Early Phase Development Considerations of Antibody-Payload Conjugates

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Presentation Overview

- GBI history and capabilities
- Requirements for a successful biologics drugs design and manufacturing
- Case studies:
  - Antibody-drug conjugate – Client A
  - Radioimmunoconjugate – Client B
- Conclusion

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History

- Spun-off from the Goodwin Institute of Cancer Research in 1992
- A quarter century of experience and expertise in the Contract Development and Manufacturing of Biologics; the earliest fully integrated CDMO globally from early phase development to late stage clinical trials
- Over 400 projects with more than 150 clients
- Acquired by Wallace Pharmaceuticals, India (Wallace Group of Pharma Companies) in December, 2004

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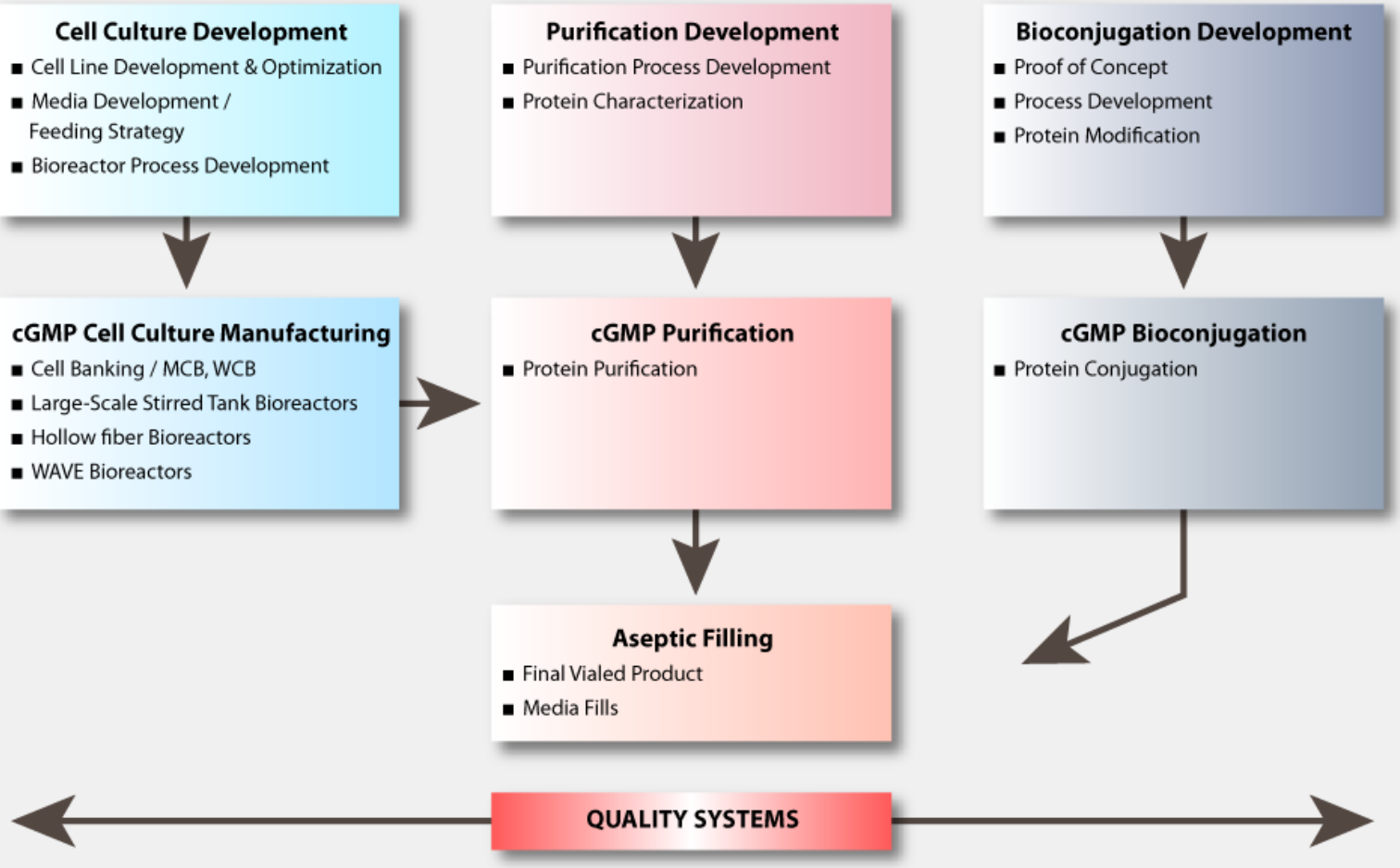
Technology Focus



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Considerations for a Successful ADC – From a CDMO Perspective

- Design Considerations
  - Anatomy/components of an ADC – mAb, linker & payload
  - Target
  - Potency
  - Mechanism of action
  - PK/PD
  - In vivo stability
- Manufacturing strategy
  - Screening, optimization, scale-up and conformance runs
  - Product quality/compliance – free payloads, solvents
  - Stability – storage buffer, temperature and excipients
  - Process economics – cost of goods

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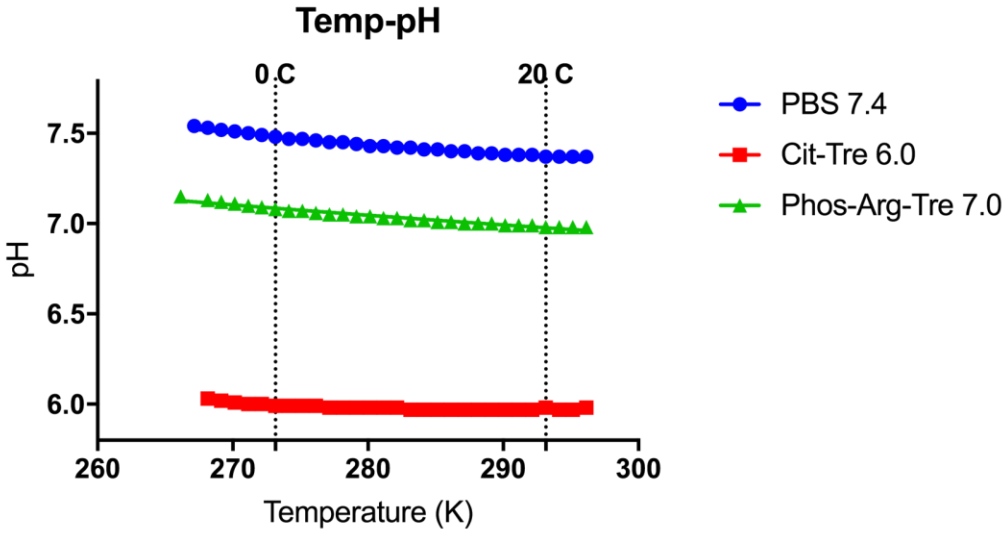
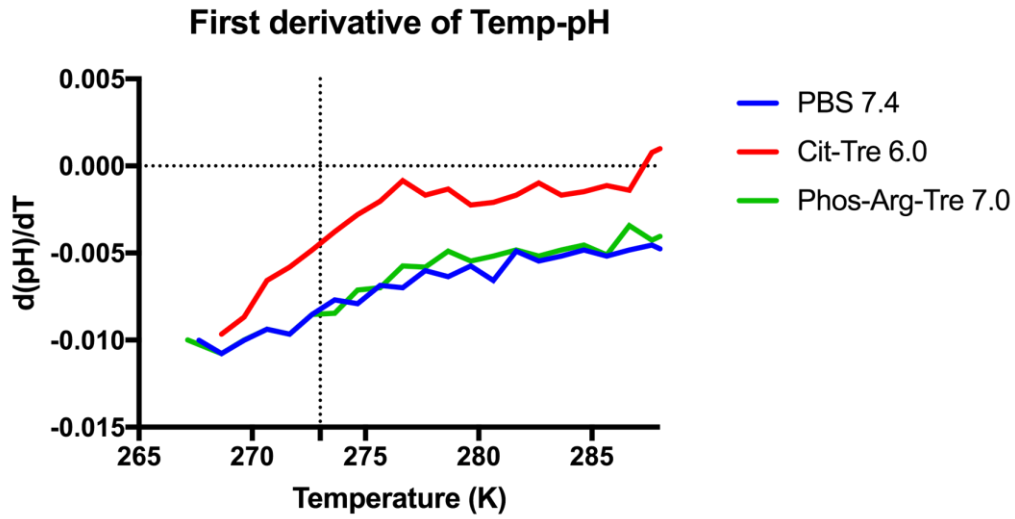
Formulation Considerations





Phos: Phosphate
Cit: Citrate
Tre: Trehalose
Arg: Arginine

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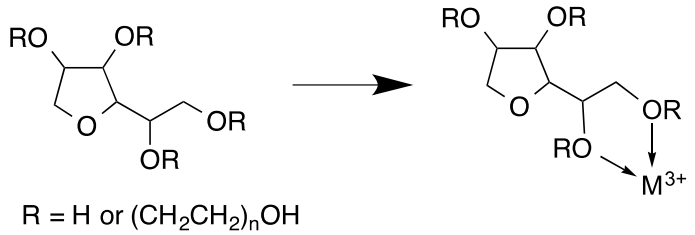
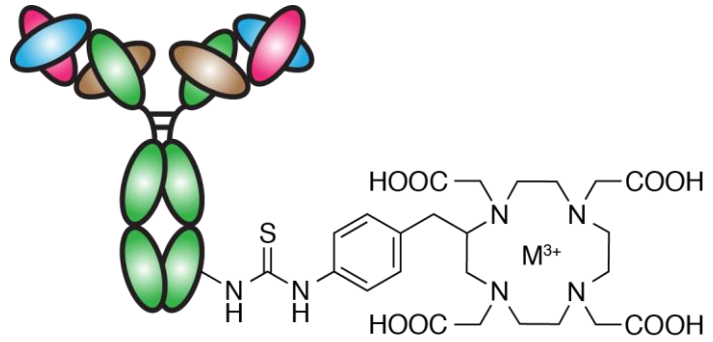
Miscellaneous Considerations

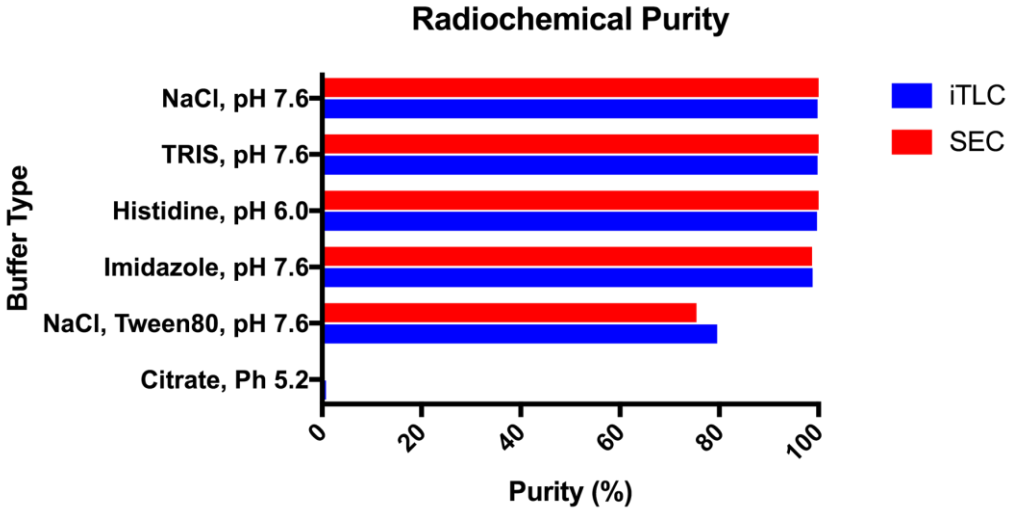
- DOTA-based metal coordination
  - M^{3+} = Lu^{3+}, In^{3+}, Ga^{3+}, Y^{3+}
- Inhibition of DOTA:M^{3+} coordination
  - Citrate: Strong chelator
  - Imidazole/histidine: Weak chelator
  - Polysorbate interference



R = H or $(CH_2CH_2)_nOH$



mAb-DOTA:M^{3+}



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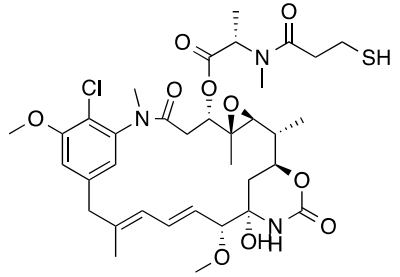
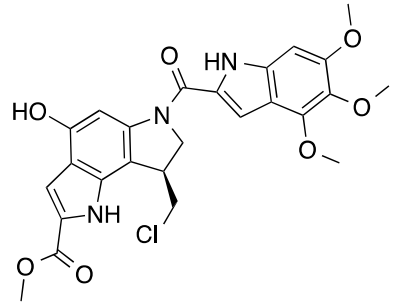
Anti-HAAH ADC – Client A

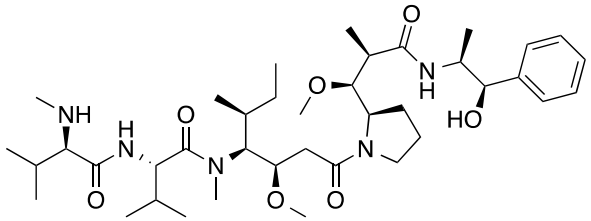
Name	Payload Type
DM1	Maytansine
MMAE	Monomethyl auristatin E
DUO	Duocarmycin SA



Maytansine



Duocarmycin SA



Monomethyl auristatin E

- PAN-622: Anti-HAAH mAb
- HAAH: Human aspartyl (asparaginyl) β-hydroxylase

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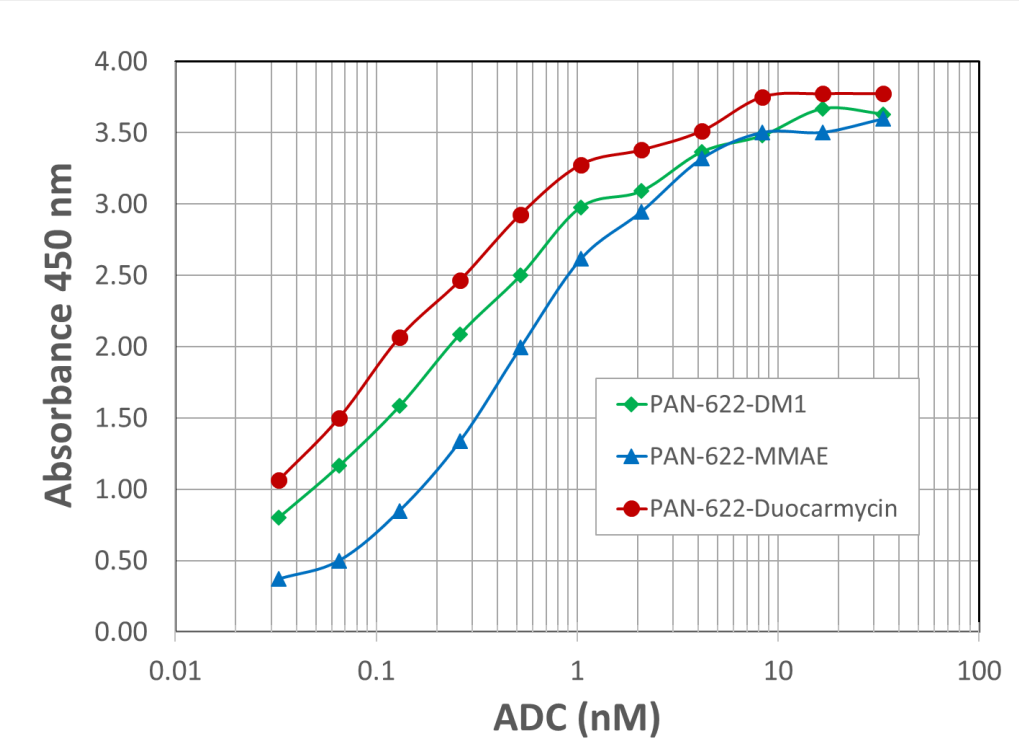
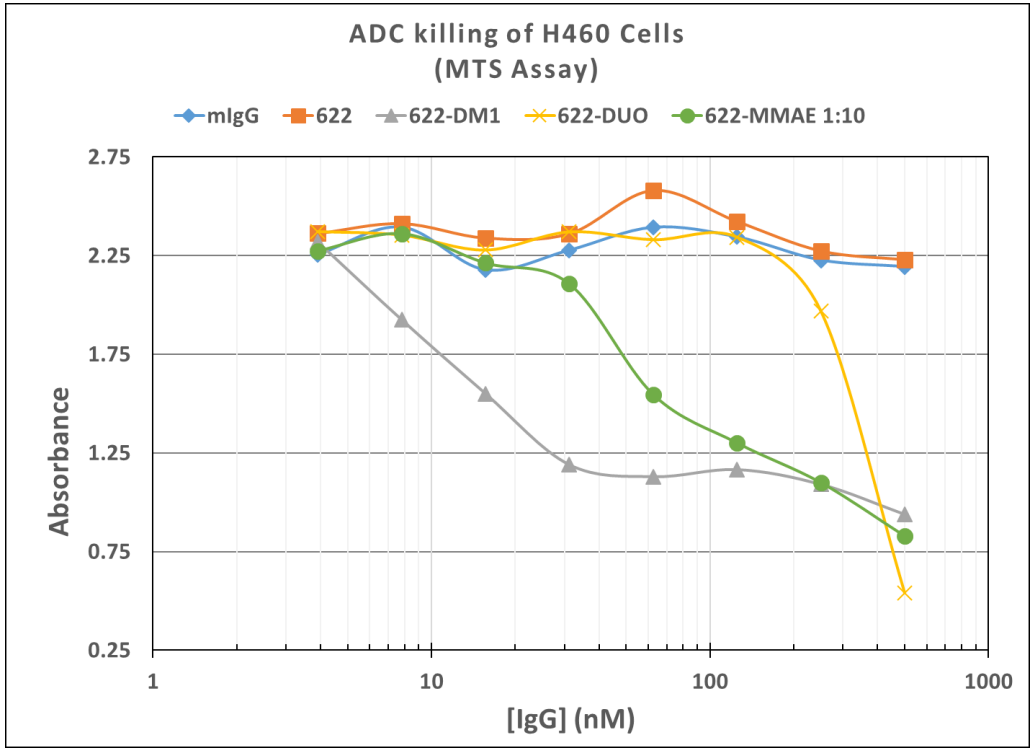
Potency Screening – Client A





K Malhotra, et al, AACR-NCI-EORTC Molecular Targets and Cancer Therapeutics, October, 2017

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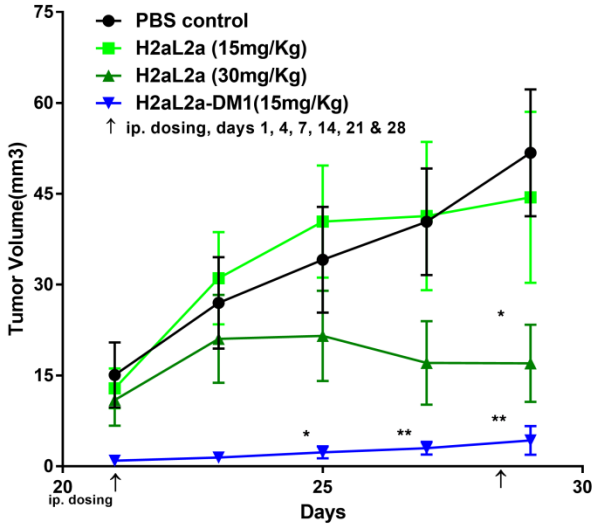
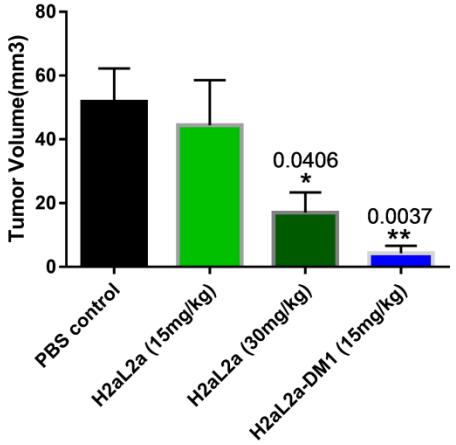
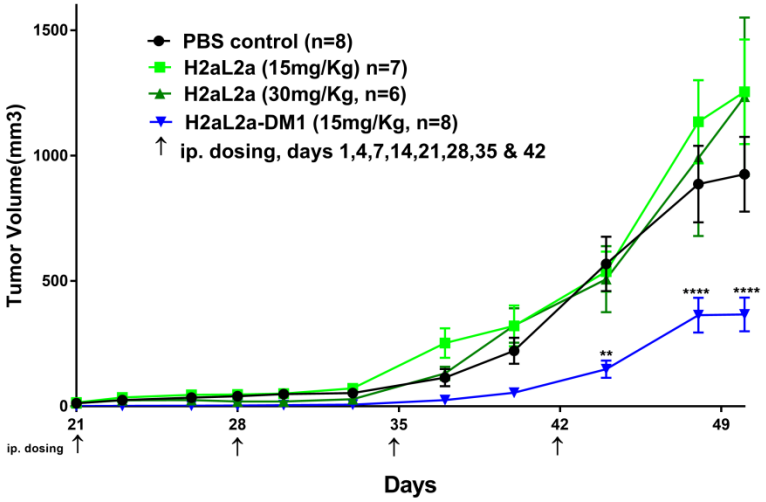
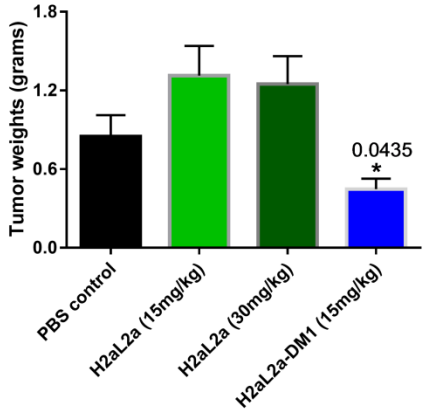
Proof-of-Concept In Vivo Study – Client B









* Unpaired t test of PBS Versus hJAA-F11-DM1

Target:
Thomsen-Friedenreich Antigen (TF-Ag)

Cell line:
MDA-MB 231 (TNBC)

H2aL2a-DM1
Dosing:
24h PTI
15 mg/kg I.P.
Q.Wk.

Tati et al, *Neoplasia*, 2017 Sep;19(9):716-733

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Conclusions

- CDMO considerations
  - Goodwin is highly experienced in developing strategies for the manufacture of ADCs for clinical trials.
- Formulation considerations
  - Buffer components and excipients compatibility with metal-chelation chemistry
- Pre-clinical evaluation
  - Anti-TF-Ag ADC has considerable antitumor effect on proof-of-concept animal models.

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Thank You

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