

Editorial

Dear Readers,

In this issue we bring you exciting news about turning procrastinating monkeys to workaholics; extension of the use of Abbott's arthritis drug and news of drug companies moving biotech work to India.

Chairman Otto delivers his quarterly message. Christophe will be telling us about recent changes to the ESACT 'Amember' database which will enable members to manage their membership details. And there are 2 reports on the Singapore Biologics Manufacturing Conference and the 227th ACS meeting that were held in April.

Merlin brings news about European Biotech investments, Wyeth's new facility at Grange Castle and Ireland's new National Bioprocessing Institute. There is also a call for an organising committee for ESACT 21, announcement of MIT's new President and news from CTM Biotech. Till the next one... enjoy!



Steve Oh, Chief Editor

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A Word from the Chairman

Following the end of August, a busy, and hopefully successful autumn is sure to start. Since the last ESACT Newsletter, news is light. As you remember, ESACT together with ACTIP submitted a project as part of the Marie Curie Programme - Marie Curie Host Fellowships for Early Stage Research Training (EST) - entitled: "Development and optimisation of industrial (large scale) animal cell technology and downstream processing of biologicals" (AC Training). I can inform you that this proposal was not accepted. This is regrettable not only because of the time invested, but also because there is a real need for such a programme. In this context, the urgent need for specialists in animal cell technology for the biotech industry was very clearly stated in a U.K. government-sponsored report (Bioscience 2015: Improving National Health, Increasing National Wealth), published on November 17, 2003, by the Bioscience Innovation and Growth Team. The main point is that despite the UK lead in developing biopharmaceuticals, its manufacturing prowess lags behind mainland Europe. Only a few UK biotech firms have set up their own manufacturing facilities, although manufacturing expenses represent between 20% and 25% of the value of a typical biopharmaceutical drug, signifying that many U.K. companies lose millions of revenues per year. One of the reasons for this situation is that the emphasis is too much on product development and the science base rather than on manufacturing. Process science is not seen as a sexy area leading to a shortage of people trained in this area and therefore a shortage of expert staff indispensable for running production plants.

Unfortunately, a similar situation can be found in many other European countries. Thus the following conclusion might be drawn that the training situation in animal cell technology is sufficiently unsatisfying that the EU commission should take measures via the Framework Programmes (Marie Curie Programmes). However, it seems, as indicated by the U.K. sponsored Bioscience 2015 report, that training to "produce" highly qualified staff for the European Biotech Industry is not sexy enough and not innovative enough.

The only glimmer of light on the EU horizon is the fact that, in principle, the EU commission plans to put more emphasis on industrial appli-

cations (in general, on the application which is almost always a product of fundamental research) in the 7th Framework Programme (start 2007) - hopefully. If not, Europe will further loose with respect to our friends and colleagues from North America and East Asia.

In this context, ESACT together with ACTIP will try to influence on the choice of topics to be included in the 7th Framework Programme in order to get a reference to animal cell technology. In any case, I would like to say here that the present situation should not hinder us and the ESACT community to further animal cell technology, and every ESACT member should remember one of ESACT's mission statements:

Financial and administrative support to selected training courses, additional specialist meetings and publications in Animal Cell Technology.

At the end of these lines, a more positive and immediate outlook concerns the next scientific meetings in the near future, which are listed later in this issue. They are a good opportunity to meet again to discuss science and perhaps also actions to take to improve the present training situation in Europe, perhaps in front of a beer. With these words I wish you a very fruitful autumn.

Otto-Wilhelm Merten

Future Meetings

Quality on the move: Dynamics of the European Pharmacopoeia

4-6 October 2004, Hilton Hotel, Budapest, Hungary. Information: www.pheur.org

5th International Conference on Systems Biology

October 9-13, 2004, Heidelberg, Germany. Information: www.ICSB2004.org

The 8th European Biotechnology Crossroads

October 27-29, Marseille, France. Information: (+33) 4 95 09 38 00, Fax : (+33) 4 95 09 38 01. www.mcocongres.com

XII Annual Congress of the European Society of Gene Therapy

4-7 November 2004, Tampere, Finland

Information: www.esgt.org

3rd Recombinant Protein Production - A comparative view on host physiology

November 11-13, 2004 Tavira, Algarve, Portugal. Information: IBET, Alexandra Azevedo
E m a i l x a n a @ i t q b . u n l . p t ,
P h o n e : + 3 5 1 2 1 4 4 6 9 3 6 2 ,
www.ibet.pt/3rdRecProtProd/

17th JAACT Meeting

November 15-18 November, 2004 in Nagoya, Japan. <http://www.nubio.nagoya-u.ac.jp/jaact04>.

World Life Sciences Forum, BioVision

April 11-15, 2005, Lyon, France
Information: www.biovision.org

And the next ESACT Meeting:

June 5-9, 2005, Harrogate, U.K. Information: www.esact2005.org

No Slacking for Work-Shy Monkeys

Procrastinating monkeys were turned into workaholics using a gene treatment to block a key brain compound, U.S. researchers reported recently through *Reuters*.

Blocking cells from receiving dopamine made the monkeys work harder at a task -- and they were better at it, too, the U.S. government researchers found.

Dr. Barry Richmond and colleagues at the National Institute of Mental Health used a new genetic technique to block the D2 gene.

"The gene makes a receptor for a key brain messenger chemical, dopamine," Richmond said in a statement. Dopamine is a message carrying chemical associated with rewards, movement and a variety of other important functions.

"The gene knockdown triggered a remarkable transformation in the simian work ethic. Like many of us, monkeys normally slack off initially in working toward a distant goal," he added.

For their study, Richmond and colleague used seven rhesus monkeys. They had to push a lever in response to visual cues on a projection screen, and got a drop of water as a reward.

"They work more efficiently -- make fewer errors -- as they get closer to being rewarded. But without the dopamine receptor, they consistently stayed on-task and made few errors, because they could no longer learn to use visual cues to predict how their work was going to get them a reward."

Writing in the Proceedings of the National Academy of Sciences, Richmond and colleagues said they were trying to figure out how D2 is involved in a type of learning.

Humans and monkeys both use this learning, which involves looking at how much work there is, visually, and deciding how long it will take to complete it.

Monkeys and humans both tend to wait until the last possible minute to finish up the work, and become very adept at estimating how long they have.

Molecular geneticist Edward Ginns created a DNA antisense agent that tricked brain cells into turning off their D2 receptors -- which are molecular doorways used by dopamine to get into cells.

Although some employers might take a distinct interest in the work, the NIMH team said they are hoping to understand mental illness.

"In this case, it's worth noting that the ability to associate work with reward is disturbed in mental disorders, including schizophrenia, mood disorders and obsessive-compulsive disorder, so our finding of the pivotal role played by this gene and circuit may be of clinical interest," Richmond said.

"For example, people who are depressed often feel nothing is worth the work. People with obsessive-compulsive disorder work incessantly; even when they get rewarded they feel they must repeat the task. In mania, people will work feverishly for rewards that aren't worth the trouble to most of us." **SO**

Abbott arthritis drug wins physical-function use

U.S. regulators have approved use of Abbott Laboratories Inc.'s popular Humira rheumatoid arthritis drug to help patients perform everyday activities, not just control pain and inflammation, the drugmaker said on Tuesday according to Ransdell Pierson (Reuters).

Humira was approved in 2002 to treat symptoms, including pain and fatigue, and inhibit progression of structural damage in adults who have failed to benefit from other medicines for rheumatoid arthritis, the less-common form of the disease.

In rheumatoid arthritis, which affects an estimated 1 percent of the population, the body's immune system attacks joints. It is potentially more crippling than osteoarthritis, the more common form of arthritis caused by wear and tear of joints.

Abbott said the U.S. Food and Drug Administration will now also allow it to market the drug to improve physical function, such as walking, bathing and grooming, in patients with moderate to severe rheumatoid arthritis.

Abbott expects 2004 sales of Humira to exceed \$800 million, fueling earnings growth. It poses a stiff challenge to Wyeth's Enbrel and Johnson & Johnson's Remicade, older injectable treatments that also block an inflammation-causing protein called tumor necrosis factor.

Bruce Cranna, a drug analyst for Leerink Swann, said many patients are already taking Humira to treat physical symptoms, and the approval for that use is just a helpful formality.

"So the expanded approval will probably not affect Humira's sales," said Cranna, who expects them to soar to \$1.2 billion next year.

Abbott said the widened approval was based on a lengthy ongoing trial in which patients began taking Humira after failing to adequately benefit from a standard arthritis treatment called methotrexate.

Patients began showing signs of improved physical function within two weeks of taking Humira, and improvements have been maintained through two years of treatment, Abbott said. **SO**

Drug Firms Move Biotech Work to India

By S. Srinivasan, Associated Press Writer

India's Trade Body says drug makers in the United States and Europe are increasingly moving clinical trials and research work to India, which helped Indian firms earn \$54 million in revenue in the last fiscal year.

"India is being taken seriously as a biotech outsourcing destination," said Kiran Mazumdar-Shaw, who heads the Association of Biotech Led Enterprises, a grouping of India's biotechnology firms.

For years, American and European companies have farmed out software development, engineering design and back-office work to firms in India and other countries that have lower wages and plenty of skilled workers.

India earns about \$12.5 billion annually from information technology outsourcing and revenues are growing at 30 percent per year. More than half of Fortune 500 firms outsource some part of their work to India.

"The practice of passing on jobs in drug development research, analysis of research data and clinical trials to India is a new but growing trend," Shaw said.

Revenue from work outsourced by Western companies accounted for more than 13 percent of India's biotechnology exports of \$395 million in the year that ended March 31.

Britain's GlaxoSmithKline, German drug maker Bayer, Aventis of France, and U.S.-based Pfizer Inc. are some of the companies that have already begun outsourcing work to India.

In five years, Indian firms are expected to be earning annual revenues of \$5 billion from outsourcing of biotechnology-related services, Shaw said. "We see outsourcing in this area growing exponentially over the next few years and giving us the same success that India had in software."

India's biotechnology trade body: <http://www.ableindia.org>. **SO**

Changes in the ESACT members administration

We will soon be migrating the ESACT members database to a completely new system, which will be accessible online at <http://www.esact.org/amember>.

Until now our members personal information was stored in an Access database on a PC at the ESACT office and was maintained by Bryan Griffiths. The new management software system – called Amember - will be entirely web-based and the principle advantages of this new database are:

- Members will have access to their own personal information online with a personal user-name/password and will be able to update this information themselves and renew their membership with a single click.
- This software will also allow restricted access to ESACT documents (latest issue of the Newsletter, society documents such as members book in PDF) and to a private discussion forum.
- At the expiration of the membership period, reminders will be sent out automatically by email.
- For the administration we will be dealing with one unique centralised list, the software also serves as a mailing system and as a financial reporting tool.

The security of this database is as good as the previous one:

- Members do not have access to the entire database and cannot see other's private information (unless we decide to publish part of this info in the form of a PDF member list for example).
- No information in this database and in the pages restricted to members is accessible to non-members. (including emails).
- Only a very few people will have access to the administration side of the database: the web-master, the ESACT office (Bryan) and chosen members of the executive committee (chairman, treasurer, secretary).

Migration process

Very soon after the entire database is transferred to the new system, each member will receive by email his unique username and password (randomly generated for each member, this password can be changed by the member).

For the usernames we will be using the member's last name (i.e. "losberger") and a combination of the first initial and last name for members with the same name (i.e. "rsmith"). Although this user-name can be changed by the members, we recommend that you don't modify them at least in the beginning to avoid confusion.

Once the login details have been sent, members should immediately check the status of their membership by logging on <http://www.esact.org/amember>. We will be migrating all the members including those whose membership has expired since 2001. The complete period of membership will be indicated in the "payment history" on the personal information screen.

Of course, members are invited to renew their membership if necessary.

Payment of membership fees

At the moment there is no change in the methods of payment of the membership fees. We continue to accept payments by credit card and by bank transfer as in the past. The forms and complete description of the process are available on our website at <http://www.esact.org/membership.html>

In the near future we will probably implement internet online payment features. The new management software already includes this possibility, but we would like to discuss this a little more



(eventually in the ESACT private forum) before we change.

The screenshot shows the ESACT website's 'Members Only Pages'. At the top left is the ESACT logo. The header text reads 'The European Society for Animal Cell Technology' and 'Members Only Pages'. The main heading is 'Your Membership Information'. Below this, there are several sections: 'Your subscriptions' with links for 'Membership', 'Member's Place', and 'Members Book'; a 'Logout' link and a 'Change Password/Edit Profile' link; an 'Add/Renew Subscription' section with a dropdown menu labeled '** Select Product **' and an 'Order' button; and a 'Your payment history' section containing a table. Below the table is a note explaining that a zero amount was generated during a database transfer in 2004. At the bottom, it says '© ESACT, 2004' and 'Powered by aMember.Pro'.

Product	Period	Payment System	Amount
Membership	13/07/2004 13/07/2014		€0.00

Screen capture: The Membership Information screen shows (left side) your subscriptions with links to the related pages and documents, (top right) a link to access and change your profile, (middle right) a drop-down menu to renew your subscription and (bottom right) your subscription history.

Contact

As always with the implementation of new software there will probably be problems and bugs, accessibility problems and maybe some strange messages sent out by mistake. If anything is unclear, if you encounter any problem or anything that you think is strange, please contact me directly at admin@esact.org, whatever the problem is.

Amember website: <http://www.amember.com/scripts/amember/>

Christophe Losberger, ESACT web manager

Singapore Biologics Manufacturing

Some 200 participants attended this conference in April, 2004 with a good mix from industry and academia. It was also an east-meet-west gathering with representatives from Asia (including Korea, Malaysia, China, India and Singapore), Australia, Europe and the US. The conference was jointly organised by the Bioprocessing Technology Institute (BTI), Singapore and the organisers of the "Interlaken Conference on Advances in Production of Biologics" conference series.

The conference venue was excellent for its logistics arrangement and the catering was befitting of Singapore's reputation as a gourmet

paradise. Highlighted below are selected talks from different sessions and the author's personal impression of the talks. It was a difficult selection since all the talks were of a high standard so the selection was probably biased towards the author's interests more than an objective selection.

Session 1: Cell Engineering

Randal J. Kaufman, University of Michigan Medical School, USA

Randy gave the first plenary lecture at the conference. He spoke about the cellular response to unfolded protein in the endoplasmic reticu-



lum (ER). The ER folding machinery is a function of the amount of proteins that require folding, and various internal and external stress conditions that can activate signaling pathways for adaptive responses. These signaling pathways are known as the unfolded protein response (UPR). The UPR has ubiquitous effects. It is responsible for the stress response in the ER due to the accumulation of unfolded proteins in mammalian cell recombinant protein expression. If the ER stress is not relieved, the cells undergo a shift towards cell-death pathways. The UPR is also implicated in glucose homeostasis (failure of which leads to diabetes) and B lymphocyte differentiation. In addition, many human diseases such as Alzheimer's, result from protein misfolding. Randy presented his work on three ER transmembrane proteins (PERK, IRE1 and ATF6) regulating the UPR. While I fully appreciated the importance of his work, I must admit that the actual details on how PERK, IRE1 and ATF6 function in the pathways were a tad too much to digest.

Jennie P. Mather, Raven Biotechnologies Inc, USA

Jennie started Raven Biotechnologies five years ago. To date the company has developed a number of platform technologies to complement each step in the discovery of new drug targets. They have proprietary methods to select and maintain tissue specific stem cell lines to "freeze" the phenotype of the intact cells, which are then used to raise monoclonal antibodies. These antibodies are screened against normal and tumor tissues and used in various assays to screen for the antigens they bind to. The novelty of the method is the use of intact cells to present cell surface antigens, thus widening the potential target sets and the probability of finding novel targets. Due to the large number of antibodies that can be generated in this method, rapid, high volume, effective methods for screening were developed. Any suitable candidates which have passed through the rigorous screening methods would be developed further for preclinical testing. Raven has a few antibodies in the pipeline against cancer targets, going into preclinical soon.

Martin Fussenegger, ETH, Switzerland

Martin introduced an interesting concept to increase the productivity of mammalian cells by using a transgene control system to "switch" on the production phase in the cells after the cell expansion phase. No addition of chemicals is required, only tobacco smoke for the induction! Smoking isn't that bad after all! By the way, the molecule responsible is acetaldehyde, an FDA-approved food additive also found in tobacco smoke.

Park Tai Hyun, Seoul National University, Korea

Tai Hyun presented a fascinating tale on the discovery of the anti-apoptotic properties of the 30K protein found in silkworm hemolymph. This was first observed when apoptosis was inhibited in cell culture containing silkworm hemolymph. The active component was isolated and a database search found a match with a group of "30K proteins". Expression of the 30K protein in HEK293 and CHOK1 cells led to the inhibition of apoptosis, hence demonstrating a new anti-apoptosis strategy for cell line engineering. Wondering how did they get interested in studying silkworm hemolymph in the first place?!

Session 2: Mammalian cell culture manufacturing

John Machulski, Lonza Biopharmaceuticals

Lonza recently built the world's first cell culture production facility at the 20,000L scale in Portsmouth. The facility covers 28,000 m² and can support multi-product campaigns up to 65 batches a year. The timeline for this project was fairly aggressive. The engineering design for the plant began in Oct 2000. By Nov 2003, all the mechanical engineering phases had been completed. Currently Lonza is validating its facility to be ready for GMP production by Aug 2004. He gave a good run-down of the progress of the project as well as the bottlenecks and lessons learnt. The take-home message for me was the importance of communication and effective project teams during various stages of project execution. No special formula for Lonza's success,

just doing the fundamental things right, which is always the most difficult.

Hermann Allgaier, LSMW GmbH, Germany

Hermann presented the findings of a study that compared two large-scale mammalian cell culture facility designs. The first design is the integrated monosuite facility which housed two large upstream and downstream suites with adequate product changeover procedures in place. The other design is a multiple suites facility with several upstream and downstream suites that will allow concurrent manufacturing campaigns. Each train is complete in itself. In terms of building space and equipment, the multiple suites facility occupied a bigger floor area to house more equipment and ancillaries such as supply and return corridor compared to the monosuite facility. As a result product changeover can take place with no down time whereas one week downtime was necessitated for changeover of products in the monosuite facility. The advantage of the monosuite facility is that investment is some 20% less than that for the multiple suites facility. The monoclonal antibody output for the monosuite facility is 10% less. In conclusion, the selection of facility designs has an impact on investment considerations and the cost of goods. The local conditions, which were not considered in Hermann's study, will also play a part to influence the selection decision.

In a separate talk, *Roland Heinrich* (Wyeth Biopharma) reported that the Wyeth investment at a green field site in Ireland is based on an integrated monosuite facility design. In their calculations the main contributor to the cost of goods is the planned utilisation of the new plant.

John Crowley, DSM Biologics, the Netherlands

Whenever there is a speaker from DSM Biologics, we know the topic will be on the human cell line Per.C6! It shows dedication and commitment from the company to develop the cell line and make it commercially viable. John's latest results showed that the productivity of the cell line can reach up to 2.4 g/L, a respectable figure. They have also optimised a continuous perfusion process (all process parameters are proprietary, of course!) to attain cell density of 5×10^7 cells/ml with no change in product glycosylation pattern.

Session 3: Protein purification, stability and formulation

There was good coverage on the topic of large-scale production of plasmids for therapeutic purposes with representatives from Gencell and Boehringer Ingelheim each tempting the audience with snippets of their proprietary technology. Gencell's technology included a high copy number plasmid vector for specially engineered bacterial strains; triple helix affinity chromatography (known as THAC) and corresponding assay methods. THAC is based on sequence specific binding of an oligonucleotide covalently attached on chromatography media to a target sequence on the plasmid. Major drawback of this technology is the slow kinetics and hence long contact time required for binding to take place.

Boehringer Ingelheim developed a semicontinuous alkaline lysis system without the use of RNase. Besides conventional liquid chromatography using bead media, they pioneered the use of monolithic supports with high dynamic capacity for plasmid DNA and high flow rates for the ion exchange chromatography steps. The monolithic media could be scaled up to 8L for commercial production.

Session 4: Building a future bio-industry

As the conference is held in Singapore, the organisers took the liberty to include this session, which emitted a strong flavour of a public relations promotion campaign. This author took the further liberty of expounding on the theme here. The main focus of the session is to showcase Singapore's efforts to develop the biomedical sciences from encouraging R&D in national research institutes (such as the BTI, Genome Institute of Singapore, etc.) and private companies to setting up biomanufacturing infrastructures. On the research front, progress has been made in the fields of media development for a protein-free chemically defined media, anti-apoptotic cocktails to prolong cell viability, transcriptome analysis of mammalian cells in culture to discover cell engineering targets for the prevention of cell apoptosis and several initiatives in downstream processing and product analysis such as glycosylation. In the area of biomanufacturing, A-Bio Pharma Pte. Ltd. (www.a-bio.com) is a recent spin-off from the Bioprocessing Technology Institute (previously known as the Bioprocessing Technology Centre). It is a contract manufacturing

organisation with full GMP capabilities including QC/QA functions and manufacturing activities in compliance with cGMP guidelines, as well as process development capabilities. It is a multiple suites facility occupying approximately 6800 m² for the production of biopharmaceuticals using mammalian cell lines.

Session 6: Considerations in regulatory compliance

Robin Thorpe, National Institute for Biological Standards and Control, UK

Robin has extensive experience in the development and validation of bioassays, assays that measure the response of living systems (such as cells) to a biological substance. Bioassays are typically used to measure the potency of the product but may be used for product identification and development. He spoke on the importance of using appropriate biological standards for bioassays to reduce the variability in the biological activity estimates and allow comparison of results across different laboratories. As a biological substrate often demonstrates multiple effects, careful selection must be made for a relevant biological response to be measured for the bioassay. In other words, one should be able to derive a dose-response curve.

Hope you enjoyed reading my account of the conference as much as I enjoyed writing it.

Dr. Lai Wen Bin, Group Leader, Purification Process Development. ABIO.

227th ACS National Meeting Division of Biochemical Technology

The latest ACS National Meeting was held in Anaheim between March 28 and April 1, 2004.

Stem Cell

Sean Palecek from University of Wisconsin presented a novel method for cryopreserving human ES cells. The cells were preserved by pouring matrigel over adherent ES cell colonies 1 day prior to freezing and frozen together with the matrigel. This was reported to improve cell survival compared to current techniques and limit cell differentiation. The same group also reported that mechanical straining of hES cell inhibited differentiation. Adherent hES cells were repeatedly strained over a piston-like device. Gene expression profiling of the strained cells showed that IGFBP7 was repressed in the strained cells.

Peter Zandstra's group reported work comparing growth of mouse ES cells in tissue culture flasks, as aggregate suspension cultures and on microcarriers. Glass coated polystyrene microcarriers was found to support growth of the cells better than cytodex beads, with doubling times equivalent to the tissue culture flask controls. Microcarrier cultures in spinner flasks reportedly reached 10⁶ cells/mL while maintaining Oct 4 expression. Aggregate suspensions grew much slower than tissue culture flask controls.

Tor Jensen of Northwestern University reported on their group's work to immobilize hematopoietic cytokines to the culture surface. They reported that immobilized insulin was more potent than soluble insulin for hematopoietic stem cells.

Benjamin Youn from University of Calgary, Pharmaceutical Production Research Facility (PPRF) presented their work on mammary epithelial stem cells. Their proprietary serum-free media enabled the growth of these stem cells as suspension in 2L bioreactors. The same group also presented a poster on serum-free suspension growth of the mesenchymal stem cells, where they revealed that their media was supplemented with bFGF and PDGF.

A group from the National Tsing Hua University, Taiwan, presented a poster on the expansion of hematopoietic stem cells in serum-free medium. The system was serum and stroma-free and contained the following serum substitutes: 1.5 g/L BSA, 4.39 mg/mL insulin, 60 mg/mL transferrin

and 25.94 mM beta-mercaptoethanol. In addition, it had a cytokine cocktail of 8.46 ng/mL TPO, 4.09 ng/mL IL-3, 15 ng/mL SCF, 6.73 ng/mL FL, 0.78 ng/mL IL-6, 3.17 ng/mL G-CSF and 1.30 ng/mL GM-CSF in IMDM basal media.

Expression Engineering

Martin Fussenegger from ETH, Zurich presented work on the engineering of a cell line where translation can be controlled in CHO cells. While many studies have focused on producing large quantities of the message of the desired product genes, knowledge on efficiently processing the gene transcripts (e.g. translation) has not been adequately dealt with. The work is based on the binding of CNBP (cellular nucleic acid binding protein) or La to TOP (terminal oligopyrimidine) elements. TOP elements adopt a specific hairpin structure which prevents ribosome binding and translation-initiation. Binding of CNBP or La to TOP stops the TOP-mediated translation block. This translation control system has been published in *Biotech. Bioeng.* (2003, 81, 1). At the conclusion of his talk, Fussenegger speculated that while engineering of the transcription, viability (apoptosis), cell cycle and now the translation machinery have been attempted, the next challenge would be to engineer the secretion machinery of the cell in order to improve product titers beyond current levels.

Animal Cell Culture

There were generally very few “novel” technologies presented in this area. Several presentations by industry representatives highlighted the use of inclined settlers coupled with continuous perfusion to achieve high cell density. Medium enrichment enabled even higher densities to be reached without diluting the product.

Mark Wesson from Protein Design Labs presented a fed-batch process for producing humanized antibodies from NSO cells. The improvement to their proprietary process apparently hinged on reducing the osmolality of the feed media by reducing the salt content and increasing the glucose concentration.

Jeremy Tong from Lonza presented their experience with the use of disposable technologies in a cGMP manufacturing process. The advantages of using disposable systems are its robustness and ease of use. The trade-off is the significant increase in consumable cost. They also reported that, in their experience, the use of disposable linings suffered from the persistent risk of tearing. A close interaction with the custom manufacturer for the disposable systems would be essential for this technology to succeed.

Centecor presented a poster on the use of the Dargip Cellferm-pro as a quick way to evaluate the effects of media, clonal differences or culture conditions in a scaled-down bioreactor system. The Cell-ferm-pro consists of eight independently-controlled 1L bioreactors inside an incubator. The results obtained from the system were comparable to a 3L bioreactor.

Bioprocessors Corp presented their microfluidic cell culture device that could be used for massively parallel experimentation to optimize media or culture conditions. However, their device is still not commercially available yet.

Dr. Victor Wong, Scientist, Bioprocessing Technology Institute

New Members

PAUL ABEL, Discovery Biology HDG, PFIZER; MICHAEL BORYS, Cell Culture Manufacturing, GALA BIOTECH; LEDA CASTILHO, FEDERAL UNIV. of RIO de JANEIRO; MADIHA DEROUAZI, EPFL; BEATRICE GOXE, Product & Development, EUROSCREEN; DERMOT PEARSON, Commercial Operations, DELTA BIOTECHNOLOGY Ltd; JAKOB H RASMUSSEN, MAXYGEN; JOAQUIM VIVES, UNIVERSITY of EDINBURGH; KATHRYN WOODS, PFIZER GLOBAL RES.& DEV.

Biopharmaceutical Investment

A recent report from *Tornado Insider* found that European companies in the Biopharmaceuticals sector have already this year nearly beaten the total amount of funding raised in 2003 (€590 million). With more than 4 months to run in 2004, it looks like the €585 million invested to date will increase significantly and cause a major uplift for the industry. *Biotechnology and Healthcare* as a whole has not overachieved in such a spectacular fashion, only managing 80% of total 2003 funding in this year to date. However, it remains the main destination for venture finance in 2004, as it has secured 36% of total investment in Europe this year. Interest is being fuelled by the upturn in biotech equities markets, the reopening of IPO possibilities and the fact that listed companies and 'big pharma' are on the prowl for infill and pipeline-boosting acquisitions. These factors combine to help investor confidence for future exit opportunities with successful companies.

Tornado Insider's data show a 2004 trend towards Biopharmaceuticals companies being funded at earlier stages than in 2003, when investors continued to be relatively risk-averse by placing more cash in established projects. 18.9% of capital invested this year has been in seed and first-round investment, whereas in 2003 the figure was 13.6%. Second rounds dropped nearly 5% from 35.4% (2003) to 31.7% (2004), while third-round funding remains almost unchanged at around 24%. This change in funding trends has probably been helped by the relatively low levels of early-stage funding in recent years, which has allowed more interesting new projects to accumulate in the pipeline.

2004 top 5 countries (Biopharmaceuticals)

Country	Total amount (€million)
Germany	154.9
UK	133.2
France	105.3
Switzerland	78.6
Denmark	33.2

Q2 2004 was a very good quarter for European Biopharmaceuticals investments with 33 companies securing €361.5 million - the biggest quarter ever recorded by Tornado Insider for that sector. In Q2, 12 German companies secured €126.8 million of Biopharmaceuticals financing. This took Germany to the overall number one position in 2004 to date with €154.9 million, ahead of both the UK (€133.2 million) and France (€105.3 million). MG

New Biopharmaceutical Facility nears Completion

Located opposite a castle ruin and surrounding by newly seeded grass lawns, nibbled on by lanky hares, is Wyeth BioPharma's Grange Castle facility – soon to be the largest in the world. The project was announced by An Tanaiste, Mary Harney, T.D. on 4 April 2000, and is due to launch its first product in summer 2005. The Grange Castle site was selected in the face of stiff competition from other locations, including sites in Puerto Rico and Singapore. However, Ireland was already

familiar to Wyeth, which has operated in the country for the past 27 years and currently employs 1,700 people at its plants in Newbridge, Askeaton, and Sligo. The Grange Castle facility in Dublin will be the largest single-site biotechnology Campus in the world, employing up to 1,300 people. The multi-product could cost as much as \$2 billion upon completion and biopharmaceutical drugs are a rapidly growing segment of Wyeth's business. Enbrel® (etanercept) will be the facility's first product which will help to meet the growing demand for the product. Enbrel® is an innovative medicine that has been used by over 250,000 people worldwide across its approved uses: rheumatoid arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and psoriasis.

The Wyeth BioPharma Campus at Grange Castle will comprise 3 separate facilities — a drug development facility, a drug substance facility, and a drug product facility. The Drug Development Facility will move products from the research pipeline to commercial manufacturing. It will coordinate and validate the technologies and procedures required to migrate the products and processes from the laboratory to the commercial production stage. The Drug Substance Facility will perform the beginning and intermediate stages of manufacture of cell culture products for worldwide distribution. It will be a multi-product facility that will include media preparation, fermentation, and purification stages of manufacture. In the Finished Product Facility the finished products are placed in vials for end sale as sterile products. The primary steps of the finishing process are formulation, vial preparation, filling, capping, and inspection. I am working as part of the Development Operations team with responsibilities including the process validation of the cell culture facility. The state-of-the-art facility includes 6 12,500 L stirred tank bioreactors.



Schematic of the layout of Wyeth BioPharma, Grange Castle, Ireland

Enbrel was the first Food and Drug Administration approved treatment for psoriatic arthritis and has been available for clinical use in the US since late 1998. Enbrel acts as a competitive inhibitor of tumour necrosis factor-alpha (TNF- α), a proinflammatory cytokine strongly implicated in the pathogenesis of psoriasis and psoriatic arthritis. TNF- α plays a critical role in the activation of the innate and acquired immune responses, but the persistence of the immune response and inappropriate production of TNF- α seen in psoriasis and psoriatic arthritis leads to chronic inflammation, tissue damage, and excessive keratinocyte proliferation. Etanercept is a fully human dimeric fusion protein consisting of the extracellular ligand-binding domain of the human 75 kilodalton (kDa) TNF- α receptor linked to the Fc portion of human immunoglobulin G1 (IgG1). Despite the presence of an Fc region, etanercept does not promote complement-mediated cell lysis in vitro. The etanercept protein is produced in a Chinese hamster ovary (CHO) expression system and consists of 934 amino acids, with an apparent molecular weight of 150 kDa. Etanercept inhibits the activity of TNF- α by competitively binding to this proinflammatory cytokine and preventing interactions with its cell surface receptors. The dimeric nature of etanercept permits binding of the protein to two free, or receptor-bound molecules of TNF- α at an affinity 50 to 1000 times that of soluble monomeric forms of the TNF- α receptor. The increased binding affinity of etanercept is likely to play a key role in the increased TNF- α -inhibitory activity observed with dimeric forms of the recombinant receptor compared to naturally occurring monovalent forms. **MG**

Ireland Announces Creation of National Bioprocessing Institute

IDA Ireland is inviting proposals from collaborative groups of academic institutions to undertake the establishment of the National Institute for Bioprocessing Research and Training. IDA Ireland is the Irish Government agency with responsibility for securing new investment from overseas in manufacturing and internationally traded services sectors. It also encourages existing investors to expand and develop their businesses.

Following wide consultation in US and Europe with businesses and academia in the biotechnology industry and taking into account the key educational and industrial issues identified, it was announced in July that that Ireland should make a strategic competitive investment and establish a national bioprocessing research, education, training and service facility. The facility should have three primary functions.

- Training and education in Bioprocessing
- Research in Bioprocessing Technologies
- Scale up capability to service the research, training, education and service needs of the Institute's stakeholders.

It is envisaged that the Institute will be a state of the art national facility designed to:

- Provide, in conjunction with academic institutions, a substantive output of people with high level best practice skills across the spectrum of bioprocessing activities, applicable in a real time scale up environment.
- Undertake academic/industry collaborative research with an emphasis on advancing knowledge in bioprocessing technologies and techniques, the technical problems of scale up and related issues.
- Give Ireland a competitive advantage and act as a magnet of attraction for further significant investment in the biopharmaceutical industry in Ireland, from both overseas and indigenous companies.
- Encourage the development of the existing foreign owned and indigenous biopharmaceutical sector and the establishment of new start up ventures in Ireland.

I will be keeping an eye on activities and report next issue on further developments. **MG**

Call for an Organising Committee for ESACT 21, 2009

ESACT organizes its General Meeting every two years in a European Country. As you know, previous meetings took place in Tylösand/S (2001) and in Granada/E (2003), and in 2005 we will meet in Harrogate/U.K. and in three years in Eastern Germany. The reason for the choice of the differ-



ent places are various:

- **ESACT** needs a member willing to take over the task of organizing such a meeting, of course, with the help of the **ESACT** Executive Committee (as a group with the know-how of organizing **ESACT** Meetings) and a professional congress organization (for organizing all non-scientific matters of an **ESACT** Meeting), in addition, general guidelines for the preparation of an **ESACT** meeting (established by F. Godia, the meeting chairman of the Granada Meeting) are available,
- The choice of a nice, preferably new place/city for organizing the meeting,
- A congress centre adapted to the needs of an **ESACT** Meeting (it should have a place/auditorium for about 750 participants and space for the trade exhibition as well as for the poster sessions (ideally about 2000m² altogether),
- The possibility to lodge all participants and exhibitors nearby to the congress centre, ideally at the same place.

The next **ESACT** Meeting for which **ESACT** is searching for an organizer is the **ESACT** 2009 Meeting. For those of you who are willing to organize this meeting, please, send a proposition containing a venue, the focus and the objectives of the meeting. As the domain of genomics and proteomics becomes one key activity in modern animal cell technology, there might be a session, keynote lecture and/or invited lecture on this matter. Other important developments, such as gene therapy, tissue engineering and, in particular, stem cell technology might also have a keynote or an invited lecture.

The proposition should be sent to me or our secretary (Alain Bernard) within the next six months.

Please, do not hesitate to send in your proposition, or contact me to discuss your ideas.

Otto-Wilhelm Merten

First woman to head MIT

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Susan Hockfield, a neurobiologist and current provost at Yale University, will succeed Charles M. Vest as the Massachusetts Institute of Technology's (MIT) 16th president, the school announced last week (August 26). Hockfield will be the first woman and the first life scientist to lead the traditionally male-dominated engineering school.

Of her election, Hockfield said in a statement released by MIT, "From my first conversations in the search process, the institute's central themes—the pursuit of truth, integrity, and the great meritocracy—have resonated with my own core values. This remarkable community's curiosity, intellectual commitment, and passionate determination to solve problems have brought immeasurable benefit to humankind. It is an enormous honor and a very great privilege to have been selected to join this effort as MIT's next president."

Her research focused on the development of the mammalian brain and central nervous system. One of the first scientists to use monoclonal antibody technology to study the brain, she discovered a family of cell surface proteins whose expression corresponds with neuronal activity early in an animal's development. She has also studied central nervous system gliomas and identified a gene and its protein products that influence the movement of cancer cells in the brain.

Her background will further MIT's attempts to bridge the gap between its technology and engineering strengths and the burgeoning field of life sciences, the Boston Globe editorialized last week

Vest, Hockfield's predecessor, announced his resignation last December after 14 years of service to the institute. **MG**



CTM Announce New Appointment

On the 25th August 2004 CTM announced the appointment of Malcolm Brattle as Non-Executive Director. CTM BioTech Ltd, the provider of process development services to the bio-pharma industry, today announces the appointment of Malcolm Brattle as Non-Executive Director.

Malcolm has a wealth of experience in the successful provision of bio-pharmaceutical services. His previous position was that of Sales and Marketing Director for Q-One Biotech, a biologicals safety testing company he co-founded some 14 years ago. Prior its sale to BioReliance, Q-One employed approx. 250 employees based in the UK and the US.

David Gough, Chairman of CTM, commented 'I am delighted to welcome Malcolm to the team at CTM BioTech. His previous experience in, and knowledge of, the sector will prove valuable to the company as we look to develop into a leader in the field of bio-pharma process development. That someone with Malcolm's experience should wish to join CTM is a fantastic validation of our positioning and potential'

Essentially CTM is looking to bridge the gap between what bio-pharma companies are able to do in-house and what CMOs can do by way of the production of clinical trial material.

The company specialises in the upstream and downstream development of GMP compliant procedures and in the manufacture of small quantities of non-GMP product derived from eukaryotic and prokaryotic client cell lines.

CTM also offer consultancy services to advise organisations as to how best develop their products in a GMP-compliant way and project management services to help client companies in their selection and management of appropriately qualified and experienced CMOs.

In addition to bank and private investment funding, CTM Biotech has also benefited from the support of Babraham Bioscience Technologies (BBT) Ltd's BioConcepts programme. BioConcepts is partly funded by the East of England Development Agency as a regional Enterprise Hub.

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MG



Malcolm Brattle

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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