THE ESACT NEWSLETTER

Published by the

European Society for Animal Cell Technology

Issue: September 2003

CONTENTS

EDITORIAL - SARS & Granada

Dear Readers,

In the short space of 6 months, a little known coronavirus took the half the world by storm, panicking the populace from Hong Kong (also known as SAR, the Special Administration Region) to Toronto. What a terrible personal and economic toll it took on nations such as China, Vietnam, Taiwan, HK, Singapore and Canada! Air travel became severely restricted, and on a personal front, 10 of us from the Bioprocessing Technology Centre were unable to come to the 18th ESACT meeting as a result. Thankfully, SARS has now ebbed away, for the moment…

Recapping events in Spain, we hear of some other world changing proposals from our Chairman Otto and committee members, who have projected a vision of a **Global Society, ISACT** for the benefit of all of us interested in animal cell technology. These are steps which have to be planned **care-full-y**, as ESACT was formed over 2 decades of hard work with steadfast team members. We shall need this same **stoutness of heart and sacrificial commitment** from the younger scientists to serve a much larger membership. Please feedback to us at committee@esact.org your feelings and opinions as we consider this intent. The more constructive and vociferous the better!

Inside this issue, exciting scientific developments from Granada are summarised by Otto, Alain, Merlin, and winners of the ESACT poster awards. There are 2 invited articles on glycosylation and genetic immunotherapy from Dr. Rudd and Dr. Pelegrin respectively. We are starting a new concept of short articles from companies, with Newlabs contributing the first. Finally we find humour in a tense period with some true SARS jokes and welcome new members to our fraternity. Enjoy & send us mail!

Your Chief Editor, Steve Oh

A Word from the Chairman

The last General Assembly which took place during the 18th ESACT Meeting (in Granada/E) has decided on the composition of the new ESACT Executive Commitee. Two members of the old Committee (Elisabeth Lindner-Olsson and Manuel Carrondo) who have been active for ESACT and have served on the Committee for several years stepped down. Both had taken the heavy burden of organizing an ESACT Meeting: Elisabeth the Tylösand-Meeting, which took place in June 2001 and Manuel the Vilamoura-Meeting which was organized in May 1996. Both meetings were great successes and were appreciated because of their scientific contents but also because of fantastic venues, Tylösand at the Kattegat in Scandinavia, and Vilamoura in the Algarve at the Atlantic Ocean. Here, I would like give a **heartfelt thank you** to both for their investment in furthering the aims of ESACT.

The two new members of the ESACT Executive Committee are Rod Smith and Hansjörg Hauser. Rod was already associated with the Executive Committee because as the organizer of the 2005 Meeting which will take place in Harrogate in the U.K., he had to be member. Now, he is the official meeting organizer of the 2005 Meeting. For many years however, with some interruptions, Hansjörg was associated with ESACT because he was a member of the Executive Committee and also participated in the scientific committees of several ESACT Meetings. He has agreed to be the meeting chairman of ESACT 2007, which will take place somewhere in Germany. I would like to welcome both new/old members of the committee and I wish both all the best for the heavy task of being meeting chairmen of the next meetings. Another modification in the committee is the change of our treasurer. Martin Fussenegger is our new treasurer. He has the heavy responsibility of preserving our finance and in trying to keep the expenses as low as possible. This change was necessary because Elisabeth stepped down as Treasurer.

It is evident that the new committee will most certainly follow in the footsteps of the old one. The connection to other societies, such as JAACT, ESGT, ACTIP or EFB, should be continued, however, only when this can benefit our members. As you know from previous newsletters but also during the last General Assembly, the objective of ESACT is to further animal cell technology by all means imaginable. Along this line ESACT in collaboration with ACTIP proposed and submitted last year to the EU an EoI (expression of interest) for financial support in establishing a training program for ACT specialists/researchers interested in industrial careers. Although the commission, bombarded by some 15000 EoIs which were submitted in the context of the 6th framework programme, rejected our intention, we do not think that the effort was in vain. As a follow up action, ESACT together with ACTIP is trying to put together a research training network in the frame of the Marie Curie Programme with the objective to train PhDs and Postdocs in large scale animal cell technology. This training network will consist of university institutes as well as biotech companies allowing training to take place in an academic as well as in an industrial environment. A very important feature of such a training network, if approved, is the fact that the commission is covering practically all expenses. The next deadline for submission of such a project is middle of November 2003.

Another point which has to be addressed during the next term of the ESACT Executive Committee is the question of the status of ESACT. As you remember, the committee proposed a modification of the constitution aiming to abolish the associated membership status. The last General Assembly which was organized during the 18th ESACT Meeting in Granada voted for this modification signifying that ESACT has now a unique membership status. Exception to this is the honorary membership status which is granted to few and selected persons in honor of their contributions to ACT and/or the society.

The visibility of ESACT has increased dramatically over the last 10 years and it has become more obvious that ESACT represents the leading society at an ***international*** level for animal cell technology. This and other factors have given birth to the idea that maybe in the future an *International Society for Animal Cell Technology* (an ISACT) could be created. And of course then, ESACT would have a major role to play. Also, it appears that our American friends involved in the *Cell Culture Engineering Conferences* would actually be very much in support of such a move, since it would help them to maintain a scientific forum that appeared to be more difficult to maintain over the last few years.

Two options for such a development exists:-
a) ESACT might become the ISACT or
b) ESACT becomes the driving force for the creation of an ISACT.

These possibilities will be discussed during the current term of the Executive Committee. **In this regard I would like to ask our members to**

express <u>their opinions</u> on this matter. Future and new developments always have their pros and cons.

The transformation of ESACT into ISACT can easily happen solely by modifying the constitution of ESACT. On the other hand the management of such a society will inevitably differ from the current ESACT management and the executive committee may have to be organized following the model of IABs. The meetings might then be organized as it is actually the case: in even years in North America using the format of the actual Cell Culture Engineering Conferences and in odd years in Europe using the format of the ESACT Meetings.

ISACT may also come to be totally independent of ESACT, or it may become an umbrella organisation under which for example AMericanSACT, ESACT, JAACT societies are organized. This will probably take more time, however, it my have certain advantages such as the organization of meetings and the management of the smaller societies. The ESACT Meetings will always be organized as usual in the uneven years by ESACT (together with ISACT). Whatever the case may be it will be necessary that the actual Committee together with some ESACT-members or scientists working in animal cell technology and currently located overseas, get together and initiate a discussion on this matter. As you see there are several possibilities directly and indirectly affecting the fate of ESACT. For this reason we would like to get feedback from everybody on this matter.

Finally, I would like to welcome our new co-editor of the ESACT-Newsletters, **Merlin Goldman**, who has the task together with Steve Oh to produce the Newsletters three times a year. The editorial board is highly motivated and has great ideas about face-lifting the Newsletter. In this context, I would like to mention one point which was discussed during the last General Assembly of ESACT. As the postage for sending the ESACT Newsletters is rather elevated, it was proposed to send the Newsletters via electronic mailing and to keep the classical postal distribution only for those who have no access to email or who have a restricted access not allowing download of the Newsletters. Therefore I would like to ask all readers to inform us if they would like to continue receiving the Newsletters via classical postal distribution. In cases where we do not get any information, future sending of the ESACT Newsletters (from December 2003 onwards) will be done by electronic mailing.

For those of you, whose holidays are starting, I wish you all the best. For those returning from holidays, have a good and successful start.

20/07/03 Otto-Wilhelm MERTEN

Minutes of the 18th ESACT General Assembly in Granada

The last General Assembly was held during the Granada meeting on May 13th, at 13:00. Approximately 50 attendees were present. A summary of the outcome is given below.

Otto Merten reported on the development of ESACT during the last two years: services from the ESACT society to the ESACT members: organization of the general scientific meetings, of interim meetings: ESGT, EFB sponsored meetings, Newsletter, publications, website and JIN, support for trainings, bursaries and travel supports for participation of young scientists at ESACT Meetings, etc.

Otto also introduced the recently appointed Newsletter co-editor Dr Merlin Goldman and acknowledged the generous gesture of many Asian colleagues (in particular, the other Newsletter co-editor Dr Steve Oh) to not attend the Granada meeting in order to eliminate risk of SARS spreading.

Elisabeth Lindner-Olsson reported on the actual state of the account with a balance of the UK account close to 100,000 £. Alain Bernard reported on the membership status with (as of April 2003), 280 full members, 78 associates, and 8 honorary members.

There was a plea to all members to send their modified contact data in case of changes as the last general e-mailing identified 37 wrong e-mails.

The newly elected Executive Committee has the following composition:
Ordinary members
H.Hauser
F. Godia
Stefanos Grammatikos
Florian Wurm

Officers, nominated by the previous ESACT Executive Committee are:
Otto-Wilhelm Merten (Chairman)
Alain Bernard (Secretary)
M. Fussenegger (Treasurer)
R. Smith (Meeting Organizer of the 19th ESACT Meeting)

Otto Merten, on behalf of the whole Executive Committee thanked the leaving members: -
Elisabeth Lindner-Olsson (ex-treasurer and Tylosand Meeting Secretary)
Manuel Carrondo (ex-chairman and Vilamoura Meeting Secretary)
for their dedication and contribution to the society during the past several years.

The proposed modification, aimed at suppressing the status of "Associate" members and transforming it into "Full" members, thereby eliminating the distinction based on geographical location was accepted by a massive positive response. Two new honorary members: B. Griffiths, C. MacDonald were also almost unanimously approved. The new Executive committee will meet next December 1st.

Alain Bernard, ESACT Secretary

Introduction to ESACT Granada meeting

The biannual conference of ESACT was held in Granada Spain between the 11 and 14th of May 2003. It attracted over 680 delegates, 6 main and 26 additional sponsors, 193 posters submissions (171 presented), 57 trade exhibitors and many jokes about the discovery of America. This was ESACT's 18th and largest conference and was held in the impressive Palacio de Congresso de Granada. The meeting's theme was "Animal Cell Technology Meets Genomics" to recognise the impact of the tools of the genomic sciences.

The Organising Committee was chaired by Francese Godia who kept the event running smoothly and was seen on the dance floor despite earlier protestations to the contrary. In addition to a good mix of topics and speakers - it was good to see a number of new as well as female presenters - there was a healthy social programme. A trip to the Alhambra Palace revealed its colourful tiled mosaics, reflective pools and expansive views across the city. We also enjoyed an evening of traditional Spanish music from an instrumental 3 piece as well as a variety of dancing at the gala dinner.

The following report will provide a flavour of the talks presented at the meeting. More detailed conference proceedings will be sent to all delegates. Those who didn't attend but would like a copy should contact Bryan Griffiths (contact details on the back page). There were 6 keynote lectures which covered topics such as gene expression, stem cell therapy, animal models, protein folding and cancer therapy. The conference opened with a Genomics Workshop

The poster session was organised into subject areas and prizes awarded in honour of Lisa Hunt, who met an untimely death a few months before the meeting. The prizes sponsored by Hoffman La Roche were awarded in ascending order to Heiko Meents, Thomas Noll and Ana V. Carvalhal.

Merlin Goldman

Report on the 18th ESACT-Meeting: Animal Cell Technology meets Genomics (Granada, Spain May 11-14, 2003)

The largest meeting in the history of ESACT was the 18th ESACT Meeting organized by Quico (F. Godia) in Granada in the middle of May 2003. The choice of the conference facilities and timing of the event were ideal for our stay in the pleasant Andalusian city with its history where the orient (the Mores) met the occident. Not only was the architecture and the landscape, in particular the white mountains of the Sierra Nevada, beautiful, but so was the whole meeting. Merlin has already given some statistics on the conference which indicates that ESACT meetings have become world meetings in animal cell technology, mainly due to the quality and quantity of presentations, the number of participants and the support of the exhibitors.

As Merlin has mentioned there were **6 keynote lectures**:

H. Bujard (ZMBH, Heidelberg/D) spoke on controlling the expression of genes in eukaryotes, on switch sequences (such as the cre/lox or the FLP/FRT systems), individual expression systems (Tet on/off), and the problem of leakiness in inducible systems.

Y. Barrandon (EPFL/CHUV, Lausanne/CH) spoke on stem cells and skin morphogenesis for cell therapy. Whereas clonogenic keratinocytes from human epidermis can only sustain epidermal renewal, it could be shown that adult corneal, limbal, conjunctival, vaginal, and oesophageal cells also respond to skin morphogenic signals by forming an epidermis, sebaceous glands and hair follicles.

N. Benvenisty (Hebrew Univ., Jerusalem/Israel) gave a lecture on human embryonic stem cells from the inner cell mass of blastocytes. These cells are the most interesting ones for transplantation with or without genetic modification. His group has identified 8 growth factors which can be used separately or together in various combinations to

direct the differentiation of the cells down one or another pathway. The differentiation was assayed by the expression of various cell specific molecular markers that cover all embryonic germ layers and a dozen different tissues.

M. Mahumbres (replaced M. Barbacid (Centro Nacional de Investigaciones Oncologicas, Madrid/E)) talked on new animal models for cancer drug discovery.

R. Kaufman (Howard Hughes Medical Institute, Ann Arbor/MI, USA) talked on the Unfolded Protein Response (UPR), its physiological role and its impact on the regulation of the production and/or the quality of several transcription factors. The UPR adaptive responses include expanding the ER capacity and efficiency for protein folding, increasing the degradation efficiency of unfolded proteins, and preventing the synthesis of additional unfolded proteins. The UPR is orchestrated by the coordinate transcriptional activation of multiple genes, a general decrease in translation initiation, and a concomitant shift in the mRNAs that are translated. This complex network of physiological responses to ER stress is regulated by three ER transmembrane proteins: IRE1, PERK and ATF6. These proteins are proximal sensors that regulate the production and/or quality of a set of transcriptional factors. IRE1 is a protein kinase/endoribonuclease that initiates splicing of XBP1 mRNA to produce a basic leucine zipper-containing transcriptional activator. ATF6 is cleaved upon UPR activation to release a cytosolic fragment that migrates to the nucleus to induce transcription of ER stress response genes. Finally, PERK is a protein kinase that phosphorylates the alpha subunit of eukaryotic translation initiation factor 2 to inhibit protein synthesis. Paradoxically, PERK-mediated translational attenuation also induces the translation of ATF4 mRNA, encoding another basic leucine zipper-containing transcription factor. In multicellular organisms, if these adaptive responses are not sufficient to relieve the ER stress, the cell enters one of the cell-death pathways – apoptosis or necrosis. Numerous studies support that these pathways contribute to adaptation as well as pathogenesis in diverse disease states. Recent gene deletion studies in mice have elucidated the requirement for the IRE1 and PERK pathways in development and organism responses to environmental stress.

A. Ullrich (Max Planck Institut für Biochemie, Martinsried/D) gave an overview on the developments in cancer research and treatment during the last 20 years. This long term activity has led to the first specific oncogene based therapeutic, 'Herceptin', for the treatment of mammary carcinoma. He presented new and recent developments such as the characterisation of Flk-1/VEGFR2 (involved in cancer development and metastasis) as a critical signalling element in tumour angiogenesis which represents the basis for the development of novel anti-angiogenesis therapies for a broad spectrum of cancers. It seems that in any case the original transforming event is the weak point of a cancer and that the omission/repair of the transforming event (e.g. deactivation of an oncogene) might be an approach for treatment.

Session 1: Cellular Mechanisms

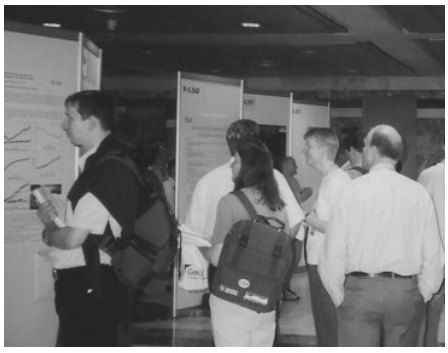
B. Palsson (Univ. California, La Jolla/CA, USA) gave an overview in the use of in silico models for the description of genome-scale networks. Such models can be used to interpret and predict genotype-phenotype relationships. Such models were developed for E. coli (the E. coli i2K model because it integrates 2000 ORFs of E. coli) and yeast. **M. Wu** (Imperial College, London/U.K.) presented a study on the effect of osmotic pressure on gene expression in GS-NS0 cells using DNA microarrays. By changing the osmotic pressure in the medium about 200 genes were up or down-regulated. **D. Hacker et al.** (EPFL, Lausanne/CH) presented results on the utility of genetic approaches to modify epigenetic pathways to increase stable and transient transgene expression in mammalian cells. Whereas the GAM1 protein (a histone deacetylase inhibitor) had only little effect on the transient gene expression in 293 cells, GAM1 increased the stable and transient expression of recombinant proteins (GFP, IgG) in CHO cells by 2 to 4-fold. GAM1 has cell and promoter specificity. **W.-S. Hu** (Univ. Minnesota, Minneapolis, USA) presented a comprehensive approach by combining genomic and proteomic tools and physiological studies to identify and isolate relevant genes in order to understand those key genetic alterations which are important for the development of new cell lines and new processes. **P. Rudd** (Oxford Univ., Oxford/U.K.) presented an overview on the different functions of carbohydrate moieties of glycoproteins, and gave several examples e.g. IgGs (about 19 glyco-isoforms per IgG), secretory IgA, and on a broadly neutralizing natural human monoclonal antibody against HIV-1, which has a novel domain swapped structure. Only this antibody can bind to the carbohydrate epitope on the GP120. **M. Valer et al.** (Agilent Technologies, Waldbronn/D) presented a microfluidic chip based system which can be used for different analytical applications: flow cytometric analysis (e.g. apoptotic cells, living cells), electrophoresis (e.g. monitoring DNA fragmentation as a parameter for apoptosis).

Session 2: Cell Based Therapies.

D. Möbest et al. (Chirurgische Universitätsklinik, Freiburg/D) presented the use of a fructose supplemented medium for the cultivation of tenocytes. These cells produce an extracellular matrix which is rather different from that produced by tenocytes cultivated in a glucose supplemented medium. The use of fructose favours the production of collagen I and III (major extracellular matrix components of tendon tissue); however, the cell growth was reduced by about 50%. A two step feeding regime (cell growth in the presence of glucose, matrix formation in the presence of fructose) might be of great interest (in general for all explanted cells which have to be amplified and then re-implanted) because growth phase and differentiation phase and matrix formation can be separated. **H.R. Bohnenkamp & T. Noll** (Forschungszentrum Jülich/D) developed a standardised and optimised generation method of monocyte derived dendritic cells (moDC). The cultivation of CD14+ monocytes enriched via immunomagnetic beads, in X-VIVO 15 in the presence of GM-CSF, IL-4 for 6 days, followed by 2 days of cultivation in the presence of TNF-α and PGE2 lead to matured moDC. Such a protocol results in highly mature DCs suitable for clinical application. **V. Jäger et al.** (GBF, Braunschweig/D) reported on a new bone-specific DNA microarray for the simultaneous determination of the expression of 58 different tissue specific genes on the transcription level. It covers specific transcription factors, extracellular matrix, attachment proteins, cytokines, their corresponding receptors and control genes for characterizing the 3D cultivation of osteogenic cells. In parallel, non-invasive methods were developed to prevent damage to bone implants during optimisation of the culture conditions and routine cultivation.

Session 3: Gene Based Therapeutics.

M. Schweitzer (Paul Ehrlich Inst. Langen/D) replaced K. Cichutek and presented an overview on the development and regulation of gene transfer medical products. The ongoing trials are based on the use of the following vectors: 50.2% MLV, 18.4% AdV, lipofection 17.7%. In Germany, 55 clinical gene therapy trials are performed: 38 for cancer treatment (21 for immunotherapy), 5 for the treatment of infectious diseases (e.g. HIV), 1 for the treatment of a monogenic inherited disorder, 5 for treating cardiovascular diseases and 5 concern marker gene transfers. The recent trend has seen a decrease in the number submissions of new dossiers. The following problems have been observed: insertional oncogenes in a SCID-γc trial in France, tumour induction following NFGR expression via MLV-derived vectors in CD34+ mice cells and AAV seems to be able to induce tumours in transgenic mice. **S. Kochanek** (Univ. Ulm, Ulm/D) gave an overview on the developmental and production issues of adenoviral vectors. It is known that the injection of adenoviral vectors (non-gutted) can lead to strong immune responses, for instance when injected into the liver, and it could be shown that the inactivation/removal of Kupffer cells from the liver leads to an elimination of this response and therefore to a long term expression of the transgenes to be expressed (as shown for the expression of Factor VIII in the liver of mice). Presently three different cell lines can be used for the production of adenoviral vectors: 293 (neuroepithelial), PERC6 (retinoblast), N52.E6 and N52.F4 (amniocytes). All cells are of human origin. Whereas the usefulness of 293 cells is affected by the production of RCAs when large quantities of vectors have to be produced, this is not the case for the other cell lines, because the overlap of vector sequences and sequences for the establishment of the packaging cells can be avoided. The N52 cells have been established by the group of Kochanek by cloning the pSTK146 plasmid into human amniocytes. These cells are easily transfectable and can be easily transformed. The N52 clones are E1A/E1B positive and produce 50,000 particles/cell or 2000 infectious particles per cell. For the N52.E6 clone a MCB and a WCB have been established and characterised. **A. Kamen et al**. (BRI, NRC, Montreal/Canada) presented production and optimization issues of adenoviral vector production using 293 cells. Amongst others they presented the establishment of a 293 clone containing pyruvate carboxylase (PYC) which led to an enhanced cellular metabolism due to an improved coupling between glycolysis and the Krebs cycle. In normal 293 cells, 86% of the glucose is metabolised to lactate and about 3% via the pentose phosphate cycle. The expression of PYC led to a reduced accumulation of lactate and ammonia. In addition, methods to increase reactor productivity for adenoviral vectors were presented using a perfusion reactor which gave a high vector titre and higher cell specific production rate.



S. Forestell et al. (Onyx Pharmaceuticals, Richmond/CA, USA) presented a new generation of oncolytic AdV vectors. Onyx has developed new packaging cell lines which remove the need for a recombination event: H1299 and a HeLa S based producer cell line. The HeLa S based cell line is more interesting than the H1299 cell line because high vector titres can be produced. In a CF-10, 2-3 x 10^{13} particles/l were obtained. Under perfusion conditions, these values can even be increased to 3-5 x 10^{14} viral particles/l. H1299 is only efficient when a feeding regime is used. HeLa S cells are à priori not excluded from use for gene therapy purposes (view of FDA and industry consultants). A very important issue, however, is the elimination of host cell DNA which has to be done by downstream processing of the viral vectors. **P. Cruz et al.** (IBET, Oeiras/P) presented a study on MLV vector stability and inactivation mechanisms. They have observed envelope shedding only for amphotropic MLV vectors whereas for GaLV pseudotyped MLV vectors a complete disintegration but no shedding was observed.

Session 5: Biopharmaceuticals

V. Sandig et al. (ProBioGen, Berlin/D) presented a new heterohybridoma cell line for the high level expression of heterologous genes. The original cell line produced IgM at levels of 30 to 100 µg/ml (45 pg/cell day). The high level expression of recombinant proteins was achieved by targeting the human IgH locus using the FLP/FRT exchange system. This locus is located on the human chromosome 14. They were able to establish a mother clone (the G cell line) which can be used for the rapid establishment of producer cells of rec. proteins. These new producer clones are characterized by homogeneous expression levels of recombinant proteins. **N. Mermod et al.** (Univ. Lausanne, Lausanne/CH) presented the use of MAR elements (5'-matrix attachment region) in order to increase the expression of heterologous proteins in CHO cells. MAR elements open closed chromatin loops and vice versa. The expression of MAR in cis or in cis and trans led to much better recombinant protein expression than cells without MAR. This increase was observed for stable as well as transient protein production. The observed increase in the expression level of stable producer cell lines showed long term stability. **H. Schellekens** (Utrecht University, Utrecht/NL) presented a lecture on bioequivalence and the immunogenicity of biopharmaceuticals. Problems can occur for many reasons e.g. scale-up, change of the production site and introduction of generics because all these modifications can have an adverse effect on the molecule and finally on the behaviour of the molecule in the patient (leading to a immunological reaction). Whereas the use of a new production site for β-IFN led to better product which was less immunogenic, the use of EPO in Europe and Australia (EPREX) led to the appearance of pure red cell aplasia in some patients (1 of 500 patients developed antibodies against EPO). The EPO treatment was stopped; however, some of the patients are still dependent on red cell transfusion. This was not observed in the USA, and the only difference between both products were the production site and the fact that the stabilizer of the US product (HSA) was replaced by another one (TWEEN 80/glycerol). In addition the product for the European and Australian market is used SC. As the Sorbitol 80 concentration was above the critical micelle concentration, micelle formation appeared in EPREX, and EPO was located in the micelles. Such micelles look like viral particles and may activate the immune system. The conclusion is that the main problem seems to be the final formulation of the biologic and that in the future, clinical trials will be necessary for biogenerics. **D. Galbraith** (Q-One, Glasgow/Scotland) presented the actual state of and prospects for the use of insect cells as substrate for the production of biotherapeutics. The most common used cell lines are: S. frudgiperda, T. ni, Bombyx mori, and Mamestra brassicae. One product used as a veterinary vaccine is based on the envelope glycoprotein E2 to prevent swine fever in piglets. This vaccine is produced in 500/1000 l reactors under serum-free conditions. The CVMP requirements were: 5 production batches, integrity tests of the sterile filters, validation of the production method and inactivation of the baculovirus. No inactivation studies with model viruses was required, there was also no need to test for insect viruses. The freedom of adventitious viruses in the MCB (Sf9) and virus stock had to be shown. **P. Alves et al.** (IBET, Oeiras/P) presented the production of VLPs (virus like particles) in Sf9 cells as a means of production of a rotavirus vaccine. They used a stirred tank reactor, performed serum-free cultures and infected the cultures at a density of 2 x 10^6 c/ml with a MOI of 10. Actually they produce the VLPs by co-infecting the Sf9 cells with at least two different baculoviruses at a ratio of 1/1 (for VP2 and VP6) which for the moment proved to be more efficient than when a multigene baculovirus (Bac2/6) was used. Future work will be directed at getting the correct stoichiometry between VPs and particle stability. **P. Umaña et al.** (GlycArt Biotechnology AG, Zürich/CH) discussed the engineering of cell lines to produce more humanised glycosylation of recombinant proteins. They expressed β 1, 4-N-acetylglucosaminyltransferase III (which is not expressed in CHO, in NS0 nor in SP2/0 cells, but which is important for bisecting glycosylation) in CHO cells. Monoclonal antibodies produced in such cells showed an increased activity in an

ADCC assay. **C. Goudar et al.** (Bayer Crop., Berkeley/CA) presented a quasi real time metabolic flux analysis for optimizing industrial production processes and studying the effect of the variation of several process parameters (such as pH or pO_2). The actual process is run at a perfusion rate of 1 to 15 reactor volumes per day for a duration of 3 to 7 months. The cell density ranged between 20 x 10^6 and 60 x 10^6 cells/ml. They performed the following on-line monitoring: mass-spectrometry, OUR-CER, in situ microscopy, and off-line analysis for glucose, lactate, glutamine, NH_3 and amino acids. **S. Bengio et al.** (Ciphergen, Cergy/F) presented the applications of surface enhanced laser desorption ionization for protein expression analysis and fast purification optimization from cell culture and fermentation media. **L.A. Palomares et al.** (UNAM, Cuernavaca/Mexico) presented scale-up strategies for animal cell technology. **J. Aunins** (Merck Res. Labs., West Point/PA) presented Merck's AdV programme for the production of a HIV vaccine (gag, pol, and nef expressed via the adenovirus system, CMV as promoter). The planned dose is 10^{11} viral particles/dose, X3 for each HIV protein, X3 for 3 successive vaccinations. The planned production is 10^{20} particles per year. The problems to be faced are the genetic stability of the vector as well as the scale of production (a 10,000 – 20,000 l batch process). Only the FMDV vaccine had been produced at this scale up to now. The process has to be simple and easy. The production vehicle is the PER C6 cell line grown in suspension under serum free conditions. The cells are aneuploid and tumorgenic in an immunodeficient animal model. This signifies that safety tests have to be performed and the cellular DNA has to be eliminated during downstream processing. The following optimal culture conditions have been established: pH 6.8 (for cell growth), 7.2 (for virus production); temperature 33°C (for cell growth) and 36-37°C for AdV-production. **O.-W. Merten**

Roles for glycosylation in the immune system

Pauline M. Rudd and Raymond A. Dwek of the Glycobiology Institute, Department of Biochemistry, University of Oxford, South Parks Road, Oxford OX1 3QU, UK

Specific sugars are required for glycoproteins to access the calnexin/caleticulin folding pathway

Most of the key molecules involved in the innate and adaptive immune response are glycoproteins. The N- and O-linked glycans play important roles in recognition events that are critical for the biological functions of the proteins. In the endoplasmic reticulum (ER), all glycoproteins carry the $Glc_1Man_{9-7}GlcNAc_2$ glycan that can bind to the lectin-like quality control chaperones, calnexin (Clx) and calreticulin (Clr). The terminal glucose (Glc) residue is essential for binding the glycoprotein to these chaperones and is finally removed only when the protein is fully folded. One protein that folds using the Clx pathway is the major histocompatibility class I (MHC I) which, in humans, contains one N-linked glycan. Following the association of the MHCI heavy chains with 2microglobulin in the ER, the $Glc_1Man_{9-7}GlcNAc_2$ glycoform of MHCI is released from Clx and binds to Clr. In an adaptation of the Clx/Clr folding pathway, the loading of MHCI peptide antigens takes place in a multipeptide complex which only dissociates when the peptide groove is filled. This event signals that the peptide loaded MHCI (pMHCI) is 'fully folded', the final glucose residue is permanently removed from the glycan and pMHCI transits to the surface of the antigen presenting cell (APC).

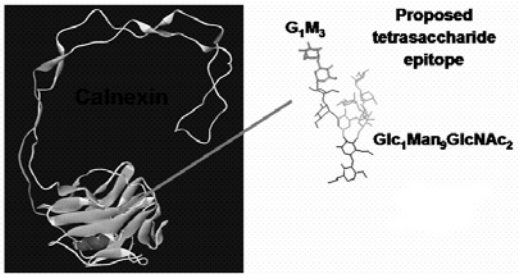


Figure 1 Self sugars are recognised by membrane bound calnexin (on left) during protein folding.

Glycans play a significant role in the APC/T cell synapse.

The large sizes of oligosaccharides shield proteins such as the T cell receptor from proteases and from non-specific interactions. The formation of the cell adhesion pair between CD2 and CD48 is assisted by a glycan that is located in the membrane proximal region on CD2. This sugar serves to orient the binding face of CD2 towards that of CD48. Also in the synapse, the O-linked glycans on CD8 extend its protein stalk so that the CD8 binding domain is suspended at the optimal distance from the T cell surface to locate the binding site on MHCI attached to the APC.

Specific glycan epitopes provide SIgA1 with binding sites for bacteria

Secretory IgA1 (sIgA1) is a multi-polypeptide complex consisting of a secretory component (SC) covalently attached to dimeric IgA containing one joining (J) chain. The N-glycans on the H chains present terminal GlcNAc and mannose residues which are normally masked by SC. When exposed by disrupting the SC-H chain non covalent

interactions, the terminal oligosaccharide residues can bind mannose binding lectin. The O-glycan regions on the heavy (H) chains of sIgA1 and the SC N-glycans have adhesin-binding glycan epitopes including galactose linked β1-4 and β1-3 to GlcNAc, fucose linked α1-3 and α1-4 to GlcNAc and α1-2 to galactose, and α2-3 and α2-6 linked sialic acids. These glycan epitopes provide SIgA1 with multiple glycan sites to which bacteria can bind, thus enabling SIgA to participate in both innate and adaptive immunity [16]. Specific agalactosyl glycoforms of IgG, present in increased amounts in rheumatoid arthritis, can, when clustered also activate the complement pathway through engaging the mannose binding lectin.

Glycosylation is the human immunodeficiency virus' Achilles heel

Viruses usually surround themselves with a heavily glycosylated envelope. Viruses have no glycosylation machinery of their own and simply highjack that of the host, masking potential antigenic epitopes with sugars that are invisible to the host's immune system. A new paradigm for antigen recognition has emerged from the remarkable finding that an unusual cluster of mannose residues on the HIV gp120 envelope glycoprotein are recognised by a novel domain swapped antibody. The broadly neutralising 2G12 IgG antibody, isolated from a patient's serum, has four closely spaced potential combining sites and may suggest a novel means of targeting clustered glycan arrays on a range of pathogens or tumour cells.

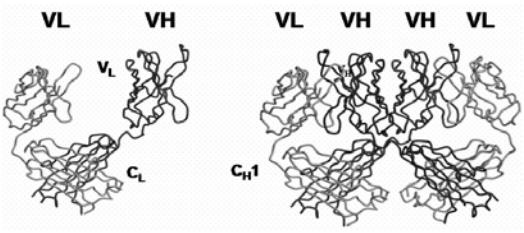


Figure 2 2G12 crystal structure reveals a domain swapped Fab dimmer.

Glycosylation processing is cell type specific

Recombinant glycoproteins, often expressed for use as pharmaceuticals or in modeling physiological processes, will be glycosylated differently in different cell lines. It is important to recognise this aspect of animal cell technology otherwise altered glycosylation patterns may result in the unexpected loss or gain of function of the protein. For example, modifying glycosylation may improve the efficacy of therapeutic antibodies, decrease their life time in the serum or introduce antigenic epitopes. An understanding of the principles of Glycobiology allows possible outcomes to be predicted and glycosylation to be manipulated to achieve particular goals.

Monoclonal Antibody Based Genetic Immunotherapy

Mireia Pelegrin and Marc Piechaczyk at the Institute of Molecular Genetics, UMR5535-IFR122, CNRS, 1919, route de Mende, 34293 - Montpellier Cedex 05, France

Monoclonal antibodies (mAb) have an enormous potential for treating a wide range of diseases including cancer, viral infections, transplant rejection, autoimmunity, toxic shock and rheumatoid arthritis to name a few. Since the discovery of mAb in 1975, several generations of antibody-based therapeutic approaches have successively been tested. The poor efficiency of the first mAb used in the clinic (mostly linked to the murine origin of mAb that triggered a strong human anti-murine immune response) tempered the initial excitement created by this technology. However, after nearly two decades of disappointment, mAb have finally appeared as viable and powerful drugs (1). The emergence of mAb as real therapeutics has been rendered possible due to the development of new technologies allowing the production of fully human antibodies overcoming in this way the intrinsic limitations of mouse mAb. To date, the US Food and Drug Administration have approved 12 of them and at least 400 other mAb are in clinical trials worldwide (1).

However, although satisfactory for short-term applications, direct intravenous injection creates difficulties for long treatment because: (i) the mild to severe side-effects associated with infusion, (ii) the possible anti-idiotypic response resulting from repeated injections of large doses of antibodies and (iii) the high costs of *in vitro* produced proteins certified for human use. Moreover, injection of large doses of mAb is followed by rapid clearance during the post-infusion period, which results in great variations in the bioavailability of these therapeutic agents and may have negative consequences on the efficiency of treatments and, in some occurrences, be toxic for patients. *In vivo* production of ectopic antibodies through new gene/cell therapy based approaches, might be used in place of intravenous injection to overcome these limitations.

Our laboratory has demonstrated the feasibility of sustained *in vivo* production of mAb by engineered cells using a variety of approaches such as: (i) the grafting of *ex-vivo* genetically modified cells (including myoblasts, fibroblasts and keratinocytes) (2-4), (ii) the implantation of antibody-producing

cells encapsulated within immunoprotective devices made of cellulose sulphate (5) and (iii) direct *in vivo* gene transfer of mAb genes by using both viral and non-viral gene transfer approaches (6). Importantly, we have also provided evidence of the therapeutic value of this approach by protecting mice from developing a lethal retroviral disease (7).

The major limitations that mAb-based gene/cell therapy may meet is the development of an immune response developing against, on one side, the ectopic mAb, whatever the technology used for gene transfer/production, and/or, on the other side, antibody-producing cells. However, a cytotoxic response against antibody-producing cells is unlikely to occur because secreted antibodies, if they are of human origin (or if they originate from the same species as that in which experiments are conducted in the case of preclinical studies), are molecules of the self. Supporting this view, our studies performed in immunocompetent mice showed long-term mAb *in vivo* production (from several months up to two years) upon grafting of genetically altered cells, *in vivo* gene transfer as well as implantation of encapsulated mAb-producing cells. Moreover, no humoral anti-idiotypic responses were observed upon grafting of engineered myogenic cells or upon implantation of cellulose sulphate capsules containing hybridoma cells.

Our work thus provides the technical basis for a new gene/cell therapy approach which is potentially applicable to a large number of illnesses. Anti-viral and anti-tumour cell surveillance and chronic disease treatments will probably constitute its first applications. Optimization of *in vivo* mAb production and validation of the therapeutic potential of the approach in a variety of preclinical studies is required before any human application. To reach this goal, establishment of cell lines validated for human use and amenable to both genetic modification and encapsulation constitutes a promising approach that would offer advantages, not only in terms of therapeutic efficiency, but also at the level of safety. Also, recombinant virus as well as non-viral *in vivo* gene transfer methods might represent an interesting alternative provided that safety issues are solved properly and antibody genes expressed for long periods of time.

1. Gura, T. (2002) *Nature* **417,** 584-6.
2. Noel, D., Pelegrin, M., Marin, M., Biard, P. M., Ourlin, J. C., Mani, J. C. & Piechaczyk, M. (1997) *Hum. Gene Ther.* **8,** 1219-29.
3. Noel, D., Pelegrin, M., Brockly, F., Lund, A. H. & Piechaczyk, M. (2000) *J Invest Dermatol* **115,** 740-5.
4. Noel, D., Dazard, J. E., Pelegrin, M., Jacquet, C. & Piechaczyk, M. (2002) *J Invest Dermatol* **118,** 288-94.
5. Pelegrin, M., Marin, M., Noël, D., Del Rio, M., Saller, R., Günzburg, W., Stange, S., Steffen, M. & Piechaczyk, M. (1998) *Gene Therapy* **5,** 828-834.
6. Noel, D., Pelegrin, M., Kramer, S., Jacquet, C., Skander, N. & Piechaczyk, M. (2002) *Hum Gene Ther* **13,** 1483-93.
7. Pelegrin, M., Marin, M., Oates, A., Noel, D., Saller, R., Salmons, B. & Piechaczyk, M. (2000) *Hum Gene Ther* **11,** 1407-15.

19th ESACT Meeting "Animal Cell Technology - Cell Processes for Cell Products"

The 19th ESACT meeting will be held in the UK at the Harrogate International Centre on June 5th -9th 2005.

The preparations are already underway and proceeding well at present. The Trade and General Meeting committee's have already met and the Scientific organisers will meet next month. The venue at Harrogate is an ideal one for an ESACT meeting and will accommodate us all very well. Harrogate is a floral market town in North Yorkshire with access to the Yorkshire Moors and the Yorkshire Dales. It has good airport links to Europe and the USA and excellent rail links to London. The 19th ESACT Meeting aims to build on the successful 18th Meeting held in Granada 2003.

There is an outline theme for the "Animal Cell Technology- Cell Processes for Cell Products".
This theme covers all aspects of the animal cell technology process for example from cell line generation to the delivery of therapeutic products and all those activities in-between. It is anticipated that all scientists working the biotechnology arena can visualise how their work fits in with this theme and hopefully encourage them to submit their work for verbal and poster presentations.

The Scientific committee will meet and agree the session topics which will be announced in January 2004. With the input from the animal cell technology scientific groups throughout the world we will have a good, exciting and informative meeting in June 2005. I look forward to the next few months and to meeting with you all in Harrogate June 5th-9th 2005 at the 19th ESACT meeting.

If you any queries or suggestions at this time please feel free to contact myself or anyone in the listed committees below.

Dr Rod Smith
CTM BioTech
0(44)1223-496070
rodney.smith@ctmbiotech.co.uk
General Meeting Organisation
Glenda Bland Global Meeting Planning
Tracey Zecchini Astex Technology
Trade Committee
Fiona Godsman Q1
John Bonham-Carter Adaptive Biosystems

Scientific Committee
Prof. Jurgen Lehman University of Bielefeld
Prof. Glyn Stacey NIBSC
Prof. Mohamed Al-Rubeai University of Birmingham
Prof. Martin Fussenegger ETH
Dr. Dave Venables Q1
Dr. Rob Arathoon Genentech

Poster Winners

Nathalie Chatzissavidou and Paula Marques Alves organised the poster competition with some willing participants to help judge the large number of posters on show. A final two dozen were selected and grouped together before the final judging panel made their final decision. The winners were announced at the gala dinner and received prizes donated by Hoffman La Roche. The winners were

1st Prize: Ana V. Carvalhal
Cell growth arrest by nucleotides, nucleosides and bases as a tool for improved production of recombinant proteins (P-1.10).

Ana works in the Instituto de Biologia Experimental e Tecnológica / Instituto de Tecnologia Química e Biológica in Oeiras, Portugal and worked in collaboration with Sónia Sá Santos1, Matthias Haurry and Manuel J.T. Carrondo.

Arresting cell growth and thus decreasing cell division potentially lessens the chance for genetic drift in the cell population; this would be of utmost importance for the consistent production of biopharmaceuticals during long periods. Different methods for cell growth arrest and synchronization have been reported; nevertheless, they have been poorly explored and are far from being usable for the production of recombinant proteins by animal cells. The modulation of the cell cycle through chemical synchronization would represent a strong strategy for industry. The drawback of the addition of well known synchronizing agents, such as chemotherapeutics, is that they cause a disproportionate accumulation of cellular constituents, leading to cell death. The use of compounds that are naturally synthesized by the cell, as is the case of nucleotides, is shown, in this work, to be a promising tool.

The addition of purines and pyrimidines were tested using a CHO cell line producing the enzyme SEAP. From the chemical alternatives tested, AMP was the most promising compound for protein production improvement: it reduced cell growth and maintained the culture with high cell viability for long periods, while increasing SEAP specific productivity 3-fold. The use of CHO and BHK mammalian cells producing Factor VII and the use of an insect cell line (Sf9) showed that the effect of AMP addition seems to be independent of the r-protein and cell line. With the addition of AMP an initial accumulation of cells at the G1 and S phase was accompanied by the increase of the protein specific productivity. Addition of known synchronizing drugs and application of environmental cell growth arrest strategies (depletion of nutrients and by-product accumulation) also effectively arrested CHO cell growth.

For further work see Carvalhal et al. 2003 Biotechnol Prog 19(1):69-83

2nd Prize: Dr Thomas Noll
Membrane-separated cocultivation of cord blood hematopoietic stem cells with stromal cell lines (P-2.13)

Thomas works in the Institute of Biotechnology in Jülich, Germany and worked in collaboration with Tina Fischbach.

Cord blood hematopoietic stem and progenitor cells (HSPC) represent an important cell source for transplantation of cancer patients after high dose chemotherapy if autologous cells are not suitable (e.g. patients with hematopoietic malignancies) and no adult allogeneic donor is available. The main disadvantage of cord blood is the low number of cells obtained due to the small volume of blood collectable from umbilical cords. Without an expansion of the HSPC transplantation is mostly limited to juvenile patients. We developed a novel small scale membrane bioreactor for parallelized membrane-separated cocultivation of HSPC with stromal cells. This system imitates the natural hematopoietic environment with stromal growth factors, ECM components and direct cell-cell contact between HSPC and stromal cells while maintaining a physical separation of the cells

The mini membrane bioreactor consists of a turning insert for conventional 12-well plates, wherein a thin, porous polyethylene membrane is fixed.

Murine stromal cells adhere to the underside on the membrane and HSPC are co-cultured on top of it. Soluble factors and stromal extensions traverse the membrane, whereas cell bodies are retained. Thus, stroma directly supports HSPC expansion without contaminating the future transplant. Purified $CD34^+$ cells are cultured for 7 days in X-Vivo10 supplemented with four cytokines (Tpo, SCF, IL-3 and FL). Many important parameters have been investigated using this system (membrane material, pore size, type of stromal cells, cell density, agitation, feeding, etc.). With the novel membrane reactor we are able to expand HSPC to high cell densities. On average, after 7 days total cells and progenitor cells (CFC) expand 242 and 29fold. Early progenitors (CAFC) could even be expanded 39-fold.

3rd Prize: Heiko Meents

Dicistronic Expression Units for Simultaneous Apoptosis Engineering and Product Expression in CHO-DG44 Cells Adapted for Growth in Serum-free Media (P-1.21)

Heiko works at the Institute of Biotechnology, Swiss Federal Institute of Technology, in Zurich, Switzerland and collaborated with B Enenkel and Martin Fussenegger

We have constructed dicistronic expression vectors for one-step anti-apoptosis engineering and product expression. Expression units encoding the soluble intercellular adhesion molecule 1 (sICAM), a potential therapeutic for treatment of the common cold, and bcl-2/bcl-x_L were integrated and amplified in Chinese hamster ovary- (CHO) DG44 cells adapted for anchorage-independent growth in serum-free media. sICAM expression was translated in a cap-dependent and survival gene expression in a cap-independent manner based on the encephalomyocarditis virus (EMCV) internal ribosome entry site (IRES). Batch cultivations of engineered CHO-DG44 cells containing amplified transgene expression units exhibited improved viability and delayed onset of apoptosis compared to cell lines harboring monocistronic control constructs. bcl-x_L-mediated apoptosis protection was significantly higher compared to bcl-2-based survival engineering. High-level expression of bcl-2 and bcl-x_L seem to be required to compensate for increased mitochondria numbers found to be associated with production cell lines grown in serum-free medium.

For further work see Meents et al. 2002 Biotechnol Bioeng 80:706-716.

Stability Testing of Biopharmaceutical Proteins and Plasmids used in Gene Therapy

As a part of the pharmaceutical development process, the stability of drug substances and products is one of the main issues addressed by the regulatory authorities. Tissue-derived and biotechnological products as well as plasmids used in gene therapies are often particularly sensitive to environmental factors. Therefore, much effort must be spent to determine the stability of these products under various conditions. This requires the development of a thoroughly planned stability testing study program.

The objective of a stability study is to determine the exact conditions for storage as well as the shelf life at these conditions for the drug product and to be able to recommend a re-test period for the drug substance. The biopharmaceutical product is evaluated under various environmental storage conditions that test its thermal stability and, if applicable, its sensitivity to moisture. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment and subsequent use. It also provides insight into the consequences of what may occur if the recommended storage conditions are not maintained.

The extent of a stability program depends on the actual status of the product in the drug development chain. Accelerated storage conditions are used to determine the limit and tolerances of the drug product. The data from these studies also provides valuable information concerning the effect of short term exposures outside of the normal label storage conditions such as might occur during shipment. The accelerated stability study must be over a 6 month period. The shelf life of the drug product should be determined in a detailed, long term stability study. This study should cover at least 12 months and should be performed on at least three different lots.

The characteristics of the product which are determined during the stability study should provide assurance that any changes in the identity, purity, and potency of the product can be detected. The set of analytical methods to be used should, therefore, investigate appropriate physicochemical, biochemical, and immunochemical attributes. For assessing the purity aspect, a quantification of the active ingredients, degradation products, and any process impurities should be performed. For monitoring the potency of the product, a suitable bioassay should be used to determine the function of an active ingredient throughout its shelf life. Other product characteristics such as visual

appearance, time for dissolution or reconstitution, pH and sterility should also be tested. All methods which are used need to be validated before submission to the authorities. Due to the large amount of analytical work and often limited in-house resources, more and more pharmaceutical companies are frequently contracting these stability studies to an outside testing laboratory.

Dr. Andreas Richter (NewLab BioQuality AG)
www.newlab.de

Future Meetings

International Stem Cell Conference, 28th – 30th Oct. 2003, Singapore. Tel: +65 6297 7633 E-mail: ISCC2003@wwconvention.com.sg
11th Annual Meeting of the European Society of Gene Therapy - Nov 14-17, 2003 - Edinburgh, UK www.esgt.org Chairmen: David Porteous, Chris Boyd. Organisation: Congrex Sweden AB, P.O. Box 5619, SE-114 86 Stockholm, Sweden. E-mail: esgt@congrex.se - Phone: + 46 8 459 6600 - Fax: + 46 8 661 9125
Annual Meeting of American Institute of Chemical Engineers: Advances in Cell Culture Processing - Nov, 16-21, 2003 - San Francisco, CA, USA. http://www.aiche.org/Annualapp/previewmodule/SessionDetail.asp?SessionCode=TM002
Organisers: James Piret and Ron Taticek
Cell Culture Engineering IX - March 7-12, 2004 - Cancun, Mexico www.engconfintl.org/4ac.html (O. Ramirez, Natl. Autonomous University; Lynne Krummen, Genentech)
Singapore Biologics Manufacturing Conference, 19th – 21st April 2004. Tel: +65 6295 5790 E-mail: ims@inmeet.com.sg Website: www.sbmc.org.sg

Joke Corner (Special on SARS)

Following the fear of SARS, came the humour, a natural reaction of the population in the hard-hit areas of the world. Here are a few instances to infect the reader with LARS, Laughter Acute Respectless Syndrome

One day at Tan Tock Seng Hospital - Center for Communicable Disease, SINGAPORE

This story was told by a nurse...and she swears this really happened on her ward.
A man suspected of SARs is lying in bed with a mask over his mouth. A young auxiliary nurse appears to sponge his face and hands. Nurse," he mumbles from behind the mask, ***"Are my ******* black?"***
Embarrassed the young nurse replies, "I don't know sir, I'm only here to wash your face and hands."
He struggles again to ask, "*Nurse, Are my ******* black*?"
Again the nurse replies, "I can't tell. I'm only here to wash your face and hands."
The Head Nurse was passing and saw the man getting a little distraught so she marched over to inquire what was wrong.
"*Nurse*," he mumbled, "*Are my ******* black*?" Being a nurse of long-standing, the Head Nurse was undaunted.
She whipped back the bedclothes, pulled down his pajama trousers, had a right good look, pulled up the pajamas, replaced the bedclothes and announced, Nothing wrong with your testicles!!!"
At this the man pulled off his mask and asked again, ***"I SAID.... Are my TESTS RESULTS BACK .....!! ???"***

Doctors
A British doctor says "Medicine in my country is so advanced that we can take a kidney out of one man, put it in another and have him looking for work in six weeks."
A German doctor says, "That's nothing, we can take a lung out of one person, put it in another and have him looking for work in four weeks."
A Russian doctor says, "In my country medicine is so advanced we can take half a heart out of one person put it in another and have them both looking for work in two weeks."
The Chinese doctor, not to be outdone, says, "You guys are way behind. We just took a man with no brain, put him in the Governor house of Hong Kong, and now half the city is looking for work."

Quote from a doctor at the height of testing SARS

"When you see a mountain of stool samples, it can be quite daunting. You lose your appetite,"
Dr. Ling Ai Ee, Senior Consultant with the Singapore General Hospital's Virology section.

New members

ESACT would like to welcome the following new members;

Hagit Amitai (Compugen, Israel); Louise Barnes (University of Manchester, UK); Rene Brecht (ProBioGen AG, Germany); Geraldine Buhrkohl (Xenova Research Ltd., UK); Steven Chamow (Abgenix Inc., USA); Myung-Sam Cho (Bayer Biotechnology, USA); Damian Fletcher (Unipath Ltd., UK); Elke Fressler (Rentschler Biotechnologie GmbH, Germany); Jacques Gerard (GlaxoSmithKline Bio, Belgium); Fiona Godsman (Q-One Biotech Ltd., UK); Jens Jacob Hansen (Novo Nordisk A/S, Denmark);David Jones (Crucell, The Netherlands);Stephan Kalway (Lonza Biologics, UK); Uwe Koenig (Beckman Coulter GmbH, Germany); Olga Khochtchenko (Russian Academy of Medical Sciences); Guy de Martynoff (BioProtein Technologies SA, France); Petra Meissner (Micromet AG, Germany); Nic Mermod (University of Lausanne, Switzerland); Fred Meuwly (Laboratoires Serono, Switzerland); Alexander Nagel (ProBioGen AG, Germany);Dirk-Jan Opselten (Crucell Holland BV, The Netherlands); Kurt Russ (Rentschler Biotechnologie GmbH, Germany); Peter Schlenke (Rentschler Biotechnologie GmbH, Germany); Yves-Jacques Schneider (Universite Catholique de Louvain, Belgium); Hilary Van Valkenburgh (GlaxoSmithKline, USA).

ESACT Secretariat

A reminder that 2003 subscription fees are now due 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 Euros (= £13)

Please remember when paying by credit card to include the **security number** (3 digit on the reverse on the card usually on signature strip; 4 digits for Amex) and **post/zip code** of billing address. **Bryan Griffiths**

Please note the ESACT OFFICE email address is **esact@griff.evesham.net.** Also, as courier services etc. do not recognise PO Box addresses the following ESACT Office address should be used **PO BOX 1723, 5 Bourne Gardens, Porton, Salisbury, Wilts., SP4 0PL, UK**

ESACT INFORMATION

COMMITTEE MEMBERS

Chairman: Otto-Wilhelm MERTEN
Généthon III
Gene Therapy Programme
1 rue de l'Internationale, BP 60
F-91002 Evry Cedex 2
France
Tel: (+33) 1 6947 259
Fax: (+33)1 6947 2838
omerten@genethon.fr

Secretary: Alain BERNARD
Serono Biotech Center
Route de FENIL Z1B
1804 CORSIER-sur-VEVEY
Switzerland
Tel.: (+41) 21 923 23 57
Fax: (+41) 21 923 20 13
Alain.Bernard@Serono.com

Treasurer: Martin FUSSENEGGER
ETH Honnerberg
HPT
CH8093 Zurich
Switzerland
Tel.: (+41) 1633 3448
Fax: (+41) 1633 1051
fussenegger@biotech.biol.ethz.ch

Meeting Secretary: Rodney SMITH
CTM BioTech
England, UK
0(44)1223-496070
rodney.smith@ctmbiotech.co.uk

Committee Members:

Francesc GODIA
Universitat Autonoma de Barcelona,
Dept. d'Enginyeria Quimica,
Edifici C,
E-08193 Bellaterra (Barcelona)
Spain
Tel: (+34) 93 5812692
Fax: (+34) 93 5812013
francesc.godia@uab.es

Stefanos GRAMMATIKOS
Boehringer Ingleheim Pharm.
84 397 Biberach an der Riss
Germany
Tel.: (+49) 7351 544022
Fax: (+49) 7351 844022
stefanos.grammatikos@bc.boehringer-ingelheim.com

Hansjorg HAUSER
GBF
Masheroder weg 1
D-38124 Braunschweig
Germany
Tel: (+49) 531 6181250
Fax: (+49) 531 6181262
hha@gbf.de

Committee Members continued:

Florian WURM
EPFL,
Dept. de Chimie,
Centre de Biotechnologie,
CH-1015 Lausanne
Switzerland
Tel: (+41) 21 693 6141
Fax: (+41) 21 693 6140
Florian.Wurm@epfl.ch

ESACT Office: Bryan GRIFFITHS
PO Box 1723
5 Bourne Gardens
Porton, Salisbury
Wilts SP4 0PL, UK
Tel.: (+44) 1 980 610 405
Fax: (+44) 1 980 610 405
esact@griff.evesham.net

Web Site Manager Christophe LOSBERGER
Serono Pharmaceutical
Research Institute
14 Chemin des Aulx
CH-1228 Plan-des-Ouates
Geneva, Switzerland
Tel: (+41) 22 70 69637
Fax: (+41) 22 79 46965
christophe.losberger@serono.com

Newsletter Editor: Steve OH
Fax: +65 67754933
btcohs@btc.a-star.edu.sg

Newsletter Co-Editor: Merlin H GOLDMAN
Tel: +44 (0)131 472 4704
merlin@magnetical.com

Membership Subscriptions
We propose the following alternative payment methods:

Master, Visa, Access, Delta Eurocard, Amex or
1. 20 Euro per year paid by cheque drawn on a UK bank*.
2. USD 25.00 per year if drawn on any other bank*.

Note:
We recommend you consider payment of more than one year's subscription at a time so as to minimise local bank charges to your account.

Newsletter Correspondence/Contributions:
Correspondence for publication in the ESACT Newsletter, meeting reports and comments should be sent direct to the Newsletter Editor.

PLEASE NOTIFY THE ESACT OFFICE OF ANY ADDRESS CHANGES/TEL/FAX/email etc.