MAB CANCER THERAPY PRODUCTION PLANT

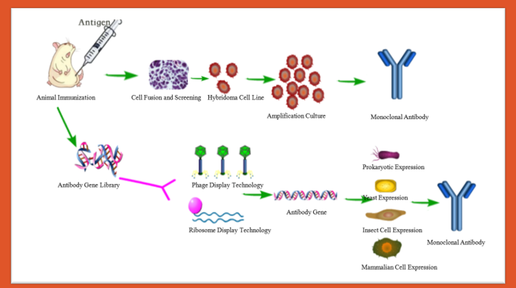
The objective of this project was to generate a preliminary design for a monoclonal antibody plant that produces one tonne of product annually.

INTRODUCTION

A preliminary design for a monoclonal antibody plant has been requested for the AIChE design competition. Current market growth of monoclonal antibodies (Mabs) is expected to double in the next fifteen years and contract manufacturing must be increased to meet demand. Competitors in the industry, such as Genentech™, have similar processes and have market caps exceeding 5 billion dollars. Therefore, there is ample economic opportunity to expand into the Mab market. The proposed plant was designed to produce 1000 kg of Mab annually based on a reactor yield of 1 – 2 g-L^{-1} . The bioreactor capacity is expected to increase to 8 – 12 g-L^{-1} over the course of production. Hence, the facility has a capability to repurpose multiple bioreactors for different cell lines so that additional capacity can be contracted out once there is an increase in reactor yield. Within the current facility, cells are grown within the seed train and then used to inoculate the bioreactor. The biomass is then removed through filtration and centrifugation. Final purification is then conducted through protein A chromatography and ultrafiltration and virial inactivation is achieved between chromatography and polishing.

MOTIVATION

The product protein, a monoclonal antibody (Mab), is being studied for colon cancer, breast cancer, neovascular glaucoma, and macular degeneration treatment. Cancer is projected to be the first approved application for the product.



A current marketed Mab of this nature is Avastin™ (bevacizumab). This Mab targets the Vascular Endothelial Growth Factor pathway, which is utilized by tumors to advance blood vessel growth. Blocking this pathway inhibits this out of control growth; thus, blood vessel growth related health issues can be treated. CHO cells are grown to produced 97% humanized antibodies to prevent human immune system rejection.

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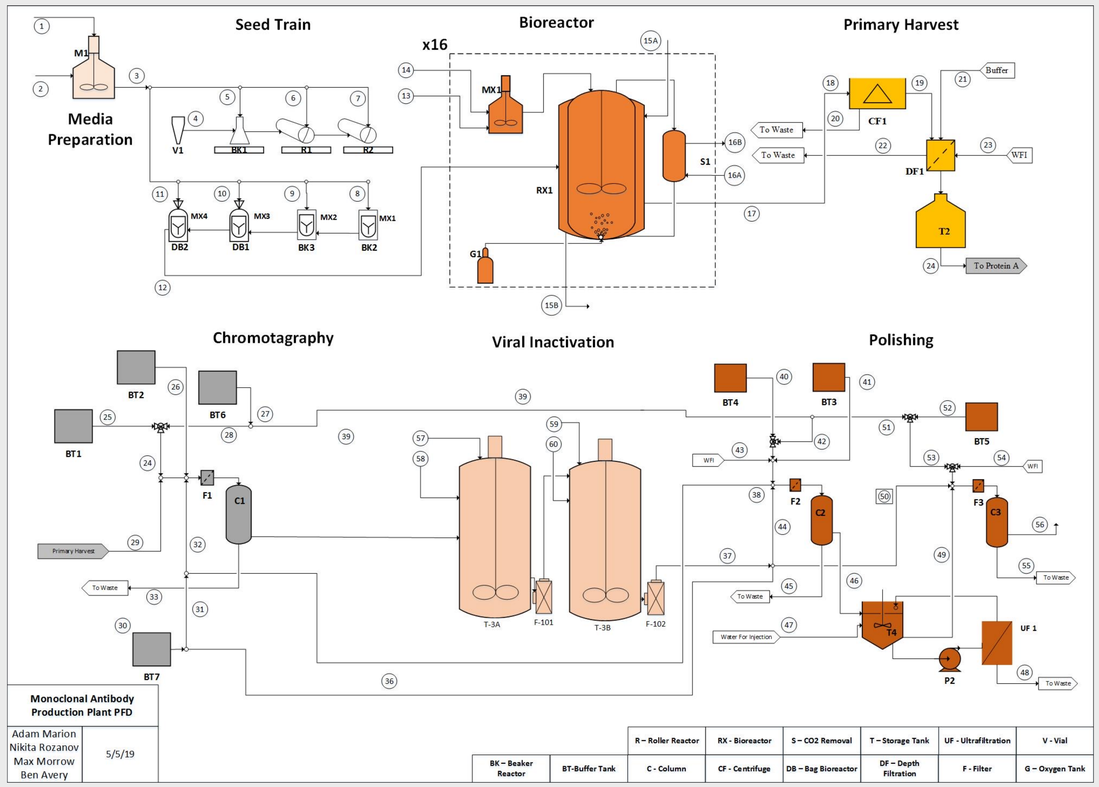


Media Development

Goal:
- Robust (multiple cell lines)
- Limit cell damage
- Low inhibitor production
- More contributing cells
- High protein to media ratio
- High production rate

Method:
- Plackett-Burman statistical approach
- Powder addition to water

Seed Train

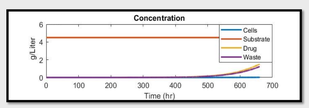
Goal:
- Increase cell density for bioreactor inoculation

Method:
- Batch growth in media
- Increasing reactor sizes
- Powder addition to water
- Completely disposable

Bioreactor

Goal:
- Maximize product production
- Maintain high cell concentrations

Method:
- Monod kinetics



Primary Harvest

Goal:
- Removal of insoluble particles

Method:
- Disc Stack Centrifugation
- Depth Filtration: disposable absolute filtration and adsorption

Chromatography

Goal:
- Capture and purify the protein product from clarified broth

Method:
- Choose resin (capture species) with high binding capacity, lifetime, yield, and productivity
- Run three cycles per batch to recover protein

Viral Inactivation

Goal:
- Safety step
- Remove or deactivate remaining viruses with protein

Method:
- Detergent treatment
- Low pH treatment
- Absolute microfiltration

Polishing

Goal:
- Final purification to achieve pharmaceutical standards

Method:
- Dead end filtration
- Cation Exchange
- Dia-/Ultra-filtration
- Anion Exchange

Miscellaneous

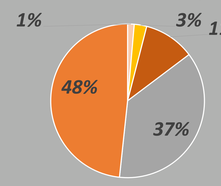
Storage
- Cryogenic storage of protein for up to a year

Clean/Steam in Place
- Cleaning procedures with acidic/alkaline solutions for FDA validation

Kill Tanks
- Heating organic waste (80°C) to make waste safe to dispose into the sewage

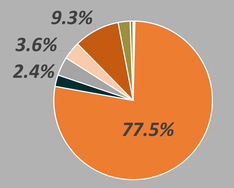
ECONOMIC ANALYSIS

Annual Utility Costs: $57,000,000



Viral Inactivation	$800,000
Primary Harvest	$1,500,000
Polishing	$6,100,000
Chromatography	$21,000,000
Bioreactor	$27,500,000

Capital Costs: $34,000,000



Media Preparation	$40,000
Seed Train	$80,000
Bioreactor	$26,000,000
Primary Harvest	$750,000
Chromatography	$1,200,000
Viral Inactivation	$1,200,000
Final Polishing	$3,000,000
Waste Disposal	$800,000
Final Storage	$200,000

HAZARD AND HEALTH

Minimize	Several small reactors not a single large reactor.
Moderate	Final Storage at -10°C not -80°C
Substitute	Water-Ethanol Mixture for cooling not liquid N_2
Simplify	Disposable seed train components over CIP/SIP

FUTURE WORK AND RECOMMENDATIONS

We recommend to complete the preliminary analysis of this design future engineers must:

- Confirm Economic analysis integrating efficiency and uncertainty.
- Model the system in a professional version of SuperPro Designer™ by Intellegen® rather than the restricted version.
- Evaluate the systems performance at the at optimized bioreactor yields.
- More harshly scrutinize regulations that could effect the project conclusions.

Based on preliminary analysis, this plant is profitable and viable, therefore it is recommended to move to the detailed phase of development.