# Comparative Analysis of De Novo Antibody Design Platforms: JAM-2, Chai-2, Origin-1, RFAntibody, and Latent-X2

With First-Ever Immunogenicity Data and Macrocyclic Peptide Design

Comprehensive Review of Generative AI Approaches
for Therapeutic Antibody Discovery

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**Abstract**

The field of computational antibody design has undergone a paradigm shift with the emergence of generative artificial intelligence platforms capable of designing therapeutic antibodies de novo. This comprehensive analysis examines five leading approaches: **JAM-2** from Nabla Bio, **Chai-2** from Chai Discovery, **Origin-1** from AbSci, **RFAntibody** from the Baker Lab, and **Latent-X2** from Latent Labs. We systematically compare their architectures, training methodologies, target selection strategies, and experimental validation results. JAM-2 demonstrates the highest reported hit rates (39% for VHH-Fc). Chai-2 achieves remarkable structural accuracy (<1.7 Å RMSD) and first-in-class functional GPCR agonist design. Origin-1 addresses the challenging "zero-prior" epitope problem. RFAntibody provides atomic-level precision validated by cryo-EM with full open-source availability. **Latent-X2** introduces three critical advances: (1) the first-ever immunogenicity data on AI-designed antibodies (10 human donors, ex vivo), (2) the highest design efficiency (4–24 designs per target), and (3) macrocyclic peptide design capability that matches or exceeds trillion-compound mRNA display libraries. Special emphasis is placed on oncology applications and clinical translation readiness. This analysis provides a framework for understanding the current landscape and future directions of AI-driven antibody therapeutics.

**Keywords:** de novo antibody design, generative AI, diffusion models, therapeutic antibodies, oncology, immunogenicity, macrocyclic peptides, structure prediction

# Contents

# 1 Introduction

Therapeutic antibodies represent one of the most successful classes of biopharmaceuticals, with over 100 approved products generating annual revenues exceeding $200 billion [Kaplon et al., 2024]. Traditionally, antibody discovery has relied on immunization campaigns, phage display, or hybridoma technology—approaches that are time-consuming, expensive, and often converge on limited epitope diversity [Bradbury et al., 2011].

The emergence of deep learning has fundamentally transformed protein structure prediction, exemplified by AlphaFold2's breakthrough in the CASP14 competition [Jumper et al., 2021]. This success has catalyzed efforts to extend these capabilities from structure prediction to structure generation, enabling the computational design of proteins with novel functions [Watson et al., 2023].

In 2024-2026, five distinct platforms have emerged as leading approaches for de novo antibody design:

1. **JAM-2** (Joint Atomic Modeling) from Nabla Bio: A general-purpose design system achieving double-digit hit rates across diverse targets [Nabla Bio, 2025].

2. **Chai-2** from Chai Discovery: An all-atom foundation model demonstrating atomically accurate predictions and functional GPCR agonist design [Chai Discovery, 2025].

3. **Origin-1** from AbSci: A platform specifically targeting "zero-prior" epitopes lacking structural precedent [AbSci, 2026].

4. **RFAntibody** from the Baker Lab: An RFdiffusion-based approach with cryo-EM-validated atomic precision [Bennett et al., 2025].

5. **Latent-X2** from Latent Labs: A frontier model with first-ever immunogenicity data and macrocyclic peptide capability [Latent Labs, 2025].

This review provides a systematic comparison of these platforms across multiple dimensions: architectural design, training methodology, target selection strategy, performance metrics, immunogenicity assessment, and oncology applications.

# 2 Antibody Biology Primer

Before examining computational design approaches, we provide an overview of antibody structure, function, and traditional discovery methods. This context is essential for understanding both the challenges these AI platforms address and the metrics by which they are evaluated.

## 2.1 Antibody Structure and Function

Antibodies (immunoglobulins) are Y-shaped glycoproteins produced by B cells as part of the adaptive immune response. Their primary function is to recognize and bind specific molecular targets (antigens) with high affinity and specificity, thereby neutralizing pathogens or marking them for destruction by other immune cells.

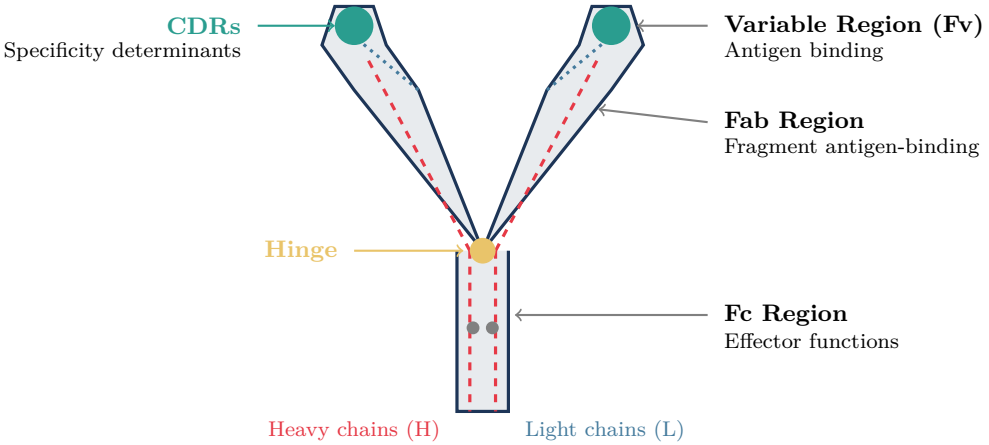


Figure 1: **Immunoglobulin G (IgG) structure.** The canonical antibody consists of two heavy chains (H, red dashed) and two light chains (L, blue dotted) arranged in a Y-shape. The Fab regions contain the variable domains responsible for antigen binding, with specificity determined by the complementarity-determining regions (CDRs, green). The Fc region mediates effector functions including complement activation and Fc receptor binding. Glycosylation sites (gray) in the Fc region influence pharmacokinetics and effector function.

### 2.1.1 Structural Hierarchy

The IgG antibody (the dominant therapeutic format) comprises:

- **Heavy Chains (H):** Two identical ∼450 amino acid chains, each containing one variable domain ($V_H$) and three constant domains ($C_H1$, $C_H2$, $C_H3$).
- **Light Chains (L):** Two identical ∼220 amino acid chains, each containing one variable domain ($V_L$) and one constant domain ($C_L$). Either kappa ($\kappa$) or lambda ($\lambda$) type.
- **Disulfide Bonds:** Inter-chain disulfides link H-H and H-L chains; intra-chain disulfides stabilize immunoglobulin domains.
- **Hinge Region:** Flexible linker between Fab and Fc, enabling bivalent binding to spatially separated epitopes.

### 2.1.2 Complementarity-Determining Regions (CDRs)

The antigen-binding site (paratope) is formed by six hypervariable loops—three from $V_H$ (HCDR1, HCDR2, HCDR3) and three from $V_L$ (LCDR1, LCDR2, LCDR3). These CDRs determine binding specificity:

Table 1: CDR characteristics and their roles in antigen recognition.

| CDR | Length Range | Variability | Role in Binding |
|---|---|---|---|
| HCDR1 | 5–7 aa | Moderate | Often contacts antigen; canonical structures |
| HCDR2 | 16–19 aa | Moderate | Broad antigen contact; some canonical structures |
| HCDR3 | 3–30+ aa | **Highest** | Primary specificity determinant; no canonical structures |
| LCDR1 | 10–17 aa | Moderate | Antigen contact; canonical structures |
| LCDR2 | 7 aa | Low | Limited antigen contact |
| LCDR3 | 7–11 aa | Moderate | Antigen contact; canonical structures |

**HCDR3** is of particular importance for computational design: it is the most variable in both length and sequence, lacks predictable canonical structures, and typically makes the most extensive contacts with the antigen. Accurate modeling and design of HCDR3 represents a key challenge for all platforms reviewed here.

### 2.2 Alternative Antibody Formats

Beyond conventional IgG, several alternative formats are relevant to computational design:

Table 2: Antibody formats and their characteristics.

| Format | Size (kDa) | Chains | Valency | Key Features |
|---|---|---|---|---|
| IgG (mAb) | ∼150 | 4 (2H + 2L) | Bivalent | Full effector function; long half-life |
| Fab | ∼50 | 2 (H + L) | Monovalent | No Fc; shorter half-life |
| scFv | ∼25 | 1 (linked) | Monovalent | Single-chain; bacterial expression |
| VHH (Nanobody) | ∼15 | 1 | Monovalent | Camelid-derived; high stability |
| VHH-Fc | ∼80 | 2 | Bivalent | Nanobody + Fc; combines advantages |

**VHH (Nanobodies):** Derived from camelid heavy-chain-only antibodies, VHHs consist of a single variable domain (∼110 amino acids). Their advantages include:

- Small size enabling tissue penetration and access to cryptic epitopes
- High thermostability and solubility
- Amenable to bacterial expression (no glycosylation required)
- Extended HCDR3 loops can penetrate concave epitopes (e.g., enzyme active sites)

JAM-2, Chai-2, and Latent-X2 all demonstrate strong performance in VHH/VHH-Fc formats, which may reflect the reduced complexity of single-domain design.

### 2.3 Macrocyclic Peptides

**Beyond antibodies**, macrocyclic peptides represent an emerging modality for targeting intracellular proteins:

- **Size:** Typically 6–20 amino acids cyclized via backbone or side-chain linkages
- **Advantages:** Cell permeability, access to intracellular targets, oral bioavailability potential
- **Traditional discovery:** mRNA display (RaPID) screens $>10^{12}$ compounds over months
- **AI approach:** Latent-X2 designs macrocycles using the same architecture as antibodies

## 3 Architectural Approaches

### 3.1 Overview of Design Paradigms

The five platforms represent distinct architectural philosophies for antibody generation, as illustrated in Figure 2.

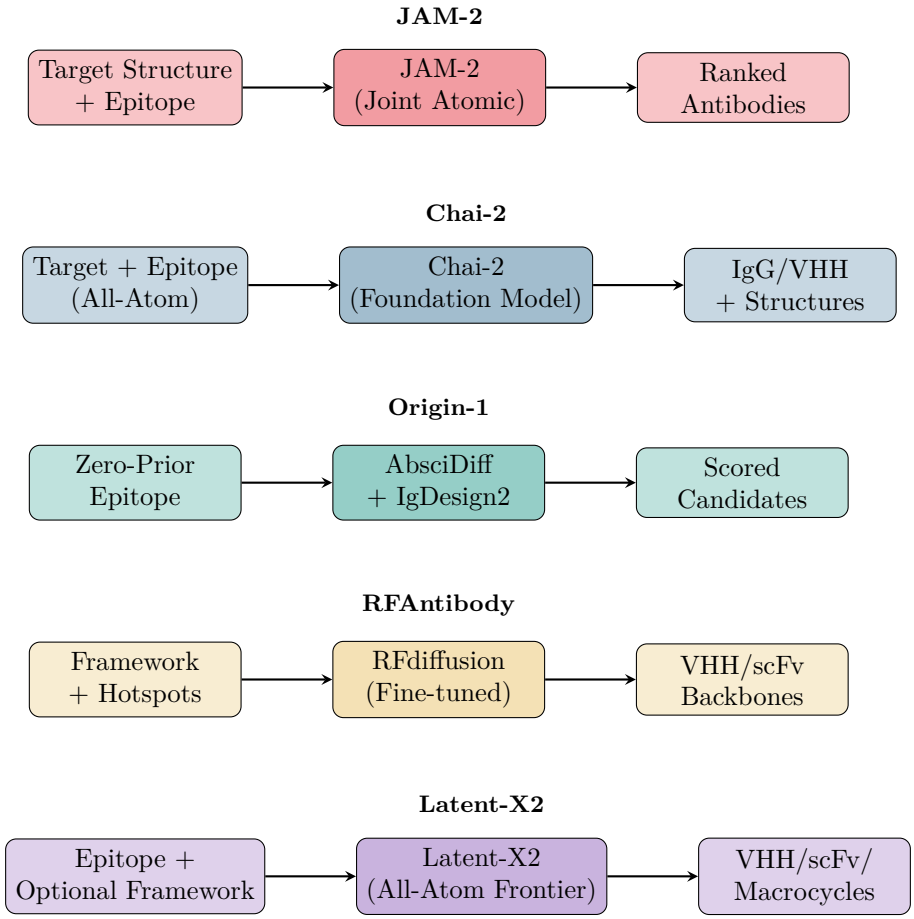


Figure 2: Schematic comparison of the five de novo antibody design pipelines. Each platform takes different input specifications and employs distinct generative architectures. Latent-X2 is unique in generating both antibody fragments and macrocyclic peptides from a unified architecture.

### 3.2 JAM-2: Joint Atomic Modeling

JAM-2 represents Nabla Bio's second-generation antibody design system. The system operates as a general-purpose de novo designer capable of generating both VHH-Fc and full-length mAb formats.

**Key Architectural Features:**

- Zero-shot design capability without target-specific training
- Complete CDR generation (IMGT definition) plus adjacent framework residues
- Generates ranked design sets (typically 45 designs per target per format)
- Design cycle completion in 2–3 days computationally

The system outputs novel sequences with >95% having RMSD >10 Å to the closest structure in SAbDab, demonstrating genuine novelty.

### 3.3 Chai-2: All-Atom Foundation Model

Chai-2 builds upon Chai-1, Chai Discovery's multimodal foundation model that demonstrated competitive performance with AlphaFold3 on structure prediction benchmarks.

**Key Architectural Features:**

- All-atom resolution modeling (not just backbone)
- Atomic-level reasoning about binding interfaces
- Direct full-length IgG format design
- Framework selection using well-characterized VH3-23 and VH3-66 germlines

### 3.4 Origin-1: Zero-Prior Epitope Targeting

Origin-1 addresses a specific challenge: targeting epitopes that lack any structural precedent from antibody-antigen or protein-protein complexes.

**Platform Components:**

1. **AbsciDiff**: All-atom structure generation via diffusion, fine-tuned from Boltz-1
2. **IgDesign2**: GNN encoder + causal transformer decoder for sequence design
3. **AbsciBind**: Modified AlphaFold-Multimer scoring protocol for design selection

### 3.5 RFAntibody: Diffusion-Based Backbone Generation

RFAntibody extends the RFdiffusion framework with antibody-specific fine-tuning and a multi-stage pipeline.

**Pipeline Components:**

1. **RFdiffusion (fine-tuned)**: Backbone generation with framework conditioning
2. **ProteinMPNN**: CDR sequence design with fixed framework sequences
3. **RoseTTAFold2 (fine-tuned)**: Structure prediction and filtering

A distinguishing feature is the MIT license, making it the only fully open-source option.

### 3.6 Latent-X2: All-Atom Frontier Model

**Latent-X2** from Latent Labs represents the newest entrant with several distinctive capabilities.

**Key Architectural Features:**

- All-atom generative model for joint sequence-structure generation
- Zero-shot design across VHH, scFv, *and macrocyclic peptides*
- Epitope conditioning with optional framework specification
- Multi-modality without task-specific fine-tuning
- Highest design efficiency reported (4–24 designs per target)

**Unique Capabilities:**

- **First immunogenicity testing:** Ex vivo T-cell assays in human donor panels
- **Macrocycle design:** Same architecture generates peptide macrocycles
- **Ultra-high efficiency:** 4–24 designs per target vs. 45–9,000+ for other platforms

# 4 Performance Metrics and Validation

## 4.1 Hit Rate Comparison

Hit rate—the percentage of computational designs that yield experimental binders—represents the primary metric of design efficacy.

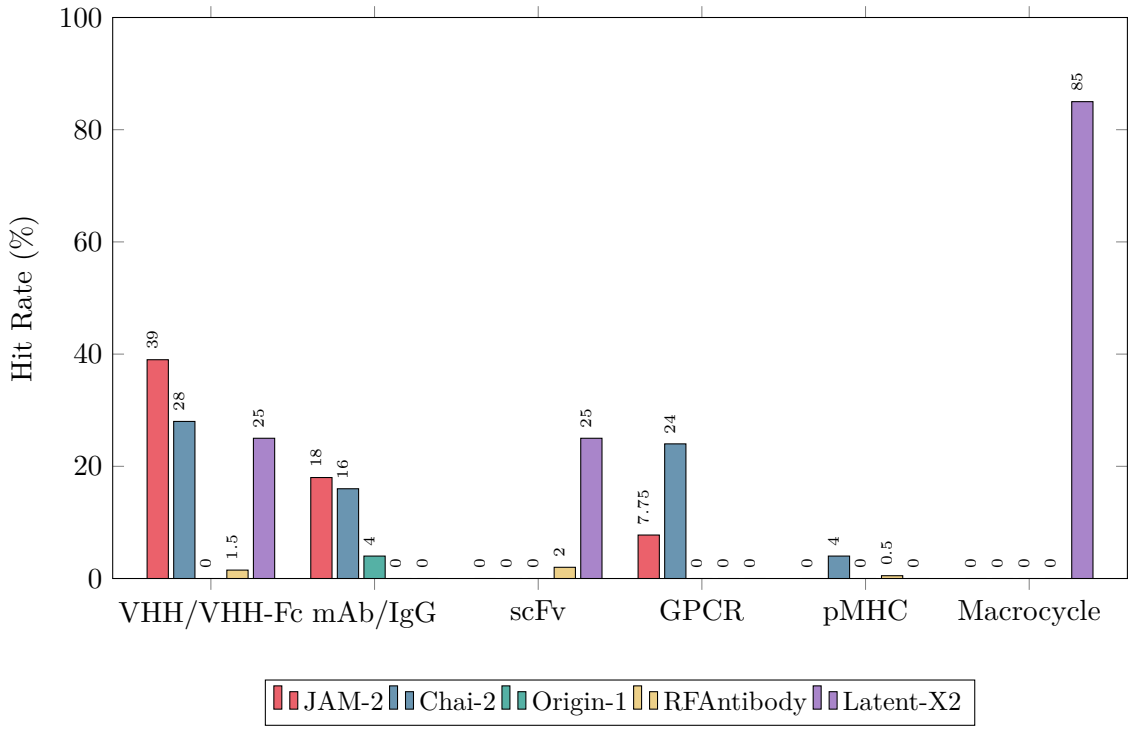


Figure 3: Hit rates across antibody formats and target categories. Values represent approximate averages where multiple targets were tested. Zero indicates format/category not tested or no hits reported. Latent-X2 macrocycle hit rate represents average of PHD2 (90%) and K-Ras G12D (80%) campaigns.

## 4.2 Binding Affinity Comparison

Table 3: Best reported binding affinities across platforms.

| Platform | Target | Best $K_D$ | Format |
|---|---|---|---|
| JAM-2 | TrkA | <100 pM | VHH-Fc (avid) |
| JAM-2 | CXCR4 | 1.4 nM | VHH-Fc |
| JAM-2 | VEGFR2 | 3.3 nM | VHH-Fc |
| Chai-2 | CCR8 | 453 pM | VHH-Fc |
| Chai-2 | KRAS G12V pMHC | 1.5 nM | IgG |
| Origin-1 | IL36RN | 89 nM | mAb (optimized) |
| RFAntibody | VEGFR2 | 1.4 nM | scFv |
| RFAntibody | PHOX2B pMHC | 400 nM | scFv |
| **Latent-X2** | **HDAC8** | **26.2 pM** | scFv |
| Latent-X2 | 1433B | 2.75 nM | VHH |
| Latent-X2 | PHD2 (macrocycle) | 1.54 nM | Macrocycle |
| Latent-X2 | K-Ras G12D | 5.43 $\mu$M | Macrocycle |

Latent-X2's 26.2 pM affinity against HDAC8 represents the tightest binding reported by any de novo antibody design platform to date.

### 4.3 Design Efficiency

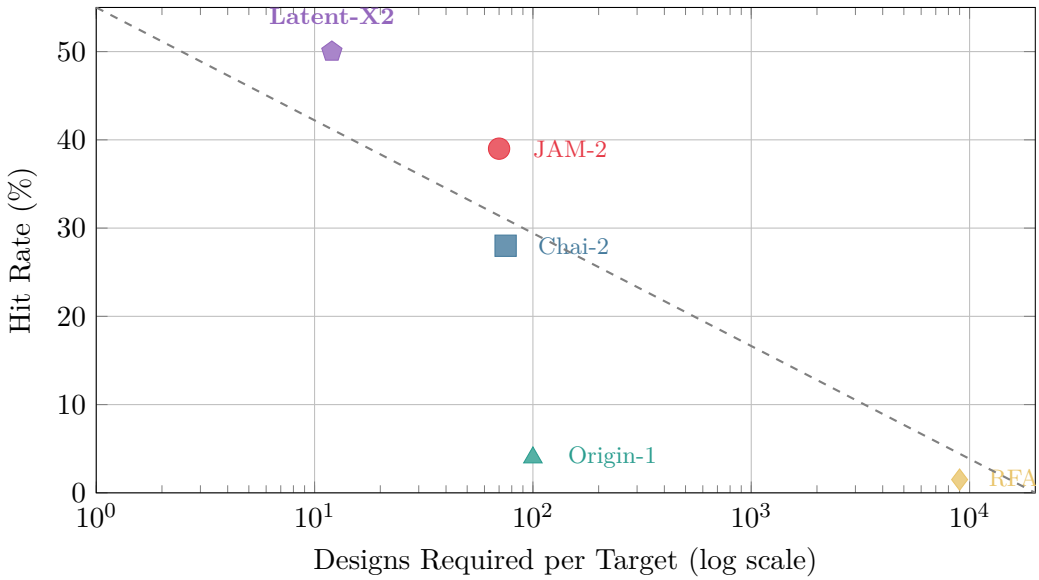


Figure 4: Design efficiency landscape. Latent-X2 occupies the upper-left "sweet spot" with the highest hit rate (50% target-level) and fewest designs required (4–24 per target). The dashed line represents an idealized efficiency frontier.

### 4.4 Structural Validation

Cryo-electron microscopy provides the gold standard for validating computational predictions. Table 4 summarizes structural validation results.

Table 4: Cryo-EM structural validation across platforms.

| Platform | Complex | Resolution | Global RMSD | Interface RMSD |
|---|---|---|---|---|
| Chai-2 | S1433B | 2.9 Å | 0.41 Å | 0.54 Å |
| | CSF1 | 3.3 Å | — | 1.9 Å |
| | EFNA5 | 3.9 Å | 1.7 Å | — |
| | IL20 | 3.3 Å | — | — |
| | EPCR | 3.5 Å | — | — |
| Origin-1 | COL6A3 | 3.0 Å | 2.56 Å | 0.96 Å |
| | AZGP1 | 3.1 Å | 1.79 Å | 1.35 Å |
| RFAntibody | Influenza HA | 3.0 Å | 1.45 Å | — |
| | TcdB-scFv6 | 3.6 Å | 0.9 Å | — |
| | TcdB-VHH | 4.6 Å | — | — |
| | SARS-CoV-2 RBD* | 3.9 Å | *Failed* | *Failed* |
| JAM-2 | — | No cryo-EM reported | | |
| **Latent-X2** | — | **No cryo-EM reported** | | |

*Design failure: correct epitope but incorrect binding mode.

**Note:** The absence of cryo-EM validation for Latent-X2 represents a significant gap in

structural characterization. While binding affinities are well-documented, atomic-level structural confirmation of the designed binding modes remains pending.

### 4.5 Developability Assessment

Drug-like properties are essential for therapeutic development.

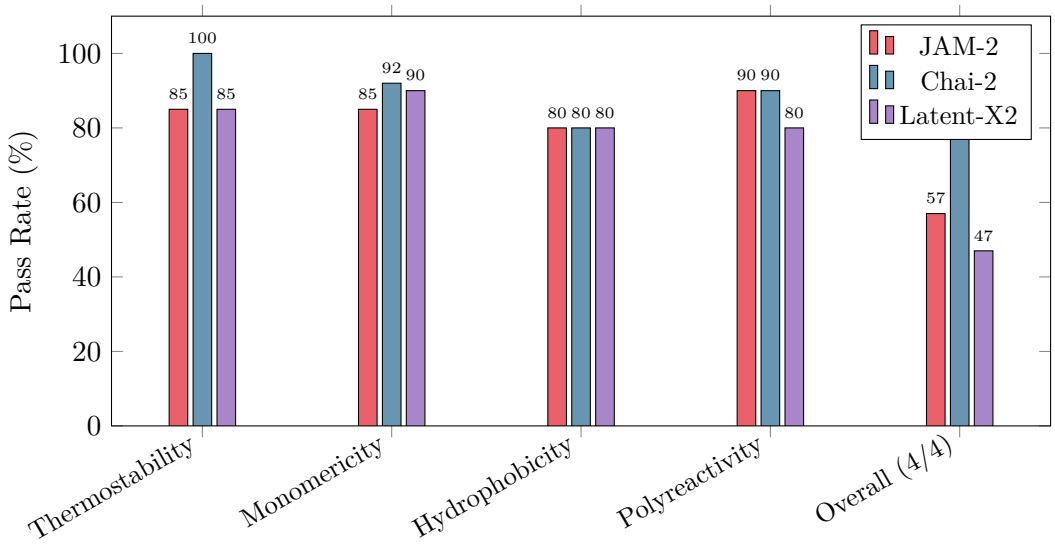


Figure 5: Developability pass rates for JAM-2, Chai-2, and Latent-X2. Origin-1 and RFAntibody reported limited developability data. Latent-X2 reports 47% pass all 4 metrics but 80% pass 3/4 metrics. All platforms use thermostability threshold of >60°C.

## 5 Immunogenicity Assessment

**This section presents the first-ever immunogenicity data on AI-designed antibodies.**

### 5.1 Context: Why Immunogenicity Matters

Immunogenicity—the potential for a therapeutic protein to elicit an immune response—is a leading cause of clinical failure for biologic drugs:

- **Anti-drug antibodies (ADAs)** can neutralize therapeutic efficacy
- **Altered pharmacokinetics:** Accelerated clearance reduces exposure
- **Safety concerns:** Anaphylaxis, infusion reactions, cross-reactivity
- **Clinical attrition:** Multiple candidates have failed in late-stage trials due to immunogenicity

Prior to Latent-X2, *no AI-designed antibody had been assessed for immunogenic potential.*

### 5.2 Study Design

Latent-X2 conducted ex vivo immunogenicity testing:

Table 5: Latent-X2 immunogenicity study design.

| Parameter | Details |
|---|---|
| Target | TNFSF9 (4-1BB ligand) |
| Test articles | 4 AI-designed VHH binders |
| Control | Caplacizumab (approved VHH therapeutic) |
| Donor panel | 10 healthy human donors |
| Cell type | Peripheral blood mononuclear cells (PBMCs) |
| Timepoints | 48 hours, 120 hours |
| Assays | T-cell proliferation, cytokine release (6 cytokines) |

### 5.3 Results

Table 6: Immunogenicity results for Latent-X2 VHH designs.

| Readout | AI-Designed VHHs | Caplacizumab | Positive Control |
|---|---|---|---|
| T-cell proliferation (48h) | No increase | No increase | Increased |
| T-cell proliferation (120h) | No increase | No increase | Increased |
| IFN-$\gamma$ | Not elevated | Not elevated | Elevated |
| IL-6 | Not elevated | Not elevated | Elevated |
| IL-10 | Not elevated | Not elevated | Elevated |
| IL-16 | Not elevated | Not elevated | Elevated |
| TNF-$\alpha$ | Not elevated | Not elevated | Elevated |

**Key Finding:** All four AI-designed VHHs showed immunogenic profiles comparable to the FDA-approved therapeutic caplacizumab.

### 5.4 Critical Limitations

**Scientific Caveats**

The following limitations must be considered when interpreting these results:

1. **Ex vivo only:** These are not in vivo animal studies or clinical trials
2. **Small donor panel:** 10 donors may miss rare responders (clinical trials use larger panels)
3. **Single target:** Results from TNFSF9 binders may not generalize to other targets
4. **No ADA testing:** Anti-drug antibody formation was not assessed
5. **Short timepoints:** Chronic dosing effects not evaluated
6. **Technical note:** IL-8 occasionally exceeded detection limits

**Animal studies and clinical trials remain necessary before any conclusions about clinical safety.**

### 5.5 Significance

Despite the limitations, this represents a meaningful milestone:

- First systematic assessment of AI-designed antibody immunogenicity

- Results are reassuring (comparable to approved drug) rather than concerning
- Establishes a methodology for future immunogenicity screening
- Addresses a key investor/regulatory question: "Has anyone even checked?"

# 6 Beyond Antibodies: Macrocyclic Peptide Design

Latent-X2 is unique among the platforms reviewed in its ability to design macrocyclic peptides using the same generative architecture as antibodies.

## 6.1 Why Macrocycles Matter

- **Intracellular access:** Unlike antibodies, macrocycles can penetrate cell membranes
- **Challenging targets:** Protein-protein interactions, transcription factors, "undruggable" oncoproteins
- **KRAS:** The most frequently mutated oncogene, intracellular, historically undruggable

## 6.2 Traditional Macrocycle Discovery: mRNA Display

The RaPID (Random non-standard Peptides Integrated Discovery) system represents the state-of-the-art:

- Library size: $>10^{12}$ unique sequences
- Timeline: Several months for a typical campaign
- Requires specialized expertise and facilities
- Has generated multiple clinical candidates

## 6.3 Latent-X2 vs. mRNA Display: Head-to-Head Comparison

Table 7: Macrocycle design: Latent-X2 vs. RaPID mRNA display.

| Metric | Latent-X2 | RaPID mRNA Display | Fold Difference |
|---|---|---|---|
| ***PHD2 (EGLN1) Target*** | | | |
| Library/designs tested | 10 | $>10^{12}$ | $10^{11}\times$ fewer |
| Hit rate | 90% | $\sim$0.000002% | — |
| Best $K_D$ | **1.54 nM** | 729 nM | **470× better** |
| ***K-Ras G12D Target*** | | | |
| Library/designs tested | 10 | $>10^{12}$ | $10^{11}\times$ fewer |
| Hit rate | 80% | $\sim$0.0000005% | — |
| Best $K_D$ | 5.43 $\mu$M | 5.53 $\mu$M | Comparable |
| GTP-state selectivity | Yes | Yes | — |

## 6.4 Implications

1. **11 orders of magnitude reduction** in experimental search space
2. **Comparable or superior affinities** with computational design
3. **Timeline compression** from months to weeks

4. **Modality flexibility:** Same platform designs antibodies AND macrocycles

This suggests AI-driven macrocycle design may transform discovery for intracellular targets similarly to how AI is transforming antibody discovery for extracellular targets.

# 7 Oncology Applications

Oncology represents the primary application domain for de novo antibody design, encompassing traditional targets and emerging modalities.

## 7.1 Comprehensive Oncology Target Table with OpenTargets Annotations

Table 8: Oncology Targets: Platform Performance with OpenTargets Disease Associations.

| Target | Platform | Affinity | Disease Assoc. | Drugs | Clinical Context |
|---|---|---|---|---|---|
| ***Immune Checkpoints*** | | | | | |
| PD-L1 | JAM-2 | Low nM | 1,996 | 13 | Pembrolizumab, durvalumab, atezolizumab approved |
| ***Receptor Tyrosine Kinases*** | | | | | |
| VEGFR2 | JAM-2 | 3.3 nM | 1,397 | 69 | Ramucirumab approved; validated target |
| TrkA | JAM-2 | <100 pM | 1,244 | 12 | Larotrectinib tumor-agnostic approval |
| FGFR1 | Chai-2 | — | 1,653 | 18 | Futibatinib approved for cholangiocarcinoma |
| ***Oncology GPCRs*** | | | | | |
| CXCR4 | JAM-2 | 1.4 nM | 1,500 | 8 | Metastasis driver; plerixafor approved |
| CXCR4 | Chai-2 | 164 nM* | 1,500 | 8 | First computational GPCR agonist |
| CCR8 | Chai-2 | 453 pM | 259 | 0 | Tumor Treg marker; first-in-class opportunity |
| GPRC5D | Chai-2 | 189 nM | 91 | 1 | Talquetamab approved Aug 2023 (myeloma) |
| ***Neoepitopes / pMHC*** | | | | | |
| KRAS G12V | Chai-2 | 1.5 nM | 1,801 | 12 | Single-residue specificity; TCR-mimetic |
| TP53 R175H | Chai-2 | — | 3,277 | 5 | Most mutated tumor suppressor |
| PHOX2B | RFAntibody | 400 nM | — | 0 | Neuroblastoma driver |
| ***Latent-X2 Oncology Targets (NEW)*** | | | | | |
| **HDAC8** | **Latent-X2** | **26.2 pM** | **353** | **355** | Epigenetic regulator; neuroblastoma, AML |
| PHD2/EGL | Latent-X2 | 1.54 nM† | 362 | 29 | Hypoxia regulator; HIF pathway |

Continued on next page

Table 8 – continued

| Target | Platform | Affinity | Disease Assoc. | Drugs | Clinical Context |
|---|---|---|---|---|---|
| MMP2 | Latent-X2 | 77 nM | 1,744 | 9 | Metastasis; extracellular matrix |
| K-Ras G12D | Latent-X2 | 5.43 $\mu$M$^{\dagger}$ | 1,801 | 12 | Most common KRAS mutation; direct binding |
| TNFSF9 | Latent-X2 | 31.1 nM | 209 | 0 | Immuno-oncology; immunogenicity tested |
| OSM | Latent-X2 | 3.26 $\mu$M | 478 | 0 | Tumor microenvironment; IL-6 family |
| ***Zero-Prior Targets*** | | | | | |
| FOLR1 | Origin-1 | — | 402 | 3 | Mirvetuximab soravtansine approved 2022 |
| IL36RN | Origin-1 | 89 nM | 245 | 0 | Tumor microenvironment modulation |

*EC50 for agonist activity. $^{\dagger}$Macrocyclic peptide format. Disease associations and drug counts from Open-Targets Platform (January 2026).

### 7.2 KRAS Targeting: Two Approaches Compared

KRAS mutations are present in ∼25% of all human cancers. Two platforms have demonstrated KRAS targeting through distinct mechanisms:

Table 9: KRAS targeting comparison: Chai-2 vs. Latent-X2.

| Aspect | Chai-2 | Latent-X2 |
|---|---|---|
| Mutation targeted | G12V | G12D |
| Modality | IgG antibody | Macrocyclic peptide |
| Mechanism | pMHC-targeting (TCR-mimetic) | Direct protein binding |
| Presentation | HLA-A*03:01 | N/A (intracellular) |
| Best affinity | 1.5 nM | 5.43 $\mu$M |
| Hit rate | 4% (2/50) | 80% (8/10) |
| Specificity | WT/G12D discrimination | GTP-state selective |
| Cellular access | Extracellular (pMHC) | Potentially intracellular |

These complementary approaches illustrate how AI platforms are tackling the KRAS problem from multiple angles.

### 7.3 GPCR Targets in Oncology

G protein-coupled receptors represent historically “undruggable” targets with significant oncology relevance.

Table 10: GPCR targeting across platforms with oncology relevance.

| Target | Platform | Hit Rate | Best $K_D$ | Oncology Relevance |
|---|---|---|---|---|
| GPRC5D | Chai-2 | 48% | 189 nM | Multiple myeloma (talquetamab) |
| CXCR4 | JAM-2 | 11.7% | 1.4 nM | Metastasis, tumor microenvironment |
| CXCR4 | Chai-2 | 11% | 164 nM* | First functional GPCR agonist |
| CCR8 | Chai-2 | 50% | 453 pM | Tumor-infiltrating Tregs; 0 approved |

*EC50 for partial agonist activity.

**Note:** Latent-X2 has not demonstrated GPCR targeting capability.

# 8 Clinical Translation Readiness

Table 11: Clinical translation readiness across platforms.

| Milestone | JAM-2 | Chai-2 | Origin-1 | RFAntibody | Latent-X2 |
|---|---|---|---|---|---|
| In vitro binding | ✓ | ✓ | ✓ | ✓ | ✓ |
| Developability | ✓ | ✓ | Partial | Limited | ✓ |
| Cryo-EM validation | Limited | ✓ (5) | ✓ (2) | ✓ (4) | **None** |
| Functional activity | Partial | ✓ | ✓ | Partial | Not reported |
| Ex vivo immunogenicity | None | None | None | None | ✓ **(10 donors)** |
| In vivo efficacy | None | None | None | None | None |
| IND-enabling studies | None | None | None | None | None |

**Key observations:**

- No platform has demonstrated in vivo efficacy or completed IND-enabling studies
- Latent-X2 is the only platform with immunogenicity data, but lacks structural validation
- Chai-2 has the most comprehensive structural validation (5 cryo-EM structures)
- The field collectively requires animal studies to progress toward clinical translation

# 9 Comparative Analysis

## 9.1 Strengths and Limitations

Table 12: Comparative strengths and limitations of each platform.

| Platform | Key Strengths | Limitations |
|---|---|---|
| **JAM-2** | • Highest hit rates (39% VHH-Fc)<br>• Comprehensive developability (57% pass all 4)<br>• GPCR orthosteric targeting<br>• Large-scale validation (923+ designs) | • Architecture not disclosed<br>• No pMHC targeting demonstrated<br>• Proprietary/not available<br>• No cryo-EM validation |
| **Chai-2** | • Atomic accuracy (<1 Å HCDR3)<br>• First functional GPCR agonists<br>• Single-residue pMHC discrimination<br>• Best structural validation (5 cryo-EM) | • Not publicly available<br>• Lower hit rates than JAM-2<br>• No immunogenicity data |
| **Origin-1** | • Zero-prior epitope capability<br>• All-atom diffusion generation<br>• Functional antagonist design | • Lower hit rates (4/10 targets)<br>• Initial $\mu$M affinities<br>• Requires optimization |
| **RFAntibody** | • Open-source (MIT license)<br>• Atomic precision validated<br>• Reproducible | • Low hit rates (0-2%)<br>• Requires 9,000+ designs<br>• Design failures occur |
| **Latent-X2** | • **First immunogenicity data**<br>• Highest efficiency (4–24 designs)<br>• Best affinity (26.2 pM)<br>• Macrocycle capability<br>• Multi-modality from single architecture | • **No cryo-EM validation**<br>• Immunogenicity ex vivo only<br>• Single target for immunogenicity<br>• No GPCR targeting shown<br>• Not open source |

## 9.2 Platform Selection Guide

Table 13: Platform selection based on use case.

| Use Case | Recommended | Rationale |
|---|---|---|
| GPCR targeting | JAM-2, Chai-2 | Demonstrated success with functional activity |
| pMHC / neoepitope | Chai-2 | Single-residue discrimination validated |
| Zero-prior epitopes | Origin-1 | Specialized capability |
| Academic / open source | RFAntibody | MIT license, reproducible |
| Fastest iteration | Latent-X2 | 4–24 designs per target |
| Immunogenicity priority | Latent-X2 | Only platform with data |
| Intracellular targets | Latent-X2 | Macrocycle capability |
| Structural validation required | Chai-2 | Most cryo-EM structures |

# 10 Discussion

## 10.1 Convergent Themes

Despite distinct architectural approaches, several convergent themes emerge:

1. **Diffusion/generative models as foundation**: Four of five platforms employ generative approaches.

2. **All-atom modeling**: Moving beyond backbone-only to all-atom resolution appears critical.

3. **Epitope conditioning**: Explicit epitope specification enables targeted interface design.

4. **Efficiency improvements**: Design counts have dropped from 9,000+ to as few as 4–24.

### 10.2 Novel Contributions from Latent-X2

Latent-X2 introduces three advances not seen in prior platforms:

1. **Immunogenicity testing**: First systematic assessment, even if limited to ex vivo
2. **Design efficiency**: 4–24 designs per target represents >100× improvement over RFAntibody
3. **Modality flexibility**: Same architecture for antibodies and macrocycles

However, the absence of structural validation (cryo-EM) represents a significant gap that should be addressed in future work.

### 10.3 Implications for Drug Discovery

The demonstrated capabilities have significant implications:

1. **Timeline compression**: Traditional 12–24 months reduced to 4–8 week cycles.
2. **Target expansion**: GPCRs, pMHCs, and intracellular targets now accessible.
3. **Epitope control**: Systematic epitope coverage from the outset.
4. **Early immunogenicity screening**: May become standard practice.
5. **Modality choice**: Antibody vs. macrocycle can be a design parameter.

### 10.4 Limitations and Gaps

Critical gaps remain across the field:

- **In vivo validation**: No platform has demonstrated in vivo efficacy or PK.
- **Clinical immunogenicity**: Ex vivo data does not predict clinical outcomes.
- **Manufacturing**: Large-scale production unvalidated.
- **Reproducibility**: Most platforms not publicly available.
- **IND pathway**: No candidates have entered formal regulatory development.

## 11 Conclusions

The emergence of JAM-2, Chai-2, Origin-1, RFAntibody, and Latent-X2 marks a transformative moment in antibody therapeutics:

1. **Five platforms** now demonstrate practical de novo antibody design capability.
2. **Hit rates of 15–50%** are achievable, representing 10–100× improvements over early methods.
3. **Drug-like affinities** (picomolar to single-digit nanomolar) achievable without optimization.
4. **Challenging targets**—GPCRs, pMHC neoepitopes, intracellular proteins—are now accessible.

5. **First immunogenicity data** suggests AI-designed antibodies may have acceptable profiles.

6. **Macrocycle capability** extends AI design beyond antibodies to intracellular targets.

The field is transitioning from "can we design antibodies computationally?" to "how do we optimally deploy these capabilities *and prove they are safe*?"

The path to clinical validation remains the critical next step. We anticipate the first IND applications for AI-designed de novo antibodies within 18–24 months.

## References


Bennett, N.R., Watson, J.L., Ragotte, R.J., et al. (2025). Atomically accurate de novo design of antibodies with RFdiffusion. *Nature*, published online. https://www.biorxiv.org/content/10.1101/2024.03.14.585103v1.full.pdf

Bradbury, A.R., Sidhu, S., Dübel, S., McCafferty, J. (2011). Beyond natural antibodies: the power of in vitro display technologies. *Nature Biotechnology*, 29(3):245–254.

Chai Discovery Team (2025). Drug-like antibody design against challenging targets with atomic precision. *bioRxiv*, doi:10.1101/2025.11.29.691346.

Jumper, J., Evans, R., Pritzel, A., et al. (2021). Highly accurate protein structure prediction with AlphaFold. *Nature*, 596(7873):583–589.

Kaplon, H., Crescioli, S., Chenoweth, A., et al. (2024). Antibodies to watch in 2024. *mAbs*, 16(1):2297450.

Latent Labs (2025). Latent-X2: A frontier model for de novo antibody and macrocycle design with immunogenicity assessment. Technical Report. https://www.latentlabs.com/wp-content/uploads/2025/12/Latent-X2-Technical-Report.pdf

Nabla Bio (2025). JAM-2: Fully computational design of drug-like antibodies with high success rates. Technical Report. https://nabla-public.s3.us-east-1.amazonaws.com/2025_Nabla_JAM2.pdf

AbSci Corporation (2026). Origin-1: a generative AI platform for de novo antibody design against novel epitopes. *bioRxiv*, doi:10.64898/2026.01.14.699389. https://www.absci.com/wp-content/uploads/2026/01/260114_Origin1_Final_Submission.pdf

Watson, J.L., Juergens, D., Bennett, N.R., et al. (2023). De novo design of protein structure and function with RFdiffusion. *Nature*, 620(7976):1089–1100.