

CLAIMS

1. ~~A polypeptide comprising an Fc region of a human IgG and an antigen binding region, wherein the Fc region comprises a CH2 and a CH3 domain, said Fc region comprising a (i) first mutation and a (ii) second mutation corresponding to the following amino acid positions in human IgG1 according to EU numbering:
 - i. ~~first mutation at E430, E345 or S440, with the proviso that the mutation in S440 is S440Y or S440W; and~~
 - ii. ~~second mutation at K322 or P329.~~~~
2. ~~The polypeptide according to claim 1, wherein the first mutation is selected from the group consisting of: E430G, E345K, E430S, E430F, E430T, E345Q, E345R, E345Y, S440W and S440Y.~~
3. ~~The polypeptide according to claim 1, wherein the first mutation is selected from E430G or E345K.~~
4. ~~The polypeptide according to any one of the preceding claims, wherein the second mutation is selected from the group consisting of: K322E, K322D, K322N, P329H, P329K, P329R, P329D, P329E, P329F, P329G, P329I, P329L, P329M, P329N, P329Q, P329S, P329T, P329V, P329W P329A and P329Y.~~
5. ~~The polypeptide according to any one of the preceding claims, wherein the second mutation is K322E.~~
6. ~~The polypeptide according to any one of the preceding claims 1 to 4, wherein the second mutation is selected from the group of: P329R, P329K and P329D.~~
7. ~~The polypeptide according to any one of the preceding claims, wherein the Fc region comprises one or more further mutations.~~
8. ~~The polypeptide according to any one of the preceding claims, wherein the Fc region comprises one or more further mutations in the CH2 or CH3 domain.~~

- ~~9. The polypeptide according to claim 7 or 8, wherein the Fc region comprises a further mutation in the CH3 domain corresponding to position K439 or where the first mutation is not at position S440 the further mutation may be at position S440.~~
- ~~10. The polypeptide according to claim 9, wherein the further mutation is selected from S440K or K439E.~~
- ~~11. The polypeptide according to any one of the preceding claims, wherein the Fc region comprises at most ten mutations, such as nine mutations, such as eight mutations, such as seven mutations, such as six mutations; such as five mutations, such as four mutations, such as three mutations or such as two mutations.~~
- ~~12. The polypeptide according to any one of the preceding claims, wherein the polypeptide has an Fc effector function which is decreased by at least 20%, such as by at least 30% or at least 40%, or at least 50% or by at least 60% or by at least 70%, or by at least 80% or by at least 90% compared to a parent polypeptide which is identical to the polypeptide with the same first mutation but without the second mutation.~~
- ~~13. The polypeptide according to any one of the preceding claims, wherein the polypeptide does not induce an Fc effector function.~~
- ~~14. The polypeptide according to claims 12 to 13, wherein the Fc effector function is selected from the following group; complement dependent cytotoxicity (CDC), complement dependent cell mediated cytotoxicity (CDCC), complement activation, antibody dependent cell mediated cytotoxicity (ADCC), antibody dependent cell mediated phagocytosis (ADCP), C1q binding and FcγR binding.~~
- ~~15. The polypeptide according to any one of the preceding claims, wherein the polypeptide is an antibody, monospecific antibody, bispecific antibody or multispecific antibody.~~

~~16. The polypeptide according to any one of the preceding claims, wherein the Fc region is a human IgG1, IgG2, IgG3, IgG4, IgE, IgD, IgM, IgA isotype or a mixed isotype.~~

~~17. The polypeptide according to any one of the preceding claims, wherein the Fc region is a human IgG1 isotype.~~

~~18. The polypeptide according to any one of the preceding claims, wherein the polypeptide is a human antibody, humanized antibody or chimeric antibody.~~

~~19. The polypeptide according to any one of the preceding claims, wherein the antigen binding region binds to a member of the TNFR-SF.~~

~~20. The polypeptide according to claim 19, wherein the TNFR-SF does not comprise an intracellular death domain.~~

~~21. The polypeptide according to claim 19, wherein the member of the TNFR-SF is selected from the group of: FAS, DR4, DR5, TNFR1, DR6, DR3, EDAR, and NGFR.~~

~~22. The polypeptide according to claim 20, wherein the TNFR-SF is selected from the group of: OX40, CD40, CD30, CD27, 4-1BB, RANK, TACI, BLySR, BCMA, RELT and GITR.~~

~~23. A method of decreasing an Fc-effector function of a polypeptide comprising an Fc-region of a human immunoglobulin and an antigen binding region, wherein the Fc-region comprises a CH2 and CH3 domain, said Fc-region comprising a (i) first mutation corresponding to the following positions in human IgG1 according to EU-numbering: E430, E345 or S440, which method comprises introducing a (ii) second mutation corresponding to the following positions in human IgG1 according to EU-numbering: K322 or P329.~~

~~24. The method according to claim 23, wherein the first mutation is selected from the group consisting of: E430G, E345K, E430S, E430F, E430T, E345Q, E345R, E345Y, S440W and S440Y.~~

- ~~25. The method according to claims 23 or 24, wherein the first mutation is selected from E430G or E345K.~~
- ~~26. The method according to claims 23 to 25, wherein the second mutation is selected from the group consisting of: K322E, K322D, K322N, P329H, P329K, P329R, P329D, P329E, P329F, P329G, P329I, P329L, P329M, P329N, P329Q, P329S, P329T, P329V, P329W, P329A and P329Y.~~
- ~~27. The method according to any of claims 23 to 26, wherein the second mutation is selected from the group of: K322E, P329R, P329K and P329D.~~
- ~~28. The method according to any one of claims 23 to 27, wherein the Fc region comprises one or more further mutations in the CH3 domain.~~
- ~~29. The method according to claim 28, wherein the Fc region comprises a further mutation in the CH3 domain corresponding to one of the following positions in human IgG1 according to EU numbering: S440 or K439.~~
- ~~30. The method according to claim 29, wherein the further mutation is selected from S440K or K439E.~~
- ~~31. The method according to any one of claims 23 to 30, wherein the Fc effector function is decreased by at least 20%, such as by at least 30% or at least 40%, or at least 50% or by at least 60% or by at least 70%, or by at least 80% or by at least 90% compared to a parent polypeptide which is identical to the polypeptide with the same first mutation but without the second mutation.~~
- ~~32. The method according to any one of claims 23 or 31, wherein the Fc effector function is selected from the following group; complement dependent cytotoxicity (CDC), complement dependent cell mediated cytotoxicity (CDCC), antibody dependent cell mediated cytotoxicity (ADCC), antibody dependent cell mediated phagocytosis (ADCP), C1q binding and FcγR binding.~~

- ~~33. The method according to claims 32, wherein ADCC is decreased by at least 20%, at least 50%, at least 60%, at least, 70%, at least, 80%, at least, 90%, at least 100% compared to a comparison antibody which is identical to the antibody except that it does not comprise the second mutation.~~
- ~~34. A composition comprising at least one polypeptide according to any one of claims 1-22.~~
- ~~35. The composition according to claim 34 comprising one or more polypeptides according to any one of the preceding claims.~~
- ~~36. The composition according to any one of claims 34 to 35, which comprises a first polypeptide and a second polypeptide as defined in any one of the preceding claims 1-22.~~
- ~~37. The composition according to any one of claims 36, which comprises a first polypeptide comprising a first antigen binding region and a first Fc region, a second polypeptide or antibody comprising second antigen binding region and a second Fc region, wherein the first and second Fc region comprises (i) a first mutation, (ii) a second mutation, (iii) a further mutation, wherein the mutations corresponds to the following amino acid positions in human IgG1, according to EU numbering:~~
- ~~(i) — a first mutation E430, E345 or S440, with the proviso that the mutation in S440 is S440Y or S440W;~~
- ~~(ii) — a second mutation at E322 or P329;~~
- ~~(iii) — a further mutation at K439 or S440, with the proviso that if the further mutation is at S440 then the first mutation is not at S440, with the proviso that the first and second Fc region does not comprise a further mutation in the same amino acid position.~~
- ~~38. The composition according to any one of the claims 36 to 37, wherein said first polypeptide and said second polypeptide bind different epitopes on one or more members of the TNFR-SF with an intracellular death domain selected from the following group consisting of: TNFR1, FAS, DR3, DR4, DR5, DR6, NGFR and EDAR.~~

- ~~39. The composition according to any one of the claims 36 to 37, wherein said first polypeptide and said second polypeptide bind different epitopes on one or more members of the TNFR-SF without an intracellular death domain, such as OX40, CD40, CD30, CD27, 4-1BB, RANK, TACI, BLySR, BCMA, RELT and GITR.~~
- ~~40. The composition according to any one of the claims 36 to 37, wherein said first polypeptide binding to one member of the TNFR-SF without an intracellular death domain, such as OX40, CD40, CD30, CD27, 4-1BB, RANK, TACI, BLySR, BCMA, RELT and GITR does not block binding of said second antibody binding to one member of the TNFR-SF without an intracellular death domain, such as OX40, CD40, CD30, CD27, 4-1BB, RANK, TACI, BLySR, BCMA, RELT and GITR.~~
- ~~41. The composition according to any one of the claims 34 to 40, wherein said first polypeptide and said second polypeptide are present in the composition at a 1:49 to 49:1 molar ratio, such as a 1:1 molar ratio, a 1:2 molar ratio, a 1:3 molar ratio, a 1:4 molar ratio, a 1:5 molar ratio, a 1:6 molar ratio, a 1:7 molar ratio, a 1:8 molar ratio, a 1:9 molar ratio, a 1:10 molar ratio, a 1:15 molar ratio, a 1:20 molar ratio, a 1:25 molar ratio, a 1:30 molar ratio, a 1:35 molar ratio, a 1:40 molar ratio, a 1:45 molar ratio, a 1:50 molar ratio, a 50:1 molar ratio, a 45:1 molar ratio, a 40:1 molar ratio, a 35:1 molar ratio, a 30:1 molar ratio, a 25:1 molar ratio, a 20:1 molar ratio, a 15:1 molar ratio, a 10:1 molar ratio, a 9:1 molar ratio, a 8:1 molar ratio, a 7:1 molar ratio, a 6:1 molar ratio, a 5:1 molar ratio, a 4:1 molar ratio, a 3:1 molar ratio, a 2:1 molar ratio.~~
- ~~42. The composition according to any one of the claims 34 to 40, wherein said first polypeptide and said second polypeptide and/or any additional polypeptide are present in the composition at an equimolar ratio.~~
- ~~43. The composition according to any one of the claims 34 to 42, wherein the composition is a pharmaceutical composition.~~

- ~~44. A polypeptide according to any of claims 1-22 or a composition according to any of claims 34-43 for use as a medicament.~~
- ~~45. A polypeptide according to any of claims 1-22 or a composition according to any of claims 34-44 for use in the treatment of cancer, autoimmune disease, inflammatory disease or infectious disease.~~
- ~~46. A method of treating an individual having a disease comprising administering to said individual an effective amount of an antibody or composition according to any of the preceding claims.~~
- ~~47. The method according to claim 46, wherein the disease is selected from the group of: cancer, autoimmune disease, inflammatory disease and infectious disease.~~
- ~~48. The method according to any one of claims 46 to 47, comprising further administering an additional therapeutic agent.~~
- ~~49. The method according to claim 48, wherein the additional therapeutic agent is one or more anti-cancer agent(s) selected from the group consisting of chemotherapeutics (including but not limited to paclitaxel, temozolomide, cisplatin, carboplatin, oxaliplatin, irinotecan, doxorubicin, gemcitabine, 5-fluorouracil, pemetrexed), kinase inhibitors (including but not limited to sorafenib, sunitinib or everolimus), apoptosis modulating agents (including but not limited to recombinant human TRAIL or birinapant), RAS inhibitors, proteasome inhibitors (including but not limited to bortezomib), histone deacetylase inhibitors (including but not limited to vorinostat), nutraceuticals, cytokines (including but not limited to IFN- γ), antibodies or antibody mimetics (including but not limited to anti-EGFR, anti-IGF-1R, anti-VEGF, anti-CD20, anti-CD38, anti-HER2, anti-PD-1, anti-PD-L1, anti-CTLA4, anti-CD40, anti-CD137, anti-GITR antibodies and antibody mimetics), antibody drug conjugates.~~

~~50. A kit of parts comprising a polypeptide, or composition according to any one of the preceding claims, wherein said polypeptide, or composition is in one or more containers such as vials.~~

~~51. The kit of parts according to claim 50, wherein the polypeptide or composition according to any one of the preceding claims is for simultaneous, separate or sequential use in therapy.~~

~~52. Use of a polypeptide or a composition according to any of the previous claims 1-43 for the manufacture of a medicament for treatment of a disease.~~

~~53. Use according to claim 52, wherein the disease is cancer, autoimmune disease, inflammatory disease or infectious disease.~~

CLAIMS

1. An invention not claimed in any divisional application.