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Enabling a Healthier World

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Biologics

# Bioconjugates

Where chemistry and biology meet  
Sanna Fowler PhD  
Head of Strategy and Innovation

Lonza | EPFL 24 Sept 2024

Public



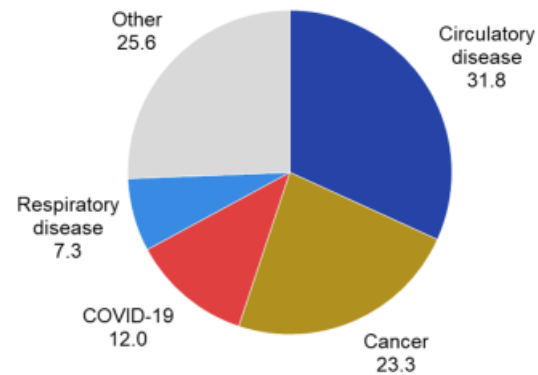
# What is an ADC?

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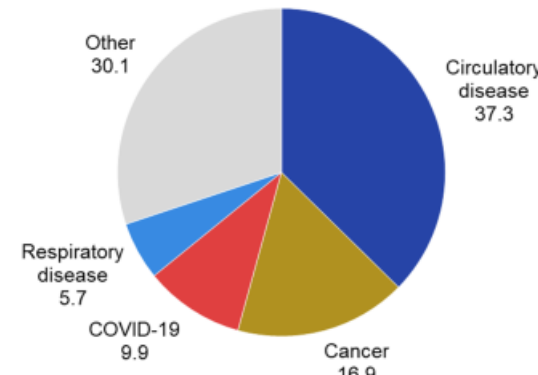


# Major Causes of Death in Europe

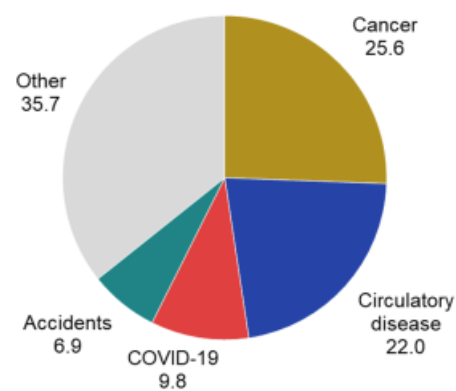
Males aged 65 years and over



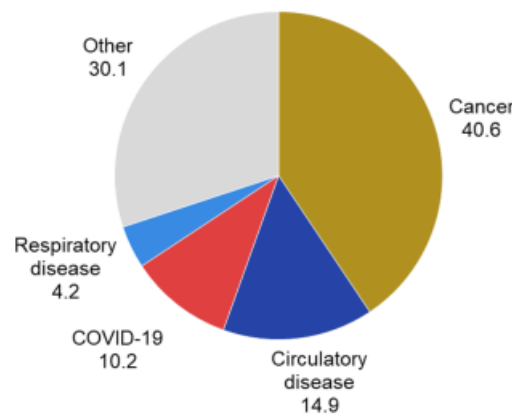
Females aged 65 years and over



Males aged less than 65 years



Females aged less than 65 years



|                                                                                                          | Therapy                                                                                           | Mechanism                                                    | Disadvantages                                                             |
|----------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|--------------------------------------------------------------|---------------------------------------------------------------------------|
| <b>Irradiation</b><br>  | Locally applied nuclear radiation damages the genetic makeup of cells                             | Affect all cells, damages primarily cells with fast division | Undetected metastases are not treated. Healthy cells are affected as well |
| <b>Chemotherapy</b><br> | Synthetic or natural substances prevent cell division or damage their genetic makeup (incl. mAbs) | Affect all cells, damages primarily cells with fast division | Healthy cells are affected as well                                        |
| <b>Surgery</b><br>    | Cancer cells are removed                                                                          | Selective for cancer cells                                   | Undetected metastases are not treated                                     |

# Enabling targeted drug delivery

## Paul Ehrlich's dream

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Nobel Laureate Paul Ehrlich, 1854 – 1915  
“Founder of chemotherapy”

## magic bullet noun

### Definition of *magic bullet*

- 1 : a substance or therapy capable of destroying pathogens (such as bacteria or cancer cells) or providing an effective remedy for a disease or condition without deleterious side effects

Only targeting  
unhealthy tissue

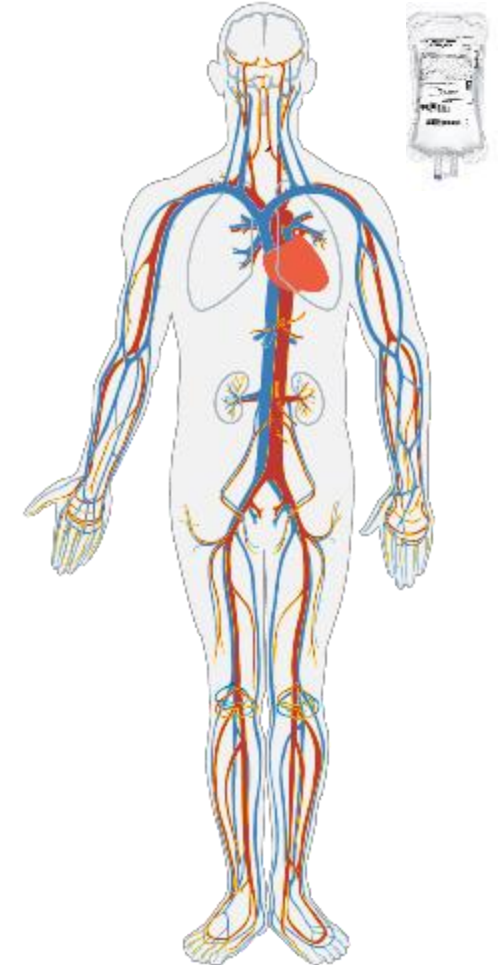


Selectivity

The drug has the  
desired effect



Efficacy



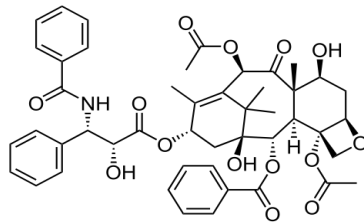
## Chemicals vs biopharmaceuticals - Traditional cancer therapy options



## Small molecules

- > mode of action: killing of dividing cells

## Paciltaxel



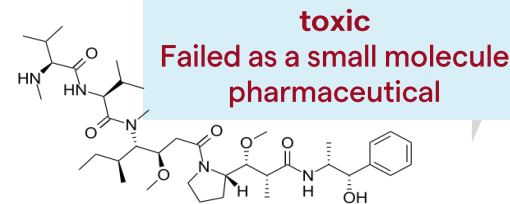
Derived from pacific yew

LD<sub>50</sub>: 12 mg/kg  
Microtubule-binder



- > higher potency → typically more side effects on healthy cells

## Monomethylauristatin E



Derived from mollusk

LD<sub>50</sub>: ca 1 mg/kg  
Tubuline inhibitor



## Antibodies

- > fulfill the promise of **highly selective** drugs
- > Limitation: may have **low efficacy**

## Examples on the market:

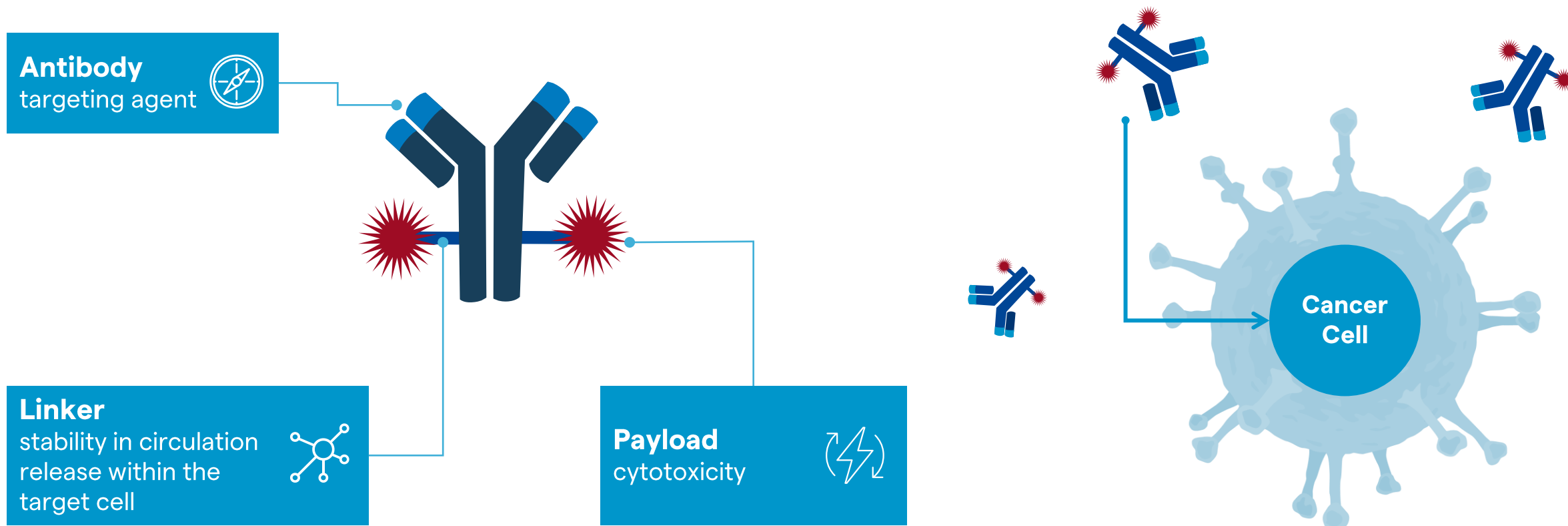
- **Herceptin** - breast cancer
- **Avastin** - colon cancer
- **Rituxan** - lymphoma





# Antibody drug conjugates (ADCs)

Best of both worlds – combining selectivity and cytotoxicity



**highly potent cytotoxic compounds can be safely delivered to the cancer cell**

# How the chemistry is evolving

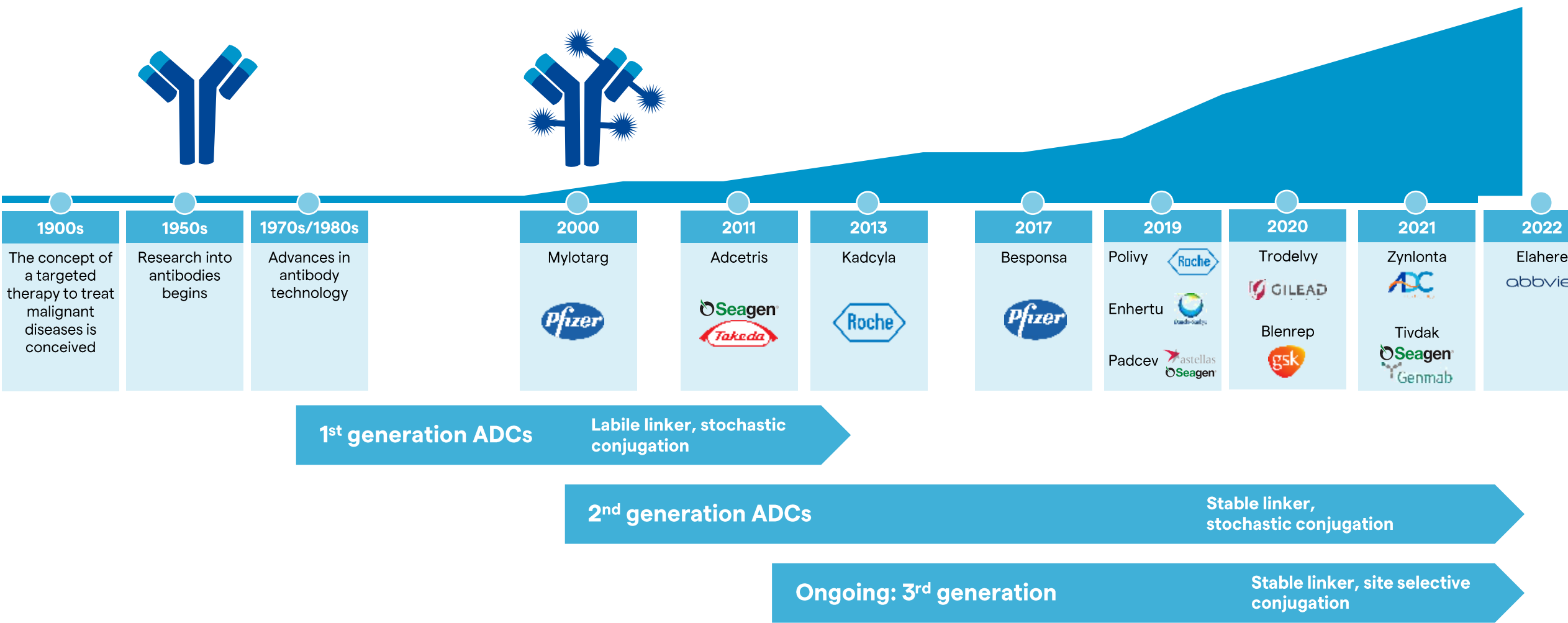
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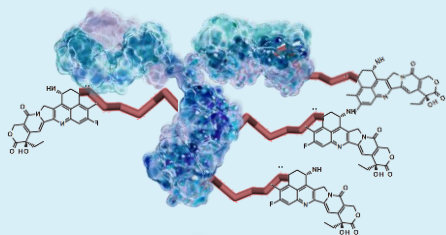
# History of ADCs

New technologies paved the way to a wave of approvals



## 1<sup>st</sup> generation ADCs

*E.g. Lysine-amide conjugates*

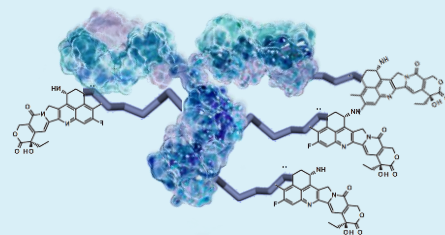


- + Fast release of the payloads in cancer cells
- Release of payloads in the blood stream → lower tolerability
- DAR 0 molecules inhibit the binding to the cancer cell → lower efficacy
- High DAR molecules tend to aggregate → lower tolerability

Labile linker  
stochastic conjugation

## 2<sup>nd</sup> generation ADCs

*Eg Cysteine-maleimide conjugation*

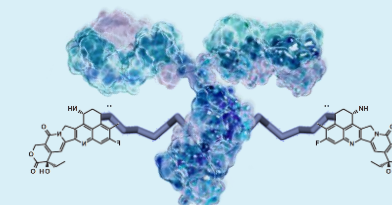


- + Fast release of the payloads in cancer cells
- DAR 0 molecules inhibit the binding to the cancer cell → lower efficacy
- High DAR molecules tend to aggregate → lower tolerability

Stable linker  
stochastic conjugation

## 3<sup>rd</sup> generation ADCs

*Site specific*

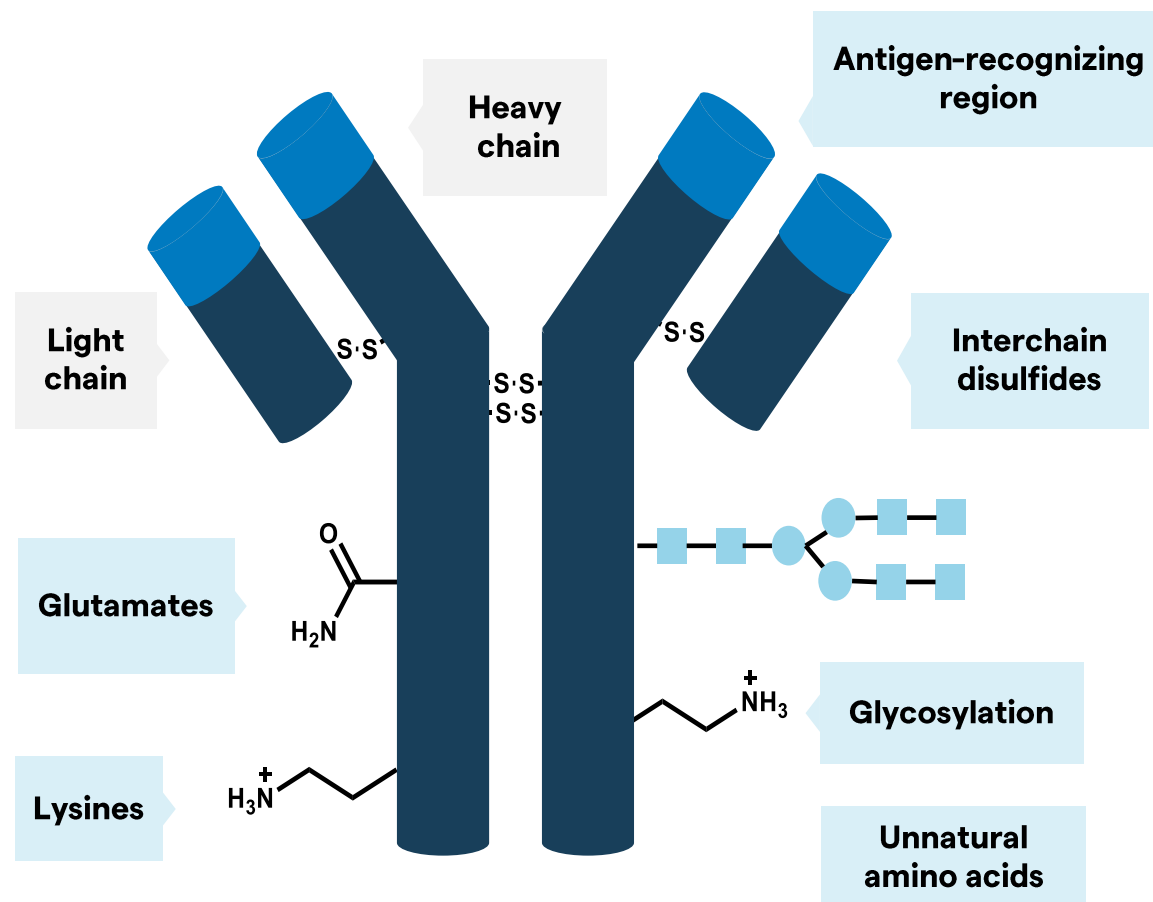


- + Fast release of the payloads in cancer cells
- + Tailored DAR value for the specific payload used → maximized tolerability and efficacy
  - DAR1, DAR2: highly potent payloads
  - DAR4, DAR8: moderately potent payloads

Stable linker  
site selective conjugation

# Conjugation technologies

## Chemical handles on an antibody



✓ **lysines**

stochastic conjugation

✓ **interchain disulfides**

stochastic conjugation, disulfide re-bridging

✓ **glutamates**

enzymatic conjugation

✓ **glycosylation**

glycan engineering

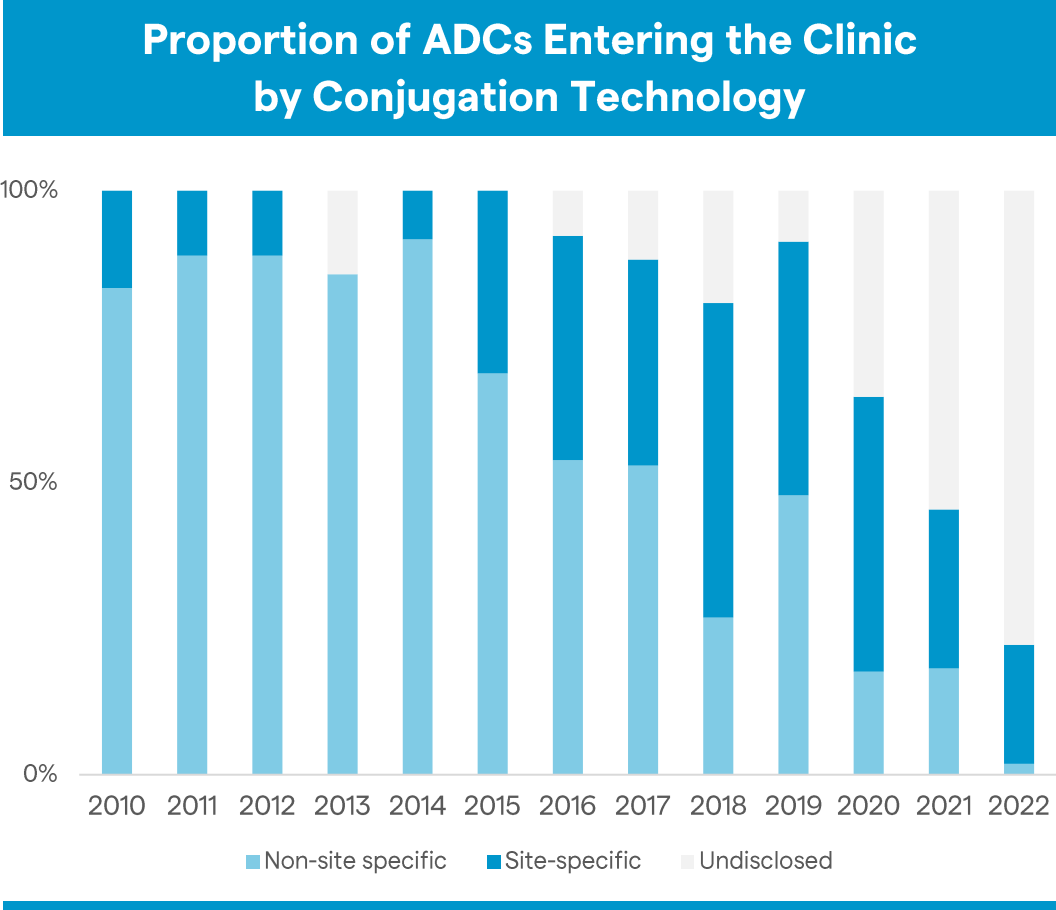
✓ **Unnatural amino acids**

Antibody expression with novel handles

...and many different chemistries and alternative anchor point to the protein

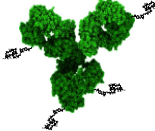
# Technology Landscape ADCs

## Bioconjugation technologies: Perspectives and trends



Source:  
Beacon Targeted Therapies (2023), [www.beacon-intelligence.com](http://www.beacon-intelligence.com)

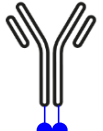
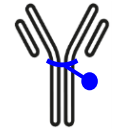
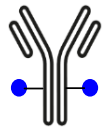
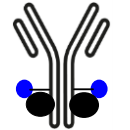
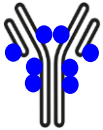
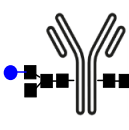
### 2010

|                                   |                                                                                     |                                                 |                                                                                     |
|-----------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------|-------------------------------------------------------------------------------------|
| Stochastic conjugation to lysines |  | Stochastic conjugation to interchain disulfides |  |
|                                   | e.g., Kadcycla                                                                      |                                                 | e.g., Adcetris                                                                      |

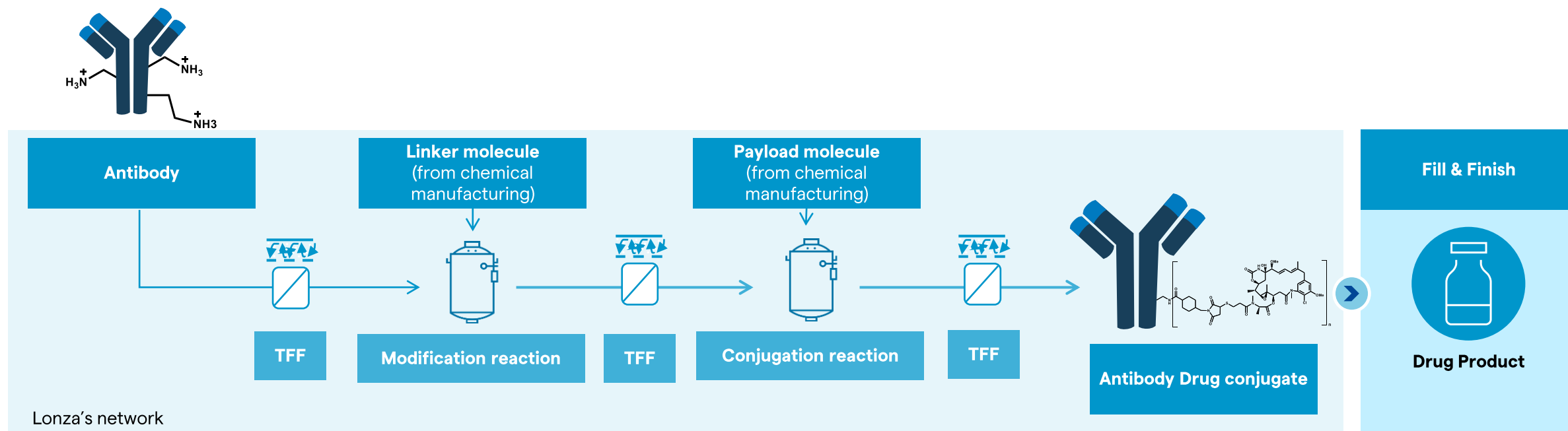
Trend towards site-specific conjugation

Diversification of technologies

### 2021 – Future

|                                                 |                                                                                       |                                     |                                                                                       |                            |                                                                                       |
|-------------------------------------------------|---------------------------------------------------------------------------------------|-------------------------------------|---------------------------------------------------------------------------------------|----------------------------|---------------------------------------------------------------------------------------|
| Stochastic conjugation to interchain disulfides |    | Site-specific enzymatic conjugation |    | Disulfide rebridging       |    |
| Stochastic conjugation to lysines               |   | Engineered cysteines                |   | Affinity based conjugation |   |
| DAR8 technologies                               |  | Glycan remodeling                   |  | Click chemistry            |  |

# Stochastic lysine conjugation

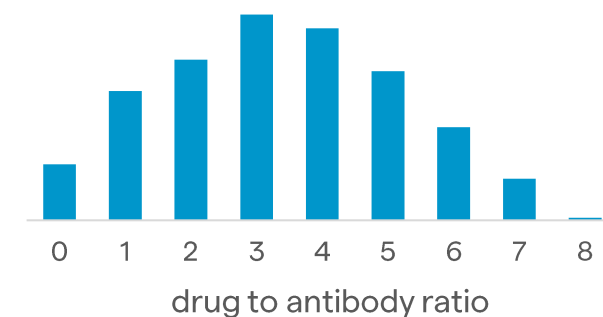


> An antibody (IgG1) scaffold contains over 80 lysine residues

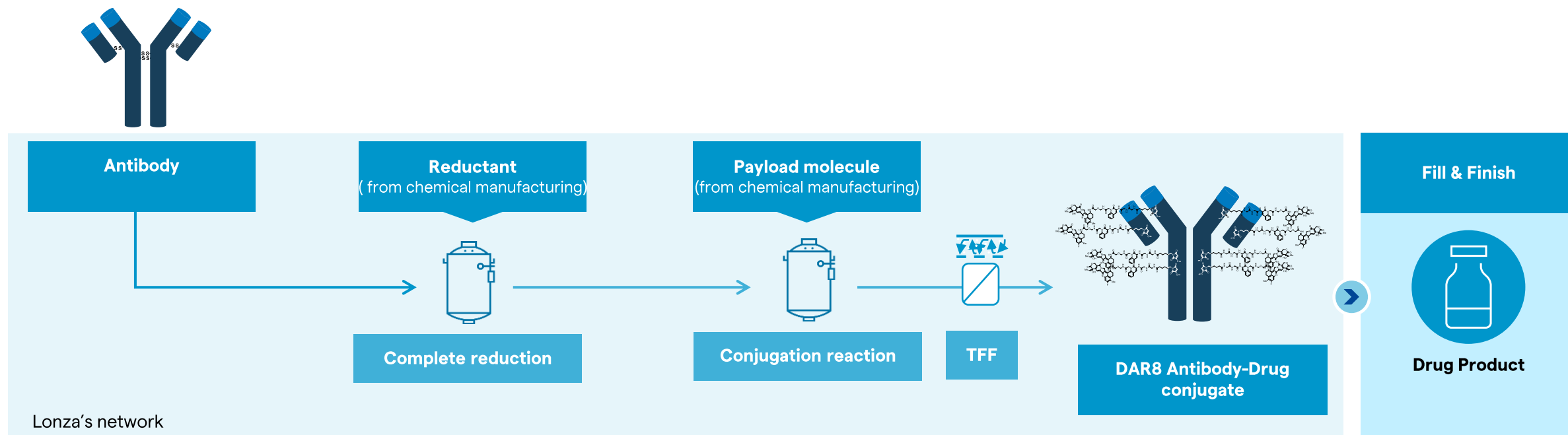
> Product is a mixture of **differently substituted antibody drug conjugates**

> Derivatization can be controlled by the process

> Average drug to antibody ratio (DAR): 3.5



# Site-selective cysteine conjugation

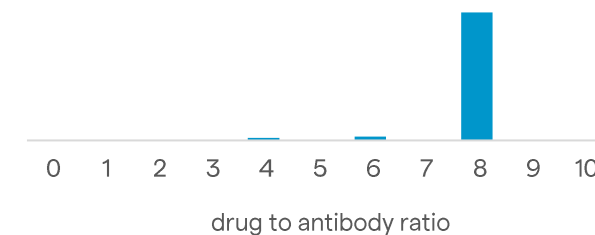


> IgG1 antibody: four interchain disulfides

> Drug to antibody ratio (DAR): ~8.0

> Complete reduction – complete conjugation allows for homogenous conjugation

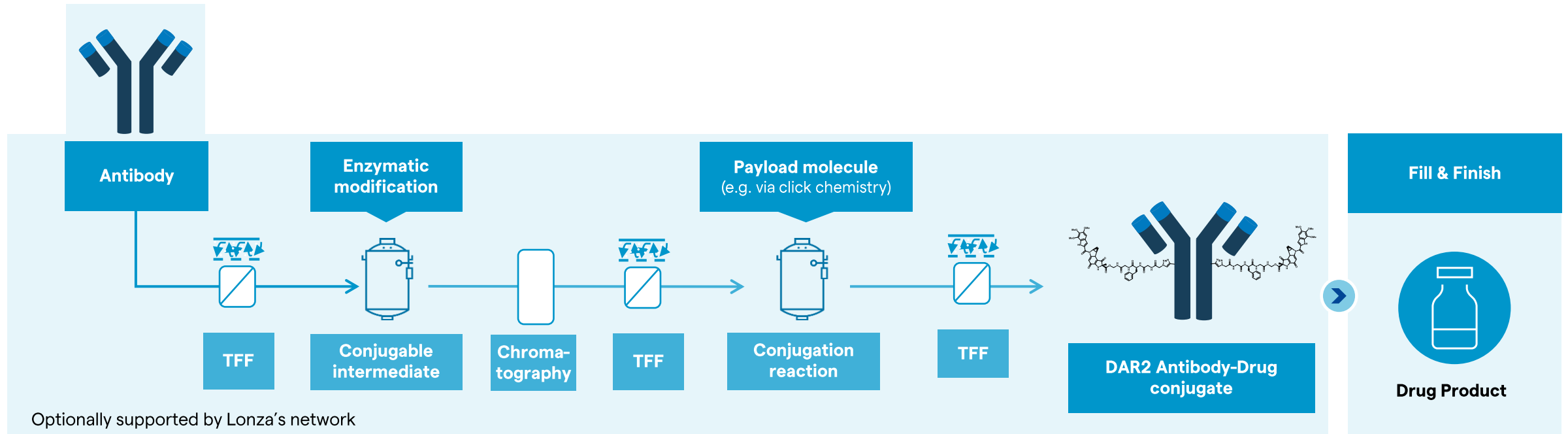
> **Site selective** conjugation technology





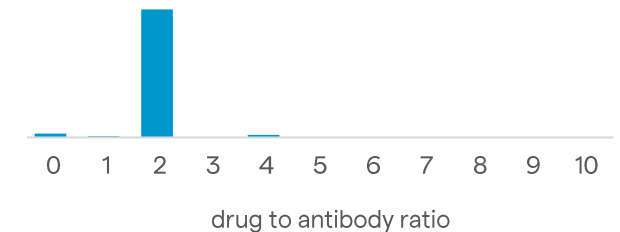
# Site selective conjugation process

## Example: enzymatic conjugation



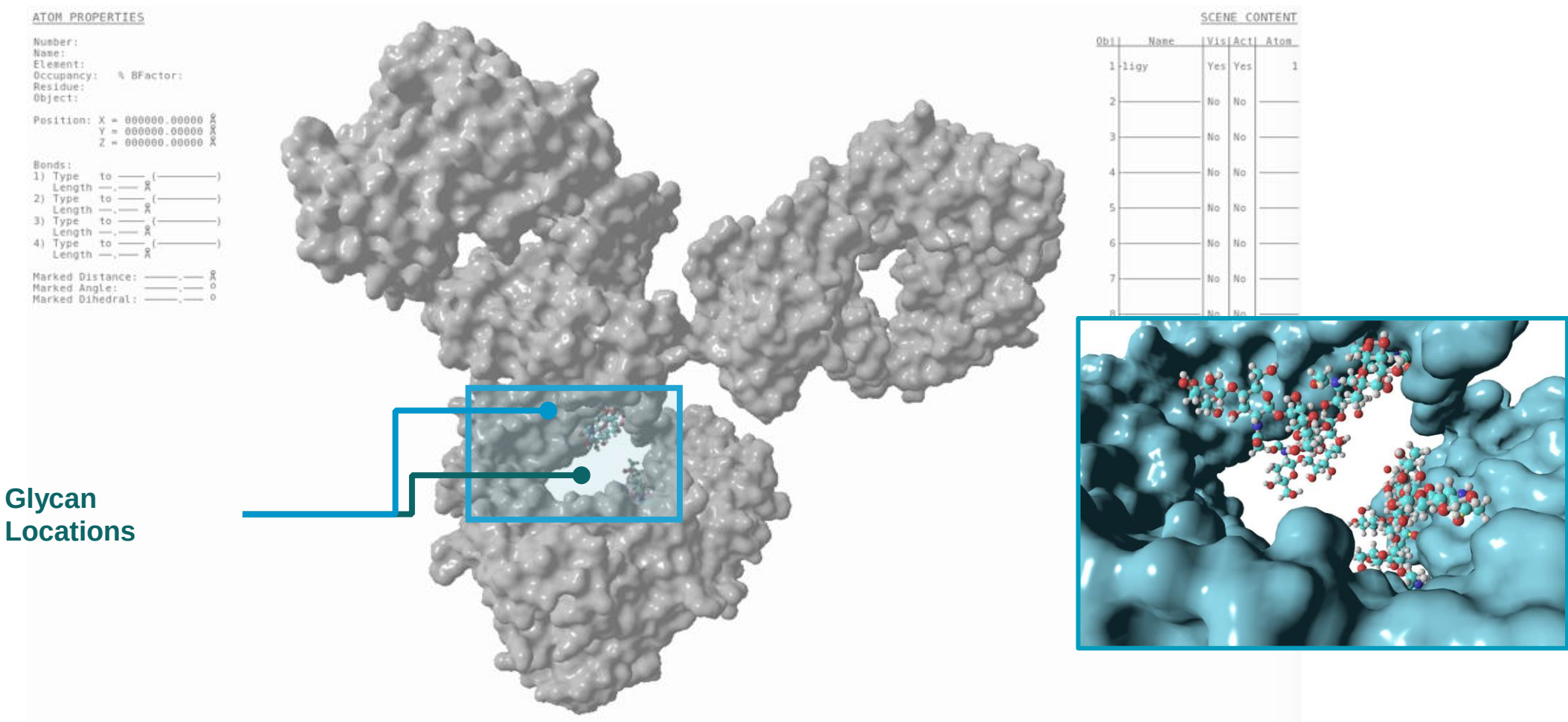
- > Standard antibody or engineered antibody
- > Highly selective enzymatic modification at a specific site on the conserved mAb backbone

- > Drug to antibody ratio (DAR): 2.0, 4.0 or above
- > **Site selective** conjugation technology

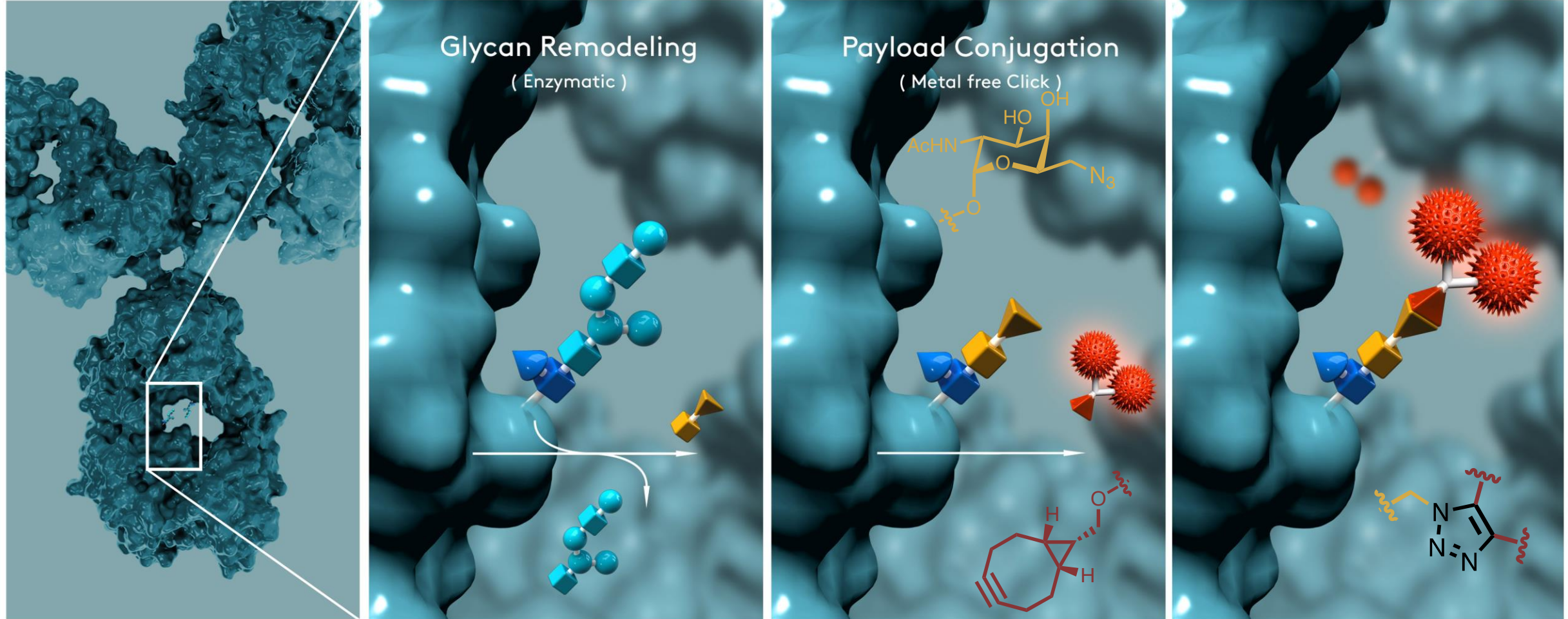


# Synaffix GlycoConnect™

The Glycan Pocket is a Special Place to Hide ADC Payloads

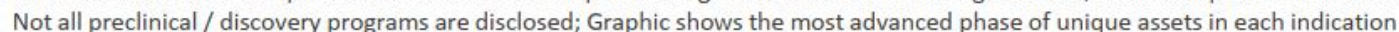


Glycan  
Locations



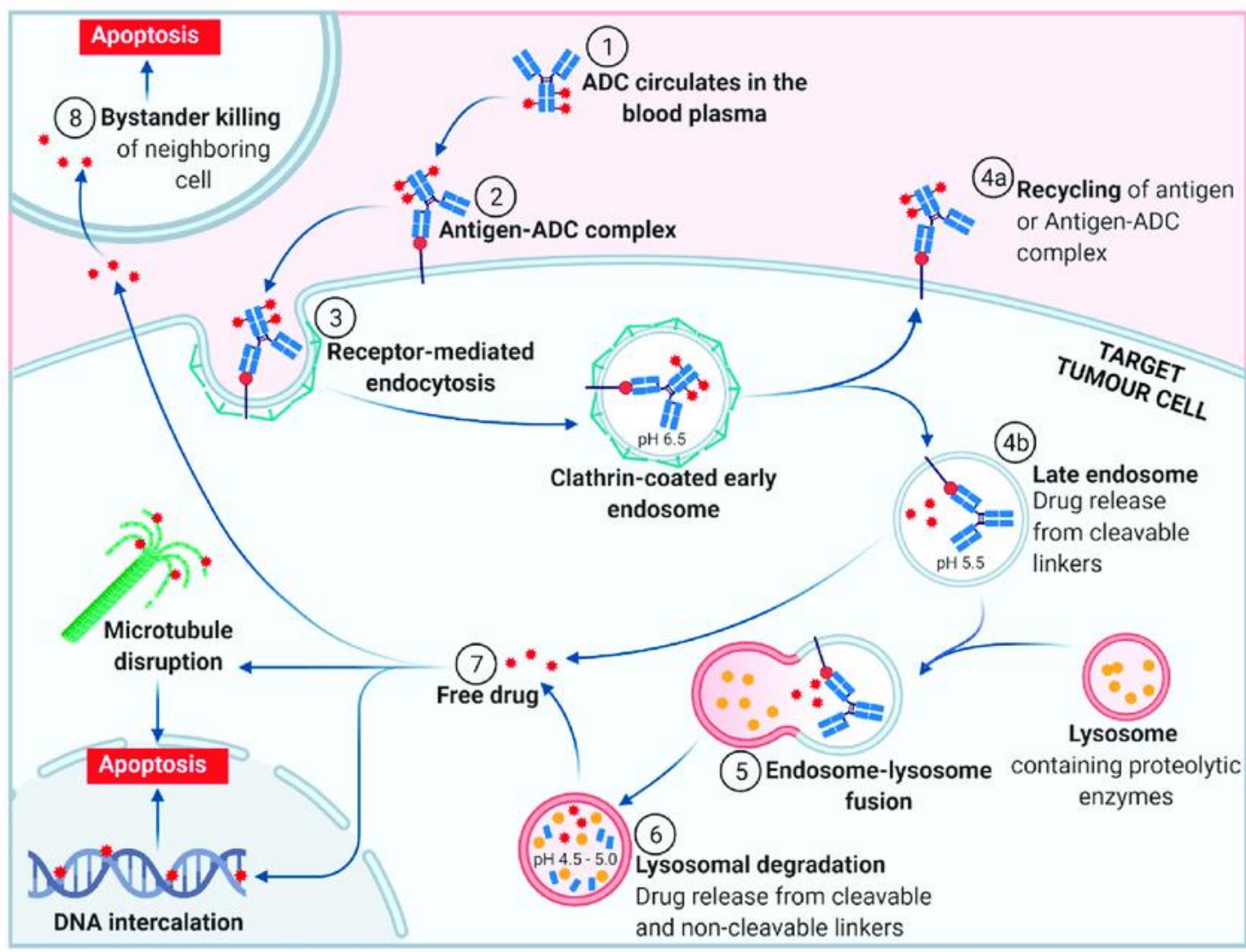
# Disease targets and clinical pipelines







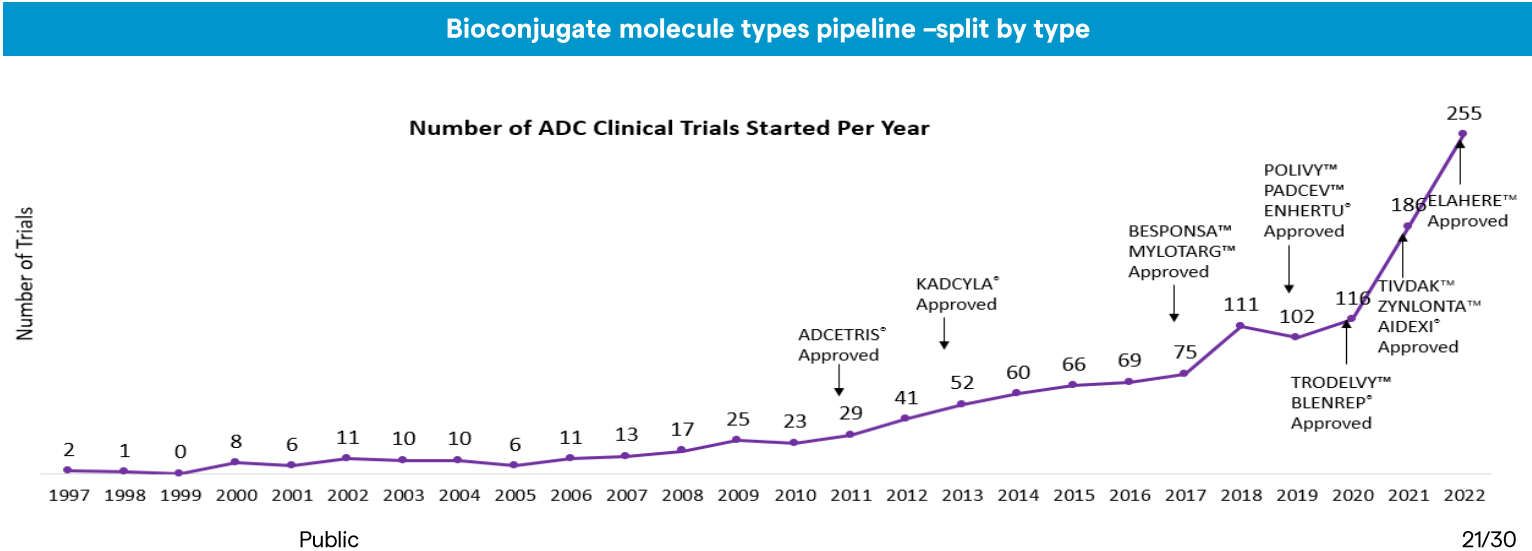
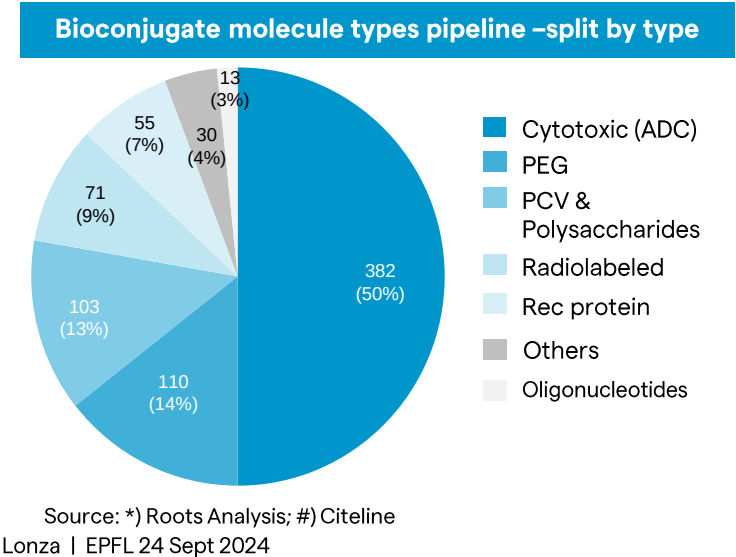
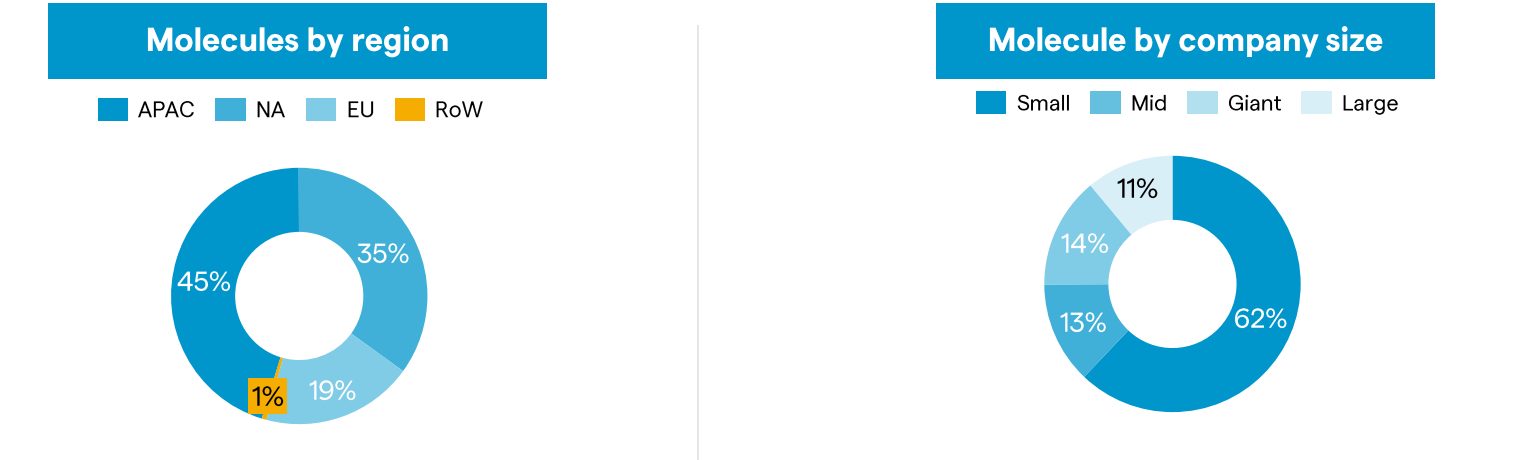
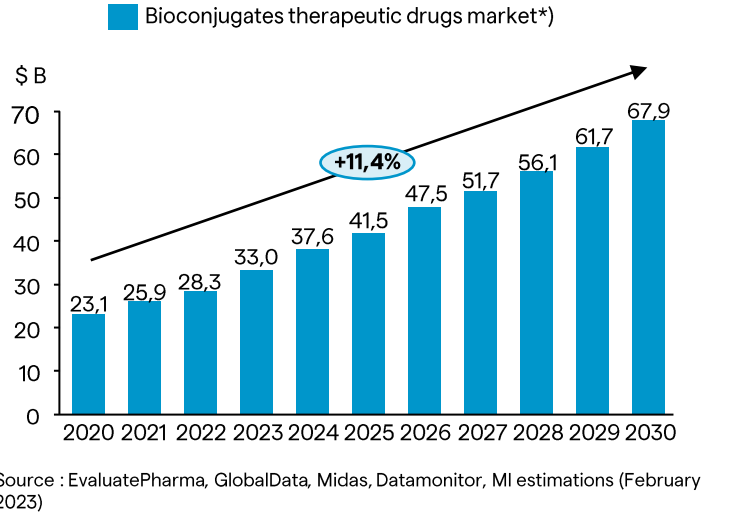
# Mode of Action



An Insight into FDA Approved Antibody-Drug Conjugates for Cancer Therapy - Scientific Figure on ResearchGate. Available from: [https://www.researchgate.net/figure/The-general-mechanism-of-action-of-an-antibody-drug-conjugate-ADC-Adapted-from\\_fig1\\_354898747](https://www.researchgate.net/figure/The-general-mechanism-of-action-of-an-antibody-drug-conjugate-ADC-Adapted-from_fig1_354898747) [accessed 13 Sept 2024]

# The Bioconjugates Market

## Diverse and Growing





# Novel bioconjugates

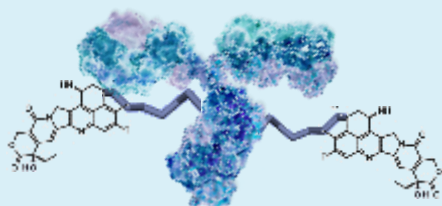
# Enabling targeted drug delivery

## Applications beyond antibody drug conjugates for cancer treatment

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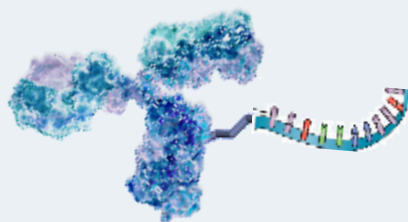
Biologics

Antibody drug conjugates  
DAR 1-8 payload agnostic

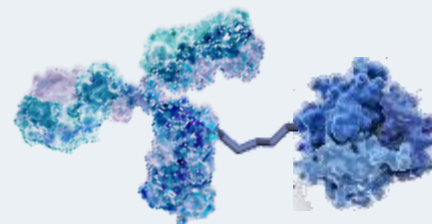


Validated modality

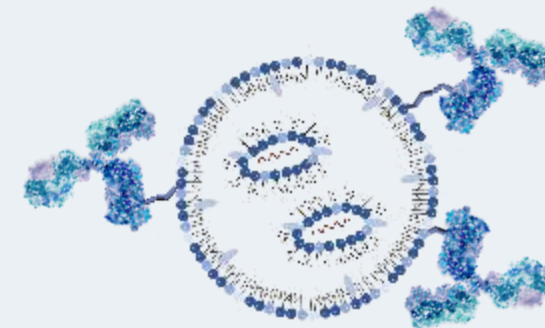
Antibody siRNA conjugates  
targeted siRNA delivery



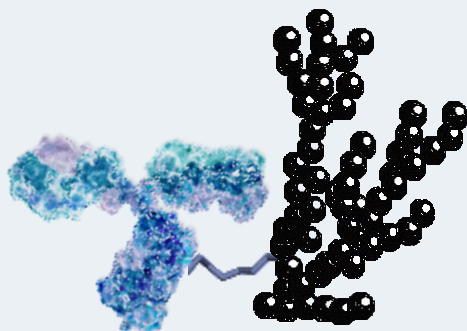
Antibody immunoconjugate  
e.g. interleukin conjugates for immunotherapy



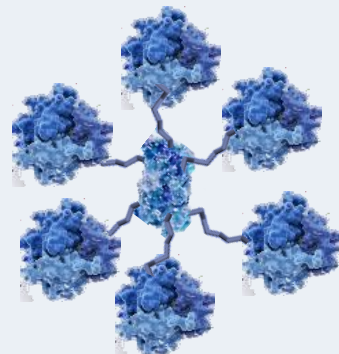
Antibody conjugated nanoparticles  
e.g. targeted LNPs for mRNA delivery



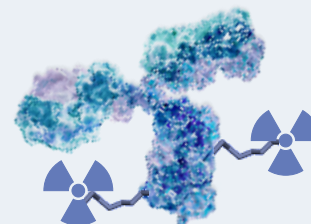
Antibody biopolymer conjugates  
Extend half life



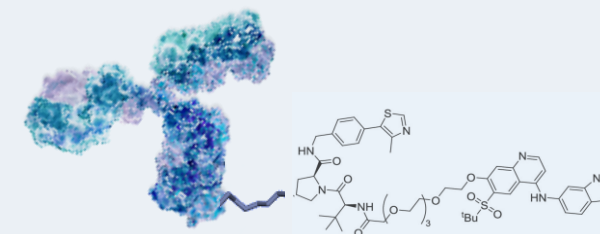
Bioconjugate vaccines  
Multiple serotypes



Radioimmunoconjugates  
Diagnostics and Treatment



Antibody PROTAC  
Targeted protein degradation





## Technology diversification



### Targeting moiety

- Antibody
- Bispecific antibody
- Nanobody

- DARpin
- Aptamer
- scFV



### Bioconjugation

- Stochastic
- Site specific
- Enzymatic conjugation

- Affinity-based conjugation
- DAR optimization
- Cleavable linkers



### Effective modality

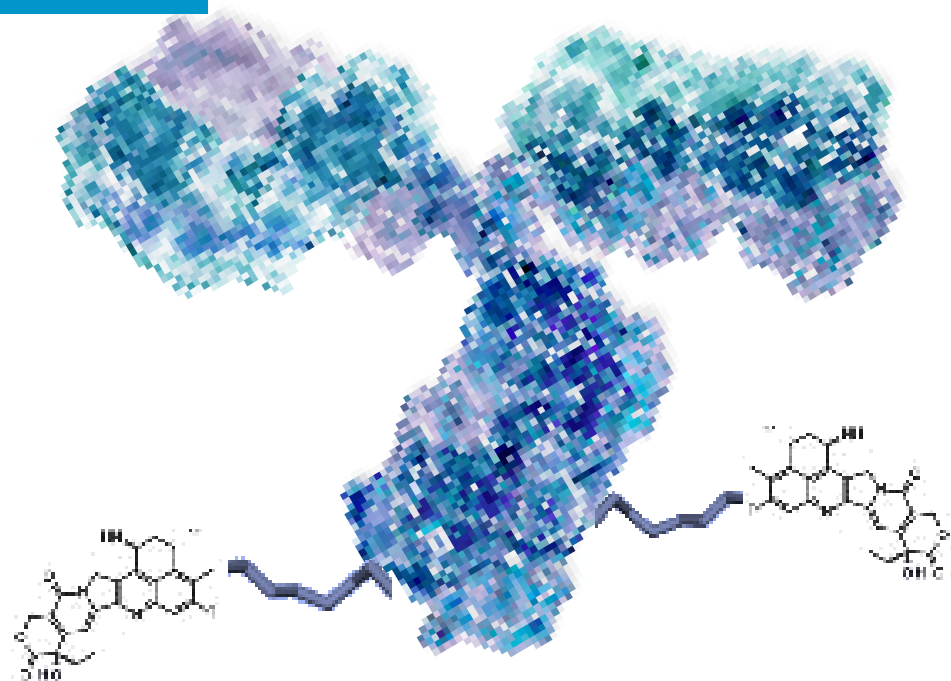
- Chelator – radioisotope
- Cytotoxic small molecule
- siRNA

- Immunostimulants e.g. interleukins
- Antibiotics
- ...

# The Challenges of Manufacturing Bioconjugates

## Antibody

Biologic production



## Linker

small molecule – chemical  
manufacturing

## Payload

small molecule –  
chemical manufacturing  
High containment due  
to cytotoxicity

## Conjugation

- Complex supply chain – managing elements from several sources
- Single source
- High cost ‘ingredients’
- Complex handling due to cytotoxicity (double grade clean rooms & gowning)
- Solvent handling
- Extensive waste handling infrastructure



# Careers in Bioconjugates

# Job Profile

## Bioprocess Engineer

- Responsible for entire processes for clinical and commercial manufacturing projects, ensuring **on-time delivery** and production within strict **safety and quality standards**
- Lead a team for preparation, **manufacturing execution**, cleaning and changeover in the suite
- Including tech transfer support, material planning, **document and batch record preparation**, training and **troubleshooting, deviation handling**
- **Liaise with customers** for their process and ensure delivery to the highest standards
- **Optimize manufacturing** where possible to increase throughput and support with innovation

Profile: Masters or PhD in bioprocess or chemical engineering. Some experience in industry helps (eg internship)



# Job Profile

## Manufacturing Science and Technology (MSAT) Scientist

- Responsible for the tech transfer of a customer process from development into manufacturing
- Manages the transfer of information, process related risks and change control
- Guides the customer for scale up, approval and optimization
- Works closely with different departments such as manufacturing, development, quality assurance and control
- Ensures right first-time process technology transfer and manufacturability in cooperation with the project cross-functional team
- Delivers process know-how, scientific expertise as well as operational excellence

Profile: Masters or PhD in bioprocessing, chemistry, biology etc. Some experience in industry helps (eg internship)



# Job Profile

## Analytical Development and Process Development

- Typically works with early phase companies and novel molecules
- Develops analytical methods essential for safe release of the final drug
- Identifies solutions for scale up from lab bench into small scale manufacturing
- Critical for getting a new drug into clinical trials
- Works closely with operations, MSAT and quality
- Closely linked to innovation and may support new technology screening

Profile: PhD in bioprocessing, chemistry, biology etc.

