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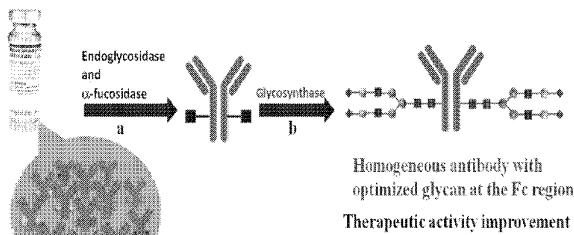
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- (72) Inventors: **WU, Chung-Yi**; No. 78-1, Dongshi Street, Xi-Zhi District, New Taipei City, 221 (CN). **MA, Che**; c/o Academia Sinica, 128 Academia Road, Section 2, Nankang, Taipei, 11529 (CN).
- (74) Agent: **NORTON, Vicki**; Duane Morris LLP, Suite 2900, 750 B Street, San Diego, California 92101 (US).
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- (71) Applicant: **ACADEMIA SINICA**; 128 Academia Road, Section 2, Nankang, Taipei, 11529 (CN).
- (72) Inventor: and
- (71) Applicant : **WONG, Chi-Huey** [US/US]; P.O. Box 8154, Rancho Santa Fe, California 92067 (US).

[Continued on next page]

(54) Title: COMPOSITIONS AND METHODS RELATING TO UNIVERSAL GLYCOFORMS FOR ENHANCED ANTIBODY EFFICACY



Heterogeneous Antibodies
More than 50 glycans on Fc Asn297

Fig. 1a

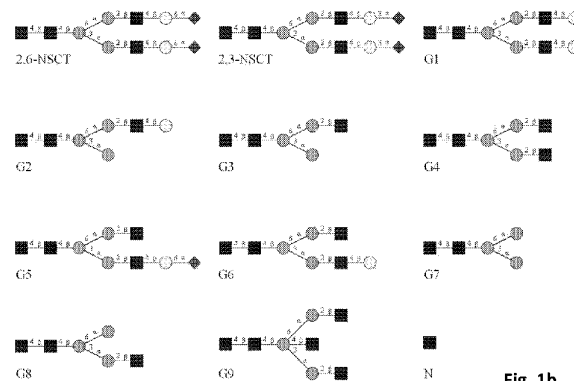


Fig. 1b

(57) Abstract: The present disclosure relates to glycoproteins, particularly monoclonal antibodies, comprising a glycoengineered Fc region, wherein said Fc region comprises an optimized N-glycan having the structure of Sia₂(α2-6)Gal₂GlcNAc₂Man₃GlcNAc₂. The glycoengineered Fc region binds FcγRIIA or FcγRIIIA with a greater affinity, relative to comparable monoclonal antibodies comprising the wild-type Fc region. The monoclonal antibodies of the invention are particularly useful in preventing, treating, or ameliorating one or more symptoms associated with a disease, disorder, or infection where an enhanced efficacy of effector cell function (e.g., ADCC) mediated by FcγR is desired, e.g., cancer, autoimmune, infectious disease, and in enhancing the therapeutic efficacy of therapeutic antibodies the effect of which is mediated by ADCC.

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**COMPOSITIONS AND METHODS RELATING TO UNIVERSAL GLYCOFORMS
FOR ENHANCED ANTIBODY EFFICACY**

RELATED APPLICATIONS

[0001] This applications claims the benefit of priority to US provisional applications US Serial No. (USSN) 62/003,136, filed May 27, 2014, USSN 62/003,104, filed May 27, 2014, USSN 62/003,908, filed May 28, 2014, USSN 62/020,199, filed July 2, 2014, and USSN 62/110,338, filed January 30, 2015. The contents of each of which is hereby incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

[0002] Antibody-based therapies have a proven record of efficacy against many diseases including inflammatory disorders, cancers, infectious diseases, and solid organ transplant rejection. Currently more than 40 therapeutic monoclonal antibodies (mAbs) are approved for clinical use in USA, EU and several other countries. Most of them are for therapy of cancer and immune diseases. Examples of therapeutic antibodies with anti-tumor activities include anti-CD20, anti-Her2, anti-EGFR, anti-CD40, anti-CTLA-4, and anti-PD-1 antibodies.

[0003] Most of therapeutic antibodies are monoclonal and prepared by the hybridoma technology in which transgenic humanized mice were incorporated to express murine/human chimeric or humanized antibodies to avoid undesired immunological responses derived from species difference. Recently, the development of fully human antibodies has become a major trend and its impressive progress is beneficial from the utilization of phage-displayed antibody libraries or single B cells.

[0004] Like many other mammalian proteins, antibodies are heterogeneously glycosylated, and the glycosylation in the Fc region has been an important issue in the development of efficacious and safe therapeutic monoclonal antibodies because the glycan can significantly affect the antibody's activity through interaction with the Fc receptors. Consequently, there is a need for the development of homogeneous monoclonal antibodies with well-defined Fc-glycan to understand these interactions and to improve the safety and efficacy in medication. Toward this goal, it has been reported that the removal of the core fucose residue would enhance the antibody-dependent cellular cytotoxicity (ADCC) activity of IgGs due to the increased interaction between Fc-glycan and human FcγRIIIa receptor. The two FDA approved glyco-engineered antibodies, mogamulizumab (POTELLIGENT[®]) and obinutuzuman (GA101), are defucosylated antibodies in which POTELLIGENT[®] was produced by the FUT8 knockout CHO

cell line and GA101 was from the GnT-III overexpressing system. In addition, more Fc γ IIIa was expressed on the monocytes of long-term RA, and the tendency of more fucosylation was also found in the IgG heavy chain of RA patients, implying the possibility of RA treatment and remission with afucosylated pharmaceutical antibodies, which not only neutralize proinflammatory cytokines but also compete with autologous autoantibodies for Fc γ IIIa.

[0005] Thus, it is of great interest to generate therapeutic monoclonal antibodies with optimized Fc glycoforms.

SUMMARY OF THE INVENTION

[0006] The present disclosure is based on the discovery of glyco-optimized Fc for monoclonal antibodies, specifically a homogeneous population of monoclonal antibodies (“glycoantibodies”). The optimized glycoform exhibits an enhanced efficacy of effector cell function (e.g., ADCC).

[0007] The term “glycoantibodies” was coined by the inventor, Dr. Chi-Huey Wong, to refer to a homogeneous population of monoclonal antibodies (preferably, therapeutic monoclonal antibodies) having a single, uniform N-glycan on Fc. The individual glycoantibodies comprising the homogeneous population are substantially identical, bind to the same epitope, and contain the same Fc glycan with a well-defined glycan structure and sequence.

[0008] "Substantially identical" means the objects being compared have such close resemblance as to be essentially the same - as understood by one having ordinary skill in the art. "Substantially identical" encompasses "identical".

[0009] As used herein, the term “glycoantibodies” (“GAbs”) refers to a homogeneous population of IgG molecules having the same N-glycan on Fc. The term “glycoantibody” (“GAb”) refers to an individual IgG molecule in the glycoantibodies.

[0010] Accordingly, one aspect of the present disclosure relates to a composition of a homogeneous population of monoclonal antibodies comprising a single, uniform N-glycan on Fc, wherein the structure is an optimized N-glycan structure for enhancing the efficacy of effector cell function.

[0011] In preferred embodiments, the N-glycan is attached to the Asn-297 of the Fc region.

[0012] In preferred embodiments, wherein the N-glycan consists of the structure of Sia₂(α -6)Gal₂GlcNAc₂Man₃GlcNAc₂.

[0013] The glycoantibodies described herein may be produced *in vitro*. The glycoantibodies may be generated by Fc glycoengineering. In certain embodiments, the glycoantibodies are enzymatically or chemoenzymatically engineered from the monoclonal antibodies obtained by mammalian cell culturing.

[0014] In some embodiments, the Fc region of the glycoantibodies described herein exhibits an increased binding affinity for Fc γ RIIA or Fc γ RIIIA relative to a wild-type Fc region in the corresponding monoclonal antibodies.

[0015] In some embodiments, the glycoantibodies described herein exhibit an enhanced antibody-dependent cell mediated cytotoxicity (ADCC) activity relative to wild-type immunoglobulins.

[0016] In some embodiments, the glycoantibodies are selected from a group consisting of human IgG1, IgG2, IgG3, and IgG4.

[0017] The monoclonal antibodies may be humanized, human or chimeric.

[0018] The glycoantibodies described herein may bind to an antigen associated with cancers, autoimmune disorders, inflammatory disorders or infectious diseases.

[0019] In some embodiments, the glycoantibody described herein is a glycoengineered anti-CD20. In some examples, the glycoantibody described herein is a glycoengineered Rituximab (Rituxan[®]).

[0020] In some embodiments, the glycoantibody described herein is a glycoengineered anti-HER2. In some examples, the glycoantibody described herein is a glycoengineered Trastuzumab (Herceptin[®]).

[0021] In some embodiments, the glycoantibody described herein is a glycoengineered anti-TNF α . In some examples, the glycoantibody described herein is a glycoengineered Adalimumab (Humira[®]).

[0022] In some embodiments, the glycoantibody described herein is a glycoengineered F16 antibodies.

[0023] Another aspect of the present disclosure features a pharmaceutical composition comprising a composition of glycoantibodies described herein and a pharmaceutically acceptable carrier. The pharmaceutical composition may be used in therapeutics such as oncology, autoimmune disorders, inflammatory disorders and infectious diseases.

[0024] In some embodiments, the pharmaceutical composition is used for preventing, treating, or ameliorating one or more symptoms associated with a disease, disorder, or infection where an enhanced efficacy of effector cell function (e.g., ADCC) mediated by Fc γ R is desired, e.g., cancer, autoimmune, infectious disease, and in enhancing the therapeutic efficacy of therapeutic antibodies the effect of which is mediated by ADCC.

[0025] Disclosed herein also include methods for enhancing antibody-dependent cell mediated cytotoxicity (ADCC) activity, the method comprising administering to a subject an amount of glycoantibodies described herein.

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