

# From 1 g/L to 3 g/L: Rapid Process Development for Phase II Clinical Production of XmAb™2513

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## Abstract

XmAb™2513, a monoclonal antibody achieved by application of Xencor's XmAb™ technology, exhibits significantly enhanced potency and efficacy against target lymphomas relative to the unmodified antibody, and is currently being moved into Phase I clinical study. To support pre-clinical and Phase I clinical studies for XmAb2513, we developed a CHO cell line and an animal-component-free (ACF) cell culture process that produces a final titer of 1-1.3 g/mL within 6 months. This process has been successfully scaled up at 250L- and 1200L-scale bioreactors. At Xencor, a continuous effort was made to improve production of XmAb2513 in order to meet an increasing demand of XmAb2513 for Phase II clinical studies and beyond. The cell culture process was optimized from three directions: basal medium, feed composition, and timing for temperature shift. With collaboration with the SAFC Biosciences, a new animal-component-free medium was developed in less than 4 months using the SAFC Biosciences' high-throughput screening technology and statistical Design-of-Experiment method. The new basal medium enhanced XmAb2513 production by 2-fold compared to the old basal medium. The antibody titer was further increased >2-fold by applying an ACF feed that was developed at Xencor. Earlier temperature shift prior to reaching a peak viable cell density shows benefit to enhancing expression of XmAb2513 although peak viable cell density is lower. Optimization in these three areas has led to a new cell culture process that produces > 3 g/L of XmAb2513. This presentation will elucidate the strategies applied in the process development and will report results obtained.

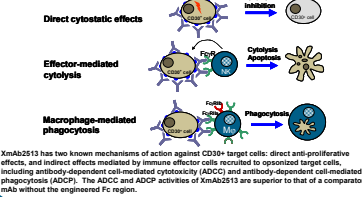
## XmAb™2513

XmAb2513, targeting CD30, is the Xencor lead antibody optimized using the XmAb™ technology. This technology applies the novel method of human string content optimization to the Fv region to enhance affinity for antigen and the advanced Fc engineering to the Fc region to increase affinity for the FcγRIIIA receptor, resulting in XmAb2513 antibody with significant increases in both potency and efficacy relative to the murine-human chimeric antibody cAC10 with no Fc-receptor binding enhancement.

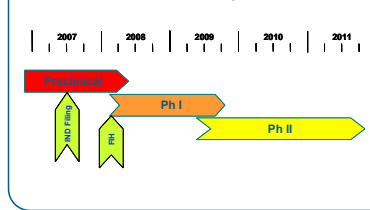
### XmAb2513 clinical indications:

- ◆ Hodgkin's Disease
  - Current patients = 131,000
  - 15% non-responders to current therapies = 19,650
  - New patients per year = 7,880
- ◆ Late effects
  - 15% non-responders to current therapies = 1182
  - Increased risk of secondary cancers with standard care (chemo+radiation)
  - Increased risk of cardiovascular disease
- ◆ Anaplastic Large Cell Lymphoma
  - New cases per year = 1280 - 2560

## XmAb™2513: Multiple Mechanisms of Actions against CD30+ Cells

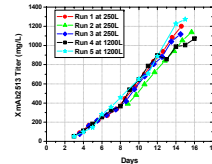


## XmAb™2513: Development Timeline



## Cell Culture Process for Phase I Clinical Production

- ◆ CHO cell line
- ◆ Fed-batch process
  - Chemical-defined medium
  - Proprietary glucose feed
  - Glutamine feed
  - Temperature shift
  - Final titers of 1-1.3 g/L in 14-16 days cultivation



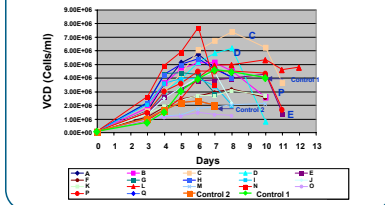
## Process Optimization for Phase II Clinical Production

- ◆ Compositions of batch medium
- ◆ Composition of feeds
- ◆ Temperature shift

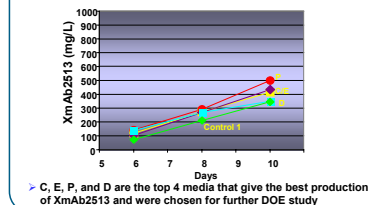
SAFC high-throughput screening and DOE method

- ▶ Use the CHO cell line for XmAb2513 production
- ▶ Screen 19 different media available at SAFC Biosciences
- ▶ Monitor viable cell density and viability
- ▶ Monitor protein titer of XmAb2513
- ▶ Compare cell growth profiles and protein titers
- ▶ Choose 4 media that give best production for XmAb2513 for further Design of Experiments (DOE)

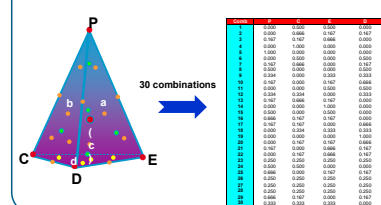
## Medium Development for Phase II Clinical Production



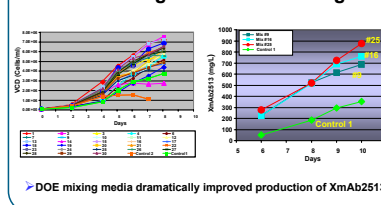
## Medium Development for Phase II Clinical Production



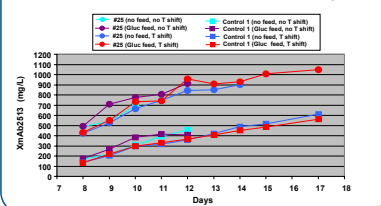
## DOE Design



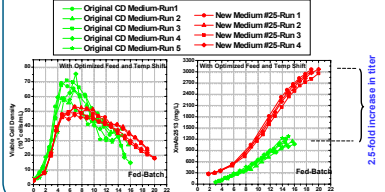
## DOE Mixing Medium Screening



## #25 Medium Improved XmAb2513 Production by 2-fold



## Optimized Medium/Optimized Feed/Temperature Shift Dramatically Enhanced XmAb2513 Production



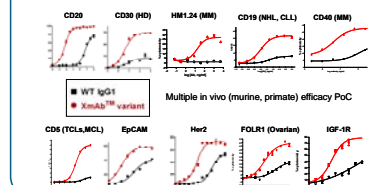
## Summary

- ◆ The XmAb™2513 engineered antibody has been shown to have enhanced potency and efficacy compared to IgG1 antibodies.
- ◆ The cell culture process used for Phase I clinical production of XmAb2513 applied a chemical-defined medium that is commercially available and achieved 1-1.3 g/L of protein titers at 250L and 1200L scales.
- ◆ SAFC's high-throughput screening and statistical Design-of-Experiment has led to an optimized basal medium (#25) that doubled XmAb2513 production in batch production and fed-batch with feeding glucose compared to the original basal medium (control 1).
- ◆ Optimization of the feed composition and application of temperature shift further enhanced XmAb2513 production by ~2.5-fold.
- ◆ A new cell culture process with a final titer of >3 g/L has been developed for future Phase II clinical production.

## Acknowledgements

We thank the many Xencor employees who supported this work. We greatly appreciate the SAFC Biosciences team for their effort in developing the #25 medium.

## XmAb™ Broad Target Applicability for Enhancing Cytotoxic Potency



## Xencor is the Leader in Antibody Fc Optimization

- ◆ Higher Fc affinity well established as enhancing antibody efficacy
  - Carron (Blood 2005), Weng and Levy (JCO 2005), Musolino (AACR 2007)
- ◆ Set of well characterized Fc variants on hand and ready to be rapidly applied to any antibody
  - Specific Fc can be chosen for desired enhancement capabilities
- ◆ XmAb™ Fc technology capabilities
  - Enhanced cytotoxic potency
  - Improved half-life
  - Immune system regulation
  - Focused NGA by Fc silencing
  - Broad & early intellectual property
  - Broad therapeutic applicability

**Xencor Partnerships**

Contact: [mzhu@xencor.com](mailto:mzhu@xencor.com); [www.Xencor.com](http://www.Xencor.com)