FairJourneyBio

Accelerating Drug Discovery:
De-Risking Complex Multi-specific and Multi-format Biologics with a CMC-Predictive Mammalian Display Platform.

Kothai Parthiban [1]; Manon Fuchs [1]; Alexander Fullwood [1]; Manjunath Hegde [1]; Jonathan C. Seaman [1]; Cyril V. Privezentzev [1]; Marc van Dijk [1];
[1] FairJourney Biologics, Rua Delfim Ferreira, 760. 4100-199 Porto, Portugal

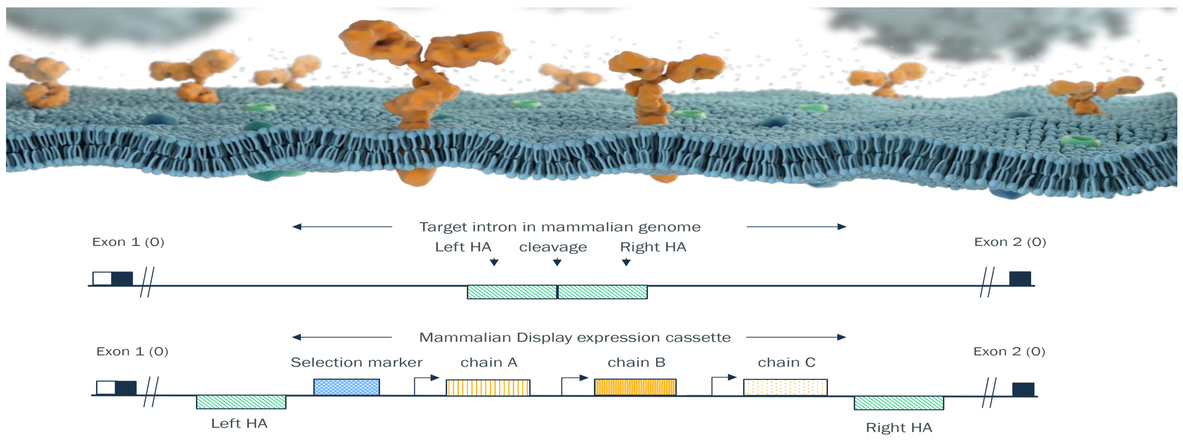
The development of novel multispecific biologics is hampered by an 'Innovation-Complexity Paradox': to efficiently target complex disease, one may need to deploy complex formats. The struggle to turn innovative formats into manufacturable products is a major efficiency bottle neck. Sequential optimization of individual 'building blocks' is costly, time-consuming, and high-risk because it is unpredictive of the CMC properties of assembled complex constructs.

We have developed a proprietary, clinically validated Mammalian Display platform that overcomes this flaw by enabling simultaneous multi-parameter optimization in the final format, as demonstrated across symmetric and asymmetric bispecific antibodies. Using precise single-copy gene integration into a defined locus, the platform leverages native mammalian proteostasis pathways as a universal, format-independent quality control sensor. Surface display level correlates directly with developability attributes, such as aggregation propensity. We have observed how this technology powerfully predicts CMC performance across multiple formats.

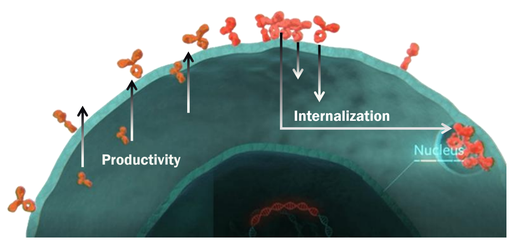
We demonstrate the power of Mammalian Display with a best-in-class enzyme inhibitor case study, where the platform simultaneously optimized antibody affinity (<15 pM), specificity (>106-fold), and developability for subcutaneous administration, paving the way for the molecule to rapidly progress to phase III clinical trials.

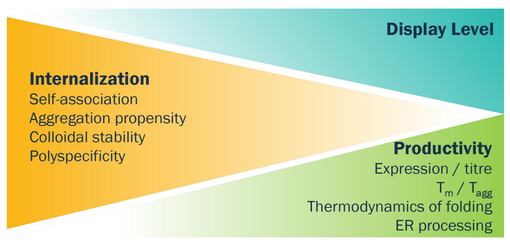
This "de-risking by design" approach selects 'elite' candidates, enabling the molecule to quickly move from discovery to clinic and solving the core challenges for the next generation of complex therapeutics.

PRECISE SINGLE-COPY INTEGRATION PROVIDES TRANSCRIPTIONAL NORMALISATION



DISPLAY CORRELATES WITH BIOPHYSICAL PROPERTIES IN SOLUTION

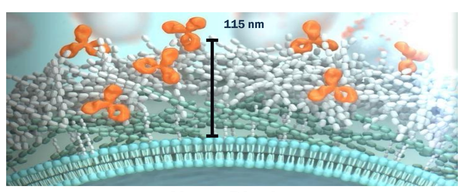




Antibody	Expression yield (mg/L)	T_m (° C)	T_{agg} (° C)	C-max (mg/mL)	IgG display level (MFI)
MEDI-1912[1] Parental	33.2	71.5	73.2	1.4	681
MEDI-1912 (STT)[1] Improved	52.8	70.8	74.8	>29	12352
Ang2mAb[2] Parental	13.4	63.8	65.0	>21	539
Ang2mAb (C49T)[2] Improved	34.4	66.5	65.2	>18	14586

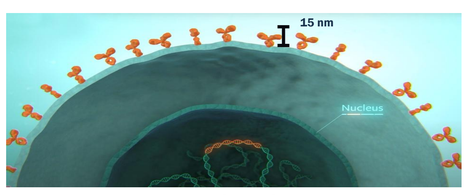
1. Dobson et al (2016), *Scientific Reports:* 6, 38644
2. Buchanan et al (2013), *mAbs:* 5, 255-26

MAMMALIAN DISPLAY SHOWS CLEARER DISTINCTION BETWEEN "GOOD" AND "BAD" MOLECULES COMPARED TO YEAST DISPLAY

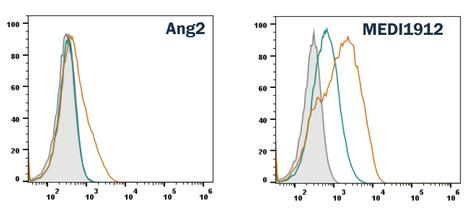


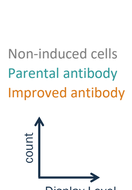
Yeast Display

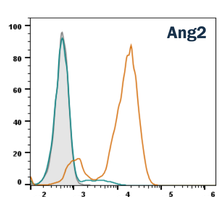
VERSUS

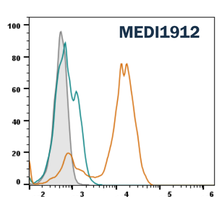


Mammalian Display



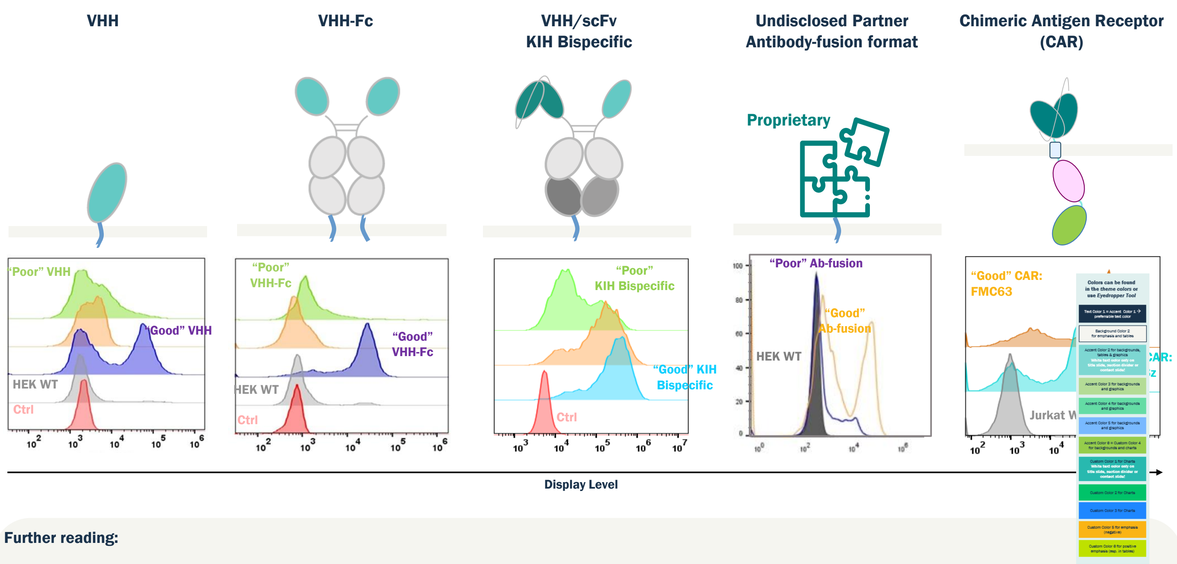






IgG yeast display by Wozniak-Knopp & Ruker (Department of Biotechnology, BOKU)

A UNIVERSAL QUALITY CONTROL PLATFORM FOR ANY COMPLEX FORMAT



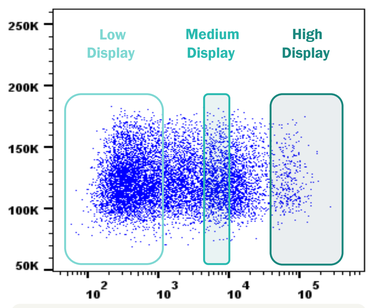
Further reading:

A comprehensive search of functional sequence space using large mammalian display libraries created by gene editing.
Parthiban et al (2019), *MAbs*: 11(5): 884-898.

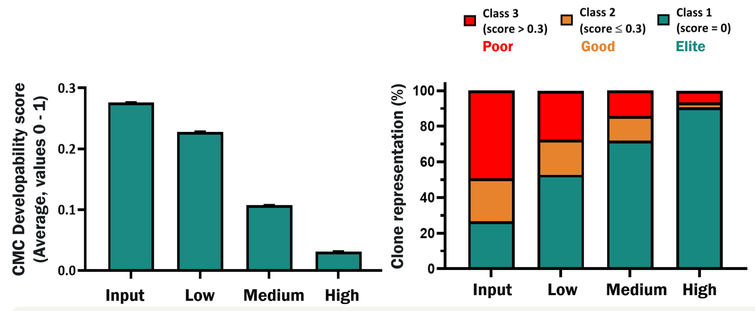
Beyond affinity: selection of antibody variants with optimal biophysical properties and reduced immunogenicity from mammalian display libraries.
Dyson et al (2020), *MAbs*: 12(1): 1829335

Advancements in mammalian display technology for therapeutic antibody development and beyond: current landscape, challenges, and future prospects.
Slavny & Hegde et al (2024),
Front. Immunol.: 15: 1664-3224

CASE STUDY 1: MAMMALIAN-DISPLAY-LEVEL BASED SELECTIONS IDENTIFY THE MOST DEVELOPABLE MOLECULES FROM A POOL OF >110 CMC-STAGE BIOLOGICS



FACS gating of MD library
according to antibody display level

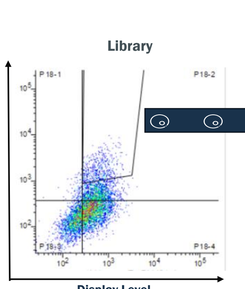


NGS analysis of sorted populations
clone distribution in low, medium and high antibody display populations compared to input control

Mammalian surface display level is a highly predictive marker of performance in late-stage CMC assessment, enabling the distinction between "good" and "elite" clones

CASE STUDY 2: SELECTION OF OPTIMAL BOCOCIZUMAB VARIANTS WITHOUT DEVELOPABILITY AND IMMUNOGENICITY ISSUES BASED ON IGG DISPLAY LEVEL

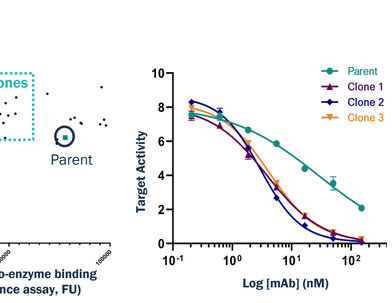
Identification of hydrophobic and positive charged regions → **Mutagenesis library + Mammalian Display selection (display level & binding)** → **Characterization and immunogenicity assessment of most enriched clones**



FACS gating for superior binding & developability

Clone name	AC-SINS (nm)	Vr in HPLC-SEC (mL)	Expression yield (mg/L)	DLS Zav (40mg/mL)
NSR-5A10i	5	1.49	N/A	**N/A**
Bococizumab	**31**	1.61	69	**41.3**
NEI	5	1.49	198	**14.2**
EEH	4	1.49	198	**15.2**
NEE	4	1.48	190	**15.1**
Alirocumab	4	1.50	50	**16.1**

Biophysical characterization: Self-interaction (AC-SINS), post-purification yields and DLS scores of bococizumab & variant antibodies.



Proliferation of CD4+ T cells by bococizumab reduced in variants selected by Mammalian Display.

The most enriched variants exhibit improved biophysical properties across multiple metrics and ablated immunogenicity in vitro

CASE STUDY 3: OPTIMIZATION OF ENZYME INHIBITOR TO BEST-IN-CLASS ANTIBODY WITH EXQUISITE SPECIFICITY, POTENCY AND DEVELOPABILITY PROPERTIES

1st FACS gate for improved on-target binding | **2nd FACS gate for reduced off-target binding** | **Monoclonal IgG screen** | ***Ex vivo* potency determination**

Simultaneous FACS gating for
1) display level, 2) improved on-target binding, 3) reduced off-target binding

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