NucSys Newsletter,

Issue No. 5. – The Asymptotic Recursion

April 2008

'Asymptotic recursion' was a phrase used in the final NucSys grant application. Carsten and I were collating the comments of many people, and this phrase appeared in a description of the modelling training. I can't exactly remember who suggested this but pretty sure his initials are HW.

At the time I thought that sounds great, without too precise an idea what it meant; I think that's called Grantsmanship.

As time has gone on I have come back to this phrase because I think it's at the heart of what we're trying to do.

First some definitions, from Wikipedia;

Asymptotic theory; '….. a formal series of functions which has the property that truncating the series after a finite number of terms provides an approximation to a given function as the argument of the function tends towards a particular, often infinite, point'.

Recursion; '….. a method of defining functions in which the function being defined is applied within its own definition. In plain English the directions on a shampoo bottle: 1. Lather, 2. Rinse, 3. Repeat'.

This process of **asymptotic recursion** is occurring at many levels in our network. Scientifically, in the NucSys network, this means the process of iteration between wet and dry lab experimentation as we develop models, test them, and input new experimentally-derived values and insight into generate the next generation of models. With each recursive round of modelling and experimentation the outputs approximate ever closer to a precise representation of reality. This is essentially washing our hair moving ever closer to clean hair.

The same process is also occurring in terms of interactions between the teams of different disciplines. We have had an ongoing dialogue between the different teams that goes back several years. The first iteration was the recognition that the nuclear receptors acted as interactive network, and that the phenotypic consequences of their actions could not be explained by a reductionist interpretation of their actions. Rather, modelling approaches that explained receptor behaviour collectively and in process terms would most likely generate the greatest insight.

This dialogue has passed through several iterations with the PIs, and now the ESRs adding their voices. Over the last few network meetings the iterations of this process have occurred more frequently and precisely. We have moved from recognizing the need to apply systems biology tools, to understanding, a little, of each other's disciplines and needs.

Through email over the last six weeks this process has developed more momentum and detail. The ESRs at VU have made significant progress to develop a number of important models of nuclear receptor function. **Alexey Kolodkin** (VU) has focused on the topic of nucleo-cytoplasmic shuttling and receptor signalling. This model will be tested and validated in co-operation the teams at SUR and OUL. Similarly **Katja Rybakova** (VU) is developing a model of PPAR-induced transcription initiation of gene expression using biological data from **Tatjana Degenhardt** (KUO).

To drive this process forward further **Frank Bruggeman** (VU) and I will be seeking and compiling model requirement summaries for each team as a prelude to deciding upon further modelling priorities at the Berlin meeting in June.

In this way our network is undertaking a process of asymptotic recursion towards model development!

MJC April 2008

PI Network News

Meeting Report

Eighth International Conference on Systems Biology, Long Beach, October 2007. http://www.icsb-2007.org/index.html

Carsten and I, and approximately 800 other scientists, attended this highly diverse conference last autumn to consider *in silico*, *in vitro* and *in vivo* issues in model prokaryotes and eukaryotes, and including human cell systems.

On day 1 **Clarie Tomlin** (http://www.eecs.berkeley.edu/~tomlin/) illustrated the concept of the asymptotic recursion very powerfully with her work on planar cell polarity in the development of the drosophila wing. The impetus for the work was to overcome the limitation of intuitive interpretation of complex data sets, which can easily lead to the wrong interpretation.

The biological challenge within this system is to define the mechanisms that allow cells to assess their position in the developing wing and asymmetrically develop cilia. Many of the important signalling molecules were established from traditional molecular approaches and included for example, Dsh and Fz. Her group considered how the polarity may arise from either global signals or local inputs. They established a model and then drew feedback from the research community (apparently some of it quite robust!), and re-fined the model to three different levels of sophistication. A discrete model in which components were static; a hybrid model with the same components but the relationships expressed in differential equations; and a continuous model which also accounted for diffusion of molecules.

Such modelling also revealed the limitations of experimental approaches where a static output as an endpoint does not capture the dynamic nature of the system. Importantly further refinement of the model generated an algorithm with lead to non-intuitive predictions about the regulation of the systems and allowed for novel biological findings[1]

This theme, of asymptotic recursive modelling was developed by many other workers and permeated the session on Network Structure and regulation that, of course, was highly relevant to the modelling goals of NucSys.

[1] K. Amonlirdviman, N. A. Khare, D. R. P. Tree, W.-S. Chen, J. D. Axelrod, and C. J. Tomlin, Mathematical Modeling of Planar Cell Polarity to Understand Domineering Nonautonomy. Science 307 5708:423-426, 21 Jan 2005.

Several workers, such as **Jonathon Weissman** (http://weissmanlab.ucsf.edu/) introduced the concept of biology without bias. And dissected signaling processes in yeast with large scale siRNA approaches combined with micro-array and phenotype data to generate an epistatic mini array profile (E-MAP), which can allocate new functions to known genes, uncover the roles of previously uncharacterized proteins, and define how biochemical pathways and proteins interact with one another.

Other workers in the same session focussed around modelling mammalian networks such as those controlled by receptor tyrosine kinases. For example, **Ami Citri** from the lab of **Yosef Yarden** http://www.weizmann.ac.il/Biological_Regulation/ presented modeling approaches to the EGFR network and described its classical bow-tie structure, the redundancy, robustness and network motifs inherit within the structure that predict much of the biological signaling capacity observed in real systems[2].

Carsten Carlberg presented the rational and merits for modelling the nuclear receptor network and the research and training goals of the *NucSys* network. From an unscientific survey of the attendees it seemed that few groups were modelling nuclear receptor function in human systems.

Perhaps the clearest example of how such knowledge and understanding will be exploited in biomedicine was presented by **Alexis Borisy** of a biotech start-up company called CominatoR_x http://www.combinatorx.com/. He outlined their approach to systems medicine as an attempt to break away from the reductionist view where single therapeutic targets might be hit by 'magic bullets'. Instead they utilize a rational approach using drug combinations to probe network topology and identify novel nodal control points to target. The company had clearly made significant investments in establishing a comprehensive drug library of all FDA approved drugs (approximately 2500 lead compounds), defining models to test efficacy and applying appropriate synergy scores. These approaches had already reveled a number of synergies and highlighted their tissue specificity.

There was a significant educational flavour to the meeting, with training workshops on software and modelling approaches. I spoke with **Joshua Ho**, who had a selected talk on gene-regulatory networks in bacteria and is a PhD student at the University of Sydney, Australia. I asked Joshua about his background and view of the field of SB.

MJC. How did you arrive in the field of Systems Biology? ***JH***. I did a double major in computer science and biochemistry for my undergraduate degree. I started systems biology research during my last year of my undergraduate (honors) year, in which I applied network analysis and modeling tools to study the evolution of gene regulatory networks. Now I am continuing my interest in systems biology of gene expression in my PhD.

MJC. What training do value most you in your PhD? ***JH***. The one thing I value most in my current PhD training is the unique combination of hands-on wet-lab molecular biology training and dry-lab

[2] Citri A, Yarden Y. EGF-ERBB signalling: towards the systems level. Nat Rev Mol Cell Biol. 2006 Jul;7(7):505-16. Review.

computational/statistical/mathematical training. In addition, I am jointly supervised by a mathematician and a medical scientist, which really helps me to view systems biology from different perspectives.

MJC. What are the major limitations to modeling events in mammalian systems? ***JH***. The lack of clean data and detailed knowledge of the actual molecular biology processes are the main limitations in modeling mammalian systems.

MJC. The first NucSys graduates will be looking for jobs in about 12 months. Do you think they will find jobs easily in either academia or industry? ***JH***. Yes, I believe these graduates will find job easily as systems biology is such a rapidly expanding field. In particular, the combination of wet and dry skills should have given them a competitive edge in finding a good appointment.

Selected highlights of the meeting are being published in partnership with the journal Molecular Systems Biology (http://www.nature.com/msb/focus/icsb/index.html)

ESR Network news.

Team 1, Prof. Carlberg, University of Kuopio, Finland.

ESR1: Tatjana Degenhardt, (4/06 to 3/09)

Published papers

1. Malinen M., Saramäki A., Ropponen A., **Degenhardt T**., Väisänen S. and **Carlberg C**. Distinct HDACs regulate the transcriptional response of human cyclin-dependent kinase inhibitor genes to Trichostatin A and 1α,25-dihydroxyvitamin D_3 (2008) Nucleic Acids Res.36:121-32

Meetings Report:

Masterclass Nutrigenomics: From molecules to life, November 2007, Wageningen, Netherlands

I had a poster presentation there: Involvement of PPARa and PGC-1a in the regulation of heme biosynthesis

Master lecturer Professor John Mathers on Epigenetics and Nutrition. The course gave a very good introduction to how important it is to understand that there is a clear link between nutrition and epigenetic regulation. Additionally, there were talks about different methods/approaches to study the influence of nutrition on our genes, proteins and metabolites. It was very nice to see the possibilities of proteomics and metabolomics. Those fields are not yet as advanced as genomics but they are developing rapidly. Other sessions dealt with microarray analysis and the advantages/disadvantages of mouse models.

We as students also had the possibility to discuss our approaches and results with the presentation of our posters and time between the sessions.

ESR2: Aleksandra Tomaszewska (12/06 to 11/09)

Meeting reports

Early this year I attended C-category course for researchers using experimental animals. It gave me an overview on what can I expect from this kind of experiments. After two weeks of lectures and hands on experience of injections, anaesthesia and euthanasia I think I learned the limitations of using animals in research. I would recommend this course for all ESRs working with animal samples or planning to work with animals. It gives a background from ethics and international laws concerning animal rights as well as animal welfare. After attending group works and passing the final exam all the students received an international certificate, which is very useful if you're planning to work with the animals in the future.

Team 2, Drs Campbell & Bunce, University of Birmingham, UK

ESR3: Sebastiano Battaglia, (3/06 to 2/09)

Meeting Report

Keystone Symposia: Nuclear Receptors at Whistler, British Columbia: 30th March – 4th April 2008

Deciphering and targeting nuclear receptor co-repressor specificity in prostate cancer. Poster

The last four days of March I had the luck to be at the "Keystone Symposia – Nuclear Receptor: Steroids" in Whistler, about 150km outside Vancouver. This conference gathered people from all over the world working on nuclear receptors, both orphans and steroids, to share the last findings in matter of gene regulation and transcription factor activity in physiology and diseases. Impressive genome wide studies to find ER responsive elements and Chip-Seq technologies dominated most of the presentations during the meeting; poster sessions gave instead the possibility to loads of young students to present their work, mostly on GR/ER activity in breast cancer MCF7 cells and AR function in prostate cancer. Big guys such as Myles Brown, Mitchell Lazar and Robert Roeder presented massive amounts of data (also obtained with very expensive experiments) about ER and FOXA1 in breast cancer, physiology of the NCoR/SMRT complex and TRAP220/MED1 function (Pedro Rocha's favourite protein). Those presentations, loads of other talks/ posters and Whistler's small skiing paradise made this meeting pretty unique, and stimulating; a very good place where I'd like to go again.

ESR4: Pedro Velica, (9/06 to 8/09)

Meeting reports

The 2008 Leukemia Research Fund Forum for Translational Research in London "Normal and Leukaemic haematopoietic stem cells", London March 2008 was an one day meeting concerning the translational aspects of normal and leukemic hematopoietic stem cells. Many speakers focused on the biology and markers of the normal stem cells, often drifting to less translational fields. One very interesting talk by Timm Schroeder (Helmholtz Centre in Munich) presented a recently developed software capable of tracking movement and replication of single cells in a continuously monitored tissue culture dish (keeping huge amounts of information!). The talks that did approach more translational topics (such as the one by Tessa Holyoake, Univ of Glasgow) added some novel potential clinical targets to the leukemic stem cell knowledge.

Team 3, Prof. van Leeuwen, Erasmus University Medical Centre, Rotterdam The Netherlands

ESR5: Claudia Bruedigam (3/06 to 2/09)

Meeting abstracts

Annual meeting of NVCB 2007

The peroxisome proliferator-activated receptor γ ligand rosiglitazone stimulates human osteoblast differentiation.

(Oral presentation)

The annual meeting of the Dutch society for calcium and bone metabolism brings together basic and clinical researchers working at institutes in The Netherlands and Belgium. Latest results from cell biological and genetic studies focussing on major factors controlling bone metabolism are shared. The main focus this time were cellular signalling pathways that mediate signal transduction in bone. In addition, the so far hardly studied osteocyte cell type has been proposed to orchestrate bone resorption and formation. This meeting is of value for researchers that are working in the bone field in the Netherlands or Belgium as it offers the possibility to present and discuss data, and to establish collaborations with colleagues from research institutes neighbouring cities.

ESR 6: Viola Woeckel

Meetings reports

Dutch Society of Calcium and Bone Metabolism 2007

Abstract for talk: Evidence that vitamin D controls different processes in early and late human osteoblast differentiation

This was my first meeting with people from other labs (besides NucSys), so it was a nice experience to get to know atmospheres and talk with people you probably would never get the idea of

talking to. Although I already was in the field of bone and calcium metabolism for 10 months I still learned a lot about our field of work. We got hints for further investigations and were supported in what we do.

Team 4, Profs Goldfarb & Gibson and Dr. Plant, University of Surrey, UK

ESR7: Ellen Wiedemann, (9/06 to 8/09)

Keystone Symposia: Nuclear Receptors at Whistler, British Columbia: 30th March – 4th April 2008

"Temporal And Ligand Dependent Sub-cellular Localization Of The Nuclear Receptors PXR, VDR, PPARalpha And RXRalpha In Human Liver And Intestinal Cell Lines" Poster

This was the first joint conference I attended and there is one good thing and one bad thing about them. The good thing is: you have the choice and the bad thing is: you have the choice.

The atmosphere of the conference was very casual but with serious science behind the doors. Most lectures started without any introduction which made it sometimes hard to get into them. The main focus of the meeting was AR and ER and the cancers they are involved in.

The only disappointment was that lectures with very interesting abstracts were changed without notice which led to there being no lectures about PXR.

In my poster I presented my data about the sub-cellular localization of the nuclear receptors PXR, VDR, PPARα and RXRα in human liver and intestinal cell lines.

One very interesting lecture with the title "Systems biology of nuclear receptors and coregulators" showed that NCoR/HDAC3 interaction is not required for development but is required for normal circadian rhythm, glucose and lipid metabolism. Another lecture illustrated that SRC2 is able to function as co-activator as well as co-repressor, depending on the context of the target gene. "Role of Protein Folding in Coactivator Function" gave you an idea about the folding in CBP/p300; it demonstrated that the folding takes place upon complex forming.

British Toxicology Society at University of Surrey, UK: 6th-9th April 2008 "Temporal And Ligand Dependent Sub-cellular Localization Of The Nuclear Receptors PXR, VDR, PPARalpha And RXRalpha In Human Liver And Intestinal Cell Lines" Oral Communication

Team 5, Prof. Westerhoff and Drs. Bruggeman & Bakker, Vrije Universiteit Amsterdam, The Netherlands

ESR8: Katja Rybakova, (7/06 to 6/09)

Meeting reports:

2nd ElSyS conference in Enschede, the Netherlands, February 24th -26th

Rybakova K.N., Degenhardt T., Bruggeman F.J., Carlberg C. and Westerhoff H.V. The mechanism of nuclear receptor (PPARβ/δ) mediated

transcription activation of the human PDK4 gene.

Oral presentation

ESF-UB Conference on Systems Biology, St Feliu de Guixols, Spain, 12-17 April 2008.

Rybakova K.N., Degenhardt T., Mone M.J., Bruggeman F.J., Westerhoff H.V. and Carlberg C. Nuclear receptor-induced transcription dynamics of the human PDK4 gene: combined experimental and modeling study.

Poster presentation

This was a very inspiring conference in which we had the opportunity to hear the talks of the leading researches in Systems Biology field from both Europe and the USA. Many of the presentations were dedicated to the mammalian cell biology. What made it especially interesting was that it had an equal representation of researches practicing the bottom-up (using available biochemical information for building a detailed kinetic model of the network) and top-down (using large scale "–omics" data to infer hypothesis about network structure and function) approaches.
On one hand, the bottom-up approach makes it possible to make very accurate and predictive models of a single pathway or even two interacting pathways; for example, MAP kinase, NF-κB or osmotic shock signaling pathways. However, these models are usually not enough to achieve the understanding of the whole cell level functioning that is desirable for medical applications. On the other hand, the top down approach which aims precisely at that does not provide valuable insights so far despite generating large amount of data. It is not clear if there is a fundamental obstacle that prevents the top-down approach from being successful or the reason is the lack of correct approach to design and interpret such experiments. Indeed, the Systems Biology done in prokaryotes suggests that it is possible to modularize the whole cellular network and predict its behavior in a coherent fashion. Unfortunately, for multi-cellular eukaryotes to do so remains a challenge.

ESR9: Alexey Kolodkin. (7/06 to 6/09).

ElSyS conference in Enschede, the Netherlands, February 24th -26th

Poster presentation:

Design principles of glucocorticoid receptor signalling: benefit of importin export and multi-site differential regulation.

This great event was organized by GeNeYous, the Genomics Network for Young Scientists. Everything took place in the forest, on the university campus with beautiful football fields. The only pity thing is that we had absolutely no time to enjoy these fields, as the schedule was a bit oversaturated with many interesting meetings. One of the key topics was systems biology. The session on systems biology included talks by Prof. Steve Oliver, Dr. Jorrit Hornberg and Prof. Han de Winde. There was also a session on career development and the practical seminar on development of creative thinking. At the poster session I got very important feedback on our work.

Team 6, Dr. Kersten and Prof. Müller, Wageningen University, The Netherlands.

ESR 10: Anastasia Georgiadi (08/06 to 07/09)

Graduation from the MSc programme on Human nutrition, specialization on Nutrition and Genomics, Wageningen University, the Netherlands. September 2007

5th annual conference of the society for heart and vascular metabolism. June 18-20 (2007). Abstract for poster:

Characterizing the PPARalpha dependent transcriptome in murine heart

As I'm getting specialized on gene regulation by fatty acids in the heart, this meeting was of great value to me. Through my poster presentation I had the opportunity to interact with experts in the field of heart health research and to take valuable comments on the results of my research concerning the role of fatty acids on heart physiology.

Presentation in meetings/courses:

PhD tour October 13th to 25th (2007). I participated in a PhD tour in U.S universities of the Northwest part of the U.S.A. This educational trip is organized by the PhD students of the department of human nutrition of Wageningen University every two years. This year included different destinations in the U.S.A like Harvard university, Tufts, Cornell, Pennsylvania state university and many others. My presentation took place at Cornell university on **"The role of PPARalpha in gene regulation in mouse heart"**. In addition the whole trip provided a broad overview of post doctoral possibilities in the U.S.A.

Courses:

Advanced Statistics on Experimental design of Human and Animal Studies 13th-15th of February (2008).

Team 7, Dr. Hakkola and Prof. Pelkonen, University of Oulu, Finland

ESR 11: Marcin Buler (1/07 to 12/09)

Team 8, Profs Verstuyf and Bouillon, Katholieke Universiteit Leuven, Belgium

ESR 12: Carsten Kriebitzsch (09/06 to 08/09)

Meeting Reports

Gene expression profiling in $VitD_3$ treated MC3T3-E1 mouse osteoblasts – poster presentation:

The Epiphamy symposium (symposium on Epigenetics and Pharmacogenomics) took place on the 26th of October 2007 in Ghent. I attended the meeting to get some more insights into Epigenetics and

the links between DNA methylation and cancer development. The meeting addressed a variety of different topics. The introduction addressed the issue of the basic mechanisms of DNA methylation in mammals. The later sessions focused more on the origin, extend and the implications of the cancer epigenome and clinical implications. During the break posters were presented and it was possible to come in contact with other scientists and have discussions about the presented data. The last session gave scientist with the most interesting posters the opportunity to present their novel data and findings in short oral presentations like "The transcription repressor NIPP1 is a novel player in EZH2-mediated gene silencing" or "GATA4 en GATA5 as tumor suppressors and biomarkers in colorectal cancer".

T*eam 9, Drs. Mazzatti* & *Mayes, Unilever R&D, United Kingdom*

ESR13: Oita Radu Cristian (1/07 to 12/09)

In January I participated in a SPARK workshop organized and sponsored by Unilever. The aim was to understand the contribution of mitochondrial dysfunction to physiologic changes that perpetuate metabolic deregulation related to obesity, diabetes, and ageing by bringing together specialists from academia and industry.

The workshop focusing mainly on the following issues: (i) the physiological consequences of mitochondrial dysfunction on glycemic regulation, energy expenditure, and the ageing phenotype; (ii) the key mechanistic determinants of mitochondrial [dys]function; (iii) future insights exploring the potential for intervention strategies to prevent or reverse mitochondrial decline and promote the maintenance of glycemic regulation and metabolic integrity in ageing.

Other issues discussed were also the roles of mitochondrial DNA mutations, the effects of changes in mitochondria mass, number, or functional capacity, the connections between uncoupling of oxidative phosphorylation and ATP production, and finally the alterations to the mitochondrial membrane structure.

Also recently I had the opportunity to participate in an industry workshop organized by EBI-EMBL in Hinxton (Cambridge, UK) whose goal was to introduce the EBI databases of 3D protein structures to the average researcher in biology and medicine. The workshop mainly utilised the *Macromolecular Structure Database* **(MSD)**, a global database within the *Protein Data Bank* framework **(PDB)**, but secondarily discussed other software applications like **PDBsum, ProFunc and SAS**.

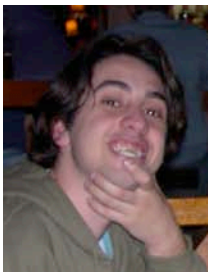
MSD is a manually curated integrative relational database, which allows searching and visualisation of published and validated 3D structures or of the possible, algorithmic-predicted structures of recently discovered proteins. **MSD** also allows searching and identification of catalytic sites, surfaces, fold matching, ligands and predicts putative function. Additionally, the database allows data mining in a user-

friendly environment. **MSD** can be accessed by selecting the following link: *http://www.ebi.ac.uk/msd/*.

Team 10, Prof. Muñoz and Dr. González-Sancho, Instituto de Investigaciones Biomédicas, Spain

ESR 14: Fabio Pires (10/06 to 09/09)

Team 11, Dr. Heinrich Schrewe, Max-Planck Institute for Molecular Genetics, Germany.



ESR 15: Pedro Rocha (09/06 to 08/09)

Keystone Meeting, February; Regulatory Mechanisms in Eukaryotic Transcription **Mouse Models to Study Mediator Functions in Transcriptional Activation.**

The Keystone meeting dealt with varied topics connected all to regulation of gene expression. It had sessions leading with basic transcriptional mechanisms like activation of the pre-initiation complex and transcriptional elongation; transcriptional silencing; nuclear architecture and how the cell can modulate long-range effects. Recent genome wide studies of chromatin modifications or ES cell reprogramming were also discussed. To my personal interest there were very interesting talks about specificity of co-activators function. On a personal note the poster sessions were the most interesting part of the meeting. Not only because they allowed discussing my own project with the world leaders in the topic but also because I could learn a lot of how other people with different backgrounds tackle the same problems I am interested in.

Team 12, Dr. Kay Colston, St. George's Hospital Medical School, UK

ESR 16: Carole Brosseau (11/06 to 10/09)

Meetings Attended

Research day at SGUL, London, UK (5^{th} of December 2007)

On the 5th of December 2007 I attended the Research Day at the St George's University of London. This day includes contributions from all Divisions at St George's as well as from the South West London Academic Network partners, Kingston University and Royal Holloway. Consequently, there was a varied programme of oral presentations and poster presentations that highlight the diversity of research activity at the three sites. The first talk I was very interested in was about the transport pathway of the malaria parasite. This talk was about a research project that focuses on a calcium transporter (PfATP6), which is a primary target of the most important anti-malaria drugs available, the artemisinins. Another very

interested presentation was about valproic acid, a medicine used in the treatment of epilepsy and more recently Alzheimer's disease. More specifically, the study was an investigation to explain the mechanism of this drug using Dictyostelium as a model.
During this meeting, I made a poster presentation for which I was awarded a poster prize.
This is the abstract: Effects of Vitamin D treatment on VDR target gene expression in breast cancer.

Team 13, Prof. Cross and Drs Kallay & Thalhammer, Medical University of Vienna, Austria

ESR 17: Thomas Nittke (04/06 to 03/09)

Papers

Nutritional Calcium Modulates Colonic Expression Of Vitamin D Receptor And Pregnane X Receptor Target Genes **Thomas Nittke**, Stephan Selig, **Enikö Kallay**, **Heide S. Cross** (2007) Molecular Nutrition & Food Research, (in press)

Team 14, Dr. Luciano Adorini, BioXell S.p.A., Italy

ESR 18: Gilles Laverny (10/06 to 09/09)

Papers

Penna G, Amuchastegui S, **Laverny G**, **Adorini L**. Vitamin D receptor agonists in the treatment of autoimmune diseases: selective targeting of myeloid but not plasmacytoid dendritic cells. J Bone Miner Res. 2007 Dec 22 Suppl 2:V69-73.

Adorini L., A. S., Corsiero E., **Laverny G.,** Le Meur T. and Penna G. Vitamin D receptor agonists as anti-inflammatory agents. Expert Rev. Clin. Immunol. 3, 477-489 (2007).

Group Publications 1/11/07 to 30/4/08

Bold = PI

Bold and underlined = ESR

1. Heinäniemi, M. & **Carlberg, C.** Screening for PPAR responsive modules in cancer. (2008) *PPAR Res.* (In Press).

2. Malinen, M., Saramäki, A., Ropponen, A., **Degenhardt, T.,** Väisänen, S. & **Carlberg, C.** Distinct HDACs regulate the transcriptional response of human cyclin-dependent kinase inhibitor genes to trichostatin A and 1α,25-dihydroxyvitamin D_3. (2008) *Nucl. Acids Res.* **36**, 121-132

3. **Campbell, M.J., Carlberg, C**. & Koeffler, H.P. A role for PPARγ in cancer therapy. (2008) *PPAR Res.* In Press.

4. Thorne J & **Campbell MJ** The Vitamin D Receptor in Cancer (2008). *Proceedings of the Nutrition Society* vol. 67, no. 2 (May 2008 issue).

5. Boult JKR, Hughes S, **Campbell MJ** & Tselepis C. (2008) Oesophageal adenocarcinoma is associated with a deregulation in the MYC/MAX/MAD network *British Journal of Cancer* (In Press)

6. Tiziani S, Emwas AH, Lodi A, Ludwig C, **Bunce CM,** Viant MR & Günther UL. Optimized metabolite extraction from blood serum for (1)H nuclear magnetic resonance spectroscopy. *Anal Biochem*. 2008 Feb 5

7. Langdahl BL, **Uitterlinden AG**, Ralston SH, Trikalinos TA, Balcells S, Brandi ML, Scollen S, Lips P, Lorenc R, Obermayer-Pietsch B, Reid DM, Armas JB, Arp PP, Bassiti A, Bustamante M, Husted LB, Carey AH, Pérez Cano R, Dobnig H, Dunning AM, Fahrleitner-Pammer A, Falchetti A, Karczmarewicz E, Kruk M, **van Leeuwen JP**, Masi L, van Meurs JB, Mangion J, McGuigan FE, Mellibovsky L, Mosekilde L, Nogués X, Pols HA, Reeve J, Renner W, Rivadeneira F, van Schoor NM & Ioannidis JP; APOSS investigators; DOPS investigators; EPOS investigators; EPOLOS investigators; FAMOS investigators; LASA investigators; ERGO investigators; for the GENOMOS Study. Large-scale analysis of association between polymorphisms in the transforming growth factor beta 1 gene (TGFB1) and osteoporosis: The GENOMOS study. *Bone*. 2007 Dec 3;

8. Sniekers YH, Weinans H, Bierma-Zeinstra SM, **van Leeuwen JP** & van Osch GJ. Animal models for osteoarthritis: the effect of ovariectomy and estrogen treatment - a systematic approach. *Osteoarthritis Cartilage*. 2008 Feb 14;

9. Sniekers YH, Intema F, Lafeber FP, van Osch GJ, **van Leeuwen JP**, Weinans H & Mastbergen SC. A role for subchondral bone changes in the process of osteoarthritis; a micro-CT study of two canine models. *BMC Musculoskelet Disord*. 2008 Feb 12;9:20.

10. Eijken M, Meijer IM, Westbroek I, Koedam M, Chiba H, Uitterlinden AG, Pols HA & **van Leeuwen JP**. Wnt signaling acts and is regulated in a human osteoblast differentiation dependent manner. *J Cell Biochem*. 2008 Jan 9;

11. Botter SM, van Osch GJ, Waarsing JH, van der Linden JC, Verhaar JA, Pols HA, **van Leeuwen JP** & Weinans H. Cartilage damage pattern in relation to subchondral plate thickness in a collagenase-induced model of osteoarthritis. *Osteoarthritis Cartilage*. 2008 Apr;16(4):506-14.

12. **Westerhoff HV**, **Kolodkin A**, Conradie R, Wilkinson SJ, **Bruggeman FJ**, Krab K, van Schuppen JH, Hardin H, **Bakker BM,** Moné MJ, **Rybakova KN**, Eijken M, van Leeuwen HJ & Snoep JL. Systems biology towards life in silico: mathematics of the control of living cells. *J Math Biol*. 2008 Feb 16;

13. **Westerhoff HV**. Signalling control strength. *J Theor Biol*. 2007 Dec 5;

14. Jonker CM, Snoep JL, Treur J, **Westerhoff HV** & Wijngaards WC. BDI-modelling of complex intracellular dynamics. *J Theor Biol*. 2008 Mar 7;251(1):1-23.

15. Haanstra JR, Stewart M, Luu VD, van Tuijl A, **Westerhoff HV** & Clayton C, **Bakker BM**. Control and regulation of gene expression: quantitative analysis of the expression of phosphoglycerate kinase in bloodstream form Trypanosoma brucei. *J Biol Chem*. 2008

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