

Innovations in Bioprocess Engineering in CNY

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How Bioprocess Engineering Can Make a Difference – 2 examples

Amgen, Inc (1983)

- 60-70 people, mostly molecular biologists and protein chemists
- No engineers
- Operational funds for 1-2 years
- Many product ideas based on recombinant proteins

Amgen, Inc (1983)

- Luria broth fermentation process (~ 2 OD or ~ 50 mg/liter recombinant protein)
- Pilot plant with 10 ten liter fermentors
- 7,000 liter fermentor purchased but not yet installed for Chicago GMP facility

Amgen, Inc (1983)

- *E. coli* K-12 host strain
- Suspected susceptibility to growth inhibition by acetate
- Previous attempts to grow cells to high cell density in batch process failed

Fermentation Design

- Choice of reactor system – batch, fed-batch, continuous
- Influenced by:
 - Organism stability
 - Oxygen transfer requirements
 - $N = k_L a(C^* - C_L)$
 - Heat transfer requirements
 - $Q_f = 0.12 Q_{O_2}$
 - Product yield

High Cell Density Growth – General Approach

- Use of defined minimal media
- Selection of appropriate specific growth rate
- Carbon nutrient limitation in fed-batch mode

Process Development Methodology

- Establish growth kinetics
- Determine growth yield
 - Design media
- Optimize for growth and expression

Escherichia coli example

- Chemostat growth to determine acetate accumulation profile vs. specific growth rate and calculation of growth yield and maintenance coefficients
- Design of medium to support high cell density growth
- Growth of non-recombinant strain
- Growth of recombinant strain and expression of alpha interferon

Amgen, Inc (1984)

- All production remained in Thousand Oaks, CA
- 7,000 liter fermentor in Chicago sold
- Lease of building in Chicago terminated
- Amgen had capacity to pursue diverse product portfolio strategy with minimal resources and \$
- Technology was used to produce *Neupogen*, one of Amgen's two *blockbuster* drugs (over \$1 billion dollars per year in sales)

Amgen, Inc (1996)

- *Epogen* approved 1995
- Manufacturing facility running at capacity (200 g/year)
- Market grossly underestimated
- J&J had right to manufacture if we could not meet market demand
- Retail value of *Epogen* ~ \$1 million per gram

Amgen, Inc (1996)

- Manufacturing facility hemmed in by terrain and other manufacturing buildings – footprint could not expand
- Roller bottle process was capacity limiting step
- Management did not want to change to “deep tank” technology

Epogen Roller Bottle Process

- Standard roller bottles
- 200 mls per bottle
- Serum containing growth cycle followed by two basal media production cycles with DMEM/F 12 media mix
- Cells would fall off bottles, primarily during second cycle, and clog filters
- What to do?

Experimental Approach

- Characterize problem
 - Measure dissolved oxygen, CO₂, pH, glucose and lactate levels, cell viability

Experimental Data

- First cycle data okay
- Second cycle:
 - Oxygen depletion
 - CO₂ and lactate buildup, dropping pH
 - Glucose depletion
 - Cell viability decreasing

Experimental Solution

- Develop a gas permeable membrane (in roller bottle cap) allowing oxygen in, CO₂ out
- Increase phosphate concentration to provide pH buffering (to replace lost carbonate buffering capacity)
- Increase glucose concentration
- Increase duration of production cycles
- Increase number of production cycles from two to three

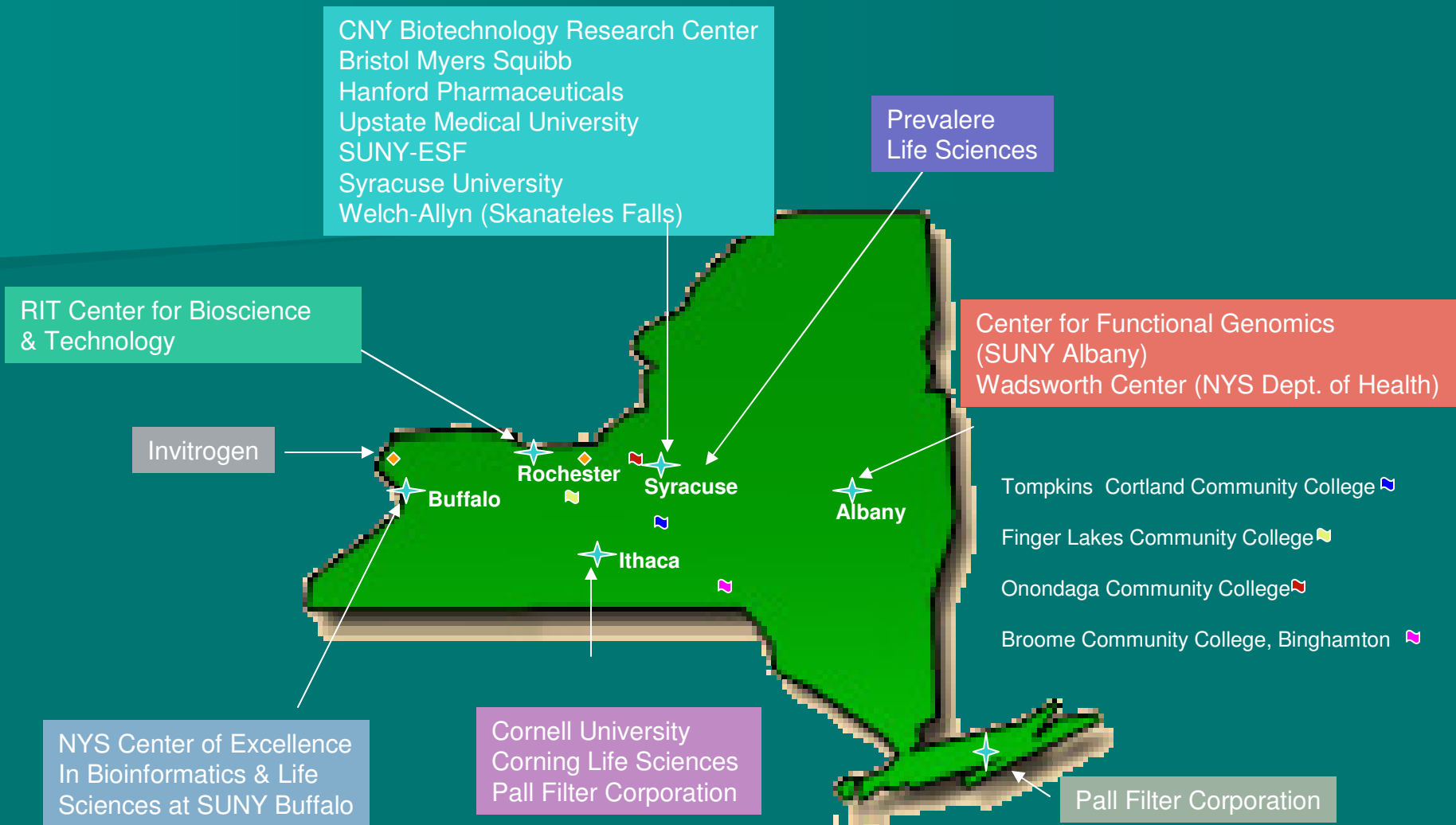
Experimental Results

- Cell numbers and viability increased
- Product titers increased 30-40%
- Plant output increased from 200 g/year to over 1,000 g/year @ \$1 million per gram
- Sales of Epogen increased to over \$1 billion per year (Amgen's other *blockbuster* drug)

Bioprocess Engineering *Does* Make a Difference

Central New York

- Opportunities for biotechnology and bioprocess engineering
 - Collaboration between academic institutions and private industry to spur economic development and growth



Upstate New York's Biosciences Corridor

Central New York Biotechnology Research Center

- A non-profit 501 c.3 corporation created through the efforts of SUNY ESF, SUNY UMU, MDA and Bristol-Myers Squibb, board includes representation from Syracuse University, Le Moyne College and other companies
- Initial seed funding of \$500,000 from BMS

Central New York Biotechnology Research Center

- \$20 million in allocated state funds for building construction
- Mission is to create economic growth through joint applied biotechnology research and development between academic institutions and the private sector

\$1 Million NASA Award CNY BRC Funded Research

Project Description	Funding Level
Repair of Spinal Cord Injuries using cultured Schwann Cells (UMU/SU)	\$120,000
Application of Gene Therapy to Blinding Retinal Diseases (UMU)	\$120,000
Biodegradable Implants for Torn Wrist Ligaments (UMU)	\$120,000
Optimization of an Electromagnetic Treatment for Osteoporosis (UMU)	\$120,000
Composite metal ceramic matrix implant materials for joint replacement (UMU)	\$120,000

\$1 Million NASA Award

CNY BRC Funded Research

Project Description	Funding Level
The Biorefinery in New York (ESF)	\$100,000
Production of Hydrogen from Woody Biomass (ESF)	\$75,000
Production of Biopolymer Thermoplastics from Woody Biomass (ESF)	\$75,000
Development of New Physical Supports for Chromatography Resins (ESF)	\$50,000
Development of Nanobrushes for Bone Repair Cement (ESF)	\$50,000

Some Relevant Biotechnology Industry Trends (relevant to CNY)

- Generic biologics, high cost of energy and increasing cost pressures on drug prices
 - More efficient manufacturing processes

CNY BRC New Project Awards

- “Optimization of a Bioprocess to Produce a r-DNA Based Human Therapeutic Product”
- \$100,000 contract process development work for Maryland based company to optimize the commercial production process for a human therapeutic (details confidential) – project completed

CNY BRC New Project Awards

- “The Use of Microporous Ceramic Composite Membrane Technology in the Improvement of Biofuels and Bioproducts Production”
- \$500,000 project, \$250,000 award from NYSERDA, 2007
- Partner with Corning, Inc., the Hilliard Corporation and SUNY ESF

Some Relevant Biotechnology Industry Trends (relevant to CNY)

- Higher Energy Costs, Global Warming, Environmental Pollution
 - Bioenergy and other products from renewable resources
 - Use of disposables in GMP and medical products manufacturing

CNY BRC New Project Awards

- “Performance Testing of a Novel Bioreactor for Ethanol Production from Cheese Whey”
- \$800,000 project, \$400,000 award from NYSERDA, 2007
- Partner with Corning, Inc., the Hilliard Corporation, Kraft Foods and SUNY ESF

CNY BRC Project Proposals

- “Evaluation of waste streams generated by New York State’s cheese industry for the production of biodegradable plastics”
- \$120,000 project, seeking a \$60,000 award from NYS Dept of Agriculture and Markets, submitted summer of 2007
- Partner with Welch Allyn, Kraft Foods and SUNY ESF

CNY BRC Project Proposals

- Ethanol Production from Combined Feed Streams from Wood Sugars and Cheese Whey
- \$120,000 project, seeking a \$60,000 award from NYS Dept of Agricultural and Markets, submitted summer of 2007
- Partner with Kraft Foods, SUNY ESF

Some Relevant Biotechnology Industry Trends (relevant to CNY)

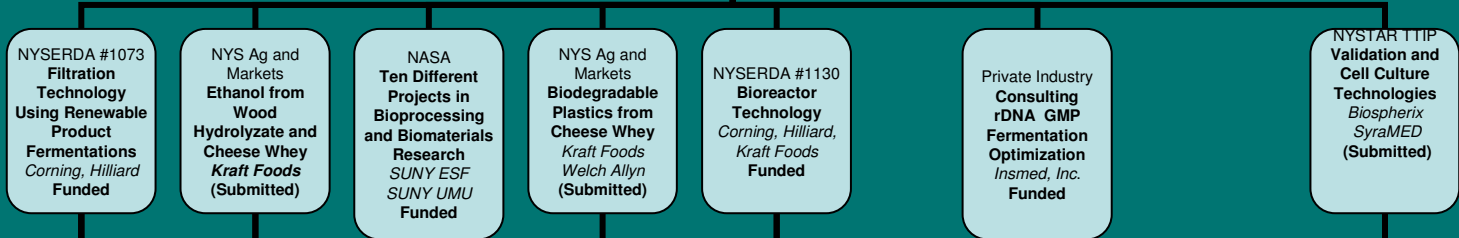
- Personalized Medicine
 - Customized stem cell preparations

CNY BRC Project Proposals

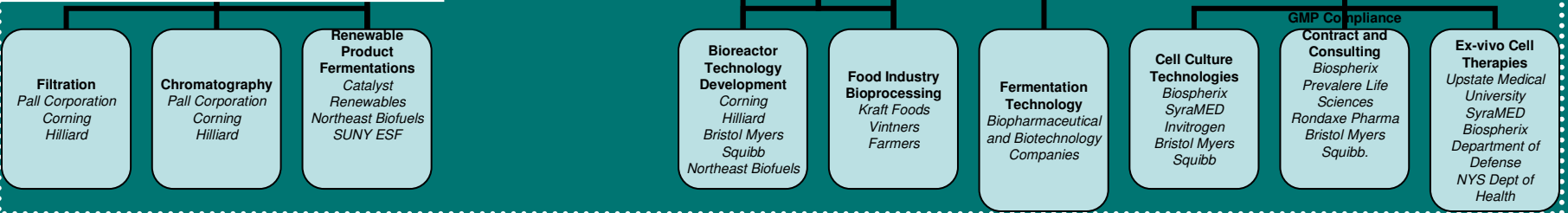
- “GMP Validation and Performance Demonstration of the Biospherix X-Vivo Incubation System”
- \$1,000,000 project, seeking a \$500,000 award from NYSTAR, in preparation
- Partner with Biospherix, LLC., Upstate Medical University, SUNY ESF

**CNY
BRC
Project
Family
Tree**

Funded and Submitted Projects



Related Future Project Areas



Other Major Funding Opportunities

- CAT Application (>\$10 million NYSTAR opportunity)
 - “CAT for Bioprocessing and Production of Biocompatible Materials” with SUNY ESF, SUNY UMU and 12 industry collaborative projects
 - *NYSTAR withdrew RFP*

Other Major Funding Opportunities

- NYS Dept of Environmental Conservation (initial \$2 million award)
 - To create center focused on sustainability and reduction of energy and resource consumption as well as reduction or elimination of hazardous substances, pollution and waste
 - Proposal in Preparation for December, 2007 submission

Future

- Continue to develop and create funded joint academic-industry projects complementary to ESF and UMU with primarily NYS companies
- Establish significant laboratory capability in bioprocessing and biotechnology using new staff and research funds
- Continue to pursue operating funds for CNY BRC

Goals for the Future

- Near term (2-5 years)
 - \$2 million per year in research programs
 - Achieve statewide reputation as the “go to” center for bioprocess engineering
 - Receive CAT or similar designation and related operational funding
 - Construct \$20 million CNY BRC building

Goals for the Future

- Longer term (5-10 years)
 - \$5 million in annual research programs
 - Achieve national reputation as the “go to” center for bioprocess engineering
 - Procure additional \$20 million in construction funds for specialized labs, possible GMP pilot plant

Thank You

