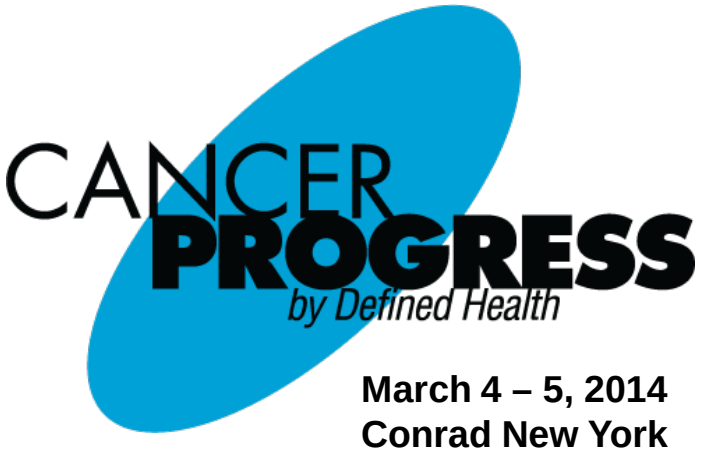
Antibody-Drug Conjugates: Supercharging the Blockbuster Antibody Class



March 4 – 5, 2014
Conrad New York

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Moderator:

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Panelists:

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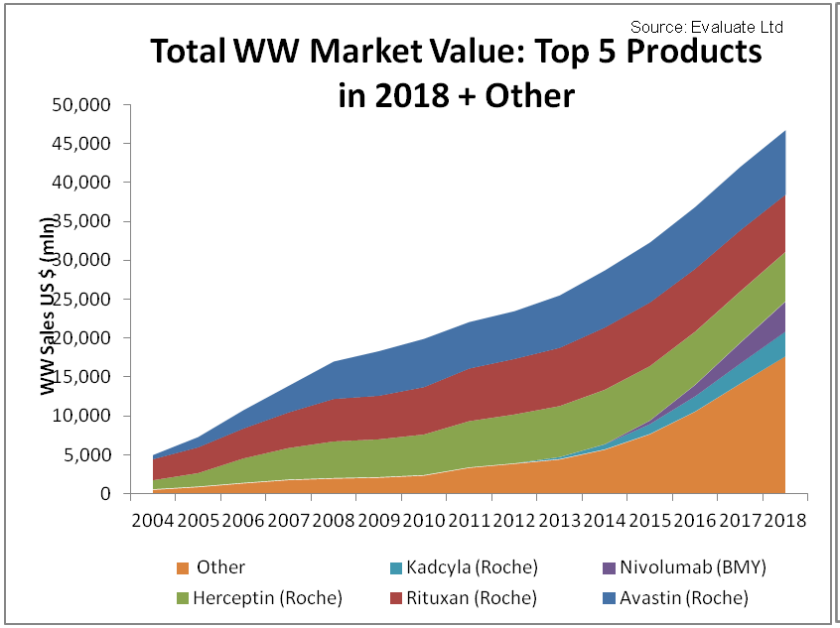
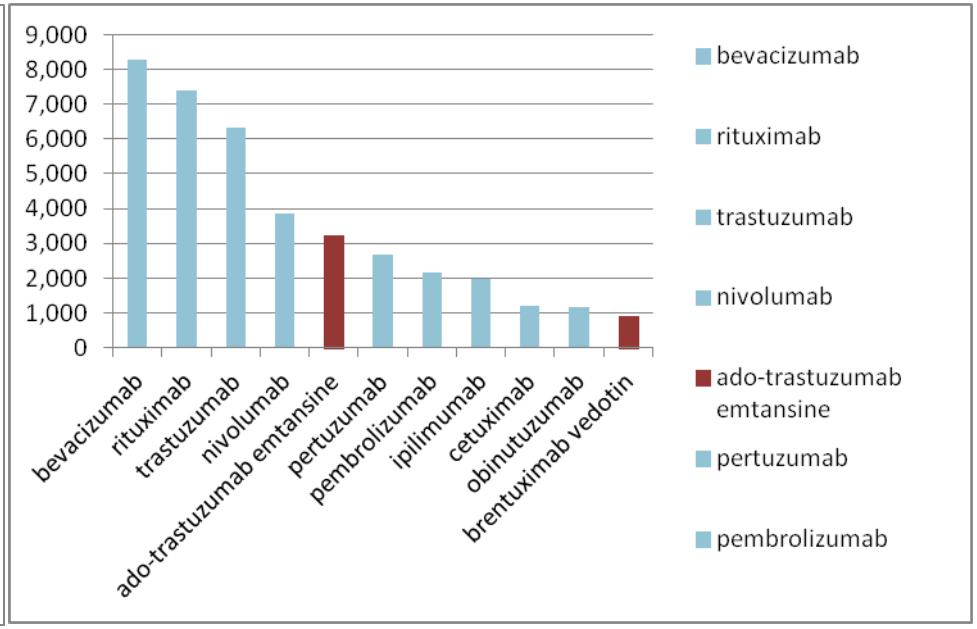
Antibody & ADC Market (to 2018)

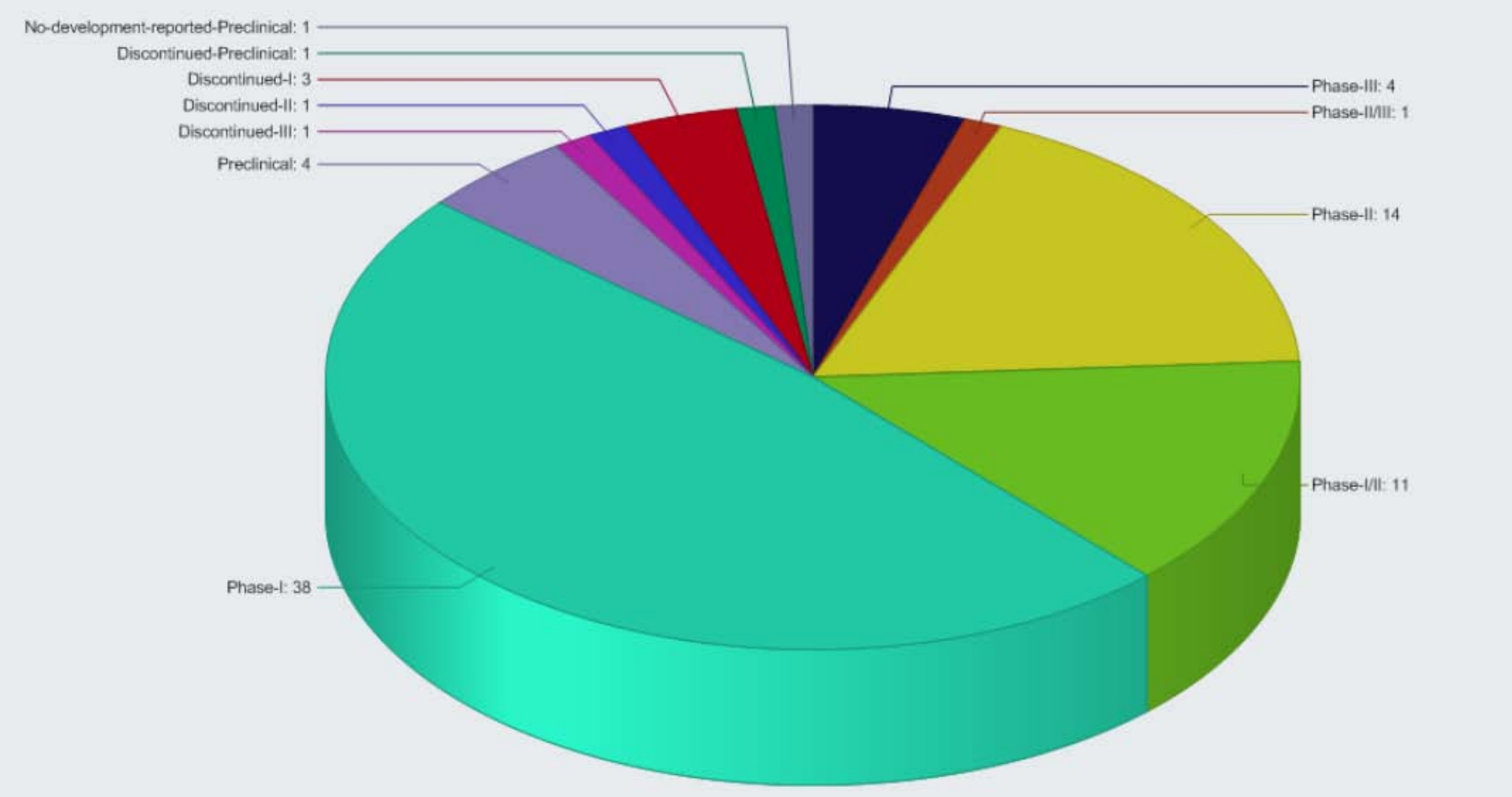




Source: EvaluatePharma, Defined Health

ADC Pipeline (WW)

Approximately Fifty drug conjugated, four radiolabeled, one toxin-labeled….



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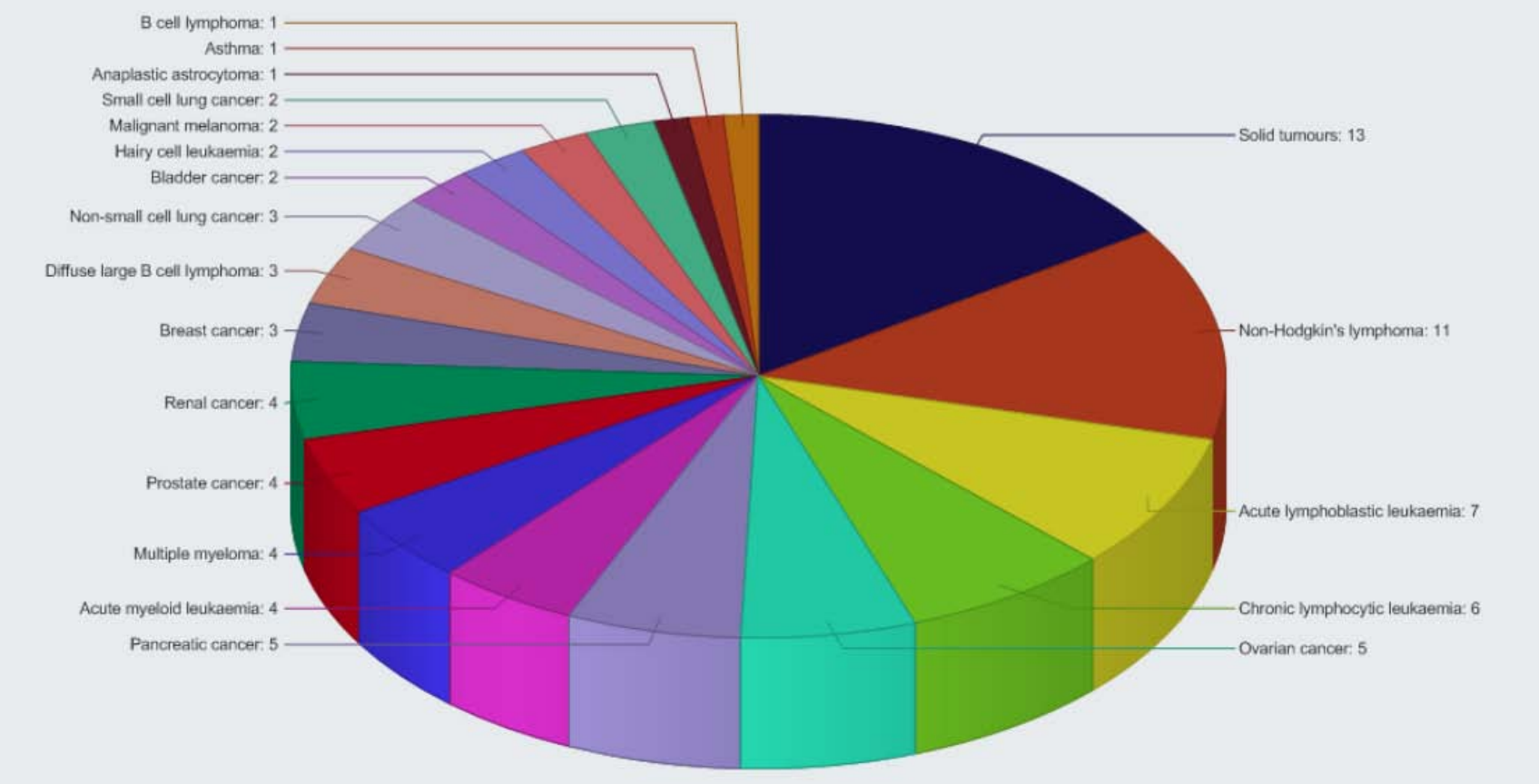

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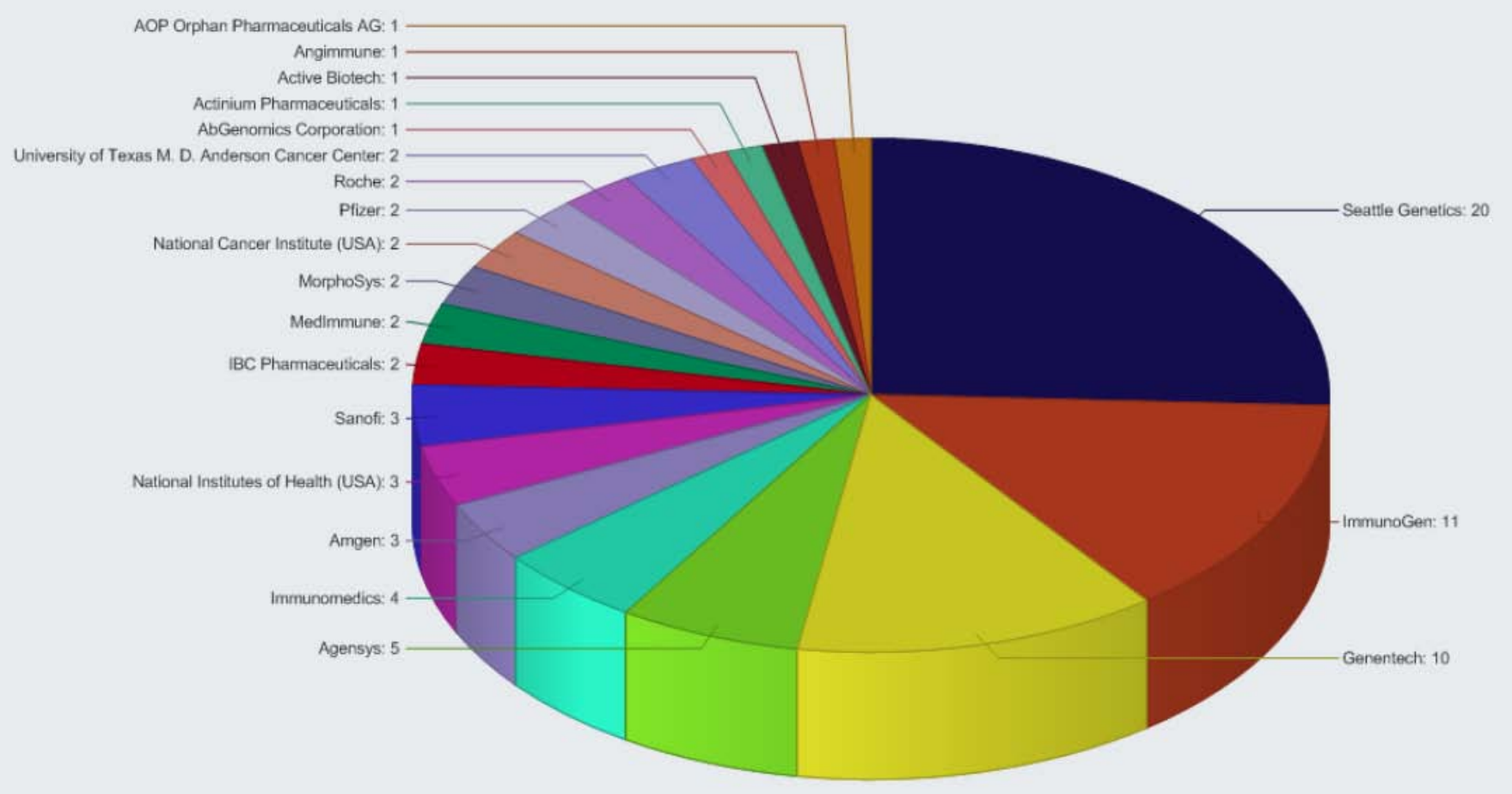

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Early Challenges

Early ADC programs suffered from several limitations:

- **Linker instability:** Early linkers were either too stable, resulting in low potency and reduced efficacy, or too unstable, resulting in poor targeting and high systemic toxicity[4]
- **Cytotoxics without sufficient potency:** Circulating serum concentrations of the ADC were not in the necessary therapeutic range
- **Inefficient internalization:** Not all antibodies were efficiently internalized, and the number of ADC molecules delivered to the target tumors was low
- **Limited expression of the target antigen:** Failure to choose an appropriate target antigen that was sufficiently over-expressed on the target cell surface led to low concentrations of the ADC inside the tumor cell
- **Immunogenicity of monoclonal antibodies:** Early conjugates employed murine or murine/chimeric (partly human) monoclonal antibodies that resulted in an immune response and the generation of human anti-murine antibodies (HAMA), preventing further treatment

Panel Topics

- What have we learned in the clinic, how can we assess early?
- How to pick a target, is expression enough, what level, and asked whether the successes and failures of programs can be attributed to the target?
  - Why antigen numbers in thousands to be effective, when CARTs need much lower antigen number?
- How to assess clinically, with maytansinoids and auristatins we know doses, but how do these doses preclinically in models translate into humans?
- How to widen the therapeutic window and is higher MTD enough?
  - Moving beyond MTD nd DLT - the off-target effects are dose-limiting, bone marrow tox, how to reduce on-target tox outside of the tumor?
- How to make ADC better including
  - sites of attachment, multiple
  - different antigen targets not just one
  - more homogenous product
- What else can we conjugate besides small molecule cytotoxics
- What else can we conjugate beside conventional antibodies and what are the effects?
- Combinability with other agents/regimens

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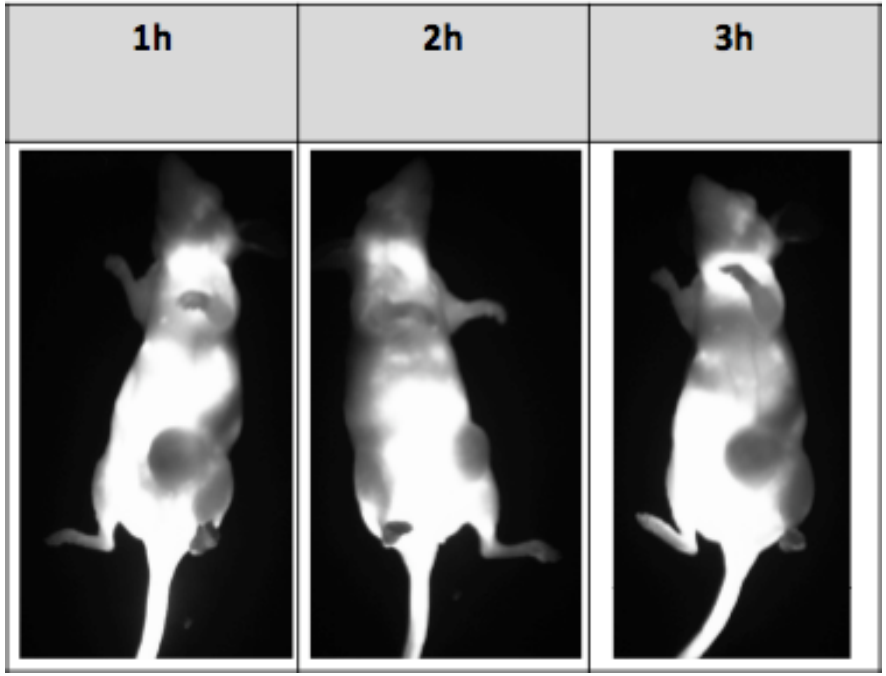
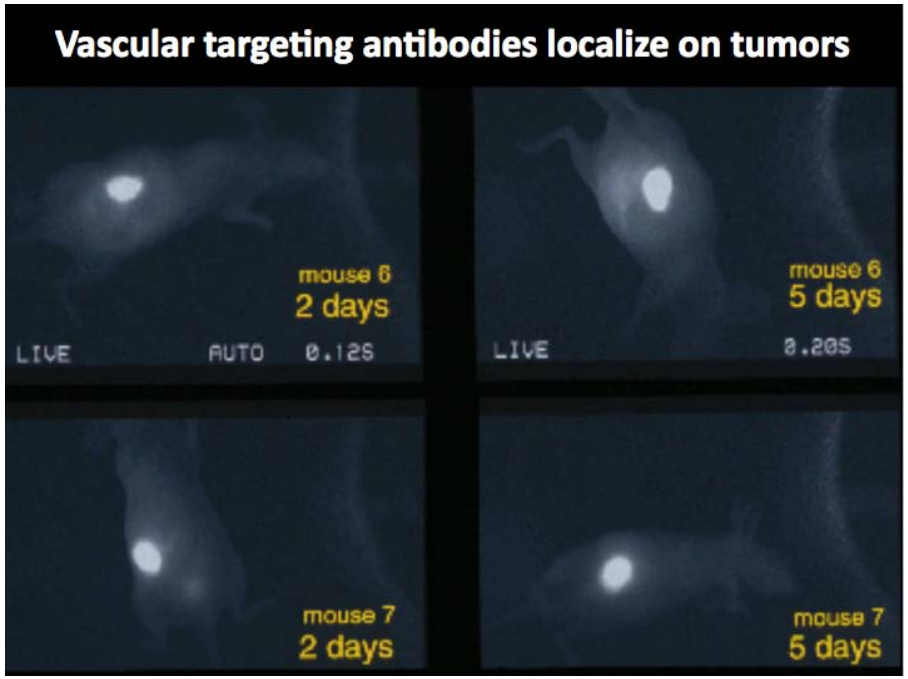
Biodistribution of Small Molecule vs. Antibody

Labeled small drug



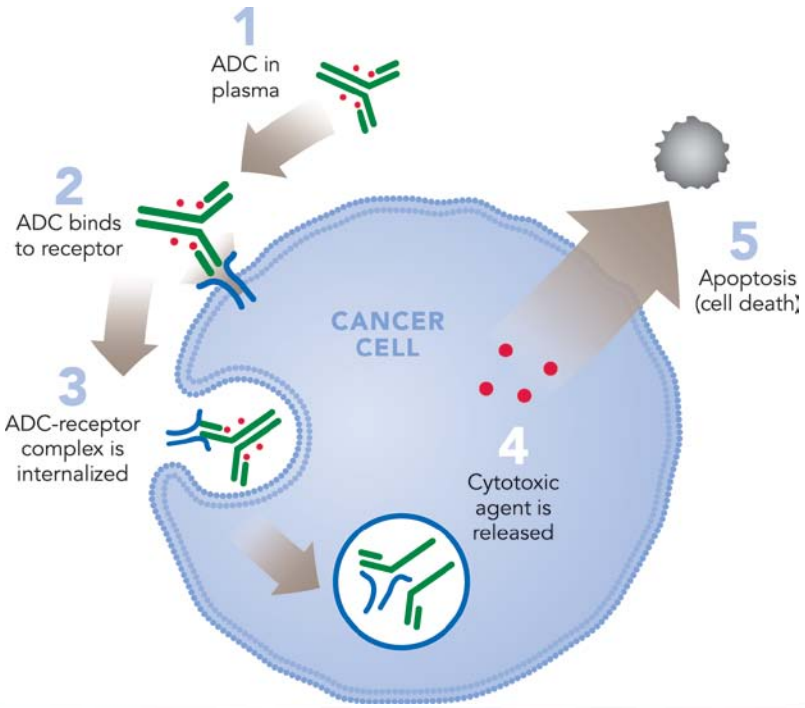
Labeled antibody



Data and slide compliments of Dario Neri

ADC Technology: Empowering Antibodies

ADCs combine the targeting ability of monoclonal antibodies with the potency of cytotoxic agents



- ADCs are designed to improve efficacy and reduce toxicity
- Potent, cytotoxic agents and stable linkers with long half-lives
- Readily scalable through simple, reproducible synthesis
- More than 20 ADC programs in clinical development using Seattle Genetics technology

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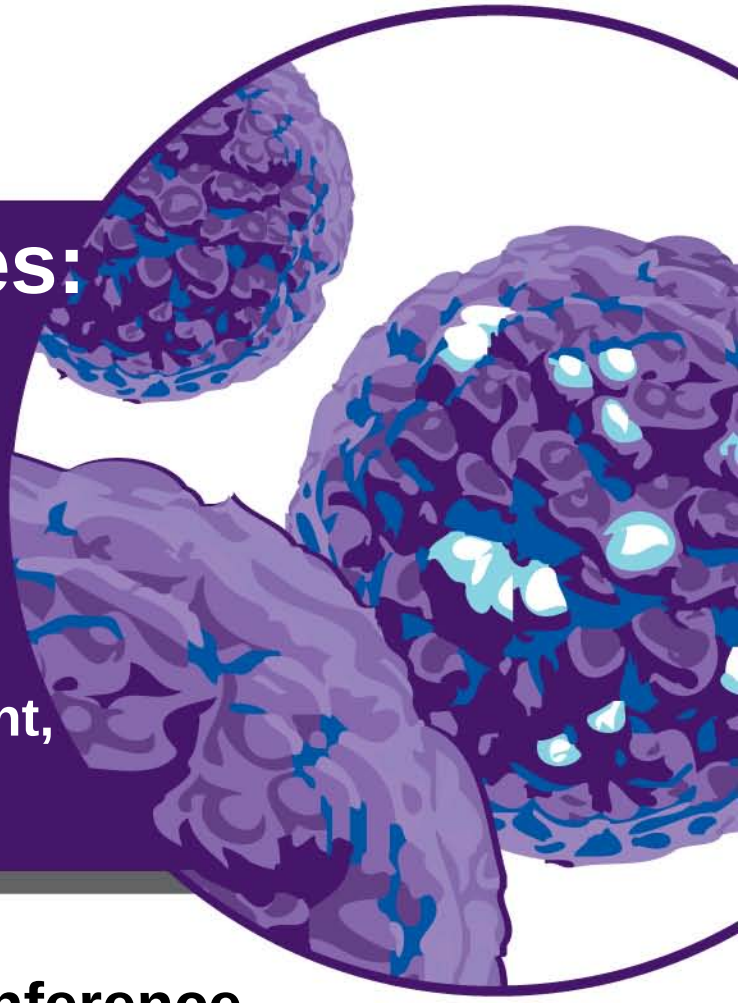

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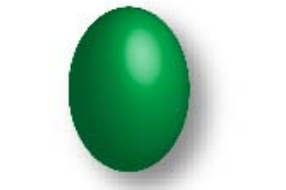
Focus Areas to Improve TIs of ADCs

- **Translation from the Clinic to Research**

- Function first
- Cancer stem cells

- Site specific conjugation

- Novel MOA linkers & payloads



Targets

Vehicles

Linkers

Payloads

- **ADC biology: Trafficking and resistance**
- **Precision medicine: Imaging, CTCs**
- **Safety improvements: On- and off- target toxicity**
- **Preclinical pharmacology: more predictive efficacy models**

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Gerber, Koehn and Abraham, Nat. Prod. Rev, 2013

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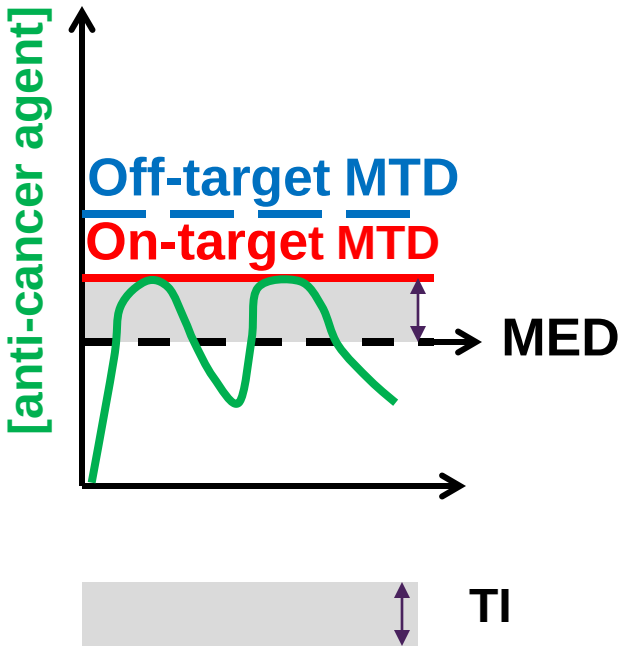
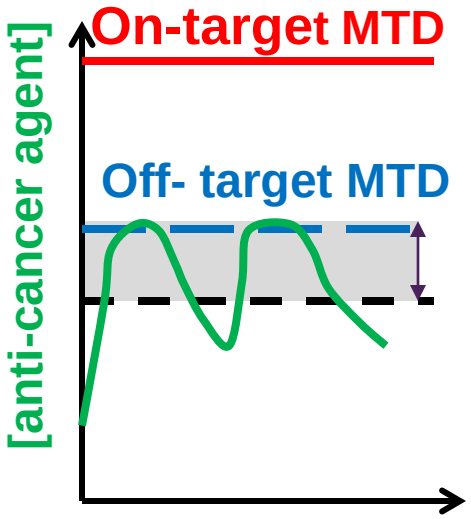
Conventional ADC targeting "dirty target"



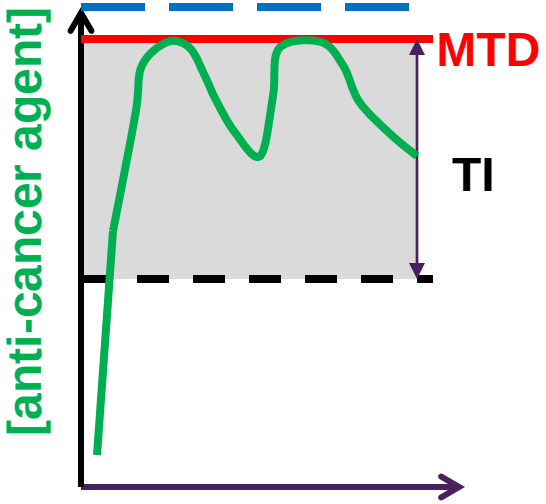
TI: Therapeutic Index
MED: Minimum Effective Dose

ADC with reduced on-target toxicity



Limited TI improvement
- Off-target toxicity
- Possible loss in potency

ADC with reduced on- and off-target toxicity



Maximal TI improvement
- Higher off-target tox levels
- Enables higher exposure and better PD

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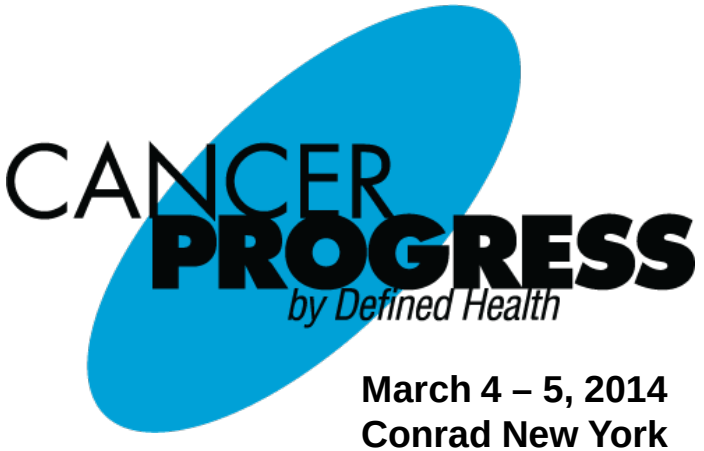
Supercharging ADCs



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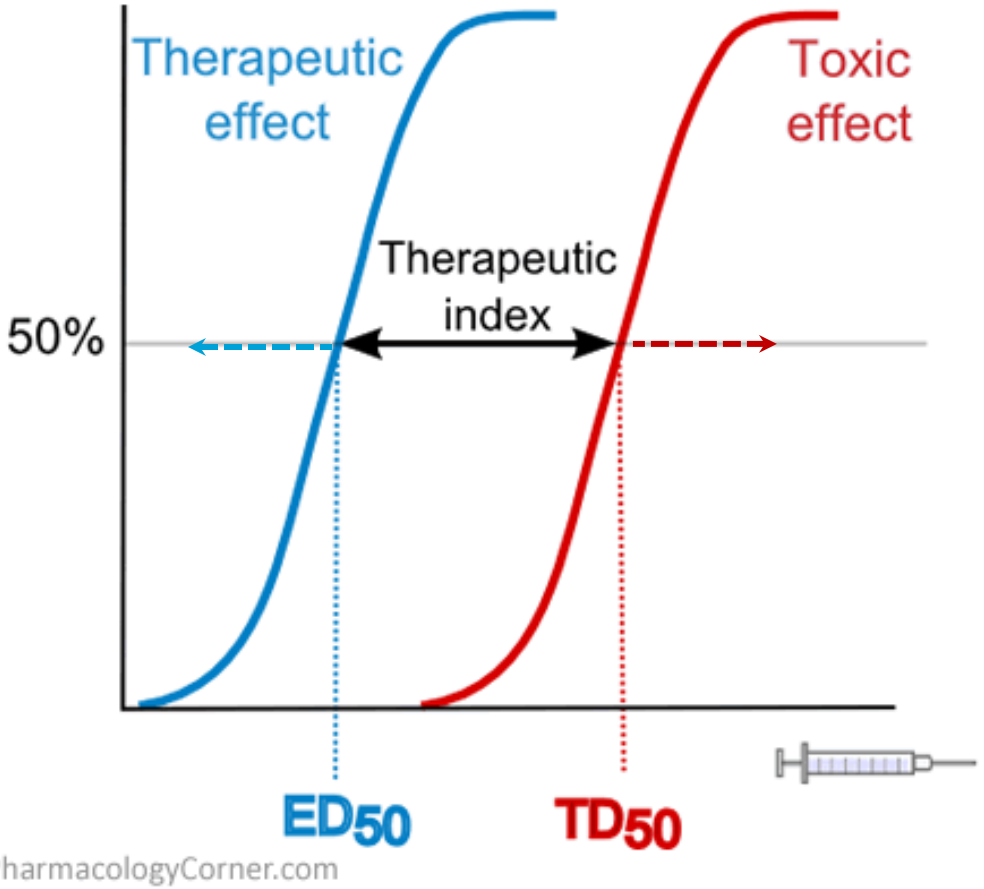
Supercharging ADCs

Efficacy is not just about potency

Efficacy is about therapeutic index



What gives rise to toxicities?

Many possibilities but include

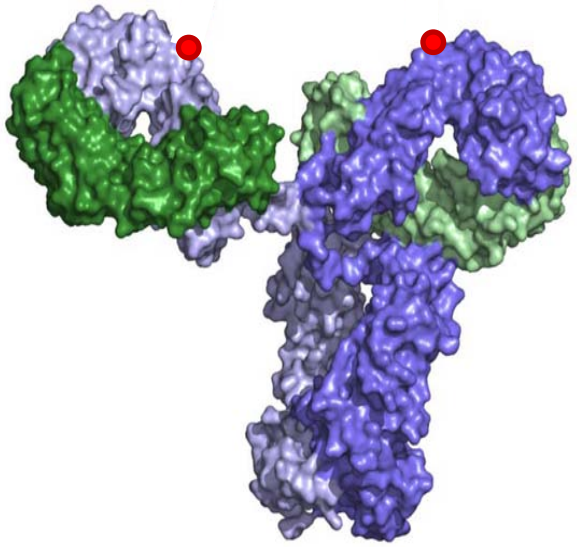
- On target
  - Antigen also expressed on normal cells
  - How do we get greater selectivity?
- Off target
  - Payload released before ADC reaches tumor target
  - ADC taken up in tissues by antigen-independent pathways
  - ADC itself is unstable
    - Component of drug product does not even bind to target
    - Drug loading destabilizes mAb structure
    - Linker not stable for long periods in circulation (t1/2 of normal mAb can be 14-21 days)

How do we increase efficacy?

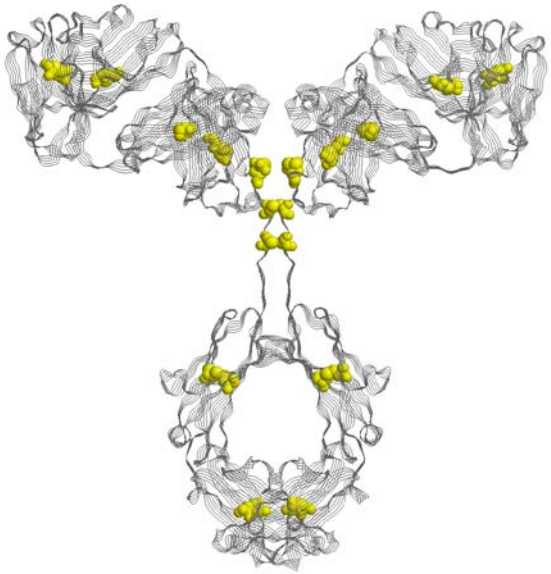
- Many possibilities but may include
  - Enhanced binding, uptake, internalization and intracellular release of drug
  - Homogeneous defined drug substance with appropriate linker and payload for the tumor cell
  - Combination of payloads that act in synergy to kill tumor cells
  - Increase payload (DAR)?

Site Specific vs Random Conjugation for ADCs

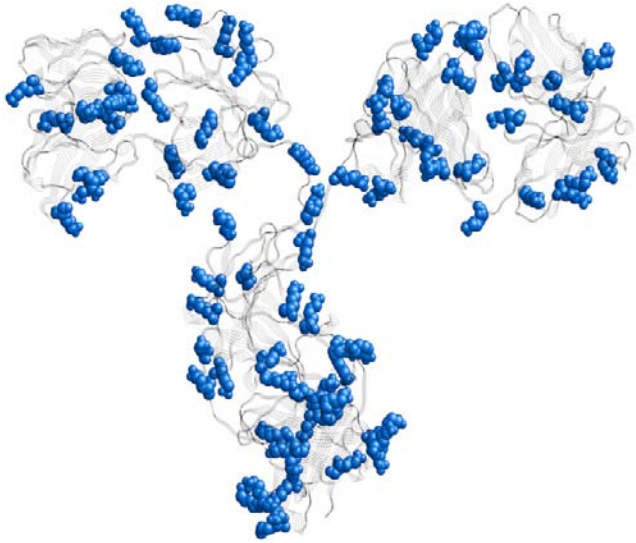
Site-specific



Cysteine



Lysine



The answer is <u>not</u> simply to add more drugs to the mAb

Know your Drug!

Increase potency

- Homogenous drug conjugate
- Optimized PK
- Site & linker payload optimized for release only upon internalization
- Bi- or multi-specific to enhance internalization
- Synergistic payloads targeting two oncogenic pathways, concomitantly released within target cell

Decrease Toxicity

- No non-active (toxic) species in drug product
- Optimized PK
- Drug only released within the tumor cell
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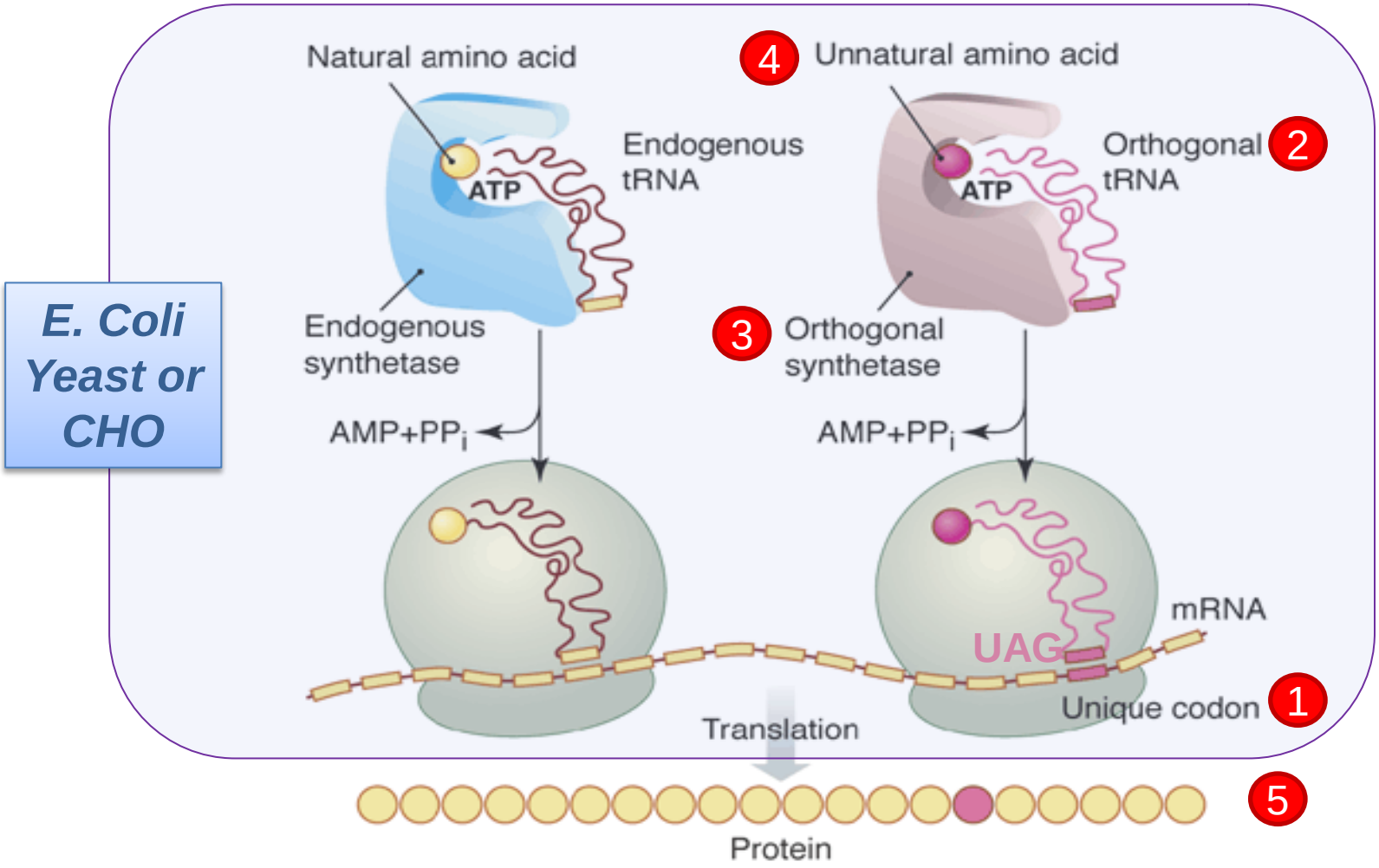
Site-Specific Incorporation of Novel Amino Acid(s) in Proteins



1: The unique codon is placed at a precise position in the DNA sequence

2 & 3 The Ambrx synthetase and tRNA and translate the DNA sequence and incorporate the non-natural amino acid 4 into the specified position in the protein, 5.

Site-Specific Conjugation to Proteins

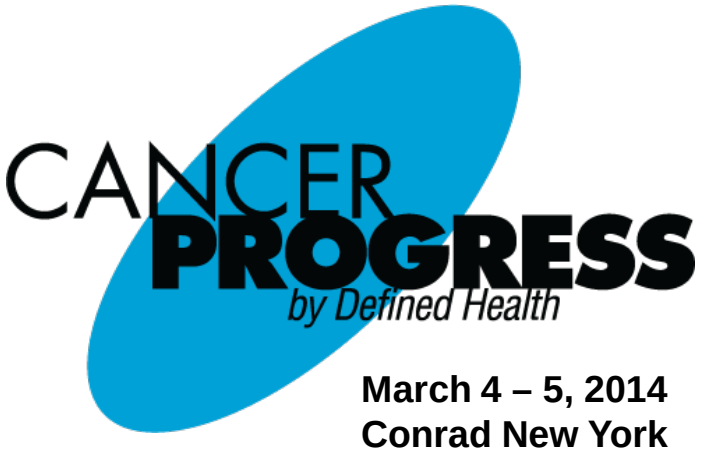
Why?

- Choose precise location without disrupting
  - Binding to ligand(s) or receptor,
  - Effector function
  - Half-life
- Introduce novel Chemistries
- Combine recombinant and chemical species for novel activities

Uses?

- mAbs for ADCs
- Bi- and multi-specific Ab formats
- Therapeutic peptides/proteins
- Redirected T cell killing
- Novel multifunctional proteins
- Subunit and live attenuated vaccines

Supercharging ADCs



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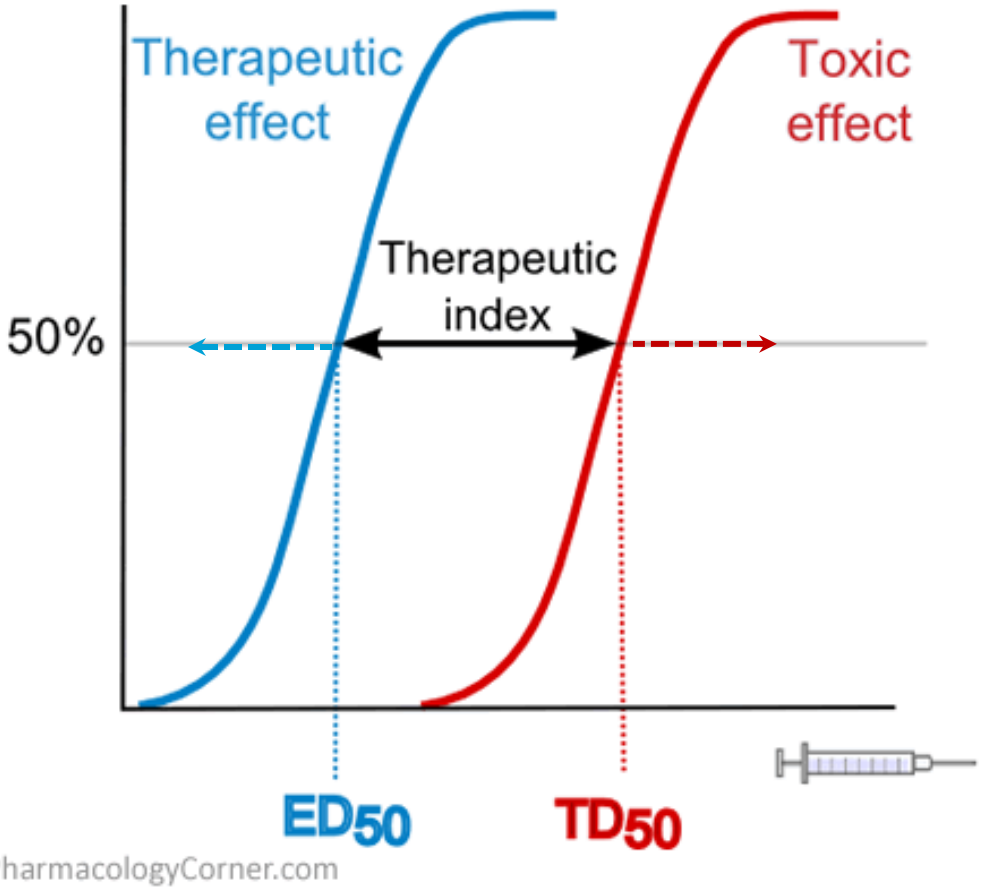

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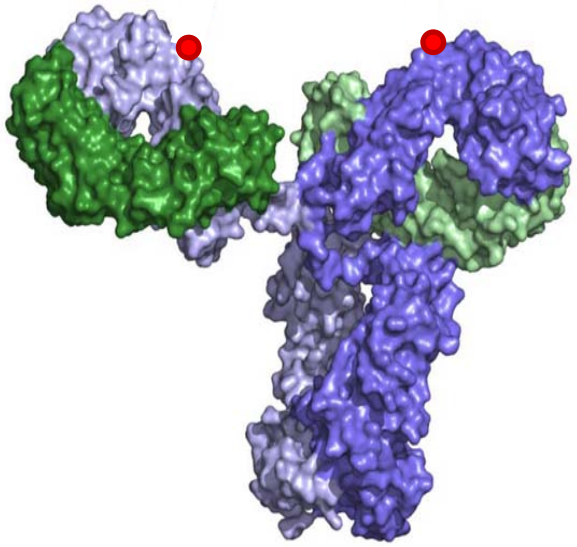

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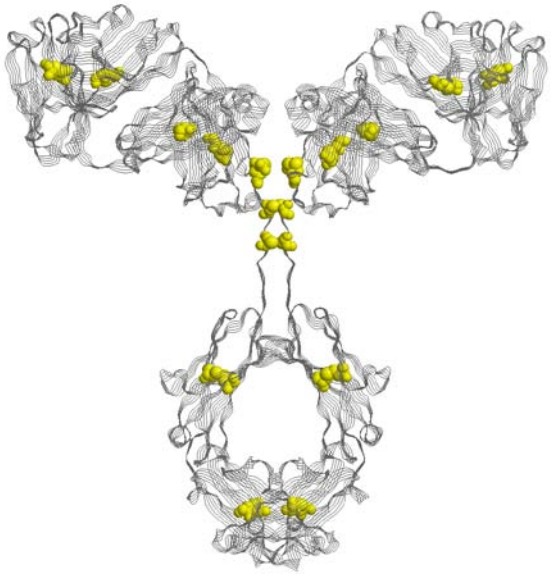

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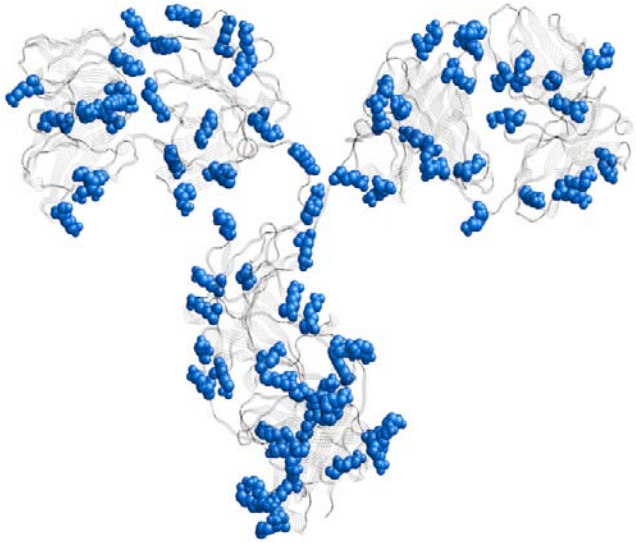

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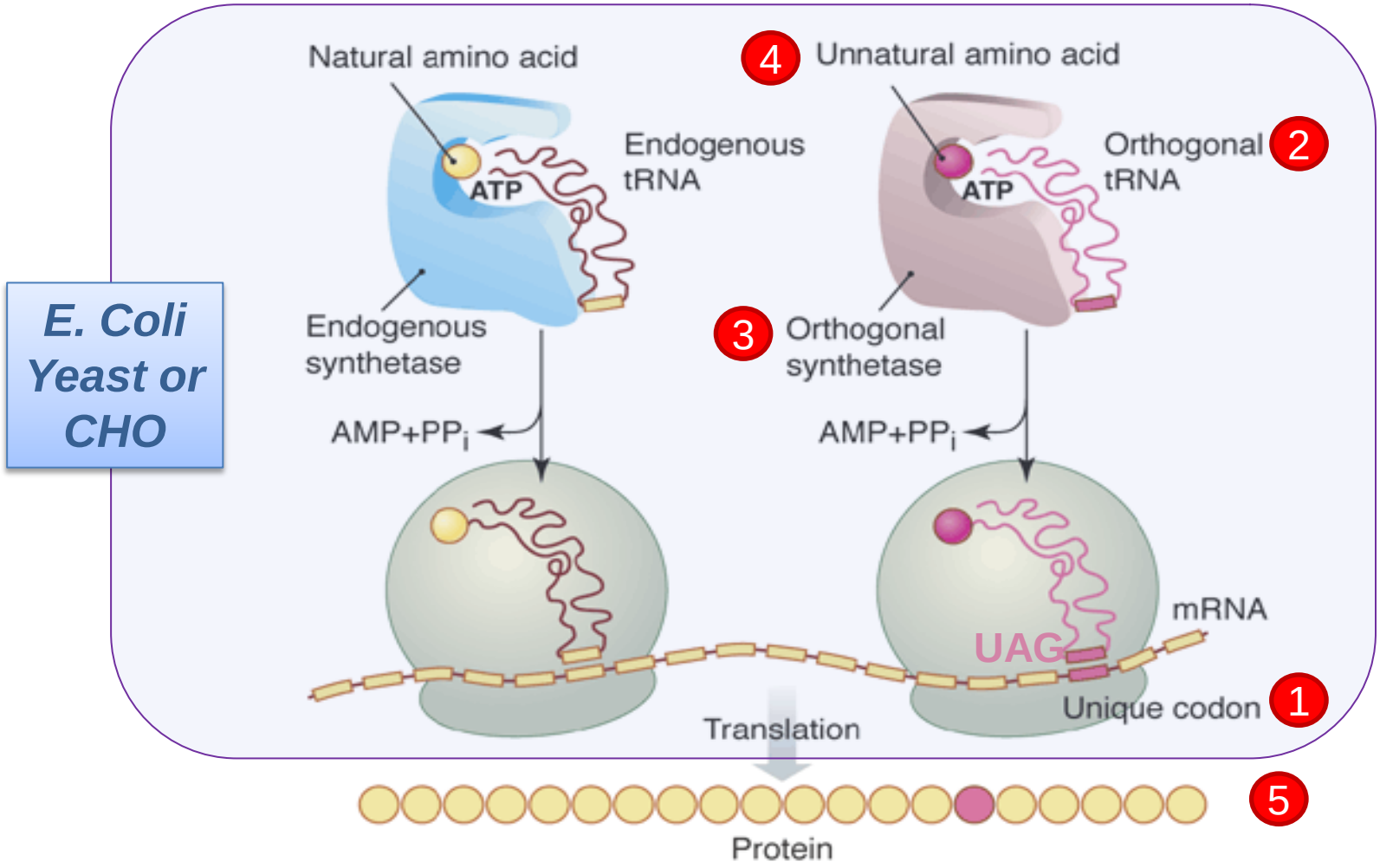

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Gerber, Koehn and Abraham, Nat. Rev. Drug Discov. 2013

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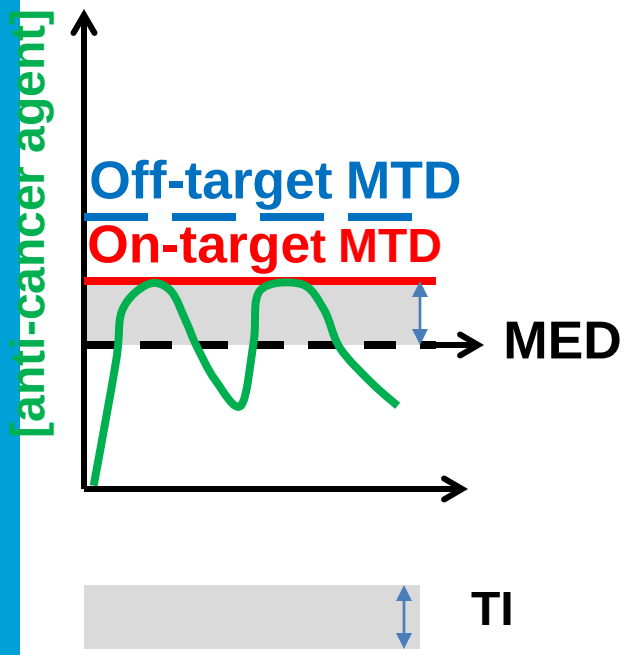

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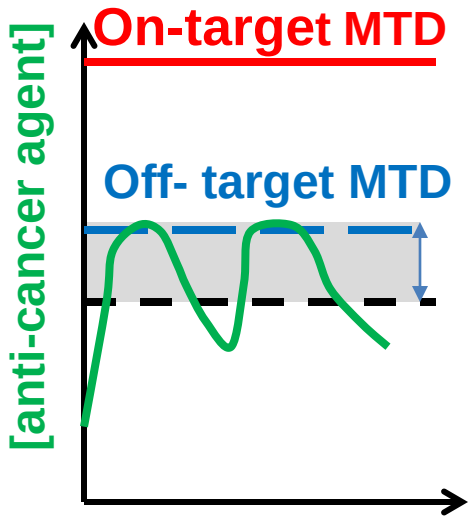

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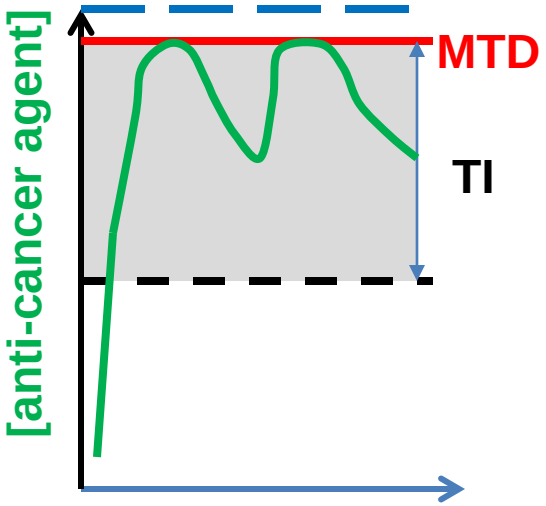

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