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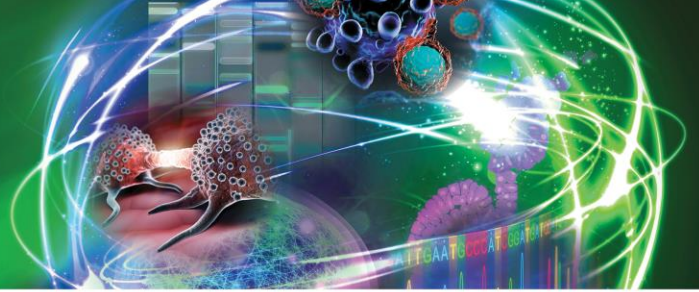
ANNUAL MEETING 2021
VIRTUAL #AACR21
APRIL 10-15, 2021 AND MAY 17-21, 2021 ★ AACR.ORG ★ AACR.ORG/AACR2021



Mechanistic evaluation of anti-DR5 IgM antibody IGM-8444 with potent tumor cytotoxicity, without *in vitro* hepatotoxicity

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Tasnim Kothambawala, Kevin C. Hart, Xingjie Chen, Melanie Desbois, Susan E. Calhoun, Poonam Yakkundi, Rodnie A. Rosete, Yuan Cao, Katie Cha, Thomas J. Matthew, Ling Wang, Paul R. Hinton, Paul D. Schnier, Miho Oyasu, Maya K. Leabman, Genevive Hernandez, Maya F. Kotturi, Eric W. Humke, Angus M. Sinclair, Bruce A. Keyt

Abstract No. 52

Disclosure Information

Beatrice T. Wang

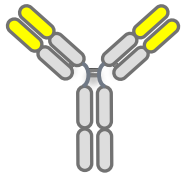
I have the following financial relationships to disclose:

Employee and Stockholder of IGM Biosciences Inc

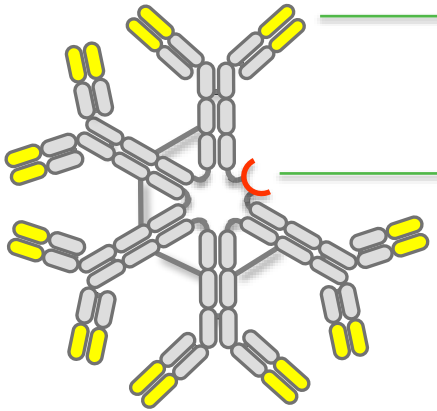
-and-

I will not discuss off label use and/or investigational use in my presentation.

High Affinity, High Avidity IgM Antibodies



IgG



IgM Pentamer

IGM-8444:

Anti-DR5 binding domain

Joining (J) chain optimized for extended serum half-life

IgM Antibodies Enhance DR5 Signaling through Efficient Receptor Clustering

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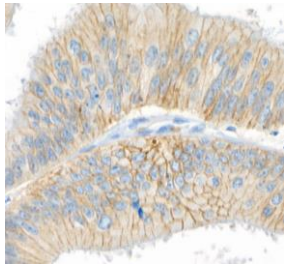
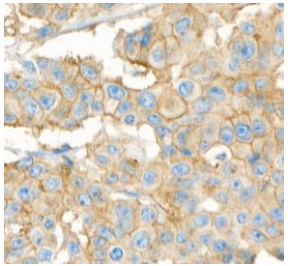
DR5 Stained Tumor Samples

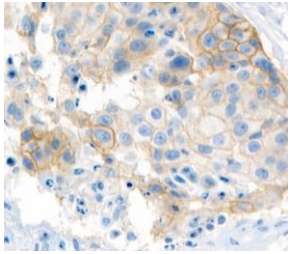
Colon Adenocarcinoma



Gastric Adenocarcinoma

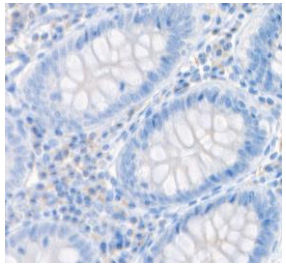


Squamous cell carcinoma

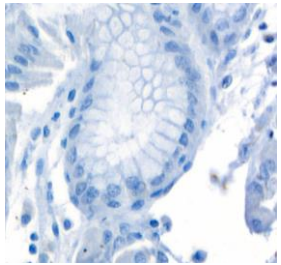


DR5 Stained Normal Tissues

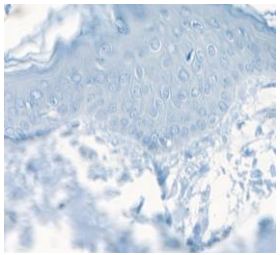
Colon

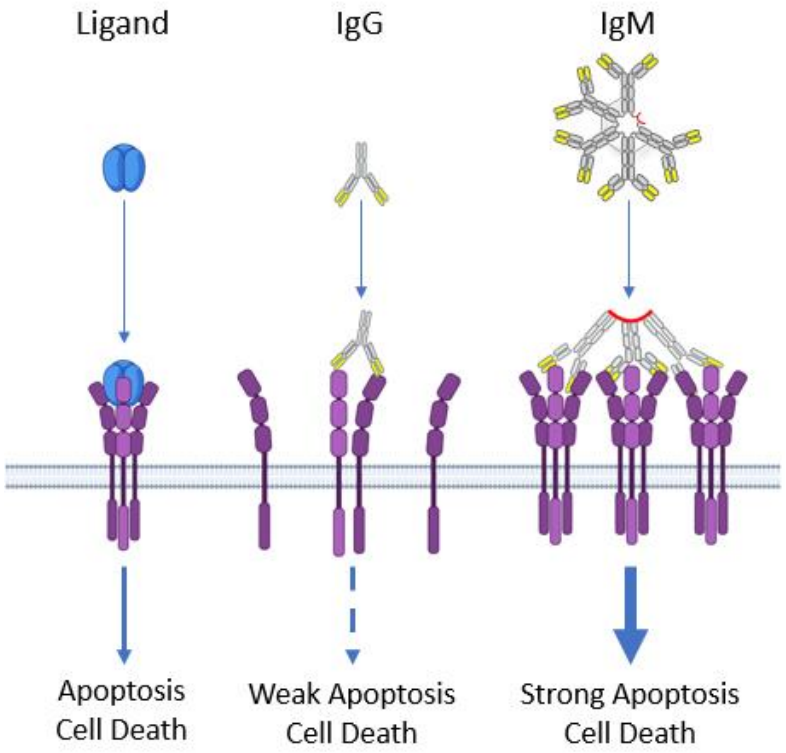


Stomach



Skin





IGM-8444 Binds Membrane Distal Cysteine Rich Domain 1 (CRD1) on DR5

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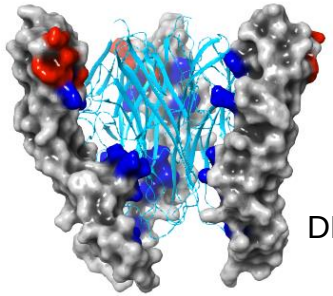
Mab-1

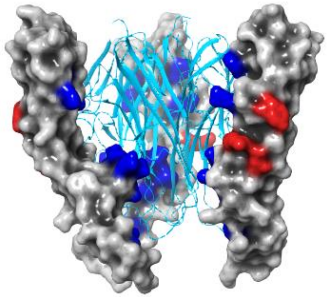


DR5

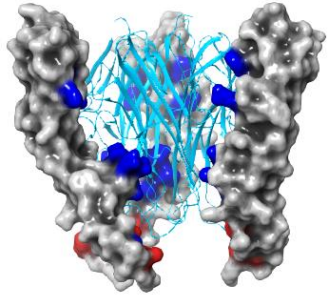
IGM-8444 was derived from Mab-1

	Mab-1	Mab-2	Mab-3	Mab-4	Mab-5
Kd, DR5-Fc (nM)	2.2	1.3	2.3	1.3	0.6
Ligand blocking	Y	N	Y	N	Y

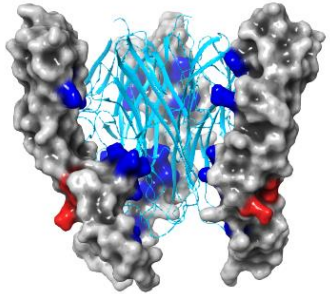
Mab-2



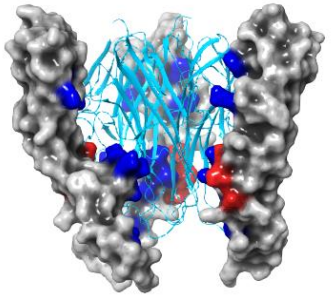
Mab-3



Mab-4



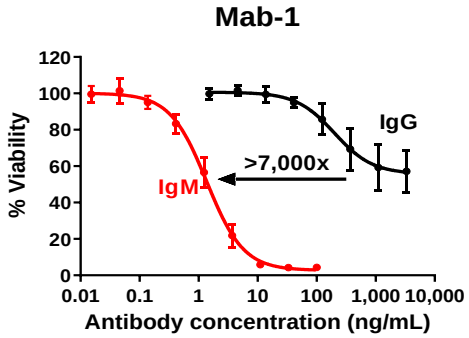
Mab-5

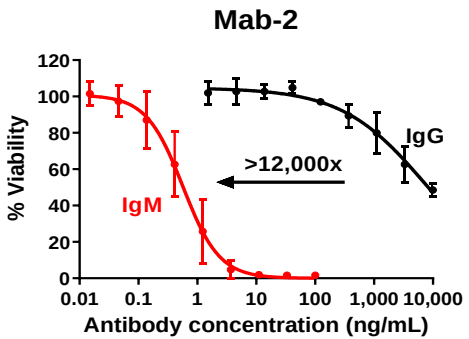


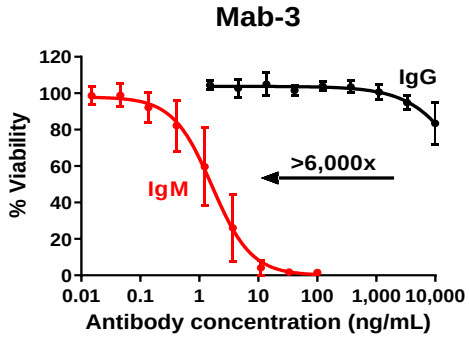
Antibody binding sites in red;
Ligand binding sites in blue

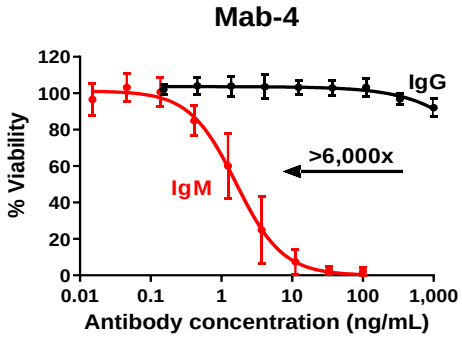
Biacore affinities determined using IgGs;
Epitopes mapped by alanine scanning using IgG Fab fragments

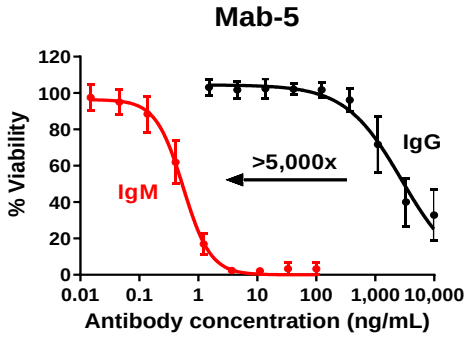
All DR5 Agonist IgM Antibodies are > 5,000-fold More Potent than IgG











- 24-hour Colo205 in vitro cytotoxicity assay

IGM-8444 was Selected for Good *In Vitro* Safety on Human Hepatocytes

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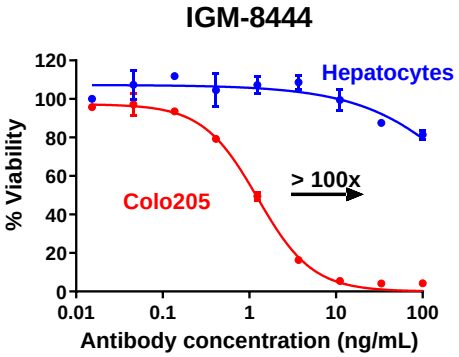
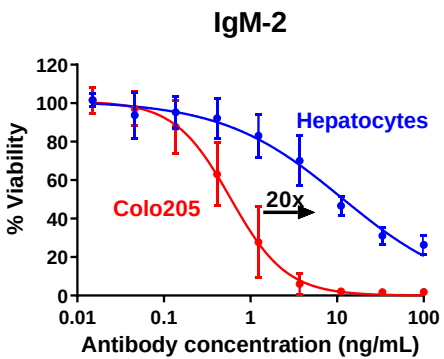
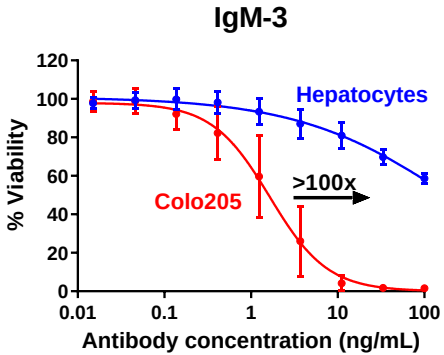
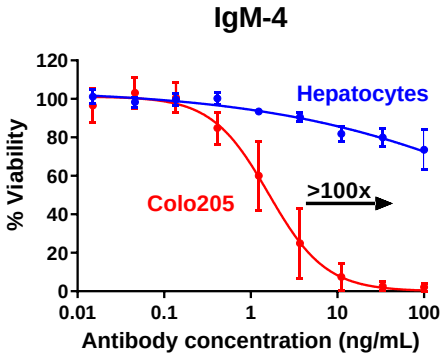
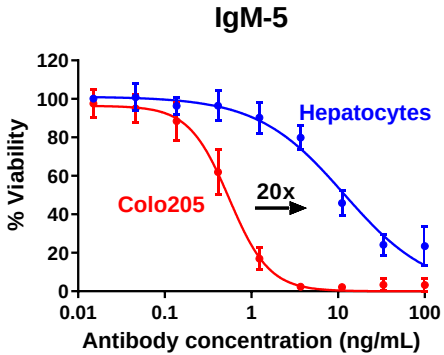






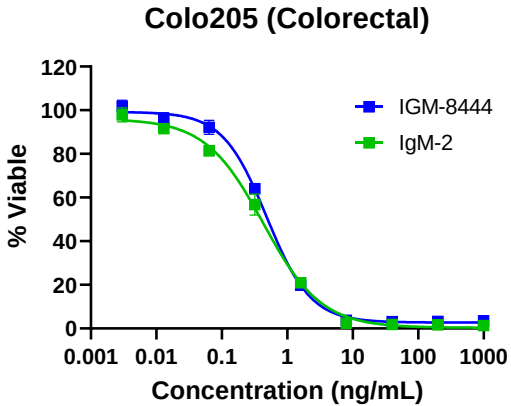


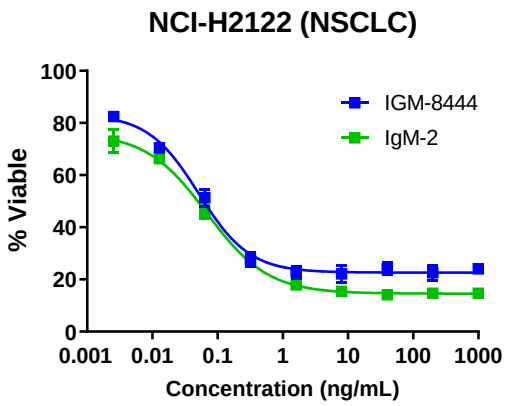


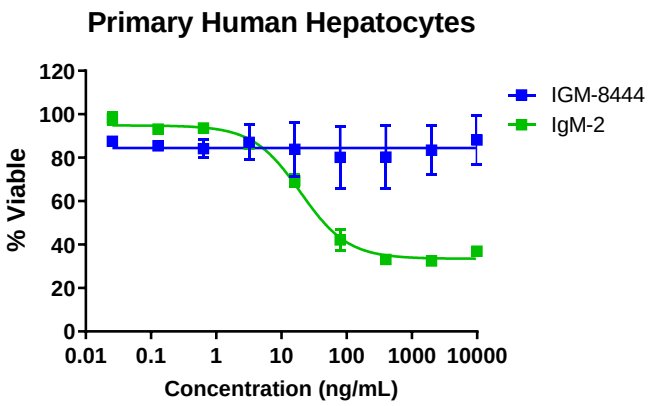
- 24-hour in vitro cytotoxicity assay comparing Colo205 cells vs primary human hepatocytes

IGM-8444 and IgM-2 Show Comparable Tumor Cytotoxicity, but Differential Hepatotoxicity

- 24-hour in vitro cytotoxicity assays







IGM-8444 Achieves Comparable Maximum Cytotoxicity with Delayed Kinetics vs. IgM-2

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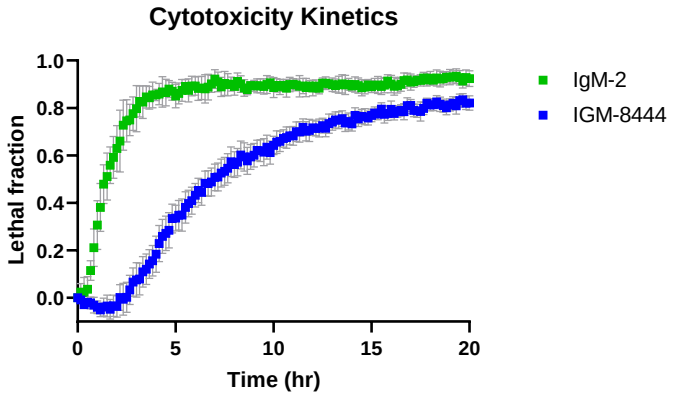
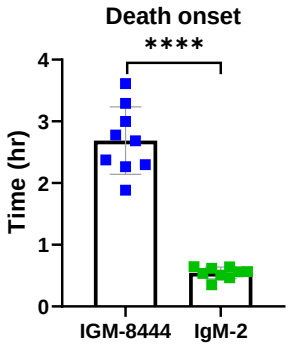
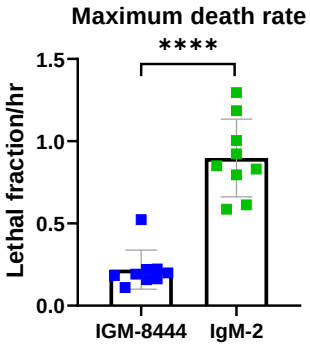
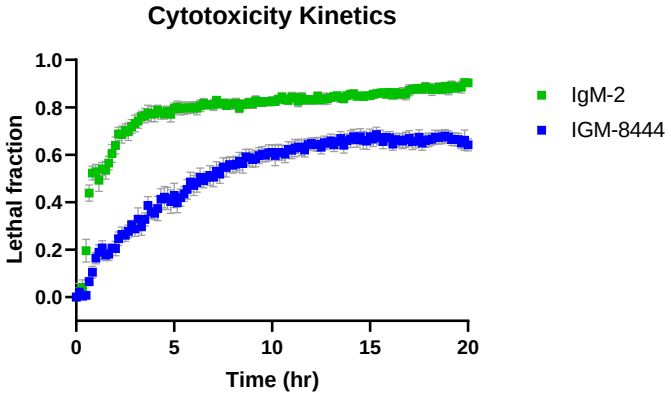
Colo205

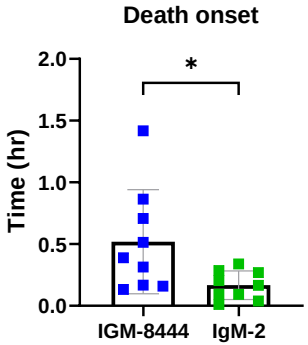


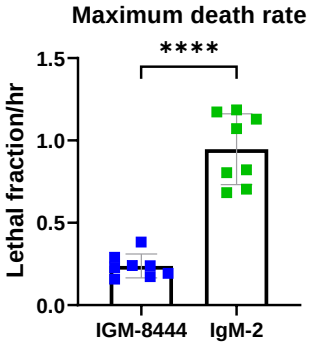




NCI-H2122



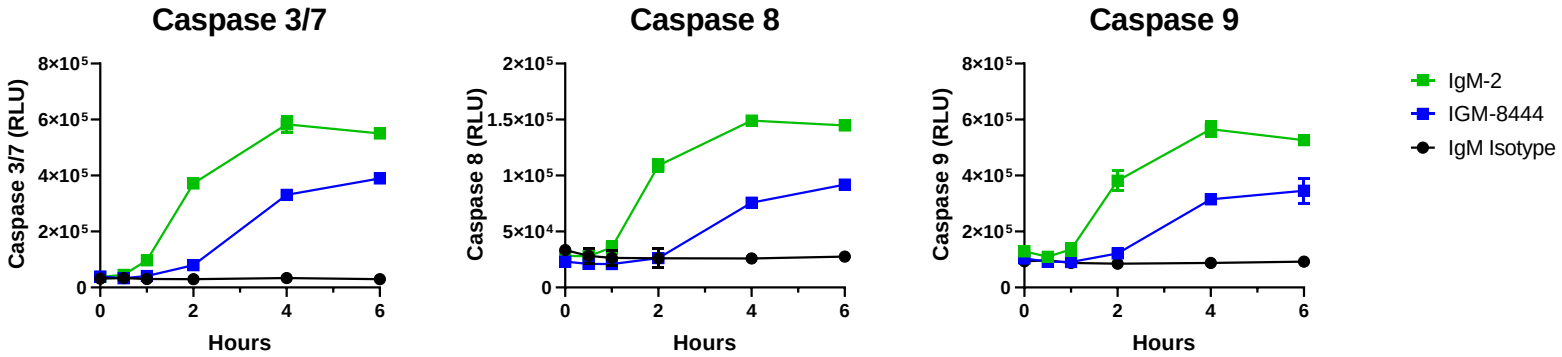




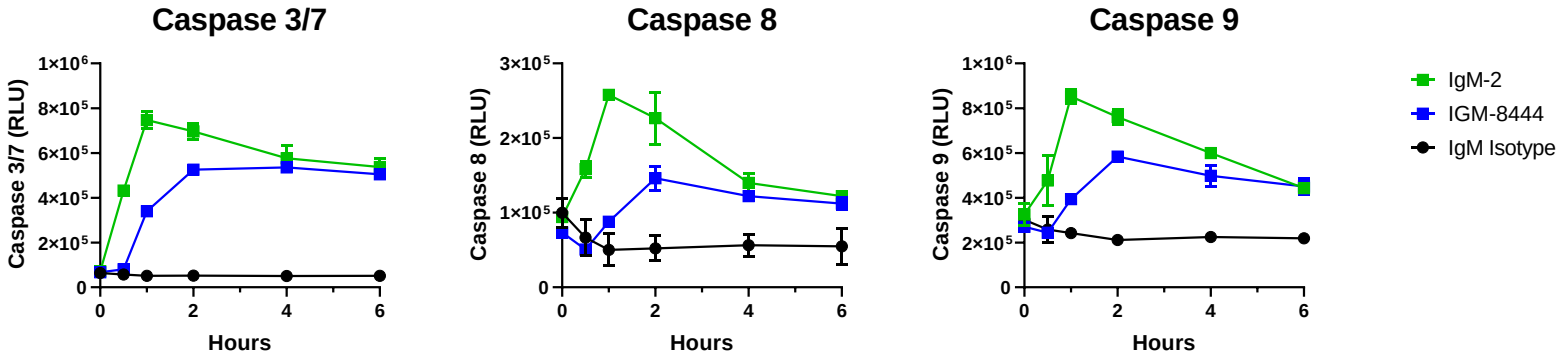
4.4 µg/mL IgM antibodies; Cells imaged every 10 min

IGM-8444 Has Slower Kinetics of Caspase Activation Compared to IgM-2

Colo205



NCI-H2122



4.4 µg/mL IgM antibodies

IGM-8444 and IgM-2 Induce DISC Caspase 8 Activation and PARP Cleavage

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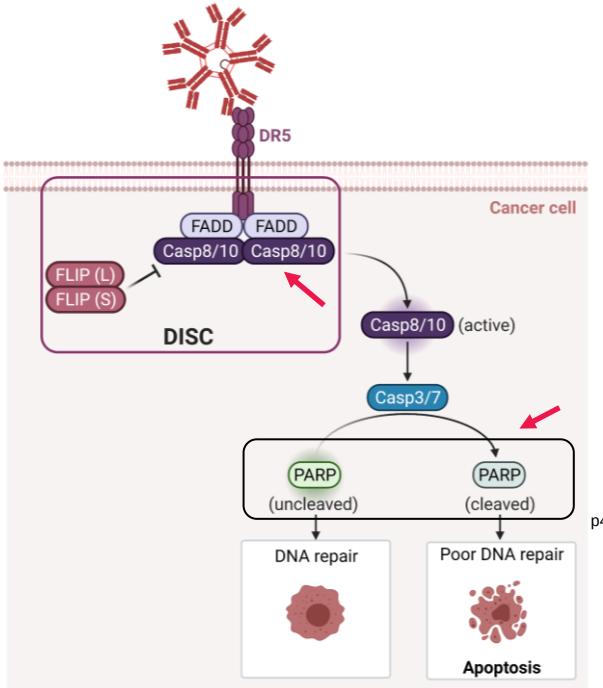
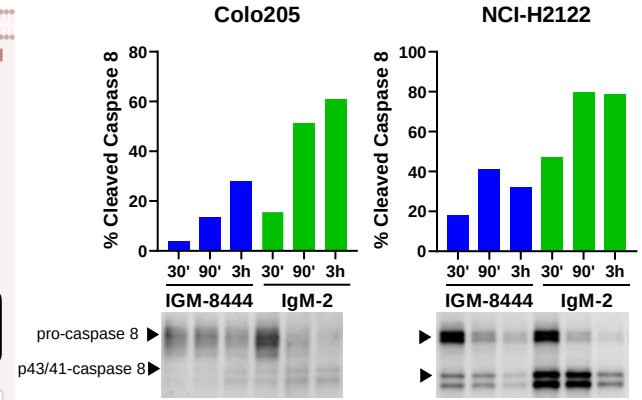
IgM-biotin for IP



Adapted from "FAS Pathway Activation Initiates Cancer Cell Apoptosis", by BioRender.com (August 2020). Retrieved from https://app.biorender.com/biorender-templates/t-5fd9408c4edb1d2833467ac1-fas-pathway-activation-initiates-cancer-cell-apoptosis

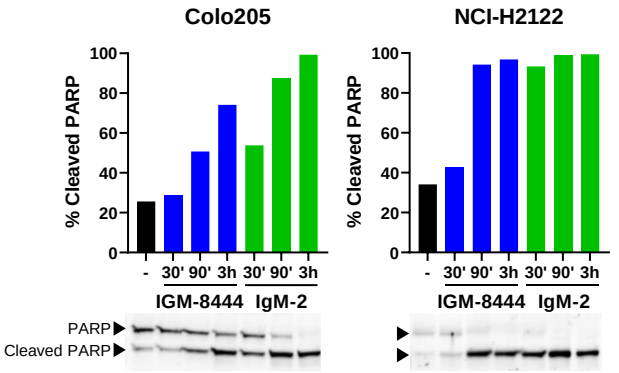
Caspase 8 at the DISC

IgM-biotin IP



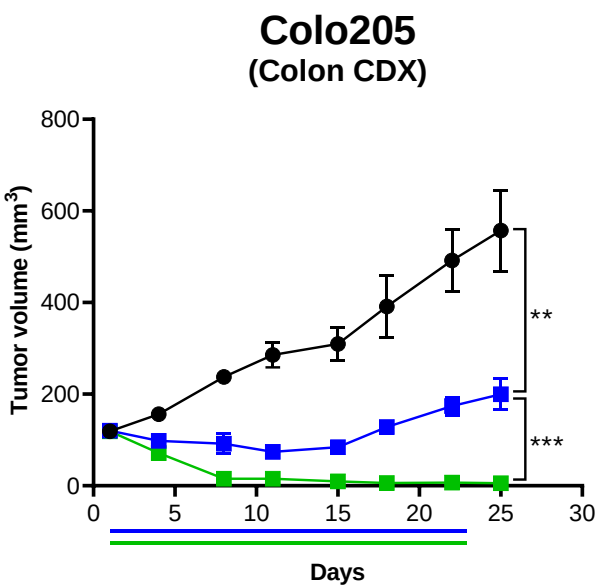
PARP

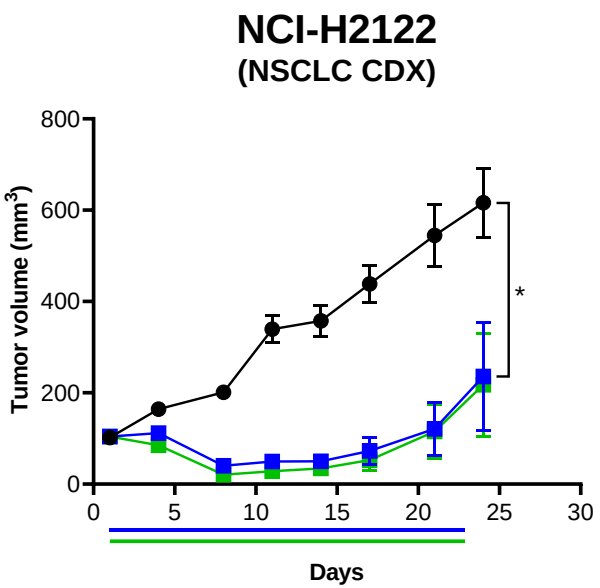
Total lysate fraction

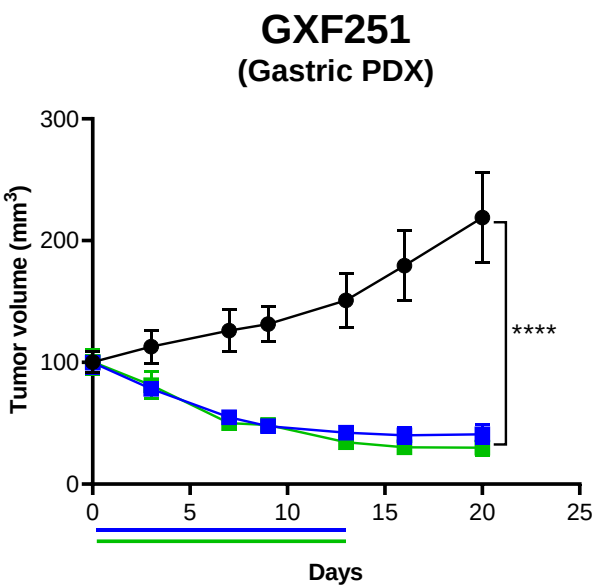


4.4 µg/mL IgM antibodies;
Caspase 8 WB: 15 µL of the DISC fraction loaded per lane;
PARP WB: 6 µg of total protein from total lysate loaded per lane

DR5 IgM Antibodies are Efficacious in Xenograft Mouse Tumor Models







Vehicle; IGM-8444 (5 mg/kg); IgM-2 (3 mg/kg)

Colo205 & NCI-H2122 Q2Dx11; GXF251 Q2Dx7

Dosing regimens were designed to match exposure for IGM-8444 & IgM-2

IGM-8444 Induces Apoptotic Biomarkers in NCI-H2122 Tumor Model *In Vivo*

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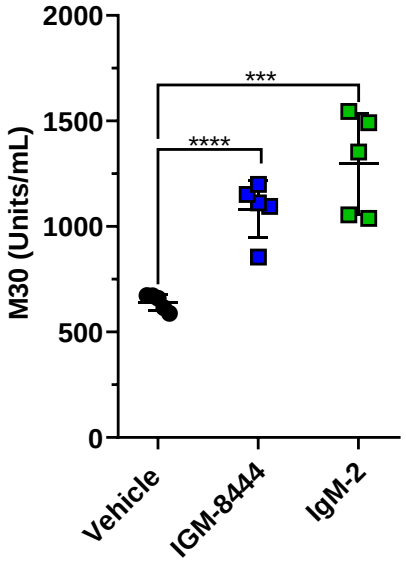
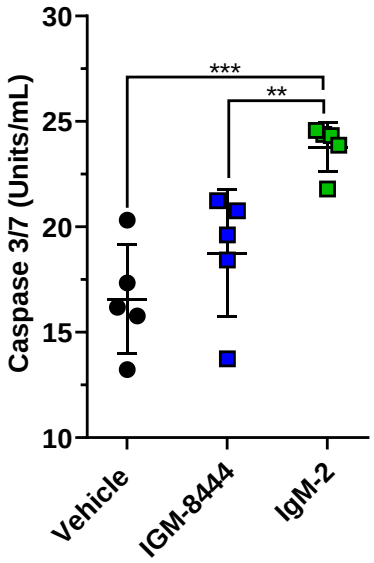
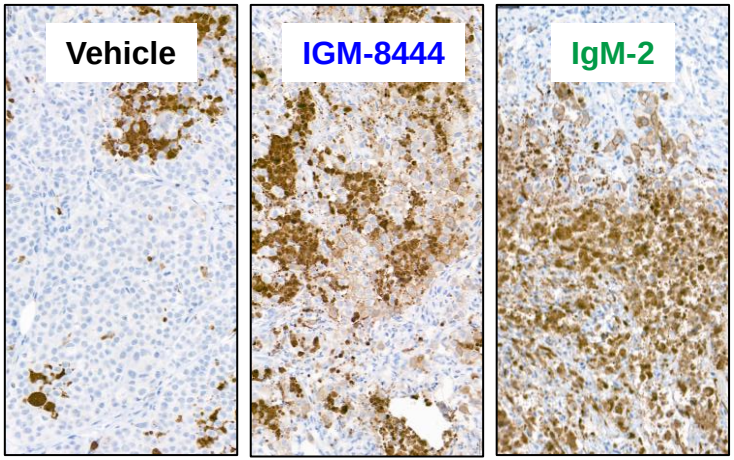
Serum M30
(caspase-cleaved CK18)



Serum Caspase 3/7



Tumor Cleaved Caspase 3



Vehicle; IGM-8444 (5 mg/kg); IgM-2 (3 mg/kg)
Serum & tumor biomarkers measured 24 hours post single dose

IGM-8444 Combination with Chemotherapy and ABT-199 Enhances In Vivo Efficacy

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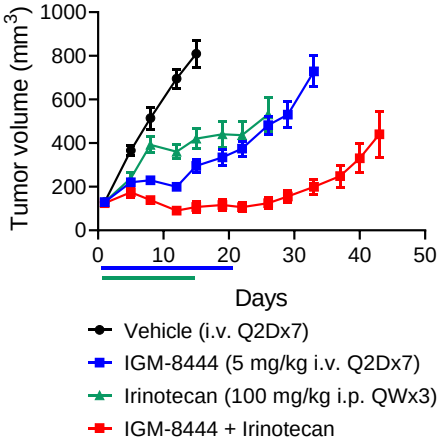
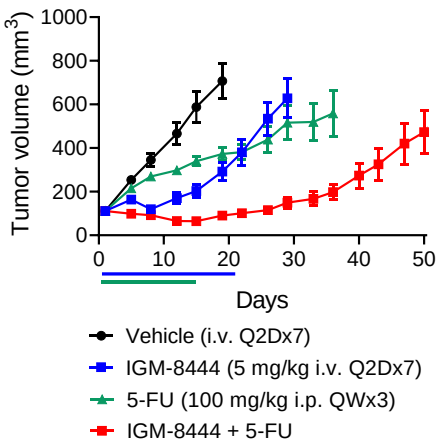
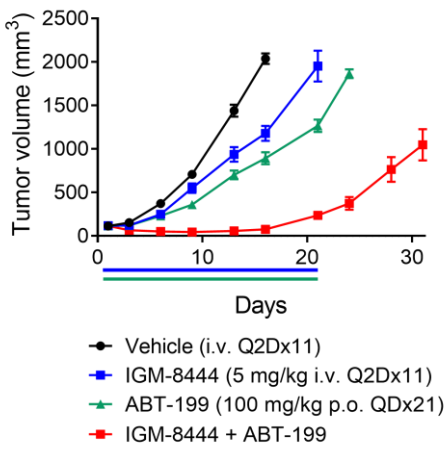
Irinotecan Combination: Colo205 colorectal model



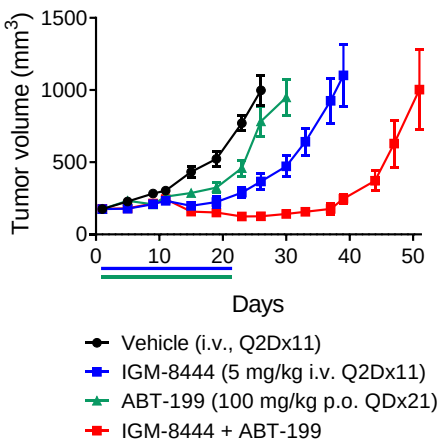
5-FU Combination: Colo205 colorectal model



ABT-199 Combination: DOHH-2 NHL model



ABT-199 Combination: MV-411 AML model



IGM-8444 Combination with Chemotherapy and ABT-199 is Safe on Hepatocytes In Vitro

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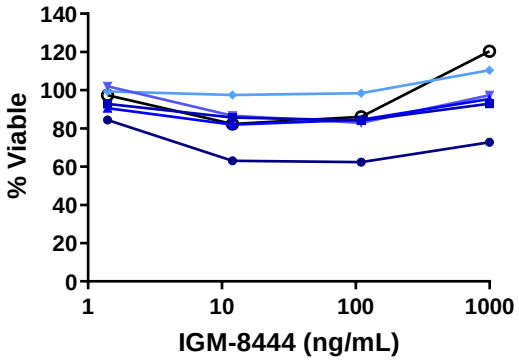
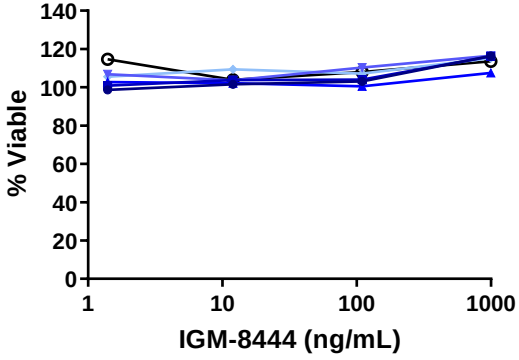
- 72-hour primary human hepatocyte in vitro cytotoxicity

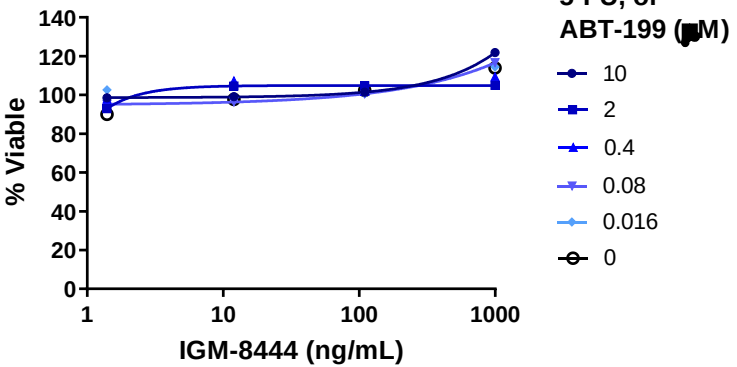
IGM-8444 + Irinotecan



IGM-8444 + 5-FU

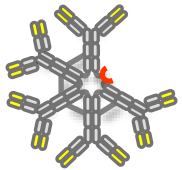


IGM-8444 + ABT-199



Summary

- IGM-8444 potently induces tumor cytotoxicity without hepatotoxicity in vitro
- IGM-8444 has comparable cytotoxicity with delayed kinetics versus IgM-2
- IGM-8444 is efficacious in vivo and induces pharmacodynamic biomarkers
- IGM-8444 repeat dosing up to 30 mg/kg x 4 doses showed no adverse events in cynomolgus monkeys
- The favorable safety profile of IGM-8444 enables combination opportunities
- IGM-8444 is currently in a Phase 1 trial as a single agent and in combination with chemotherapy (NCT04553692)



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