NucSys Newsletter,

No. 1, April 2006

Issue No. 1. This is the first issue of a biannual NucSys newsletter; principally it is designed to provide information to the Early Stage Researchers (ESRs), and associates. It will also contain information on the network and how it impacts on the wider scientific community to help the ESRs put their own research and development in a wider context. To help with this the Newsletter will highlight research occurring in the network, and also important papers and findings by other lead scientists within relevant fields.

Another role for the newsletter is to showcase the outputs and developments of NucSys to colleagues and the wider scientific community.

It also showcases our new NucSys logo.

A brief history of NucSys. The consortium was built out of several existing collaborations and was formalized at a meeting in Leuven, Belgium in November 2003. As with the development of many large scale projects the initial development was not without set-backs, not least of which was a well received, but ultimately unsuccessful bid application in 2003. Rejection, no matter how well presented is a common feature of a scientific career. Therefore the application was re-focused in line with the reviewers' comments and re-developed for submittal in 2004.

On June 24th 2005 the European Commission confirmed that NucSys had scored highly and was one of only 15 (out of approximately 350 original applications) to go through to contract negotiations. The final contract negotiations settled upon funding 18 PhD students each for 36 months, and to support the network for a 48 month period commencing January 1st 2006.

The network kick-off meeting was again held in Leuven, Belgium in January 2006 and was very successful. Approximately 35 network investigators and associated scientists attended the three day meeting. The atmosphere was understandably extremely positive and the meeting acted to integrate the teams more fully and outline current and future research results and plans.

The objectives of NucSys. The network unites a consortium of scientists who are all working at the cutting edge of their disciplines and are internationally renowned.

NucSys is focused around developing a new approach to understanding how dietary and environmental factors are sensed by the body and regulate cell processes such as growth and differentiation. Central to mediating these actions is the nuclear receptor superfamily, which act as ligand-activated transcription factors in response to a diverse range of lipophillic molecules. These include beneficial nutritional and deleterious xenobiotic components

The principal hypothesis is that the co-ordinated activities of the nuclear receptor superfamily are central to the ability of cells to sense the environment.

The main goal of the network is to *define* key components of the nuclear receptor gene regulatory network that facilitate these processes and *model* their impact on the development of aging-related syndromes and pathologies. This will be achieved by the application of systems biology mathematical tools.

This post-genomic approach seeks to unite the understanding of the activities of biological macromolecules and metabolites to generate a unified paradigm capable of describing and *predicting* complex processes in living cells and organisms. This approach requires the integration and interpretation of large volumes of data from “omics”-based studies and thus bioinformatics will form an essential component. It is anticipated that our findings will provide important momentum to the emerging field of nutrigenomics.

To achieve this NucSys is an interdisciplinary co-operative with diverse expertise to enable the mathematical description of gene-nutrient interactions and permit modelling of the impact of diet on health and the development of disease.

NucSys has three objectives;

1. To use interdisciplinary expertise to study the impact of dietary sensing by nuclear receptors on the genome, epigenome, transcriptome, proteome, metabolome and physiome.

2. To use intersectorial expertise in revealing the significance of nuclear receptor-nutrient signalling in pathological conditions associated with aging.

3. To generate an interdisciplinary and intersectorial understanding using systems biology modelling to reveal a predicative and preventative paradigm for the effect of diet upon key aspects of health within the aging European population and generate commercial realization.

Excellence in research leading to excellence in training. The Network has two functions; to undertake the research program and to train ESRs.

Therefore to compliment the research program each ESR will undertake a personalized training program which fuses research learning with taught elements. To compliment this, ESRs will be encouraged to attend relevant

workshops, meetings, and seminars outside of the network. Together these research and taught elements will develop research and generic scientific skills and allow the ESRs to develop into highly trained interdisciplinary researchers.

Network Recruitment. As of March 31st 2006 the following ESRs have been recruited:

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

ESR1: Tatjana Degenhardt, MSc degree in Biochemistry, University of Bayreuth, Germany. She did the practical part of her MSc thesis in the Carlberg team.

ESR2: to be recruited during 2006

Team 2, Dr. Moray J. Campbell, Dr. Chris Bunce, University of Birmingham, UK

ESR3: Sebastiano Battaglia, Medical Biotechnology (5 years degree) from Istituto Nazionale per lo Studio e la Cura dei Tumori of Milan.

ESR4: Pedro Velica (to start September 2006)

Team 3, Dr. Johannes P.T.M. van Leeuwen, Erasmus University Medical Centre, Rotterdam The Netherlands

ESR5: Claudia Bruedigam MSc degree in Biochemistry, University of Potsdam – Germany. Graduate student at Max Planck Institute of Molecular Plant Physiology - Germany.

ESR 6: to be recruited during 2006

Team 4, Prof. Peter Goldfarb, Prof. Gordon Gibson, Dr. Nick Plant, University of Surrey, United Kingdom

ESR7: to be recruited during 2006

Team 5, Prof. Hans V. Westerhoff, Dr. Barbara M. Bakker, Vrije Universiteit Amsterdam, The Netherlands

ESR8: position offered

ESR9: position offered

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

ESR 10: to be recruited during 2006

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

ESR 11: to be recruited during 2006

Team 8, Dr. Annemieke Verstuyf, Prof. Roger Bouillon, Katholieke Universiteit Leuven, Belgium

ESR 12: Carsten Kriebitzsch Undergraduate studies on Human Biology in Greifswald (Germany). His main subjects were Microbiology and Virology.

Team 9, Dr. Andrew Mayes, Unilever R&D, United Kingdom

ESR13: to be recruited during 2006

Team 10, Prof. Alberto Muñoz, Dr. José M. González-Sancho, Instituto de Investigaciones Biomédicas, Spain

ESR 14: Interviewing April 2006.

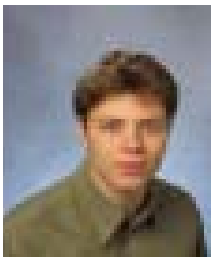
Team 11, Dr. Heinrich Schrewe, Max-Planck Institute for Molecular Genetics, Germany.

ESR 15: Pedro Rocha (to start in September 2006) MSc equivalent in Microbiology and Genetics Degree Course, Lisbon University, Portugal and subsequently Leonardo da Vinci Fellowship at Max-Planck Institute of Molecular Genetics, Berlin, Germany

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

ESR 16: Interviewing April 2006

Team 13, Prof. Heide S. Cross, Prof. Eniko Kallay, Prof. Therese Thalhammer, Medical University of Vienna, Austria



ESR 17: Thomas Nittke, MSc in Human Biology, University of Greifswald, Germany

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

ESR 18: inverviewing April 2006

Upcoming meetings. An important component of the network is for the ESRs to have access to relevant scientific meetings and therefore a regular column in the newsletter will be relevant meetings

An important date for the whole network will be the next **Network meeting in Kuopio June 30th – July 2nd** (arrival 29.6. and departure 2.7., programme to be circulated)

External meetings include

13th Vitamin D workshop, 7-12 April, Victoria, Canada

33rd European Symposium on Calcified Tissue, 10-14 May, Prague, Czech Republic

FASEB SUMMER RESEARCH CONFERENCE
Dynamic Structure of the Nuclear Hormone Receptors
http://src.faseb.org/2006/programs/AZ_02.pdf

Nuclear Receptor meeting Stockholm 2006 http://www.mednut.ki.se/conferences/

The 7th International conference on Systems Biology

http://www.icsb-2006.org/

http://ismb2006.cbi.cnptia.embrapa.br/

16th International Symposium on Microsomes and Drug Oxidations, 2006, 3-7 September 2006, Budapest, Hungary http://www.diamond-congress.hu/mdo2006/index.html

Nuclear Receptors & Disease November 1 - 5, 2006 Abstract Deadline: August 18, 2006 http://meetings.cshl.edu/meetings/nrd06.shtml

ISSX Meeting in Manchester, for the study of xenobiotics http://www.issx.org/Manchester.html

Useful websites. There are a range of highly informative websites available which compliment the research interests of the consortium and are useful reference tools.

Top of the list is the NucSys website

http://www.uku.fi/nucsys/

The Entrez suite of sites, including OMIM, which gives a current description and bibliography of almost all genes and their function. Very useful when entering new fields

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM&itool=toolbar

http://www.genecards.org/

Other useful cell signalling websites include

http://www.cellsignal.com/reference/pathway/index.asp?cookie%5Ftest=1

Signal Transduction Knowledge Environment

http://stke.sciencemag.org/

In particular the nuclear receptor superfamily is illustrated by a number of sites including the recently established NURSA site.

http://www.nursa.org/

The arena of Systems Biology is highly dynamic and still defining its scope and ambition. A ragne of websites introduce and discuss the relevant concepts

www.systems-biology.org
www.systemsbiology.org
www.bio.vu.nl

http://sbw.kgi.edu/research/sbwIntro.htm

http://celldesigner.org/

A curated database of biological pathways

http://www.reactome.org/

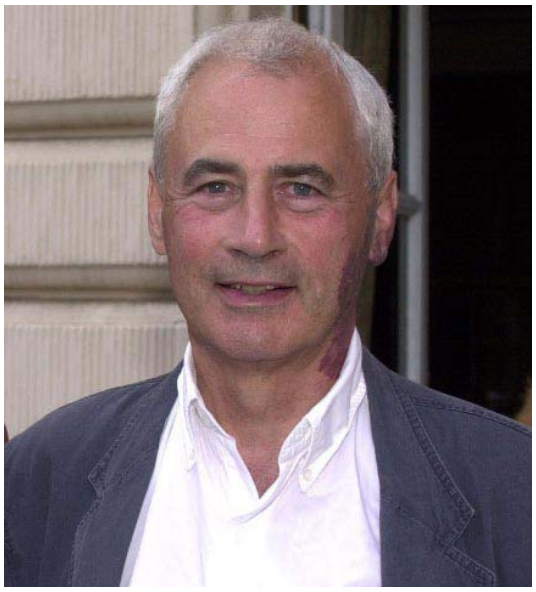
The area of nutrigenomics is well covered by sites such as

http://www.nugo.org

For those who are interested on cytochrome P450s, David Nelson's Cytochrome P450 home page is a basic tool.

http://drnelson.utmem.edu/CytochromeP450.html

Career Profiles. Increasingly scientists have very different career paths and to illustrate this each Newsletter will profile two scientists, on within the network, and one outside (suggestions welcomed), who have pursued different career paths. This issue will profile Dr. Oliver Gillie, a scientific journalist from outside of the network, and Dr. Andrew Mayes, a scientist within the network, working in industry.



Oliver Gillie is a freelance medical writer and journalist with 25 years experience working for national newspapers in the United Kingdom, such as the Independent and Sunday Times. In these papers he has written about major changes in medicine from heart transplantation to the elimination of smallpox. Over the last three years he has been engaged in researching environmental causes of chronic disease, in particular the effects of vitamin D deprivation. This has led to the publication of “Sunlight Robbery” – a report which shows how health benefits of sunlight are denied to the public by current government policy.

Oliver Gillie has won multiple awards for his journalism, including British Science Writer of the year (twice) and British National Press Awards (four times). He has written, or co-authored, 13 books on science and medicine and made two television documentaries.

1. Describe you early career

[Oliver Gillie] I graduated from Edinburgh in genetics in 1960. They were exciting times - the genetic code had just been discovered. There were more FRS's than students when I did my PhD. Studying genes and complementation in Neurospora crassa was fascinating but it did not lead anywhere. I then went to the National Institute for Medical Research, Mill Hill, and found reading The Lancet more interesting than microbial genetics. Journalism called and I was glad to turn my back on the petri dishes.

2. What is your biggest career achievement to date?

[Oliver Gillie] Most successes in journalism are very ephemeral. But I campaigned hard against smoking and asbestos at a time when tobacco and asbestos companies were still a powerful influence. I exposed the fraudulent twin studies of Sir Cyril Burt and campaigned for wholemeal bread and healthy lifestyles. But my biggest achievement was probably the launch of the first regular weekly health page on a national daily newspaper when the Independent started in 1986. There had never been such a thing before. It was a great success and within months had

been copied by every other national broadsheet.

3. What gives you most satisfaction in your career?

[Oliver Gillie] I enjoy being able to provide people with new information which is relevant to their lives and a help to them. I like to see the progress of science contributing to health. I wrote a lot about impotence at one point because it was a subject that had been so badly misunderstood by medical science. It was thought that impotence is largely psychological but now we know it is mostly caused by a failure of blood vessels. It is always exciting to see established theories overturned and exposed.

4. If you had to re-do a phase of your career or training, what would do differently and why?

[Oliver Gillie] My career has not been orthodox. I made it up as I went along. If I redid anything the outcome might be entirely different. I have no regrets.

5. Predict a Nobel prize in Physiology or Medicine for 2016

[Oliver Gillie] I have become fascinated by the importance of vitamin D as a cause of chronic disease. I believe that in the next few years it will be realized that inadequate vitamin D is as important as smoking or obesity as a cause of ill-health. Biologists have made a great mistake in thinking that genetics is so important in explaining chronic disease. Genetics will make a steady contribution to modern biochemistry but I believe that important explanations of chronic disease will come from a better understanding of environmental factors. Vitamin D may be the first of a new set of important environmental variables to be recognized. There could be a Nobel prize here for someone.

6. Systems Biology: Pot of Gold or Fools Gold?

[Oliver Gillie] When I was at the Institute of Animal Genetics in Edinburgh almost 50 years ago we thought that genes determined enzymes and enzymes determined everything else. So we tried to build models of how cells worked based on the law of mass action. Henrik Kacser, my supervisor, was recognised as having some success at doing this but it made no lasting impression on me. I think words will always be the crucial tool for describing biological systems. Why? Biological systems are discontinuous. Small bits of the system may be susceptible to mathematical treatment but if you want the big picture you have to go back to words to describe how all the elements work together.

In this issue Dr. Andrew Mayes, the leader of Unilever Team, is also profiled.

1. Describe your early career

[Andrew Mayes] I achieved a 1st Class honours in Biochemistry from the University of Edinburgh in 1994 and then did a PhD in Molecular Biology also at Edinburgh in the Lab of Professor Jean Beggs. Thesis title "Identification and Characterisation of proteins interacting with Uss1p: A Saccharomyces cerevisiae Sm-like protein." I then joined Unilever Research, Colworth, UK in 1999 as a research scientist, working on the role of Nuclear Hormone Receptors particularly PPARs on age-related conditions. In my current role within Unilever's Corporate Research department, I lead a group investigating the effect of systemic health on ageing appearance within a larger project focussed on Healthy Ageing in the over 50s.

2. What is your biggest career achievement to date?

[Andrew Mayes] Publishing in Nature from my PhD work "Tharun S, He W, Mayes AE, Lennertz P, Beggs JD, Parker R. Nature. 2000 404:515-8. Yeast Sm-like proteins function in mRNA decapping and decay."

(Also a) Unilever product in the market place containing technology I was responsible for identifying within my research program

3. What gives you most satisfaction in your career?

[Andrew Mayes] Seeing the translation of our scientific research into a form which can then benefit people in everyday life

4. If you had to re-do a phase of your career or training, what would do differently and why?

[Andrew Mayes] I would be more pro-active in the direction of my PhD research and not leave as much to my supervisor.

5. Predict a Nobel prize in Physiology or Medicine for 2016

[Andrew Mayes] Fully functional artificial limbs for humans.

6. Systems Biology: Pot of Gold or Fools Gold?

[Andrew Mayes] Pot of Gold.....if you do it right!

Group Publications 1/1/06 to 31/3/06

(PIs in Bold, ESRs underlined)

Saramäki, A., Banwell, C.M., **Campbell, M.J.** and **Carlberg, C.,** Regulation of the human p21$^{(waf1/cip1)}$ gene promoter via multiple binding sites for p53 and the vitamin D3 receptor. (2006) *Nucl. Acids Res.* 34, 543-554

Carlberg, C. and Dunlop, T.W. An integrated biological approach to nuclear receptor signaling in physiological control and disease (2006) *Crit. Rev. Eukaryotic Gene Expression* 16, 1-22

Molnár, F., Peräkylä, M. and **Carlberg, C.** Vitamin D receptor agonists specifically modulate the volume of the ligand-binding pocket. (2006) *J. Biol. Chem.* 281, in press

Yee SW, **Campbell MJ**, Simons C. (2006) Inhibition of Vitamin D_3 metabolism enhances VDR signalling in androgen-independent prostate cancer cells *Journal of Steroid Biochemistry and Molecular Biology* 2006 Feb 13;

Campbell MJ & **Colston KW** (2006). The actions of the vitamin D receptor in health and malignancy; polymorphic associations and gene regulatory actions, in '*Nutrient-Gene Interactions in Cancer*'. Book chapter, pp. 129- 173, eds Drs Sang and Froi. Pub: Taylor and Francis, CRC Press

Campbell MJ & Abedin SA (2006). Vitamin D and cancer. *Expert Review of Endocrinology and Metabolism*. **1**(2): 219-233

Ralston SH, **Uitterlinden AG**, Brandi ML, Balcells S, Langdahl BL, Lips P, Lorenc R, Obermayer-Pietsch B, Scollen S, Bustamante M, Husted LB, Carey AH, Diez-Perez A, Dunning AM, Falchetti A, Karczmarewicz E, Kruk M, **van Leeuwen JP**, Meurs JB, Mangion J, McGuigan FE, Mellibovsky L, Monte FD, Pols HA, Reeve J, Reid DM, Renner W, Rivadeneira F, Schoor NM, Sherlock RE, Ioannidis JPLarge-Scale Evidence for the Effect of the COLIA1 Sp1 Polymorphism on Osteoporosis Outcomes: The GENOMOS Study. *PLoS Med.* 2006 Feb 21;3(4):

Eijken M, Koedam M, van Driel M, Buurman CJ, Pols HA, **van Leeuwen JP**. The essential role of glucocorticoids for proper human osteoblastdifferentiation and matrix mineralization. *Mol Cell Endocrinol*. 2006 Jan 4;

Delhanty PJ, van der Eerden BC, van der Velde M, Gauna C, Pols HA, Jahr H,Chiba H, van der Lely AJ, **van Leeuwen JP.** Ghrelin and unacylated ghrelin stimulate human osteoblast growth via mitogen-activated protein kinase (MAPK)/phosphoinositide 3-kinase (PI3K) pathways in the absence of GHS-R1a. *J Endocrinol.* 2006 Jan;188(1):37-47.

van Meurs JB, Rivadeneira F, Jhamai M, Hugens W, Hofman A, **van Leeuwen JP**, Pols HA, **Uitterlinden AG**. Common genetic variation of the low-density lipoprotein receptor-related protein 5 and 6 genes determines fracture risk in elderly white men. *J Bone Miner Res*. 2006 Jan;21(1):141-50.

Aouabdi S, **Gibson G**, **Plant N**. Transcriptional regulation of the PXR gene: identification and characterization of a functional peroxisome proliferator-activated receptor alpha binding site within the proximal promoter of PXR. Drug Metab Dispos. 2006 Jan;34(1):138-44. Epub 2005 Oct 21.

F.J. Bruggeman, F.C. Boogerd, **H.V Westerhoff,** R.C. Richardson und A. Stephan, Interaktion von Biologie und Wissenschaftsphilosophie: Mechanistische Erklärungen emergenten Verhaltens von Zellen: IN: Einführung in die Philosophie der Biologie, Eds U. Krohs & G. Toepher (2006) in press.

J.J. Hornberg, **F.J. Bruggeman**, **H.V. Westerhof**f and J. Lankelma, Cancer: A Systems Biology Disease, BioSystems 83 (2006) 81-90.

M. Rautenbach, G.D. Gerstner, N.M. Vlok, J. Kulenkampff and **H.V. Westerhoff,** Analysis of concentration response curves to describe and compare the antimicrobial activity of model cationic α-helical peptides, Anal. Biochemistry (2006)

Blüthgen, N., **Bruggeman, F.J.,** Legewie, S., Herzel, H., **Westerhoff, H.V.**, Kholodenko, B.N., Effects of Sequestration on Signal Transduction Cascades, /Febs Journal/, 273, 895-906, 2006.

Rossell S, van der Weijden CC, Lindenbergh A, van Tuijl A, Francke C, **Bakker BM, Westerhoff HV**. Unraveling the complexity of flux regulation: a new method demonstrated for nutrient starvation in Saccharomyces cerevisiae. Proc Natl Acad Sci U S A. 2006 Feb 14;103(7):2166-71.

Rautenbach M, Gerstner GD, Vlok NM, Kulenkampff J, **Westerhoff HV.** Analyses of dose-response curves to compare the antimicrobial activity of modelcationic alpha-helical peptides highlights the necessity for a minimum of two activity parameters. Anal Biochem. 2006 Mar 1;350(1):81-90.

Patsouris D, Reddy JK, **Müller M, Kersten S.** (2006) PPARalpha mediates the effects of high fat diet on hepatic gene expression. *Endocrinology*. 147:1508-16.

Mandard S, Zandbergen F, van Straten E, Wahli W, Kuipers F, **Müller M**, and **Kersten S.** (2006) The fasting-induced adipose factor/angiopoietin-like protein 4 is physically associated with lipoproteins and governs plasma lipid levels and adiposity. *J. Biol. Chem*. 281:934-44.

Coecke S, Ahr H, Blaauboer BJ, Bremer S, Casati S, Castell J, Combes R, Corvi R, Crespi CL, Cunningham ML, Elaut G, Eletti B, Freidig A, Gennari A, Ghersi-Egea JF, Guillouzo A, Hartung T, Hoet P, Ingelman-Sundberg M, Munn S, Janssens W, Ladstetter B, Leahy D, Long A, Meneguz A, Monshouwer M, Morath S, Nagelkerke F, **Pelkonen O**, Ponti J, Prieto P, Richert L, Sabbioni E, Schaack B, Steiling W, Testai E, Vericat JA, Worth A. Metabolism: a bottleneck in in vitro toxicological test development. The report and recommendations of ECVAM workshop 54. Altern Lab Anim. 2006 Feb;34(1):49-84.

SanderOves D, Fernandez S, Ferrero M, **Bouillon R, Verstuyf A,** Gotor V. Versatile synthesis and biological evaluation of 1,3- diamino-substituted 1alpha,25-dihydroxyvitamin D3 analogues. Bioorg Med Chem. 2006 Feb 15;14(4):928-37. Epub 2005 Oct 4

Mouratidis PX, Dalgleish AG, **Colston KW**. Investigation of the

mechanisms by which EB1089 abrogates apoptosis induced by 9-cis retinoic acid in pancreatic cancer cells. Pancreas. 2006 Jan;32(1):93-100.

Lechner D, Bajna E, Alercreutz H and **Cross HS**. Genistein and 17,-estradiol, but not equol, regulate vitamin d synthesis in human colon and breast cancer cells Anticancer Research *26*: (2006) (In press)

Cross HS, Lipkin M, **Kallay E**, Nutrients Regulate the Colonic Vitamin D System in Mice: relevance for Human Colon Malignancy, *Recent Advances in Nutritional Sciences* (2006) (*In press*)

Marchiani S, Bonaccorsi L, Ferruzzi P, Crescioli C, Muratori M, **Adorini L**, Forti G, Maggi M, Baldi E. The vitamin D analogue BXL-628 inhibits growth factor-stimulated proliferation and invasion of DU145 prostate cancer cells. J Cancer Res Clin Oncol. 2006 Feb 17;

Landmark or provocative papers published by other groups in the same period

Important papers: Keeping on top of the key papers to emerge in the relevant fields can by difficult and time consuming. A wide range of sophisticated search tools can help with this, such as PubCrawler, Google Scholar and Scopus.

To help with this we will also list a number of stand-out papers that shape the paradigm.

1: Hammes A, Andreassen TK, Spoelgen R, Raila J, Hubner N, Schulz H, Metzger J, Schweigert FJ, Luppa PB, Nykjaer A, Willnow TE. Role of endocytosis in cellular uptake of sex steroids. Cell. 2005 Sep 9;122(5):751-62.

2. Zhu P, Baek SH, Bourk EM et al. Macrophage/Cancer cell interactions mediate hormone resistance by a nuclear receptor derepression pathway. *Cell*. 2006;124:615-629.

3. Janes KA, Lauffenburger DA. A biological approach to computational models of proteomic networks. Curr Opin Chem Biol. 2006 Feb;10(1):73-80. Epub 2006 Jan 6.

4. Carter GW, Rupp S, Fink GR, Galitski T. Disentangling information flow in the Ras-cAMP signaling network. Genome Res. 2006 Mar 13; [Epub ahead of print]

5. Kholodenko BN. Cell-signalling dynamics in time and space. Nat Rev Mol Cell Biol. 2006 Mar;7(3):165-76.

6. Rayala SK, Mascarenhas J, Vadlamudi RK, Kumar R. Altered localization of a coactivator sensitizes breast cancer cells to tumor necrosis factor-induced apoptosis. Mol Cancer Ther. 2006 Feb;5(2):230-7.