Antibody Discovery Against GPCRs: A NEW PARADIGM

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Digital Biologics

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GPCRs: Emerging Opportunities for Antibody Therapeutics

Many of the most consequential diseases, including cancers, cardiovascular diseases, atherosclerosis, and neurological disorders, are driven by proteins that have long been considered therapeutically intractable. A substantial proportion of these belong to a class of membrane-embedded receptors known as G protein-coupled receptors (GPCRs), which regulate nearly every major physiological process in the human body[1].

Targeting GPCRs has already demonstrated profound therapeutic value across a wide range of diseases. However, despite representing the largest class of druggable membrane proteins, GPCRs remain overwhelmingly exploited by small molecules, with only three therapeutic antibodies currently marketed against this vast target space. This disparity highlights a major and largely untapped opportunity.

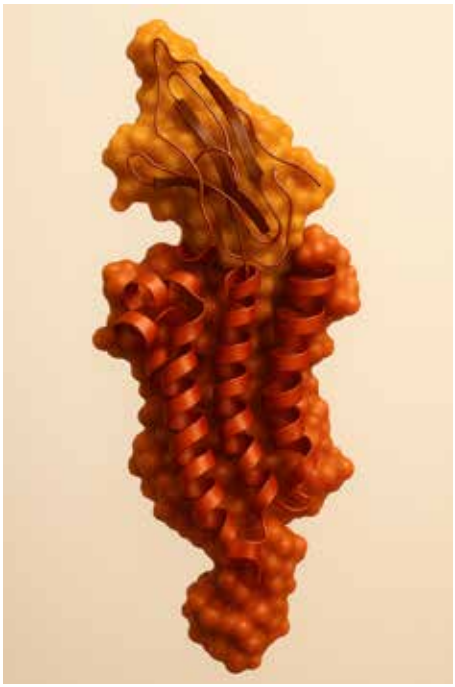
Therapeutic antibodies targeting GPCRs—including monoclonal antibodies (sdAbs), and antibody–drug conjugates (ADCs)—constitute a promising class of biologics that offer clear advantages over small molecules, including superior specificity, reduced dosing frequency, and restricted central nervous system (CNS) penetration, which may translate into improved safety profiles.

Notably, biologics (of which mAbs constitute a large proportion) exhibit a higher probability of success in drug development than small molecules – ~10–20% of biologics that enter preclinical testing ultimately reach the market, compared with ~5–10% of small-molecule drugs[2]. Moreover, biologics consistently outperform small molecules at every stage of development, with higher transition rates throughout the pipeline[3].

Despite being among the most clinically relevant drug targets known to biology, GPCRs remain largely inaccessible to conventional antibody discovery.

1. Hutchings, CJ. 2020. A review of antibody-based therapeutics targeting G protein-coupled receptors: an update. Expert Opin Biol Ther.
2. Wong et al., 2019. Estimation of clinical trial success rates and related parameters. Biostatistics.
3. Dowden & Munro, 2019. Trends in clinical success rates and therapeutic focus. Nat Rev Drug Discov.

A Persistent Bottleneck in GPCR Drug Discovery



Antibody engagement with a GPCR target.

Their complex three-dimensional structure, dynamic conformational behaviour, and membrane-embedded nature make them extraordinarily difficult to work with using traditional laboratory methods. As a result, a vast therapeutic space has remained out of reach — not because of lack of motivation, but because of fundamental limitations in how drug discovery has historically been done.

Conventional Approaches Fall Short for GPCR Targets

Classical antibody discovery relies on labour-intensive approaches, including animal immunization (hybridomas), phage display, and cell-based screening. While these methods have produced successful therapeutics (e.g. erenumab and mogamulizumab) they typically face fundamental limitations when applied to GPCRs.

A key challenge is preserving the native conformation of GPCR epitopes during antigen presentation. Hybridoma approaches often rely on extracellular domains or N-terminal fragments, which may not capture conformational epitopes present in the full receptor. Similarly, display platforms can yield binders to misfolded or non-native states due to structural disruption during antigen presentation, while single B cell cloning depends heavily on immunization strategies that successfully elicit conformationally relevant antibodies. Because these platforms were developed for soluble, stable proteins—not dynamic,

membrane-embedded GPCRs—loss of native conformation frequently leads to low hit rates, non-functional binders, and prolonged discovery timelines, increasing both cost and risk[4].

Even the current wave of AI-driven drug discovery, while powerful, is largely constrained to pattern recognition over existing biological data. When the target class itself is underrepresented in the data — as GPCRs are — these tools reach their natural limits.

Harnessing the Power of Digital Directed Evolution

Adaptive immunity solved the problem of antibody discovery by applying the principles of evolution: selection on heritable variation but, in this case, at the cellular level. The same principles that shaped life on earth are acting every minute to generate antibody variants on vast populations of B-cells that iteratively display candidates until effective solutions emerge.

Evolutionary computation uses this same logic in the digital domain. Thus, tying these two knots allows an efficient and reliable way to digital discovery at a speed and scale impossible in any laboratory.

The evolutionary algorithms in our RedQueen platform actively explore the enormous space of sequence, structure and function.

Each computational cycle generates new candidate sequences, evaluates their predicted fitness against a target, and selects the most promising for the next round — mimicking the refinement of adaptive immunity that takes generations of B-cell-mediated affinity maturation. Crucially, this process is generative rather than interpolative: it can discover solutions that have never existed in nature and that would never appear in any training dataset.

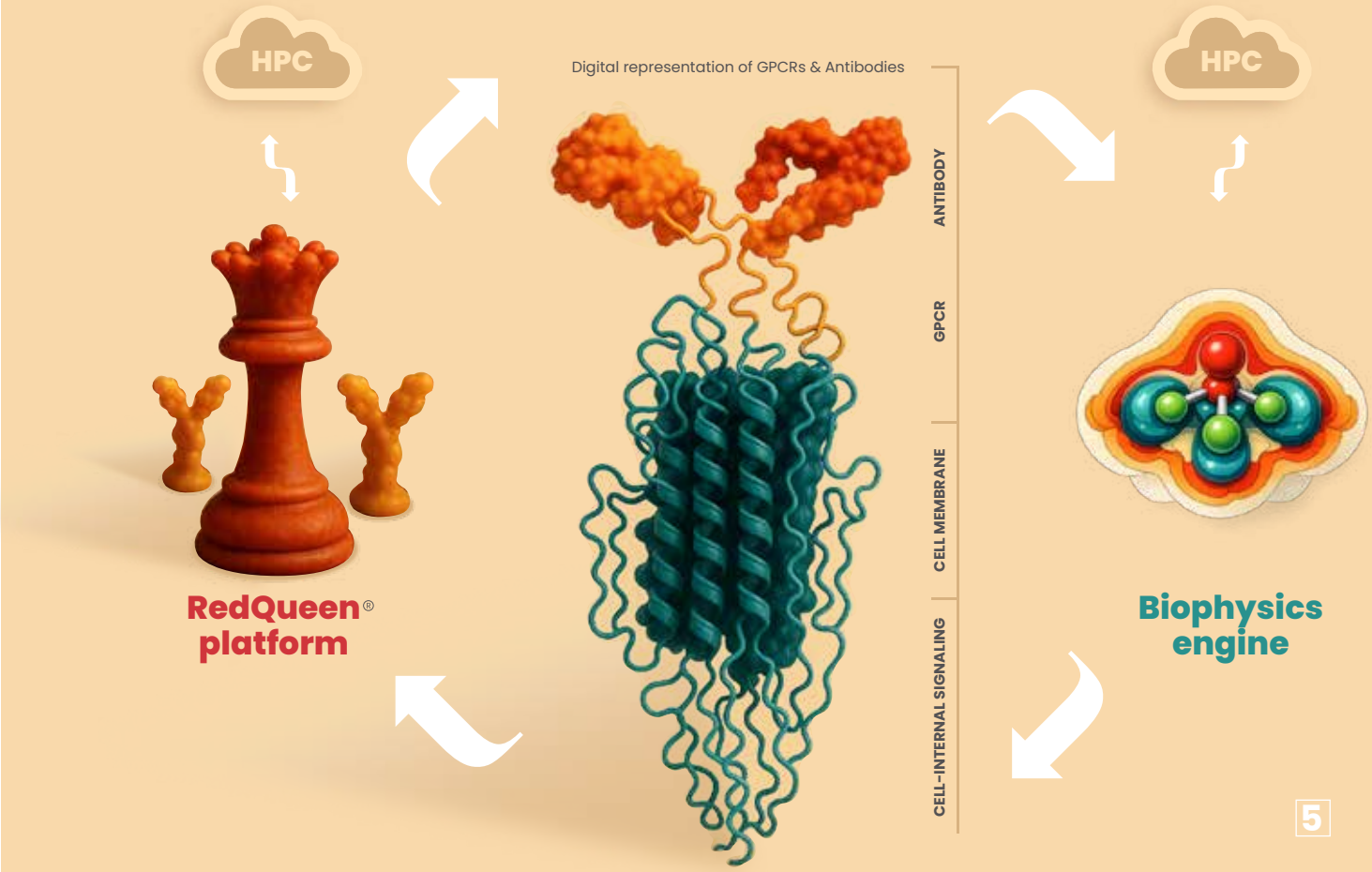
4. Xu et al., 2026. Therapeutic antibodies targeting G protein coupled receptors. Trend Pharm Scien.

Early drug discovery pipeline: The Bottlenecks for GPCRs

CLINICALLY RELEVANT	RISK OF MISFOLDING	KEY BOTTLENECK	REDUCE CONFIDENCE	ENCOURAGING OUTLOOK
STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
Target selection	**Antigen preparation**	**Antibody generation**	**Hit-to-lead**	**Preclinical models**
GPCRs are selected for their disease relevance and accessibility at the cell surface. ~34% of approved drugs target GPCRs.	GPCRs are unstable outside the membrane and easily lose the native shape required for antibody binding and assay development.	GPCRs present inherent challenges as antigens; scarce availability and poor assay scalability lead to limited screening, low hit rates, and increased discovery risk.	Low hit rates from antibody generation limit candidates, and each hit must be validated against the native receptor.	Candidates are tested *in vitro* and *in vivo*, with advancing antibodies showing high specificity and well-defined pharmacological activity.

Our solution:

Our **RedQueen Discovery Platform** moves the early discovery steps into the digital world, where the limitations of classic methods do not apply. By putting biophysical modeling first, we can go beyond AI-methods and deliver optimized antibodies for lab-testing.



At Discovery Evolution, this principle is at the core of our discovery platform, which integrates evolutionary computation with physics-based molecular modelling. By simulating the physical interactions between antibody candidates and their target receptors at an atomic level, the platform goes beyond sequence-level pattern matching to predict actual binding behaviour — delivering reliable, mechanistically grounded insights into antibody–antigen interactions. This combination of evolutionary search and physical accuracy is what allows us to operate confidently in target spaces where data-driven AI cannot.

A Digital-First Approach to Discovery

We operate at the frontier where conventional AI ends. Rather than applying machine learning to existing experimental datasets, we harness computational methods that explore biological space generatively — identifying novel antibody candidates against membrane receptors through a process grounded in the principles of molecular evolution, conducted entirely in silico.

This shift from bench to digital platform is not merely a workflow improvement. It fundamentally changes what is discoverable, how quickly, and at what cost. By removing the dependency on physical assays in the early discovery phase, we dramatically increase throughput, reduce experimental risk, and open access to target classes that have historically been off-limits.

We operate at the frontier where conventional AI ends.

We have successfully deployed **RedQueen** and found promising novel antibodies for GPCRs.

We have successfully deployed our **RedQueen** platform across 13 GPCR targets, identifying multiple novel antibody candidates. In parallel, we conducted a large-scale digital discovery campaign spanning 30 antigens, generating and evaluating thousands of antibody candidates with high developability profile. These results demonstrate the robustness, scalability, and effectiveness of our platform for antibody discovery against challenging target classes such as GPCRs.

Expanding antibody targetability across the GPCR landscape

The ability to reliably discover antibodies against GPCRs represents a significant inflection point in drug development. What was once considered a largely inaccessible target class is now emerging as one of the most attractive opportunities in biologics. With only a handful of approved antibody therapeutics against GPCRs to date, the space remains vastly underpenetrated—despite its central role in human disease.

This firmly positions Discovery Evolution as a driving force in shaping the next wave of biologics innovation.

Digital directed evolution fundamentally changes the economics and scalability of discovery. By shifting early-stage R&D into a computational framework, we reduce cost, accelerate timelines, and dramatically expand the range of viable targets. This creates a compelling opportunity to build a differentiated pipeline of first-in-class therapeutics against high-value, previously intractable GPCRs.

With the application of the **RedQueen** platform, we expect further gains in speed, precision, and, most important for the industry, success rates. This positions Discovery Evolution to not only participate in, but help define, the next wave of biologics innovation—unlocking a large and underserved therapeutic landscape with strong potential for high-value outcomes.