

# International peer review of LACDR research program: Strategic Choices Got Peer Support

**Q**uality control in Pharmaceutical Research is the rule: Good Manufacturing Practice, Good Laboratory Practice and Good Clinical Practice are nowadays-standard procedures. It is in line with these concepts that also the academic research quality is checked regularly. The LACDR has done so in the past once every 5 years by a quite extensive peer review approach. The results of these peer reviews have in the past been very helpful in the implementation of some important strategic decisions.

In February 2003 the research program of the LACDR has again been reviewed by external peers. It was the first time that this peer review was not organised by the Center itself: since last year it has become a formal requirement in the Dutch academic system. There are some rumours that this new nation-wide system was copied from the previous "privately-organised" LACDR peer reviews.

In any case, from 16 till 19 February 2003 a committee of 5 internationally renowned peers (see Box) travelled to Leiden and Amsterdam after reading the extensive documentation of the LACDR groups, describing the results of the past 6 years, as well as the plans for the 2003-2007 period. The visit took 3 days and included discussions with all the individual divisions on their past performance and their plans for the next 5 year period. The site visit by the peers was intensive

## Some quotes from the report of the 2003 LACDR Peer Review

The mission of LACDR is to be one of the leading centres in the world in learning, teaching and advancing innovative drug research. The Committee considers that this is an appropriate mission and has found that the Center and its research programmes clearly adhere to it. In view of its current position, the mission is not so much to become but to remain one of the leading centres.

The resources available to the Center are more than adequate, primarily as a result of the large amount of external financial support the staff manages to acquire and the many funding initiatives that they are involved in. The quality and extent of the laboratory and research facilities range from good to very impressive.

With almost all groups being opinion leaders in their fields, the Center has an excellent academic reputation. This is further evidenced by the large support from the Dutch organisation for scientific research, the European Union and various charities. With its many contributions to advancing drug discovery and development, the societal relevance of LACDR is very high. This is exemplified by the many collaborative projects with pharmaceutical industry and the success of the spin-off companies that were established on the basis of innovative academic research. All this results manifests in the remarkable fact that over 50% of LACDR's research and teaching budget is externally funded.

...we consider LACDR to be a very good and on many counts an excellent institute.

and inspiring for both the peers and the LACDR staff. In May 2003 the peer review committee reported to the board of the Universities on their findings.

In general, the peers were impressed by the scientific quality of

the various divisions and the committee considers the LACDR as one of the world's leading centers in the area of the pharmaceutical sciences. This is well indicated by the comments of the peers on the LACDR mission statement. The mission of

the LACDR is to be one of the leading centers in the world in learning, teaching and advancing innovative drug research. The peer review committee states in its report that "this is an appropriate mission and that it has found that the Center and its research programmes clearly adhere to it. In view of its current position, the mission is not so much to become but to remain one of the leading centers".

In the plans for the future several suggestions were made, which, with the peer review committee's support, will lead to implementation in the course of 2004 and 2005. Thus for the Leiden groups, the peer review committee strongly supported proposals to appoint new professors in Drug Delivery Technology, Analytical Biosciences and Toxicology. For the Amsterdam groups, the peers suggested additional funding for the appointment of additional assistant and associate professors. Moreover, the strongly recommended, increased university budgets for investment in equipment will make sure that the general infrastructure of the LACDR can be kept up-to-date at both sites. One area in which major innovative investments will be made is in Pharmacology/toxicogenomics (see elsewhere in the newsletter). Given these results and the innovative plans of the divisions, as well as the very positive response of the peer review committee to them, the LACDR faces the next 5-year period with a lot of confidence.

## People Awards Prizes



**Dr. Miranda van Eck**, PhD at the division of Biopharmaceutics, received the International HDL Research Award (\$220,000). Pfizer Inc. founded the International HDL Research Awards Program in 2001 to support outstanding investigators in the field of high-density lipoprotein (HDL) biology in relation to atherosclerotic disease. In 2001, Miranda already received the first cycle of funding of this Program, which is now continued, by the second cycle.

The title of her project is "Role of ABC transporters and Scavenger Receptor BI in Reverse Cholesterol Transport and Atherosclerosis".

A low level of HDL cholesterol is an important risk factor for the development of atherosclerosis. A mechanism by which HDL exerts its anti-atherogenic properties is reverse transport of cholesterol from macrophages of the arterial wall to the liver. Key regulators in HDL metabolism both in liver and macrophages are ATP-binding cassette (ABC) transporters and scavenger receptor BI (SR-BI). The award enables Miranda to investigate the potential synergistic roles of these ABC transporters and SR-BI in reverse cholesterol transport and atherosclerosis by using bone marrow transplantation and liver cell transplantation to modify the expression of these genes in macrophages and liver.



The Council of the Potchefstroom University for Christian Higher Education, South Africa, has awarded Prof. dr. Hans Junginger a honorary doctorate in pharmacy. The formal award took place on the occasion of the University's Spring graduation ceremony on 18 September 2003.



STW has awarded a grant to **Eric Biessen** (Division of Biopharmaceutics). This research project involves a collaboration between the division of Biopharmaceutics and the Department of Bio-organic Chemistry and aims at the development of novel therapeutics to treat cardiovascular disorders via a new multidisciplinary approach of phage display and organic chemistry.

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## Members of the LACDR Peer Review Committee 2003.



From right to left:

**Professor Geoffrey T. Tucker**, Head of Molecular Pharmacology & Pharmacogenetics, Division of Clinical Sciences at the University of Sheffield, UK

**Dr. Thomas A. Baillie**, Vice President of Drug Metabolism at Merck Laboratories in Westpoint, PA, USA

**Professor Jan J. Sixma**, Chairman of the committee. Former full professor of Haematology at the University Hospital of Utrecht, The Netherlands and

former President of the Health Council of the Netherlands

**Professor Sandy T. Florence**, Dean of the School of Pharmacy, University of London, UK

**Professor Philip S. Portoghese**, Former Director of Graduate Studies in Medicinal Chemistry, University of Minnesota, Minneapolis, MN, USA

**Dr Harmen Jousma**, secretary of the committee, Faculty of Mathematics and Natural Sciences, Leiden University

## Hans E. Junginger, 35 years of Pharmaceutical Science

Prof.dr. Hans Junginger will retire from his post as head of the Department of Pharmaceutical Technology of the LACDR in 2004 after 35 years in Pharmaceutical Science. Hans Junginger started his career, after graduation as pharmacist from Maximilians-University of Munich (Germany) in 1969, with his Ph.D. work at Saarland University in Saarbrücken, Germany. At that time, Pharmaceutical Technology as a separate pharmaceutical discipline had not been entirely established yet. Hans Junginger, therefore, decided on a project in Pharmaceutical Chemistry, working on the synthesis and characterisation of barbituric acid derivatives under Prof. J. Knabe. He obtained his Ph.D. in 1971 and, much to the grief of his supervisor, turned to the field of Pharmaceutical Technology for his habilitation thesis at the Technical University of Braunschweig (Germany). Working on the "Production and Characterisation of Spray Dried Products" at the department of Prof. C. Führer, he became a tenured University Docent in 1979 and later an Assistant Professor (1980) at Braunschweig. During that time, he also became interested in the preparation and structural examination of dermal application forms, such as the hydrophilic cream, described in various pharmacopoeia. After an interim professorship at München University in 1980, Hans Junginger was appointed Full Professor and Head of the Department of Pharmaceutical Technology and Dispensing at Leiden University in 1981, which at that time still was a part of Leiden's School of Pharmacy. Being one of the founding fathers of the LACDR, he be-

came the head of the Department of Pharmaceutical Technology in 1984.

During the last 20 years, he, together with the other staff members J.A. Bouwstra, J.C. Verhoef, H.E. Boddé (who passed away in 1996) and G. Borchard, built a visionary research program, which examines the possibility to deliver drugs having such unfavourable properties as high molecular weight, high hydrophilicity, etc., by application routes alternative to parenteral injection. This program included studies by dr. Boddé and dr. Bouwstra, on the biophysical characterisation and modulation of the skin barrier, continuing and far extending research started at Braunschweig University. Different delivery systems, such as non-ionic surfactant systems (niosomes), liposomes and iontophoresis, and in vitro test systems were developed. Since the late 1980's, Hans Junginger's interest turned to the use of polymers, multifunctional in nature, for the delivery of macromolecules via mucosal surfaces. These surfaces included the buccal, the intestinal, and later the pulmonary route of application. The fundamental concept of this research area is the design of non-absorbable polymers, which by interaction with the mucosal surface would increase residence time of the delivery system. At the same time, these polymers would modulate tight intercellular junctions, opening the paracellular pathway for absorption of macromolecular compounds. If possible, these polymers would protect drugs against enzymatic degradation. A lot of studies have shown the validity of the concept, using and modifying an array of polymers. The department at Leiden



University became known for its expertise using acrylic acid derivatives and various chitosans for delivering peptide drugs by the oral route. During the last five years, this was extended to preparing and successfully testing chitosan microparticles for mucosal vaccine delivery, and non-viral gene and DNA vaccine delivery by chitosan nanoparticles. This work was made possible by the staff of the department, more than 30 graduate students, over 20 post-docs and visiting scientists that were attracted to Leiden and the LACDR. It resulted in more than 250 publications in peer-reviewed journals and over 20 book chapters. As a renowned scientist and opinion leader within Pharmaceutical Sciences, Hans Junginger held numerous positions in scientific organisations, and (co) organised numerous international scientific conferences. He was given two honorary doctorates from the University of Gent (Belgium) in 1995 and Potchefstroom University (South Africa) in 2003 for his achievements. After his retirement in 2004, he is sure to stay faithful to Pharmaceutical Sciences as an "apprentice" at Philipps-Apotheke in Marburg, and as visiting professor at the Naresuan University of Phitsanulok, Thailand.

G. Borchard

## Dr Joke Bouwstra got a personal professorship in Drug Delivery Technology

Prof Dr Joke Bouwstra is responsible for the (drug transport related) skin research at the LACDR. She received her M.Sc degree in Chemistry (cum laude, 1980) at the University of Utrecht, where she also received her PhD (1985) on the subject "Thermodynamic and structural investigations of binary mixtures". After this rather physical-chemical oriented research, she became interested in the more applied field and was appointed as assistant professor at the Centre for Bio-Pharmaceutical Sciences of the LACDR. A few years later she started in the field of (trans)dermal drug delivery. The attractiveness of this research field is that it is possible to perform fundamental research, which is still very close to the application. In 1997 she became associate professor. She published more than 170 papers and book chapters in the area of drug delivery and is the inventor of three patents. She is a member of the advisory boards of Journal of Liposome Research, Pharmaceutical Research, STP-Pharma and International Journal of Pharmaceutics and an associate editor of the Journal of Investigative Dermatology. In 1996 she received the Young Investigators Award from the Controlled Release Society. In 2003 she was co-chair of the Gordon Research Conference "Barrier Function of Mammalian Skin".



fraction (Synchrotron facilities in Daresbury and Grenoble) she was able to gain detailed information on isolated stratum corneum sheets. The successful isolation of individual skin lipids followed by preparation of mixtures with systematically varying lipid composition made it possible to fully reconstruct the skin lipid structure in vitro. With this approach it was possible to unravel the role of the individual ceramides, free fatty acids, cholesterol, cholesterol sulfate and environmental parameters such as water, pH, calcium and temperature play in skin lipid organisation.

In the nineties in Leiden various electron microscopic and biophysical methods have been optimised to obtain detailed information about the ultrastructure and lipid organisation in the skin. With these techniques, which include freeze fracture electron microscopy, transmission electron microscopy, Fourier transform infrared spectroscopy, cryo-scanning electron microscopy and electron diffraction technique it is possible to study the skin ultra-

structure in man ex vivo using very small samples collected non-invasively. In addition confocal laser scanning microscopy was explored for on-line visualisation of the diffusion process in human scalp skin.

Besides studies on stratum corneum organisation also various novel drug delivery systems for passive delivery have been developed. In the late eighties Professor Joke Bouwstra initiated research on vesicles consisting entirely of surfactants. Studies were performed to examine drug transport and penetration pathways across skin. Vesicle-skin interactions were studied. These studies provided new insights in ultrastructural modulations induced by (elastic) vesicles. During the last 6 years she also started projects focussed electrochemically driven transport (iontophoresis) of several dopamine agonists, peptides and macromolecules. Very recently apomorphine delivery by iontophoresis has been explored in patients with Parkinson's disease. Recently a new series of dopamine agonists varying systematically in molecular architecture have been selected for efficient iontophoretic delivery.

Of course this broad area of research is only possible when having a close collaboration with a number of research groups. In particular the collaboration with Dr M. Ponc (Dermatology), professor M. Danhof (Department of Pharmacology), Dr H. Koerten (Center for Electron Microscopy) and late Dr H.E. Boddé (Department of Pharmaceutical Technology, deceased in 1996) has been of great importance.

## LACDR Fall Symposium

Honoring Prof.dr. H.E. Junginger

Experiments and Experiences

20 – 21 November 2003

Gorlaeus Laboratories, Lecture Hall 1

On November 21, Prof.dr. Hans E. Junginger

will retire as professor of Pharmaceutical Technology.

To Honor Prof. Junginger for his work in the area of Pharmaceutical Technology in Europe and his scientific achievements in the field, the LACDR

fall symposium is entirely dedicated to developments in Pharmaceutical Technology.

When?

The symposium will take place at

20 and 21 November 2003

Where?

The symposium will be held at the Leiden

University,

Gorlaeus Laboratories, Einsteinweg 55, 2333 CC

Leiden

Registration?

The symposium is open to everyone and free of charge (incl. lunch)

Registration is required via e-mail at  
m.ham@lacdr.leidenuniv.nl

## Prof. Wilfried Niessen joins LACDR's Division of Biomolecular Analysis

The Division of Biomolecular Analysis (chair: Prof. Dr. Hubertus Irth) has attracted Prof. Dr. Wilfried Niessen to hold a special professorship in Bioanalytical Mass Spectrometry. Prof. Niessen studied Chemistry at the Vrije Universiteit; in 1986, received his PhD at the University of Amsterdam for a thesis entitled 'Mass spectrometric detection in open tubular liquid chromatography'. From 1986 to 1996, Prof. Niessen was employed as assistant professor at LACDR's Division of Analytical Biosciences (Prof. Jan van der Greef) at Leiden University. In 1996, he established a consulting company, hyphen MassSpec that provides international training and consultancy in the area of bioanalytical mass spectrometry. Prof. Niessen is (co)author of a large number of scientific articles and author of various books and reviews on mass spectrometry.

Prof. Niessen will be involved in ongoing research projects of the Division of Biomolecular Analysis dedicated to the application of mass spectrometry in the characterization of proteins and protein-ligand interactions. His special interest lies in the area of hyphenation, i.e., the coupling of various analytical separation and detection techniques,

and in the use of mass spectrometry for structure elucidation. A major research line of the Division of Biomolecular Analysis focuses on the development of novel analytical technologies that simultaneously measure chemical (concentration, molecular mass, absorption spectra) and biochemical parameters (affinity for receptors, enzymes) of analytes. Mass spectrometry plays a crucial role in the detection and characterization of bioactive ligands. Applications of the novel techniques developed are targeted mainly towards drug discovery and early ADME research. Furthermore, the division is focusing its research activities on the development of multi-dimensional analytical methods for the trace level detection of proteins in biological matrices. Again, mass spectrometry is the most important detection technique employed in this area. Finally, Prof. Niessen will also play an important role in the Division's teaching activities, particularly in its two master programs, Pharmaceutical Sciences (jointly with the Divisions of Molecular Toxicology and Pharmacology) and Analytical Sciences (jointly with Prof. Schoenmaker's analytical research group at the University of Amsterdam).

## Genomics research at LACDR gets a boost

The LACDR currently rapidly expands its research in the Genomics area. In the past few years some LACDR groups, in particular Medical Pharmacology and Biopharmaceutics already applied (pharmaco-)genomics technology and recently published several papers that drew attention of their colleagues in the field (see below). By the end of this year the new Center for Medical Systems Biology (CMSB) will start; this is one of the four national Genomics Centers in the Netherlands and is an initiative of Leiden University, of Leiden University Medical Centre, TNO, University of Rotterdam, Vrije Universiteit Amsterdam and the Vrije Universiteit Medical Center. The CMSB, one of the two medical genomics centers of excellence recognized in 2002 by the Netherlands Genomics Initiative, has received considerable funding from the Dutch government for the start of an exciting research program. The research strategy of the CMSB is built on the premise that the systemic nature of complex diseases will only truly be uncovered if the primary disease process and the systemic response are studied as interacting biological systems. This approach uniquely enables the discovery and validation of common determinants of complex diseases, i.e. hidden biological connectivity between not obviously related diseases. By capitalizing on shared biological factors, it intends to open up multiple opportunities to improve patient care.

The LACDR in Leiden and Amsterdam will participate in this Center; the LACDR expects to make extra investments of some 3-4 Million Euro over that period in Genomics research.

**A new pharmac/toxicogenomics unit at the LACDR**

By the end of this year, the LACDR will have created a Pharmacogenomics/toxicogenomics unit at Leiden University. The CMSB will provide major support in the setting

up of this facility by providing equipment and technical support. The unit will be supervised by dr. Erno Vreugdenhil and several LACDR staff members. A number of graduate students will be involved in new initiatives in the research program. The focus at this moment will be on neurological and cardiovascular diseases and cancer as well as provide a direct link with the already ongoing programs within the divisions of Medical Pharmacology (Gene and brain function), Biopharmaceutics (Cardiovascular genomics) and Toxicology (Cancer predisposition and resistance). The new unit is expected to further boost genomic research within the LACDR in the future. The following projects are currently ongoing:

**Genes and brain function**

The current research programs in the group of Vreugdenhil and de Kloet focus on the validation of genomics strategies in stress hormone research and in collaboration with the Department of Psychiatry, LUMC on biomarkers for major depression in integrated phenotypic and genotype studies. In particular the impact of single nucleotide polymorphisms (SNPs) in stress hormone receptors on the success rate of pharmacotherapy of depressed patients, will be a major focus. Second, manipulation of gene expression of novel stress-responsive genes by classic transgenesis and siRNA technology will be implemented for in vitro and in vivo studies.

**Cardiovascular genomics**

The Genomics programme of the division of Biopharmaceutics (Van Berkel, Kuiper) concerns studies on the identification of gene expression profiles in blood monocytes and vascular lesions to predict the progression of atherosclerosis. Gene expression profiling in the monocytes and macrophages within the atherosclerotic plaque (obtained by laser capture) and the degree of atherosclerosis will be directly linked.

**Genes and brain function**

The group of De Kloet and Vreugdenhil has published several papers in the past few years. For instance, in pioneering research of the Division of Medical Pharmacology serial analysis of gene expression (SAGE) was developed for analysis discrete brain regions (Datson et al Nucleic Acids Res (1999) 27: 1300 - 1307 and adopted for identification of patterns of corticosteroid responsive genes (Datson et al. Hippocampus (2001) 11: 430-444 and Eur J Neurosci (2001) 14:1-17). Moreover, using SAGE and GeneChips potential molecular targets for treatment of stress-related brain disorders were identified in a genetically selected animal model. The latter research papers are compiled in the thesis of dr Dorine Feldker, entitled: "Towards the molecular basis of individual differences in vulnerability to stress: application of large scale gene expression profiling", which she has defended September 4 at the University of Leiden.

## Professor Jan-Åke Gustafsson Marius Tausk visiting Professor 2003

Professor Jan-Åke Gustafsson, Professor of Medical Nutrition and Director of the Center of Biotechnology, Karolinska Institute, Stockholm, was appointed to the "Marius Tausk Chair 2003" at Leiden University. N.V. Organon and the Netherlands Endocrine Society established the Marius Tausk Chair, accommodated at LACDR, at the Leiden University Medical Center (LUMC). From 1926-1967, Professor Tausk has been, as Organon Director, a strong driving force to the growth and success of Organon. He also was professor of Endocrinology in Utrecht and he has

written a number of authoritative books. In honour of Marius Tausk each year the Chair is designated to a scientist who has made an extraordinary contribution to research in the area of endocrinology.

Professor Jan-Åke Gustafsson has made hallmark contributions to molecular endocrinology. These contributions focus on molecular mechanisms of nuclear receptor actions including a classical paper on the discovery of the oestrogen b-receptor and pioneering research in nuclear co-activators and co-repressors. His recent Yin - Yang concept of opposing oestrogen receptor a- vs b-mediated

## Atherosclerosis and anti-oxidative enzyme expression

Recently, dr Twisk of the division of Biopharmaceutics applied the first generation Affymetrix microarray chips and analysed the expression of genes in the arterial wall during atherosclerotic lesion formation. As initial studies indicated major changes in the expression of enzymes involved in antioxidant defence and production of reactive oxygen species, Drs 't Hoen and Twisk subsequently quantified the mRNA expression of 16 antioxidant enzymes by real time PCR ('t Hoen, Van der Lans, Van Eck, Bijsterbosch, Van Berkel and Twisk, Circulation Research 93(2003): 262-269). Contrary to expectation, all major antioxidant enzymes showed a significant up regulation before atherosclerotic lesion formation, reaching a peak roughly coinciding with the onset of intimal thickening, but were markedly down regulated thereafter. These findings were considered remarkable in the Editorial entitled "United They Go" (Circulation Research 93(2003): 183-185) which accompanied the paper. First, the data indicate that many antioxidant enzymes are conjunctly regulated; this suggests that common responsive elements, or at least synchronous responses to different receptor or transcription factor signals, must govern the expression of these enzymes. Second, results suggest that antioxidant enzymes respond to hypercholesterolemia with a pronounced initial upregulation, which may constitute a defensive mechanism, whereas the antioxidant defences weaken significantly once atherosclerosis becomes more extensive, which may even accelerate atherosclerosis.

Subsequently expression profiles observed in monocytes collected from well-defined patient groups will be linked to the animal data possibly leading to the identification of predictive gene profiles for the manifestation of heart attacks.

**Cancer predisposition and resistance**

The theme of the program within the division of Toxicology (van de Water) is Cancer predisposition and resistance to chemotherapy, which will be performed in close collaboration with the Departments of Surgery, Pathology and Toxicology of the LUMC. It is well established that the development of cancer is driven by the accumulation of mutations in cell growth controlling genes. There is a strong correlation between inherited defects in genes encoding the DNA damage response pathways and cancer susceptibility. Defects in such genes likely also affect the response of tumor cells to therapy and (hyper)sensitivity reactions in normal cells. The incorporation of genomic and proteomics technologies into this research line will improve our insight into the relationship between loss of genome stability, cancer development, genetic predisposition and responses to anticancer therapy.

**G protein coupled receptors: signalling networks and polymorphic variance.**

G-protein coupled receptors and their ligands are the major research themes of the divisions of Medicinal Chemistry. Despite the fact that these proteins are the most favorite target in current drug discovery relatively little is known about their signaling networks. Using microarray analysis the division of Medicinal Chemistry (Leurs and Smit) is currently establishing the signaling networks of G protein coupled receptors encoded by the human cytomegalovirus. Moreover, the division has a strong interest in the characterization of known polymorphic

variants of a variety of receptor subtypes. One of the Leiden division's aims with respect to the latter is the development of a dedicated database for single nucleotide polymorphisms (SNPs) of G protein-coupled receptors (Ijzerman, Kazius). This effort is sponsored by a new Dutch initiative, the NWO BioMolecular Informatics program. In it the division collaborates with the Nijmegen CMBI and the Leiden LIACS.

**Mass Spectrometry as important tool**

Highly sophisticated technology is a prerequisite for cutting edge research in the genomics arena. Fortunately, the LACDR has 2 strong divisions with relevant expertise. The division of Analytical Biosciences (De Greef Tjaden) is a key player for the instrumental analysis focused on fingerprinting the proteome en metabolome searching for novel biomarkers related to disease etiology or to drug response. This program is stimulated by a CMSB grant to buy a 2D-linear Ion Trap Fourier Transform Mass Spectrometer (LTQ-FTMS), which yields ultra high resolution in LCMS approaches enabling not only high resolution in profiling but especially also the identification power of low concentration biomarkers present in body fluids and tissues. The first test experiments performed earlier this year have been presented at the International Mass Spectrometry Society meeting (IMSC) in Edinburgh in September 1-6, 2003.

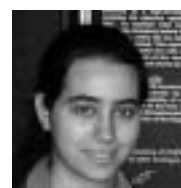
The division of Bioanalytical Chemistry (Irth et al) has also recently been investing a lot in state-of-the-art mass spectrometry equipment, as has also been acknowledged by the recent peer review committee. In order to keep up with the continuing developments and required investments the division will join forces with groups within the faculty of Earth and Life Sciences in order create a Proteomics Center in Amsterdam.



exploring the potential of cortisol antagonists as novel antidepressant drugs. One of the highlights of Gustafsson's stay will be the workshop and master class, on the topic "Molecular mechanisms of steroid action" to be held January 12 and 13, 2004 in the castle 'Oud-Poelgeest' in Oegstgeest (near Leiden). Other highlights such as the Marius Tausk lecture at the annual Endo-Neuro-Psycho meeting in Doorwerth on 2 June 2003, entitled "New paradigms in oestrogen action" underscored the success of having professor Gustafsson as Marius Tausk Visiting Professor 2003.

During his stay in Leiden professor Gustafsson is involved in the research on 'stress in the brain' of his host, professor Ron de Kloet (LACDR, Division of Medical Pharmacology),

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Laila el Jarari, student biopharmaceutical sciences and intern at the division of biopharmaceutics has won the KNCV poster-competition with her poster entitled: 'Application of the Scavenger Receptor-BI for the Selective delivery of Drugs' on March 2003.



Paola Casarosa, (Division of Medicinal Chemistry (A)) was awarded the Seroen Ian Clark-Lewis Memorial Award for the best short oral communication at the Keystone meeting on Chemokines and Chemokine receptors in Breckenridge, USA (January 7-12, 2003). She also has won the national graduate student competition of the Dutch Society for Pharmaceutical Sciences (NVFW) with her presentation entitled: "Identification of the first non-peptidic inverse agonist for a constitutively active viral-encoded G-protein coupled receptor", held on May 23 in Utrecht, The Netherlands



Remko Bakker (Division of Medicinal Chemistry A) won the Young Investigator's award for his oral presentation on "Cloning and functional characterization of new H3 receptor isoforms" at the XXXIth Annual Meeting of the European Research Society held in Noordwijkerhout in May 2003



Tim Schenk (Division of Analytical Biosciences) received the 2002 AAPS outstanding Manuscript Award in Analysis and Pharmaceutical Quality. This award recognises exemplary research published in the journal of Pharmaceutical and Biomedical Analysis (JPBA).



During the FIGON Themadag van en voor labmedewerkers' held on June 10th in Leiden, two technicians from Leiden got awards.

Gert Gooris (Division of Pharmaceutical Technology) got the Award of Technical Excellence because of his great performance during his (long) career at the division of Drug Delivery Technology.

Paula de Vos (Division of Biopharmaceutics) got the poster prize for her presentation "The protective role of interleukin-9 in atherosclerosis".



Guido Dees, Division of Medicinal Chemistry won a prize for his poster on "Homodimerization of the human H1-receptor" on the XXXIth Annual Meeting of the European Research Society held in Noordwijkerhout 7-11 May 2003.

# ULLA Summer School 2003



Summer has arrived, School's out! Remember the "good old days" back at high school, where a period of hard work and study was rewarded with the official exemption from all learning activities for many weeks. However, moving along our academic career, the association between summer and holidays became more and more disturbed. As a (more or less) sovereign scientist, voluntarily seeking for the torture of scientific puzzles, we are forced to fit our holidays in our experimental agenda. Lao-Tzu (604-531 B.C), the famous Chinese philosopher, already noticed, "A scholar who cherishes the love of comfort is not fit to be deemed a scholar", while he also stated "Abandon learning and there will be no sorrow". The ULLA consortium chose to break with this paternalistic paradigm, this "trade off" between comfort and learning and started organising a Summer (holiday) school for PhD students in Pharmaceutical sciences.

In July this year the 6th ULLA Summer School took place in Paris at the Faculté de Pharmacie of the Université de Paris Sud. About 130 PhD students of Schools of Pharmacy in Uppsala (Sweden), London (London University), Leiden (Center for Bio-Pharmaceutical Sciences), Amsterdam (Dept of Pharmacology, Vrije Universiteit), Paris (Université Paris Sud) and Copenhagen (Royal Danish School of Pharmacy) met at the Cité Internationale Universitaire de Paris, a small, miniature city with 35 guesthouses used as residences for foreign students. Drinks were organised to give all PhD students in Pharmaceutical Sciences an opportunity to get in touch with colleagues from other countries before starting their 7 days (in total 37 courses in e.g. PK/PD modeling, pulmonary drug delivery, bioinformatics, steroid action in the brain, scientific writing and presentation) of lectures. On Saturdays, a small



symposium with poster session was organized. Professor Dominique Duchêne, president of the EUFEPS showed how this organisation can (financially) stimulate pharmaceutical science and scientists. Dr. Yves Dumas, head of regulatory Liaison Europe of Aventis Pharma, offered a nice set of tips with respect to job interviews for obtaining a position in the (pharmaceutical) industry and Professor Trevor Jones, director general of the Association of the British Pharmaceutical Industry showed the state of the art of late 21st pharmaceutical science. During the poster session, the ULLA students got the opportunity to present and/or discuss their own work and scientific data of their colleagues.

Thinking of the correlation between summer and holiday, the

ULLA consortium planned some time off to get to know your fellow PhD students in a non-scientific environment. The ULLA organisation offered all students the unique possibility to watch Paris's beauty from the river itself by organising a Seine diner cruise on the Bel Ami. On Sundays, the Faculté de Pharmacie of the Université de Paris Sud arranged two walks in St. Germain des Pres quarter and Montmartre village respectively and distributed a few museum cards amongst the students.

As they say, "all that ends ends well". After two weeks of 'Study and Science' and 'Leisure and Laughter' in Paris all PhD students were invited to a farewell reception at the Faculté de Pharmacie to say goodbye and share some last moments together in Paris.

Chris de Graaf, Marjo de Graauw



Graduate students at the Cité Internationale

## Awards for former Director of Research Prof. Henk Timmerman

### Ariens Award of the Dutch Pharmacological Society

On February 13, 2003, Professor Henk Timmerman received the prestigious Ariens Award at the Annual meeting of the Dutch Pharmacological Society after his lecture entitled "Histaminic receptors, tools and targets both". The Ariens Award is presented each year and is sponsored by Yamanouchi Europe.

### Honorary member of the Royal Netherlands Society of Chemistry

During the festivities for the centennial of the Royal Netherlands Society of Chemistry, on April 15, 2003, prof. Timmerman became honorary member of the Society for his important contributions to the field of chemistry and his work for the Society. Timmerman has amongst other been chairman of the Society for some years.

### Honorary doctorate University Gadjah Mada in Yogyakarta, Indonesia

On September 3, 2003 the University Gadjah Mada in Yogyakarta, Indonesia awarded prof. Timmerman an honorary doctorate to acknowledge his contributions to the field of Medicinal Chemistry. In the eighties of 20th century Timmerman started an intensive collaboration between the Fakultas Farmasi of Gadjah Mada University and the Amsterdam branch of the LACDR. In those days there was hardly any tradition in modern drug research in Indonesia and this initiative aimed to create a national center of excellence in Yogyakarta. With help of many Dutch teachers a 'Mid Career Training in Pharmacology' was organized twice a year in Indonesia, which attracted a lot of Indonesian scientists. One of the first participants of the course, Dr. Umar Jenie, in fact acted as promotor on September, 3.



## Dr. Iwan de Esch as new Assistant Prof in Medicinal Chemistry



Since June 1, Dr. Iwan de Esch (33) has started as new assistant professor in the division of Medicinal Chemistry in Amsterdam.

De Esch has studied Organic Chemistry in Nijmegen and obtained a Ph.D. degree in Medicinal Chemistry at the Vrije Universiteit. He worked for several years as postdoc in Cambridge in the area of Computational Chemistry, whereafter he was involved in the start-up of De Novo Pharmaceuticals. In Amsterdam Dr. De Esch will have the opportunity to invest in new equipment for parallel chemistry and purification and will also try to introduce microwave-chemistry in the research program.

## Just Started

### Barbara Lussenburg

From 15 October 2002 onwards at the division of Molecular Toxicology  
Promoter: Prof.dr. N.P.E. Vermeulen  
Project: Combinatorial biochemistry: Random mutagenesis of Cytochromes P450 as a bio-catalysis tool for the generation of new lead compounds.

### Jane van Heteren

From 1 October 2002 onwards at the division of Medicinal Chemistry (Amsterdam)  
Promoter: Prof.dr. R. Leurs  
Project: Ligand-receptor interactions for chemokine receptors

### Maaïke Alderlieste

From 1 November 2002 onwards at the division of Toxicology  
Promoter: Prof.dr. G.J. Mulder  
Project: Focal adhesion kinase signaling in acute renal failure

### Joke in 't Veen

From 1 January 2003 onwards at the di-

vision of Pharmaceutical Technology  
Promoter: Prof.dr. F.W.H.M. Merkus.  
Project: Nasal Drug Delivery

### Barbara Piket

From 1 January 2003 onwards at the division of Biopharmaceutics  
Promoter: Prof.dr. Th.J.C. van Berkel.  
Project: P53-induced destabilisation and rupture of atherosclerotic lesions: mechanisms and therapeutic implications

### Vera Brinks

From 1 February 2003 onwards at the division of Medical Pharmacology  
Promoter: Prof.dr. E.R.de Kloet  
Project: Stress hormone effects on cognitive performance: an integrated behavioural and electrophysiological analysis (NWO)

### Jeroen Kazius

From 1 March 2003 onwards at the Division of Medicinal Chemistry (Leiden)  
Promoter: Prof.dr. A.P. IJzerman

Project: G-protein-coupled receptors: from sequence to function".

### Willem Engel

From 1 April onwards at the division of Analytical Biosciences  
Promoter: Prof.dr. J. van der Greef  
Project: Single cell analysis coupled to the MS

### Sylvia Le Dévédéc

From 16 June 2003 onwards at the Division of Toxicology  
Promoter: Prof.dr. G.J. Mulder  
Project: Visualization of Protein-Protein Interactions at the Cell-Matrix Interface During Migration and Invasion in Living Tumor Cells (BioScience Initiative)

### Micaela Damsten

From 1 August 2003 onwards at the Division of Molecular Toxicology  
Promoter: Nico P.E. Vermeulen  
Project: Novel screening tools for reactive intermediates

## PhD Theses

### PhD-Theses completed since October 2002

#### Chantal Appeldoorn,

Division of Biopharmaceutics  
Promoter: Prof.dr. Th.J.C. van Berkel  
Generation of P-selectin inhibitors for anti-atherothrombotic therapy

#### Tjerk J.H. Bueters,

Division of Pharmacology  
Promoter: Prof.dr. M. Danhof  
Treatment of organophosphate poisoning with adenosine A1 receptor agonists

#### Danny A. van Elswijk,

Division of Analytical Biosciences  
Promoters: Professor Jan van den Greef and Professor Hubertus Irth  
Detection of bioactive molecules in complex mixtures using on-line liquid chromatography biochemical detection coupled to mass spectrometry

#### Richard.A. Faaij,

Centre for Human Drug Research  
Promoter: Prof.dr. A.F. Cohen, Centre for Human Drug Research  
The clinical pharmacology of novel antithrombotic compounds

#### Dorine E.M. Feldker,

Division of Medical Pharmacology  
Promoter: Prof.dr. E.R. de Kloet  
Towards the molecular basis of individual differences in vulnerability to stress.

#### Bogdan I. Florea,

Division of Pharmaceutical Technology

Promoter: Professor H.E. Junginger  
Polymeric Carriers for Drug and Gene Delivery to the Airway Epithelium

#### Harm Gijsman,

Centre for Human Drug Research  
Promoters: Prof.dr. A.F. Cohen and prof.dr.G.M.J. van Kempen  
Pharmacological aspects of challenge tests of the serotonergic system of the brain

#### Merei Huigsloot,

Division of Toxicology,  
Promoter: G.J. Mulder  
Molecular mechanism of anticancer drug-induced apoptosis in breast cancer (MTLn3) cells

#### Ingrid Kamerling,

Centre for Human Drug Research  
Promoter: Prof.dr. A.F. Cohen.  
Clinical target validation for a non-peptide motilin receptor antagonist

#### Michiel Kemme,

Centre for Human Drug Research  
Promoter: Prof.dr. A.F. Cohen  
Endothelial function determined from systemic plasma concentrations: release of tissue factor pathway inhibitor and binding of tissue plasminogen activator.

#### Gailing Li,

Division of Pharmaceutical Technology  
Promoter(s): Prof.dr. H.E. Junginger and Prof.dr. M. Danhof.  
Transdermal Iontophoretic Delivery of

R-apomorphine for the treatment of patients with Parkinsons' Disease

#### Ingrid Michon,

Division of Biopharmaceutics  
Promoter: Prof.dr. Th.J.C. van Berkel  
Targeting and modulation of vascular smooth muscle cells

#### Tom Molenaar,

Division of Biopharmaceutics  
Promoter: Prof.dr. Th.J.C. van Berkel  
P-selectin: Development of antagonists and their application in mechanistic and therapeutic studies

#### Martijn Rooseboom,

Division of Molecular Toxicology  
Promoter: Prof.dr. N.P.J. Vermeulen  
Novel organoselenium prodrugs

#### Sabine van Rossenberg,

Division of Biopharmaceutics  
Promoter: Prof.dr. Th. J.C. van Berkel  
Nonviral Gene Therapy: Overcoming Extra- and Intracellular Barriers

#### Alexa Veenema (Groningen University)

Promoter(s): Prof.dr. J.M. Koolhaas and Prof.dr. E.R. de Kloet.  
Coping Style & Stressor Susceptibility. Neuroendocrine and neurochemical studies with genetically selected mouse lines.

#### Jurjen Velthuis,

Division of Toxicology  
Promoter: Prof.dr. G.J. Mulder  
Natural killer cell induced apoptosis

#### Jennifer Venhorst,

Division of Molecular Toxicology,  
Promoter: Prof.dr. N.P.J. Vermeulen  
High-Throughput Screening and Molecular Modeling of Biotransformation Enzymes

#### Sandra A.G. Visser,

Division of Pharmacology  
Promoter(s): Prof.dr. M.Danhof and Prof.dr. B. Pelletier.  
Mechanism-Based pharmacokinetic-pharmacodynamic modeling GABA A Receptor Response In vivo

#### Saco de Visser,

Centre for Human Drug Research  
Promoter: Professor A.F. Cohen  
A question based approach to drug development

## Courses and Symposia

LACDR is an active organiser of Courses and Symposia on topics that represent the specific expertise available within the Center.

### Information

For information on future events:  
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