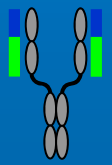
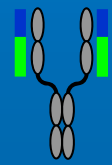
Surrobodies™ – A Novel Approach to Bispecifics…

Ramesh Bhatt, Ph.D.
Vice President of Research
Sea Lane Biotechnologies



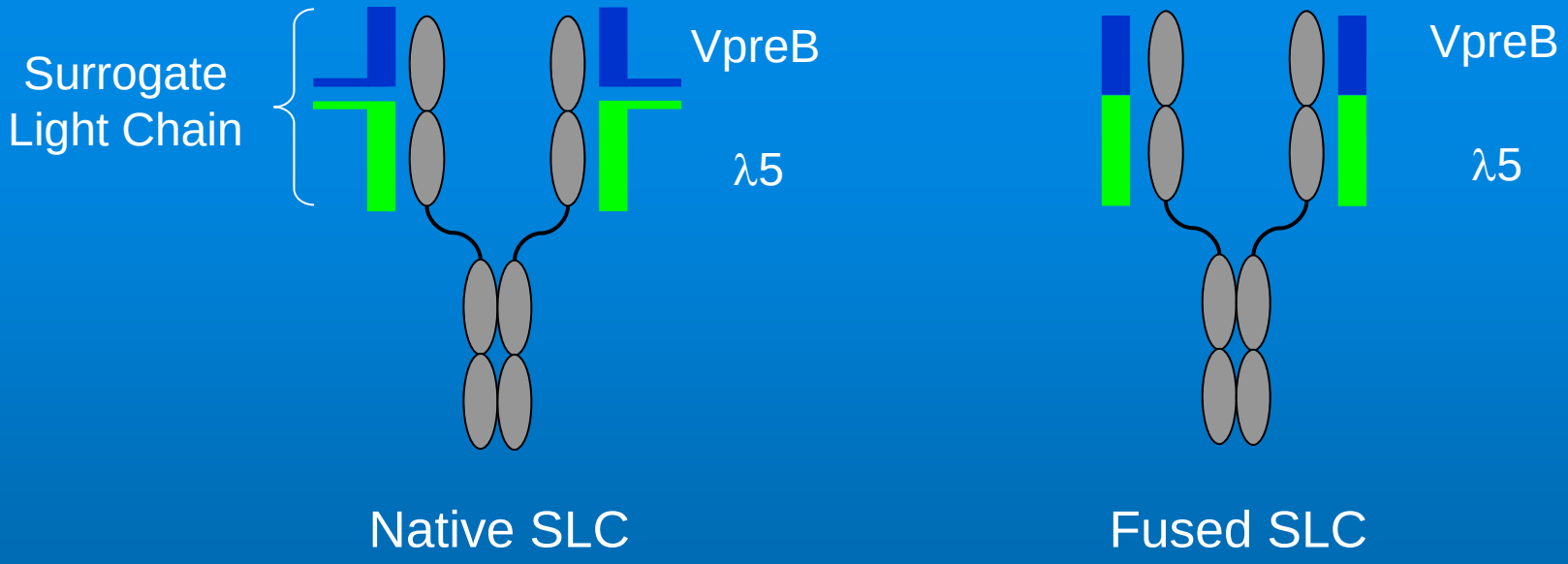


Presentation Agenda

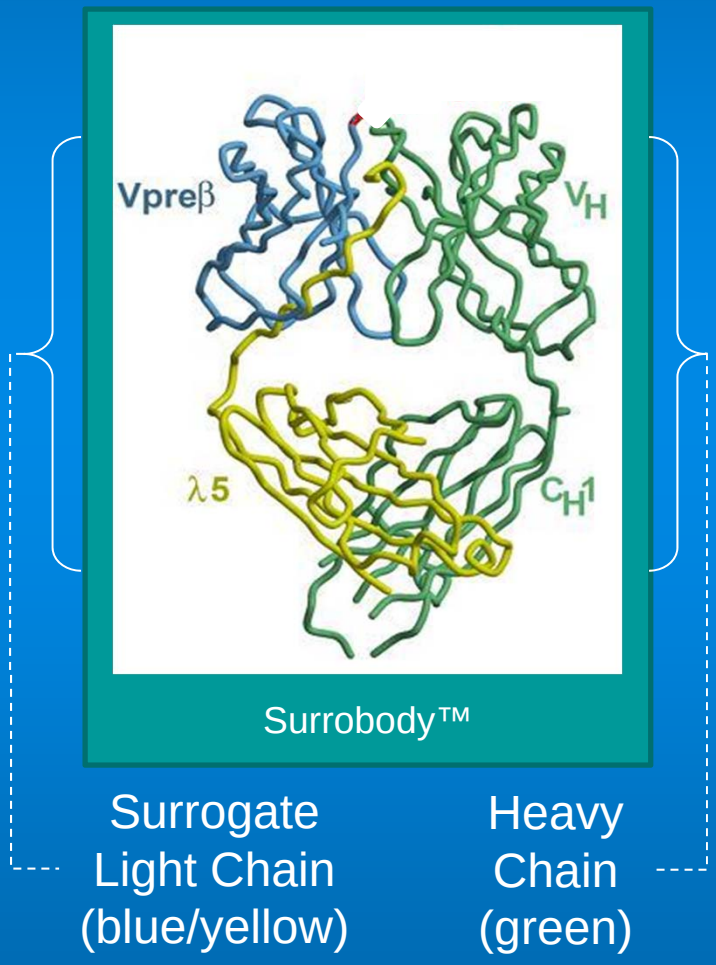
- *Introduction to Surrobody structure*
- *Surrobody advantages directly address bispecific challenges*
- *Three brief bispecific examples*
  - *Comparability to antibodies*
  - *Inhibiting soluble targets in vitro and in vivo*
  - *Targeting receptors in vitro*
- *Summary*
- *Surrobody Drug Conjugate Teaser*

Surrobodies

Highly adaptable platform inspired by endogenous human pre-B Cell Receptor

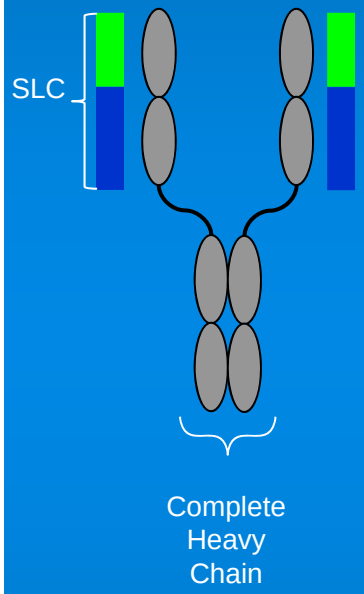


The Sea Lane Advantage



- The invariant surrogate light chain **simplifies** and **accelerates** bispecific development and enables drug conjugation for all existing and future Surrobodies
- Proprietary design of fully human, synthetic libraries mirror natural human diversity enabling rapid, high quality lead generation and simple, comprehensive optimization
- Use of naturally occurring, human germline frameworks provides consistently robust expression characteristics and should reduce immunogenic potential

General Surrobody Strengths



- Surrogate Light Chain
  - Only known universal heavy chain partner
  - Expected low immunogenicity
  - Invariant protein that simplifies all steps from discovery through manufacture
- Intact Fc
  - Imparts effector function and favorable half life
  - Known scalable production capable through Protein A
- Bispecific/Drug Conjugate Ready
  - Rapid conversion to enhanced format
- Intellectual Property
  - Granted patents protect basic structure and synthetic human library design

Synthetic Human Surrobody Library Drives Discovery

- ~28 billion productive members
- Patented human diversity productively matches frameworks and CDRs
  - Based on *functional* diversity
  - Powers companion optimization technology
- Novel library construction processes maximize library fidelity
- 12 week panning through lead ID cycle time
- Surrobodies found against 14 different therapeutic targets

Surrobodies Provide Ideal Path for Bispecific and Drug Conjugate Applications

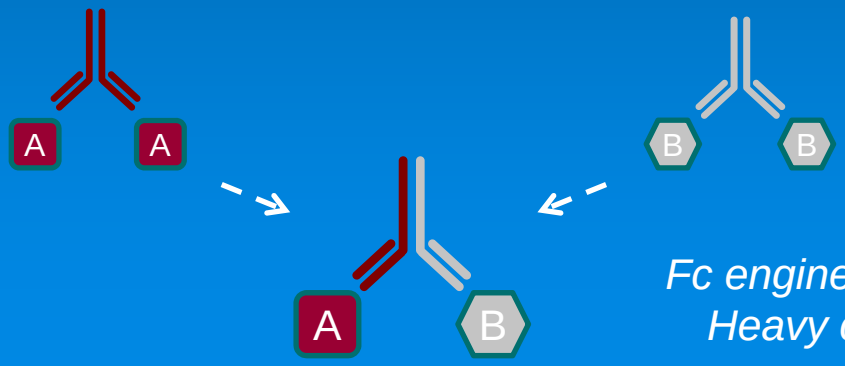
Bispecifics

- Simplified structure dramatically reduces required resources
- Antibody-like PK and other beneficial CMC qualities
- Robust *in vivo* efficacy
- Multiple bispecific formats provide unmatched flexibility

Toxin Drug Conjugation

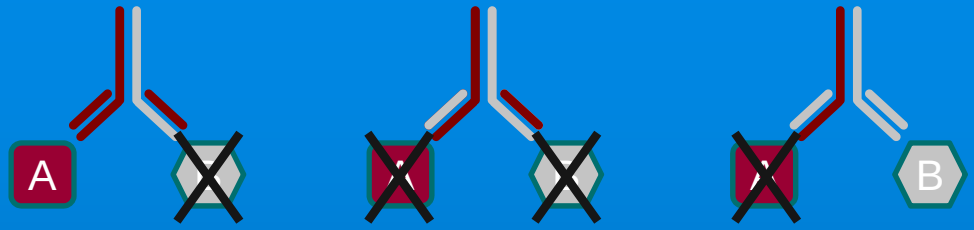
- Simplified process utilizing the universal surrogate light chain is applicable to all Surrobodies
- Bioanalytic assessment supports robust and stable conjugation
- Resulting toxin conjugated Surrobodies are highly potent

Fc Engineering Improves Bispecific Assembly but Provides an Incomplete Solution



25% Productive

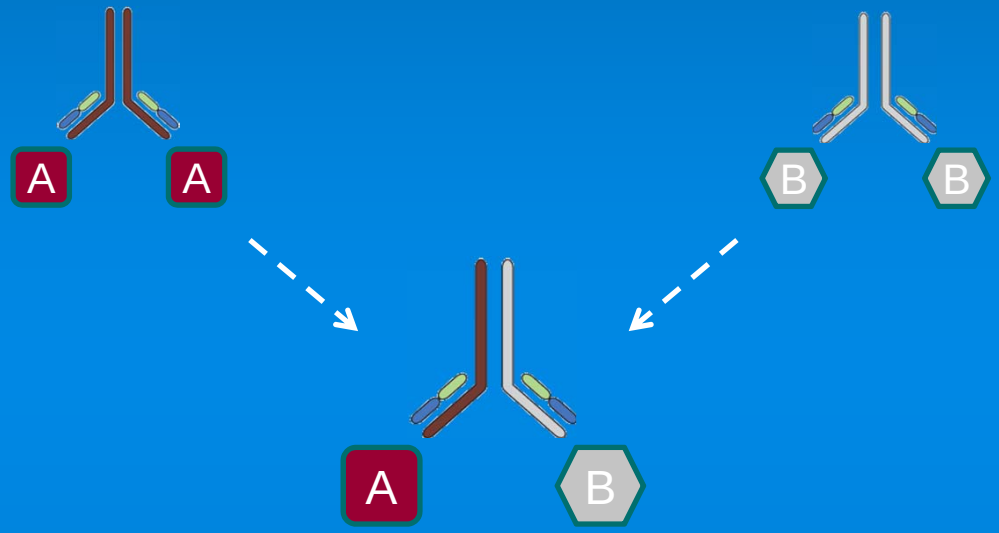
Fc engineered heteromeric Heavy chain assembly



75% Unwanted

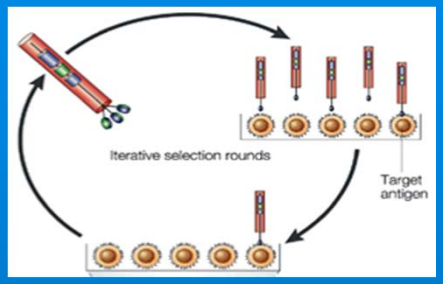
Light chain mismatching generates predominant and undesirable products

Sea Lane Advantage: The Surrogate Light Chain



Invariant surrogate light chain partnering eliminates unproductive combinations caused by mismatching of light chain/heavy chain partners

Bispecific Example #1
Comparability to Antibodies



Surrobodies Display Antibody-Like Characteristics

Biochemical

- Long term RT stability >1yr
- High level protein expression
  - Many >100mg/L in HEK293
- Stable following physical stress
  - freeze/thaw cycles
  - Low pH 3 exposure
  - Short term High temp exposure
    - at 50°C for 48 hours
  - High concentration (100mg/ml)
- All Surrobody formats maintain thermal stability profiles that are similar to commercial antibodies
  - Tm >65°C

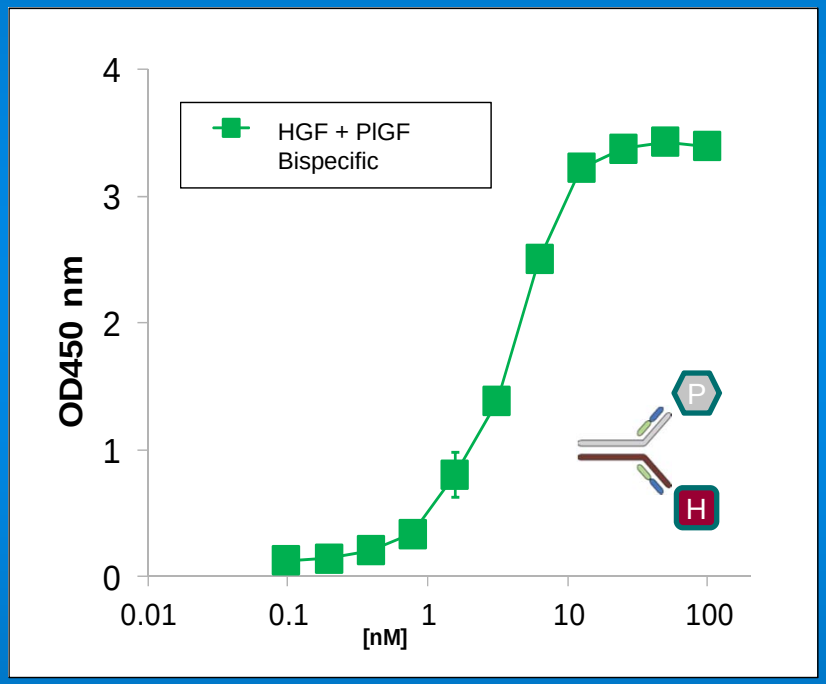
In vitro

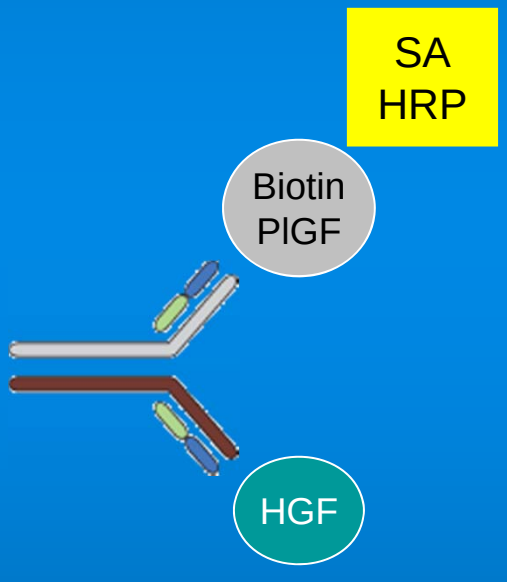
- High affinity binding (subnanomolar)
- Antagonist and Agonist activities are possible
- Broad epitopic range

In Vivo

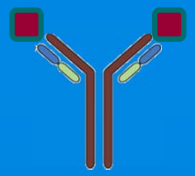
- NHP half-life ~1-2 wks
- Excellent efficacy in rodent models of disease

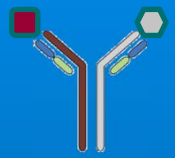
Monovalent Bispecifc Surrobodies Simultaneously Bind Two Distinct Targets





Mammalian Expressed Surrobodies Have Excellent Characteristics



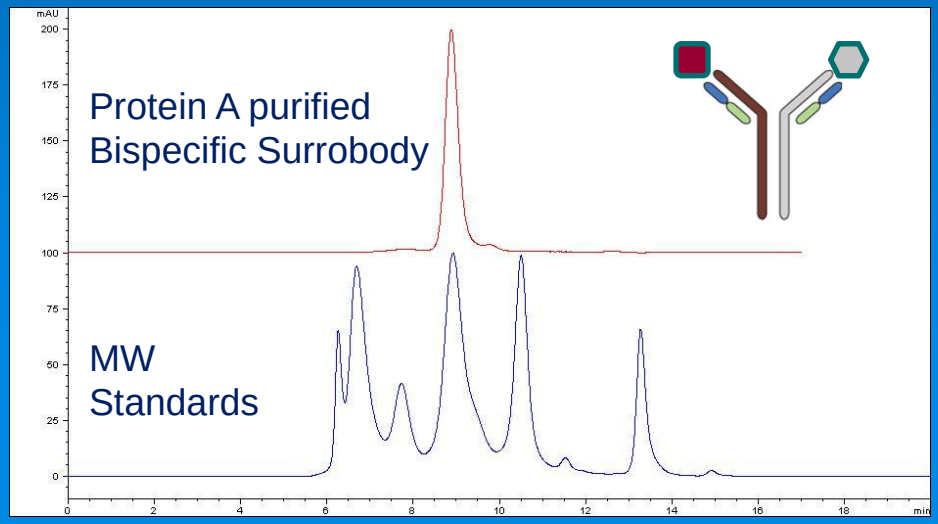


Format	Unique proteins (# preps)	Avg yield (mg/L)	Intact SgG (%)	High MW "Aggregate" (%)	Low MW "Protein" (%)	Thermal Stability (°C)	RT Stability (months)
Standard Surrobody	194 (249)	77	98.2%	1.6%	0.2%	>65	24
Bispecific Monovalent Binding	72 (82)	81	88.2%	3.4%	8.4%	>65	12

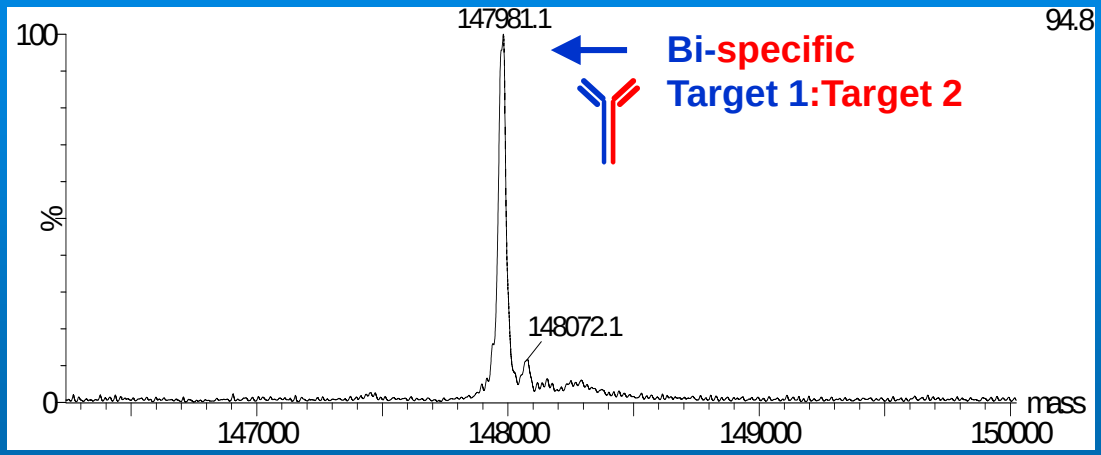
All 16 possible bispecific Vh framework combinations produce comparable yields in HEK293 transient systems

Size Exclusion and Mass Spec Show High Quality Monovalent Bispecific Complexes

SEC analysis: Cotransfection results in single peak at the appropriate size marker

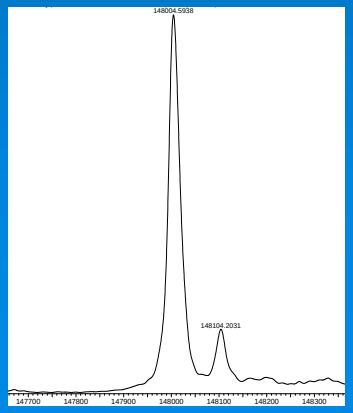


Mass Spec analysis: Virtually all heterodimeric bispecific

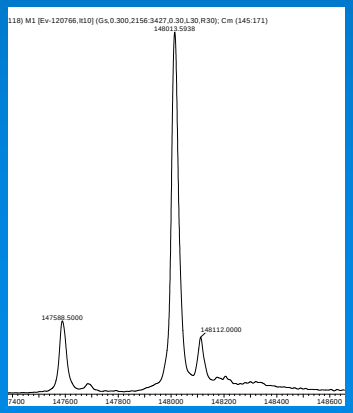


LC-MS Analysis of a Collection of Monovalent Bispecific Surrobodies

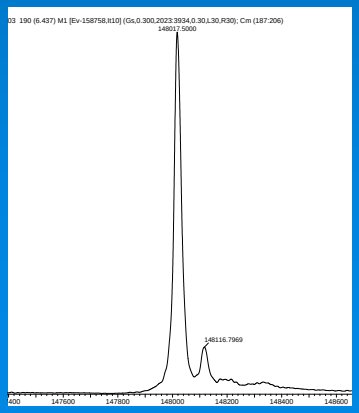
H/P



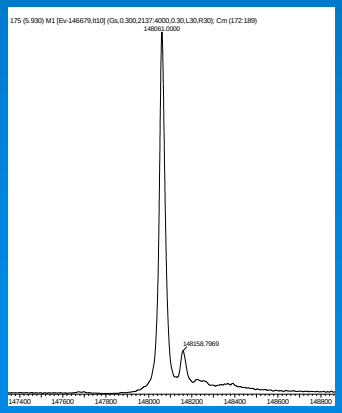
H/V

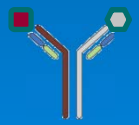


H/B5



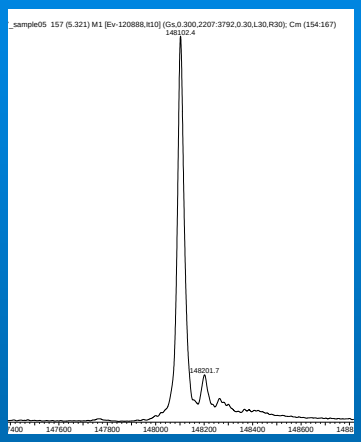
H/B6



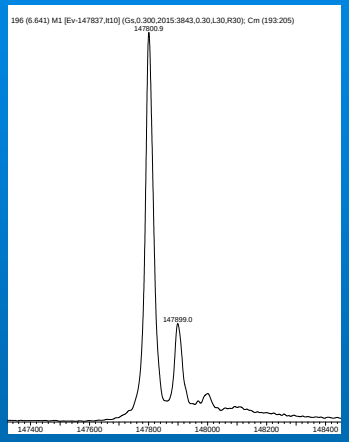


Deglycosylated proteins
(Focusing on region of intact tetramers: ~148,000 Da)

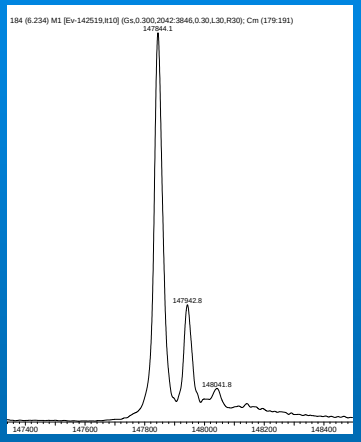
H/D



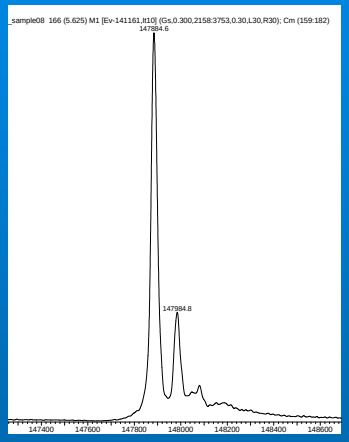
V/B5



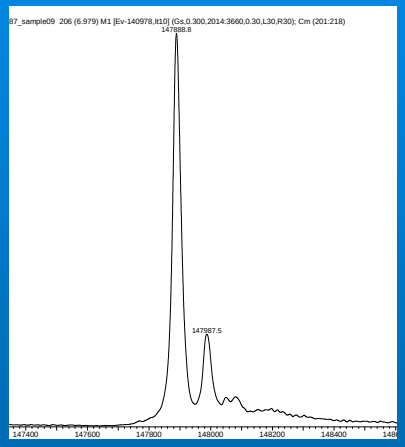
V/B6



V/D

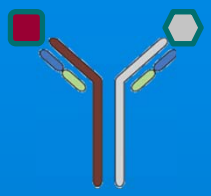


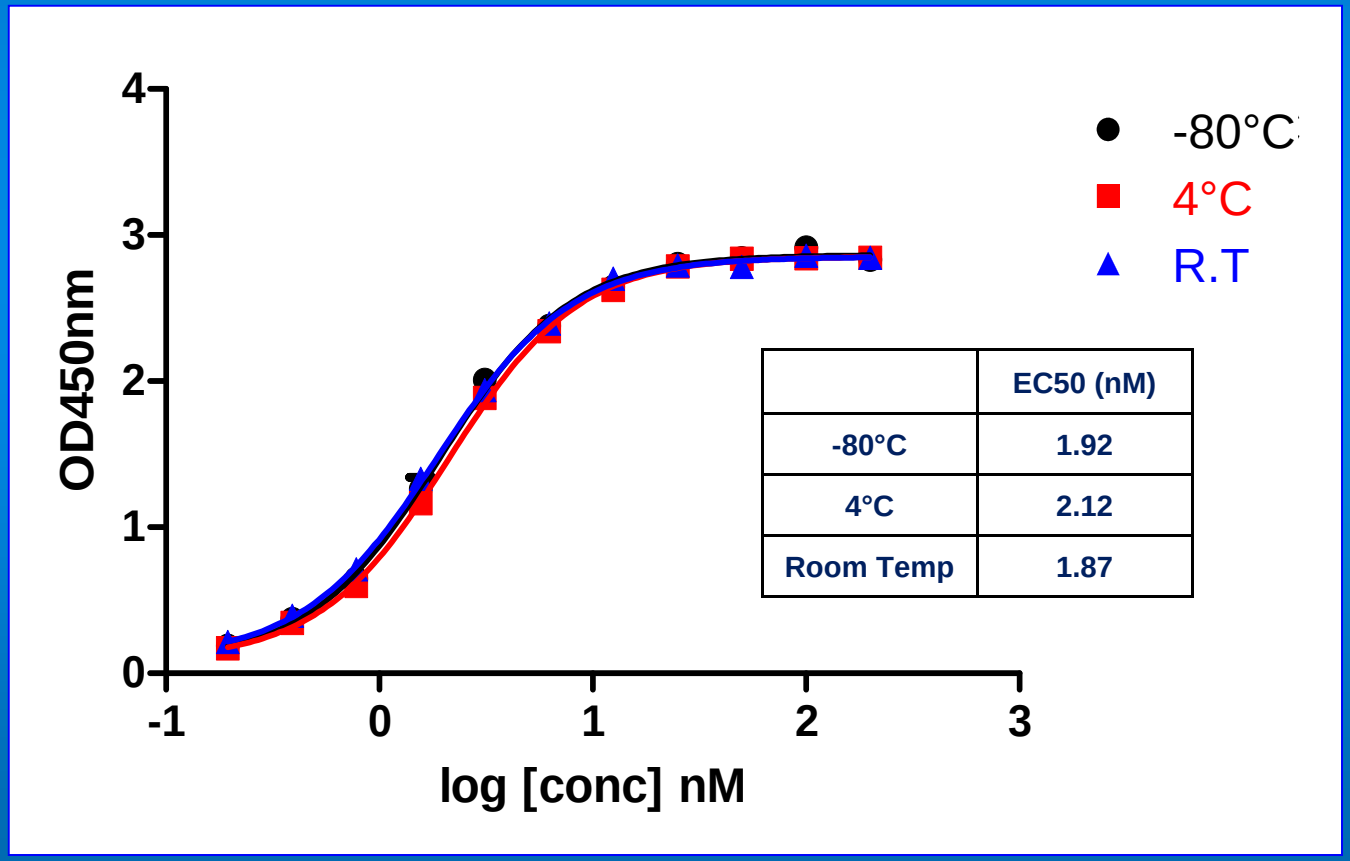
B5/D



Monovalent Bispecific Surrobodies are Stable Following Storage at Room Temp for 12 Months

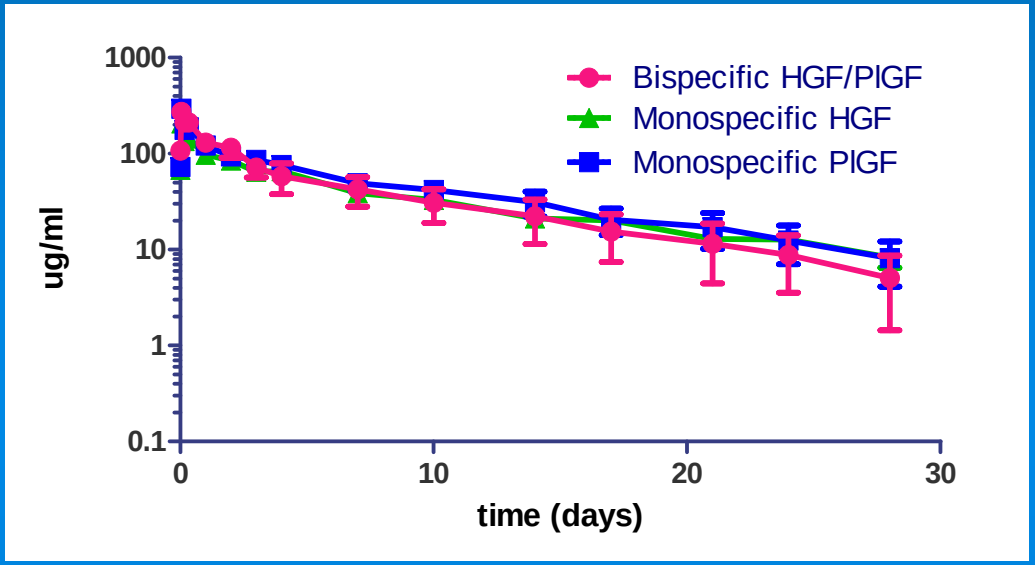
ELISA binding isotherms show no loss of activity between -80°C and room temperature.





	EC50 (nM)
-80°C	1.92
4°C	2.12
Room Temp	1.87

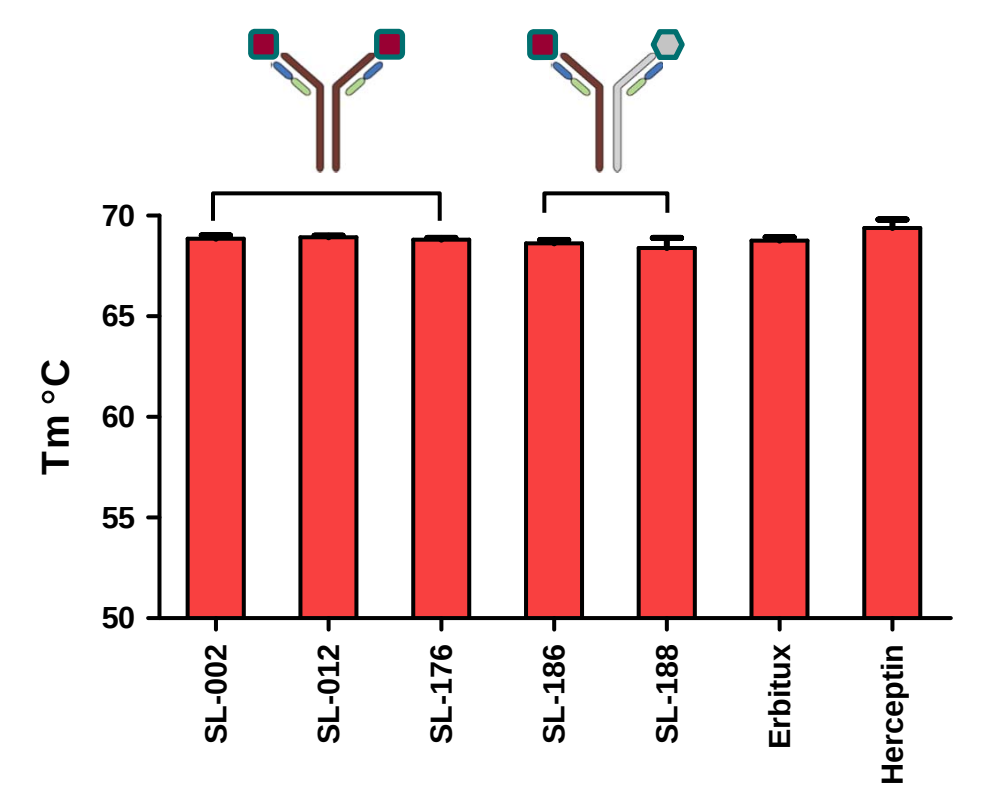
The PK Properties of Bispecific Surrobodies are Comparable to Parentals in Cynomolgus



- Naïve groups (n=3) of Cynomolgus monkeys were administered single IV dose of Surrobodies (10 mg/kg)
- Serum was tested over a 28 day period
- The overall PK properties are “Antibody-like”

Agent	Half-life (days)	Clearance (mL/hr/kg)	Vss (mL/kg)
Bispecific (HGF/PlGF)	6.04	0.42	77.2
Monospecific PlGF	6.35	0.35	78.5
Monospecific HGF	9.28	0.40	110
HGF IgG	10.88	0.19	75.6

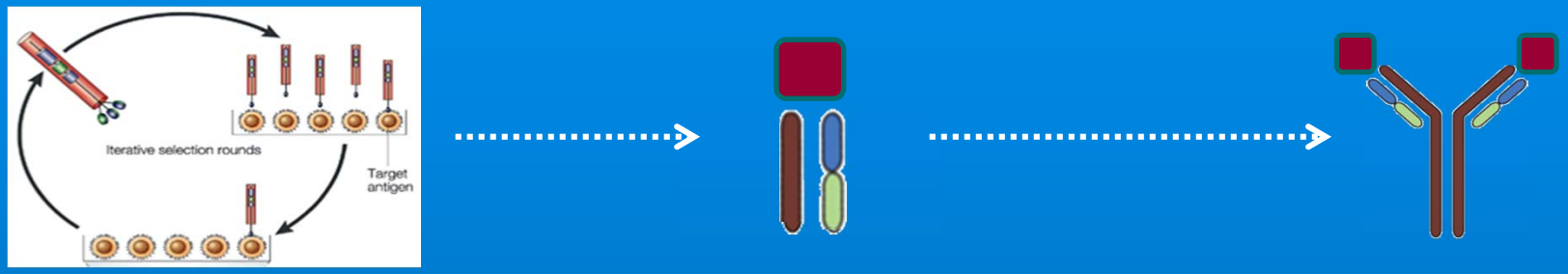
Surrobody Thermostability is Comparable to Marketed Antibodies



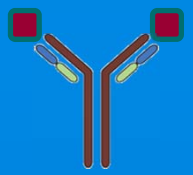
	Target	Format
SL-002	PlGF	Monospecific
SL-012	HGF	
SL-176	ErbB3	
SL-186	PlGF HGF	Bispecific v1
SL-188		Bispecific v2

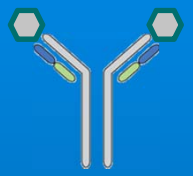
Tm was calculated in a fluorescent-based assay of agents in PBS

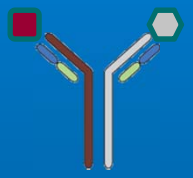
Bispecific Example #2
Targeting Two Soluble Factors in vitro and in vivo



GF x Ligand Bispecific Properties are Similar to Parental Surrobodies

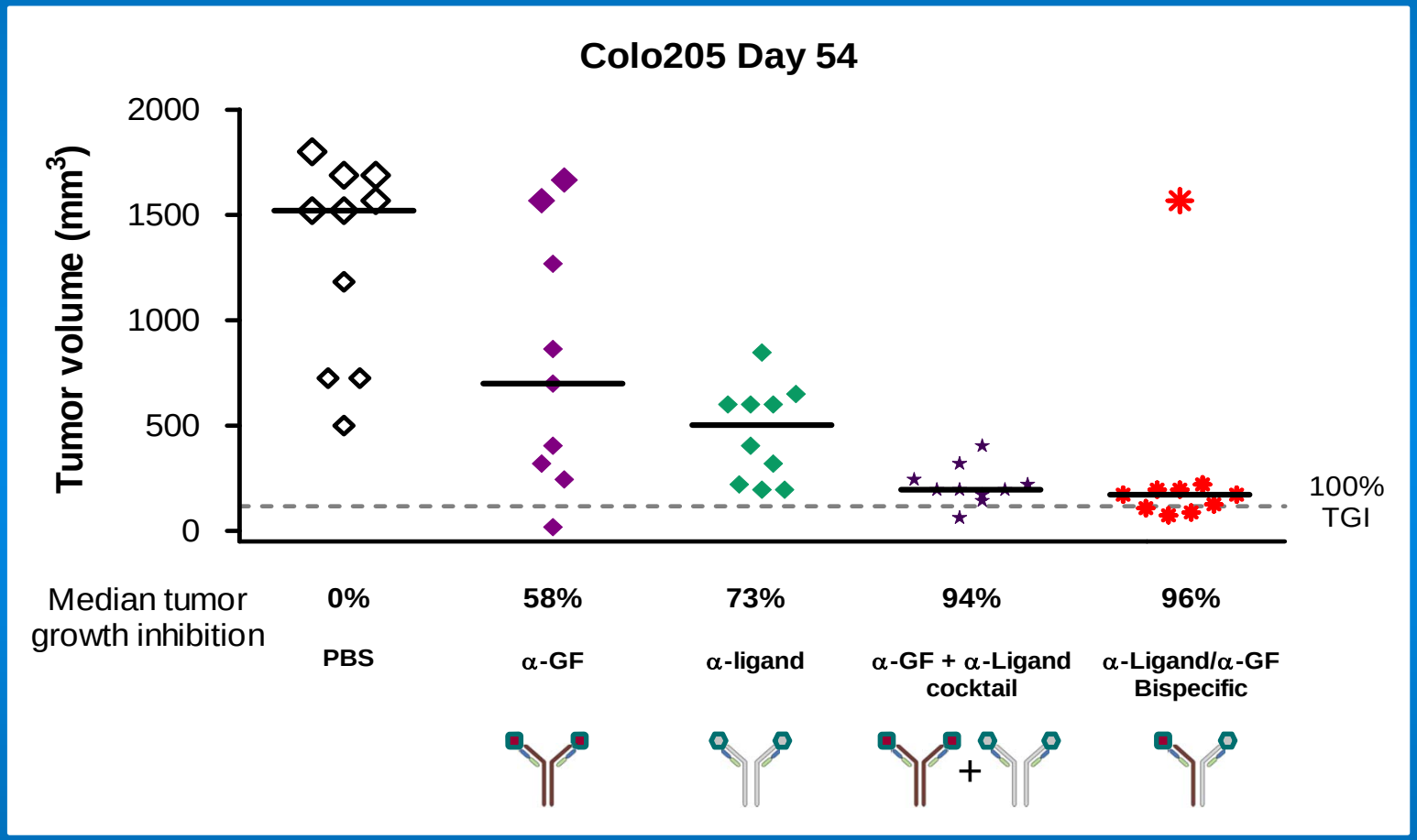






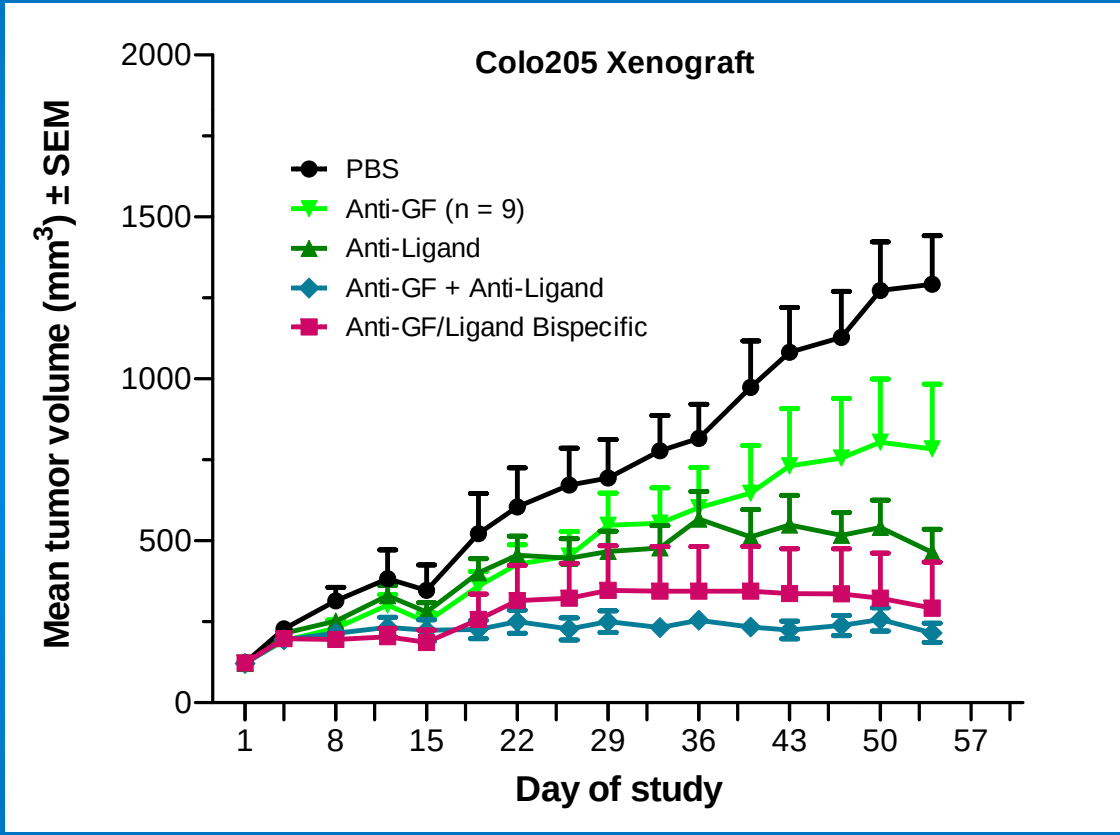
	All values [nM]				
	Ligand-1	Ligand-2		GF	
Molecule *(specificity)*	**Cell IC50**	**ELISA Binding**	**ELISA Inhibition**	**ELISA Binding**	**Cell IC50**
SL-429 *(Ligand)*	**0.281**	**0.020**	**0.156**		
SL-516 *(GF)*				**0.086**	**0.139**
SL-634 *(Ligand x GF) Monovalent Bispecific*	**Not Tested**	**0.048**	**0.955**	**0.055**	**2.602**

Anti-GF/Ligand Bispecific Captures the Synergistic Benefits of Dual Inhibition In Vivo



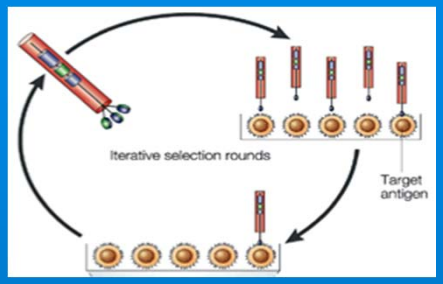
Mice were treated 2x weekly by iv injection.
Groups received 5mg/kg each, except bispecific which was 10mg/kg

Anti-GF/Ligand Bispecific Captures the Synergistic Benefits of Dual Inhibition In Vivo



Mice were treated 2x weekly by iv injection.
Groups received 5mg/kg each, except bispecific which was 10mg/kg

Bispecific Example #3
In vitro Targeting
ErbB3 x Growth Factor Receptor



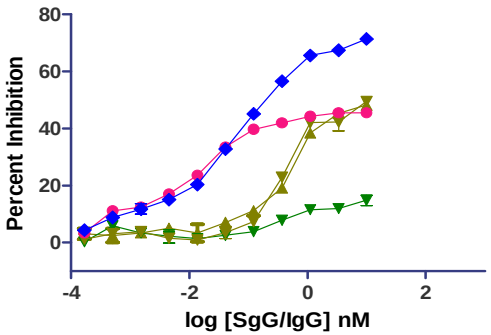
ErbB3 Summary

- ErbB3 represents a pivotal node in regulation of cell proliferation
  - Implicated in the generation of resistance to a *number* of key oncology agents
- Sea Lane's anti-ErbB3 is a potent inhibitor with a novel mechanism of action in ErbB2 overexpressing cells *(Molecular Cancer Therapeutics; July, 2012)*
- Sea Lane's anti-ErbB3 Surrobodies synergistically enhance the activity of ErbB2 and EGFR antibodies
- Bispecific ErbB3 x GFR surrobodies capably capture a similarly synergistic cocktail

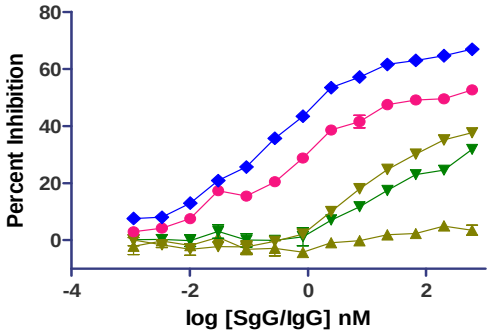
Anti-ErbB3 Surrobodies Enhance the Activity of Trastuzumab

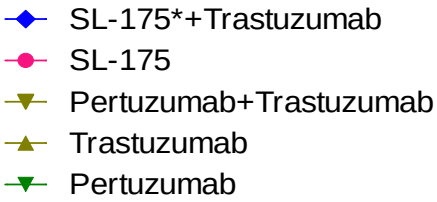
SKBR3 Cells

Unstimulated



NRG-stimulated

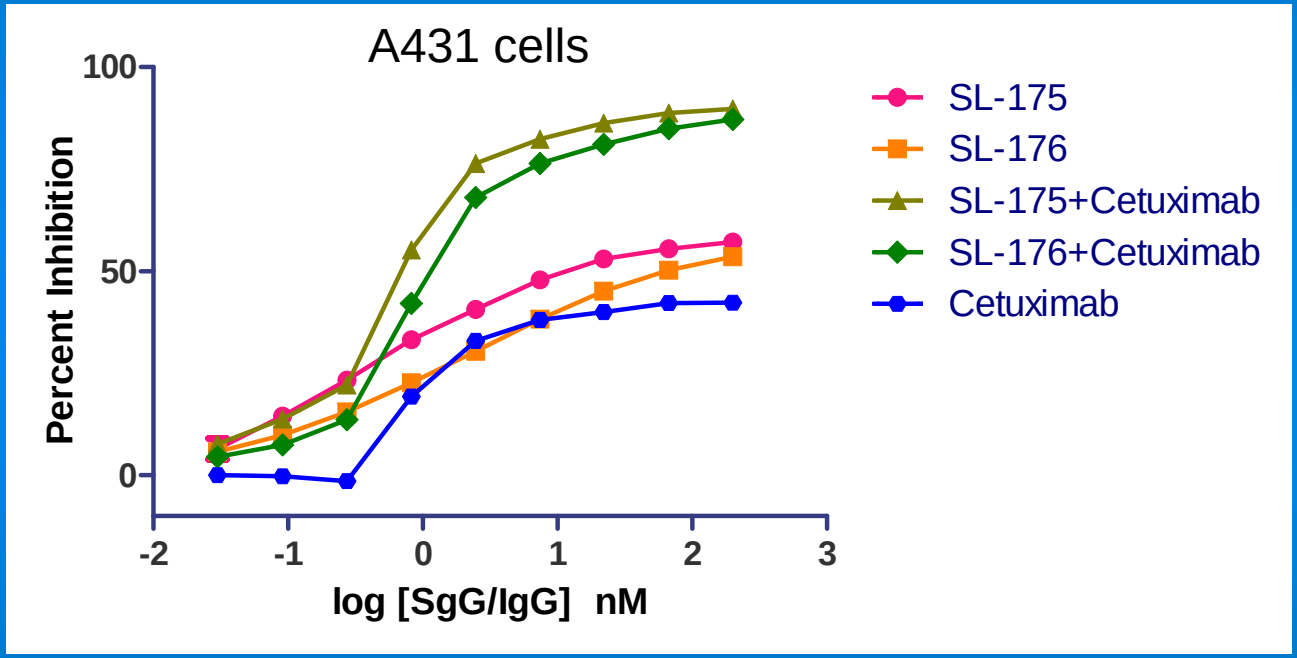




* Nearly identical results were obtained using SL-176
Foreman, et. al., Molecular Cancer Therapeutics 2012

Anti-ErbB3 Surrobody enhancement of anti-ErbB2 provides the rational basis for an ErbB3 x ErbB2 bispecific

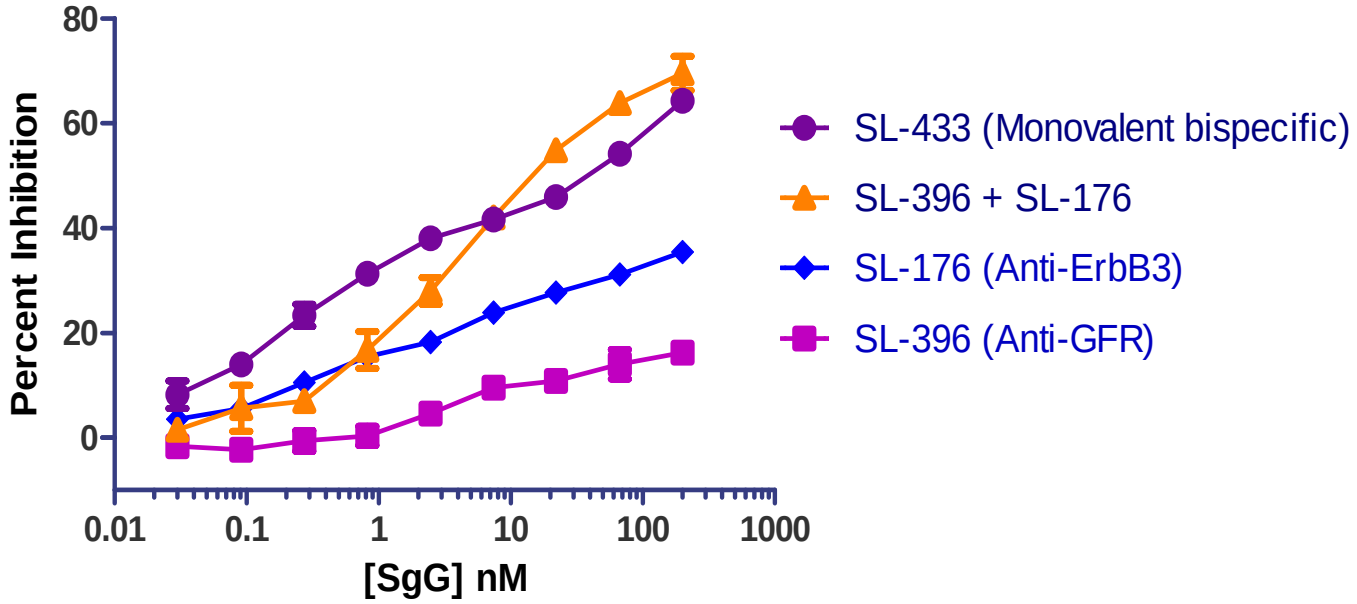
Anti-ErbB3 Surrobodies Enhance the Activity of Cetuximab

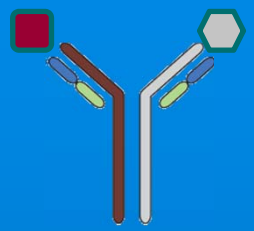


Anti-ErbB3 Surrobody enhancement of anti-EGFR provides the rational basis for an ErbB3 x EGFR bispecific

Bispecific ErbB3 x GFR Surrobody Captures Complimentary Efficacy of Parental Cocktail

Anti-GFR ( ) Surrobody combined with anti-ErbB3 ( ) Surrobody





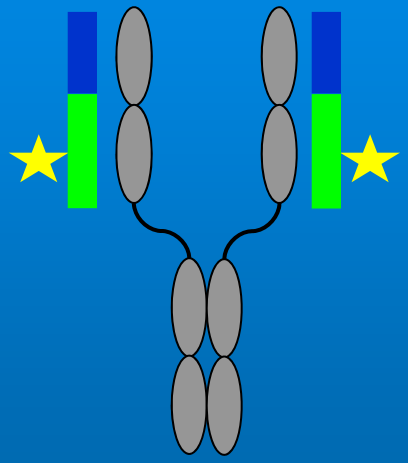
SL-433

Summary

- The Surrogate Light Chain is a natural universal Heavy Chain partner
- Sea Lane's fully human synthetic library drives Surrobody discovery
- High level, high quality transient expression accelerates Surrobodies through *in vitro* and *in vivo* research
- Bispecific Surrobodies are highly efficacious with characteristics that are comparable to antibodies
- The Surrobody structure is amenable to additional formats that enable optimal therapeutic approaches including:
  - Multivalent bispecifics
  - Drug conjugation

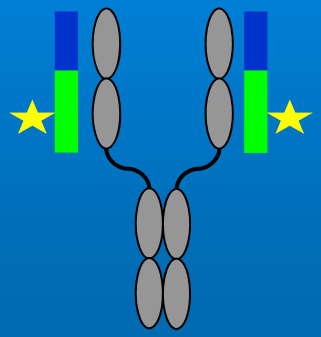
Surrobody Drug Conjugates

Boosting the anti-tumor abilities of Surrobodies



Surrobody Drug Conjugates

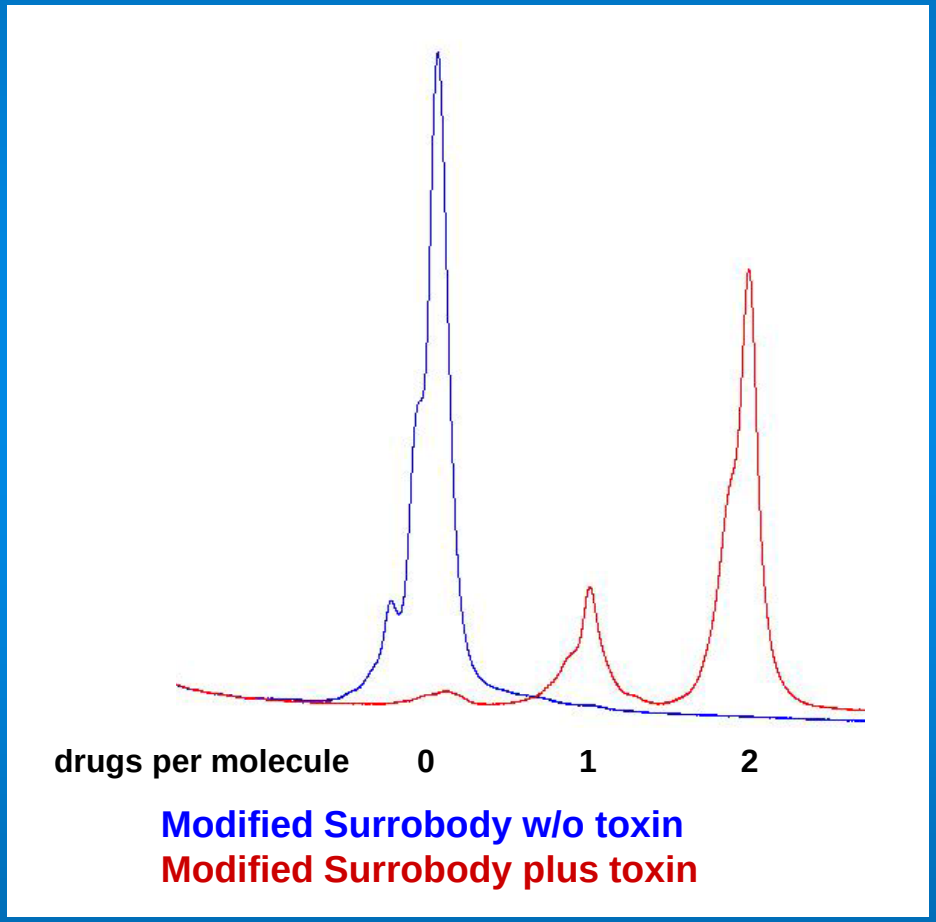
- Invariant surrogate light chain partner is the ideal site for drug conjugation
  - **ALL** Surrobodies use the **exact** same light chain
  - One solution will work across the entire platform from monospecific to bispecific agents
  - Light chain has been shown to be more desirable for conjugation than heavy chain



Surrobody Drug Conjugation Research Milestones

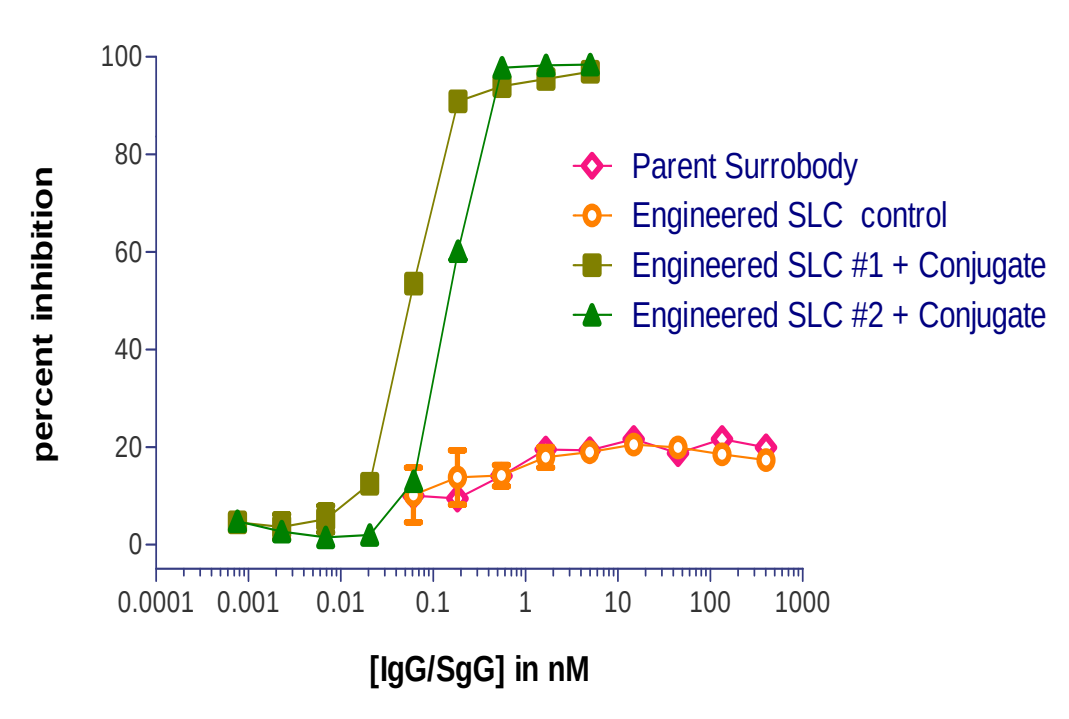
- Engineered Surrobody for drug conjugation
  - Modified surrogate light chain allows for 2 toxins per Surrobody
  - Possible to further modify to add more toxin
  - Toxin addition efficiency appears excellent
- Demonstrated cellular potencies in vitro
  - POC target: GFR driven cell proliferation
- Bispecific drug conjugation comparable to monospecific Surrobodies

Toxins Conjugate Robustly to Surrobodies



- Analysis of unoptimized Drug Conjugation shows predominance of Surrobodies containing two or one toxins per molecule
- Toxin conjugate: Monomethyl Auristatin E (MMAE)

Surrobody Drug Conjugates More Potently Inhibit In Vitro Proliferation



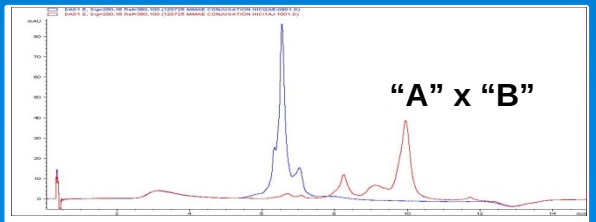
	Potency [pM]	Efficacy
Parent	0.615	20%
Engineered SLC control	0.382	19%
Engineered SLC #1 + Conjugate	0.058	96%
Engineered SLC #2 + Conjugate	0.156	99%

- Possible to modify to add more toxins
- Performs as well as, or better than toxin conjugated antibody *(not shown)*

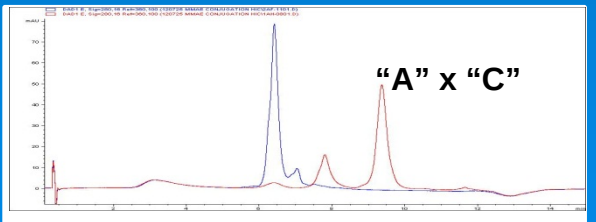
Bispecific Surrobody Toxin Conjugation is Comparable to Monospecific Conjugation

Heteromeric Fc Bispecific Surrobodies

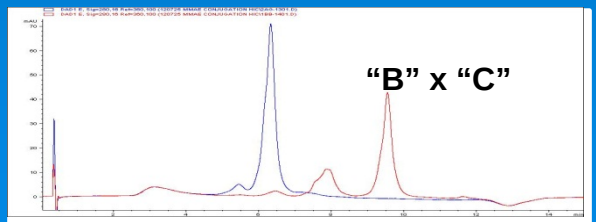
Blue tracing is Unmodified SgG
Red tracing is toxin (MMAE) conjugated



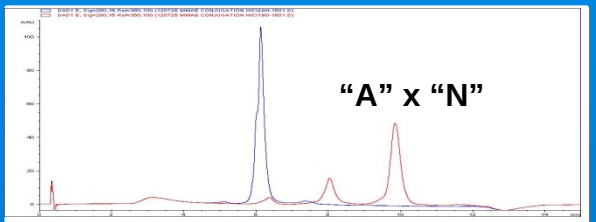
Drug per molecule 0 +1 +2



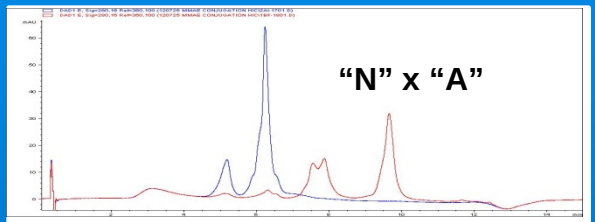
Drug per molecule 0 +1 +2



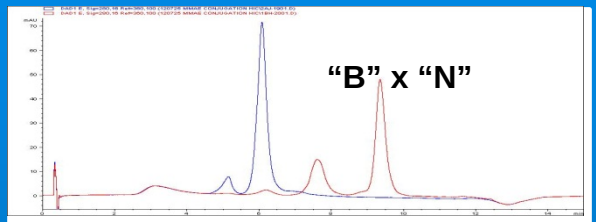
Drug per molecule 0 +1 +2



Drug per molecule 0 +1 +2



Drug per molecule 0 +1 +2



Drug per molecule 0 +1 +2

In unoptimized conjugation reactions almost all the surrobodies are conjugated with most carrying two toxin molecules

Acknowledgements

Technology Development

- Li Xu
- Sandra Wang
- Gordon Leung

Protein Sciences

- Chuck Hannum
- Hieu Tran

Discovery

- Aaron Kurtzman
- Helena Yee
- David Duffin

Program Teams

- Danying Cai
- Medini Gore
- Pamela Foreman
- Phil Kobel

Management

- Lawrence Horowitz
- Michael Horowitz

Contact Information

Sea Lane Biotechnologies

2450 Bayshore Parkway, Suite 200

Mountain View, CA 94043

USA

Michael Horowitz
GC/COO
michael.horowitz@sealanebio.com
(650) 336-1532

Ramesh Bhatt
VP of Research
ramesh.bhatt@sealanebio.com
(650) 325-7402