

Small Scale Bio-production: Beyond the Flask.

The Penridge Suite, 470 Bowes Road, London , N11 1NL , United Kingdom : 18th November 2011

"Once you can produce it in a flask, what next? The focus of this meeting will be on techniques for the bioproduction of usable quantities of biologic materials, specifically recombinant proteins, monoclonal antibodies, cytokines viruses and other secreted cellular products from eukaryotic cells. Topics covered will include expression systems, mammalian vs. insect vs. other, constitutive vs. transient expression, cell culture medium considerations and culture devices for scale-up that can be used in any laboratory. This meeting should show the fastest pathway from discovery to proof of principle and the production of 100 mgs to several grams of product"

Meeting Chair: *Professor Julian Morris*, Technical Director CFACT and Professor of Process Control, Centre for Process Analytics and Control Technology, Newcastle University, UK

This meeting has CPD accreditation

- 9:00 – 9:45 **Registration**
- 9:45 – 10:00 **Introduction by the Chair:** *Professor Julian Morris*, Technical Director CFACT and Professor of ProcessControl, Centre for Process Analytics and Control Technology, Newcastle University, UK.
- 10:00– 10:30 **Laboratory-scale production of monoclonal antibodies as immunological tools in the vaccine industry**
Vincent Dewar, GlaxoSmithKline Biologicals, Rixensart, Belgium
Monoclonal antibodies are widely used at GlaxoSmithKline Biologicals for the quantification and characterization of antigens and the quality control of vaccine lots. In the last decade, monoclonal antibodies have been produced by in vitro methods, based on a cell bank library of more than 2,500 hybridomas covering more than 200 different antigens. For production yields ranging from 10 mg to 1 g, two methods have been established, each addressing specific requirements. One is based on the double membrane bioreactor technology, the other on hollow fiber technology. This lecture aims to highlight the current needs in terms of the investment, productivity and manpower that are necessary to provide the vaccine industry with monoclonal antibodies as powerful immunological tools. The selection of a production method, depending on the goal to reach, will be described.
- 10:30 – 11:00 **Biorefining Plant Natural Products: a Synthetic Biology Approach**
Professor Robert Edwards, University of York, UK
- 11:00- 11:30 **Mid-morning break, Poster Viewing and Trade Show**
- 11:30 - 12:00 **Scalable Platforms for Adherent Cell Growth in Biopharmaceutical Manufacturing**
Dr Alun Fowler, Thermofisher, UK
Suspension cell culture has dominated the bioproduction agenda due to the prevalence of recombinant protein production. With the advent of gene therapy, regenerative medicine and a continued focus on viral vaccines, validated and scaleable systems are required for bioproduction based on adherent cell growth. We will demonstrate how these platforms are evaluated, developed and automated at production scale.
- 12:00 – 12:30 **PAT and Quality by Design – a Process SystemsEngineering View**
Professor Julian Morris, Technical Director CFACT and Professor of Process Control, Centre for Process Analytics and Control Technology, Newcastle University, UK.
Unlike in off-line assays, in-situ or on-line real-time spectroscopic measurements are almost inevitably subjected to fluctuations/variations of process variables such as temperature as well as sample compactness, instrumental effects and other external process variables and physical properties of samples. This makes the task of extracting the relevant chemical information, and ultimately reliable process understanding for process modelling and for closed loop process control and optimization,

from spectroscopic measurements well beyond being routine in pharmaceutical manufacturing. Challenges also relate to the routine integration (fusion) of analytical and process sensor based chemical and biological measurements which may be dynamic, nonlinear and of disparate forms. All these exacerbate the building robust, transferable, calibrations (models). The presentation will discuss the application of recently developed multivariate methods to enable the assured application and on-line real-time use of process analytics for process monitoring and control.

12:30–13:30 **Lunch, Poster Viewing and Trade Show**

13:30 – 14:30 **Question and Answer Session**

Delegates will be asked to submit questions to a panel of experts. Questions can be submitted before the event or on the day

14:30 – 15:00 **Process development and scale up**

Dr Stephen Pearson, Centre for Process Innovation Limited, UK

CPI is a part government funded Technology Innovation Centre focused on the delivery of large and small, private and public projects in a number of technology areas, the largest of which is in fermentation and industrial biotechnology. Home to the National Industrial Biotechnology Facility (NIBF), CPI helps industry and academia develop and scale processes for the production of enzymes and biorenewable chemicals. This talk describes what we do, how you can use CPI's facilities to support your needs and discusses some of our recent process experiences.

15:00 – 15:30 **Afternoon Tea/Coffee, Poster Viewing and Trade Show**

15:30 – 16:00 **The Use of Hollow Fiber Bioreactors for Protein and Antibody Production.**

Dr John J.S. Cadwell, President and CEO, FiberCell Systems Inc, USA

Hollow fiber bioreactors offer significant advantages vs. traditional cell culture methods and other bioreactors. Product is significantly concentrated, the use of simplified protein-free medium is facilitated, apoptosis is inhibited and protein folding can be improved. Application of hollow fiber bioreactors for the production of gram quantities or more of antibodies and proteins will be described.

16:00 - 16:30 **The use of DoE for efficient process development and scale-up**

Paul Murray, CatSci Ltd, Cardiff, UK

The use of DoE during small molecule development has shown significant benefit. These tools can be applied to all aspect of bio-production. The use of DoE and some advanced designs to support efficient development of processes will be demonstrated and discussed.

16:30 - 17:00 **Chairman's summing up.**

Keywords: monoclonal antibodies, hybridoma, recombinant protein, monoclonal antibody, production, hollow fiber., hollow fiber, double membrane, cell culture; viral vaccine; gene therapy; stem cell; scale-up, Biorefining, Design of Experiments, process scale-up, industrial biotechnology, biorenewable chemicals, enzymes.

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About the speakers

Julian Morris is Professor of Process Control at Newcastle University and Visiting Professor in the Department of Pure and Applied Chemistry at the University of Strathclyde and Director of the Centre for Process Analytics and Control Technology (CPACT). He is the immediate past Head of the School of Chemical Engineering and Advanced Materials at Newcastle University, head of the Department of Chemical and Process Engineering between 1990 and 1995, and has spent some time as Professor of Chemical Engineering at the University of Alberta in Canada. He holds positions of Associate Director of the data mining company AJM Consulting; is a member of the UK Centre for Process Innovation (CPI) Advisory Committee. His research interests include process diagnostics and condition monitoring, process performance monitoring, Process Analytical Technologies, neural networks, and advanced process control and optimisation. He has authored/co-authored over 190 articles in scientific journals, conferences and books, given over 70 invited lectures, and 50 Plenary and Keynote presentations. He is a Fellow of the Britain's Royal Academy of Engineering

Vincent Dewar is a scientist at GSK Biologicals in Belgium with more than 15 years of expertise in the field of monoclonal antibodies (MAb), including their generation and characterization. He is heading the MAb Platform and has conducted the transition from in vivo to in vitro production of MAb's at GSK Biologicals.

After a career comprising of 8 years in academia, 5 years commercial experience and the completion of a MBA, **Steven Pearson** joined CPI in 2010 as a commercial manager. He currently generates and facilitates projects within CPI to progress the development of industrial biotechnology in the UK.

Alun Fowler gained his PhD in Microbiology at Leeds University in 1997. Since then he has worked as a technical specialist for filtration in clinical, diagnostic, and laboratory applications before moving into the field of chromatography and downstream processing in a biopharmaceutical setting. Alun joined Thermo Fisher Scientific as a Bioproduction Specialist in 2010 and provides technical support to Thermo's Laboratory Products Group, with a specific focus on their Nunc and Nalgene brands.

John Cadwell has his degree in pharmacology from the University of Miami. He has held prominent positions in sales and marketing in several cell culture oriented companies prior to forming FiberCell Systems in 2000.

Paul Murray completed a degree in Natural Science and a PhD at Trinity College, Dublin. He joined AstraZeneca in 1998 working on various stages of the development. In '03 he became involved in Catalysis and set up a dedicated Catalysis Facility to support projects across R&D from ca '05. A collaboration with UoB on Predictive Catalysis was initiated - the use high quality ligand descriptors with Principal Component Analysis and experimental design to drive reaction understanding. At the end of 2010, as a result of R&D restructuring, Paul left AZ to set up CatSci - a SME focused on the development and optimisation of catalysed reactions.

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Full Abstracts

"Coproduction of biopolymers consisting of Medium chain length 3-hydroxyalkanoic Acid and Exopolysaccharide by *Pseudomonas* CMG607w of marine origin"

Nazia Jamila, Nuzhat Ahmedb, David H. Edwardsc, Hilary K.Youngc and Geof M. Gaddca

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Background

Bioplastics or polyhydroxyalkanoates (PHAs) are a special type of biomaterial. They are polyesters, produced by a range of microorganisms, cultured under different nutrient and environmental conditions. When the carbon substrate is in excess to other growth limiting nutrients like nitrogen, sulfur, phosphorus or oxygen (Madison and Huisman, 1999; Kim and Lenz, 2001; Reddy *et al.*, 2003), many microorganisms can accumulate PHAs as intracellular energy yielding and carbon storage granules. These polymers are accumulated in the form of mobile, amorphous, liquid granules of lipids that provide these microorganisms nutrients under stress conditions (Barnard and Sander, 1989; Sudesh *et al.*, 2000).

Objectives

Characterization of *Pseudomonas* CMG607w for the production Exopolysaccharides and mcl-PHA.

Methods

1. Extraction and Purification of biopolymers from *Pseudomonas* CMG607w.
2. PCR based strategy to identify *PhaC* synthase operon.

Results

Bioplastic (medium chain length polyhydroxyalkanoate) was extracted and purified from CMG607w bacterial strain isolated from sediment of Layari River out fall to Arabian sea. PHA synthesis was substrate depended in CMG607w. In presence of sodium gluconate mcl-Pha was synthesized at the rate of 42% cell dry mass. Under highly enrich conditions, co production of polysaccharide and blends of PHB/PHA were observed. PCR base strategy was used to amplify *Pha* biosynthesis operon from chromosomal DNA. In CMG607w *Pha* biosynthesis operon has *PhaC1ZC2D* (polymerase1, depolymerase, polymerase2 and hypothetical protein) genes orientation. Conserved sequences were observed in *polymerase C1* and *C2*. All gene of *Pha* operon was cloned and sequenced. *Pha* biosynthesis operon of CMG607w has 98% homology to *Pseudomonas aeruginosa* PAO1 (AE004919). GenBank accession numbers for polyhydroxyalkanoates synthase operon nucleotide sequences are from AY596787 to AY596795.

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