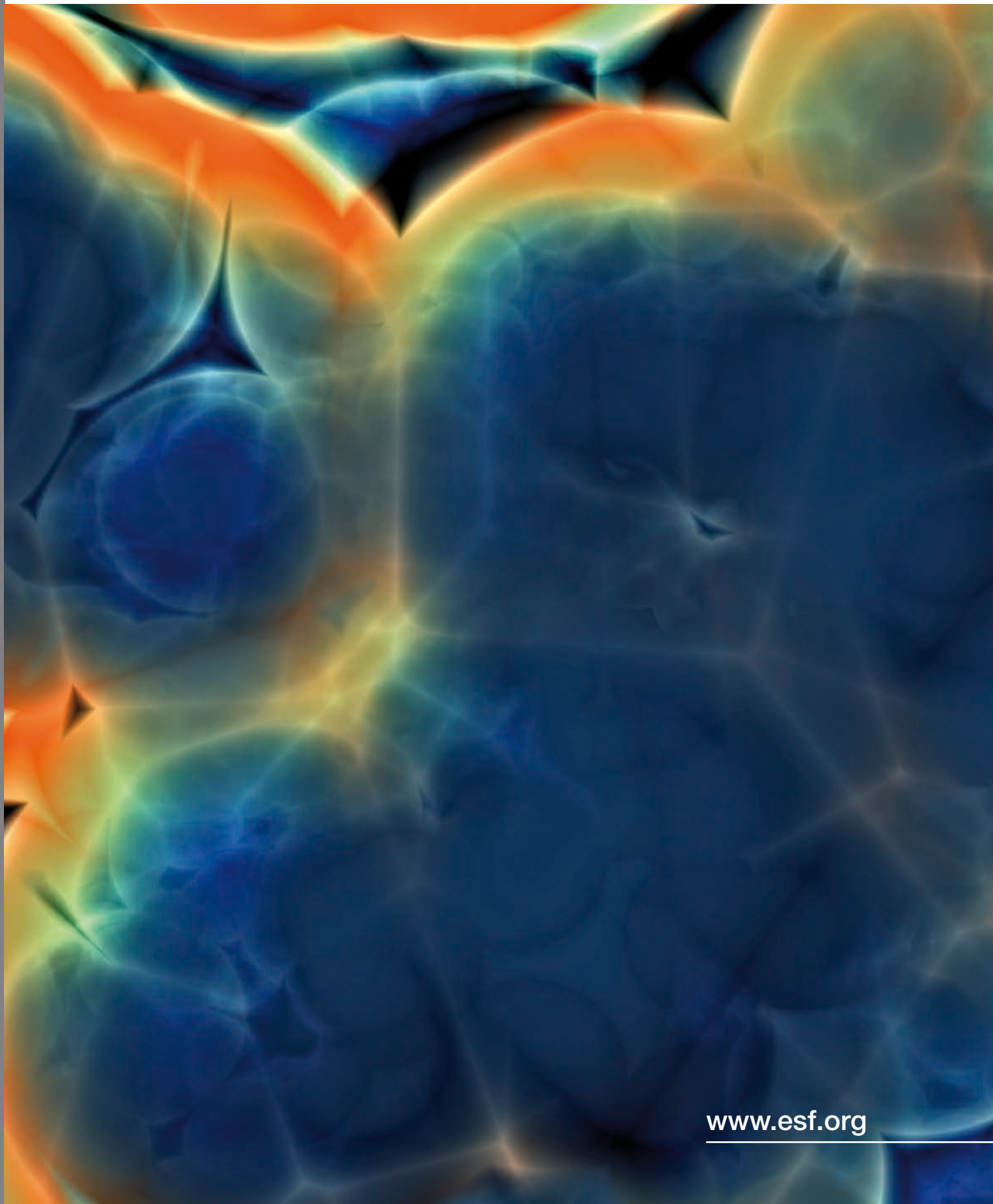


EuroDYNA Activities

Dynamic Nuclear Architecture and Chromatin Function



The European Science Foundation (ESF) was established in 1974 to create a common European platform for cross-border cooperation in all aspects of scientific research.

With its emphasis on a multidisciplinary and pan-European approach, the Foundation provides the leadership necessary to open new frontiers in European science.

Its activities include providing science policy advice (Science Strategy); stimulating cooperation between researchers and organisations to explore new directions (Science Synergy); and the administration of externally funded programmes (Science Management). These take place in the following areas: Physical and engineering sciences; Medical sciences; Life, earth and environmental sciences; Humanities; Social sciences; Polar; Marine; Space; Radio astronomy frequencies; Nuclear physics.

Headquartered in Strasbourg with offices in Brussels and Ostend, the ESF's membership comprises 77 national funding agencies, research performing agencies and academies from 30 European countries.

The Foundation's independence allows the ESF to objectively represent the priorities of all these members.



EuroDYNA¹, the European Collaborative Research (EUROCORES) Programme that aims to shed light onto the functioning of the nucleus, the control center of a cell, is now coming to an end. As the EuroDYNA Coordinator, it has been a very exciting endeavour to create a platform that offers scientists the possibility of teaming up with peers and exploring new research directions in a flexible manner. EuroDYNA has already yielded fruit and will continue to do so beyond the Programme's lifetime, thereby contributing to gaining a complete picture as to how the nucleus operates.

The Programme offers its members a diverse array of networking opportunities, of which the annual conferences have been particularly successful. This is illustrated by the fact that over the past two years 14 new collaborations have been formed between scientists across several thematic Collaborative Research Projects (CRPs), a development that otherwise would not have happened. This is also where the added value of EuroDYNA has kicked in as scientists with related yet slightly different research interests got together on a regular basis to present their data and have stimulating debates with the possibility of setting up new research initiatives. The latter was further developed through short-term visits of students between the CRP labs.

EuroDYNA has also been active beyond its boundaries, forging links with EU-networks and other EUROCORES Programmes within the same discipline and across scientific disciplines. For instance, in 2006 and 2007, two roundtable meetings took place involving members of EuroDYNA and SONS² (a EUROCORES Programme in the Physical Sciences) to facilitate cross-disciplinary exchange at the interface of molecular biology and material science/nanoscience. Within the Life Sciences, EuroDYNA investigators participated in a Mini-Symposium held by RNAQuality, a EUROCORES Programme that was launched in May 2007. Plans are underway to extend interactions between these two EUROCORES Programmes at the RNAQuality PhD summerschool, in 2008.

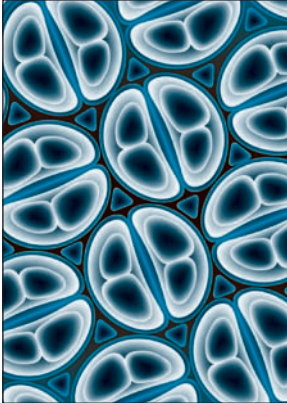
EuroDYNA is hosting its last big event at The Wellcome Trust Conference Center in Hinxton, UK from 28-31 May 2008. This final conference will highlight the scientific achievements generated during the Programme's lifetime. Specifically, the younger EuroDYNA researchers will be on stage presenting their data and will also have the opportunity to speak to leaders in the field. I have no doubt that this meeting, like the previous ones, will be successful in creating new collaborations and intensifying already existing ones, thereby providing a basis for common publications and opening new lines of research and future research grant applications.

Astrid Lunkes
EUROCORES Programme
Coordinator for EuroDYNA

¹ Dynamic Nuclear Architecture and Chromatin Function

² Self-Organised Nanostructures

EuroDYNA starts to unlock Pandora's Box of genome function



Understanding how the genome functions is one of the major challenges in biology. No small feat one might say but the implications are manifold. Detailed knowledge of the principles and mechanisms underlying the control of gene expression is vital for understanding the cause of many diseases, and for developing rational procedures for genomic engineering, including gene therapy and stem cell engineering, and for many biotechnology applications.

“People cannot expect medical applications like cures but they can expect us to describe biological pathways in more detail. This will provide us with much better tools to monitor disease, disease remission and disease progression. Essentially EuroDYNA has made a significant contribution to getting hold of molecular markers for certain conditions, one of them being cancer but this also includes ageing,” said Colin Logie, Chair of the EuroDYNA Scientific Committee.

The EUROCORES Programme EuroDYNA has approached the challenge of understanding the genome by bringing together researchers from across Europe.

“EuroDYNA has exposed me to new and different approaches to biological problems and that has made a difference. It’s made a difference to my research,” said David Shore, University of Geneva and the Project Leader of “Environmental stress-induced dynamic modulation of chromatin structure, gene expression and nuclear architecture in yeast”.

The Programme has gathered and combined expertise in many different fields of research. At a meeting in Dresden in September 2007, members of the EuroDYNA community as well as invited speakers from the US and Canada came together for a EuroDYNA-organised session. On this occasion talks focused on the subject “Chromatin and the cell cycle” and the speakers covered everything from plant cells, via *Drosophila* cells to mammalian cells.

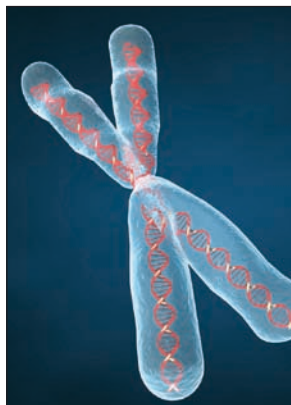
Chromatin and the Cell Cycle

The EuroDYNA Session at ELSO, Dresden, 1 September 2007

Organisers: Colin Logie and David Shore

Invited speakers:

- Mary Ann Osley (Albuquerque) - a pioneer in chromatin.
Histone metabolism, transcription and the cell cycle
- Rainer Renkawitz (Giessen), selected talk
The Drosophila insulator protein dCTCF binds to different genomic sites than Suppressor of Hairy wing, shares cofactor CP190 and is required for the function of the homeotic Bithorax complex
- Mieke van Lijsebettens (Ghent) who presented findings on cell cycle control during *A. thaliana* development. *The plant BRE1 H2B ubiquitylase has a function in cell cycle regulation during early leaf and root growth*
- Alain Verreault (Montreal), who talked about *Histone H3-Lys56 acetylation: a new twist in the chromosome cycle*
- Francis Stewart (Dresden) - an Australian recombinering pioneer.
Global analysis of histone modifications by mass spectrometry



Alain Verreault, University of Montreal and speaker at the EuroDYNA session at ELSO, focuses his research on how chemicals in the environment affect DNA. Verreault's research has many implications for the treatment of cancer using chemotherapy. He has found that a process called acetylation, when an acetyl group is added to a protein, globally affects the proteins that package DNA (known as histones) during DNA replication. Both the acetylation of histones and its timely removal are important for efficient DNA repair and cell survival in response to DNA damage. For instance, when the genes HST3 and HST4 were removed from yeast cells, acetylation could no longer be removed from histone proteins, which resulted in increased DNA damage, both spontaneous and in response to chemotherapeutic agents that damage DNA. This research could prove tremendously important to cancer treatment, but Verreault also emphasised "I suspect that other acetylation sites play a role in higher eukaryotes and more research is needed".

However, medicine is not the only area where the EuroDYNA research has implications. The regulation of plant growth is a topic of both scientific and economic importance. Understanding the molecular mechanisms behind leaf size, shape and number could result in tools to improve food and bioenergy production.

Plant leaves start to grow as a result of the activation of transcription factors, proteins that bind to DNA and initiate the transcription of DNA to RNA. In other words, transcription factors are the triggers initiating the information from DNA to be translated into proteins and peptides, which determine cell type and function in all organisms. Some of the triggers that control leaf growth have already been identified but the question many cell biologists ask is; what are the mechanisms that regulate the transcription factors? This is what Mieke Van Lijsebettens and her group "Chromatin and growth control" at the Department of Plant Systems Biology at VIB/Ghent University, Belgium are looking into.

"The leaf has been developed as an experimental system to identify upstream regulatory genes for growth by analyzing Arabidopsis mutants with altered leaf size and shape," said Van Lijsebettens during her talk in Dresden. She reported that her group had found a putative upstream regulatory gene called HISTONE MONOUBIQUITINATION 1 (HUB1) that mediates gene activation and cell cycle regulation by chromatin modification leading to the coordination of growth in multiple organ types.

For more information see the EuroDYNA website at www.esf.org/eurodyna

EuroDYNA starts to unlock Pandora's Box of genome function



Colin Logie

A moment with Colin Logie

In a recent interview, Colin Logie, Chair of the EuroDYNA Scientific Committee, talks about organising the EuroDYNA session at ELSO and about future challenges for the cell biology field and for EuroDYNA.

Why did you choose the topic “Chromatin and the cell cycle” for the EuroDYNA session at ELSO?

Although we know a lot about the cell, DNA and chromatin, we still lack insight into how it functions. To understand how things function you have to put them into context. One thing about life is that it is cell based and one thing about cells is that they are always the product of the cell division of a previous cell. So, to really understand chromosomes we really have to understand how the chromosomes behave in the cell cycle. I think during the session we saw an example of very disparate talks ending up with conclusions about chromosomes which fitted together because they fit the context of the cell cycle as the common denominator.

What, in your opinion, are the challenges in your field?

One of the frontiers of this field is to really see what happens inside living cells. We have done many beautiful experiments in the recent past (by we, I mean the Scientific Community) but what we really need is multi-molecular assembly dynamics data. These things are very difficult to see at the moment and we really need to be able to see them to find out which factors are playing roles of messengers and which ones are playing more structural roles. Essentially it boils down to physically describing the isomerisations that take place in the cell, the DNA and also in the membranes. We also need to find ways of estimating the energetic code of each transaction and of integrating these types of data over multiple length scales from the nanometer to the micrometer. From this we should be able to formulate a mathematical description of biological systems.

What's also a big challenge is our ability to monitor things at the right timescale. We know that molecules function on the level of millions as well as thousands of a second and this spans six maybe even seven orders of magnitude. Right now we don't have good modelling systems to integrate all the data at those different time and length scales and I think that's a major challenge. It's not so complicated to address this. We need durable funding of scientific research; we need to maintain and sometimes also improve career opportunities, support institutes where innovation and originality are encouraged and promote communication amongst scientists. The latter is very important and something that ESF has been doing very well. We need communication between disciplines but also within disciplines.

What can the Scientific Community expect from EuroDYNA as a collaboration?

One field which is moving forward at the moment is nanoscience. By looking in great detail using biophysical methods on single molecules we are actually studying nanomotors which are driven by ATP. The exciting application for this is that maybe one day such motors can be harvested to produce DNA-based machines. EuroDYNA's contribution in this field involves what we are doing in defining the forces that are deployed by these motors. At the moment the physical description of biology is lagging behind but we are getting there now by finding forces, distances and time.

The full podcast with Colin Logie can be found on the EuroDYNA website at www.esf.org/eurodyna

Finding a cure for cancer: the holy grail of science



Mendel Centre, Brno

At the EuroDYNA conference in Brno, Czech Republic in 2006, scientists from around Europe came together to share their research carried out in the field of genetics and cell nucleus architecture. A greater understanding of the body's building blocks might ultimately lead to a better understanding of human diseases.

Understanding DNA damage

Jiri Bartek from the Danish Cancer Society in Copenhagen in Denmark, is one step closer to understanding the route of cancer through his work on cell response to DNA damage. By using a UV laser to damage DNA strands inside tumour cells, the Copenhagen team is able to directly observe the different checkpoints in the cell.

Each time a cell divides its genetic information must be doubled in order for the genes to remain the same. A cell that is about to become tumorous can not make this genome replication and division without errors. To spot errors in the genetic material cells have evolved mechanisms to slow down or block cell division (so called cell-cycle checkpoints), promote DNA repair, or eliminate damaged, hazardous cells by engaging a cellular suicide program. How cells make the choice between life and death in response to DNA damage is critical not only for the fate of each cell, but also for avoiding life-threatening diseases such as cancer.

In cells with an early pre-tumorous change, the entire checkpoint network is activated. The system puts an end to such cells or blocks their division by a process of cellular senescence. On the other hand, defects in the DNA damage response machinery, or a phenomenon of checkpoint adaptation (when the cell arrest is long-term and not irreversible) may allow the cell to escape from the DNA damage-imposed blockade and despite its damaged DNA, it may multiply. This can give birth to a tumour.

Bartek and his team have found that if an inhibitor called Chk1 kinase is added, this ends what is called the G2-phase cell cycle checkpoint, a mechanism that is often still preserved in cancer cells, and this can tip the balance of life-or-death decisions towards cell death. This strategy might be useful to sensitise cancer cells to treatment with DNA-damaging irradiation or chemotherapeutic drugs, by eliminating the sick cells. Although a cure for cancer is still far away, this has great implication for the future of cancer research.

The team is also looking in depth at the pathways of repair in response to DNA damage and they have found that a whole host of proteins rapidly congregate in and around the damage site and begin repair. When the repair proteins fail to fully repair the DNA damage, there is a danger of the DNA lesion to be fixed as a mutation, and eventually this might lead to a cell becoming tumorous.

"If we can understand the function of these preventative proteins, we can learn how cancer develops and then better prevent or treat it", says Simon Bekker-Jensen from the Danish Cancer Society team.

Finding a cure for cancer: the holy grail of science



Understanding the pathways

The understanding of individual disease response pathways is increasing as Pavel Kovarik from the Max F. Perutz Laboratories at the University of Vienna has demonstrated. He is looking at two signalling pathways which are regulated by stress or interferon and related to immune response. Although both pathways can be activated by independent stimuli, an immune response is only obtained when both pathways are acting on the gene at the same time. This happens when the body is defending itself against pathogens and tumours. By looking at the order, location and contribution of stress and interferon induced changes on chromatin modifications (DNA damage) and nuclear architecture, our understanding of gene expression regulation will improve. This will open up new possibilities to combat disease.

Measuring radiation

There is still a lot to learn about DNA damage response. The conference emphasized that current research is only scratching the surface but EuroDYNA's efforts have brought about exciting new methods such as the ion microbeam developed by Anna Friedl and colleagues from the University of Munich.

"We want to understand what is disturbed by ionizing irradiation, and what are the cellular responses to these disturbances, in order to further understand how ionizing radiation induces cancer or cell death. People currently start to think not only about DNA damage and mutations, but also about epigenetic disturbances, for example alterations in chromatin structure, which may affect gene expression," said Friedl. "We came up with the idea of using an ion microbeam in 1999 but it has taken us a long time to make our idea happen".

By using several types of ions all with different velocities she can transmit energy levels of different strengths through a substrate and induce very precise double-strand DNA breaks. UV lasers can also be used to target individual cells or even subcellular regions, and they are cheaper and much easier to handle, but the ion beam has the advantage of using real ionizing radiation.

In reality, UV lasers would not be harmful humans but the effect from ionizing radiation (background, medical applications and so on) is inevitable. Friedl's work gives the ability to make detailed observations of the effects of ionizing radiation on individual cells, research which might ultimately give us an idea of the effects of radiation treatment on cancer patients.

"Another important point is intercellular communication. Can a cell that has experienced radiation damage give signals to undamaged cells and change the behaviour of these cells", Friedl questions.

Friedl's work is preliminary but she and her team have found a first gene product (Mdc1) that appears to be required for inhibiting mobility of damaged chromatin. If damaged chromatin were allowed to move around in the cell nucleus, chances would be higher for DNA ends from different breaks to meet, and this might increase the frequency of chromosome aberrations.

To sum up the conference, it was clear that pan-European collaboration was the driving factor making this research possible.

"It is important to note that these kind of projects require a close collaboration of nuclear physicists, cell biologists and radiobiologists", commented Friedl about her project.



Poster session, Brno

Final EuroDYNA conference at The Wellcome Trust Conference Centre in Hinxton, UK, 28-31 May 2008

The meeting will feature the scientific achievements of the Programme and have a dedicated session to discuss future directions of the field and funding opportunities between investigators and representatives of funding agencies.

More information at www.esf.org/eurodyna



The Wellcome Trust Conference Centre in Hinxton, UK

The brains behind EuroDYNA



Niels Galjart



David Shore

EUROCORES is the European Science Foundation's flagship activity. It supports interdisciplinary research in non-traditional areas, thereby opening new horizons in science. With EuroDYNA, one of the EUROCORES Programmes, coming to an end, some of the Project Leaders have shared their experiences from the Programme with us.

"Thanks to EuroDYNA, nine research projects were funded that may otherwise not have been funded. Therefore, European research in the area of nuclear dynamics and architecture has been stimulated. Without EuroDYNA I would not have been able to perform the research I have carried out over the last three years. One aspect of EuroDYNA that I like a lot is the lack of bureaucratic burden compared to other research programmes. Another very important aspect is that the EUROCORES programmes are suggested by the scientists themselves (bottom-up approach). Finally, a great added value is the willingness at ESF to stimulate discussion among scientists, by organizing conferences, workshops and brainstorm meetings. As a EuroDYNA member I have benefited enormously from this valuable resource," said Niels Galjart, Department of Cell Biology and Genetics, Erasmus University, Rotterdam and the Project Leader of "Role of multi zinc finger proteins CTCF and BORIS in the dynamic change of the nuclear architecture and chromatin function during cell cycle and differentiation".

There is no doubt that EuroDYNA has achieved some great results and many of these results stem directly from the EUROCORES Programmes' focus on networking and collaboration. David Shore, University of Geneva and the Project Leader of "Environmental stress-induced dynamic modulation of chromatin structure, gene expression and nuclear architecture in yeast" commented, "My project recently entered into collaboration with a lab in Vienna. This wouldn't have happened if it weren't for EuroDYNA. The Vienna group is interested in understanding how arsenic affects cells and of course this has important global health implications. Arsenic is a pollutant in drinking water in many places in the world. Our collaboration began at a EuroDYNA meeting in Brno; we presented a gene we were working on that's involved in growth regulation in yeast cells and also in the cellular response to stress (which is what our project is aimed at understanding) when we were approached by a researcher from the Vienna group. The Vienna researcher noticed that this gene had also come up in his studies as a regulator of the cellular response to arsenic poisoning. As a result, we got together and did some more work which has now led to a manuscript ready for submission".



Pavel Kovarik

EuroDYNA has been successful in generating new and exciting collaborations that have been hugely beneficial to the people involved. Now the scientists are focusing on what happens next. EuroDYNA is finishing but new collaborations have been set up.

“For me personally, the rather generous funding of the networking activities within EuroDYNA turned out to be very useful. Although I still maintain close links with the original members of my Collaborative Research Project (CRP), I have now made several links with members of other CRPs which are also relevant for my future research,” said Pavel Kovarik, Vienna Biocenter Institute of Microbiology and Genetics and the Project Leader of “Control of stress and interferon regulated gene expression by transcription factors, histone modification and nuclear compartmentalisation” during a recent interview.



René Ketting

This viewpoint is shared by René Ketting, Hubrecht Laboratory, Netherlands Institute for Developmental Biology and the Project Leader of “Nuclear actions of mRNAs”. “I think scientific collaboration is essential. Many of my papers have resulted from collaborations that have been forged through meetings and exchange programmes. In my experience these collaborations are formed *de novo* on very different occasions, but a collective such as EuroDYNA is certainly a good catalyst for such interactions.

EuroDYNA is likely to have established new collaborations that will start to pay off in the future. I therefore think that the impact will not be limited to just the scientific progress that has been made during the funding period but will extend far beyond.”

Find full profiles of these and other Project Leaders on the EuroDYNA website at www.esf.org/eurodyna

Collaborative Research Projects (CRPs)

Cell biology of messenger RNA biogenesis

Project Leader:

Maria do Carmo-Fonseca
University of Lisbon, Portugal

Principal Investigators:

Torben Heick Jensen
University of Aarhus, Denmark
Walter Keller
University of Basel, Switzerland
Jørgen Kjems
University of Aarhus, Denmark
Angela Krämer-Bilbe
University of Geneva, Switzerland
Ulrike Kutay
Swiss Federal Institute of Technology (ETH), Zürich, Switzerland
Marc Timmers
University of Utrecht, The Netherlands

Role of the multi zinc finger proteins CTCF and BORIS in the dynamic change of the nuclear architecture and chromatin function during cell cycle and differentiation

Project Leader:

Niels Galjart
Erasmus University, Rotterdam, The Netherlands

Principal Investigator:

Rainer Renkawitz
Justus-Liebig University, Giessen, Germany

Spatio-temporal organisation of genome surveillance in live cells

Project Leader:

Roland Kanaar
Erasmus University, Rotterdam, The Netherlands

Principal Investigators:

Jiri Bartek
Institute of Cancer Biology, Copenhagen, Denmark
Thomas Cremer
Ludwig-Maximilians University, Munich, Germany
Günther Dollinger
Munich University of Technology, Garching, Germany
Anna A. Friedl
Ludwig-Maximilians Universität, Munich, Germany
Jan H.J. Hoeijmakers
Erasmus University, Rotterdam, The Netherlands
Adriaan Houtsmuller
Erasmus University, Rotterdam, The Netherlands
Alan Robert Lehmann
University of Sussex, Brighton, United Kingdom
Jiri Lukas
Institute of Cancer Biology, Copenhagen, Denmark
Leon H.F. Mullenders
University of Leiden, The Netherlands
Wim Vermeulen
Erasmus University, Rotterdam, The Netherlands

Nuclear action of miRNAs

Project Leader:

René F. Ketting
Netherlands Institute for Developmental Biology, Utrecht, The Netherlands

Principal Investigator:

Marjori Matzke
Austrian Academy of Sciences, Vienna, Austria

Control of stress and interferon regulated gene expression by transcription factors, histone modification and nuclear compartmentalisation

Project Leader:

Pavel Kovarik
Institute of Microbiology and Genetics, Vienna, Austria

Principal Investigator:

Pavel Hozák
Institute of Molecular Genetics, Prague, Czech Republic

The role of linker histone variants and their phosphorylation in chromatin structure and function

Project Leader:

Herbert Lindner
University of Innsbruck, Austria

Principal Investigator:

Jean O. Thomas
University of Cambridge,
United Kingdom

Associated Partner:

Ingemar Rundquist
University of Linköping, Sweden

Chromatin higher order dynamics: A single molecule approach

Project Leader:

Colin Logie
University of Nijmegen, The Netherlands

Principal Investigators:

Alexander Brehm
Institute of Molecular Biology
and Tumor Research,
Philipps-University Marburg, Germany
John van Noort
University of Leiden, The Netherlands

The control of chromosome structure by cohesin/condensin complexes

Project Leader:

Jan-Michael Peters
IMP, Vienna, Austria

Principal Investigators:

Terence David Allen
Paterson Institute for Cancer Research,
Manchester, United Kingdom
Roland Eils
German Cancer Research Centre,
Heidelberg, Germany
Jan Ellenberg
EMBL, Heidelberg, Germany
Jan Löwe
Medical Research Council, Cambridge,
United Kingdom
Kim Nasmyth
University of Oxford, United Kingdom

Environmental stress-induced dynamic modulation of chromatin structure, gene expression and nuclear architecture in yeast

Project Leader:

David Shore
University of Geneva, Switzerland

Principal Investigators:

Gustav Ammerer
University of Vienna, Austria
Matthias Peter
Swiss Federal Institute of Technology
(ETH), Zürich, Switzerland

Associated Partner:

Francesc Posas
University Pompeu Fabra, Barcelona,
Spain

EuroDYNA Programme

The aim of the European Collaborative Research (EUROCORES) Scheme is to enable researchers in different European countries to develop collaboration and scientific synergy in areas where European scale and scope are required to reach the critical mass necessary for top class science in a global context. The scheme provides a flexible framework which allows national basic research funding and performing organisations to join forces to support excellent European research in and across all scientific areas. The European Science Foundation (ESF) provides scientific coordination and support for networking activities of funded scientists currently through the EC FP6 Programme, under contract no. ERAS-CT-2003-980409. Research funding is provided by participating national organisations.

www.esf.org/eurocores

The following national funding organisations support the EuroDYNA programme:

- Fonds zur Förderung der wissenschaftlichen Forschung (FWF)
Austrian Science Fund, Austria
- Grantová Agentura České republiky (GAČR)
Czech Science Foundation, Czech Republic
- Forskningsrådet for Natur og Univers (FNU)
The Danish Natural Science Research Council, Denmark
- Deutsche Forschungsgemeinschaft (DFG)
German Research Foundation, Germany
- Nederlandse organisatie voor Wetenschappelijk Onderzoek (NWO)
Netherlands Organisation for Scientific Research, The Netherlands
- Fundação para a Ciência e a Tecnologia (FCT)
Foundation for Science and Technology, Portugal
- Schweizerischer Nationalfonds (SNF)
Swiss National Science Foundation, Switzerland
- Medical Research Council (MRC), *United Kingdom*

Acknowledgements

We would like to thank the following persons for their contribution to this brochure:
The ESF Communications Unit for interviews, articles, production and proofreading.
Jackie McLelland for editing and proofreading.

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