

Ynamines as Bioorthogonal Click Handles in ADC Synthesis

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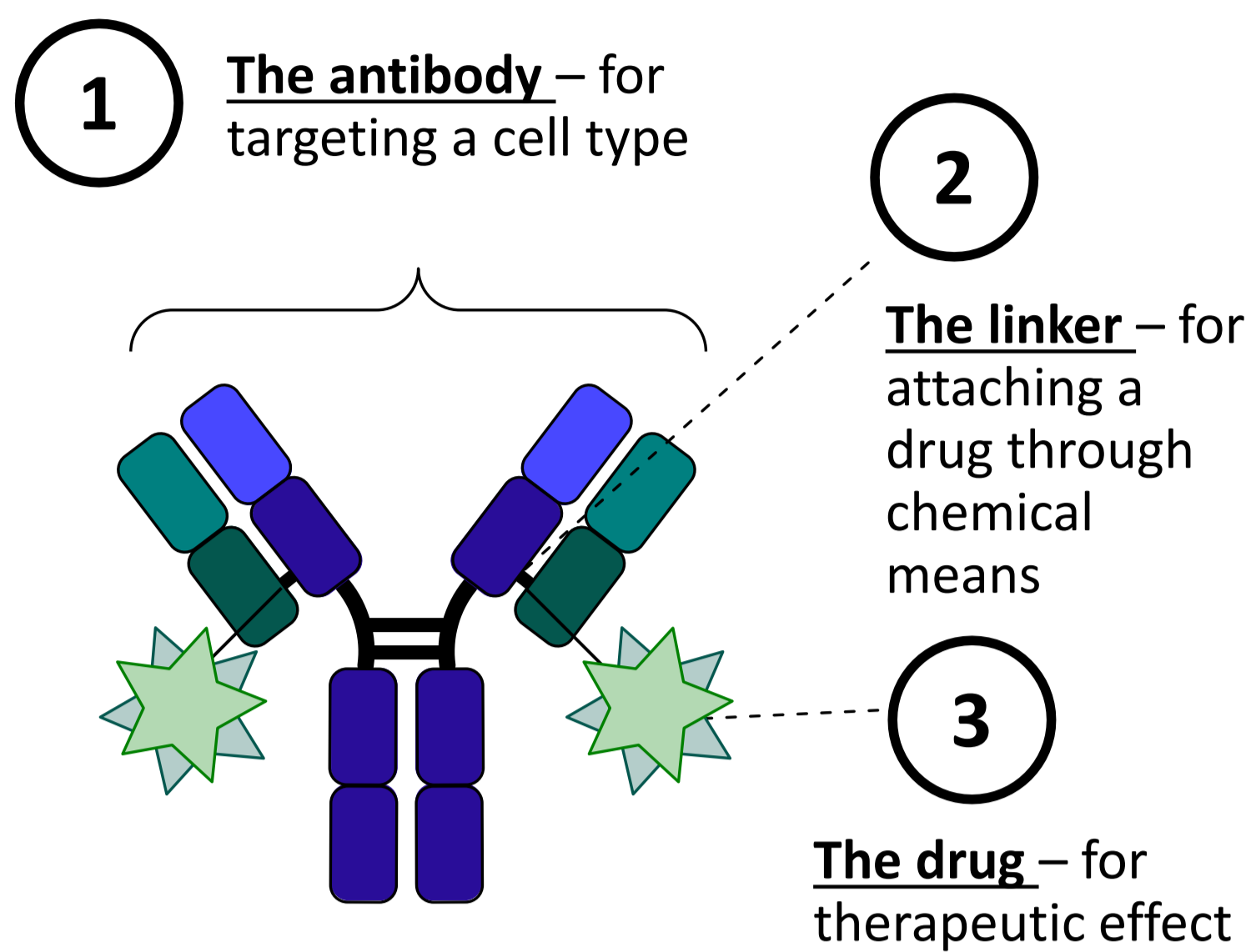
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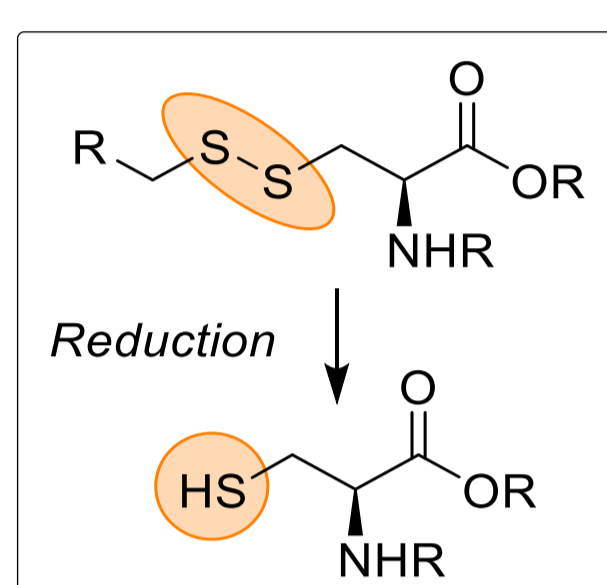


ADCs are a 'Magic Bullet' - The Future of Cancer Treatment

ADC – Simple as 1, 2, 3



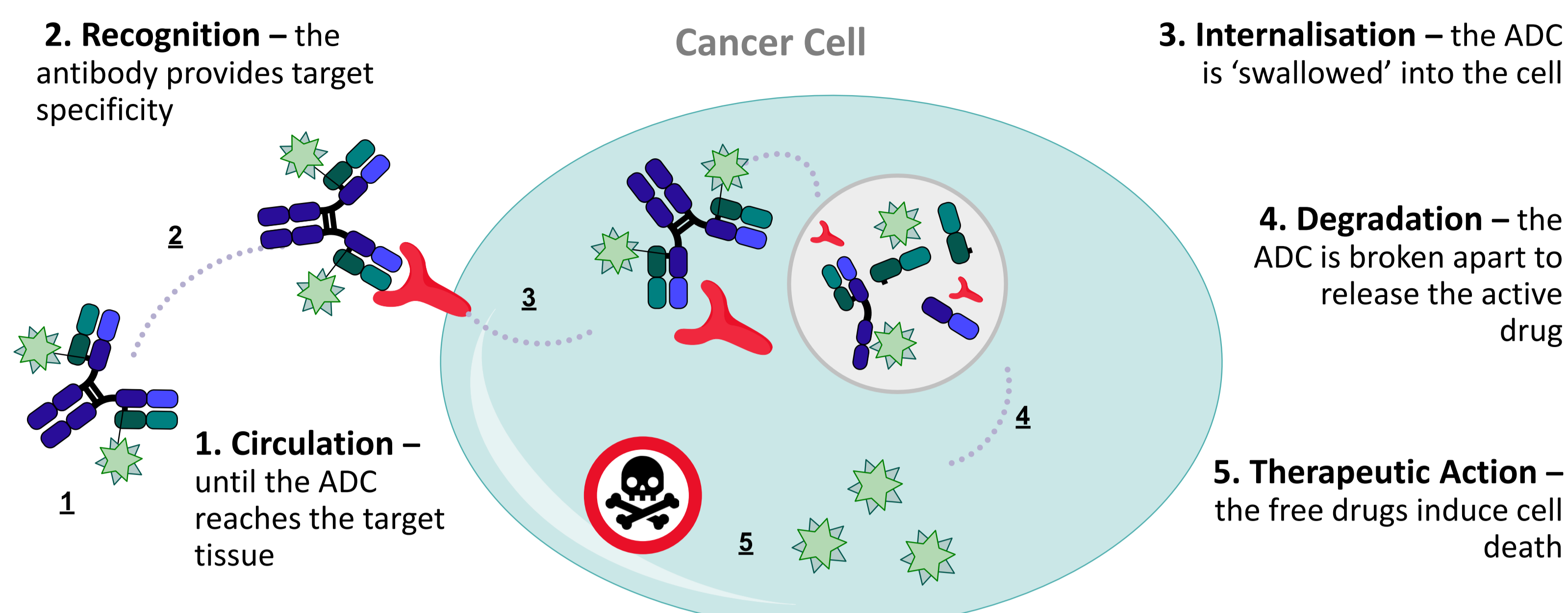
- Antibody Drug Conjugates (ADCs) are a cutting-edge therapeutic – blending biological targeting with traditional medicinal chemistry



Amino Acid Manipulation

- Amino acids are subunits of all proteins, including antibodies
- Can be modified with biological chemistry

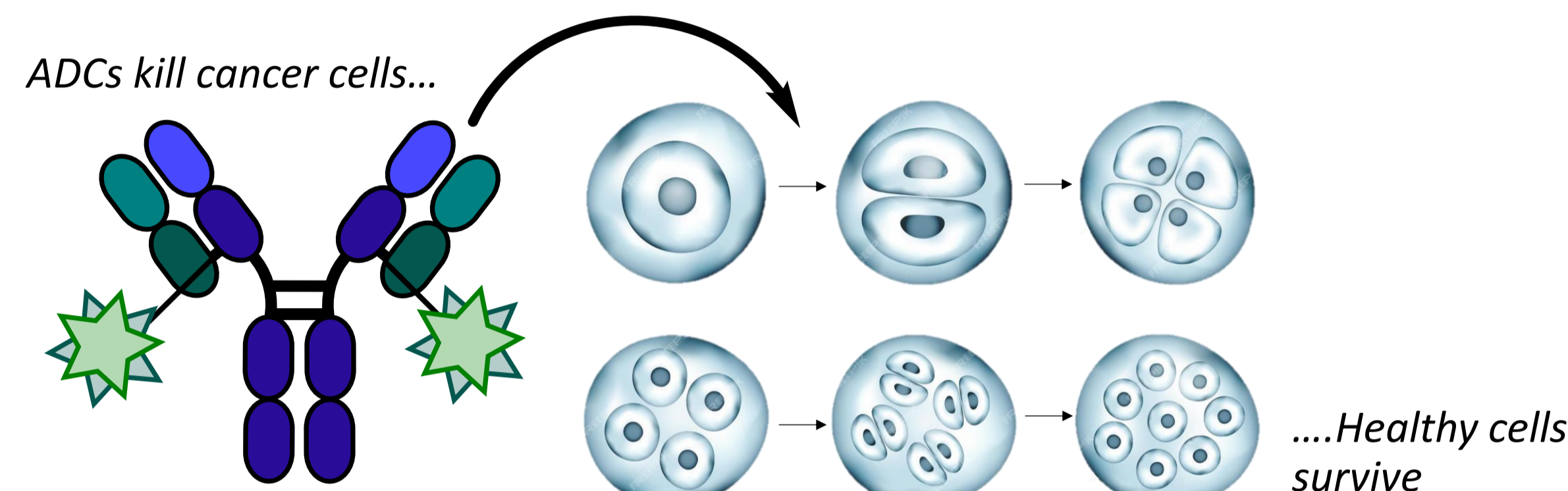
How does an ADC work?



Chemotherapy



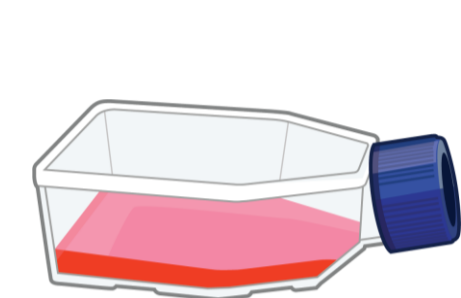
- Chemotherapy cannot distinguish between healthy and cancer cells.
- The death of healthy cells causes negative side effects for the patient



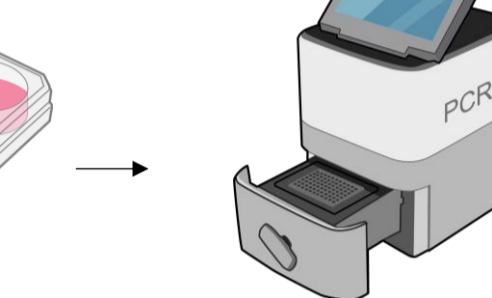
Project Aims

- Develop new methodology to produce ADCs
- Prove that these ADCs do not kill healthy cells

Grow and test cells



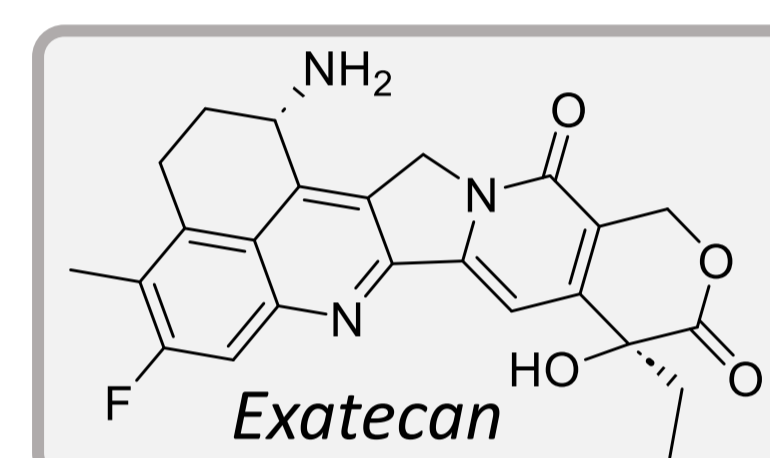
Results



Constructing the ADC – How and Why?

Why are attachment methods important?

- The 2022 Nobel Prize winner was awarded to Meldal, Sharpless and Bertozzi for click chemistry. Morten Meldal compared click chemistry to lego building blocks - 'click them together, like snap, snap, snap.'
- Click chemistry prevents messy reactions with undesired products and can be used in biological settings



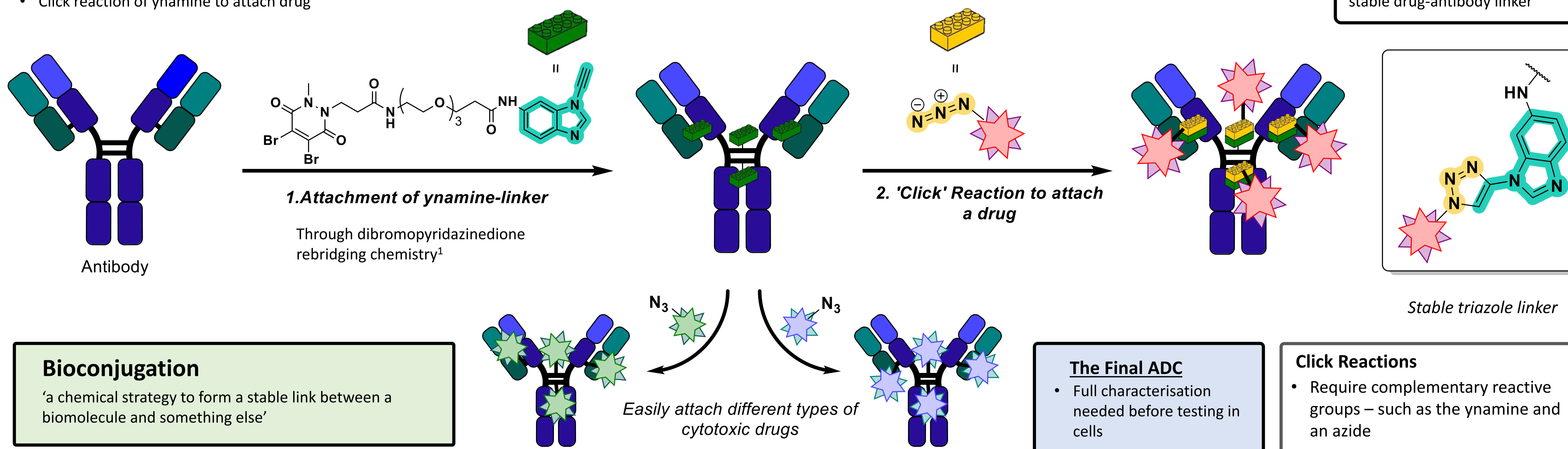
Choice of Drug

- Highly potent cytotoxins are chosen for maximal cell-killing effects
- Exatecan is a chemotherapeutic which prevents DNA replication

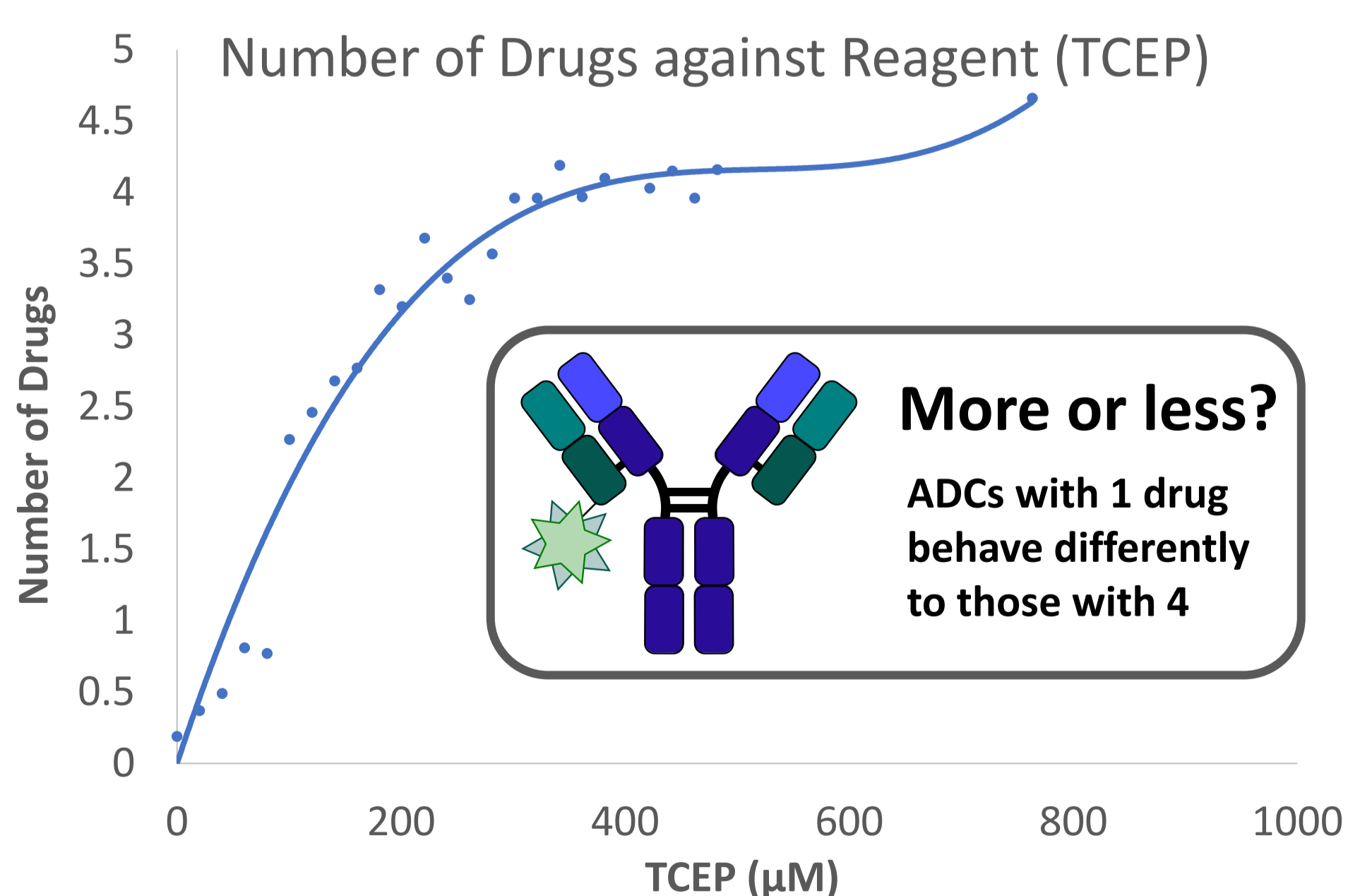


Bioconjugation Strategy

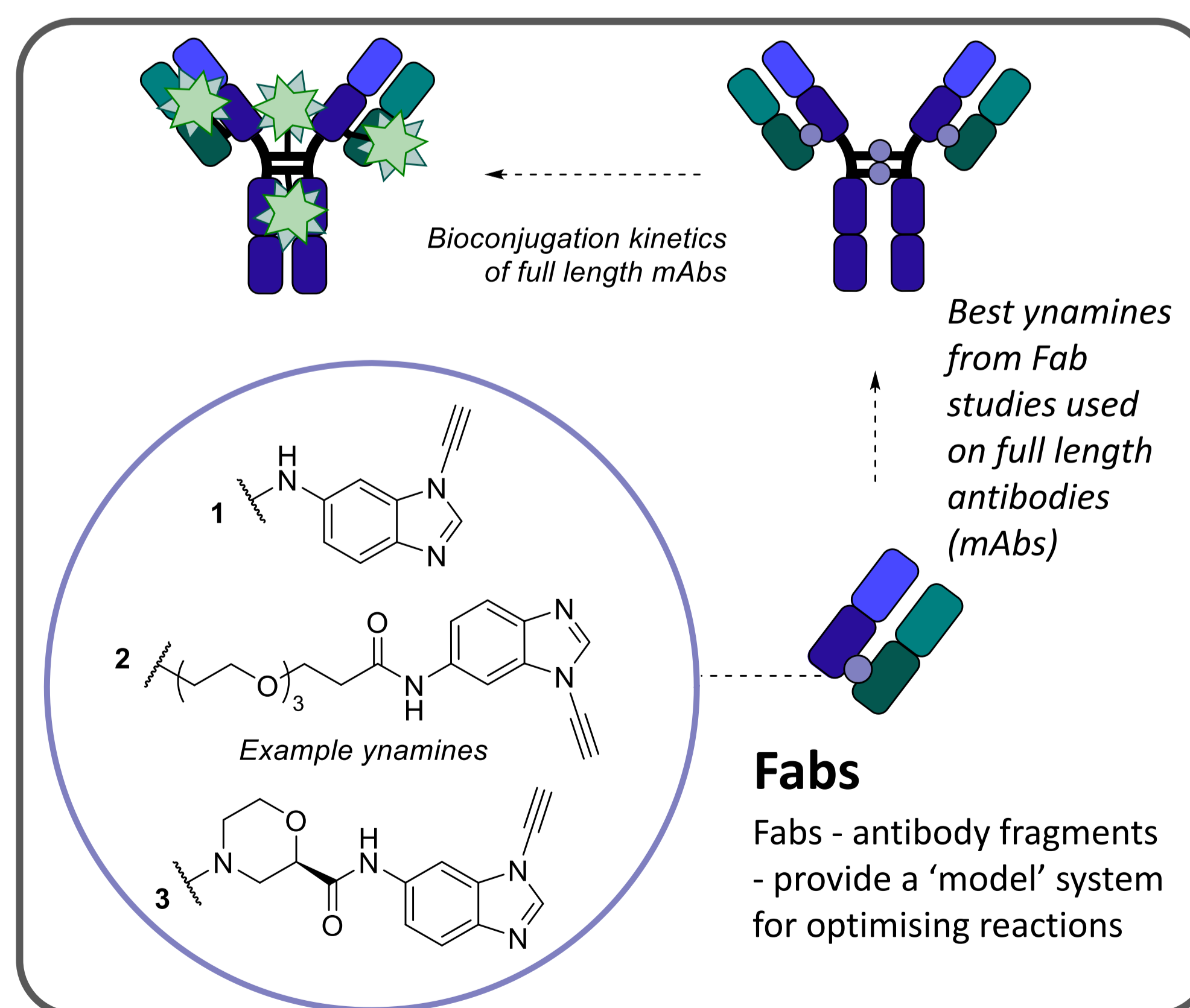
- Cysteine rebridging chemistry (reforming intermolecular bonds) to attach click handle
- Click reaction of ynamine to attach drug



The Number of Drugs per Antibody

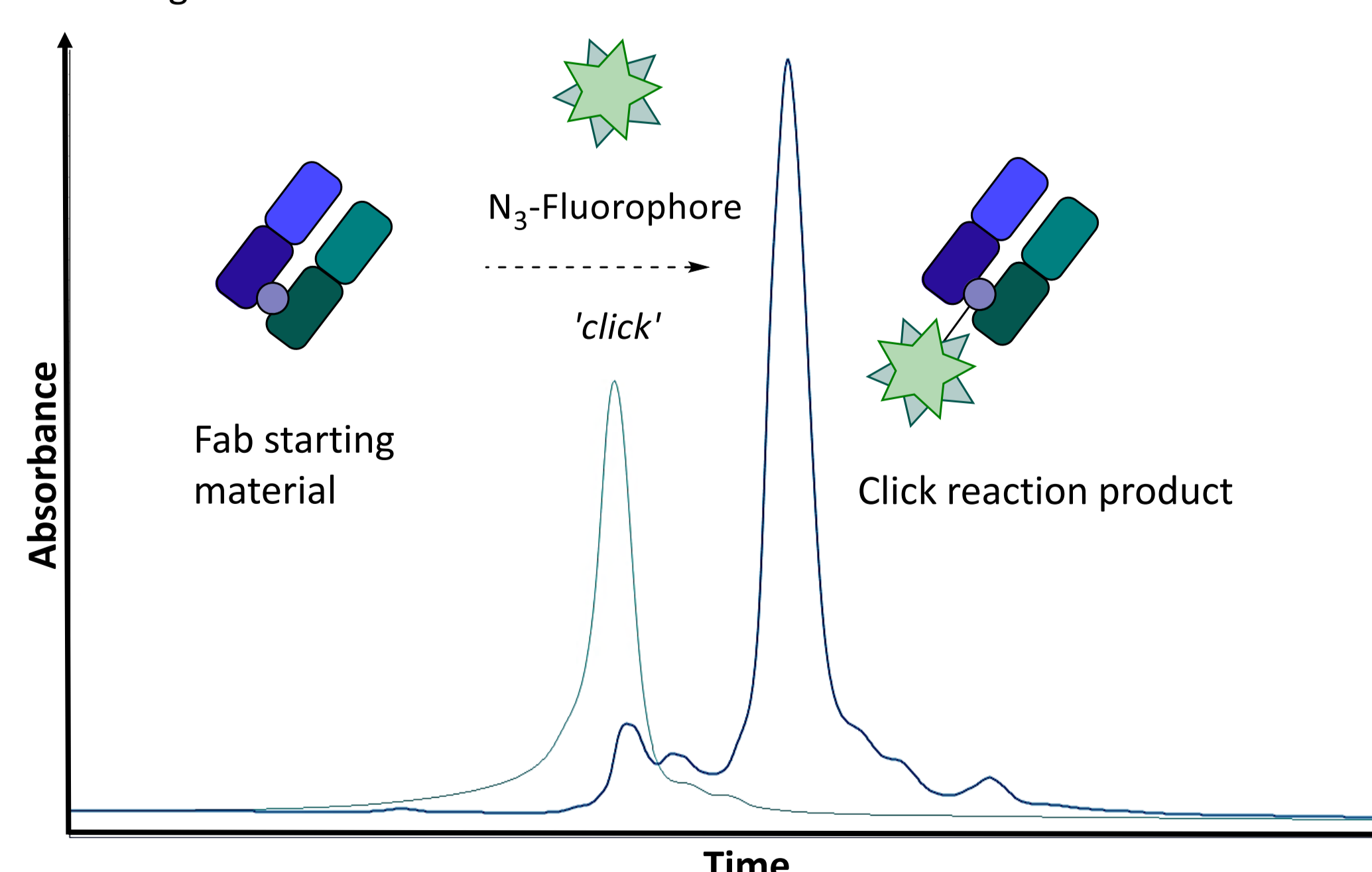


- The number of drugs per antibody has important effects on dosage, stability and therapeutic effects of the ADC
- This can be controlled by concentration of reactants during synthesis



Visualising Click Reactions

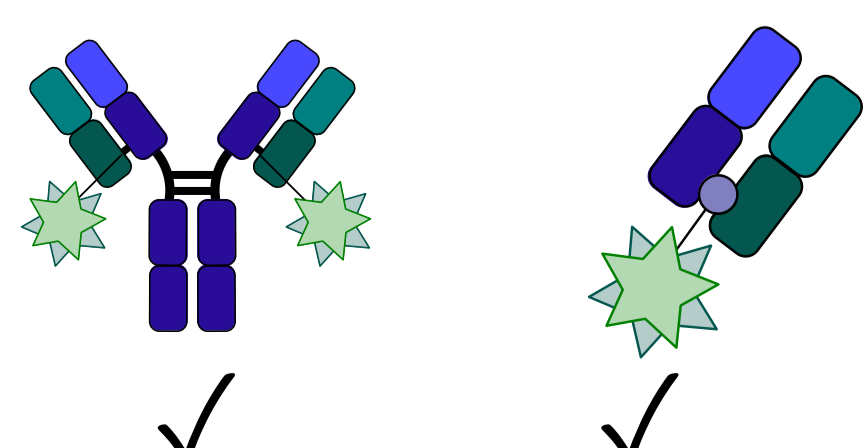
- Reaction progress can be visualised by chromatography
- ADCs have different retention times to unmodified antibodies and Fab fragments



Conclusions and Future Work

Conclusions

- Development of new method to construct ADCs achieved
- Multiple ADCs and Fab conjugates synthesised, ready for testing



Testing on Live Cells

- Testing of the ADCs on both healthy cells and cancer cells.
- Cancer cells should die, healthy cells should keep growing

