Risk Assessment of Novel Biopharmaceutical Platforms

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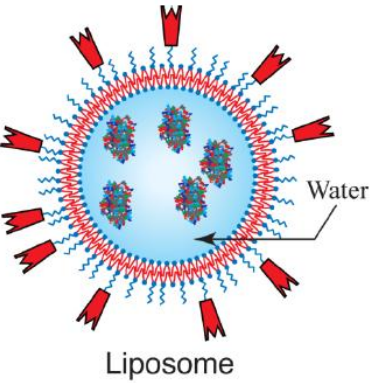
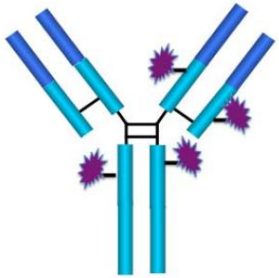
Types of Novel Biopharmaceutical Platforms

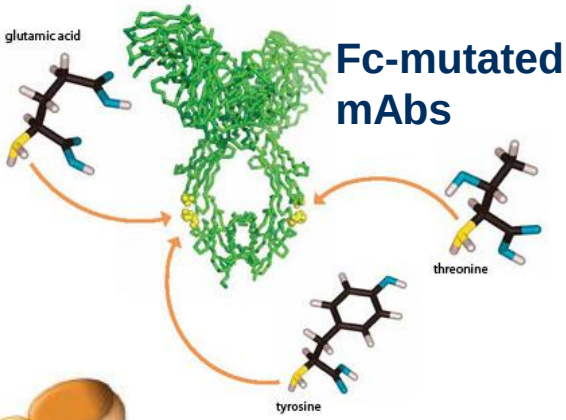
Targeted nanoparticles



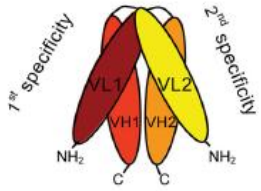


Antibody Drug Conjugates

Fc-mutated mAbs



Bispecifics



ICHS6(R1) Preclinical Safety Evaluation of Biotech-Derived Pharmaceuticals

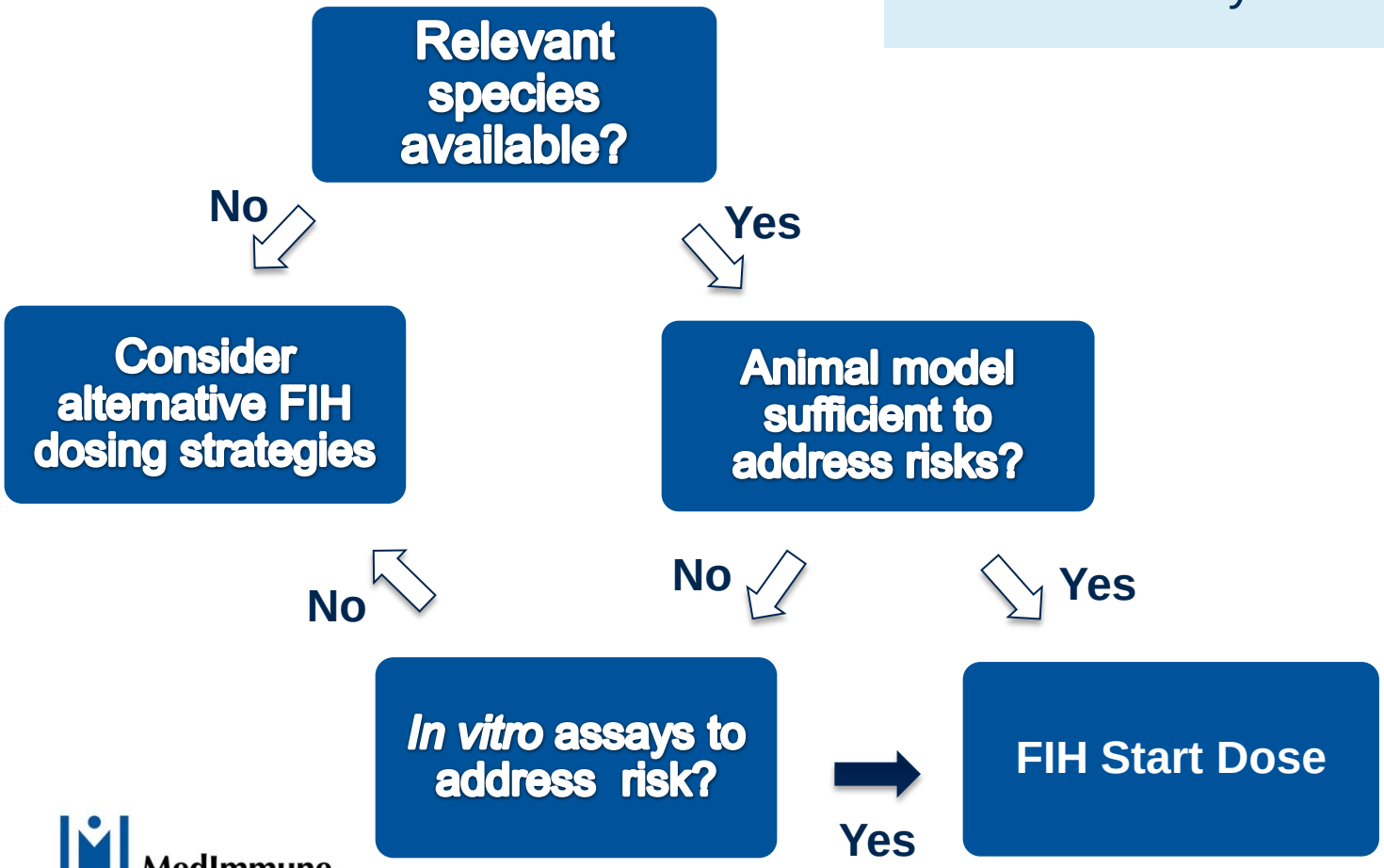
- Allows flexible approach that can be adapted as needed for new biopharmaceutical platforms
- General principles can be applied to new technologies; however, individualized approach required based on unique properties of each platform
- Often involves use of safety methods that have not yet been standardized; will continue to evolve with scientific advances

(Solaro, 2010; Trail, 2013; Chames, 2011; Brien, 2013)

General Principles for Safety Assessment of Novel Biopharmaceuticals

Scientific Case-by-Case Approach

- Building confidence that the safety data provides a reasonable assessment of the potential human safety risks



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Bispecific Formats

Engineered proteins composed of fragments of two different monoclonal antibodies

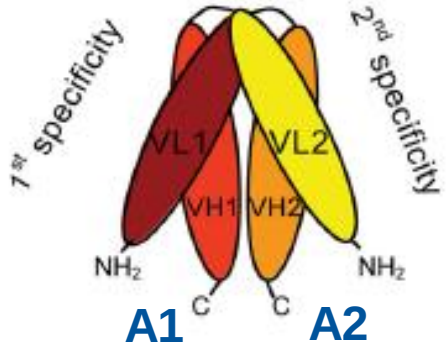
Unique Properties to be Considered

- Binds to two different antigens
- Cytokine release
- Immunogenicity
- Half-life

Bispecific monoclonal antibody

Diabody

BiTE® Molecules



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(Chames, 2011; Brien, 2013)

Case Example – MEDI-565 (AMG 211)

Bi-specific T-cell engager (BiTE®*)

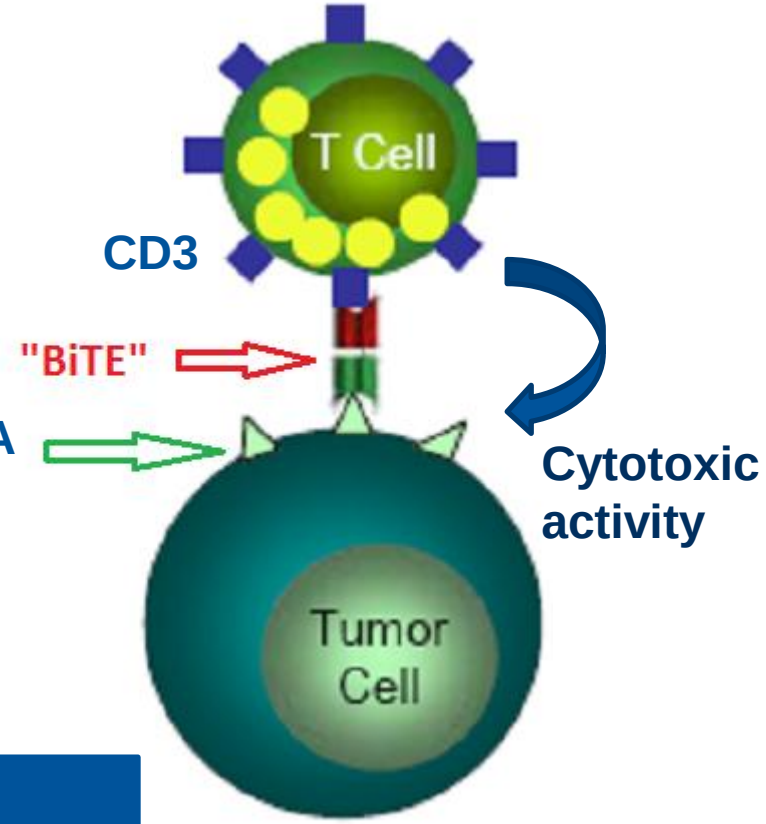
Fusion protein consisting of two scFvs

Antigen 1 – CEA (carcinoembryonic antigen)

- Highly expressed on multiple solid tumors
- Apical expression on normal tissues

Antigen 2 – CD3

- Engagement with CD3 on T cells results in activation of cytotoxic T cell response involving release of proteins such as perforin and granzyme



http://updates.clltopics.org/3528-taking-a-bite-out-of-b-cell-cancers

Unique Aspects to be Considered:

- **MEDI0565 does not cross-react with CD3 in cyno monkeys or other standard tox species**
- **Potential for cytokine release**

*BiTE® is a registered trademark of Amgen.

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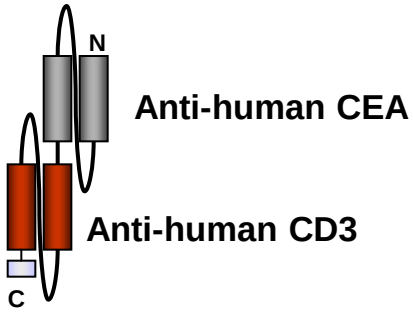
Case example courtesy of Patty Ryan

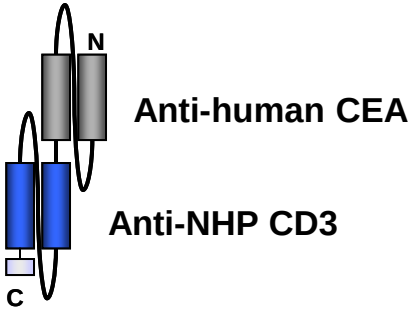
Lack of Relevant Species for Safety Testing

MEDI-565



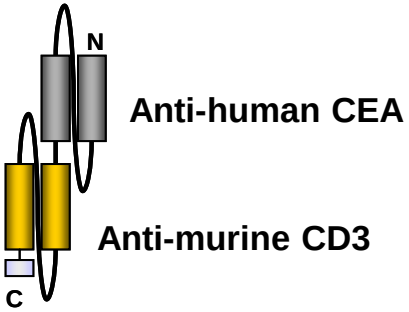
- MEDI-565 does not bind CD3 in standard tox species (i.e. monkeys or rodents)
- Binds human and chimpanzee CD3 similarly
- Chimpanzee is not a suitable tox model
- No non-specific T cell activation observed

Cyno Surrogate (cyS111)



- CyS111 binds cyno CD3 and human CEA
- CEA expression similar in cyno and human
- In vitro potency lower than MEDI-565 human
- Non-specific T cell activation observed in vitro
  - 10-fold greater binding affinity to CD3

Mouse Surrogate (hyS111)



- HyS111 binds murine CD3 and human CEA
- CEA expression similar in huCEA Tg mouse and human
- In vitro potency greater than MEDI-565
- Non-specific T cell activation observed in vitro and in vivo
  - 100-fold greater binding affinity to CD3

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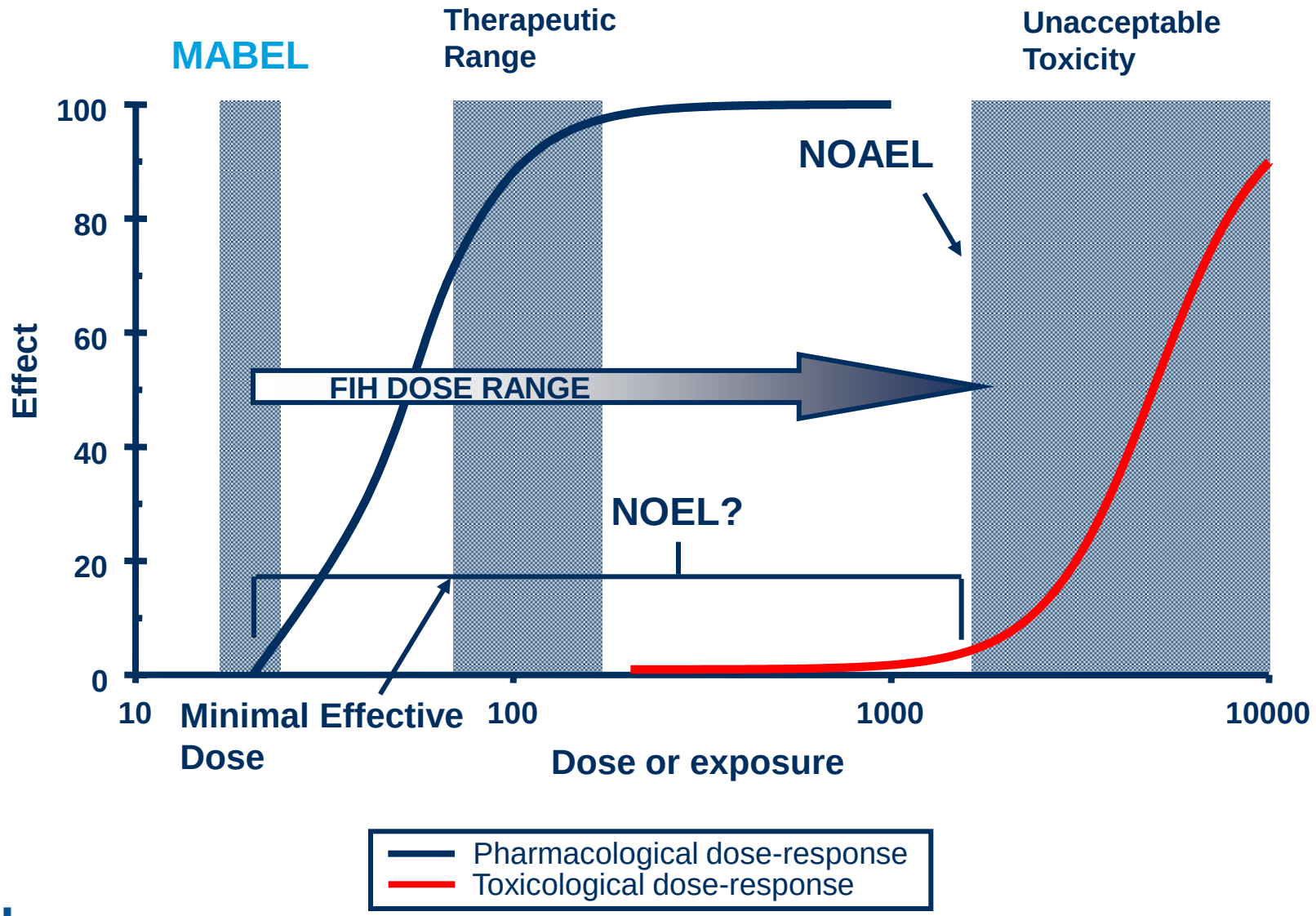
Use of Minimum Anticipated Biological Effect Level



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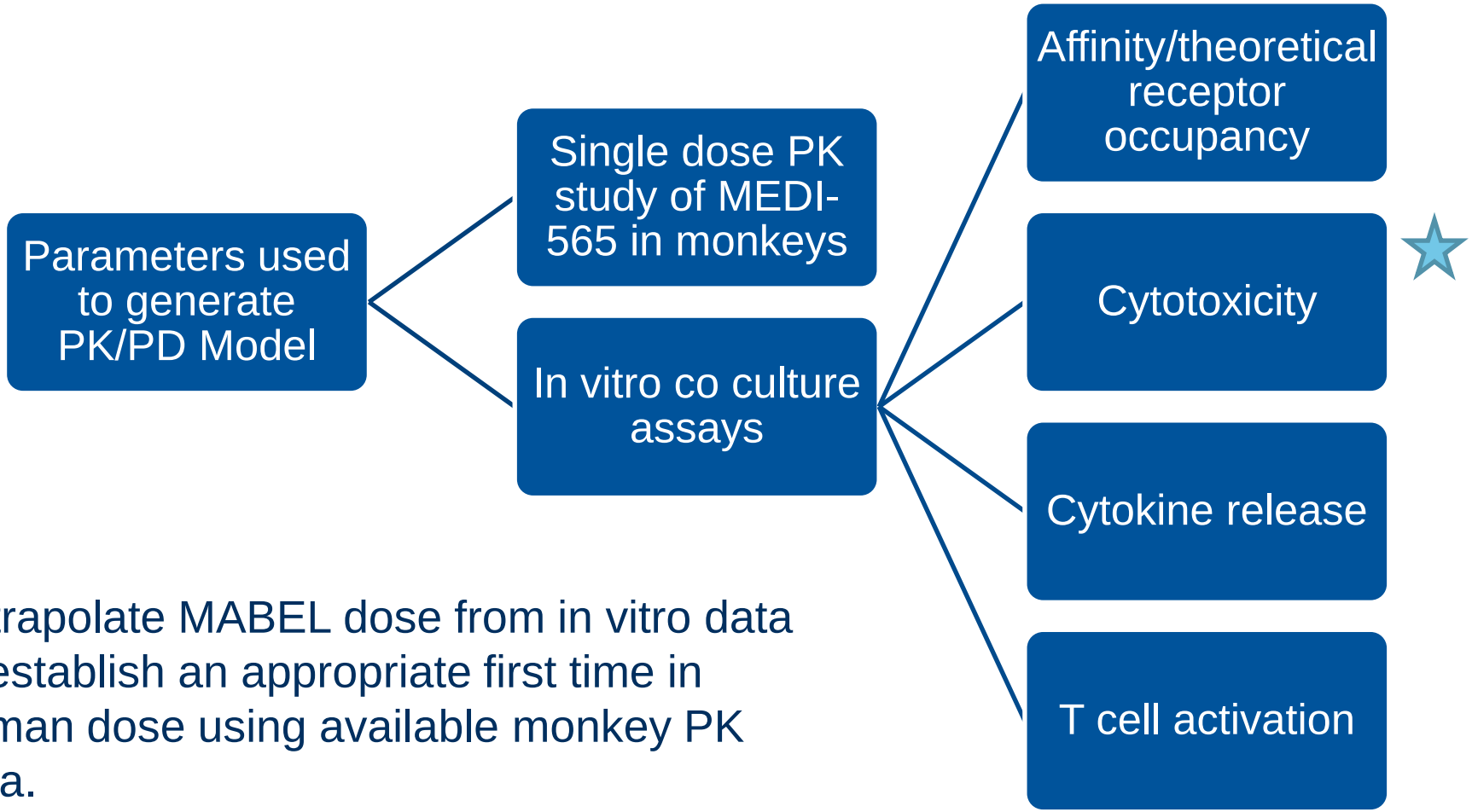
Determination of the MABEL



Extrapolate MABEL dose from in vitro data to establish an appropriate first time in human dose using available monkey PK data.

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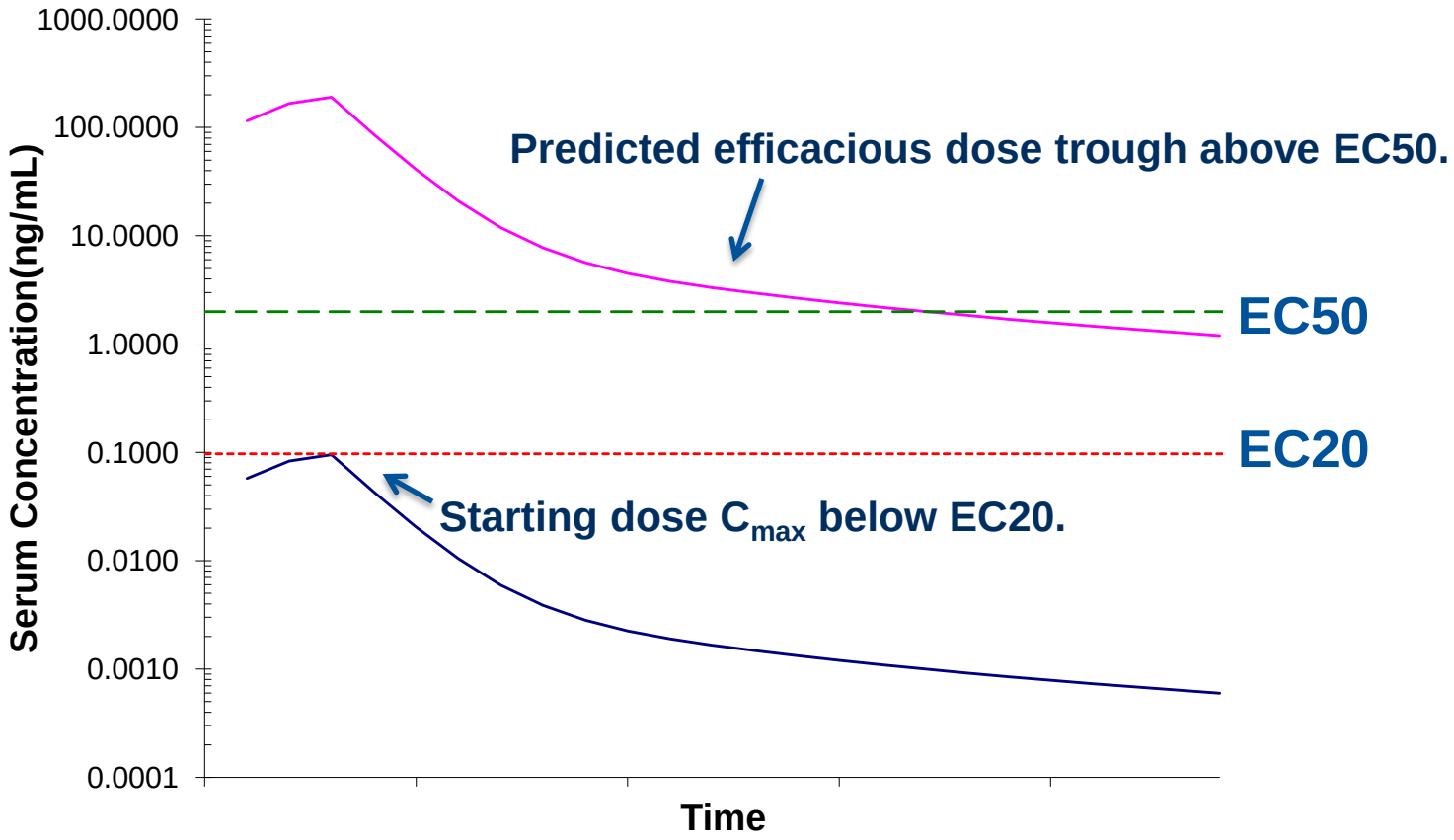
★ Most sensitive measure of pharmacological activity

Modeling for FIH Phase I Dose

- Phase I dose regimen projected based on simulated C-t profiles and in vitro MABEL



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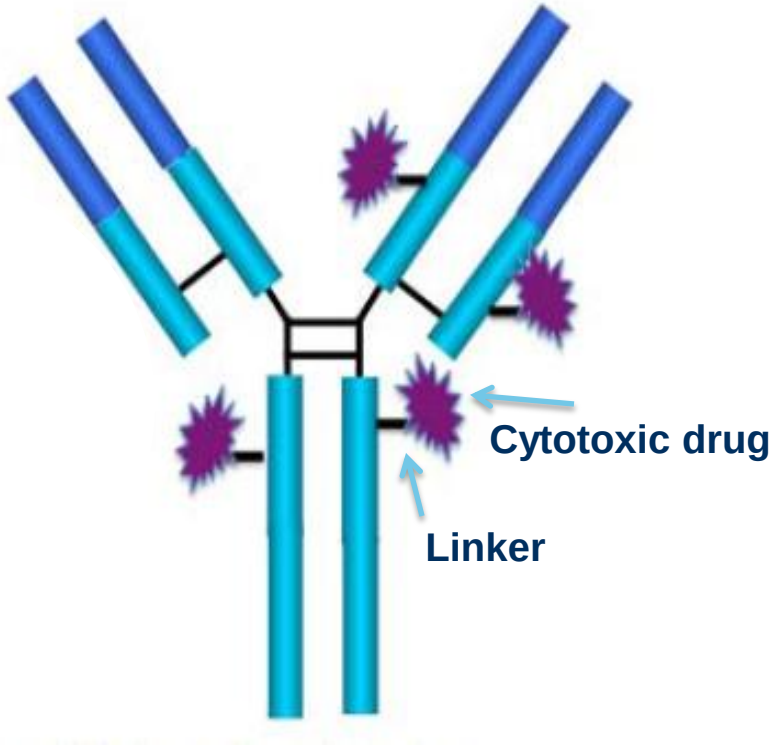
Antibody Drug Conjugates

Antibodies linked via a stable chemical linker to a highly potent cytotoxic small molecule



Unique Properties to be Considered

- Relevant species
  - On/off target toxicities
- Need to assess safety of small molecule as well as conjugate
  - Apply principles of ICHS6(R1) and ICHS9

Reference on Nonclinical Safety Testing of ADCs

Roberts et al. 2013. Considerations for the nonclinical safety evaluation of ADCs for oncology. *Regul. Toxicol. Pharmacol.*

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Mechanisms of ADC-Mediated Toxicity

	Mechanism(s)	Safety Assessment
On Target	Binding/internalization of ADC in target-expressing normal cells	In vivo toxicity must be evaluated in crossreactive species Requires understanding of normal tissue target expression
Off Target	Instability of conjugate	Off-target toxicity can be evaluated in non crossreactive species
	Nonspecific uptake into normal cells (*i.e.* Fcγ receptors, FcRn binding, pinocytosis, etc.)	
	Nonspecific binding of antibody to normal cells	

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ADC Clinical Toxicities are Mixture of 'On/Off' Target

Drug	Target	Toxin	Normal Tissue Expression	Dose-Limiting Toxicities
AGS-16M8F	ENPP3	MMAF	GI tract (glandular cells), lung (respiratory epithelial cells), kidney tubules	Thrombocytopenia
ASG-5ME	SLC44A4	MMAE	Apical expression in polarized cells in kidney and GI tract	Neutropenia; GI toxicity; Neuropathy
AVE9633	CD33	DM4	Hematopoietic cells in BM, lymphocytes, GI tract (epithelial and glandular)	Hepatotoxicity
BT-062	CD138	DM4	B cells, epithelial cells in GI tract, liver, skin, kidney, pancreas, and prostate	Hand/foot syndrome; mucositis
CDX-011	GPNMB	MMAE	Melanocytes, osteoblasts, retinal epithelial cells	Rash (hand/foot and TEN); neutropenia; peripheral neuropathy
CMC544	CD22	Calicheamicin	B cells	Thrombocytopenia, lymphopenia, neutropenia
DCDT2980S	CD22	MMAE	B cells, GI tract (glandular cells)	Neutropenia; sensory neuropathy
IMGN242	CanAg	DM4	Mutated MUC1 on tumor cells	Ocular toxicity
IMGN388	αv integrin	DM4	GI tract (epithelial cells), bile duct, melanocytes, kidney tubules/glomeruli	GI toxicity, headache, confusion
IMGN901	CD56	DM1	Peripheral nerves, neurons (cerebellum), lung (epithelial cells), glandular cells in GI, thyroid, and adrenal	Peripheral neuropathy
PSMA ADC	PSMA	MMAE	Kidney (proximal tubules) and prostate	Neutropenia
SAR3419	CD19	DM4	B cells	Ocular toxicity
SB-408075	CanAg	DM1	Mutated form of MUC1 on tumor	Elevated liver enzymes, fatigue, neutropenia; thrombocytopenia; peripheral neuropathy
SGN-35	CD30	MMAE	Activated lymphocytes	Neutropenia; thrombocytopenia; elevated liver enzymes
SGN-75	CD70	MMAF	B cells and some T cells	Neutropenia
T-DM1	HER2	DM1	Cardiac myocytes, epithelial cells in GI tract, lung, skin, and breast	Thrombocytopenia, elevated liver enzymes

Both ‘On’ and ‘Off’ Target Effects are Related to Known Toxicities of Cytotoxic Agents

Dose Limiting Toxicity	Number of ADCs (%)	Toxin				
		MMAF	MMAE	Calich	DM1	DM4
Neutropenia	8 (50%)	√	√	√	√	
Thrombocytopenia	5 (31%)	√	√	√	√	
Peripheral neuropathy	5 (31%)		√		√	
Elevated liver enzymes	4 (25%)		√		√	√
Grade 3/4 skin rash - **Mucositis, hand/foot, TEN**	2 (12%)		√	√		
Ocular toxicity	2 (12%)					√
Grade 3/4 GI toxicity	2 (12%)		√			√
Generalized symptoms - **Headache, confusion, fatigue**	2 (12%)				√	√
Lymphopenia	1 (6%)			√		

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Unique characteristics of ADCs

	ADCs	Warhead	Antibodies
Half-life	Intermediate half-life (4-6 days)	Rapid half-life (hours)	Prolonged half-life (20-21 days)
Clearance	Catabolism/target-mediated clearance of mAb Hepatic and/or renal elimination of warhead	Hepatic and/or renal elimination	Catabolism/target-mediated clearance
Biodistribution	Plasma volume	Variable	Plasma volume
Dosing schedule	Intermittent	Intermittent	Maintain steady state
Target interaction	High affinity; rapid internalization	N/A	High affinity; blocking or agonist activity

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Hybrid Approach to Safety Assessment

Studies to evaluate ADC

- **For IND submission**
  - Tissue cross reactivity (TCR) studies
  - GLP toxicology study in relevant species*
  - Stability in relevant species and human plasma
- **For BLA submission**
  - GLP chronic (3-month) repeat dose toxicology study in relevant species
  - Embryofetal development in relevant species**

Studies to evaluate warhead

- **For IND submission**
  - NonGLP Single dose rat toxicology study
- **For BLA submission**
  - Genotoxicity

*Local tolerance and safety pharmacology endpoints included in repeat dose toxicology studies as per ICHS6(R1) and ICHS9

**If warhead is a cytotoxic agent that targets rapidly dividing cells, it is possible to use literature data to inform the risk of reproductive toxicology

Summary

- Novel biopharmaceutical platforms require an individualized approach to nonclinical safety testing based on unique characteristics of each platform
- If relevant species available:
  - Consider use of animal toxicology data to set FIH start dose if animal model provides adequate assessment of potential toxicities in humans
  - Might also involve use of nonstandardized *in vitro* methods (*e.g*. cytokine release) to fully evaluate risk
- If no relevant species available:
  - Consider use of alternative strategies to set FIH start dose (*e.g*. MABEL)

Acknowledgements

- Rakesh Dixit
- Patty Ryan
- MEDI-565 team
- ADC Safety Group
- Amgen collaborators

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