# Advancing target identification and lead optimization through mechanistic toxicology: An AI-integrated approach for translational safety assessment

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## Background

Safety-driven attrition remains a major barrier in oncology drug development. For complex modalities such as antibody–drug conjugates (ADCs), toxicity arises from interactions among **target biology, linker stability, payload mechanism**, and compound physicochemical properties. Relevant mechanistic evidence is distributed across chemistry, biology, toxicology, and clinical domains. These silos limit systematic cross-domain reasoning and hinder early identification of safety liabilities. The volume and heterogeneity of life science data now exceed the capacity of manual synthesis. Standard predictive approaches often lack contextual integration across molecular, tissue, and clinical scales. Mechanistic AI frameworks enable structured integration of curated life science evidence, supporting traceable hypotheses that link ADC design features to biological and clinical outcomes. **LeapSpace and Elsevier AI Solutions** operationalize this approach through multi-agent evidence retrieval, evaluation, and mechanistic synthesis to support hypothesis-driven safety assessment in early discovery.

## Objective

To evaluate whether a multi-agent mechanistic AI framework integrating curated Elsevier Life Science Solutions, can:

- De-silo chemical, biological, toxicological, and clinical evidence relevant to **ADC design**
- Generate biologically plausible hypotheses linking **linker and payload design** to organ-level toxicity
- Enable translational interpretation by aligning preclinical mechanistic signals with clinical AE patterns
- Support evidence-attributed decision-making for **safety, efficacy, and PK optimization** during early discovery

## Mechanistic framework for ADC safety

**Evidence foundation**

**Biology**
Embiology: target biology + tissue expression

**Chemistry**
Reaxys: linker/payload chemistry +structure-property

**Safety intelligence**
PharmaPendium: tox endpoints + regulatory context

**Biomedical evidence + competitive intelligence**
Embase: biomedical evidence support (including CT.gov and PubMed (high-recall))
ScienceDirect: full-text evidence + clinical-trial publications
Scopus: competitive intelligence (comparators, trends, networks)

Chem | Bio
**Multi-Agent Reasoning**
Tox | Clin

**Outputs (traceable + decision-ready)**

| | |
|---|---|
| **Linker instability** | **Payload lipophilicity** |
| **Premature release** | **Uptake / retention** |
| **Hepatocyte exposure** | **Bone marrow exposure** |
| **ALT / AST ↑** | **Neutropenia / cytopenias** |

**Decision levers**
- Stabilize linker / tune cleavage
- Tune payload lipophilicity
- Refine target selection / expression context

Multi-agent mechanistic synthesis across curated evidence to generate traceable ADC safety hypotheses (e.g., linker stability and payload properties) to tissue exposure and clinical phenotypes, while preserving evidence attribution.

## Why mechanistic AI frameworks are needed in ADC discovery

**Evidence scale**
- Rapidly accessible
- Structured
- Full-text (articles, patents, clinical trial reports)

**Siloed context**
- Chemistry, biology, and clinical data linked
- Context-driven
- Cross-domain links are easily tracked

**ADC complexity**
- Multi-target + payload
- Joint safety drivers
- Non-linear exposure and toxicity profiles

**Translational gap**
- Preclinical signals do not always translate to clinical outcomes
- Limited early insight into human risk

**Traceable decisions**
- Evidence-linked rationale
- Explicit safety drivers
- Stable decisions across target selection and linker retention

Mechanistic AI is needed to integrate siloed discovery evidence into traceable hypotheses that connect ADC design choices to tissue exposure and translational toxicity risk.

## Operationalizing mechanistic AI with LeapSpace and Elsevier AI solutions

These solutions operationalizes this framework by coordinating chemistry, biology, toxicology, and clinical agents to:

- Retrieve curated evidence across Elsevier Life Science Solutions, with external sources as needed
- Evaluate relevance and evidence quality across domains
- Synthesize **design → exposure → organ-level** mechanistic hypotheses with traceable evidence attribution
- Inform safety, efficacy, and PK decisions through actionable design levers and comparator insight

**Query**
- Natural-language, hypothesis-driven questions
- Define modality constraints (target, linker, payload)

**Retrieve**
- Elsevier Life Science Solutions + curated tox
- PubMed + ClinicalTrials.gov + structured databases

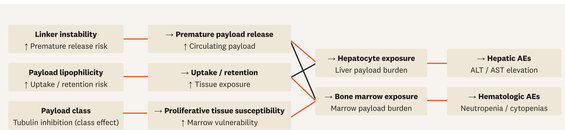
**Evaluate**
- Domain agents assess relevance & evidence quality
- Extract entities: targets, tissues, motifs, AEs

**Synthesize**
- Consensus cycles refine mechanistic hypotheses
- Link design → exposure → organ outcomes

**Optimize**
- Prioritize design levers (linker, payload, antigen)
- Inform safety, efficacy & PK decision-making

## Mechanistic mapping of ADC design to exposure-driven hepatic and hematologic liability

Highlighted design-dependent exposure pathways connecting linker/payload features to hepatic and hematologic liabilities




**Key result**
Linker instability and payload lipophilicity increase hepatocyte and bone marrow exposure, aligning with hepatic and hematologic adverse event patterns observed in similar ADCs.

Linker instability and payload lipophilicity increase hepatocyte and bone marrow exposure, supporting hepatic and hematologic risk hypotheses.

## Mechanism-to-organ injury patterns

Organ toxicities follow consistent, payload- and exposure-dependent patterns; use this mapping to anticipate liabilities and prioritize mitigation.

**Mechanistic drivers**

**Microtubule payload class (Auristatins, maytansinoids)**
Mitotic arrest; axonal transport disruption

**Linker instability / premature release**
↑ systemic free payload; off-target uptake

**Target expression in normal tissue**
On-target / off-tumor tissue injury

**Patterns are largely payload- and exposure-driven; linker stability and DAR modulate systemic payload exposure.**

**Hematologic**
Neutropenia, thrombocytopenia

**Neuropathy**
Peripheral neuropathy

**Ocular**
Keratopathy / visual symptoms (MMAF class)

**Hepatic**
ALT / AST elevations ↑ hepatotoxicity

**GI**
Diarrhea, mucositis (Topo-I prominent)

**ILD**
ILD / pneumonitis (Topo-I + combos)

## Ranked mechanistic toxicity drivers of ADCs

Integrated synthesis ranks plausible toxicity mechanisms and maps to pathways and design levers (microtubule payload focus)

**Ranked mechanisms**

1. **Payload-mediated cytotoxicity**
   Microtubule disruption → apoptosis (class-wide hematologic / neuropathy / ocular AEs)
2. **Premature payload release**
   Linker instability → systemic free payload (off-target marrow / liver exposure)
3. **On-target / off-tumor toxicity**
   Normal tissue antigen expression (therapeutic index limitation)
4. **Fc-mediated immune effects**
   ADCC / complement, hypersensitivity (patient- and construct-dependent)
5. **Catabolism / bystander toxicity**
   Lysosomal catabolites → diffusion (local collateral injury)

**Discovery decisions enabled**

Prioritize mitigation for top-ranked drivers
Payload class / DAR • Linker stability • Target expression

**Key pathways**

Microtubule inhibition | DNA damage / DDR | Topoisomerase-I inhibition | Complement / ADCC

**Computational interrogation**
- Toxicophore mapping to flag motifs linked to stress-response pathways
- Mechanistic substructure inference to connect linker/payload chemistry
- Exposure drivers → outcomes for go / no-go and design optimization decisions

Mechanistic toxicology synthesis ranks dominant ADC toxicity drivers and links them to pathways, evidence, and actionable design levers.

## Mechanism-based mitigation and lead optimization strategy

Strong mechanistic tox framing: translate drivers into what to measure next and which design levers to pull early

**Mechanistic driver → nonclinical actions → design levers**

| Mechanistic driver | Primary liability | What to measure next | Design levers |
|---|---|---|---|
| Payload class effects (microtubule) | Myelosuppression; neuropathy/ocular | Exposure–toxicity: total ADC, conjugated payload, free payload; class-specific safety screens | Select payload fit-for-indication; optimize DAR; adjust schedule |
| Linker instability / free payload | Systemic off-target marrow/liver | Human plasma stability; free payload bioanalytics; catabolite ID | Stabilize linker; use stabilized conjugation; hydrophilic linker/PEG |
| On-target / off-tumor | Tissue-specific liabilities | Tumor-normal expression (single-cell / tissue atlas); cross-reactivity panels | Refine target; tune affinity; limit bystander effect |
| Fc / immune activation (ADCC / CDC / ADA) | Infusion reactions; immune injury | FcγR binding; complement; ADA risk assessment | Fc-silent engineering; humanized scaffolds |
| Catabolism / bystander | Local collateral injury (skin / GI) | Catabolite permeability; lysosomal release kinetics | Non-cleavable linker; less permeable payload |

**Elsevier AI Solutions support evidence-attributed mechanistic synthesis and traceable decision rationale across payload, linker, target biology, and exposure**

Mechanism-based optimization strategy emphasizes exposure measurements and design levers (DAR, linker stability, conjugation strategy) to mitigate organ liabilities.

## Conclusion

- Mechanistic integration across chemistry, biology, toxicology, and clinical evidence enables earlier recognition of design-dependent **ADC toxicity drivers**
- Exposure-driven liabilities linked to **linker stability and payload properties** explain hepatic and hematologic phenotypes observed across ADC programs
- Ranked mechanistic mapping supports **actionable mitigation strategies**, including payload/DAR optimization, linker stabilization, and antigen profiling
- Structured mechanistic synthesis improves interpretability and translational confidence in **ADC discovery decisions.**

## References

- Elsevier Life Science Solutions: Embase, ScienceDirect, Scopus, Reaxys, Embiology, PharmaPendium
- Selected citations available upon request

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