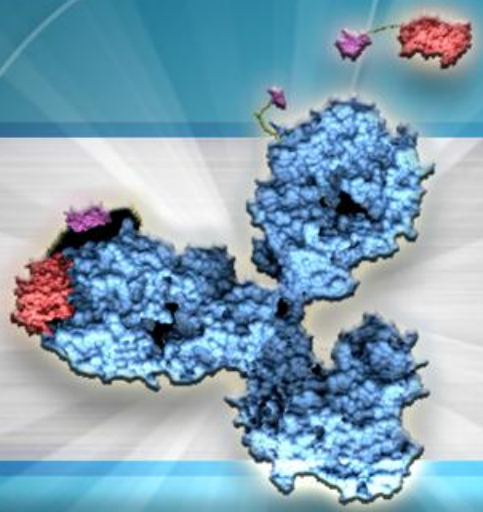
Probodies, Protease Activated Antibodies, for Disease-specific Inhibition of Notch Signaling



CytomX Therapeutics

James W. West, Ph.D.

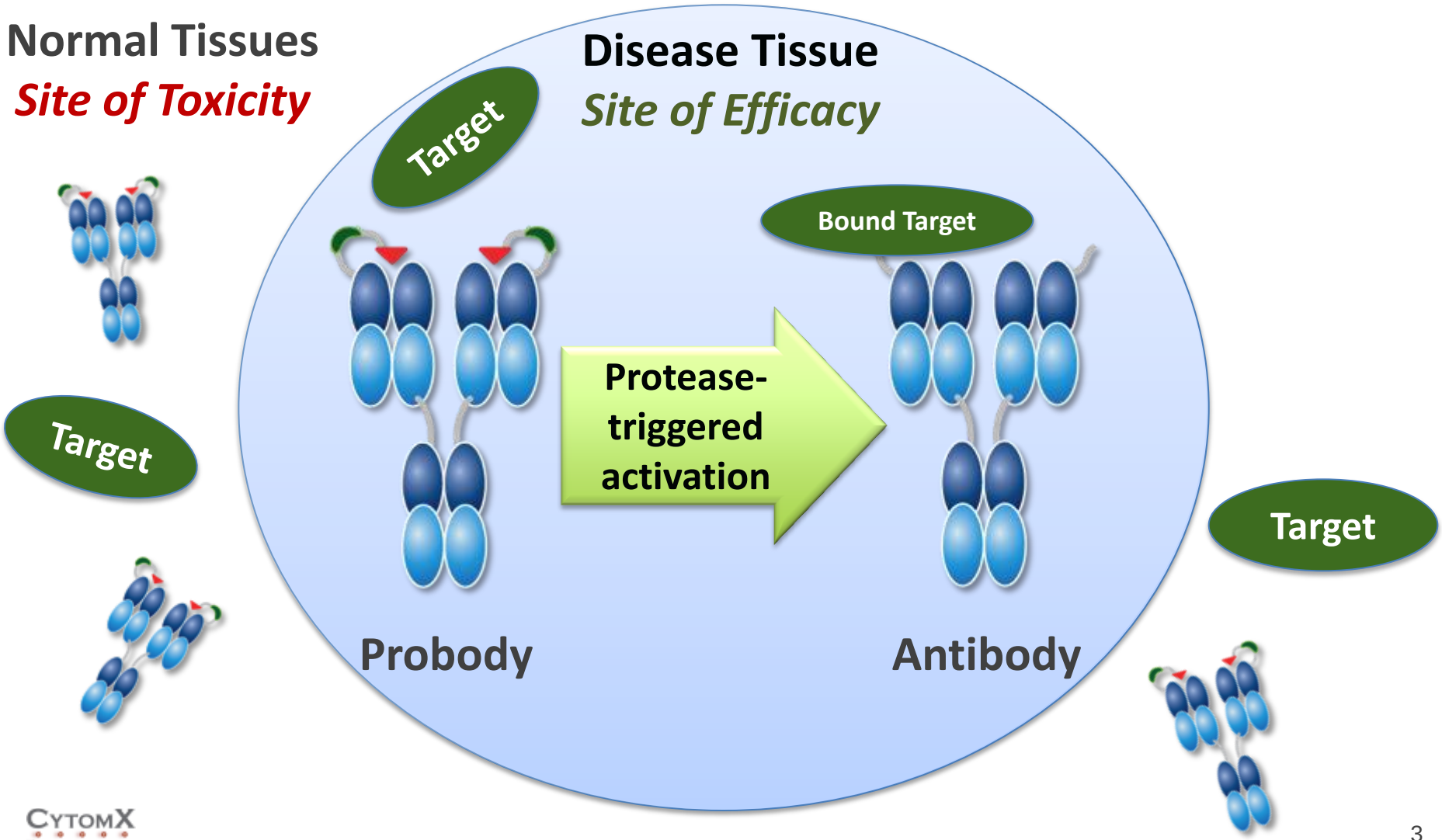
2nd international Conference
Notch Targeting in Cancer

June 29, 2012

Talk outline

- Describe what a Probody™ is, and how we make them
- Show you how converting an antibody to a Probody™ can open its therapeutic window
  - Anti-EGFR
- Describe to you why the Notch pathway is a great place to apply the Probody™ technology
  - Anti-jagged 1/2

Probody™ Platform: Masked, Protease-Activated mAbs that Specifically Target Disease Tissue

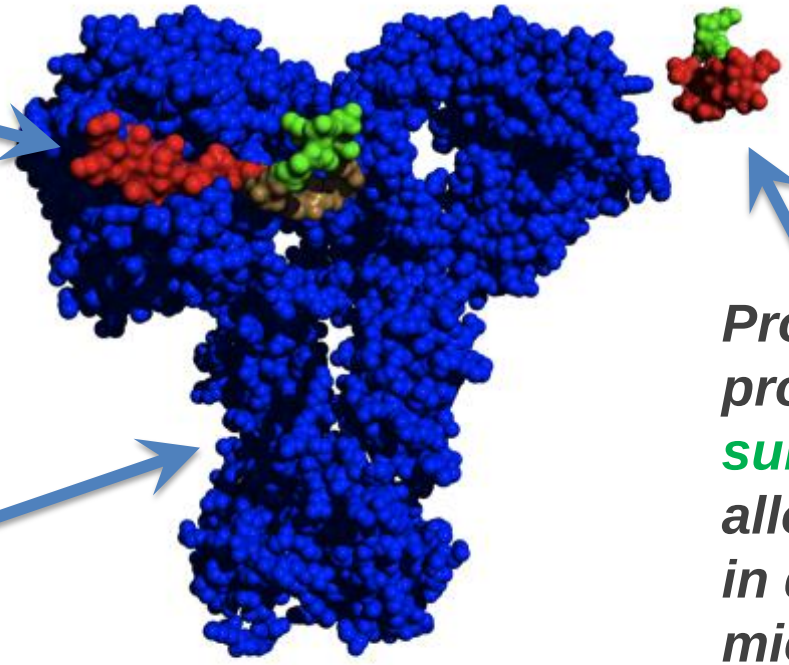


The Probody™ Platform

eCPX and CLiPS Core Platform Technologies

CDR proprietary mask ensures mAb only binds target at site of disease

eCPX



Antibody framework

CLiPS

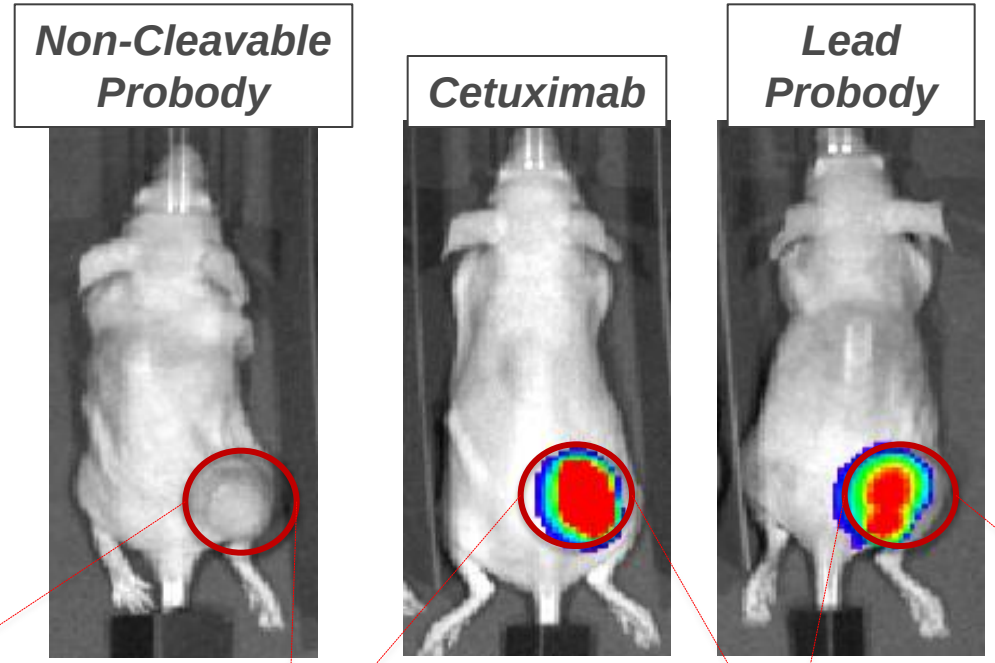
Protease cleavage of proprietary substrate linker allows mask release in disease microenvironment

CytomX Probody™ Pipeline

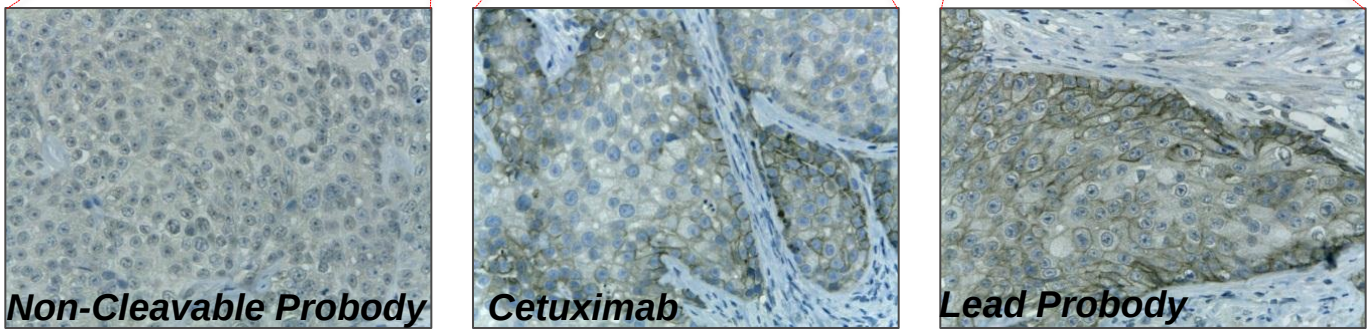
Target	Ab Opt.	Mask Opt.	Probody Lead	Probody Opt.	Candidate Selection
Oncology EGFR/ EGFR PDC					
Oncology Jagged/Delta/ Notch					
Inflammation IL-6R/GP-130					
ImmunoRx CTLA-4/PD-1/ PDL-1/CD137					
New Product Concepts					

EGFR Probody Is Activated in Tumors

Imaging of DyeLight 650 labeled Probody: Tumor specific localization



IHC staining: Activation of Probody required for binding on tumor



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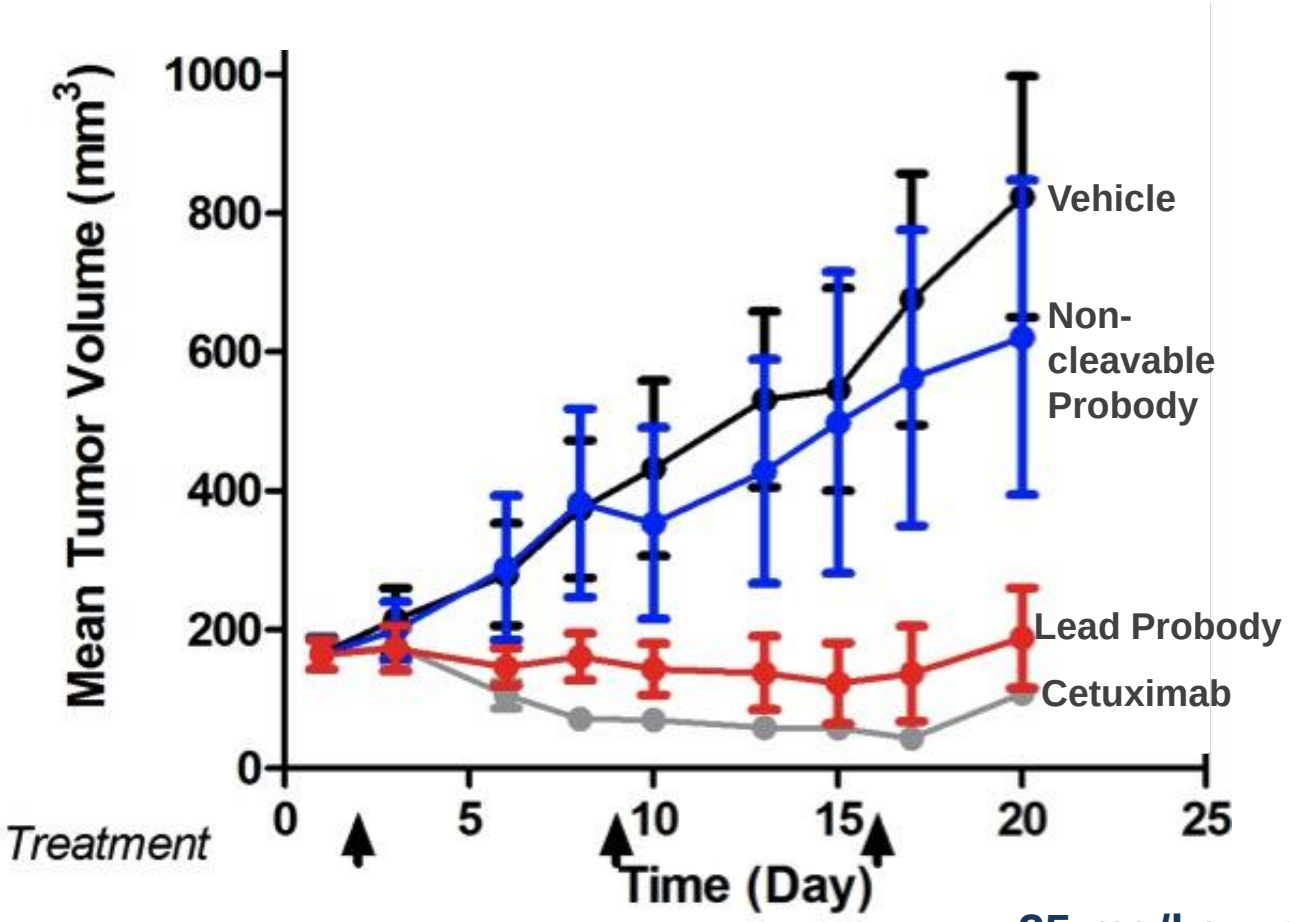
Efficacy of Lead EGFR Probody Compared to Cetuximab



- 25 mg/kg weekly
- n = 8 mice/group

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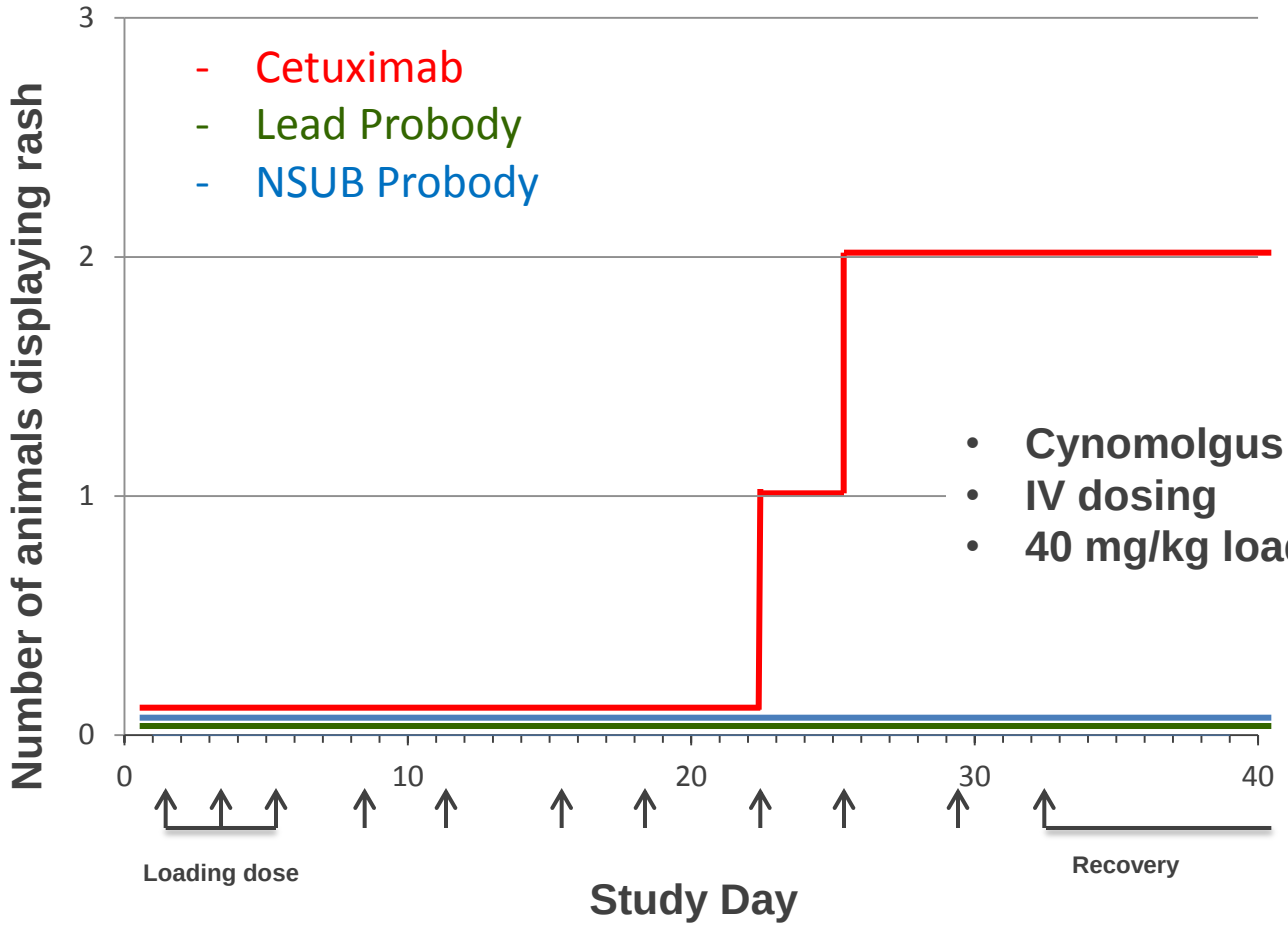
Lead EGFR Probody™ Displays Reduced Dermatologic Toxicity in Non-Human Primates



- Cynomolgus monkeys
- IV dosing
- 40 mg/kg load, 25 mg/kg wkly

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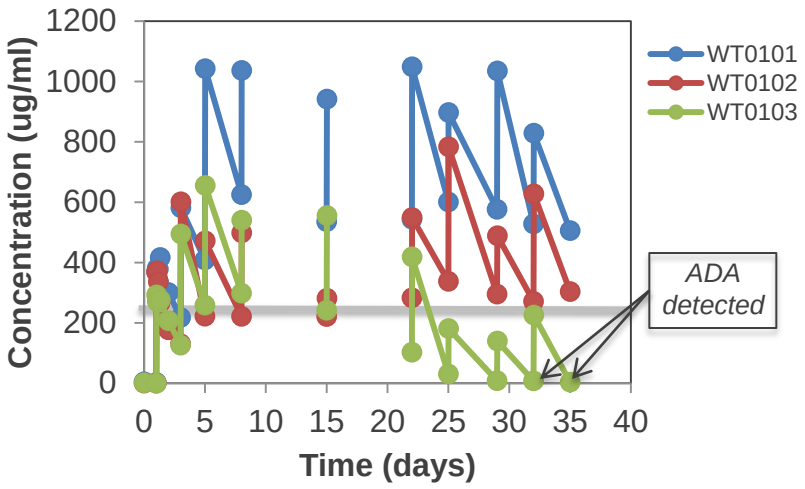
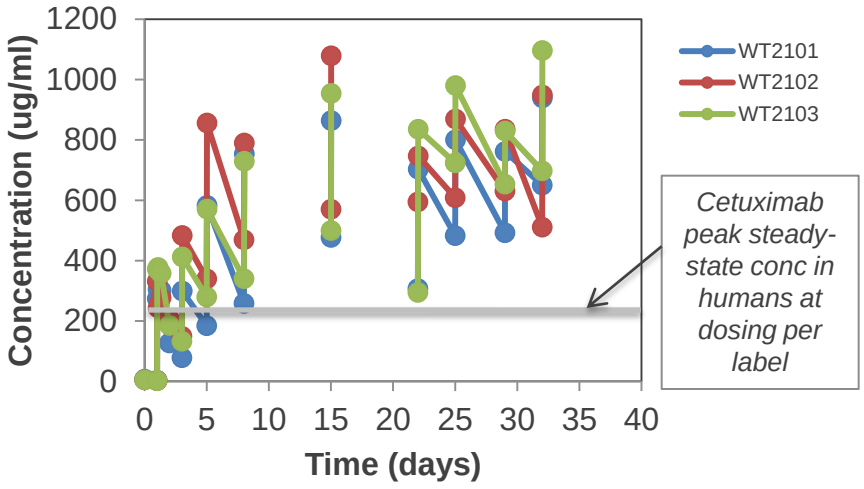
Probody Blood Levels in Non-Human Primates at 25 mg/kg Weekly Dosing After 40 mg/kg Loading

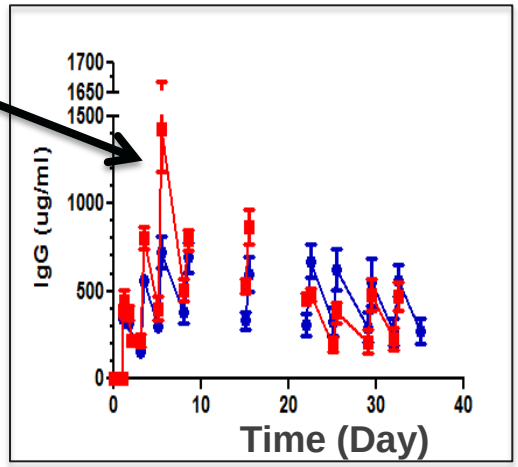
Parental mAb Blood Levels

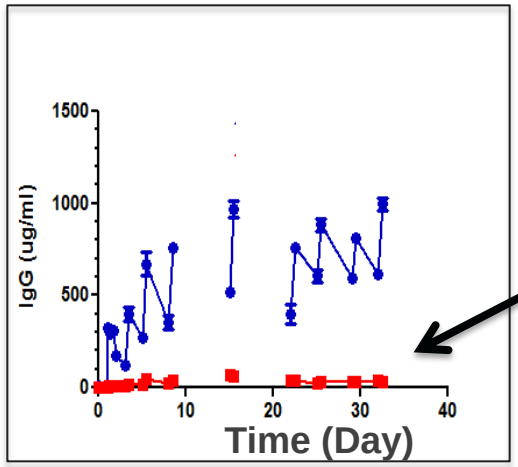


Probody Blood Levels



Active Parental mAb





Active Probody

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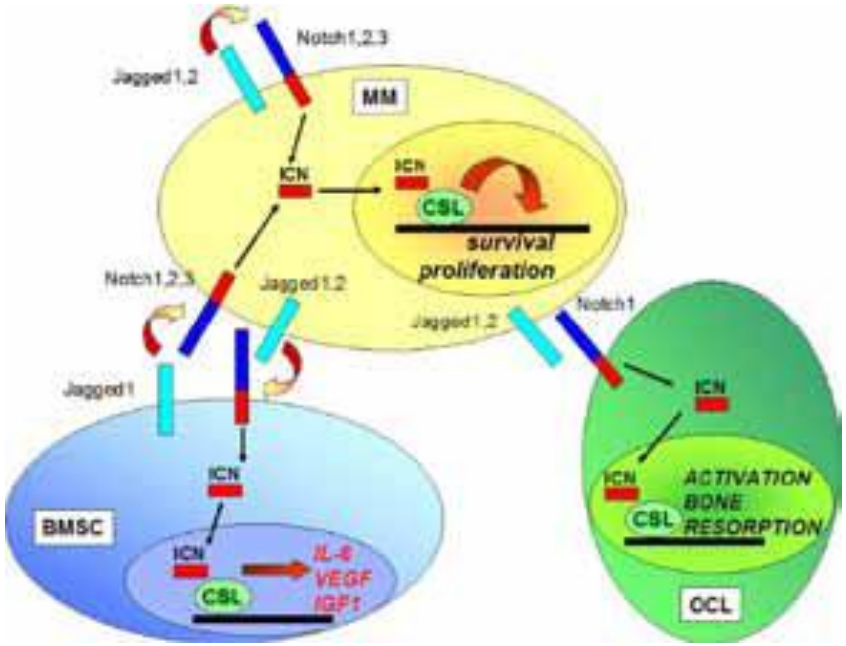
CytomX Probody™ Pipeline

Target	Ab Opt.	Mask Opt.	Probody Lead	Probody Opt.	Candidate Selection
Oncology EGFR/ EGFR PDC					
Oncology Jagged/Delta/ Notch					
Inflammation IL-6R/GP-130					
ImmunoRx CTLA-4/PD-1/ PDL-1/CD137					
New Product Concepts					

The Notch/Delta/Jagged Pathway Represents a Significant Opportunity for Probody™ Technology



Mirandola et al. 2007. Arch Onc. 17, 72-77.

- Notch signaling is critical in early development, and for maintaining the balance between proliferation and maturation of cells in adult tissues
- The dysregulation of Notch signaling has been implicated in several cancers (PC, TNB, MM) and also in fibrotic disease
- Inhibition of Jagged dependent Notch signaling (conditional knockouts and siRNA) inhibits disease progression in animal models
- **Systemic inhibition of the Notch pathway leads to toxicities that limit therapeutic benefit.**

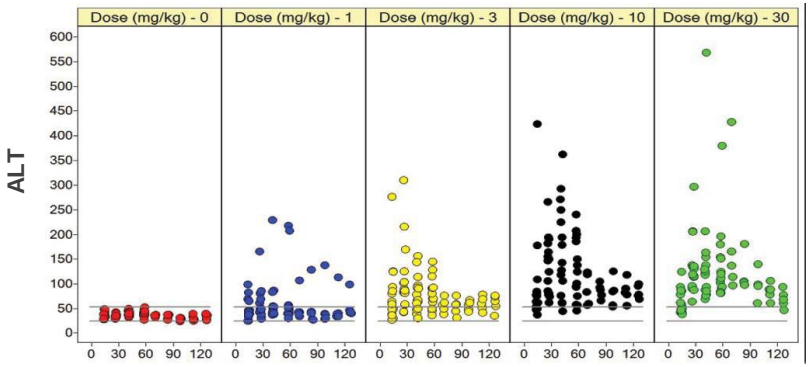
Targeting the Notch/Delta/Jagged Pathway Leads to Significant Toxicities

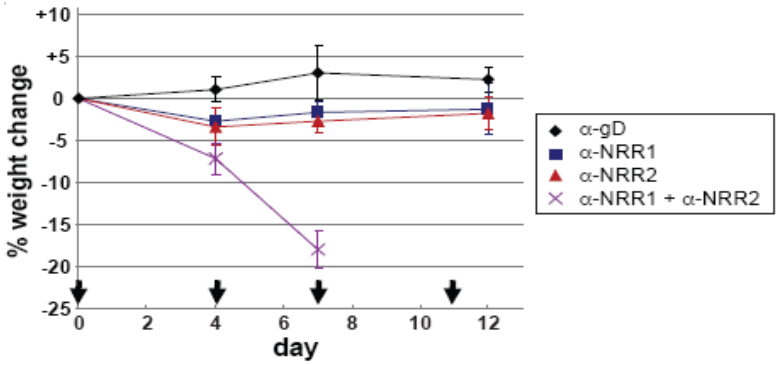
- Anti-DLL4 treatment leads to
  - Liver toxicity
  - Vascular neoplasms

  Ridgeway et al, Nature 444, 1083–1087 (2006)
- Anti-Notch1/Notch 2 treatment leads to
  - Gut toxicity
    - Goblet cell metaplasia
    - Weight loss

  Wu, et al., Nature 464, 1052-1059 (2010)
  - Inhibition of T-cell maturation
- γ secretase inhibition leads to
  - Gut toxicity
  - T-cell maturation

  Wong, et al. JBC 279, 12876-12882 (2004)





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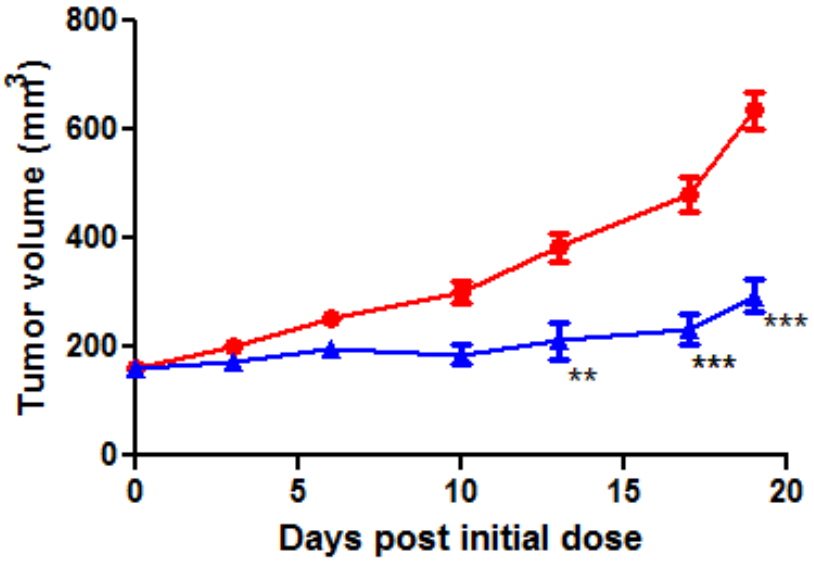
CytomX Proprietary Anti-Jagged Antibody Binds Human and Mouse Ligands

- Anti-Jagged 4D11 was engineered for
  - Sub nM affinity for Jagged 1 and Jagged 2
  - Potent inhibition of Jagged/Notch binding
  - Potent inhibition of Jagged dependent Notch signaling

Anti-Jagged 4D11 Suppresses BxPC3 Tumor Growth In Vivo



* p = 0.01
** p = 0.001
*** p = 0.0001 (two way Anova)

Dose IP; day 0, 3, 6, 10

IVIg	**20 mg/Kg**
Anti-Jagged	**20 mg/Kg**

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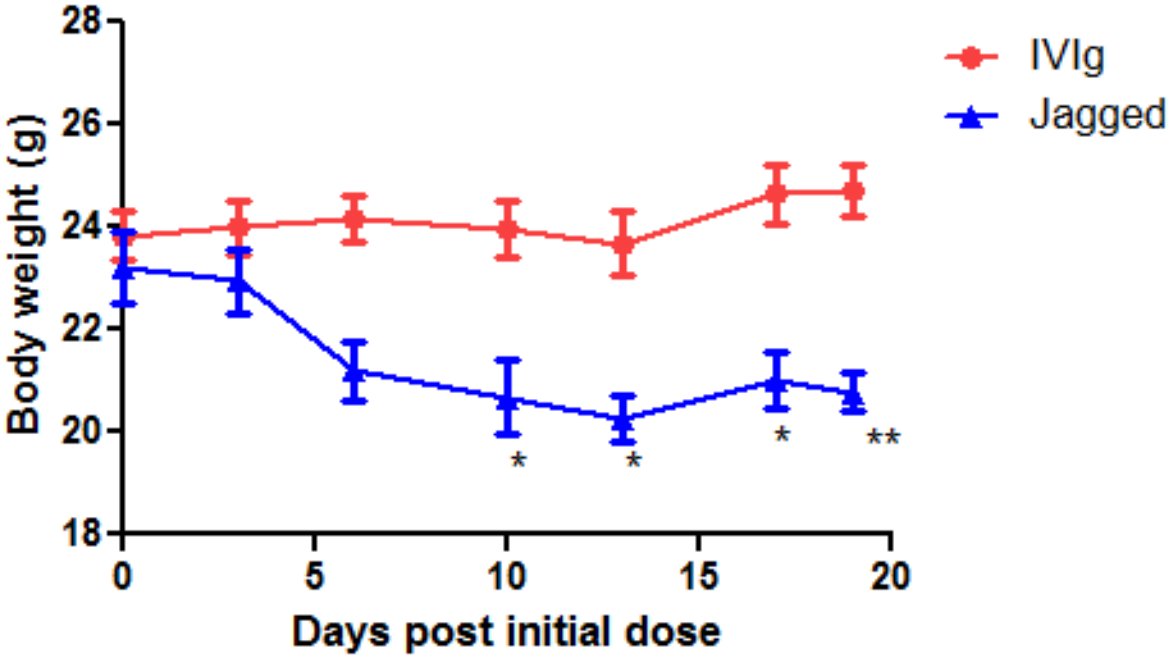
Anti-Jagged 4D11 Treated Mice Show Significant Weight Loss

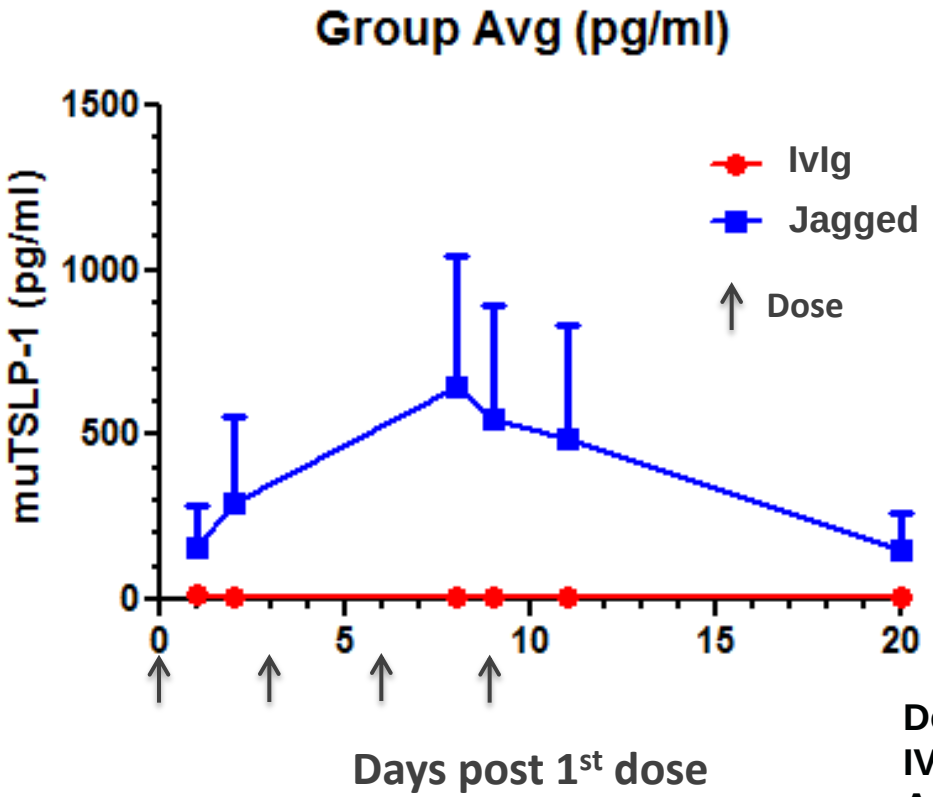


Dose IP; day 0, 3, 6, 10

IVIg	**20 mg/Kg**
Anti-Jagged	**20 mg/Kg**

Anti-Jagged Antibody 4D11 Treated Mice Show Skin Toxicity

Thymic stromal lymphopoietin (TSLP) is secreted from the skin in response to notch pathway inhibition.



Dose IP; day 0, 3, 6, 10

IVIg	**20 mg/Kg**
Anti-Jagged	**20 mg/Kg**

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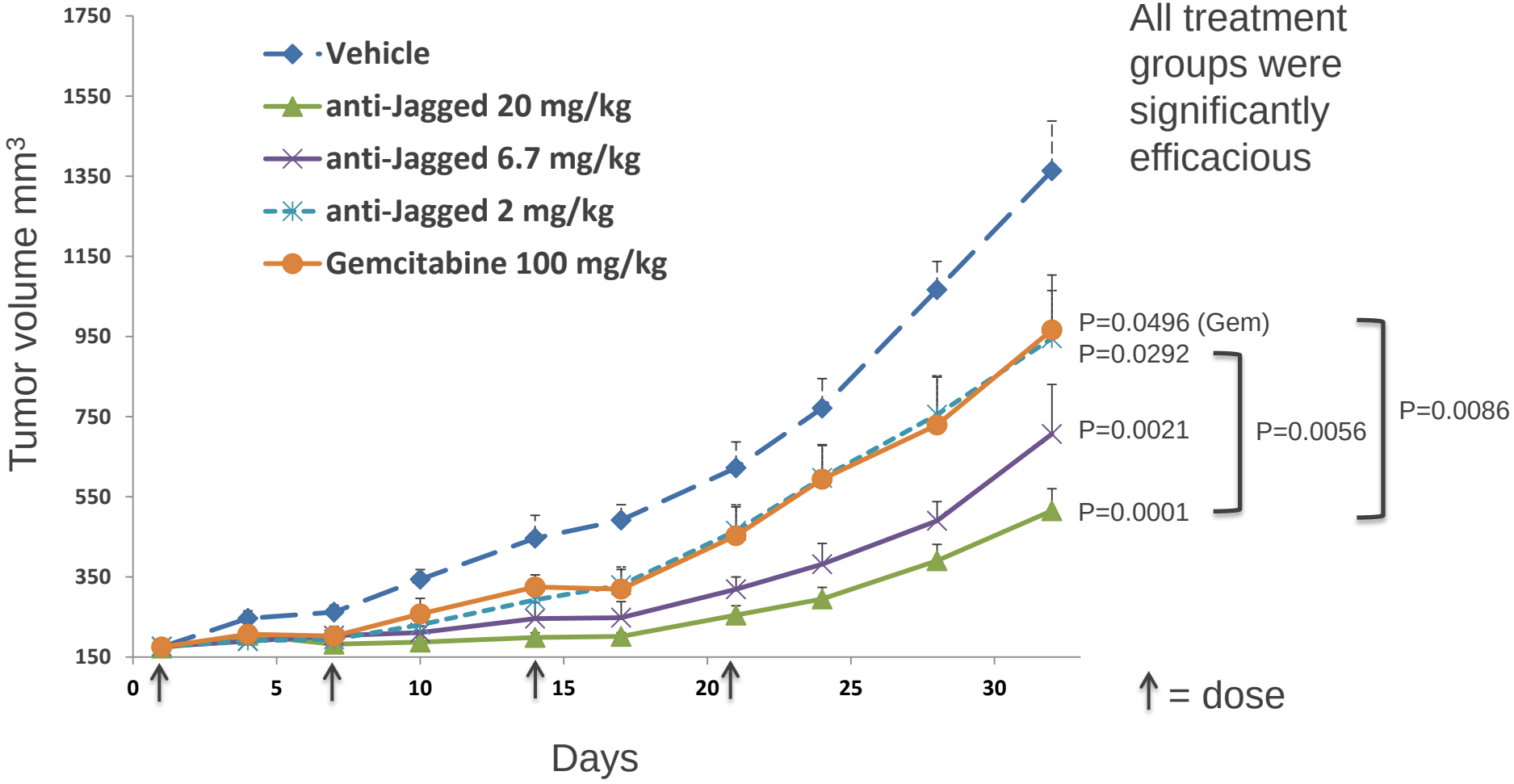
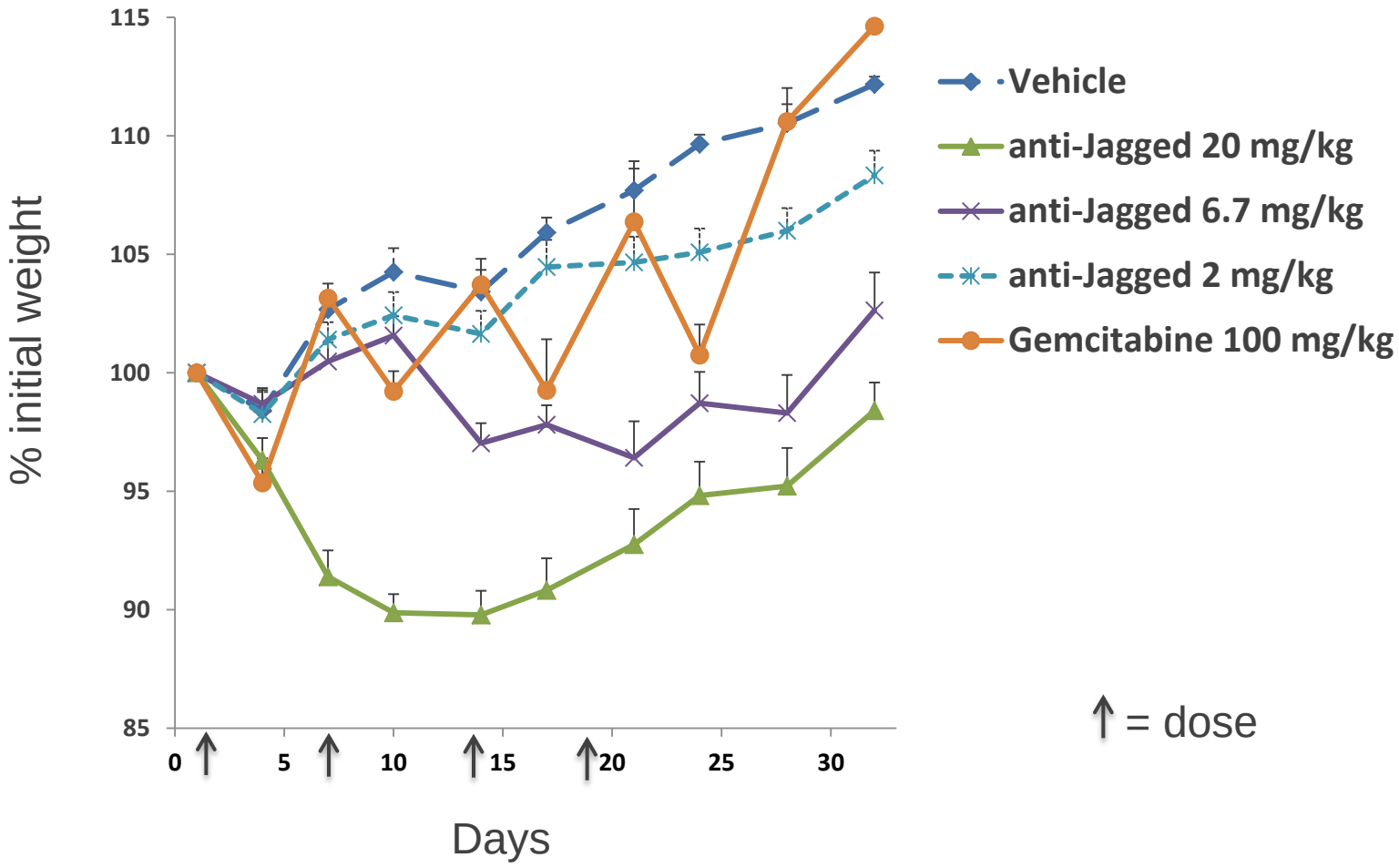
Anti-Jagged 4D11 Antibody is as Efficacious as the Standard-of-Care in a Pancreatic Model



CytomX Therapeutics

Body Weight Loss is Observed at Higher Doses of 4D11 Antibody



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Next Steps for Jagged Probody

- Characterize masking peptides for 4D11 antibody.
- Assemble Jagged Probodies with candidate substrates.
- Test Probody candidates for efficacy and safety in xenograft models.

Summary

- Anti-EGFR Probody™ shows good efficacy with no dermatologic toxixity
- Tumor growth in BxPC3 xenografts is inhibited by anti-jagged antibody 4D11.
- On-target but off-disease-tissue activity leads to gut and skin toxicities with antibody 4D11 treatment.
- Anti-Jagged Probody being developed to inhibit signaling specifically in disease tissues will unlock the potential of this therapeutic area.
- **The Probody™ Platform affords unprecedented opportunities to expand the target universe for therapeutic antibodies.**

Those who work and play well together

- **Santa Barbarians**
  - Jason Sagert
  - Kathy Kamath
  - Paul Bessette
  - Nancy Stagliano
  - Gretchen Smith
  - Stephan Moore
  - Jim West

- **San Francisco**
  - Jason Sagert
  - Stephan Moore
  - Jim West
  - Sherry LaPorte
  - Kim Tipton
  - Luc Desnoyer
  - Annie Yang
  - Chi Wang
  - Tony Liang
  - Shouchun Liu
  - Jason Gee
  - Fei Hann
  - Olga Vasilyev
  - Dan Hostetter
  - Margaret Nuygen
  - Jennifer Richardson
  - Ken Wong
  - Mike Krimm
  - Henry Lowman
  - Sean McCarthy
  - Kris Ortner
  - Carol Verser