Twist GPCR Library Series

Unlock the G-protein coupled receptor (GPCR) interactome for antibody discovery

GPCRs are ubiquitous in human biology, participating in diverse processes such as metabolism, inflammation, neurotransmission, and carcinogenesis. The Twist GPCR Library Series leverages all known GPCR-ligand interactions and existing GPCR antibody diversities to enable antibody discovery beyond existing GPCR-targeting small molecules and antibodies, which cover only 13% of the human GPCRome. This fully human synthetic library series includes the GPCR 2.0 scFv, GPCR 3.0 scFv, and VHH hShuffle GPCR libraries.

KEY BENEFITS

Produce optimized scFv or VHH antibodies

- Proven, highly manufacturable frameworks
  - Manufacturing liabilities removed
  - Low immunogenicity
- Fully human antibody sequences
- 1 x 10^{10} diversity per library

Exploit all known GPCR binding motifs

- Over 150,000+ binding motifs, including:
  - Protein ligands, peptide ligands, and peptide mimics
  - GPCR N-terminal domains and extracellular loops
  - GPCR-binding antibodies
- Diversities from all known GPCR antibodies

Synthetic library advantage

- Avoid immunization
- Focus on effective sequence space
- Screen multiple targets simultaneously
- Engineer and optimize antibodies with ease

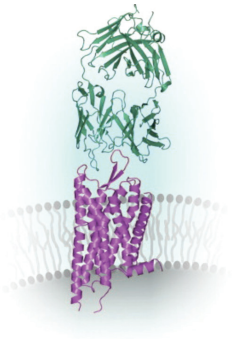
APPLICATIONS

GPCR-targeted drug discovery and development in therapeutic areas including:

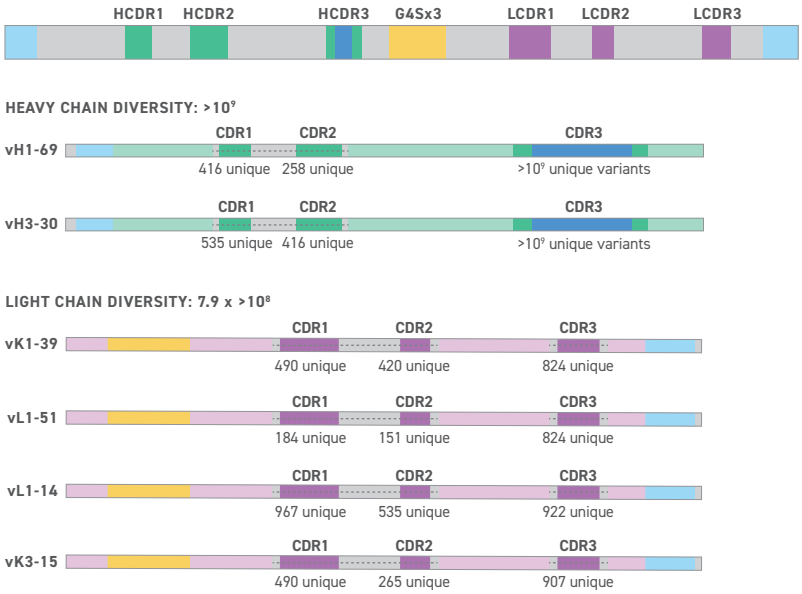
- Oncology
- Metabolic
- Inflammation
- Fibrosis
- Pain

Library Specifications

GPCR 2.0 scFv

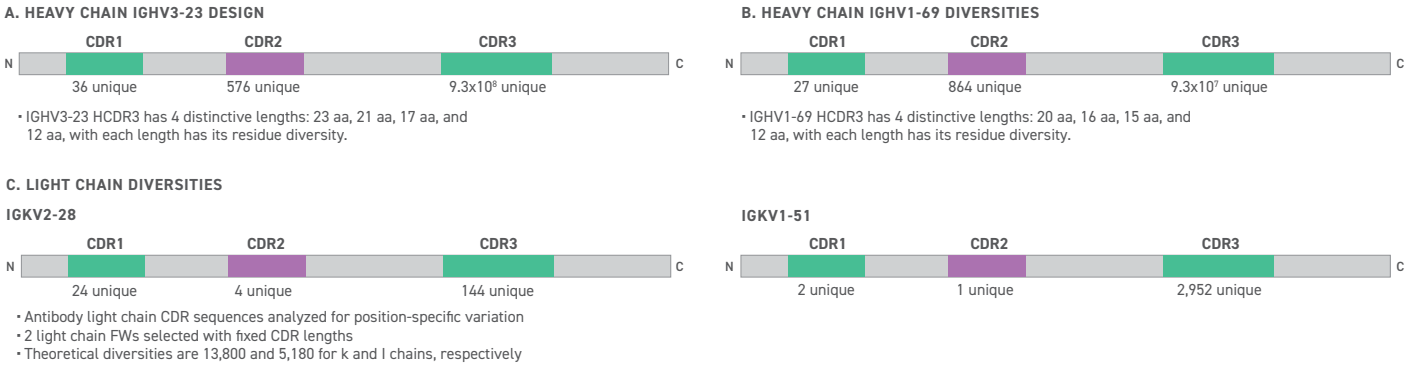


The GPCR 2.0 scFv Library integrates all known GPCR interactions with over 150,000 GPCR-binding motifs, including protein ligands, peptide ligands, peptide mimics GPCR N-terminal domains and extracellular loops, and GPCR-binding antibodies. These binding motifs were placed into five different stem regions which were selected from structural antibodies with ultra-long CDRH3. This high variation library incorporates rules of the human repertoire and has a diversity of 1x10^{10}. The library utilizes two heavy chain frameworks (VH1-69 and VH3-30) and four light chain frameworks (IGKV1-39, IGKV3-15, IGLV1-51 and IGLV2-14) which are able to tolerate these ultra-long HCDR3.



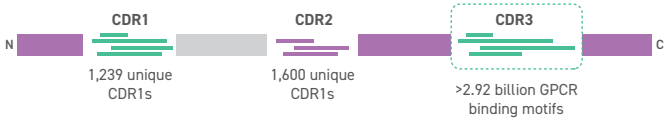
GPCR 3.0 scFv

The GPCR 3.0 scFv Library incorporates diversities from all known GPCR antibodies. Modeling based on 61 GPCR antibody sequences targeting 22 different GPCR proteins informs the design of this library. By recombining these proven antibody sequences, GPCR 3.0 scFv ensures high-quality leads. This library uses 2 heavy chain frameworks (IGVH3-23 and IGVH1-69) and 2 light chain frameworks (IGKV2-28 and IGLV1-51) and has a diversity of $1x10^{10}$.



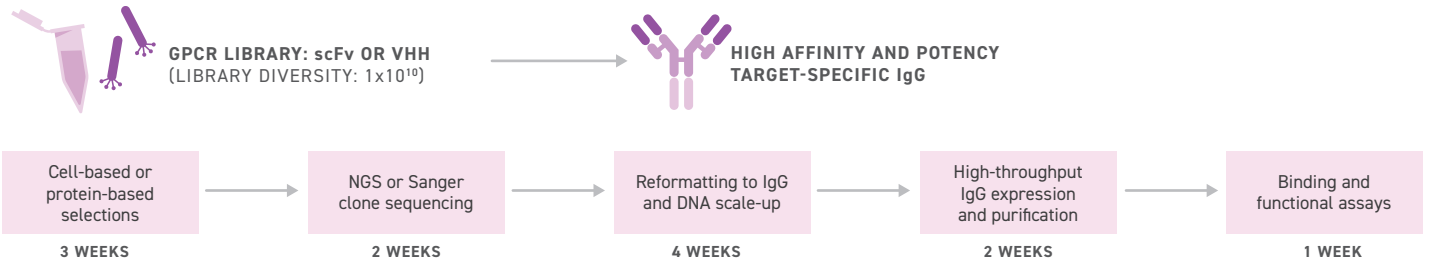
VHH hShuffle GPCR Library

The VHH hShuffle GPCR Library has a diversity of $1x10^{10}$ and transfers design elements from the GPCR 2.0 scFv Library to the highly desirable VHH format, providing access to occluded epitopes and simplifying downstream engineering and manufacturing. The design shuffles nearly 3 billion GPCR-binding motifs from GPCR 2.0 with sequences from a naïve llama repertoire (CDR1 and CDR2 regions) in the context of a partially humanized VHH framework (DP-47).



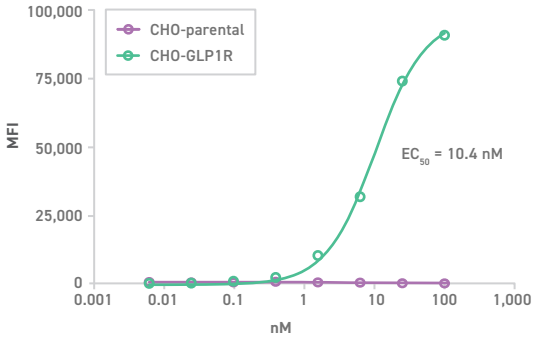
Library Panning & Screening

Go from panning to functional assays in 10–12 weeks. The process starts with phage screening a diverse Twist GPCR Library against target antigens and ends with reformatting candidate antibody fragments to full-length IgG.

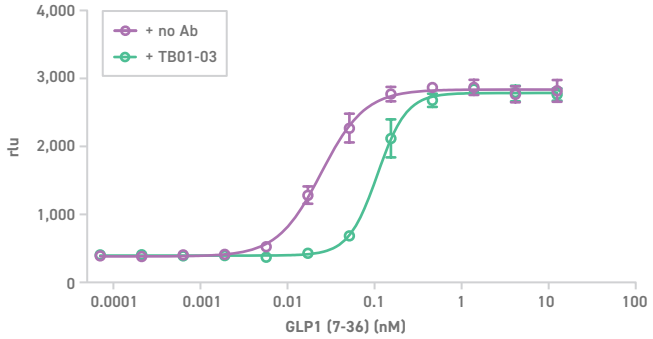


Proof of Concept Data

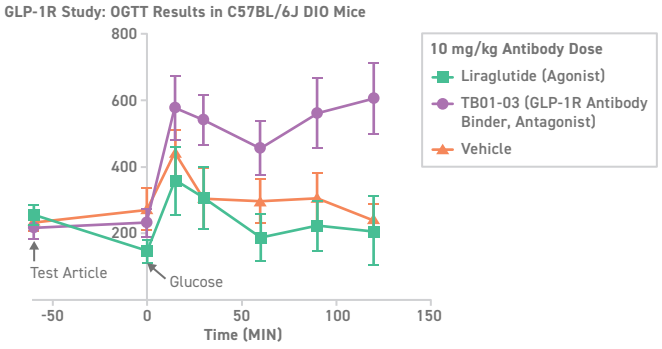
The GPCR 2.0 scFv Library was successfully panned against glucagon-like peptide-1 receptor (GLP-1R), an important target for metabolic disorders. A large number of unique clones with diverse binding affinities were identified, and TB01-3 emerged as a high-affinity, potent GLP-1R antagonist *in vitro* and *in vivo*.



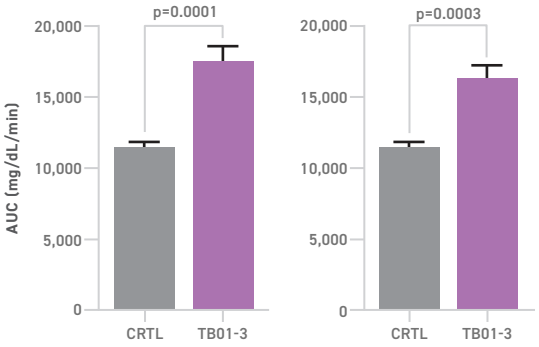
TB01-3: Binding Assays and Flow Cytometry
TB01-3 binds with nanomolar affinity to specific GPCR target-expressing CHO cells and does not bind to CHO-parental cells.



TB01-3: cAMP Assay
The functional effect of IgG binding is assessed in a cAMP assay with GPCR target-expressing cells. The presence of TB01-3 results in a negative allosteric effect.



TB01-3: *In vivo* efficacy in glucose tolerance mouse study
TB01-3 sustained high glucose levels after glucose administration in a mouse model of diet induced obesity, indicating GLP-1:GLP-1R signal blockade.



TB01-3: *In vivo* efficacy with insulin tolerance mouse study
TB01-3 stabilizes higher blood glucose levels in an insulin tolerance test using a 6 hour (left) and 19+2 hour (right) dosing regimen.