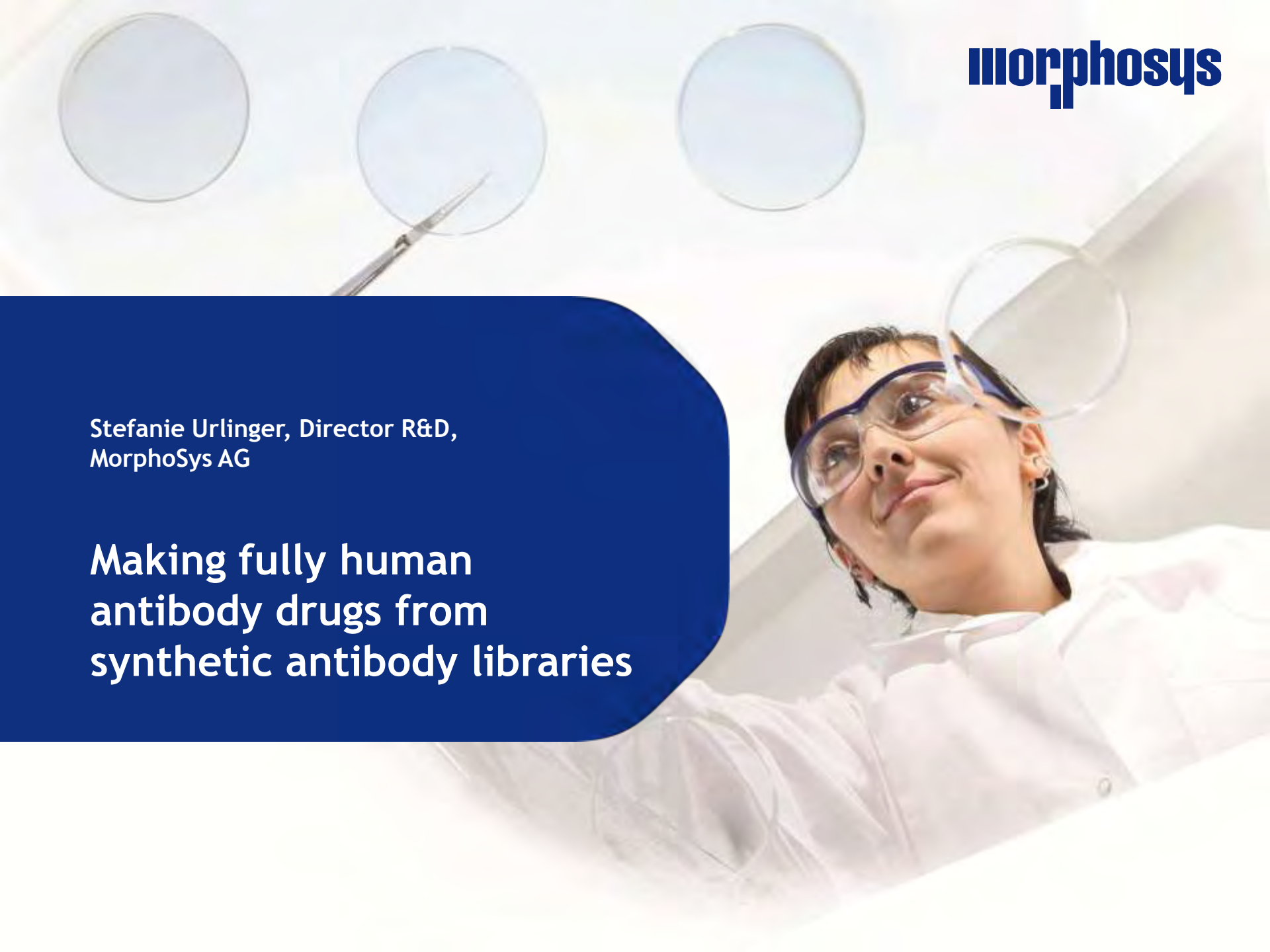
Stefanie Urlinger, Director R&D,
MorphoSys AG

Making fully human antibody drugs from synthetic antibody libraries



Introduction: MorphoSys

MorphoSys
An Overview

MorphoSys is a leader in the discovery & development of therapeutic antibodies

- Most successful antibody library technology in the industry
- Highly successful track-record of partnering with pharmaceutical companies world-wide
- Deep pipeline of proprietary and partnered therapeutic programs
- Financially strong
- New technologies to make the antibody drugs of tomorrow

The MorphoSys Pipeline
21 Clinical Programs, 81 Total

Program	Partner	Target	Indication	Discovery	Preclinic	Phase 1	Phase 2	Phase 3
Bimagrumab (BYM338)	Novartis	ActRIIB	Musculoskeletal					
Gantenerumab	Roche	Amyloid-ß	Alzheimer's Disease					
MOR103 (2 programs)	GSK	GM-CSF	Rheumatoid Arthritis Multiple Sclerosis					
Guselkumab (CNTO1959) (2 programs)	Janssen/J&J	IL23p19	Psoriasis Rheumatoid Arthritis					
BHQ880	Novartis	DKK-1	Cancer					
NOV - 3	Novartis	-	not discl.					
LFG316	Novartis	C5	Ophthalmology					
OMP-59R5	OncoMed/GSK	Notch 2	Cancer					
CNTO3157	Janssen/J&J	-	Asthma					
CNTO6785	Janssen/J&J	-	Rheumatoid Arthritis					
MOR208	-	CD19	CLL, NHL, ALL					
MOR202	Celgene/MOR	CD38	Multiple Myeloma					
BAY94-9343	Bayer Healthcare	Mesothelin (ADC)	Cancer					
BI - 1	BI	-	not discl.					
VAY736	Novartis	BAFF-R	Inflammation					
LJM716	Novartis	HER3	Cancer					
Vantictumab (OMP-18R5)	OncoMed/Bayer	Fzd 7	Cancer					
PFE - 1	Pfizer	-	Cancer					
NOV - 7	Novartis	-	Ophthalmology					
22 Programs	Various Partners	-	Various Indications					
38 Programs	Various Partners 3 Proprietary Pr.	-	Various Indications					

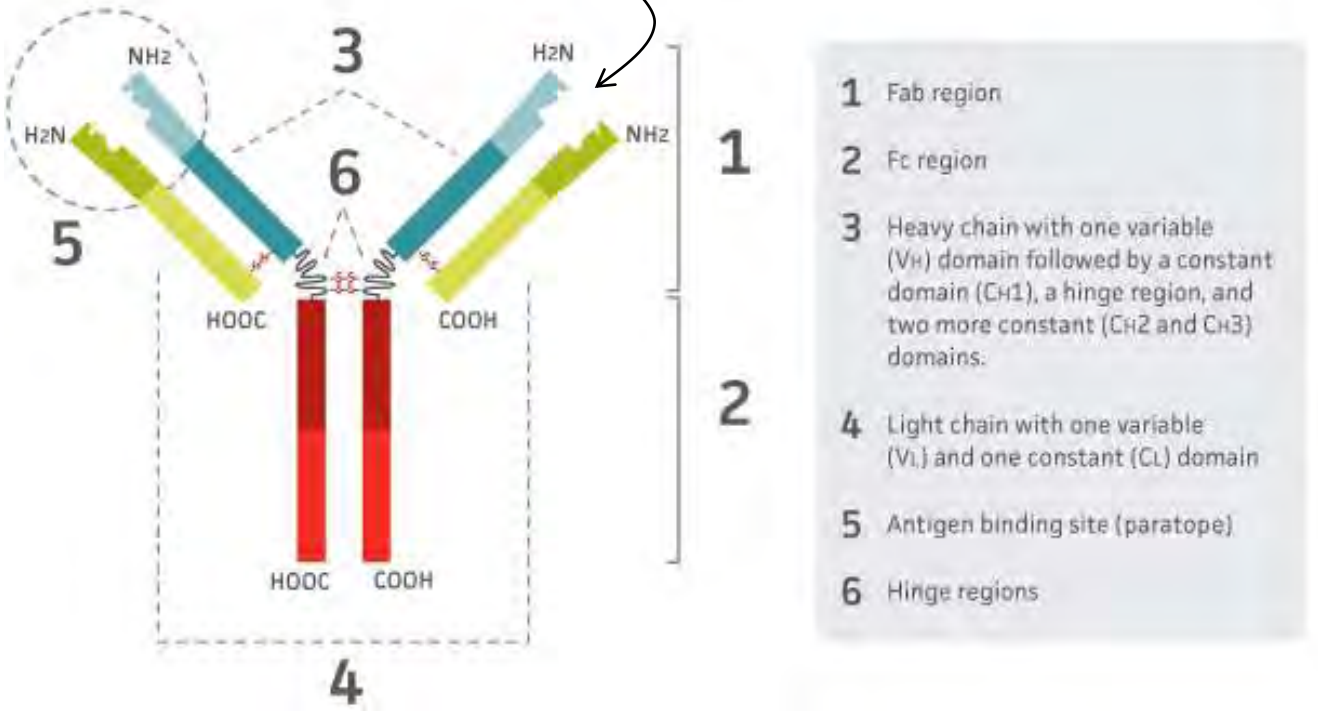
74 Partnered Programs
7 MOR Programs

Antibody Technologies

Glossary: Antibodies

Variable region (5) consists of frameworks („scaffold“) and CDRs which provide the antigen binding site

Antigen binds to hypervariable regions (= complementarity determining regions; CDRs) within Fab (1)



1 Fab region

2 Fc region

3 Heavy chain with one variable (V_H) domain followed by a constant domain (C_H1), a hinge region, and two more constant (C_H2 and C_H3) domains.

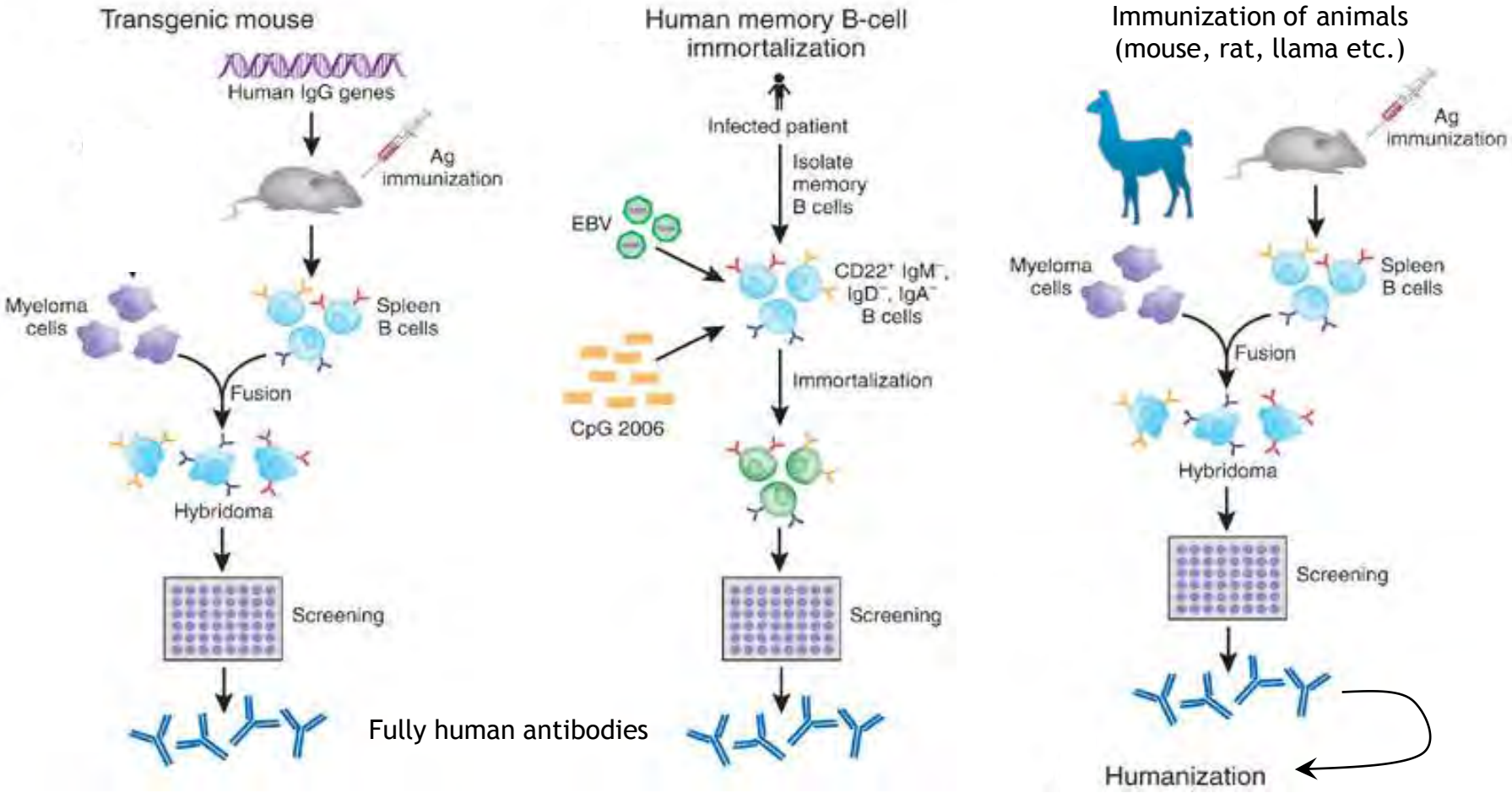
4 Light chain with one variable (V_L) and one constant (C_L) domain

5 Antigen binding site (paratope)

6 Hinge regions

Picture from: www.bioatla.com

Human Antibody Techniques:
In vivo Technologies – „Hybridoma Approaches“

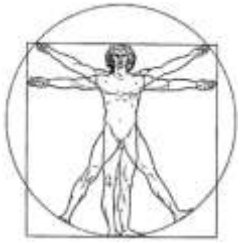


Fully human antibodies

Adapted from: Wayne A Marasco & Jianhua Sui. Nature Biotechnology 25, 1421 - 1434 (2007)

Human Antibody Techniques:
In vitro Technologies – „Antibody Display“

V-gene & CDR source



- naive
- immunized
- disease-related

mRNA isolated from B-cells

databases & publications

V-region DNA origin

natural (PCR)

semi-synthetic

synthetic (gene synthesis)

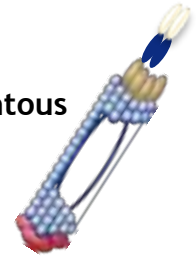
Fragment format for display

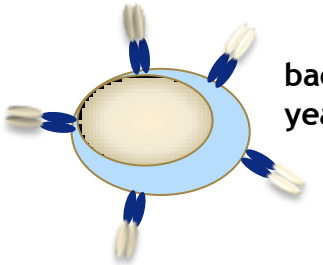
scFv

Fab

Display technology

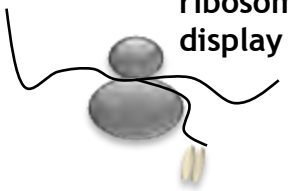
filamentous phage





bacterial or yeast display

ribosome display



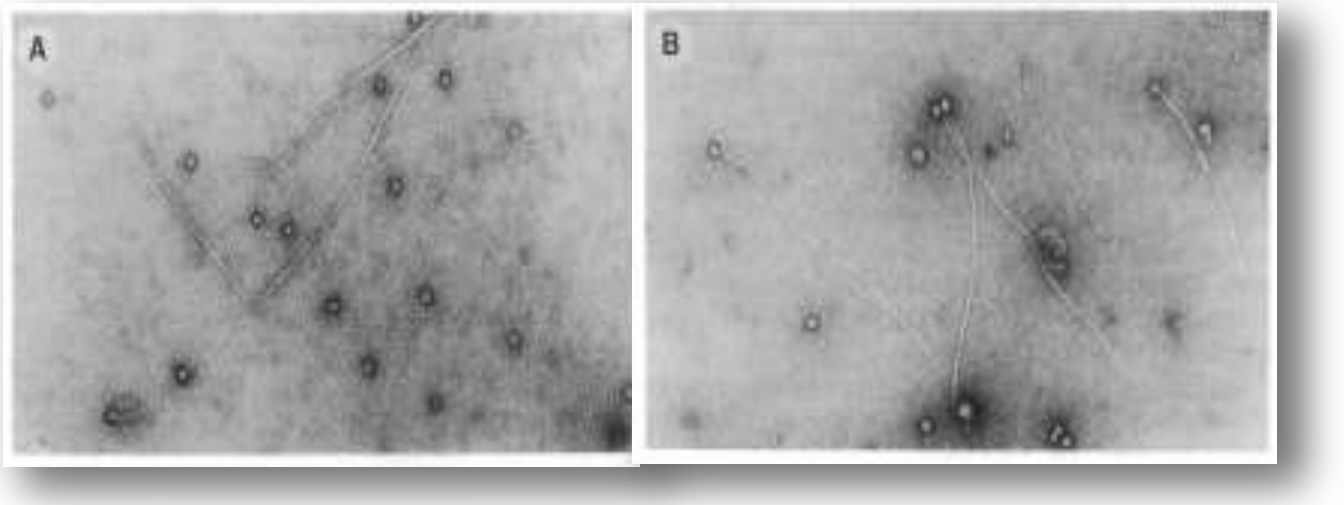
Adapted from: H.R. Hoogenboom & P. Chames.
Natural and designer binding sites made by phage display technology. Immunology Today 21 (2000) p. 371–378

MorphoSys' Technology Platforms are Based on Phage Display

Phage Display Using Filamentous Phage M13

Before selection

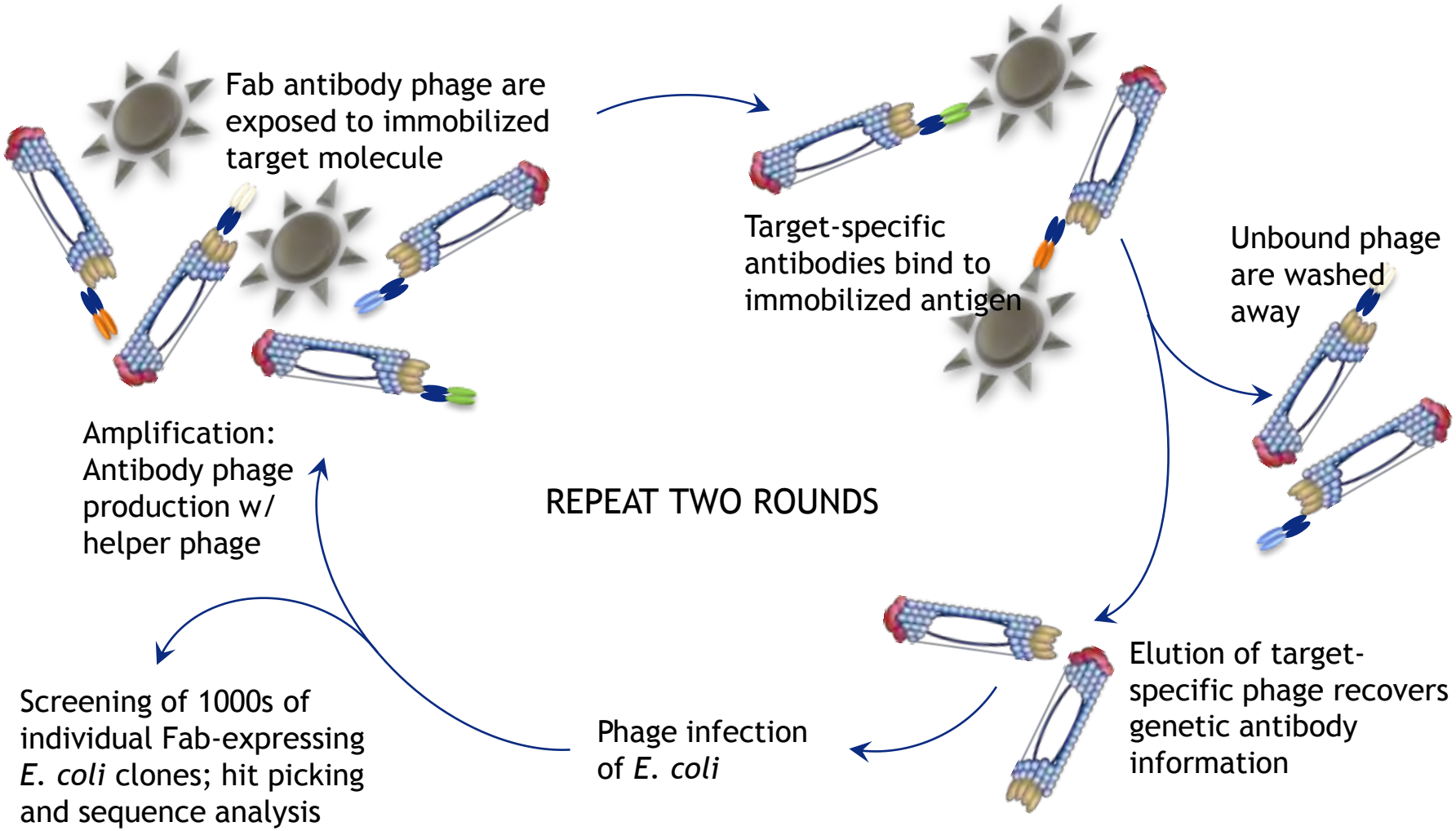
After 3rd selection round



Electron microscopy of particles from hepatitis B surface antigen and M13 filamentous phage.

Zebedee et al. (1992), PNAS 89, 3175-3179

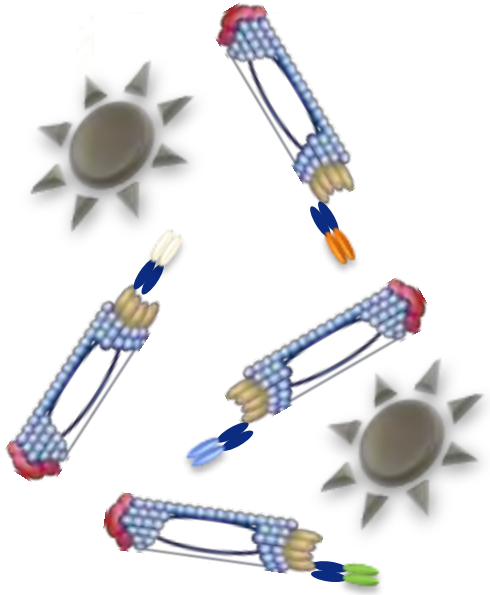
The Principle of Ylanthia Phage Display



Adapted from: Grönwall et al. 2009, J. Biotechnol. 140, 254

Tailored Selections by Phage Display

- Optimal presentation of antigen to maintain most native conformation
  - Plates vs. beads vs. selections in solution
- Alternation of antigens during panning rounds
  - Selection for cross-reactive antibodies (rodent/monkey orthologs, related proteins)
- Concentration of antigen and stringency of washing
  - Modulates affinity range of enriched antibodies
- Elution of phage with specific ligand or antibody
  - Selection of epitope-specific antibodies
- Subtraction with related antigen
  - Elimination of cross-reactive antibodies
  - Selection for epitope-specific or anti-idiotype antibodies
- Cell panning
  - Provides cell surface antigen in natural conformation and format

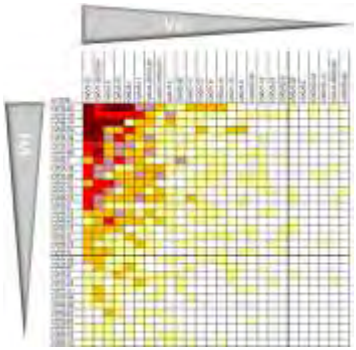


MorphoSys‘ Cutting Edge Platform: Ylanthia®

Making Synthetic, Fully Human Antibody Libraries

databases & publications with human antibody sequences

analysis of sequences, frequencies etc.



Identification of prevalent germline gene segments; frequent HC/LC pairings; common CDR sequences and conformations etc.

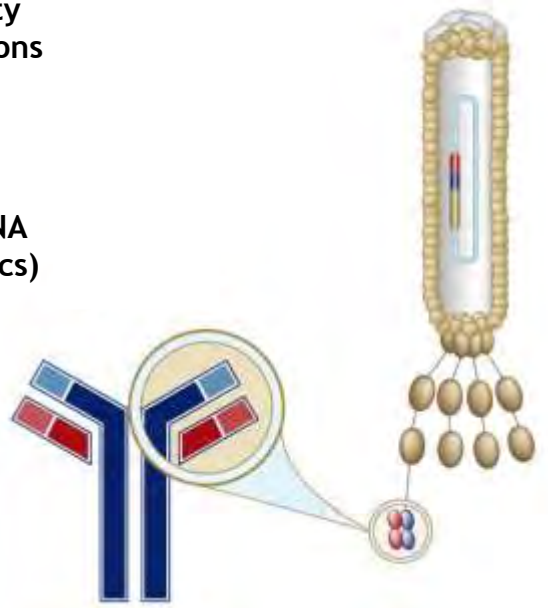
Selection of suitable variable region genes (heavy & light chain)

Design of complementarity determining regions

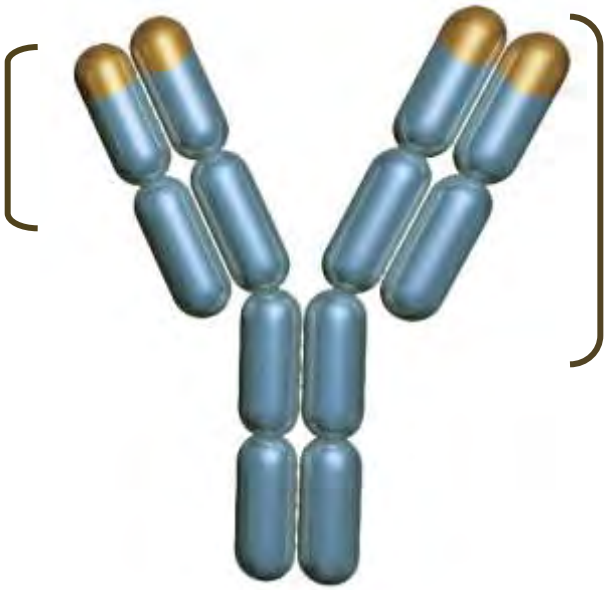
Gene synthesis

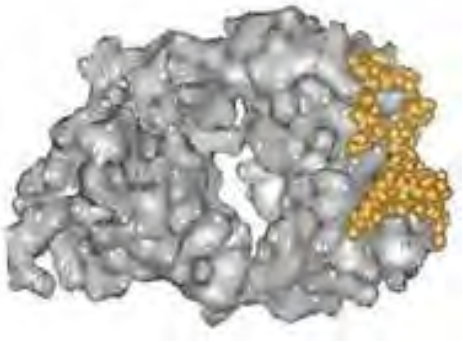
Synthesis of combinatorial DNA libraries (Slonomics)

Library cloning; antibody display on phage



MorphoSys' Antibody Libraries





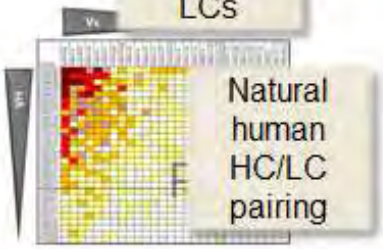
- HuCAL-scFv 1
- HuCAL-scFv 2
- HuCAL-scFv 3

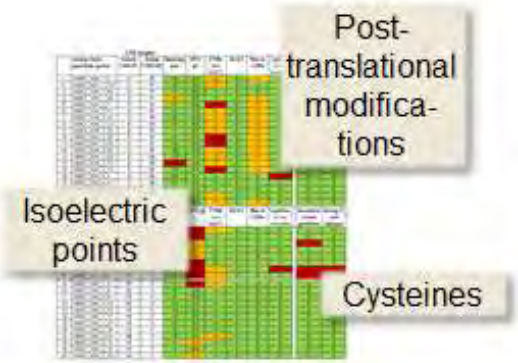
- HuCAL-Fab 1
- HuCAL-Fab 2
- HuCAL GOLD
- HuCAL PLATINUM

Ylanthia®

Ylanthia: Made for Developability

In silico **analysis of natural human antibody repertoire**





Pre-selection of 400 human HC/LC pairs: Fab and IgG1 formats

In vitro **analysis of fully human antibodies**

Production yields | Thermo-stability | Serum stability | Aggregation propensity | Physical & pH stress | Phage display

36 distinct HC/LC pairs with superior biophysical properties

Ylanthia®

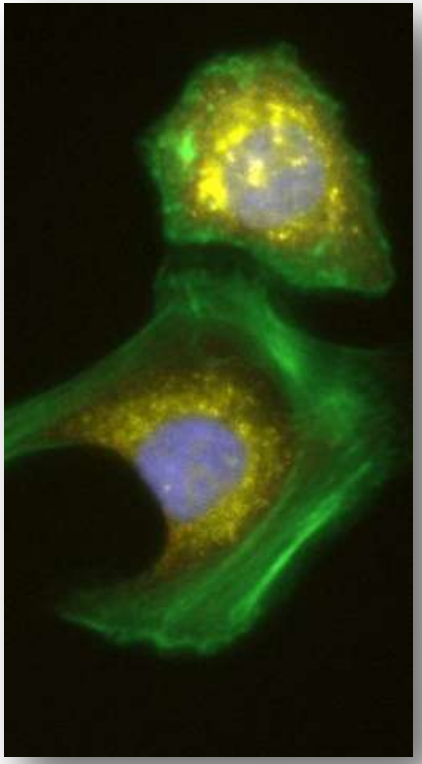
Advantages of Ylanthia vs. other Antibody Libraries

Combination of 12 heavy chains (HC), 6 lambda and 9 kappa light chains (LC)	→	Broad coverage of the natural human Ig repertoire to achieve maximum epitope diversity
… in fixed HC/LC pairing	→	Stable antibodies, T_m mainly >68°C
Reduction in post-translational modification sites (PTMs)	→	More stable and homogenous product; no need for engineering
Gene-optimized antibody sequences	→	Optimized expression levels; no internal splice sites etc
Library size of 1.3E+11 clones	→	Huge diversity of many hundreds of antibodies against each target
HC/LC “scaffolds” pre-selected for developability	→	Resulting antibodies with favorable physico-chemical properties
Almost no deviations from germline sequences	→	Minimum risk for immunogenicity

Targeting of GPCRs - Showcase: CXCR2

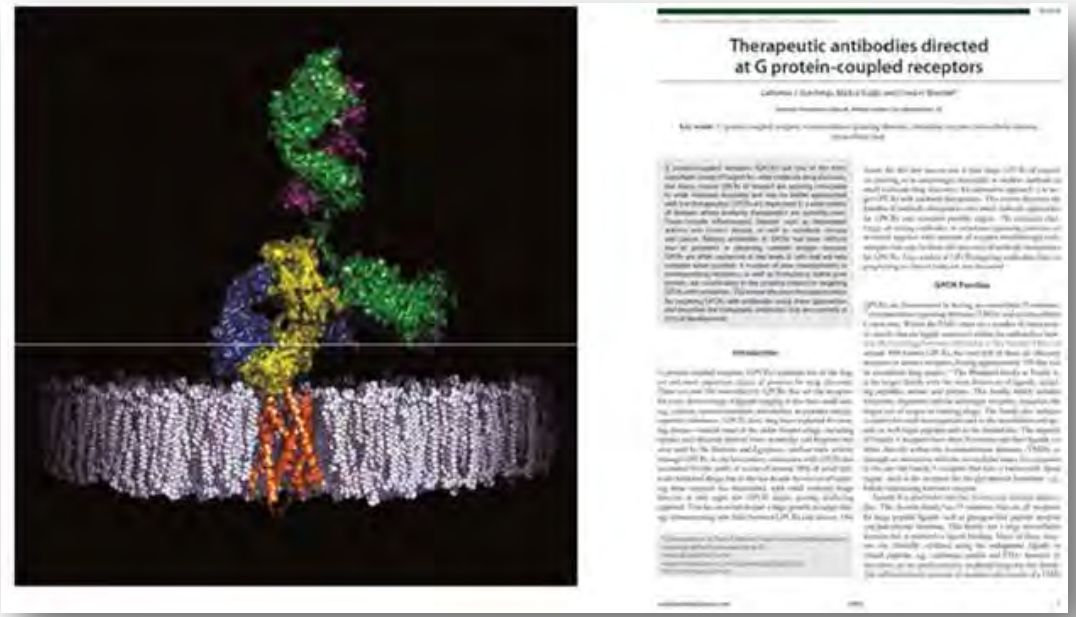
An Integrated Platform for GPCR Targeting

- The generation of specific, high quality and functionally active antibodies against GPCRs is a very complex, technically challenging task
- No all-in-one solution possible
- Instead: Portfolio of many techniques and different materials required
  - Large, high quality antibody library covering broad structural antibody repertoire: YLANTHIA
  - Presentation of target antigen in various formats
  - Complex selection strategies
  - High throughput screening, e.g., in flow cytometry
  - Broad assay portfolio



MorphoSys has all the expertise, technologies and materials required in-house to make GPCR antibody programs a success

GPCRs Offer Only Small Extracellular Area Accessible to Antibodies

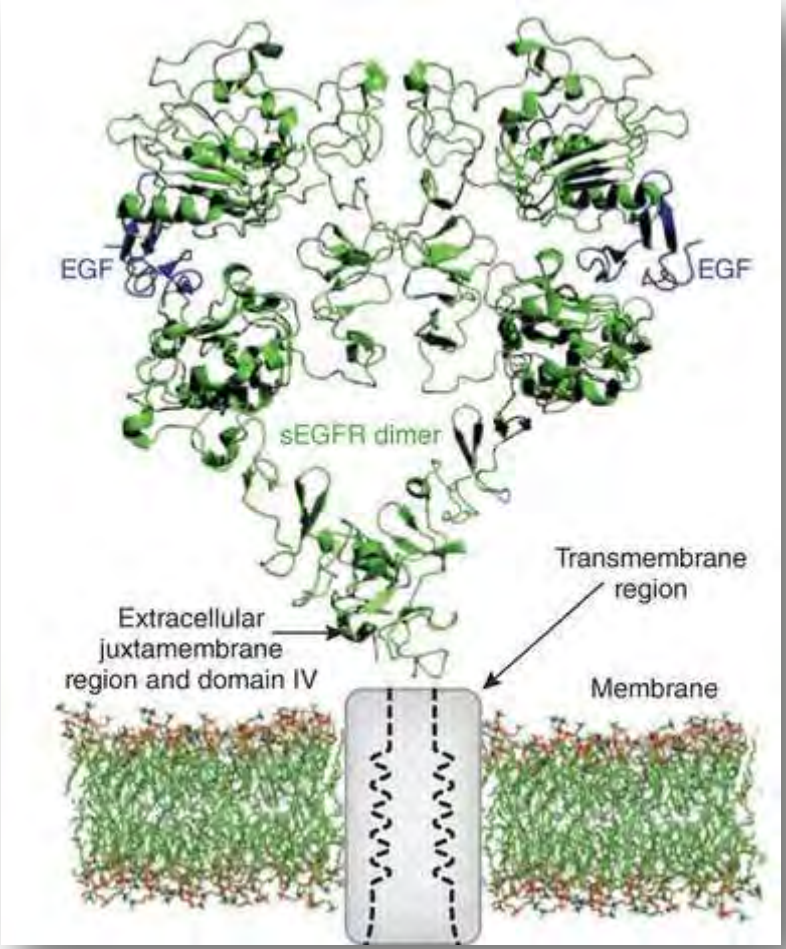


Hutchings C. et al. 2010, mAbs 2, 594-606

- G-protein coupled receptors (GPCRs) comprise a huge class of proteins
- From the known ~800 GPCRs ~350 are considered relevant targets for drug discovery
- High potential as **antibody** targets: Anti-GPCR antibodies provide …
  - High specificity by binding to extracellular regions
  - Limited access through BBB → no CNS side effects
  - Long *in vivo* half life
  - Possibility of using effector functions

Technically challenging to drive antibodies to small extracellular GPCR surface

„Standard“ Antibody Targets

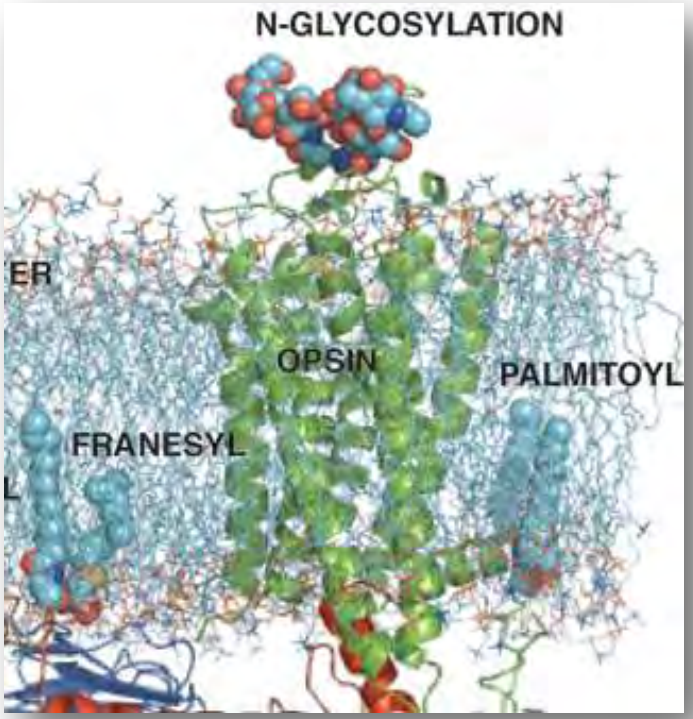


- Soluble (cytokine, chemokine, complement factors etc.)
- OR: Receptors with relatively large, hydrophilic extracellular domain (e.g., receptor tyrosine kinases, RTKs)
- Easy to target
- Well accessible during antibody selections and generation

Composite image of EGF-activated EGFR generated from known structures (no structural information for regions that link the extracellular and intracellular domains).

From Bessmann & Lemmon: Finding the missing links in EGFR (2012).
Nature Structural & Molecular Biology 19, p. 1-3

The Challenging Antibody Targets: GPCRs

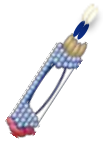
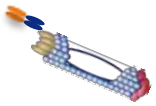
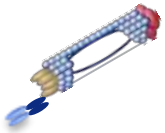
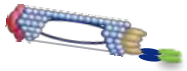


Mukhopadyay & Huber: Molecular model of an opsin-transducin complex in a lipid bilayer
From: The Sakmar Lab, Rockefeller University

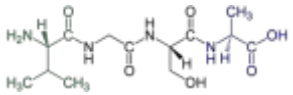
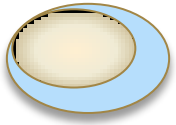
- Often only 25-30% of the protein (~100 aa) are theoretically accessible for antibodies
- All extracellular residues are very close to the membrane
- Glycosylation etc. further shield the GPCR surface
- Many GPCR antibodies lack specificity (reviewed by Michel et al., Naunyn Schmiedebergs Arch Pharmacol 2009; 379, p. 385-388)

Sophisticated approaches are needed to drive antibodies to the small, partially hidden extracellular GPCR surface

Anti-GPCR Antibodies by Phage Display

Phage display Fab library YLANTHIA
Fully human antibodies with superior biophysical properties

GPCR peptides	GPCR over-expressing cell lines	purified, stabilized GPCR in detergent	purified GPCR in lipid vesicles
			
Antibodies against:			
peptide	cell surface protein	Heptares‘ StaR	lipid-embedded GPCR
RISKS: no binding to structured GPCR loops („3D“)	RISKS: binding to proteins other than target GPCR	RISKS: Binding to TM or intracellular portion	RISKS: Binding to intra-cellular portion; hydrophobic, sticky

SOLUTION

- Combination of different antigen materials for pannings (cells, peptides, StaR etc.)
- HT flow cytometry to screen for native conformation, extracellular loops & specificity
- Antibody library producing „manufacturable“ antibodies: YLANTHIA

SOLUTION

Note: So far no success with GPCRs reconstituted in lipid vesicles

MorphoSys‘ Track Record of GPCR Targeting

		Antibody generation	Specific cell binding	Functional activity
CXCR2	class A	√	√	√
GPCR B	class A	√	√	√
GPCR C	class A	√	(√)	weak
GPCR D	class A	√	√	√
GPCR G	class Fzd	√	√	*tbd*

- **MorphoSys‘ comprehensive GPCR portfolio:**
  - Reliable generation of stable GPCR over-expressing mammalian cell lines
  - Advanced antibody selection and screening methods combining various GPCR-derived antigens
  - In depth antibody characterization, also for biophysical properties
  - Broad assay portfolio (β-arrestin, pERK1/2, internalization, ADCC, CDC, ligand binding inhibition, etc.)
  - For very difficult GPCRs (instable, low expressing) where stabilization might be needed: Partnership with Heptares

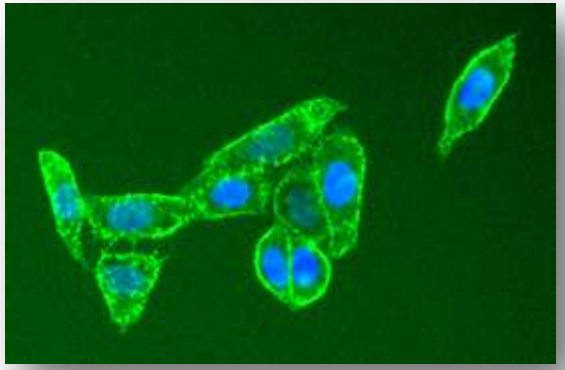
Showcase: CXCR2

- **Target:** CXCR2 is a class A GPCR belonging to the chemokine receptor family
- **Size:** 360 amino acids (N-terminus: 48 aa)
- **Ligands:** CXCR2 is the only high-affinity receptor for all pro-angiogenic chemokines (CXCL1, CXCL2, CXCL3,CXCL5, CXCL6, CXCL7, CXCL8/IL-8).
- **Physiological roles:**
  - Mobilization and recruitment of leukocytes (especially neutrophils) from the bone marrow to sites of inflammation
  - Migration of endothelial cells in angiogenesis
- **Expression**:
  - Mainly on neutrophils, but also on monocytes
  - Various cancer cells and cell lines

CXCR2: Material and Antibody Selections

GPCR material used through different rounds of antibody selections:

- Over-expressing CXCR2 cell lines only
- Combination of CXCR2 CHO cells with peptides
- Combination of CXCR2 CHO cells with virus-like particles



Cell line CHO-CXCR2 + MOR022719

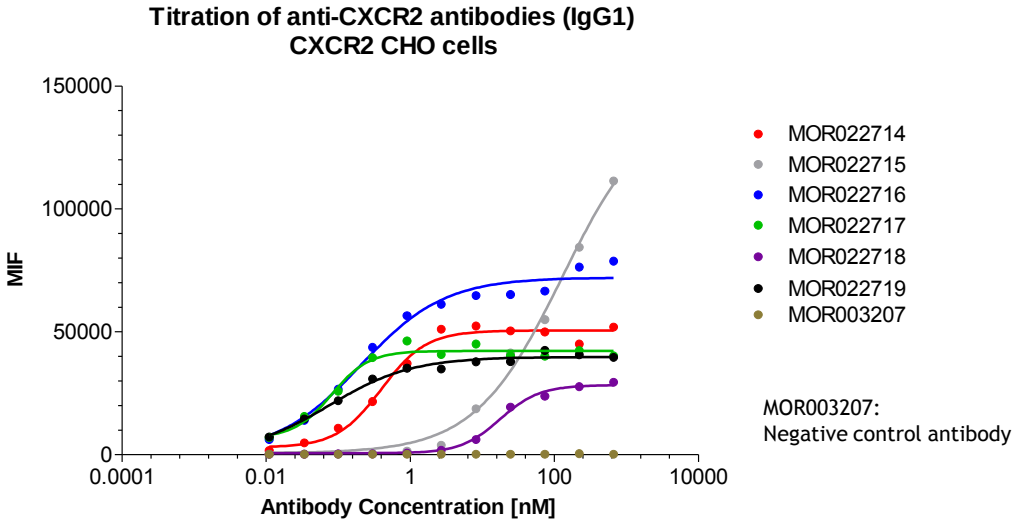
Outcome:

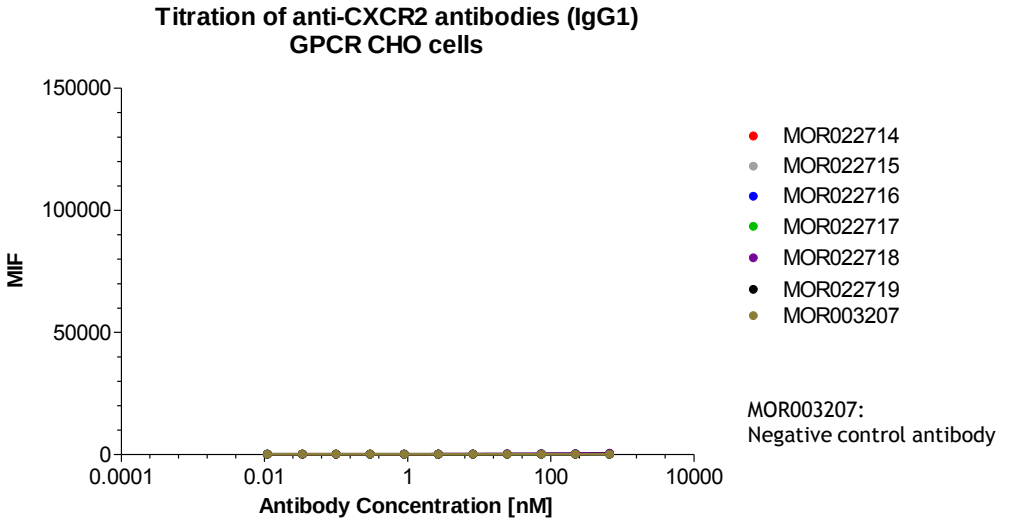
- Hundreds of CXCR2-specific fully human, cell binding hits were identified applying various selection strategies
- Sensitive and high-throughput flow cytometry assays in combination with over-expressing GPCR cell lines built up for antibody screening
- So far, six ‘front runner’ antibodies characterized in detail in Fab and IgG1 formats. Further antibodies selected to be characterized in functional and binding assays

Characterization of anti-CXCR2 Antibodies: Specific Cell Binding

Evaluation of specific cell binding:

Anti-CXCR2 antibodies were titrated on CXCR2 overexpressing CHO cells and cell binding was determined by flow cytometry





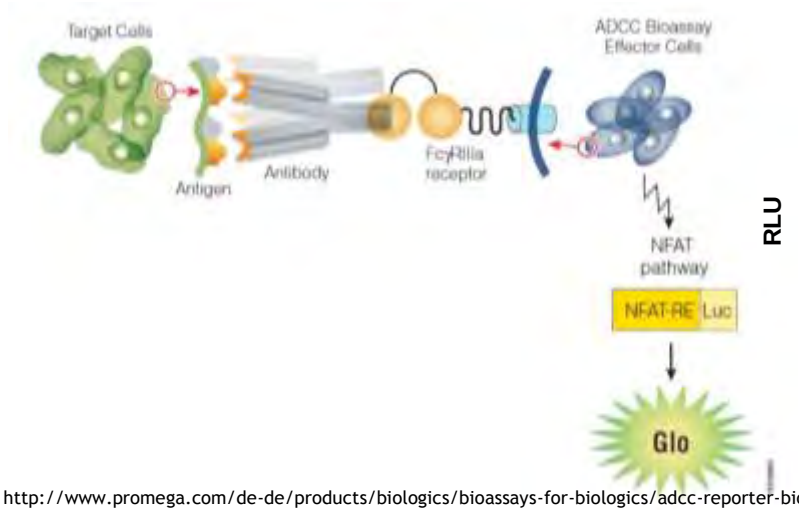
- Numerous antibodies bind selectively to CXCR2 overexpressing CHO cells
- No binding to CHO cells transfected with unrelated GPCR detectable

Characterization of anti-CXCR2 Antibodies: Induction of ADCC

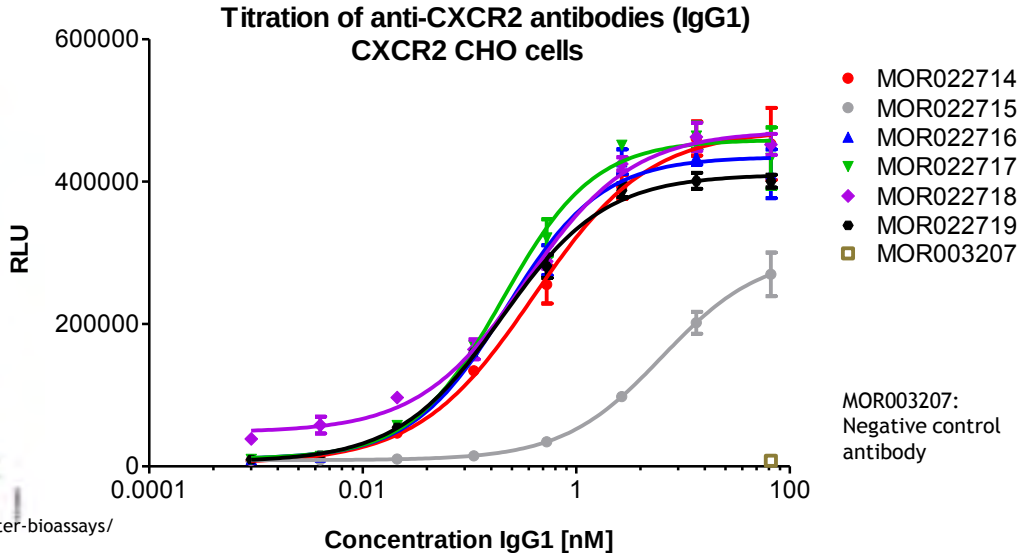
Evaluation of antibody-dependent cellular cytotoxicity (ADCC):

Standard ADCC assay with human PBMCs and flow cytometry read out might be hampered by expression of CXCR2 on PBMCs leading to substantial cell death of PBMCs

Alternative: Luciferase reporter assay with FcγRIIIa expressing cell line (Promega; good correlation to ADCC with human PBMCs shown)



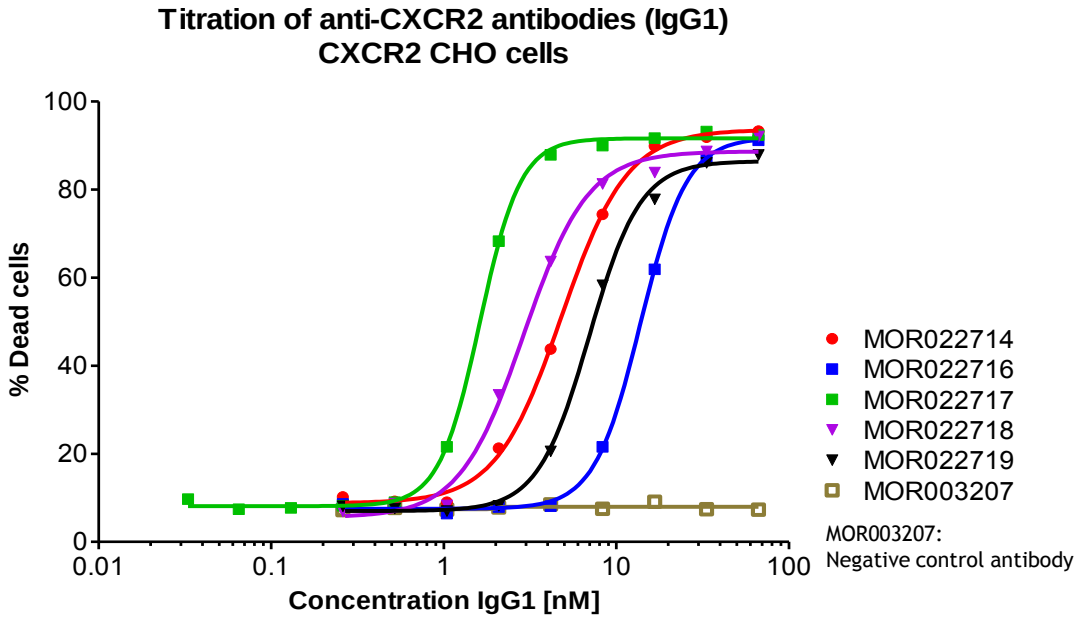
http://www.promega.com/de-de/products/biologics/bioassays-for-biologics/adcc-reporter-bioassays/



Stimulation of FcγRIIIa signaling as a measure for ADCC detected with most anti-CXCR2 antibodies

Characterization of anti-CXCR2 Antibodies: Induction of CDC

Evaluation of complement-dependent cytotoxicity (CDC):

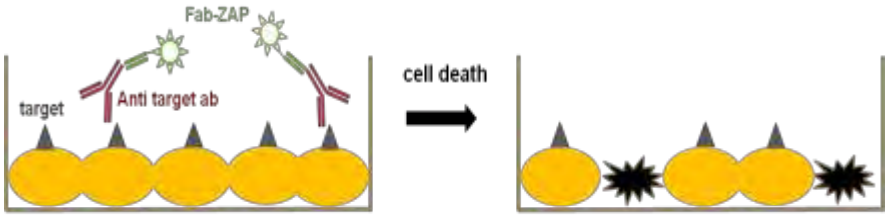


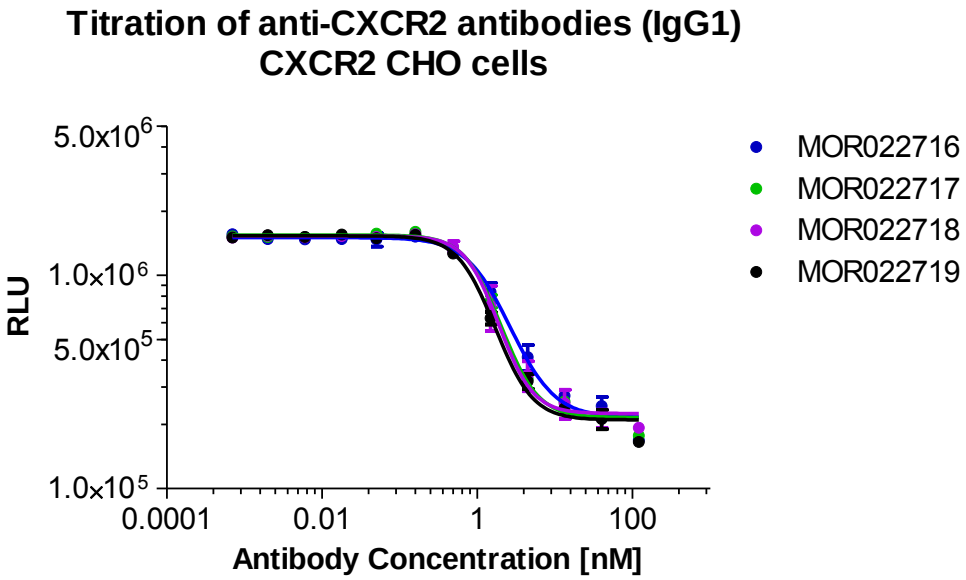
- Anti-CXCR2 antibodies mediate efficient complement-dependent cell killing of CXCR2 overexpressing CHO cells using human serum
- Maximum cell killing almost 100% with IC50 values in low nM range
- Absolutely specific for CXCR2-expressing cells (data not shown)

Characterization of anti-CXCR2 Antibodies: Efficient Internalization

Evaluation of internalization:

- Fab-ZAP is a monovalent saporin conjugate binding to human antibodies. Once the Fab-ZAP is internalized together with the primary anti-CXCR2 antibody, free saporin inactivates the ribosomes that leads to the inhibition of protein synthesis and cell death.
- Useful as measure for internalization and first filter for potential of primary antibody as antibody-drug conjugate



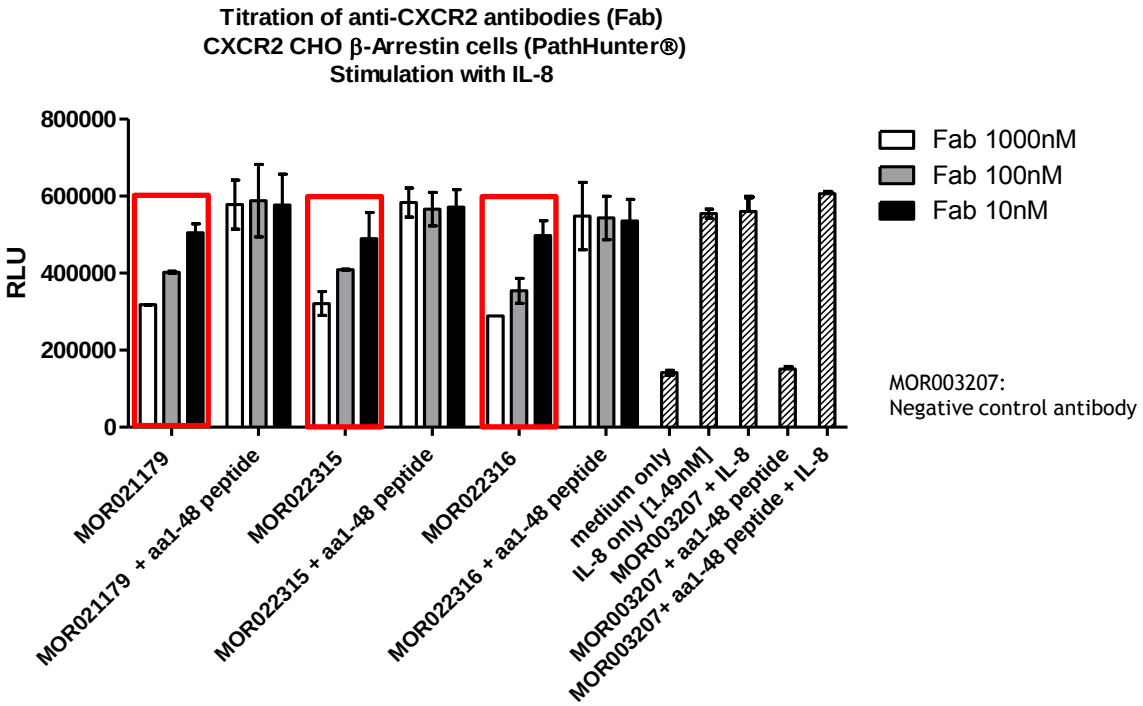


Anti-CXCR2 antibodies internalize efficiently and specifically

Characterization of anti-CXCR2 Antibodies: β-Arrestin Recruitment

Blockade of β-arrestin recruitment (PathHunter® cells, DiscoveRx):

Whole cell, functional assay that measures CXCR2 activity by detecting the interaction of β-arrestin with the activated CXCR2:



Concentration dependent inhibition of IL-8 induced β-arrestin recruitment detected with several anti-CXCR2 Fab and IgG1

MorphoSys Teams up with Heptares

MorphoSys and Heptares Sign Alliance to Develop Antibody Therapeutics Targeting GPCRs

February 13, 2013 / 7:30 am, CET

Collaboration Harnesses Heptares' StaRs® to Open up New Target Space for Therapeutic Antibodies from MorphoSys' Ylanthia® Platform

MorphoSys AG (FSE: MOR; Prime Standard Segment, TecDAX) and UK-based Heptares Therapeutics, the leading GPCR drug discovery and development company, have signed an agreement to discover novel antibody therapeutics targeting G protein-coupled receptors (GPCRs), which are membrane proteins involved in a broad range of biological processes and diseases.

"GPCRs comprise the single largest class of targets for pharmaceuticals currently on the market. Technical challenges have meant that GPCRs have been largely intractable to therapeutic antibody development. We believe that by combining Heptares' unique StaR® platform for generating stable GPCRs as antigens with our antibody discovery technology, we will be able to unlock the immense potential of therapeutic antibodies against GPCRs," commented Dr. Simon Moroney, Chief Executive Officer of MorphoSys AG.

"By creating StaRs, we believe we have overcome a major challenge facing small molecule and biologics discovery efforts focused on GPCRs. This has enabled us to create partnerships with leading pharma and biotech companies in both areas as well as to advance our own pipeline. We are therefore very excited to sign this new partnership with MorphoSys, one of the world's most advanced antibody therapeutic companies, to further leverage the power of our StaR® technology into the antibody space," said Malcolm Weir, Chief Executive Officer of Heptares.

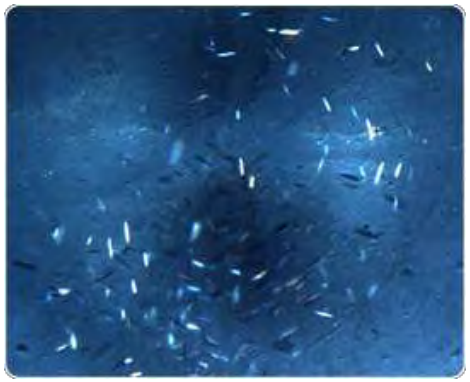
Under the terms of the agreement, Heptares will generate stabilized receptors (StaRs) for a set of GPCR disease targets proposed by MorphoSys. MorphoSys will then apply its Ylanthia antibody library to discover and develop antibody therapeutics against these StaRs. MorphoSys has the right to sublicense to third parties access to these targets in conjunction with therapeutic antibody candidates. Heptares will receive upfront and

Heptares: Collaboration Partner of MorphoSys

- Located in Welwyn Garden City, UK
- Founded in 2007 to develop and commercialize research from the MRC Laboratory of Molecular Biology (Cambridge, UK) and the National Institute of Medical Research (London, UK)
- Founders: Malcolm Weir (CEO), Fiona Marshall (CSO), Richard Henderson (Board Member), Chris Tate (Scientific Advisor)

- **Technology:**
  Stabilization, purification and crystallization of GPCRs for structure determination and structure based drug discovery

- Highly promising also for antibody generation!
- Several publications in Nature, Structure, PNAS



GPCR crystals grown by the lipidic cubic phase method at Heptares. Acknowledgements: Andrew Doré, Heptares Therapeutics Ltd.

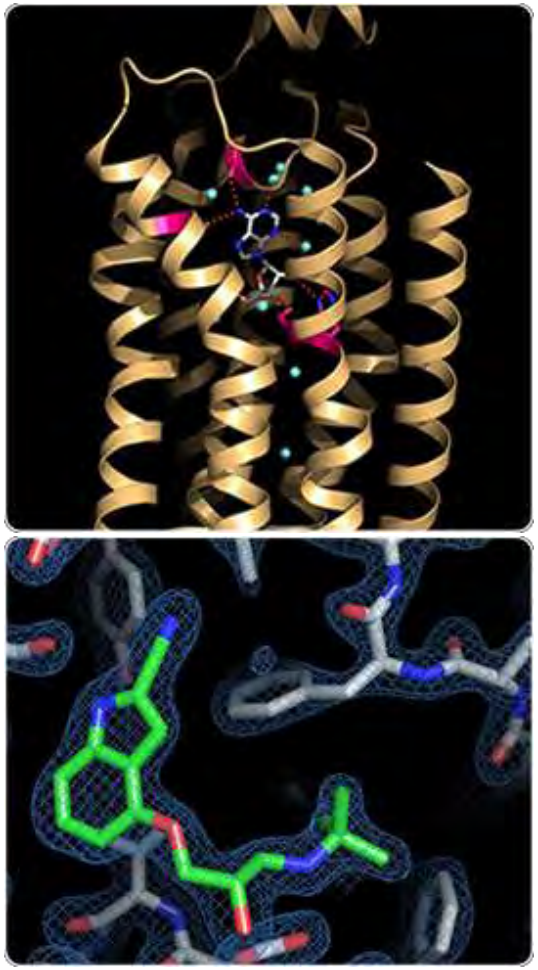
Heptares: The StaR Company

Stabilized Receptor StaR =

- GPCR contains a small number of point mutations that improve its thermostability (also in detergent), while retaining its functional and drug-binding characteristics
- StaR proteins are locked in the conformation derived from the pharmacology of the ligand used in their creation
- The stabilization make a GPCR perfectly suitable for all processes during antibody generation, such as phage display selections and screening

The MorphoSys – Heptares collaboration:

- Heptares to generate StaRs for a set of GPCR disease targets proposed by MorphoSys
- MorphoSys to apply its Ylanthia antibody library to discover & develop antibody therapeutics



1) Structure of GPCR thermostabilized in the agonist conformation and in complex with endogenous agonist ligand (grey).
2) Electron density around the cyanopindolol ligand binding site in b1AR. Acknowledgements: Warne et al, Nature. 2008.

Summary CXCR2

- Anti-CXCR2 antibodies can be generated by various selection methods: Combinations of pannings using CXCR2 over-expressing cell lines, virus like particles and peptides representing the GPCR N-terminus
- The resulting antibodies show specific CXCR2 cell surface binding, internalize quickly and mediate ADCC and CDC
- Several antibodies can antagonize IL-8 signaling as shown by inhibition of β-arrestin recruitment
- Recombinant CXCR2 can be produced, solubilized and purified in sufficient amounts and quality

- Fully human anti-GPCR antibodies directly from the antibody selections
- Potential for being therapeutic lead candidates

Thank you!