

N.A.B.C.

Need	Current treatment for neuroblastomas in children results in pain, requiring additional pain management medications and administration in hospitals.
Approach	Develop a naked GD2xB7H3 antibody. Show that molecule binding to GD2 and B7H3, kills tumors, and reduces pain.
Benefit	Scientific: Improved therapeutic windows and broader use than current therapies. Decreased pain for patients
Competition	Current approved treatment is Unituxin (Dinutuximab) developed at the NCI and distributed through ASD Healthcare.

FIG. 1

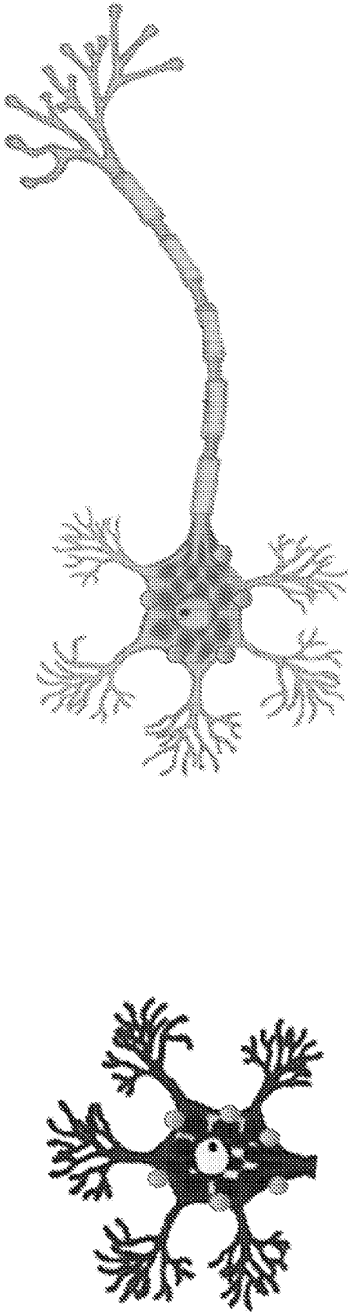
Goal

- The goal is to create a binding molecule (also referred to as “SNIPER” molecule) that will target neuroblastomas specifically and reduce off target pain associated with current therapies.
 - GD2 (Ganglioside antigen GD2)
 - A ganglioside that is expressed on cancers of neuroectodermal origin for example Neuroblastoma
 - Expressed on peripheral nerves, which can lead to off target pain in current GD2 therapies
 - B7H3 (also known as Cluster of Differentiation 276 (CD276))
 - An immune checkpoint that can inhibit t-cell function
 - B7H3 is overexpressed on many cancer cell types including neuroblastoma

FIG. 2

Cell Selectivity with SNIPER™ FIG. 3A

● GD2



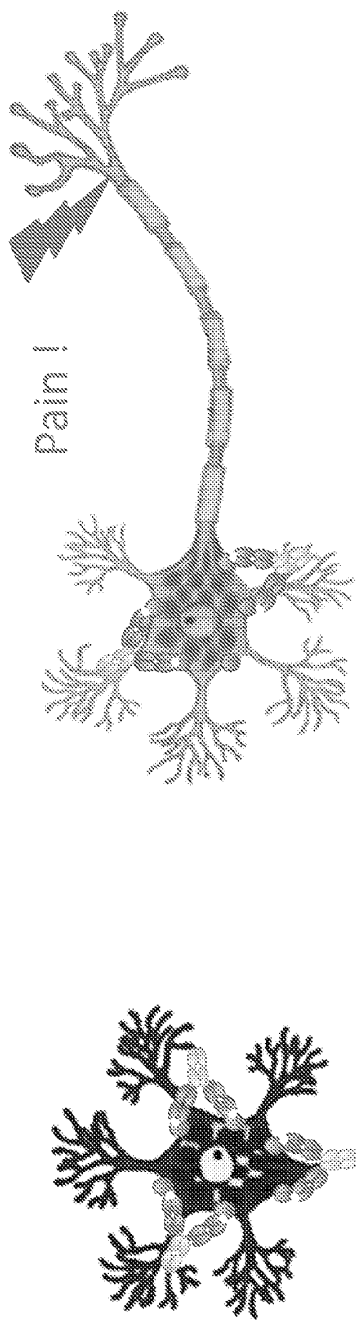
A. Neuroblastoma Cell

B. Healthy Peripheral Nerve

SNIPER™ Avoids Off Target Neurons and Pain

Cell Selectivity with SNIPER™

GD2



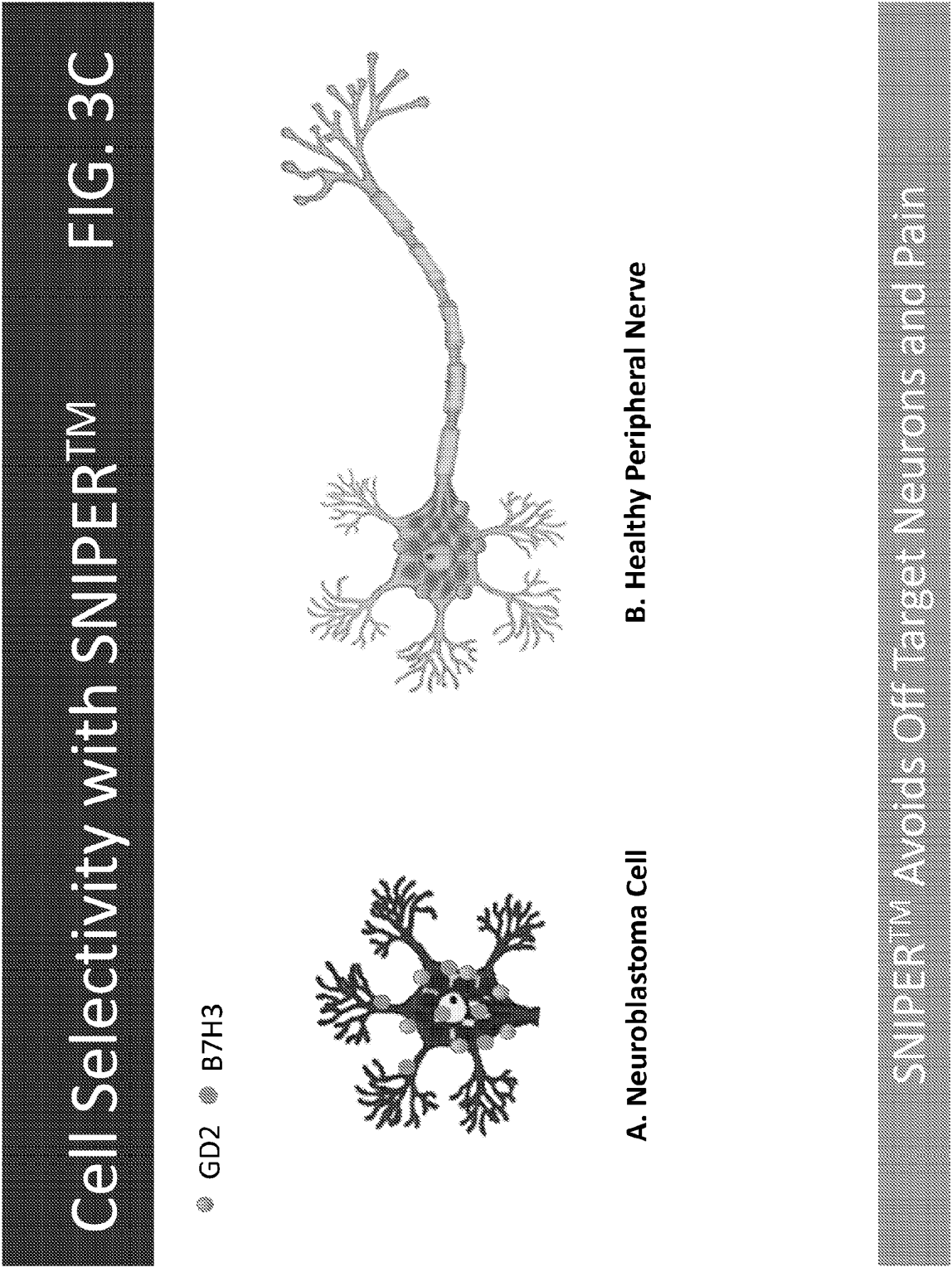
A. Neuroblastoma Cell

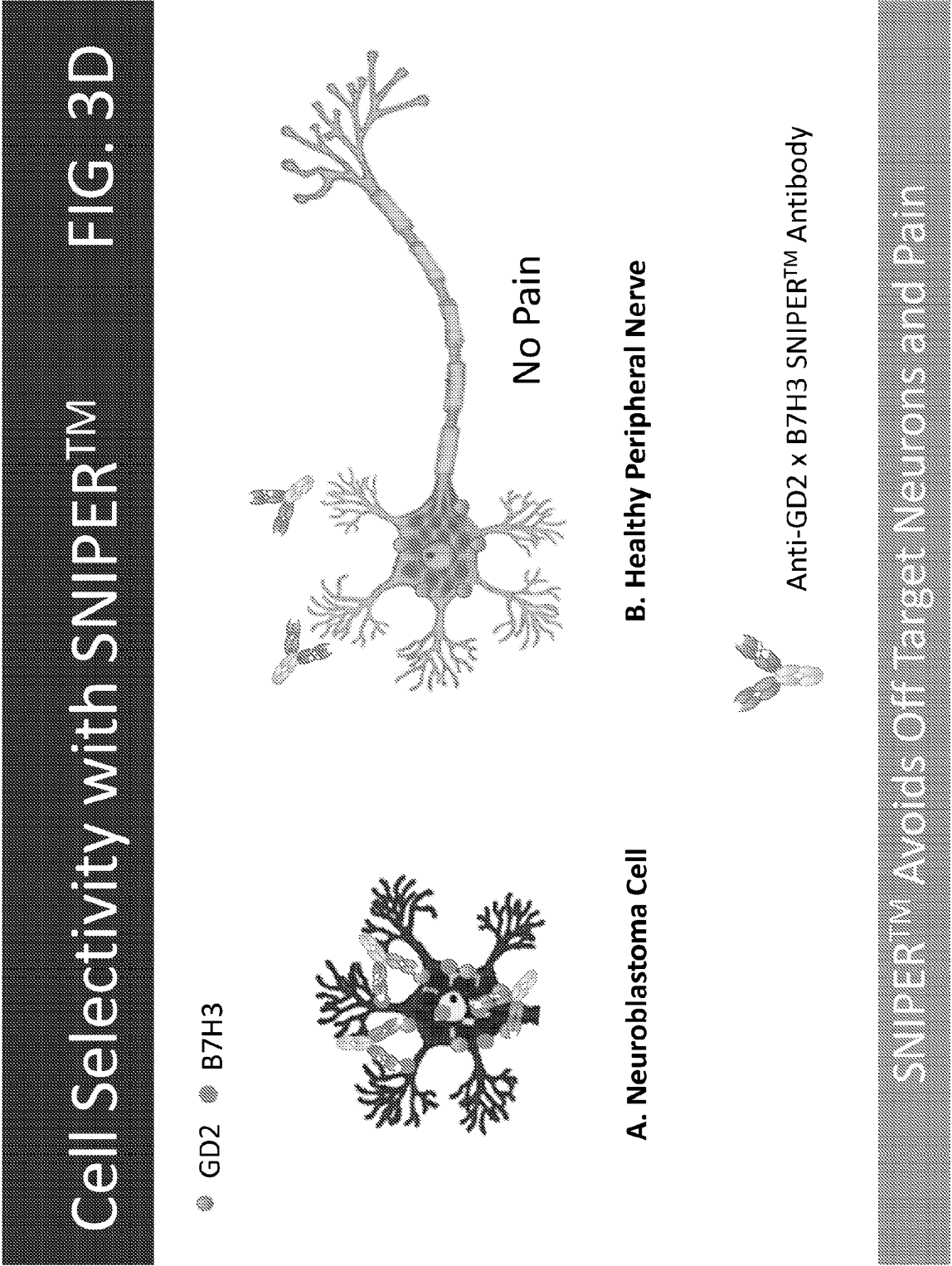
B. Healthy Peripheral Nerve



Anti-GD2 Antibody
(e.g., dinutuximab)

SNIPER™ Avoids Off Target Neurons and Pain





Project Workflow

FIG. 4

- GD2 binding arm maturation from dinutuximab
 - Binding specificity
- B7H3 binding arm discovery campaign
 - Binding specificity
- Bispecific SNIPER antibodies
 - Epitope Binning
 - Binding Specificity
 - Monovalent Affinity and Bivalent
 - Biophysical characteristics
 - ADCC Assay
 - *In vivo* pain study model

ADCC Criteria for SNIPER™

Make bispecifics (SNIPER™) antibodies from the 22 B7H3 and 2 GD2 arms selected during milestone 1 of the project and select the top candidates for testing *in vivo*.

Criteria: Using the Promega ADCC assay on a cell line expressing just GD2 (mimicking the peripheral neurons) or GD2 and B7H3 (mimicking the neuroblastoma), select candidates that show greater than >5-fold increase in the *in vitro* therapeutic window as compared to Dinutuximab.

FIG. 5

GD2 Humanized Binding Arm Sequences (with CAR mutation)

- > SEQ ID NO: 1 GD2-1 (with CAR mutation)
EVQLVESGGGLVQPGGSLRLSCAASGSSFTGYNMNWNVRQAPGKGLEWVAIDPYYGGTYADSVKGRFTISADTSKN
TAY LQMNSLRAEDTAVYYCA:GMEYWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPTVSWNSGALT
SGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVNHPKPSNTKVDKKVEPKSCDKHTCTCPCPAPELLGGPSVFLFP
PKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV
S NKAIPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSF
FLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK
- > SEQ ID NO: 2 GD2-2 (with CAR mutation)
EVQLVESGGGLVQPGGSLRLSCAASGSSFTGYNMNWNVRQAPGKGLEWVAIDPYYGGTYADSVKGRFTISADTSKN
TAY LQMNSLRAEDTAVYYCA:GMEYWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPTVSWNSGALT
SGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVNHPKPSNTKVDKKVEPKSCDKHTCTCPCPAPELLGGPSVFLFP
PKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV
S NKAIPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSF
FLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK

FIG. 6

GD2 Binding Assay

FIG. 7

- m21 human melanoma cell line, which expresses GD2 and B7H3 and B78 cell line (mouse melanoma, derived from B16-F10, expresses mGD2 and mB7H3) were used to assess the binding of the humanized GD2 binding arm (GD2-1 and GD2-2)
- GD2 monoclonal parental antibodies were compared to GD2 tool antibodies:
 - 14G2a is a monoclonal antibody reacts with human ganglioside GD2.
 - K322A is a monoclonal antibody reacts with human ganglioside GD2 where the Fc region is engineering to have a K322A mutation to reduce complement binding.
- Cells were stained with an antibody concentration of 1 ug /million cells was used for each binding assay.
- Antibody binding to m21 cell line is reported as the mean fluorescent intensity (MFI) determined by flow cytometry. MFI was normalized to the dinutuximab control which had the highest signal.

GD2 Binding Assay

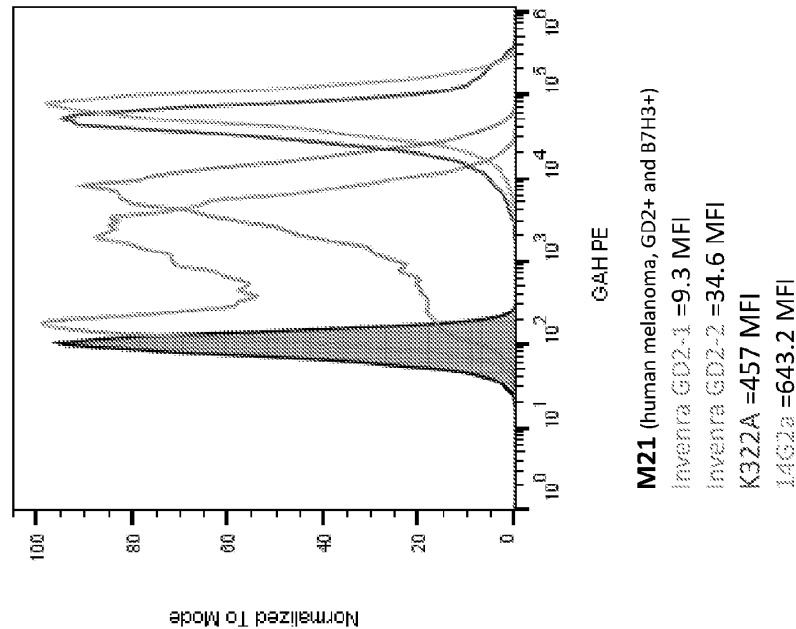


FIG. 8

GD2 Binding Assay

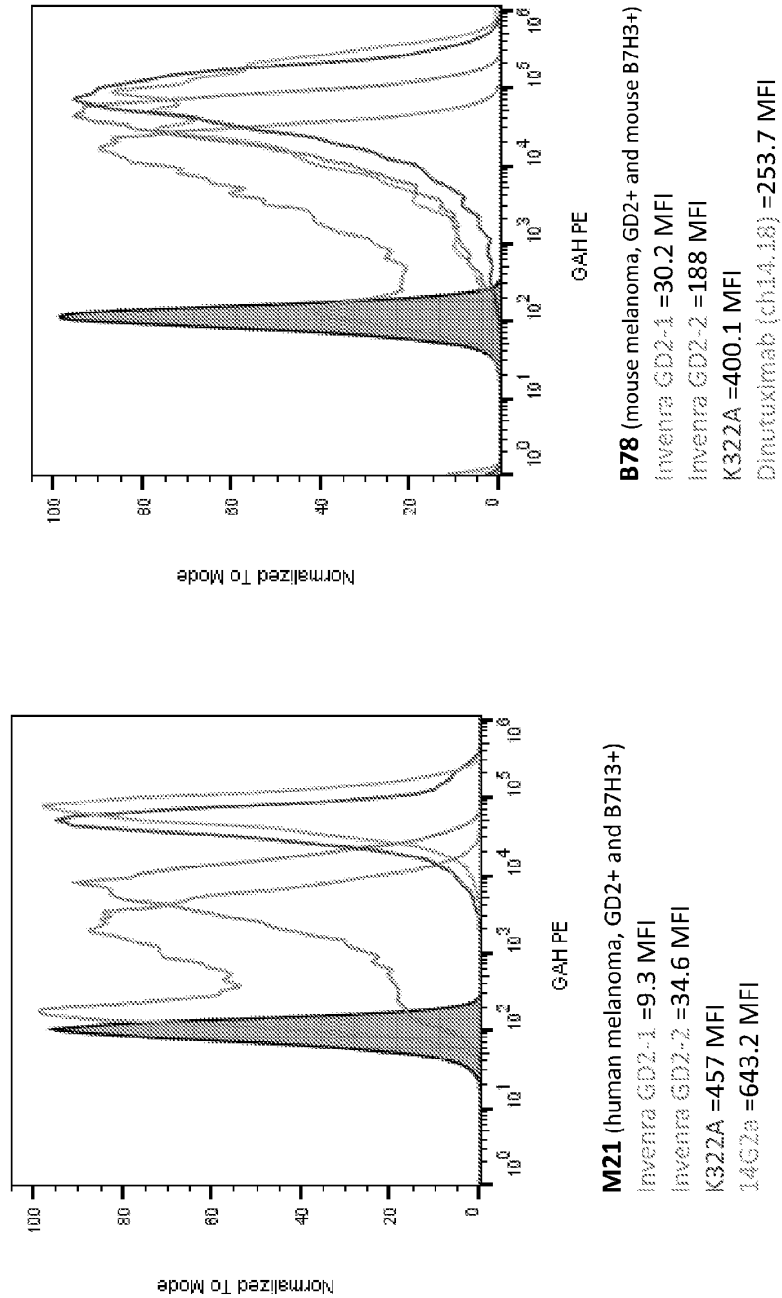


FIG. 9

Summary

- 40 B7H3 binders identified
 - 18 were excluded due to poor developability or binding
 - 22 B7H3 arms moved forward

FIG. 10

B7H3 Binding Assay

- m21 human melanoma cell line, which expresses GD2 and B7H3 and B16 cell line (no GD2, has mouse B7H3) were used to assess cell binding by flow cytometry
 - B7H3 binding arm
 - Bispecific antibodies B7H3 x GD2-1 or B7H3 x GD2-2
- Cells were stained with an antibody concentration of 1 ug /million cells was used for each binding assay.
- Antibody binding is reported as the mean fluorescent intensity (MFI) determined by flow cytometry. MFI was normalized to the dinutuximab control.

FIG. 11

B7H3 binding arm

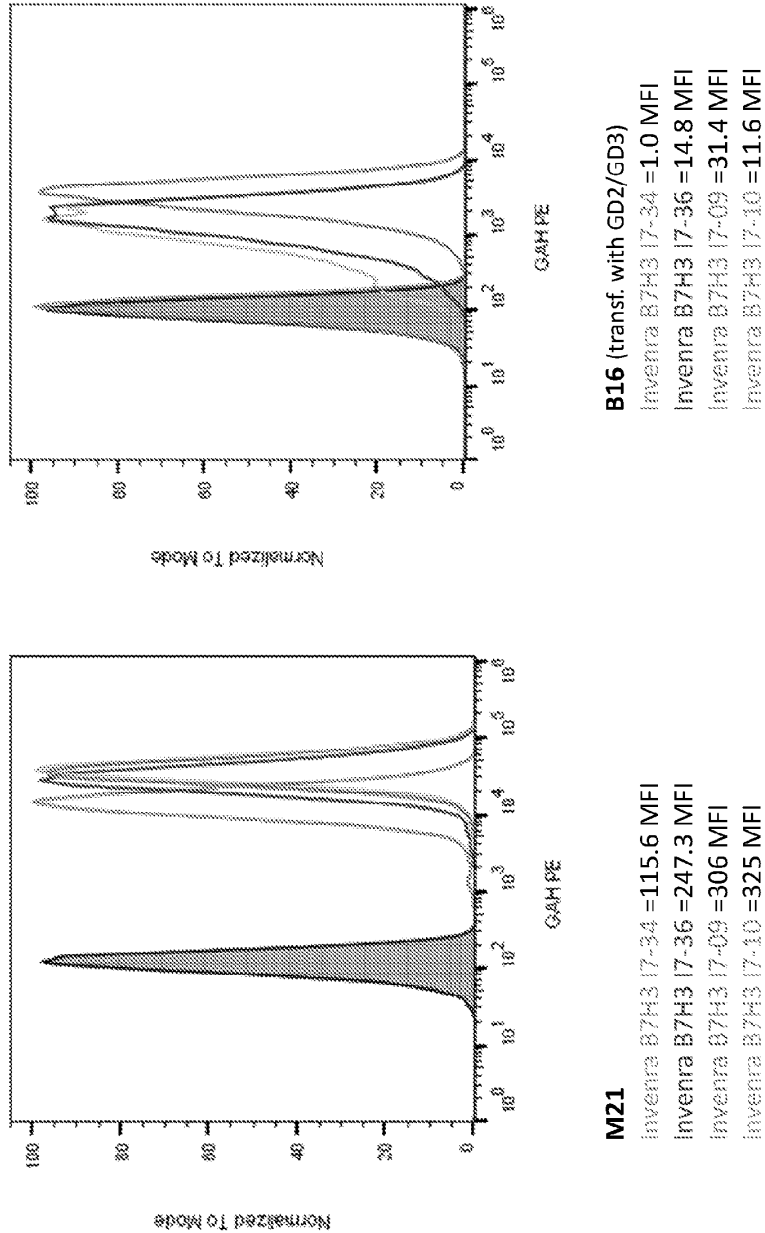


FIG. 12

B7H3 binding arm

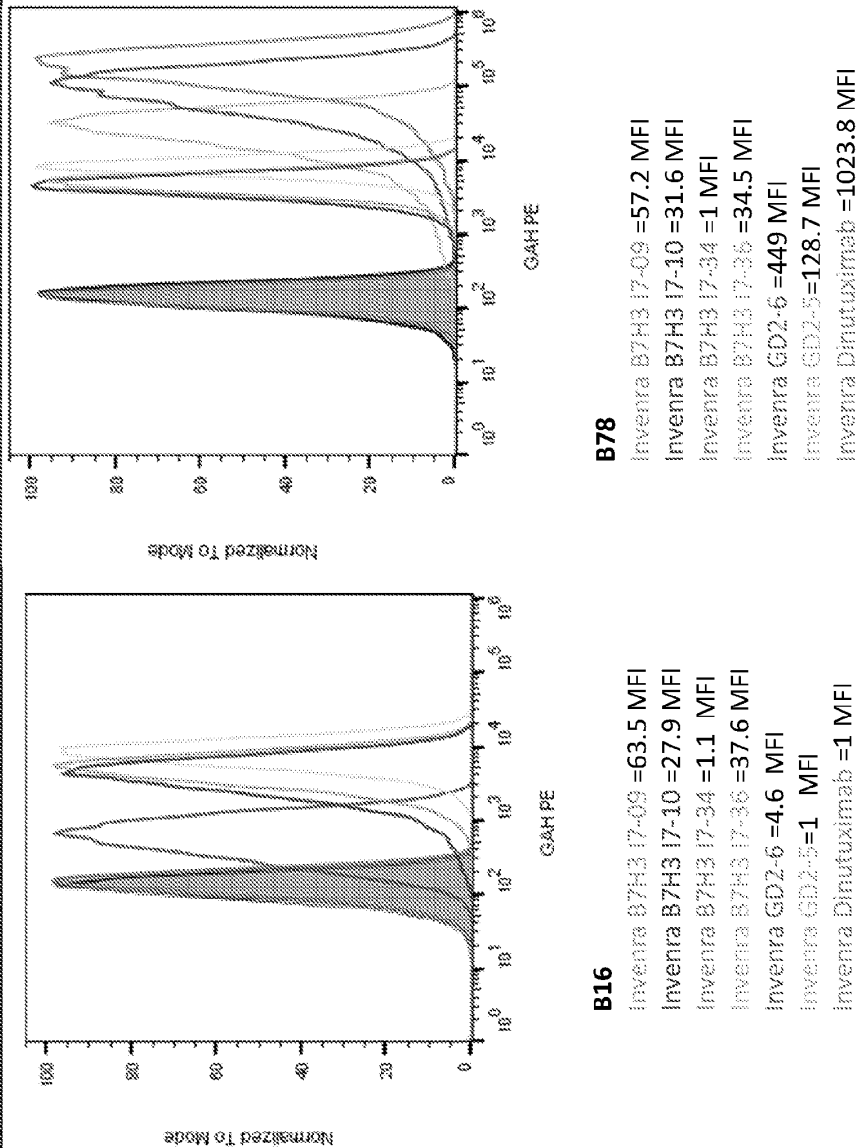


FIG. 13

Summary - GD2 and B7H3

- 2 GD2 binding arms (GD2-1 and GD2-2)
 - Humanized version of mouse mAb (Dinutuximab)
 - Common light chain for both GD2 arms
 - Single point mutation in scaffold of HC alters binding affinity
- 40 B7H3 binding arms
 - 22 B7H3 arms moved forward

FIG. 14

Bispecific B7H3 x GD2-1 or -2

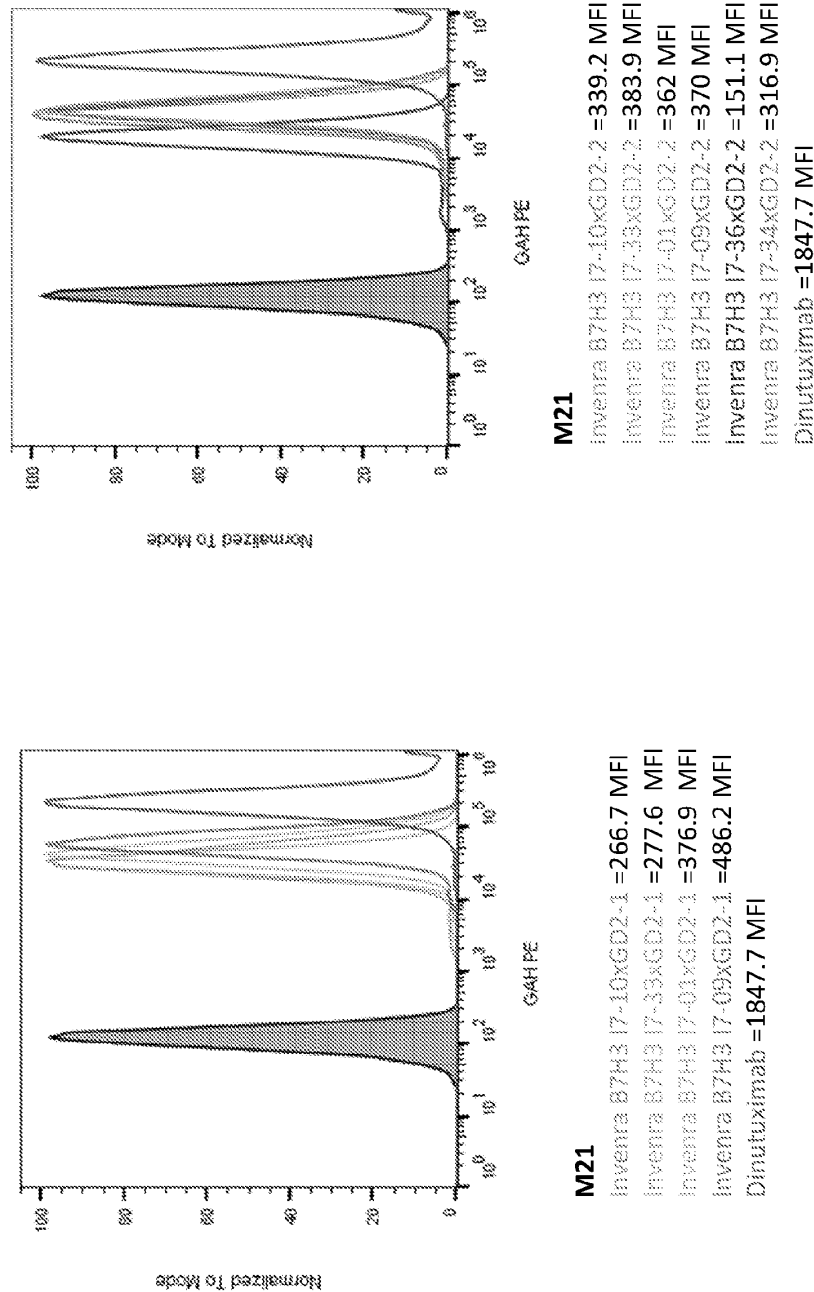


FIG. 15

Bispecific B7H3 x GD2-1 or -2

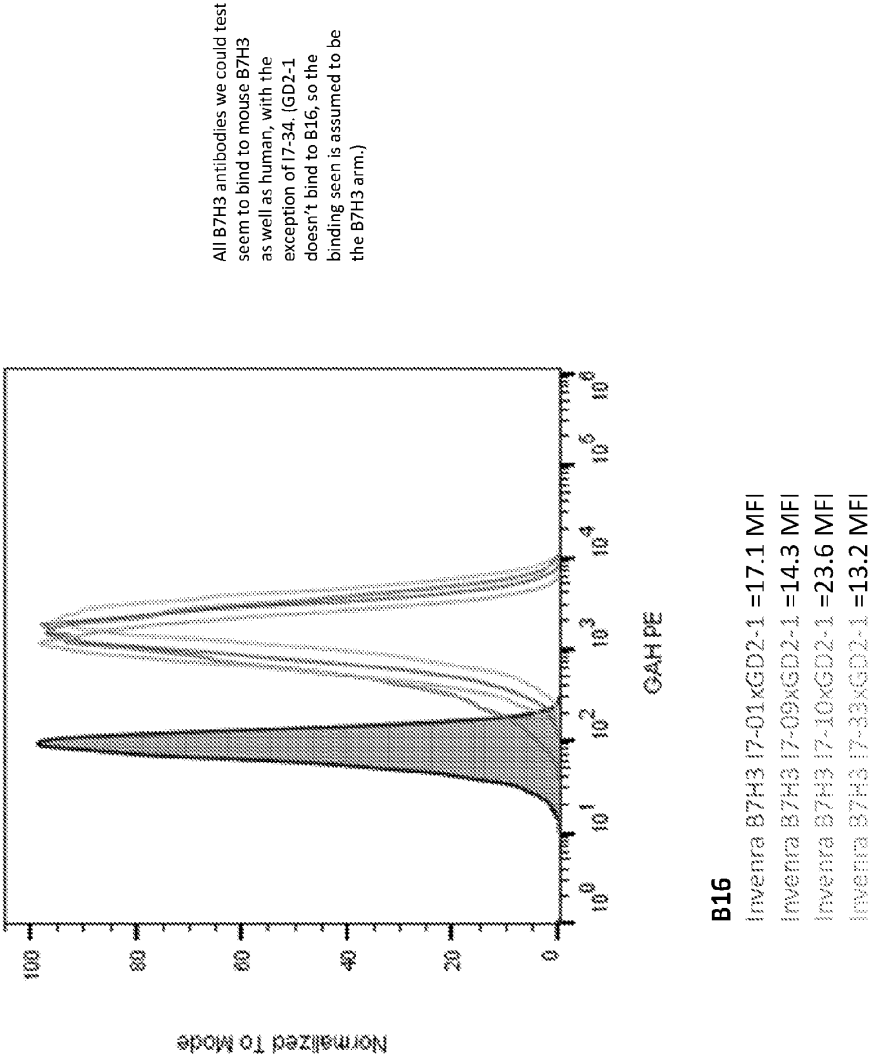


FIG. 16

Initial data on Bispecific SNIPERs

- An initial data set was collected on the 22 B7H3 x 2 GD2 (GD2-1 and GD2-2) SNIPERs
 - however we observed very little binding of the GD2 arm with these bispecific antibodies.
- We found that a mutation (CAR to CAS) in the HC (heavy chain) of the 2 selected GD2 Fabs improved binding and assembly of the bispecific SNIPER antibodies.

FIG. 17

GD2 Humanized Binding Arm Sequences (with CAS mutation)

- > SEQ ID NO: 1 (GD2-5) (with CAS mutation)
EVQLVGGGLVQPGGSLRLSCAASGSSFTGYNMNVWRQAPGKGLEWVAIDPYGGTYADSVKGRFTISADTSKN
TAY LQMNSLRAEDTAVYYCA~~Q~~GMEYWGQGT~~LV~~TVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT
VSWNSGALT SGVHTFPAVLQSSGLYSLSSVTV~~PP~~SSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP
CPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ
YNSTYRVVSVLTVLHQDWLNGKEYCKV5 NKALPAIEKTIKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV
KGFPYSDIAVEWESNGQPENNYKTTTPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQK
SLSPGK SSLQPEDFATYYCSQSTHP~~PL~~TFGQGTKEIKRTVAAPSVFIFPPSDSQLKSGTASV~~W~~CLLN
NFYPREAKVQWKVDNAL QSGNSQESVTEQDSKDSYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
- > SEQ ID NO: 2 (GD2-6)(with CAS mutation)
EVQLVGGGLVQPGGSLRLSCAASGSSFTGYNMNVWRQAPGKGLEWVAIDPYGGTYADSVKGRFTISADTSKN
TAY LQMNSLRAEDTAVYYCA~~Q~~GMEYWGQGT~~LV~~TVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT
VSWNSGALT SGVHTFPAVLQSSGLYSLSSVTV~~PP~~SSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP
CPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ
YNSTYRVVSVLTVLHQDWLNGKEYCKV5 NKALPAIEKTIKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV
KGFPYSDIAVEWESNGQPENNYKTTTPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQK
SLSPGK SSLQPEDFATYYCSQSTHP~~PL~~TFGQGTKEIKRTVAAPSVFIFPPSDSQLKSGTASV~~W~~CLLN
NFYPREAKVQWKVDNAL QSGNSQESVTEQDSKDSYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

FIG. 18

Epitope Binning

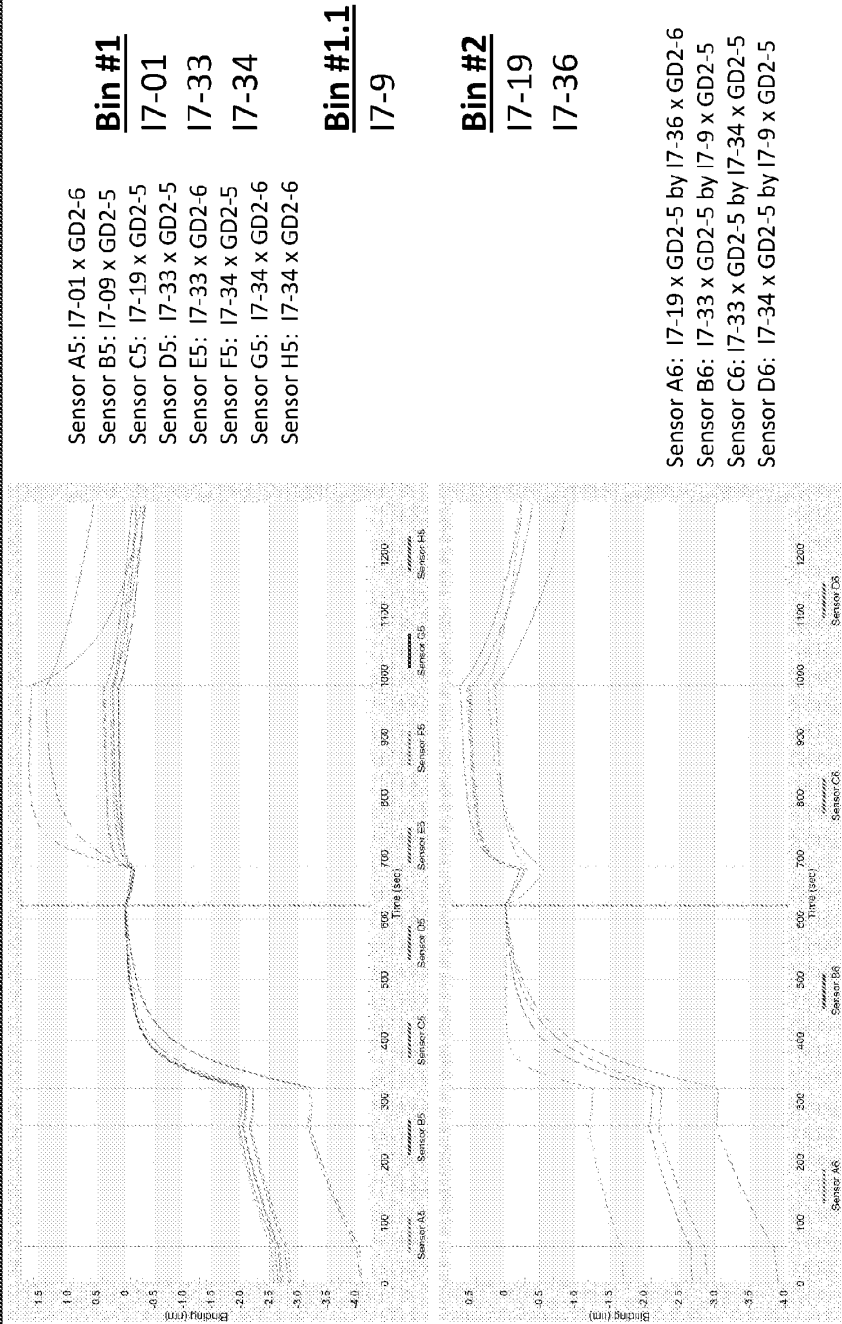


FIG. 19

New Bispecific SNIPERS

- The new GD2 arms with the CAS mutation (named GD2-5 and GD2-6) x 22 B7H3 arms were transfected into CHO cells and tested for differential binding.
- B7H3 x Dummy arm or GD2 x Dummy arm were used to look at monovalent binding. The Dummy arm did not bind in the cell lines used for testing.
- Promising candidates were re-transfected in HEK to confirm binding data and achieve better assembly.

FIG. 20

Binding Assays

- The B16-F10 is a mouse melanoma cell line was used a base cell line to make two test cell lines, “B78” and “B7H3 B78” for the binding assay.
 - “B78” – is a single positive GD2 cell line: derived from B16-F10, transduced with human GD2/GD3, and expresses endogenous mouse B7H3.
 - “B7H3 B78” – is double positive cell line for GD2/B7H3: derived from B16-F10, transduced with human GD2/GD3 and human B7H3.
- Bispecific SNIPER antibodies and were assessed for cell binding, using RFU (fluorescence) as readout.
- A monovalent antibody to B7H3, with a dummy arm to the Herceptin antigen was made and compared to the bispecific SNIPER antibody.
- Monovalent affinity to B7H3 (B7H3 Octet = nM) and Bivalent affinity to B7H3/GD2 (EC50 = nM) were determined.

FIG. 21

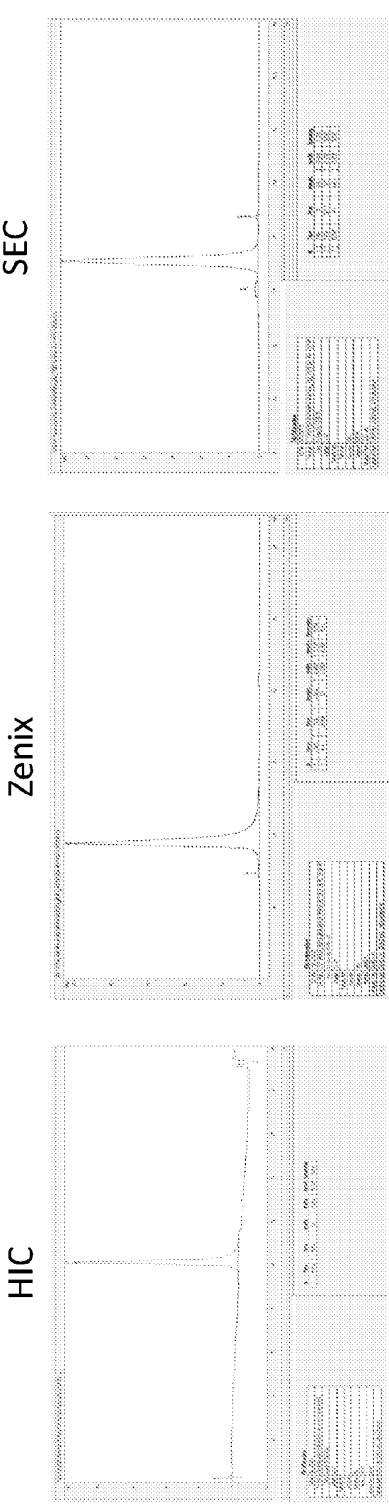
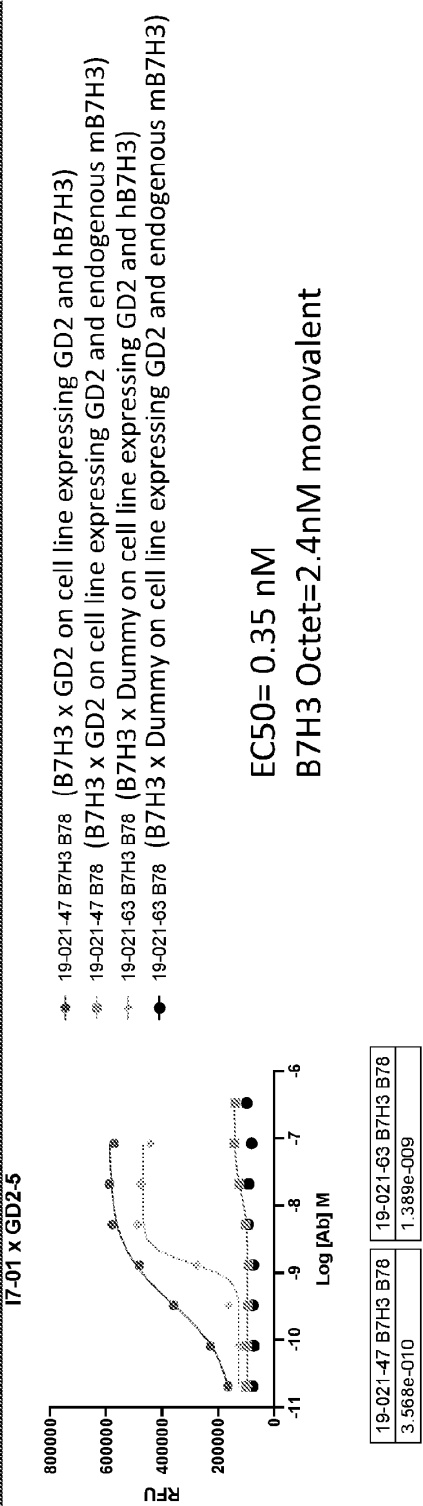
Chromatography Assays

- **“HIC” Hydrophobic interaction chromatography (HIC):** HIC was used to determine hydrophobicity and level of heterogeneity of the molecule. Delay in coming off the column indicates an increase in hydrophobicity and therefore more potential for developability risks. A strong candidate would have low hydrophobicity and be more homogeneous, showing a single peak.
- **“SEC” Size-exclusion chromatography (SEC):** SEC separates antibodies by their molecular size and was used to determine the homogeneity of the molecule. If shoulders are present this indicates higher or lower molecular weight species are present in the sample (aggregation or partially assembled product). A strong candidate show a single peak of one size.
- **“Zenix” stand-up Monolayer chromatography:** retention times are inversely related to colloidal stability. Antibodies prone to non-specific interactions, aggregation, or/and precipitation tend to have longer retention times. A strong candidate would not be delayed in the time that it comes off the column (compared to control antibodies) show a single peak of one size. Multiple peaks indicate that there are multiple species present in the sample.

FIG. 22

I7-01 x GD2-5

Binding and Chromatography



I7-01 x GD2-6

Binding and Chromatography

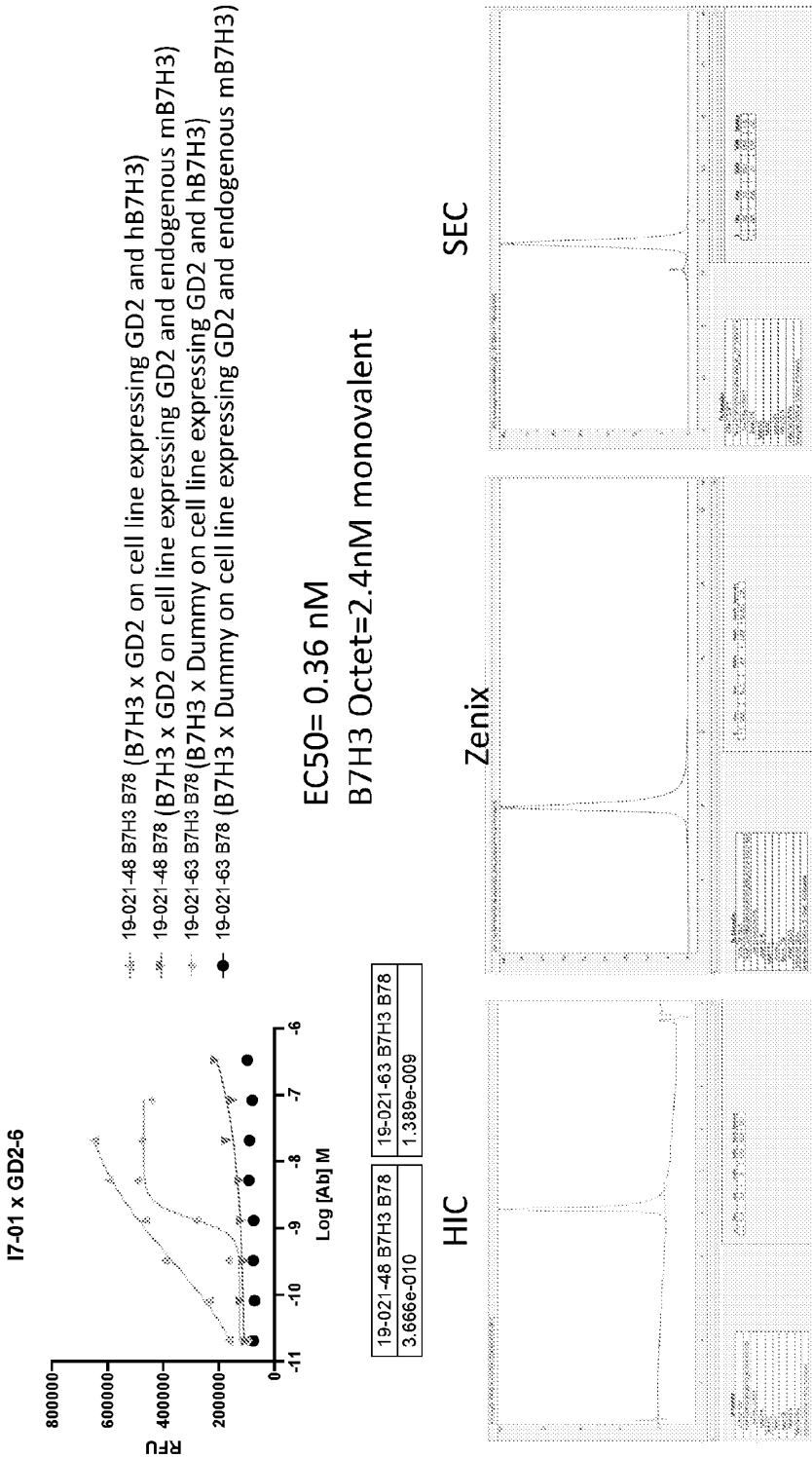


FIG. 24

17-09 x GD2-5
Binding and Chromatography

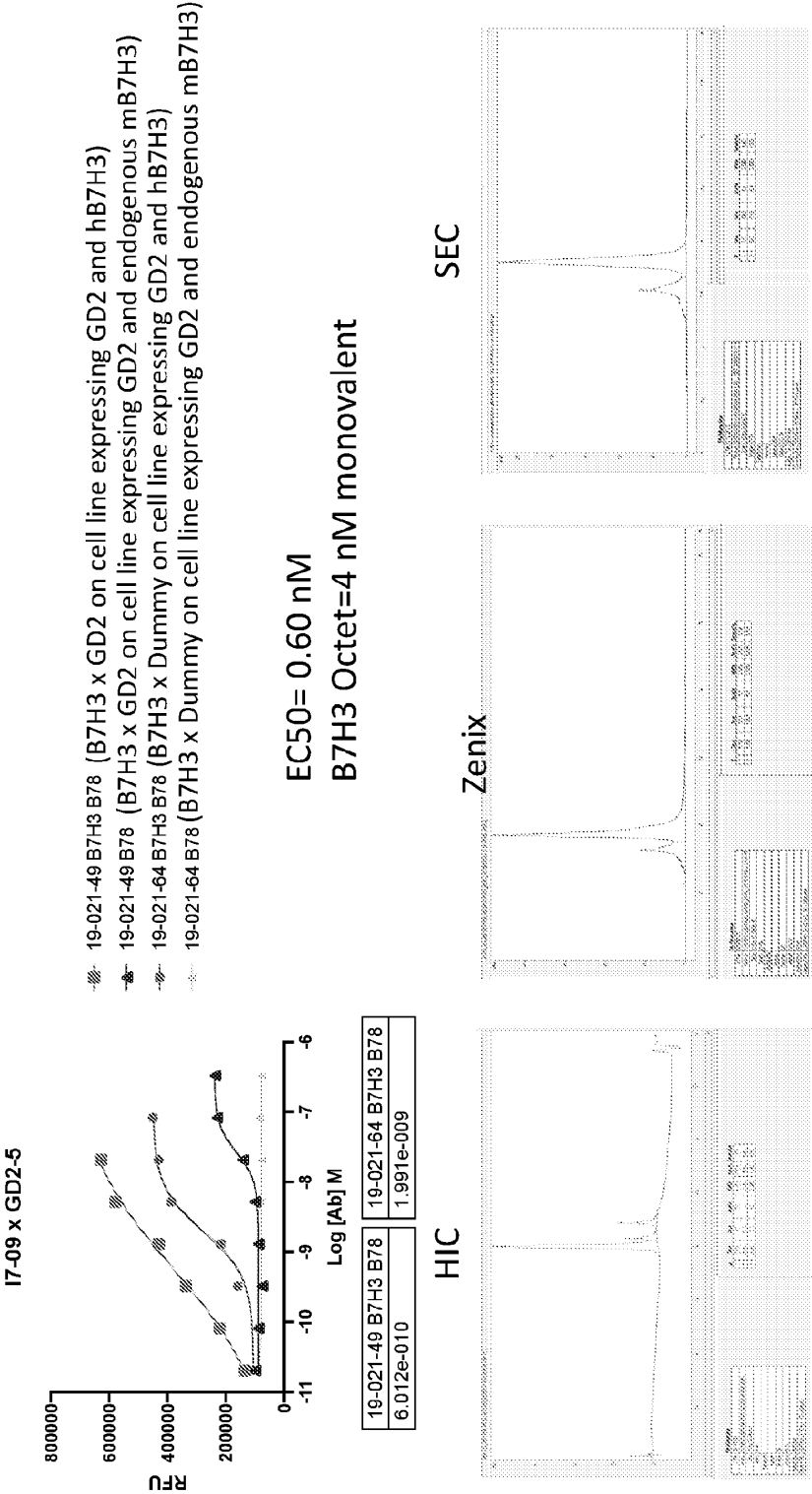


FIG. 25

17-09 x GD2-6
Binding and Chromatography

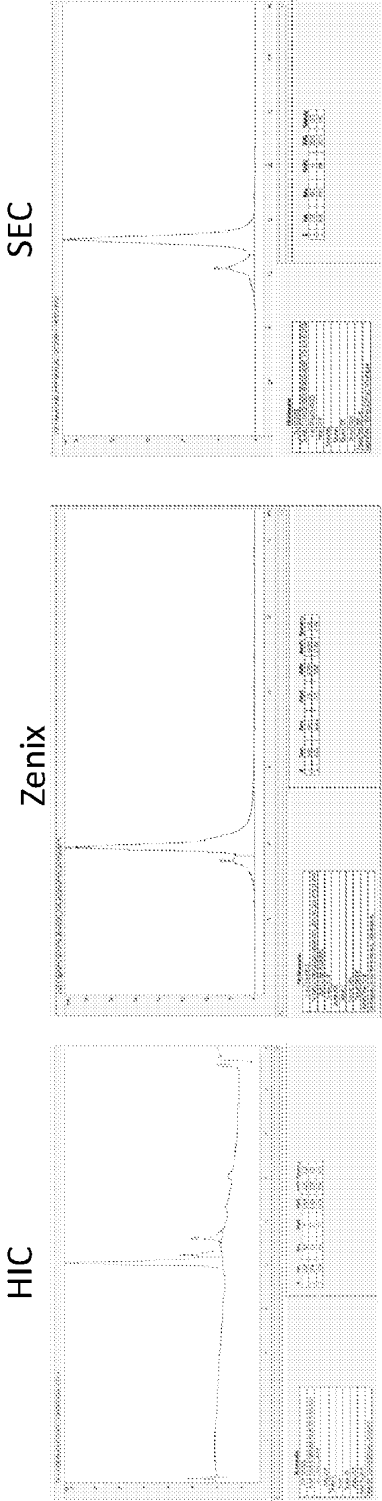
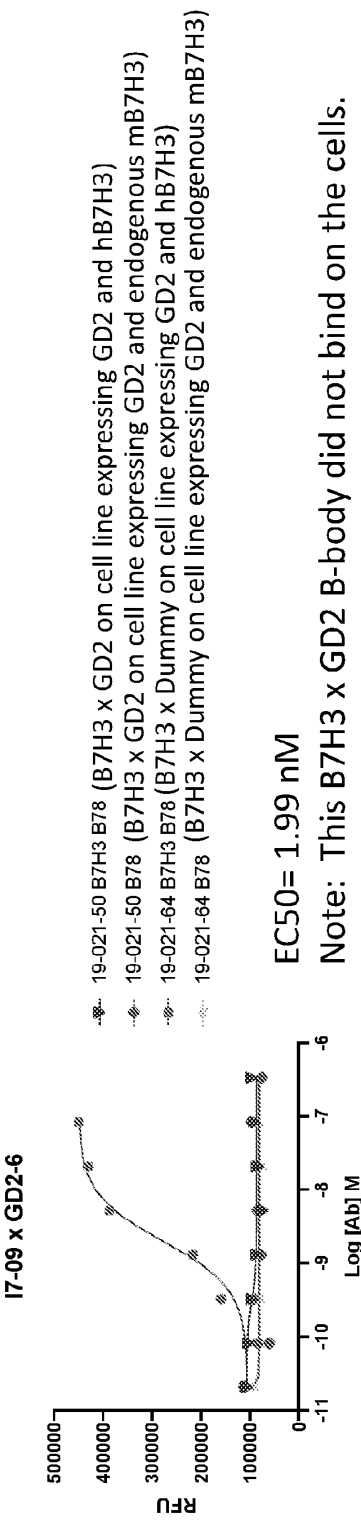
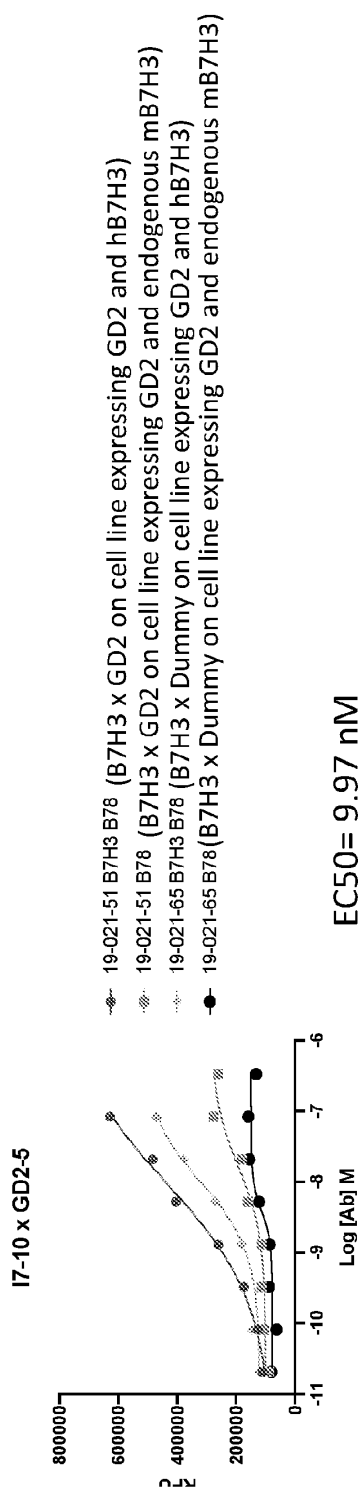


FIG. 26

I7-10 x GD2-5 Binding and Chromatography



19-021-51 B7H3 B7E	19-021-65 B7H3 B7E
9.970e-009	9.921e-009

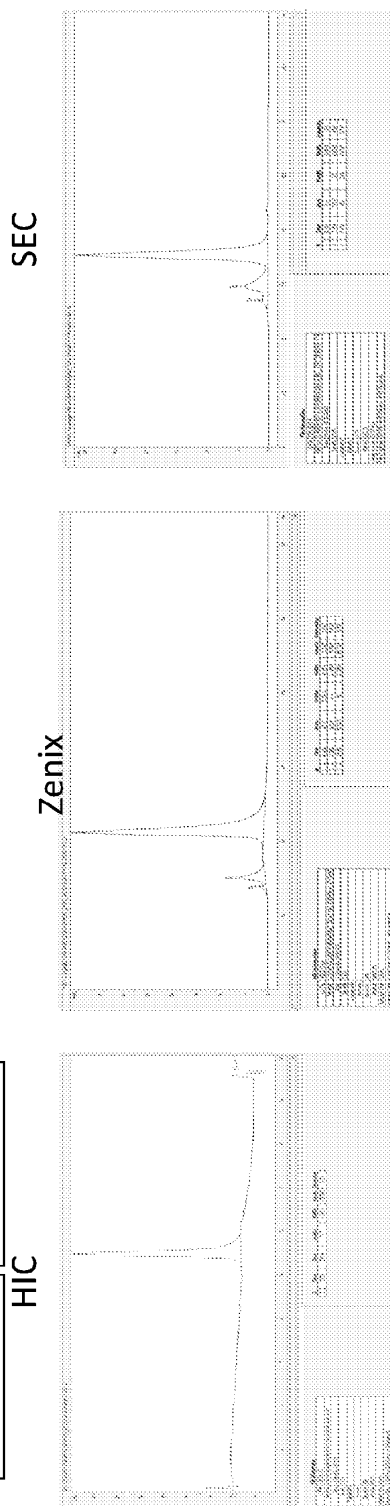
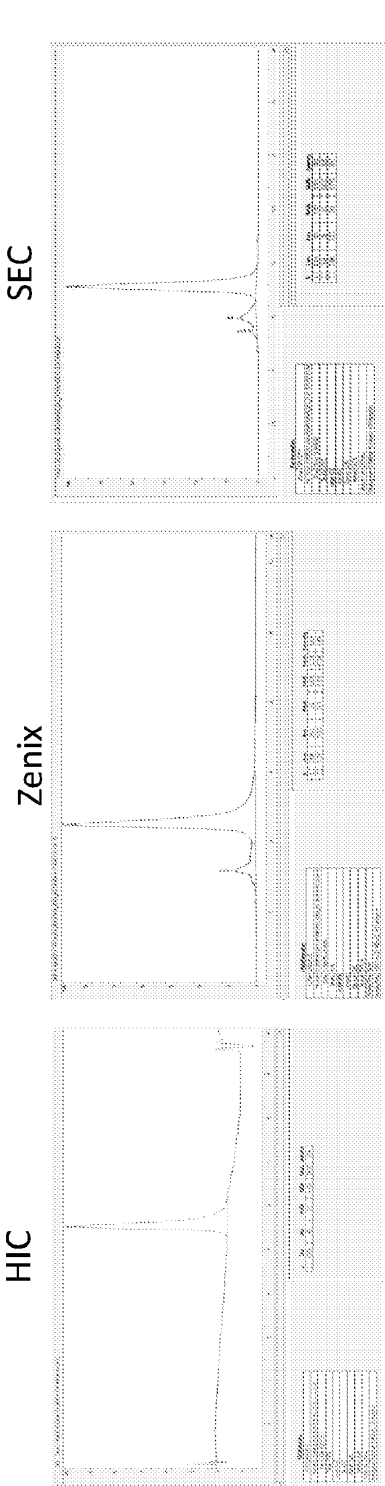
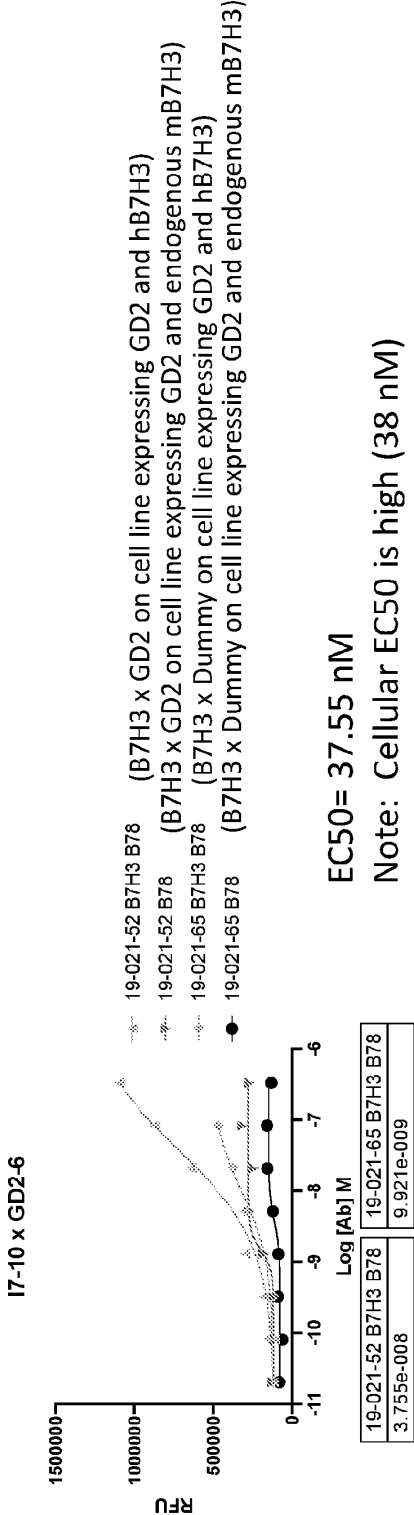


FIG. 27

I7-10 x GD2-6
Binding and Chromatography



I7-19 x GD2-5
Binding and Chromatography

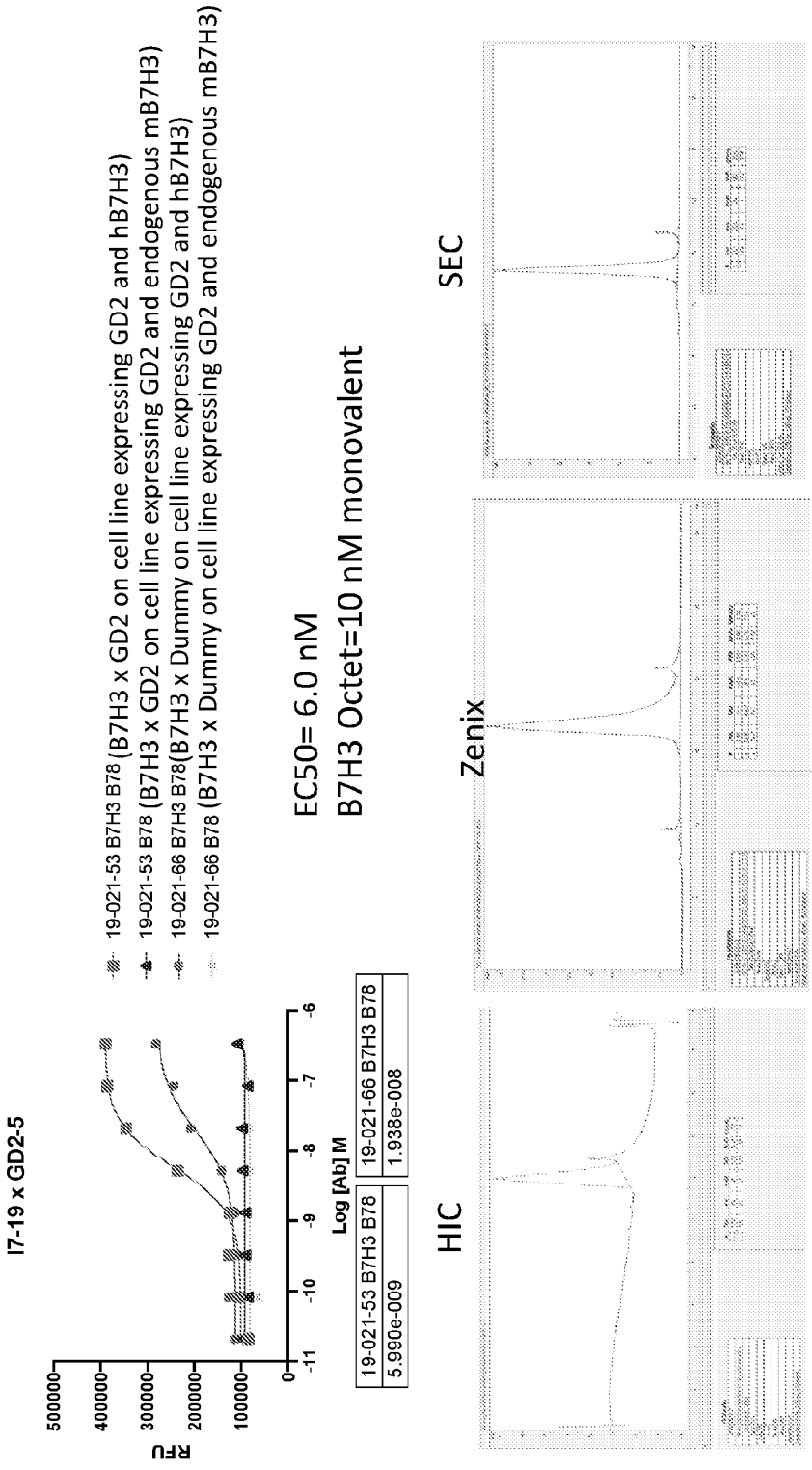


FIG. 29

I7-19 x GD2-6
Binding and Chromatography

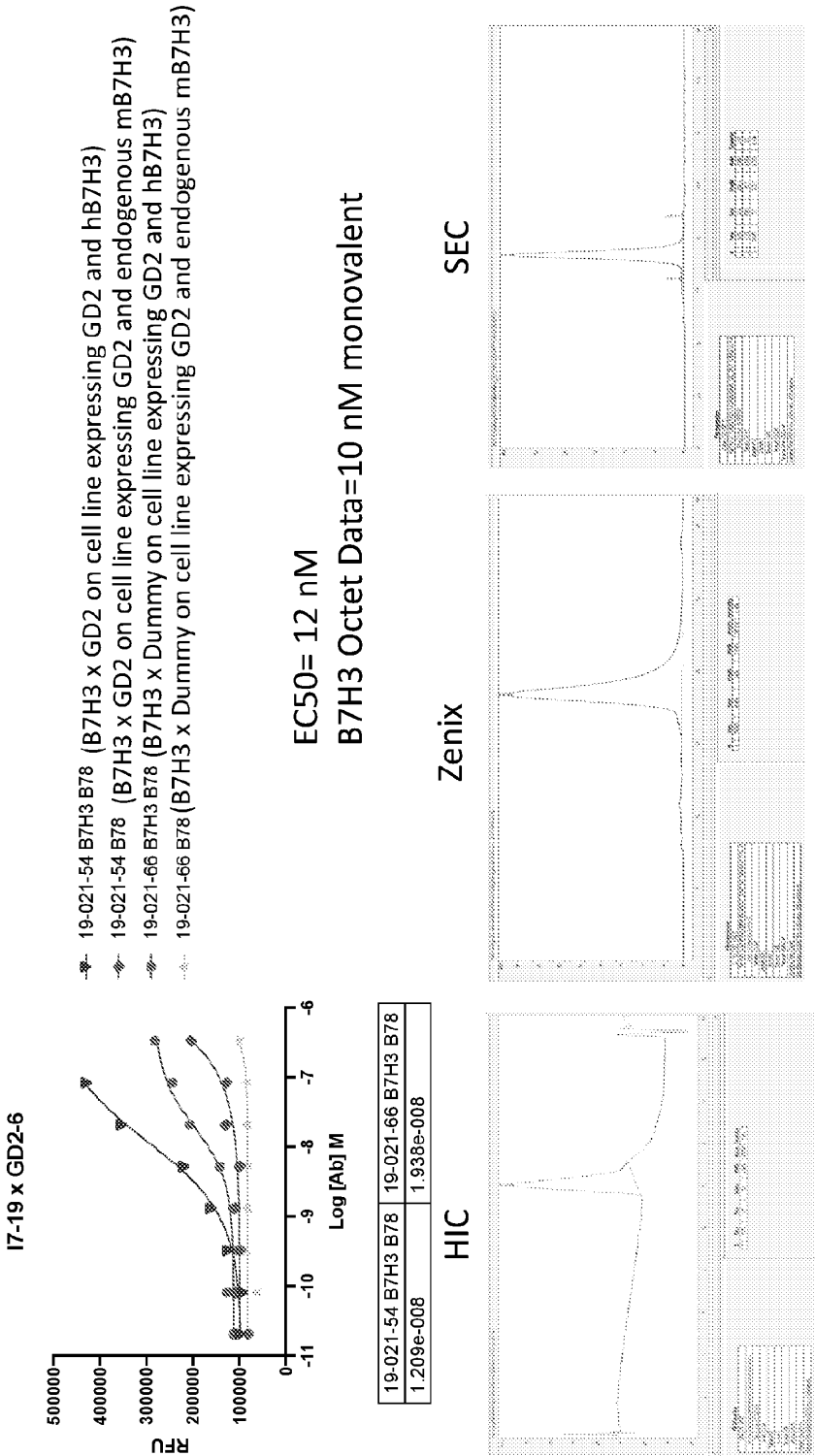


FIG. 30

17-20 x GD2-6

Binding and Chromatography

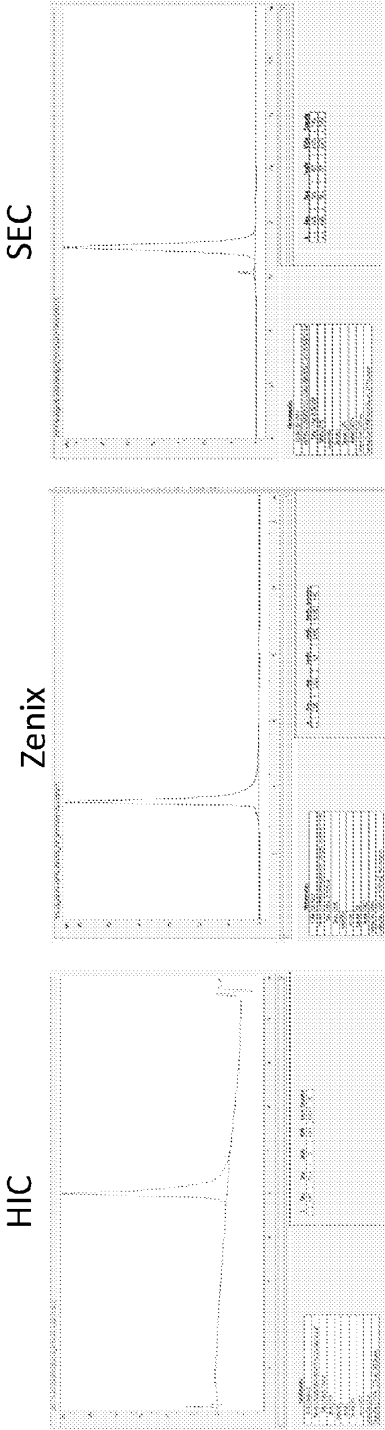
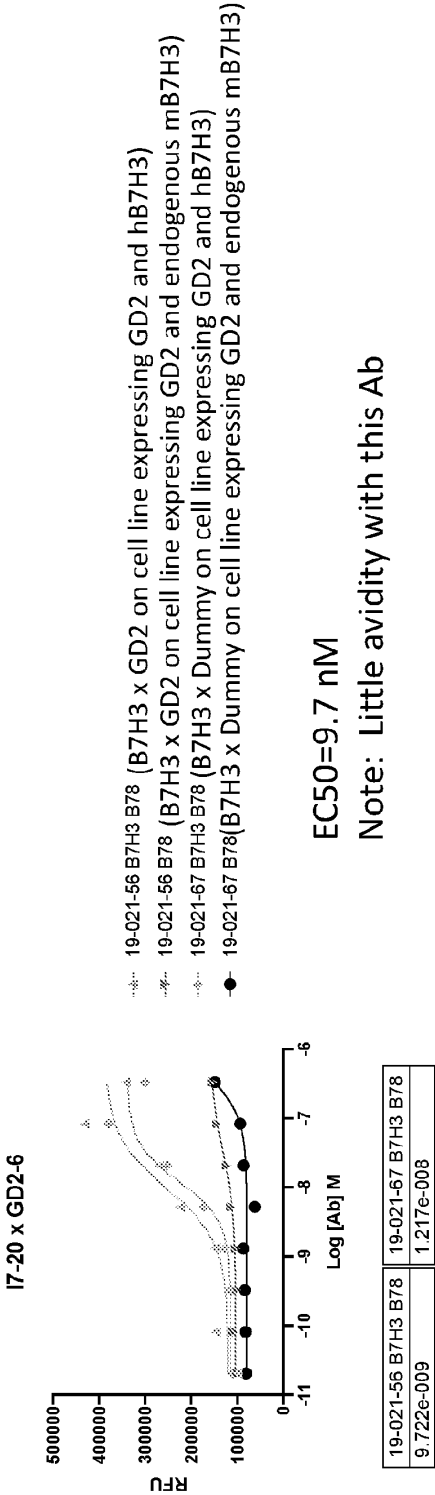


FIG. 31

17-33 x GD2-5
Binding and Chromatography

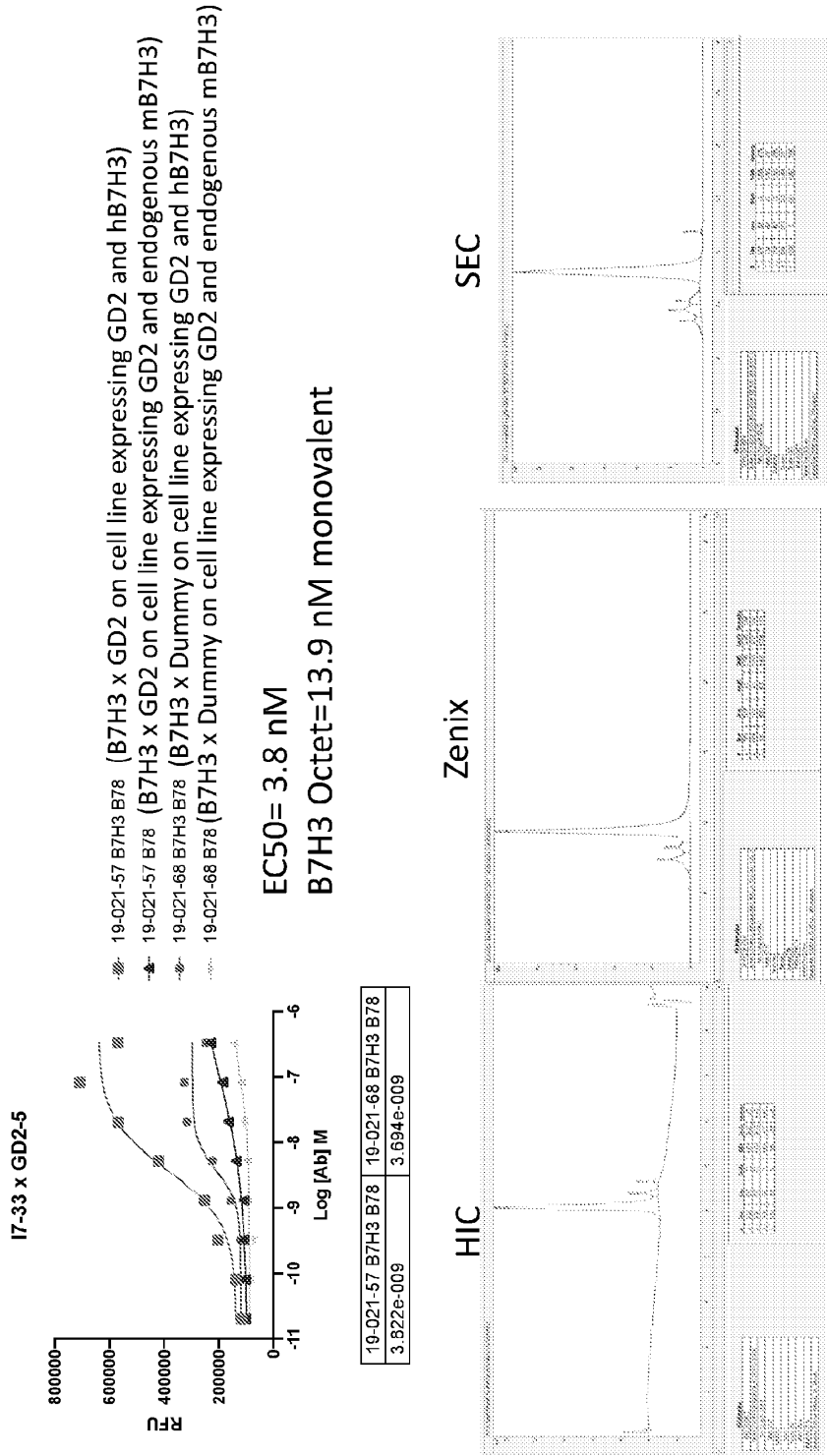


FIG. 32

I7-33 x GD2-6
Binding and Chromatography

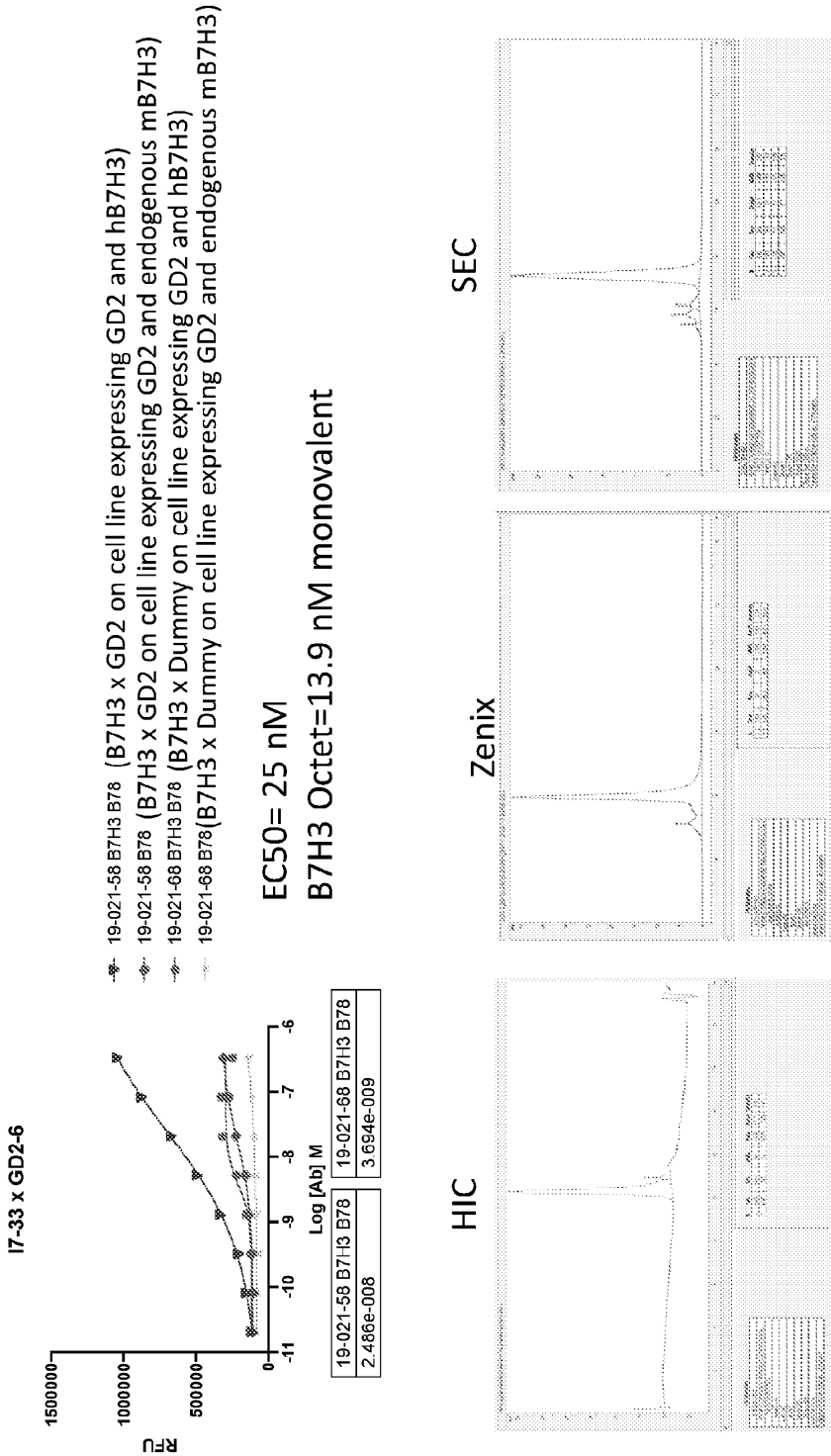
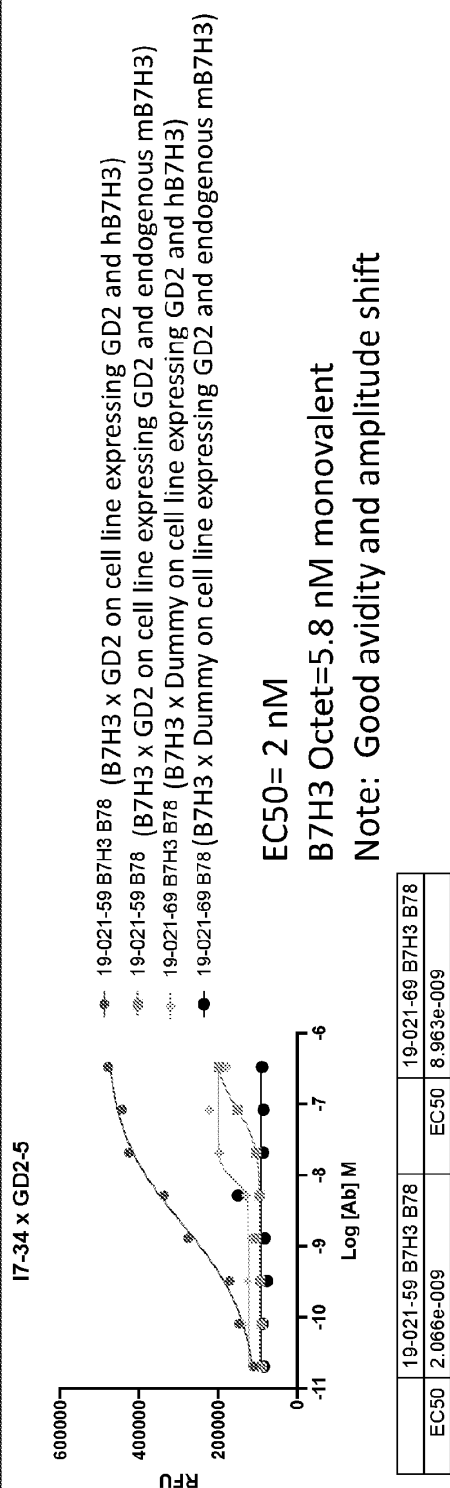
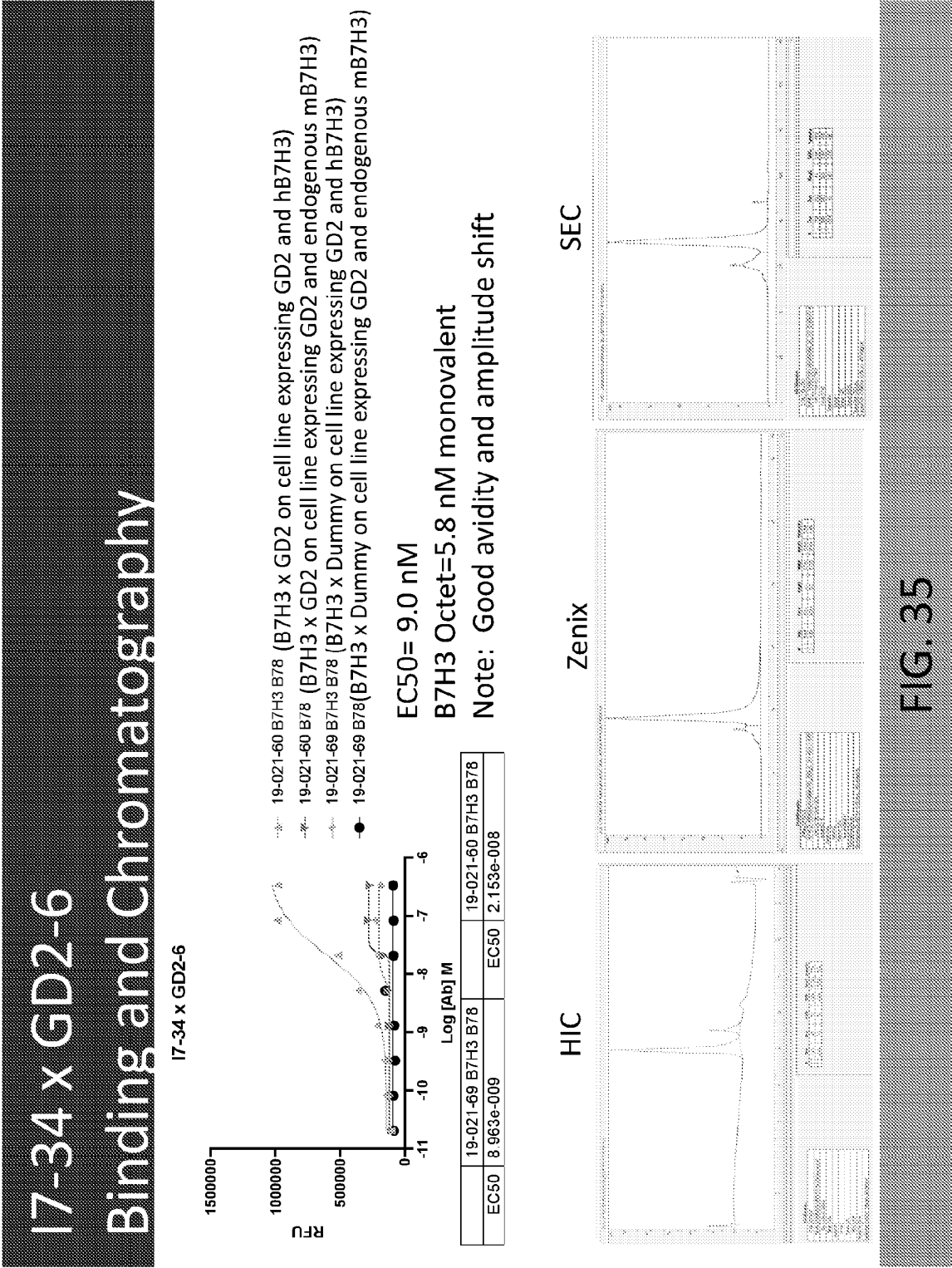


FIG. 33

I7-34 x GD2-5

Binding and Chromatography





I7-36 x GD2-5
Binding and Chromatography

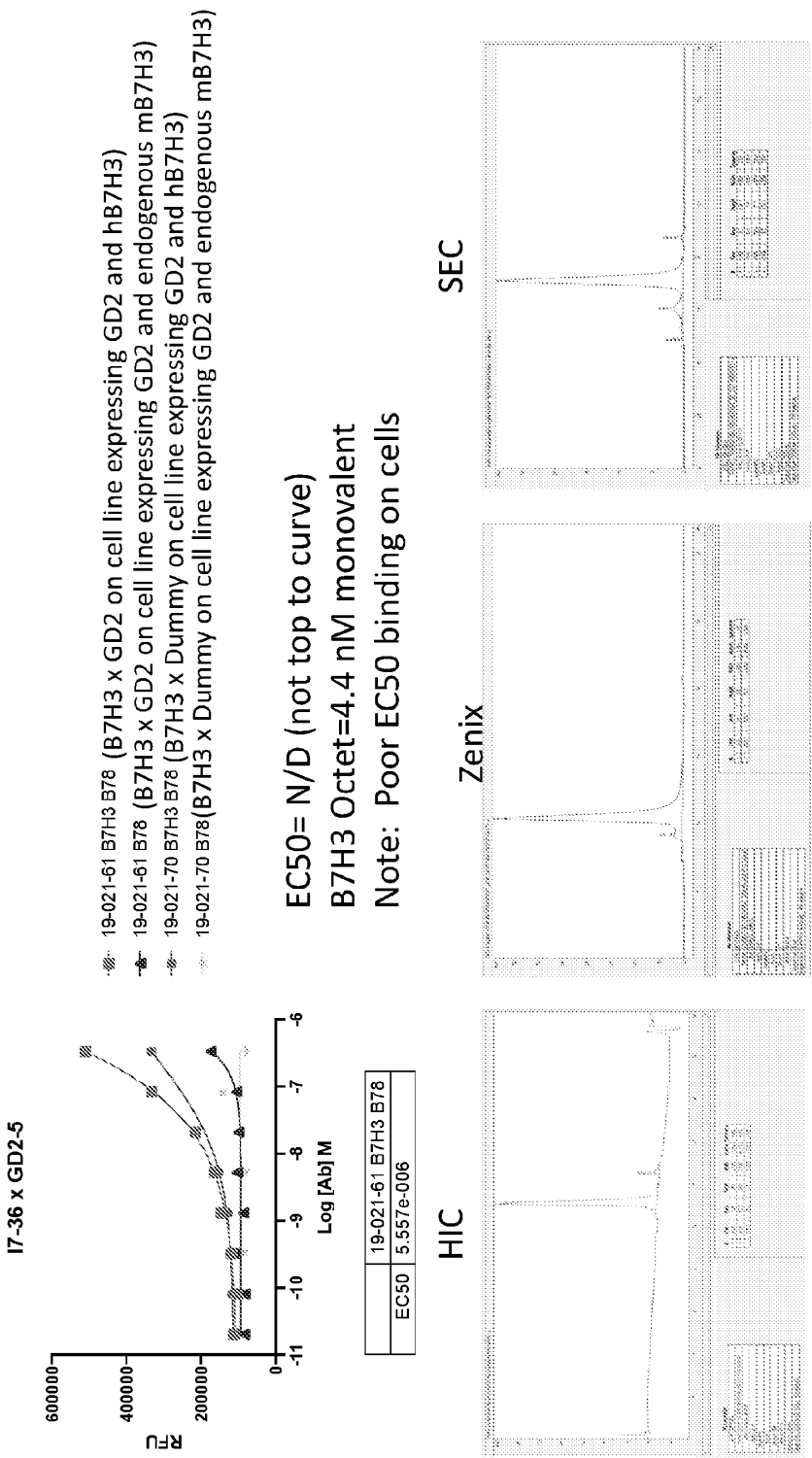
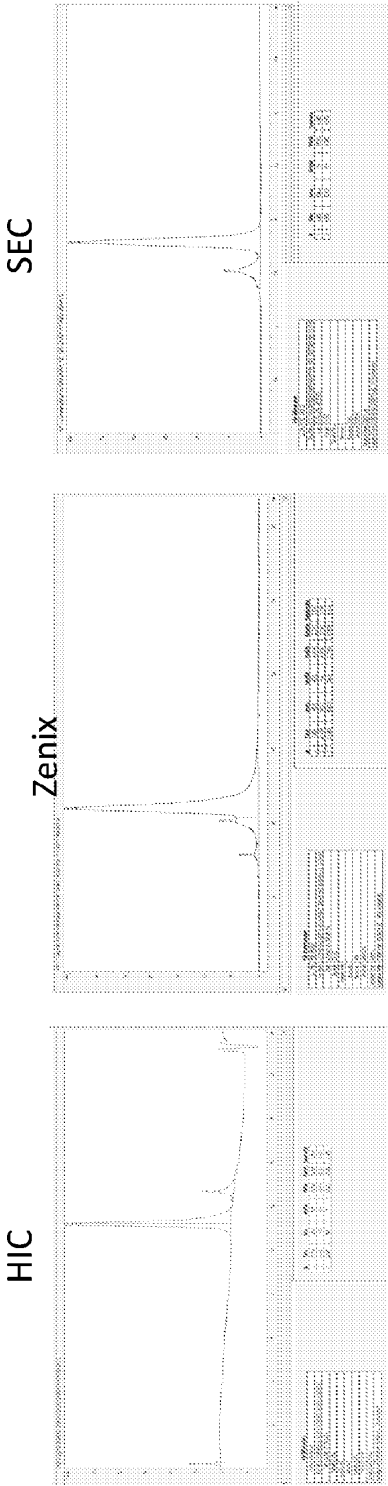
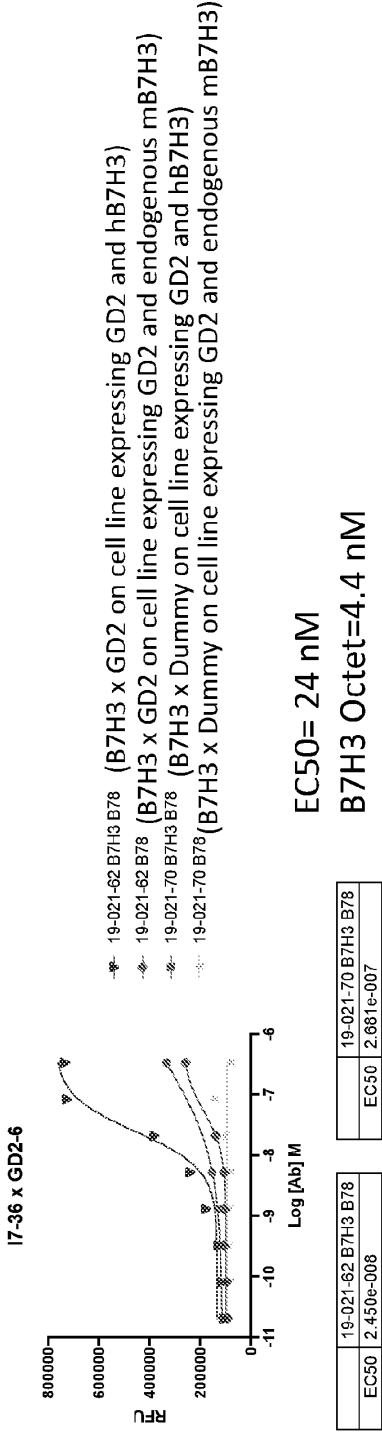


FIG. 36

17-36 x GD2-6
Binding and Chromatography



Top 9 Candidates for ADCC testing

- I7-01 x GD2-5
- I7-01 x GD2-6
- I7-09 x GD2-5
- I7-19 x GD2-5
- I7-33 x GD2-5
- I7-33 x GD2-6
- I7-34 x GD2-5
- I7-34 x GD2-6
- I7-36 x GD2-6

FIG. 38

Summary

- The top 9 candidates were tested in the Promega ADCC assay and compared to dinutuximab.
- The top candidates for *in vivo* work will be selected from these 9 candidates.

FIG. 39

ADCC Assay

- The Promega ADCC reporter gene assay was used to determine ADCC activity. The assay used an NFAT-luciferase Jurkat cell line expressing the human FcγRIIIa.
- The following cell lines were used.
 - B78 which expresses “GD2 only”. This cell line was used to simulate/model binding to peripheral neurons which express GD2 but are negative for human B7H3
 - B78 expresses murine B7H3, but most B-Bodies have low cross-reactive binding to mB7H3
 - B7H3 B78 (clone #32) which expresses high levels of human GD2 and human B7H3. This cell line was used to simulate/model a double positive tumor expressing GD2 and B7H3. (also referred to as “B7H3 + GD2”)
- Dinutuximab is used as a control. All data were normalized to Dinutuximab (set to 100%).
- The EC80 for each molecule on the double positive cell line is marked with a black dotted line.
 - On target value was defined by EC80 of double positive cell line (“B7H3 + GD2”).
 - Off target value was defined by EC80 of single positive GD2 cell line (“B78”).
- The ratio of signal observed at the EC80 for the double positive B7H3 B78 to the B78 is calculated for each molecule.

FIG. 40

Initial ADCC Results

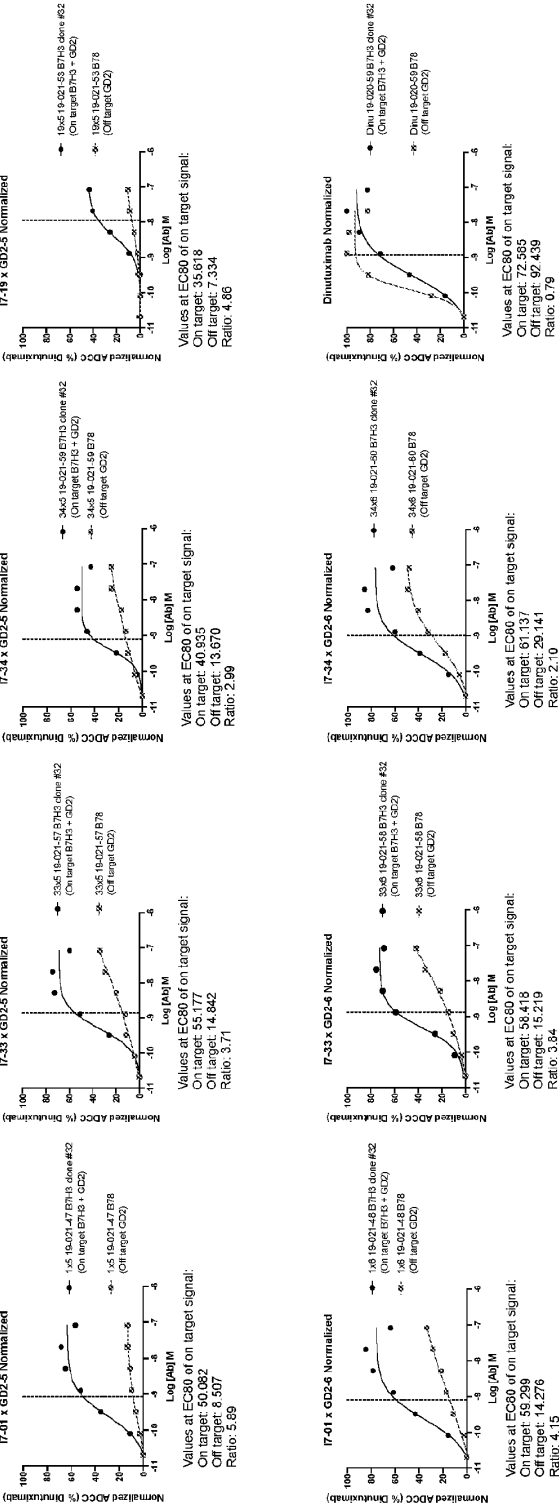


FIG. 41

Repeat ADCC Results

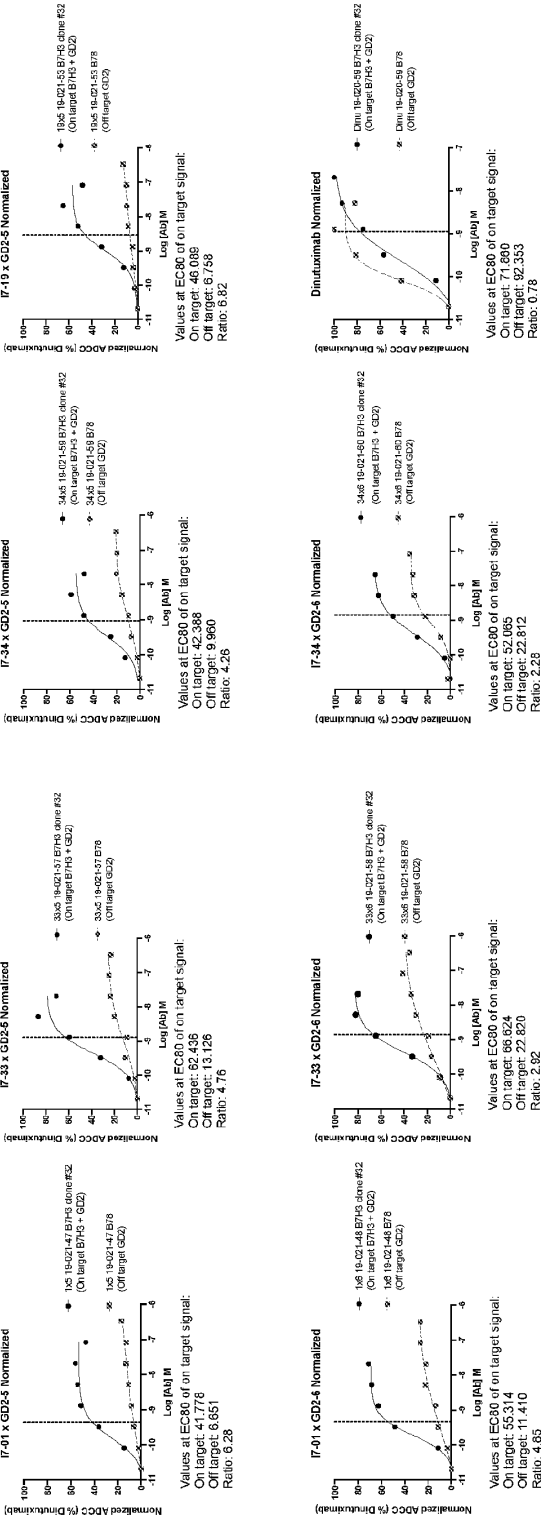


FIG. 42

Schematic of Intraplantar Model induction and Treatment

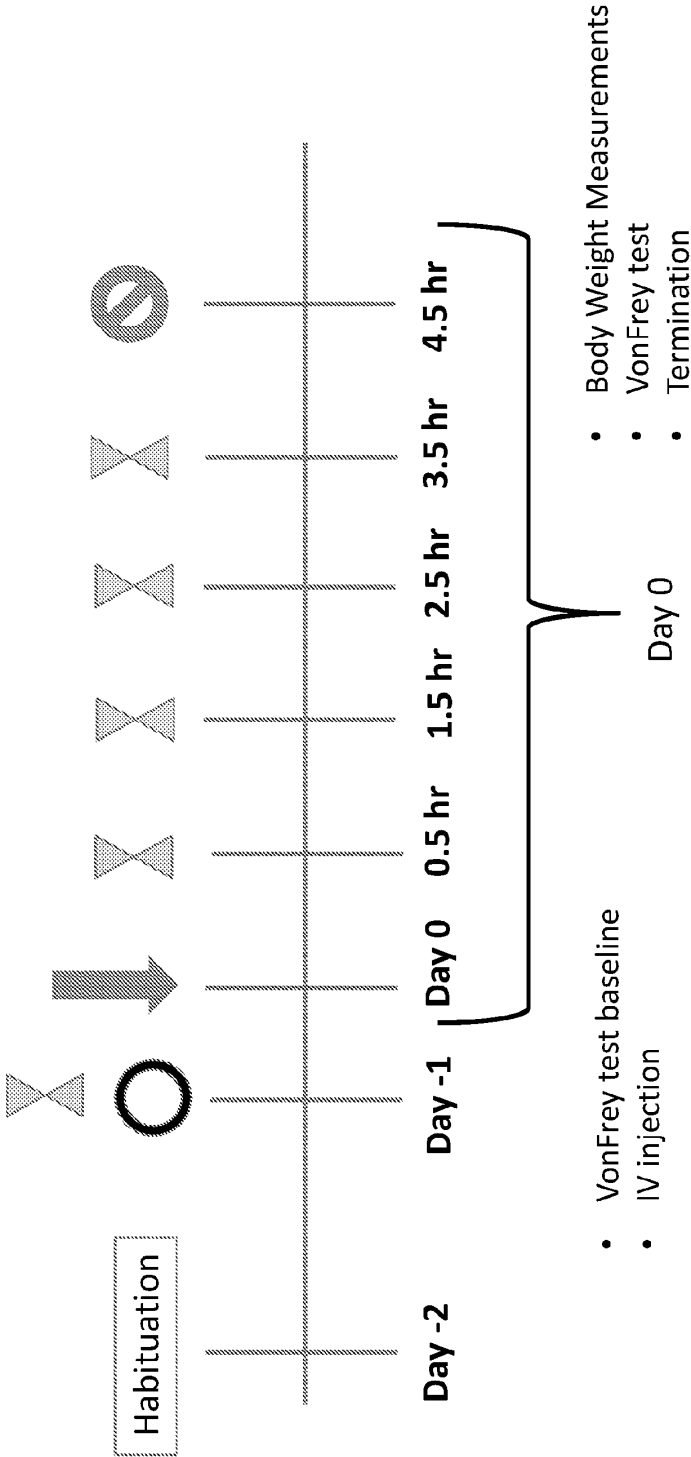
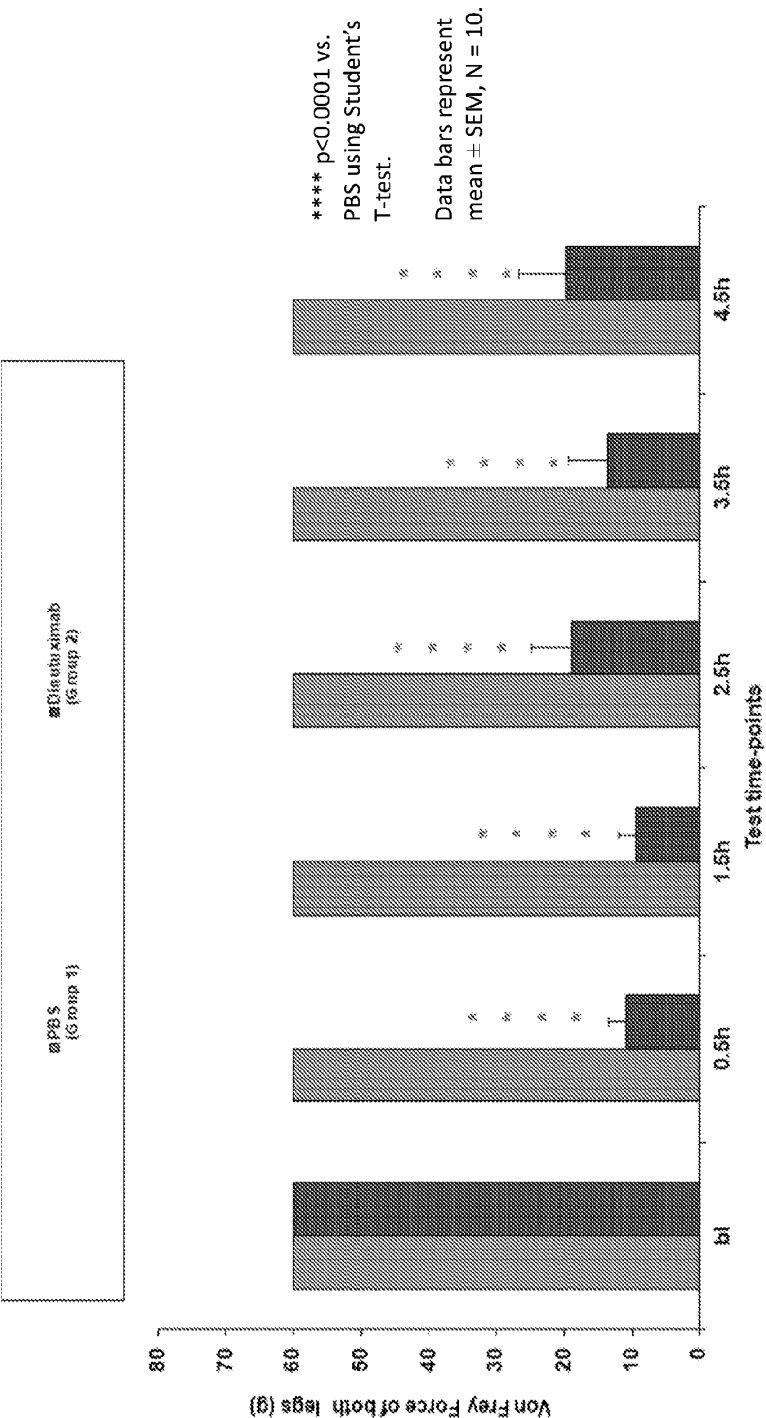


FIG. 43

Pilot Dinutuximab Pain Model Results



Dinutuximab Leads to a Reduced Pain Threshold at All Times Tested

FIG. 44

Summary

FIG. 45

- The pilot study showed a reduced pain threshold (increased pain sensitivity) for rats treated with dinutuximab.
- The goal of the larger pain study would be to show statistically less pain with the B-body™ molecule(s) compared to dinutuximab.
- Plan to run the pain study outlined in the slide above except instead of just testing dinutuximab, we will also test trastuzumab.
- SNIPER candidates selected for pain study:
 - I7-01 x GD2-5
 - I7-01 x GD2-6
 - I7-19 x GD2-5
 - I7-33 x GD2-5
 - I7-34 x GD2-5
 - dinutuximab control
 - Herceptin control

Other Indications for GD2 x B7H3 SNIPER

- Glioblastoma
- Small cell lung cancer
- Sarcomas

FIG. 46

Enhanced SNIPER - version 1.1

- SNIPER with Fc engineering to increase ADCC
- SNIPER antibody-drug conjugate (ADC)

FIG. 47

- Objective:** Targeting disialoganglioside (GD2) with monoclonal antibodies (mAb) is included as standard-of-care in high-risk pediatric-neuroblastoma. Despite high-expression in tumor cells, GD2 is also present in peripheral nerves, leading to substantial, at times dose-limiting, neuropathic-pain in many treated patients. Another molecular target B7-H3 (CD276), is also overexpressed in many cancers including neuroblastoma, but not on nerves. Our goal is to generate anti-GD2/B7-H3 bispecific antibodies (bs-mAb) that conserve high tumor avidity with significantly reduced off-target GD2-binding.

Methods: Three bispecific bs-mAb, 17.33-GD2.2, 17.34-GD2.6, and 17.36-GD2.6 were engineered to present Fab fragments with moderate affinity for GD2 or B7-H3 alone, but strong binding when combined. The bs-mAbs were conjugated to deferroxamine and radiolabeled with 89Zr for in vitro and in vivo studies. The affinities of the bs-mAbs for GD2+/B7-H3+ melanoma (MEL) cells (B78-H3), GD2+/B7-H3- MEL (B78), or GD2-/B7-H3+ MEL (B16-H3), were determined via an in vitro radioactive competitive binding assay and compared to that of monospecific anti-GD2 (dinutuximab) and anti-B7-H3 (17.36) mAbs. To assess in vivo tumor avidity, C57BL/6 mice (n=3) bearing subcutaneous B78-H3 MELs were intravenously administered 89Zr-17.33-GD2.2, 89Zr-17.34-GD2.6, 89Zr-17.36-GD2.6, or 89Zr-dinutuximab; longitudinal PET scans were acquired at 3, 24, 48, and 72 h post-injection. PET imaging of an isotype control and blocking studies were performed to confirm the specificity of the bs- mAbs in vivo. Ex vivo biodistribution was carried out following the last PET imaging timepoint. PET imaging quantification and biodistribution results were reported as percent injected activity per gram (%IA/g) of tissue.
- Results:** Competitive binding assays in B78 (GD2+/B7-H3-) or B16-H3 (GD2-/B7-H3+) cells revealed a markedly reduced binding affinity (IC50 >333 nM) for all bs-mAbs compared to the monospecific dinutuximab (IC50=49.8±12.4 nM) and 17.36 (IC50=13.0±4.5 nM) antibodies. Conversely, the bs-mAbs 17.33-GD2.2 (IC50=16.1±4.7 nM) and 17.34-GD2.6 (IC50=12.2±3.8 nM) demonstrated higher affinity for GD2+/B7-H3+ B78-H3 cells than dinutuximab (IC50=33.9±15.4 nM). In vivo PET imaging in mice bearing B78-H3 tumors confirmed elevated and persistent tumor uptake of 89Zr-17.33-GD2.2, 89Zr-17.34-GD2.6, and 89Zr-17.36-GD2.6 which peaked at 17.0±1.9, 19.3±0.7 and 18.3±1.5 %IA/g, respectively, 48-h post-injection of the radiotracers. Co-injection of non-radioactive 17.33-GD2.2 (10 mg/kg) resulted in a 46% reduction (9.1±1.7 %IA/g; p<0.0001) in tumor uptake of 89Zr-17.33- GD2.2, and together with a low tumor uptake of the 89Zr-isotype control (6.9±1.9 %IA/g) corroborated the in vivo specificity of the bs-mAb. Consistent with its lower in vitro affinity for B78-H3 cells, 89Zr-dinutuximab had significantly lower uptake (12.8±3.8 %IA/g; p<0.01) in B78-H3 tumors compared to all three bs-mAb tested.
- Conclusion:** We successfully generated bs-mAbs with high tumor avidity to GD2+/B7-H3+ cells and limited off-target binding to GD2-/B7-H3- cells. These data suggest that future testing may show improved treatment efficacy in treating patients with GD2+/B7-H3+ tumors (like neuroblastoma) with reduced neuropathic toxicity.

FIG. 48

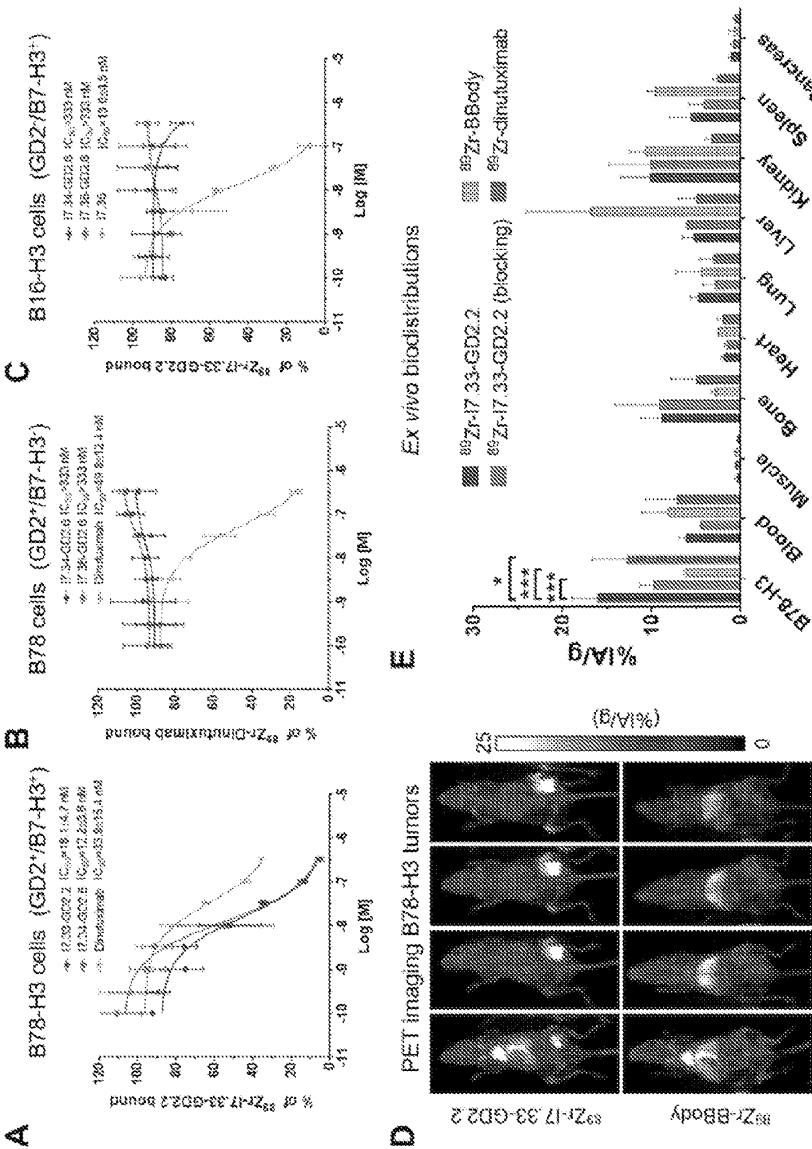


FIG. 49

Disialoganglioside GD2 is expressed on neuroblastoma, as well as many melanomas, small cell lung cancers, and sarcomas. Administration of an anti-GD2 mAb can be used for the treatment of these diseases and is part of the standard of care for neuroblastoma. While expressed on a limited number of normal tissues, GD2 is expressed on some nerve cells. As such, treatment with anti-GD2 mAb is associated with neuropathic pain. To increase tumor specificity, we have developed a bispecific SNIPER antibody, INV721, to simultaneously target two tumor antigens. One arm of the antibody is specific to GD2 and the other arm is specific to B7H3. B7H3 is overexpressed on multiple tumor types, including those listed above, with minimal expression on most normal cells and absent on nerve cells. The monovalent arms targeting GD2 and B7H3 are each low-moderate affinity, such that INV721 will only bind with high affinity when both arms of the antibody bind to their antigens on the same cell. This high-affinity binding requires expression of both GD2 and B7H23, resulting in high-specificity of the SNIPER to tumor cells. Mice bearing GD2/B7H3-expressing tumors were treated with a ^{89}Zr radio-labeled INV721 SNIPER and monitored via PET imaging. INV721- ^{89}Zr bound with high-specificity to the tumor for up to 72 hours, and relatively little INV721- ^{89}Zr uptake was observed in normal tissues. The goal of this SNIPER-antibody is to enhance the tumor-specific delivery of mAb-based treatment, which may decrease toxicity and improve efficacy for cancers expressing both GD2 and B7H3.

FIG. 50

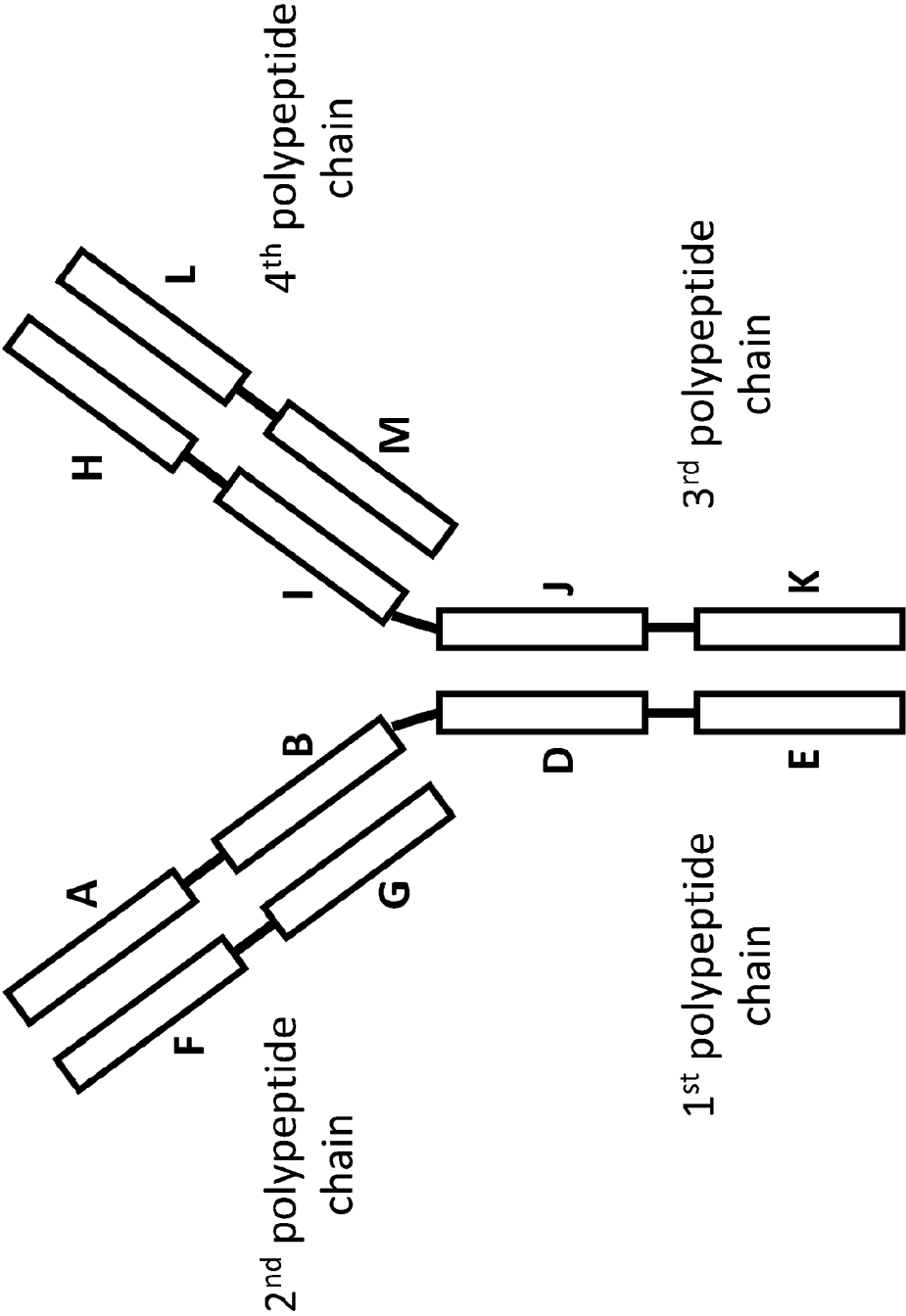


FIG. 51

- INV721 (B7H3 arm x GD2 arm)
- B7H3 arm x Non-Specific arm
- ▲ GD2 arm x Non-Specific arm

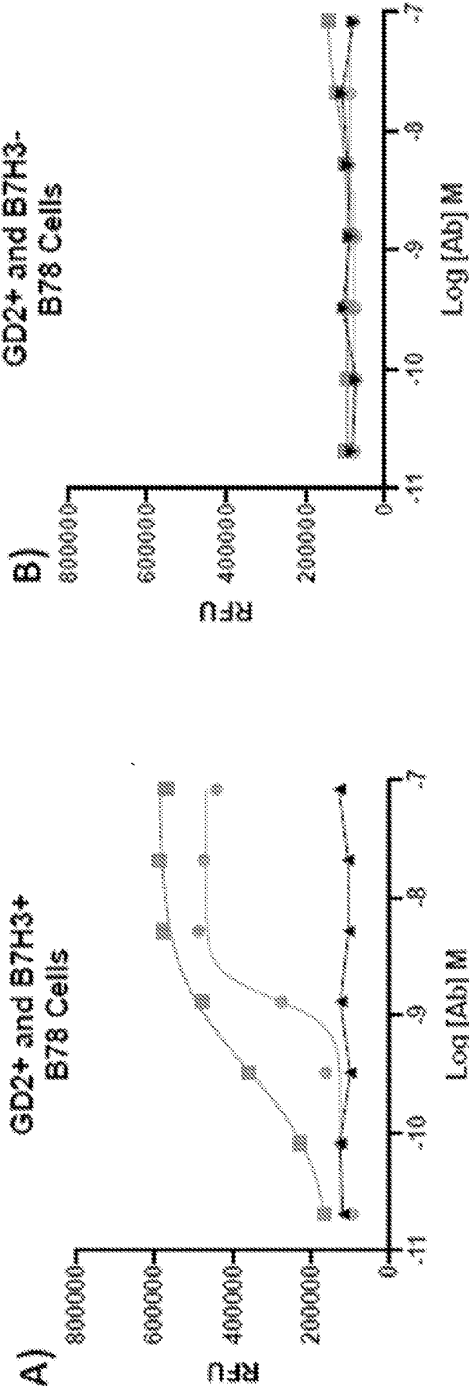


FIG. 52B

FIG. 52A

Pediatric Cancer Cell Lines				
	GD2 Expression	B7H3 Expression	GD2/B7H3 Dual Expression	INV721
CHLA20	+++	+++	+++	+++
NGP	+++	+++	++	+++
LAN1	+++	++	+	+++
LAN5	+	++	+	+++
LAN5	+++	++	+++	+++
Rd	+++	++	+++	+++

FIG. 53

Melanoma Cell Lines				
	GD2 Expression	B7H3 Expression	GD2/B7H3 Dual Expression	INV721
MEL MRA 2	-	+++	-	+++
MEL MRA 6	+	++	+	+++
MEL MRA 7	++	+++	++	+++
MEL MRA 13	++	+++	++	+++
M21	+++	+++	+++	+++
A375	+	+++	+	+++

FIG. 54

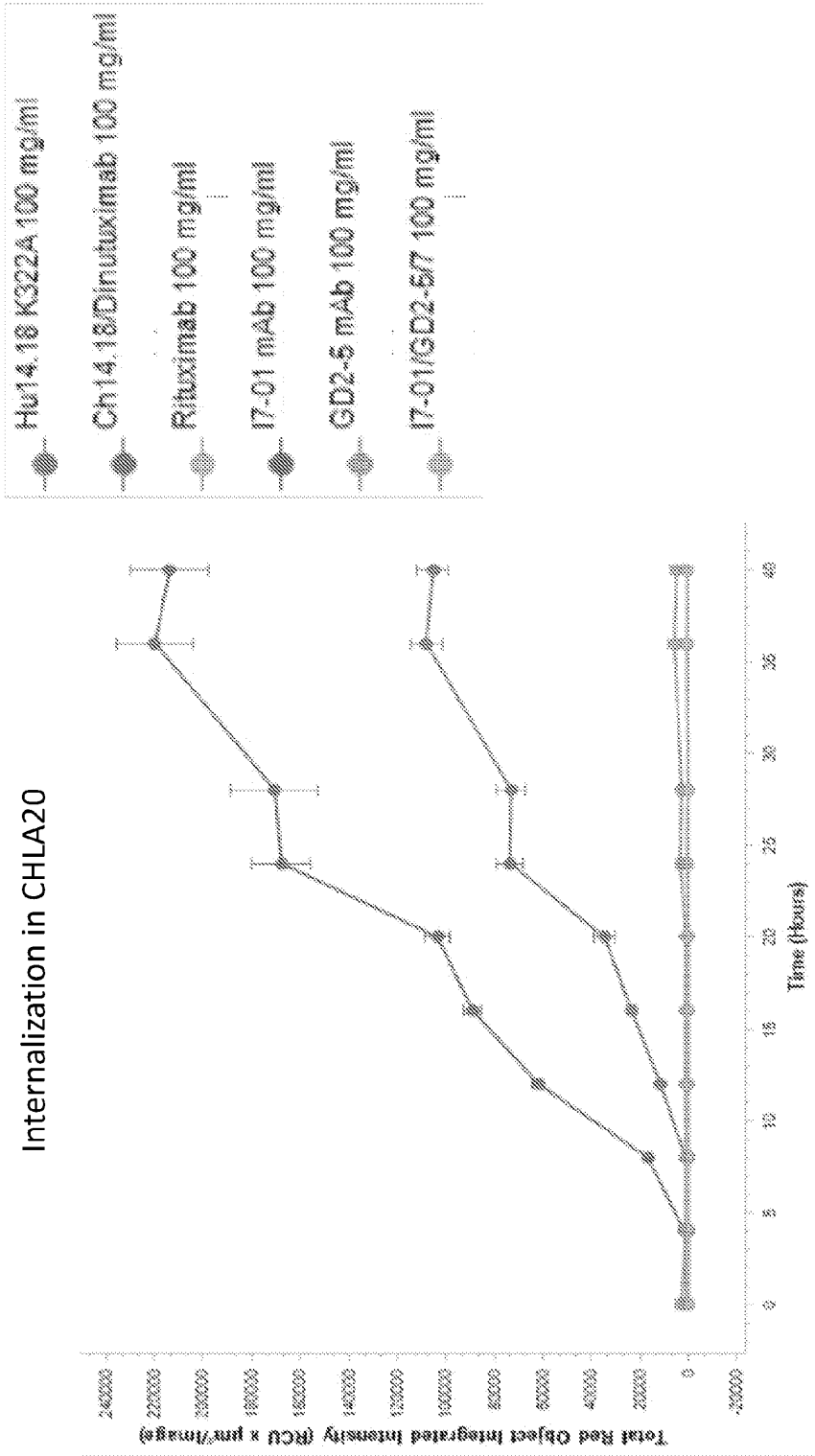


FIG. 55A

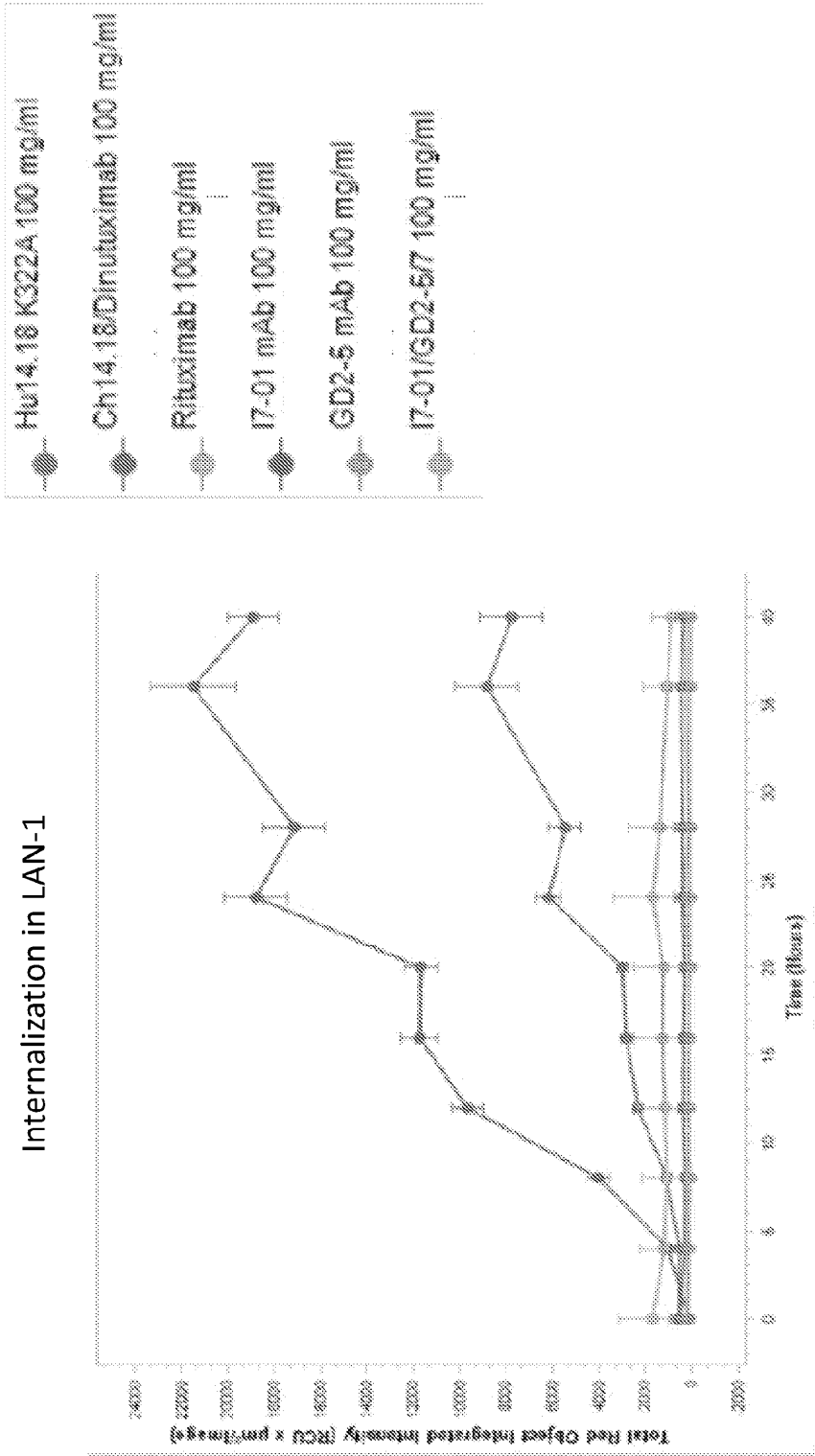


FIG. 55B

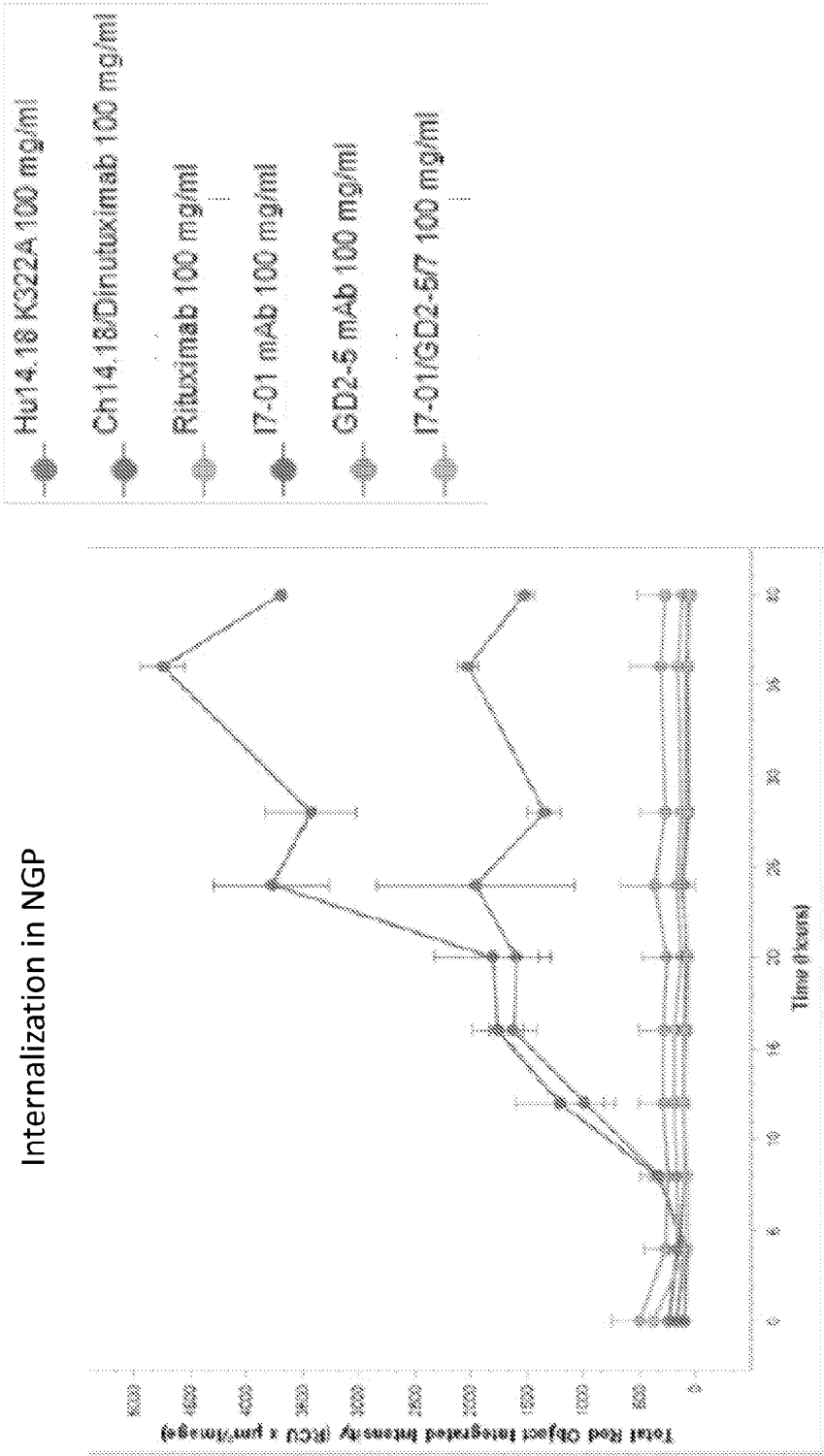


FIG. 55C

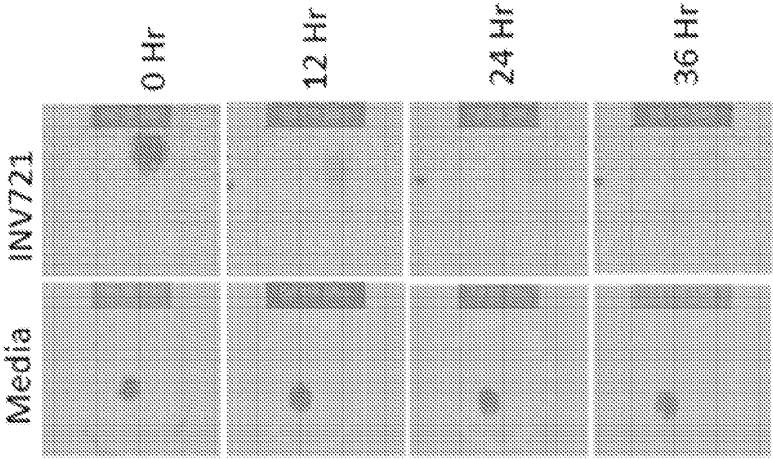


FIG. 56A

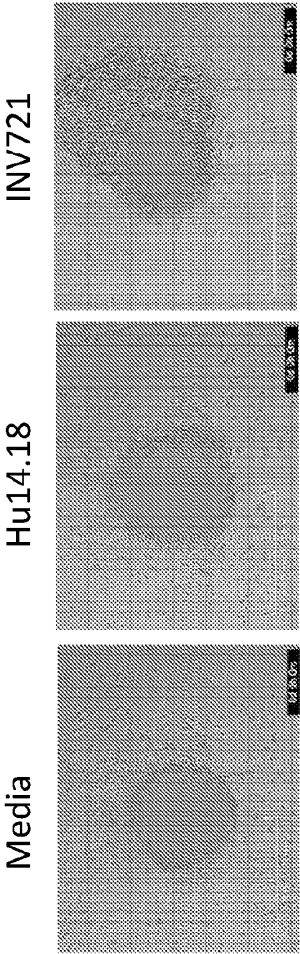


FIG. 56B

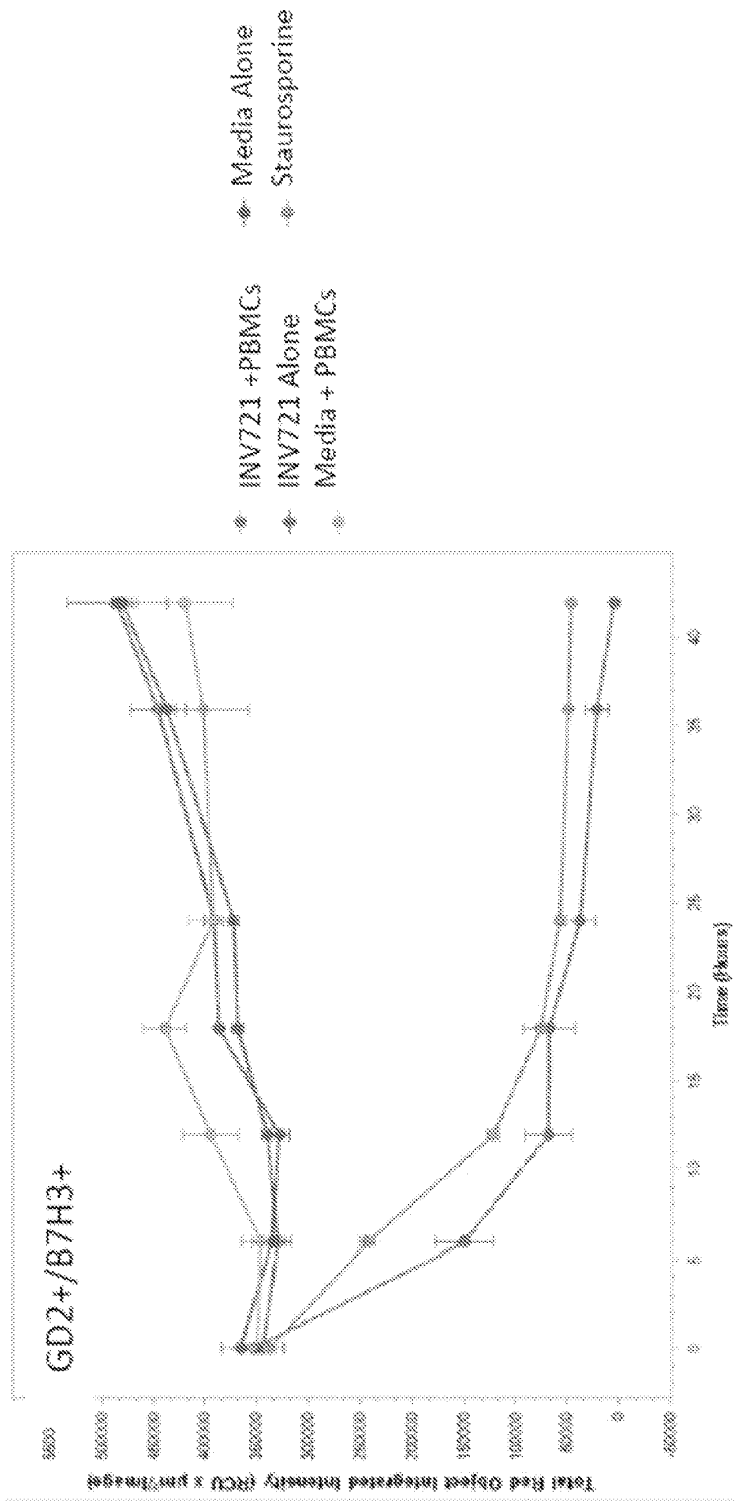


FIG. 57A

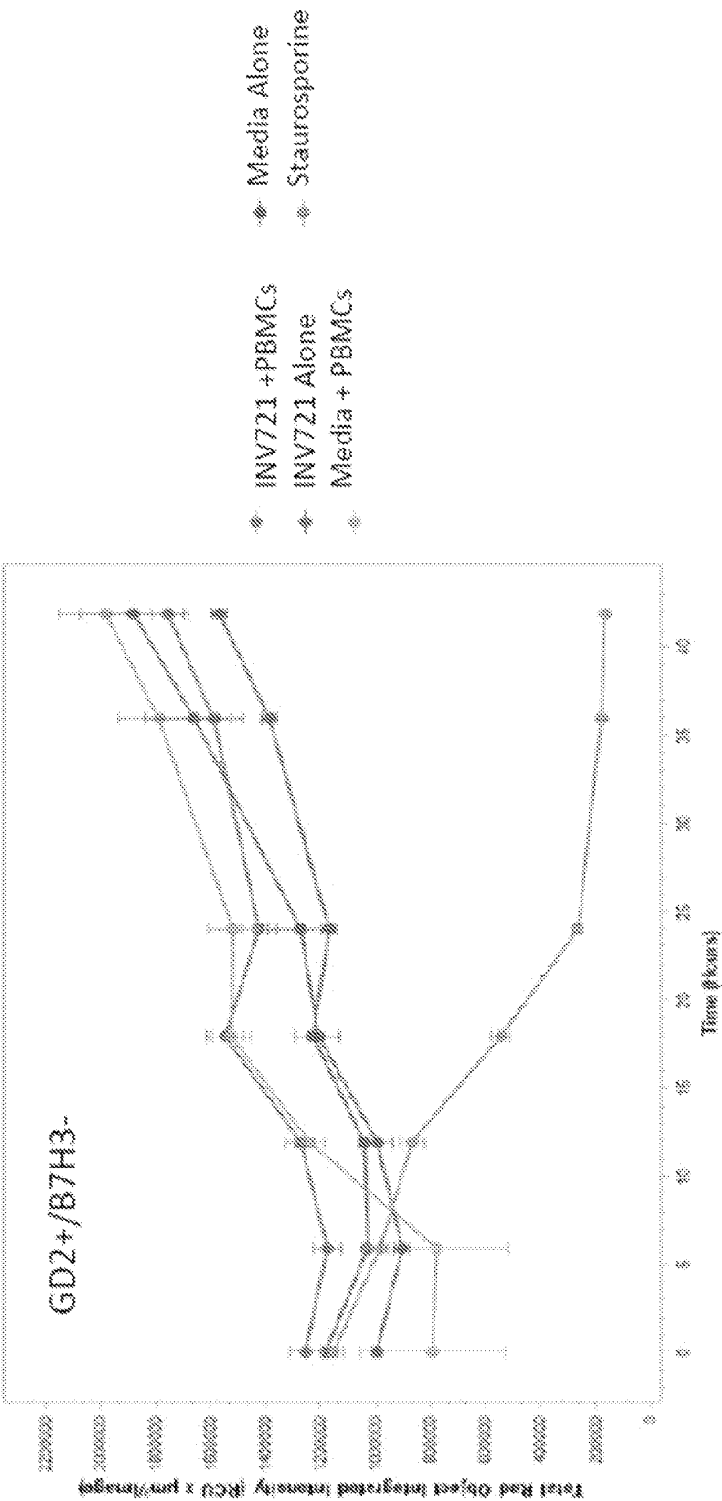


FIG. 57B

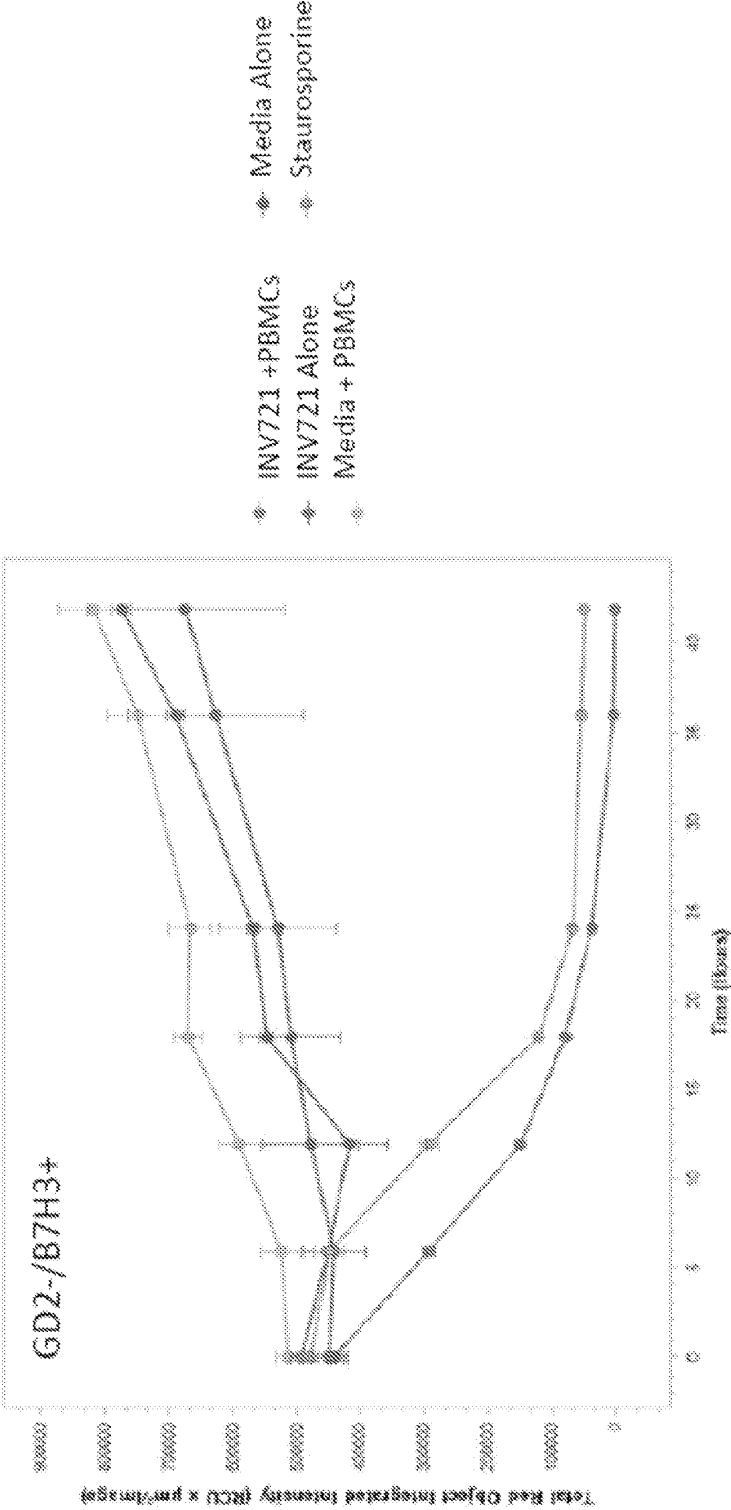


FIG. 57C

M21 cells

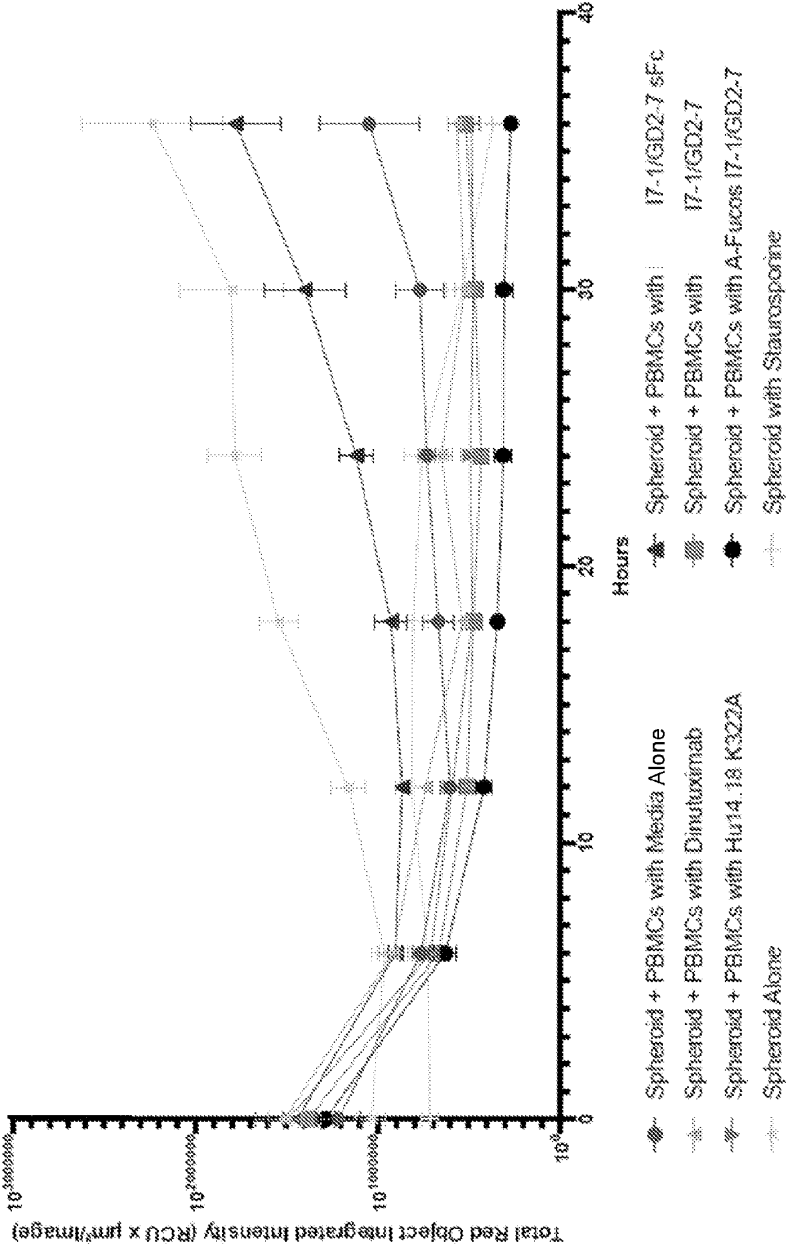


FIG. 58A

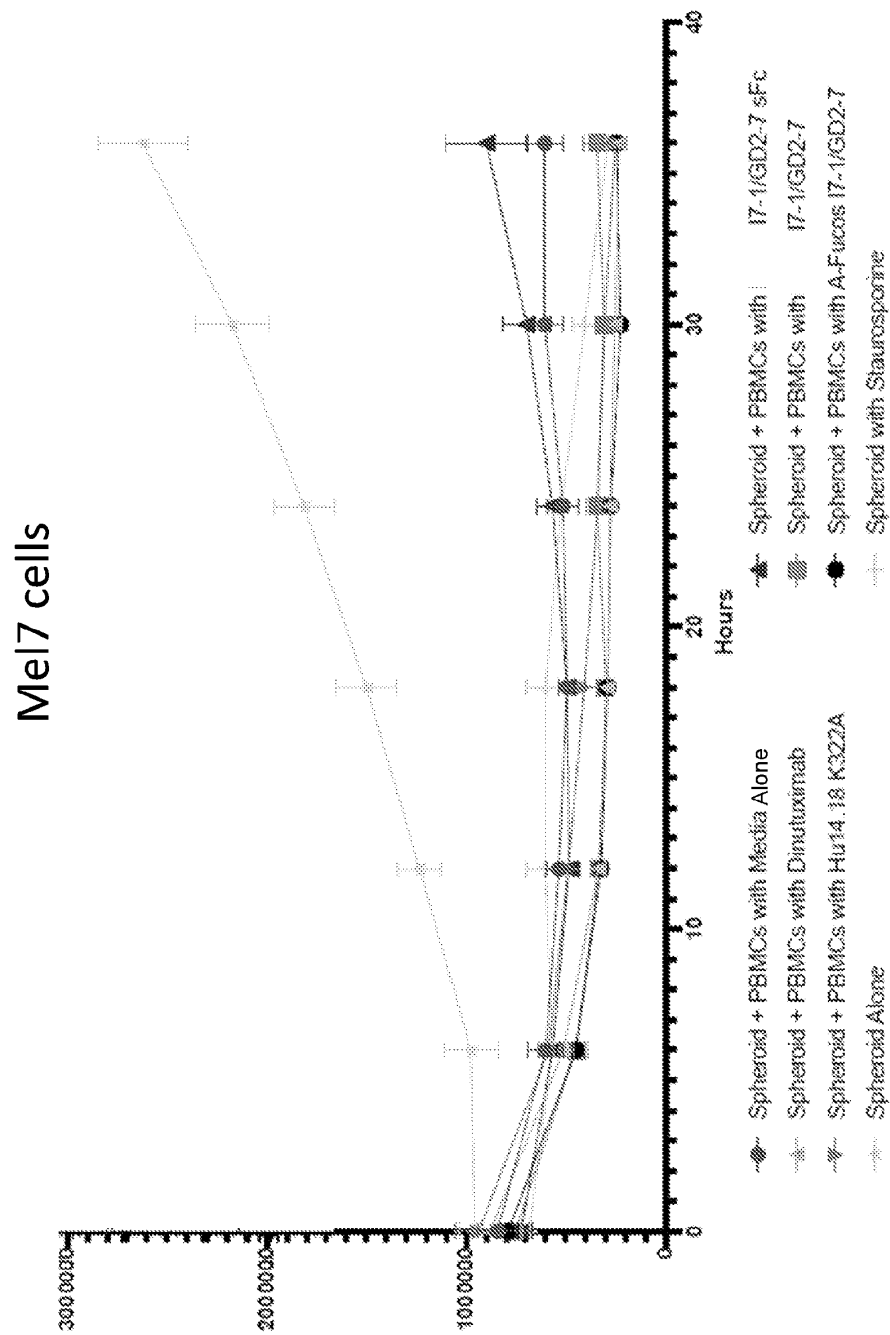


FIG. 58B

Mel13 cells

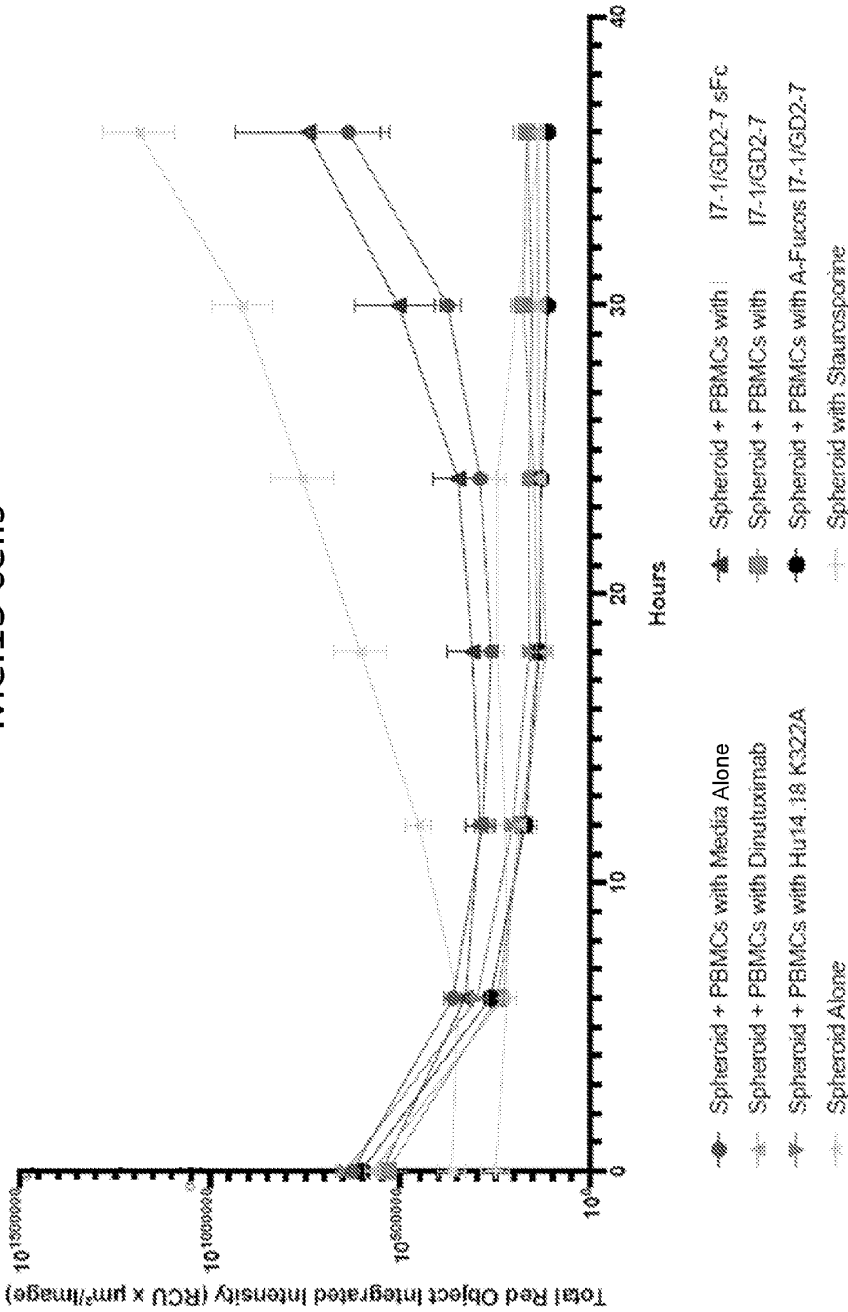


FIG. 58C

M21 cells

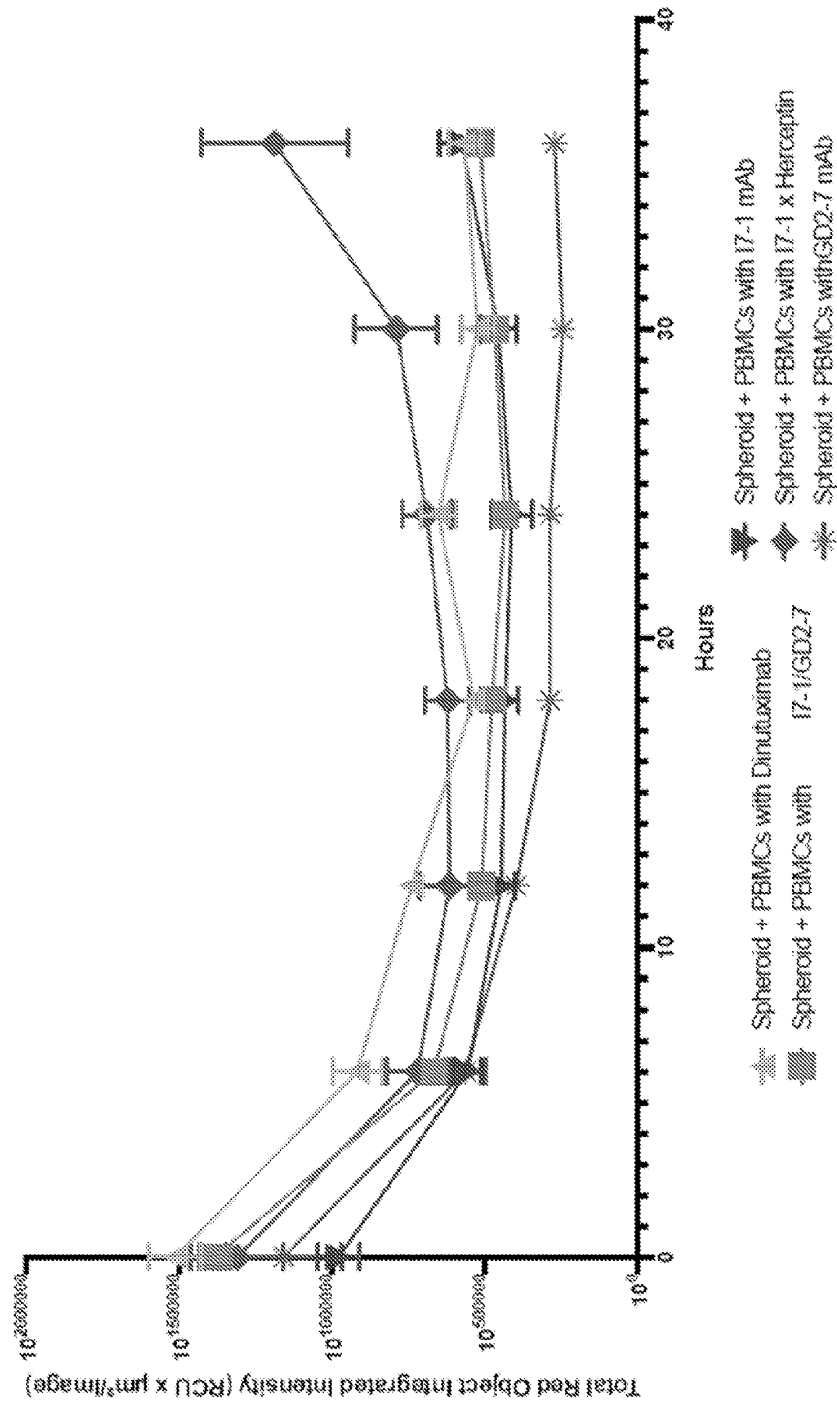


FIG. 59

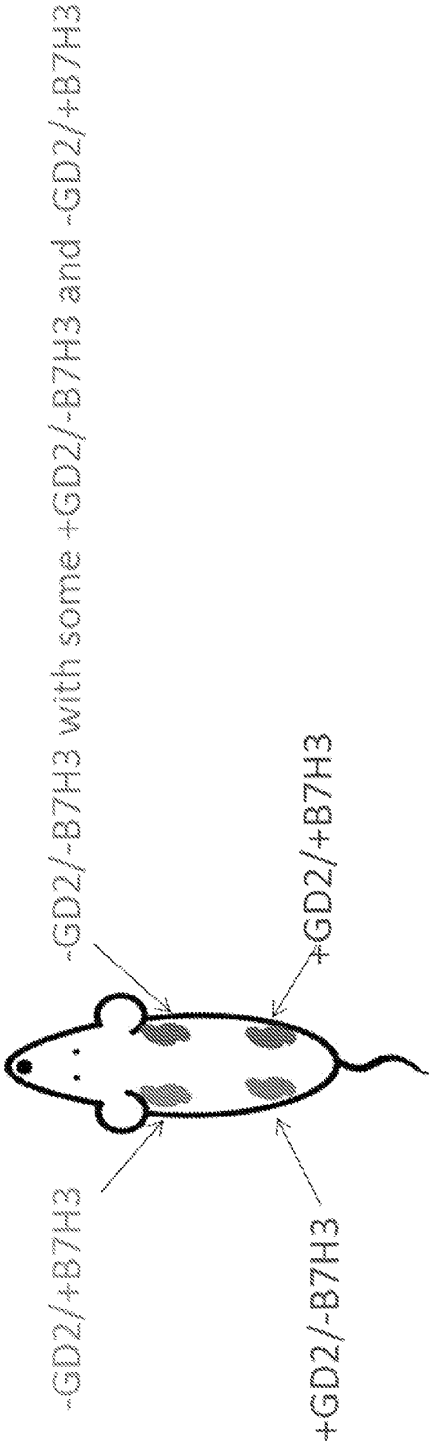
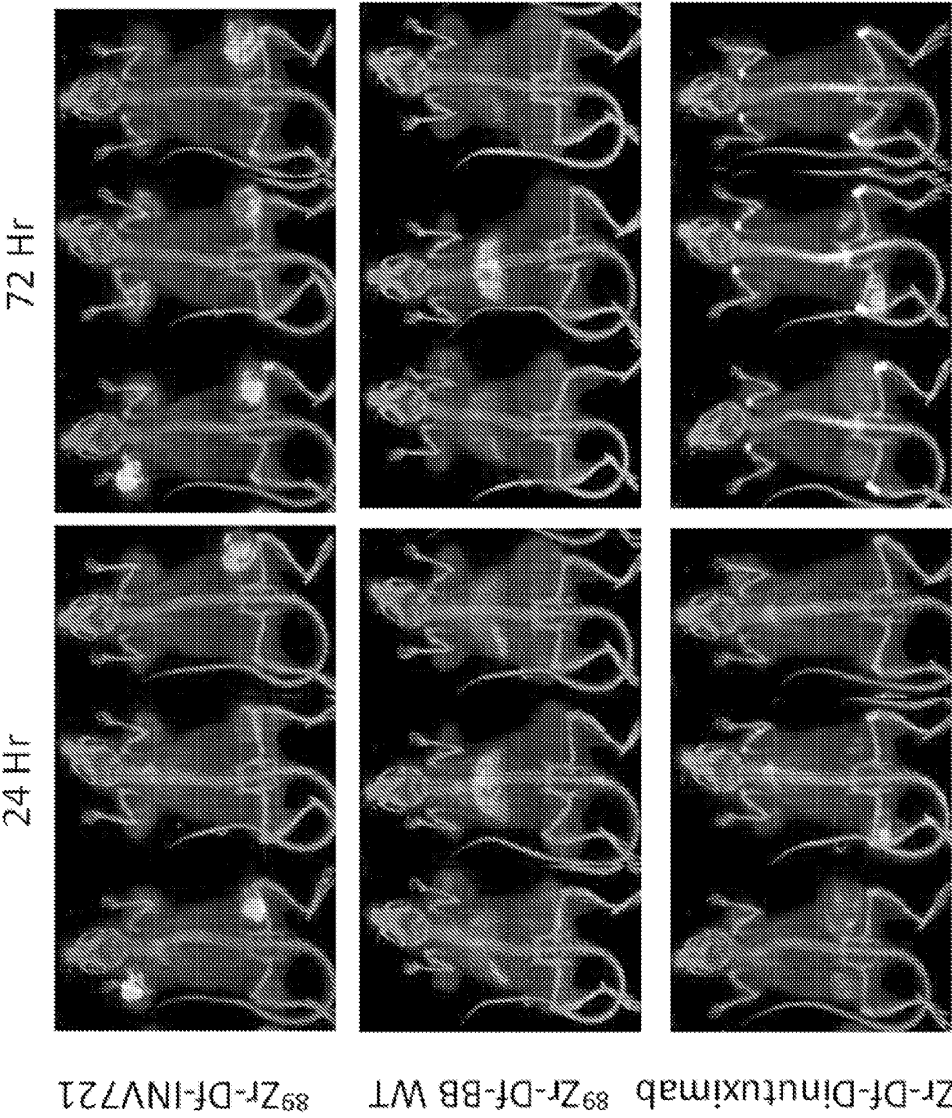


FIG. 60



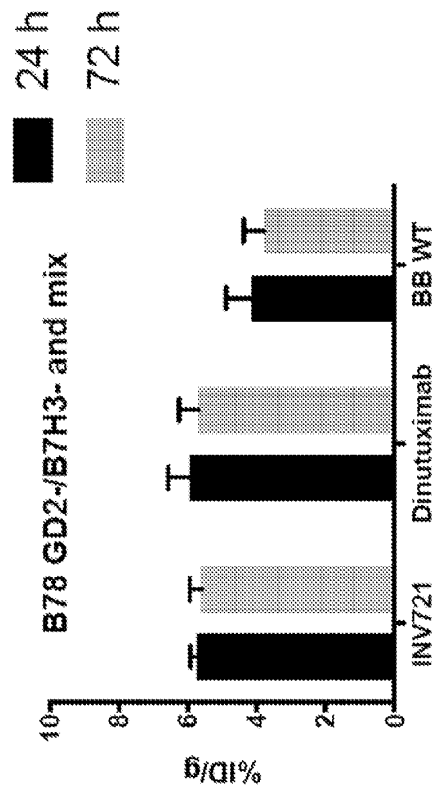


FIG. 62B

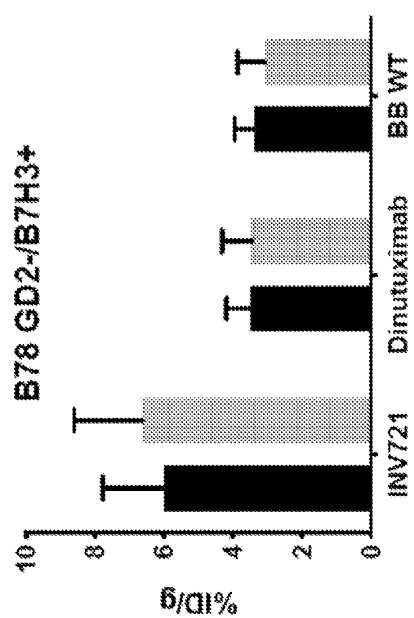


FIG. 62A

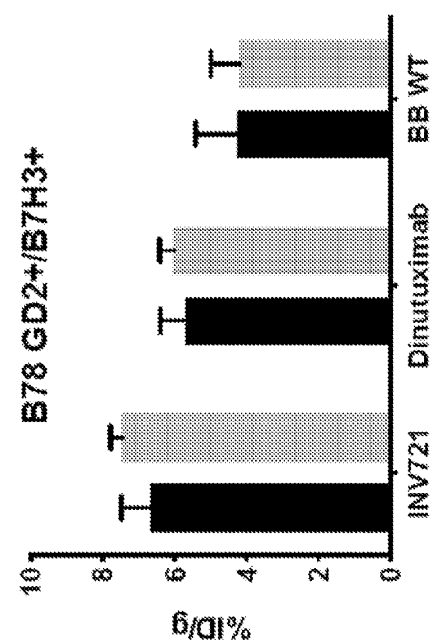


FIG. 62D

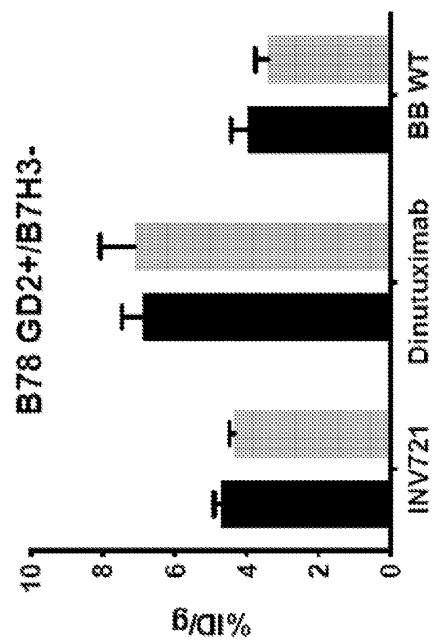


FIG. 62C

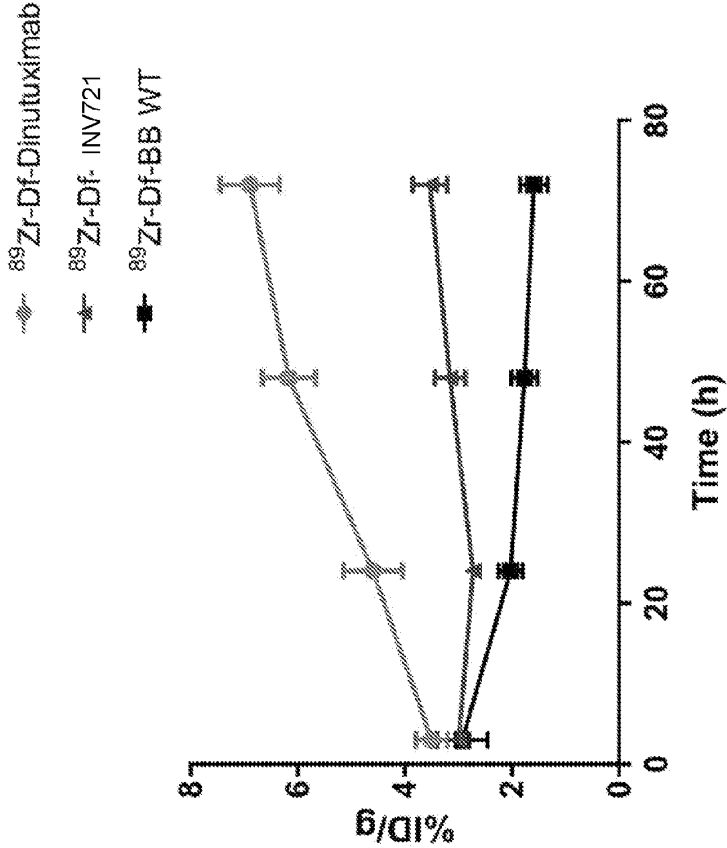


FIG. 63B

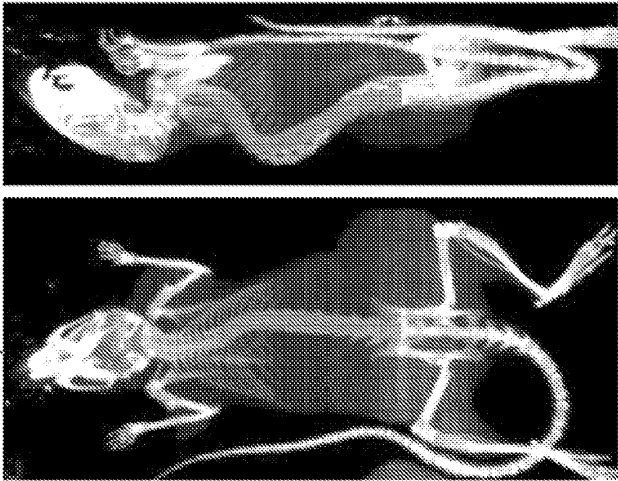


FIG. 63A

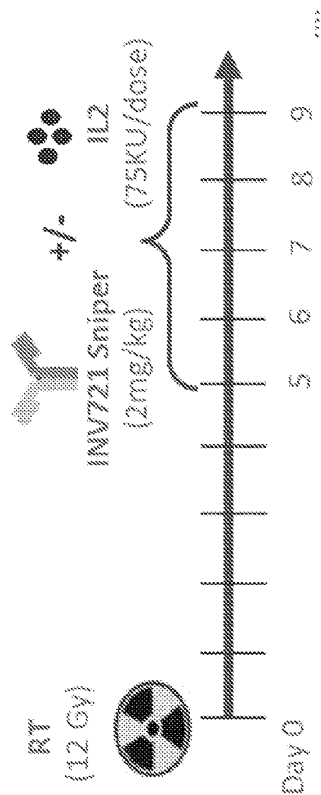


FIG. 64

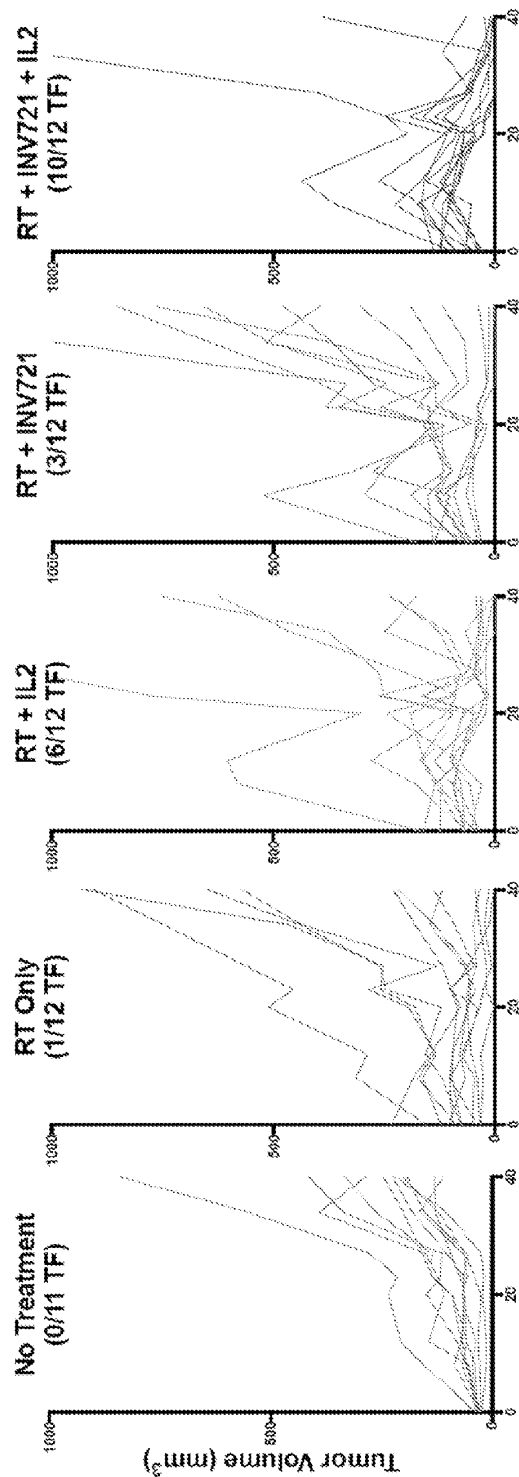


FIG. 65

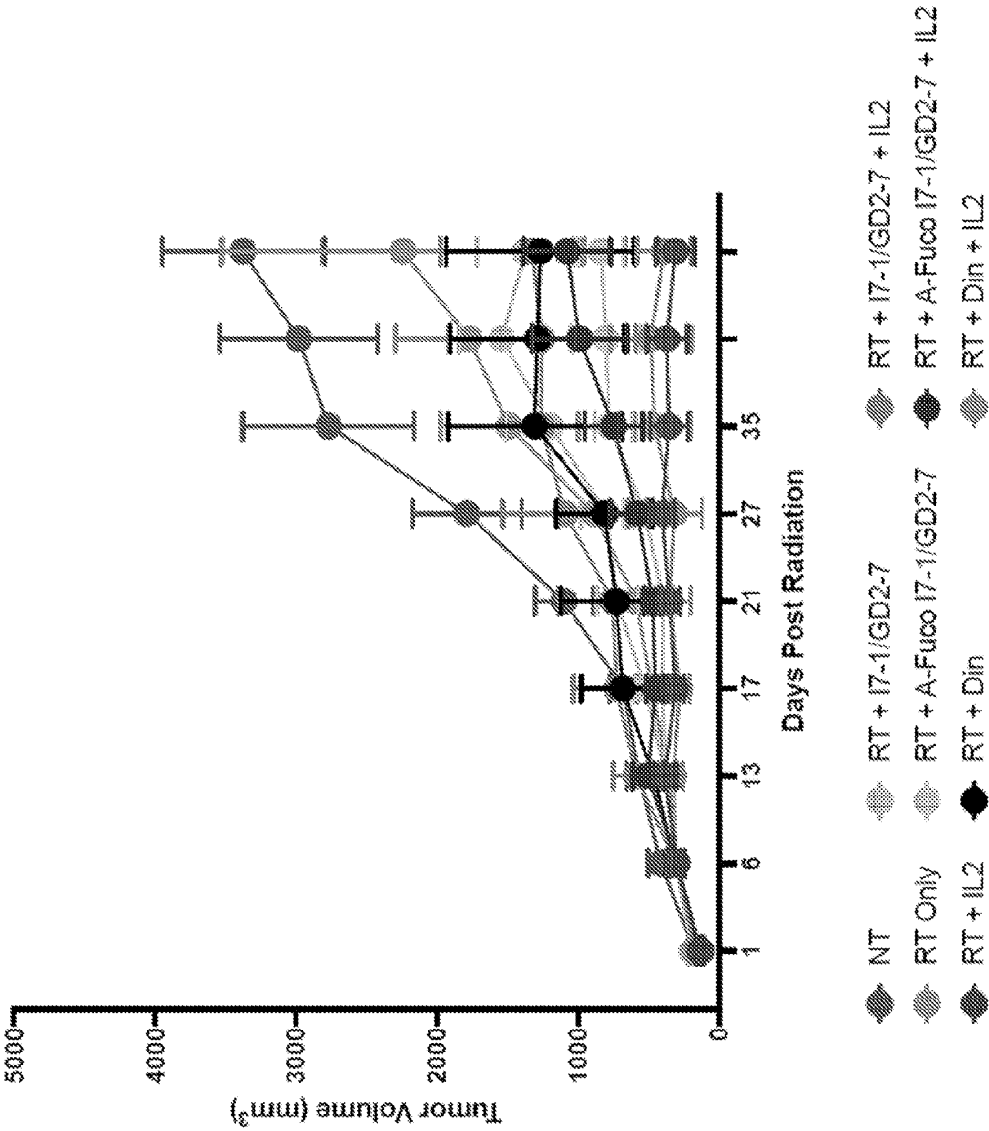


FIG. 66

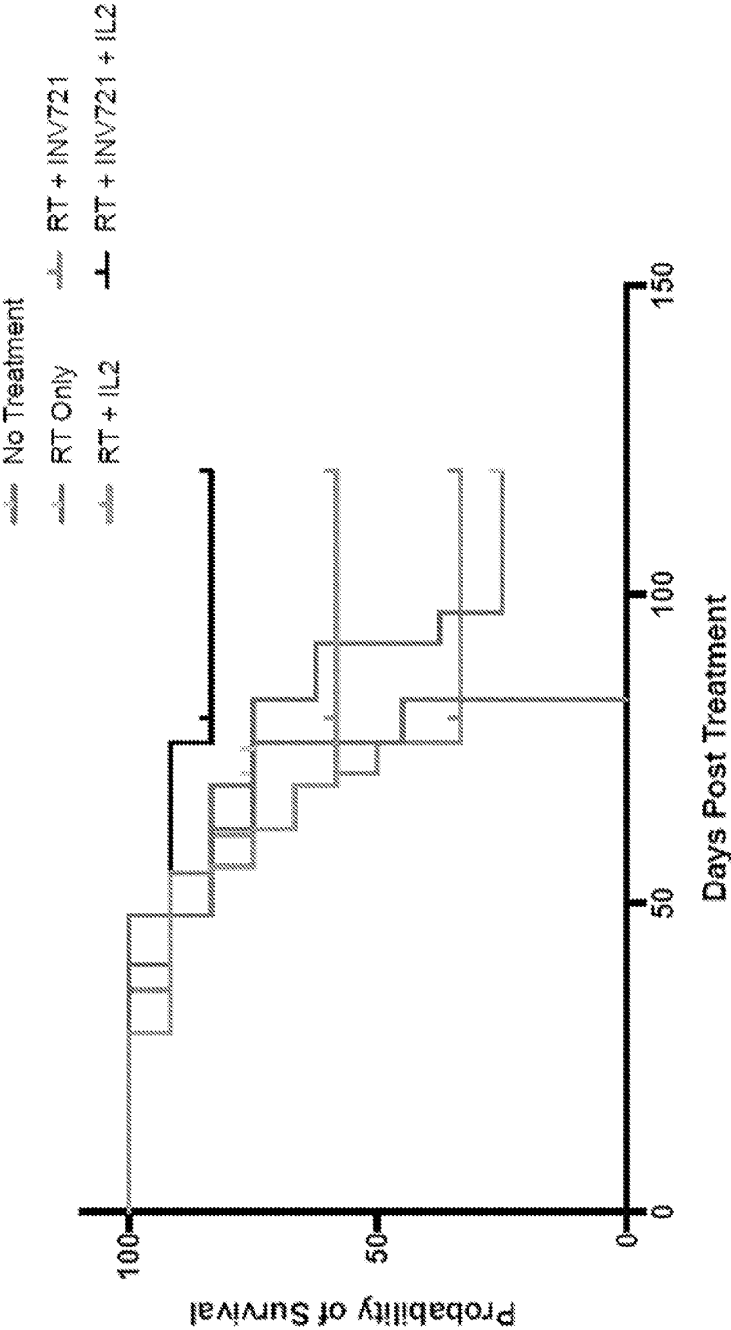


FIG. 67