

Newsletter

April 2004

Editorial

Dear Readers,

Hello there folks! As promised last year, we said we would explore changing the design of our newsletter. Hope you all like the new look, courtesy of "Merlin the Magician"!

In this issue, we have a word from the Chairman, a call for papers for ESACT 2005 (already?!?); announcement of the Animal Cell Technology forum, the latest about JIN; some updates about our ESACT website; a contribution

from Alain about Bioprocess research at Serono; a short piece about a start-up company CTM Biotech formed by Dr. Rodney Smith, and some interesting snippets of news from moi.

Enjoy!

Steve Oh, Chief Editor



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A Word from the Chairman

Another 4 months have rapidly passed since the last issue of the ESACT Newsletters appeared, and another important event in the series of animal cell culture meetings took place: the Cell Culture Engineering Conference number IX. Following tradition, this meeting started on a Sunday afternoon (7th of March 2004) and went on for five days up to Friday noon (12th of March 2004). The meeting was organized in the Paradisus Riviera Cancún Hotel some kilometres south of Cancún and many people interested in animal cell technology took the chance to take part in this meeting. The meeting was divided into 10 oral sessions, 6 workshops and 2 poster sessions and some very new aspects on stem cells, gene therapy vectors, optimisation studies, and large scale aspects of animal cell technology, to mention some of them, were presented and discussed. During the meeting, there was a very interesting keynote lecture on the Mayas (the peninsula of Yucatan is more or less the place where the Mayas lived and developed their culture, and where their descendants are still living today) and the excursion to Tulum, a Maya stronghold in use between the 13th and the 15th century, and to Xcaret gave us interesting impressions of the history of the Mayas as well as of Mexico.

In this context, I would like to thank Lynne A. Krummen from Genentech in South San Francisco/CA and Octavio T. Ramirez from the National Autonomous University of Mexico in Cuernavaca/Morelos for this nice and successful meeting in Cancún. For those who would like to participate in the next one, the Xth Cell Culture Engineering Conference will be organized near Vancouver in British Columbia; the co-organizers will be James Piret and Konstantin Konstantinov.

However, if you do not want to wait two years to go to a cell culture meeting, then I would like to recommend the 3rd European Biotechnology Workshop organized by Sabine Geisse in Ittingen/CH (in September), the "3rd meeting on recombinant protein production: a comparative view on host physiology" (joint EFB/FEMS/ESACT meeting proposal; our ex-Esact chairman and good friend Manuel Carrondo is the chairman of this event)(Algarve/P, November 2004), or the 17th JAACT Meeting (Nagoya/Japan, November 2004). And of

course it goes without saying that In addition, Rod Smith from CTM BioTech is the meeting chairman of the 19th ESACT Meeting which will take place in Harrogate/U.K. at the beginning of June 2005 with Rod Smith from CTM BioTech as the meeting chairman.

For those of you who visit the ESACT web site from time to time, you will see that the JIN-page (Job Information Network) has changed and been considerably improved. This allows a much easier posting of new jobs as soon as the posting company has registered, however, the final approval, if a new offer appears, will always be performed by Christophe Losberger, ESACT's web manager, or an authorized ESACT representative. This helps us in avoiding junk information and in bringing to our JIN users and ESACT members the most relevant up-to-date job openings. A very new feature has been introduced is that people searching for a job can also put an announcement (including a CV) onto the JIN web site. In any case, I would like to thank Christophe Losberger for his efforts to get this modification done, and Alain Miller and his company CIL Biotech, located in Mons/B, for financially supporting this modification and improvement of the JIN-features.

I recommend everybody (ESACT member and non-member) to visit ESACT's web site from time to time because a lot of useful information can be found.

Finally, some words concerning the joint project between ESACT and ACTIP. The proposal was submitted by Manuel Carrondo, the coordinator, in the frame of the Marie Curie Host Fellowships for Early Stage Research Training (EST) projects "Development and optimisation of industrial (large scale) animal cell technology and downstream processing of biologicals", the deadline for submission was the 11th of February, 2004), and now everybody is waiting for the hopefully positive news. It is evident that our first objective is to get to a functional European doctoral network in animal cell technology; however, the second objective is also to show the European Commission in Brussels that there is a need to support academic/university and industrial activities in animal cell technology, a domain which was completely forgotten in the 6th framework pro-

gramme.

With these words I wish you all the best for Easter and a very nice springtime 2004.

Otto-Wilhelm Merten

ESACT 2005 - Harrogate, June 5-9, 2005

The Call for Papers for the ESACT 2005 conference that will be held in Harrogate 5th - 9th of June 2005 is now available at <http://www.esact2005.org/documents/CallForPapers.pdf> The Abstract deadline is 3rd December 2004.

The complete and latest information concerning the meeting is available now on the website <http://www.esact2005.org>

Please contact Glenda Bland (glenda@global-meeting.co.uk) if you need any information concerning the organisation of the meeting. Please direct all scientific questions to the chairman Rodney Smith (Rod.Smith@esact.org).

The Animal Cell Technology Forum

In order to increase the potential number of participants, the ESACT has invited a number of other societies to share our discussion board on <http://www.esact.org/forum/>

The new participants are www.baculovirus.com, ESACT UK, ESGT and ETCS. Please help us build this community by visiting this forum from time to time, post questions if you have, answer questions if you can and especially spread the information among your colleagues and students.

Job Information Network

The Job Information Network (JIN) was completely renovated and now has its proper website at <http://www.jin-esact.org/>

Some of the new features are:

- New and original design
- Job providers (institutions) can manage their jobs entirely themselves online and track all the contacts they receive through JIN.
- Job seekers can post their resume, either privately and hidden just to quickly be able to apply for a job with a single click, or publicly which displays the CV on the website.
- The job publication should be quicker.
- All the contacts are through web forms and emails are completely hidden, which prevents them to be stolen and used by spammers.

This complete renovation was made possible by the generous sponsoring of CIL Biotech SA (<http://www.cilbiotech.be>), a Belgian company involved in the production and exploitation of mammalian cells, run by our colleague and ESACT member, Professor Alain Miller.

We also wish to thank Bioengineering SA (<http://www.bioengineering.ch/>) who kindly allowed us to use their pictures of bioreactors in our design and also Cobweb (<http://www.cobweb.ch/>) who has done the programming and design.

You are invited to visit the site and discover by yourself the other features not mentioned above. You are welcome to submit your resume or publish any open job positions you have in your institution, as long as they are related to Animal Cell Technology. You are sure it will be addressed to a professional and highly qualified audience.

The new JIN is only a baby, so if you find that it sometimes behaves curiously or if you have any suggestions for its future education please feel free to email your comments at admin@jin-esact.org You can also come and discuss it publicly on our forum: <http://www.esact.org/forum/viewtopic.php?t=16>

Best regards,

Christophe Losberger and Stephanos Grammatikos

JIN administrators

Manufacturing Process Development at Serono

The mission of Manufacturing Process Development at Serono is to develop processes for the production of different injectable human protein therapeutics in bulk form (or active ingredient) from preclinical stage to market supply. It is organized in several groups, each dedicated to a specific area of technical expertise.

The Cell Sciences group is spread between two labs located in Israël and Vevey, Switzerland. It focuses on the generation of cell clones expressing a variety of protein therapeutics. To this end, expression vectors for stable long-term expression of single, as well as multichain, proteins of interest are introduced in mammalian host cells. High expressing clones are isolated using automated approaches. Special emphasis is given to the



selection of such producer clones in animal-derived component free media, using state of the art technology for screening and clone development. The group is concentrating on optimal solutions from expression vectors till clone evaluation in lab scale culture flasks, with approaches including media and feed testing. Clone selection is performed not only on the basis of high expression, but, more importantly, with optimal product quality as target.

The Upstream process development group at Serono is another integral

“special emphasis on product quality”

part of the Manufacturing Process Development function, located at the Serono Biotech Center (SBC) in Vevey, Switzerland. The development facility is equipped for the manufacturing of clinical grade material. With more than 30 bioreactor of working volumes ranging from

0.5 to 250L we are developing continuous, batch and fed-batch processes. Our team of 22 employees (7 scientists) and some diploma/PhD students targets high yield, robust processes which consistently deliver the protein of interest with a special emphasis on product quality. Driven by the requirements of the process, different new technologies are investigated such as on-line process monitoring/control, immobilization technologies. Through active and good contacts with universities and companies we aim to maintain a high level of competence in the field.

After optimizing media, designing feeding strategies and development of the seed train, the scale-up to 250L pilot scale is performed. When the process has demonstrated robustness and reproducibility at this scale it is transferred either to the SBC manufacturing or to one of the various other Serono manufacturing sites.

The Downstream Development Group is another group of the Manufacturing Process Development Department and currently comprises 12 staff members (including 6 scientists, divided into two units - DSP Development and Pilot Scale Units.

Within the development unit, lab-scale processes are developed “from scratch”. The scale of the operations corresponds to the purification of 0.01 – 0.5 g of protein. The activities cover all types of chromatography, in packed bed or expanded bed modes, filtration (micro-, ultra-, nanofiltration, dead-end or tangential mode) and other techniques related to protein recovery.

Optimization studies for DSP processes currently used in manufacturing are also performed in this unit. The laboratories are equipped with state-of-the-art instruments, including fully automated

“The laboratories are equipped with state-Of-the-art equipment”



chromatography systems and ultrafiltration skids, as well as analytical HPLCs.

Purification processes are submitted to a first round of scale-up within the Pilot-scale unit. The target scale corresponds to the processing of 0.5 – 100 g of final purified protein per batch. This unit is at the hinge between the development and the manufacturing functions. Its main mission is to ensure a smooth transfer of processes between both scales by verifying, at an intermediate scale, the consistency of results in term of product yield, purity etc. Validation of processes in term of virus/DNA/contaminant clearances is also performed. The group is also responsible for the delivery of the final purification process to the various Serono manufacturing sites.



Strong emphasis is put on new technologies. The DSP Group has several external collaborations with academia, the technical services of several chromatography and filtration device suppliers and specialized subcontracting companies. The Group presently hosts several students completing their Diploma work.

Alain Bernard

Conference Report: Drug Discovery 2004

The IBC Life Sciences 8th Annual Drug Discovery Technology Conference and Exhibition was held 9-10 March in London, UK. The event had 4 themes, running in parallel: target discovery, biopharmaceuticals, lead generation and R&D business strategy. The event was well attended and had a good number of speakers from international locations and industry leading companies. I attended as a guest of the organisers and will provide a personal view of some of the talks witnessed.

Joseph Bolen (Millennium Pharmaceuticals, USA) described Millenium's transfer from genome miner to a fully fledged biotechnology company. Their strength in computational biology is still a critical tool in working on "unprecedented targets in precedent pathways." They measure internal success in the number of development candidates which make it the clinic rather than the number of drugs reaching the market. A development target should

1. Meet target product profile prediction e.g. efficacy, pathway markers, and
2. Still requires GMP synthesis and safety pharmacology and GLP gene toxicity

Millenium have invested heavily in animal imaging systems allowing them to replicate clinical systems used on human subjects. Millenium have also created a new computer algorithm, PARIS, which is used to elucidate key pathways in disease states from large data sets from clinical trials.

Ray Hill (Merck Sharp and Dohme, UK) spoke of the fall in pharma productivity and the number of unmet needs despite the success which may be due to the "easy ones being done." There are a large number of targets but genomics has been slow to effect day to day discovery. Many companies have large number of drug candidates but a purge of these can reduce these to a more realistic library. Pharma companies are now in-licensing even more, particularly from biotechnology companies, contributing as much as 40% of sales revenues.

Tim Wells (Serono, Switzerland) continued the biotech theme by repeating the growing gap between R & D expenditure (\$30 billion in 2001) and NCE approvals. Biotechnology has proved very productive, now accounting for about 25% of all NMEs and over 100 biotech compounds have now been approved. Biotech companies would like to discover the next EPO which could be a therapeu-

tic cytokine but most current candidates are antibodies. Serono believe that there is a finite resource of new proteins and perhaps only 2000 secreted proteins of which Serono have a bank of 800. However, finding the correct pharmacological activity of these proteins has proved challenging. For instance, Serostim builds lean body mass in the clinic but has no direct effect in cell culture.

Peter Senter (Seattle Genetics, USA) described his company's progress in creating what was often referred to as the 'magic bullet' – an antibody targeted cancer killing molecule. The current generation of antibody drug conjugates (ADCs) are closer than ever to reaching this goal by achieving the following characteristics:

- Antibody must have high selectivity for tumour cell antigens
- Drug component must be potent, totally synthetic and readily scaleable
- The linker must be stable and offer efficient and rapid release of active drug – usually a peptide
- Conjugation process must retain conjugate uniformity and antibody characteristics

Seattle Genetics have several of these ADCs in development as well as clinical trials.

Merlin Goldman

Most successful Y-chromosomes

The male Y-chromosome is doomed to disappear: per million years, 3-6 genes disappear from the Y-chromosome. It has been sequenced (Nature, June 2003) and currently contains not more than 78 active genes, sufficient to produce 27 proteins. The reasons of this doom and gloom are a lack of recombination and surprisingly few variations: some Y-chromosomes occur frequently, others are rare. In a nicely written article, two examples of the world's most successful Y-chromosomes are given.

Probably the world's most successful Y-chromosome is the one allegedly from the Mongolian leader Genghis Kahn, ruler of an area encompassing Asia from the Pacific Ocean until the Caspian Sea. Exactly along the borders a particular Y-chromosome is found frequently: it is most likely of Genghis Kahn and his four sons and one grandson. The reason: all men were killed and cities destroyed. Each warrior was free to do as he pleased with one exception: all pretty women were sent to Genghis Kahn. Currently, there are 16 million people with the alleged Kahn Y-chromosome. This particular Y-chromosome is not found outside the old Mongolian borders. Thus, this Y-chromosome succeeded to multiply from one copy to 16 million in only 30 generations!

An example closer to home is that of the Scottish leader Somerled of Argyll (1100), who is at the root of three Scottish clans, the MacDonalds, the MacDougalls and the MacAllisters. At present, there are close to half a million copies of Somerled's Y-chromosome; after all, he was rich, powerful, had a lot of land and attractive sons who later became the founding fathers of the three clans.

Source: Bionieuws Jan 16, 2004, and Nature, June 19, 2003

Harvard's Professor Melton derives new stem cell lines

Driven by both personal and humane concerns, Doug Melton has derived 17 new lines of embryonic stem cells, which can, in theory, be coaxed into becoming any type of adult tissue from kidneys to spinal cords.

He isolated the cells from excess fertilized eggs obtained from in-vitro fertilization clinics with their owners' permission. The eggs are grown into embryos from which the stem cells are extracted before the embryos show any signs of life. The work was done with private funds because the U.S. government limits federal funding for such research to 64 lines of frozen cells already in

existence. These restrictions come from the belief by some people that embryos are alive and that cell extraction destroys them. Most scientists do not agree with this belief.

When Melton, Thomas Dudley Cabot Professor of Natural Sciences at Harvard and Howard Hughes Medical Institute investigator, looked into the supply of frozen stem cells, he judged it wholly inadequate. Information is lacking on the viability of many of these cell lines and access to others involves restricted usage. "I could not convince myself that any of the cell lines would be available or useful," he says.

Also, some of the providers charge as much as \$5,000 for the frozen cells. Melton thinks that something so important for the potential treatment of human ills ranging from Alzheimer's and diabetes to Parkinson's and spine repair should be free to all legitimate researchers. He plans to make the new lines developed at Harvard available to such researchers.



Douglas Melton (right) and post-doctoral fellow Chad Cowan work in Melton's lab. Melton has a very personal reason for wanting to experiment with high quality stem cells. His two children, Emma, 16, and Sam, 12, have insulin-dependent, or juvenile, diabetes.

high quality stem cells. His two children, Emma, 16, and Sam, 12, have insulin-dependent, or juvenile, diabetes. They frequently inject themselves with the insulin they need to stay alive, but that does not halt the gradual organ degeneration that can eventually lead to kidney failure, blindness, and malfunctioning limbs. Melton would like to be able to use stem cells to make working insulin-secreting cells that prevent this long-term suffering for them and a million others in the United States.

Finally, careful nurturing of embryonic stem cells in the laboratory should answer many questions about the earliest stages of human development, about how we become what we are. In Melton's words, the stem cells "offer a unique window into the study of human early development."

William J. Cromie

"I am gratified that Harvard can participate in the advancement of stem cell research, which holds such enormous promise for transforming the treatment of disease," said William C. Kirby, Dean of the FAS and Edith and Benjamin Geisinger Professor of History. "Professor Melton's creation of new stem cell lines, and the University's wider collaborative efforts, can contribute significantly to worldwide research in this area."

Melton has a very personal reason for wanting to experiment with

Biopharmaceutical Development Company Makes a Flying Start

Two entrepreneurial, longstanding ESACT members have established a contract business offering services to the bio-pharmaceutical industry. Jon Mowles (Commercial Director) and Rod Smith (Scientific Director) are both former members of staff at the European Collection of Animal Cell Cultures based at Porton Down in the UK, before going their separate ways to work for a number of different bio-pharma companies.



Rod Smith

Both have long held the view that the rate determining step that often exists in bio-pharma product development lies between the research phase of product development and the need for clinical trial material. Over a glass of wine at the ESACT Tylosand meeting, they agreed that there was space in the market for a company, staffed by scientists experienced in the field of GMP production, to bridge this gap and thereafter set-about launching this new venture. CTM BioTech, set-up in August of last year, offers bio-pharmaceutical companies and research organisations a range of contract services from early stage process development and pre-clinical production through, where required, to later stage project management services. The company operates from bespoke facilities at Babraham Research Campus, in the heart of the Cambridge Bioscience cluster.



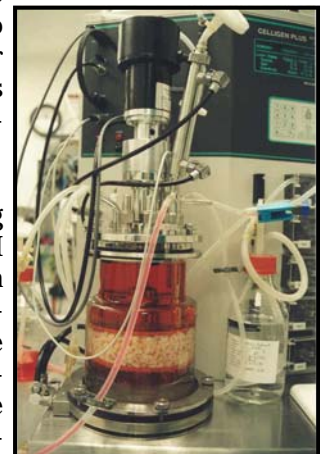
Jon Mowles

The aim of CTM is to alleviate the bottleneck that exists between a clients' in-house, research-phase of development and large-scale GMP production work by working in collaboration with laboratories to enable their products to get to the clinic in a timely, cost efficient manner. In addition to scale-up and process development, the com-

pany can provide up to 50L bioreactor capacity for not only animal cell work but also can offer expression using prokaryotic, baculovirus and Pichia systems. In the field of project management, CTM can work in partnership with client companies to offer services such as sourcing GMP production facilities, technology transfer and the management of GMP production projects.

Jon Mowles states, "A major problem that bio-science companies face is in managing the transition of their products from the laboratory bench to early stage clinical trials. They may not have the necessary skills, experience or equipment readily available. CTM Biotech's significant background in process development and optimisation means that we can bring added value to a client's project, and can facilitate their future GMP manufacturing needs. The positive response we have received to date suggests that our service offering has been very well received."

In addition to offering these services, CTM also has a research interest in the development of down-scale methodologies, in order to decrease lengthy process development times, by exploiting the miniaturisation of bioreactor systems. The development and validation of such systems has enormous potential advantages by decreasing the time, and therefore the costs, of this stage of process development. Rod Smith says 'using miniaturised systems to develop fermentation production regimes can speed up the whole development process. Many essential production parameters can be investigated quickly to provide defined critical process parameters to ensure optimal product formation. This aids not only the process as a whole but helps the product purification by having a consistent production stream at a very early stage.' Jon and Rod would be delighted to hear from



ESACT members either looking to utilise the services of CTM or to form a collaboration looking into the miniaturisation of bioreactors.

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Joke Corner

Something to activate your brain cells

man	= man overboard
board	
stand	= I understand
I	
/r/e/a/d/i/n/g/	= reading between the lines
0	= two degrees below zero
MD	
PhD	
knee	= ne-on light
light	
Ecnalg	= backward glance
dice	
Dice	= paradise
THINK	= think big !!!
ababaaabbbbbaaaabbbbababaabbaaabbbb...	long time no 'c'(see)

Conference Announcements

3rd Recombinant Protein Production

A comparative view on host physiology. 11-14 November 2004 - Tavira, Algarve, Portugal.

<http://www.ibet.pt/3rdRecProtProd/>.

Contact Alexandra Azevedo (Secretariat) at IBET, Apartado 12, 2781-901 Oeiras, Portugal, e-mail: xana@itqb.unl.pt for further details.



ESACT SECRETARIAT

A reminder that **2004** subscription fees should now have been paid and that following the rationalisation of membership (abolishing Associate Membership in favour of Full membership status) the annual Membership Fee is now the same for everyone.

€20, £13 or US\$25

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Bryan Griffiths

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