NEWSLETTER

of the European Society for Animal Cell Technology

March 2010

News

Proceedings Dresden and Dublin

The Book of Proceedings from 20th ESACT Meeting - Dresden is coming out soon. The Dublin Scientific Committee Chair, Professor Nigel Jenkins, is now inviting all the 21th ESACT poster presenters to contribute with a extended abstract (3 pages max) to the Dublin proceedings book. The deadline is April 9, 2010. For more information please contact ESACT Dublin Secretariat, Ms Bernadette Douglas (Margaret.Beggan@dcu.ie).

2010 Elmer Gaden Award

E. Terry Papoutsakis and former group member Ryan Senger (now an Assistant Professor at Virginia Tech, are honored with the 2010 Elmer Gaden Award by Biotechnology & Bioengineering and John Wiley & Sons, Inc. for their paper:"Genome-Scale Model for Clostridium acetobutylicum: Part I. Metabolic Network Resolution and Analysis".

Biotechnology and Bioengineering, Volume **101**, Issue 5, 2008, Pages 1036–1052 DOI 10.1002/bit.22010.

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Contributions should be sent to eletter@esact.org

Synthetic Biology - what is it?

In cell culture technology we hope to make useful products and we think that key to this is a complete and "happy" cell. When our cells are happy then they work well for us, i.e. they work for example as protein production machines. However and maybe one day, this could be done in an entirely different way. The "black-box" - our cells - could be replaced by a true biological machine where we know every part involved and could modify or optimize it for our purposes to fit better to the final product intended. So, are we able to design such a machine? At least some attempts have been made in the past towards this goal. As Martin Fussenegger, our highly respected chairman said, small successes have been sold with some (too much?) hype.

In any case, if you want to read more about this highly fascinating and maybe still very provocative new field, please read the commentary Professor Fussenegger has recently published in Nature (*Nature* **463**, 301-302 (21 January 2010))

JIN - our service offer to the industry and interested cell culture professionals for finding matching interests.

The JIN is apparently becoming more and more successful and the website is heavily utilized. We are still looking, however, for sponsor companies who would help us to pay for the costly program that ESACT has supported since its establishment several years ago. In return for a sponsor contribution the logo of the sponsor company will be displayed on the web site.

→ http://www.jin-esact.org

ESACT 2009 Workshops

Brian Kelley

21st ESACT Dublin Participants had the opportunity to attend, once again, the traditional series of **Workshops** organized before the Official Opening of the ESACT Meeting. This edition covered several relevant topics of Animal Cell Technology:

Workshop 1: PAT and other recent developments in regulations (organized Sadettin Ozturk, Centocor, U.S.A. and Nigel Jenkins, NIRBT, Ireland);

Workshop 2: Innovative media products for the 21st century biopharmaceutical industry (organized by Steve Profit, SAFC U.S.A.),

Workshop 3: The impact of high titer feedstreams on monoclonal antibody purification (organized by Brian Kelley, Genentech U.S.A.) and,

Workshop 4: Advances in genomics and proteomics (organized by Wei-Shou Hu University of Minnesota and Tim Charlebois, Wyeth U.S.A.)

In this newsletter edition we acknowledge Brian Kelly contribution and publish his overview and summary of Workshop 3.

The Impact of High-Titer Feedstreams on Monoclonal Antibody Purification

Brian Kelley
Vice President, Bioprocess Development
Genentech, Inc.

This workshop focused on the impact of high-titer fed-batch processes used for production of monoclonal antibodies (mAbs), first addressing the challenges these cell culture advance present to the purification process. Next, the group reviewed high-level process economics and the question of what additional benefits are gained in pressing for ever higher process titers.

Current surveys of industrial mAb processes from published literature and conference reports indicate that it is now common to achieve product titers of 2 – 5 g/L after a 10 – 14 day fed-batch process. Optimized processes using exceptional cell lines have been demonstrate to approach 10 g/L in extended fed-batch processes (usually 17-21 days) by several companies. These high titers will exceed the capacity of the purification trains in most cGMP production facilities, at least when matched to purification technology developed several years ago for the first generation of recombinant therapeutic mAbs. An informal audience poll confirmed that many had heard of the purification bottleneck, and had developed cell culture processes that exceeded the limits of these older purification processes.

To address these limits, facility fit models are developed to determine which unit operations cause the purification bottleneck. An example was shared which evaluated solution volume, pool volumes, length of each chromatographic and filtration step, and bulk drug substance volume. Typical constraints identified from models of some of the world's largest cell culture facilities suggest that solution volume, pool volume, and bulk concentration limits are common. Using older mAb purification platform processes, some facilities cannot handle even 3 or 4 g/L titers, hence the observation that cell culture productivity can exceed purification capacity.

Next, several examples of successful purification debottlenecking were shared. One key focus is to increase the concentration of the chromatographic resin loadings, and to avoid in-process dilutions which condition the product pool for the next step. This strategy minimizes the total solution volume required per gram of product produced (one published benchmark for a highly optimized process was 2L per gm as well as minimizes product pool volumes, and reduces column cycling thus decreasing processing time.

A second example changed the process design basis from 'every gram counts' to 'bigger batches win'. By allowing modest reductions in step yield as a degree of freedom, and not enforcing the strict yield maximization of past purification processes, a greater mass of product can be purified per batch, thus increasing plant productivity. For a Protein A capture step, increasing the binding capacity from 20 to 55 g/L and reducing the pool volume from 3 to 2 column volumes may cause a reduction in the step yield from the typical high values (98% can be achieved) to 95% or less, but increases the product concentration in the pool four-fold, and thus relieves a constraint for plants that have small Protein A product pool tanks.

Another approach argued that increasing the chromatographic bed height and reducing the flowrate serve to increase binding capacities further; early processes had opposite design criteria as they were developed to handle dilute, large volume harvests. New chromatographic resins and filters enable these significantly higher loading capacities, thus enabling the next generation of processes to handle 50 or even 100 kg batches from facilities with 12 – 25kL bioreactors (well in excess of 4 g/L titers).

With such simple debottlenecking approaches becoming established in the industry, non-conventional unit operations such as precipitation, crystallization, simulated moving bed chromatography, etc. may not be required to increase plant capacities. A design basis for a plant having 6 x 12kL bioreactors running at 5 g/L could produce 8 tons of mAb per year, using columns which are only 1m in diameter. (Putting this in perspective, the global demand for therapeutic mAbs and Fc fusion proteins was estimated to be approximately 7 tons in 2008.) More advanced processes using just two chromatographic steps, or semi-continuous operation were also seen to offer little in terms of increased capacity or cost reduction for current facilities.

The group then discussed the impact that high-titer processes can have on product quality. One participant has experienced increased product aggregation, and the conference program included a presentation on disulfide bond reduction during harvest (although it was noted that this process did not have very high titers, other groups have seen this problem get worse with increasing titer). Others commented on the challenges that increased levels of cell debris cause to the harvest and clarification steps. Process changes from a low-titer Phase I to a high-titer Phase III process could include shifts in acidic variant profiles; while these do not always alter product safety or efficacy they may introduce comparability hurdles during development. Each of these issues argue for carefully considering the benefits of high-titer processes before assuming that higher titers are always better.

This led to several exchanges on Factories of the Future (FoF), a conceptual design based on multiple 2kL single-use bioreactors. While such facilities would significantly reduce capital investment, the kilograms harvested per batch would not strain state-of-the-art purification trains, even at 10 g/L or higher. It is the total kg per batch which should be the purification design comparison in the FoFs vs. conventional large-scale bioreactor facilities, not the product titer alone.

Lastly, a review of simplistic process economics suggested that as titers have risen from 1 to 5 g/L, the cost of goods for very-large scale plants is likely to drop from $200 - 300/g to $40 – 80/g. The raw material costs for the purification train are small (as low as $4/g), as will be all raw materials on a per-gram basis for high-titer processes which take advantage of economies of scale from extant facilities with bioreactors of 12kL volume or larger.

One participant offered that product change-over costs are significant; minimizing the down time for a large facility is a key objective. This will reward platform processes which use similar unit operations and design bases, which could be established rapidly for the next generation of purification platforms. Non-conventional purification (or cell culture) unit operations may be challenging to incorporate into a facility that is designed for the current mix of products.

A provocative question closed the workshop; if we throttle back the drive for ever-higher titers, does this suggest that our most significant cell culture development challenge is over? The counter argument suggested that investing in establishing a more fundamental understanding of many aspects of industrial cell culture mAb processes (metabolic flux modeling and cell metabolism, -omics approaches to understand biochemical pathways as well as product expression and secretion, etc.), we may arrive at a comfortable equilibrium where modest titers are sufficient to satisfy all but the largest blockbuster markets at an acceptable cost of goods, and that the processes will be inherently robust and capable of consistently delivering a product of high quality. A counterpoint was raised, that driving to higher titers enables technological advances which could ensure that moderate titer targets are more easily achieved. Several participants felt that product quality should be a continued focus of process development groups, and perhaps increased in emphasis in comparison to high titers.

The workshop closed without bloodshed, and the lone purification engineer was lucky to have escaped alive.

9th PEACe Conference

Georg Schmid

9th Conference on Protein Expression in Animal Cells (PEACe) September 19-23, 2009 (Jackson Hole, Wyoming, USA)

This series of conferences evolved from its origins in 1992 with a meeting on "Baculovirus and Insect Cell Expression" in Interlaken and an initial conference in 1997 on "Transient Gene Expression" held in Jersey, Channel Islands, into a regular event that takes place every second year. Since the days of these early and more highly specialized meetings the conference topics have been expanded to include a significantly wider scientific scope and for the sixth meeting in Mont Tremblant, Canada, in 2003 the present meeting title Protein Expression in Animal Cells (PEACe) was introduced.

http://www.peace-conference.org/

In September 2009 around 140 colleagues from academia and industry attended the latest meeting in Jackson Hole, Wyoming. As a purposeful small meeting it encourages discussions right after the individual presentations and provides plenty of time for interactions with colleagues during coffee breaks, meals and the poster sessions. The organizing committee with its chairman Tom Kost (GSK) did a great job in putting together a very stimulating and diverse program covering the broad range of cell culture expression systems in use today. The sessions covered transient protein production, engineering for stable cell lines, post-translational modifications, large-scale bioprocessing and alternative expression systems.

In the following I will give an outline of the scientific program and summarize a number of select presentations:

- **Transient Protein Production**

Bob Ames (GSK Collegeville) presented the principles of the BacMam technology, i.e. the use of recombinant baculoviruses to support transient gene expression in mammalian cells (The Tao of BacMam). He reviewed pressures facing the pharmaceutical industry and related how discovery groups are struggling to meet the demand for new reagents and assays to support drug discovery. Described how BacMam-based transient gene delivery is an effective solution to generate cell-based assays amenable to high throughput screening and presented data to support the concept that the system provides unparalleled experimental flexibility. He presented how BacMam has been implemented across GSK R&D and concluded with information about improvements to the system, including newest generation of expression vectors and engineering of host cells to increase their susceptibility to transduction. **Yves Durocher (NRC Montreal)** compared PEI based transient transfection in 293EBNA and CHO cells. (1) The 293EBNA clone 6E in combination with the pTT5 vector (4.4 kb) yields 150 to 250 mg/L of mAb at 6 days post-transfection (+/– oriP has a 3-4 fold effect on expression). (2) Data on a newly generated CHO-EBNA1 cell clone (3E7) was also presented. EBNA1 expression was stable w/o selection pressure over 4 months. GFP expression levels for CHO 3E7 and "normal" CHO using a pTT-GFP vector were compared. Expression levels were increased 4-5 fold. Similar improvements in titer were observed for secreted alkaline phosphatase (SEAP). mAb expression levels in CHO-3E7 reached 150 mg/L within 12 days.

- **Stable Cell Lines & Cell Engineering**

The effect of iterative transfections of MAR elements plus transgene were the topic of **Nic Mermod's (University of Lausanne)** talk. Such double transfections yielded high-producing (qp 20-80 pg/cell.d) CHO DG44 clones. The timing of the second transfection is critical (cell cycle dependent). The integration occurs into the first loci, whereby the second plasmid is transported to the nucleaus more efficiently. **Bhaskar Thyagarajan (Invitrogen)** introduced a novel site-specific integration method. The phiC31 integrase is derived from a Streptomyces bacteriophage, it is functional in mammalian cells without the addition of any co-factors. The integrase recombines attachment sites that are non-identical. However, screening multiple clones to find integrations in

identical sites would be still needed. Thus, a specific R4 target cell line with a pre-placed acceptor site was created in 293 cells.

- **Protein Expression & Secretion**

Colin Hebert (University of Maryland) spoke about the use of interfering RNA in the baculovirus expression system (esp. HighFive cells). For example, *Trichoplusia ni* caspase-1 (a protease involved in apoptosis) was silenced with in vitro synthesized dsRNA resulting in increased protein production. Subsequently, for a cell line stably expressing in vivo RNAi, caspase-1 enzymatic activity was reduced by 90%. These cells demonstrated superior viabilities and 2x higher protein yields (GFP) when compared to standard HighFive cells. **Sean Evans (GTC Biotherapeutics)** reported on antithrombin III production in transgenic goats (ATryn). This product, the first licensed transgenic animal produced recombinant protein, received EMEA approval in 2006 and FDA approval in 2009. Using the goat beta casein expression vector antibodies are expressed at 5-15 g/L in the milk. This translates into 0.6-7.2 kg/yr per goat

- **Post-Translational Modification**

Mike Butler (University of Manitoba) covered huIFNbeta production. The observed aggregation could be reduced by lowering the expression temperature at day 7 in fed-batch cultures and also by employing cell-retention (perfusion) technology. Reduced residence time resulted in less aggregation similar to less proteolytic degradation observed for protease sensitive products. **Tim Edmunds (Genzyme)** reported on different strategies to manipulate glycosylation of hormones and antibodies to reduce heterogeneity and improve efficacy (thyroid stimulating hormone, antithrombin III, glucocerebrosidase). Co-expression of glycosyltransferases and using specific inhibitors were exemplified, e.g. fucose modification was accomplished by the addition of kifunensine (2 µg/mL) to cultures. For antibodies this approach resulted in similar yields, however, for other proteins reduced yields were seen.

- **Alternative Cell Systems**

Paula Alves (IBET, Lisbon) spoke about "Bioengineering long term neuronal and hepatocyte spheroid cultures for pre-clinical research". Three cell types were covered: (1) Primary cultures of brain cells as 3-D cultures/aggregates and development of cryopreservation protocols for brain cell aggregates (in alginate, 80% recovery). (2) 2-D and 3-D hepatocyte cultures as aggregates and in alginate beads including functional assessment for albumin production, urea secretion, Phase I and Phase II (UGTs) enzyme activities. (3) Expansion of stem cell-derived neurons for toxicology, screening and therapy. **Andre Choo (BTI, Singapore)** described the generation of a panel of mAbs against novel cell surface markers on human embryonic stem cells (hESCs). One of the antibodies, mAb84, is shown to be a cytotoxic IgM antibody that selectively kills hESCs by oncosis (not apoptosis). It can be used for eliminating contaminating hESCs from the differentiated cell population by chromatographic purification (purging). This may be relevant in a clinical setting. Micro-algae as a platform for the production of therapeutic proteins were introduced by **Stephen Mayfield (Scripps)**. Most proteins in photosynthetic organisms are made in the chloroplasts, however, little post-translational modifications take place. The eukaryotic green algae *Chlamydomonas reinhardtii* can synthesize and assemble several proteins/hormones in transgenic chloroplasts. Varying but significant amounts of these proteins are found to be bioactive. One example was a full-length anti-anthrax IgG1. Heavy and light chain proteins expressed in the chloroplast accumulated as soluble proteins that assemble into complexes containing two heavy and two light chain proteins.

- **Large Scale Bioprocessing**

Two presentations here focused on the baculovirus insect cell expression system. While **Sergei Zolotukin's (University of Florida)** talk covered an inducible production system for recombinant adeno-associated virus (rAAV) vectors to be used in gene therapy, **Marguerite Deschamps (GSK Rixensart)** gave a high-level account on Cervarix production (GlaxoSmithKline Biologicals' cervical cancer vaccine). Quality and safety assessment of cells and

viruses were described. Recombinant capsid HPV-16 and HPV-18 L1 gene products are expressed in *Trichoplusia ni* insect cells which are assembled into virus-like particles (VLPs). Antigen characterization included various assays for structural integrity and similarity to native HPV virions, e.g. secondary structure determination by CD and FT-IR. VLPs demonstrated a size and structure similar to HPV (ca. 50 nm, morphological analyses), high binding affinity with neutralizing antibodies, etc. At the level of drug substance - besides the standard assays – baculovirus presence and clearance have to be demonstrated. DNA < 4 pg/dose. HCPs < 0.1%. Several additional VLP based vaccines (e.g. against the flu) are in development by GSK. The *Trichoplusia ni* cells used for production are devoid of alphanodavirus RNA. The EBx cell based platform was presented by **Majid Mehtali (Vivalis)**. The whole company has been built around the use of avian stem cells (indefinite self renewal, genetically stable) as biological substrate. The use of duck EB66 cells was exemplified for the expression of therapeutic proteins and VLPs. During the derivation of EB66 cells several stem cell markers (like Nanog, Oct-4) were assessed, telomerase activity remained high, stability was shown by karyotyping. Cells grow to 45 x 10E6 cells/mL (SAGB medium) with a doubling time of 15 h. Product examples include: mumps and pox VLPs. With regard to protein production it was shown/claimed that neither NGNA nor Gal alpha1-3 Gal linkages were present and little fucosylation occurs. Fed-batch IgG concentrations reached 0.7 g/L after 8 days (special promoter used). Low amounts of NH4 and lactate are generated, cells don't require glutamine, only glucose.

PEACe Lectures: John Rossi (City of Hope, Duarte) spoke about the treatment of HIV infections by other approaches than by the currently used small molecule drug therapy (HAART), namely by hematopoetic stem cell and systemic RNA based therapies. **Verne Luckow (Neal Gerber Eisenberg)** gave an update on the proposed legislation regulating the approval of Follow-on Biologics.

Short Talk Session/Workshop/Posters: A short talk session and a workshop covering e.g. the latest developments for Crucell's PER.C6 technology and demonstrating the progress for Ajinomoto's Corynex expression platform (using Corynebacteria as host) complemented the program. Additionally ca. 40 posters on stable cell line development (platforms and case studies), utilization of site-specific recombination approaches for production cell lines, viral vector production, transient gene expression, BacMam and insect cell expression systems and FACS-assisted analysis for high-producers, etc. were on display.

The **10th Conference on Protein Expression in Animal Cells (PEACe)** is scheduled to take place near **Lisbon in September 2011**. I strongly encourage you to check any upcoming announcements for this meeting and consider your active participation.

Georg Schmid
F. Hoffmann-La Roche
My thanks go to Ken Lundstrom and Tom A. Kost for their comments

Invitation to the 5th European *Bio*Technology Workshop in Ittingen/CH

The European *Bio*Technology Workshop (ETW) meeting has established itself in previous years as a congregation of dedicated scientists working in academia as well as in industrial settings throughout Europe (but also from abroad), sharing common interests in eukaryotic cell culture, recombinant protein expression and novel cell systems and applications. Since the first launch in year 2000, this community has reconvened regularly in the marvellous location of the "Kartause Ittingen", a Carthusian cloister in Switzerland close to Zurich.

As the 5th anniversary of this event in September is nearing, scientists interested in joining are invited to register for the workshop via our website (www.etw2010.ch); we welcome newcomers as well as repeaters warmly. This years' edition has a special focus on biopharmaceuticals in research and pre-clinical development (antibodies, therapeutic proteins and new scaffolds). Please be aware that a contribution to the program in the form of an abstract for oral or poster presentation is highly appreciated to ensure a high quality meeting with lively interactions and discussions. Likewise, attendance is limited to about 70 people – thus, do not wait too long to register. We look forward to seeing you (again) in Ittingen!

Sabine Geisse, Holger Heine, Alfred Engel

and Martin Fussenegger

Introduction of JAACT2010 Sapporo

Dear Colleagues

It is our great pleasure to announce that the 23rd Annual and International Meeting of Japanese Association for Animal Cell Technology (JAACT2010) will be held at Hokkaido University Conference Hall in Sapporo in Hokkaido, Japan, on September 1-4, 2010. The slogan is "Animal Cell Technology from Asia to World" and there will be a special symposium by researchers in Asian countries. This meeting will focus on animal cell technology concerning health care, foods, pharmaceuticals production, regenerative medicine, and so on. We invite academic and industrial scientists from all over the world to make the JAACT2010 truly successful and scientifically fruitful.

Hokkaido is the northern most island in Japan and abundant in wild nature, flowers, and greenery. Located on almost the same latitude as Milan in Italy, Toronto in Canada and Marseille in France, the capital of Hokkaido, Sapporo, has the same daylight hours as these cities. Sapporo is a young city where the Ainu, a people indigenous to Japan, used to live. Western culture was introduced from the very outside of land reclamation during the Meiji era. It has developed into the nation's fifth largest city. Portland in the U.S., Munich in Germany, Shenyang in China and Novosibirsk in Russia are its sister cities. Sapporo and Hokkaido wait for your visit.

Please visit the homepage → http://jaact2010.jaact.org/

Deadlines

Application of presentation: 18:00 (JST), May 14, 2010
Abstract submission: 18:00 (JST), May 31, 2010
On-line registration: 18:00 (JST), July 31, 2010
JST (Japan Standard Time)

Sincerely yours,
Mutsumi Takagi, Ph.D.
Chairperson of JAACT2010

Correspondence

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ESACT 2011

22nd Meeting
Vienna, Austria
May 15th – 18th, 2011
Hofburg Convention Centre
Chairs: Hermann Katinger and Nicole Borth
www.ESACT2011.org (starting in 2010)
For further information: ESACT2011@boku.ac.at

JAACT2010

	Sep. 1 (Wed)	Sep. 2 (Thu)	Sep. 3 (Fri)	Sep. 4 (Sat)
Morning		Plenary Lecture-1 *"Glycoblotting method reveals new promising biomarkers during cell differentiation"* Prof. Shin-Ichiro Nishimura (Hokkaido University) Symposium-3 *"Advanced technologies in cell engineering"*	Plenary Lecture-2 " ESACT Lecture" Symposium-6 *"Advanced technologies in cell culture process development"*	Plenary Lecture-3 *"Stem cell biology: past, present and future topics"* Dr. Shinichi Nishikawa (Riken) Symposium-8 *" Noninvasive estimation of cell quality for transplantation"* Technical Seminar
Lunch Time		Luncheon Seminar-1	Luncheon Seminar-2	Luncheon Seminar-3
Afternoon	*(Registration)* Opening Remarks Murakami Memorial Lecture Symposium-1 *"Water and Life"* Symposium-2 *"Animal cell technology in Asian countries"*	Symposium-4 *"ESACT symposium"* Poster and Oral Session Symposium-5 *"Novel culture supplement for mammalian cell culture"*	Technical seminar Poster and Oral Session Symposium-7 *"Serum-free culture of human stem cells"*	Closing Remarks
Evening	*Get-together Party*		*Banquet*	

New members C Losberger

ESACT welcomes the following new members:

Aguiar Marcelo	Institute for Technological Research
Augusto Elisabeth	IPT- Institute for Technological Research
Bulloch Alexander	Life Technologies Ltd
Conradt Harald S.	GlycoThera GmbH
Deeter Scott	InVitria
Dormond Edwige	Syngenta
Galosy Sybille	Pfizer Inc
Haredy Ahmad	Osaka Univeristy
Huang Yao-ming	Biogen Idec Inc
Kelley Brian	Genentech
Kölln Johanna	MorphoSys AG
Kremer Matt	Artelis s.a.
Lorenz Verena	Celonic GmbH
Makagiansar Helena	Biogen Idec, Inc
MALARD Dominique	MABIO
McCarron Caroline	Institute of Technology, Tralee
Mulcahy Tony	DSM Biologics
nelson kim	CRB
Poppema Maaike	Centocor B.V.
Soderblom Tore	CMC Biologics A/S
Storms Scott	Irvine Scientific
Tao Lina	DASGIP
Tebbe Hermann	Roche diagnostics GmbH
Uhlenküken Jochen	Company
Want Andrew	Loughborough University
Wilms Burkhard	Novartis Pharma AG
wolton david	Vivalis
Yokota Masami	Astellas Pharma Inc.
Zindel Heiner	hameln rds

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