

Novel cancer treatments with TLR7/8 Agonists

The present invention relates to a unit dosage form comprising a therapeutically effective amount of a TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof; to a
5 TLR7/8 agonist conjugate for use in the treatment of cancer, wherein the TLR7/8 agonist conjugate is administered via intratumoral administration in a dose ranging from 0.3 mg to 3 mg of TLR7/8 agonist per tumor; and to specific conjugates of resiquimod and related aspects.

Toll-like receptor (TLR) agonists can elicit anti-tumor activity by activating innate immune
10 cells and promoting a proinflammatory microenvironment (Aznar et al., J Immunol. 2017 Jan 1;198(1):31-39; Marabelle et al., Ann Oncol. 2017 Dec 1;28(suppl_12): xii33-xii43; Hamid et al., Oncologist. 2020 Mar;25(3):e423-e438). Local delivery of TLR agonists has shown encouraging preclinical and clinical anti-tumor activity (Hamid et al., Oncologist. 2020 Mar;25(3):e423-e438; et al., Blood.2015;126:1452-1461; Clark et al., Am J Clin
15 Dermatol.2014;15:197-216).

However, intratumoral (IT) delivery of unmodified TLR agonists such as resiquimod, a TLR7/8 agonist, can lead to rapid diffusion from the tumor, resulting in acute systemic drug exposure and transient but high levels of peripheral proinflammatory cytokines, thus limiting
20 anti-tumor benefit and increasing risk of cytokine-driven adverse effects.

Similarly, in clinical studies of resiquimod administered orally, resiquimod at a systemic concentration of about 4 ng/mL was well tolerated, whereas systemic toxicity was observed at higher doses. Side effects were consistent with systemic cytokine induction, including fever,
25 headache, shivering, and lymphopenia (Journal of Hepatology 47 (2007) 174–182)

Thus, there is a need for a more efficacious and safer treatment with TLR agonists and it is an object of the present invention to at least partially overcome the shortcomings of current treatment options with TLR agonists.

30

In a first aspect the present invention relates to a unit dosage form comprising a therapeutically effective amount of a TLR7/8 agonist conjugate or pharmaceutically acceptable salt thereof, wherein the TLR7/8 agonist conjugate comprises one or more TLR 7/8 agonist moieties

reversibly conjugated to a polymeric moiety and wherein the unit dosage form comprises 0.3 mg to 3 mg of TLR7/8 agonist.

5 In a second aspect the present invention relates to a TLR7/8 agonist conjugate for use in the treatment of cancer, wherein the TLR7/8 agonist conjugate comprises one or more TLR7/8 agonist moieties reversibly conjugated to a polymeric moiety, wherein the cancer is a solid tumor and wherein the TLR7/8 agonist conjugate is administered via intratumoral administration in a dose ranging from 0.3 mg to 3 mg of TLR7/8 agonist per tumor.

10 Surprisingly, a robust upregulation of biomarkers was observed in 4 patient tumor lesions intratumorally injected with the TLR 7/8 agonist conjugate demonstrating activation of local tumor immunity, across different tumor types. These biomarkers of activation of local and abscopal immunity by TLR7/8 agonist include altered expression of Type-I interferon related genes and altered expression of genes otherwise involved in the TLR7/8 signaling pathway.
15 Specific biomarkers of activation of local and abscopal immunity by TLR7/8 agonist include upregulation of the genes CXCL10, IFNB1, IRF1, IRF3, IRF4, IRF7, IRF8, STAT1, STAT2 in biopsies of patient tumors after treatment compared to baseline.

In addition, consistent upregulation of biomarkers of activation was also observed in 2 tumor
20 lesions which had not been injected with the TLR 7/8 agonist conjugate but were derived from patients who had undergone intratumoral injection with the TLR 7/8 agonist conjugate in other tumor lesions demonstrating activation of abscopal immunity. Of note, on-treatment biopsies were obtained 7 days post dose, suggesting prolonged immune activation maintained for more than a week after each dose. Furthermore, sustained immune activation is seen with repeat
25 dosing in injected tumors from 3 patients.

Furthermore, following intratumoral injection of the TLR7/8 agonist conjugate into a single tumor lesion at up to 0.5 mg per lesion C_{max} values were generally below 150 pg/mL and well below levels reported in the literature to be associated with cytokine release syndrome (~4000
30 pg/mL). Thus, the risk of systemic side effects is greatly reduced.

Within the present invention the terms are used having the meaning as follows.

As used herein, the term “dose” or “unit dose” refers to the predetermined amount of the drug, such as TLR7/8 agonist, administered at one time to produce a certain degree of biological response in a patient. The dose of a drug is governed by its inherent potency and in this case, it is a therapeutic dose or therapeutic unit dose. It is understood that the unit dosage form of the present invention comprises one dose or one unit dose of the TLR7/8 agonist.

Doses can be administered once or multiple times. Drug can be administered for at least six months, a year, two years, until the cancer is cured or indefinitely. Treatment may start upon diagnosis of the cancer. It is understood that treatment may last until the death of the patient.

If a dose is determined for a particular drug, such as a TLR7/8 agonist conjugate of formula (A-3) or (A-6), then the dose can be used as a guide for other TLR7/8 agonist conjugates, such that the dose or other reversible conjugates is the same by moles of TLR7/8 agonist as that for the TLR7/8 agonist of formula (A-3) or (A-6). Such guidance is particularly useful when the other conjugate releases a TLR7/8 agonist moiety with a release half-life within plus or minus 20% of that of the conjugate of TLR7/8 agonist of formula (A-3) or (A-6).

The treatments and methods of the present invention can also be used for treating a population of patients having cancer. Such a population can include at least 10, 100 or 1000 patients or may represent all patients at a particular institution.

Although clinical trials can be useful for determining doses and dosage regimens de novo, the present methods can also be performed not in the course of a clinical trial.

As used herein, the term “dosage form” refers to the physical form that comprises the active pharmaceutical ingredient in combination with selected additional ingredients or excipients and which is intended to be delivered to sites of action within the body by various routes of drug administration. It also refers to the physical form in which a precise mixture of active pharmaceutical ingredients and excipients are presented to help administration and delivery to the sites of action, achieve rapid onset of action and improve bioavailability. As used herein, the term “unit dosage form” refers to a dosage form configured for a single administration to a patient, i.e. a unit dosage form comprises one dose. For example, a unit dosage form can be a single vial or the container containing an amount of drug suitable for a single administration.

As used herein, the term “dosage regimen” is the combination of dose, and frequency with which a drug is administered. Dosage regimen can also include a route of administration (e.g., intratumoral) and/or duration of administration.

- 5 As used herein, the terms “treating” and “treatment” refer to curing, reducing or inhibiting further deterioration of at least one sign or symptom of a disease or stabilizing at least one sign or symptom of disease and can be determined by comparing sign(s) and symptom(s) in an individual patient before (baseline) and after receiving treatment or by comparing a population of treated patients to a control population as in a clinical trial or trial with an animal model.

10

As used herein, the term “drug” refers to a substance used in the treatment, cure, prevention or diagnosis of a disease or used to otherwise enhance physical or mental well-being of a patient. If a drug is conjugated to another moiety, the moiety of the resulting product that originated from the drug is referred to as “drug moiety”.

15

- As used herein the terms “immune checkpoint inhibitor” and “immune checkpoint antagonist” are used synonymously and refer to compounds that interfere with the function of, or inhibit binding of ligands that induce signaling through, cell-membrane expressed receptors that inhibit inflammatory immune cell function upon receptor activation. Such compounds may for example be biologics, such as antibodies, nanobodies, probodies, anticalins or cyclic peptides, or small molecule inhibitors.

20

- As used herein the term “T cells” refers to a type of immune cell that plays a central role in the adaptive immune response. T cells are distinguished from other immune cells by the presence of either an $\alpha\beta$ or $\gamma\delta$ T cell receptor (TCR) on their cell surface. T cells also express CD3 – a protein complex critical for TCR signaling. $\alpha\beta$ T cells can be divided into either CD4, CD8, or CD4/CD8 double negative subsets. Due to the high surface density of CD4 and CD8 on CD4⁺ and CD8⁺ T cells, CD4 and CD8 alone can often be used to identify CD4⁺ and CD8⁺ T cells respectively. Following activation via TCR recognition of cognate antigen presented by MHC molecules, T cells can mature and divide to generate effector or memory T cells. Memory T cells are a subset of T cells that have previously encountered and responded to their cognate antigen. Such T cells can recognize pathogenic antigens, such as antigens derived from bacteria or viruses, as well as cancer-associated antigens. T cells can be identified by a person skilled in the art by using phenotypic techniques such as flow cytometry. Phenotypic markers used to

25

30

identify T cells are generally conserved in mammals and include CD3, TCR α , TCR β , TCR δ , CD4, and CD8. Phenotypic markers used to identify memory T cells can vary by species and by tissue, but may include cell surface markers such as CD45RO, LY6C, CD44, and CD95.

- 5 As used herein, the term “intratumoral administration” refers to a mode of administration, in which the drug is administered directly into tumor tissue. The term “intratumoral administration” may in certain embodiments also refer to administration pre- or post-resection into or onto the tumor bed. When tumor boundary is not well defined, it is also understood that intratumoral administration includes administration to tissue adjacent to the tumor cells (“peri-
- 10 tumoral administration”). Exemplary tumors for intratumoral administration are solid tumors and lymphomas, which are disclosed in more detail elsewhere herein. Administration may occur via injection.

- As used herein the term “baseline tissue” refers to a tissue sample taken from, or adjacent to,
- 15 the area to be treated prior to treatment. For example, a biopsy of tissue to be treated can be taken immediately prior to treatment. It is understood that it may not always be possible to take a reference sample from the respective area prior to treatment, so the term “baseline tissue” may also refer to a non-treated control tissue that may be taken from a comparable location from the same animal or may be taken from a comparable location of a different animal of the
- 20 same species. It is understood that the term “animal” also covers human and in certain embodiments means mouse, rat, non-human primate or human.

- As used herein the term “anti-tumor activity” means the ability to inhibit a tumor from growing larger, i.e. tumor growth inhibition or tumor stasis, or the ability to cause a reduction in the size
- 25 of a tumor, i.e. tumor regression.

- Any reference to a biologic drug herein, i.e., to a drug manufactured in, extracted from, or semisynthesized from biological sources such as a protein drug, also covers biosimilar versions of said drug.

30

For a drug containing a TLR7/8 agonist and other components, such as the TLR7/8 reversibly conjugated to a polymeric moiety, dose can be given with respect to mass or moles of the TLR7/8 agonist moiety or to the entire drug, e.g., to the TLR7/8 agonist conjugate. Unless otherwise apparent from the context, dosages for TLR7/8 agonist conjugates are given with

respect to the TLR7/8 agonist moiety. Thus, the phrases “0.5 mg of TLR7/8 agonist” and “0.5 mg of TLR7/8 agonist conjugate” are used synonymously to give a dose of the TLR7/8 agonist conjugate based on the amount of TLR7/8 agonist moieties, which is 0.5 mg.

- 5 It is understood that the conjugates of the present invention are prodrugs.

As used herein the term “prodrug” refers to a drug moiety reversibly and covalently connected to a specialized protective group through a reversible prodrug linker moiety which is a linker moiety comprising a reversible linkage with the drug moiety and wherein the specialized
10 protective group alters or eliminates undesirable properties in the parent molecule. This also includes the enhancement of desirable properties in the drug and the suppression of undesirable properties. The specialized non-toxic protective group may also be referred to as “carrier”, such as for example Z. A prodrug releases the reversibly and covalently bound drug moiety in the form of its corresponding drug. In other words, a prodrug is a conjugate comprising a drug
15 moiety, which is covalently and reversibly conjugated to a carrier moiety via a reversible linker moiety, such as for example -L¹-, which covalent and reversible conjugation of the carrier to the reversible linker moiety is either directly or through a spacer, such as for example -L²-. The reversible linker may also be referred to as “reversible prodrug linker”. Such conjugate may release the formerly conjugated drug moiety in the form of a free drug, in which case the
20 reversible linker or reversible prodrug linker is a traceless linker.

As used herein, the term “free form” of a drug means the drug in its unmodified, pharmacologically active form.

- 25 As used herein the term “spacer” refers to a moiety that connects at least two other moieties with each other.

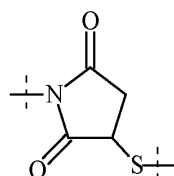
As used herein, the terms “reversible”, “reversibly”, “degradable” or “degradably” with regard to the attachment of a first moiety to a second moiety means that the linkage that connects said
30 first and second moiety is cleavable under physiological conditions, which physiological conditions are aqueous buffer at pH 7.4 and 37°C, with a half-life ranging from one day to three months, such as from two days to two months, such as from three days to one month. Such cleavage is in certain embodiments non-enzymatically. Accordingly, the term “stable” with regard to the attachment of a first moiety to a second moiety means that the linkage that

connects said first and second moiety exhibits a half-life of more than three months under physiological conditions.

As used herein, the term “reagent” means a chemical compound, which comprises at least one functional group for reaction with the functional group of another chemical compound or drug. It is understood that a drug comprising a functional group is also a reagent.

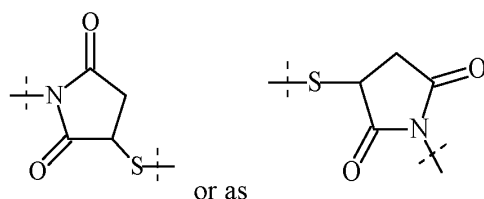
As used herein, the term “moiety” means a part of a molecule, which lacks one or more atom(s) compared to the corresponding reagent. If, for example, a reagent of the formula “H-X-H” reacts with another reagent and becomes part of the reaction product, the corresponding moiety of the reaction product has the structure “H-X-” or “-X-”, whereas each “-” indicates attachment to another moiety. Accordingly, a drug moiety, such as TLR7/8 agonist moiety, is released from a reversible linkage as a drug, such as a TLR7/8 agonist drug.

It is understood that if the chemical structure of a group of atoms is provided and if this group of atoms is attached to two moieties or is interrupting a moiety, said chemical structure can be attached to the two moieties in either orientation, unless explicitly stated otherwise. For example, a moiety “-C(O)N(R¹)-” can be attached to two moieties or interrupting a moiety either as “-C(O)N(R¹)-” or as “-N(R¹)C(O)-”. Similarly, a moiety



20

can be attached to two moieties or can interrupt a moiety either as



The term “substituted” as used herein means that one or more -H atom(s) of a molecule or moiety are replaced by a different atom or a group of atoms, which are referred to as “substituent”.

25

As used herein, the term “substituent” in certain embodiments refers to a moiety selected from the group consisting of halogen, -CN, -COOR^{x1}, -OR^{x1}, -C(O)R^{x1}, -C(O)N(R^{x1}R^{x1a}), -S(O)₂N(R^{x1}R^{x1a}), -S(O)N(R^{x1}R^{x1a}), -S(O)₂R^{x1}, -S(O)R^{x1}, -N(R^{x1})S(O)₂N(R^{x1a}R^{x1b}), -SR^{x1}, -N(R^{x1}R^{x1a}), -NO₂, -OC(O)R^{x1}, -N(R^{x1})C(O)R^{x1a}, -N(R^{x1})S(O)₂R^{x1a}, -N(R^{x1})S(O)R^{x1a}, -N(R^{x1})C(O)OR^{x1a}, -N(R^{x1})C(O)N(R^{x1a}R^{x1b}), -OC(O)N(R^{x1}R^{x1a}), -T⁰, C₁₋₅₀ alkyl, C₂₋₅₀ alkenyl, and C₂₋₅₀ alkynyl; wherein -T⁰, C₁₋₅₀ alkyl, C₂₋₅₀ alkenyl, and C₂₋₅₀ alkynyl are optionally substituted with one or more -R^{x2}, which are the same or different and wherein C₁₋₅₀ alkyl, C₂₋₅₀ alkenyl, and C₂₋₅₀ alkynyl are optionally interrupted by one or more groups selected from the group consisting of -T⁰-, -C(O)O-, -O-, -C(O)-, -C(O)N(R^{x3})-, -S(O)₂N(R^{x3})-, -S(O)N(R^{x3})-, -S(O)₂-, -S(O)-, -N(R^{x3})S(O)₂N(R^{x3a})-, -S-, -N(R^{x3})-, -OC(OR^{x3})(R^{x3a})-, -N(R^{x3})C(O)N(R^{x3a})-, and -OC(O)N(R^{x3})-;

-R^{x1}, -R^{x1a}, -R^{x1b} are independently of each other selected from the group consisting of -H, -T⁰, C₁₋₅₀ alkyl, C₂₋₅₀ alkenyl, and C₂₋₅₀ alkynyl; wherein -T⁰, C₁₋₅₀ alkyl, C₂₋₅₀ alkenyl, and C₂₋₅₀ alkynyl are optionally substituted with one or more -R^{x2}, which are the same or different and wherein C₁₋₅₀ alkyl, C₂₋₅₀ alkenyl, and C₂₋₅₀ alkynyl are optionally interrupted by one or more groups selected from the group consisting of -T⁰-, -C(O)O-, -O-, -C(O)-, -C(O)N(R^{x3})-, -S(O)₂N(R^{x3})-, -S(O)N(R^{x3})-, -S(O)₂-, -S(O)-, -N(R^{x3})S(O)₂N(R^{x3a})-, -S-, -N(R^{x3})-, -OC(OR^{x3})(R^{x3a})-, -N(R^{x3})C(O)N(R^{x3a})-, and -OC(O)N(R^{x3})-;

each T⁰ is independently selected from the group consisting of phenyl, naphthyl, indenyl, indanyl, tetralinyl, C₃₋₁₀ cycloalkyl, 3- to 10-membered heterocyclyl, and 8- to 11-membered heterobicyclyl; wherein each T⁰ is independently optionally substituted with one or more -R^{x2}, which are the same or different;

each -R^{x2} is independently selected from the group consisting of halogen, -CN, oxo (=O), -COOR^{x4}, -OR^{x4}, -C(O)R^{x4}, -C(O)N(R^{x4}R^{x4a}), -S(O)₂N(R^{x4}R^{x4a}), -S(O)N(R^{x4}R^{x4a}), -S(O)₂R^{x4}, -S(O)R^{x4}, -N(R^{x4})S(O)₂N(R^{x4a}R^{x4b}), -SR^{x4}, -N(R^{x4}R^{x4a}), -NO₂, -OC(O)R^{x4}, -N(R^{x4})C(O)R^{x4a}, -N(R^{x4})S(O)₂R^{x4a}, -N(R^{x4})S(O)R^{x4a}, -N(R^{x4})C(O)OR^{x4a}, -N(R^{x4})C(O)N(R^{x4a}R^{x4b}), -OC(O)N(R^{x4}R^{x4a}), and C₁₋₆ alkyl; wherein C₁₋₆ alkyl is optionally substituted with one or more halogen, which are the same or different;

each $-R^{x3}$, $-R^{x3a}$, $-R^{x4}$, $-R^{x4a}$, $-R^{x4b}$ is independently selected from the group consisting of -H and C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different.

- 5 In certain embodiments a maximum of 6 -H atoms of an optionally substituted molecule are independently replaced by a substituent, e.g. 5 -H atoms are independently replaced by a substituent, 4 -H atoms are independently replaced by a substituent, 3 -H atoms are independently replaced by a substituent, 2 -H atoms are independently replaced by a substituent, or 1 -H atom is replaced by a substituent.

10

As used herein, the term “hydrogel” means a hydrophilic or amphiphilic polymeric network composed of homopolymers or copolymers, which is insoluble due to the presence of hydrophobic interactions, hydrogen bonds, ionic interactions and/or covalent chemical crosslinks. The crosslinks provide the network structure and physical integrity. In certain
15 embodiments the hydrogel is insoluble due to the presence of covalent chemical crosslinks.

20

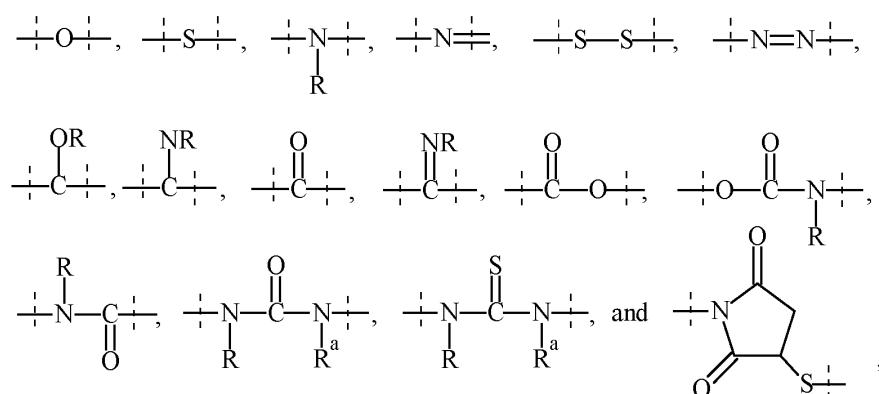
As used herein the term “about” in combination with a numerical value is used to indicate a range ranging from and including the numerical value plus and minus no more than 25% of said numerical value, such as no more than plus and minus 20% of said numerical value or such as no more than plus and minus 10% of said numerical value. For example, the phrase
25 “about 200” is used to mean a range ranging from and including 200 +/- 25%, i.e., ranging from and including 150 to 250; such as 200 +/- 20%, i.e., ranging from and including 160 to 240; such as ranging from and including 200 +/-10%, i.e., ranging from and including 180 to 220. It is understood that a percentage given as “about 50%” does not mean “50% +/- 25%”, i.e., ranging from and including 25 to 75%, but “about 50%” means ranging from and including
30 37.5 to 62.5%, i.e., plus and minus 25% of the numerical value which is 50. In case the range covered by “about X” is defined by one or two fractions at one or both ends of the range and it is clear that only integers are suitable values, the one or two fractions are rounded using the “round half up” rule to obtain the nearest integer.

The term “approx.” is used synonymously with “about”.

As used herein, the term “polymer” means a molecule comprising repeating structural units, i.e., the monomers, connected by chemical bonds in a linear, circular, branched, crosslinked or dendrimeric way or a combination thereof, which may be of synthetic or biological origin or a combination of both. The monomers may be identical, in which case the polymer is a homopolymer, or may be different, in which case the polymer is a heteropolymer. A heteropolymer may also be referred to as a “copolymer” and includes, for example, alternating copolymers in which monomers of different types alternate, periodic copolymers, in which monomers of different types are arranged in a repeating sequence; statistical copolymers, in which monomers of different types are arranged randomly; block copolymers, in which blocks of different homopolymers consisting of only one type of monomers are linked by a covalent bond; and gradient copolymers, in which the composition of different monomers changes gradually along a polymer chain. It is understood that a polymer may also comprise one or more other moieties, such as, for example, one or more functional groups. The term “polymer” also relates to a peptide or protein, even though the side chains of individual amino acid residues may be different. It is understood that for covalently crosslinked polymers, such as hydrogels, no meaningful molecular weight ranges can be provided.

As used herein, the term “polymeric” refers to a reagent or a moiety comprising one or more polymers or polymer moieties. A polymeric reagent or moiety may optionally also comprise one or more other moieties, which in certain embodiments are selected from the group consisting of:

- C₁₋₅₀ alkyl, C₂₋₅₀ alkenyl, C₂₋₅₀ alkynyl, C₃₋₁₀ cycloalkyl, 3- to 10-membered heterocyclyl, 8- to 11-membered heterobicycyl, phenyl, naphthyl, indenyl, indanyl, and tetralinyl;
- branching points, such as -CR<, >C< or -N<; and
- linkages selected from the group comprising



wherein

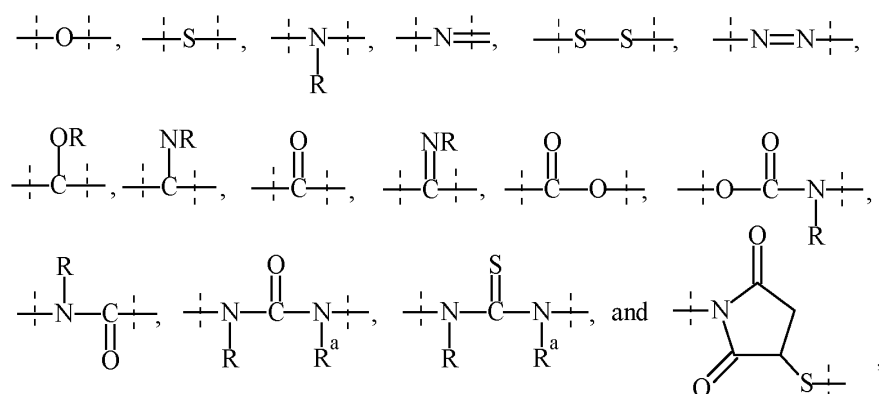
dashed lines indicate attachment to the remainder of the moiety or reagent, and

-R and -R^a are independently of each other selected from the group consisting of -H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, 2-methylbutyl, 2,2-dimethylpropyl, n-hexyl, 2-methylpentyl, 3-methylpentyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl and 3,3-dimethylpropyl; and which moieties and linkages are optionally further substituted.

10 In certain embodiments a polymeric reagent or moiety may optionally also comprise one or more other moieties, which in certain embodiments are selected from the group consisting of:

- C₁₋₅₀ alkyl, C₂₋₅₀ alkenyl, C₂₋₅₀ alkynyl, C₃₋₁₀ cycloalkyl, 3- to 10-membered heterocyclyl, 8- to 11-membered heterobicyclyl, phenyl, naphthyl, indenyl, indanyl, and tetralinyl; and

- linkages selected from the group comprising



wherein

dashed lines indicate attachment to the remainder of the moiety or reagent, and

-R and -R^a are independently of each other selected from the group consisting of -H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, 2-methylbutyl, 2,2-dimethylpropyl, n-hexyl, 2-methylpentyl, 3-methylpentyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl and 3,3-dimethylpropyl; and
5 which moieties and linkages are optionally further substituted.

The person skilled in the art understands that the polymerization products obtained from a polymerization reaction do not all have the same molecular weight, but rather exhibit a molecular weight distribution. Consequently, the molecular weight ranges, molecular weights,
10 ranges of numbers of monomers in a polymer and numbers of monomers in a polymer as used herein, refer to the number average molecular weight and number average of monomers, i.e. to the arithmetic mean of the molecular weight of the polymer or polymeric moiety and the arithmetic mean of the number of monomers of the polymer or polymeric moiety.

15 Accordingly, in a polymeric moiety comprising “x” monomer units any integer given for “x” therefore corresponds to the arithmetic mean number of monomers. Any range of integers given for “x” provides the range of integers in which the arithmetic mean numbers of monomers lie. An integer for “x” given as “about x” means that the arithmetic mean numbers of monomers lie in a range of integers of x +/- 25%, such as x +/- 20% or such as x +/- 10%.

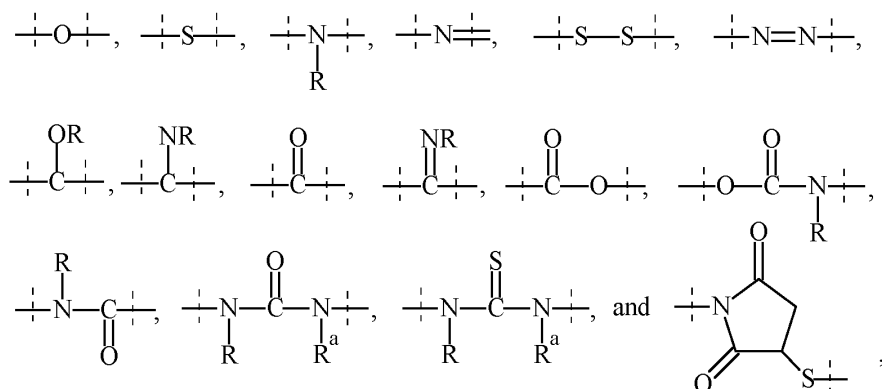
20

As used herein, the term “number average molecular weight” means the ordinary arithmetic mean of the molecular weights of the individual polymers.

As used herein, the term “PEG-based” in relation to a moiety or reagent means that said moiety or reagent comprises PEG. Such PEG-based moiety or reagent comprises at least 10% (w/w) PEG, such as at least 20% (w/w) PEG, such as at least 30% (w/w) PEG, such as at least 40% (w/w) PEG, such as at least 50% (w/w), such as at least 60 (w/w) PEG, such as at least 70% (w/w) PEG, such as at least 80% (w/w) PEG, such as at least 90% (w/w) PEG, or such as at least 95% (w/w) PEG. The remaining weight percentage of the PEG-based moiety or reagent
25 may be other moieties, such as those selected from the group consisting of:
30

- C₁₋₅₀ alkyl, C₂₋₅₀ alkenyl, C₂₋₅₀ alkynyl, C₃₋₁₀ cycloalkyl, 3- to 10-membered heterocyclyl, 8- to 11-membered heterobicyclyl, phenyl, naphthyl, indenyl, indanyl, and tetralinyl; and

- linkages selected from the group consisting of



The terms “poly(alkylene glycol)-based”, “poly(propylene glycol)-based” and “hyaluronic acid-based” are used accordingly.

The term “interrupted” means that a moiety is inserted between two carbon atoms or – if the insertion is at one of the moiety’s ends – between a carbon or heteroatom and a hydrogen atom.

As used herein, the term “C₁₋₄ alkyl” alone or in combination means a straight-chain or branched alkyl moiety having 1 to 4 carbon atoms. If present at the end of a molecule, examples of straight-chain or branched C₁₋₄ alkyl are methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl. When two moieties of a molecule are linked by the C₁₋₄ alkyl, then examples for such C₁₋₄ alkyl groups are -CH₂-, -CH₂-CH₂-, -CH(CH₃)-, -CH₂-CH₂-CH₂-, -CH(C₂H₅)-, -C(CH₃)₂-. Each hydrogen of a C₁₋₄ alkyl carbon may optionally be replaced by a substituent as defined above. Optionally, a C₁₋₄ alkyl may be interrupted by one or more moieties as defined below.

As used herein, the term “C₁₋₆ alkyl” alone or in combination means a straight-chain or branched alkyl moiety having 1 to 6 carbon atoms. If present at the end of a molecule, examples of straight-chain and branched C₁₋₆ alkyl groups are methyl, ethyl, n-propyl, isopropyl, n-butyl,

isobutyl, sec-butyl, tert-butyl, n-pentyl, 2-methylbutyl, 2,2-dimethylpropyl, n-hexyl, 2-methylpentyl, 3-methylpentyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl and 3,3-dimethylpropyl. When two moieties of a molecule are linked by the C₁₋₆ alkyl group, then examples for such C₁₋₆ alkyl groups are -CH₂-, -CH₂-CH₂-, -CH(CH₃)-, -CH₂-CH₂-CH₂-, -CH(C₂H₅)- and -C(CH₃)₂-. Each hydrogen atom of a C₁₋₆ carbon may optionally be replaced by a substituent as defined above. Optionally, a C₁₋₆ alkyl may be interrupted by one or more moieties as defined below.

Accordingly, “C₁₋₁₀ alkyl”, “C₁₋₂₀ alkyl” or “C₁₋₅₀ alkyl” means an alkyl chain having 1 to 10, 1 to 20 or 1 to 50 carbon atoms, respectively, wherein each hydrogen atom of the C₁₋₁₀, C₁₋₂₀ or C₁₋₅₀ carbon may optionally be replaced by a substituent as defined above. Optionally, a C₁₋₁₀ or C₁₋₅₀ alkyl may be interrupted by one or more moieties as defined below.

As used herein, the term “C₂₋₆ alkenyl” alone or in combination means a straight-chain or branched hydrocarbon moiety comprising at least one carbon-carbon double bond having 2 to 6 carbon atoms. If present at the end of a molecule, examples are -CH=CH₂, -CH=CH-CH₃, -CH₂-CH=CH₂, -CH=CHCH₂-CH₃ and -CH=CH-CH=CH₂. When two moieties of a molecule are linked by the C₂₋₆ alkenyl group, then an example for such C₂₋₆ alkenyl is -CH=CH-. Each hydrogen atom of a C₂₋₆ alkenyl moiety may optionally be replaced by a substituent as defined above. Optionally, a C₂₋₆ alkenyl may be interrupted by one or more moieties as defined below.

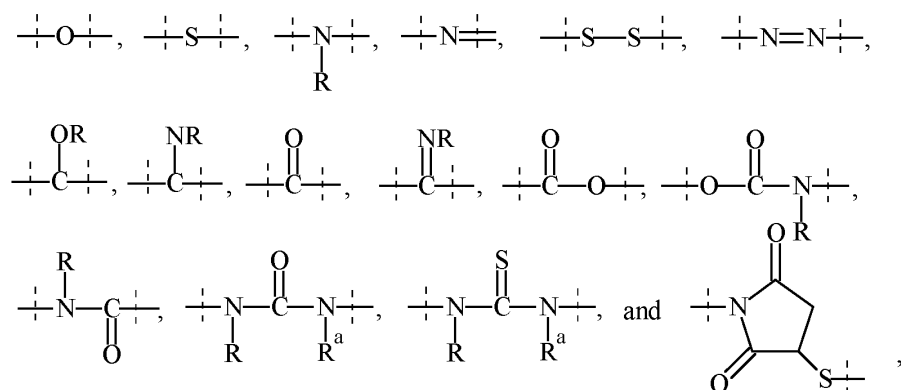
Accordingly, the terms “C₂₋₁₀ alkenyl”, “C₂₋₂₀ alkenyl” or “C₂₋₅₀ alkenyl” alone or in combination mean a straight-chain or branched hydrocarbon moiety comprising at least one carbon-carbon double bond having 2 to 10, 2 to 20 or 2 to 50 carbon atoms, respectively. Each hydrogen atom of a C₂₋₁₀ alkenyl, C₂₋₂₀ alkenyl or C₂₋₅₀ alkenyl group may optionally be replaced by a substituent as defined above. Optionally, a C₂₋₁₀ alkenyl, C₂₋₂₀ alkenyl or C₂₋₅₀ alkenyl may be interrupted by one or more moieties as defined below.

As used herein, the term “C₂₋₆ alkynyl” alone or in combination means a straight-chain or branched hydrocarbon moiety comprising at least one carbon-carbon triple bond having 2 to 6 carbon atoms. If present at the end of a molecule, examples are -C≡CH, -CH₂-C≡CH, CH₂-CH₂-C≡CH and CH₂-C≡C-CH₃. When two moieties of a molecule are linked by the alkynyl group, then an example is -C≡C-. Each hydrogen atom of a C₂₋₆ alkynyl group may

optionally be replaced by a substituent as defined above. Optionally, one or more double bond(s) may occur. Optionally, a C₂₋₆ alkynyl may be interrupted by one or more moieties as defined below.

- 5 Accordingly, as used herein, the term "C₂₋₁₀ alkynyl", "C₂₋₂₀ alkynyl" and "C₂₋₅₀ alkynyl" alone or in combination means a straight-chain or branched hydrocarbon moiety comprising at least one carbon-carbon triple bond having 2 to 10, 2 to 20 or 2 to 50 carbon atoms, respectively. Each hydrogen atom of a C₂₋₁₀ alkynyl, C₂₋₂₀ alkynyl or C₂₋₅₀ alkynyl group may optionally be replaced by a substituent as defined above. Optionally, one or more double bond(s) may occur.
- 10 Optionally, a C₂₋₁₀ alkynyl, C₂₋₂₀ alkynyl or C₂₋₅₀ alkynyl may be interrupted by one or more moieties as defined below.

- As mentioned above, a C₁₋₄ alkyl, C₁₋₆ alkyl, C₁₋₁₀ alkyl, C₁₋₂₀ alkyl, C₁₋₅₀ alkyl, C₂₋₆ alkenyl, C₂₋₁₀ alkenyl, C₂₋₂₀ alkenyl, C₂₋₅₀ alkenyl, C₂₋₆ alkynyl, C₂₋₁₀ alkynyl, C₂₋₂₀ alkenyl or C₂₋₅₀ alkynyl may optionally be interrupted by one or more moieties which may be selected from the group consisting of
- 15



wherein

dashed lines indicate attachment to the remainder of the moiety or reagent; and

- 20 -R and -R^a are independently of each other selected from the group consisting of -H and C₁₋₆ alkyl.

- As used herein, the term "C₃₋₁₀ cycloalkyl" means a cyclic alkyl chain having 3 to 10 carbon atoms, which may be saturated or unsaturated, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl, cyclooctyl, cyclononyl or cyclodecyl. Each hydrogen
- 25

atom of a C₃₋₁₀ cycloalkyl carbon may be replaced by a substituent as defined above. The term "C₃₋₁₀ cycloalkyl" also includes bridged bicycles like norbornane or norbornene.

The term "8- to 30-membered carbopolycyclyl" or "8- to 30-membered carbopolycycle" means
5 a cyclic moiety of two or more rings with 8 to 30 ring atoms, where two neighboring rings share at least one ring atom and that may contain up to the maximum number of double bonds (aromatic or non-aromatic ring which is fully, partially or un-saturated). In one embodiment an 8- to 30-membered carbopolycyclyl means a cyclic moiety of two, three, four or five rings. In another embodiment an 8- to 30-membered carbopolycyclyl means a cyclic moiety of two,
10 three or four rings.

As used herein, the term "3- to 10-membered heterocyclyl" or "3- to 10-membered heterocycle" means a ring with 3, 4, 5, 6, 7, 8, 9 or 10 ring atoms that may contain up to the maximum number of double bonds (aromatic or non-aromatic ring which is fully, partially or un-saturated) wherein at least one ring atom up to 4 ring atoms are replaced by a heteroatom selected from the group consisting of sulfur (including -S(O)-, -S(O)₂-), oxygen and nitrogen (including =N(O)-) and wherein the ring is linked to the rest of the molecule via a carbon or nitrogen atom. Examples for 3- to 10-membered heterocycles include but are not limited to
15 aziridine, oxirane, thiirane, azirine, oxirene, thiirene, azetidine, oxetane, thietane, furan, thiophene, pyrrole, pyrroline, imidazole, imidazoline, pyrazole, pyrazoline, oxazole, oxazoline, isoxazole, isoxazoline, thiazole, thiazoline, isothiazole, isothiazoline, thiadiazole, thiadiazoline, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, imidazolidine, pyrazolidine, oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, thiadiazolidine, sulfolane, pyran, dihydropyran, tetrahydropyran, imidazolidine, pyridine, pyridazine, pyrazine, pyrimidine,
20 piperazine, piperidine, morpholine, tetrazole, triazole, triazolidine, tetrazolidine, diazepane, azepine and homopiperazine. Each hydrogen atom of a 3- to 10-membered heterocyclyl or 3- to 10-membered heterocyclic group may be replaced by a substituent.

As used herein, the term "8- to 11-membered heterobicyclyl" or "8- to 11-membered
30 heterobicycle" means a heterocyclic moiety of two rings with 8 to 11 ring atoms, where at least one ring atom is shared by both rings and that may contain up to the maximum number of double bonds (aromatic or non-aromatic ring which is fully, partially or un-saturated) wherein at least one ring atom up to 6 ring atoms are replaced by a heteroatom selected from the group consisting of sulfur (including -S(O)-, -S(O)₂-), oxygen and nitrogen (including =N(O)-) and

wherein the ring is linked to the rest of the molecule via a carbon or nitrogen atom. Examples for an 8- to 11-membered heterobicycle are indole, indoline, benzofuran, benzothiophene, benzoxazole, benzisoxazole, benzothiazole, benzisothiazole, benzimidazole, benzimidazoline, quinoline, quinazoline, dihydroquinazoline, quinoline, dihydroquinoline, tetrahydroquinoline, decahydroquinoline, isoquinoline, decahydroisoquinoline, tetrahydroisoquinoline, dihydroisoquinoline, benzazepine, purine and pteridine. The term 8- to 11-membered heterobicycle also includes spiro structures of two rings like 1,4-dioxo-8-azaspiro[4.5]decane or bridged heterocycles like 8-aza-bicyclo[3.2.1]octane. Each hydrogen atom of an 8- to 11-membered heterobicycyl or 8- to 11-membered heterobicycle carbon may be replaced by a substituent.

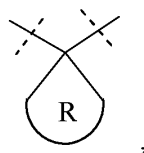
Similarly, the term “8- to 30-membered heteropolycyclyl” or “8- to 30-membered heteropolycycle” means a heterocyclic moiety of more than two rings with 8 to 30 ring atoms, such as of three, four or five rings, where two neighboring rings share at least one ring atom and that may contain up to the maximum number of double bonds (aromatic or non-aromatic ring which is fully, partially or unsaturated), wherein at least one ring atom up to 10 ring atoms are replaced by a heteroatom selected from the group of sulfur (including -S(O)-, -S(O)₂-), oxygen and nitrogen (including =N(O)-) and wherein the ring is linked to the rest of a molecule via a carbon or nitrogen atom.

20

It is understood that the phrase “the pair R^x/R^y is joined together with the atom to which they are attached to form a C₃₋₁₀ cycloalkyl or a 3- to 10-membered heterocyclyl” in relation with a moiety of the structure

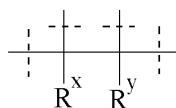


means that R^x and R^y form the following structure:

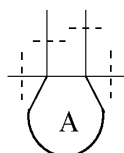


wherein R is C₃₋₁₀ cycloalkyl or 3- to 10-membered heterocyclyl.

It is also understood that the phrase “the pair R^x/R^y is joint together with the atoms to which they are attached to form a ring A” in relation with a moiety of the structure



means that R^x and R^y form the following structure:



5

As used herein, "halogen" means fluoro, chloro, bromo or iodo. In certain embodiments halogen is fluoro or chloro.

- 10 As used herein, the term “functional group” means a group of atoms which can react with other groups of atoms. Exemplary functional groups are carboxylic acid, primary amine, secondary amine, tertiary amine, maleimide, thiol, sulfonic acid, carbonate, carbamate, hydroxyl, aldehyde, ketone, hydrazine, isocyanate, isothiocyanate, phosphoric acid, phosphonic acid, haloacetyl, alkyl halide, acryloyl, aryl fluoride, hydroxylamine, disulfide, sulfonamides, 15 sulfuric acid, vinyl sulfone, vinyl ketone, diazoalkane, oxirane, and aziridine.

- In case the conjugates of the present invention comprise one or more acidic or basic groups, the invention also comprises their corresponding pharmaceutically or toxicologically acceptable salts, in particular their pharmaceutically utilizable salts. Thus, the conjugates of the 20 present invention comprising acidic groups can be used according to the invention, for example, as alkali metal salts, alkaline earth metal salts or as ammonium salts. More precise examples of such salts include sodium salts, potassium salts, calcium salts, magnesium salts or salts with ammonia or organic amines such as, for example, ethylamine, ethanolamine, triethanolamine, amino acids, and quaternary ammonium salts, like tetrabutylammonium or 25 cetyl trimethylammonium. Conjugates of the present invention comprising one or more basic groups, i.e. groups which can be protonated, can be present and can be used according to the invention in the form of their addition salts with inorganic or organic acids. Examples for suitable acids include hydrogen chloride, hydrogen bromide, phosphoric acid, sulfuric acid, nitric acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acids, oxalic

acid, acetic acid, tartaric acid, lactic acid, salicylic acid, benzoic acid, formic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, malic acid, sulfaminic acid, phenylpropionic acid, gluconic acid, ascorbic acid, isonicotinic acid, citric acid, adipic acid, trifluoroacetic acid, and other acids known to the person skilled in the art. For the person skilled in the art further methods are known for converting the basic group into a cation like the alkylation of an amine group resulting in a positively-charge ammonium group and an appropriate counterion of the salt. If the conjugates of the present invention simultaneously comprise acidic and basic groups, the invention also includes, in addition to the salt forms mentioned, inner salts or betaines (zwitterions). The respective salts can be obtained by customary methods, which are known to the person skilled in the art like, for example by contacting these prodrugs with an organic or inorganic acid or base in a solvent or dispersant, or by anion exchange or cation exchange with other salts. The present invention also includes all salts of the conjugates of the present invention which, owing to low physiological compatibility, are not directly suitable for use in pharmaceuticals but which can be used, for example, as intermediates for chemical reactions or for the preparation of pharmaceutically acceptable salts.

The term "pharmaceutically acceptable" means a substance that does not cause harm when administered to a patient and in certain embodiments means approved by a regulatory agency, such as the EMA (Europe) and/or the FDA (US) and/or any other national regulatory agency for use in animals, such as for use in humans.

As used herein, the term "excipient" refers to a diluent, adjuvant, or vehicle with which the therapeutic, such as a drug or prodrug, is administered. Such pharmaceutical excipient may be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, including but not limited to peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred excipient when the pharmaceutical composition is administered orally. Saline and aqueous dextrose are preferred excipients when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions are preferably employed as liquid excipients for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, mannitol, trehalose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, hyaluronic acid, propylene glycol, water, ethanol and the like. The pharmaceutical composition, if desired,

can also contain minor amounts of wetting or emulsifying agents, pH buffering agents, like, for example, acetate, succinate, tris, carbonate, phosphate, HEPES (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid), MES (2-(*N*-morpholino)ethanesulfonic acid), or may contain detergents, like Tween, poloxamers, poloxamines, CHAPS, Igepal, or amino acids like, for example, glycine, lysine, or histidine. These pharmaceutical compositions can take the form of solutions, suspensions, emulsions, tablets, pills, capsules, powders, sustained-release formulations and the like. The pharmaceutical composition can be formulated as a suppository, with traditional binders and excipients such as triglycerides. Oral formulation can include standard excipients such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Such compositions will contain a therapeutically effective amount of the drug or drug moiety, together with a suitable amount of excipient so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

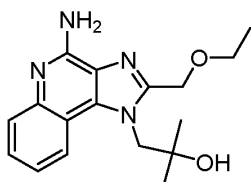
The term “peptide” or “polypeptide” as used herein refers to a chain of at least 2 and up to and including 50 amino acid monomer moieties, which may also be referred to as “amino acid residues”, linked by peptide (amide) linkages. The amino acid monomers may be selected from the group consisting of proteinogenic amino acids and non-proteinogenic amino acids and may be D- or L-amino acids. The term “peptide” also includes peptidomimetics, such as peptoids, beta-peptides, cyclic peptides and depsipeptides and covers such peptidomimetic chains with up to and including 50 monomer moieties.

As used herein, the term “protein” refers to a chain of more than 50 amino acid monomer moieties, which may also be referred to as “amino acid residues”, linked by peptide linkages, in which preferably no more than 12000 amino acid monomers are linked by peptide linkages, such as no more than 10000 amino acid monomer moieties, no more than 8000 amino acid monomer moieties, no more than 5000 amino acid monomer moieties or no more than 2000 amino acid monomer moieties.

In general, the terms “comprise” or “comprising” also encompasses “consist of” or “consisting of”.

In certain embodiments the TLR7/8 agonist of the first, second and third embodiment is selected from the group consisting of CL075, CL097, poly(dT), resiquimod (R-848, VML600, S28463), MEDI9197 (3M-052), NKTR262, DV1001, IMO4200, IPH3201 and VTX1463.

- 5 In certain embodiments the TLR7/8 agonist of the first, second and third embodiment is resiquimod. Resiquimod has the following structure:



- In certain embodiments a unit dosage form of the first aspect comprises a therapeutically effective amount of a TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients. In such case the unit dosage form comprises a pharmaceutical formulation comprising a therapeutically effective amount of a TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof.
- 10 A unit dosage form of the first aspect comprises in certain embodiments 0.5 mg TLR7/8 agonist. In certain embodiments a unit dosage form of the first aspect comprises 1 mg TLR7/8 agonist. In certain embodiments a unit dosage form of the first aspect comprises 2 mg TLR7/8 agonist. A unit dosage form of the first aspect comprises in certain embodiments 0.5 mg TLR7/8 agonist and one or more excipients. In certain embodiments a unit dosage form of the first aspect comprises 1 mg TLR7/8 and one or more excipients. In certain embodiments a unit dosage form of the first aspect comprises 2 mg TLR7/8 and one or more excipients. It is understood that if the unit dosage form comprises for example 0.5 mg TLR7/8 agonist, such dose of 0.5 mg TLR7/8 is a unit dose.
- 15 20 25 In certain embodiments a unit dosage form of the first aspect comprises 0.5 mg resiquimod. In certain embodiments a unit dosage form of the first aspect comprises 1 mg resiquimod. In certain embodiments a unit dosage form of the first aspect comprises 2 mg resiquimod. In certain embodiments a unit dosage form of the first aspect comprises 0.5 mg resiquimod and one or more excipients. In certain embodiments a unit dosage form of the first aspect comprises 2 mg resiquimod and one or more excipients.
- 30

In certain embodiments the unit dosage form of the first aspect comprises a pharmaceutical formulation comprising the TLR7/8 agonist and the pharmaceutical formulation is a dry formulation, such as a lyophilized formulation. Such dry formulation is resuspended prior to administration to a patient using a liquid such as sterile water or a sterile buffer. Such resuspended formulation is in certain embodiments a suspension.

In certain embodiments the unit dosage form of the first aspect comprises a pharmaceutical formulation comprising the TLR7/8 agonist and the pharmaceutical formulation is a liquid formulation, such as a suspension.

10

In certain embodiments the unit dosage form of the first aspect comprises the TLR7/8 agonist conjugate in a volume ranging from 0.1 ml to 2 ml. In certain embodiments the unit dosage form of the first aspect comprises the TLR7/8 agonist conjugate in a volume ranging from 0.2 ml to 1.5 ml. In certain embodiments the unit dosage form of the first aspect comprises the TLR7/8 agonist conjugate in a volume of 0.25 ml. In certain embodiments the unit dosage form of the first aspect comprises the TLR7/8 agonist conjugate in a volume of 0.5 ml. In certain embodiments the unit dosage form of the first aspect comprises the TLR7/8 agonist conjugate in a volume of 1 ml.

20 In certain embodiments the unit dosage form of the first aspect comprises the TLR7/8 agonist conjugate in a volume ranging from 0.1 ml to 2 ml and the TLR7/8 agonist is resiquimod. In certain embodiments the unit dosage form of the first aspect comprises the TLR7/8 agonist conjugate in a volume ranging from 0.2 ml to 1.5 ml and the TLR7/8 agonist is resiquimod. In certain embodiments the unit dosage form of the first aspect comprises the TLR7/8 agonist conjugate in a volume of 0.25 ml and the TLR7/8 agonist is resiquimod. In certain
25 embodiments the unit dosage form of the first aspect comprises the TLR7/8 agonist conjugate in a volume of 0.5 ml and the TLR7/8 agonist is resiquimod. In certain embodiments the unit dosage form of the first aspect comprises the TLR7/8 agonist conjugate in a volume of 1 ml and the TLR7/8 agonist is resiquimod.

30

In certain embodiments a unit dosage form of the first aspect comprises 0.5 mg of the TLR7/8 agonist in a volume of 1 ml. In certain embodiments a unit dosage form of the first aspect comprises 0.5 mg of the TLR7/8 agonist in a volume of 0.25 ml. In certain embodiments a unit dosage form of the first aspect comprises 1 mg of the TLR7/8 agonist in a volume of 2 ml. In

certain embodiments a unit dosage form of the first aspect comprises 1 mg of the TLR7/8 agonist in a volume of 0.5 ml.

5 In certain embodiments a unit dosage form of the first aspect comprises 0.5 mg of the TLR7/8 agonist, which TLR7/8 agonist is resiquimod, in a volume of 1 ml. In certain embodiments a unit dosage form of the first aspect comprises 0.5 mg of the TLR7/8 agonist, which TLR7/8 agonist is resiquimod, in a volume of 0.25 ml. In certain embodiments a unit dosage form of the first aspect comprises 1 mg of the TLR7/8 agonist, which TLR7/8 agonist is resiquimod, in a volume of 2 ml. In certain embodiments a unit dosage form of the first aspect comprises 1
10 mg of the TLR7/8 agonist, which TLR7/8 agonist is resiquimod, in a volume of 0.5 ml.

In certain embodiments the unit dosage form is a vial, a dual-chamber cartridge, an ampoule or a syringe comprising the unit dose.

15 In certain embodiments the unit dosage form is vial comprising the unit dose. Such vial may be a vial with a stopper, such as a bromo-butyl stopper, and a seal cap, such as an aluminium seal cap. In certain embodiments the vial is a glass vial, such as a type 1 glass vial. Such a vial may have a size of 1 ml, 2 ml or 5 ml, for example.

20 In certain embodiments the unit dosage form is stored at a temperature ranging from -80°C to +25°C. In certain embodiments the unit dosage form is stored at a temperature ranging from -80°C to 10°C. In certain embodiments the unit dosage form is stored at a temperature ranging from -80°C to -60°C. In certain embodiments the unit dosage form is stored at a temperature ranging from -30°C to -15°C. In certain embodiments the unit dosage form is
25 stored at a temperature ranging from 0°C to +10°C. In certain embodiments the unit dosage form is stored at about -80°C. In certain embodiments the unit dosage form is stored at -80°C. In certain embodiments the unit dosage form is stored at about -20°C. In certain embodiments the unit dosage form is stored at -20°C. In certain embodiments the unit dosage form is stored at a temperature ranging from 2°C to 8°C.

30

In certain embodiments the unit dosage form of the first aspect is a vial comprising the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof. In certain embodiments the unit dosage form of the first aspect is a vial comprising 0.5 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof. In certain embodiments the unit dosage form of

the first aspect is a vial comprising 1 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof. In certain embodiments the unit dosage form of the first aspect is a vial comprising 2 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof.

- 5 In certain embodiments the unit dosage form of the first aspect is a vial comprising the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients. In certain embodiments the unit dosage form of the first aspect is a vial comprising 0.5 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients. In certain embodiments the unit dosage form of the first aspect is a vial comprising
- 10 1 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients. In certain embodiments the unit dosage form of the first aspect is a vial comprising 2 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients.
- 15 In certain embodiments the unit dosage form of the first aspects is a vial comprising TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and the content of the vial is lyophilized. In certain embodiments the unit dosage form of the first aspects is a vial comprising 0.5 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and the content of the vial is lyophilized. In certain embodiments the unit dosage form
- 20 of the first aspects is a vial comprising 1 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and the content of the vial is lyophilized. In certain embodiments the unit dosage form of the first aspects is a vial comprising 2 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and the content of the vial is lyophilized.
- 25 In certain embodiments the unit dosage form of the first aspect is a vial comprising TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients and the content of the vial is lyophilized. In certain embodiments the unit dosage form of the first aspect is a vial comprising 0.5 mg of the TLR7/8 agonist conjugate or a pharmaceutically
- 30 acceptable salt thereof and one or more excipients and the content of the vial is lyophilized. In certain embodiments the unit dosage form of the first aspect is a vial comprising 1 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients and the content of the vial is lyophilized. In certain embodiments the unit dosage form of the first aspect is a vial comprising 2 mg of the TLR7/8 agonist conjugate or a

pharmaceutically acceptable salt thereof and one or more excipients and the content of the vial is lyophilized.

5 In certain embodiments the unit dosage form of the first aspects is a vial comprising TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and the content of the vial is a liquid, such as a suspension. In certain embodiments the unit dosage form of the first aspects is a vial comprising 0.5 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and the content of the vial is a liquid, such as a suspension. In certain embodiments the unit dosage form of the first aspects is a vial comprising 1 mg of the TLR7/8 agonist
10 conjugate or a pharmaceutically acceptable salt thereof and the content of the vial is a liquid, such as a suspension. In certain embodiments the unit dosage form of the first aspects is a vial comprising 2 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and the content of the vial is a liquid, such as a suspension.

15 In certain embodiments the unit dosage form of the first aspect is a vial comprising TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients and the content of the vial is a liquid, such as a suspension. In certain embodiments the unit dosage form of the first aspect is a vial comprising 0.5 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients and the content of the vial
20 is a liquid, such as a suspension. In certain embodiments the unit dosage form of the first aspect is a vial comprising 1 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients and the content of the vial is a liquid, such as a suspension. In certain embodiments the unit dosage form of the first aspect is a vial comprising 2 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or
25 more excipients and the content of the vial is a liquid, such as a suspension.

In certain embodiments the unit dosage form of the first aspect is a vial comprising the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof, wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dosage form of the first aspect is a vial comprising
30 0.5 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof, wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dosage form of the first aspect is a vial comprising 1 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof, wherein the TLR7/8 agonist is resiquimod. In certain embodiments the

unit dosage form of the first aspect is a vial comprising 2 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof, wherein the TLR7/8 agonist is resiquimod.

5 In certain embodiments the unit dosage form of the first aspect is a vial comprising the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients, wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dosage form of the first aspect is a vial comprising 0.5 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients, wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dosage form of the first aspect is a vial comprising 1 mg of the
10 TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients, wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dosage form of the first aspect is a vial comprising 2 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients, wherein the TLR7/8 agonist is resiquimod.

15 In certain embodiments the unit dosage form of the first aspect is a vial comprising the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof, wherein the TLR7/8 agonist is resiquimod and the content of the vial is lyophilized. In certain embodiments the unit dosage form of the first aspect is a vial comprising 0.5 mg of the TLR7/8 agonist conjugate or a
20 pharmaceutically acceptable salt thereof, wherein the TLR7/8 agonist is resiquimod and the content of the vial is lyophilized. In certain embodiments the unit dosage form of the first aspect is a vial comprising 1 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof, wherein the TLR7/8 agonist is resiquimod and the content of the vial is lyophilized. In certain embodiments the unit dosage form of the first aspect is a vial comprising 2 mg of the
25 TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof, wherein the TLR7/8 agonist is resiquimod and the content of the vial is lyophilized.

In certain embodiments the unit dosage form of the first aspect is a vial comprising the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients,
30 wherein the TLR7/8 agonist is resiquimod and the content of vial is lyophilized. In certain embodiments the unit dosage form of the first aspect is a vial comprising 0.5 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients, wherein the TLR7/8 agonist is resiquimod and the content of vial is lyophilized. In certain embodiments the unit dosage form of the first aspect is a vial comprising 1 mg of the TLR7/8

agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients, wherein the TLR7/8 agonist is resiquimod and the content of vial is lyophilized. In certain embodiments the unit dosage form of the first aspect is a vial comprising 2 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients,
5 wherein the TLR7/8 agonist is resiquimod and the content of vial is lyophilized.

In certain embodiments the unit dosage form of the first aspect is a vial comprising the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof, wherein the TLR7/8 agonist is resiquimod and the content of the vial is a liquid, such as a suspension. In certain embodiments
10 the unit dosage form of the first aspect is a vial comprising 0.5 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof, wherein the TLR7/8 agonist is resiquimod and the content of the vial is a liquid, such as a suspension. In certain embodiments the unit dosage form of the first aspect is a vial comprising 1 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof, wherein the TLR7/8 agonist is
15 resiquimod and the content of the vial is a liquid, such as a suspension. In certain embodiments the unit dosage form of the first aspect is a vial comprising 2 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof, wherein the TLR7/8 agonist is resiquimod and the content of the vial is a liquid, such as a suspension.

20 In certain embodiments the unit dosage form of the first aspect is a vial comprising the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients, wherein the TLR7/8 agonist is resiquimod and the content of vial is a liquid, such as a suspension. In certain embodiments the unit dosage form of the first aspect is a vial comprising 0.5 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one
25 or more excipients, wherein the TLR7/8 agonist is resiquimod and the content of vial is a liquid, such as a suspension. In certain embodiments the unit dosage form of the first aspect is a vial comprising 1 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients, wherein the TLR7/8 agonist is resiquimod and the content of vial is a liquid, such as a suspension. In certain embodiments the unit dosage form of the first aspect
30 is a vial comprising 2 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients, wherein the TLR7/8 agonist is resiquimod and the content of vial is a liquid, such as a suspension.

In certain embodiments the unit dosage form of the first aspect is a dual-chamber cartridge comprising the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof in a first chamber. In certain embodiments the unit dosage form of the first aspect is a dual-chamber cartridge comprising 0.5 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof in a first chamber. In certain embodiments the unit dosage form of the first aspect is a dual-chamber cartridge comprising 1 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof in a first chamber. In certain embodiments the unit dosage form of the first aspect is a dual-chamber cartridge comprising 2 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof in a first chamber.

10

In certain embodiments the unit dosage form of the first aspect is a dual-chamber cartridge comprising the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients in a first chamber. In certain embodiments the unit dosage form of the first aspect is a dual-chamber cartridge comprising 0.5 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients in a first chamber. In certain embodiments the unit dosage form of the first aspect is a dual-chamber cartridge comprising 1 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients in a first chamber. In certain embodiments the unit dosage form of the first aspect is a dual-chamber cartridge comprising 2 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients in a first chamber.

20

In certain embodiments the unit dosage form of the first aspect is a dual-chamber cartridge comprising the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof in the first chamber and wherein the content of said first chamber is lyophilized. In certain embodiments the unit dosage form of the first aspect is a dual-chamber cartridge comprising 0.5 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof in the first chamber and wherein the content of said first chamber is lyophilized. In certain embodiments the unit dosage form of the first aspect is a dual-chamber cartridge comprising 1 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof in the first chamber and wherein the content of said first chamber is lyophilized. In certain embodiments the unit dosage form of the first aspect is a dual-chamber cartridge comprising 2 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof in the first chamber and wherein the content of said first chamber is lyophilized.

25

30

In certain embodiments the unit dosage form of the first aspect is a dual-chamber cartridge comprising the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients in the first chamber and wherein the content of said first chamber is lyophilized. In certain embodiments the unit dosage form of the first aspect is a dual-chamber cartridge comprising 0.5 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients in the first chamber and wherein the content of said first chamber is lyophilized. In certain embodiments the unit dosage form of the first aspect is a dual-chamber cartridge comprising 1 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients in the first chamber and wherein the content of said first chamber is lyophilized. In certain embodiments the unit dosage form of the first aspect is a dual-chamber cartridge comprising 2 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients in the first chamber and wherein the content of said first chamber is lyophilized.

In certain embodiments the unit dosage form of the first aspect is a dual-chamber cartridge comprising the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof in a first chamber, wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dosage form of the first aspect is a dual-chamber cartridge comprising 0.5 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof in a first chamber, wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dosage form of the first aspect is a dual-chamber cartridge comprising 1 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof in a first chamber, wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dosage form of the first aspect is a dual-chamber cartridge comprising 2 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof in a first chamber, wherein the TLR7/8 agonist is resiquimod.

In certain embodiments the unit dosage form of the first aspect is a dual-chamber cartridge comprising the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients in a first chamber, wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dosage form of the first aspect is a dual-chamber cartridge comprising 0.5 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients in a first chamber, wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dosage form of the first aspect is a dual-chamber cartridge comprising 1 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or

more excipients in a first chamber, wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dosage form of the first aspect is a dual-chamber cartridge comprising 2 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients in a first chamber, wherein the TLR7/8 agonist is resiquimod.

5

In certain embodiments the unit dosage form of the first aspect is a dual-chamber cartridge comprising the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof in the first chamber, wherein the TLR7/8 agonist is resiquimod and wherein the content of said first chamber is lyophilized. In certain embodiments the unit dosage form of the first aspect is a dual-chamber cartridge comprising 0.5 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof in the first chamber, wherein the TLR7/8 agonist is resiquimod and wherein the content of said first chamber is lyophilized. In certain
10 embodiments the unit dosage form of the first aspect is a dual-chamber cartridge comprising 1 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof in the first chamber, wherein the TLR7/8 agonist is resiquimod and wherein the content of said first
15 chamber is lyophilized. In certain embodiments the unit dosage form of the first aspect is a dual-chamber cartridge comprising 2 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof in the first chamber, wherein the TLR7/8 agonist is resiquimod and wherein the content of said first chamber is lyophilized.

20

In certain embodiments the unit dosage form of the first aspect is a dual-chamber cartridge comprising the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients in the first chamber, wherein the TLR7/8 agonist is resiquimod and wherein the content of said first chamber is lyophilized. In certain embodiments the unit dosage form
25 of the first aspect is a dual-chamber cartridge comprising 0.5 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients in the first chamber, wherein the TLR7/8 agonist is resiquimod and wherein the content of said first chamber is lyophilized. In certain embodiments the unit dosage form of the first aspect is a dual-chamber cartridge comprising 1 mg of the TLR7/8 agonist conjugate or a
30 pharmaceutically acceptable salt thereof and one or more excipients in the first chamber, wherein the TLR7/8 agonist is resiquimod and wherein the content of said first chamber is lyophilized. In certain embodiments the unit dosage form of the first aspect is a dual-chamber cartridge comprising 2 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable

salt thereof and one or more excipients in the first chamber, wherein the TLR7/8 agonist is resiquimod and wherein the content of said first chamber is lyophilized.

5 In all embodiments the second chamber of a dual-chamber cartridge may comprise buffer or water for resuspension.

In certain embodiments the unit dosage form of the first aspect comprises a pharmaceutical formulation comprising the TLR7/8 agonist, such as resiquimod, and the pharmaceutical formulation is a liquid formulation or a resuspended formulation with a concentration ranging
10 from 0.5 mg TLR7/8 agonist, such as resiquimod, per ml to 2 mg TLR7/8 agonist, such as resiquimod, per ml. In certain embodiments the concentration is 0.5 mg TLR7/8 agonist, such as resiquimod, per ml. In certain embodiments the concentration is 1 mg TLR7/8 agonist, such as resiquimod, per ml.

15 In certain embodiments the unit dosage form of the first aspect is for use in the treatment of cancer, in particular of a solid tumor. In certain embodiment the unit dose of the unit dosage form of the first aspect is administered via intratumoral injection, such as by using a fanning technique. In certain embodiments the solid tumor is selected from the group consisting of lip and oral cavity cancer, oral cancer, liver cancer/hepatocellular cancer, primary liver cancer,
20 lung cancer, lymphoma, malignant mesothelioma, malignant thymoma, skin cancer, intraocular melanoma, metastatic squamous neck cancer with occult primary, childhood multiple endocrine neoplasia syndrome, mycosis fungoides, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, oropharyngeal cancer, ovarian cancer, pancreatic cancer, parathyroid cancer, pheochromocytoma, pituitary tumor, adrenocortical carcinoma,
25 AIDS-related malignancies, anal cancer, bile duct cancer, bladder cancer, brain and nervous system cancer, breast cancer, bronchial adenoma/carcinoid, gastrointestinal carcinoid tumor, carcinoma, colorectal cancer, endometrial cancer, esophageal cancer, extracranial germ cell tumor, extragonadal germ cell tumor, extrahepatic bile duct cancer, gallbladder cancer, gastric (stomach) cancer, gestational trophoblastic tumor, head and neck cancer, hypopharyngeal
30 cancer, islet cell carcinoma (endocrine pancreas), kidney cancer/renal cell cancer, laryngeal cancer, pleuropulmonary blastoma, prostate cancer, transitional cell cancer of the renal pelvis and ureter, retinoblastoma, salivary gland cancer, sarcoma, Sezary syndrome, small intestine cancer, genitourinary cancer, malignant thymoma, thyroid cancer, Wilms' tumor and cholangiocarcinoma. In certain embodiments the solid tumor is selected from the group

consisting of squamous cell carcinoma of the head and neck (SCCHN); HPV-associated cancers, such as anal, vulvar, cervical, penile and vaginal cancers; melanomas; pancreatic cancer and breast cancer, such as triple-negative breast cancer (TNBC). In certain embodiments the solid tumor is selected from the group consisting of pancreatic cancer, prostate cancer, melanoma, SCCHN, cutaneous squamous cell cancer (cSCC) and cervical cancer. In certain embodiments the solid tumor is a pancreatic cancer. In certain embodiments the solid tumor is prostate cancer. In certain embodiments the solid tumor is a melanoma. In certain embodiments the solid tumor is a SCCHN. In certain embodiments the solid tumor is a cSCC. In certain embodiments the solid tumor is cervical cancer.

10

In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every two to four weeks. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every two weeks. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every three weeks. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every four weeks.

20

In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every five weeks. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every six weeks. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every seven weeks. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every eight weeks. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every nine weeks. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every ten weeks. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every twelve weeks.

30

In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every six months. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every seven months.

- 5 In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every eight months. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every nine months. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every ten months. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every eleven months. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient once a year.

15

In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered at a frequency dependent on disease progression.

- 20 In certain embodiments the unit dose is 0.5 mg TLR7/8 agonist per tumor. In certain embodiments the unit dose is 1 mg TLR7/8 agonist per tumor. Such unit dose may be administered via intratumoral injection, such as by using a fanning technique.

- In certain embodiments the treatment of cancer comprises administration of the unit dose to one tumor of the patient. In certain embodiments the treatment of cancer comprises administration of the unit dose to more than one tumor of the patient, such as to two tumors, three tumors, four tumors or five tumors or to all tumors of a patient that have a sufficient size and are accessible for treatment. If the treatment comprises administration to more than one tumor per patient, such administrations may occur within at most four hours, such as within 25 three hours, within two hours or within one hour. In certain embodiments administration to more than one tumor occurs consecutively without breaks between administrations. In certain embodiments administrations to different tumors of a patient occur at different times, such that for example the time between one administration and the following administration ranges from one day to three weeks and is in certain embodiments one week, two weeks or three weeks.

30

In certain embodiments the treatment comprises one administration of a unit dose to a tumor of the patient, such as a dose of 0.5 mg TLR7/8 agonist, such as resiquimod, per tumor, which unit dose is administered as one intratumoral injection. In certain embodiments the treatment
5 comprises repeated administrations of a unit dose to a tumor of the patient, such as repeated administrations of 0.5 mg TLR7/8 agonist, such as resiquimod, per tumor administered via intratumoral injection, wherein each unit dose is administered as one intratumoral injection. Such treatment with repeated administrations per tumor means in certain embodiment two, three, four, five, six, seven, eight, nine, ten, eleven, twelve or more administrations to a
10 particular tumor of the patient. In certain embodiments more than one tumor of the patient are treated with such repeated administrations.

In certain embodiments the unit dose of the unit dosage form of the first aspect comprises 0.5 mg of the TLR7/8 agonist conjugate and is for use in the treatment of cancer, wherein the unit
15 dose is administered to the patient every two to four weeks. In certain embodiments the unit dose of the unit dosage form of the first aspect comprises 0.5 mg of the TLR7/8 agonist conjugate and is for use in the treatment of cancer, wherein the unit dose is administered to the patient every two weeks. In certain embodiments the unit dose of the unit dosage form of the first aspect comprises 0.5 mg of the TLR7/8 agonist conjugate and is for use in the treatment
20 of cancer, wherein the unit dose is administered to the patient every three weeks. In certain embodiments the unit dose of the unit dosage form of the first aspect comprises 0.5 mg of the TLR7/8 agonist conjugate and is for use in the treatment of cancer, wherein the unit dose is administered to the patient every four weeks.

25 In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every two to four weeks via intratumoral administration. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every two weeks via intratumoral administration. In certain embodiments the unit
30 dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every three weeks via intratumoral administration. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every four weeks via intratumoral administration.

In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every two to four weeks via intratumoral administration. In certain
5 embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every two weeks via intratumoral administration. In certain
10 embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every three weeks via intratumoral administration. In certain
15 embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every four weeks via intratumoral administration.

15 In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every two to four weeks via intratumoral administration using a fanning technique. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every two weeks via intratumoral administration using a
20 fanning technique. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every three weeks via intratumoral administration using a fanning technique. In certain
25 embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every four weeks via intratumoral administration using a fanning technique.

In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every two to four weeks via intratumoral administration using a
30 fanning technique. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every two weeks via intratumoral administration using a fanning technique. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose

comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every three weeks via intratumoral administration using a fanning technique. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient
5 every four weeks via intratumoral administration using a fanning technique.

In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every two to four weeks and wherein the treatment is a cotreatment with an immune checkpoint inhibitor, which may
10 be given prior to, together with or after administration of the TLR7/8 agonist conjugate. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every two weeks and wherein the treatment is a cotreatment with an immune checkpoint inhibitor, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate. In certain
15 embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every three weeks and wherein the treatment is a cotreatment with an immune checkpoint inhibitor, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate. In certain
20 embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every four weeks and wherein the treatment is a cotreatment with an immune checkpoint inhibitor, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate.

In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the
25 treatment of cancer, wherein the unit dose comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every two to four weeks and wherein the treatment is a cotreatment with an immune checkpoint inhibitor, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose
30 comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every two weeks and wherein the treatment is a cotreatment with an immune checkpoint inhibitor, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose comprises 0.5 mg TLR7/8 agonist conjugate and is

administered to the patient every three weeks and wherein the treatment is a cotreatment with an immune checkpoint inhibitor, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose
5 comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every four weeks and wherein the treatment is a cotreatment with an immune checkpoint inhibitor, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate.

In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the
10 treatment of cancer, wherein the unit dose is administered to the patient every two to four weeks and wherein the treatment is a cotreatment with an inhibitor of PD-1 or an inhibitor of PD-L1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every
15 two weeks and wherein the treatment is a cotreatment with an inhibitor of PD-1 or an inhibitor of PD-L1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every three weeks and wherein the treatment is a cotreatment with an inhibitor of PD-1 or an
20 inhibitor of PD-L1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every four weeks and wherein the treatment is a cotreatment with an inhibitor of PD-1 or an inhibitor of PD-L1, which may be given prior to, together with or after administration of
25 the TLR7/8 agonist conjugate.

In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every two to four weeks and wherein the treatment is a cotreatment
30 with an inhibitor of PD-1 or an inhibitor of PD-L1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every two weeks and wherein the treatment is a cotreatment with an inhibitor of PD-1 or an inhibitor of

PD-L1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every three weeks and wherein the treatment is a cotreatment with an inhibitor of PD-1 or an inhibitor of PD-L1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every four weeks and wherein the treatment is a cotreatment with an inhibitor of PD-1 or an inhibitor of PD-L1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate.

An inhibitor of PD-1 (programmed cell death protein 1) may be selected from the group consisting of pembrolizumab, nivolumab, pidilizumab, AMP-224, BMS-936559, cemiplimab and PDR001. An inhibitor of PD-L1 (programmed cell death ligand 1) may be selected from the group consisting of MDX-1105, MEDI4736, atezolizumab, avelumab, BMS-936559 and durvalumab.

In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every two to four weeks and wherein the treatment is a cotreatment with an inhibitor of PD-1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every two weeks and wherein the treatment is a cotreatment with an inhibitor of PD-1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every three weeks and wherein the treatment is a cotreatment with an inhibitor of PD-1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every four weeks and wherein the treatment is a cotreatment with an inhibitor of PD-1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate.

In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every two to four weeks and wherein the treatment is a cotreatment with an inhibitor of PD-1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every two weeks and wherein the treatment is a cotreatment with an inhibitor of PD-1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every three weeks and wherein the treatment is a cotreatment with an inhibitor of PD-1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every four weeks and wherein the treatment is a cotreatment with an inhibitor of PD-1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate.

20

In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every two to four weeks and wherein the treatment is a cotreatment with an inhibitor of PD-L1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every two weeks and wherein the treatment is a cotreatment with an inhibitor of PD-L1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every three weeks and wherein the treatment is a cotreatment with an inhibitor of PD-L1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every four weeks and wherein the treatment is a cotreatment with

25

30

an inhibitor of PD-L1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate.

In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dosage comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every two to four weeks and wherein the treatment is a cotreatment with an inhibitor of PD-L1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dosage comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every two weeks and wherein the treatment is a cotreatment with an inhibitor of PD-L1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dosage comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every three weeks and wherein the treatment is a cotreatment with an inhibitor of PD-L1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dosage comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every four weeks and wherein the treatment is a cotreatment with an inhibitor of PD-L1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate.

In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every two to four weeks and wherein the treatment is a cotreatment with pembrolizumab, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every two weeks and wherein the treatment is a cotreatment with pembrolizumab, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every three weeks and wherein the treatment is a cotreatment with pembrolizumab, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate. In certain embodiments the unit dose of the unit dosage form of the

first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every four weeks and wherein the treatment is a cotreatment with pembrolizumab, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate.

5

In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dosage comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every two to four weeks and wherein the treatment is a cotreatment with pembrolizumab, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dosage comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every two weeks and wherein the treatment is a cotreatment with pembrolizumab, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dosage comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every three weeks and wherein the treatment is a cotreatment with pembrolizumab, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dosage comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every four weeks and wherein the treatment is a cotreatment with pembrolizumab, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate.

Pembrolizumab may be given as per the prescription information, such as 200 mg pembrolizumab per intravenous infusion, for example every three weeks. The infusion time may range from 15 minutes to 4 hours, such as from 30 minutes to one hour and is typically about 30 minutes. In general, pembrolizumab is administered with the dose, administration frequency and form of administration approved for a given indication.

30

In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every two to four weeks and wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose

is administered to the patient every two weeks and wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every three weeks and wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every four weeks and wherein the TLR7/8 agonist is resiquimod.

In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dosage comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every two to four weeks and wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dosage comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every two weeks and wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dosage comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every three weeks and wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every four weeks and wherein the TLR7/8 agonist is resiquimod.

20

In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every two to four weeks via intratumoral administration and wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every two weeks via intratumoral administration and wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every three weeks via intratumoral administration and wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every four weeks via intratumoral administration and wherein the TLR7/8 agonist is resiquimod.

30

In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dosage comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every two to four weeks via intratumoral administration and wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dosage comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every two weeks via intratumoral administration and wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dosage comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every three weeks via intratumoral administration and wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dosage comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every four weeks via intratumoral administration and wherein the TLR7/8 agonist is resiquimod.

In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every two to four weeks via intratumoral administration using a fanning technique and wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every two weeks via intratumoral administration using a fanning technique and wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every three weeks via intratumoral administration using a fanning technique and wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every four weeks via intratumoral administration using a fanning technique and wherein the TLR7/8 agonist is resiquimod.

In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dosage comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every two to four weeks via intratumoral administration using a fanning technique and wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein

the unit dosage comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every two weeks via intratumoral administration using a fanning technique and wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dosage comprises 0.5 mg
5 TLR7/8 agonist conjugate and is administered to the patient every three weeks via intratumoral administration using a fanning technique and wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dosage comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every four weeks via intratumoral administration using a fanning
10 technique and wherein the TLR7/8 agonist is resiquimod.

In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every two to four weeks and wherein the treatment is a cotreatment with an immune checkpoint inhibitor, which may
15 be given prior to, together with or after administration of the TLR7/8 agonist conjugate and wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every two weeks and wherein the treatment is a cotreatment with an immune checkpoint inhibitor, which may be given prior to, together with or after
20 administration of the TLR7/8 agonist conjugate and wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every three weeks and wherein the treatment is a cotreatment with an immune checkpoint inhibitor, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate and
25 wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every four weeks and wherein the treatment is a cotreatment with an immune checkpoint inhibitor, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate and wherein the TLR7/8 agonist is resiquimod.
30

In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dosage comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every two to four weeks and wherein the treatment is a cotreatment with an immune checkpoint inhibitor, which may be given prior to, together with

or after administration of the TLR7/8 agonist conjugate and wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dosage comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every two weeks and wherein the treatment is a
5 cotreatment with an immune checkpoint inhibitor, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate and wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dosage comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every three weeks and wherein the treatment is a
10 cotreatment with an immune checkpoint inhibitor, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate and wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dosage comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every four weeks and wherein the treatment is a
15 cotreatment with an immune checkpoint inhibitor, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate and wherein the TLR7/8 agonist is resiquimod.

In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the
20 treatment of cancer, wherein the unit dose is administered to the patient every two to four weeks and wherein the treatment is a cotreatment with an inhibitor of PD-1 or an inhibitor of PD-L1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate and wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit
25 dose is administered to the patient every two weeks and wherein the treatment is a cotreatment with an inhibitor of PD-1 or an inhibitor of PD-L1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate and wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every
30 three weeks and wherein the treatment is a cotreatment with an inhibitor of PD-1 or an inhibitor of PD-L1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate and wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every four weeks and wherein the treatment is a

cotreatment with an inhibitor of PD-1 or an inhibitor of PD-L1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate and wherein the TLR7/8 agonist is resiquimod.

- 5 In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dosage comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every two to four weeks and wherein the treatment is a cotreatment with an inhibitor of PD-1 or an inhibitor of PD-L1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate and wherein the TLR7/8
- 10 agonist is resiquimod. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dosage comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every two weeks and wherein the treatment is a cotreatment with an inhibitor of PD-1 or an inhibitor of PD-L1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate and wherein the
- 15 TLR7/8 agonist is resiquimod. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dosage comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every three weeks and wherein the treatment is a cotreatment with an inhibitor of PD-1 or an inhibitor of PD-L1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate and
- 20 wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dosage comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every four weeks and wherein the treatment is a cotreatment with an inhibitor of PD-1 or an inhibitor of PD-L1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate and wherein the TLR7/8 agonist is resiquimod.
- 25

Examples for the inhibitor of PD-1 and PD-L1 are as described elsewhere herein.

- 30 In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every two to four weeks and wherein the treatment is a cotreatment with an inhibitor of PD-1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate and wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to

the patient every two weeks and wherein the treatment is a cotreatment with an inhibitor of PD-1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate and wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every three weeks and wherein the treatment is a cotreatment with an inhibitor of PD-1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate and wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every four weeks and wherein the treatment is a cotreatment with an inhibitor of PD-1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate and wherein the TLR7/8 agonist is resiquimod.

In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dosage comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every two to four weeks and wherein the treatment is a cotreatment with an inhibitor of PD-1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate and wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dosage comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every two weeks and wherein the treatment is a cotreatment with an inhibitor of PD-1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate and wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dosage comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every three weeks and wherein the treatment is a cotreatment with an inhibitor of PD-1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate and wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dosage comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every four weeks and wherein the treatment is a cotreatment with an inhibitor of PD-1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate and wherein the TLR7/8 agonist is resiquimod.

- In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every two to four weeks and wherein the treatment is a cotreatment with an inhibitor of PD-L1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate and wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every two weeks and wherein the treatment is a cotreatment with an inhibitor of PD-L1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate and wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every three weeks and wherein the treatment is a cotreatment with an inhibitor of PD-L1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate and wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every four weeks and wherein the treatment is a cotreatment with an inhibitor of PD-L1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate and wherein the TLR7/8 agonist is resiquimod.
- In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dosage comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every two to four weeks and wherein the treatment is a cotreatment with an inhibitor of PD-L1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate and wherein the TLR7/8 agonist is resiquimod.
- In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dosage comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every two weeks and wherein the treatment is a cotreatment with an inhibitor of PD-L1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate and wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dosage comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every three weeks and wherein the treatment is a cotreatment with an inhibitor of PD-L1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate and wherein the TLR7/8 agonist is resiquimod. In certain

embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dosage comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every four weeks and wherein the treatment is a cotreatment with an inhibitor of PD-L1, which may be given prior to, together with or after administration of the
5 TLR7/8 agonist conjugate and wherein the TLR7/8 agonist is resiquimod.

In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every two to four weeks and wherein the treatment is a cotreatment with pembrolizumab, which may be given prior to,
10 together with or after administration of the TLR7/8 agonist conjugate and wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every two weeks and wherein the treatment is a cotreatment with pembrolizumab, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate and
15 wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every three weeks and wherein the treatment is a cotreatment with pembrolizumab, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate and wherein the TLR7/8 agonist is resiquimod. In certain
20 embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dose is administered to the patient every four weeks and wherein the treatment is a cotreatment with pembrolizumab, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate and wherein the TLR7/8 agonist is resiquimod.

25 In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dosage comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every two to four weeks and wherein the treatment is a cotreatment with pembrolizumab, which may be given prior to, together with or after
30 administration of the TLR7/8 agonist conjugate and wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dosage comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every two weeks and wherein the treatment is a cotreatment with pembrolizumab, which may be given prior to, together with or after administration of the

TLR7/8 agonist conjugate and wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dosage comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every three weeks and wherein the treatment is a cotreatment with
5 pembrolizumab, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate and wherein the TLR7/8 agonist is resiquimod. In certain embodiments the unit dose of the unit dosage form of the first aspect is for use in the treatment of cancer, wherein the unit dosage comprises 0.5 mg TLR7/8 agonist conjugate and is administered to the patient every four weeks and wherein the treatment is a cotreatment with
10 pembrolizumab, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate and wherein the TLR7/8 agonist is resiquimod.

The dose, administration frequency and form of administration of pembrolizumab is as described elsewhere herein.

15

In a second aspect the present invention relates to a TLR7/8 agonist conjugate for use in the treatment of cancer, wherein the TLR7/8 agonist conjugate comprises one or more TLR7/8 agonist moieties reversibly conjugated to a polymeric moiety, wherein the cancer is a solid tumor and wherein the TLR7/8 agonist conjugate is administered via intratumoral
20 administration in a dose ranging from 0.3 mg to 3 mg of TLR7/8 agonist per tumor. In certain embodiments the dose administered to a tumor via intratumoral injection in the second aspect is 0.5 mg of TLR7/8 agonist per tumor. In certain embodiments the dose administered to a tumor via intratumoral injection in the second aspect is 1 mg of TLR7/8 agonist per tumor. In certain embodiments the dose administered to a tumor via intratumoral injection in the second
25 aspect is 2 mg of TLR7/8 agonist per tumor.

In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is administered intratumorally using a fanning technique.

30 In certain embodiments the present invention relates to a TLR7/8 agonist conjugate for use in the treatment of cancer, wherein the TLR7/8 agonist conjugate comprises one or more TLR7/8 agonist moieties reversibly conjugated to a polymeric moiety, wherein the cancer is a solid tumor and wherein the TLR7/8 agonist conjugate is administered via intratumoral administration in a dose ranging from 0.3 mg to 3 mg of TLR7/8 agonist per tumor and wherein

the TLR7/8 agonist is resiquimod. In certain embodiments the dose administered to a tumor via intratumoral injection in the second aspect is 0.5 mg of TLR7/8 agonist per tumor and wherein the TLR7/8 agonist is resiquimod. In certain embodiments the dose administered to a tumor via intratumoral injection in the second aspect is 1 mg of TLR7/8 agonist per tumor and
5 wherein the TLR7/8 agonist is resiquimod. In certain embodiments the dose administered to a tumor via intratumoral injection in the second aspect is 2 mg of TLR7/8 agonist per tumor and wherein the TLR7/8 agonist is resiquimod.

In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is
10 administered in a volume ranging from 0.1 ml to 2 ml. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is administered in a volume ranging from 0.2 ml to 1.5 ml. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is administered in a volume of 0.25 ml. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is administered in a volume of 0.5 ml. In certain embodiments the
15 TLR7/8 agonist conjugate for use of the second aspect is administered in a volume of 1 ml.

In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is administered in a volume ranging from 0.1 ml to 2 ml and the TLR7/8 agonist is resiquimod. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is
20 administered in a volume ranging from 0.2 ml to 1.5 ml and the TLR7/8 agonist is resiquimod. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is administered in a volume of 0.25 ml and the TLR7/8 agonist is resiquimod. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is administered in a volume of 0.5 ml and the TLR7/8 agonist is resiquimod. In certain the TLR7/8 agonist
25 conjugate for use of the second aspect is administered in volume of 1 ml and the TLR7/8 agonist is resiquimod.

In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is administered in a dose of 0.5 mg of the TLR7/8 agonist in a volume of 0.5 ml. In certain
30 embodiments the TLR7/8 agonist conjugate for use of the second aspect is administered in a dose of 0.5 mg of the TLR7/8 agonist in a volume of 1 ml. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is administered in a dose of 0.5 mg of the TLR7/8 agonist in a volume of 0.25 ml. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is administered in a dose of 1 mg of the TLR7/8 agonist in a volume of 1

ml. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is administered in a dose of 1 mg of the TLR7/8 agonist in a volume of 2 ml. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is administered in a dose of 1 mg of the TLR7/8 agonist in a volume of 0.5 ml.

5

In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is administered in a dose of 0.5 mg of the TLR7/8 agonist, which TLR7/8 agonist is resiquimod, in a volume of 0.5 ml. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is administered in a dose of 0.5 mg of the TLR7/8 agonist, which TLR7/8 agonist is resiquimod, in a volume of 1 ml. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is administered in a dose of 0.5 mg of the TLR7/8 agonist, which TLR7/8 agonist is resiquimod, in a volume of 0.25 ml. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is administered in a dose of 1 mg of the TLR7/8 agonist, which TLR7/8 agonist is resiquimod, in a volume of 1 ml. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is administered in a dose of 1 mg of the TLR7/8 agonist, which TLR7/8 agonist is resiquimod, in a volume of 2 ml. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is administered in a dose of 1 mg of the TLR7/8 agonist, which TLR7/8 agonist is resiquimod, in a volume of 0.5 ml.

20

In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a vial comprising the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a vial comprising 0.5 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a vial comprising 1 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a vial comprising 2 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof.

30

In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a vial comprising the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a vial comprising 0.5 mg of the TLR7/8 agonist conjugate or

a pharmaceutically acceptable salt thereof and one or more excipients. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a vial comprising 1 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a vial comprising 2 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients.

In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a vial comprising TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and the content of the vial is lyophilized. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a vial comprising 0.5 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and the content of the vial is lyophilized. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a vial comprising 1 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and the content of the vial is lyophilized. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a vial comprising 2 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and the content of the vial is lyophilized.

In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a vial comprising TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and the content of the vial is a liquid, such as a suspension. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a vial comprising 0.5 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and the content of the vial is a liquid, such as a suspension. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a vial comprising 1 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and the content of the vial is a liquid, such as a suspension. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a vial comprising 2 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and the content of the vial is a liquid, such as a suspension.

In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a vial comprising TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients and the content of the vial is lyophilized. In certain embodiments

the TLR7/8 agonist conjugate for use of the second aspect is provided in a vial comprising 0.5 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients and the content of the vial is lyophilized. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a vial comprising 1 mg of the
5 TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients and the content of the vial is lyophilized. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a vial comprising 2 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients and the content of the vial is lyophilized.

10

In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a vial comprising TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients and the content of the vial is a liquid, such as a suspension. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in
15 a vial comprising 0.5 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients and the content of the vial is a liquid, such as a suspension. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a vial comprising 1 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients and the content of the vial is a liquid, such
20 as a suspension. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a vial comprising 2 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients and the content of the vial is a liquid, such as a suspension.

25 In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a vial comprising the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof, wherein the TLR7/8 agonist is resiquimod. In certain the TLR7/8 agonist conjugate for use of the second aspect is provided in a vial comprising 0.5 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof, wherein the TLR7/8 agonist is
30 resiquimod. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a vial comprising 1 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof, wherein the TLR7/8 agonist is resiquimod. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a vial comprising 2 mg

of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof, wherein the TLR7/8 agonist is resiquimod.

In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided
5 in a vial comprising the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof
and one or more excipients, wherein the TLR7/8 agonist is resiquimod. In certain embodiments
the unit dosage form of the first aspect is a vial comprising 0.5 mg of the TLR7/8 agonist
conjugate or a pharmaceutically acceptable salt thereof and one or more excipients, wherein
the TLR7/8 agonist is resiquimod. In certain embodiments the TLR7/8 agonist conjugate for
10 use of the second aspect is provided in a vial comprising 1 mg of the TLR7/8 agonist conjugate
or a pharmaceutically acceptable salt thereof and one or more excipients, wherein the TLR7/8
agonist is resiquimod. In certain embodiments the TLR7/8 agonist conjugate for use of the
second aspect is provided in a vial comprising 2 mg of the TLR7/8 agonist conjugate or a
pharmaceutically acceptable salt thereof and one or more excipients, wherein the TLR7/8
15 agonist is resiquimod.

In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided
in a vial comprising the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt
thereof, wherein the TLR7/8 agonist is resiquimod and the content of the vial is lyophilized. In
20 certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in
a vial comprising 0.5 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable
salt thereof, wherein the TLR7/8 agonist is resiquimod and the content of the vial is lyophilized.
In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided
in a vial comprising 1 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable
25 salt thereof, wherein the TLR7/8 agonist is resiquimod and the content of the vial is lyophilized.
In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided
in a vial comprising 2 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable
salt thereof, wherein the TLR7/8 agonist is resiquimod and the content of the vial is lyophilized.

30 In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided
in a vial comprising the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt
thereof, wherein the TLR7/8 agonist is resiquimod and the content of the vial is a liquid, such
as a suspension. In certain embodiments the TLR7/8 agonist conjugate for use of the second
aspect is provided in a vial comprising 0.5 mg of the TLR7/8 agonist conjugate or a

pharmaceutically acceptable salt thereof, wherein the TLR7/8 agonist is resiquimod and the content of the vial is a liquid, such as a suspension. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a vial comprising 1 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof, wherein the TLR7/8 agonist is resiquimod and the content of the vial is a liquid, such as a suspension. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a vial comprising 2 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof, wherein the TLR7/8 agonist is resiquimod and the content of the vial is a liquid, such as a suspension.

In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a vial comprising the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients, wherein the TLR7/8 agonist is resiquimod and the content of vial is lyophilized. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a vial comprising 0.5 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients, wherein the TLR7/8 agonist is resiquimod and the content of vial is lyophilized. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a vial comprising 1 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients, wherein the TLR7/8 agonist is resiquimod and the content of vial is lyophilized. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a vial comprising 2 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients, wherein the TLR7/8 agonist is resiquimod and the content of vial is lyophilized.

25 In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a vial comprising the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients, wherein the TLR7/8 agonist is resiquimod and the content of vial is a liquid, such as a suspension. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a vial comprising 0.5 mg of the TLR7/8 agonist conjugate
30 or a pharmaceutically acceptable salt thereof and one or more excipients, wherein the TLR7/8 agonist is resiquimod and the content of vial is a liquid, such as a suspension. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a vial comprising 1 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients, wherein the TLR7/8 agonist is resiquimod and the content of vial

is a liquid, such as a suspension. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a vial comprising 2 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients, wherein the TLR7/8 agonist is resiquimod and the content of vial is a liquid, such as a suspension.

5

In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a dual-chamber cartridge comprising the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof in a first chamber. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a dual-chamber cartridge comprising 0.5 mg of the
10 TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof in a first chamber. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a dual-chamber cartridge comprising 1 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof in a first chamber. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a dual-chamber cartridge
15 comprising 2 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof in a first chamber.

In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a dual-chamber cartridge comprising the TLR7/8 agonist conjugate or a pharmaceutically
20 acceptable salt thereof and one or more excipients in a first chamber. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a dual-chamber cartridge comprising 0.5 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients in a first chamber. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a dual-chamber cartridge
25 comprising 1 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients in a first chamber. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a dual-chamber cartridge comprising 2 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients in a first chamber.

30

In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a dual-chamber cartridge comprising the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof in the first chamber and wherein the content of said first chamber is lyophilized. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect

is provided in a dual-chamber cartridge comprising 0.5 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof in the first chamber and wherein the content of said first chamber is lyophilized. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a dual-chamber cartridge comprising 1 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof in the first chamber and wherein the content of said first chamber is lyophilized. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a dual-chamber cartridge comprising 2 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof in the first chamber and wherein the content of said first chamber is lyophilized.

10

In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a dual-chamber cartridge comprising the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients in the first chamber and wherein the content of said first chamber is lyophilized. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a dual-chamber cartridge comprising 0.5 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients in the first chamber and wherein the content of said first chamber is lyophilized. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a dual-chamber cartridge comprising 1 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients in the first chamber and wherein the content of said first chamber is lyophilized. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a dual-chamber cartridge comprising 2 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients in the first chamber and wherein the content of said first chamber is lyophilized.

25

In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a dual-chamber cartridge comprising the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof in a first chamber, wherein the TLR7/8 agonist is resiquimod. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a dual-chamber cartridge comprising 0.5 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof in a first chamber, wherein the TLR7/8 agonist is resiquimod. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a dual-chamber cartridge comprising 1 mg of the TLR7/8 agonist conjugate or a pharmaceutically

30

acceptable salt thereof in a first chamber, wherein the TLR7/8 agonist is resiquimod. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a dual-chamber cartridge comprising 2 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof in a first chamber, wherein the TLR7/8 agonist is resiquimod.

5

In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a dual-chamber cartridge comprising the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients in a first chamber, wherein the TLR7/8 agonist is resiquimod. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a dual-chamber cartridge comprising 0.5 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients in a first chamber, wherein the TLR7/8 agonist is resiquimod. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a dual-chamber cartridge comprising 1 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients in a first chamber, wherein the TLR7/8 agonist is resiquimod. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a dual-chamber cartridge comprising 2 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients in a first chamber, wherein the TLR7/8 agonist is resiquimod.

20

In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a dual-chamber cartridge comprising the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof in the first chamber, wherein the TLR7/8 agonist is resiquimod and wherein the content of said first chamber is lyophilized. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a dual-chamber cartridge comprising 0.5 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof in the first chamber, wherein the TLR7/8 agonist is resiquimod and wherein the content of said first chamber is lyophilized. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a dual-chamber cartridge comprising 1 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof in the first chamber, wherein the TLR7/8 agonist is resiquimod and wherein the content of said first chamber is lyophilized. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a dual-chamber cartridge comprising 2 mg of the TLR7/8 agonist conjugate or a

30

pharmaceutically acceptable salt thereof in the first chamber, wherein the TLR7/8 agonist is resiquimod and wherein the content of said first chamber is lyophilized.

In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided
5 in a dual-chamber cartridge comprising the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients in the first chamber, wherein the TLR7/8 agonist is resiquimod and wherein the content of said first chamber is lyophilized. In certain
10 embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a dual-chamber cartridge comprising 0.5 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients in the first chamber, wherein the TLR7/8
15 agonist is resiquimod and wherein the content of said first chamber is lyophilized. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a dual-chamber cartridge comprising 1 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients in the first chamber, wherein the TLR7/8
20 agonist is resiquimod and wherein the content of said first chamber is lyophilized. In certain embodiments the TLR7/8 agonist conjugate for use of the second aspect is provided in a dual-chamber cartridge comprising 2 mg of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients in the first chamber, wherein the TLR7/8
agonist is resiquimod and wherein the content of said first chamber is lyophilized.

20

In all embodiments the second chamber of a dual-chamber cartridge may comprise buffer or water for resuspension.

The TLR7/8 agonist conjugate for use of the second aspect is in certain embodiments for use
25 in the treatment of a solid tumor. In certain embodiment TLR7/8 agonist of the second aspect is administered via intratumoral injection, such as by using a fanning technique. In certain
embodiments the solid tumor is selected from the group consisting of lip and oral cavity cancer, oral cancer, liver cancer/hepatocellular cancer, primary liver cancer, lung cancer, lymphoma, malignant mesothelioma, malignant thymoma, skin cancer, intraocular melanoma, metastatic
30 squamous neck cancer with occult primary, childhood multiple endocrine neoplasia syndrome, mycosis fungoides, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, oropharyngeal cancer, ovarian cancer, pancreatic cancer, parathyroid cancer, pheochromocytoma, pituitary tumor, adrenocortical carcinoma, AIDS-related malignancies, anal cancer, bile duct cancer, bladder cancer, brain and nervous system cancer, breast cancer,

bronchial adenoma/carcinoid, gastrointestinal carcinoid tumor, carcinoma, colorectal cancer, endometrial cancer, esophageal cancer, extracranial germ cell tumor, extragonadal germ cell tumor, extrahepatic bile duct cancer, gallbladder cancer, gastric (stomach) cancer, gestational trophoblastic tumor, head and neck cancer, hypopharyngeal cancer, islet cell carcinoma
5 (endocrine pancreas), kidney cancer/renal cell cancer, laryngeal cancer, pleuropulmonary blastoma, prostate cancer, transitional cell cancer of the renal pelvis and ureter, retinoblastoma, salivary gland cancer, sarcoma, Sezary syndrome, small intestine cancer, genitourinary cancer, malignant thymoma, thyroid cancer, Wilms' tumor and cholangiocarcinoma. In certain
10 embodiments the solid tumor is selected from the group consisting of squamous cell carcinoma of the head and neck (SCCHN); HPV-associated cancers, such as anal, vulvar, cervical, penile and vaginal cancers; melanomas; pancreatic cancer and breast cancer, such as triple-negative breast cancer (TNBC).

In certain embodiments the TLR7/8 agonist for use of the second aspect is administered to the
15 patient every two to four weeks. In certain embodiments the TLR7/8 agonist for use of the second aspect is administered to the patient every two weeks. In certain embodiments the TLR7/8 agonist for use of the second aspect is administered to the patient every three weeks. In certain embodiments the TLR7/8 agonist for use of the second aspect is administered to the patient every four weeks.

20

In certain embodiments the TLR7/8 agonist for use of the second aspect is administered to the patient every two to four weeks and the treatment is a cotreatment with an immune checkpoint inhibitor, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate. In certain embodiments the TLR7/8 agonist for use of the second aspect is
25 administered to the patient every two weeks and the treatment is a cotreatment with an immune checkpoint inhibitor, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate. In certain embodiments the TLR7/8 agonist for use of the second aspect is administered to the patient every three weeks and the treatment is a cotreatment with an immune checkpoint inhibitor, which may be given prior to, together with or after
30 administration of the TLR7/8 agonist conjugate. In certain embodiments the TLR7/8 agonist for use of the second aspect is administered to the patient every four weeks and the treatment is a cotreatment with an immune checkpoint inhibitor, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate.

In certain embodiments the TLR7/8 agonist for use of the second aspect is administered to the patient every two to four weeks and wherein the treatment is a cotreatment with an inhibitor of PD-1 or an inhibitor of PD-L1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate. In certain embodiments the TLR7/8 agonist for use of the second aspect is administered to the patient every two weeks and wherein the treatment is a cotreatment with an inhibitor of PD-1 or an inhibitor of PD-L1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate. In certain embodiments the TLR7/8 agonist for use of the second aspect is administered to the patient every three weeks and wherein the treatment is a cotreatment with an inhibitor of PD-1 or an inhibitor of PD-L1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate. In certain embodiments the TLR7/8 agonist for use of the second aspect is administered to the patient every four weeks and wherein the treatment is a cotreatment with an inhibitor of PD-1 or an inhibitor of PD-L1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate.

15

An inhibitor of PD-1 (programmed cell death protein 1) may be selected from the group consisting of pembrolizumab, nivolumab, pidilizumab, AMP-224, BMS-936559, cemiplimab and PDR001. An inhibitor of PD-L1 (programmed cell death ligand 1) may be selected from the group consisting of MDX-1105, MEDI4736, atezolizumab, avelumab, BMS-936559 and durvalumab.

20

In certain embodiments the TLR7/8 agonist for use of the second aspect is administered to the patient every two to four weeks and wherein the treatment is a cotreatment with an inhibitor of PD-1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate. In certain embodiments the TLR7/8 agonist for use of the second aspect is administered to the patient every two weeks and wherein the treatment is a cotreatment with an inhibitor of PD-1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate. In certain the TLR7/8 agonist for use of the second aspect is administered to the patient every three weeks and wherein the treatment is a cotreatment with an inhibitor of PD-1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate. In certain embodiments the TLR7/8 agonist for use of the second aspect is administered to the patient every four weeks and wherein the treatment is a cotreatment with an inhibitor of PD-1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate.

25

30

In certain embodiments the TLR7/8 agonist for use of the second aspect is administered to the patient every two to four weeks and wherein the treatment is a cotreatment with an inhibitor of PD-L1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate. In certain embodiments the TLR7/8 agonist for use of the second aspect is administered to the patient every two weeks and wherein the treatment is a cotreatment with an inhibitor of PD-L1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate. In certain embodiments the TLR7/8 agonist for use of the second aspect is administered to the patient every three weeks and wherein the treatment is a cotreatment with an inhibitor of PD-L1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate. In certain embodiments the TLR7/8 agonist for use of the second aspect is administered to the patient every four weeks and wherein the treatment is a cotreatment with an inhibitor of PD-L1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate.

In certain embodiments the TLR7/8 agonist for use of the second aspect is administered to the patient every two to four weeks and wherein the treatment is a cotreatment with pembrolizumab, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate. In certain embodiments the TLR7/8 agonist for use of the second aspect is administered to the patient every two weeks and wherein the treatment is a cotreatment with pembrolizumab, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate. In certain embodiments the TLR7/8 agonist for use of the second aspect is administered to the patient every three weeks and wherein the treatment is a cotreatment with pembrolizumab, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate. In certain embodiments the TLR7/8 agonist for use of the second aspect is administered to the patient every four weeks and wherein the treatment is a cotreatment with pembrolizumab, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate.

The dose, administration frequency and form of administration of pembrolizumab is as described elsewhere herein.

In a third aspect the present invention relates to a method of treating cancer, the method comprising the step of administering to a patient in need thereof a pharmaceutically effective

dose of a TLR7/8 agonist conjugate, wherein the TLR7/8 agonist conjugate comprises one or more TLR 7/8 agonist moieties reversibly conjugated to a polymeric moiety and wherein the pharmaceutically effective dose ranges from 0.3 mg to 3 mg of TLR7/8 agonist. In certain embodiments the pharmaceutically effective dose is 0.5 mg TLR7/8 agonist. In certain
5 embodiments the pharmaceutically effective dose is 1 mg.

In certain embodiments the method of the third aspect comprises the step of intratumorally administering the pharmaceutically effective dose, which ranges from 0.3 to 3 mg of TLR7/8 agonist per tumor. In certain embodiments the effective dose is 0.5 mg TLR7/8 agonist per
10 tumor. In certain embodiments the effective dose is 1 mg per tumor.

In certain embodiments the TLR7/8 agonist of the third aspect is resiquimod.

In certain embodiments the intratumoral administration is an intratumoral injection. In certain
15 embodiments such intratumoral injection uses a fanning technique.

In certain embodiments the pharmaceutically effective dose of the third aspect is provided in a volume ranging from 0.1 ml to 2 ml. In certain embodiments the pharmaceutically effective dose of the third aspect is provided in a volume ranging from 0.2 ml to 1.5 ml. In certain
20 embodiments the pharmaceutically effective dose of the third aspect is provided in a volume of 0.25 ml. In certain the pharmaceutically effective dose of the third aspect is provided in a volume of 0.5 ml. In certain embodiments the pharmaceutically effective dose of the third aspect is provided in a volume of 1 ml.

25 In certain embodiments the pharmaceutically effective dose of the third aspect is provided in a vial. In certain embodiments the pharmaceutically effective dose of the third aspect is provided in a dual-chamber cartridge.

In certain embodiments the pharmaceutically effective dose of the third aspect is provided in
30 the form of a pharmaceutical formulation. In certain embodiments such pharmaceutical formulation is provided as a dry formulation, such as in the form of a lyophilized formulation. Such lyophilized formulation is resuspended before administration to the patient to yield a resuspended formulation, which may be a solution or suspension. In certain embodiments the pharmaceutical formulation is provided as a liquid, such as a suspension formulation. In certain

embodiments the pharmaceutical formulation is provided as a suspension formulation. In certain embodiments the pharmaceutical formulation is provided as a suspension formulation which is stored at a temperature ranging from -80°C to 12°C. In certain embodiments the pharmaceutical formulation is provided as a suspension formulation which is stored at a temperature of about -20°C.

In certain embodiments the cancer of the third aspect is a solid tumor. In certain embodiments the solid tumor is selected from the group consisting of lip and oral cavity cancer, oral cancer, liver cancer/hepatocellular cancer, primary liver cancer, lung cancer, lymphoma, malignant mesothelioma, malignant thymoma, skin cancer, intraocular melanoma, metastatic squamous neck cancer with occult primary, childhood multiple endocrine neoplasia syndrome, mycosis fungoides, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, oropharyngeal cancer, ovarian cancer, pancreatic cancer, parathyroid cancer, pheochromocytoma, pituitary tumor, adrenocortical carcinoma, AIDS-related malignancies, anal cancer, bile duct cancer, bladder cancer, brain and nervous system cancer, breast cancer, bronchial adenoma/carcinoid, gastrointestinal carcinoid tumor, carcinoma, colorectal cancer, endometrial cancer, esophageal cancer, extracranial germ cell tumor, extragonadal germ cell tumor, extrahepatic bile duct cancer, gallbladder cancer, gastric (stomach) cancer, gestational trophoblastic tumor, head and neck cancer, hypopharyngeal cancer, islet cell carcinoma (endocrine pancreas), kidney cancer/renal cell cancer, laryngeal cancer, pleuropulmonary blastoma, prostate cancer, transitional cell cancer of the renal pelvis and ureter, retinoblastoma, salivary gland cancer, sarcoma, Sezary syndrome, small intestine cancer, genitourinary cancer, malignant thymoma, thyroid cancer, Wilms' tumor and cholangiocarcinoma. In certain embodiments the solid tumor is selected from the group consisting of squamous cell carcinoma of the head and neck (SCCHN); HPV-associated cancers, such as anal, vulvar, cervical, penile and vaginal cancers; melanomas; pancreatic cancer and breast cancer, such as triple-negative breast cancer (TNBC).

In certain embodiments the pharmaceutically effective dose of the third aspect is administered to the patient every two to four weeks. In certain embodiments the pharmaceutically effective dose of the third aspect is administered to the patient every two weeks. In certain embodiments the pharmaceutically effective dose of the third aspect is administered to the patient every three weeks. In certain embodiments the pharmaceutically effective dose of the third aspect is administered to the patient every four weeks.

In certain embodiments the pharmaceutically effective dose of the third aspect is administered to the patient every two to four weeks and the treatment is a cotreatment with an immune checkpoint inhibitor, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate. In certain embodiments the pharmaceutically effective dose of the third aspect is administered to the patient every two weeks and the treatment is a cotreatment with an immune checkpoint inhibitor, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate. In certain the pharmaceutically effective dose of the third aspect is administered to the patient every three weeks and the treatment is a cotreatment with an immune checkpoint inhibitor, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate. In certain the pharmaceutically effective dose of the third aspect is administered to the patient every four weeks and the treatment is a cotreatment with an immune checkpoint inhibitor, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate.

In certain embodiments the immune checkpoint inhibitor of the third aspect is an inhibitor of PD-1 or an inhibitor of PD-L1. An inhibitor of PD-1 (programmed cell death protein 1) may be selected from the group consisting of pembrolizumab, nivolumab, pidilizumab, AMP-224, BMS-936559, cemiplimab and PDR001. An inhibitor of PD-L1 (programmed cell death ligand 1) may be selected from the group consisting of MDX-1105, MEDI4736, atezolizumab, avelumab, BMS-936559 and durvalumab.

In certain embodiments the immune checkpoint inhibitor is an inhibitor of PD-1. In certain embodiments the immune checkpoint inhibitor is pembrolizumab.

In the following sections the TLR7/8 agonist conjugate of all aspects of the present invention will be described in further detail.

The TLR7/8 agonist conjugate comprises a polymeric moiety Z to which one or more moieties $-L^2-L^1-D$ are conjugated, wherein each $-L^2-$ is individually a chemical bond or a spacer moiety; each $-L^1-$ is individually a linker moiety to which $-D$ is reversibly and covalently conjugated; and each $-D$ is a TLR7/8 agonist.

The one or more moieties $-L^2-L^1-D$ are covalently conjugated to Z. In certain embodiments the one or more moieties $-L^2-L^1-D$ are stably conjugated to Z. If Z is a hydrogel it is understood that the number of moieties $-L^2-L^1-D$ conjugated to such hydrogel carrier is too large to specify.

- 5 In certain embodiments -D is a TLR7/8 agonist selected from the group consisting of CL075, CL097, poly(dT), resiquimod (R-848, VML600, S28463), MEDI9197 (3M-052), NKTR262, DV1001, IMO4200, IPH3201 and VTX1463.

In certain embodiments -D is resiquimod.

10

In certain embodiments at least some moieties -D of the conjugate are resiquimod, such as about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90% or 100%, i.e. all, of the moieties -D present in the conjugate.

- 15 In certain embodiments the conjugate comprises only one type of moiety -D, i.e. all moieties -D of the conjugate are identical. In certain embodiments the conjugate comprises more than one type of -D, such as 2, 3, 4, 5, 6, 7, 8, 9 or 10 different types of -D.

- If the conjugate comprises more than one type of -D, all moieties -D may be conjugated to the same type of $-L^1-$ or may be conjugated to different types of $-L^1-$, i.e. a first type of -D may be conjugated to a first type of $-L^1-$, a second type of -D may be conjugated to a second type $-L^1-$, and so on. In certain embodiments all moieties $-L^1-$ are of the same type, i.e. have the same structure. Alternatively, individual moieties -D of the same type may be conjugated to different types of moiety $-L^1-$. The use of different moieties $-L^1-$ allows for release of the conjugated drug moieties -D with different release kinetics. For example, a first linker moiety $-L^1-$ may have a short half-life and thus provides drug release within a shorter time after administration to a patient than a second linker moiety $-L^1-$ which may have a longer half-life. Using different moieties $-L^1-$ with different release half-lives allows for an optimized dosage regimen of one or more drugs.

25
30

The moiety $-L^1-$ is conjugated to -D via a functional group of -D, which functional group is in certain embodiments selected from the group consisting of carboxylic acid, primary amine, secondary amine, thiol, sulfonic acid, carbonate, carbamate, hydroxyl, aldehyde, ketone, hydrazine, isothiocyanate, phosphoric acid, phosphonic acid, acryloyl, hydroxylamine, sulfate,

vinyl sulfone, vinyl ketone, diazoalkane, guanidine, aziridine, amide, imide, imine, urea, amidine, guanidine, sulfonamide, phosphonamide, phosphoramidate, hydrazide and selenol. In certain embodiments -L¹- is conjugated to -D via a functional group of -D selected from the group consisting of carboxylic acid, primary amine, secondary amine, thiol, sulfonic acid, carbonate, carbamate, hydroxyl, aldehyde, ketone, hydrazine, isothiocyanate, phosphoric acid, phosphonic acid, acryloyl, hydroxylamine, sulfate, vinyl sulfone, vinyl ketone, diazoalkane, guanidine, amidine and aziridine. In certain embodiments -L¹- is conjugated to -D via a functional group of -D selected from the group consisting of hydroxyl, primary amine, secondary amine, amidine and carboxylic acid.

10

In certain embodiments -L¹- is conjugated to -D via a hydroxyl group of -D.

In certain embodiments -L¹- is conjugated to -D via a primary amine group of -D.

15

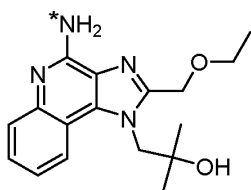
In certain embodiments -L¹- is conjugated to -D via a secondary amine group of -D.

In certain embodiments -L¹- is conjugated to -D via a carboxylic acid group of -D.

In certain embodiments -L¹- is conjugated to -D via an amidine group of -D.

20

If -D is resiquimod, -L¹- is in certain embodiments conjugated to -D via its aromatic amine, i.e. the amine functional group marked with the asterisk



25 The moiety -L¹- can be connected to -D through any type of linkage, provided that it is reversible. In certain embodiments -L¹- is connected to -D through a linkage selected from the group consisting of amide, ester, carbamate, acetal, aminal, imine, oxime, hydrazone, disulfide, acylguanidine, acylamidine, carbonate, phosphate, sulfate, urea, hydrazide, thioester, thiophosphate, thiosulfate, sulfonamide, sulfoamidine, sulfaguanidine, phosphoramidate, phosphoamidine, phosphoguanidine, phosphonamide, phosphonamidine, phosphoguanidine,

30

phosphonate, borate and imide. In certain embodiments -L¹- is connected to -D through a linkage selected from the group consisting of amide, ester, carbonate, carbamate, acetal, aminal, imine, oxime, hydrazone, disulfide, acylamidine and acylguanidine. In certain
 5 embodiments -L¹- is connected to -D through a linkage selected from the group consisting of amide, ester, carbonate, acylamide and carbamate. It is understood that some of these linkages may not be reversible *per se*, but that in the present invention neighboring groups present in -L¹- render these linkages reversible.

10 In certain embodiments -L¹- is connected to -D through an ester linkage.

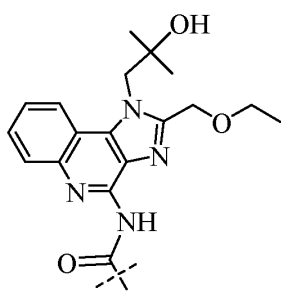
In certain embodiments -L¹- is connected to -D through a carbonate linkage.

In certain embodiments -L¹- is connected to -D through an acylamidine linkage.

15 In certain embodiments -L¹- is connected to -D through a carbamate linkage.

In certain embodiments -L¹- is connected to -D through an amide linkage.

20 If -D is resiquimod, the linkage between -D and -L¹- is in certain embodiments through an amide linkage, in which the aromatic amine functional group of -D forms an amide linkage with a carbonyl (-C(=O)-) of -L¹-



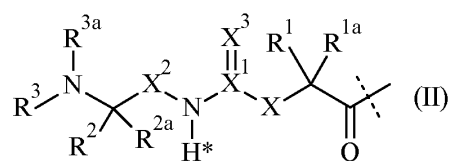
wherein the dashed line indicates attachment to the remainder of -L¹-.

25 In certain embodiments cleavage of the linkage between -D and -L¹- occurs with a release half-life under physiological conditions (aqueous buffer, pH 7.4, 37°C) of at least 3 days, such as at least 4 days, at least 5 days, at least 6 days, at least 7 days, at least 8 days, at least 9 days, at

least 10 days, at least 12 days, at least 15 days, at least 17 days, at least 20 days or at least 25 days.

The moiety $-L^1-$ is a linker moiety from which $-D$ is released in its free form, i.e. generally in the form of $D-H$ or $D-OH$. Such moieties are also known as “prodrug linkers” or “reversible prodrug linkers” and are known in the art, such as for example the reversible linker moieties disclosed in WO 2005/099768 A2, WO 2006/136586 A2, WO 2011/089216 A1, WO 2013/024053 A1, WO 2011/012722 A1, WO 2011/089214 A1, WO 2011/089215 A1, WO 2013/024052 A1 and WO 2013/160340 A1, which are incorporated by reference herewith.

In one embodiment $-L^1-$ has a structure as disclosed in WO 2009/095479 A2. Accordingly, in certain embodiments the moiety $-L^1-$ is of formula (II):



wherein the dashed line indicates attachment to a nitrogen of $-D$ by forming an amide bond;

$-X-$ is $-C(R^4R^{4a})-$; $-N(R^4)-$; $-O-$; $-C(R^4R^{4a})-C(R^5R^{5a})-$; $-C(R^5R^{5a})-C(R^4R^{4a})-$; $-C(R^4R^{4a})-N(R^6)-$; $-N(R^6)-C(R^4R^{4a})-$; $-C(R^4R^{4a})-O-$; $-O-C(R^4R^{4a})-$; or $-C(R^7R^{7a})-$;

X^1 is C; or S(O);

$-X^2-$ is $-C(R^8R^{8a})-$; or $-C(R^8R^{8a})-C(R^9R^{9a})-$;

$=X^3$ is $=O$; $=S$; or $=N-CN$;

$-R^1$, $-R^{1a}$, $-R^2$, $-R^{2a}$, $-R^4$, $-R^{4a}$, $-R^5$, $-R^{5a}$, $-R^6$, $-R^8$, $-R^{8a}$, $-R^9$, $-R^{9a}$ are independently selected from the group consisting of $-H$; and C_{1-6} alkyl;

$-R^3$, $-R^{3a}$ are independently selected from the group consisting of $-H$; and C_{1-6} alkyl, provided that in case one of $-R^3$, $-R^{3a}$ or both are other than $-H$ they are connected to N to which they are attached through an sp^3 -hybridized carbon atom;

$-R^7$ is $-N(R^{10}R^{10a})$; or $-NR^{10}-(C=O)-R^{11}$;

$-R^{7a}$, $-R^{10}$, $-R^{10a}$, $-R^{11}$ are independently of each other $-H$; or C_{1-6} alkyl;

optionally, one or more of the pairs $-R^{1a}/-R^{4a}$, $-R^{1a}/-R^{5a}$, $-R^{1a}/-R^{7a}$, $-R^{4a}/-R^{5a}$, $-R^{8a}/-R^{9a}$ form a chemical bond;

optionally, one or more of the pairs $-R^1/-R^{1a}$, $-R^2/-R^{2a}$, $-R^4/-R^{4a}$, $-R^5/-R^{5a}$, $-R^8/-R^{8a}$, $-R^9/-R^{9a}$ are joined together with the atom to which they are attached to form a C_{3-10} cycloalkyl; or 3- to 10-membered heterocyclyl;

optionally, one or more of the pairs $-R^1/-R^4$, $-R^1/-R^5$, $-R^1/-R^6$, $-R^1/-R^{7a}$, $-R^4/-R^5$, $-R^4/-R^6$, $-R^8/-R^9$, $-R^2/-R^3$ are joined together with the atoms to which they are attached to form a ring A;

optionally, R^3/R^{3a} are joined together with the nitrogen atom to which they are attached to form a 3- to 10-membered heterocycle;

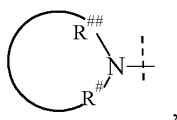
A is selected from the group consisting of phenyl; naphthyl; indenyl; indanyl; tetralinyl; C_{3-10} cycloalkyl; 3- to 10-membered heterocyclyl; and 8- to 11-membered heterobicyclyl; and

wherein $-L^1-$ is substituted with at least one $-L^2-$ and wherein $-L^1-$ is optionally further substituted, provided that the hydrogen marked with the asterisk in formula (II) is not replaced by $-L^2-$ or a substituent.

Preferably $-L^1-$ of formula (II) is substituted with one moiety $-L^2-$.

In one embodiment $-L^1-$ of formula (II) is not further substituted.

It is understood that if $-R^3/-R^{3a}$ of formula (II) are joined together with the nitrogen atom to which they are attached to form a 3- to 10-membered heterocycle, only such 3- to 10-membered heterocycles may be formed in which the atoms directly attached to the nitrogen are sp^3 -hybridized carbon atoms. In other words, such 3- to 10-membered heterocycle formed by $-R^3/-R^{3a}$ together with the nitrogen atom to which they are attached has the following structure:



wherein

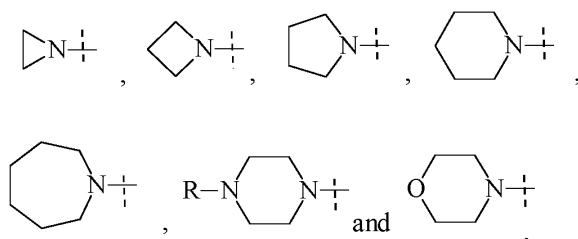
the dashed line indicates attachment to the rest of $-L^1-$;

the ring comprises 3 to 10 atoms comprising at least one nitrogen; and

$R^{\#}$ and $R^{##}$ represent an sp^3 -hybridized carbon atom.

It is also understood that the 3- to 10-membered heterocycle may be further substituted.

Exemplary embodiments of suitable 3- to 10-membered heterocycles formed by $-R^3/-R^{3a}$ of
 5 formula (II) together with the nitrogen atom to which they are attached are the following:

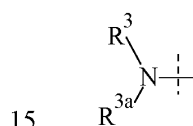


wherein

dashed lines indicate attachment to the rest of the molecule; and

10 $-R$ is selected from the group consisting of $-H$ and C_{1-6} alkyl.

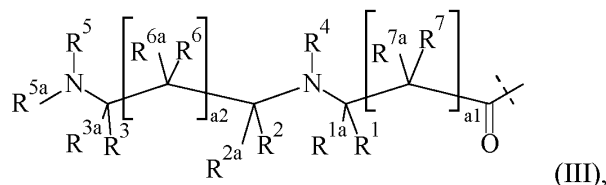
$-L^1-$ of formula (II) may optionally be further substituted. In general, any substituent may be used as far as the cleavage principle is not affected, i.e. the hydrogen marked with the asterisk in formula (II) is not replaced and the nitrogen of the moiety



of formula (II) remains part of a primary, secondary or tertiary amine, i.e. $-R^3$ and $-R^{3a}$ are independently of each other $-H$ or are connected to $-N<$ through an sp^3 -hybridized carbon atom.

In one embodiment $-R^1$ or $-R^{1a}$ of formula (II) is substituted with $-L^2-$. In another
 20 embodiment $-R^2$ or $-R^{2a}$ of formula (II) is substituted with $-L^2-$. In another embodiment $-R^3$ or $-R^{3a}$ of formula (II) is substituted with $-L^2-$. In another embodiment $-R^4$ of formula (II) is substituted with $-L^2-$. In another embodiment $-R^5$ or $-R^{5a}$ of formula (II) is substituted with $-L^2-$. In another embodiment $-R^6$ of formula (II) is substituted with $-L^2-$. In another embodiment $-R^7$ or $-R^{7a}$ of formula (II) is substituted with $-L^2-$. In another embodiment $-R^8$ or $-R^{8a}$ of formula
 25 (II) is substituted with $-L^2-$. In another embodiment $-R^9$ or $-R^{9a}$ of formula (II) is substituted with $-L^2-$. In another embodiment $-R^{10}$ or $-R^{10a}$ of formula (II) is substituted with $-L^2-$. In another embodiment $-R^{11}$ of formula (II) is substituted with $-L^2-$.

In certain embodiments -L¹- has a structure as disclosed in WO2016/020373A1. Accordingly, in certain embodiments the moiety -L¹- is of formula (III):



5 wherein

the dashed line indicates attachment to a primary or secondary amine or hydroxyl of -D by forming an amide or ester linkage, respectively;

-R¹, -R^{1a}, -R², -R^{2a}, -R³ and -R^{3a} are independently of each other selected from the group consisting

10 of -H, -C(R⁸R^{8a}R^{8b}), -C(=O)R⁸, -C≡N, -C(=NR⁸)R^{8a}, -CR⁸(=CR^{8a}R^{8b}), -C≡CR⁸ and -T; -R⁴, -R⁵ and -R^{5a} are independently of each other selected from the group consisting of -H, -C(R⁹R^{9a}R^{9b}) and -T;

a1 and a2 are independently of each other 0 or 1;

15 each -R⁶, -R^{6a}, -R⁷, -R^{7a}, -R⁸, -R^{8a}, -R^{8b}, -R⁹, -R^{9a}, -R^{9b} are independently of each other selected from the group consisting of -H, halogen, -CN, -COOR¹⁰, -OR¹⁰, -C(O)R¹⁰, -C(O)N(R¹⁰R^{10a}), -S(O)₂N(R¹⁰R^{10a}), -S(O)N(R¹⁰R^{10a}), -S(O)₂R¹⁰, -S(O)R¹⁰, -N(R¹⁰)S(O)₂N(R^{10a}R^{10b}), -SR¹⁰, -N(R¹⁰R^{10a}), -NO₂, -OC(O)R¹⁰, -N(R¹⁰)C(O)R^{10a}, -N(R¹⁰)S(O)₂R^{10a}, -N(R¹⁰)S(O)R^{10a}, -N(R¹⁰)C(O)OR^{10a}, -N(R¹⁰)C(O)N(R^{10a}R^{10b}), -OC(O)N(R¹⁰R^{10a}), -T, C₁₋₂₀ alkyl, C₂₋₂₀ alkenyl, and C₂₋₂₀ alkynyl; wherein -T, C₁₋₂₀ alkyl, C₂₋₂₀ alkenyl, and C₂₋₂₀ alkynyl are optionally substituted with one or more -R¹¹,

20 which are the same or different and wherein C₁₋₂₀ alkyl, C₂₋₂₀ alkenyl, and C₂₋₂₀ alkynyl are optionally interrupted by one or more groups selected from the group consisting of -T-, -C(O)O-, -O-, -C(O)-, -C(O)N(R¹²)-, -S(O)₂N(R¹²)-, -S(O)N(R¹²)-, -S(O)₂-, -S(O)-, -N(R¹²)S(O)₂N(R^{12a})-, -S-, -N(R¹²)-, -OC(OR¹²)(R^{12a})-, -N(R¹²)C(O)N(R^{12a})-, and -OC(O)N(R¹²)-;

25 each -R¹⁰, -R^{10a}, -R^{10b} is independently selected from the group consisting of -H, -T, C₁₋₂₀ alkyl, C₂₋₂₀ alkenyl, and C₂₋₂₀ alkynyl; wherein -T, C₁₋₂₀ alkyl, C₂₋₂₀ alkenyl, and C₂₋₂₀ alkynyl are optionally substituted with one or more -R¹¹, which are the same or different and wherein C₁₋₂₀ alkyl, C₂₋₂₀ alkenyl, and C₂₋₂₀ alkynyl are optionally

30

- interrupted by one or more groups selected from the group consisting of -T-, -C(O)O-, -O-, -C(O)-, -C(O)N(R¹²)-, -S(O)₂N(R¹²)-, -S(O)N(R¹²)-, -S(O)₂-, -S(O)-, -N(R¹²)S(O)₂N(R^{12a})-, -S-, -N(R¹²)-, -OC(OR¹²)(R^{12a})-, -N(R¹²)C(O)N(R^{12a})-, and -OC(O)N(R¹²)-;
- 5 each T is independently of each other selected from the group consisting of phenyl, naphthyl, indenyl, indanyl, tetralinyl, C₃₋₁₀ cycloalkyl, 3- to 10-membered heterocyclyl, and 8- to 11-membered heterobicyclyl; wherein each T is independently optionally substituted with one or more -R¹¹, which are the same or different;
- each -R¹¹ is independently of each other selected from halogen, -CN, oxo (=O), -COOR¹³, -OR¹³, -C(O)R¹³, -C(O)N(R¹³R^{13a}), -S(O)₂N(R¹³R^{13a}), -S(O)N(R¹³R^{13a}), -S(O)₂R¹³, -S(O)R¹³, -N(R¹³)S(O)₂N(R^{13a}R^{13b}), -SR¹³, -N(R¹³R^{13a}), -NO₂, -OC(O)R¹³, -N(R¹³)C(O)R^{13a}, -N(R¹³)S(O)₂R^{13a}, -N(R¹³)S(O)R^{13a}, -N(R¹³)C(O)OR^{13a}, -N(R¹³)C(O)N(R^{13a}R^{13b}), -OC(O)N(R¹³R^{13a}), and C₁₋₆ alkyl; wherein C₁₋₆ alkyl is optionally substituted with one
- 10 or more halogen, which are the same or different;
- each -R¹², -R^{12a}, -R¹³, -R^{13a}, -R^{13b} is independently selected from the group consisting of -H, and C₁₋₆ alkyl; wherein C₁₋₆ alkyl is optionally substituted with one or more halogen, which are the same or different;
- optionally, one or more of the pairs -R¹/-R^{1a}, -R²/-R^{2a}, -R³/-R^{3a}, -R⁶/-R^{6a}, -R⁷/-R^{7a} are
- 20 joined together with the atom to which they are attached to form a C₃₋₁₀ cycloalkyl or a 3- to 10-membered heterocyclyl;
- optionally, one or more of the pairs -R¹/-R², -R¹/-R³, -R¹/-R⁴, -R¹/-R⁵, -R¹/-R⁶, -R¹/-R⁷, -R²/-R³, -R²/-R⁴, -R²/-R⁵, -R²/-R⁶, -R²/-R⁷, -R³/-R⁴, -R³/-R⁵, -R³/-R⁶, -R³/-R⁷, -R⁴/-R⁵, -R⁴/-R⁶, -R⁴/-R⁷, -R⁵/-R⁶, -R⁵/-R⁷, -R⁶/-R⁷ are joint together with the atoms to which they are
- 25 attached to form a ring A;
- A is selected from the group consisting of phenyl; naphthyl; indenyl; indanyl; tetralinyl; C₃₋₁₀ cycloalkyl; 3- to 10-membered heterocyclyl; and 8- to 11-membered heterobicyclyl;
- 30 wherein -L¹- is substituted with at least one -L²- and wherein -L¹- is optionally further substituted.

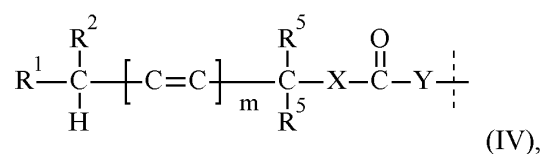
The optional further substituents of -L¹- of formula (III) are preferably as described above.

Preferably -L¹- of formula (III) is substituted with one moiety -L²-.

In one embodiment -L¹- of formula (III) is not further substituted.

- 5 In another embodiment -L¹- has a structure as disclosed in EP1536334B1, WO2009/009712A1, WO2008/034122A1, WO2009/143412A2, WO2011/082368A2, and US8618124B2, which are herewith incorporated by reference.

- 10 In another embodiment -L¹- has a structure as disclosed in US8946405B2 and US8754190B2, which are herewith incorporated by reference. Accordingly, in certain embodiments -L¹- is of formula (IV):



wherein

- 15 the dashed line indicates attachment to -D through a functional group of -D selected from the group consisting of -OH, -SH and -NH₂;

m is 0 or 1;

- 20 at least one or both of -R¹ and -R² is/are independently of each other selected from the group consisting of -CN, -NO₂, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkenyl, optionally substituted alkynyl, -C(O)R³, -S(O)R³, -S(O)₂R³, and -SR⁴,

one and only one of -R¹ and -R² is selected from the group consisting of -H, optionally substituted alkyl, optionally substituted arylalkyl, and optionally substituted heteroarylalkyl;

- 25 -R³ is selected from the group consisting of -H, optionally substituted alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, -OR⁹ and -N(R⁹)₂;

-R⁴ is selected from the group consisting of optionally substituted alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, and optionally substituted heteroarylalkyl;

- 30 each -R⁵ is independently selected from the group consisting of -H, optionally substituted alkyl, optionally substituted alkenylalkyl, optionally substituted

alkynylalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl;

-R⁹ is selected from the group consisting of -H and optionally substituted alkyl;

-Y- is absent and -X- is -O- or -S-; or

5 -Y- is -N(Q)CH₂- and -X- is -O-;

Q is selected from the group consisting of optionally substituted alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl;

optionally, -R¹ and -R² may be joined to form a 3 to 8-membered ring; and

10 optionally, both -R⁹ together with the nitrogen to which they are attached form a heterocyclic ring;

wherein -L¹- is substituted with at least one -L²- and wherein -L¹- is optionally further substituted.

15 Only in the context of formula (IV) the terms used have the following meaning:

The term “alkyl” as used herein includes linear, branched or cyclic saturated hydrocarbon groups of 1 to 8 carbons, or in some embodiments 1 to 6 or 1 to 4 carbon atoms.

20 The term “alkoxy” includes alkyl groups bonded to oxygen, including methoxy, ethoxy, isopropoxy, cyclopropoxy, cyclobutoxy, and similar.

The term “alkenyl” includes non-aromatic unsaturated hydrocarbons with carbon-carbon double bonds.

25

The term “alkynyl” includes non-aromatic unsaturated hydrocarbons with carbon-carbon triple bonds.

30 The term “aryl” includes aromatic hydrocarbon groups of 6 to 18 carbons, preferably 6 to 10 carbons, including groups such as phenyl, naphthyl, and anthracenyl. The term “heteroaryl” includes aromatic rings comprising 3 to 15 carbons containing at least one N, O or S atom, preferably 3 to 7 carbons containing at least one N, O or S atom, including groups such as pyrrolyl, pyridyl, pyrimidinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, quinolyl, indolyl, indenyl, and similar.

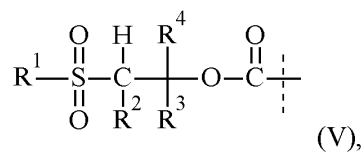
In some instance, alkenyl, alkynyl, aryl or heteroaryl moieties may be coupled to the remainder of the molecule through an alkylene linkage. Under those circumstances, the substituent will be referred to as alkenylalkyl, alkynylalkyl, arylalkyl or heteroarylalkyl, indicating that an
 5 alkylene moiety is between the alkenyl, alkynyl, aryl or heteroaryl moiety and the molecule to which the alkenyl, alkynyl, aryl or heteroaryl is coupled.

The term “halogen” includes bromo, fluoro, chloro and iodo.

- 10 The term “heterocyclic ring” refers to a 4 to 8 membered aromatic or non-aromatic ring comprising 3 to 7 carbon atoms and at least one N, O, or S atom. Examples are piperidiny, piperaziny, tetrahydropyrany, pyrrolidine, and tetrahydrofurany, as well as the exemplary groups provided for the term “heteroaryl” above.
- 15 When a ring system is optionally substituted, suitable substituents are selected from the group consisting of alkyl, alkenyl, alkynyl, or an additional ring, each optionally further substituted. Optional substituents on any group, including the above, include halo, nitro, cyano, -OR, -SR, -NR₂, -OCOR, -NRCOR, -COOR, -CONR₂, -SOR, -SO₂R, -SONR₂, -SO₂NR₂, wherein each R is independently alkyl, alkenyl, alkynyl, aryl or heteroaryl, or two R groups
 20 taken together with the atoms to which they are attached form a ring.

Preferably -L¹- of formula (IV) is substituted with one moiety -L²-.

In another embodiment -L¹- has a structure as disclosed in WO2013/036857A1, which is
 25 herewith incorporated by reference. Accordingly, in certain embodiments -L¹- is of formula (V):



wherein

the dashed line indicates attachment to -D through an amine functional group of -D;

- R¹ is selected from the group consisting of optionally substituted C₁-C₆ linear, branched, or cyclic alkyl; optionally substituted aryl; optionally substituted heteroaryl; alkoxy; and -NR⁵₂;
- R² is selected from the group consisting of -H; optionally substituted C₁-C₆ alkyl; optionally substituted aryl; and optionally substituted heteroaryl;
- R³ is selected from the group consisting of -H; optionally substituted C₁-C₆ alkyl; optionally substituted aryl; and optionally substituted heteroaryl;
- R⁴ is selected from the group consisting of -H; optionally substituted C₁-C₆ alkyl; optionally substituted aryl; and optionally substituted heteroaryl;
- each -R⁵ is independently of each other selected from the group consisting of -H; optionally substituted C₁-C₆ alkyl; optionally substituted aryl; and optionally substituted heteroaryl; or when taken together two -R⁵ can be cycloalkyl or cycloheteroalkyl;
- wherein -L¹- is substituted with at least one -L²- and wherein -L¹- is optionally further substituted.

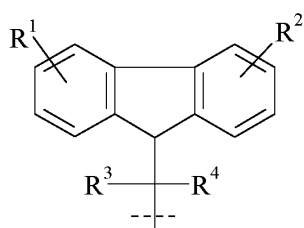
Only in the context of formula (V) the terms used have the following meaning:

- “Alkyl”, “alkenyl”, and “alkynyl” include linear, branched or cyclic hydrocarbon groups of 1-8 carbons or 1-6 carbons or 1-4 carbons wherein alkyl is a saturated hydrocarbon, alkenyl includes one or more carbon-carbon double bonds and alkynyl includes one or more carbon-carbon triple bonds. Unless otherwise specified these contain 1-6 C.
- “Aryl” includes aromatic hydrocarbon groups of 6-18 carbons, preferably 6-10 carbons, including groups such as phenyl, naphthyl, and anthracene. “Heteroaryl” includes aromatic rings comprising 3-15 carbons containing at least one N, O or S atom, preferably 3-7 carbons containing at least one N, O or S atom, including groups such as pyrrolyl, pyridyl, pyrimidinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, quinolyl, indolyl, indenyl, and similar.
- The term “substituted” means an alkyl, alkenyl, alkynyl, aryl, or heteroaryl group comprising one or more substituent groups in place of one or more hydrogen atoms. Substituents may generally be selected from halogen including F, Cl, Br, and I; lower alkyl including linear, branched, and cyclic; lower haloalkyl including fluoroalkyl, chloroalkyl, bromoalkyl, and iodoalkyl; OH; lower alkoxy including linear, branched, and cyclic; SH; lower alkylthio

including linear, branched and cyclic; amino, alkylamino, dialkylamino, silyl including alkylsilyl, alkoxysilyl, and arylsilyl; nitro; cyano; carbonyl; carboxylic acid, carboxylic ester, carboxylic amide, aminocarbonyl; aminoacyl; carbamate; urea; thiocarbamate; thiourea; ketone; sulfone; sulfonamide; aryl including phenyl, naphthyl, and anthracenyl; heteroaryl including 5-member heteroaryls including as pyrrole, imidazole, furan, thiophene, oxazole, thiazole, isoxazole, isothiazole, thiadiazole, triazole, oxadiazole, and tetrazole, 6-member heteroaryls including pyridine, pyrimidine, pyrazine, and fused heteroaryls including benzofuran, benzothiophene, benzoxazole, benzimidazole, indole, benzothiazole, benzisoxazole, and benzisothiazole.

Preferably -L¹- of formula (V) is substituted with one moiety -L²-.

In another embodiment -L¹- has a structure as disclosed in US7585837B2, which is herewith incorporated by reference. Accordingly, in certain embodiments -L¹- is of formula (VI):



(VI),

wherein

the dashed line indicates attachment to -D through an amine functional group of -D;

R¹ and R² are independently selected from the group consisting of hydrogen, alkyl, alkoxy, alkoxyalkyl, aryl, alkaryl, aralkyl, halogen, nitro, -SO₃H, -SO₂NHR⁵, amino, ammonium, carboxyl, PO₃H₂, and OPO₃H₂;

R³, R⁴, and R⁵ are independently selected from the group consisting of hydrogen, alkyl, and aryl;

wherein -L¹- is substituted with at least one -L²- and wherein -L¹- is optionally further substituted.

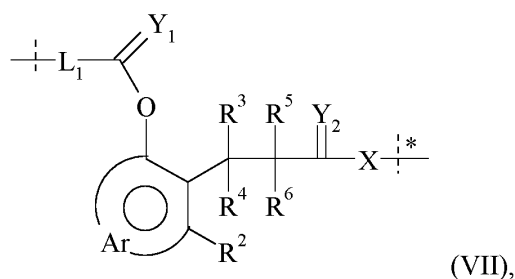
Suitable substituents for formulas (VI) are alkyl (such as C₁₋₆ alkyl), alkenyl (such as C₂₋₆ alkenyl), alkynyl (such as C₂₋₆ alkynyl), aryl (such as phenyl), heteroalkyl, heteroalkenyl, heteroalkynyl, heteroaryl (such as aromatic 4 to 7 membered heterocycle) or halogen moieties.

Only in the context of formula (VI) the terms used have the following meaning:

The terms “alkyl”, “alkoxy”, “alkoxyalkyl”, “aryl”, “alkaryl” and “aralkyl” mean alkyl radicals of 1-8, preferably 1-4 carbon atoms, e.g. methyl, ethyl, propyl, isopropyl and butyl, and aryl radicals of 6-10 carbon atoms, e.g. phenyl and naphthyl. The term “halogen” includes bromo, fluoro, chloro and iodo.

Preferably $-L^1-$ of formula (VI) is substituted with one moiety $-L^2-$.

10 In another embodiment $-L^1-$ has a structure as disclosed in WO2002/089789A1, which is herewith incorporated by reference. Accordingly, in certain embodiments $-L^1-$ is of formula (VII):



wherein

15 the dashed line indicates attachment to $-D$ through an amine functional group of $-D$;
 L_1 is a bifunctional linking group,
 Y_1 and Y_2 are independently O, S or NR^7 ;
 R^2 , R^3 , R^4 , R^5 , R^6 and R^7 are independently selected from the group consisting of
hydrogen, C_{1-6} alkyls, C_{3-12} branched alkyls, C_{3-8} cycloalkyls, C_{1-6} substituted alkyls,
20 C_{3-8} substituted cycloalkyls, aryls, substituted aryls, aralkyls, C_{1-6} heteroalkyls,
substituted C_{1-6} heteroalkyls, C_{1-6} alkoxy, phenoxy, and C_{1-6} heteroalkoxy;
Ar is a moiety which when included in formula (VII) forms a multisubstituted aromatic
hydrocarbon or a multi-substituted heterocyclic group;
X is a chemical bond or a moiety that is actively transported into a target cell, a
25 hydrophobic moiety, or a combination thereof,
y is 0 or 1;
wherein $-L^1-$ is substituted with at least one $-L^2-$ and wherein $-L^1-$ is optionally further
substituted.

Only in the context of formula (VII) the terms used have the following meaning:

The term “alkyl” shall be understood to include, e.g. straight, branched, substituted C₁₋₁₂ alkyls, including alkoxy, C₃₋₈ cycloalkyls or substituted cycloalkyls, etc.

5

The term “substituted” shall be understood to include adding or replacing one or more atoms contained within a functional group or compounds with one or more different atoms.

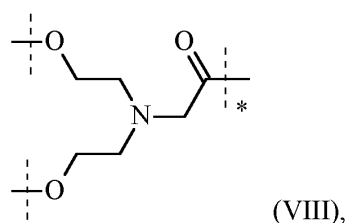
Substituted alkyls include carboxyalkyls, aminoalkyls, dialkylaminos, hydroxyalkyls and mercaptoalkyls; substituted cycloalkyls include moieties such as 4-chlorocyclohexyl; aryls include moieties such as naphthyl; substituted aryls include moieties such as 3-bromo-phenyl; aralkyls include moieties such as toluyll; heteroalkyls include moieties such as ethylthiophene; substituted heteroalkyls include moieties such as 3-methoxythiophene; alkoxy includes moieties such as methoxy; and phenoxy includes moieties such as 3-nitrophenoxy. Halo- shall be understood to include fluoro, chloro, iodo and bromo.

15

Preferably -L¹- of formula (VII) is substituted with one moiety -L²-.

In certain embodiments -L¹- comprises a substructure of formula (VIII)

20



wherein

the dashed line marked with the asterisk indicates attachment to a nitrogen of -D by forming an amide bond;

the unmarked dashed lines indicate attachment to the remainder of -L¹-; and

25

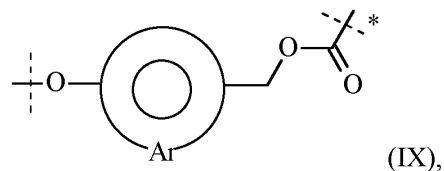
wherein -L¹- is substituted with at least one -L²- and wherein -L¹- is optionally further substituted.

Preferably -L¹- of formula (VIII) is substituted with one moiety -L²-.

30

In one embodiment -L¹- of formula (VIII) is not further substituted.

In certain embodiments $-L^1-$ comprises a substructure of formula (IX)



wherein

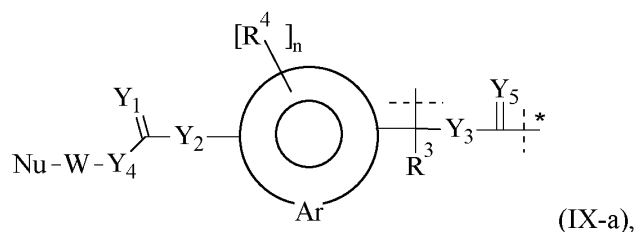
- 5 the dashed line marked with the asterisk indicates attachment to a nitrogen of $-D$ by forming a carbamate bond;
the unmarked dashed lines indicate attachment to the remainder of $-L^1-$; and
wherein $-L^1-$ is substituted with at least one $-L^2-$ and wherein $-L^1-$ is optionally further substituted.

10

Preferably $-L^1-$ of formula (IX) is substituted with one moiety $-L^2-$.

In one embodiment $-L^1-$ of formula (IX) is not further substituted.

- 15 In certain embodiments $-L^1-$ is of formula (IX-a):



wherein

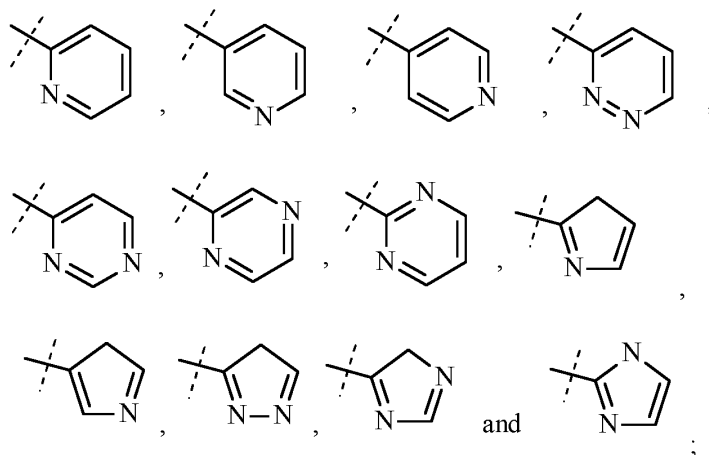
- the dashed line marked with the asterisk indicates attachment to a nitrogen of $-D$ and
the unmarked dashed line indicates attachment to $-L^2-$;
20 n is 0, 1, 2, 3, or 4;
 $=Y_1, =Y_5$ are independently of each other selected from the group consisting of $=O$ and $=S$;
 $-Y_2-$ is selected from the group consisting of $-O-$ and $-S-$;
 $-Y_3-$ is selected from the group consisting of $-O-$ and $-S-$;
25 $-Y_4-$ is selected from the group consisting of $-O-$, $-NR^5-$ and $-C(R^6R^{6a})-$;

$-R^3$, $-R^5$, $-R^6$, $-R^{6a}$ are independently of each other selected from the group consisting of -H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, 2-methylbutyl, 2,2-dimethylpropyl, n-hexyl, 2-methylpentyl, 3-methylpentyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl and 3,3-dimethylpropyl;

5 $-R^4$ is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, 2-methylbutyl, 2,2-dimethylpropyl, n-hexyl, 2-methylpentyl, 3-methylpentyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl and 3,3-dimethylpropyl;

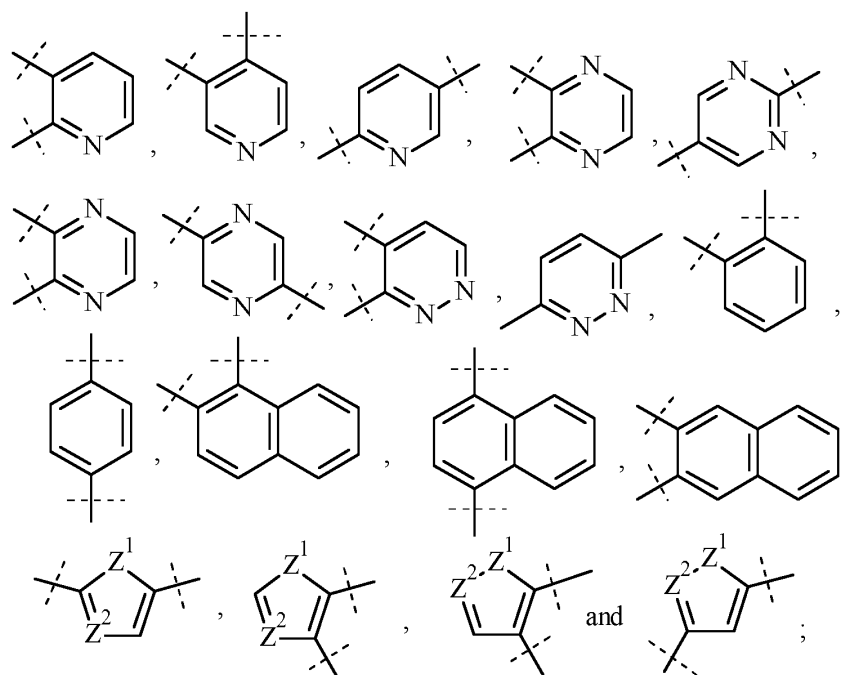
10 $-W-$ is selected from the group consisting of C_{1-20} alkyl optionally interrupted by one or more groups selected from the group consisting of C_{3-10} cycloalkyl, 8- to 30-membered carbopolycyclyl, 3- to 10-membered heterocyclyl, $-C(O)-$, $-C(O)N(R^7)-$, $-O-$, $-S-$ and $-N(R^7)-$;

$-Nu$ is a nucleophile selected from the group consisting of $-N(R^7R^{7a})$, $-N(R^7OH)$, $-N(R^7)-N(R^{7a}R^{7b})$, $-S(R^7)$, $-COOH$,



15

$-Ar-$ is selected from the group consisting of



wherein

dashed lines indicate attachment to the remainder of $-L^1$ -,

$-Z^1$ is selected from the group consisting of $-O$ -, $-S$ - and $-N(R^7)$ -, and

5 $-Z^2$ is $-N(R^7)$ -, and

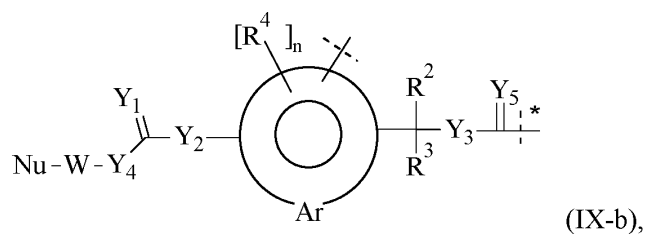
$-R^7$, $-R^{7a}$, $-R^{7b}$ are independently of each other selected from the group consisting of $-H$,

C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl;

wherein $-L^1$ is optionally further substituted.

10 In one embodiment $-L^1$ of formula (IX-a) is not further substituted.

In certain embodiments $-L^1$ is of formula (IX-b):



wherein

the dashed line marked with the asterisk indicates attachment to a nitrogen of -D and the unmarked dashed line indicates attachment to -L²-;

n is 0, 1, 2, 3, or 4;

=Y₁, =Y₃ are independently of each other selected from the group consisting of =O and =S;

-Y₂- is selected from the group consisting of -O- and -S-;

-Y₃- is selected from the group consisting of -O- and -S-;

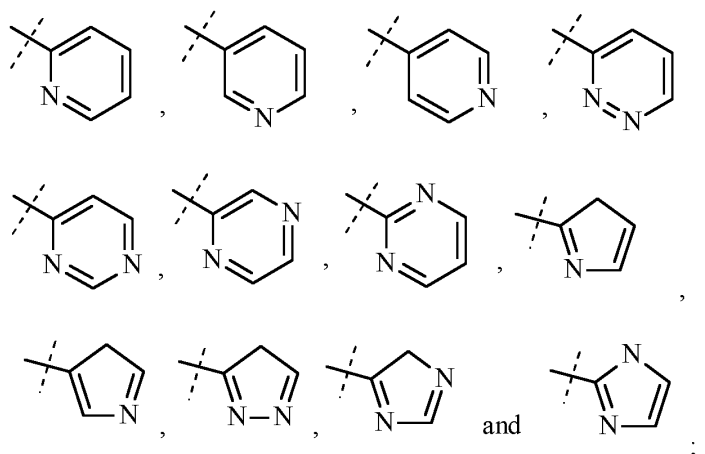
-Y₄- is selected from the group consisting of -O-, -NR⁵- and -C(R⁶R^{6a})-;

-R², -R³, -R⁵, -R⁶, -R^{6a} are independently of each other selected from the group consisting of -H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, 2-methylbutyl, 2,2-dimethylpropyl, n-hexyl, 2-methylpentyl, 3-methylpentyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl and 3,3-dimethylpropyl;

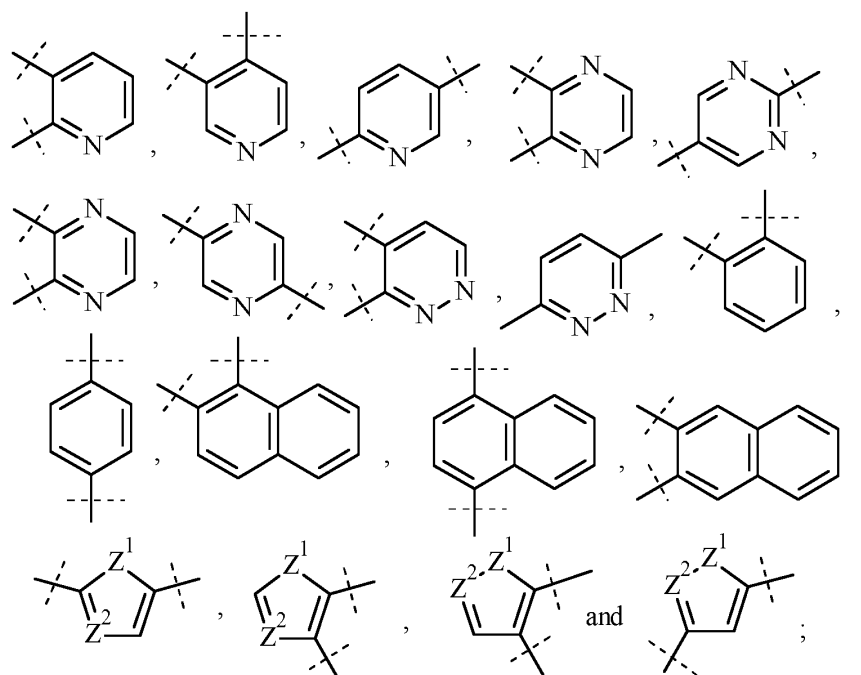
-R⁴ is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, 2-methylbutyl, 2,2-dimethylpropyl, n-hexyl, 2-methylpentyl, 3-methylpentyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl and 3,3-dimethylpropyl;

-W- is selected from the group consisting of C₁₋₂₀ alkyl optionally interrupted by one or more groups selected from the group consisting of C₃₋₁₀ cycloalkyl, 8- to 30-membered carbopolycyclyl, 3- to 10-membered heterocyclyl, -C(O)-, -C(O)N(R⁷)-, -O-, -S- and -N(R⁷)-;

-Nu is a nucleophile selected from the group consisting of -N(R⁷R^{7a}), -N(R⁷OH), -N(R⁷)-N(R^{7a}R^{7b}), -S(R⁷), -COOH,



-Ar- is selected from the group consisting of



wherein

dashed lines indicate attachment to the remainder of -L¹-,

-Z¹- is selected from the group consisting of -O-, -S- and -N(R⁷)-, and

5 -Z²- is -N(R⁷)-; and

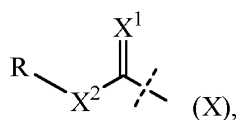
-R⁷, -R^{7a}, -R^{7b} are independently of each other selected from the group consisting of -H,

C₁₋₆ alkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl;

wherein -L¹- is optionally further substituted.

10 In one embodiment -L¹- of formula (IX-b) is not further substituted.

In certain embodiments -L¹- is of formula (X)



wherein

15 the dashed line indicates attachment to a nitrogen of an amine functional group of -D;

=X¹ is selected from the group consisting of =O, =S and =N;

-X²- is selected from the group consisting of -O-, -S- and -N-;

-R is C₁₋₅₀ alkyl, which C₁₋₅₀ alkyl is optionally interrupted by one or more groups selected from the group consisting of -T-, -C(O)O-, -O-, -C(O)-, -C(O)N(R^{z1})-, -S(O)₂N(R^{z1})-, -S(O)N(R^{z1})-, -S(O)₂-, -S(O)-, -N(R^{z1})S(O)₂N(R^{z1a})-, -S-, -N(R^{z1})-, -OC(OR^{z1})(R^{z1a})-, -N(R^{z1})C(O)N(R^{z1a})-, and -OC(O)N(R^{z1})-; and which

5 C₁₋₅₀ alkyl is optionally substituted with one or more -R^{z2};

each T is independently selected from the group consisting of phenyl, naphthyl, indenyl, indanyl, tetralinyl, C₃₋₁₀ cycloalkyl, 3- to 10-membered heterocyclyl, 8- to 11-membered heterobicycyl, 8- to 30-membered carbopolycyclyl, and 8- to 30-membered heteropolycyclyl; wherein each T is independently optionally substituted with one or

10 more -R^{z2}, which are the same or different;

each -R^{z2} is independently selected from the group consisting of halogen, -CN, oxo (=O), -COOR^{z3}, -OR^{z3}, -C(O)R^{z3}, -C(O)N(R^{z3}R^{z3a}), -S(O)₂N(R^{z3}R^{z3a}), -S(O)N(R^{z3}R^{z3a}), -S(O)₂R^{z3}, -S(O)R^{z3}, -N(R^{z3})S(O)₂N(R^{z3a}R^{z3b}), -SR^{z3}, -N(R^{z3}R^{z3a}), -NO₂, -OC(O)R^{z3}, -N(R^{z3})C(O)R^{z3a}, -N(R^{z3})S(O)₂R^{z3a}, -N(R^{z3})S(O)R^{z3a}, -N(R^{z3})C(O)O

15 R^{z3a}, -N(R^{z3})C(O)N(R^{z3a}R^{z3b}), -OC(O)N(R^{z3}R^{z3a}), and C₁₋₆ alkyl; wherein C₁₋₆ alkyl is optionally substituted with one or more halogen, which are the same or different; and

each -R^{z1}, -R^{z1a}, -R^{z3}, -R^{z3a} and -R^{z3b} is independently selected from the group consisting of -H, and C₁₋₆ alkyl, wherein C₁₋₆ alkyl is optionally substituted with one or more halogen, which are the same or different;

20 wherein -L¹- is substituted with at least one -L²- and wherein -L¹- is optionally further substituted.

In certain embodiments -L¹- is substituted with one -L²-.

25

In one embodiment -L¹- of formula (X) is not further substituted.

In certain embodiments =X¹ of formula (X) is selected from the group consisting of =N and =O. In certain embodiments =X¹ of formula (X) is =N. In certain embodiments =X¹ of formula

30 (X) is =O.

In certain embodiments -X²- of formula (X) is selected from the group consisting of -N- and -O-. In certain embodiments -X²- of formula (X) is -N-. In certain embodiments -X²- of formula (X) is -O-.

In certain embodiments $=X^1$ of formula (X) is $=N$ and $-X^2-$ of formula (X) is $-O-$. In certain embodiments $=X^1$ of formula (X) is $=O$ and $-X^2-$ of formula (X) is $-N-$. In certain embodiment $=X^1$ of formula (X) is $=N$ and $-X^2-$ of formula (X) is $-N-$. In certain embodiments $=X^1$ of formula (X) is $=O$ and $-X^2-$ of formula (X) is $-O-$.

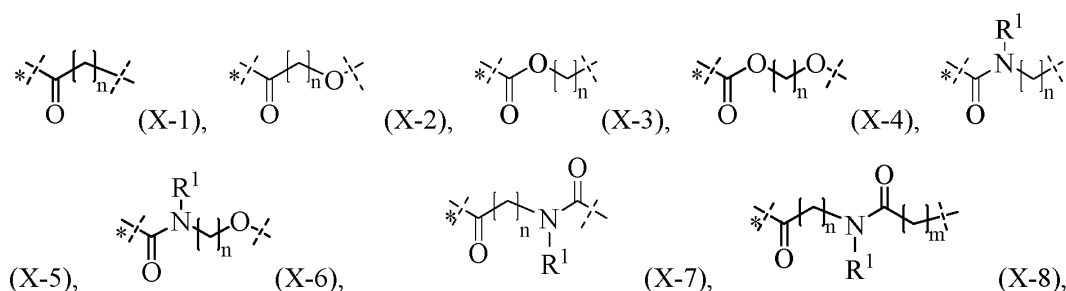
In certain embodiments $-R$ of formula (X) is C_{1-20} alkyl, which C_{1-20} alkyl is optionally interrupted by one or more groups selected from the group consisting of $-T-$, $-C(O)O-$, $-O-$, $-C(O)-$, $-C(O)N(R^{z1})-$, $-S(O)_2N(R^{z1})-$, $-S(O)N(R^{z1})-$, $-S(O)_2-$, $-S(O)-$, $-S-$, $-N(R^{z1})-$, $-OC(OR^{z1})(R^{z1a})-$, $-N(R^{z1})C(O)N(R^{z1a})-$, and $-OC(O)N(R^{z1})-$; and which C_{1-20} alkyl is optionally substituted with one or more $-R^{z2}$;

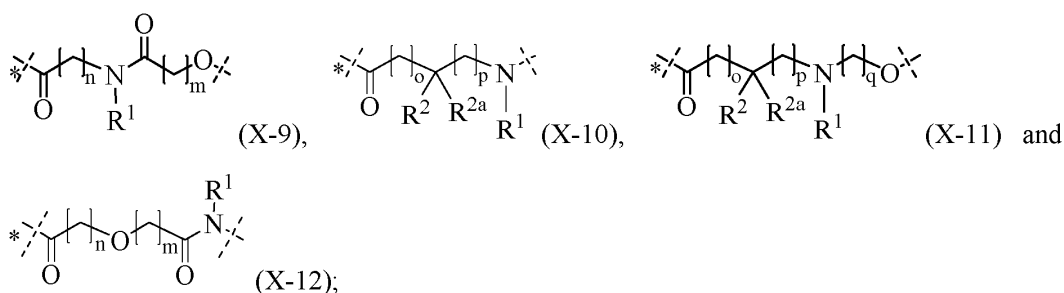
each $-R^{z1}$ and $-R^{z1a}$ is independently selected from the group consisting of $-H$, and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

each T is independently selected from the group consisting of phenyl, naphthyl, indenyl, indanyl, tetralinyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl, 8- to 11-membered heterobicycyl, wherein each T is independently optionally substituted with one or more $-R^{z2}$, which are the same or different;

each $-R^{z2}$ is independently selected from the group consisting of halogen, and C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different.

In certain embodiments the moiety of formula (X) is selected from the group consisting of formula (X-1), (X-2), (X-3), (X-4), (X-5), (X-6), (X-7), (X-8), (X-9), (X-10), (X-11) and (X-12)





wherein

the dashed line marked with the asterisk indicates attachment to a nitrogen of an amine functional group of -D;

the unmarked dashed line indicates attachment to -L²-;

-R¹ is selected from the group consisting of -H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl and C₂₋₁₀ alkynyl;

-R² and -R^{2a} are independently selected from the group consisting of -H, halogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl and C₂₋₁₀ alkynyl;

n is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 and 25;

m is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 and 25;

o is an integer selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10;

p is an integer selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10; and

q is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 and 25.

- 20 In certain embodiments n of formula (X-1), (X-2), (X-3), (X-4), (X-5), (X-6), (X-7), (X-8), (X-9) or (X-12) is 1. In certain embodiments n of formula (X-1), (X-2), (X-3), (X-4), (X-5), (X-6), (X-7), (X-8), (X-9) or (X-12) is 2. In certain embodiments n of formula (X-1), (X-2), (X-3), (X-4), (X-5), (X-6), (X-7), (X-8), (X-9) or (X-12) is 3. In certain embodiments n of formula (X-1), (X-2), (X-3), (X-4), (X-5), (X-6), (X-7), (X-8), (X-9) or (X-12) is 4. In certain
- 25 embodiments n of formula (X-1), (X-2), (X-3), (X-4), (X-5), (X-6), (X-7), (X-8), (X-9) or (X-12) is 5. In certain embodiments n of formula (X-1), (X-2), (X-3), (X-4), (X-5), (X-6), (X-7), (X-8), (X-9) or (X-12) is 6. In certain embodiments n of formula (X-1), (X-2), (X-3), (X-4), (X-5), (X-6), (X-7), (X-8), (X-9) or (X-12) is 7. In certain embodiments n of formula (X-1), (X-2), (X-3), (X-4), (X-5), (X-6), (X-7), (X-8), (X-9) or (X-12) is 8. In certain embodiments n

of formula (X-1), (X-2), (X-3), (X-4), (X-5), (X-6), (X-7), (X-8), (X-9) or (X-12) is 9. In certain embodiments n of formula (X-1), (X-2), (X-3), (X-4), (X-5), (X-6), (X-7), (X-8), (X-9) or (X-12) is 10.

- 5 In certain embodiments m of formula (X-8), (X-9) or (X-12) is 1. In certain embodiments m of formula (X-8), (X-9) or (X-12) is 2. In certain embodiments m of formula (X-8), (X-9) or (X-12) is 3. In certain embodiments m of formula (X-8), (X-9) or (X-12) is 4. In certain embodiments m of formula (X-8), (X-9) or (X-12) is 5. In certain embodiments m of formula (X-8), (X-9) or (X-12) is 6. In certain embodiments m of formula (X-8), (X-9) or (X-12) is 7.
- 10 In certain embodiments m of formula (X-8), (X-9) or (X-12) is 8. In certain embodiments m of formula (X-8), (X-9) or (X-12) is 9. In certain embodiments m of formula (X-8), (X-9) or (X-12) is 10.

- In certain embodiments o of formula (X-10) or (X-11) is 0. In certain embodiments o of formula (X-10) or (X-11) is 1. In certain embodiments o of formula (X-10) or (X-11) is 2. In certain embodiments o of formula (X-10) or (X-11) is 3. In certain embodiments o of formula (X-10) or (X-11) is 4. In certain embodiments o of formula (X-10) or (X-11) is 5. In certain embodiments o of formula (X-10) or (X-11) is 6. In certain embodiments o of formula (X-10) or (X-11) is 7. In certain embodiments o of formula (X-10) or (X-11) is 8. In certain
- 20 embodiments o of formula (X-10) or (X-11) is 9. In certain embodiments o of formula (X-10) or (X-11) is 10.

- In certain embodiments p of formula (X-10) or (X-11) is 0. In certain embodiments p of formula (X-10) or (X-11) is 1. In certain embodiments p of formula (X-10) or (X-11) is 2. In certain
- 25 embodiments p of formula (X-10) or (X-11) is 3. In certain embodiments p of formula (X-10) or (X-11) is 4. In certain embodiments p of formula (X-10) or (X-11) is 5. In certain embodiments p of formula (X-10) or (X-11) is 6. In certain embodiments p of formula (X-10) or (X-11) is 7. In certain embodiments p of formula (X-10) or (X-11) is 8. In certain embodiments p of formula (X-10) or (X-11) is 9. In certain embodiments p of formula (X-10) or (X-11) is 10.
- 30

In certain embodiments q of formula (X-11) is 1. In certain embodiments q of formula (X-11) is 2. In certain embodiments q of formula (X-11) is 3. In certain embodiments q of formula (X-11) is 4. In certain embodiments q of formula (X-11) is 5. In certain embodiments q of formula

(X-11) is 6. In certain embodiments q of formula (X-11) is 7. In certain embodiments q of formula (X-11) is 8. In certain embodiments q of formula (X-11) is 9. In certain embodiments q of formula (X-11) is 10.

- 5 In certain embodiments $-R^1$ of formula (X-5), (X-6), (X-7), (X-8), (X-9), (X-10), (X-11) or (X-12) is -H. In certain embodiments $-R^1$ of formula (X-5), (X-6), (X-7), (X-8), (X-9), (X-10), (X-11) or (X-12) is C_{1-10} alkyl, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, 2-methylbutyl, 2,2-dimethylpropyl, n-hexyl, 2-methylpentyl, 3-methylpentyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl or 3,3-dimethylpropyl. In certain
- 10 embodiments $-R^1$ of formula (X-5), (X-6), (X-7), (X-8), (X-9), (X-10), (X-11) or (X-12) is C_{2-10} alkenyl. In certain embodiments $-R^1$ of formula (X-5), (X-6), (X-7), (X-8), (X-9), (X-10), (X-11) or (X-12) is C_{2-10} alkynyl.

- In certain embodiments $-R^2$ of formula (X-10) or (X-11) is -H. In certain embodiments $-R^2$ of
- 15 formula (X-10) or (X-11) is halogen, such as fluoro or chloro. In certain embodiments $-R^2$ of formula (X-10) or (X-11) is C_{1-10} alkyl, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, 2-methylbutyl, 2,2-dimethylpropyl, n-hexyl, 2-methylpentyl, 3-methylpentyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl or 3,3-dimethylpropyl. In certain embodiments $-R^2$ of formula (X-10) or (X-11) is C_{2-10} alkenyl, such as C_2 alkenyl, C_3
- 20 alkenyl, C_4 alkenyl, C_5 alkenyl or C_6 alkenyl. In certain embodiments $-R^2$ of formula (X-10) or (X-11) is C_{2-10} alkynyl, such as C_2 alkynyl, C_3 alkynyl, C_4 alkynyl, C_5 alkynyl or C_6 alkynyl.

- In certain embodiments $-R^{2a}$ of formula (X-10) or (X-11) is -H. In certain embodiments $-R^{2a}$ of
- 25 formula (X-10) or (X-11) is halogen. In certain embodiments $-R^{2a}$ of formula (X-10) or (X-11) is C_{1-10} alkyl, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, 2-methylbutyl, 2,2-dimethylpropyl, n-hexyl, 2-methylpentyl, 3-methylpentyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl or 3,3-dimethylpropyl. In certain embodiments $-R^{2a}$ of formula (X-10) or (X-11) is C_{2-10} alkenyl, such as C_2 alkenyl, C_3 alkenyl, C_4 alkenyl, C_5 alkenyl or C_6 alkenyl. In certain embodiments $-R^{2a}$ of formula (X-10) or (X-11) is C_{2-10} alkynyl, such
- 30 as C_2 alkynyl, C_3 alkynyl, C_4 alkynyl, C_5 alkynyl or C_6 alkynyl.

In certain embodiments at least one of $-R^2$ and $-R^{2a}$ of formula (X-10) and (X-11) is not -H.

In certain embodiments $-L^1$ - is of formula (X-1). In certain embodiments $-L^1$ - is of formula (X-1) with $n = 1$. In certain embodiments $-L^1$ - is of formula (X-1) with $n = 2$. In certain embodiments $-L^1$ - is of formula (X-1) with $n = 3$. In certain embodiments $-L^1$ - is of formula (X-1) with $n = 4$. In certain embodiments $-L^1$ - is of formula (X-1) with $n = 5$.

5

In certain embodiments $-L^1$ - is of formula (X-2). In certain embodiments $-L^1$ - is of formula (X-2) with $n = 1$. In certain embodiments $-L^1$ - is of formula (X-2) with $n = 2$. In certain embodiments $-L^1$ - is of formula (X-2) with $n = 3$. In certain embodiments $-L^1$ - is of formula (X-2) with $n = 4$. In certain embodiments $-L^1$ - is of formula (X-2) with $n = 5$.

10

In certain embodiments $-L^1$ - is of formula (X-3). In certain embodiments $-L^1$ - is of formula (X-3) with $n = 1$. In certain embodiments $-L^1$ - is of formula (X-3) with $n = 2$. In certain embodiments $-L^1$ - is of formula (X-3) with $n = 3$. In certain embodiments $-L^1$ - is of formula (X-3) with $n = 4$. In certain embodiments $-L^1$ - is of formula (X-3) with $n = 5$.

15

In certain embodiments $-L^1$ - is of formula (X-4). In certain embodiments $-L^1$ - is of formula (X-4) with $n = 1$. In certain embodiments $-L^1$ - is of formula (X-4) with $n = 2$. In certain embodiments $-L^1$ - is of formula (X-4) with $n = 3$. In certain embodiments $-L^1$ - is of formula (X-4) with $n = 4$. In certain embodiments $-L^1$ - is of formula (X-4) with $n = 5$.

20

In certain embodiments $-L^1$ - is of formula (X-5). In certain embodiments $-L^1$ - is of formula (X-5) and $-R^1$ is -H. In certain embodiments $-L^1$ - is of formula (X-5) and $-R^1$ is methyl. In certain embodiments $-L^1$ - is of formula (X-5) and $-R^1$ is ethyl. In certain embodiments $-L^1$ - is of formula (X-5) and n is 1. In certain embodiments $-L^1$ - is of formula (X-5) and n is 2. In certain
25 embodiments $-L^1$ - is of formula (X-5) and n is 3. In certain embodiments $-L^1$ - is of formula (X-5), $-R^1$ is -H and n is 1. In certain embodiments $-L^1$ - is of formula (X-5), $-R^1$ is -H and n is 2. In certain embodiments $-L^1$ - is of formula (X-5), $-R^1$ is -H and n is 3. In certain embodiments $-L^1$ - is of formula (X-5), $-R^1$ is methyl and n is 1. In certain embodiments $-L^1$ - is of formula (X-5), $-R^1$ is methyl and n is 2. In certain embodiments $-L^1$ - is of formula (X-5), $-R^1$
30 is methyl and n is 3.

In certain embodiments $-L^1$ - is of formula (X-6). In certain embodiments $-L^1$ - is of formula (X-6) and $-R^1$ is -H. In certain embodiments $-L^1$ - is of formula (X-6) and $-R^1$ is methyl. In certain embodiments $-L^1$ - is of formula (X-6) and $-R^1$ is ethyl. In certain embodiments $-L^1$ - is of

formula (X-6) and n is 1. In certain embodiments -L¹- is of formula (X-6) and n is 2. In certain
embodiments -L¹- is of formula (X-6) and n is 3. In certain embodiments -L¹- is of formula (X-
6), -R¹ is -H and n is 1. In certain embodiments -L¹- is of formula (X-6), -R¹ is -H and n is 2.
In certain embodiments -L¹- is of formula (X-6), -R¹ is -H and n is 3. In certain
5 embodiments -L¹- is of formula (X-6), -R¹ is methyl and n is 1. In certain embodiments -L¹- is
of formula (X-6), -R¹ is methyl and n is 2. In certain embodiments -L¹- is of formula (X-6), -R¹
is methyl and n is 3.

In certain embodiments -L¹- is of formula (X-7). In certain embodiments -L¹- is of formula (X-
10 7) and -R¹ is -H. In certain embodiments -L¹- is of formula (X-7) and -R¹ is methyl. In certain
embodiments -L¹- is of formula (X-7) and -R¹ is ethyl. In certain embodiments -L¹- is of
formula (X-7) and n is 1. In certain embodiments -L¹- is of formula (X-7) and n is 2. In certain
embodiments -L¹- is of formula (X-7) and n is 3. In certain embodiments -L¹- is of formula (X-
7), -R¹ is -H and n is 1. In certain embodiments -L¹- is of formula (X-7), -R¹ is -H and n is 2.
15 In certain embodiments -L¹- is of formula (X-7), -R¹ is -H and n is 3. In certain
embodiments -L¹- is of formula (X-7), -R¹ is methyl and n is 1. In certain embodiments -L¹- is
of formula (X-7), -R¹ is methyl and n is 2. In certain embodiments -L¹- is of formula (X-7), -R¹
is methyl and n is 3.

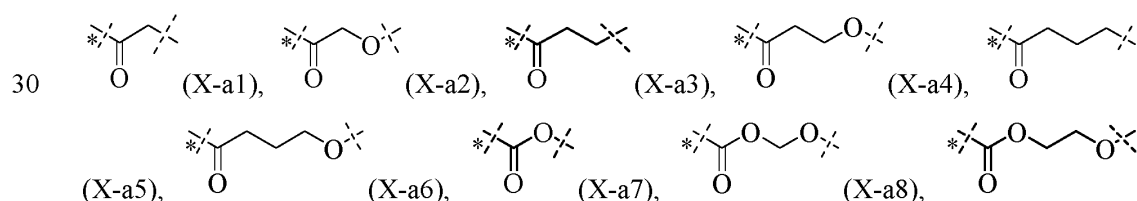
20 In certain embodiments -L¹- is of formula (X-8). In certain embodiments -L¹- is of formula (X-
8) and -R¹ is -H. In certain embodiments -L¹- is of formula (X-8) and -R¹ is methyl. In certain
embodiments -L¹- is of formula (X-8) and -R¹ is ethyl. In certain embodiments -L¹- is of
formula (X-8) and n is 1. In certain embodiments -L¹- is of formula (X-8) and n is 2. In certain
embodiments -L¹- is of formula (X-8) and n is 3. In certain embodiments -L¹- is of formula (X-
25 8) and m is 1. In certain embodiments -L¹- is of formula (X-8) and m is 2. In certain
embodiments -L¹- is of formula (X-8) and m is 3. In certain embodiments -L¹- is of formula
(X-8), -R¹ is -H, n is 1 and m is 1. In certain embodiments -L¹- is of formula (X-8), -R¹ is -H,
n is 1 and m is 2. In certain embodiments -L¹- is of formula (X-8), -R¹ is -H, n is 1 and m is 3.
In certain embodiments -L¹- is of formula (X-8), -R¹ is -H, n is 2 and m is 1. In certain
30 embodiments -L¹- is of formula (X-8), -R¹ is -H, n is 2 and m is 2. In certain
embodiments -L¹- is of formula (X-8), -R¹ is -H, n is 2 and m is 3. In certain
embodiments -L¹- is of formula (X-8), -R¹ is -H, n is 3 and m is 1. In certain
embodiments -L¹- is of formula (X-8), -R¹ is -H, n is 3 and m is 2. In certain
embodiments -L¹- is of formula (X-8), -R¹ is -H, n is 3 and m is 3.

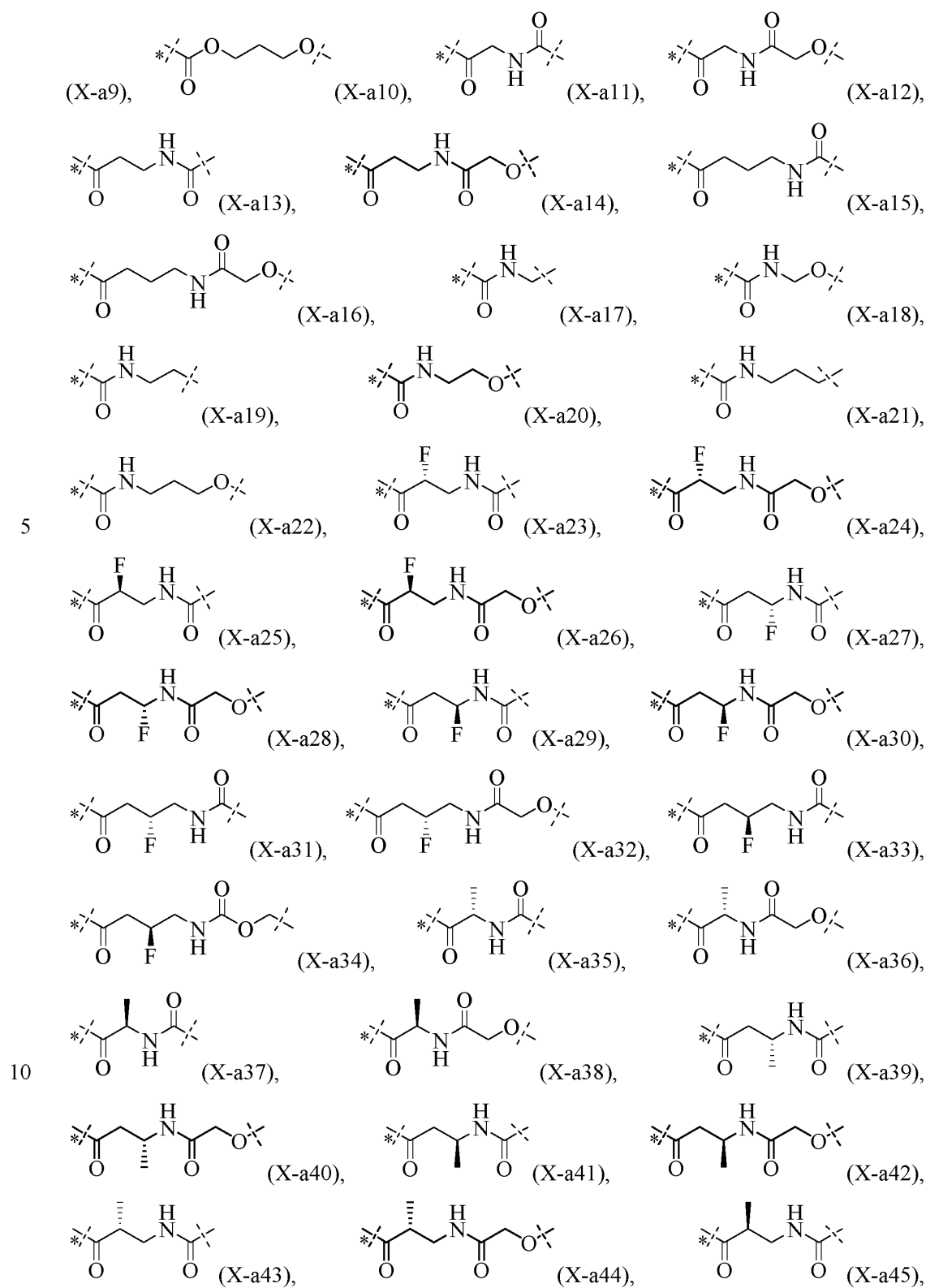
In certain embodiments $-L^1$ is of formula (X-9). In certain embodiments $-L^1$ is of formula (X-9) and $-R^1$ is -H. In certain embodiments $-L^1$ is of formula (X-9) and $-R^1$ is methyl. In certain
5 embodiments $-L^1$ is of formula (X-9) and $-R^1$ is ethyl. In certain embodiments $-L^1$ is of formula (X-9) and n is 1. In certain embodiments $-L^1$ is of formula (X-9) and n is 2. In certain
embodiments $-L^1$ is of formula (X-9) and n is 3. In certain embodiments $-L^1$ is of formula (X-9) and m is 1. In certain embodiments $-L^1$ is of formula (X-9) and m is 2. In certain
embodiments $-L^1$ is of formula (X-9) and m is 3. In certain embodiments $-L^1$ is of formula (X-9), $-R^1$ is -H, n is 1 and m is 1. In certain embodiments $-L^1$ is of formula (X-9), $-R^1$ is -H,
10 n is 1 and m is 2. In certain embodiments $-L^1$ is of formula (X-9), $-R^1$ is -H, n is 1 and m is 3. In certain embodiments $-L^1$ is of formula (X-9), $-R^1$ is -H, n is 2 and m is 1. In certain
embodiments $-L^1$ is of formula (X-9), $-R^1$ is -H, n is 2 and m is 2. In certain
embodiments $-L^1$ is of formula (X-9), $-R^1$ is -H, n is 2 and m is 3. In certain
embodiments $-L^1$ is of formula (X-9), $-R^1$ is -H, n is 3 and m is 1. In certain
15 embodiments $-L^1$ is of formula (X-9), $-R^1$ is -H, n is 3 and m is 2. In certain
embodiments $-L^1$ is of formula (X-9), $-R^1$ is -H, n is 3 and m is 3.

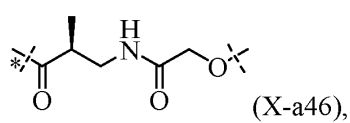
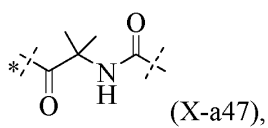
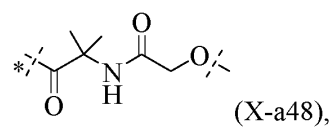
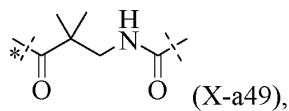
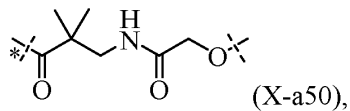
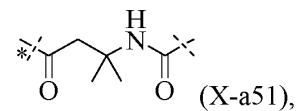
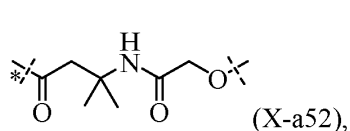
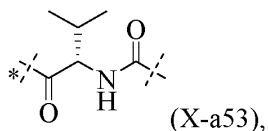
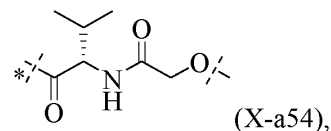
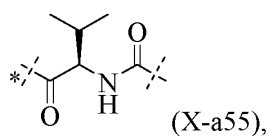
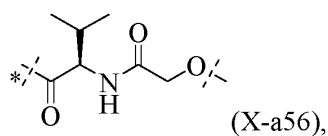
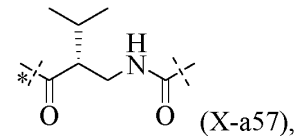
In certain embodiments $-L^1$ is of formula (X-10). In certain embodiments $-R^1$ of formula (X-10) is -H. In certain embodiments o of formula (X-10) is 0. In certain embodiments o of
20 formula (X-10) is 1. In certain embodiments o of formula (X-10) is 2. In certain embodiments o of formula (X-10) is 3. In certain embodiments p of formula (X-10) is 0. In certain
embodiments p of formula (X-10) is 1. In certain embodiments p of formula (X-10) is 2. In
certain embodiments p of formula (X-10) is 3. In certain embodiments $-R^2$ of formula (X-10)
is -H. In certain embodiments $-R^2$ of formula (X-10) is halogen, such as fluor. In certain
25 embodiments $-R^2$ of formula (X-10) is methyl. In certain embodiments $-R^2$ of formula (X-10)
is ethyl. In certain embodiments $-R^2$ of formula (X-10) is *n*-propyl. In certain embodiments $-R^2$
of formula (X-10) is isopropyl. In certain embodiments $-R^2$ of formula (X-10) is 2-
methylpropyl. In certain embodiments $-R^2$ of formula (X-10) is 2-methylpropyl. In certain
embodiments $-R^2$ of formula (X-10) is 1-methylpropyl. In certain embodiments $-R^{2a}$ of formula
30 (X-10) is -H. In certain embodiments both $-R^2$ and $-R^{2a}$ of formula (X-10) are methyl. In certain
embodiments $-R^2$ of formula (X-10) is fluor and $-R^{2a}$ of formula (X-10) is -H. In certain
embodiments $-R^2$ of formula (X-10) is isopropyl and $-R^{2a}$ of formula (X-10) is -H. In certain
embodiments $-R^2$ of formula (X-10) is 2-methylpropyl and $-R^{2a}$ of formula (X-10) is -H.

- In certain embodiments $-L^1$ - is of formula (X-11). In certain embodiments $-R^1$ of formula (X-11) is -H. In certain embodiments $-R^1$ of formula (X-11) is methyl. In certain embodiments $-R^1$ of formula (X-11) is ethyl. In certain embodiments o of formula (X-11) is 0. In certain embodiments o of formula (X-11) is 1. In certain embodiments o of formula (X-11) is 2. In certain embodiments p of formula (X-11) is 0. In certain embodiments p of formula (X-11) is 1. In certain embodiments p of formula (X-11) is 2. In certain embodiments $-R^2$ of formula (X-11) is -H. In certain embodiments $-R^2$ of formula (X-11) is halogen, such as fluor. In certain embodiments $-R^2$ of formula (X-11) is methyl. In certain embodiments $-R^2$ of formula (X-11) is ethyl. In certain embodiments $-R^2$ of formula (X-11) is *n*-propyl. In certain embodiments $-R^2$ of formula (X-11) is isopropyl. In certain embodiments $-R^2$ of formula (X-11) is 2-methylpropyl. In certain embodiments $-R^2$ of formula (X-11) is 2-methylpropyl. In certain embodiments $-R^2$ of formula (X-11) is 1-methylpropyl. In certain embodiments $-R^{2a}$ of formula (X-11) is -H. In certain embodiments both $-R^2$ and $-R^{2a}$ of formula (X-11) are methyl. In certain embodiments $-R^2$ of formula (X-11) is fluor and $-R^{2a}$ of formula (X-11) is -H. In certain embodiments $-R^2$ of formula (X-11) is isopropyl and $-R^{2a}$ of formula (X-11) is -H. In certain embodiments $-R^2$ of formula (X-11) is 2-methylpropyl and $-R^{2a}$ of formula (X-11) is -H. In certain embodiments q of formula (X-11) is 1. In certain embodiments q of formula (X-11) is 2. In certain embodiments q of formula (X-11) is 3.
- In certain embodiments $-L^1$ - is of formula (X-12). In certain embodiments L^1 - is of formula (X-12) and n is 1. In certain embodiment L^1 - is of formula (X-12) and n is 2. In certain embodiments L^1 - is of formula (X-12) and n is 3. In certain embodiments L^1 - is of formula (X-12) and m is 1. In certain embodiment L^1 - is of formula (X-12) and m is 2. In certain embodiments L^1 - is of formula (X-12) and m is 3. In certain embodiments L^1 - is of formula (X-12) and both n and m are 1. In certain embodiments L^1 - is of formula (X-12) and $-R^1$ is -H. In certain embodiments L^1 - is of formula (X-12) and $-R^1$ is methyl. In certain embodiments L^1 - is of formula (X-12) and $-R^1$ is ethyl.

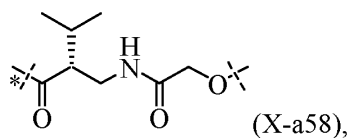
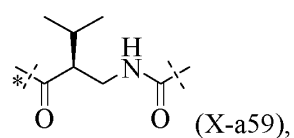
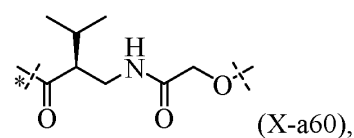
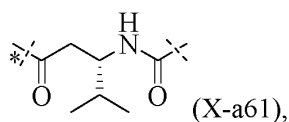
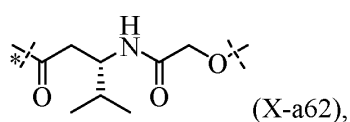
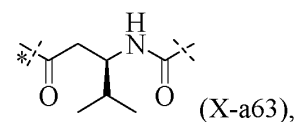
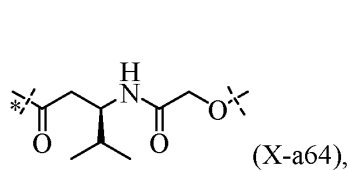
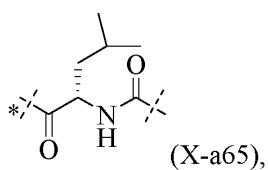
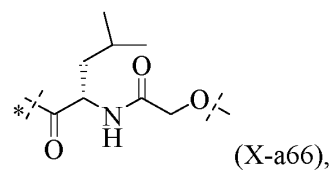
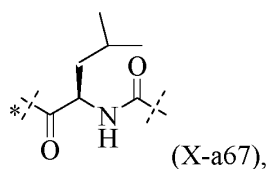
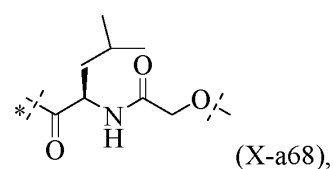
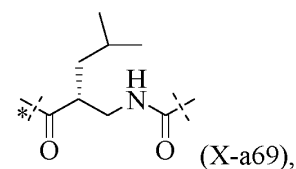
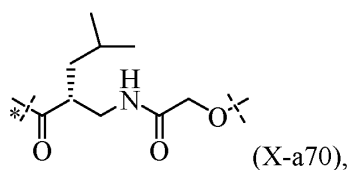
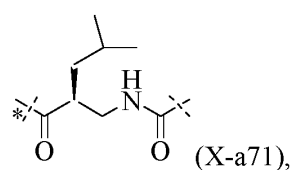
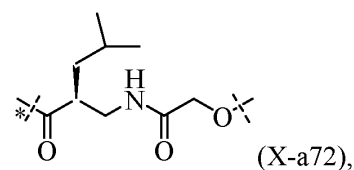
In certain embodiments $-L^1$ - is selected from the group consisting of



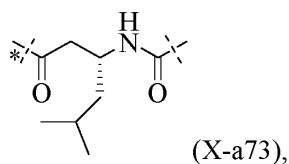
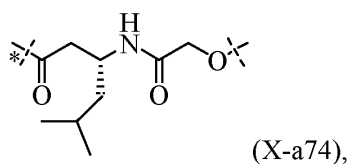
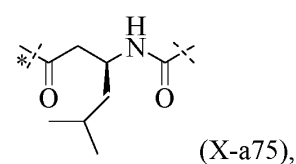


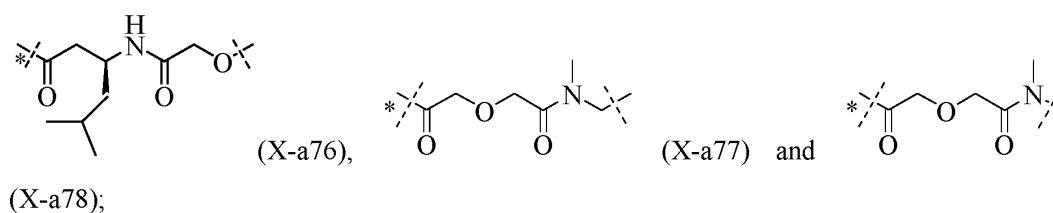


5



10





wherein

- 5 the dashed line marked with the asterisk indicates attachment to a nitrogen of an amine functional group of -D; and
the unmarked dashed line indicates attachment to -L².

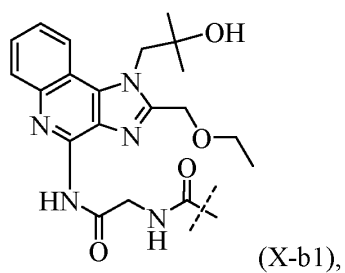
In certain embodiments -L¹- is of formula (X-a1). In certain embodiments -L¹- is of formula (X-a2). In certain embodiments -L¹- is of formula (X-a3). In certain embodiments -L¹- is of formula (X-a4). In certain embodiments -L¹- is of formula (X-a5). In certain embodiments -L¹- is of formula (X-a6). In certain embodiments -L¹- is of formula (X-a7). In certain embodiments -L¹- is of formula (X-a8). In certain embodiments -L¹- is of formula (X-a9). In certain embodiments -L¹- is of formula (X-a10). In certain embodiments -L¹- is of formula (X-a11). In certain embodiments -L¹- is of formula (X-a12). In certain embodiments -L¹- is of formula (X-a13). In certain embodiments -L¹- is of formula (X-a14). In certain embodiments -L¹- is of formula (X-a15). In certain embodiments -L¹- is of formula (X-a16). In certain embodiments -L¹- is of formula (X-a17). In certain embodiments -L¹- is of formula (X-a18). In certain embodiments -L¹- is of formula (X-a19). In certain embodiments -L¹- is of formula (X-a20). In certain embodiments -L¹- is of formula (X-a21). In certain embodiments -L¹- is of formula (X-a22). In certain embodiments -L¹- is of formula (X-a23). In certain embodiments -L¹- is of formula (X-24). In certain embodiments -L¹- is of formula (X-a25). In certain embodiments -L¹- is of formula (X-a26). In certain embodiments -L¹- is of formula (X-a27). In certain embodiments -L¹- is of formula (X-a28). In certain embodiments -L¹- is of formula (X-a29). In certain embodiments -L¹- is of formula (X-a30). In certain embodiments -L¹- is of formula (X-a31). In certain embodiments -L¹- is of formula (X-a32). In certain embodiments -L¹- is of formula (X-a33). In certain embodiments -L¹- is of formula (X-a34). In certain embodiments -L¹- is of formula (X-a35). In certain embodiments -L¹- is of formula (X-a36). In certain embodiments -L¹- is of formula (X-a37). In certain embodiments -L¹- is of formula (X-a38). In certain embodiments -L¹- is of formula (X-a39). In certain embodiments -L¹- is of formula (X-a40). In certain

embodiments -L¹- is of formula (X-a41). In certain embodiments -L¹- is of formula (X-a42). In certain embodiments -L¹- is of formula (X-a43). In certain embodiments -L¹- is of formula (X-a44). In certain embodiments -L¹- is of formula (X-a45). In certain embodiments -L¹- is of formula (X-a46). In certain embodiments -L¹- is of formula (X-a47). In certain
5 embodiments -L¹- is of formula (X-a48). In certain embodiments -L¹- is of formula (X-a49). In certain embodiments -L¹- is of formula (X-a50). In certain embodiments -L¹- is of formula (X-a51). In certain embodiments -L¹- is of formula (X-a52). In certain embodiments -L¹- is of formula (X-a53). In certain embodiments -L¹- is of formula (X-a54). In certain
10 embodiments -L¹- is of formula (X-a55). In certain embodiments -L¹- is of formula (X-a56). In certain embodiments -L¹- is of formula (X-a57). In certain embodiments -L¹- is of formula (X-a58). In certain embodiments -L¹- is of formula (X-a59). In certain embodiments -L¹- is of formula (X-a60). In certain embodiments -L¹- is of formula (X-a61). In certain
15 embodiments -L¹- is of formula (X-a62). In certain embodiments -L¹- is of formula (X-a63). In certain embodiments -L¹- is of formula (X-a64). In certain embodiments -L¹- is of formula (X-a65). In certain embodiments -L¹- is of formula (X-a66). In certain embodiments -L¹- is of formula (X-a67). In certain embodiments -L¹- is of formula (X-a68). In certain
20 embodiments -L¹- is of formula (X-a69). In certain embodiments -L¹- is of formula (X-a70). In certain embodiments -L¹- is of formula (X-a71). In certain embodiments -L¹- is of formula (X-a72). In certain embodiments -L¹- is of formula (X-a73). In certain embodiments -L¹- is of formula (X-a74). In certain embodiments -L¹- is of formula (X-a75). In certain
embodiments -L¹- is of formula (X-a76). In certain embodiments -L¹- is of formula (X-a77). In certain embodiments -L¹- is of formula (X-a78).

In certain embodiments release half-life, i.e. the time in which half of all moieties -D are
25 released from -L¹-, is pH independent, in particular independent for a pH ranging from about 6.8 to about 7.4. Such pH-independent release is advantageous, because pH in tumor tissue may vary and such pH-independence allows for a more uniform and thus more predictable drug release.

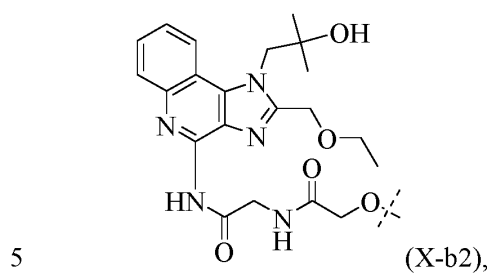
30 It was surprisingly found that moieties -L¹- of formula (X-a11) and (X-a12) have a release half-life that is independent of pH for a pH ranging from 6.8 to 7.4.

In certain embodiments the moiety -L¹-D is of formula (X-b1)



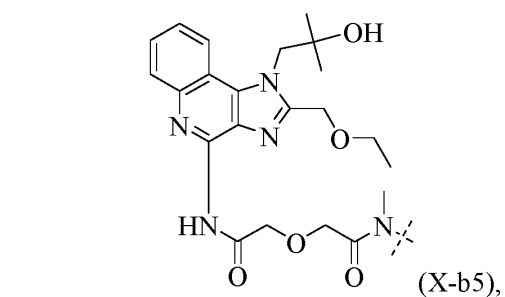
wherein the dashed line indicates attachment to $-L^2-$.

In certain embodiments the moiety $-L^1-D$ is of formula (X-b2)



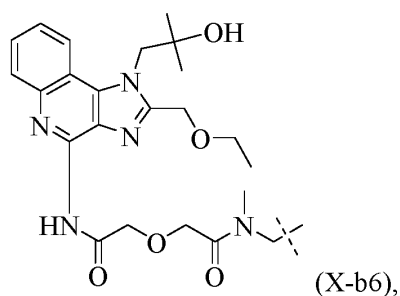
wherein the dashed line indicates attachment to $-L^2-$.

In certain embodiments the moiety $-L^1-D$ is of formula (X-b5)



wherein the dashed line indicates attachment to $-L^2-$.

In certain embodiments the moiety $-L^1-D$ is of formula (X-b6)



wherein the dashed line indicates attachment to $-L^2-$.

In the conjugates of the present invention $-L^2-$ is a chemical bond or a spacer moiety. In certain embodiments $-L^2-$ does not comprise a reversible linkage, i.e. all linkages in $-L^2-$ are stable linkages. In certain embodiments $-L^1-$ is connected to $-L^2-$ via a stable linkage. In certain
 5 embodiments $-L^2-$ is connected to $-Z$ via a stable linkage.

In certain embodiments $-L^2-$ is a chemical bond.

In certain embodiments $-L^2-$ is a spacer moiety.

10

In certain embodiments $-L^2-$ is a spacer moiety selected from the group consisting of $-T-$, $-C(O)O-$, $-O-$, $-C(O)-$, $-C(O)N(R^{y1})-$, $-S(O)_2N(R^{y1})-$, $-S(O)N(R^{y1})-$, $-S(O)_2-$, $-S(O)-$, $-N(R^{y1})S(O)_2N(R^{y1a})-$, $-S-$, $-N(R^{y1})-$, $-OC(OR^{y1})(R^{y1a})-$, $-N(R^{y1})C(O)N(R^{y1a})-$, $-OC(O)N(R^{y1})-$, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl; wherein $-T-$,
 15 C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally substituted with one or more $-R^{y2}$, which are the same or different and wherein C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally interrupted by one or more groups selected from the group consisting of $-T-$, $-C(O)O-$, $-O-$, $-C(O)-$, $-C(O)N(R^{y3})-$, $-S(O)_2N(R^{y3})-$, $-S(O)N(R^{y3})-$, $-S(O)_2-$, $-S(O)-$, $-N(R^{y3})S(O)_2N(R^{y3a})-$, $-S-$, $-N(R^{y3})-$, $-OC(OR^{y3})(R^{y3a})-$, $-N(R^{y3})C(O)N(R^{y3a})-$,
 20 and $-OC(O)N(R^{y3})-$;

$-R^{y1}$ and $-R^{y1a}$ are independently of each other selected from the group consisting of $-H$, $-T$, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl; wherein $-T$, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally substituted with one or more $-R^{y2}$, which are the same or different, and
 25 wherein C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally interrupted by one or more groups selected from the group consisting of $-T-$, $-C(O)O-$, $-O-$, $-C(O)-$, $-C(O)N(R^{y4})-$, $-S(O)_2N(R^{y4})-$, $-S(O)N(R^{y4})-$, $-S(O)_2-$, $-S(O)-$, $-N(R^{y4})S(O)_2N(R^{y4a})-$, $-S-$, $-N(R^{y4})-$, $-OC(OR^{y4})(R^{y4a})-$, $-N(R^{y4})C(O)N(R^{y4a})-$, and $-OC(O)N(R^{y4})-$;

30 each T is independently selected from the group consisting of phenyl, naphthyl, indenyl, indanyl, tetralinyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl, 8- to 11-membered heterobicycyl, 8- to 30-membered carbopolycyclyl, and 8- to 30-membered heteropolycyclyl; wherein each T is independently optionally substituted with one or more $-R^{y2}$, which are the same or different;

each $-R^{y2}$ is independently selected from the group consisting of halogen, $-CN$, oxo ($=O$), $-COOR^{y5}$, $-OR^{y5}$, $-C(O)R^{y5}$, $-C(O)N(R^{y5}R^{y5a})$, $-S(O)_2N(R^{y5}R^{y5a})$, $-S(O)N(R^{y5}R^{y5a})$, $-S(O)_2R^{y5}$, $-S(O)R^{y5}$, $-N(R^{y5})S(O)_2N(R^{y5a}R^{y5b})$, $-SR^{y5}$, $-N(R^{y5}R^{y5a})$, $-NO_2$, $-OC(O)R^{y5}$,
 5 $-N(R^{y5})C(O)R^{y5a}$, $-N(R^{y5})S(O)_2R^{y5a}$, $-N(R^{y5})S(O)R^{y5a}$, $-N(R^{y5})C(O)OR^{y5a}$, $-N(R^{y5})C(O)N(R^{y5a}R^{y5b})$, $-OC(O)N(R^{y5}R^{y5a})$, and C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different; and

each $-R^{y3}$, $-R^{y3a}$, $-R^{y4}$, $-R^{y4a}$, $-R^{y5}$, $-R^{y5a}$ and $-R^{y5b}$ is independently selected from the group
 10 consisting of $-H$, and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different.

In certain embodiments $-L^2-$ is a spacer moiety selected from $-T-$, $-C(O)O-$, $-O-$, $-C(O)-$, $-C(O)N(R^{y1})-$, $-S(O)_2N(R^{y1})-$, $-S(O)N(R^{y1})-$, $-S(O)_2-$,
 15 $-S(O)-$, $-N(R^{y1})S(O)_2N(R^{y1a})-$, $-S-$, $-N(R^{y1})-$, $-OC(OR^{y1})(R^{y1a})-$, $-N(R^{y1})C(O)N(R^{y1a})-$, $-OC(O)N(R^{y1})-$, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl; wherein $-T-$, C_{1-20} alkyl, C_{2-20} alkenyl, and C_{2-20} alkynyl are optionally substituted with one or more $-R^{y2}$, which are the same or different and wherein C_{1-20} alkyl, C_{2-20} alkenyl, and C_{2-20} alkynyl are optionally interrupted by one or more groups selected from the group consisting of $-T-$, $-C(O)O-$, $-O-$,
 20 $-C(O)-$, $-C(O)N(R^{y3})-$, $-S(O)_2N(R^{y3})-$, $-S(O)N(R^{y3})-$, $-S(O)_2-$, $-S(O)-$, $-N(R^{y3})S(O)_2N(R^{y3a})-$, $-S-$, $-N(R^{y3})-$, $-OC(OR^{y3})(R^{y3a})-$, $-N(R^{y3})C(O)N(R^{y3a})-$, and $-OC(O)N(R^{y3})-$;

$-R^{y1}$ and $-R^{y1a}$ are independently of each other selected from the group consisting of $-H$, $-T$, C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl; wherein $-T$, C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10}
 25 alkynyl are optionally substituted with one or more $-R^{y2}$, which are the same or different, and wherein C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl are optionally interrupted by one or more groups selected from the group consisting of $-T-$, $-C(O)O-$, $-O-$, $-C(O)-$, $-C(O)N(R^{y4})-$, $-S(O)_2N(R^{y4})-$, $-S(O)N(R^{y4})-$, $-S(O)_2-$, $-S(O)-$, $-N(R^{y4})S(O)_2N(R^{y4a})-$, $-S-$, $-N(R^{y4})-$, $-OC(OR^{y4})(R^{y4a})-$, $-N(R^{y4})C(O)N(R^{y4a})-$, and $-OC(O)N(R^{y4})-$;

30

each T is independently selected from the group consisting of phenyl, naphthyl, indenyl, indanyl, tetralinyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl, 8- to 11-membered heterobicyclyl, 8- to 30-membered carbopolycyclyl, and 8- to 30-membered heteropolycyclyl;

wherein each T is independently optionally substituted with one or more $-R^{y2}$, which are the same or different;

$-R^{y2}$ is selected from the group consisting of halogen, $-CN$, oxo
 5 $(=O)$, $-COOR^{y5}$, $-OR^{y5}$, $-C(O)R^{y5}$, $-C(O)N(R^{y5}R^{y5a})$, $-S(O)_2N(R^{y5}R^{y5a})$, $-S(O)N(R^{y5}R^{y5a})$,
 $-S(O)_2R^{y5}$, $-S(O)R^{y5}$, $-N(R^{y5})S(O)_2N(R^{y5a}R^{y5b})$, $-SR^{y5}$, $-N(R^{y5}R^{y5a})$, $-NO_2$, $-OC(O)R^{y5}$, $-N(R^{y5})$
 $C(O)R^{y5a}$, $-N(R^{y5})S(O)_2R^{y5a}$, $-N(R^{y5})S(O)R^{y5a}$, $-N(R^{y5})C(O)OR^{y5a}$, $-N(R^{y5})C(O)N(R^{y5a}R^{y5b})$,
 $-OC(O)N(R^{y5}R^{y5a})$, and C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with one or more
 10 halogen, which are the same or different; and

each $-R^{y3}$, $-R^{y3a}$, $-R^{y4}$, $-R^{y4a}$, $-R^{y5}$, $-R^{y5a}$ and $-R^{y5b}$ is independently of each other selected from
 the group consisting of $-H$, and C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with one
 or more halogen, which are the same or different.

15 In certain embodiments $-L^2-$ is a spacer moiety selected from the group consisting
 of $-T-$, $-C(O)O-$, $-O-$, $-C(O)-$, $-C(O)N(R^{y1})-$, $-S(O)_2N(R^{y1})-$, $-S(O)N(R^{y1})-$, $-S(O)_2-$,
 $-S(O)-$, $-N(R^{y1})S(O)_2N(R^{y1a})-$, $-S-$, $-N(R^{y1})-$, $-OC(OR^{y1})(R^{y1a})-$,
 $-N(R^{y1})C(O)N(R^{y1a})-$, $-OC(O)N(R^{y1})-$, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl; wherein $-T-$,
 C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally substituted with one or more $-R^{y2}$,
 20 which are the same or different and wherein C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are
 optionally interrupted by one or more groups selected from the group consisting of $-T-$,
 $-C(O)O-$, $-O-$, $-C(O)-$, $-C(O)N(R^{y3})-$, $-S(O)_2N(R^{y3})-$, $-S(O)N(R^{y3})-$, $-S(O)_2-$,
 $-S(O)-$, $-N(R^{y3})S(O)_2N(R^{y3a})-$, $-S-$, $-N(R^{y3})-$, $-OC(OR^{y3})(R^{y3a})-$, $-N(R^{y3})C(O)N(R^{y3a})-$,
 and $-OC(O)N(R^{y3})-$;

25 $-R^{y1}$ and $-R^{y1a}$ are independently selected from the group consisting of $-H$, $-T$, C_{1-10} alkyl, C_{2-10}
 alkenyl, and C_{2-10} alkynyl;

each T is independently selected from the group consisting of phenyl, naphthyl, indenyl,
 30 indanyl, tetralinyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl, 8- to 11-membered
 heterobicyclyl, 8- to 30-membered carbopolycyclyl, and 8- to 30-membered heteropolycyclyl;

each $-R^{y2}$ is independently selected from the group consisting of halogen, and C_{1-6} alkyl; and

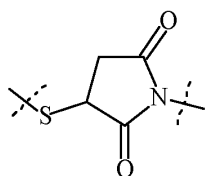
each $-R^{y3}$, $-R^{y3a}$, $-R^{y4}$, $-R^{y4a}$, $-R^{y5}$, $-R^{y5a}$ and $-R^{y5b}$ is independently of each other selected from the group consisting of $-H$, and C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different.

- 5 In certain embodiments $-L^2-$ is a C_{1-20} alkyl chain, which is optionally interrupted by one or more groups independently selected from $-O-$, $-T-$ and $-C(O)N(R^{y1})-$; and which C_{1-20} alkyl chain is optionally substituted with one or more groups independently selected from $-OH$, $-T$ and $-C(O)N(R^{y6}R^{y6a})$; wherein $-R^{y1}$, $-R^{y6}$, $-R^{y6a}$ are independently selected from the group consisting of H and C_{1-4} alkyl and wherein T is selected from the group consisting of phenyl, naphthyl, indenyl, indanyl, tetralinyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl, 8- to 11-membered heterobicycyl, 8- to 30-membered carbopolycyclyl, and 8- to 30-membered heteropolycyclyl.

In certain embodiments $-L^2-$ has a molecular weight ranging from 14 g/mol to 750 g/mol.

15

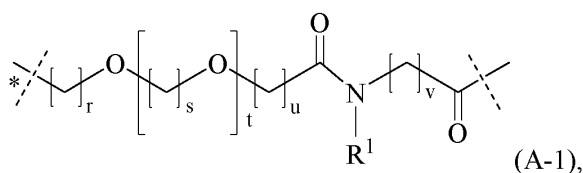
In certain embodiments $-L^2-$ comprises a moiety selected from



In certain embodiments $-L^2-$ has a chain lengths of 1 to 20 atoms.

- 20 As used herein the term “chain length” with regard to the moiety $-L^2-$ refers to the number of atoms of $-L^2-$ present in the shortest connection between $-L^1-$ and $-Z$.

In certain embodiments $-L^2-$ is of formula (A-1)



25

wherein

the dashed line marked with the asterisk indicates attachment to $-L^1-$,

the unmarked dashed line indicates attachment to Z ,

- r is selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10;
s is selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10;
t is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10;
u is selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10;
5 v is selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10; and
-R¹ is selected from the group consisting of -H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl and C₂₋₁₀ alkynyl.

In certain embodiments r of formula (A-1) is 1. In certain embodiments r of formula (A-1) is
10 2. In certain embodiments r of formula (A-1) is 3. In certain embodiments r of formula (A-1)
is 4. In certain embodiments r of formula (A-1) is 5. In certain embodiments r of formula (A-
1) is 6. In certain embodiments r of formula (A-1) is 7. In certain embodiments r of formula
(A-1) is 8. In certain embodiments r of formula (A-1) is 9. In certain embodiments r of formula
(A-1) is 10.

15 In certain embodiments s of formula (A-1) is 1. In certain embodiments s of formula (A-1) is
2. In certain embodiments s of formula (A-1) is 3. In certain embodiments s of formula (A-1)
is 4. In certain embodiments s of formula (A-1) is 5. In certain embodiments s of formula (A-
1) is 6. In certain embodiments s of formula (A-1) is 7. In certain embodiments s of formula
20 (A-1) is 8. In certain embodiments s of formula (A-1) is 9. In certain embodiments s of formula
(A-1) is 10.

In certain embodiments t of formula (A-1) is 1. In certain embodiments t of formula (A-1) is
2. In certain embodiments t of formula (A-1) is 3. In certain embodiments t of formula (A-1)
25 is 4. In certain embodiments t of formula (A-1) is 5. In certain embodiments t of formula (A-
1) is 6. In certain embodiments t of formula (A-1) is 7. In certain embodiments t of formula
(A-1) is 8. In certain embodiments t of formula (A-1) is 9. In certain embodiments t of formula
(A-1) is 10.

30 In certain embodiments u of formula (A-1) is 1. In certain embodiments u of formula (A-1) is
2. In certain embodiments u of formula (A-1) is 3. In certain embodiments u of formula (A-1)
is 4. In certain embodiments u of formula (A-1) is 5. In certain embodiments u of formula (A-
1) is 6. In certain embodiments u of formula (A-1) is 7. In certain embodiments u of formula

(A-1) is 8. In certain embodiments u of formula (A-1) is 9. In certain embodiments u of formula (A-1) is 10.

In certain embodiments v of formula (A-1) is 1. In certain embodiments v of formula (A-1) is 2. In certain embodiments v of formula (A-1) is 3. In certain embodiments v of formula (A-1) is 4. In certain embodiments v of formula (A-1) is 5. In certain embodiments v of formula (A-1) is 6. In certain embodiments v of formula (A-1) is 7. In certain embodiments v of formula (A-1) is 8. In certain embodiments v of formula (A-1) is 9. In certain embodiments v of formula (A-1) is 10.

10

In certain embodiments $-R^1$ of formula (A-1) is -H. In certain embodiments $-R^1$ of formula (A-1) is methyl. In certain embodiments $-R^1$ of formula (A-1) is ethyl. In certain embodiments $-R^1$ of formula (A-1) is n-propyl. In certain embodiments $-R^1$ of formula (A-1) is isopropyl. In certain embodiments $-R^1$ of formula (A-1) is n-butyl. In certain embodiments $-R^1$ of formula (A-1) is isobutyl. In certain embodiments $-R^1$ of formula (A-1) is sec-butyl. In certain embodiments $-R^1$ of formula (A-1) is tert-butyl. In certain embodiments $-R^1$ of formula (A-1) is n-pentyl. In certain embodiments $-R^1$ of formula (A-1) is 2-methylbutyl. In certain embodiments $-R^1$ of formula (A-1) is 2,2-dimethylpropyl. In certain embodiments $-R^1$ of formula (A-1) is n-hexyl. In certain embodiments $-R^1$ of formula (A-1) is 2-methylpentyl. In certain embodiments $-R^1$ of formula (A-1) is 3-methylpentyl. In certain embodiments $-R^1$ of formula (A-1) is 2,2-dimethylbutyl. In certain embodiments $-R^1$ of formula (A-1) is 2,3-dimethylbutyl. In certain embodiments $-R^1$ of formula (A-1) is 3,3-dimethylpropyl.

20

In certain embodiments r of formula (A-1) is 1, s of formula (A-1) is 2, t of formula (A-1) is 2, u of formula (A-1) is 1, v of formula (A-1) is 2 and $-R^1$ of formula (A-1) is -H.

25

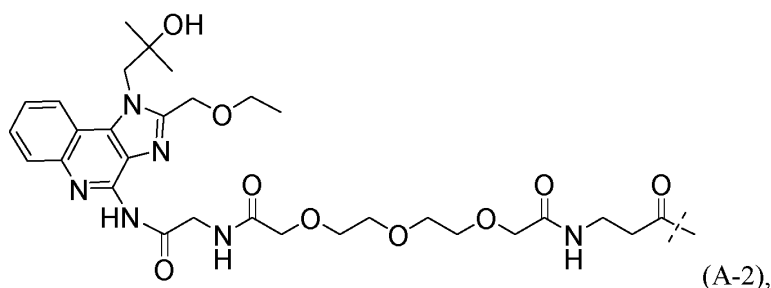
In certain embodiments r of formula (A-1) is 1, s of formula (A-1) is 2, t of formula (A-1) is 3, u of formula (A-1) is 1, v of formula (A-1) is 2 and $-R^1$ of formula (A-1) is -H.

In certain embodiments r of formula (A-1) is 1, s of formula (A-1) is 2, t of formula (A-1) is 4, u of formula (A-1) is 1, v of formula (A-1) is 2 and $-R^1$ of formula (A-1) is -H.

30

In certain embodiments r of formula (A-1) is 1, s of formula (A-1) is 2, t of formula (A-1) is 5, u of formula (A-1) is 1, v of formula (A-1) is 2 and $-R^1$ of formula (A-1) is -H.

In certain embodiments the moiety D-L¹-L²- is of formula (A-2):



wherein

- 5 the dashed line indicates attachment to Z.

In certain embodiments Z comprises a polymer.

- 10 In certain embodiments Z is not degradable. In certain embodiments Z is degradable. A degradable moiety Z has the effect that the carrier moiety degrades over time which may be advantageous in certain applications.

- 15 In certain embodiments Z is a hydrogel. Such hydrogel may be degradable or may be non-degradable, i.e. stable. In certain embodiments such hydrogel is degradable. In certain embodiments such hydrogel is non-degradable.

- In certain embodiments such hydrogel Z comprises a polymer selected from the group consisting of 2-methacryloyl-oxyethyl phosphocholins, poly(acrylic acids), poly(acrylates), poly(acrylamides), poly(alkyloxy) polymers, poly(amides), poly(amidoamines), poly(amino acids), poly(anhydrides), poly(aspartamides), poly(butyric acids), poly(glycolic acids), polybutylene terephthalates, poly(caprolactones), poly(carbonates), poly(cyanoacrylates), poly(dimethylacrylamides), poly(esters), poly(ethylenes), poly(alkylene glycols), such as poly(ethylene glycols) and poly(propylene glycol), poly(ethylene oxides), poly(ethyl phosphates), poly(ethyloxazolines), poly(glycolic acids), poly(hydroxyethyl acrylates), poly(hydroxyethyl-oxazolines), poly(hydroxymethacrylates), poly(hydroxypropylmethacrylamides), poly(hydroxypropyl methacrylates), poly(hydroxypropyloxazolines), poly(iminocarbonates), poly(lactic acids), poly(lactic-co-glycolic acids), poly(methacrylamides), poly(methacrylates), poly(methyloxazolines),
- 20
- 25

poly(organophosphazenes), poly(ortho esters), poly(oxazolines), poly(propylene glycols), poly(siloxanes), poly(urethanes), poly(vinyl alcohols), poly(vinyl amines), poly(vinylmethylethers), poly(vinylpyrrolidones), silicones, celluloses, carbomethyl celluloses, hydroxypropyl methylcelluloses, chitins, chitosans, dextrans, dextrans, gelatins, 5 hyaluronic acids and derivatives, functionalized hyaluronic acids, mannans, pectins, rhamnogalacturonans, starches, hydroxyalkyl starches, hydroxyethyl starches and other carbohydrate-based polymers, xylans, and copolymers thereof.

In certain embodiments Z is a poly(alkylene glycol)-based hydrogel, such as a poly(propylene glycol)-based hydrogel or a poly(ethylene glycol)-based (PEG-based) hydrogel, or a 10 hyaluronic acid-based hydrogel.

In certain embodiments Z is a PEG-based hydrogel. Such PEG-based hydrogel may be degradable or may be non-degradable, i.e. stable. In certain embodiments such PEG-based 15 hydrogel is degradable. In certain embodiments such PEG-based hydrogel is non-degradable. Suitable hydrogels are known in the art. Examples are WO2006/003014, WO2011/012715 and WO2014/056926, which are herewith incorporated by reference.

In certain embodiments such PEG-based hydrogel comprises a plurality of backbone moieties 20 that are crosslinked via crosslinker moieties $-CL^P-$. Optionally, there is a spacer moiety $-SP^1-$ between a backbone moiety and a crosslinker moiety. In certain embodiments such spacer $-SP^1-$ is defined as described above for $-L^2-$.

In certain embodiments a backbone moiety has a molecular weight ranging from 1 kDa to 20 25 kDa.

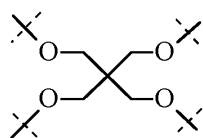
In certain embodiments a backbone moiety is of formula (pA)

30 $B^*-(A-Hyp)_x$ (pA),
wherein
 B^* is a branching core,
A is a PEG-based polymer,
Hyp is a branched moiety,
x is an integer of from 3 to 16;

and wherein each backbone moiety is connected to one or more crosslinker moieties and to one or more moieties $-L^2-$, which crosslinker moieties and moieties $-L^2-$ are connected to Hyp, either directly or through a spacer moiety.

- 5 In certain embodiments B^* of formula (pA) is selected from the group consisting of polyalcohol moieties and polyamine moieties. In certain embodiments B^* of formula (pA) is a polyalcohol moiety. In certain embodiments B^* of formula (pA) is a polyamine moiety.

- 10 In certain embodiments the polyalcohol moieties for B^* of formula (pA) are selected from the group consisting of a pentaerythritol moiety, tripentaerythritol moiety, hexaglycerine moiety, sucrose moiety, sorbitol moiety, fructose moiety, mannitol moiety and glucose moiety. In certain embodiments B^* of formula (pA) is a pentaerythritol moiety, i.e. a moiety of formula



, wherein dashed lines indicate attachment to $-A-$.

- 15 In certain embodiments the polyamine moieties for B^* of formula (pA) is selected from the group consisting of an ornithine moiety, diaminobutyric acid moiety, tryllysine moiety, tetralysine moiety, pentalysine moiety, hexalysine moiety, heptalysine moiety, octalysine moiety, nonalysine moiety, decalysine moiety, undecalysine moiety, dodecalysine moiety, tridecalysine moiety, tetradecalysine moiety and pentadecalysine moiety. In certain
20 embodiments B^* of formula (pA) is selected from the group consisting of an ornithine moiety, diaminobutyric acid moiety and a tryllysine moiety.

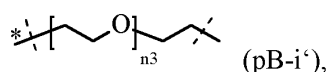
- A backbone moiety of formula (pA) may consist of the same or different PEG-based moieties $-A-$ and each moiety $-A-$ may be chosen independently. In certain embodiments all
25 moieties $-A-$ present in a backbone moiety of formula (pA) have the same structure. It is understood that the phrase “have the same structure” with regard to polymeric moieties, such as with regard to the PEG-based polymer $-A-$, means that the number of monomers of the polymer, such as the number of ethylene glycol monomers, may vary due to the polydisperse nature of polymers. In certain embodiments the number of monomer units does not vary by
30 more than a factor of 2 between all moieties $-A-$ of a hydrogel.

In certain embodiments each -A- of formula (pA) has a molecular weight ranging from 0.3 kDa to 40 kDa; e.g. from 0.4 to 30 kDa, from 0.4 to 25 kDa, from 0.4 to 20 kDa, from 0.4 to 15 kDa, from 0.4 to 10 kDa or from 0.4 to 5 kDa. In certain embodiments each -A- has a molecular weight from 0.4 to 5 kDa. In certain embodiments -A- has a molecular weight of about 0.5 kDa. In certain embodiments -A- has a molecular weight of about 1 kDa. In certain
5 embodiments -A- has a molecular weight of about 2 kDa. In certain embodiments -A- has a molecular weight of about 3 kDa. In certain embodiments -A- has a molecular weight of about 5 kDa.

10 In certain embodiments -A- of formula (pA) is of formula (pB-i)
 $-(\text{CH}_2)_{n1}(\text{OCH}_2\text{CH}_2)_n\text{X}-$ (pB-i),
 wherein
 n1 is 1 or 2;
 n is an integer ranging from 3 to 250, such as from 5 to 200, such as from 8 to 150 or
 15 from 10 to 100; and
 X is a chemical bond or a linkage covalently linking A and Hyp.

 In certain embodiments -A- of formula (pA) is of formula (pB-ii)
 $-(\text{CH}_2)_{n1}(\text{OCH}_2\text{CH}_2)_n(\text{CH}_2)_{n2}\text{X}-$ (pB-ii),
 20 wherein
 n1 is 1 or 2;
 n is an integer ranging from 3 to 250, such as from 5 to 200, such as from 8 to 150 or
 from 10 to 100;
 n2 is 0 or 1; and
 25 X is a chemical bond or a linkage covalently linking A and Hyp.

In certain embodiments -A- of formula (pA) is of formula (pB-i')

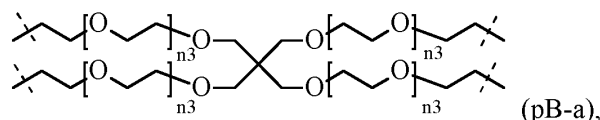


 wherein
 30 the dashed line marked with the asterisk indicates attachment to B*,
 the unmarked dashed line indicates attachment to -Hyp; and
 n3 is an integer ranging from 10 to 50.

In certain embodiments n_3 of formula (pB-i') is 25. In certain embodiments n_3 of formula (pB-i') is 26. In certain embodiments n_3 of formula (pB-i') is 27. In certain embodiments n_3 of formula (pB-i') is 28. In certain embodiments n_3 of formula (pB-i') is 29. In certain embodiments n_3 of formula (pB-i') is 30.

5

In certain embodiments a moiety $B^*-(A)_4$ is of formula (pB-a)



wherein

dashed lines indicate attachment to Hyp; and

each n_3 is independently an integer selected from 10 to 50.

In certain embodiments n_3 of formula (pB-a) is 25. In certain embodiments n_3 of formula (pB-a) is 26. In certain embodiments n_3 of formula (pB-a) is 27. In certain embodiments n_3 of formula (pB-a) is 28. In certain embodiments n_3 of formula (pB-a) is 29. In certain embodiments n_3 of formula (pB-a) is 30.

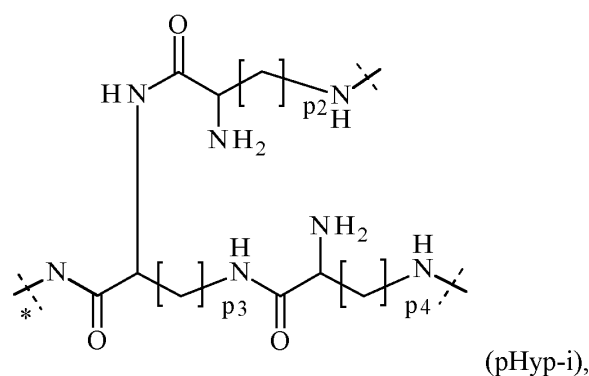
A backbone moiety of formula (pA) may consist of the same or different dendritic moieties -Hyp and that each -Hyp can be chosen independently. In certain embodiments all moieties -Hyp present in a backbone moiety of formula (pA) have the same structure.

20

In certain embodiments each -Hyp of formula (pA) has a molecular weight ranging from 0.3 kDa to 5 kDa.

In certain embodiments -Hyp is selected from the group consisting of a moiety of formula (pHyp-i)

25



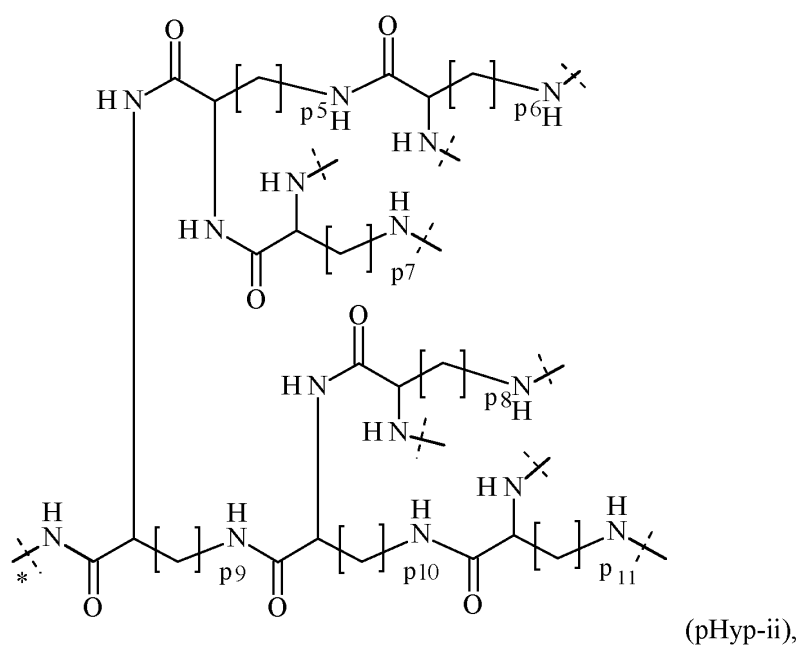
wherein

the dashed line marked with the asterisk indicates attachment to -A-,

the unmarked dashed lines indicate attachment to a spacer moiety -SP¹-, a crosslinker moiety -CL^p- or to -L²-; and

p2, p3 and p4 are identical or different and each is independently of the others an integer from 1 to 5;

a moiety of formula (pHyp-ii)



wherein

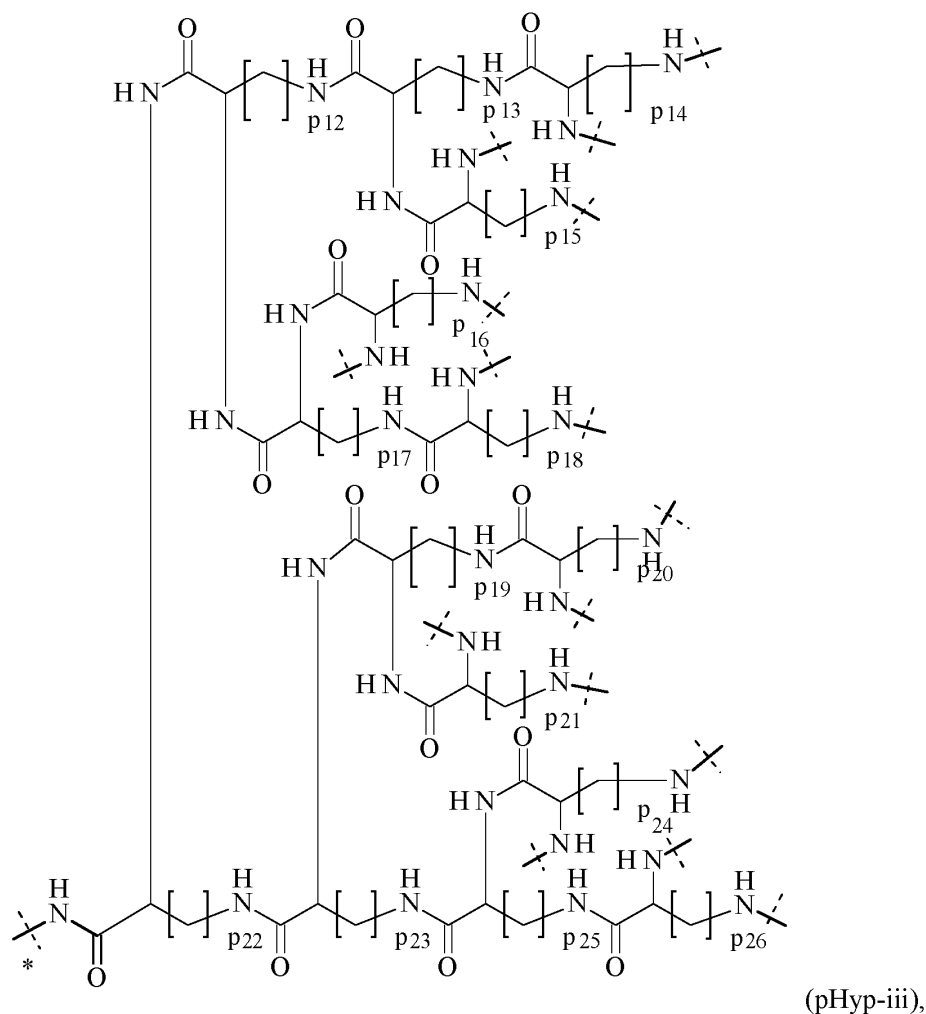
the dashed line marked with the asterisk indicates attachment to -A-,

the unmarked dashed lines indicate attachment to a spacer moiety -SP¹-, a crosslinker moiety -CL^p- or to -L²-; and

p5 to p11 are identical or different and each is independently of the others an integer from 1 to 5;

5

a moiety of formula (pHyp-iii)



wherein

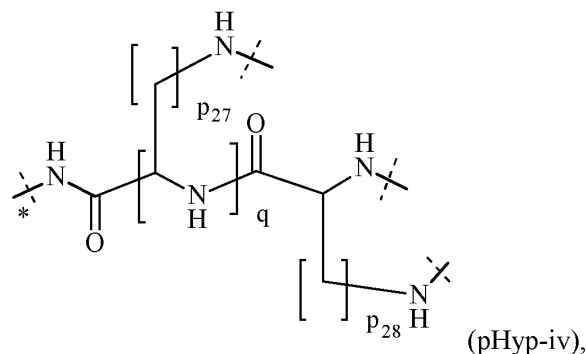
the dashed line marked with the asterisk indicates attachment to -A-,

10

the unmarked dashed lines indicate attachment to a spacer moiety -SP¹-, a crosslinker moiety -CL^p- or to -L²-; and

p12 to p26 are identical or different and each is independently of the others an integer from 1 to 5; and

a moiety of formula (pHyp-iv)



5 wherein

the dashed line marked with the asterisk indicates attachment to -A-,

the unmarked dashed lines indicate attachment to a spacer moiety -SP¹-, a crosslinker moiety -CL^p- or to -L²-;

10 p27 and p28 are identical or different and each is independently of the other an integer from 1 to 5; and

q is an integer from 1 to 8;

wherein the moieties (pHyp-i) to (pHyp-iv) may at each chiral center be in either R- or S-configuration.

15

In certain embodiments all chiral centers of a moiety (pHyp-i), (pHyp-ii), (pHyp-iii) or (pHyp-iv) are in the same configuration. In certain embodiments all chiral centers of a moiety (pHyp-i), (pHyp-ii), (pHyp-iii) or (pHyp-iv) are in R-configuration. In certain embodiments all chiral centers of a moiety (pHyp-i), (pHyp-ii), (pHyp-iii) or (pHyp-iv) are in S-configuration.

20

In certain embodiments p2, p3 and p4 of formula (pHyp-i) are 4.

In certain embodiments p5 to p11 of formula (pHyp-ii) are 4.

25 In certain embodiments p12 to p26 of formula (pHyp-iii) are 4.

In certain embodiments q of formula (pHyp-iv) is 2 or 6. In certain embodiments q of formula (pHyp-iv) q is 6.

In certain embodiments p27 and p28 of formula (pHyp-iv) are 4.

5

In certain embodiments -Hyp of formula (pA) comprises a branched polypeptide moiety.

In certain embodiments -Hyp of formula (pA) comprises a lysine moiety. In certain embodiments each -Hyp of formula (pA) is independently selected from the group consisting of a trilycine moiety, tetralysine moiety, pentalysine moiety, hexalysine moiety, heptalysine moiety, octalysine moiety, nonalysine moiety, decalysine moiety, undecalysine moiety, dodecalysine moiety, tridecalysine moiety, tetradecalysine moiety, pentadecalysine moiety, hexadecalysine moiety, heptadecalysine moiety, octadecalysine moiety and nonadecalysine moiety.

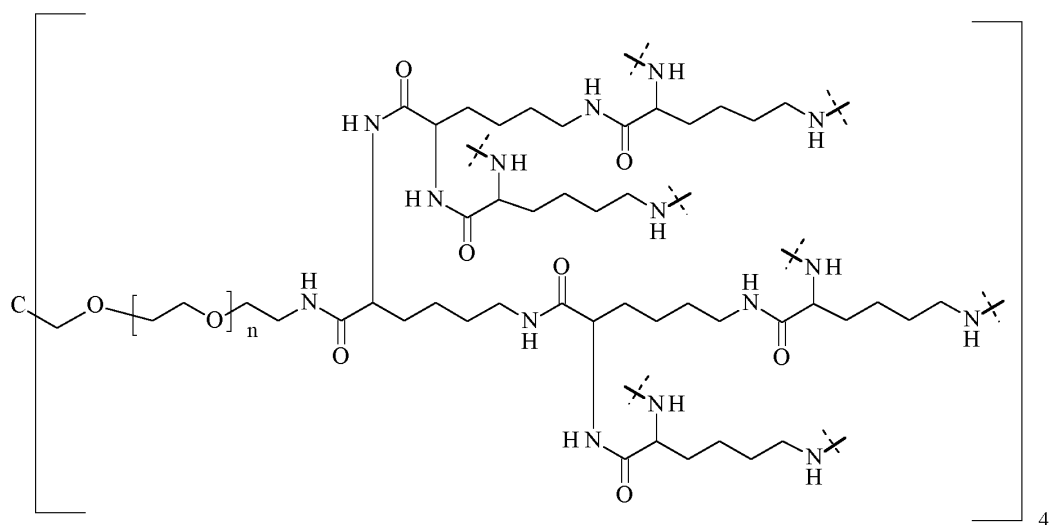
15

In certain embodiments -Hyp comprises 3 lysine moieties. In certain embodiments -Hyp comprises 7 lysine moieties. In certain embodiments -Hyp comprises 15 lysine moieties. In certain embodiments -Hyp comprises heptalysiny.

In certain embodiments x of formula (pA) is 3. In certain embodiments x of formula (pA) is 4. In certain embodiments x of formula (pA) is 6. In certain embodiments x of formula (pA) is 8.

20

In certain embodiments the backbone moiety is of formula (pC1)



(pC1),

wherein

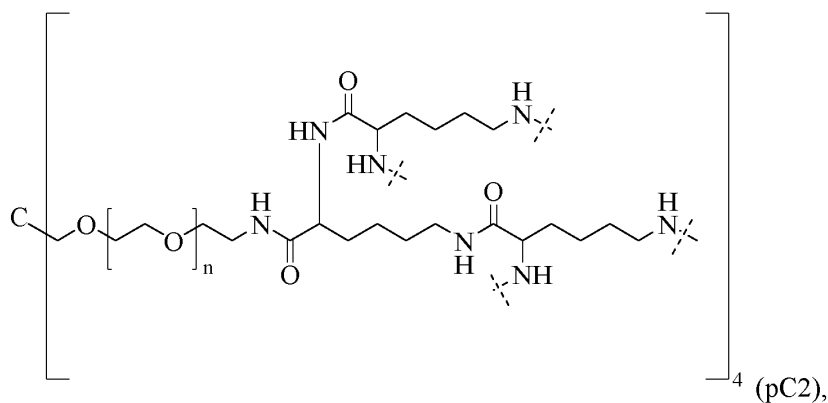
dashed lines indicate attachment to a spacer moiety -SP¹-, a crosslinker moiety -CLᵖ- or

to -L²-; and

n ranges from 10 to 40.

In certain embodiments n of formula (pC1) is about 28.

In certain embodiments the backbone moiety is of formula (pC2)



wherein

dashed lines indicate attachment to a spacer moiety -SP¹-, a crosslinker moiety -CLᵖ- or

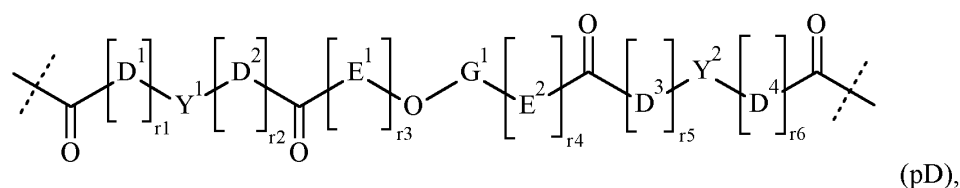
to -L²-; and

n ranges from 10 to 40.

In certain embodiments there is no spacer moiety $-SP^1-$ between a backbone moiety and a crosslinker moiety $-CL^P-$, i.e. $-CL^P-$ is directly linked to $-Hyp$.

The crosslinker $-CL^P-$ of the PEG-based hydrogel is in certain embodiments poly(alkylene glycol) (PAG)-based. In certain embodiments the crosslinker is poly(propylene glycol)-based. In certain embodiments the crosslinker $-CL^P-$ is PEG-based.

In certain embodiments such PAG-based crosslinker moiety $-CL^P-$ is of formula (pD)

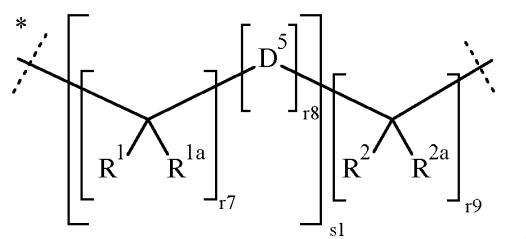


10

wherein

dashed lines indicate attachment to a backbone moiety or to a spacer moiety $-SP^1-$;

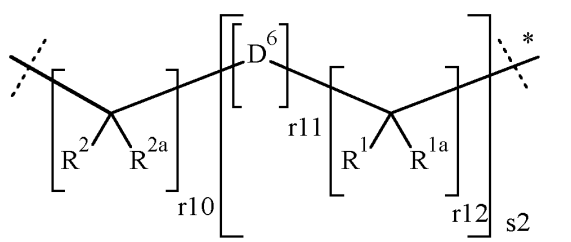
$-Y^1-$ is of formula



15

wherein the dashed line marked with the asterisk indicates attachment to $-D^1-$ and the unmarked dashed line indicates attachment to $-D^2-$;

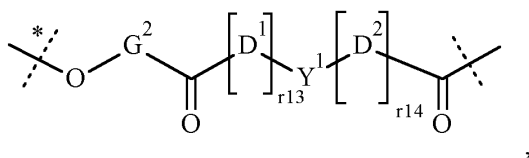
$-Y^2-$ is of formula



20

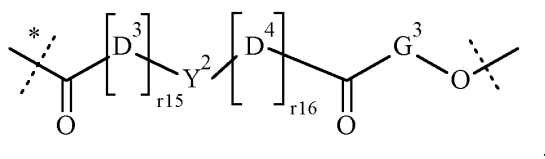
wherein the dashed line marked with the asterisk indicates attachment to $-D^4-$ and the unmarked dashed line indicates attachment to $-D^3-$;

$-E^1-$ is of formula



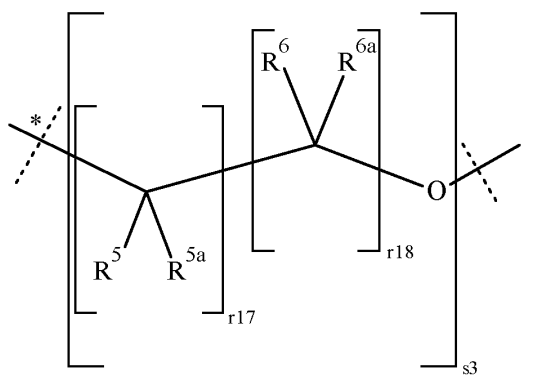
wherein the dashed line marked with the asterisk indicates attachment to $-(C=O)-$ and the unmarked dashed line indicates attachment to $-O-$;

5 $-E^2-$ is of formula



wherein the dashed line marked with the asterisk indicates attachment to $-G^1-$ and the unmarked dashed line indicates attachment to $-(C=O)-$;

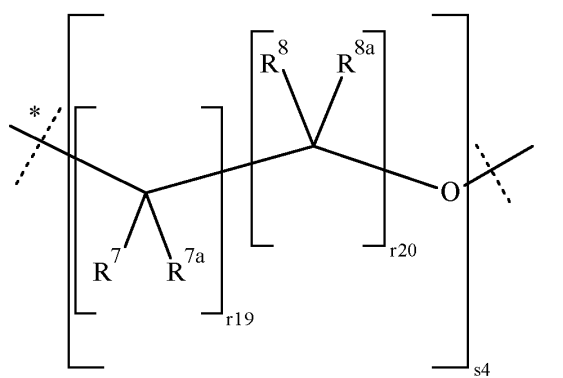
10 $-G^1-$ is of formula



wherein the dashed line marked with the asterisk indicates attachment to $-O-$ and the unmarked dashed line indicates attachment to $-E^2-$;

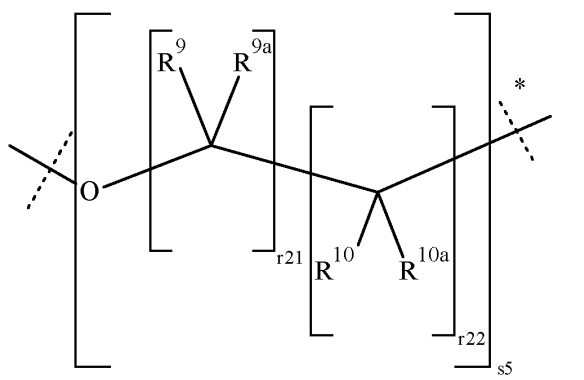
15 $-G^2-$ is of formula

119



wherein the dashed line marked with the asterisk indicates attachment to -O- and the unmarked dashed line indicates attachment to -(C=O)-;

5 -G³- is of formula



wherein the dashed line marked with the asterisk indicates attachment to -O- and the unmarked dashed line indicates attachment to -(C=O)-;

10 -D¹-, -D²-, -D³-, -D⁴-, -D⁵- and -D⁶- are identical or different and each is independently of the others selected from the group comprising -O-, -NR¹¹-, -N⁺R¹²R^{12a}-, -S-, -(S=O)-, -(S(O)₂)-, -C(O)-, -P(O)R¹³-, -P(O)(OR¹³) and -CR¹⁴R^{14a}-;

15 -R¹-, -R^{1a}-, -R²-, -R^{2a}-, -R³-, -R^{3a}-, -R⁴-, -R^{4a}-, -R⁵-, -R^{5a}-, -R⁶-, -R^{6a}-, -R⁷-, -R^{7a}-, -R⁸-, -R^{8a}-, -R⁹-, -R^{9a}-, -R¹⁰-, -R^{10a}-, -R¹¹-, -R¹²-, -R^{12a}-, -R¹³-, -R¹⁴ and -R^{14a} are identical or different and each is independently of the others selected from the group consisting of -H and C₁₋₆ alkyl;

optionally, one or more of the pairs -R¹/-R^{1a}-, -R²/-R^{2a}-, -R³/-R^{3a}-, -R⁴/-R^{4a}-, -R¹/-R²-, -R³/-R⁴-, -R^{1a}/-R^{2a}-, -R^{3a}/-R^{4a}-,

$-R^{12}/-R^{12a}$, and $-R^{14}/-R^{14a}$ form a chemical bond or are joined together with the atom to which they are attached to form a C_{3-8} cycloalkyl or to form a ring A or are joined together with the atom to which they are attached to form a 4- to 7-membered heterocyclyl or 8- to 11-membered heterobicycyl or adamantyl;

5

A is selected from the group consisting of phenyl, naphthyl, indenyl, indanyl and tetralinyl;

$r_1, r_2, r_5, r_6, r_{13}, r_{14}, r_{15}$ and r_{16} are independently 0 or 1;

10

$r_3, r_4, r_7, r_8, r_9, r_{10}, r_{11}, r_{12}$ are independently 0, 1, 2, 3, or 4;

$r_{17}, r_{18}, r_{19}, r_{20}, r_{21}$ and r_{22} are independently 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10;

15

s_1, s_2, s_4, s_5 are independently 1, 2, 3, 4, 5 or 6; and

s_3 ranges from 1 to 900.

In certain embodiments s_3 ranges from 1 to 500. In certain embodiments s_3 ranges from 1 to 200.

20

In certain embodiments r_1 of formula (pD) is 0. In certain embodiments r_1 of formula (pD) is 1. In certain embodiments r_2 of formula (pD) is 0. In certain embodiments r_2 of formula (pD) is 1. In certain embodiments r_5 of formula (pD) is 0. In certain embodiments r_5 of formula (pD) is 1.

25

In certain embodiments r_1, r_2, r_5 and r_6 of formula (pD) are 0.

In certain embodiments r_6 of formula (pD) is 0. In certain embodiments r_6 of formula (pD) is 1. In certain embodiments r_{13} of formula (pD) is 0. In certain embodiments r_{13} of formula (pD) is 1. In certain embodiments r_{14} of formula (pD) is 0. In certain embodiments r_{14} of formula (pD) is 1. In certain embodiments r_{15} of formula (pD) is 0. In certain embodiments r_{15} of formula (pD) is 1. In certain embodiments r_{16} of formula (pD) is 0. In certain embodiments r_{16} of formula (pD) is 1.

30

In certain embodiments r3 of formula (pD) is 1. In certain embodiments r3 of formula (pD) is 2. In certain embodiments r4 of formula (pD) is 1. In certain embodiments r4 of formula (pD) is 2. In certain embodiments r3 and r4 of formula (pD) are both 1. In certain embodiments r3 and r4 of formula (pD) are both 2. In certain embodiments r3 and r4 of formula (pD) are both 3.

In certain embodiments r7 of formula (pD) is 0. In certain embodiments r7 of formula (pD) is 1. In certain embodiments r7 of formula (pD) is 2. In certain embodiments r8 of formula (pD) is 0. In certain embodiments r8 of formula (pD) is 1. In certain embodiments r8 of formula (pD) is 2. In certain embodiments r9 of formula (pD) is 0. In certain embodiments r9 of formula (pD) is 1. In certain embodiments r9 of formula (pD) is 2. In certain embodiments r10 of formula (pD) is 0. In certain embodiments r10 of formula (pD) is 1. In certain embodiments r10 of formula (pD) is 2. In certain embodiments r11 of formula (pD) is 0. In certain embodiments r11 of formula (pD) is 1. In certain embodiments r11 of formula (pD) is 2. In certain embodiments r12 of formula (pD) is 0. In certain embodiments r12 of formula (pD) is 1. In certain embodiments r12 of formula (pD) is 2.

In certain embodiments r17 of formula (pD) is 1. In certain embodiments r18 of formula (pD) is 1. In certain embodiments r19 of formula (pD) is 1. In certain embodiments r20 of formula (pD) is 1. In certain embodiments r21 of formula (pD) is 1.

In certain embodiments s1 of formula (pD) is 1. In certain embodiments s1 of formula (pD) is 2. In certain embodiments s2 of formula (pD) is 1. In certain embodiments s2 of formula (pD) is 2. In certain embodiments s4 of formula (pD) is 1. In certain embodiments s4 of formula (pD) is 2.

In certain embodiments s3 of formula (pD) ranges from 5 to 500. In certain embodiments s3 of formula (pD) ranges from 10 to 250. In certain embodiments s3 of formula (pD) ranges from 12 to 150. In certain embodiments s3 of formula (pD) ranges from 15 to 100. In certain embodiments s3 of formula (pD) ranges from 18 to 75. In certain embodiments s3 of formula (pD) ranges from 20 to 50.

[illegible]

of formula (pD) is methyl. In certain embodiments -R^{10a} of formula (pD) is ethyl. In certain
embodiments -R¹¹ of formula (pD) is -H. In certain embodiments -R¹¹ of formula (pD) is
methyl. In certain embodiments -R¹¹ of formula (pD) is ethyl. In certain embodiments -R¹² of
formula (pD) is -H. In certain embodiments -R¹² of formula (pD) is methyl. In certain
5 embodiments -R¹² of formula (pD) is ethyl. In certain embodiments -R^{12a} of formula (pD) is -H.
In certain embodiments -R^{12a} of formula (pD) is methyl. In certain embodiments -R^{12a} of
formula (pD) is ethyl. In certain embodiments -R¹³ of formula (pD) is -H. In certain
embodiments -R¹³ of formula (pD) is methyl. In certain embodiments -R¹³ of formula (pD) is
ethyl. In certain embodiments -R¹⁴ of formula (pD) is -H. In certain embodiments -R¹⁴ of
10 formula (pD) is methyl. In certain embodiments -R¹⁴ of formula (pD) is ethyl. In certain
embodiments -R^{14a} of formula (pD) is -H. In certain embodiments -R^{14a} of formula (pD) is
methyl. In certain embodiments -R^{14a} of formula (pD) is ethyl.

In certain embodiments -D¹⁻ of formula (pD) is -O-. In certain embodiments -D¹⁻ of formula
15 (pD) is -NR¹¹-. In certain embodiments -D¹⁻ of formula (pD) is -N⁺R¹²R^{12a}-. In certain
embodiments -D¹⁻ of formula (pD) is -S-. In certain embodiments -D¹⁻ of formula (pD)
is -(S=O). In certain embodiments -D¹⁻ of formula (pD) is -(S(O)₂)-. In certain
embodiments -D¹⁻ of formula (pD) is -C(O)-. In certain embodiments -D¹⁻ of formula (pD) is
-P(O)R¹³-. In certain embodiments -D¹⁻ of formula (pD) is -P(O)(OR¹³)-. In certain
20 embodiments -D¹⁻ of formula (pD) is -CR¹⁴R^{14a}-.

In certain embodiments -D²⁻ of formula (pD) is -O-. In certain embodiments -D²⁻ of formula
(pD) is -NR¹¹-. In certain embodiments -D²⁻ of formula (pD) is -N⁺R¹²R^{12a}-. In certain
embodiments -D²⁻ of formula (pD) is -S-. In certain embodiments -D²⁻ of formula (pD)
25 is -(S=O). In certain embodiments -D²⁻ of formula (pD) is -(S(O)₂)-. In certain
embodiments -D²⁻ of formula (pD) is -C(O)-. In certain embodiments -D²⁻ of formula (pD) is
-P(O)R¹³-. In certain embodiments -D²⁻ of formula (pD) is -P(O)(OR¹³)-. In certain
embodiments -D²⁻ of formula (pD) is -CR¹⁴R^{14a}-.

In certain embodiments -D³⁻ of formula (pD) is -O-. In certain embodiments -D³⁻ of formula
(pD) is -NR¹¹-. In certain embodiments -D³⁻ of formula (pD) is -N⁺R¹²R^{12a}-. In certain
embodiments -D³⁻ of formula (pD) is -S-. In certain embodiments -D³⁻ of formula (pD)
is -(S=O). In certain embodiments -D³⁻ of formula (pD) is -(S(O)₂)-. In certain
embodiments -D³⁻ of formula (pD) is -C(O)-. In certain embodiments -D³⁻ of formula (pD)

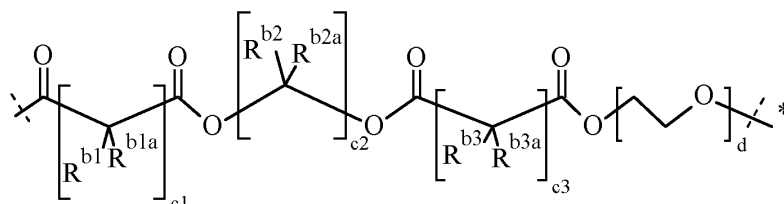
is $-P(O)R^{13}$ -. In certain embodiments $-D^3$ - of formula (pD) is $-P(O)(OR^{13})$ -. In certain embodiments $-D^3$ - of formula (pD) is $-CR^{14}R^{14a}$ -.

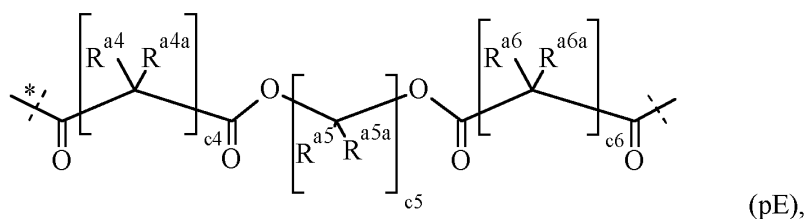
In certain embodiments $-D^4$ - of formula (pD) is $-O$ -. In certain embodiments $-D^4$ - of formula (pD) is $-NR^{11}$ -. In certain embodiments $-D^4$ - of formula (pD) is $-N^+R^{12}R^{12a}$ -. In certain embodiments $-D^4$ - of formula (pD) is $-S$ -. In certain embodiments $-D^4$ - of formula (pD) is $-(S=O)$ -. In certain embodiments $-D^4$ - of formula (pD) is $-(S(O)_2)$ -. In certain embodiments $-D^4$ - of formula (pD) is $-C(O)$ -. In certain embodiments $-D^4$ - of formula (pD) is $-P(O)R^{13}$ -. In certain embodiments $-D^4$ - of formula (pD) is $-P(O)(OR^{13})$ -. In certain
 10 embodiments $-D^4$ - of formula (pD) is $-CR^{14}R^{14a}$ -.

In certain embodiments $-D^5$ - of formula (pD) is $-O$ -. In certain embodiments $-D^5$ - of formula (pD) is $-NR^{11}$ -. In certain embodiments $-D^5$ - of formula (pD) is $-N^+R^{12}R^{12a}$ -. In certain embodiments $-D^5$ - of formula (pD) is $-S$ -. In certain embodiments $-D^5$ - of formula (pD) is $-(S=O)$ -. In certain embodiments $-D^5$ - of formula (pD) is $-(S(O)_2)$ -. In certain embodiments $-D^5$ - of formula (pD) is $-C(O)$ -. In certain embodiments $-D^5$ - of formula (pD) is $-P(O)R^{13}$ -. In certain embodiments $-D^5$ - of formula (pD) is $-P(O)(OR^{13})$ -. In certain embodiments $-D^5$ - of formula (pD) is $-CR^{14}R^{14a}$ -.

In certain embodiments $-D^6$ - of formula (pD) is $-O$ -. In certain embodiments $-D^6$ - of formula (pD) is $-NR^{11}$ -. In certain embodiments $-D^6$ - of formula (pD) is $-N^+R^{12}R^{12a}$ -. In certain embodiments $-D^6$ - of formula (pD) is $-S$ -. In certain embodiments $-D^6$ - of formula (pD) is $-(S=O)$ -. In certain embodiments $-D^6$ - of formula (pD) is $-(S(O)_2)$ -. In certain embodiments $-D^6$ - of formula (pD) is $-C(O)$ -. In certain embodiments $-D^6$ - of formula (pD) is $-P(O)R^{13}$ -. In certain embodiments $-D^6$ - of formula (pD) is $-P(O)(OR^{13})$ -. In certain
 25 embodiments $-D^6$ - of formula (pD) is $-CR^{14}R^{14a}$ -.

In one embodiment $-CL^p$ - is of formula (pE)





wherein

dashed lines marked with an asterisk indicate the connection point between the upper and the lower substructure,

5 unmarked dashed lines indicate attachment to a backbone moiety or to a spacer moiety -SP¹-;

-R^{b1}, -R^{b1a}, -R^{b2}, -R^{b2a}, -R^{b3}, -R^{b3a}, -R^{b4}, -R^{b4a}, -R^{b5}, -R^{b5a}, -R^{b6} and -R^{b6} are independently selected from the group consisting of -H and C₁₋₆ alkyl;

c1, c2, c3, c4, c5 and c6 are independently selected from the group consisting of 1, 2,
10 3, 4, 5 and 6;

d is an integer ranging from 2 to 250.

In certain embodiments d of formula (pE) ranges from 3 to 200. In certain embodiments d of formula (pE) ranges from 4 to 150. In certain embodiments d of formula (pE) ranges from 5 to
15 100. In certain embodiments d of formula (pE) ranges from 10 to 50. In certain embodiments d of formula (pE) ranges from 15 to 30. In certain embodiments d of formula (pE) is about 23.

In certain embodiments -R^{b1} and -R^{b1a} of formula (pE) are -H. In certain embodiments -R^{b1} and -R^{b1a} of formula (pE) are -H. In certain embodiments -R^{b2} and -R^{b2a} of formula (pE) are -H.
20 In certain embodiments -R^{b3} and -R^{b3a} of formula (pE) are -H. In certain embodiments -R^{b4} and -R^{b4a} of formula (pE) are -H. In certain embodiments -R^{b5} and -R^{b5a} of formula (pE) are -H. In certain embodiments -R^{b6} and -R^{b6a} of formula (pE) are -H.

In certain embodiments -R^{b1}, -R^{b1a}, -R^{b2}, -R^{b2a}, -R^{b3}, -R^{b3a}, -R^{b4}, -R^{b4a}, -R^{b5}, -R^{b5a}, -R^{b6} and -R^{b6}
25 of formula (pE) are all -H.

In certain embodiments c1 of formula (pE) is 1. In certain embodiments c1 of formula (pE) is 2. In certain embodiments c1 of formula (pE) is 3. In certain embodiments c1 of formula (pE) is 4. In certain embodiments c1 of formula (pE) is 5. In certain embodiments c1 of formula
30 (pE) is 6.

In certain embodiments c2 of formula (pE) is 1. In certain embodiments c2 of formula (pE) is 2. In certain embodiments c2 of formula (pE) is 3. In certain embodiments c2 of formula (pE) is 4. In certain embodiments c2 of formula (pE) is 5. In certain embodiments c2 of formula (pE) is 6.

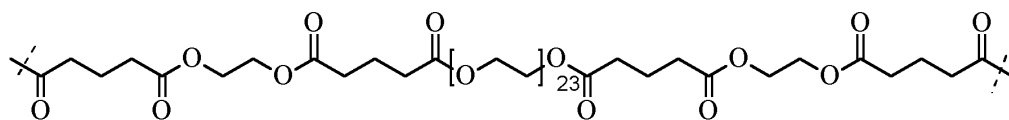
In certain embodiments c3 of formula (pE) is 1. In certain embodiments c3 of formula (pE) is 2. In certain embodiments c3 of formula (pE) is 3. In certain embodiments c3 of formula (pE) is 4. In certain embodiments c3 of formula (pE) is 5. In certain embodiments c3 of formula (pE) is 6.

In certain embodiments c4 of formula (pE) is 1. In certain embodiments c4 of formula (pE) is 2. In certain embodiments c4 of formula (pE) is 3. In certain embodiments c4 of formula (pE) is 4. In certain embodiments c4 of formula (pE) is 5. In certain embodiments c4 of formula (pE) is 6.

In certain embodiments c5 of formula (pE) is 1. In certain embodiments c5 of formula (pE) is 2. In certain embodiments c5 of formula (pE) is 3. In certain embodiments c5 of formula (pE) is 4. In certain embodiments c5 of formula (pE) is 5. In certain embodiments c5 of formula (pE) is 6.

In certain embodiments c6 of formula (pE) is 1. In certain embodiments c6 of formula (pE) is 2. In certain embodiments c6 of formula (pE) is 3. In certain embodiments c6 of formula (pE) is 4. In certain embodiments c6 of formula (pE) is 5. In certain embodiments c6 of formula (pE) is 6.

In certain embodiments a crosslinker moiety -CL^p- is of formula (pE-i)



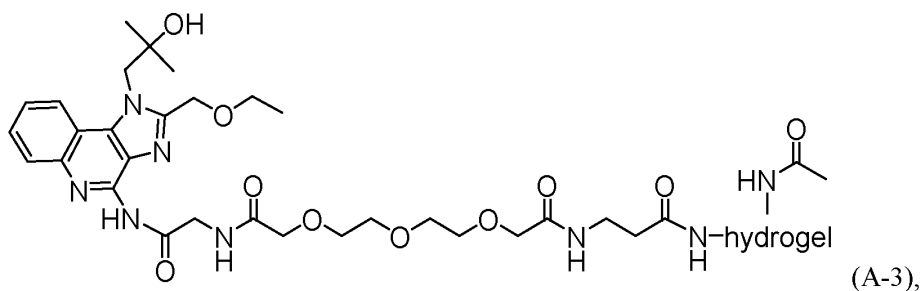
(pE-i),
30 wherein

dashed lines indicate attachment to a backbone moiety or to a spacer moiety -SP¹-.

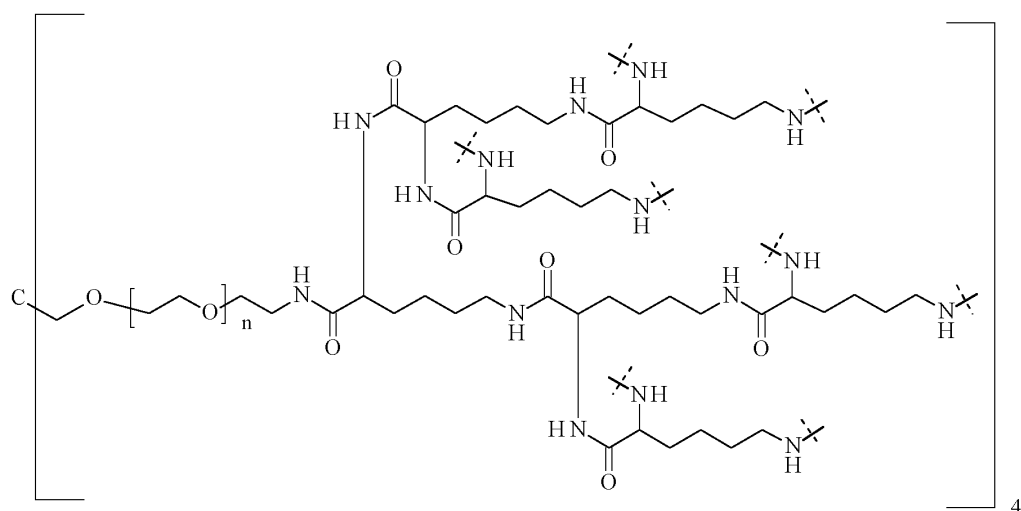
In certain embodiments -Z is a hyaluronic acid-based hydrogel. Such hyaluronic acid-based hydrogels are known in the art, such as for example from WO2018/175788, which is incorporated herewith by reference.

5

In certain embodiments the TLR7/8 agonist conjugate is of formula (A-3)



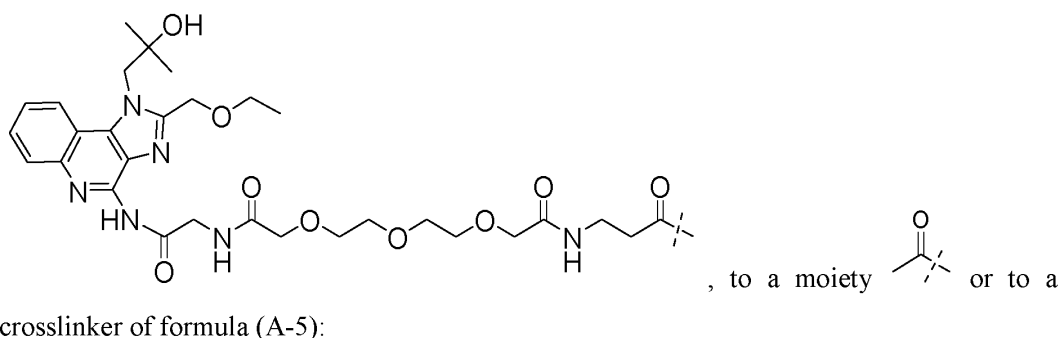
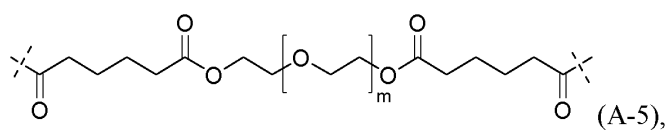
wherein “hydrogel” is a hydrogel comprising backbone moieties of formula (A-4):



10

(A-4),

wherein n ranges from approx. 25 to 29 and dashed lines indicate attachment to either a moiety



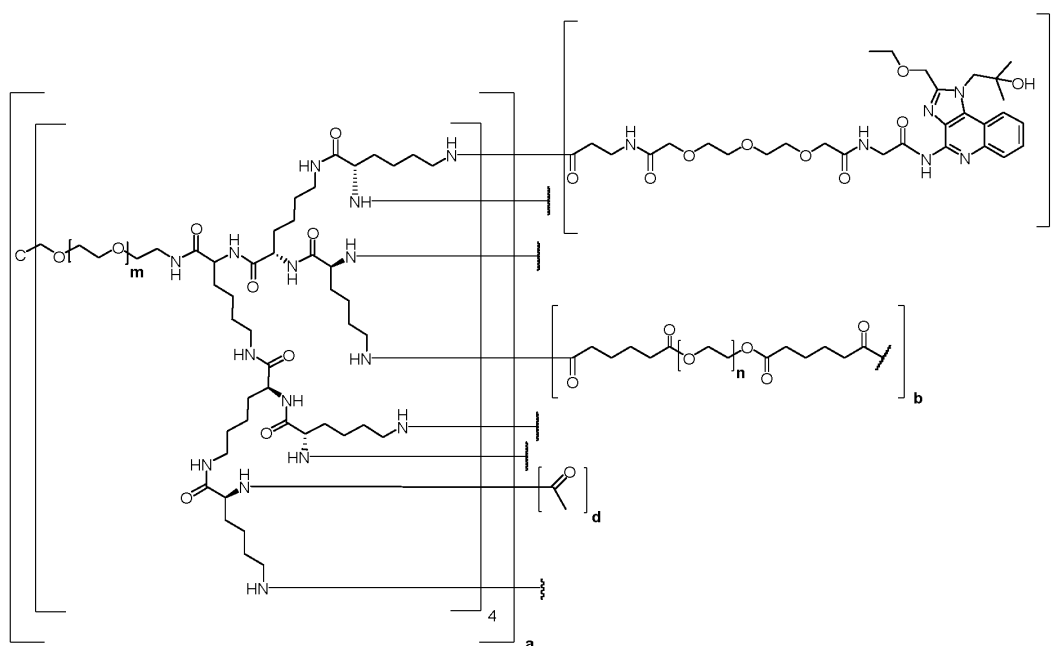
wherein m ranges from approx. 41 to 45 and the dashed lines in (A-5) indicate attachment to a backbone moiety of formula (A-4).

In certain embodiments n of formula (A-4) is approx. 28. In certain embodiments n of formula (A-5) is approx. 27.

In certain embodiments m of formula (A-5) is approx. 44. In certain embodiments m of formula (A-5) is approx. 45.

In certain embodiments n of formula (A-4) is approx. 28 and m of formula (A-5) is approx. 45.

In certain embodiments the TLR7/8 agonist conjugate is of formula (Ai-6):



(Ai-6),

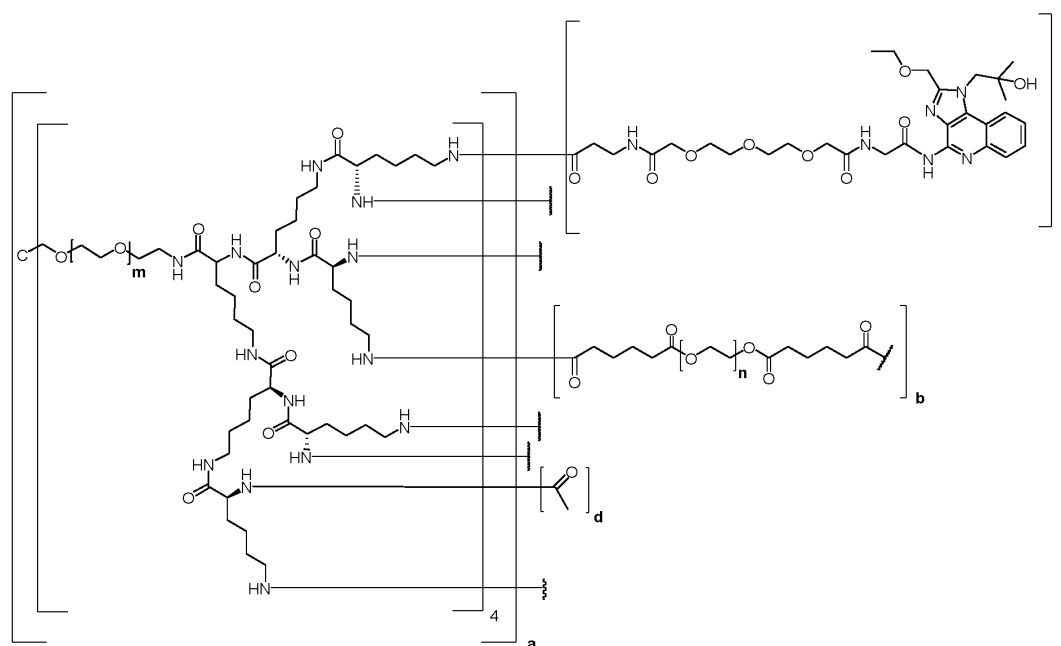
wherein

m ranges from approx. 25 to 29;

5 n ranges from approx. 41 to 45;

“a” denotes a backbone moiety, “b” denotes a crosslinker moiety, “c” denotes a reversibly conjugated resiquimod moiety and “d” denotes an acetamide moiety; and the ratio of moieties “a” : “b” : “c” : “d” in the conjugate is approx. 1:13:c:d with c + d = 6.

10 In certain embodiments the TLR7/8 agonist conjugate is of formula (A-6):



(A-6),

wherein

m ranges from approx. 25 to 29;

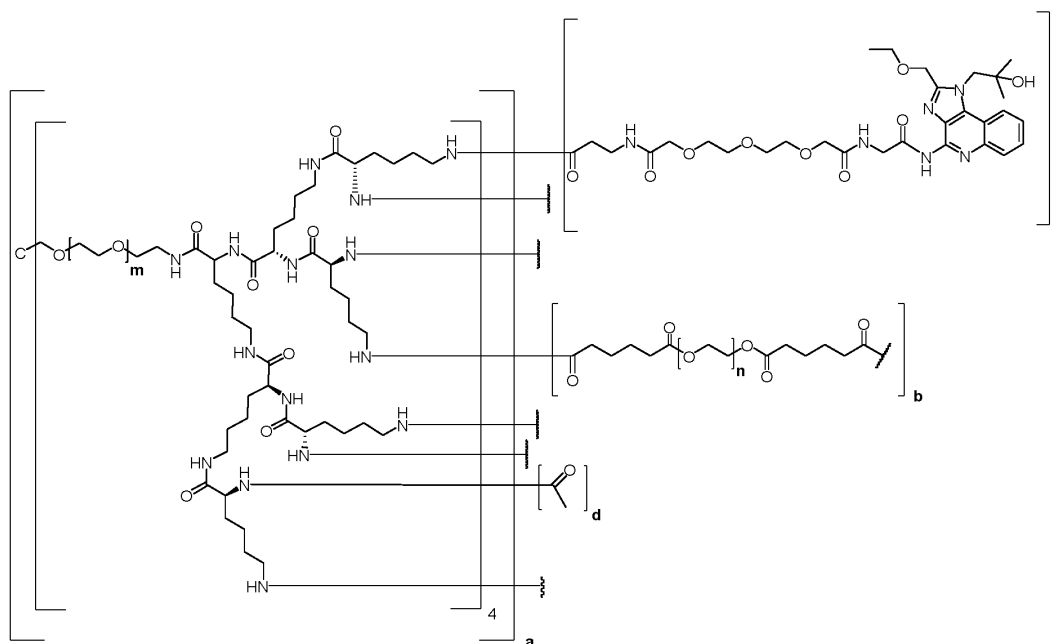
5 n ranges from approx. 41 to 45;

“a” denotes a backbone moiety, “b” denotes a crosslinker moiety, “c” denotes a reversibly conjugated resiquimod moiety and “d” denotes an acetamide moiety; and the ratio of moieties “a” : “b” : “c” : “d” in the conjugate is approx. 1:13:2:4.

10 It is understood that wavy lines indicate attachment to further moieties “b”, “c” or “d”, which for simplification were not shown.

In certain embodiments the ratio of “a” : “b” : “c” : “d” in (A-6) is approx. 1:13:2.4:3.6.

15 In certain embodiments the TLR7/8 agonist conjugate is of formula (A-7):



(A-7),

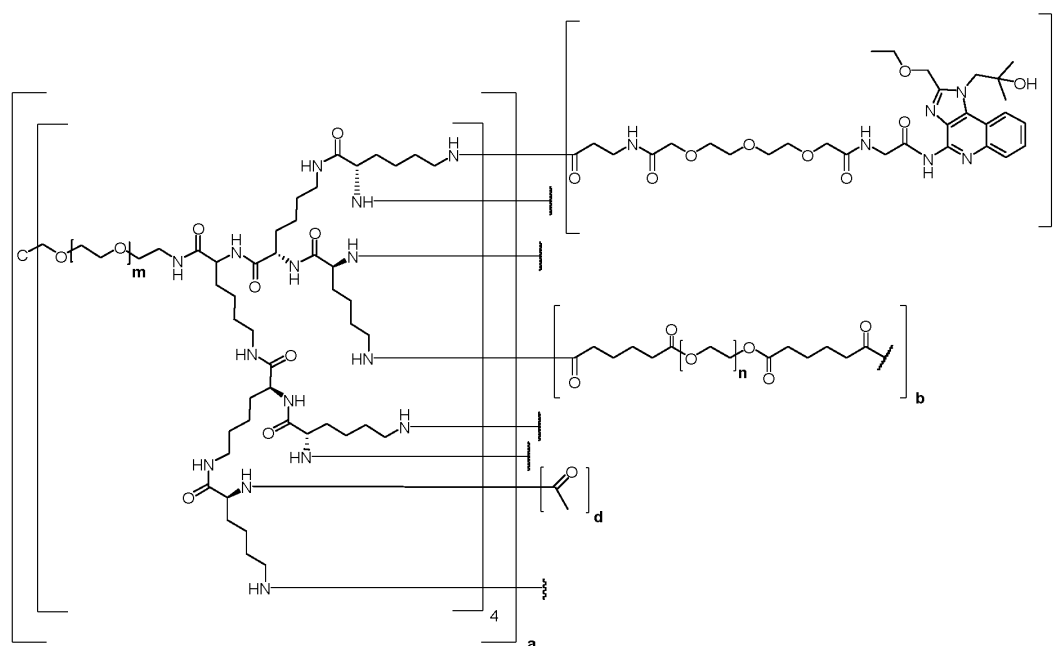
wherein

m ranges from approx. 25 to 29;

5 n ranges from approx. 41 to 45;

“a” denotes a backbone moiety, “b” denotes a crosslinker moiety, “c” denotes a reversibly conjugated resiquimod moiety and “d” denotes an acetamide moiety; and the ratio of moieties “a” : “b” : “c” : “d” in the conjugate is approx. 1:13:4:2.

10 In certain embodiments the TLR7/8 agonist conjugate is of formula (A-8):



(A-8),

wherein

m ranges from approx. 25 to 29;

5 n ranges from approx. 41 to 45;

“a” denotes a backbone moiety, “b” denotes a crosslinker moiety, “c” denotes a reversibly conjugated resiquimod moiety and “d” denotes an acetamide moiety; and the ratio of moieties “a” : “b” : “c” : “d” in the conjugate is approx. 1:13:3:3.

10 In a fourth aspect the present invention relates to a conjugate of formula (A-3).

In a fifth aspect the present invention relates to a conjugate of formula (A-6). In certain embodiments the conjugate of the fifth aspect as a ratio of “a” : “b” : “c” : “d” of approx. 1:13:2.4:3.6.

15

In a sixth aspect the present invention relates to a conjugate of formula (A-7).

In a seventh aspect the present invention relates to a conjugate of formula (A-8).

20 In an eighth aspect the present invention relates to a conjugate of formula (Ai-6).

In a ninth aspect the present invention relates to a pharmaceutical formulation comprising one or more TLR7/8 agonist conjugate of formula (Ai-6), (A-6), (A-7) or (A-8) or a pharmaceutically acceptable salt thereof. In certain embodiments such pharmaceutical formulation is a dry formulation, such as a lyophilized formulation. In certain embodiments
5 such pharmaceutical formulation is a suspension.

In certain embodiments the pharmaceutical formulation comprises the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof in a concentration ranging from 0.5 mg to 2 mg TLR7/8 agonist per ml. In certain embodiments the pharmaceutical formulation
10 comprises the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof in a concentration of 1 mg TLR7/8 agonist per ml. In certain embodiments the pharmaceutical formulation comprises the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof in a concentration of 2 mg TLR7/8 agonist per ml.

15 In certain embodiments the conjugate of the fourth, fifth, sixth, seventh or eighth aspect or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation of the ninth aspect is for use as a medicament. In certain embodiments such medicament is for the treatment of cancer, in particular a solid tumor. In certain embodiments such solid tumor is selected from the group consisting of lip and oral cavity cancer, oral cancer, liver cancer/hepatocellular
20 cancer, primary liver cancer, lung cancer, lymphoma, malignant mesothelioma, malignant thymoma, skin cancer, intraocular melanoma, metastatic squamous neck cancer with occult primary, childhood multiple endocrine neoplasia syndrome, mycosis fungoides, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, oropharyngeal cancer, ovarian cancer, pancreatic cancer, parathyroid cancer, pheochromocytoma, pituitary tumor,
25 adrenocortical carcinoma, AIDS-related malignancies, anal cancer, bile duct cancer, bladder cancer, brain and nervous system cancer, breast cancer, bronchial adenoma/carcinoid, gastrointestinal carcinoid tumor, carcinoma, colorectal cancer, endometrial cancer, esophageal cancer, extracranial germ cell tumor, extragonadal germ cell tumor, extrahepatic bile duct cancer, gallbladder cancer, gastric (stomach) cancer, gestational trophoblastic tumor, head and
30 neck cancer, hypopharyngeal cancer, islet cell carcinoma (endocrine pancreas), kidney cancer/renal cell cancer, laryngeal cancer, pleuropulmonary blastoma, prostate cancer, transitional cell cancer of the renal pelvis and ureter, retinoblastoma, salivary gland cancer, sarcoma, Sezary syndrome, small intestine cancer, genitourinary cancer, malignant thymoma, thyroid cancer, Wilms' tumor and cholangiocarcinoma.

In certain embodiments the solid tumor is selected from the group consisting of squamous cell carcinoma of the head and neck (SCCHN); HPV-associated cancers, such as anal, vulvar, cervical, penile and vaginal cancers; melanomas; pancreatic cancer and breast cancer, such as triple-negative breast cancer (TNBC). In certain embodiments the solid tumor is selected from the group consisting of pancreatic cancer, prostate cancer, melanoma, SCCHN, cutaneous squamous cell cancer (cSCC) and cervical cancer. In certain embodiments the solid tumor is a pancreatic cancer. In certain embodiments the solid tumor is prostate cancer. In certain embodiments the solid tumor is a melanoma. In certain embodiments the solid tumor is a SCCHN. In certain embodiments the solid tumor is a cSCC. In certain embodiments the solid tumor is cervical cancer. In certain embodiments the medicament is administered via intratumoral injection, such as by using a fanning technique.

In certain embodiments such medicament is administered to a patient at a dose ranging from 0.3 mg to 3 mg of TLR7/8 agonist per tumor. In certain embodiments such medicament is administered at a dose ranging from 0.3 mg to 3 mg of TLR7/8 agonist per tumor via intratumoral injection. In certain embodiment the medicament is administered at a dose of 0.5 mg of TLR7/8 agonist per tumor. In certain embodiment the medicament is administered at a dose of 0.5 mg of TLR7/8 agonist per tumor via intratumoral injection. In certain embodiment the medicament is administered at a dose of 1 mg of TLR7/8 agonist per tumor. In certain embodiment the medicament is administered at a dose of 1 mg of TLR7/8 agonist per tumor via intratumoral injection. In certain embodiments the medicament is administered using a fanning technique.

In certain embodiments the medicament is administered to a patient every two to four weeks. In certain embodiments the medicament is administered to a patient every three weeks. In certain embodiments the medicament is administered to a patient every two weeks. In certain embodiments the medicament is administered to a patient every four weeks.

In certain embodiments the medicament is administered to a patient every five weeks. In certain embodiments the medicament is administered to a patient every six weeks. In certain embodiments the medicament is administered to a patient every seven weeks. In certain embodiments the medicament is administered to a patient every eight weeks. In certain embodiments the medicament is administered to a patient every nine weeks. In certain

embodiments the medicament is administered to a patient every ten weeks. In certain
embodiments the medicament is administered to a patient every twelve weeks. In certain
embodiments the medicament is administered to a patient every six months. In certain
embodiments the medicament is administered to a patient every seven months. In certain
5 embodiments the medicament is administered to a patient every eight months. In certain
embodiments the medicament is administered to a patient every nine months. In certain
embodiments the medicament is administered to a patient every ten months. In certain
embodiments the medicament is administered to a patient every eleven months. In certain
embodiments the medicament is administered to a patient once a year. In certain embodiments
10 the medicament is administered to a patient at a frequency dependent on disease progression.

In certain embodiments the medicament is administered to one tumor of the patient. In certain
embodiments the medicament is administered to more than one tumor of the patient, such as to
two tumors, three tumors, four tumors or five tumors or to all tumors of a patient that have a
15 sufficient size and are accessible for treatment. In certain embodiments treatment of one tumor
leads to an abscopal effect in one or more untreated tumors.

In certain embodiments the medicament is administered to a patient in a cotreatment with an
inhibitor of PD-1 or an inhibitor of PD-L1, which may be given prior to, together with or after
20 administration of the medicament.

In certain embodiments the medicament is administered to a patient in a cotreatment with an
inhibitor of PD-1, which may be given prior to, together with or after administration of the
medicament. An inhibitor of PD-1 may be selected from the group consisting of
25 pembrolizumab, nivolumab, pidilizumab, AMP-224, BMS-936559, cemiplimab and PDR001.
An inhibitor of PD-L1 may be selected from the group consisting of MDX-1105, MEDI4736,
atezolizumab, avelumab, BMS-936559 and durvalumab. In certain embodiments the inhibitor
of PD-1 is pembrolizumab. Details regarding the administration of pembrolizumab are as
described elsewhere herein.

30 In certain embodiments the medicament is provided in a vial. Such vial may be a vial with a
stopper, such as a bromo-butyl stopper, and a seal cap, such as an aluminium seal cap. In certain
embodiments the vial is a glass vial, such as a type 1 glass vial. Such a vial may have a size of
1 ml, 2 ml or 5 ml, for example. In certain embodiments the vial has a size of 2 ml. In certain

embodiments the vial has a size of 1 ml. In certain embodiments the vial has a size of 5 ml. In certain embodiments such vial comprises a unit dose. Such unit dose comprises in certain embodiments 0.5 mg of TLR7/8 agonist. In certain embodiments the unit dose is a liquid, such as a suspension, which has a volume ranging from 0.1 to 1.5 ml. In certain embodiments the unit dose is provided as a suspension and has a volume of 0.5 ml.

Embodiments for the tumor to which the medicament is administered are as described elsewhere herein.

In certain embodiments the conjugate of the fourth, fifth, sixth, seventh or eighth aspect or the pharmaceutical formulation of the ninth aspect is for use in the treatment of cancer, such as of a solid tumor.

In certain embodiments such solid tumor is selected from the group consisting of lip and oral cavity cancer, oral cancer, liver cancer/hepatocellular cancer, primary liver cancer, lung cancer, lymphoma, malignant mesothelioma, malignant thymoma, skin cancer, intraocular melanoma, metastatic squamous neck cancer with occult primary, childhood multiple endocrine neoplasia syndrome, mycosis fungoides, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, oropharyngeal cancer, ovarian cancer, pancreatic cancer, parathyroid cancer, pheochromocytoma, pituitary tumor, adrenocortical carcinoma, AIDS-related malignancies, anal cancer, bile duct cancer, bladder cancer, brain and nervous system cancer, breast cancer, bronchial adenoma/carcinoid, gastrointestinal carcinoid tumor, carcinoma, colorectal cancer, endometrial cancer, esophageal cancer, extracranial germ cell tumor, extragonadal germ cell tumor, extrahepatic bile duct cancer, gallbladder cancer, gastric (stomach) cancer, gestational trophoblastic tumor, head and neck cancer, hypopharyngeal cancer, islet cell carcinoma (endocrine pancreas), kidney cancer/renal cell cancer, laryngeal cancer, pleuropulmonary blastoma, prostate cancer, transitional cell cancer of the renal pelvis and ureter, retinoblastoma, salivary gland cancer, sarcoma, Sezary syndrome, small intestine cancer, genitourinary cancer, malignant thymoma, thyroid cancer, Wilms' tumor and cholangiocarcinoma.

In certain embodiments the solid tumor is selected from the group consisting of squamous cell carcinoma of the head and neck (SCCHN); HPV-associated cancers, such as anal, vulvar, cervical, penile and vaginal cancers; melanomas; pancreatic cancer and breast cancer, such as triple-negative breast cancer (TNBC). In certain embodiments the solid tumor is selected from

the group consisting of pancreatic cancer, prostate cancer, melanoma, SCCHN, cutaneous squamous cell cancer (cSCC) and cervical cancer. In certain embodiments the solid tumor is a pancreatic cancer. In certain embodiments the solid tumor is prostate cancer. In certain embodiments the solid tumor is a melanoma. In certain embodiments the solid tumor is a SCCHN. In certain embodiments the solid tumor is a cSCC. In certain embodiments the solid tumor is cervical cancer. In certain embodiments the medicament is administered via intratumoral injection, such as by using a fanning technique.

In certain embodiments the conjugate of the fourth, fifth, sixth, seventh or eighth aspect or the pharmaceutical formulation of the ninth aspect is for use in the treatment of cancer, such as a solid tumor, and is administered at a dose ranging from 0.3 mg to 3 mg of TLR7/8 agonist per tumor, such as at a dose of 0.5 mg of TLR7/8 agonist per tumor. In certain embodiments administration is a dose of 1 mg of TLR7/8 agonist per tumor. In certain embodiments administration is a dose of 2 mg of TLR7/8 agonist per tumor.

In certain embodiments the conjugate of the fourth, fifth, sixth or seventh aspect or the pharmaceutical formulation of the eighth aspect is for use in the treatment of cancer and is administered to a patient every two to four weeks, such as for example every three weeks. In certain embodiments administration of the conjugate or the pharmaceutical formulation to a patient occurs every two weeks. In certain embodiments administration of the conjugate or the pharmaceutical formulation to a patient occurs every four weeks.

In certain embodiments administration of the conjugate or the pharmaceutical formulation to a patient occurs every five weeks. In certain embodiments administration of the conjugate or the pharmaceutical formulation to a patient occurs every six weeks. In certain embodiments administration of the conjugate or the pharmaceutical formulation to a patient occurs every seven weeks. In certain embodiments administration of the conjugate or the pharmaceutical formulation to a patient occurs every eight weeks. In certain embodiments administration of the conjugate or the pharmaceutical formulation to a patient occurs every nine weeks. In certain embodiments administration of the conjugate or the pharmaceutical formulation to a patient occurs every ten weeks. In certain embodiments administration of the conjugate or the pharmaceutical formulation to a patient occurs every twelve weeks. In certain embodiments administration of the conjugate or the pharmaceutical formulation to a patient occurs every six months. In certain administration of the conjugate or

the pharmaceutical formulation to a patient occurs every seven months. In certain embodiments administration of the conjugate or the pharmaceutical formulation to a patient occurs every eight months. In certain embodiments administration of the conjugate or the pharmaceutical formulation to a patient occurs every nine months. In certain embodiments administration of the conjugate or the pharmaceutical formulation to a patient occurs every ten months. In certain
5 embodiments administration of the conjugate or the pharmaceutical formulation to a patient occurs every eleven months. In certain embodiments administration of the conjugate or the pharmaceutical formulation to a patient occurs once a year. In certain embodiments administration of the conjugate or the pharmaceutical formulation to a patient occurs at a
10 frequency dependent on disease progression.

In certain embodiments the conjugate of the fourth, fifth, sixth, seventh or eighth aspect or the pharmaceutical formulation of the ninth aspect is for use in the treatment of cancer and the conjugate or the pharmaceutical formulation is administered to one tumor of a patient. In
15 certain embodiments the conjugate of the fourth, fifth, sixth, seventh or eighth aspect or the pharmaceutical formulation of the ninth aspect is for use in the treatment of cancer and the conjugate or the pharmaceutical formulation is administered to more than one tumor of the patient, such as to two tumors, three tumors, four tumors or five tumors or to all tumors of a patient that have a sufficient size and are accessible for treatment. In certain embodiments
20 treatment of one tumor leads to an abscopal effect in one or more untreated tumors.

In certain embodiments the conjugate of the fourth, fifth, sixth, seventh or eighth aspect or the pharmaceutical formulation of the ninth aspect is for use in the treatment of cancer and the treatment is a cotreatment with an inhibitor of PD-1 or an inhibitor of PD-L1, which may be
25 given prior to, together with or after administration of the conjugate or the pharmaceutical formulation. In certain embodiments the treatment is a cotreatment with an inhibitor of PD-1, which may be given prior to, together with or after administration of the conjugate or the pharmaceutical formulation. Such inhibitor of PD-1 may be selected from the group consisting of pembrolizumab, nivolumab, pidilizumab, AMP-224, BMS-936559, cemiplimab and
30 PDR001 and is in certain embodiments pembrolizumab. Details regarding the administration of pembrolizumab are as described elsewhere herein.

In certain embodiments the conjugate of the fourth, fifth, sixth, seventh or eighth aspect or the pharmaceutical formulation of the ninth aspect is for use in the treatment of cancer and the

TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation is provided in a vial. Such vial may be a vial with a stopper, such as a bromo-butyl stopper, and a seal cap, such as an aluminium seal cap. In certain embodiments the vial is a glass vial, such as a type 1 glass vial. Such a vial may have a size of 1 ml, 2 ml or 5 ml, for example. In certain embodiments the vial has a size of 2 ml. In certain embodiments the vial has a size of 1 ml. In certain embodiments the vial has a size of 5 ml. In certain embodiments such vial comprises a unit dose.

In certain embodiments the conjugate of the fourth, fifth, sixth, seventh or eighth aspect or the pharmaceutical formulation of the ninth aspect is administered at a dose ranging from 0.3 mg to 3 mg per tumor and said dose is provided in a volume ranging from 0.1 ml to 2 ml. In certain embodiments the conjugate of the fourth, fifth, sixth, seventh or eighth aspect or the pharmaceutical formulation of the ninth aspect is administered at a dose ranging from 0.3 mg to 3 mg per tumor and said dose is provided in a volume ranging from 0.2 ml to 1.5 ml. In certain embodiments the conjugate of the fourth, fifth, sixth, seventh or eighth aspect or the pharmaceutical formulation of the ninth aspect is administered at a dose ranging from 0.3 mg to 3 mg per tumor and said dose is provided of 0.25 ml. In certain embodiments the conjugate of the fourth, fifth, sixth, seventh or eighth aspect or the pharmaceutical formulation of the ninth aspect is administered at a dose ranging from 0.3 mg to 3 mg per tumor and said dose is provided in a volume of 0.5 ml. In certain embodiments the conjugate of the fourth, fifth, sixth, seventh or eighth aspect or the pharmaceutical formulation of the ninth aspect is administered at a dose ranging from 0.3 mg to 3 mg per tumor and said dose is provided in a volume of 1 ml.

In certain embodiments the conjugate of the fourth, fifth, sixth, seventh or eighth aspect or the pharmaceutical formulation of the ninth aspect is administered at a dose 0.5 mg per tumor and said dose is provided in a volume ranging from 0.1 ml to 2 ml. In certain embodiments the conjugate of the fourth, fifth, sixth, seventh or eighth aspect or the pharmaceutical formulation of the ninth aspect is administered at a dose of 0.5 mg per tumor and said dose is provided in a volume ranging from 0.2 ml to 1.5 ml. In certain embodiments the conjugate of the fourth, fifth, sixth, seventh or eighth aspect or the pharmaceutical formulation of the ninth aspect is administered at a dose of 0.5 mg per tumor and said dose is provided of 0.25 ml. In certain embodiments the conjugate of the fourth, fifth, sixth, seventh or eighth aspect or the pharmaceutical formulation of the ninth aspect is administered at a dose of 0.5 mg per tumor

and said dose is provided in a volume of 0.5 ml. In certain embodiments the conjugate of the fourth, fifth, sixth, seventh or eighth aspect or the pharmaceutical formulation of the ninth aspect is administered at a dose of 0.5 mg per tumor and said dose is provided in a volume of 1 ml.

5

In certain embodiments the conjugate of the fourth, fifth, sixth, seventh or eighth aspect or the pharmaceutical formulation of the ninth aspect is administered at a dose 1 mg per tumor and said dose is provided in a volume ranging from 0.1 ml to 2 ml. In certain embodiments the conjugate of the fourth, fifth, sixth, seventh or eighth aspect or the pharmaceutical

10 formulation of the ninth aspect is administered at a dose of 1 mg per tumor and said dose is

provided in a volume ranging from 0.2 ml to 1.5 ml. In certain embodiments the conjugate of the fourth, fifth, sixth, seventh or eighth aspect or the pharmaceutical formulation of the ninth aspect is administered at a dose of 1 mg per tumor and said dose is provided of 0.25 ml. In

15 certain embodiments the conjugate of the fourth, fifth, sixth, seventh or eighth aspect or the pharmaceutical formulation of the ninth aspect is administered at a dose of 1 mg per tumor and

said dose is provided in a volume of 0.5 ml. In certain embodiments the conjugate of the fourth, fifth, sixth, seventh or eighth aspect or the pharmaceutical formulation of the ninth aspect is administered at a dose of 1 mg per tumor and said dose is provided in a volume of 1 ml.

20 In certain embodiments the conjugate of the fourth, fifth, sixth or seventh aspect is for use in the treatment of a solid tumor, wherein the conjugate is administered via intratumoral injection using a fanning technique at a dose of 0.5 mg per tumor.

25 In certain embodiments the conjugate of the fourth, fifth, sixth, seventh or eighth aspect or the pharmaceutical formulation of the ninth aspect is for use in the treatment of a solid tumor, wherein the conjugate is administered every three weeks via intratumoral injection at a dose of 0.5 mg per tumor.

30 In certain embodiments the conjugate of the fourth, fifth, sixth, seventh or eighth aspect or the pharmaceutical formulation of the ninth aspect is for use in the treatment of a solid tumor, wherein the conjugate is administered via intratumoral injection at a dose of 0.5 mg per tumor and wherein the treatment is a cotreatment with pembrolizumab.

In certain embodiments the conjugate the fourth, fifth, sixth, seventh or eighth aspect or the pharmaceutical formulation of the ninth aspect is for use in the treatment of a solid tumor, wherein the conjugate is administered via intratumoral injection at a dose of 0.5 mg per tumor and wherein the treatment is a cotreatment with pembrolizumab, wherein pembrolizumab is administered every three weeks, either prior to, together with or after administration of the conjugate of the fourth, fifth, sixth, seventh or eighth aspect or the pharmaceutical formulation of the ninth aspect.

In certain embodiments the conjugate of the fourth, fifth, sixth, seventh or eighth aspect or the pharmaceutical formulation of the ninth aspect is for use in the treatment of a solid tumor, wherein the conjugate is administered via intratumoral injection at a dose of 0.5 mg per tumor and wherein the treatment is a cotreatment with pembrolizumab, wherein pembrolizumab is administered every three weeks via intravenous injection at a dose of 200 mg, either prior to, together with or after administration of the conjugate of the fourth, fifth, sixth, seventh or eighth aspect or the pharmaceutical formulation of the ninth aspect.

In certain embodiments the conjugate of the fourth, fifth, sixth, seventh or eighth aspect or the pharmaceutical formulation of the ninth aspect is for use in the treatment of a solid tumor, wherein the conjugate is administered via intratumoral injection using a fanning technique at a dose of 0.5 mg per tumor and wherein the treatment is a cotreatment with pembrolizumab, wherein pembrolizumab is administered every three weeks via intravenous injection at a dose of 200 mg, either prior to, together with or after administration of the conjugate the fourth, fifth, sixth, seventh or eighth aspect or the pharmaceutical formulation of the ninth aspect.

In certain embodiments the conjugates of fourth, fifth, sixth, seventh or eighth aspect or the pharmaceutical formulation of the ninth aspect are for use in the manufacture of a medicament. In certain embodiments the medicament is for the treatment of cancer, such as for the treatment of a solid tumor.

In certain embodiments such solid tumor is selected from the group consisting of lip and oral cavity cancer, oral cancer, liver cancer/hepatocellular cancer, primary liver cancer, lung cancer, lymphoma, malignant mesothelioma, malignant thymoma, skin cancer, intraocular melanoma, metastatic squamous neck cancer with occult primary, childhood multiple endocrine neoplasia syndrome, mycosis fungoides, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer,

neuroblastoma, oropharyngeal cancer, ovarian cancer, pancreatic cancer, parathyroid cancer, pheochromocytoma, pituitary tumor, adrenocortical carcinoma, AIDS-related malignancies, anal cancer, bile duct cancer, bladder cancer, brain and nervous system cancer, breast cancer, bronchial adenoma/carcinoid, gastrointestinal carcinoid tumor, carcinoma, colorectal cancer, endometrial cancer, esophageal cancer, extracranial germ cell tumor, extragonadal germ cell tumor, extrahepatic bile duct cancer, gallbladder cancer, gastric (stomach) cancer, gestational trophoblastic tumor, head and neck cancer, hypopharyngeal cancer, islet cell carcinoma (endocrine pancreas), kidney cancer/renal cell cancer, laryngeal cancer, pleuropulmonary blastoma, prostate cancer, transitional cell cancer of the renal pelvis and ureter, retinoblastoma, salivary gland cancer, sarcoma, Sezary syndrome, small intestine cancer, genitourinary cancer, malignant thymoma, thyroid cancer, Wilms' tumor and cholangiocarcinoma.

In certain embodiments the solid tumor is selected from the group consisting of squamous cell carcinoma of the head and neck (SCCHN); HPV-associated cancers, such as anal, vulvar, cervical, penile and vaginal cancers; melanomas; pancreatic cancer and breast cancer, such as triple-negative breast cancer (TNBC). In certain embodiments the solid tumor is selected from the group consisting of pancreatic cancer, prostate cancer, melanoma, SCCHN, cutaneous squamous cell cancer (cSCC) and cervical cancer. In certain embodiments the solid tumor is a pancreatic cancer. In certain embodiments the solid tumor is prostate cancer. In certain embodiments the solid tumor is a melanoma. In certain embodiments the solid tumor is a SCCHN. In certain embodiments the solid tumor is a cSCC. In certain embodiments the solid tumor is cervical cancer. In certain embodiments the medicament is administered via intratumoral injection, such as by using a fanning technique.

In certain embodiments such medicament is administered to a patient at a dose ranging from 0.3 mg to 3 mg of TLR7/8 agonist per tumor. In certain embodiments such medicament is administered at a dose ranging from 0.3 mg to 3 mg of TLR7/8 agonist per tumor via intratumoral injection. In certain embodiment the medicament is administered at a dose of 0.5 mg of TLR7/8 agonist per tumor. In certain embodiment the medicament is administered at a dose of 0.5 mg of TLR7/8 agonist per tumor via intratumoral injection. In certain embodiment the medicament is administered at a dose of 1 mg of TLR7/8 agonist per tumor. In certain embodiment the medicament is administered at a dose of 1 mg of TLR7/8 agonist per tumor via intratumoral injection. In certain embodiments the medicament is administered via

intratumoral injection. In certain embodiments the medicament is administered using a fanning technique.

In certain embodiments the medicament is administered to a patient every two to four weeks.

- 5 In certain embodiments the medicament is administered to a patient every three weeks. In certain embodiments the medicament is administered to a patient every two weeks. In certain embodiments the medicament is administered to a patient every four weeks.

- 10 In certain embodiments the medicament is administered to a patient every five weeks. In certain embodiments the medicament is administered to a patient every six weeks. In certain embodiments the medicament is administered to a patient every seven weeks. In certain embodiments the medicament is administered to a patient every eight weeks. In certain embodiments the medicament is administered to a patient every nine weeks. In certain
15 embodiments the medicament is administered to a patient every ten weeks. In certain embodiments the medicament is administered to a patient every twelve weeks. In certain embodiments the medicament is administered to a patient every six months. In certain embodiments the medicament is administered to a patient every seven months. In certain embodiments the medicament is administered to a patient every eight months. In certain
20 embodiments the medicament is administered to a patient every nine months. In certain embodiments the medicament is administered to a patient every ten months. In certain embodiments the medicament is administered to a patient every eleven months. In certain embodiments the medicament is administered to a patient once a year. In certain embodiments the medicament is administered to a patient at a frequency dependent on disease progression.

- 25 In certain embodiments the medicament is administered to one tumor of the patient. In certain embodiments the medicament is administered to more than one tumor of the patient, such as to two tumors, three tumors, four tumors or five tumors or to all tumors of a patient that have a sufficient size and are accessible for treatment. In certain embodiments treatment of one tumor leads to an abscopal effect in one or more untreated tumors.

30

In certain embodiments the medicament is administered to a patient in a cotreatment with an inhibitor of PD-1 or an inhibitor of PD-L1, which may be given prior to, together with or after administration of the medicament.

- In certain embodiments the medicament is administered to a patient in a cotreatment with an inhibitor of PD-1, which may be given prior to, together with or after administration of the medicament. An inhibitor of PD-1 may be selected from the group consisting of pembrolizumab, nivolumab, pidilizumab, AMP-224, BMS-936559, cemiplimab and PDR001.
- 5 An inhibitor of PD-L1 may be selected from the group consisting of MDX-1105, MEDI4736, atezolizumab, avelumab, BMS-936559 and durvalumab. In certain embodiments the inhibitor of PD-1 is pembrolizumab. Details regarding the administration of pembrolizumab are as described elsewhere herein.
- 10 In certain embodiments the medicament is provided in a vial. Such vial may be a vial with a stopper, such as a bromo-butyl stopper, and a seal cap, such as an aluminium seal cap. In certain embodiments the vial is a glass vial, such as a type 1 glass vial. Such a vial may have a size of 1 ml, 2 ml or 5 ml, for example. In certain embodiments the vial has a size of 2 ml. In certain embodiments the vial has a size of 1 ml. In certain embodiments the vial has a size of 5 ml.
- 15 In certain embodiments such vial comprises a unit dose. Such unit dose comprises in certain embodiments 0.5 mg of TLR7/8 agonist. In certain embodiments the unit dose is a liquid, such as a suspension, which has a volume ranging from 0.1 to 1.5 ml. In certain embodiments the unit dose is provided as a suspension and has a volume of 0.5 ml.
- 20 In another aspect the present invention relates to a method of treating a patient having cancer, wherein the method comprises the step of administering a pharmaceutically effective amount of the TLR7/8 agonist conjugate of the fourth, fifth, sixth, seventh or eighth aspect or the pharmaceutical formulation of the ninth aspect to the patient. In certain embodiments the cancer is a solid tumor. In certain embodiments the cancer is selected from the group consisting of
- 25 lip and oral cavity cancer, oral cancer, liver cancer/hepatocellular cancer, primary liver cancer, lung cancer, lymphoma, malignant mesothelioma, malignant thymoma, skin cancer, intraocular melanoma, metastatic squamous neck cancer with occult primary, childhood multiple endocrine neoplasia syndrome, mycosis fungoides, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, oropharyngeal cancer, ovarian cancer,
- 30 pancreatic cancer, parathyroid cancer, pheochromocytoma, pituitary tumor, adrenocortical carcinoma, AIDS-related malignancies, anal cancer, bile duct cancer, bladder cancer, brain and nervous system cancer, breast cancer, bronchial adenoma/carcinoid, gastrointestinal carcinoid tumor, carcinoma, colorectal cancer, endometrial cancer, esophageal cancer, extracranial germ cell tumor, extragonadal germ cell tumor, extrahepatic bile duct cancer, gallbladder cancer,

gastric (stomach) cancer, gestational trophoblastic tumor, head and neck cancer, hypopharyngeal cancer, islet cell carcinoma (endocrine pancreas), kidney cancer/renal cell cancer, laryngeal cancer, pleuropulmonary blastoma, prostate cancer, transitional cell cancer of the renal pelvis and ureter, retinoblastoma, salivary gland cancer, sarcoma, Sezary syndrome, small intestine cancer, genitourinary cancer, malignant thymoma, thyroid cancer, Wilms' tumor and cholangiocarcinoma.

In certain embodiments the solid tumor is selected from the group consisting of squamous cell carcinoma of the head and neck (SCCHN); HPV-associated cancers, such as anal, vulvar, cervical, penile and vaginal cancers; melanomas; pancreatic cancer and breast cancer, such as triple-negative breast cancer (TNBC). In certain embodiments the solid tumor is selected from the group consisting of pancreatic cancer, prostate cancer, melanoma, SCCHN, cutaneous squamous cell cancer (cSCC) and cervical cancer. In certain embodiments the solid tumor is a pancreatic cancer. In certain embodiments the solid tumor is prostate cancer. In certain embodiments the solid tumor is a melanoma. In certain embodiments the solid tumor is a SCCHN. In certain embodiments the solid tumor is a cSCC. In certain embodiments the solid tumor is cervical cancer. In certain embodiments the medicament is administered via intratumoral injection, such as by using a fanning technique.

In certain embodiments the conjugate of the fourth, fifth, sixth, seventh or eighth aspect or the pharmaceutical formulation of the ninth aspect is administered to the patient at a dose ranging from 0.3 mg to 3 mg of TLR7/8 agonist per tumor, such as at a dose of 0.5 mg of TLR7/8 agonist per tumor. In certain embodiments administration is a dose of 1 mg of TLR7/8 agonist per tumor. In certain embodiments administration is a dose of 2 mg of TLR7/8 agonist per tumor. Such dose is a pharmaceutically effective amount or pharmaceutically effective dose.

In certain embodiments the conjugate of the fourth, fifth, sixth or seventh aspect or the pharmaceutical formulation of the eighth aspect is for use in the treatment of cancer and is administered to the patient every two to four weeks, such as for example every three weeks. In certain embodiments administration of the conjugate or the pharmaceutical formulation to the patient occurs every two weeks. In certain embodiments administration of the conjugate or the pharmaceutical formulation to the patient occurs every four weeks.

In certain embodiments administration of the conjugate or the pharmaceutical formulation to the patient occurs every five weeks. In certain embodiments administration of the conjugate or the pharmaceutical formulation to the patient occurs every six weeks. In certain embodiments administration of the conjugate or the pharmaceutical formulation to the patient occurs every
5 every seven weeks. In certain embodiments administration of the conjugate or the pharmaceutical formulation to the patient occurs every every eight weeks. In certain embodiments administration of the conjugate or the pharmaceutical formulation to the patient occurs every nine weeks. In certain embodiments administration of the conjugate or the pharmaceutical formulation to the patient occurs every ten weeks. In certain embodiments
10 administration of the conjugate or the pharmaceutical formulation to a patient occurs every twelve weeks. In certain embodiments administration of the conjugate or the pharmaceutical formulation to the patient occurs every six months. In certain administration of the conjugate or the pharmaceutical formulation to the patient occurs every seven months. In certain embodiments administration of the conjugate or the pharmaceutical formulation to the patient
15 occurs every eight months. In certain embodiments administration of the conjugate or the pharmaceutical formulation to the patient occurs every nine months. In certain embodiments administration of the conjugate or the pharmaceutical formulation to the patient occurs every ten months. In certain embodiments administration of the conjugate or the pharmaceutical formulation to the patient occurs every eleven months. In certain embodiments administration
20 of the conjugate or the pharmaceutical formulation to the patient occurs once a year. In certain embodiments administration of the conjugate or the pharmaceutical formulation to the patient occurs at a frequency dependent on disease progression.

In certain embodiments the conjugate of the fourth, fifth, sixth, seventh or eighth aspect or the
25 pharmaceutical formulation of the ninth aspect is administered to one tumor of the patient. In certain embodiments the conjugate of the fourth, fifth, sixth, seventh or eighth aspect or the pharmaceutical formulation of the ninth aspect is administered to more than one tumor of the patient, such as to two tumors, three tumors, four tumors or five tumors or to all tumors of the patient that have a sufficient size and are accessible for treatment. In certain embodiments
30 treatment of one tumor leads to an abscopal effect in one or more untreated tumors.

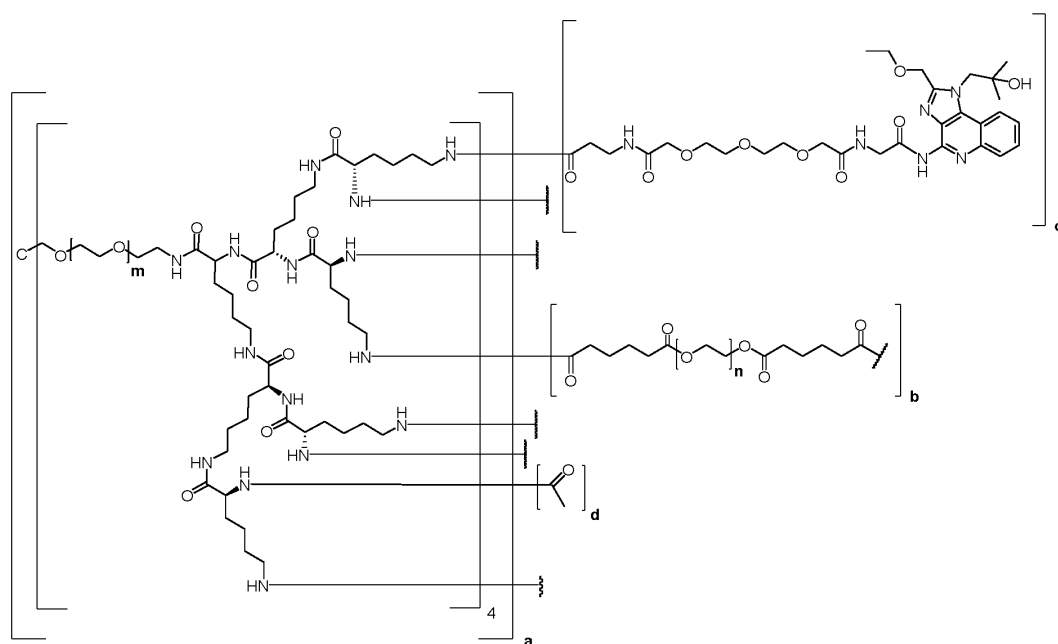
In certain embodiments the method of treatment is a cotreatment with an inhibitor of PD-1 or an inhibitor of PD-L1, which may be given prior to, together with or after administration of the conjugate or the pharmaceutical formulation. In certain embodiments the method is a

cotreatment with an inhibitor of PD-1, which may be given prior to, together with or after administration of the conjugate or the pharmaceutical formulation. Such inhibitor of PD-1 may be selected from the group consisting of pembrolizumab, nivolumab, pidilizumab, AMP-224, BMS-936559, cemiplimab and PDR001 and is in certain embodiments pembrolizumab. Details regarding the administration of pembrolizumab are as described elsewhere herein.

- In certain embodiments the conjugate of the fourth, fifth, sixth, seventh or eighth aspect or the pharmaceutical formulation of the ninth aspect is provided in a vial. Such vial may be a vial with a stopper, such as a bromo-butyl stopper, and a seal cap, such as an aluminium seal cap.
- 10 In certain embodiments the vial is a glass vial, such as a type 1 glass vial. Such a vial may have a size of 1 ml, 2 ml or 5 ml, for example. In certain embodiments the vial has a size of 2 ml. In certain embodiments the vial has a size of 1 ml. In certain embodiments the vial has a size of 5 ml. In certain embodiments such vial comprises a unit dose.
- 15 In a further aspect the present invention relates to a TLR7/8 agonist conjugate for use in the treatment of cancer, in particular of a solid tumor, wherein administration of a pharmaceutically effective dose leads to a plasma concentration of the TLR7/8 agonist of less than 4000 pg/ml, such as of less than 2000 pg/ml, of less than 1000 pg/ml, of less than 750 pg/ml or of less than 500 pg/ml. In certain embodiments the TLR7/8 agonist conjugate is administered via
- 20 intratumoral injection, such as by using a fanning technique. In certain embodiments the TLR7/8 agonist conjugate is administered at a dose ranging from 0.3 to 3 mg of the TLR7/8 agonist, such as at a dose of 0.5 mg of TLR7/8 agonist or 1 mg of TLR7/8 agonist. In certain embodiments the TLR7/8 agonist conjugate is administered to a patient every 2 to 4 weeks, such as every 3 weeks. In certain embodiments the TLR7/8 agonist conjugate is administered
- 25 in a cotreatment with an inhibitor of PD-1 or PD-L1, such as pembrolizumab.

The TLR7/8 agonist conjugate, examples for solid tumors, doses, administration frequencies, volumes and details regarding the cotreatment are as described elsewhere herein.

- 30 (01) A TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof of formula (Ai-6):



(Ai-6),

wherein

m ranges from approx. 25 to 29;

5 n ranges from approx. 41 to 45;

“a” denotes a backbone moiety, “b” denotes a crosslinker moiety, “c” denotes a reversibly conjugated resiquimod moiety and “d” denotes an acetamide moiety; and the ratio of moieties “a” : “b” : “c” : “d” in the conjugate is approx. 1:13:c:d with c + d = 6.

(02) The TLR7/8 agonist or a pharmaceutically acceptable salt thereof of paragraph (01),
10 wherein the ratio of moieties “a” : “b” : “c” : “d” in the conjugate is approx. 1:13:3:3.

(03) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof of paragraph (01), wherein the ratio of moieties “a” : “b” : “c” : “d” in the conjugate is approx. 1:13:2:4.

(04) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof of paragraph (01), wherein the ratio of moieties “a” : “b” : “c” : “d” in the conjugate is approx. 1:13:4:2.

15 (05) A pharmaceutical formulation comprising one or more TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof of any one of paragraphs (01) to (04).

(06) The pharmaceutical formulation of paragraph (05), wherein pharmaceutical formulation is a dry formulation.

20 (07) The pharmaceutical formulation of paragraph (05) or (06), wherein the pharmaceutical formulation is a lyophilized formulation.

- (08) The pharmaceutical formulation of paragraph (05), wherein the pharmaceutical formulation is a suspension.
- (09) The pharmaceutical formulation of paragraph (08), wherein the pharmaceutical formulation comprises the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof in a concentration ranging from 0.5 mg to 2 mg TLR7/8 agonist per ml.
- (10) The pharmaceutical formulation of paragraph (08) or (09), wherein the pharmaceutical formulation comprises the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof in a concentration of 1 mg TLR7/8 agonist per ml.
- (11) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof of any one of paragraphs (01) to (04) or the pharmaceutical formulation of any one of paragraphs (05) to (10) for use as a medicament.
- (12) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of paragraph (11), wherein the medicament is for the treatment of cancer, such as a solid tumor.
- (13) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of paragraph (12), wherein the solid tumor is selected from the group consisting of lip and oral cavity cancer, oral cancer, liver cancer/hepatocellular cancer, primary liver cancer, lung cancer, lymphoma, malignant mesothelioma, malignant thymoma, skin cancer, intraocular melanoma, metastatic squamous neck cancer with occult primary, childhood multiple endocrine neoplasia syndrome, mycosis fungoides, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, oropharyngeal cancer, ovarian cancer, pancreatic cancer, parathyroid cancer, pheochromocytoma, pituitary tumor, adrenocortical carcinoma, AIDS-related malignancies, anal cancer, bile duct cancer, bladder cancer, brain and nervous system cancer, breast cancer, bronchial adenoma/carcinoid, gastrointestinal carcinoid tumor, carcinoma, colorectal cancer, endometrial cancer, esophageal cancer, extracranial germ cell tumor, extragonadal germ cell tumor, extrahepatic bile duct cancer, gallbladder cancer, gastric (stomach) cancer, gestational trophoblastic tumor, head and neck cancer, hypopharyngeal cancer, islet cell carcinoma (endocrine pancreas), kidney cancer/renal cell cancer, laryngeal cancer, pleuropulmonary blastoma, prostate cancer, transitional cell cancer of the renal pelvis and ureter, retinoblastoma, salivary gland cancer, sarcoma, Sezary syndrome, small intestine cancer, genitourinary cancer, malignant thymoma, thyroid cancer, Wilms' tumor and cholangiocarcinoma.

- (14) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of paragraph (12) or (13), wherein the cancer is selected from the group consisting of squamous cell carcinomas of the head and neck (SCCHN), HPV-associated cancers, melanomas, pancreatic cancer and breast cancer.
- 5 (15) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of paragraphs (12) to (14), wherein the medicament is administered at a dose ranging from 0.3 mg to 3 mg of TLR7/8 agonist per tumor.
- 10 (16) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of paragraphs (12) to (15), wherein the medicament is administered at a dose of 0.5 mg of TLR7/8 agonist per tumor.
- (17) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of paragraphs (11) to (16), wherein the medicament is administered to a patient every two to four weeks.
- 15 (18) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of paragraphs (11) to (17), wherein the medicament is administered to a patient every three weeks.
- (19) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of paragraphs (12) to (19), wherein the medicament is administered via intratumoral injection.
- 20 (20) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of paragraph (19), wherein the medicament is administered via intratumoral injection using a fanning technique.
- (21) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of paragraphs (12) to (20), wherein the medicament is administered to one tumor of the patient.
- 25 (22) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of paragraphs (12) to (21), wherein the medicament is administered to more than one tumor of the patient, such as to two tumors, three tumors, four tumors or five tumors or to all tumors of a patient that have a sufficient size and are accessible for treatment.
- 30 (23) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of paragraphs (12) to (22), wherein treatment of one tumor leads to an abscopal effect in one or more untreated tumors.

- 5 (24) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of paragraphs (12) to (23), wherein medicament is administered to a patient in a cotreatment with an inhibitor of PD-1 or an inhibitor of PD-L1, which may be given prior to, together with or after administration of the medicament.
- (25) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of paragraphs (12) to (24), wherein the medicament is administered to a patient in is a cotreatment with an inhibitor of PD-1, which may be given prior to, together with or after administration of the medicament.
- 10 (26) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of paragraph (24) or (25), wherein the inhibitor of PD-1 is selected from the group consisting of pembrolizumab, nivolumab, pidilizumab, AMP-224, BMS-936559, cemiplimab and PDR001.
- 15 (27) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of paragraphs (24) to (26), wherein the inhibitor of PD-1 is pembrolizumab.
- (28) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of paragraphs (11) to (27), wherein the medicament is provided in a vial.
- 20 (29) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of paragraph (28), wherein the vial is a type 1 glass vial.
- (30) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of paragraph (28) or (29), wherein the vial has a size
- 25 of 1 ml, 2 ml or 5 ml.
- (31) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof of any one of paragraphs (01) to (04) or the pharmaceutical formulation of any one of paragraphs (05) to (10) for use in the treatment of cancer, such as of a solid tumor.
- 30 (32) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of paragraph (31), wherein the solid tumor is selected from the group consisting of lip and oral cavity cancer, oral cancer, liver cancer/hepatocellular cancer, primary liver cancer, lung cancer, lymphoma, malignant mesothelioma, malignant thymoma, skin cancer, intraocular melanoma, metastatic squamous neck cancer with occult primary, childhood multiple endocrine neoplasia

- syndrome, mycosis fungoides, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, oropharyngeal cancer, ovarian cancer, pancreatic cancer, parathyroid cancer, pheochromocytoma, pituitary tumor, adrenocortical carcinoma, AIDS-related malignancies, anal cancer, bile duct cancer, bladder cancer, brain and nervous system cancer, breast cancer, bronchial adenoma/carcinoid, gastrointestinal carcinoid tumor, carcinoma, colorectal cancer, endometrial cancer, esophageal cancer, extracranial germ cell tumor, extragonadal germ cell tumor, extrahepatic bile duct cancer, gallbladder cancer, gastric (stomach) cancer, gestational trophoblastic tumor, head and neck cancer, hypopharyngeal cancer, islet cell carcinoma (endocrine pancreas), kidney cancer/renal cell cancer, laryngeal cancer, pleuropulmonary blastoma, prostate cancer, transitional cell cancer of the renal pelvis and ureter, retinoblastoma, salivary gland cancer, sarcoma, Sezary syndrome, small intestine cancer, genitourinary cancer, malignant thymoma, thyroid cancer, Wilms' tumor and cholangiocarcinoma.
- (33) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of paragraph (31) or (32), wherein the cancer is selected from the group consisting of squamous cell carcinoma of the head and neck (SCCHN), HPV-associated cancers, melanomas, pancreatic cancer and breast cancer.
- (34) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of paragraphs (31) to (33), wherein the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation is administered at a dose ranging from 0.3 mg to 3 mg of TLR7/8 agonist per tumor.
- (35) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of paragraphs (31) to (34), wherein the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation is administered at a dose of 0.5 mg of TLR7/8 agonist per tumor.
- (36) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of paragraphs (31) to (35), wherein the TLR7/8 agonist or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation is administered to a patient every two to four weeks.
- (37) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of paragraphs (31) to (36), wherein the

TLR7/8 agonist or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation is administered to a patient every three weeks.

- 5 (38) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of paragraphs (31) to (37), wherein the TLR7/8 agonist or the pharmaceutical formulation is administered via intratumoral injection.
- 10 (39) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of paragraphs (31) to (38), wherein the TLR7/8 agonist or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation is administered via intratumoral injection using a fanning technique.
- (40) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of paragraphs (31) to (39), wherein the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation is administered to one tumor of a patient.
- 15 (41) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of paragraphs (31) to (39), wherein the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation is administered to more than one tumor of the patient, such as to two tumors, three tumors, four tumors or five tumors or to all tumors of a patient
- 20 that have a sufficient size and are accessible for treatment.
- (42) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of paragraphs (31) to (41), wherein treatment of one tumor leads to an abscopal effect in one or more untreated tumors.
- 25 (43) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of paragraphs (31) to (42), wherein the treatment is a cotreatment with an inhibitor of PD-1 or an inhibitor of PD-L1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation.
- 30 (44) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of paragraphs (31) to (43), wherein the treatment is a cotreatment with an inhibitor of PD-1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation.

- (45) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of paragraph (43) or (44), wherein the inhibitor of PD-1 is selected from the group consisting of pembrolizumab, nivolumab, pidilizumab, AMP-224, BMS-936559, cemiplimab and PDR001.
- 5 (46) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of paragraphs (43) to (45), wherein the inhibitor of PD-1 is pembrolizumab.
- (47) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of paragraphs (31) to (46), wherein the
- 10 TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation is provided in a vial.
- (48) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of paragraph (47), wherein the vial is a type 1 glass vial.
- 15 (49) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of paragraph (47) or (48), wherein the vial has a size of 1 ml, 2 ml or 5 ml.
- (50) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof of any one of paragraphs (01) to (04) or the pharmaceutical formulation of any one of paragraphs
- 20 (05) to (10) for use in the manufacture of a medicament.
- (51) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of paragraph (50), wherein the medicament is for the treatment of cancer, such as for the treatment of a solid tumor.
- (52) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the
- 25 pharmaceutical formulation for use of paragraph (51), wherein the solid tumor is selected from the group consisting of lip and oral cavity cancer, oral cancer, liver cancer/hepatocellular cancer, primary liver cancer, lung cancer, lymphoma, malignant mesothelioma, malignant thymoma, skin cancer, intraocular melanoma, metastatic squamous neck cancer with occult primary, childhood multiple endocrine neoplasia
- 30 syndrome, mycosis fungoides, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, oropharyngeal cancer, ovarian cancer, pancreatic cancer, parathyroid cancer, pheochromocytoma, pituitary tumor, adrenocortical carcinoma, AIDS-related malignancies, anal cancer, bile duct cancer, bladder cancer, brain and nervous system cancer, breast cancer, bronchial adenoma/carcinoid, gastrointestinal

- carcinoid tumor, carcinoma, colorectal cancer, endometrial cancer, esophageal cancer, extracranial germ cell tumor, extragonadal germ cell tumor, extrahepatic bile duct cancer, gallbladder cancer, gastric (stomach) cancer, gestational trophoblastic tumor, head and neck cancer, hypopharyngeal cancer, islet cell carcinoma (endocrine pancreas), kidney cancer/renal cell cancer, laryngeal cancer, pleuropulmonary blastoma, prostate cancer, transitional cell cancer of the renal pelvis and ureter, retinoblastoma, salivary gland cancer, sarcoma, Sezary syndrome, small intestine cancer, genitourinary cancer, malignant thymoma, thyroid cancer, Wilms' tumor and cholangiocarcinoma.
- 5
- (53) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of paragraph (51) or (52), wherein the cancer is selected from the group consisting of squamous cell carcinoma of the head and neck (SCCHN), HPV-associated cancers, melanomas, pancreatic cancer and breast cancer.
- 10
- (54) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of paragraphs (51) to (53), wherein the medicament is administered at a dose ranging from 0.3 mg to 3 mg of TLR7/8 agonist per tumor.
- 15
- (55) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of paragraphs (51) to (54), wherein the medicament is administered at a dose of 0.5 mg of TLR7/8 agonist per tumor.
- 20
- (56) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of paragraphs (50) to (55), wherein the medicament is administered to a patient every two to four weeks.
- (57) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of paragraphs (50) to (56), wherein the medicament is administered to a patient every three weeks.
- 25
- (58) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of paragraphs (51) to (57), wherein the medicament is administered via intratumoral injection.
- (59) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of paragraph (58), wherein the medicament is administered via intratumoral injection using a fanning technique.
- 30
- (60) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of paragraphs (51) to (59), wherein the medicament is administered to one tumor of the patient.

- (61) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of paragraphs (51) to (59), wherein the medicament is administered to more than one tumor of the patient, such as to two tumors, three tumors, four tumors or five tumors or to all tumors of a patient that have a sufficient size and are accessible for treatment.
- (62) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of paragraphs (51) to (61), wherein treatment of one tumor leads to an abscopal effect in one or more untreated tumors.
- (63) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of paragraphs (51) to (62), wherein the medicament is administered to a patient in a cotreatment with an inhibitor of PD-1 or an inhibitor of PD-L1, which may be given prior to, together with or after administration of the medicament.
- (64) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of paragraphs (51) to (63), wherein the is administered to a patient in a cotreatment with an of PD-1, which may be given prior to, together with or after administration of the medicament.
- (65) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of paragraph (63) or (64), wherein the inhibitor of PD-1 is selected from the group consisting of pembrolizumab, nivolumab, pidilizumab, AMP-224, BMS-936559, cemiplimab and PDR001.
- (66) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of paragraphs (63) to (65), wherein the inhibitor of PD-1 is pembrolizumab.
- (67) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of paragraphs (50) to (66), wherein the medicament is provided in a vial.
- (68) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of paragraph (67), wherein the vial is a type 1 glass vial.
- (69) The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of paragraph (67) or (68), wherein the vial has a size of 1 ml, 2 ml or 5 ml.

- (70) A method of treating a patient having cancer, wherein the method comprises the step of administering a pharmaceutically effective amount of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof of any one of paragraphs (01) to (04) or the pharmaceutical formulation of any one of paragraphs (05) to (10) to the patient.
- 5 (71) The method of paragraph (70), wherein the cancer is selected from the group consisting of lip and oral cavity cancer, oral cancer, liver cancer/hepatocellular cancer, primary liver cancer, lung cancer, lymphoma, malignant mesothelioma, malignant thymoma, skin cancer, intraocular melanoma, metastatic squamous neck cancer with occult primary, childhood multiple endocrine neoplasia syndrome, mycosis fungoides, nasal cavity and
- 10 paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, oropharyngeal cancer, ovarian cancer, pancreatic cancer, parathyroid cancer, pheochromocytoma, pituitary tumor, adrenocortical carcinoma, AIDS-related malignancies, anal cancer, bile duct cancer, bladder cancer, brain and nervous system cancer, breast cancer, bronchial adenoma/carcinoid, gastrointestinal carcinoid tumor, carcinoma, colorectal cancer,
- 15 endometrial cancer, esophageal cancer, extracranial germ cell tumor, extragonadal germ cell tumor, extrahepatic bile duct cancer, gallbladder cancer, gastric (stomach) cancer, gestational trophoblastic tumor, head and neck cancer, hypopharyngeal cancer, islet cell carcinoma (endocrine pancreas), kidney cancer/renal cell cancer, laryngeal cancer, pleuropulmonary blastoma, prostate cancer, transitional cell cancer of the renal pelvis
- 20 and ureter, retinoblastoma, salivary gland cancer, sarcoma, Sezary syndrome, small intestine cancer, genitourinary cancer, malignant thymoma, thyroid cancer, Wilms' tumor and cholangiocarcinoma.
- (72) The method of paragraph (70) or (71), wherein the cancer is selected from the group consisting of squamous cell carcinoma of the head and neck (SCCHN), HPV-associated
- 25 cancers, melanomas, pancreatic cancer and breast cancer.
- (73) The method of any one of paragraphs (70) to (72), wherein the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation is administered to the patient at a dose ranging from 0.3 mg to 3 mg of TLR7/8 agonist per tumor.
- 30 (74) The method of any one of paragraphs (70) to (73), wherein the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation is administered to the patient at a dose of 0.5 mg of TLR7/8 agonist per tumor.

- (75) The method of any one of paragraphs (70) to (74), wherein the TLR7/8 agonist or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation is administered to a patient every two to four weeks.
- (76) The method of any one of paragraphs (70) to (75), wherein the TLR7/8 agonist or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation is administered to a patient every three weeks.
- (77) The method of any one of paragraphs (70) to (76), wherein the TLR7/8 agonist or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation is administered via intratumoral injection.
- (78) The method of any one of paragraphs (70) to (77), wherein the TLR7/8 agonist or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation is administered via intratumoral injection using a fanning technique.
- (79) The method of any one of paragraphs (70) to (78), wherein the TLR7/8 agonist or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation is administered to one tumor of the patient.
- (80) The method of any one of paragraphs (70) to (78), wherein the TLR7/8 agonist or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation is administered to more than one tumor of the patient, such as to two tumors, three tumors, four tumors or five tumors or to all tumors of a patient that have a sufficient size and are accessible for treatment.
- (81) The method of any one of paragraphs (70) to (80), wherein treatment of one tumor leads to an abscopal effect in one or more untreated tumors.
- (82) The method of any one of paragraphs (70) to (81), wherein the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation is administered in a cotreatment with an inhibitor of PD-1 or an inhibitor of PD-L1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation.
- (83) The method of any one of paragraphs (70) to (82), wherein the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation is administered in a cotreatment with an inhibitor of PD-1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation.

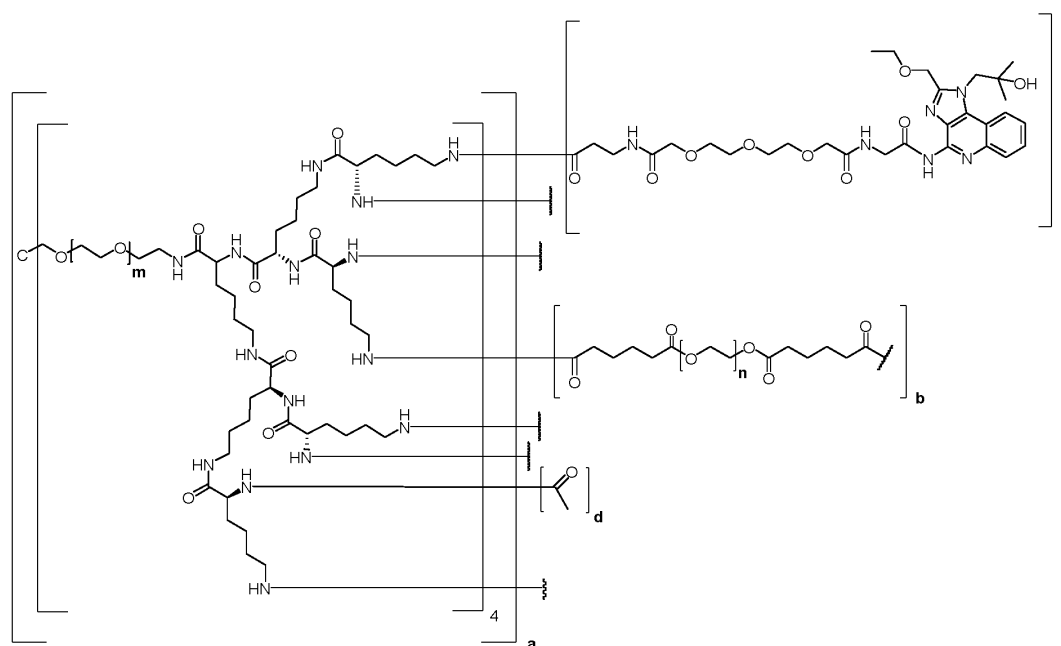
- (84) The method of paragraph (82) or (83), wherein the inhibitor of PD-1 is selected from the group consisting of pembrolizumab, nivolumab, pidilizumab, AMP-224, BMS-936559, cemiplimab and PDR001.
- (85) The method for use of any one of paragraphs (82) to (84), wherein the inhibitor of PD-1 is pembrolizumab.
- (86) The method of any one of paragraphs (70) to (85), wherein the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation is provided in a vial.
- (87) The method of paragraph (86), wherein the vial is a type 1 glass vial.
- (88) The method of paragraph (86) or (87), wherein the vial has a size of 1 ml, 2 ml or 5 ml.
- (89) A TLR7/8 agonist conjugate for use in the treatment of cancer, in particular of a solid tumor, wherein administration of a pharmaceutically effective dose leads to a plasma concentration of the TLR7/8 agonist of less than 4000 pg/ml.
- (90) The TLR7/8 agonist conjugate for use of paragraph (89), wherein the plasma concentration of the TLR7/8 agonist is less than 2000 pg/ml.
- (91) The TLR7/8 agonist conjugate for use of paragraph (89) or (90), wherein the plasma concentration of the TLR7/8 agonist is less than 1000 pg/ml.
- (92) The TLR7/8 agonist conjugate for use of any one of paragraphs (89) to (91), wherein the plasma concentration of the TLR7/8 agonist is less than 750 pg/ml.
- (93) The TLR7/8 agonist conjugate for use of any one of paragraphs (89) to (92), wherein the plasma concentration of the TLR7/8 agonist is less than 500 pg/ml.
- (94) The TLR7/8 agonist conjugate for use of any one of paragraphs (89) to (93), wherein the solid tumor is selected from the group consisting of lip and oral cavity cancer, oral cancer, liver cancer/hepatocellular cancer, primary liver cancer, lung cancer, lymphoma, malignant mesothelioma, malignant thymoma, skin cancer, intraocular melanoma, metastatic squamous neck cancer with occult primary, childhood multiple endocrine neoplasia syndrome, mycosis fungoides, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, oropharyngeal cancer, ovarian cancer, pancreatic cancer, parathyroid cancer, pheochromocytoma, pituitary tumor, adrenocortical carcinoma, AIDS-related malignancies, anal cancer, bile duct cancer, bladder cancer, brain and nervous system cancer, breast cancer, bronchial adenoma/carcinoid, gastrointestinal carcinoid tumor, carcinoma, colorectal cancer, endometrial cancer, esophageal cancer, extracranial germ cell tumor, extragonadal germ cell tumor, extrahepatic bile duct cancer, gallbladder cancer, gastric (stomach) cancer, gestational

- 5 trophoblastic tumor, head and neck cancer, hypopharyngeal cancer, islet cell carcinoma (endocrine pancreas), kidney cancer/renal cell cancer, laryngeal cancer, pleuropulmonary blastoma, prostate cancer, transitional cell cancer of the renal pelvis and ureter, retinoblastoma, salivary gland cancer, sarcoma, Sezary syndrome, small intestine cancer, genitourinary cancer, malignant thymoma, thyroid cancer, Wilms' tumor and cholangiocarcinoma.
- 10 (95) The TLR7/8 agonist conjugate of any one of paragraphs (89) to (94), wherein the solid tumor is selected from the group consisting of squamous cell carcinoma of the head and neck (SCCHN), HPV-associated cancers, melanomas, pancreatic cancer and breast cancer.
- (96) The TLR7/8 agonist conjugate of any one of paragraphs (89) to (95), wherein the TLR7/8 agonist conjugate is administered via intratumoral injection.
- (97) The TLR7/8 agonist conjugate of paragraph (96), wherein the intratumoral injection is via a fanning technique.
- 15 (98) The TLR7/8 agonist conjugate of any one of paragraphs (89) to (97), wherein the TLR7/8 agonist conjugate is administered every two to four weeks.
- (99) The TLR7/8 agonist conjugate of any one of paragraphs (89) to (98), wherein the TLR7/8 agonist conjugate is administered every three weeks.
- 20 (100) The TLR7/8 agonist conjugate of any one of paragraphs (89) to (99), wherein the TLR7/8 agonist is administered at a dose ranging from 0.3 mg to 3 mg of TLR7/8 agonist per tumor.
- (101) The TLR7/8 agonist conjugate of any one of paragraphs (89) to (100), wherein the TLR7/8 agonist conjugate is administered at a dose of 0.5 mg of TLR7/8 agonist per tumor.

25

Examples

Compound 1 has the following structure:



(A-6),

wherein

m ranges from approx. 25 to 29;

5 n ranges from approx. 41 to 45;

“a” denotes a backbone moiety, “b” denotes a crosslinker moiety, “c” denotes a reversibly conjugated resiquimod moiety and “d” denotes an acetamide moiety; and the ratio of moieties “a” : “b” : “c” : “d” in the conjugate is approx. 1:13:2:4;

10 and can be manufactured as described for hydrogel 14 in WO2020/141221.

Note: Experiments and resulting data are reported in past tense, even though at the time of filing the clinical trial was ongoing.

15 **Example 1**

Data shown herein is from a Phase 1/2, open-label, multi-center, first-in-human dose escalation and dose expansion study of compound 1, delivered by IT injection, for participants aged 18 years and older with locally advanced or metastatic solid tumors. The clinical trial is listed on www.clinicaltrials.gov under the ClinicalTrials.gov Identifier: NCT04799054.

20

Participants must have:

- At least 2 measurable lesions;
 - Lesion(s) for IT injection must be between 20 mm and 50 mm (inclusive) in the longest diameter when selected for injection; and
 - Lesion(s) for IT injection must be easily and safely accessible (for example, cutaneous or subcutaneous, palpable, and/or lesions visualized by ultrasound).
- The study uses a standard 3+3 design to investigate a range of dose levels of compound 1 as monotherapy or in combination with pembrolizumab.

Part 1: Monotherapy Dose Escalation

Part 1 included participants with advanced solid tumors that have progressed on or were intolerant of available standard of care treatment options or have disease for which there is no standard of care therapy. Compound 1 starting dose (Dose Level 1) was administered IT every 3 weeks. Upon disease progression, the addition of pembrolizumab every 3 weeks was allowed if deemed appropriate by the investigator.

Part 2: Combination Dose Escalation with Pembrolizumab

Part 2 started after Part 1 Dose Level 1 has passed safety evaluation. Compound 1 was given in a staggered dosing schedule in combination with pembrolizumab at 200 mg in Cycle 1 only (specifically, pembrolizumab is given 7 days after compound 1). After Cycle 1 (28 days), compound 1 was given together with pembrolizumab at 200 mg every 3 weeks in subsequent cycles (21 days).

For Part 1 and Part 2: There were at least 48 hours after dosing of the first participant before any subsequent participant is enrolled in a given cohort. This allows for evaluation of the first participant (defined as sentinel participant) in each dose cohort for any potential serious acute local or systemic reactions.

Doses are summarized in Table 1.

Table 1: Dose levels of Parts 1 and 2

Compound 1 (Parts 1 and 2) ¹		Pembrolizumab (for Part 2) ⁵
---	--	---

Dose Level ³	Dose Per Lesion ⁴	Number of Injected Lesions	Total Injected Dose/Patient	200 mg Q3W
Dose level 1	0.3	1	0.3 mg	
Dose level 2	0.5	Up to 2	0.5 – 1.0 mg	
Dose level 3	1	Up to 3	1.0 – 3.0 mg	
Dose level 4	2	Up to 3	2.0 – 6.0 mg	
Dose level 5	4	Up to 3	4.0 – 12.0 mg	

Abbreviations: mg = milligram; Q3W = every 3 weeks.

¹ All lesions chosen for intratumoral injections in an individual participant were treated at the same procedure setting on the same day.

³ Dose levels refer to resiquimod equivalent dose levels with the dose being administered per tumor site. With the exception of Dose Level 1, dose levels for subsequent cohorts may have been adjusted (escalated or de-escalated) based on clinical and available PK/PD observations. Each level was evaluated by the Safety Review Committee (SRC) after safety and available PK/PD data from the DLT period of a minimum of 3 participants enrolled to receive a dose level.

⁴ Compound 1 was given Q3W in Part 1 and Cycle 2 onwards in Part 2 (of note, Cycle 1 in Part 2 is 28 days long due to staggered dosing of Compound 1 and pembrolizumab)

⁵ If dose limiting toxicities were observed at any one dose level, dose may have been de-escalated in the same cohort or the previous dose level may have been reopened to enrollment to ensure the availability of safety and PK/PD data for a minimum of 6 participants for RP2D decision. Upon disease progression in Part 1, the addition of pembrolizumab was permitted at the discretion of the Investigator and after discussion with and approval from the Medical Monitor.

20 **Part 3: Combination Dose Expansion (Phase 2)**

In Part 3, compound 1 was given at the RP2D determined from Part 2 along with pembrolizumab at 200 mg every 3 weeks (Q3W). The number of indication-specific dose expansion cohorts was determined by a combination of clinical data seen from Parts 1 and 2, treatment landscape for a certain indication, and/or compelling scientific rationale.

25

Number of Participants: Approximately 40 participants were enrolled in total for Parts 1 and 2. Each expansion cohort in Part 3 was based on Simon-2-stage design and enrolled up to

approximately 50 participants, depending on benchmark ORR data in each indication. Table 2 shows the patient disposition.

Table 2: Patient disposition. Tumor types and number of prior lines of anti-cancer therapy

	Monotherapy (n=5)	Combination (n=3)
Tumor types (# prior lines of anti-cancer therapy)	Melanoma (2) Melanoma (3) Melanoma (3) TNBC (5) Pancreatic (5)	Melanoma (2) Basal Cell Carcinoma (2) Pancreatic (2)
Prior anti-PD(L)1	4 (80%)	2 (67%)

5

Results

To date (December 2021), no dose-limiting toxicities were observed. In the safety-evaluable population (n=8) so far there was no indication of systemic side effects related to compound 1. Of note, the only related adverse event reported was transient injection site related reactions (Grade 1/2). This was reported in 2 out of 5 patients treated with monotherapy, and no injection site reactions have been reported so far for the 3 patients treated with combination treatment. Table 3 provides the safety summary.

10

Table 3: Safety Summary

Overview of Safety	Monotherapy (n=5)		Combination (n=3)	
Subjects with at least 1 AE	4 (80%)		2 (67%)	
Subjects with at least one SAE	3 (60%)	Related: 0	1 (33%)	Related: 0
Subjects with at least one ≥ 3 AE	3 (60%)	Related: 0	1 (33%)	Related: 0
Subjects with an AE leading to study drug withdrawn or study discontinuation	0		0	
Subjects with Death related to AE	0		0	

15

Efficacy:

	Tumor type (# prior lines of anti-cancer therapy)	Prior PD(L)1	Best Overall Response per RECIST v1.1 (latest assessment), study status
Monotherapy (dose level 1)	Melanoma (2)	yes	uPR (week 27), ongoing
Combination with pembro (dose level 1)	Pancreatic cancer (2)	no	SD (week 9), ongoing
Combination with pembro (dose level 1)	Basal cell carcinoma (2)	yes	SD (week 9), ongoing

Melanoma Patient: uPR (week 27)

Target lesions				
	Baseline	wk9	wk18	wk27
Injected (mm)	25	24	24	30
Non-injected (mm)	11	10	9	0

3 core biopsies of injected lesion at week 27 after 9 cycles showed tumor found in up to 50% of total tissue; focal foreign material (hydrogel carrier) was surrounded by granulomatous inflammation.

Punch biopsy at non-injected lesion location showed mild chronic inflammation, reactive changes, no evidence of malignancy.

10

Pancreatic cancer SD (week 9)

Target lesions	Baseline	wk9
Injected once in Cycle 1 (mm)	22	30
Non-injected (mm)	90	
Injected since Cycle 2 (mm)		90

3 core biopsies of injected lesion at week 7 after 1 dose showed no tumor present; minimal lymphohistiocytic reaction was observed.

Basal cell carcinoma Patient SD (week 9)

Target lesions	Baseline	wk9
Injected once in Cycle 1 (mm)	42	47.5
Non-injected (mm)	17	18.4

5

3mm punch biopsy (5mm deep) of injected lesion at week 9 after 3 cycles showed atypical basaloid proliferation at base of biopsy. No evidence of malignancy were detected.

PK Measurements

- 10 Resiquimod systemic concentration was determined following IT administration of compound 1 at a dose of 0.3 and 0.5 mg per lesion. The mean systemic half-life of resiquimod released from the intratumoral administered depot was 6.5 days. C_{max} values were generally below 150 pg/mL and well below levels reported in the literature to be associated with cytokine release syndrome (~4000 pg/mL). Table 4 show the results of the resiquimod plasma concentration
- 15 measurements.

Table 4: Resiquimod plasma concentration measurements

Dose	Time	N	Plasma conc	SD
(μ g)	(day)		(pg/mL)	(pg/mL)
300	0	6		
	0.021	6	63.7	38.8
	0.083	6	63.7	31.5
	0.167	6	63.2	43.7
	1	6	52.5	72.2
	3	6	51.5	59.3
	7	6	49.1	67.8
	14	5	33.6	58.9
	21	5	20.2	40.9
500	0	1	<LLOQ	
	0.021	1	14.5	
	0.083	1	32.4	
	1	1	62.1	

	3	1	121	
	7	1	85.7	
	14	1	47.4	
	21	1	38.8	

Resiquimod and O-Desethyl Resiquimod:

Plasma samples were spiked with an internal standard (IS) (resiquimod-d5 and O-desethyl resiquimod-d6) followed by supported liquid extraction (SLE) with ethyl acetate using SLE+ plates. The analytes were then separated from remaining endogenous compounds on an Acquity UPLC HSS T3 C18 (50 x 2.1 mm, 1.8 μ m) and analyzed using positive electrospray ionization (ESI) tandem mass spectrometry (MS/MS) in multiple reaction monitoring mode (MRM). The resiquimod and O-desethyl resiquimod calibration range is 2.00 to 2,500 pg/mL. The concentrations of resiquimod and O-desethyl resiquimod in plasma were calculated using weighed ($1/X^2$) linear regression from plasma calibration standards.

Gene expression

Gene expression was evaluated by NanoString® technology using the Nanostring nCounter® Human Immunology V2 Panel. Tumor biopsies collected prior to first dosing with compound 1 (pre-dose) and 7 days after first dosing (C1D8) were formalin fixed and paraffin embedded followed by analysis. The absolute gene expression counts were adjusted by technical negative and positive controls and normalized to Housekeeping genes (genes that have a consistent and stable expression level) contained in the nCounter® Human Immunology V2 Panel. Fold change in expression from pre-dose to C1D8 expression was calculated and log2 transformed.

20

Patients were treated with intratumoral injection of compound 1 dosed into a single tumor lesion at either 0.3 mg per lesion (Dose level 1) or 0.5 mg per lesion (Dose level 2).

Patient	1	2	3	4	5	6
IRF7	1.7	3.5	3.5	4.1	3.5	1.8
CXCL10	0.6	6.7	7.2	12	1.4	3.6
STAT1	0.5	3.5	4.4	3.4	0.5	2.7
STAT2	1.2	2.6	3	1.4	0.9	0.9
IRF1	-0.6	2.5	1.7	0.8	2	2.3
IRF3	-0.1	0.3	4.9	-1	1.9	0.8

IRF4	-0.1	1.5	6.3	0.8	0.8	-0.1
IRF5	-0.7	2.4	4.7	0.2	1.2	1.2
IRF8	-0.6	2.9	1.7	1.9	-0.4	0.3
IFNB1	0.5	1	2.4	5.7	-0.1	-0.3
IFNA1/13	-0.4	1.5	-2.9	-0.4	-0.1	-0.1
IFNA2	-0.2	0.7	-3.3	-1.7	3.8	-0.3
JAK1	-0.5	0.4	0.5	0.6	0.6	0.7

Table showing log2 fold changes of tumoral gene expression 7 days post first compound 1 dose. (>0 = increased expression, 0 = no change, <0 = decreased expression)

Biomarker measurements

- 5 Gene expression was evaluated by NanoString® technology using the Nanostring nCounter® Human Immunology V2 Panel. Tumor biopsies collected prior to first dosing with compound 1 (pre-dose) and 7 days after first dosing (C1D8) were formalin fixed and paraffin embedded followed by analysis. The absolute gene expression counts were adjusted by technical negative and positive controls and normalized to Housekeeping genes (genes that have a consistent and
- 10 stable expression level) contained in the nCounter® Human Immunology V2 Panel. Fold change in expression from pre-dose to C1D8 expression was calculated and log2 transformed.

Patients were treated with intratumoral injection of compound 1 dosed into a single tumor lesion at either 0.3 mg per lesion (Dose level 1) or 0.5 mg per lesion (Dose level 2). 3 weeks

15 thereafter patients were treated with intratumoral injection of compound 1 dosed into a single tumor lesion at either 0.3 mg per lesion (Dose level 1) or 0.5 mg per lesion (Dose level 2) In addition, selected patients received intravenous treatment with pembrolizumab dosed at 200 mg per patient 1 week after the first dose of compound 1 and 3 weeks after the first dose of compound 1.

20

Sustained immune activation following repeat administration of compound 1 was observed. Gene expression remained elevated after second administration, indicating no down-regulation of immune activation.

- 25 In conclusion, compound 1 was administered at 300 µg and 500 µg per lesion to patients with solid tumors. At these dose levels signs of activity in three out of three evaluable patients

including those previously treated with checkpoint inhibitors were observed. Compound 1 demonstrated monotherapy activity and consistent and robust target engagement, as measured by biomarkers.

- 5 Compound 1 was well-tolerated, with transient, mild injection site-related reactions (Grade 1/2) are the only related AEs. In patients treated with compound 1, no systemic side effects related to compound 1 was reported, consistent with low systemic exposure of resiquimod.

- 10 Compound 1 has the potential for sustained immune activation and systemic anti-tumor response with infrequent dosing using dose levels of 300 µg and 500 µg per lesion.

Updated Results:

- As of September 21, 2022, 23 patients were enrolled in the dose escalation: 9 to monotherapy and 14 to combination therapy. The following results are based on this data cutoff and may differ from the December 2021 data as more information is gathered.
- 15

Patient Baseline Demographics and Clinical Characteristics

Monotherapy (Part 1)

Demographics	Dose		
	0.3 mg/lesion (n=3)	0.5 mg/lesion (n=6)	Total (N=9)
Age (years), median (min, max)	60 (58, 66)	65 (42, 75)	63 (42, 75)
Sex			
Male	2	4	6
Female	1	2	3
Race			
Asian	0	1	1
Black	1	0	1
White	2	5	7
Ethnicity			
Hispanic or Latino	0	1	1
Not Hispanic or Latino	3	5	8
ECOG Performance Status			

Grade 0	2	2	4
Grade 1	1	4	5
Prior Anti-PD1 Therapy (Yes), n (%)	2 (66.7)	4 (66.7)	6 (66.7)
Number of Prior Lines of Systemic Therapy, median (min, max)	5 (2,5)	3 (2,4)	3 (2,5)
Tumor Types			
Head and Neck Squamous Cell	0	1	1
Melanoma	1	2	3
Pancreatic Cancer	1	1	2
Cutaneous Squamous Cell	0	1	1
Other	1	1	2

Abbreviation: ECOG Eastern Cooperative Oncology Group

Combination with Pembrolizumab (Part 2)

Demographics	Dose		
	0.3 mg/lesion (n=3)	0.5 mg/lesion (n=11)	Total (N=14)
Age (years), median (min, max)	49 (47,66)	70 (43, 86)	69 (43, 86)
Sex			
Male	1	7	8
Female	2	4	6
Race			
Asian	0	0	0
Black	0	0	0
White	3	11	14
Ethnicity			
Hispanic or Latino	0	1	1
Not Hispanic or Latino	3	10	13
ECOG Performance Status			
Grade 0	2	2	4
Grade 1	1	9	10
Prior Anti-PD1 Therapy (Yes), n (%)	2 (66.7)	7 (63.6)	9 (64.3)

Number of Prior Lines of Systemic Therapy, median (min, max)	2 (2,2)	2 (1,3)	2 (1,3)
Tumor Types			
Head and Neck Squamous Cell	0	2	2
Melanoma	1	2	3
Pancreatic Cancer	1	0	1
Cutaneous Squamous Cell	0	1	1
Other	1	6	7

Abbreviation: ECOG Eastern Cooperative Oncology Group

Safety

Compound 1 was well tolerated as monotherapy and in combination with pembrolizumab at both 0.3 mg/lesion and 0.5 mg/lesion doses. All treatment related adverse events to compound 1 were grades 1 and 2, except one grade 3 injection site reaction. One dose-limiting toxicity (Grade 3 injection site reaction) was observed in a patient receiving 0.5 mg/lesion and pembrolizumab.

Table 4: Safety Summary

	Monotherapy (Part1)		Combination with Pembrolizumab (Part 2)	
	0.3 mg/lesion (n=3)	0.5 mg/lesion (n=6)	0.3 mg/lesion (n=3)	0.5 mg/lesion (n=11)
Patients with $\geq$ related SAE or related grade 3 or higher TEAE	0	0	1 (Grade 3 hyperglycemia related to pembrolizumab)	1 (SAE: Grade 3 injection site reaction)
TEAE leading to study drug interruption any cycle	1 (Grade 3 gluteal pain not related to compound 1)	1 (Grade 3 aspiration pneumonia)	0	2 (Grade 3 seizure not related to compound 1; 1, grade 3 injection)

		not related to compound 1)		site reaction related to compound 1)
TEAE leading to compound 1 withdrawn	0	0	0	0
TEAE leading to death	0	0	0	0

Abbreviations: SAE serious adverse events; TEAE treatment emergent adverse events

Efficacy: Preliminary efficacy data show clinical response to compound 1 occurred in 2 out of 13 response evaluable patients with one abscopal (non-injected lesion) effect.

5

Table 5: Best Overall Response

Study Drug	Tumor type	Prior anti-PD(L)1therapy	Best Overall Response per RECIST v 1.1
Monotherapy (0.3 mg/lesion)	Melanoma	yes	PR with abscopal effect (based on pathology review)
Monotherapy (0.5 mg/lesion)	Melanoma	yes	NE
Monotherapy (0.5 mg/lesion)	Melanoma	yes	SD
Monotherapy (0.5 mg/lesion)	Head and Neck Squamous Cell	yes	SD
Monotherapy (0.5 mg/lesion)	Pancreatic	no	PD
Monotherapy (0.5 mg/lesion)	Colon Mixed Adenoneuroendocrine	no	PD
Combination with pembrolizumab (0.3 mg/lesion)	Basal Cell Carcinoma	yes	SD
Combination with pembrolizumab (0.3 mg/lesion)	Melanoma	yes	PD
Combination with pembrolizumab (0.3 mg/lesion)	Pancreatic	no	SD
Combination with pembrolizumab (0.5 mg/lesion)	Melanoma	yes	PR

Combination with pembrolizumab (0.5 mg/lesion)	Leiomyosarcoma	no	SD
Combination with pembrolizumab (0.5 mg/lesion)	Adenoid cystic carcinoma	no	NE
Combination with pembrolizumab (0.5 mg/lesion)	Melanoma	yes	PD

Abbreviations: RECIST Response Evaluation Criteria in Solid Tumors; CR complete response; PR partial response; SD stable disease; PD progressive disease; NE not evaluable

- Out of the 23 patients dosed, four patients continue with treatment with compound 1 and three patients received compound 1 for longer than 24 weeks.

Study Drug	Tumor type	Duration on compound 1 (days)*
Monotherapy (0.3 mg/lesion)	Melanoma	316
Monotherapy (0.3 mg/lesion)	Pancreatic	22
Monotherapy (0.3 mg/lesion)	Breast cancer	1
Monotherapy (0.5 mg/lesion)	Melanoma	22
Monotherapy (0.5 mg/lesion)	Melanoma	208
Monotherapy (0.5 mg/lesion)	Squamous cell	21
Monotherapy (0.5 mg/lesion)	Head and Neck Squamous Cell	106
Monotherapy (0.5 mg/lesion)	Pancreatic	1
Monotherapy (0.5 mg/lesion)	Colon Mixed Adenoneuroendocrine	26
Combination with pembrolizumab (0.3 mg/lesion)	Basal Cell Carcinoma	49
Combination with pembrolizumab (0.3 mg/lesion)	Melanoma	71
Combination with pembrolizumab (0.3 mg/lesion)	Pancreatic	71
Combination with pembrolizumab (0.5 mg/lesion)	Melanoma (and Cutaneous Squamous Cell)	231 (ongoing)

Combination with pembrolizumab (0.5 mg/lesion)	Leiomyosarcoma	116
Combination with pembrolizumab (0.5 mg/lesion)	Adenoid cystic carcinoma	1
Combination with pembrolizumab (0.5 mg/lesion)	Melanoma	51
Combination with pembrolizumab (0.5 mg/lesion)	Melanoma	50
Combination with pembrolizumab (0.5 mg/lesion)	Head and Neck Squamous Cell	49
Combination with pembrolizumab (0.5 mg/lesion)	Mesothelioma	32 (ongoing)
Combination with pembrolizumab (0.5 mg/lesion)	Head and Neck Squamous Cell	1 (ongoing)
Combination with pembrolizumab (0.5 mg/lesion)	Liposarcoma	1
Combination with pembrolizumab (0.5 mg/lesion)	Sarcoma	1 (ongoing)
Combination with pembrolizumab (0.5 mg/lesion)	Colon	1

*Duration is calculated from the time of first administration to the time of the last administration. If the subject only received one administration the duration of treatment is one day.

5 PK Measurements

Resiquimod systemic concentration was determined following IT administration of compound 1 at a dose of 0.3 and 0.5 mg per lesion. The updated results are based on the data obtained in 17 patients. There were no significant differences between the two different doses. The mean systemic half-life of resiquimod released from the intratumoral administered depot was approximately 9 days. $C_{\max}$ values were generally below 150 pg/mL and well below levels reported in the literature to be associated with cytokine release syndrome (~4000 pg/mL). There was no observed interaction with pembrolizumab.

Biomarker measurements

Sustained immune gene activation following repeat administration of compound 1 was observed and no difference was seen between the 0.3 mg/lesion and 0.5 mg/ lesion doses. Specifically, there was a 7.4 times increase in IRF7 gene expression, 37.4 times increase in CXCL 10 gene expression, 4.7 times increase in STAT1 gene expression and 12.8 times increase in MX1 gene expression when comparing levels from cycle 1 day 8 to pre-treatment screening values in injected tumor lesions indicating sustained TLR7/8 pathway and interferon pathway gene activation. Sustained upregulation of expression of HLA genes was also observed with a 3.3 times increase in HLA-B gene expression and 3.7 fold increase in HLA-C gene expression when comparing cycle 1 day 8 levels to pre-treatment screening values in injected tumor lesions. Upregulation of gene signatures for cytotoxic immune cells (CD8 T cell and NK cell) but not regulatory T cells was also observed in the injected lesions. Gene expression remained elevated after a second administration, indicating sustained immune activation. Increases in plasma CXCL10 and TNF-alpha protein levels were found to be statistically significant at cycle 1 day 8 compared to pre-dose plasma concentrations documenting sustained elevated immune activation for at least one week after treatment. In one patient, a paired biopsy sample of a non-injected lesion demonstrated a 2.8 times increase in CD8 positive T cells, 16.8 fold increase in CD68 positive macrophages and no increase in FoxP3 positive regulatory T cells when comparing cycle 1 day 8 to cycle 2 day 8.

20

Conclusion

Compound 1 was administered at 0.3 mg and 0.5 mg per lesion both as monotherapy and in combination with pembrolizumab to patients with solid tumors. Compound 1 is well tolerated with the majority of adverse events of Grade 1 or 2 per CTCAE v. 5 (Common Terminology Criteria for Adverse Events). There was one DLT observed of a Grade 3 injection site reaction in the 0.5 mg/lesion of compound 1 in combination with pembrolizumab. Compound 1 demonstrates clinical activity both as monotherapy and in combination with pembrolizumab in heavily treated advanced solid tumor patients with one abscopal (non-injected lesion) effect observed. PK and biomarker data suggest no difference between the two tested doses of compound 1 with low systemic concentrations of resiquimod and sustained activation of immune markers. Based on this data, the recommended phase 2 dose is 0.5 mg/ lesion of compound 1, both as monotherapy and in combination with pembrolizumab.

30

Abbreviations

AE	Adverse event
C _{max}	Maximum concentration
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting toxicities
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
FDA	United States Food and Drug Administration
HPV	Human papillomavirus
IT	Intratumoral
mg	Milligram
NE	not evaluable
PD	Pharmacodynamic/s
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death ligand 1
PEG	Poly(ethylene glycol)
PR	Partial response
Q3W	Every 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 Dose
SAE	Serious adverse event
SCCHN	Squamous cell carcinoma of the head and neck
SRC	Safety Review Committee
TEAE	Treatment emergent adverse events
TLR	Toll-like receptor
TNBC	Triple-negative breast cancer

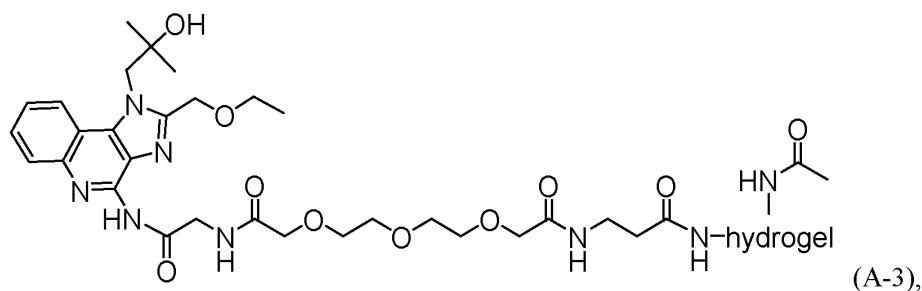
Claims

1. A unit dosage form comprising a therapeutically effective amount of a TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof, wherein the TLR7/8 agonist
5 conjugate comprises one or more TLR 7/8 agonist moieties reversibly conjugated to a polymeric moiety and wherein the unit dosage form comprises 0.3 mg to 3 mg of TLR7/8 agonist.
2. The unit dosage form of claim 1, wherein the unit dosage form comprises 0.5 mg TLR7/8
10 agonist.
3. The unit dosage form of claim 1, wherein the unit dosage form comprises 1 mg TLR7/8 agonist.
- 15 4. The unit dosage form of any one of claims 1 to 3, wherein the unit dosage form comprises the TLR7/8 agonist conjugate in a volume ranging from 0.1 ml to 2 ml.
5. The unit dosage form of any one of claims 1 to 4, wherein the unit dosage form comprises the TLR7/8 agonist conjugate in a volume of 0.5 ml.
- 20 6. The unit dosage form of any one of claims 1 to 4, wherein the unit dosage form comprises the TLR7/8 agonist conjugate in a volume of 1 ml.
7. The unit dosage form of any one of claims 1 to 4, wherein the unit dosage form comprises
25 the TLR7/8 agonist conjugate in a volume of 0.25 ml.
8. The unit dosage form of any one of claims 1 to 7, wherein the TLR7/8 agonist is resiquimod.
- 30 9. The unit dosage form of any one of claims 1 to 8, wherein the polymeric moiety is a hydrogel.
10. The unit dosage form of any one of claims 1 to 9, wherein the polymeric moiety is a PEG-based hydrogel.
- 35 11. The unit dosage form of any one of claims 1 to 10, wherein the unit dosage form is a vial comprising the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof.

12. The unit dosage form of any one of claims 1 to 10, wherein the unit dosage form is a dual-chamber cartridge comprising the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof.

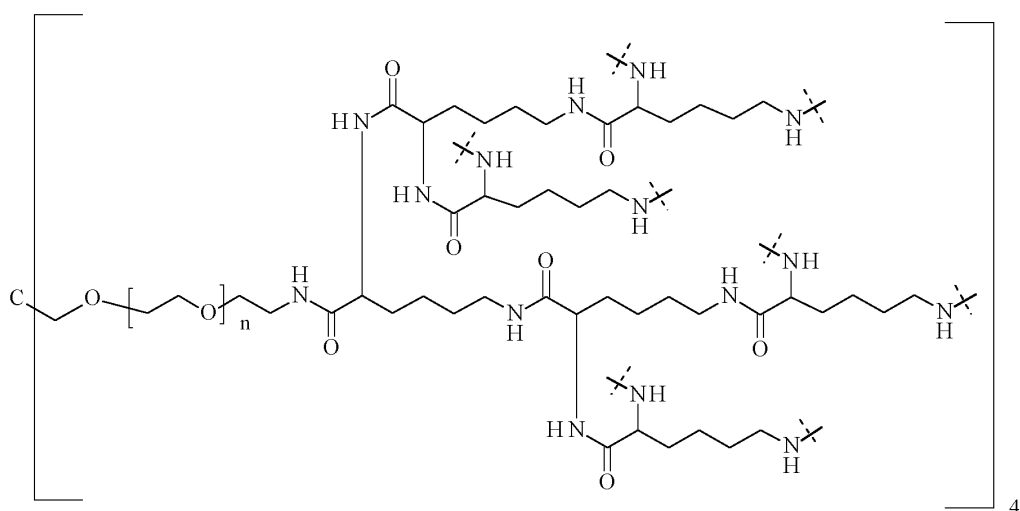
5

13. The unit dosage form of any one of claims 1 to 12, wherein the TLR7/8 agonist conjugate is of formula (A-3)



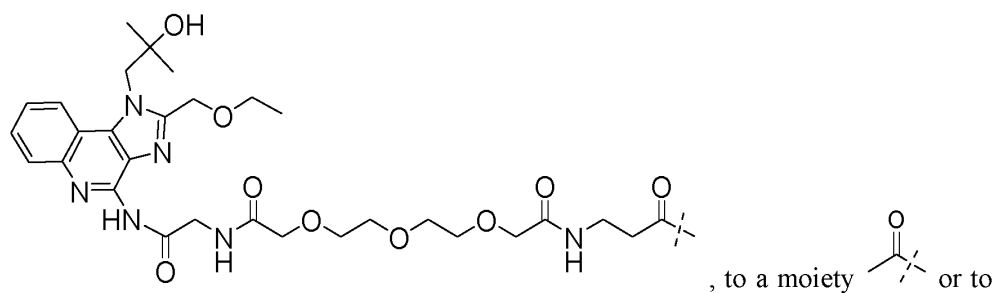
wherein “hydrogel” is a hydrogel comprising backbone moieties of formula (A-4):

10

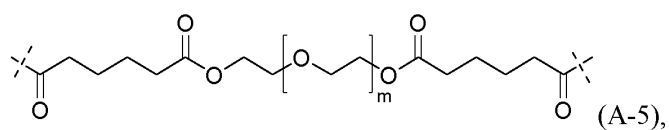


(A-4),

wherein n ranges from approx. 25 to 29 and dashed lines indicate attachment to either a moiety



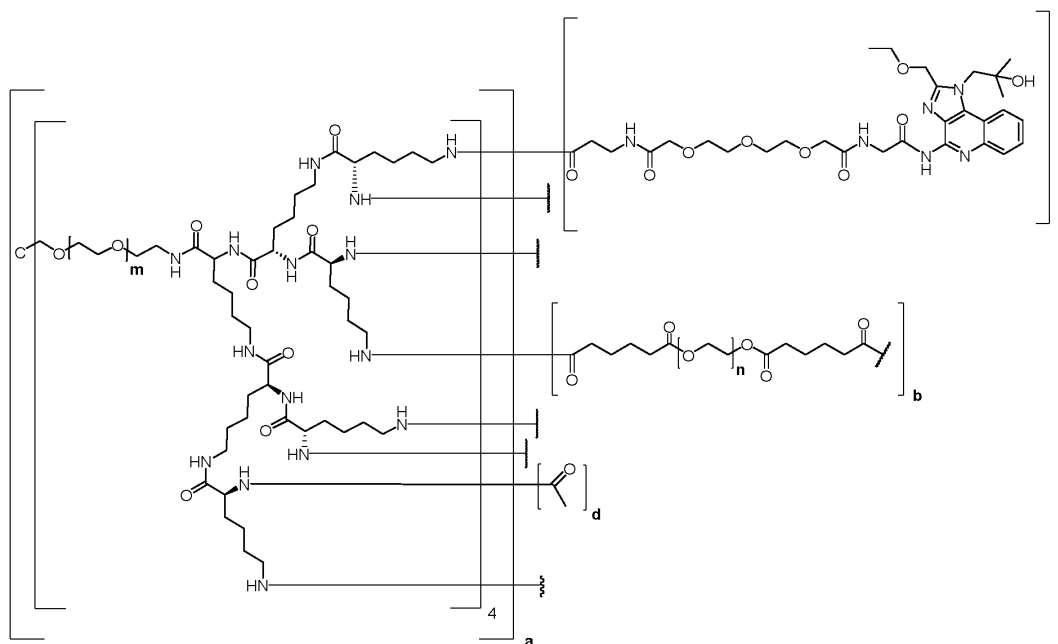
a crosslinker of formula (A-5):



wherein m ranges from approx. 41 to 45 and the dashed lines in (A-5) indicate attachment to a backbone moiety of formula (A-4).

5

14. The unit dosage form of any one of claims 1 to 13, wherein the TLR7/8 agonist conjugate is of formula (Ai-6):



10

wherein

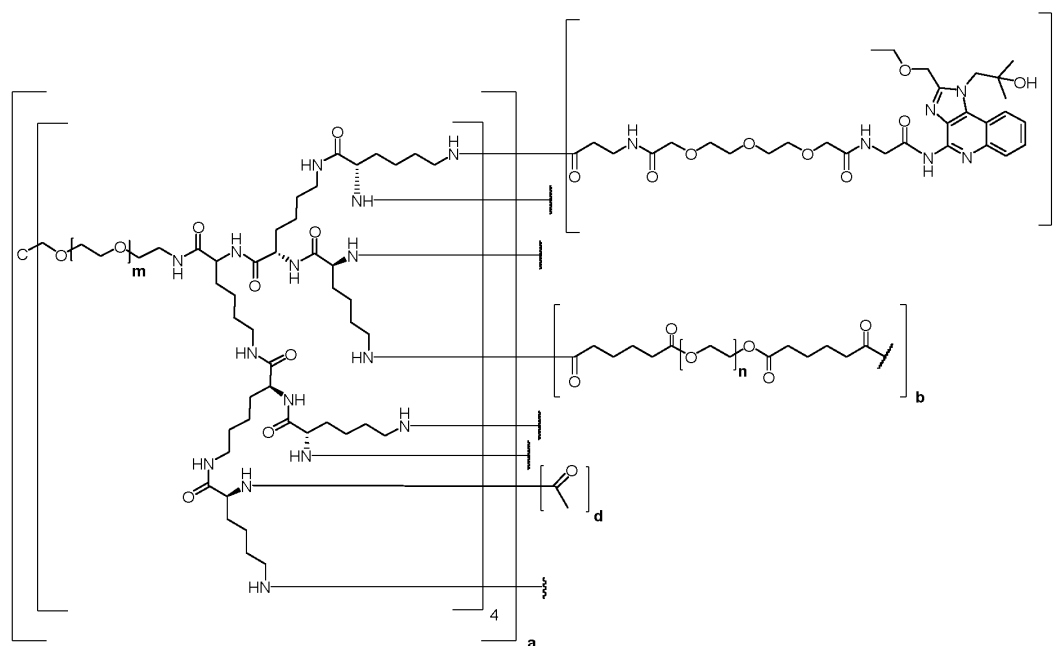
m ranges from approx. 25 to 29;

n ranges from approx. 41 to 45;

“a” denotes a backbone moiety, “b” denotes a crosslinker moiety, “c” denotes a reversibly conjugated resiquimod moiety and “d” denotes an acetamide moiety; and the ratio of moieties “a” : “b” : “c” : “d” in the conjugate is approx. 1:13:c:d with c + d = 6.

5

15. The unit dosage form of any one of claims 1 to 14, wherein the TLR7/8 agonist conjugate is of formula (A-8):



(A-8),

wherein

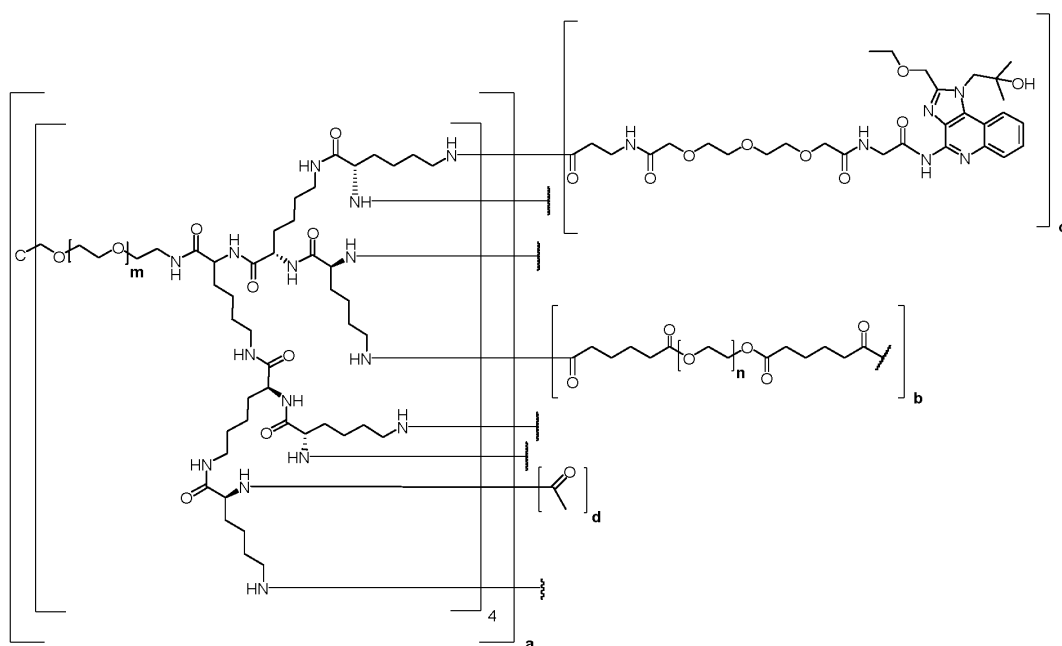
m ranges from approx. 25 to 29;

n ranges from approx. 41 to 45;

“a” denotes a backbone moiety, “b” denotes a crosslinker moiety, “c” denotes a reversibly conjugated resiquimod moiety and “d” denotes an acetamide moiety; and

the ratio of moieties “a”:"b”:"c”:"d” in the conjugate is approx. 1:13:3:3.

16. The unit dosage form of any one of claims 1 to 14, wherein the TLR7/8 agonist conjugate is of formula (A-6):



(A-6),

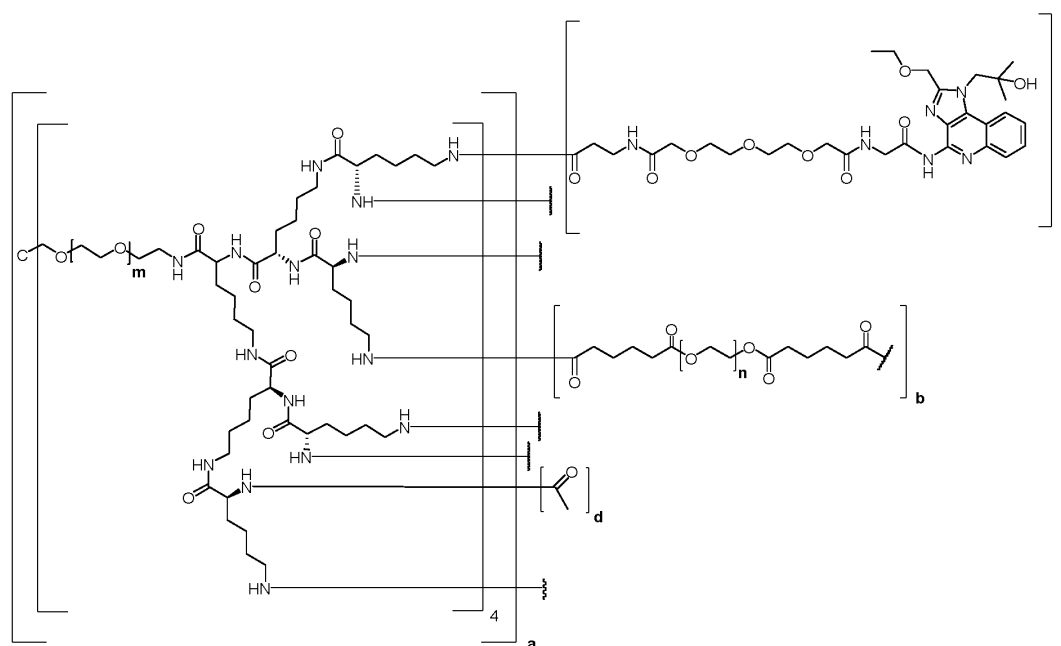
wherein

m ranges from approx. 25 to 29;

5 n ranges from approx. 41 to 45;

“a” denotes a backbone moiety, “b” denotes a crosslinker moiety, “c” denotes a reversibly conjugated resiquimod moiety and “d” denotes an acetamide moiety; and the ratio of moieties “a” : “b” : “c” : “d” in the conjugate is approx. 1:13:2:4.

- 10 17. The unit dosage form of any one of claims 1 to 14, wherein the TLR7/8 agonist conjugate is of formula (A-7):



(A-7),

wherein

m ranges from approx. 25 to 29;

5 n ranges from approx. 41 to 45;

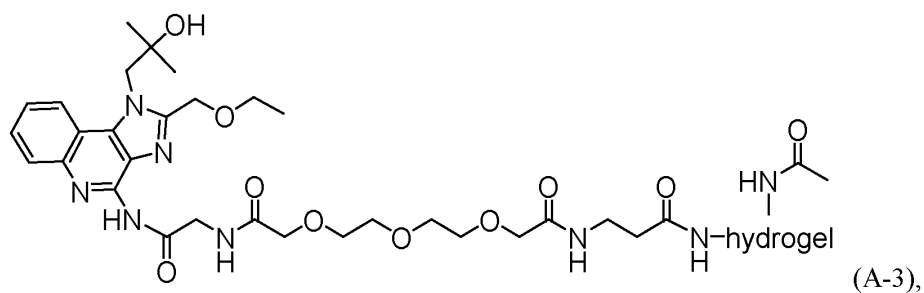
“a” denotes a backbone moiety, “b” denotes a crosslinker moiety, “c” denotes a reversibly conjugated resiquimod moiety and “d” denotes an acetamide moiety; and the ratio of moieties “a” : “b” : “c” : “d” in the conjugate is approx. 1:13:4:2.

- 10 18. The unit dosage form of any one of claims 1 to 17, wherein the unit dosage form comprises the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients.
- 15 19. The unit dosage form of any one of claims 1 to 18 for use in the treatment of cancer.
20. The unit dosage form for use of claim 19, wherein the cancer is a solid tumor.
21. The unit dosage form for use of claim 19 or 20, wherein the unit dose of the unit dosage form is administered via intratumoral injection.
- 20 22. The unit dosage form for use of claim 21, wherein the intratumoral injection is performed using a fanning technique.

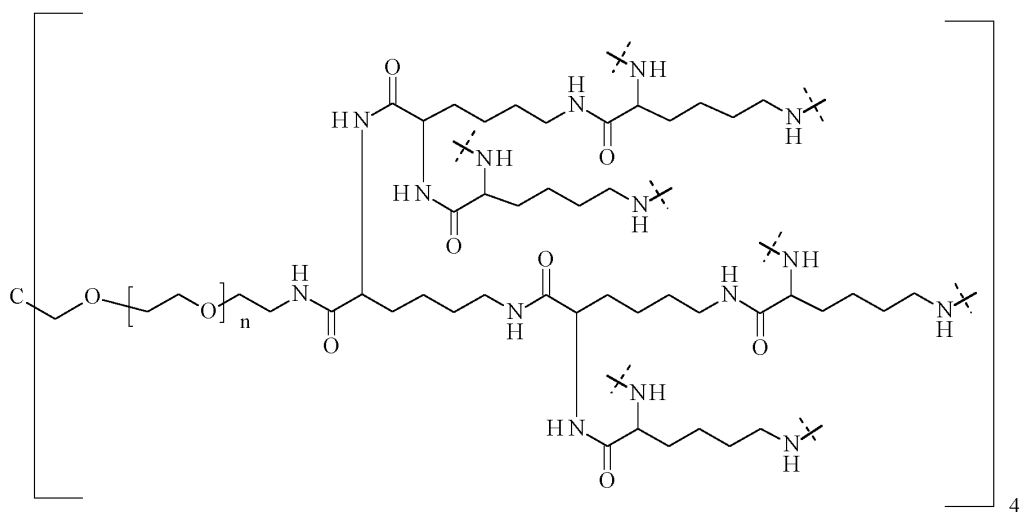
23. The unit dosage form for use of any one of claims 19 to 22, wherein the unit dose is administered every two to four weeks.
- 5 24. The unit dosage form for use of any one of claims 19 to 23, wherein the unit dose is administered every three weeks.
- 10 25. The unit dosage form for use of any one of claims 20 to 24, wherein the solid tumor is selected from the group consisting of lip and oral cavity cancer, oral cancer, liver cancer/hepatocellular cancer, primary liver cancer, lung cancer, lymphoma, malignant mesothelioma, malignant thymoma, skin cancer, intraocular melanoma, metastatic squamous neck cancer with occult primary, childhood multiple endocrine neoplasia syndrome, mycosis fungoides, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, oropharyngeal cancer, ovarian cancer, pancreatic cancer, 15 parathyroid cancer, pheochromocytoma, pituitary tumor, adrenocortical carcinoma, AIDS-related malignancies, anal cancer, bile duct cancer, bladder cancer, brain and nervous system cancer, breast cancer, bronchial adenoma/carcinoid, gastrointestinal carcinoid tumor, carcinoma, colorectal cancer, endometrial cancer, esophageal cancer, extracranial germ cell tumor, extragonadal germ cell tumor, extrahepatic bile duct cancer, 20 gallbladder cancer, gastric (stomach) cancer, gestational trophoblastic tumor, head and neck cancer, hypopharyngeal cancer, islet cell carcinoma (endocrine pancreas), kidney cancer/renal cell cancer, laryngeal cancer, pleuropulmonary blastoma, prostate cancer, transitional cell cancer of the renal pelvis and ureter, retinoblastoma, salivary gland cancer, sarcoma, Sezary syndrome, small intestine cancer, genitourinary cancer, 25 malignant thymoma, thyroid cancer, Wilms' tumor and cholangiocarcinoma.
26. The unit dosage form for use of any one of claims 20 to 25, wherein the solid tumor is selected from the group consisting of pancreatic cancer, prostate cancer, melanoma, SCCHN, cutaneous squamous cell cancer (cSCC) and cervical cancer.
- 30 27. The unit dosage form for use of any one of claims 19 to 26, wherein the TLR7/8 agonist conjugate is administered to one tumor of a patient.
28. The unit dosage form for use of any one of claims 19 to 26, wherein the TLR7/8 agonist 35 conjugate is administered to more than one tumor of a patient.

29. The unit dosage form for use of any one of claims 19 to 28, wherein administration of the TLR7/8 agonist conjugate to one tumor leads to an abscopal effect in one or more untreated tumors.
- 5 30. The unit dosage form for use of any one of claims 19 to 29, wherein the treatment is a cotreatment with an immune checkpoint inhibitor, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate.
- 10 31. The unit dosage form for use of any one of claims 19 to 30, wherein the treatment is a cotreatment with an inhibitor of PD-1 or an inhibitor of PD-L1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate.
- 15 32. The unit dosage form for use of any one of claims 19 to 31 wherein the treatment is a cotreatment with an inhibitor of PD-1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate.
- 20 33. The unit dosage form for use of any one of claims 19 to 32, wherein the treatment is a cotreatment with pembrolizumab, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate.
34. The unit dosage form for use of claim 33, wherein pembrolizumab is administered via intravenous injection every three weeks.
- 25 35. A TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof for use in the treatment of cancer, wherein the TLR7/8 agonist conjugate comprises one or more TLR7/8 agonist moieties reversibly conjugated to a polymeric moiety, wherein the cancer is a solid tumor and wherein the TLR7/8 agonist conjugate is administered via intratumoral administration in a dose ranging from 0.3 mg to 3 mg of TLR7/8 agonist per tumor.
- 30 36. The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof for use of claim 35, wherein the TLR7/8 agonist conjugate is administered in a dose of 0.5 mg of TLR7/8 agonist per tumor.

37. The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof for use of claim 35, wherein the TLR7/8 agonist conjugate is administered in a dose of 1 mg of TLR7/8 agonist per tumor.
- 5 38. The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof for use of any one of claims 35 to 37, wherein the dose is administered in a volume ranging from 0.1 ml to 2 ml.
39. The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof for use of
10 any one of claims 35 to 38, wherein the dose is administered in a volume of 0.5 ml.
40. The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof for use of any one of claims 35 to 38, wherein the dose is administered in a volume of 1 ml.
- 15 41. The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof for use of any one of claims 35 to 38, wherein the dose is administered in a volume of 0.25 ml.
42. The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof for use of any one of claims 35 to 41, wherein the TLR7/8 agonist conjugate or a pharmaceutically
20 acceptable salt thereof is provided as a pharmaceutical formulation comprising one the TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof and one or more excipients.
43. The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof for use of
25 any one of claims 35 to 42, wherein the TLR7/8 agonist is resiquimod.
44. The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof for use of any one of claims 35 to 43, wherein the polymeric moiety is a hydrogel.
- 30 45. The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof for use of any one of claims 35 to 44, wherein the polymeric moiety is a PEG-based hydrogel.
46. The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof for use of any one of claims 35 to 45, wherein the TLR7/8 agonist conjugate is of formula (A-3)

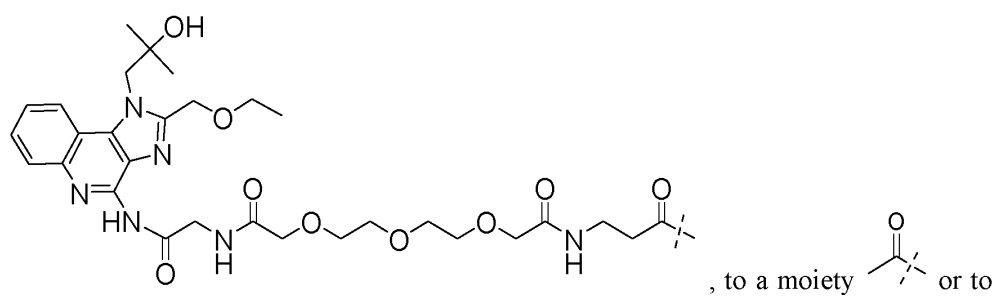


wherein “hydrogel” is a hydrogel comprising backbone moieties of formula (A-4):

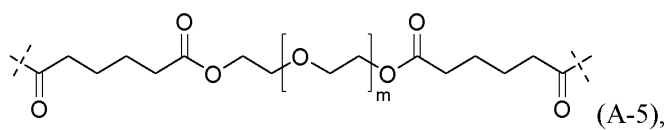


(A-4),

wherein n ranges from approx. 25 to 29 and dashed lines indicate attachment to either a moiety

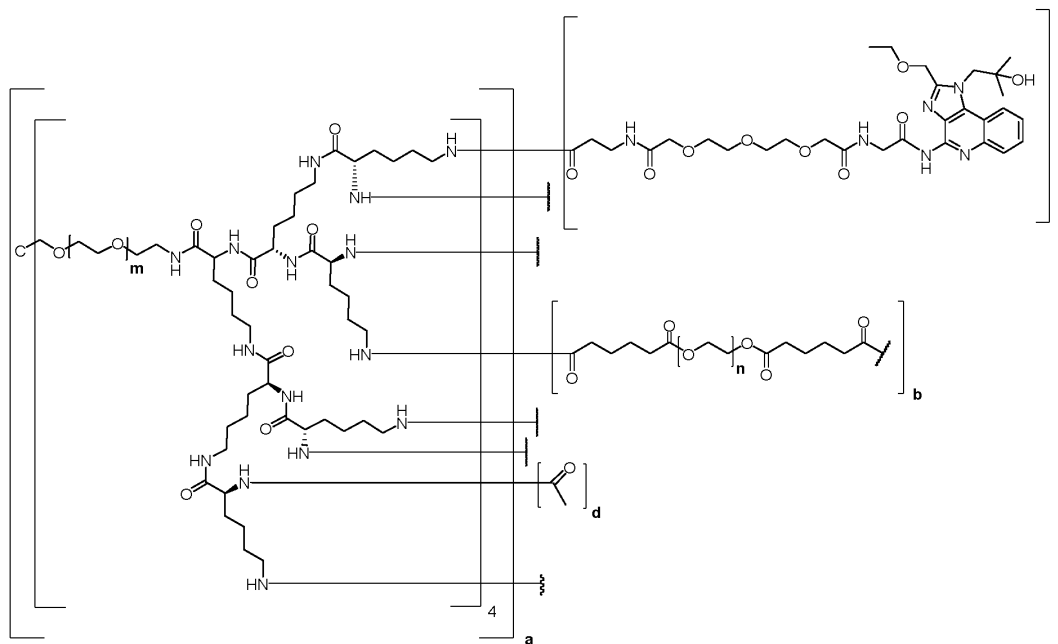


a crosslinker of formula (A-5):



wherein m ranges from approx. 41 to 45 and the dashed lines in (A-5) indicate attachment to a backbone moiety of formula (A-4).

47. The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof for use of any one of claims 35 to 46, wherein the TLR7/8 agonist conjugate is of formula (Ai-6):



(Ai-6),

wherein

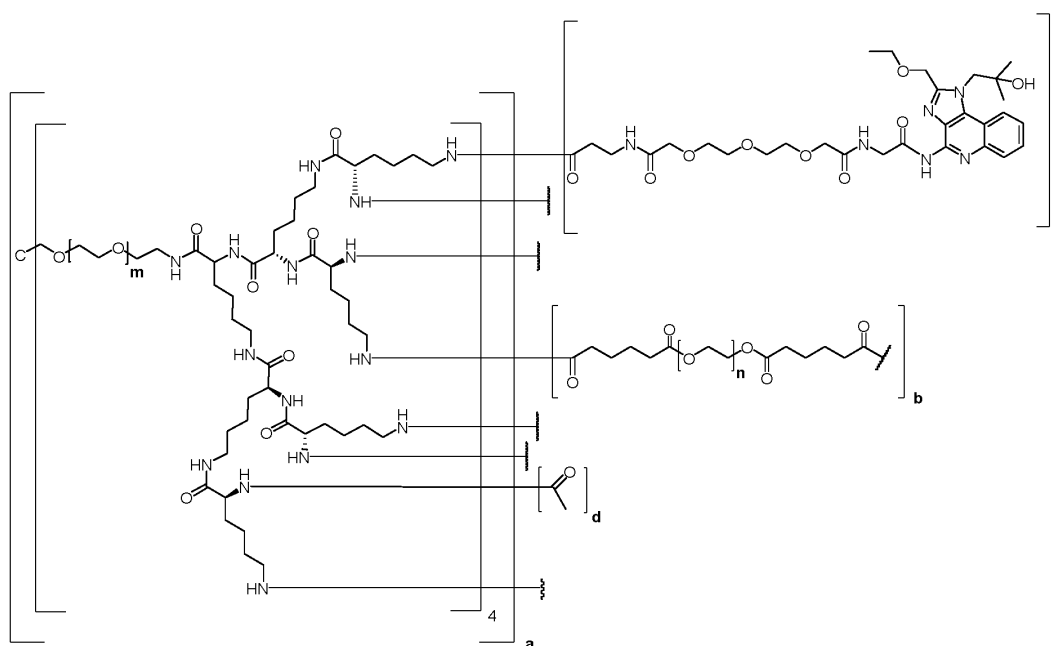
m ranges from approx. 25 to 29;

n ranges from approx. 41 to 45;

“a” denotes a backbone moiety, “b” denotes a crosslinker moiety, “c” denotes a reversibly conjugated resiquimod moiety and “d” denotes an acetamide moiety; and the ratio of moieties “a”:“b”:“c”:“d” in the conjugate is approx. 1:13:c:d with c + d = 6.

15

48. The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof for use of any one of claims 35 to 47, wherein the TLR7/8 agonist conjugate is of formula (A-8):



(A-8),

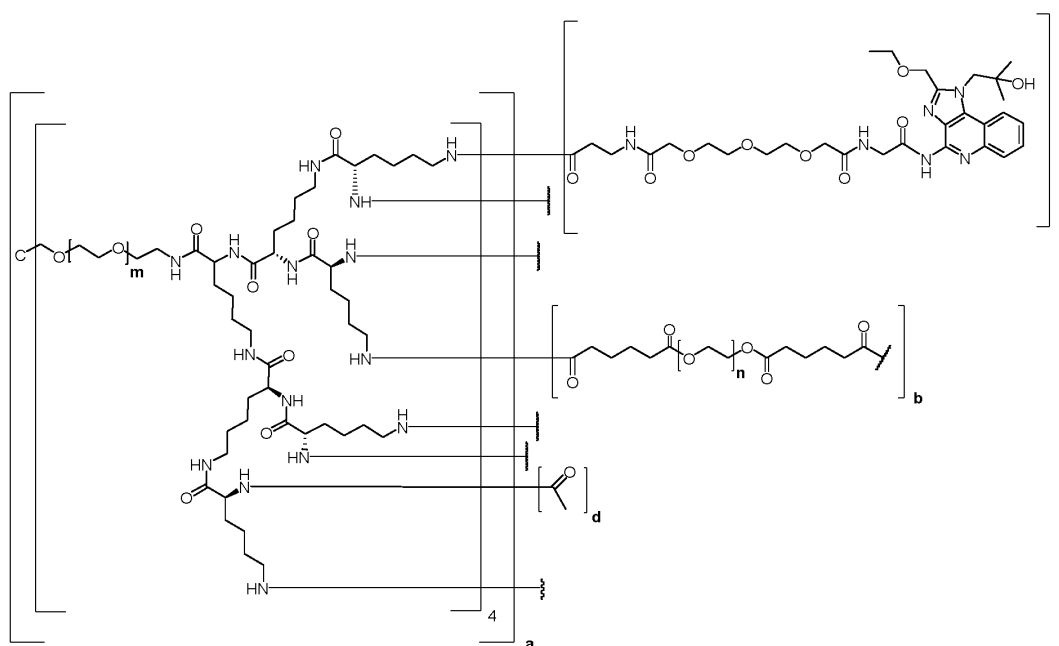
wherein

m ranges from approx. 25 to 29;

5 n ranges from approx. 41 to 45;

“a” denotes a backbone moiety, “b” denotes a crosslinker moiety, “c” denotes a reversibly conjugated resiquimod moiety and “d” denotes an acetamide moiety; and the ratio of moieties “a”:“b”:“c”:“d” in the conjugate is approx. 1:13:3:3.

- 10 49. The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof for use of
any one of claims 35 to 47, wherein the TLR7/8 agonist conjugate is of formula (A-6):



(A-6),

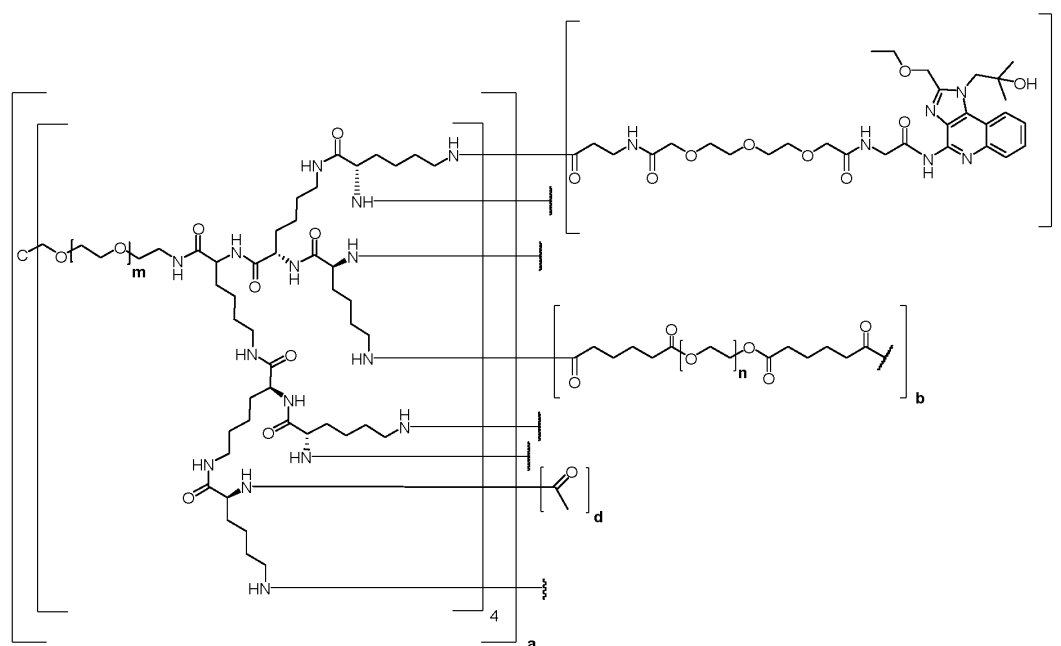
wherein

m ranges from approx. 25 to 29;

5 n ranges from approx. 41 to 45;

“a” denotes a backbone moiety, “b” denotes a crosslinker moiety, “c” denotes a reversibly conjugated resiquimod moiety and “d” denotes an acetamide moiety; and the ratio of moieties “a” : “b” : “c” : “d” in the conjugate is approx. 1:13:2:4.

10 50. The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof for use of any one of claims 35 to 47, wherein the TLR7/8 agonist conjugate is of formula (A-7):



(A-7),

wherein

m ranges from approx. 25 to 29;

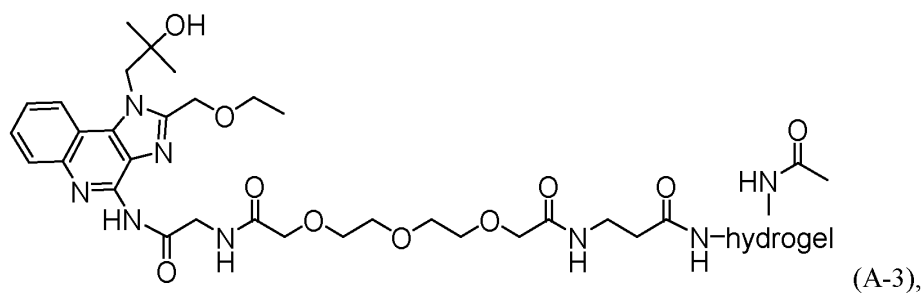
5 n ranges from approx. 41 to 45;

“a” denotes a backbone moiety, “b” denotes a crosslinker moiety, “c” denotes a reversibly conjugated resiquimod moiety and “d” denotes an acetamide moiety; and the ratio of moieties “a” : “b” : “c” : “d” in the conjugate is approx. 1:13:4:2.

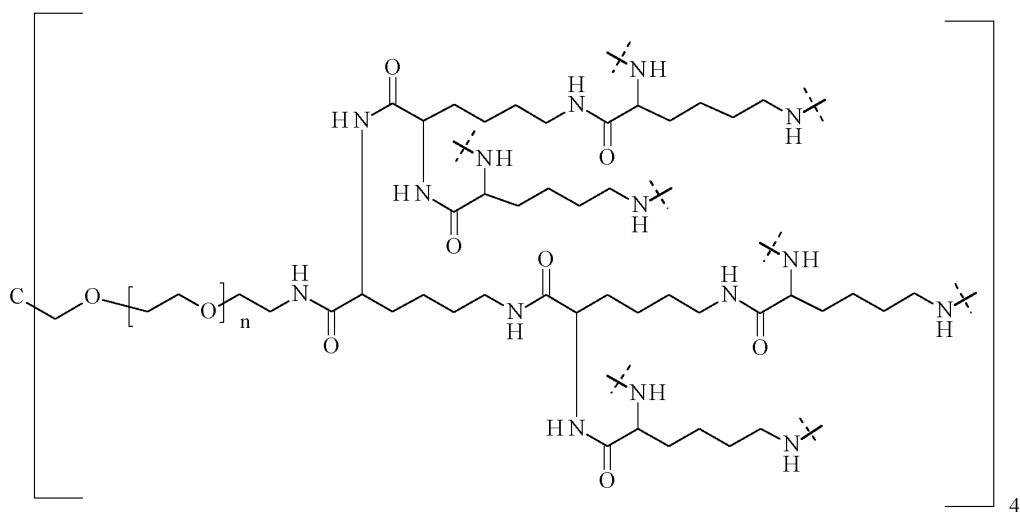
- 10 51. The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof for use of any one of claims 35 to 50, wherein the dose is provided in a vial.
52. The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof for use of any one of claims 35 to 50, wherein the dose is provided in a dual-chamber cartridge.
- 15 53. TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof for use of any one of claims 35 to 52, wherein the intratumoral injection is performed using a fanning technique.
- 20 54. The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof for use of any one of claims 35 to 53, wherein the dose is administered every two to four weeks.

55. The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof for use of any one of claims 35 to 54, wherein the dose is administered every three weeks.
56. The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof for use of any one of claims 35 to 55, wherein the solid tumor is selected from the group consisting of lip and oral cavity cancer, oral cancer, liver cancer/hepatocellular cancer, primary liver cancer, lung cancer, lymphoma, malignant mesothelioma, malignant thymoma, skin cancer, intraocular melanoma, metastatic squamous neck cancer with occult primary, childhood multiple endocrine neoplasia syndrome, mycosis fungoides, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, oropharyngeal cancer, ovarian cancer, pancreatic cancer, parathyroid cancer, pheochromocytoma, pituitary tumor, adrenocortical carcinoma, AIDS-related malignancies, anal cancer, bile duct cancer, bladder cancer, brain and nervous system cancer, breast cancer, bronchial adenoma/carcinoid, gastrointestinal carcinoid tumor, carcinoma, colorectal cancer, endometrial cancer, esophageal cancer, extracranial germ cell tumor, extragonadal germ cell tumor, extrahepatic bile duct cancer, gallbladder cancer, gastric (stomach) cancer, gestational trophoblastic tumor, head and neck cancer, hypopharyngeal cancer, islet cell carcinoma (endocrine pancreas), kidney cancer/renal cell cancer, laryngeal cancer, pleuropulmonary blastoma, prostate cancer, transitional cell cancer of the renal pelvis and ureter, retinoblastoma, salivary gland cancer, sarcoma, Sezary syndrome, small intestine cancer, genitourinary cancer, malignant thymoma, thyroid cancer, Wilms' tumor and cholangiocarcinoma.
57. The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof for use of any one of claims 35 to 56, wherein the solid tumor is selected from the group consisting of pancreatic cancer, prostate cancer, melanoma, SCCHN, cutaneous squamous cell cancer (cSCC) and cervical cancer.
58. The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof for use of any one of claims 35 to 57, wherein the TLR7/8 agonist conjugate is administered to one tumor of a patient.
59. The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof for use of any one of claims 35 to 57, wherein the TLR7/8 agonist conjugate is administered to more than one tumor of a patient.

60. The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof for use of any one of claims 35 to 59, wherein administration of the TLR7/8 agonist conjugate to one tumor leads to an abscopal effect in one or more untreated tumors.
- 5 61. The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof for use of any one of claims 35 to 60, wherein the treatment is a cotreatment with an immune checkpoint inhibitor, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate.
- 10 62. The TLR7/8 conjugate or a pharmaceutically acceptable salt thereof for use of any one of claims 35 to 61, wherein the treatment is a cotreatment with an inhibitor of a PD-1 or an inhibitor of PD-L1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate.
- 15 63. The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof for use of any one of claims 35 to 62, wherein the treatment is a cotreatment with an inhibitor of PD-1, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate.
- 20 64. The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof for use of any one of claims 35 to 63, wherein the treatment is a cotreatment with pembrolizumab, which may be given prior to, together with or after administration of the TLR7/8 agonist conjugate.
- 25 65. The TLR7/8 agonist conjugate or a pharmaceutically acceptable salt thereof for use of claim 64, wherein the pembrolizumab is administered via intravenous injection every three weeks.
- 30 66. A conjugate or a pharmaceutically acceptable salt thereof of formula (A-3)

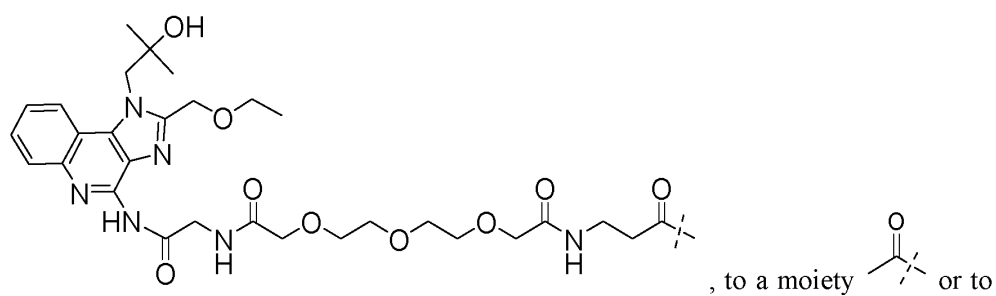


wherein “hydrogel” is a hydrogel comprising backbone moieties of formula (A-4):

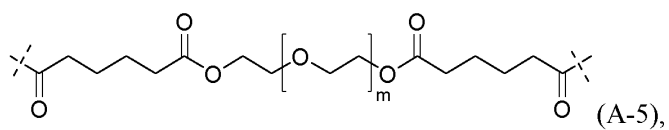


(A-4),

wherein n ranges from approx. 25 to 29 and dashed lines indicate attachment to either a moiety

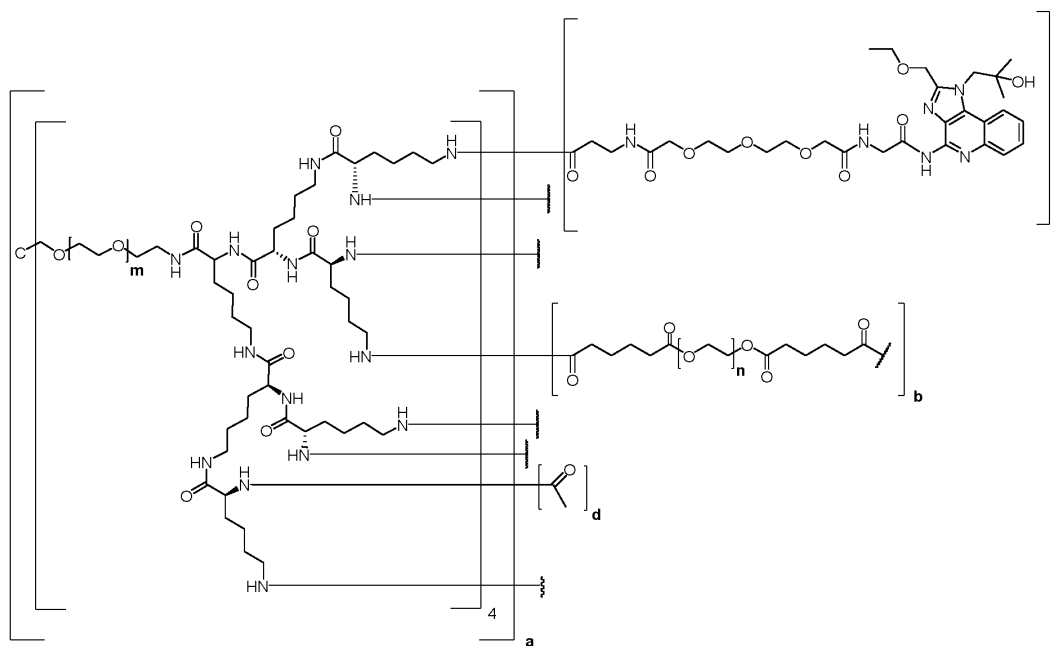


a crosslinker of formula (A-5):



wherein m ranges from approx. 41 to 45 and the dashed lines in (A-5) indicate attachment to a backbone moiety of formula (A-4).

67. The conjugate or a pharmaceutically acceptable salt thereof of claim 42, wherein the conjugate is of formula (A-6)



(A-6),

wherein

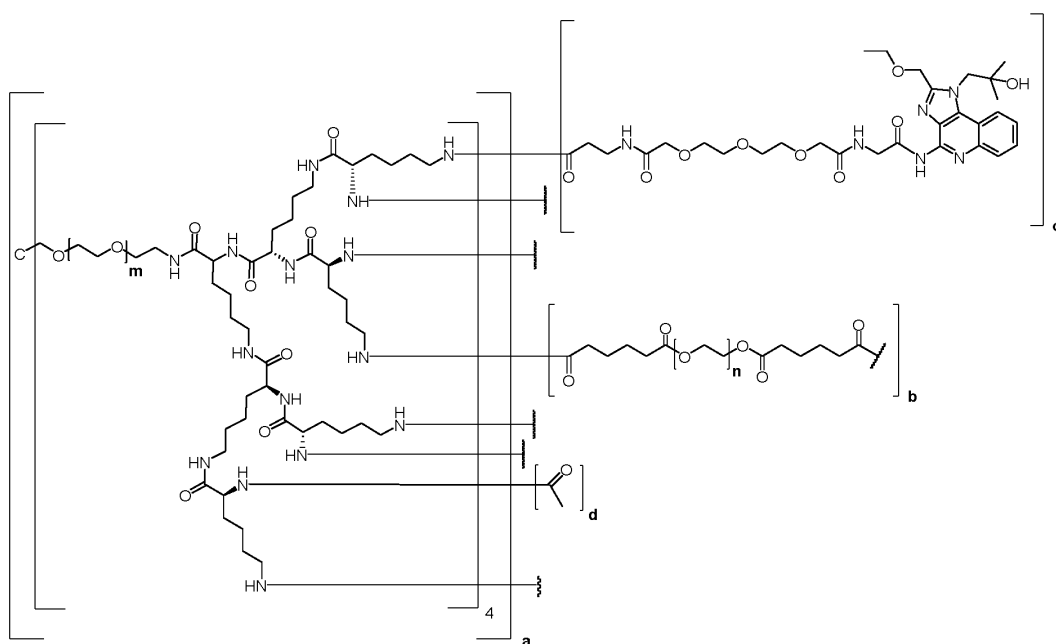
m ranges from approx. 25 to 29;

n ranges from approx. 41 to 45;

“a” denotes a backbone moiety, “b” denotes a crosslinker moiety, “c” denotes a reversibly conjugated resiquimod moiety and “d” denotes an acetamide moiety; and the ratio of moieties “a” : “b” : “c” : “d” in the conjugate is approx. 1:13:2:4.

68. The conjugate or a pharmaceutically acceptable salt thereof of claim 43, wherein the ratio of “a” : “b” : “c” : “d” is approx. 1:13:2.4:3.6.

69. A conjugate or a pharmaceutically acceptable salt thereof of formula (Ai-6)



(Ai-6),

wherein

m ranges from approx. 25 to 29;

5 n ranges from approx. 41 to 45;

“a” denotes a backbone moiety, “b” denotes a crosslinker moiety, “c” denotes a reversibly conjugated resiquimod moiety and “d” denotes an acetamide moiety; and the ratio of moieties “a” : “b” : “c” : “d” in the conjugate is approx. 1:13:c:d with c + d = 6.

10 70. The conjugate or a pharmaceutically acceptable salt thereof of claim 69, wherein the ratio of moieties “a” : “b” : “c” : “d” in the conjugate is approx. 1:13:3:3.

71. The conjugate or a pharmaceutically acceptable salt thereof of claim 69, wherein the ratio of moieties “a” : “b” : “c” : “d” in the conjugate is approx. 1:13:2:4.

15

72. The conjugate or a pharmaceutically acceptable salt thereof of claim 69, wherein the ratio of moieties “a” : “b” : “c” : “d” in the conjugate is approx. 1:13:4:2.

73. A pharmaceutical formulation comprising one or more conjugate or a pharmaceutically acceptable salt thereof of any one of claims 66 to 72 and one or more excipients.

20

74. The conjugate or a pharmaceutically acceptable salt thereof of any one of claims 66 or 72 or the pharmaceutical formulation of claim 73 for use as a medicament.
75. The conjugate or a pharmaceutically acceptable salt thereof of any one of claims 66 or 72 or the pharmaceutical formulation of claim 73 for use in the treatment of a cancer.
76. The conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of claim 75, wherein the cancer is a solid tumor.
77. The conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of claim 75 or 76, wherein the conjugate is administered at a dose ranging from 0.3 mg to 3 mg per tumor.
78. The conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of claims 75 to 77, wherein the conjugate is administered at a dose of 0.5 mg per tumor.
79. The conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of claims 75 to 78, wherein the conjugate is administered in a volume ranging from 0.1 to 2 ml.
80. The conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of claims 75 to 79, wherein the conjugate is administered in a volume of 1 ml.
81. The conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of claims 75 to 79, wherein the conjugate is administered in a volume of 0.25 ml.
82. The conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of claims 75 to 81, wherein the conjugate is administered via intratumoral injection.

83. The conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of claim 82, wherein the intratumoral injection uses a fanning technique.
- 5 84. The conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of claims 75 to 83, wherein the conjugate is administered to the patient every two to four weeks.
- 10 85. The conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of claims 75 to 84, wherein the conjugate is administered to the patient every three weeks.
- 15 86. The conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of claims 75 to 85, wherein the solid tumor is selected from the group consisting of lip and oral cavity cancer, oral cancer, liver cancer/hepatocellular cancer, primary liver cancer, lung cancer, lymphoma, malignant mesothelioma, malignant thymoma, skin cancer, intraocular melanoma, metastatic squamous neck cancer with occult primary, childhood multiple endocrine neoplasia syndrome, mycosis fungoides, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, oropharyngeal cancer, ovarian cancer, pancreatic cancer, parathyroid cancer, pheochromocytoma, pituitary tumor, adrenocortical carcinoma, AIDS-related malignancies, anal cancer, bile duct cancer, bladder cancer, brain and nervous system cancer, breast cancer, bronchial adenoma/carcinoid, gastrointestinal carcinoid tumor, carcinoma, colorectal cancer, endometrial cancer, esophageal cancer, 20 extracranial germ cell tumor, extragonadal germ cell tumor, extrahepatic bile duct cancer, gallbladder cancer, gastric (stomach) cancer, gestational trophoblastic tumor, head and neck cancer, hypopharyngeal cancer, islet cell carcinoma (endocrine pancreas), kidney cancer/renal cell cancer, laryngeal cancer, pleuropulmonary blastoma, prostate cancer, transitional cell cancer of the renal pelvis and ureter, retinoblastoma, salivary gland cancer, sarcoma, Sezary syndrome, small intestine cancer, genitourinary cancer, 30 malignant thymoma, thyroid cancer, Wilms' tumor and cholangiocarcinoma.
87. The conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of claims 75 to 86, wherein the solid tumor is selected

from the group consisting of pancreatic cancer, prostate cancer, melanoma, SCCHN, cutaneous squamous cell cancer (cSCC) and cervical cancer.

- 5 88. The conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of claims 75 to 87, wherein the conjugate is administered to one tumor of a patient.
- 10 89. The conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of claims 75 to 87, wherein the conjugate is administered to more than one tumor.
- 15 90. The conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of claims 75 to 89, wherein administration of the conjugate to one tumor leads to an abscopal effect in one or more untreated tumors.
- 20 91. The conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of claims 75 to 90, wherein the treatment is a cotreatment with an inhibitor of PD-1 or PD-L1, which may be given prior to, together with or after administration of conjugate.
- 25 92. The conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of claims 75 to 91, wherein the treatment is a cotreatment with an inhibitor of PD-1, which may be given prior to, together with or after administration of the conjugate.
- 30 93. The conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of any one of claims 75 to 92, wherein the treatment is a cotreatment with pembrolizumab, which may be given prior to, together with or after administration of the conjugate.
94. The conjugate or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of claim 93, wherein the pembrolizumab is administered via intravenous infusion at a dose of 200 mg.

95. The conjugate or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable salt thereof or the pharmaceutical formulation for use of claim 93 or 94, wherein the pembrolizumab is administered every three weeks.