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Twist Biopharma: antibody candidates against GPCR therapeutic targets

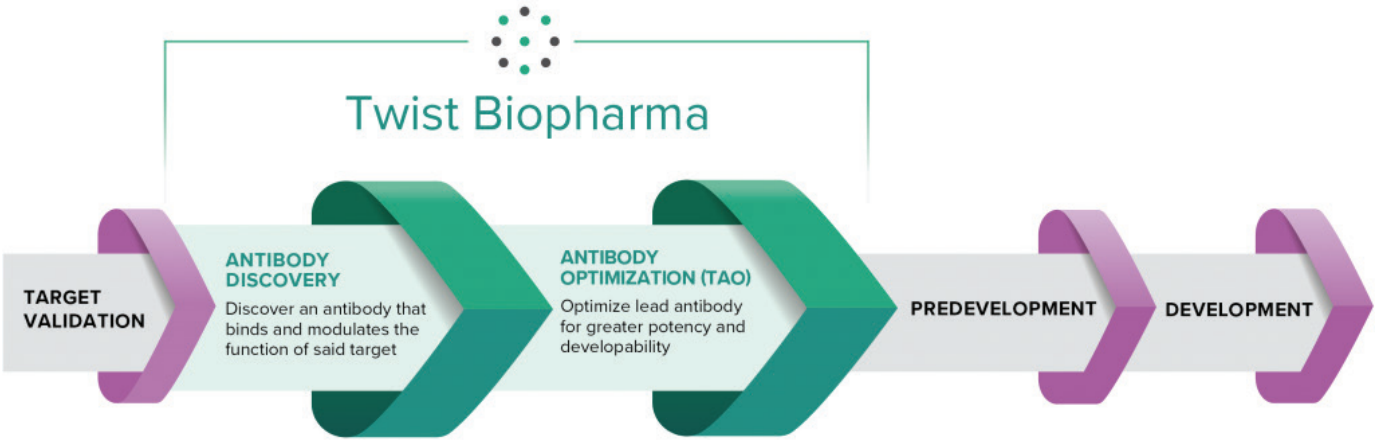
Immunotherapy has the potential to treat a wide variety of conditions, from autoimmune disease to cancer. However, the discovery of potential antibody therapeutics against key receptor proteins remains a major challenge for the traditional immunisation approaches currently available on the market. Twist Biopharma, an arm of Twist Bioscience, was built to overcome this bottleneck by leveraging Twist Bioscience's world-leading oligonucleotide synthesis platform to build high-quality antibody discovery libraries for better therapeutic discovery and development.

Recently, Twist Biopharma announced the discovery and preclinical validation of optimised, fully-human, highly-potent antibody leads against two hard-todrug receptors, including immune checkpoint inhibitor ADORA2A and bloodsugar controller GLP1R. Both antibodies are immediately available for licensing.

Twist Bioscience's high throughout oligonucleotide synthesis technology allows Twist Biopharma to rapidly build antibody discovery libraries from large volumes of oligonucleotides synthesized with base-by-base precision, and include only the sequences that occur naturally in the human body to minimise toxicity and improve pharmacokinetic properties.

By avoiding the use of randomisation (e.g. NNK bases or error-prone PCR) in the library construction process, Twist Biopharma's libraries exhibit tight uniformity, minimal bias, and even variant representation, properties that have allowed us to miniaturize and automate our phage display-driven discovery pipeline.

The libraries are also flexible in that they can be built into a variety of antibody scaffolds, such as IgG, scFv, Fab, and VHH, making Twist Biopharma uniquely situated to discover antibody candidates against hard-to-drug targets.



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How Twist Biopharma fits into the antibody discovery workflow One immuno-oncology target, ADORA2A, operates as an adenosine receptor and immune checkpoint protein that prevents the inappropriate activation of T-cells.

Unfortunately, in the context of cancer, the normal, immunosuppressive role of a checkpoint protein is counterproductive, as it can prevent a T-cell from destroying a tumour cell. Blocking its activity with a checkpoint inhibitor allows cytotoxic T-cells to destroy their tumour cell targets – effectively allowing the patient's immune system to fight back and destroy cancer.

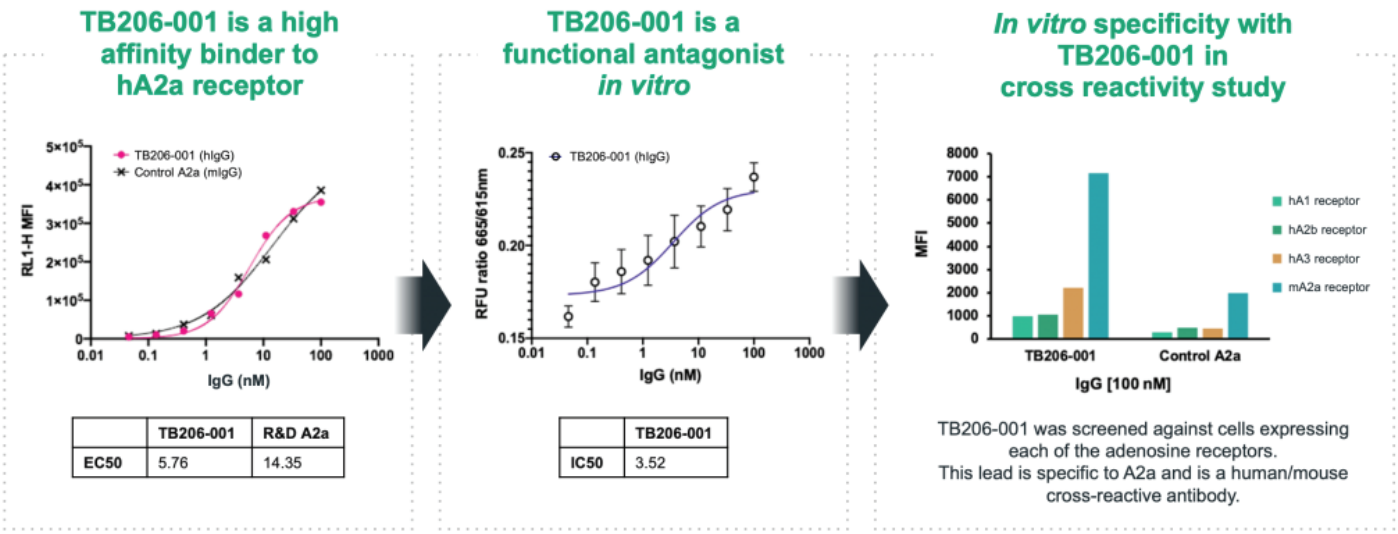
Immune checkpoint blockades are one of the newest pillars of cancer therapeutic development. Current examples in the literature for targeting ADORA2A involve small molecule antagonists1. Selective antibody binders of ADORA2A are therefore a largely untapped, exciting immunotherapeutic candidate. Using its proprietary biologics discovery and optimization platform, Twist Biopharma identified a potent high-affinity antibody, TB206-001, amongst other promising leads. In vitro and in vivo testing demonstrated efficacy in animal models of cancer.

Initial in vitro assays show that TB206-001 binds with high affinity to both human and mouse ADORA2A and has an IC5015-fold lower than a currently available, potent small-molecule inhibitor of ADORA2A, ZM-241,3852. This is a significant advance representing the first high-affinity antagonistic anti-ADORA2A antibody to enter the therapeutic development market.

TB206-001 possesses an EC50 of 5.76, showing it is a high-affinity binder to ADORA2A (left). TB206-001 possesses an IC50 of 3.52, showing it is a potent antagonist (center). Cross-reactivity studies show TB206-001 is specific to ADORA2A and is a human/mouse cross-reactive antibody.

Twist Biopharma also produced therapeutic antibody candidates against GLP1R, a receptor involved in the regulation of insulin secretion3. The company identified potent, high-affinity both GLP1R agonists and antagonists, which are now poised for further development as potential immunotherapies for obesity and hypoglycemia, respectively. GLP1R is also a target for the treatment of diabetes and metabolic disorders. Preclinical data on the group of GLP1R antibodies were published in a peer-reviewed article in mAbs.

These development-ready anti-ADORA2A and anti-GLP1R antibody candidates are immediately available for licensing from Twist Biopharma for further development. In addition, Twist Biopharma offers a suite of antibody discovery and optimization capabilities for partners looking to identify and optimize biologics of all modalities against specific disease targets.



	TB206-001	R&D A2a
EC50	5.76	14.35

	TB206-001
IC50	3.52

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There are several advantages to partnering with Twist Biopharma. “We understand every antibody discovery project is unique, and have the tools and expertise to tailor our services and workflows to the needs of each individual project. Our high-precision, highly diverse oligonucleotide libraries maximize hit-rate and expedite the process of antibody discovery. A typical discovery cycle takes only eight weeks, which allows a company the ability to explore more antibody space in less time. This translates into lower costs and failure rates, which ultimately means our partners can bring products to market much more quickly” explains Twist CEO, Emily LeProust.

Over the course of the coming year, Twist Biopharma plans to generate new high-quality libraries, as well as develop new antibody therapies against hardto-drug targets.

REFERENCES

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To learn more, please visit Twist Bioscience.

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