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Innovations in Bispecific Antibodies

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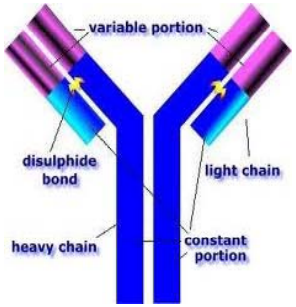
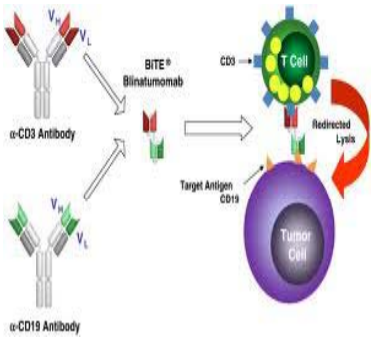
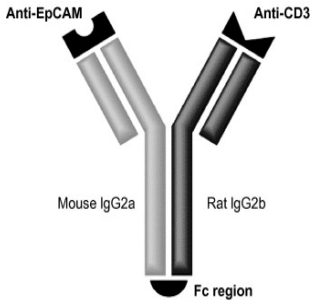
Introduction to Bispecific Antibodies







- 1958: The Foundation of Innovation: Noble Prize winning work by Rodney Porter with the structure of immunoglobulin
  - Two almost identical antigen binding Fabs nurtured the idea of artificially constructing bispecific antibody
- 1960-1997: Over 150 publications with Five International Conferences on Bispecific Antibodies describing various bispecific targets, engineering and CMC innovations; however,
  - Tremendous excitement but not a single approved bispecific antibody yet: poor yield, stability, high toxicity and poor efficacy in clinical trials of early bispecific Mabs
- 1997: The Next Key Breakthrough: Single-chain bispecific CD19X CD3 Mab (blinatumomab)-BiTE (Micromet/Amgen) based on work by Mack et al. 1995 (PNAS 92:617-621)
  - Robust efficacy in Acute Lymphoblastic Leukemia who had relapsed following treatment with standard front-line chemotherapy or allogeneic stem cell transplant
    - Validation of BiTE technology
- Explosion of Bispecific Formats and yet only a single approved bispecific mAb (trifunctional)-
- 2009: To date, catumaxomab (anti-EpCAM X CD3) is the only bispecific mAb approved for treatment of malignant ascites by EMEA in 2009 (Fresenius Biotech)

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Opportunities

Bispecific mAb

- Design flexibility with various formats: able to combine multiple targets
- Highly specific and effective targeting
- High avidity like target interactions allowing better efficacy
- Toxicity can be reduced by engineering differential potency in one mAb
- Cost of one mAb vs. combining two separate expensive mAbs will be substantially less and attractive to payers

Combination of mAbs

- Convenience of dosing and flexibility with dosing schedule (simultaneous, sequential etc.) to reduce toxicities
- Fixed combinations with enhanced efficacy and reduced toxicities are potentially attainable
- Business case for combining two expensive antibodies can only be made in terminal cancers or other debilitating diseases with very few options

Antibodies Mixture (Fixed Ratio)

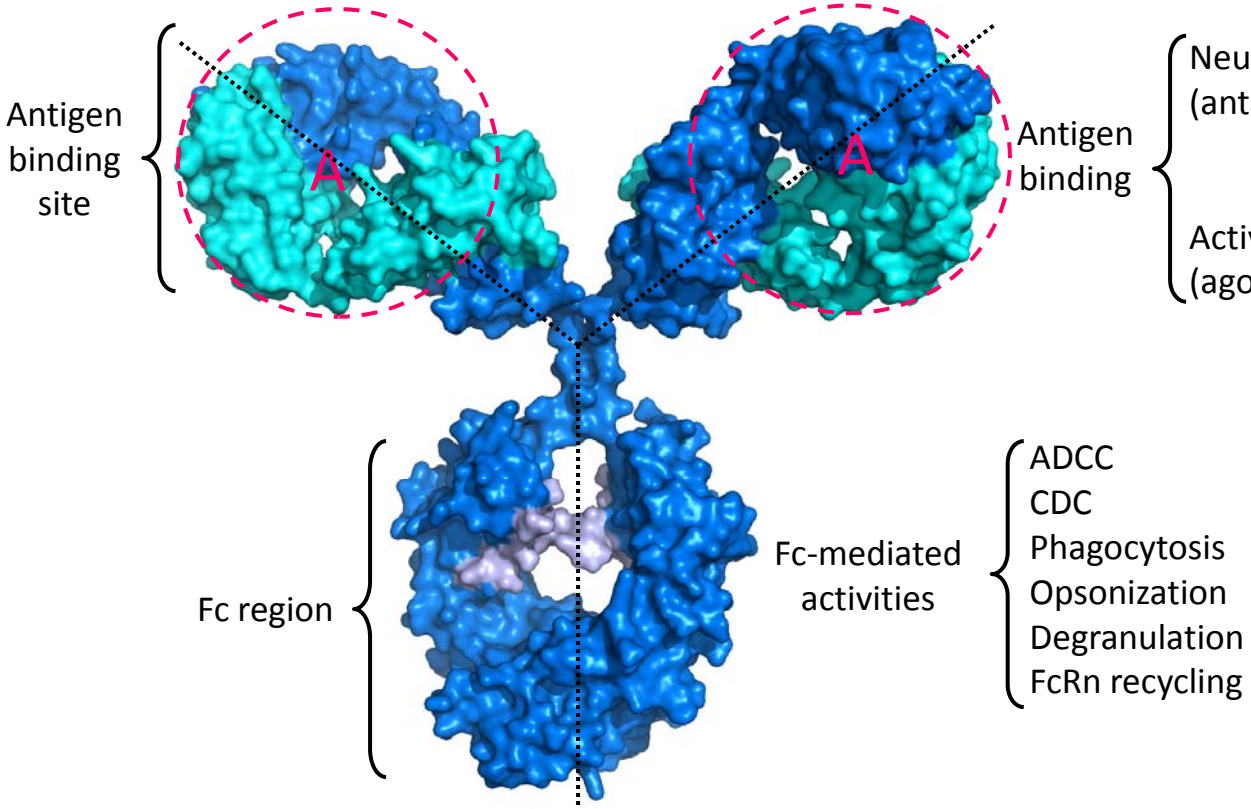
Pros

- **Synergistic/additive/potentiation activities**
  - Targeting non-overlapping epitopes (e.g., Symphogen's anti-EGFR mAbs mixture) may broaden efficacy
  - Targeting different MOAs to achieve broader efficacy
- **Opportunities to manage resistance mechanisms**
  - Resistance and escape pathways
- **Opportunities to improve therapeutic index by adjusting the ratio of antibodies in the mixture**

Cons

- Fixed ratio of antibodies mixture may not allow flexibility in doses and schedules of individual monotherapy
- May enhance toxicities of mixture of single target antibodies with overlapping DLTs
- Substantial CMC and manufacturing challenges
- Business case for mixture of antibodies is most favorable in terminal cancers or difficult to treat infections

Natural Antibodies Have Certain Limitations



One antibody one antigen paradigm

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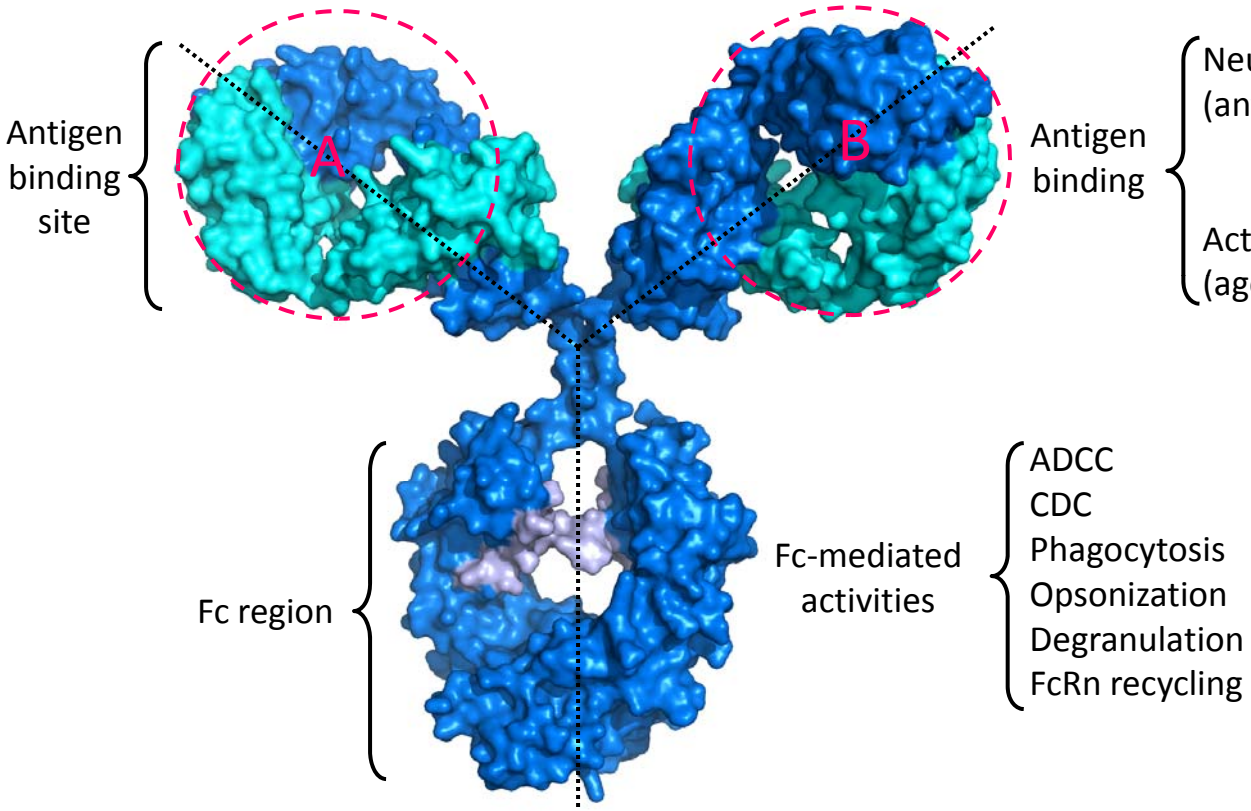
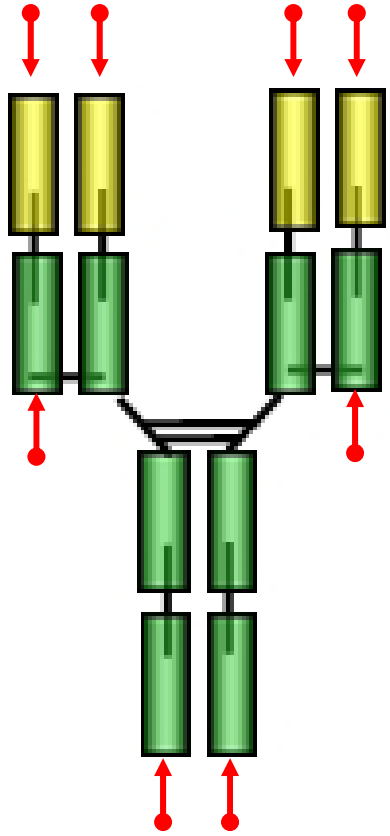
Natural Antibodies Have Certain Limitations



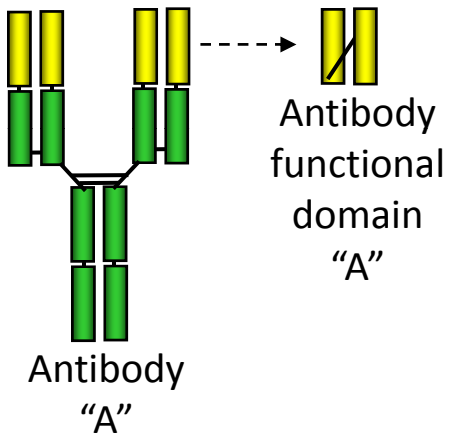
Breaking the paradigm:
"one antibody one antigen" to "one antibody two antigens"

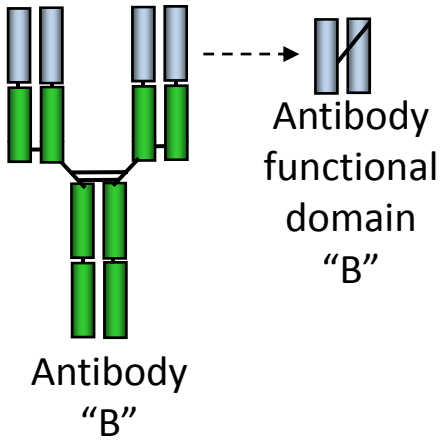
Breaking the Paradigm of a Perfect Antibody Symmetry



Functional binding sites can be branched out or inserted into the antibody modular domains

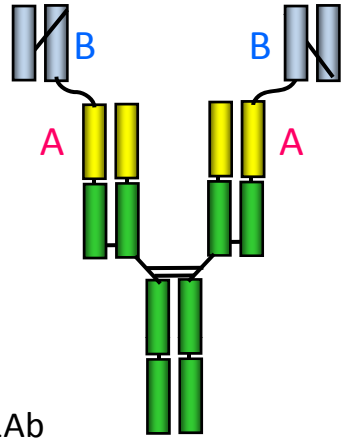
What are the functional domains that can be branched out or inserted into the antibody modular domains?





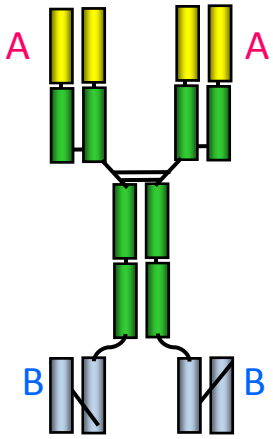
Antibody functional domains retain specificity and affinity of the parental antibodies and can be used to build "bispecificity" into antibodies.

Bispecific bivalent antibodies at MedImmune



1Ab

2Ab



3Ab

Potential Safety Concerns with Bispecific mAbs

Target-PD Related

- Cross-linking of two target binding sites with blood cells (e.g., platelets, neutrophils) or off-target issues (Fc related) leading to unknown toxicities

•Enhancement in overlapping toxicities (e.g., EGFR inhibitors/VEGF inhibitor- case study presented)

• Altered PK and disposition leading to unknown differential toxicities and or reduced efficacy

Intrinsic and Off-Target Toxicities

•Bispecific backbone or format related

•Immunogenicity to unnatural mAb formats or CMC issues (e.g., aggregation)

• Non-specific non-target based interactions (off-target toxicities)

•CMC related issues (e.g., aggregation) leading to unexpected toxicities

Pharmacokinetic & Disposition Challenges to Bispecific mAbs

Smaller size bispecific mAbs with no FcRn binding (e.g., BiTE)

- Very short half-life requiring prolonged infusions or frequent administrations to maintain desired PD
- High immunogenicity to non-human Fab sequences limiting efficacy
- High off-target tissue distribution and greater opportunities for off-target toxicities

Full length bispecific IgG mAbs

- Intact FcRn binding
- Soluble ligand vs. receptor targeting or combinations
- May have shorter half-life when compared to natural IgG mAb
  - Disproportionate binding to one target vs. other (sink effect) dependent on target expression
  - Reduced FcRn recycling due to bulky structures
  - Altered tissue distribution leading to decrease in circulating plasma levels

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Case Studies of Bispecific Antibodies

Anti-*P. aeruginosa* Psl/PcrV Bispecific Antibody for Serious *P. aeruginosa* Disease

EGFR x IGFR Bispecific

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A Novel Multi-Mechanistic Monoclonal Antibody Format for Treating *Pseudomonas aeruginosa* Infections

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A bispecific PslxPcrV antibody for the treatment of *P. aerigunosa* infections: Key messages

- We used a phenotypic, target-independent approach, including the use of B-cells of convalescing patients, to identify functionally active antibodies against a novel epitope, Psl, on the surface of *P. aerigunosa*
- We developed a novel bispecific format to generate a drug candidate that is superior to an oligoclonal approach for treatment of *P. aerigunosa* infections

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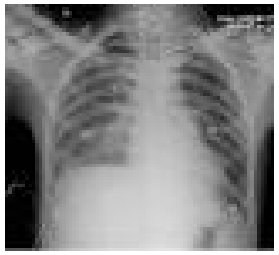
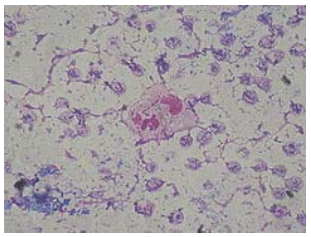
Pseudomonas aeruginosa & Bispecific Background





- **Pseudomonas aeruginosa**
  - It is a Gram-negative, aerobic, rod-shaped bacterium with unipolar motility
  - An opportunistic human pathogen, P. aeruginosa is also an opportunistic pathogen of plants
  - P. aeruginosa is often preliminarily identified by its pearlescent appearance and grape-like or tortilla-like odor in vitro.
  - P. aeruginosa is capable of growth in diesel and jet fuel, where it is known as a hydrocarbon-using microorganism (or "HUM bug"), causing microbial corrosion
  - An opportunistic, nosocomial pathogen of immunocompromised individuals, P. aeruginosa typically infects the pulmonary tract, urinary tract, burns, wounds, and also causes other blood infections

- **Unmet Medical Need *Pseudomonas aeruginosa* and Ventilator Associated Pneumonia (VAP)**
  - Nosocomial pneumonia is the leading cause of death from hospital-acquired infections
  - Nearly 1/3 of patients intubated for 48 hr or more develop VAP
  - Patients with VAP due to P. aeruginosa have an attributable mortality >40%
  - >20% of PA isolates from US ICUs were resistant to imipenem and 30% were resistant to fluorquinolones

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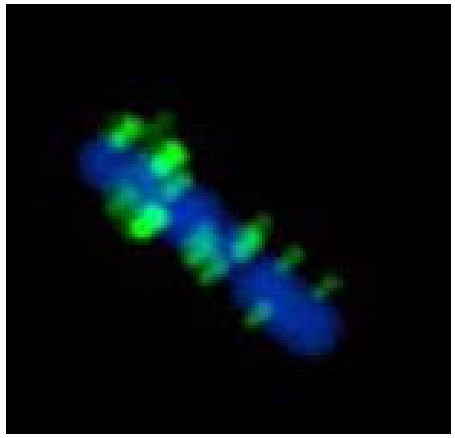
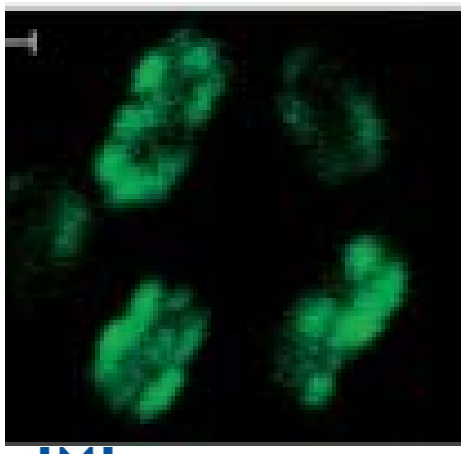
Anti-PcrV/Psl Combination & Multispecific Rationale

PcrV



Psl



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PcrV: Virulence factor

MOA: Prevents toxin injection into host cells

High affinity mAb to low density target

- **Potential to engage both surface targets with mAbs having unique MOAs, without competition**
- **Expression of both targets is coordinated but in opposite directions.**
- **96% of strains express either or both targets**

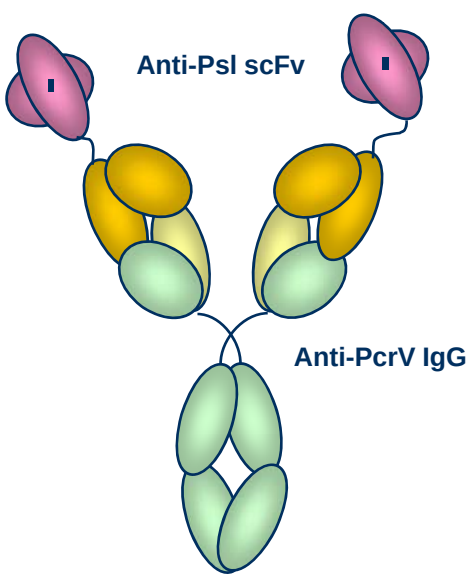
Psl: Persistence factor

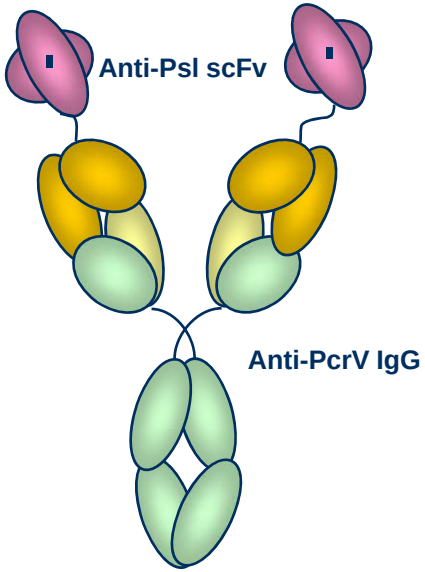
MOA: Promotes opsonophagocytic killing and blocks cell adherence

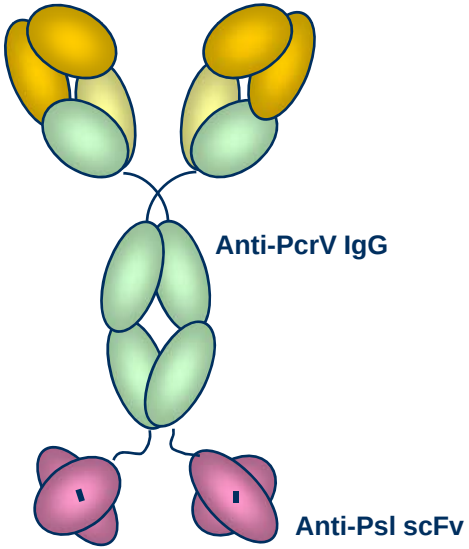
Low affinity mAb to high density target

Bispecific antibody formats

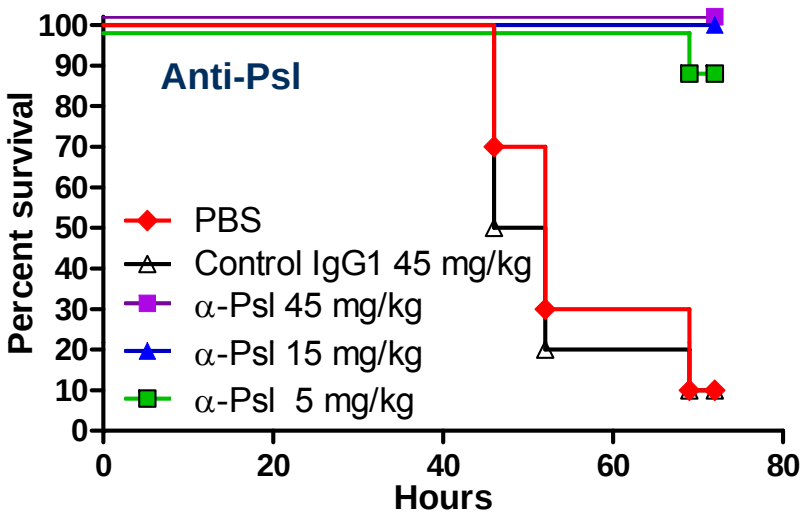
- **Mixture of Anti-Psl + anti-PcrV mAbs**
  - Combine anti-cytolytic, OPK and anti-adherence MOAs
- **Multi-specific antibody constructs**

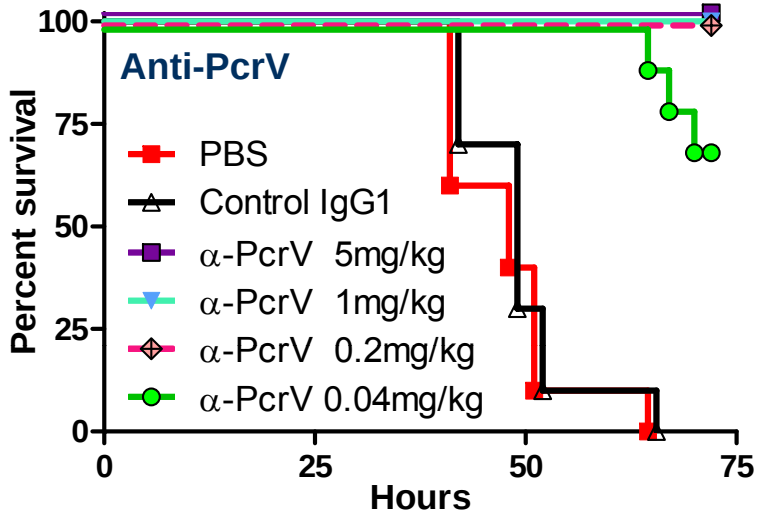






Anti-PsI and Anti-PcrV mAbs are highly active in *P. aeruginosa* infection models

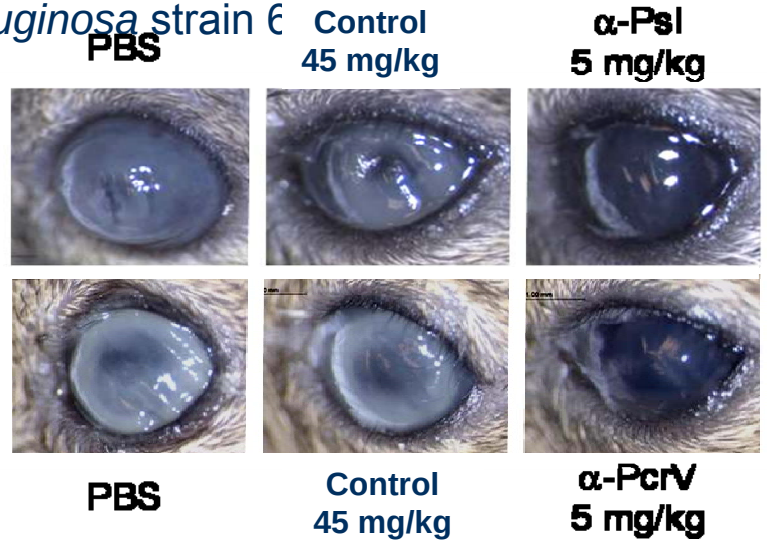




Mouse Acute Pneumonia Model - mAbs administered IP, 24 hours prior to infection with ~10 x LD100 of cytotoxic *P. aeruginosa* strain 6

Mouse keratitis model

mAbs administered IP, 16 hours prior to corneal scratch and infection with 10^6 CFUs.



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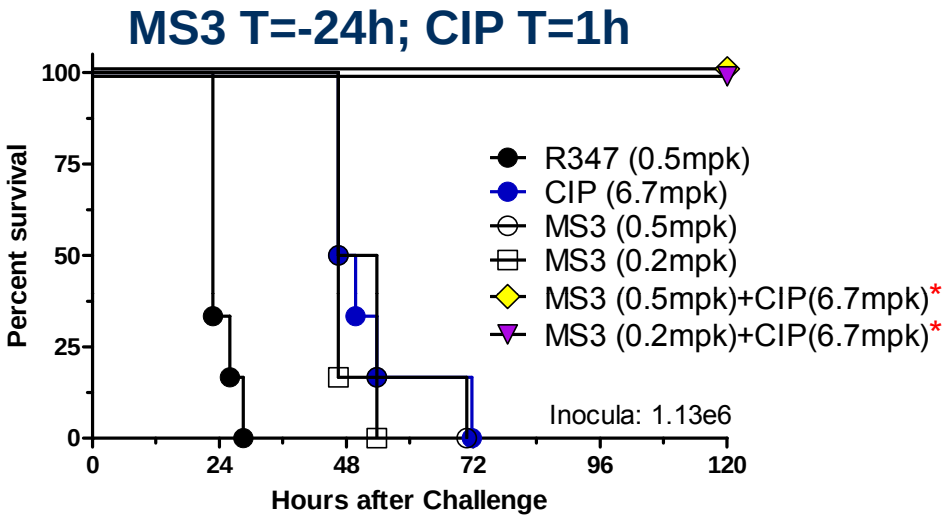
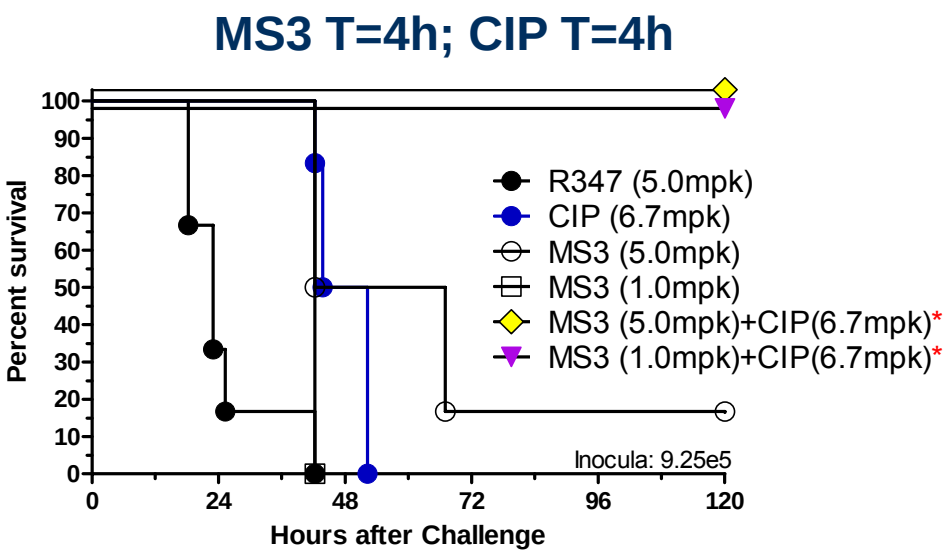
Antibody/Antibiotic adjunctive therapy protects mice from lethal pneumonia (*in vivo* synergy)



- Sub-protective antibody dose makes *P. aeruginosa* infection easier to treat with sub-protective antibiotic dose

*Log Rank: $P<0.0005$

- MS3 + CIP rescue mice from lethal pneumonia when dosed at 4 hrs post-infection
- Similar results observed with meropenem



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Ashley Keller, Jamese Hilliard

Multi-specific (MS) and mixture (rpAb) comparison in the *P. aeruginosa* acute pneumonia model

120 hr post-infection (strain 6206)
Parentheses indicate total number of animals

Percent protection against lethal 6206 (O11-ExoU$^+$) challenge in mouse pneumonia model

	Antibody Dose (mg/kg)							
Antibody	**15**	**10**	**5**	**2**	**1**	**0.5**	**0.2**	**0.1**
anti-PcrV	-	-	80 (10)	-	20 (10)	10 (10)	0 (10)	-
anti-Psl	0 (10)	-	0 (10)	-	0 (10)	-	-	-
MS1			70 (10)		10 (10)	0 (10)	0 (10)	
MS2	-	80 (10)	40 (20)	-	10 (20)	0 (20)	0 (20)	-
MS3	**-**	**-**	**100 (60)**	**-**	**88 (60)**	**60 (60)**	**10 (60)**	**-**
	(mg/kg each mAb)							
Mixture			**5**	**2**	**1**	**0.5**	**0.2**	**0.1**
Anti Psl + Anti PcrV	**-**	**-**	**100 (10)**	**100 (40)**	**78 (40)**	**15 (40)**	**-**	**3 (40)**

- MS3 and mixture are superior to monoprophylaxis
- MS3 construct at least comparable or better than mixture
- Isobologram analysis indicates potent synergy when comparing MS3 vs. individual mAbs

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Executive Summary

- Novel bispecific antibody provides:
  - Protection against multiple pathogenic activities of *P. aeruginosa*
  - Broad *P. aeruginosa* coverage independent of serotype or antibiotic resistance
  - Potent efficacy in several different prevention and treatment infection models
  - **Synergistic activity when combined with antibiotics**
  - **Low safety concerns due to absence of host cell target**
  - Lack of disruption of beneficial microbiome or promotion of antibiotic resistance
  - **High expression level, excellent thermostability with strong protease resistance**

- **Can be developed for prevention or treatment**
  - Both TPPs are commercially viable
  - Additional information required to choose between strategic alternatives
  - Same IND filing and Phase 1 regardless of strategy

Safety Challenges to Bispecific Antibodies

Potential Safety Concerns with Bispecific mAbs

Target-PD Related

- Cross-linking of two target binding sites with blood cells (e.g., platelets, neutrophils) or off-target issues (Fc related) leading to unknown toxicities

- Enhancement in overlapping toxicities (e.g., EGFR inhibitors/VEGF inhibitor- case study presented)

- Altered PK and disposition leading to unknown differential toxicities and or reduced efficacy

Intrinsic and Off-Target Toxicities

- Bispecific backbone or format related

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- CMC related issues (e.g., aggregation) leading to unexpected toxicities

Pharmacokinetic & Disposition Challenges to Bispecific mAbs

Smaller size bispecific mAbs with no FcRn binding (e.g., BiTE)

- Very short half-life requiring prolonged infusions or frequent administrations to maintain desired PD
- High immunogenicity to non-human Fab sequences limiting efficacy
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Full length bispecific IgG mAbs

- Intact FcRn binding
- Soluble ligand vs. receptor targeting or combinations
- May have shorter half-life when compared to natural IgG mAb
  - Disproportionate binding to one target vs. other (sink effect) dependent on target expression
  - Reduced FcRn recycling due to bulky structures
  - Altered tissue distribution leading to decrease in circulating plasma levels

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Case study of MEDI-6348:

Investigational EGFR and IGF-1R Bispecific Mab

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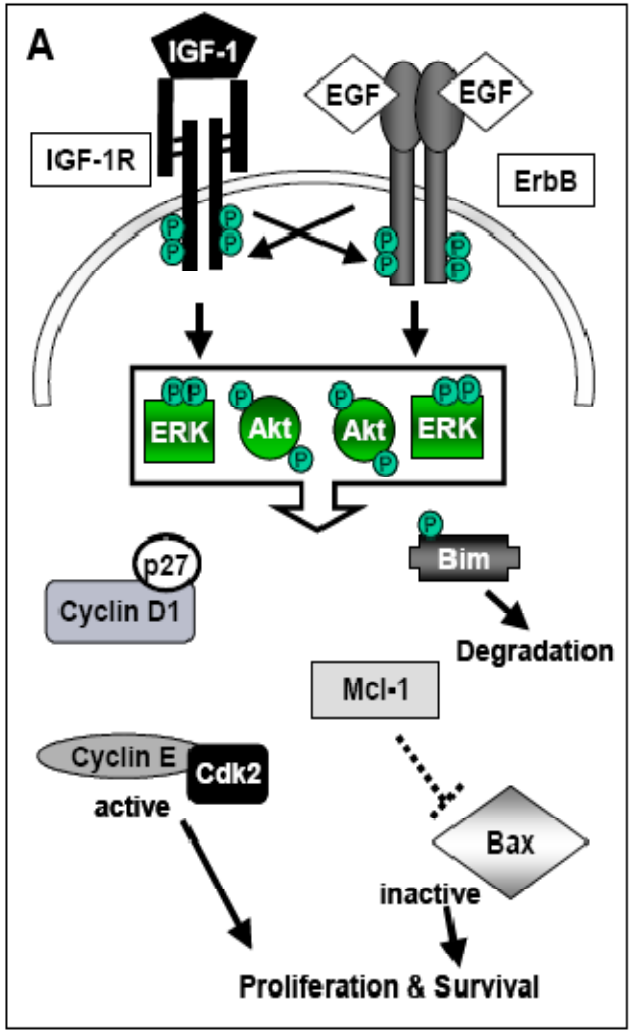
Target Rationale/Impact on Patients: Why target both EGFR and IGF1R?



Wilsbacher *et al.*, 2008

- **Multiple shared indications**
- **Non-overlapping toxicity**
- **Resistance**
  - Evade innate / avoid acquired
  - k-ras mutant CRC patients:
    - Anti-EGFR resistant
- Anti-IGF1R sensitive?
  - NSCLC:
- **Patient population may benefit:**
  - Broader range?
  - Effective with both primary and mets?
- **Two targets hit by one drug**
  - ↓cost of goods→ reduced price?

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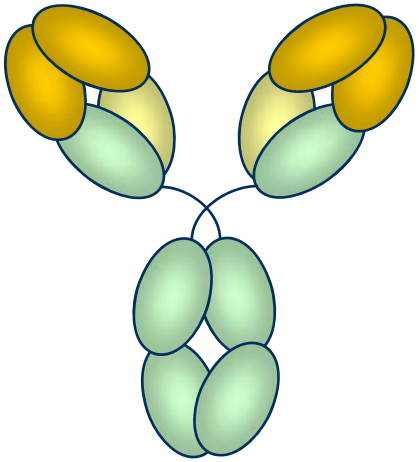
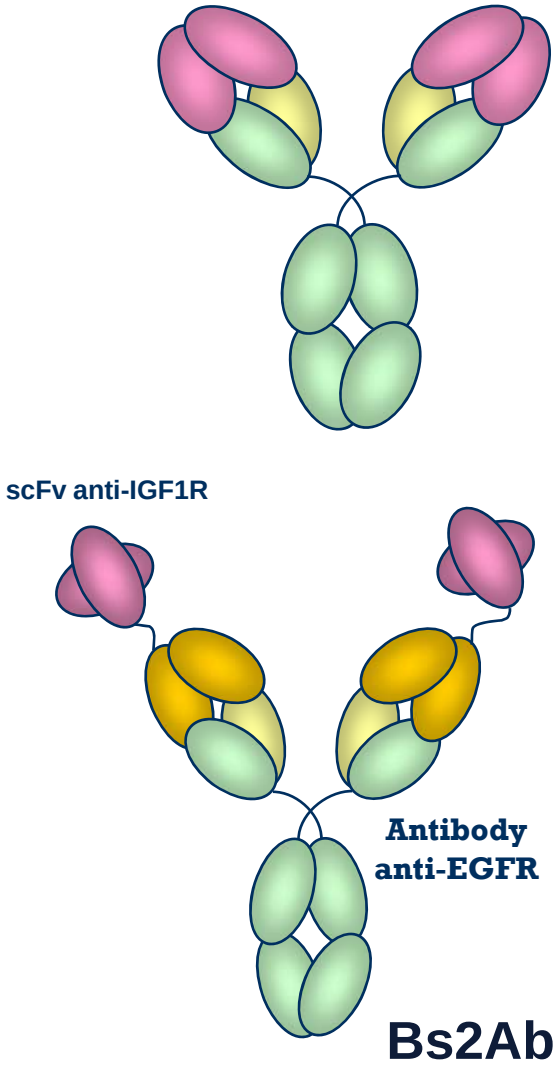
Parental arm antibodies and bi-specifics construction

EGFR arm



PaniX, human IgG1k antibody (variable domains from Panitumumab)

- **cross-reactivity: human, cyno**
- **K_D for EGFR: 253 pM**



Bs2Ab

IGF1R arm

- **cross-reactivity: human, mouse, cyno**
- **K_D for IGF1R: 297 pM**

- **variable domains engendered as scFv in the bispecifics**

TZ1-1A, human IgG1l antibody (discovered at Medi-Cambridge)

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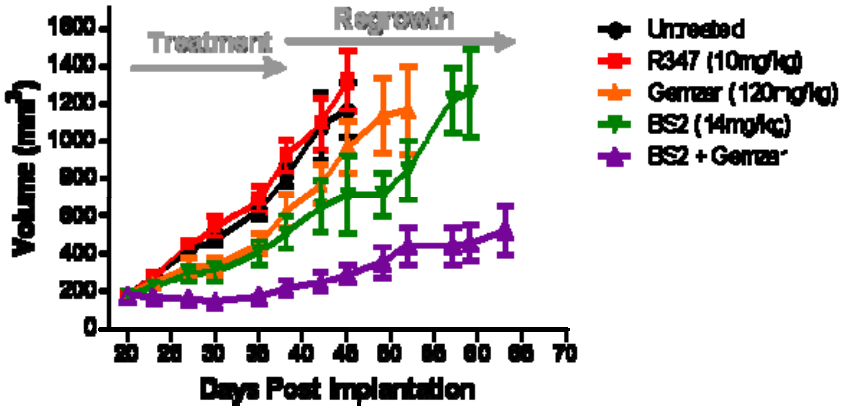
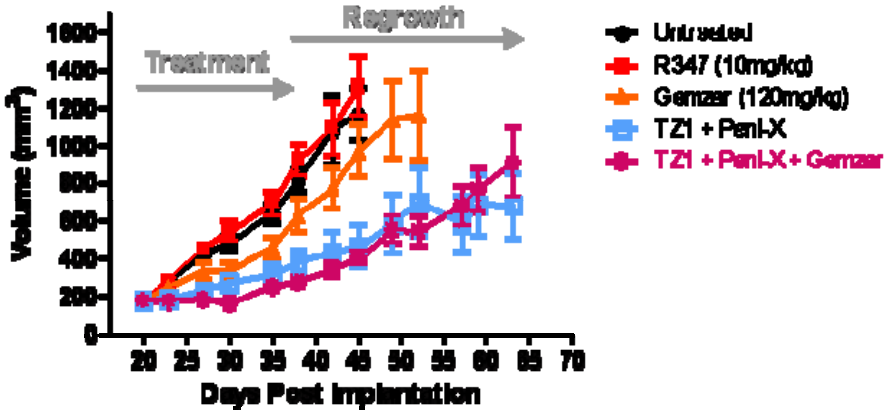
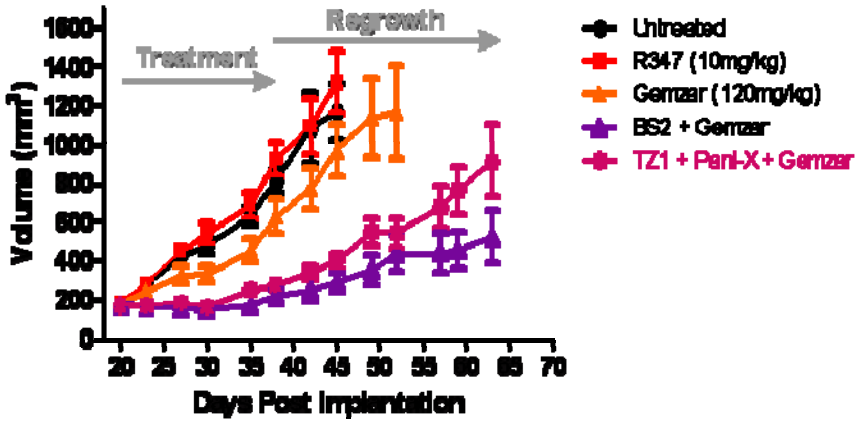
MEDI6348 Shows Superior *In Vivo* Activity to Either SOC or a Combination of Parental Abs

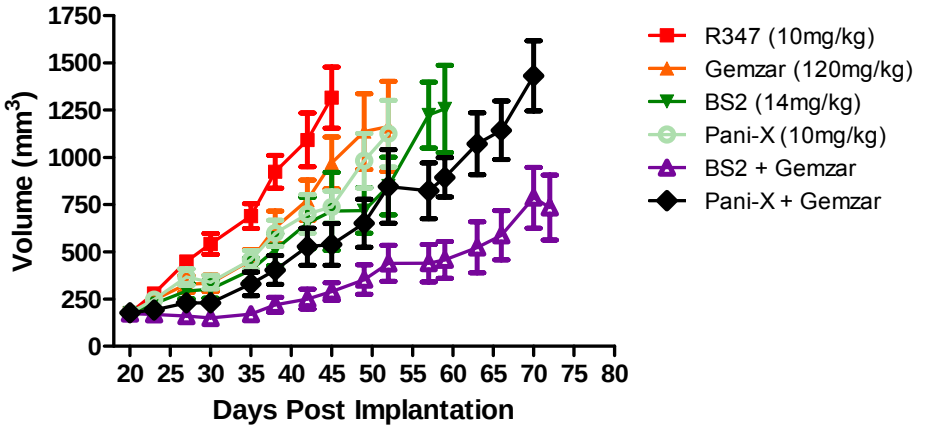
MEDI6348 Enhances SOC



A Combination of Parental Abs Does Not Enhance SOC







MEDI6348 is superior to either EGFR / SOC or an SOC combination of Abs.

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BxPC3 Pancreatic adenocarcinoma xenografts

Non-GLP Repeat-Dose Toxicity and Toxicokinetics Study in Cynomolgus Monkey (Study 8231530)

Group	Treatment	Route	No. of Doses	Dose (mg/kg)	Number	
1	Control IV	IV	5	0	4 to 6	Tox + PK/PD
2	EGFR/IGFR Bi-specific	IV	5	7.5	6	Tox
3	EGFR/IGFR Bi-specific	IV	5	15	6	Tox
4	EGFR/IGFR Bi-specific	IV	5	30	6	Tox
5	EGFR/IGFR Bi-specific	IV	1	7.5	4	PK/PD
6	Panitumumab	IV	1	7.5	4	PK/PD

- Toxicology Arm
  - Dose: IV, once weekly for 5 weeks (total 5 doses)
  - EGFR/IGFR Bi-Specific Dose Level: 7.5, 15, or 30 mg/kg

Low Dose:

- A dose of 7.5 mg/kg resulted in skin toxicity in some repeat-dose toxicity studies with panitumumab

High Dose:

- A dose of 30 mg/kg resulted in skin toxicity in some animals in repeat-dose toxicity studies with panitumumab
- Inclusion of a dose > 30 mg/kg dose of EGFR/IGFR bi-specific may provide limited information due to early morbidity/mortality

MEDI6348-Related Adverse Findings

- 30 mg/kg:
  - Day 1: in 3/6 monkeys clinical signs of ataxia, hypoactivity, dilated pupils, recumbency shortly after bolus dose; mortality in 1/6 animal (~20 minutes after bolus dose)

  - ➢ Updated study design: antihistamine (diphenhydramine) pre-treatment control & high dose (30 mg/kg) groups

  - Day 8: in 2 monkeys that had reactions on Day 1 had clinical signs of ataxia, hypoactivity, recumbency, respiratory distress, and morbidity shortly after the end of infusion dose
    - Pre-treatment with diphenhydramine did not prevent clinical signs
    - Treatment with IV epinephrine, IM diphenhydramine, IV hydrocortisone sodium succinate were unsuccessful in reversing severity of clinical signs

MEDI6348-Related Adverse Findings

- 15 mg/kg:
  - Day 8: in 1/6 animals clinical signs of ataxia, hypoactivity, and excessive salivation ~ 30 min after end of infusion dose
    - Treatment with IV epinephrine, IM diphenhydramine, IV hydrocortisone sodium succinate helped reverse the severity of clinical signs

- Updated study design: antihistamine (diphenhydramine), steroid (dexamethasone) and NSAID (carprofen) pre-treatment all dose groups and reduced the high dose to 15 mg/kg

- No additional adverse reactions following dosing from Day 15 to end of study

MEDI6348 Histopathology Summary

- Test article-related gross and microscopic findings were only observed in three 30 mg/kg animals that died or were euthanized *in extremis*
- There were no changes in organ weights
- Gross findings were red to dark red discolorations of the lung
- Associated microscopic findings in the lungs were hemorrhage/congestion/edema in all three animals, and fibrin thrombi (alveolar septa) in the two animals euthanized on Day 8
- Additional findings included marked congestion of liver in all three animals, focal cardiac myofiber degeneration in the two animals euthanized on Day 8
- Cause of death for all three animals was attributed to “pulmonary compromise”

MEDI6348 Non-GLP Investigative Tox Study in Cynomolgus Monkey Pre-treated with Carprofen, Diphenhydramine, and Dexamethasone (Study 8243711)

Group	Treatment	Route	No. of Doses	Dose (mg/kg)	Number
1	Control IV	IV	5	0	3
2	MEDI6348	IV	5	30	6
3	Panitumumab	IV	5	21	6

- Pre-treat with Carprofen (NSAID), Diphenhydramine (Antihistamine), and Dexamethasone (steroid)
- Dose: IV, once weekly for 5 weeks (total 5 doses)
  - MEDI6348 Dose of 30 mg/kg because that dose resulted in effects following IV administration in previous study and dose considered sufficient to evaluate the potential for adverse skin effects and to result in effects on the IGF1R pathway (Gualberto, 2010).
  - Panitumumab Dose of 21-mg/kg once weekly dose of panitumumab was selected to result in equivalent molar binding of the EGFR target compared to the 30-mg/kg dose of MEDI6348 and dose anticipated to result in skin effects (panitumumab BLA).
    - EGFR binding by 1 mg of MEDI6348 is approximately 72% of the EGFR binding by 1 mg of panitumumab
- Tox (obs, ECGs, clin path, organ weights, histopath), PK/PD/IM, Soluble Factors (cytokines, histamine, C3a), punch biopsies, insulin & growth factor

MEDI6348 Study 8243711 Post-Dose Findings: 30 mg/kg MEDI6348

- Day 1:
  - Three animals had reversible hypoactivity
- Day 8 (~15 minutes following end of infusion):
  - Animal I07476 was hypoactive, unresponsive, slow and ataxic when removed from cage, strong heartbeat but labored respiration, restless, ventrally recumbent, decreased body temperature (35.2 C) which recovered
    - Veterinarian classified the findings as a "transient allergic-type reaction"
- Day 22 (~15 minutes following end of infusion):
  - Animal I07476 was hypoactive, laterally recumbent, unresponsive, irregular/rapid respiration, pale mucous membranes
    - Veterinarian administered epinephrine and diphenhydramine and the animal became slightly more responsive but was still lethargic and ataxic
    - Animal euthanized due to moribund condition
    - Macroscopic observations consistent with those for moribund animals in Study 8231530

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MEDI6348-Related Adverse Findings Summary

- No-Observed-Adverse-Effect-Level (NOAEL) = 7.5 mg/kg
- Highest-Non-Severely-Toxic-Dose (HNSTD) = 15 mg/kg (animal which had reaction responded to treatment and recovered)
- MEDI6348 doses ≥ 7.5 mg/kg resulted in suppression of free IGF1R and soluble EGFR levels supporting that both arms of the bi-specific were active in cynomolgus monkey
  - There were no effects on serum glucose, insulin, or growth hormone levels or skin noted in MEDI6348 treated animals

Pathogenesis of Lung Lesions: Hypothesis Test Results

- Lesions in the lungs were relatively nonspecific but suggest circulatory shock, of the distributive type (hypovolemia due to vascular dilatation)

Hypothesis	Test	Results
Endotoxemia	Endotoxin levels	Level on SoT sufficiently low
MEDI6348 aggregation	Aggregation test with monkey plasma	Purity evaluated prior to dosing and within appropriate range
Direct endothelial damage	Pathology	No histopathology evidence
Pre-existing predisposing conditions (e.g. infections)	Pathology	No histopathology evidence
Immune Complex-mediated anaphylaxis	ADA Histamine levels, C3a levels	No ADA in AE animals
IgE-mediated anaphylaxis	ADA, histamine, total IgE	No clear changes at time of AE
Basophil activation and/or degranulation	Basophil activation test Histamine levels	MEDI6348 did not activate monkey or human basophils in vitro
Cytokine storm	Cytokine levels	No clear changes at time of AE
Complement activation	C3a levels	**Changes noted at 30 mg/kg**

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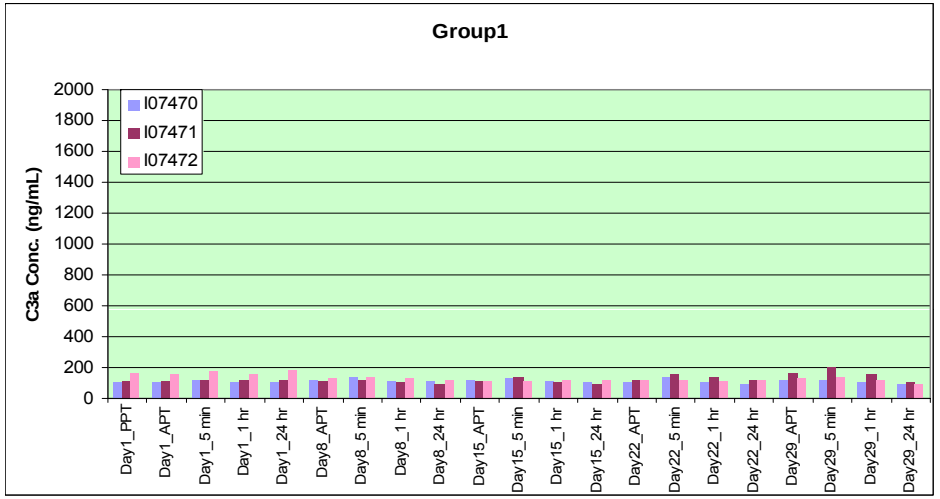
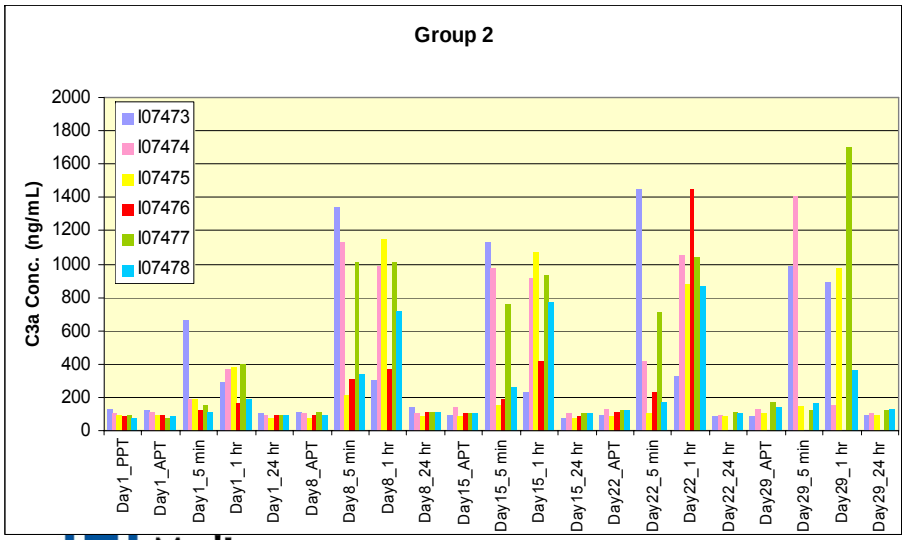
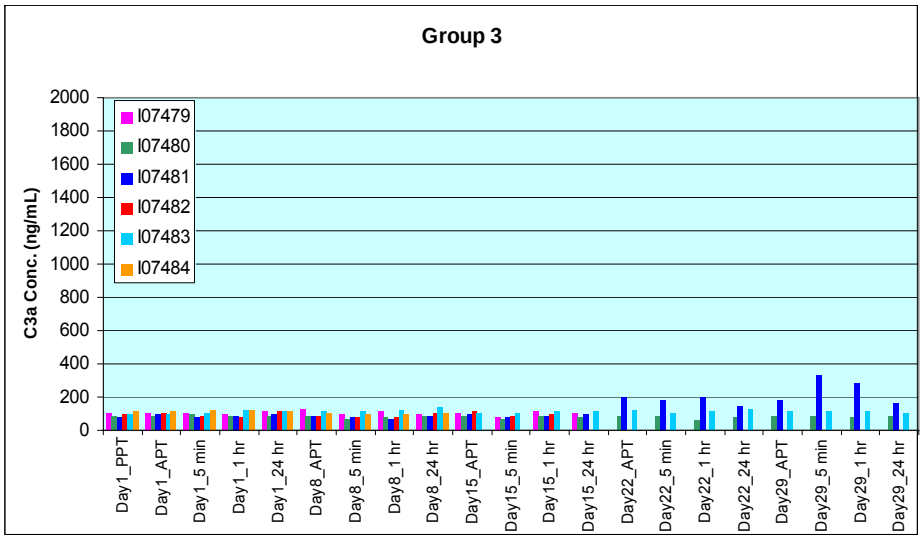
Summary of C3a Evaluation
MEDI6348 Cynomolgus Monkey Study 8243711 Study

C3a concentration in K2EDTA plasma with Futhan-175 was measured by BD ELISA kit. The LLOD is 31 ng/mL.

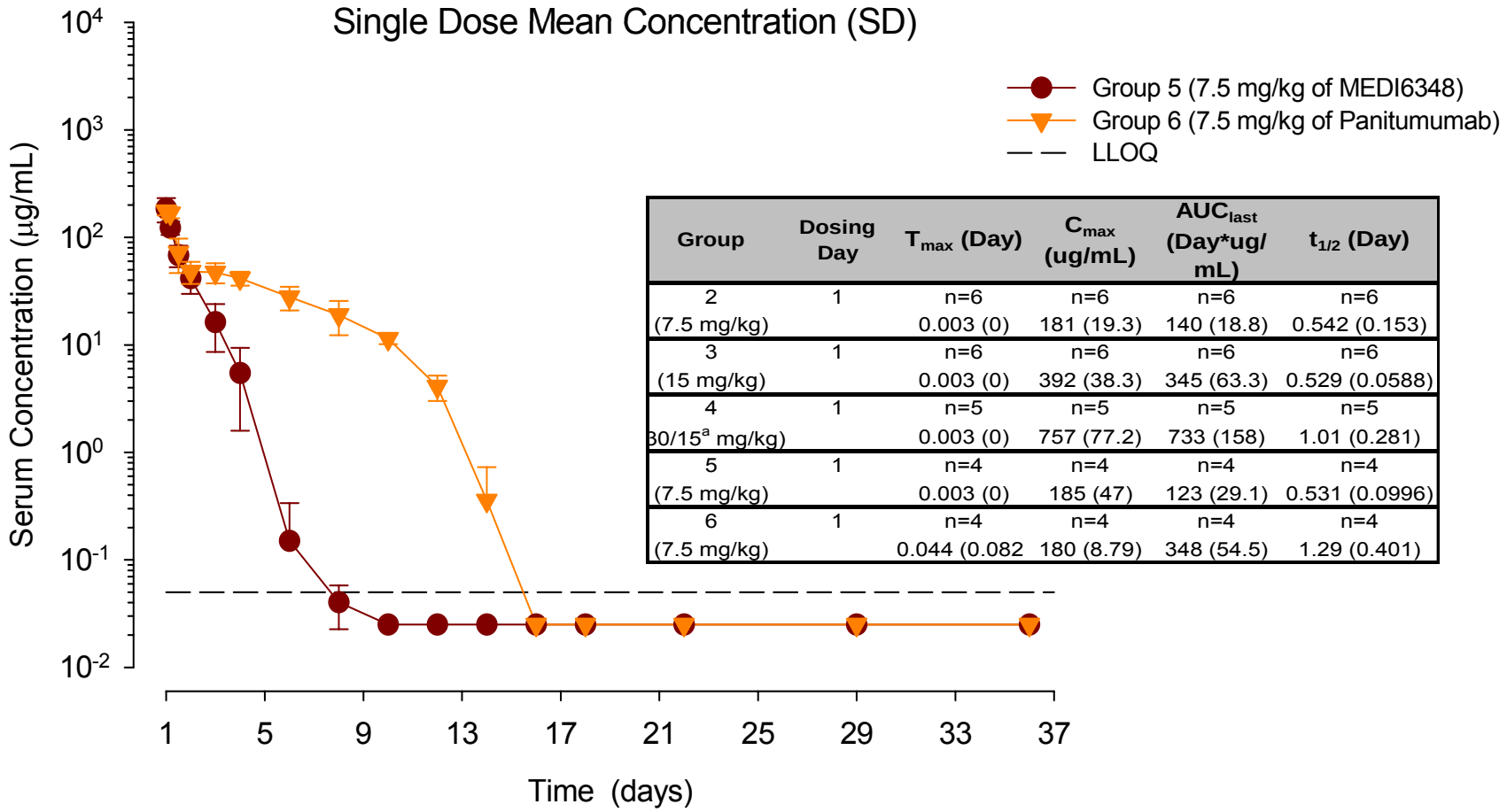
Drug induced C3a upregulation was detected from Group 2. There is no significant difference between animal I07476 and the other animals in the same group.







PK Properties of MEDI6348



Group	Dosing Day	T_{max} (Day)	C_{max} (ug/mL)	AUC_{last} (Day*ug/mL)	$t_{1/2}$ (Day)
2 (7.5 mg/kg)	1	n=6 0.003 (0)	n=6 181 (19.3)	n=6 140 (18.8)	n=6 0.542 (0.153)
3 (15 mg/kg)	1	n=6 0.003 (0)	n=6 392 (38.3)	n=6 345 (63.3)	n=6 0.529 (0.0588)
4 30/15[a] mg/kg)	1	n=5 0.003 (0)	n=5 757 (77.2)	n=5 733 (158)	n=5 1.01 (0.281)
5 (7.5 mg/kg)	1	n=4 0.003 (0)	n=4 185 (47)	n=4 123 (29.1)	n=4 0.531 (0.0996)
6 (7.5 mg/kg)	1	n=4 0.044 (0.082	n=4 180 (8.79)	n=4 348 (54.5)	n=4 1.29 (0.401)

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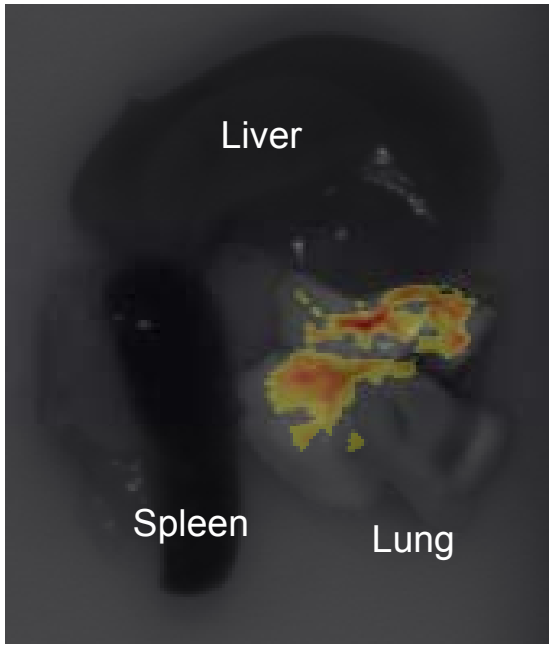
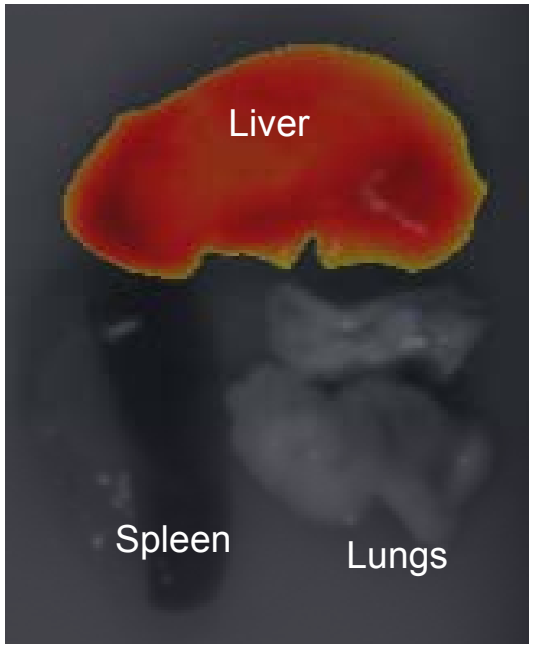
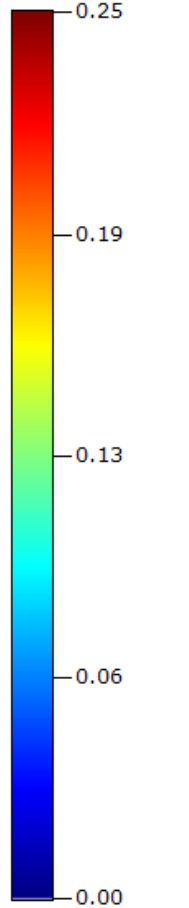
Biodistribution 24hrs post injection in Tumor Bearing Nude Mice

R347-AF-680



Medi6348-AF750





[Count/Energy]
24 hrs - 24hr
Group:6084-5

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ID# 6084

MEDI6348 PK and PD Summary

- Abnormal clearance was observed following single dose of MEDI6348
- Terminal half-life ranged from 0.5 to 1.3 day post first dose
- Faster clearance compared to panitumumab
- No evidence of saturating the target sink at 30 mg/kg dose level in monkey
- Dose-dependent suppression of both mIGF1R and sEGFR receptors in blood
  - 30 mg/kg of MEDI6348 maintain suppression of sEGFR for 7 days
  - 15 mg/kg of MEDI6348 maintain suppression of mIGF1R for 7 days
- No effects on fasted serum glucose/insulin levels and no rash observed following administration of 30 mg/kg MEDI6348 for 4 wks
  - Effects on glucose/insulin levels have been reported following administration of figitumumab (anti-IGF1R Mab) and rash was observed following administrations of 21 mg/kg panitumumab

Safety and PK Characteristics of EGFR-1 (E), IGF-1R (I) and MEDI-6348 (EI) mAbs

Panitumumab (EGFR-1R)	IGF-1R (Figitumumab)	MEDI6348
• Diarrhea, skin lesions (erythema, ulceration, necrosis)), electrolyte imbalance, myocardial degeneration, lymphoid organs atrophy, mucosal hyperplasia	•Hyperglycemia, anorexia, hyperuricemia, increased LFTs •Hematological toxicities, including cytopenias	•No skin toxicities, no hyperglycemia or hematological toxicities •Anaphylactoid reactions leading to mortality/moribundity •Pulmonary pathology secondary to infusion-type anaphylactic shock
•Half life of 3-6 days EMEA, 2007	•Half-life of > 6 days	•Half life of ≤ 1 day

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Conclusions

- Novel bispecific mAbs offer a great promise in maximizing the potential of combination biologics/targets through a single mAb.
- Smart engineering approaches are needed to optimize valency, potency, avidity and half-life of bispecific IgG like mAbs to attain the best efficacy of combination biologics therapies.
- To minimize toxicity (potentiation, additive or synergistic) resulting from the simultaneous hit of two targets or redirected effector cells, targets with overlapping toxicities should be avoided or affinities/potencies should be reengineered to minimize low dose toxicities.
- On and off-target toxicities and PK-PD resulting from the modulation of two targets should be carefully evaluated very early in drug development.

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