Sneak Peek

CMC for Antibody-Drug Conjugates

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Summary

Future Trends

- The development of new ADC technologies: more targeted, effective, and less toxic.
- The approval of new ADC drugs: Regulatory agency will approve more ADC drugs in trial.
- The expansion of ADC drugs into new indications: Current evaluations in wider range cancers.

Key Examples of Success and Failures

- Some of the most successful ADC drugs on the market include:
  - Kadcyla: A drug used to treat breast cancer.
  - Adcetris: A drug used to treat Hodgkin lymphoma.
  - Mylotarg: A drug used to treat acute myeloid leukemia.

- Some of the ADC drugs that have failed in clinical trials include:
  - Rova-T: A drug used to treat breast cancer.
  - BAY 1053192: A drug used to treat solid tumors.
  - PF-06647210: A drug used to treat bladder cancer.

Mechanisms of Action

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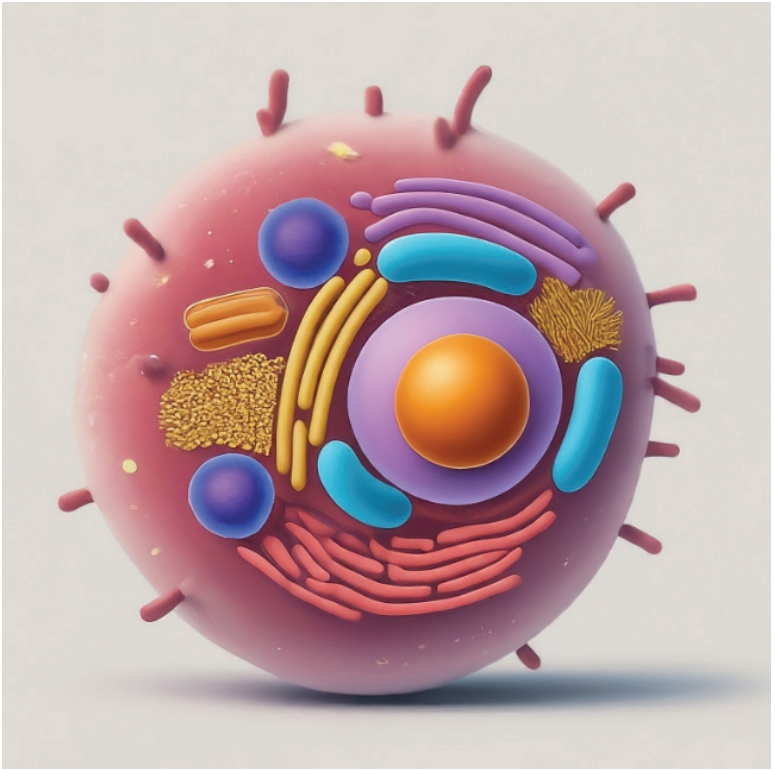
Intracellular ADCs

Successful ADCs utilize an intracellular mechanism:

- Binding to Receptor: ADCs are designed to target specific receptors overexpressed on the surface of cancer cells. When an ADC encounters its target receptor, the antibody component binds specifically to the receptor with high affinity.
- Internalization Mechanisms: After binding to the receptor, the ADC-receptor complex is internalized into the cell via several mechanisms



The rate of internalization can vary depending on factors such as the receptor expression level, the affinity of the antibody for the receptor, and the specific endocytic pathway utilized.

Overall, the efficacy of an ADC depends on the careful design of its components, including the antibody, linker, and cytotoxic payload, as well as the specific cellular mechanisms involved in its internalization, trafficking, and cytotoxic action.

Mechanisms of Action - Internalization Ranking & Significance

Ranking:

- In terms of speed: Receptor-mediated endocytosis and clathrin-mediated endocytosis are generally faster than caveolae-mediated endocytosis.
- In terms of conversion rate to the endosomal pathway: Receptor-mediated endocytosis and clathrin-mediated endocytosis have higher conversion rates compared to caveolae-mediated endocytosis.

Influence on ADC Efficacy:

- The internalization mechanism can indeed influence the overall efficacy of an ADC.
- Faster internalization rates may lead to more rapid delivery of the ADC to the endosomal pathway, increasing the likelihood of lysosomal degradation and release of the cytotoxic payload.
- Additionally, mechanisms with higher conversion rates to the endosomal pathway may ensure more efficient trafficking of the ADC to sites of lysosomal degradation, enhancing its cytotoxic effects.

Therefore, ADCs designed to exploit internalization mechanisms with rapid speed and high conversion rates to the endosomal pathway may exhibit enhanced efficacy in cancer cell killing. However, the choice of internalization mechanism should also consider other factors such as the expression level and distribution of the target receptor on cancer cells, as well as potential off-target effects on normal cells.

Drug Programme Failure: stages of failure and rates

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60% of therapeutics don't work and >92% of clinical trials fail

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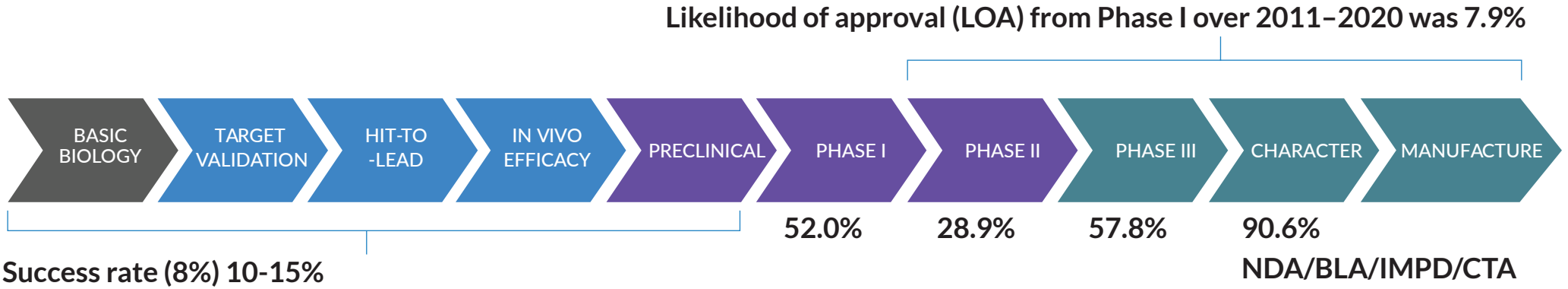

PhII failures:

- clinical efficacy (40%–50%)
- unmanageable toxicity (30%)
- poor drug-like properties (10%–15%)
- lack of commercial needs and poor strategic planning (10%)

- Drug development → market access 13 years.
- >$100bn lost for the pharmaceutical industry

The small molecule generics success rate 95%, Biosimilar success rate is 50–75%. (reference here)

The developmental risks are also higher in the case of biosimilar drugs. Market size $31bn 2023.

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Regulatory trends for ADCs

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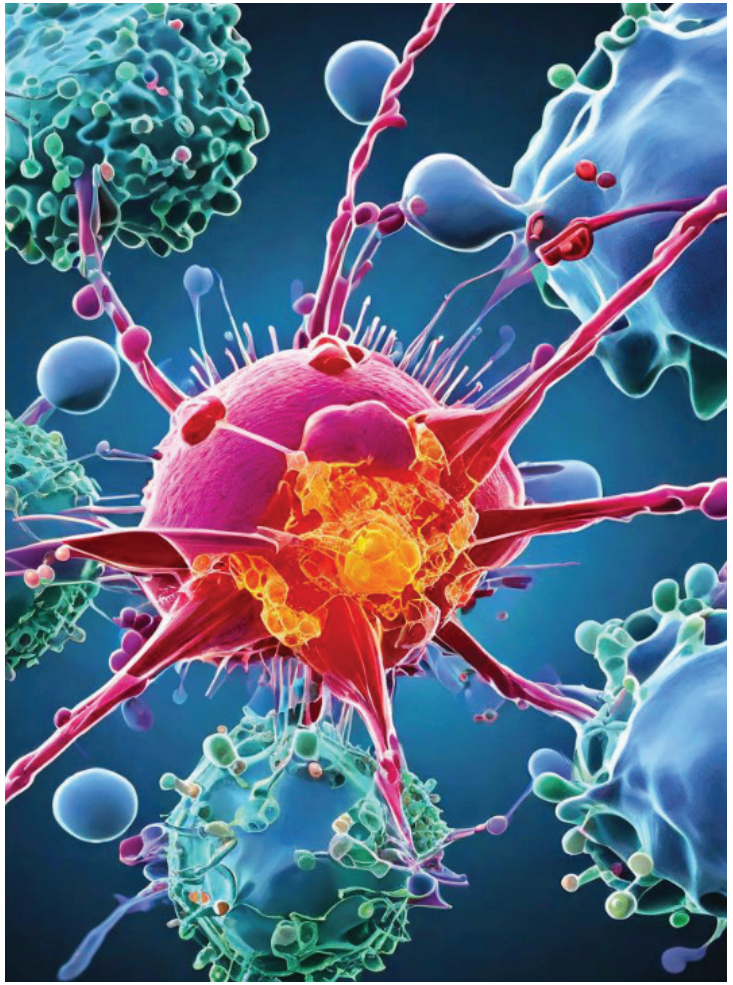
Some recent trends and considerations related to the regulatory landscape for Biologics

For Antibody-Drug Conjugates (ADCs), both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have issued specific guidance documents to provide regulatory recommendations and requirements for the development, manufacturing, and evaluation of Biologics and mAbs.

But not yet specifically about CMC requirements for ADC products. There is a recent Pharmacology Guide though Recommendations for: PK: Assessment of the ADC, its components (antibody, linker, and payload), and their metabolites.PD: Evaluation of the ADC's mechanism of action, including target binding, payload delivery, and antitumor activity.
Safety: Considerations for toxicity assessment, including off-target effects and payload-related toxicities.Clinical Trial Design: Recommendations for dose selection, patient population, and endpoints.



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