Figure 5 is a sequence (SEQ ID NO: 363) showing an Fc fusion protein that was used as an immunogen to generate antigen binding proteins; the immunogen comprises the extracellular domain (ECD) of human β-Klotho fused to an IgG1 Fc via a Gly_5 linker (SEQ ID NO: 379); the β-Klotho component is in capitals, the linker is italic and underlined and the Fc is in lower case letters.

Figure 6 is a SDS PAGE gel showing the level of purity achieved from preparations of a soluble FGF21 receptor complex comprising FGFR1c ECD-Fc and β-Klotho ECD-Fc, which was employed as an immunogen to generate antigen binding proteins.

Figure 7 is a series of plots generated from an ELK-luciferase reporter assay as described herein performed on recombinant CHO clone 2E10, demonstrating the ability of some of the antigen binding proteins to induce FGF21-like signaling in recombinant CHO cells expressing a FGF21 receptor complex comprising FGFR1c and β–Klotho.

Figure 8 is a series of plots generated from an ERK1/2 phosphorylation assay as described herein, demonstrating the ability of some of the antigen binding proteins to induce FGF21-like signaling in rat L6 cells. The X-axis is the concentrations of the antigen binding proteins and the Y-axis is the percentage of phosphorylated ERK1/2 of total ERK1/2.

Figure 9 is a series of plots generated from an ERK1/2 phosphorylation assay as described herein, demonstrating that antigen binding protein-mediated FGF21-like signaling in L6 cells is FGFR1c/β-Klotho specific.

Figure 10 is a series of plots generated from an ERK phosphorylation assay as described herein, demonstrating that some antigen binding proteins are able to induce FGF21-like signaling in human adipocyte cells.

Figure 11A~~a~~-11C is a series of binding sensorgrams (response units vs time) demonstrating that some of the antigen binding proteins that induce FGF21-mediated signaling bind to human β-Klotho at two different but partially overlapping binding sites represented by 24H11 (Group A) and 17D8 (Group B), while antigen binding proteins that do not induce FGF21-mediated signaling (2G10, 1A2) do not bind to these sites.

FIGS. 11D-11F are a series of binding sensorgrams (response units vs time) demonstrating a third binding site on human β-Klotho that was identified for Group C antigen binding proteins represented by 39F7.

FIG. 11G is a table summarizing epitope binning.~~Figure 11b is a series of binding sensorgrams (response units vs time) demonstrating a third binding site on human β-Klotho that was identified for Group C antigen binding proteins represented by 39F7.~~

example (and as shown in Figure 11), two representative agonistic FGF21 receptor antibodies (24H11 and 17D8) and one non-functional FGF21 receptor binding antibodies (1A2.1) were immobilized on the sensor chip surface. Soluble human FGFR1c/β–Klotho ECD-Fc complex or β–Klotho was then captured on the immobilized antibody surfaces. Finally, several of the test FGF21 receptor antibodies were injected individually over the captured soluble human FGF21 receptor or β–Klotho. If the injected antibody recognizes a distinct binding site relative to that recognized by the immobilized antibody, a second binding event will be observed. If the antibodies recognize very similar binding site, no more binding will be observed.

As shown in (Figures 11A to 11C), there are two distinct yet partially overlapping binding sites for the agonistic antibodies tested. One site is covered by 24H11, 21H2, 18B11.1 and 17C3 (Group A) and the other site covered by 17D8, 12E4 and 18G1 (Group B). The two non-functional antibodies 2G10 and 1A2, bind to different sites from each other and are distinct from the two sites covered by the agonistic antibodies in Group A and B. Other functional antibodies binding to Group A epitope included 20D4, 22H5, 16H7, 40D2 and 46D11. Two other functional antibodies 26H11 and 37D3 were shown by this method to bind the same site covered by the Group B antibodies. In addition, a third binding site for functional antibodies was identified for 39F11, 39F7 and 39G5 (group C) which appeared to be distinct from Group A and B binding sites (Figures ~~11B~~11D to 11F).

Another Biacore analysis was carried out with biotinylated-FGF21 immobilized on the sensor ship. 10 nM soluble β–Klotho was then passed over the chip alone or mixed with the individual test antibodies at 100nM. (Figure 12) showed that several agonistic antibodies in group A (24H11, 18B11, 17C3) and antibody 12E4 (from group B) competed significantly with FGF21 in binding to soluble β–Klotho whereas the non-functional antibodies 2G10 and 1A2 and several other functional antibodies did not show competition binding with FGF21.

Figure ~~11C~~ 11G summarizes the ~~binning~~ binding results obtained.

EXAMPLE 9

RECOGNITION OF NATIVE AND DENATURES STRUCTURES

The ability of disclosed antigen binding proteins to recognize denatured and native structures was investigated. The procedure and results were as follows.

CLAIMS

What is claimed is:

1. An isolated antibody that induces FGF21-mediated signaling and comprises a heavy and light chain comprising the amino acid sequences of SEQ ID NO: 14 and SEQ ID NO: 32.

2. An isolated antibody that induces FGF21-mediated signaling and comprises CDRs comprising the amino acid sequences of SEQ ID NOs: 122, 133, 148, 166, 176, and 188.

3. An isolated antibody that induces FGF21-mediated signaling and comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 68 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 50.

4. An isolated antibody that induces FGF21-mediated signaling and comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 32 and a light chain comprising the amino acid sequence of SEQ ID NO: 387.

5. An isolated antibody that induces FGF21-mediated signaling and comprises a light chain comprising the amino acid sequence of SEQ ID NO: 14 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 390.

6. An isolated antibody that induces FGF21-mediated signaling and comprises a light chain comprising the amino acid sequence of SEQ ID NO: 14 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 391.

7. An isolated antibody that induces FGF21-mediated signaling and comprises a light chain comprising the amino acid sequence of SEQ ID NO: 14 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 392.

8. An isolated antibody that induces FGF21-mediated signaling and comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 32 and a light chain comprising the amino acid sequence of SEQ ID NO: 385 or SEQ ID NO: 386.

9. An isolated antibody that induces FGF21-mediated signaling and comprises a light chain comprising the amino acid sequence of SEQ ID NO: 387 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 391.

10. A pharmaceutical composition comprising an antibody of any one of claims 1-9 in admixture with a pharmaceutically acceptable carrier thereof.

CLAIMS

What is claimed is:

1. An isolated antibody that induces FGF21-mediated signaling and comprises SEQ ID NO: 14 and SEQ ID NO: 32.

2. An isolated antibody that induces FGF21-mediated signaling and comprises SEQ ID NO: 385.

3. An isolated antibody that induces FGF21-mediated signaling and comprises SEQ ID NO: 386.

4. An isolated antibody that induces FGF21-mediated signaling and comprises SEQ ID NO: 387.

5. An isolated antibody that induces FGF21-mediated signaling and comprises SEQ ID NO: 390

6. An isolated antibody that induces FGF21-mediated signaling and comprises SEQ ID NO: 391.

7. An isolated antibody that induces FGF21-mediated signaling and comprises SEQ ID NO: 392.

8. An isolated antibody that induces FGF21-mediated signaling and comprises SEQ ID NO: 385 and SEQ ID NO: 386.

9. An isolated antibody that induces FGF21-mediated signaling and comprises SEQ ID NO: 387 and SEQ ID NO: 391.

10. The isolated antibody 16H7 capable of inducing FGF21-mediated signaling.

11. A pharmaceutical composition comprising one or more antigen binding proteins of claim 1 in admixture with a pharmaceutically acceptable carrier thereof.

12. A pharmaceutical composition comprising an antigen binding proteins of claims 1-10 in admixture with a pharmaceutically acceptable carrier thereof.