UPSTREAM PROCESS DEVELOPMENT FOR GBR 1302, A BISPECIFIC ANTIBODY BASED ON GLENMARK'S PROPRIETARY BEAT® FORMAT

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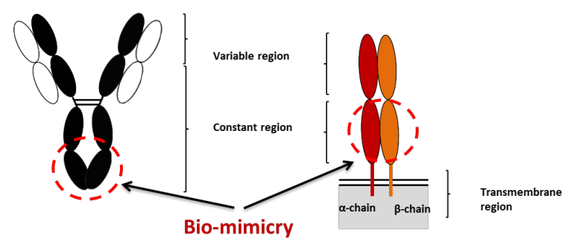
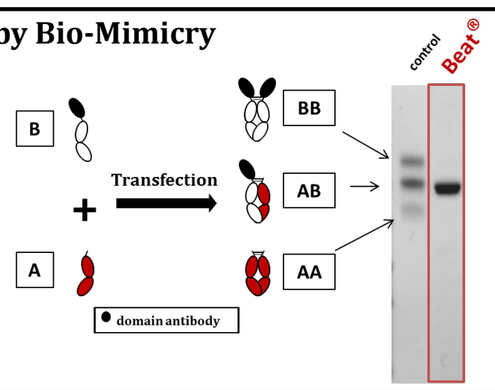
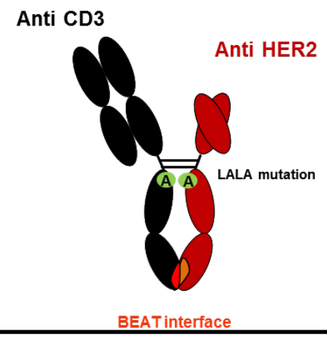
Glenmark Pharmaceutical's BEAT® (Bispecific Engagment by Antibodies based on T-cell receptor) platform is a novel bispecific heavy chain heterodimerization platform based on a unique concept of bio-mimicry. Using our BEAT® platform, we have developed a BEAT antibody –GBR 1302- designed to effectively recruit cytotoxic T cells against HER2 positive breast cancer cells including trastuzumab-resistant breast cancer cell lines. GBR1302 is composed of three different subunits (HC, scFV-FC and LC) that are expressed in recombinant CHO-S cells. Herein, we describe the upstream process development of an industrial scalable process.

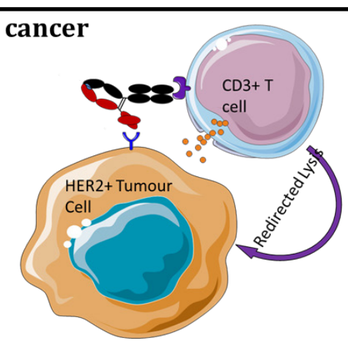
BEAT® Bispecific Antibody: Hc heterodimerization by Bio-Mimicry





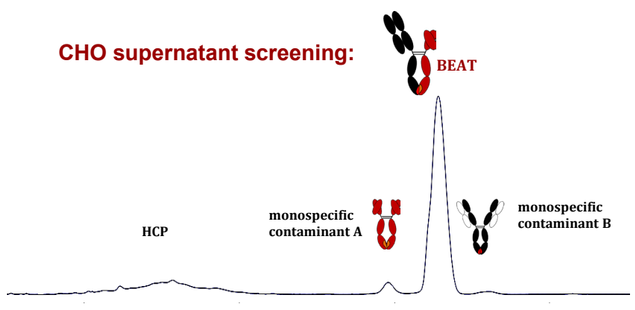
GBR 1302: first BEAT® in the clinic for HER2+ cancer

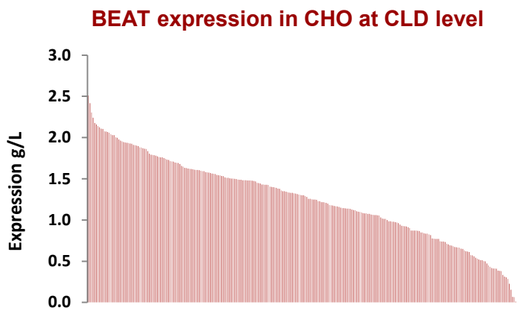


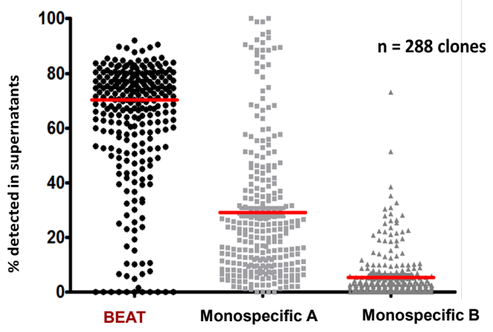


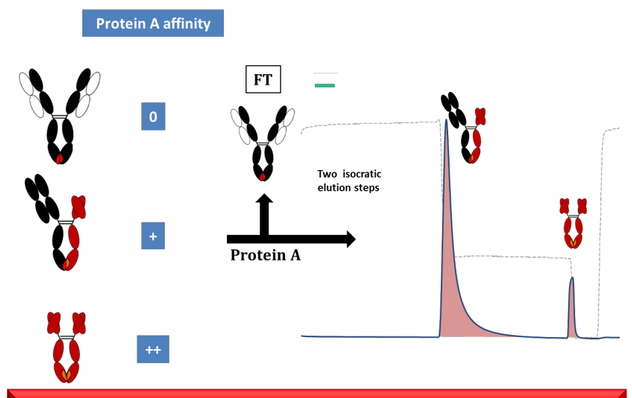
Mechanism of action of GBR 1302: Redirected lysis (RDL)

The BEAT® Platform in a nutshell:









Up to 90 % bispecific product secreted

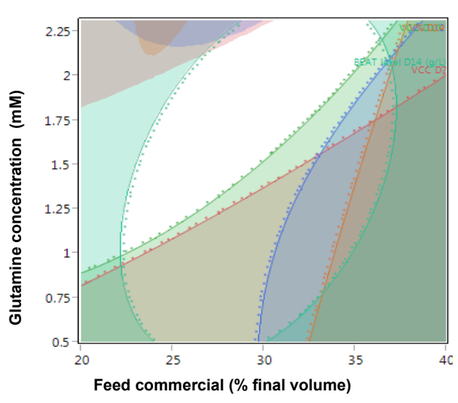
Built-in protA approach
Standard mAb purification process

USP process development for GBR1302

DOE based on media and feed optimization → 5 L intermediate scale → 50L / 250L (GMP) scales

Small-scale process development for GBR1302

Model built with the statistical software JMP 11.0
The figure below shows the response contours obtained for L-Glutamine and added feed quantity



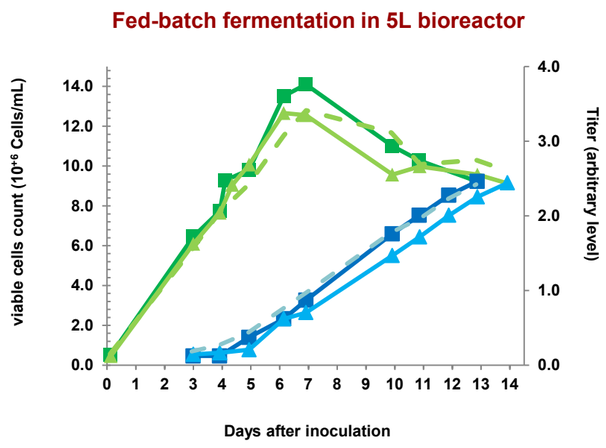
Response
VCC D7 (x 10^{+6} C/mL)
VCC D10 (x 10^{+6} C/mL)
V% D12 (%)
V% D14(%)
BEAT level D14 (g/L)

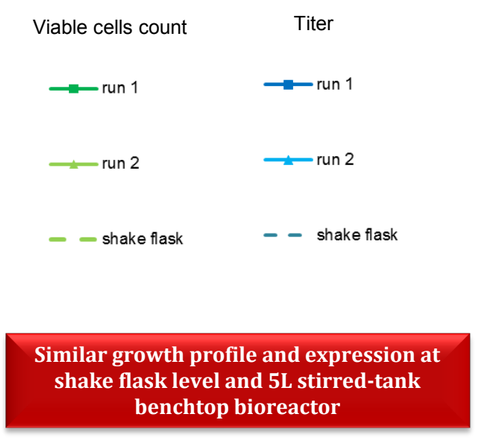
Factors
Feed quantity [% final volume]
First feeding day
Initial glutamine concentration [mM]

Selection of an optimal process for all candidates

Intermediate scale (5L sSTB) development for GBR1302

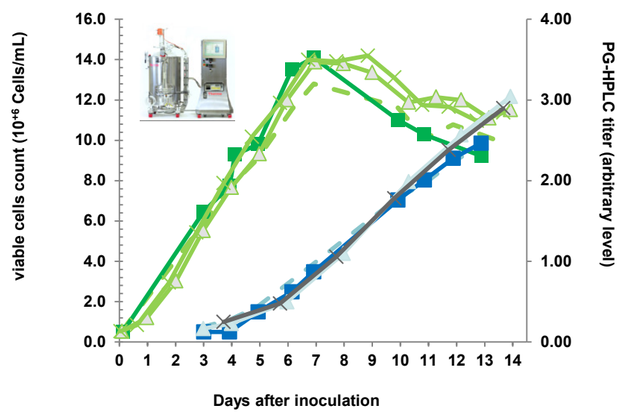
- Media and feed selected on small-scale model
- Establishment of a controlled process (gasing strategy optimization, pH, temperature)

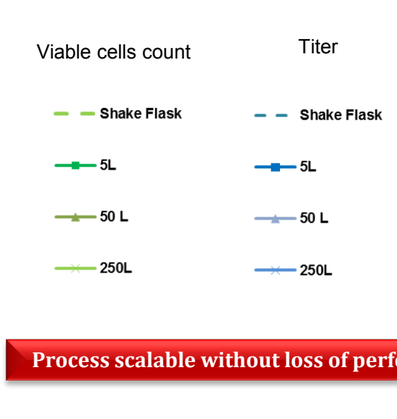




Similar growth profile and expression at shake flask level and 5L stirred-tank benchtop bioreactor

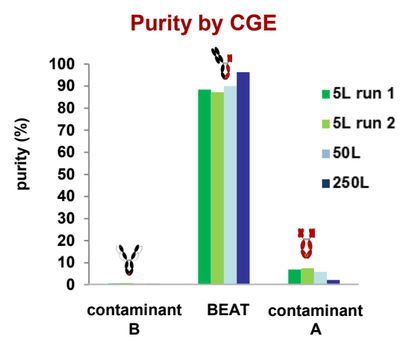
Scalable process to 50L and 250L bioreactor (GMP)

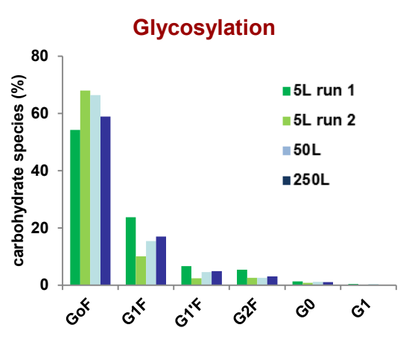


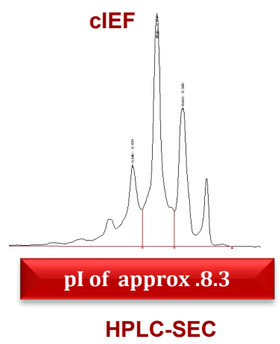


Process scalable without loss of performance

GBR1302 quality attributes



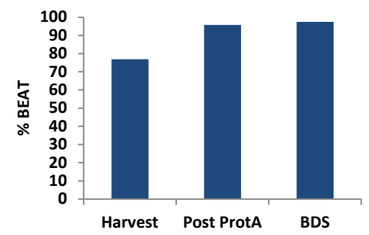


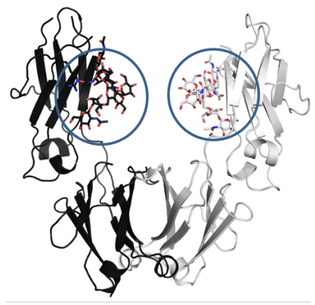


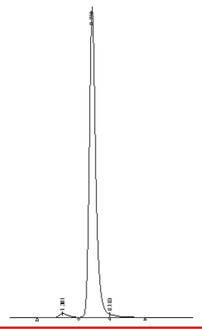
pI of approx .8.3

HPLC-SEC

Robust product formation







> 97% purity post purification

Standard CHO glycosylation profile

Aggregate level (≤2%)

- **The BEAT platform was designed for the robust, rapid and cost-effective development of bispecific antibodies. The format maintains all the benefits brought by an antibody scaffold whilst bringing a "plug and play" approach to the generation of therapeutic products.**
- **GBR 1302 is the first BEAT developed by Glenmark for the treatment of HER2+ cancers.**
- **Following a fast-track upstream process development a 5L stirred-tank bioreactor process could be established for GBR 1302 stable cell lines. This process was successfully scaled up to 50L and 250L scale without loss of performance. The level of bispecific product formation was not affected by the scale of production. The quality attributes of GBR 1302 were found very similar compared to a standard IgG produced using the same host cell (typical CHO glycosylation pattern, pI, level of aggregation < 2%).**
- **The excellent manufacturing attributes of GBR1302 allows further clinical development as a treatment for HER2 positive cancers. Entry in phase I is expected in 2015.**