intestine. Healthy mice, in contrast, showed a weak intestinal response, affecting metabolic functions such as lipid and glucose metabolism and insulin resistance, with no evidence of systemic effects. The results illustrate how the need for tumor surveillance is met by a milk constituent that preferentially targets tumor cells, in predisposed hosts without detrimental effects in a healthy host background. The response to BAMLET in extra-intestinal tissues further suggested a more general role of alpha-lactalbumin for tissue development in the newborn and in tumor surveillance.

Based on the evidence collected, it is clear that the complexes have a systemic impact, changing the overall tumor environment. As set out below, the inventors have produced evidence of both a shift in genetic expression in response to administration of the complexes and a physiological impact. Further, whereas most cancer therapies are directed at a single point of attack, for example by targeting one specific gene, the complexes of the invention have a remarkably broad efficacy, tackling cancers via multiple routes. This enables the complexes to be useful in targeting many different cancers, including metastases.

The inventors have also identified that administration of the complexes provides long term protection from cancers.

The inventors have further identified other systemic effects, particularly metabolic effects. Such effects have been found in otherwise healthy animals. The effects may impact cancer development and / or the general progress of cancer patients due to the reduction of conditions secondary to cancer that significantly impact health. The effects also demonstrate the usefulness of the complexes in treating such conditions when they are unrelated to cancer.

SUMMARY

The disclosure provides a complex for use in various therapeutic applications, and methods of treatment using the complex, or pharmaceutical compositions comprising the complex. The complex is particularly useful for treating malignant transformations, particularly cancer, especially where such transformations are found at a site distant from the site of administration of the complex.

The complex comprises a polypeptide having a sequence of a naturally occurring alpha-lactalbumin, or a functional variant thereof; or a peptide of up to 50 amino acids comprising an alpha-helical domain of said polypeptide; and a fatty acid or lipid or salt thereof.

There is provided a complex as defined for use in tumor surveillance. Further provided is a complex as defined for use in altering the tumor environment. Also provided is a method of

treating or preventing cancer, comprising the step of tumor surveillance and/or the step of altering the tumor environment.

Tumor surveillance means the identification of cancerous or pre-cancerous cells, or other indicators of cancer or a pre-cancerous state. It may also include initiating a response to the presence of such cells or indicators, for example by altering the tumor environment.

Altering the tumor environment means modifying the conditions that affect tumor development or progression, for example, but not limited to, immune cells, signalling molecules, extracellular matrix, blood supply. It can refer to the tumor microenvironment, i.e., the environment surrounding a tumor, or to the broader environment of the body. In particular, altering the tumor environment means modifying the tumor environment such that tumor development, progression or metastasis is reduced or prevented, or the likelihood of tumor development, progression or metastasis is reduced or prevented.

There is provided a complex as defined for use in the prevention or treatment, particularly treatment, of cancer; wherein the complex is for administration at a first site and the cancer is at a second site.

Also provided is a method of preventing or treating cancer, particularly treating, comprising the step of administering an effective amount of the complex or a pharmaceutical composition comprising the complex to a subject having cancer, or a predisposition to, or an increased likelihood of developing a cancer, wherein the complex or composition is for administration to a first site, and the cancer is at a second site.

In one aspect, the disclosure provides use of a complex comprising a polypeptide having a sequence of a naturally occurring alpha-lactalbumin, or a functional variant thereof; or a peptide of up to 50 amino acids comprising an alpha-helical domain of said polypeptide; and a fatty acid or lipid or salt thereof, in the preparation of a pharmaceutical composition for the treatment or prevention of cancer; wherein the treatment or prevention comprises the complex to be administered at a first site, and wherein the cancer is at a second site.

The complex or a composition comprising the complex is for administration to a first site on or in the body. By this, we mean that the complex is formulated for administration to a particular site, for example it is formulated for peroral, intravesical, intracerebral or topical administration.

The cancer is found at a second site. For example, the cancer is found in one or more of the nasal passage, the GI tract (e.g., in one or more of the oral cavity, the stomach, the colon, the bowel), the brain, the lung, the kidney, the vagina, the bladder, the liver, the skin, the breast, the prostate and/or the ovary.

In particular, the cancer may be found in the lung, the kidney or the liver. Preferably it is found in the lung. Alternatively, it may be found in the kidney. Alternatively, it may be found in the liver.

In some examples, the second site is not one or more of the nasal passage, the GI tract (in one or more of the oral cavity, the stomach, the colon, the bowel), the brain, the lung,

the kidney, the vagina, the bladder, the liver, the skin, the breast, the prostate and/or the ovary. In particularly, in some examples it is not the nasal passage. In some examples, it is not the GI tract. In some examples, it is not the brain. In some examples, it is not the lung. In some examples, it is not the kidney. In some examples, it is not the vagina. In some examples, it is not the bladder. In some examples, it is not the liver. In some examples, it is not the skin. In some examples, it is not the breast. In some examples, it is not the prostate. In some examples, it is not the ovary.

The first and second sites are preferably different and, more preferably are remote from one another, *i.e.*, are found in different parts of the body or in different systems. For example, where the complex is for administration perorally, the cancer is not a cancer of the GI tract. Table 1 provides further examples of the first and second sites.

		Second site (location of cancer)											
		Nasal passage	GI tract	Brain	Lung	Kidney	Vagina	Bladder	Liver	Skin	Breast	Prostate	Ovary
First site (route of administration)	Intranasal		X	X		X	X	X	X	X	X	X	X
	Peroral (administration to the GI tract)	X		X	X	X	X	X	X	X	X	X	X
	Intracerebral	X	X		X	X	X	X	X	X	X	X	X
	Inhalation		X	X		X	X	X	X	X	X	X	X
	Perfusion to kidney	X	X	X	X		X	X	X	X	X	X	X
	Intravaginal	X	X	X	X	X		X	X	X	X	X	X
	Intravesical	X	X	X	X	X	X		X	X	X	X	X
	Perfusion to liver	X	X	X	X	X	X	X		X	X	X	X
	Topical (to skin)	X	X	X	X	X	X	X	X		X	X	X
	Intraductal	X	X	X	X	X	X	X	X	X		X	X
	Perfusion to prostate	X	X	X	X	X	X	X	X	X	X		X
	Direct to ovary	X	X	X	X	X	X	X	X	X	X	X	
	Intravenous	X	X	X	X	X	X	X	X	X	X	X	X

Table 1. Routes of administration and cancer to be treated.

The treatment or prevention of cancer may comprise the step of tumor surveillance and/or altering the tumor environment.

Also provided is a complex as described previously, for use as a checkpoint inhibitor, particularly an inhibitor of PD-1. The disclosure provides the complex for use in the prevention or treatment, particularly treatment, of PD-L1 positive cancers or other cancers that are susceptible to PD-1 targeting.

The disclosure further provides a method of preventing or treating a cancer that is PD-L1 positive, or is otherwise susceptible to PD-1 targeting, comprising administering a therapeutically effective amount of the complex, or a composition comprising the complex, to a subject in need thereof.

In another aspect, the disclosure provides use of a complex comprising a polypeptide having a sequence of a naturally occurring alpha-lactalbumin, or a functional variant thereof; or a peptide of up to 50 amino acids comprising an alpha-helical domain of said polypeptide; and a fatty acid or lipid or salt thereof, in the preparation of a pharmaceutical composition for use as a checkpoint inhibitor, particularly an inhibitor of PD-1, or for use in the prevention or treatment, particularly treatment, of PD-L1 positive cancers or other cancers that are susceptible to PD-1 targeting.

The cancer may be found at any site in the body, for example at any of the sites listed in relation to the other examples of the disclosure.

The complex may be for administration via any suitable route, such as those described in relation to other examples of the disclosure. It may be for administration directly to the site of the cancer, or for administration at a different site. For example, the complex may be for administration perorally for the treatment of PD-L1 positive cancers in the GI tract, or elsewhere in the body, such as the liver, lung or kidney.

The cancer may be a primary cancer or a metastasis.

Also provided by the disclosure is a complex as previously described, for use in the prevention, reduction, or treatment of metastasis.

The disclosure further provides a method of preventing or treating metastatic cancer, comprising administering a therapeutically effective amount of the complex, or a composition comprising the complex, to a subject in need thereof.

In another aspect, the disclosure provides use of a complex comprising a polypeptide having a sequence of a naturally occurring alpha-lactalbumin, or a functional variant thereof; or a peptide of up to 50 amino acids comprising an alpha-helical domain of said polypeptide; and

a fatty acid or lipid or salt thereof, in the preparation of a pharmaceutical composition for the prevention, reduction, or treatment of metastasis.

The primary tumor from which the metastasis arises, or the metastasis itself may be found at any site in the body, for example at any of the sites listed in relation to the other examples of the disclosure.

The complex may be for administration via any suitable route, such as those described in relation to other examples of the disclosure. It may be for administration directly to the site of the primary cancer or the metastasis, or for administration at a different site. For example, the complex may be for administration perorally for the prevention, reduction or treatment of metastatic cancers in, or arising from cancers in the GI tract. Or it may be for prevention, reduction or treatment of metastatic cancers, or arising from cancers, elsewhere in the body, such as the liver, lung or kidney.

The prevention, reduction, or treatment of metastasis may comprise the step of tumor surveillance and/or altering the tumor environment.

In another aspect, there is provided use of a complex comprising a polypeptide having a sequence of a naturally occurring alpha-lactalbumin, or a functional variant thereof; or a peptide of up to 50 amino acids comprising an alpha-helical domain of said polypeptide; and a fatty acid or lipid or salt thereof, in the preparation of a pharmaceutical composition for tumor surveillance and/or altering the tumor environment.

Also provided by the disclosure is a complex as previously described, for use in the treatment or prevention of metabolic-related conditions, such as insulin resistance, type II diabetes, metabolic syndrome, non-alcoholic fatty acid liver disease, cirrhosis, high blood pressure. The complex may be used to modulate insulin tolerance or sensitivity, lipid metabolism and / or glucose metabolism and is therefore useful in the treatment of conditions arising from challenges with such processes.

The disclosure further provides a method of treating such metabolic-related conditions, comprising administering a complex as defined to a subject.

Such metabolic conditions may be related to the presence of cancer, for example they may be secondary to cancer, or may be independent thereof. The complex is particularly useful for improving the health of a subject having cancer, by treating the cancer, or treating conditions secondary to the cancer, or both. Accordingly, the disclosure provides a complex as previously described, for use in the treatment or prevention of metabolic-related conditions, such as insulin resistance, type II diabetes, metabolic syndrome, non-alcoholic fatty acid liver disease, cirrhosis, high blood pressure, in a subject that has, or has previously had, cancer. Also provided is a complex as previously described, for use in the treatment or prevention of metabolic-related conditions, such as insulin resistance, type II diabetes, metabolic syndrome, non-alcoholic fatty acid liver disease, cirrhosis, high blood pressure, in a subject that does not have, or has not had cancer.

The complex

The complex comprises a polypeptide having a sequence of a naturally occurring alpha-lactalbumin, or a functional variant thereof; or a peptide of up to 50 amino acids comprising an alpha-helical domain of said polypeptide, and a fatty acid or lipid or salt thereof.

In one example, the polypeptide has a sequence of a naturally occurring alpha-lactalbumin, preferably a human or bovine alpha-lactalbumin, more preferably a bovine alpha-lactalbumin.

In one example, the alpha-helical domain is the Alpha 1 (residues 1-39) or Alpha 2 (residues 81-123) domain of human alpha-lactalbumin, being of of SEQ ID NO 3 or SEQ ID NO 4; KQFTK **X**ELSQLLKDIDGYGGIALPELI **X**TMFHTSGYDTQ (SEQ ID NO 3)

LDDDITDDIM **X**AKKILDIKGIDYWLAHKAL**X**TEKLEQWL **X**EKL (SEQ ID NO 4) where X is an amino acid residue other than cysteine.

In an example, the complex comprises a peptide of about or less than 45, 42, or 40 amino acids, in particular 39 amino acids, preferably corresponding to the Alpha 1 domain of human alpha-lactalbumin.

In one example, the functional variant consists of a sequence lacking disulfide bonds. In one example, the functional variant consists of a sequence in which cysteine residues in the native alpha-lactalbumin are changed to other amino acid residues, preferably alanine residues.

In one example, the fatty acid or lipid or salt thereof is a fatty acid or salt thereof. In one example, the fatty acid or salt thereof is oleic acid or an oleate salt.

In one example, the polypeptide has the sequence of bovine alpha-lactalbumin and the fatty acid or salt thereof is oleic acid or an oleate salt.

The polypeptide present in the complex may have the sequence of an α-lactalbumin or a variant thereof as described above.

The complex may be referred to as a biologically active complex. As used herein, the term "biologically active" means that the complex has a biological activity, which is different from, or stronger than the individual components. In particular, the complex is able to induce cell death in particular selectively in tumor cells and/or has a bactericidal or antiviral effect not seen with the native protein including for example monomeric α-lactalbumin forms, although other therapeutic effects may be available.

The expression "variant" refers to proteins or polypeptides having a similar biological function but in which the amino acid sequence differs from the base sequence from which it is derived in that one or more amino acids within the sequence are substituted for other amino acids. Amino acid substitutions may be regarded as "conservative" where an amino acid is replaced with a different amino acid with broadly similar properties. Non-conservative substitutions are where amino acids are replaced with amino acids of a different type.

By "conservative substitution" is meant the substitution of an amino acid by another amino acid of the same class, in which the classes are defined as follows:

Class	Amino acid examples
Nonpolar:	A, V, L, I, P, M, F, W
Uncharged polar:	G, S, T, C, Y, N, Q

Class	Amino acid examples
Acidic:	D, E
Basic:	K, R, H.

As is well known to those skilled in the art, altering the primary structure of a peptide by a conservative substitution may not significantly alter the activity of that peptide because the side-chain of the amino acid which is inserted into the sequence may be able to form similar bonds and contacts as the side chain of the amino acid which has been substituted out. This is so even when the substitution is in a region which is critical in determining the peptide's conformation.

Non-conservative substitutions are possible provided that these do not interrupt the function of the DNA binding domain polypeptides. Broadly speaking, fewer non-conservative substitutions will be possible without altering the biological activity of the polypeptides.

Determination of the effect of any substitution (and, indeed, of any amino acid deletion or insertion) is wholly within the routine capabilities of the skilled person, who can readily determine whether a variant polypeptide retains the fundamental properties and activity of the basic protein. For example, when determining whether a variant of the polypeptide falls within the scope of the disclosure, the skilled person will determine whether complexes comprising the variant retain biological activity (e.g., tumor cell death) of complexes formed with unfolded forms of the native protein and the polypeptide has at least 60%, preferably at least 70%, more preferably at least 80%, yet more preferably 90%, 95%, 96%, 97%, 98%, 99% or 100% of the native protein.

Variants of the polypeptide may comprise or consist essentially of an amino acid sequence with at least 70% identity, for example at least 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 96%, 97%, 98% or 99% identity to a native protein sequence such as an alpha-lactalbumin or lysozyme sequence.

The level of sequence identity is suitably determined using the BLASTP computer program with the native protein sequences as the base sequence. This means that native protein sequences form the sequence against which the percentage identity is determined. The BLAST software is publicly available at http://blast.ncbi.nlm.nih.gov/Blast.cgi (accessible on 12 March 2009).

In a particular example, the polypeptide is an α-lactalbumin such as human, bovine or ovine α-lactalbumin. Whilst variants of these as described above may be useful in the

disclosure, for nutraceutical use in particular, it may be preferable to utilize the native proteins in the products. A particular example used human α-lactalbumin. In another example, the α-lactalbumin is bovine α-lactalbumin. The sequence of a wide range of α-lactalbumins is known in the literature, for example as shown in Watanabe *et al.,* J. Vet Med Sci, (2000) 62(11); 1217-1219.

In another example, the polypeptide comprises a recombinant protein having the sequence of α-lactalbumin or a fragment thereof but which lacks intra-molecular disulfide bonds or cross-links. By ensuring that the recombinant protein lacks intra-molecular disulfide crosslinks, the molecule will be three-dimensionally non-native and completely inactive in terms of its original endogenous biological activity. This is achieved by changing cysteine residues in the native α-lactalbumin to other residues, in particular alanine residues. Preferably all cysteine residues will be changed to other residues, such as alanine residues. In particular the recombinant protein is based upon the sequence of human α-lactalbumin but α-lactalbumin from other sources, including bovine or ovine α-lactalbumin may be used to derive the recombinant protein.

In a particular example, the polypeptide is a recombinant protein having the sequence of native mature α-lactalbumin but which has all of the cysteines found at positions 6, 28, 61, 73, 77, 91, 111 and 120 in the full length sequence of mature human α-lactalbumin mutated to other amino acids, such as alanine, which do not give rise to disulphide bridges. Thus, a particular of a protein that may be utilised in accordance with the disclosure comprises a protein of SEQ ID NO 1.

KQFTK**A**ELSQLLKDIDGYGGIALPELI**A**TMFHTSGYDTQAIVENNESTEYGLFQISNKLW**A**
KSSQVPQSRNI**A**DIS**A**DKFLDDDITDDIM**A**AKKILDIKGIDYWLAHKAL**A**TEKLEQWL**A**E
KL (SEQ ID NO 1)

where the bold type indicates positions of mutations of cysteines in native human α-lactalbumin.

As reported in WO2010079362, additional amino acid residues, for example up to 20 amino acids, may be attached at N and/or C terminal of the protein, if convenient, for example for expression purposes. Thus in particular, a recombinant protein as shown in SEQ ID NO. 1 but with an additional methionine at the N-terminus (SEQ ID NO 2 shown below) has been used in the complex of the disclosure.

MKQFTK**A**ELSQLLKDIDGYGGIALPELI**A**TMFHTSGYDTQAIVENNESTEYGLFQISNKL
W**A**KSSQVPQSRNI**A**DIS**A**DKFLDDDITDDIM**A**AKKILDIKGIDYWLAHKAL**A**TEKLEQWL
AEKL (SEQ ID NO 2)

The polypeptide used in the complex is suitably in pure form, and is suitably prepared using conventional methods of peptide synthesis or by recombinant expression. In particular, DNA encoding the required recombinant α-lactalbumin can be inserted into suitable expression vectors such as plasmids, which can then be employed to transform host cells, for example, prokaryotic cells such as *E. coli* or eukaryotic cells such as particular insect cells using conventional methods.

Suitable fatty acids or lipids include those known to provide biologically active complexes. These include fatty acids, for example as described in WO2008058547. Where salts are used, these are suitably water soluble salt. Particular examples of suitable salts may include alkali or alkaline earth metal salts. In a particular example, the salt is an alkali metal salt such as a sodium- or potassium salt. Where used in pharmaceuticals, the salts will be pharmaceutically acceptable.

Particular examples of fatty acids or lipids used in the present disclosure are those having from 4-30, for example from 6 to 28, such as from 8 to 26 carbon atoms. In particular examples, the fatty acid or lipid has from 10 to 24, such as from 12 to 22, for example from 14 to 20 carbon atoms. In particular, the fatty acid or lipid will have 16, 17, 18 or 20 carbon atoms. The fatty acids may be saturated or unsaturated.

In particular however, the complexes of the disclosure utilize fatty acids or salts of fatty acids having 18 carbon atoms. In one example, the complexes of the disclosure utilize fatty acids or salts of fatty acids having 18 carbon atoms and wherein the fatty acid chain is unsaturated. In one example, the fatty acid or salt of the fatty acid is a C18:1 fatty acid or salt thereof. A specific example is a C18:1 fatty acid or salt thereof of formula $CH_3(CH_2)_7CH=CH(CH_2)_7COOH$ or $CH_3(CH_2)_7CH=CH(CH_2)_7COO^-$. In one example, the fatty acid or salt thereof is oleic acid or oleate salt.

The complex may be prepared using methods similar to those described for example in WO99/26979, WO2008/138348, WO2010/131237, WO2014/023976, WO2018/210759, and WO2022/073982 the content of which is incorporated herein by reference. Not only has it been found that complexes can be prepared by contacting unfolded α-lactalbumin or derivatives thereof with co-factors in particular oleic acid or salts thereof under ion exchange conditions such as those found on an ion exchange column, but also incubation of solutions of α-lactalbumin or derivatives thereof with a co-factor at elevated temperatures, for example of from 50-80°C, for example from 50-70°C and in particular between 55-60°C will result in the production of suitable complexes for use in the disclosure.

These methods however have generally focused on attempting to recreate the conditions in which the protein becomes unfolded and complexed with oleic ions. Such work has focused

on using pure proteins including recombinant variant versions of the base proteins to facilitate the production of active complexes. Such starting materials however can also increase the cost of production.

It is known that complexes obtained using α-lactalbumin from sources other than human milk, and in particular, BAMLET, obtained using bovine α-lactalbumin shows a qualitatively similar effects on cells and in particular on tumor cells as HAMLET (see for instance, Rammer et al. (2010) Mol. Cancer Ther. 9(1) 24-32). Therefore, effects demonstrated hereinafter using BAMLET would be similarly observed if HAMLET or compositions based upon HAMLET are used instead of BAMLET.

Dosage

The amount of complex administered to an individual will depend upon a variety of factors including the nature of the composition as well as the risk factor. However, as a general rule, when administered perorally, from 1mg to 20g/dose of the biologically active complex is used for each administration, which is suitably administered daily. The daily dose may be, for example, at least or about 1mg, 2mg, 5mg, 10mg, 15mg, 20mg, 25mg, 50mg, 75mg, 100mg, 200mg, 300mg, 400mg, 500mg, 750mg, 1g, 2g, 3g, 4g, 5g, 7.5g, 10g, 12.5g, 15g, or 17.5g. Alternatively, or additionally, the daily dose may be less than 25g, 22.5g, 20g, 17.5g, 15g, 10g, 7.5g, 5g, 4g, 3g, 2g, 1g, 750mg, 500mg, 400mg, 300mg, 200mg, 100mg, 75mg, 50mg, 25mg, 20mg, 15mg, 10mg or 5mg. Alternatively, the complex may be for administration in a dosage of 0.1g to 1g per kg of bodyweight, daily. It may be for administration in a dosage of at least or about 0.1g, 0.2g, 0.3g, 0.4g, 0.5g, 0.6g, 0.g, 0.8g, 0.9g or 1g per kg of bodyweight, daily. Alternatively, or additionally, it may be for administration in a dosage of less than 1.5g, 1g, 0.9g, 0.8g, 0.7g, 0.6g 0.5g, 0.4g, 0.3g, 0.2g, 0.1 per kg of bodyweight, daily.

Food and beverage compositions

The complex or pharmaceutical composition may be in the form of a beverage, particularly drinking water, or a foodstuff, such as baby-food, or as an additive or component for a beverage or foodstuff, such as a powder for mixing into a drink, for example, in the manner of a protein shake. Such food and beverage compositions may be produced using standard techniques. Similarly, the complex or pharmaceutical composition may be in the form of a composition for providing parental or, preferably, intravenous nutrition.

The disclosure also provides a foodstuff, beverage, food additive or other nutritional composition comprising the complex as defined, particularly for use in treating cancer or a metabolic-related condition, as described in earlier examples of the disclosure.

CLAIMS

1. Use of a complex comprising a polypeptide having a sequence of a naturally occurring alpha-lactalbumin, or a functional variant thereof; or a peptide of up to 50 amino acids comprising an alpha-helical domain of said polypeptide; and a fatty acid or lipid or salt thereof, in the preparation of a pharmaceutical composition for the treatment or prevention of cancer; wherein the treatment or prevention comprises the complex to be administered at a first site, and wherein the cancer is at a second site.

2. Use of a complex comprising a polypeptide having a sequence of a naturally occurring alpha-lactalbumin, or a functional variant thereof; or a peptide of up to 50 amino acids comprising an alpha-helical domain of said polypeptide; and a fatty acid or lipid or salt thereof, in the preparation of a pharmaceutical composition for use as a checkpoint inhibitor, particularly an inhibitor of PD-1, or the prevention or treatment, particularly treatment, of PD-L1 positive cancers or other cancers that are susceptible to PD-1 targeting.

3. Use of a complex comprising a polypeptide having a sequence of a naturally occurring alpha-lactalbumin, or a functional variant thereof; or a peptide of up to 50 amino acids comprising an alpha-helical domain of said polypeptide; and a fatty acid or lipid or salt thereof, in the preparation of a pharmaceutical composition for the prevention, reduction, or treatment of metastasis.

4. Use of a complex comprising a polypeptide having a sequence of a naturally occurring alpha-lactalbumin, or a functional variant thereof; or a peptide of up to 50 amino acids comprising an alpha-helical domain of said polypeptide; and a fatty acid or lipid or salt thereof, in the preparation of a pharmaceutical composition for tumor surveillance and/or altering the tumor environment.

5. The use according to any of claims 2, 3 or 4, wherein the complex is to be administered at a first site and the cancer is at a second site.

6. The use according to any preceding claim, wherein the complex or pharmaceutical composition is to be administered to one of nasal passage, the GI tract, the brain, the lung, the kidney, the vagina, the bladder, the liver, the skin, the breast, the prostate and/or the ovary; and/or wherein the cancer is found in one or more of nasal passage, the GI tract, the brain, the lung, the kidney, the vagina, the bladder, the liver, the skin, the breast, the prostate and/or the ovary..

7. The use according to any preceding claim, wherein the site of administration of the complex or pharmaceutical composition and the site of the cancer are different;

optionally wherein the site of administration of the complex or pharmaceutical composition and the site of the cancer are remote from one another.

8. The use according to any preceding claim, wherein the cancer is primary cancer; or wherein the cancer is a metastasis.

9. The use according to any of claims 2, 3 or 8, wherein the site of administration of the complex or pharmaceutical composition and the site of the cancer are the same.

10. The use according to any preceding claim, wherein the polypeptide has a sequence of a naturally occurring alpha-lactalbumin, particularly a human or bovine alpha-lactalbumin; optionally wherein the polypeptide has a sequence of a bovine alpha-lactalbumin.

11. The use according to any preceding claim, wherein the alpha-helical domain is the Alpha 1 (residues 1-39) or Alpha 2 (residues 81-123) domain of human alpha-lactalbumin, being of SEQ ID NO 3 or SEQ ID NO 4;
KQFTK **X**ELSQLLKDIDGYGGIALPELI **X**TMFHTSGYDTQ (SEQ ID NO 3)
LDDDITDDIM **X**AKKILDIKGIDYWLAHKAL**X**TEKLEQWL **X**EKL (SEQ ID NO 4), where X is an amino acid residue other than cysteine.

12. The use according to any preceding claim, wherein the functional variant consists of a sequence lacking disulfide bonds; and/or wherein the functional variant consists of a sequence in which cysteine residues in the naturally occurring alpha-lactalbumin are changed to other amino acid residues, preferably alanine residues.

13. The use according to any preceding claim, wherein the fatty acid or lipid or salt thereof is a fatty acid or salt thereof, particularly oleic acid or an oleate salt.

14. The use according to any preceding claim, wherein the polypeptide has the sequence of bovine alpha-lactalbumin and the fatty acid or salt thereof is oleic acid or an oleate salt.

15. The use according to any preceding claim, wherein the complex or pharmaceutical composition is in the form of a beverage, a foodstuff, an additive or component for a beverage or foodstuff, or another a nutritional composition.