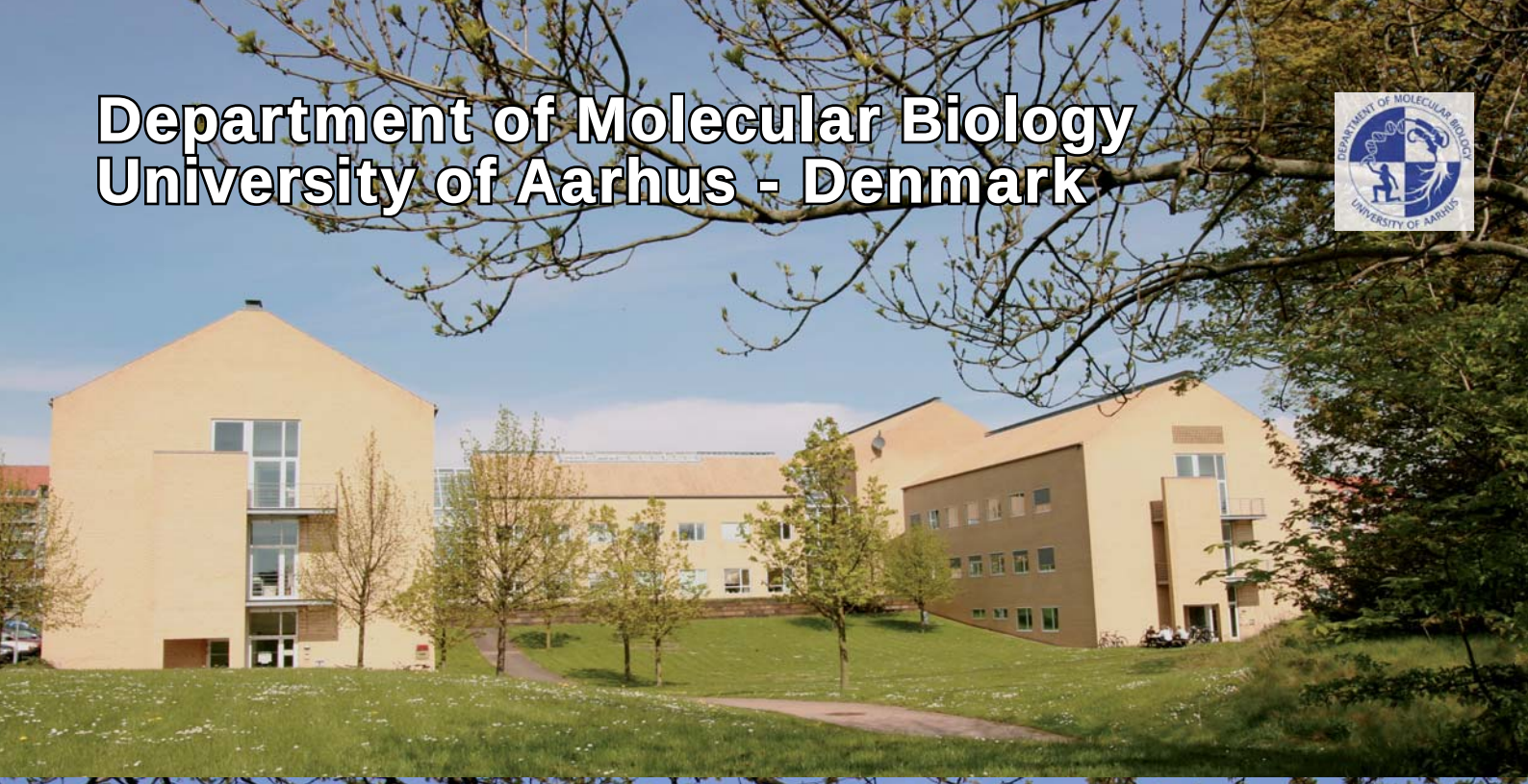
Department of Molecular Biology
University of Aarhus - Denmark



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MBI's 40th Anniversary - 4 June 2008

Preface

Characteristis of the 40 years old Department of Molecular Biology

by Erik Østergaard Jensen
Head of Department

The Department of Molecular Biology can celebrate its 40th anniversary. In many aspects, our Department shares characteristics which could be found among forty-year-old persons. It is full of vitality, experienced, ready for new challenges, calm, responsible, self-confident, open-minded and ambitious. However, it is important to realize that each person at the Department contributes with her/his unique qualities to this profile.

Full of vitality

A successful generation shift has introduced many dynamic group leaders to the Department with a pronounced tradition for collaboration and respect for each other. This has already proven successful for sustaining a highly respected Department and will be important for future challenges. More than 120 PhD students and young post-docs also contribute significantly to the vitality of the Department

Experienced

The Department hosts a number of senior scientists who contribute with important networks, a wealth of experimental and teaching experience, and they can tell the story of molecular biology, forming the foundation for young scientists.
The support staff at the Department also has a lot experience. The technicians are the focal point of our laboratories and they make sure that no valuable information or material is lost. The workshops keep all our equipment up and going.

Ready for new challenges

A few years ago it was decided that engineering should be part of the Faculty of Science. The Department took up the challenge and has launched a biotechnology bachelor study programme, and at present we are preparing an MSc degree programme in process technology to be offered in 2009 and is in the process of establishing a new engineering-based research area.

Calm

During the recent years, several new administrative systems have been imposed at the Department: a new accounting system, a database for publications and activities, new websites, electronic calendars, etc. The introduction of these systems has been very stressful and has required lot of patience for all the users. Thanks to a very dedicated support staff, these systems are now running and are in general very helpful.

Responsible

Last year, 165 students were enrolled at the three study programmes offered by the Department. Molecular Medicine was launched in 2007, Biotechnology in 2006 and Molecular Biology in 2002. The establishment of these new study programmes with the large number of students has only been possible because all teachers including PhD students have shown responsibility for their share of the teaching load, and the overall work has been very well coordinated, from individual courses to study programmes.
The education of the 83 PhD students presently enrolled at the Department also requires a dedicated contribution from supervisors and committee members organizing the education.

Self-confident

A number of our researchers have applied for prestigious national and international grants, and with great success. The Department is a partner in more than 10 EU and NIH research programmes; the Department is heading three Centres of Excellence by the Danish National Research Foundation and is a major partner in two other Centres of Excellence out of a total of 38 national centres.

Open-minded

The major part of the research at the Department is related to health issues. When Molecular Medicine was announced to be a focus area at the University in 2005, the Department initiated a collaboration with the Faculty of Health Sciences. It has previously proven difficult to integrate these different research traditions in formal structures. However, we now have a new study programme in Molecular Medicine with contributions from both Faculties and a PhD field in Molecular Medicine

Ambitious

Several groups at our Department are recognized worldwide for their research, we have started three new study programmes within the past six years and we educate PhD students who are accepted as post-docs at high-ranking universities.
But we can get even better if we work together for the same goal and take responsibility for each other. It is important that all groups at the Department can benefit from the very successful groups. This could be done by strategic collaborations and applications that can improve the general level of funding at the Department, ensuring that all groups can afford to educate Master and PhD students. The financially strong groups can also be the driving force for core facilities that all groups can benefit from. A better infrastructure to support the preparation of applications would also contribute to more and high-quality applications.

In conclusion, the Department Molecular Biology is a very healthy and strong 40 years old Department with all the skills and resources required to meet the challenges in a period of time where competition is the mantra.

40 years with Molecular Biology

by Niels Ole Kjeldgaard at the 25th Anniversary of the Department (1968-1993) - and Erik Østergaard Jensen (1993-2008)

The Molecular Biology Department was established during an especially favourable time for Danish research. Throughout Denmark it was recognized that research and education were central issues for the country's economic and cultural future, and that the majority of the population should have the opportunity to take an education to the highest possible level. During the 1950s it was decided to expand the existing universities and departments of higher learning as well as to found new universities.

An auspicious start

The University of Aarhus was part of this picture, and during 1960 it was decided that its biology teaching should be broadened to include subjects that were previously taught only at the University of Copenhagen. At the beginning of the 1960s, professorships in Zoology. Botany and Genetics were established so that teaching to Bachelor and Master levels in the Biological Sciences could begin. At this time a typical department's personnel consisted of one Professor, one Head of Department and two to three Associate Professors. Thus, the faculty's plan in 1966 was that the biology department as a whole should have 13 Professors, 15 Heads of Department and 39 Associate Professors. Naturally there were also major building plans.

In the autumn of 1965 the Faculty of Science set up a committee to study the requirements for expansion of the Biology teaching at the University of Aarhus. In addition to the Professor of Botany from Aarhus University Dr. Kai Larsen, the committee included four Professors from the University of Copenhagen: Dr. C. Barker Joergensen (Zoophysiology), Dr. Morten Lange (Botany), Dr. Ole Maaloe (Microbiology) and Dr. K. G. Wingstrand (Zoology). The committee unanimously supported the expansion plan and it was suggested that Professor-ships and Departments be set up in the fields of Genetics, Plant Physiology, Zoophysiology and Molecular Biology. It was a time when the Ministry could meet the financial demands so in 1966 a Professor of Genetics was appointed, followed in June 1967 with the appointments of Professors of Plant Physiology and Molecular Biology.

Biology teaching began with selected students continuing to follow courses in Copenhagen. It was very important for securing a good teaching base in Aarhus that the Faculty recognized that it could be a catastrophic start if the new subjects were immediately overwhelmed by high student numbers. Therefore, an agreement was made that students, even after the new departments were set up, could still, after selection, continue to study in Copenhagen until satisfactory buildings could accommodate them in Aarhus. This decision was an important basis for the successful expansion of our Department in that attention was paid to the development of the subject matter rather than the pressure of teaching when it came to appointing Department staff.

Niels Ole Kjeldgaard was the first Professor to be appointed at the new Department for Molecular Biology in 1967

The first steps

The middle of the 1960s saw huge University building projects. The Mathematics Department was about to be completed and from October 1968 it was able to provide space for the Molecular Biology Department that was founded by the University Senate on the 5th of June 1968. The Department was housed in the H-wing at one end of the attic, while Micropalæontology was housed at the other end. During 1967 the Geneticists had likewise found housing with the Mathematicians while the Department for Plant Physiology came under the wing of the Botanists in the offshoot of the Natural History Museum.

The building plans for laboratories and teaching facilities were completed in 1967. They foresaw a chain of buildings in the eastern part of what then was a military parade ground and garages. The financing for the first link in this chain was in order, the plan for the 3200 square meters Biology 1 building was finalized and the invitation to submit tenders took place in December 1967.

It was originally planned that this building should house Plant Physiology, Genetics and Molecular Biology. In the meantime the Geneticists' primary interests had moved towards population genetics and they wished to have their own building attached to Mathematics.

The new Biology II building was built in 1973

Kjeld Marcker employed as Professor in Biochemistry in 1969

The Faculty had earmarked a Professorship for Biochemistry, and in May 1969, Kjeld Marcker was appointed to this position. It was obvious that a Biochemistry Department should be housed in the Biology I building which was completed in the summer of 1970. Kjeld Marcker and I agreed that there was no advantage in having two Departments and that we should join forces in a Department for Molecular Biology. In June 1970, Staffan Magnusson came to be Head of Division for Protein Chemistry.

It was still a time for optimism, even though a student revolution had shaken both the world and the University, resulting in a new kind of governing body. A newly drawn up plan for the next building in the Biology complex was completed in the summer of 1970 and the biology expansion prognosis for 1975 called for a scientific staff of 17 Professorships, 17 Departmental Heads, 60 Associate Professors, 8 Guest Professors and 70 Post Graduates as well as buildings amounting to 31,000 square meters and an annual uptake of 150 students.

Staffan Magnusson employed as Head of Division for Protein Chemistry in 1970

Scientific Activities

Already during the first couple of years, research at the Department was faring well. It was concentrated on three main fields: Regulation of RNA synthesis in bacteria; control mechanisms for protein synthesis in eukaryotic cells; the amino acid sequence of prothrombin. The money for buying apparatus was included in the money given for the building, while the scientific positions that were earmarked for the Department allowed us not only to appoint Danish researchers but also to invite foreign guests. In the summer of 1970, Professor Eugene Goldwasser from the University of Chicago was invited to hold a series of lectures on cell differentiation, while in 1971 Professor Masayasu Nomura from the University of Wisconsin came to the Department as Guest Professor. At the same time our international contacts were strengthened when we organized the first Linderstroem-Lang conference on "Informational Structures" in August 1971 as well as two EMBO courses and symposia on "Mammalian Protein Synthesis" in June 1972 and 1973.

Problems build up

The boundless optimism for expansion that had marked the Department's inauguration could not continue. At the beginning of the 1970s grants for staff positions and buildings were no longer plentiful.

Biology II had been planned and the project went ahead more or less according to plan but the financial situation regarding further buildings in the biology complex was discouraging.

In connection with the general building fever, the University's building programme included a new addition to the Chemistry Department on the allotments on the other side of Langelandsgade. The Ministry of Education had acquired this land in 1968 and the Building Inspector for the locality had a drawn-up plan for Chemistry II already in the summer of 1971. In the spring of 1972, the Faculty saw the possibility of creating the necessary space for Biology by moving the Department for Molecular Biology to Chemistry II. This building should house teaching facilities as well as a the Group of Biostructural Chemistry, which was to be established at the Chemistry Department.

The Department's acceptance of the Faculty's plan raised a storm of unforeseen problems. The other Biology Institutes protested strongly against moving Molecular Biology from the planned complex. Even the Department for Genetics was against this plan. The good relations that existed between the Rector and some Biologists meant that on several occasions the Rector would override the Faculty's decisions. The democratic conflict between the Faculty's majority and individual Biologists resulted in the Rector cancelling the planned building of Chemistry II and sacrificing the relatively huge investment in the project. This created a very tense atmosphere that also

caused a reduction in the amount of space allotted to Molecular Biology in Biology II.

Under the heated conflict, the architect C.F. Moeller submitted a very optimistic time plan of under two years for the completion of the Biology III building, though there was still a lack of funds and no teaching facilities for 2nd-part students of Biology. Therefore, in 1973, Copenhagen University confirmed that Aarhus students could continue in Copenhagen until 1975. Over the entrance to Biology III, which houses the teaching localities, is written "Built in the years 1977-1979"!

The move to Biology II took place in the spring of 1974. The Department had its first graduate in 1973 and its first PhD was given in 1974, and gradually all studies could be taken in Aarhus. From about 1983, the Department's graduate production reached a relatively constant level.

Recent times

Economic problems put a brake on the planned further expansion of Biology though we still had time to dream. Biology IV, that also appeared in the overall building plans and had already had its own building committee, is now a twenty-year old dream that remains unfulfilled.

It was first when the Science Park was built that in 1991 with a contribution from the Bioregulatory Research Centre that it became possible to ease the rapidly accumulating space problems in Biology I and II. Kjeld Marcker's group was able to secure satisfactory space by moving to Gustav Wieds Vej. Later, in 1992, one of the protein groups under the leadership of Torben Ellebæk Petersen, also moved, supported by the food technology programme FØTEK. These moves have naturally served to ease the space problem for the Department but at the same time they have resulted in thinning out of the research potential in the original Department and a change in the research environment.

Therefore, on the occasion of the 25th anniversary of the founding of the Department it must be a big wish that the old plans for the construction of a new research and teaching building will soon be fulfilled.

Scientific staff

Within the faculties that were created after 1972 there was a wish to set up larger Department administrative units. This led to the Department of Plant Physiology amalgamating with the Department for Molecular Biology in the spring of 1976. Professor Poul Larsen died in the summer of 1976 and in keeping with the desire to restrict spending, this professorship was lost and has never been replaced. In 1983, a group from the then Department for Genetics and Ecology moved across to the Department for Molecular Biology. Even though, on paper, staff numbers were growing and the Department gained new research fields, there was no dramatic change for Molecular Biology.

A recruiting plan for research has over the years brought the Department new staff positions at a slow pace. On the other hand, the Department suffered a severe loss on the death of Staffan Magnusson in 1990, and filling this vacancy is proving a long drawn out affair. The optimistic goal for the expansion of Biology, from 1975, is still along way from fulfilment.

Although until now I have named only the scientific staff, it does not mean that the allocation of technical and administrative personnel was more generous. This has followed the same pattern with the desired number far from the reality.

The Department's research and research funding

Despite limited space and despite much needed extra positions, the Department's research has fully lived up to expectations and has attained much world recognition. For example, it is worth mentioning that in 1973 the NOVO prize was given to Kjeld Marcker and in 1984 to Staffan Magnusson.

While the Department was being established, it was taken for granted that the financing of the University's departments would also cover the cost of research. However, during the recession, the funding from the University was unable to keep up with demand and it became more and more necessary to look for external funding. In the beginning of the 1970s the funding system was gradually changed to what was called a two-stringed system consisting of University and Research Council.

While it has become more expensive to carry out research, the continuing financial depletion of the Universities and the increased demand from the Research Council has meant that the two-stringed system has gradually become multi-stringed – consisting of project grants as well as private and international funding. Funding requirements have naturally meant that researchers must take into consideration the research topics that are currently popular and this has a tendency towards uniformity. The special project grants have become necessary for the continued existence of the Department's research. The Biotechnology Programme of 1987-1990 supported many of the Department's groups after the establishment of the Bioregulatory Research Centre just as the Biotechnology Centre for Plants had. In agreement with the central administration's implicit belief that change also improves the possibilities for good scientific collaboration, the earlier Centres, after a 5-year period, were replaced by the Centre for Human Gene Research, the Centre for Biomembrane Research, and the Centre for Plant Biotechnology,

Special programmes for MD Foods and FØTEK have given important general contributions to the funding of the Department's research. Similarly, private funds, especially The Cancer Society and The Carlsberg Fund have given important contributions in the form of research funding and stipends. Finally, international research must not be forgotten. Originally it was The National Institutes of Health that provided important support for protein chemistry research. Later, several of the Institute's research groups have taken part in a number of EU-research programmes.

25 years of Molecular Biology

In 1972, the first recombinant DNA molecules were constructed at Stanford University in California, and in 1973 a foreign DNA fragment was inserted in a plasmid and then transferred to *Eschericia coli* bacteria. These trials and the rapid technological development in Molecular Biology that has occurred over the past 20 years have had profound consequences for the Department of Molecular Biology, not only that laboratory personnel must now wear yellow lab coats to make believe that the work is dangerous.

Some traditional researchers believe that Molecular Biology is a thing of the past, but the development that started in the late 1970s has clearly shown the importance of having detailed knowledge of the cell's molecular mechanisms.

The Department for Molecular Biology has at all times been in the forefront of progress here in Denmark. The Department's scientific production and the large number of graduates, post-graduates and PhDs that have passed through have, to a high degree, influenced the development of Molecular Biology in Denmark, and have without doubt, reached the goal that was set 25 years ago.

The past 15 years of the Department of Molecular Biology (MBI):
A department on the move

by Erik Østergaard Jensen

MBI at different locations

The merger between the Biostructural Chemistry Group and the MBI in 1996 is one of the most important events in the recent history of the Department. Brian F.C. Clark founded the Biostructural Chemistry group in 1974, and his group's research has over the years been closely related to the activities at the MBI with a strong focus on the structural aspects of macromolecules. Three new wings were added to the Science Park in 1996 hosting the Biostructural Chemistry Group and two additional groups from the the MBI University Campus. Thus since 1996, the MBI has been divided physically into two equally sized units, the University Campus unit with focus on molecular biology and the Science Park unit with focus on proteins and plants. The structural biological research has now become an important and integrated part of many of the ongoing research projects at the MBI and is an example of a successful merger.


MBI - Science Park Unit


MBI - Campus Unit

Ever since the housing of the MBI's research groups in different locations, it has been our dream to get one house for all MBI's activities including the related study programmes. However, the successful expansion of the activities at the MBI has made the fulfilment of this dream almost impossible since the space available either at the Science Park or at Campus is not sufficient to house the more than 400 staff and students working at the MBI. To be realistic, the move of the University Hospital to Skejby in 10 years will be the only potential possibility to get one address in the foreseeable future. However, during the recent years the MBI has acquired some more space: a whole floor from Geology at Campus, a building from the Cancer Society at the Science Park and a whole floor at the Science Park. However, a very recent investigation of the space distribution at the Faculty of Science clearly demonstrated an urgent need for more space at the MBI, a conclusion the research groups at the MBI have known for years. A take-over of the remaining part of the Science Park by the Faculty of Science will be the most obvious immediate solution to solve part of this problem.


Science Park - Pavilion 3


Science Park - Pavilion 12

Several new study programmes

The Department has contributed to the education of molecular biology students from the very beginning; however until recently the students were enrolled either as biology or chemistry students. In 2002 the Department became the master of its own house by the introduction of a new bachelor programme in molecular biology with several different flavours, the human biology being the most popular. A total of 37 students were enrolled in the molecular biology study programme in 2003.

A recent initiative taken by the Faculty of Science, the Engineering College of Aarhus and the County of Aarhus resulted in the establishment of the Aarhus Graduate School of Engineering. The MBI decided to join the initiative and agreed to offer a technical bachelor in Biotechnology in 2006 and a Master of Science in Engineering in process technology to be launched in 2009. A group of teachers from the MBI took on the responsibility to develop the new study programme, and in collaboration with the Engineering College of Aarhus, we could welcome 22 engineering students in 2006.

In 2005, the University announced Molecular Medicine to be a focus area. A major part of the research at the MBI is within the scope of molecular medicine. The MBI therefore decided to be an important player in this initiative, and in collaboration with the Faculty of Health Sciences, we established a bachelor and a master study programme in Molecular Medicine. Several of our established courses were remodelled to provide the most relevant background for the new study programme, and new courses were established. The study programme was offered for the first time in 2007, and we got many more applications than the set limit of 60 students.

Very recently the MBI has contributed significantly to the establishment of an MSc study programme in Molecular Nutrition and Food Technology, a study programme offered by the Faculty of Agricultural Sciences.

The recent years have been very busy setting up new study programmes and courses with several different external partners – in 2007 we accepted 165 students in our three study programmes. Thus within a very short period of time, the MBI has increased the production of student study years from 180 in 2000 to 364 in 2007, the highest number at the Faculty of Science! And we have only seen the tip of the iceberg due to the large number of new study programmes. The big challenge for the future is to keep the high standards with an increasing number of students and to optimize all the new study programmes.

The MBI seminar programme with prominent speakers including several Nobel Prize Laureates is part of the study plan

The number of PhD students has increased from 50 in 2000 to more than 80 in 2008. More attention has been paid to the education of PhD students over the recent years. Every student is now associated with a small committee of external and internal advisors that regularly gives feed-back on their project. An honours' programme has been initiated to recruit highly qualified bachelor students who can subsequently be enrolled as Phd students.

Strong research groups at the MBI

The tenured scientific staff has increased from 28 to 34 over the past 13 years (17 new appointments and 11 retirements). The appointed associate and full professors have primarily consolidated and expanded the established research fields. However, one exception is the recruitment of a professor in biotechnology to support the new engineering study programme. None of the four founders of molecular biology and structural chemistry are employed at the Department any longer. Staffan Magnusson died in 1990, Niels Ole Kjeldgaard retired in 1994 and died in 2006, Kjeld Marcker retired in 2002 and Brian F.C. Clark retired in 2007, but is still associated with the Department. Another very important person for the Department, Jens Nyborg, died in 2005. We all owe them a lot for what they started.

The Department is presently divided into the following research fields: DNA Processing, RNA & Viruses, Cellular Signalling & Development, Plant Molecular Biology, Structural Biology, Protein Function, Protein Interactions, and Molecular Nutrition. However, numerous collaborative projects exist between these research fields. The profiling of the Department towards the university has been difficult, illustrated by the fact that until 2003, no professors had been appointed at the MBI except for the founders. However, this has changed over the past five years where seven professors have been appointed. The national awareness of the research at the MBI has also increased dramatically over the past few years. The research at the MBI has always been of high standards, but for a period some 5-10 years ago, we had strong competition from other universities in Denmark. The present state of our high research quality is well illustrated by the fact that the MBI is heading three Centres of Excellence by the Danish National Research Foundation and is major partners in two other Centres of Excellence out of a total of 38 national centres.

The establishment of the iNANO Centre at the Faculty of Science in 2002 has resulted in new - more technology-driven - research directions at the MBI. The MBI has also fostered several spin-off companies during the past 15 years like Borean Pharma, Cobento and Plantic; however the survival rate is low due to difficulties in attracting venture capital, and thus only Cobento exists today. The MBI is also one of the more active Departments when it comes to invention disclosures, last year being involved in 1/5 of all disclosures at the University

The new iNano building

External funding is the basis for all research at the MBI, and for the past 15 years external funding has increased from 25 M DKK to 73 M DKK. Thus, as a whole the Department is doing excellently, but the figures also hide large differences between the individual research groups. The national and international competition have become much more tough, and even groups with a solid publication record can have problems in attracting money for their research and education of Master and PhD students. This might have the consequence that some research programmes must be terminated and new have to be developed in areas with better funding. On a small scale this is probably healthy, but we also face the risk that some - less trendy projects - will die even if they scientifically are potentially very interesting.

Infrastructure

On the administrative side we have been challenged by a new accounting system, a database to register publications and activities, and latest an electronic calendar. However, after some years of running-in, the benefits are now becoming evident, and no doubt professional computer systems are required to manage the increasing number of students, staff and funding.

In 2003 the Danish Parliament passed a new law concerning the management of the universities. As a consequence, the Head of Department was appointed by the Dean in 2004 and not as previously elected by the scientific staff. Another consequence was a replacement of the Departmental board with a Departmental Council advising the Head of Department.

The past 15 years can best described as the period where molecular biology has become an integrated part of many different disciplines rather than being a specialized topic. At the Department we have experienced a successful generation shift, taking the best of - but not limited by - the traditions at the MBI. There is a pronouced collaborative spirit at our Department and this augers well for our future when facing the increasing international and national competition.

Plant Molecular Biology

Professor Jens Stougaard
Associate Professor Bjarne Jochimsen

Our research in plant molecular biology focuses on cellular mechanisms controlling organ development, cellular communication systems and mineral nutrition in the model plants *Lotus japonicus* and *Arabidopsis thaliana*. For comparative studies of regulatory and signal transduction mechanisms, zebrafish has also been included among the experimental organisms. The research activities is embedded in the Centre for Carbohydrate Recognition and Signalling (CARB) funded as a Centre of Excellence by the Danish National Research Foundation. CARB includes collaborators at University of Otago, Leiden University and University of Copenhagen and this international team applies interdisciplinary approaches such as molecular genetics, biochemistry, crystallography, carbohydrate chemistry, nanobioscience and bioinformatics to investigate cellular processes from the level of molecules to the level of living organisms.
The CARB Centre aims to understand interactions between cells and organisms by investigating the role of carbohydrates exposed on cell surfaces, and polysaccharide signal molecules secreted as part of a complex interaction between organisms. Characterisation of such cellular communication systems is important for understanding factors determining pathogenesis of microorganisms as well as immune responses, symbiosis and cell-to-cell signalling involved in the development and functioning of multicellular organisms.

Identification of a new class of LysM lipochitin-oligosaccharide receptors in the rhizobium-legume interaction coupled with the ability to manipulate both the ligand and the individual domains of the receptor experimentally has opened new opportunities for functional analysis of polysaccharide receptors. LysM domains are widespread and appear to possess an unusual flexibility in ligand-binding specificity combined with a possible multi-domain mode of ligand binding. Structural and functional characterisation of human, zebrafish and plant LysM domains, their ligand-binding properties and their mechanisms for converting recognition into signalling and cellular responses, is therefore of broad scientific interest and a central theme in the Centre's activities. Effective plant and bacterial genetic methods are used to identify components recognising exo- and lipopolysaccharides exposed on cell surfaces. Cell response mechanisms related to plant hormone signalling and control of the cell cycle is integrated into these cell-to-cell signalling studies. The interaction between cell cycle activation and cell differentiation is of particular interest for understanding development and cancer. Combining an assortment of genome information and technologies available in the model organisms, the aim is to take the analysis of signalling processes in multicellular organisms to a new level, distinguishing events in tissues, cells and nuclei and to establish an understanding of fundamental life-processes in animals, humans and plants.

Adding colour and flavour to the activities food related processes in seed development and plant uptake and deposition of iron are

also investigated. A diverse set of physiological methods, proteomics and genetics is used in these studies aimed at improving the nutritional quality of seeds and improving the content of available iron and other minerals in plants. The natural diversity in legumes like the model plant *Lotus japonicus* and common bean is one of the sources investigated in an attempt to contribute towards breeding of better plants for food and feed.

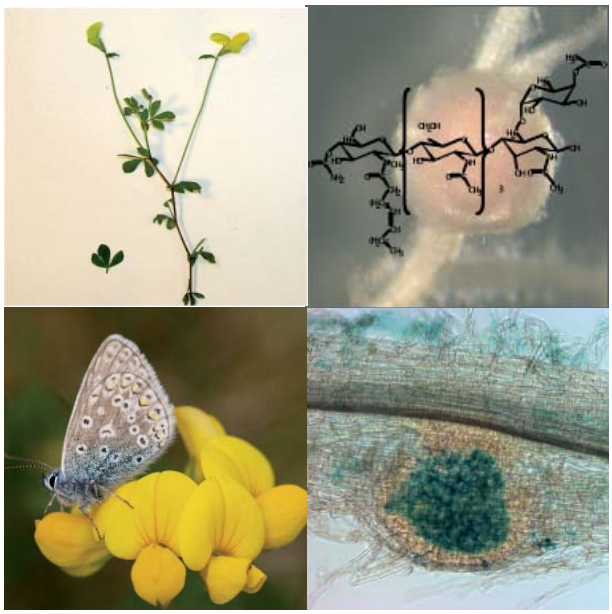
Radutoiu, S., Madsen, L.H, Madsen, E.B, Felle, H., Umehara, Y., Grønlund, M., Kaneko, T., Sato, S., Tabata, S., Sandal N. and Stougaard, J. (2003) Plant recognition of symbiotic bacteria requires two LysM receptor-like kinases. Nature 425, 585-592.

Madsen, E.B., Madsen, L.H., Radutoiu, S., Olbryt, M., Rakwalska, M., Szczyglowski, K., Kaneko, T., Sato, S., Tabata, S., Sandal, N. and Stougaard, J. (2003) A receptor-like kinase gene involved in legume perception of rhizobial signal molecules. Nature, 425, 637-640.

Tirichine L., Imaizumi-Anraku H., Yoshida S., Murakami Y., Madsen L.H., Miwa H., Nakagawa T., Sandal N., Albrektsen A., Kawaguchi M., Downie A., Sato S., Tabata S., Kouchi H.,Parniske M., Kawasaki S. and Stougaard J. (2006) Deregulation of a Ca2+/calmodulin-dependent kinase leads to spontaneous nodule development. Nature 441, 1153-1156.

Tirichine, L., Sandal, N., Madsen, L.H., Radutoiu, S., Albrektsen, A., Sato, S., Asamizu, E., Tabata, S. and Stougaard J. (2007) A gain of function mutation in a cytokinin receptor triggers spontaneous root nodule organogenesis. Science 315, 104-107.

Radutoiu S., Madsen L.H, Esben Madsen B., Jurkiewicz A., Fukai E., Quistgaard EMH, Albrektsen A.S., James E.K, Thirup S., and Stougaard J (2007. LysM domains mediate lipochitin-oligosaccharide recognition and Nfr genes extend the symbiotic host range. EMBO J 26, 3923- 3935.



Protein function

Professor Claus Oxvig
Associate Professor Peter Andreasen
Associate Professor Kim Kusk Mortensen
Associate Professor Lars Sottrup-Jensen
Associate Professor Hans Chr. Thøgersen
Associate Professor Hans Uffe Sperling-Petersen

Our current research programs focus on biological systems regulated by proteolysis, all relevant to human physiology. We study fundamental biochemical problems, but whenever possible, we make connections between basic biochemistry and human disease. Protein design and combinatorial protein biochemistry is our second major research focus. We generate e.g. monoclonal antibodies, useful in the development of diagnostic methods and novel therapeutic approaches.

The problems we try to solve are approached experimentally using a wide variety of modern biochemical methods. The area of expertise covered by members of our laboratories is broad, ranging from classical protein chemistry and biophysical analysis to modern techniques of molecular and cellular biology. Recently, we have implemented the zebrafish as a vertebrate model system of human physiology. We are actively engaged in national and international collaborative projects with other laboratories.

Zebrafish

Proteolytic regulation

Approximately 2% of human genes encode proteolytic enzymes. The regulation by specific proteolytic cleavage is common in biological systems, emphasizing its importance. We have a longstanding interest in biological systems that function to regulate e.g. cellular growth and homeostasis, mainly systems that are relevant in human reproduction and cardiovascular function, but also human disease such as cancer and arteriosclerosis. Our general experimental strategy is 1) to connect knowledge of protein structure with biochemical function, 2) to analyze such function in cell-based model systems, and 3) to explore its physiological role in animal models. We seek to connect basic knowledge with human disease in order to understand pathological mechanisms, or to develop novel methods of diagnosis or novel therapeutic strategies. Our research lies mainly within three biological systems: The insulin-like growth factor system (CO), the plasminogen activator system (PA), and the complement system (LSJ).

- The insulin-like growth factors (IGFs) are polypeptides with effects on cell proliferation and differentiation. The IGFs bind to the IGF receptor, but six homologous binding proteins, IGFBP-1 to -6, have higher affinities for the IGFs and therefore inhibit receptor stimulation. However, bioactive IGF can be released by specific proteolytic cleavage of the IGFBPs. By this mechanism, the metalloproteinase PAPP-A controls the activity of IGF in many normal tissues, and also

in cardiovascular disease and cancer. We study how this system functions at the cell surface, and we are interested in several associated extracellular regulatory mechanisms. Knowledge of such principles can be used in the development of novel diagnostic methods and drugs. For example, the direct inhibition of IGF signaling is a novel therapeutic strategy in cancer treatment. However, specific inhibition of growth promoting proteolytic activity, i.e. inhibition of PAPP-A, represents a valuable alternative, in particular because unintended interference with other signaling pathways, e.g. insulin signaling, is avoided by such approach. We therefore develop inhibitors of PAPP-A as prototype protein drugs to provide proof-of-concept in animal models (zebrafish and mouse) of human disease.

• Plasmin is an extracellular serine protease which is able to degrade many extracellular proteins. Plasmin is important in turn-over of extracellular matrix. Plasmin is generated by proteolytic activation of the ubiquitous zymogen plasminogen. The activation can be catalysed by either of two serine proteases. Tissue-type plasminogen activator (tPA) catalyses plasminogen activation in blood, whereas urokinase-type plasminogen activator (uPA) catalyses plasminogen activation in tissues. Plasmin as well as the plasminogen activators are regulated by specific proteinaceous inhibitors, i.e., alpha2-antiplasmin and plasminogen activator inhibitor-1 (PAI-1). uPA-catalysed plasminogen activation is particularly interesting in relation to invasive growth and metastasis by malignant tumours. The group was established in Aarhus in 1989. The main contributions have been in studies of transcriptional regulation of PAI-1 expression; plasminogen activators in milk; uPA and PAI-1 as prognostic markers in cancers; PAI-1 inhibitory mechanism; molecular mechanisms of endocytosis of serine protease-serpin complexes; PAI-1 as a regulator of cell migration; PAI-1 expressing cell types in tumours; PAI-1 and uPA inactivators. During its time in the department, the group has published exactly 100 papers which have been quoted more than 5,500 times.

• The complement system is part of the effector branch of the immune system. Upon complement activation, targets such as invading microorganisms become destined to destruction and elimination. The system consists of more than 30 plasma and membrane proteins, several of which are proteinases or substrates. We are principally interested in understanding the relationship between structure and function of complement proteins. Recently, we have contributed to the determination of high resolution structures of entire complement proteins.

Protein design

The primary aims of our protein engineering & design efforts are 1) to provide tools for biochemical analysis of protein synthesis (KKM, HUSP), and 2) to develop tools for protein production and the utilization of recombinant proteins (HCT). As a blueprint in our engineering efforts, we seek inspiration in the many cases were established structural (and functional) protein modules are used repeatedly in the evolution of complex multifunctional proteins.

• Many protein factors are involved in the process of translation in prokaryotes. The initiation process involves mRNA, the ribosomal subunits,

three initiation factors, IF1, IF2, and IF3, and fMet-tRNAfMet. Although the three-dimensional structures of most of the components are known at the atomic level, many aspects of the initiation process are still to be understood. We try to understand biochemical and structural details by means of several approaches. One approach involves the generation of antibodies – mono- and polyclonal as well as phage displayed single chain antibodies – against the initiation factors. Recently, we have also contributed with structural data using both NMR and SAXS. Additionally, we exploit the process of protein synthesis in our continuous effort to develop more efficient vectors for heterologous expression in *E. coli*, a scientific field, where we are at the cutting edge worldwide. Other projects in the laboratory are focusing on design, production and characterization of designed enzymes and self-assembling protein structures.

• Early research in sequence-specific proteolysis (in blood coagulation) led to Factor Xa being recognized as the first usable tool for efficient cleavage of fusion proteins, and more recently even more efficient proteases have been developed for this purpose. Structural studies of other mosaic proteins (e.g. tetranectin) provided a starting point for devising numerous new hybrid proteins, multimerised, or armed with tetranectin-derived binding modules with new binding properties rivaling those of antibodies in terms of

Figure

Zebrafish embryo, 36 hours post fertilization. Development of the fertilized egg can be observed directly and progresses fast – segmentation begins at 10h and following 24h, the heart is beating. The zebrafish has many other advantages which makes is an attractive model organism in e.g. developmental studies and drug development.

specificity and affinity. Most of this exploitation research was carried out in a spin-out company (Borean A/S), which eventually was sold off in bits, bringing in revenues in excess of 250 million Danish kroner in toto. Future research will seek to explore further ways of constructing new enhanced affinity tag / ligand systems that will further enhance the utility of the toolkit available to anyone with a need to manipulate recombinant protein products in research or for any other purpose.

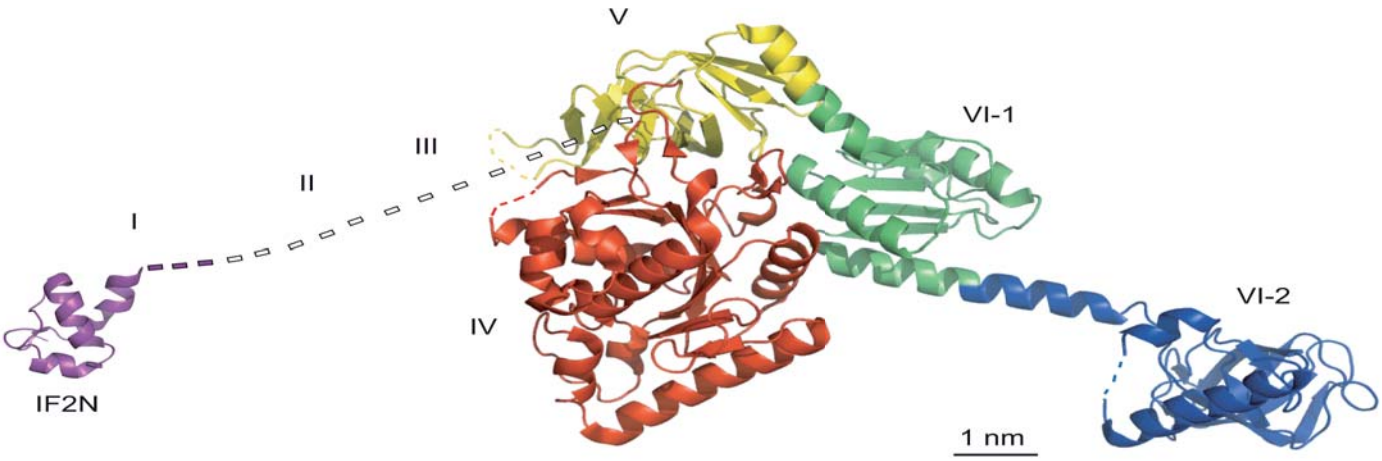
Fynbo CH, Lorentsen RH, Etzerodt M, Thøgersen HC, Holtet TL (2005) Characterization of a recombinant granzyme B derivative as a "restriction" protease. Protein Expr. Purif. 39, 209-18.

Fredslund F, Jenner L, Husted LB, Nyborg J, Andersen GR, Sottrup-Jensen L (2006) The structure of bovine complement component 3 reveals the basis for thioester function. J. Mol. Biol. 361, 115-27.

Hansen, M, Wind, T, Blouse, GE, Christensen, A, Petersen, HH, Kjelgaard, S, Mathiasen, L, Holtet, TL, Andreasen, PA (2005) A urokinase-type plasminogen activator-inhibiting cyclic peptide with an unusual P2 residue and an extended protease binding surface demonstrates new modalities for enzyme inhibition. J. Biol. Chem. 280, 38424-37.

Mikkelsen JH, Gyrup C, Kristensen P, Overgaard MT, Poulsen CB, Laursen LS, Oxvig C (2008) Selective inhibition of the proteolytic activity of pregnancy-associated plasma protein-A by targeting substrate exosite binding. J. Biol. Chem., 283, 16772-80.

Rasmussen LC, Oliveira CL, Jensen JM, Pedersen JS, Sperling-Petersen HU, Mortensen KK (2008) Solution structure of C-terminal *Escherichia coli* translation initiation factor IF2 by small-angle X-ray scattering. Biochemistry 47, 5590-8.



Cellular signalling and development

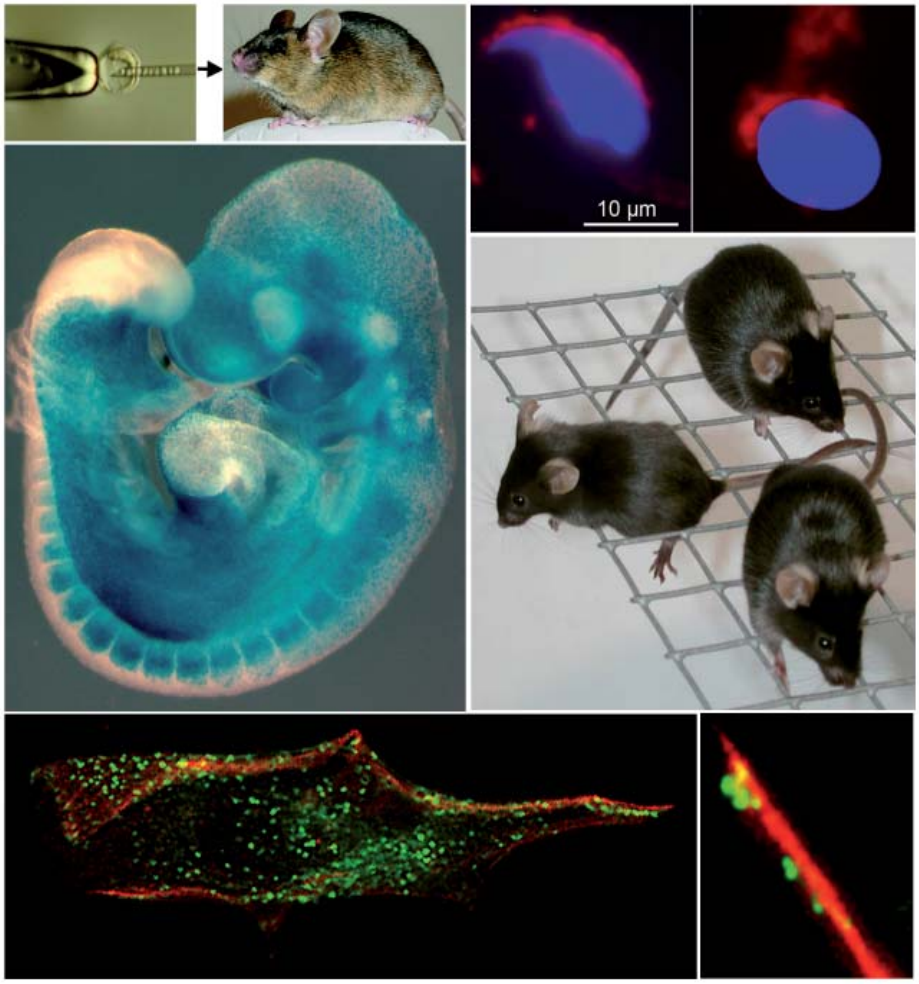
Associate Professor Ernst-Martin Füchtbauer
Associate Professor Just Justesen
Associate Professor Pia Møller Martensen
Associate Professor Lene Pedersen
Associate Professor Thomas Schmitt-John

Development and maintenance of multicellular organisms requires a coordinate communication between cells. This communication secures that cells behave appropriate according to their position in the body and maintain proper homeostasis. Disturbance of this communication may result in aberrant differentiation, malformation, tumor development or cellular degeneration. Extracellular signalling molecules such as interferons and inorganic phosphate activate cascades of intracellular signal transduction pathways thus regulating gene expression and thereby controlling processes like growth, differentiation and/or antiviral and immunological reactions. Intracellular trafficking is equally important in these processes and for viral infection. Our groups are covering topics within the fields of development and cell signalling, intracellular trafficking and virus-cell interactions through a number of research projects.

The Molecular Embryology group (**Ernst-Martin Füchtbauer**) is interested in the genetic regulation of embryonic development and cellular differentiation. The function of genes is investigated by mutational analysis in which the consequences of different mutations are investigated. The group has ample experience in different methods to generate genetically modified mice and therefore offers, within the framework of the 'Danish Center for Transgenic Mice', collaboration possibilities to other researchers interested in using these techniques. Organ development and cellular differentiation are complex processes which are related to many diseases. The research projects of the group cover many techniques like histological and molecular analysis of murine embryos, testing transcription control in tissue culture cells, investigating cancer development in mice with mutated tumor suppressor genes and development of stem cell therapy in muscular dystrophy.

The Protein Synthesis and Interferon Signalling group (**Just Justesen**) is interested in interferon stimulated genes that are involved in regulation of translation in protein synthesis. The 2-5A synthetases are coded by the OAS genes. 2-5A synthetases make 2'-5' linked oligonucleotides that in turn activate RNase L, which then acts on RNA, in particular of viral origin, but also ribosomal RNA. The significance of having a number of OAS variants is studied by looking at enzymatic properties and at how the OAS family has evolved from simple animals like marine sponges, sea squirt, mussels and snails. Furthermore, tryptophanyl tRNA synthetase (coded by WARS), which is strongly induced by immune interferon (gamma) is also investigated. Splice variants of WARS may play a role as an inhibitor of angiogenesis. It is clear that the amino terminus of the human WARS is associated with the interferon system whereas the canonical ligase activity resides in the carboxyterminus, which is strongly conserved through evolution from prokaryotes to eukaryotes.

The Apoptosis and Interferon Signalling group (**Pia Møller Martensen**) is interested in the apoptotic properties and regulation of the ISG12 family of small membrane proteins up-regulated by type 1 interferon. This family of mitochondrial BH3-like proteins are novel key players in the apoptotic pathway induced by interferon. Insights into the apoptotic pathways initiated by ISG12 proteins are based on putative interactions partners in the cell. Up-regulation of one of the ISG12 genes has been detected during pregnancy, in several cancer types as well as in psoriasis. Endometriosis is a painful gynaecological disease defined as the implantation of endometrium-like cells outside their normal location in the uterus. Due to their regulation and apoptotic properties, the ISG12 family of proteins might be involved in the development of endometriosis. The research projects of this group



cover mammalian cell culture and baculovirus expression combined with molecular analyses of proteins, RNA and DNA as well as analysis of tissue samples.

Laboratory of Interdiciplinary Research (**Lene Pedersen**) is interested in the role of inorganic phosphate (Pi) and type III sodium-dependent Pi transporters in cellular signalling and normal and pathologic cellular processes, stem cells in cell therapy, and the interplay between retrovirus and their host cells with focus on cell entry and gene delivery/therapy. A recent interest is on the roles of Pi and Pi transporters in osteoblastic differentiation of mesenchymal stem and preosteoblastic cells as well as in the pathologic differentiation of human vascular smooth muscle cells to an osteoblast-like phenotype. The Pi transporters are receptors for retrovirus, which we exploit in our studies on function and regulation of the transporters. On the virus side, focus is on receptor and co-receptor interactions of retroviruses infecting human cells and on identification of entry routes and vesicle trafficking used by retroviruses and HIV-1 to infect cells and cross cellular barriers.

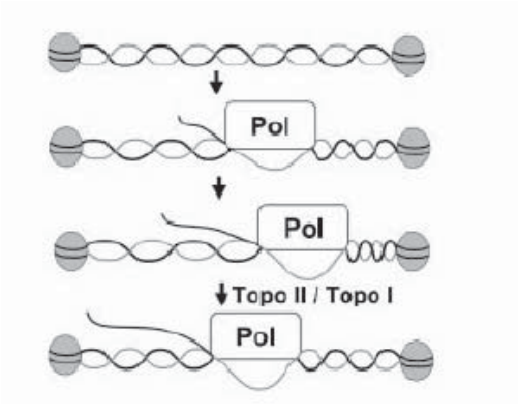
The Neurogenetics group (**Thomas Schmitt-John**) is interested in the genetic, biochemical- and cellular basis of neurodegenerative diseases of the neuromuscular system. Recently we identified a novel disease gene responsible for motor neuron degeneration in a mouse model for human motor neuron diseases. This gene encodes a vesicle traffic factor and thus, the intracellular vesicle traffic appears to play a critical role in motor neuron degeneration. Our group investigates the intracellular vesicle traffic in the context of neurodegeneration as well as disease associated gene regulation, using genetic, biochemical and cell biological techniques in vitro, in mammalian cell culture, and in genetically modified mice. Furthermore, the research projects of the Neurogenetics group comprise the analysis of murine spermatogenesis defect, resembling the human globozoospermia, a male infertility syndrome. The molecular cause of this spermatogenesis defect is also associated with factors of the retrograde vesicle traffic.

DNA processing

Associate Professor Anni H. Andersen
Associate Professor Tinna V. Stevnsner
Associate Professor Birgitta R. Knudsen

DNA topoisomerases

The double helical nature of DNA leads to a number of topological problems in the form of under- or over-winding of the DNA helix, i.e. negative or positive supercoiling, whenever the DNA strands are separated to expose the genetic code e.g. during replication and transcription (see Fig. 1). If such problems remain unsolved, the DNA metabolic processes of the cell will stop and the cell will consequently die. It is therefore not surprising that all living organisms contain enzymes, the DNA topoisomerases, which are specialized in regulating the DNA topology and, hence, are essential for the survival of all cells. In addition to the important biological functions of these enzymes, the topoisomerases are the cellular targets for important anti-cancer chemotherapeutica, which is why they are of great clinical interest.



Figur 1. Exposition of the genetic code contained in DNA leads to the accumulation of positive supercoils in front of, and negative supercoils behind the polymerase. The supercoiling needs to be removed by a DNA topoisomerase to allow completion of the polymerase extension.

Common for all topoisomerases is that they relax supercoiled DNA by introducing transient breaks in the DNA double helix. Based on their mechanism of action they can be divided into two types, the type I enzymes, which introduce single-stranded breaks and the type II enzymes, which cleave both strands of the DNA helix. In our group, we are focusing on the mechanistic and biological functions of both type I and II topoisomerases. By combining specialized *in vitro* methods and macromolecular visualization techniques (SAXS, Cryo-TEM and AFM) with *in vivo* model systems in yeast *S. cerevisiae* or mammalian cell lines we have gained a detailed understanding of the multiple functions of the topoisomerases.
Some of our ongoing projects focus on the functions of topoisomerases in DNA replication, transcription and post-transcriptional gene regulation. To study the topoisomerase function in DNA replication we are using yeast as a model to monitor replication in cells lacking the endogenous topoisomerase I and/or topoisomerase II gene. The replication process in these cells is analyzed by chromatin immunoprecipitation, qPCR, 2D gel-electrophoresis, FACS-analysis. Also, potential DNA damage caused by replication fork stalling is investigated.

The functions of DNA topoisomerases in transcription and transcriptional regulation have been investigated by use of the microarray technology. We have examined global genome expression in cells lacking topoisomerase I, topoisomerase II or both enzymes and compared to the expression levels obtained in normal cells. One of the interesting observations in the microarray analysis is that lack of topoisomerase activity specifically affects genes which are located close to areas in the genome that are attached to the nuclear membrane and the nuclear pore complex. More detailed studies of the implications of this attachment for the effect of DNA topology on gene expression are now in progress.

The functions of topoisomerase I in post-transcriptional gene regulation have been investigated in terms of its effect on pre-mRNA splicing. Previous studies have shown that topoisomerase I, in addition to DNA relaxation, catalyzes SR-protein specific

phosphorylation, whereby it may affect pre-mRNA splicing. To test this hypothesis we have compared the splicing pattern in human cells as a function to topoisomerase I activity using splice-specific microarrays. These investigations have shown that the splice pattern of important cancer relevant transcripts such as p53 and BRCA1 are altered upon down regulation of topoisomerase I expression. Presently, the exact function of topoisomerase I in p53 and BRCA1 splicing is addressed in specialized assays.

The Molecular Biology of Aging

Statistically, old age is associated with at marked increase in a number of diseases, the so-called age-related diseases. These include cancer, diabetes, cardiovascular diseases and neurodegenerative diseases. The molecular biological causes for aging are as yet unknown but several theories have been put forward to explain the phenomenon of aging.

One of these theories involves certain cellular organelles – the mitochondria. The last steps of the cellular energy production are performed in the mitochondria via oxidative phosphorylation. As a consequence of this process, highly reactive by-products the so-called free radicals are formed. Free radicals may damage the DNA of mitochondria, leading to a decrease in the essential mitochondria functioning (see Fig. 2). DNA repair mechanisms, which can recognize and remove DNA damage, are found both in the cell nucleus and in the mitochondria.

Using different molecular biological techniques, including immuno-staining, immuno-precipitation, repair activity assays and array-studies we are investigating, how DNA repair mechanisms are regulated and altered by age. In particular, we are focusing on processes in different part of the brain and its synapses, which are essential for inter-neuron communication. As model systems we are using premature aging syndromes, as these are well suited for the investigations of aging related processes.

- Andersen, FF, Knudsen, B, Frøhlich, RF, Krüger, D, Bungert, J, Agbandje-McKenna, M, McKenna, R, Juul, S, Koch, J, Rubinstein, J, Guldbrandtsen, B, Hede, MS, Karlsson, G, Andersen, AH, Knudsen, BR (2008) Assembly and structural analysis of a covalently closed nano-scale DNA cage. Nucleic Acids Res. 36, 1113-9.
- Frøhlich, RF, Veigaard, C, Andersen, FF, McClenton, AK, Gentry, AC, Andersen, AH, Osheroff, N, Stevnsner, T, Knudsen, BR (2007) Tryptophane-205 of human topoisomerase I is essential for camptothecin inhibition of negative but not positive supercoil removal. Nucleic Acids Res. 35, 6170-80.
- Oestergaard VH, Giangiacomo L, Bjergbaek L, Knudsen BR, Andersen AH. Hindering the strand passage reaction of human topoisomerase IIalpha without disturbing DNA cleavage, ATP hydrolysis, or the operation of the N-terminal clamp. J Biol Chem. 2004 279, 28093-9.
- Oestergaard, VH, Knudsen, BR, Andersen, AH (2004) Dissecting the cell-killing mechanism of the topoisomerase II-targeting drug ICRF-193. J Biol Chem. 279, 28100-5.
- Weissman, L, de Souza-Pinto, NC, Stevnsner, T, Bohr, VA (2007) DNA repair, mitochondria and neurodegeneration. Neuroscience 145, 1318-1329.

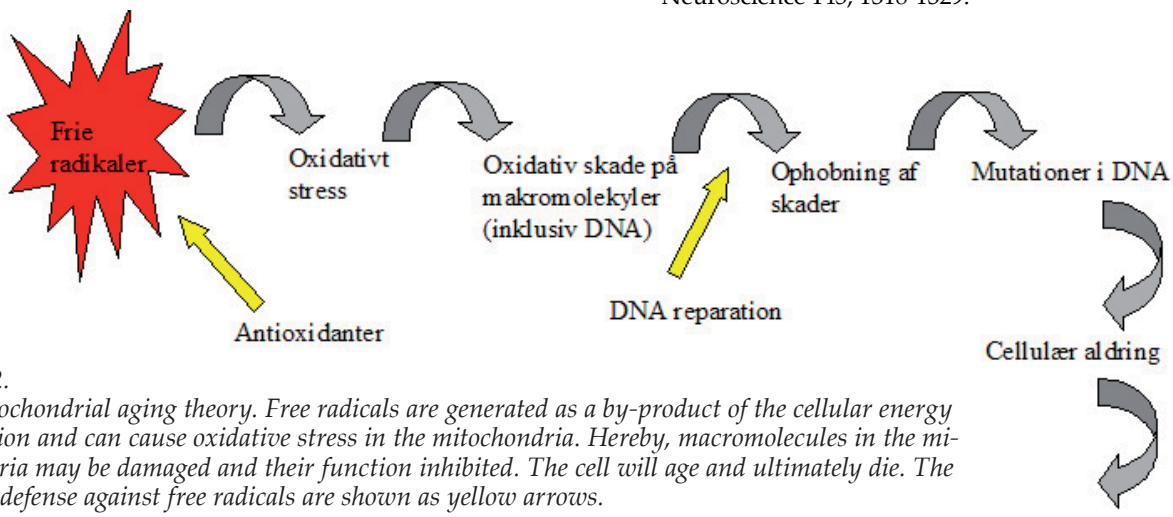


Figure 2.
The mitochondrial aging theory. Free radicals are generated as a by-product of the cellular energy production and can cause oxidative stress in the mitochondria. Hereby, macromolecules in the mitochondria may be damaged and their function inhibited. The cell will age and ultimately die. The cellular defense against free radicals are shown as yellow arrows.

RNA and virus

Professor Jørgen Kjems
Professor Finn Skou Pedersen
Associate Professor Bjarne Bonvén
Associate Professor Torben Heick Jensen
Associate Professor Poul Jørgensen
Associate Professor Jan Egebjerg Jensen

The laboratory of Associate Professor **Torben Heick Jensen**, who is also the director of the Danish National Research Foundation "Centre for mRNP Biogenesis and Metabolism", investigates effects on gene expression occurring at the co- and post-transcriptional levels. During transcription mRNA is processed by enzymes and packaged with proteins into mRNP particles. These are the entities undergoing nuclear export and cytoplasmic translation. Improper mRNP formation leads to nuclear retention and subsequent nuclear degradation of the mRNA in a process involving the 3'-5' exonucleolytic RNA exosome. Using both yeast and human cells, the laboratory studies the "molecular battle" between productive events of mRNP formation and destruction by mRNP quality control. Lately, these analyses have led to the discovery of new degradation pathways as well as a whole new class of RNAs.

Professor **Jørgem Kjems**' group has developed novel types of RNA based therapeutics including in vivo stabilized siRNA with decreased off-target effects, aptamers and bifunctional RNA oligonucleotides. Using mice as model systems we can deliver siRNAs to the lung by the means of various nanocarriers designs and consequently down regulate cellular and viral genes or reach inflamed tissue as a treatment for rheumatoid arthritis. Another active area we are focusing on is the incorporation of drugs into biodegradable polymeric nanoparticles to be use in 3D scaffolds for tissue engineering. The inclusion of cell specific ligands and "biological triggers" into the nanocarrier design are used for modulation of cellular drug trafficking and in vivo delivery. We have also used SELEX to select 2'F-modified RNA aptamers that bind strongly and highly specifically to human oncoproteins with very high affinity and block processes implicated in formation of metastases.

Professor **Finn S. Pedersen**'s group work with various aspects of retrovirus-host interactions. One line of research concerns the induction of lymphomas and leukemias in mice by proviral insertional mutagenesis, where we have developed novel mouse models of altered disease specificity, identified novel target genes for multi-step oncogenesis, and investigated how proviral insertion may deregulate such genes. A second line of research concerns the interaction of the virus with the host cell during specific steps of the replication cycle such as for example the production and packaging of viral genomes into particles or viral entry into target cells. Part of this work exploits knowledge of viral replication for gene technological purposes. A third line of research concerns the identification of endogenous retroviruses inherent to the human genome and analysis of the possible role of those in human physiology.

Selected References

Saguez C., Schmid M., Olesen J.R., Ghazy M., Poulsen M.B., Nasser T., Moore C. and Jensen T.H.: Nuclear mRNA surveillance in THO/sub2 mutants is triggered by inefficient polyadenylation. Molecular Cell (2008), 31(1):91-103.

Damgaard C.K., Kahns S., Lykke-Andersen S., Nielsen A.L., Jensen T.H. and Kjems J.: A 5' splice site enhances the recruitment of basal transcription initiation factors *in vivo*. Molecular Cell (2008) 29(2): 271-278.

Rougemaille M., Olesen J.R., Thomsen R., Seraphin B., Libri D. and Jensen T.H.: Dissecting mechanisms of mRNA surveillance in THO/sub2 complex mutants. EMBO J. (2007) 26(9): 2317-2326.

Bramsen, J.B., Lauersen, M.B., Damgaard, C.K., Willsen, S.L., Wengel, J., and Kjems, J.: Improved silencing properties of small interfering RNAs with segmented sense strand. Nucleic Acids Res. 35:5886-97, 2007.

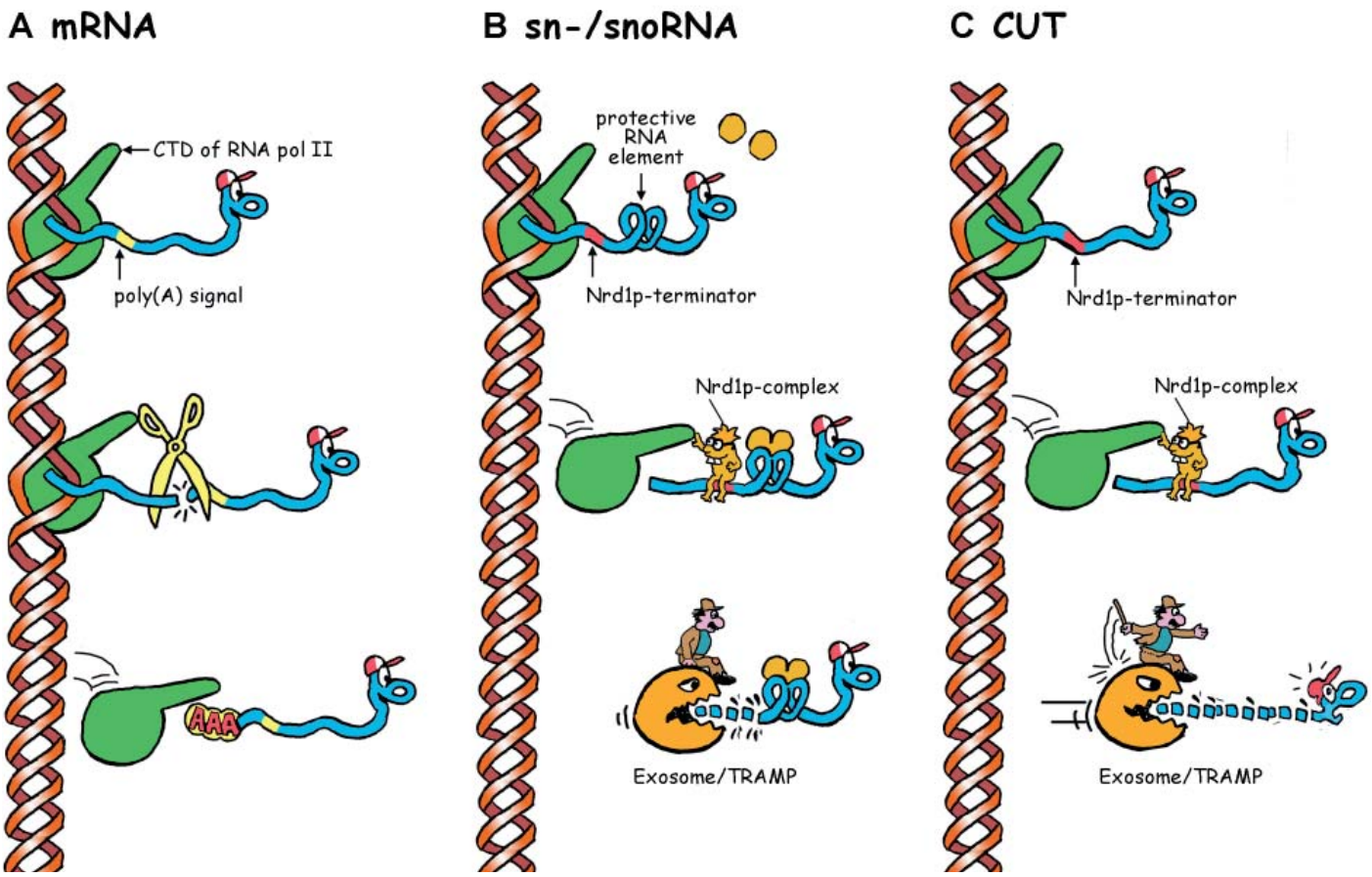
Rahbek, U.L., Howard. K.A., Oupicky, D., Dong,M., Nielsen, A.F., Raarup, M-R., Besenbacher,F. , Kjems, J.: Intracellular siRNA and precursor miRNA trafficking using Bioresponsive Copolypeptides. J. Gene Med. 10:81-93, 2008.

Odadzica, D., Bramsen, J.B., Bus; C., Kjems, J., and Engels, J.W.: Synthesis of 2`-O-modified Adenosine Building Blocks and application for RNA Interference. Bioorg. Med. Chem. 16:518-29, 2008.

Torarinsson, E., Yao, Z. , Wiklund E.D. , Bramsen, J.B. , Hansen, C., Kjems, J., Tommerup, N., Ruzzo, W.L.and Gorodkin, J.: Comparative genomics beyond sequence based alignments: RNA structures in the ENCODE regions. Genome Res. 18:242-51, 2008.

Glud SZ, Sørensen AB, Andrulis M, Wang B, Kondo E, Jessen R, Krenacs L, Stelkovics E, Wabl M, Serfling E, Palmetshofer A, Pedersen FS.: A tumor-suppressor function for NFATc3 in T-cell lymphomagenesis by murine leukemia virus. Blood. Nov 15;106(10):3546-52, 2005.

Figure: Processes removing unwanted RNA from the cell

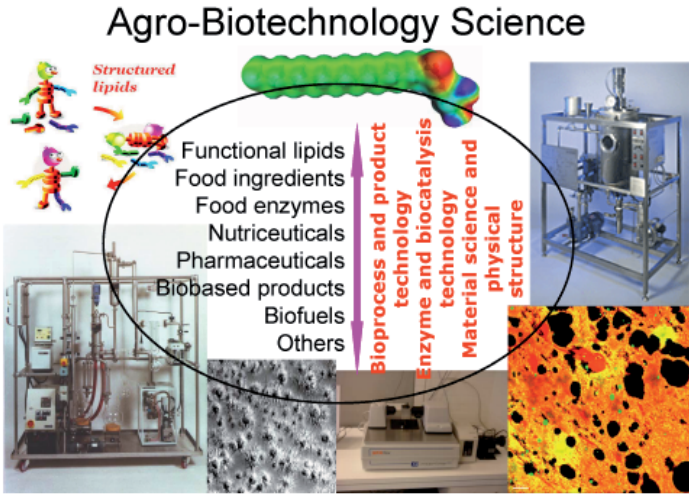


Molecular nutrition

Professor Xuebing Xu
Associate Professor Torben Ellebæk Petersen
Associate Professor Esben Skipper Sørensen

Agro-Biotechnology Science

Agro-Biotechnology Science Group (**Xuebing Xu**) has long strong research in enzyme technology and lipid product/process development. The research involves in enzymatic technology development for functionalisation of traditional fat stuffs as well as tailor-making of structured lipids for health and nutrition. Physical characterization of lipids and products as well as process monitoring technology represents another focused area. Sustainable enzymology and green solvent technology become a recent focus in research, including pioneering research concerning ionic liquid-mediated enzymatic modification of bulky oils and fats for ingredients or biofuels processing. The research profile covers model-assisted design of task-specific ionic liquids, protocol design, separation and scale-up technology. The new opportunity for value-added utilisation of lipids and agricultural products from green solvents (SCCO2 and ionic liquids) has greatly expanded the research into polar lipids, lipid-associated carbohydrates and lipid-related pharmaceuticals, with strong consideration of sustainability and environmental impact.



The group's vision is to conduct and foster interdisciplinary research to offer a knowledge foundation for the production of value-enhanced secondary agricultural products and food ingredients by means of modern biotechnology. The basic objective is to explore practical technology that contributes to a sustainable growth of agricultural products and food industry in the Danish society, based on high-quality basic and applied research.

The group's research can be highlighted with following phrases such as (1) Lipid processing and new utilization of lipid resource; (2) Industrial biotechnology for designing lipids; (3) Sustainable enzymology and green solvent technology; (4) Quality control and characterization of food lipids; (5) Polar lipids and lipid-associated carbohydrates; (6) Innovative utilization of agricultural products; (7) Food nanotechnology; (8) Food ingredients and lipid-related pharmaceuticals; and (9) biobased products and biofuels.

Guo Z., Lue B.-M, Thomasen K., Meyer A.S. and Xu X. Predictions of flavonoid solubility in ionic liquids by COSMO-RS: experimental verification, structural elucidation, and solvation characterization, Green Chem. 9: 1362-1373 (2007).

Marianne L. Damstrup, Jens Abildskov, Søren Kiil, Anker D. Jensen, Flemming V. Sparsø and Xuebing Xu. Process Development of Continuous Glycerolysis in Immobilized Enzyme Packed Reactor for industrial applied Monoacylglycerol Production, J. Agric. Food Chem. 55 (19): 7786-7792 (2007).

Zhang H., Mu H., Xu X. Monitoring lipase-catalyzed butterfat interesterification with rapeseed oil by Fourier transform near-infrared spectroscopy, Anal. Bioanal. Chem. 386:1889–1897 (2006).

Bioactive Milk Proteins

The Protein Chemistry Laboratory (**Torben Ellebæk Petersen & Esben Skipper Sørensen**), which houses the bioactive milk protein research group, was established in 1992 as a result of a series of grants from the Danish Dairy Research Foundation and the national FØTEK research program. At present the group consists of five senior researchers, three post-docs, four Ph.D.-students, three technicians and a number of master and project students.

The major research theme of the group is structural and functional characterization of bioactive milk proteins - and several for milk hitherto unknown proteins have been identified and characterized at the laboratory in the past 15 years.

The laboratory hosts a number of basic science research projects on milk and mammary gland biology. Likewise the group is also leading and conducting more applied research projects which aim at developing food ingredients, functional foods, nutraceuticals and other products based on bioactive milk proteins. In that connection the group has a long and strong record of collaboration with industrial partners in taking basic science all the way to patenting and commercial product.

The research group has published more than hundred articles in internationally peer-reviewed journals and several patents have been filled on the purification and utilization of bioactive milk proteins.

A series of patents on the purification and function of the cytokine osteopontin, which can be purified from milk in relatively large quantities, have been filed. Several projects on the industrial scale production of osteopontin and its role and potential use in products stimulating the immune response, wound healing processes and inhibition of bacterial growth are currently undertaken at the laboratory. Osteopontin is now a commercial product and is marketed by Arla Foods for use in e.g. infant formulas and oral hygiene applications.

The milk fat membrane fraction of milk is an excellent source for purification of membrane proteins which are otherwise very difficult to obtain in sufficient amounts for structural and functional characterization. Hence a number of projects on these membrane proteins (mucins, lactadherin, CD36 etc.) are ongoing in the group. E.g. a study aims at characterizing the inhibiting effect these membrane proteins have on the infectivity of virus and bacteria in the intestinal system.

Another protein characterized at the laboratory, EPV20, was found to be homologous with the human NPC-2 protein, which is a pivotal factor in intracellular cholesterol transport. Studies are ongoing to elucidate whether this milk protein can influence cholesterol transport in cellular systems and animal models.

Another project at the laboratory under the theme of molecular nutrition, but not directly linked to milk research, is the investigation of vitamin B12 and its binding proteins and receptors. This project is another example of research from the laboratory which has been led to commercialization through the establishment of the biotech company Cobento A/S.

Bojsen A, Buesa J, Montava R, Kvistgaard AS, Kongsbak MB, Petersen TE, Heegaard CW, Rasmussen JT. Inhibitory activities of bovine macromolecular whey proteins on rotavirus infections *in vitro* and *in vivo*. Journal of Dairy Science 90:66-74 (2007).

Agnholt, J., Kelsen, J., Schack, L., Hvas, C.L., Dahlerup, J.F., and Sørensen, E.S. Osteopontin, a protein with cytokine-like properties, associated with inflammation and stimulation of T cell cytokine production in Crohn's disease. Scandinavian Journal of Immunology. 65: 453-60 (2007).

Christensen B, Nielsen MS, Haselmann KF, Petersen TE, Sørensen ES. Post-translationally modified residues of native human osteopontin are located in clusters: identification of 36 phosphorylation and five O-glycosylation sites and their biological implications. Biochemical Journal 390:285-92 (2005).

Protein interactions

Professor Jan Johannes Enghild
Professor Daniel Otzen
Lektor Torsten Kristensen

The research combines modern analytical methods with classical protein chemistry techniques methods to characterize covalent and non-covalent changes to proteins and the consequences for their biological functions. We use a dual approach in our hypothesis driven research. Firstly, we characterize protein structure and function to reveal the mechanisms behind observed protein-protein and protein-ligand interactions. This research is geared towards answering important basic questions of protein structure and mechanism. Secondly, we study perturbations of normal physiology in order to investigate the significance of our structural observations. In addition, we employ proteomics methods aimed at discovery science research to tease apart more complex questions. Discovery science is characterized by non-selective gathering of information characterizing a particular biological system. The gathered results are subsequently analyzed with the hope that significant characteristics will emerge to provide insight into the mechanism and function of the system. This approach contrasts significantly with hypothesis-driven science, but we believe that discovery- and hypothesis-driven sciences are complementary approaches that, when used in combination, can advance the speed of knowledge generation.

Protein modifications

This research team focuses on proteolysis, post-translational modifications and, evaluation of protein folding/stability, oxidation, the role that particular proteins play in the formation of plaques or fibrils and the interactions between soluble and insoluble proteins. Some of the headlines for the research include:

- Functional genomics and proteomics.
- Extracellular matrix homeostasis.
- Proteases and inhibitors.
- Free radicals and antioxidant enzymes.
- Formation of plaques or fibrils.
- Protein aggregation.
- Insoluble proteins and their interactions with other proteins.
- Characterization of post-translational modifications.

Conformational transitions in proteins

Our aim is to understand the structural transitions that accompany protein binding to membranes (both integral or peripheral membrane proteins, including antimicrobial peptides and protein-detergent complexes) and pathological/functional protein aggregation. Using state-of-the-art spectroscopic techniques we quantify the energetics, stoichiometry and kinetics of the associated conformational changes to understand how the conformational landscapes of proteins, and thus the formation of different structures, can be "tuned" by the environment and vice versa. Ultimately we want to be able to prevent the physiological accumulation of harmful protein aggregates of the types seen in Parkinson's and Alzheimer's Disease. Headlines include:

- Structure and stability of states along the aggregation pathway of proteins involved in neurodegenerative diseases
- Understanding and harnessing beneficial protein aggregation, e.g. bacterial amyloid
- Characterization of the mode of action of antimicrobial peptides
- Understanding how lipids and detergents modulate the folding and stability of integral membrane proteins

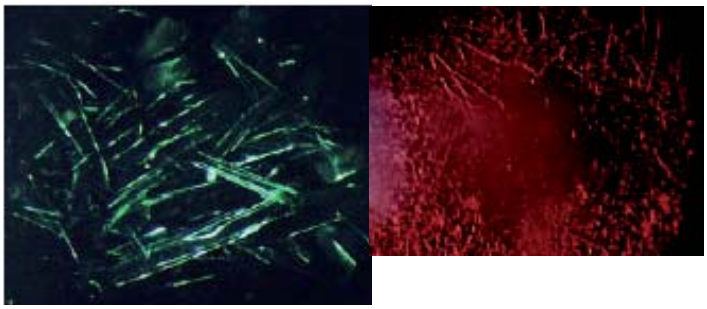


Figure: Aggregates of the Fas4 domain of TGFBIP with the mutation causing lattice corneal dystrophy formed in vitro (left) resemble the "needle-like" structures formed by the full-length TGFBIP protein as seen in the cornea of a patient suffering from lattice corneal dystrophy (right).

Topic: Ocular transparency

The research group is part of the Center for Insoluble Protein Structures (inSPIN) supported by the Danish National Research Foundation (Danmarks Grundforskningsfond). One research area is ocular transparency with special focus on the cornea, a specialized tissue in the front part of the eye. This tissue is normally transparent. However, a range of diseases compromise transparency and results in significant impairment of sight or even blindness, including corneal dystrophies established by the aggregation of the protein transforming growth-growth factor beta-induced protein (TGFBIp) in the tissue. We currently study this system by bottom-up (protein analyses) and top-down (proteomics) approaches:

- We have characterized TGFBIp purified from the cornea and generated a range of recombinant proteins representing natural variants which mediates the aggregation of the protein in the cornea. Our studies link "test tube" properties measured by spectroscopic approaches with observed physiological features.

- Together with Professor Jan Skov Pedersen we have shown that wildtype and mutant TGFBIp have different tendencies to form higher order structures in solution.

- In collaboration with Professor Niels Christian Nielsen we have determined the three dimensional structure of TGFBIp with solution NMR and initiated studies by solid-state NMR to analyze mutants which form aggregates in the cornea. These studies will support the development of compounds that can inhibit the aggregation and thus hopefully prohibit the impairment of sight of individuals affected by the mutations in TGBIp.

- The corneal proteome has been described by 2D gel electrophoresis and liquid mass spectrometry. These studies have generated a map of proteins present in the corneal tissue which can be applied in further research project and have shown that a number of plasma proteins are transported actively into the tissue.

- Using a special laser-mediated dissection technique, we have isolated deposit-rich sections of the corneal tissue, which we will analyze by mass spectrometryto elucidate the composition of the protein aggregates.

- With Professor Søren Keiding we are developing techniques to study the structure of proteins *in vivo* using non-invasive Coherent Anti-Raman Scattering microscopy. This can be applied both to TGFBIp deposits and benign amyloid deposits in bacteria.

Pedersen, J. S., and Otzen, D. E. Amyloid - A state in many guises: survival of the fittest fibril fold, Protein Science 17, 1-9 (2008).

Otzen, D. E., and Nielsen, P. H. We find them here, we find them there: Functional bacterial amyloid, Cell. Mol. Life Sci. 65, 910-927 (2008).

Pedersen, J. S., Dikov, D., Flink, J. L., Hjuler, H. A., Christiansen, G., and Otzen, D. E. The changing face of glucagon fibrillation: Structural polymorphism and conformational imprinting, Journal of Molecular Biology 355, 501-523 (2006).

Mogensen, J. E., Tapadar, D., Schmidt, M. A., and Otzen, D. E. Barriers to folding of the Transmembrane Domain of the *Escherichia coli* Autotransporter Adhesin involved in diffuse adherence, Biochemistry 44, 4533-4545 (2005).

Valnickova Z, Petersen S.V., Nielsen S.B., Otzen D.E., Enghild J.J. Heparin binding induces a conformational change in pigment epithelium-derived factor. J Biol Chem. 2;282(9):6661-7 (2007).

Valnickova Z, Sanglas L, Arolas J.L, Pallarés I., Guevara T., Solà M., Kristensen T., Enghild J. J., Avilés F. X., Gomis-Rüth F. X. Structure of activated thrombin-activatable fibrinolysis inhibitor, a molecular link between coagulation and fibrinolysis. Molecular Cell 22;31(4):598-606 (2008).

Molecular interventions

Suresh Rattan, PhD, Dr.scient.
Peter Kristensen, PhD
Anders Olsen, PhD

Cellular processes are regulated by interactions between different macromolecules. Basic understanding of normal and pathological processes can be gained by manipulation of such molecular interactions, which also provide a point of intervention. Occurrence of damage in macromolecules is intrinsic to the basic molecular processes of life. Alterations in gene expression levels and the degree of molecular damage are often causative events leading to unique phenotypes. These include muscular, skeletal and neuronal degenerative diseases, cancer, failure of the immune system, altered angiogenesis, metabolic disorders and hormonal deficiencies. Since studies of the molecular events are often hampered by the complexity of the human body, much basic knowledge can be best obtained by taking advantage of various model systems, followed by validation in higher systems or organisms. Additionally, single cell analyses in complex systems can assist further advancement in this respect. Within our groups, the focus is mainly at elucidating the molecular mechanisms leading to ageing and age-related malfunctions, such as vascular and mental impairments. Development of novel technologies and biotechnological reagents combined with experimental model systems to address questions regarding the occurrence and accumulation of molecular damage, and interventions are integral to this research.

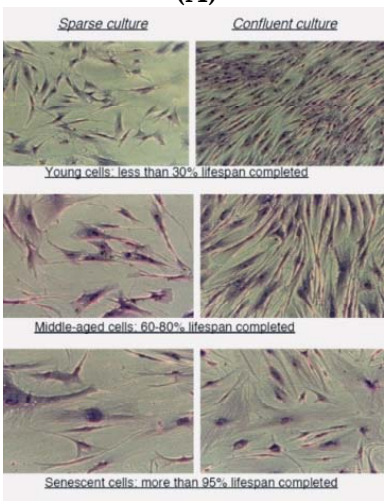
Cellular Ageing group (**Suresh Rattan**) is using the experimental model system, the "Hayflick system" of long-term serially subculturing of normal diploid human cells which have a limited proliferative capacity. Cell types used are epidermal fibroblasts and keratinocytes, bone marrow stem cells and osteoblasts, and vascular- and micro-vascular endothelial cells. Macromolecular damages, specially the oxidative damage to proteins, alterations in proteasomes and lysosomes), and alterations in cellular responses to stress through heat shock proteins, hemeoxygenase, and antioxidant pathways are being studied. Various interventions include testing the effects of synthetic and natural compounds (for example, cytokinins, polyphenols and spices), and establishing the beneficial effects of mild stress, termed hormesis, on preventing or slowing down the accumulation of molecular damage. Other hormetic interventions such as nutritional components, mechanical stretching and exercise are being investigated to elucidate the effects and mechanisms of mild stress on cellular lifespan, wound healing, angiogenesis, and sugar-induced accelerated molecular damage accumulation.

Phage display group (**Peter Kristensen**) The central dogma in molecular biology states that it is impossible to derive a unique gene sequence from a protein sequence due to the degeneracy of the genetic code. However, the technique of phage display is one example of a technique where it is possible to link genotype and phenotype. The application of phage display opens up the possibility of creating large libraries of different proteins (for example, antibodies). We are utilising such antibody-generating systems as a discovery tool, to identify important biological networks and biomarkers. We are isolating antibodies which are capable of modulating blood vessel formation. By intervention in the process of formation of new blood vessels, we have in mice models demonstrated that tumor development is delayed. Also we are aiming to increase our understanding of the age-related decline in the ability to form new blood vessels. An important area of our research is to develop tools which are capable of analysing gene expression at the single cell level, again this mainly rely on the application of the phage display technology. The last area of interest covers the development of methods which can be applied in areas of industrial importance, such as the development of proteins with novel catalytic properties or changed stabilities. Thus we have been able to devise methods relying of Darwinian selection of enzymes with higher thermostability.

***C. elegans* group** (**Anders Olsen**) The main focus of the *C. elegans* research group is to investigate the mechanistic relationship between cancer and ageing

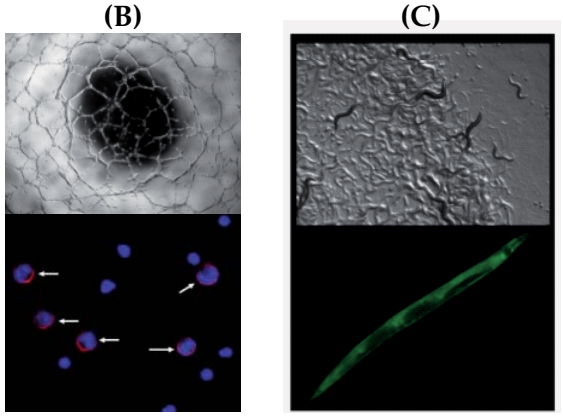
using the soil nematode *Caenorhabditis elegans*. *C. elegans* is an excellent model system for ageing studies. More than 100 gene mutations have been shown to influence the nematode lifespan and a large fraction of these "Age genes" share identity with genes of known function in other species. We are particularly interested in the role of tumor suppressors and checkpoint proteins in the ageing process. To prevent cancer, cells are equipped with surveillance systems that detect damage and stop cells from dividing. These surveillance systems are collectively called cellular checkpoints. We have made the discovery that inactivation of some checkpoint proteins can increase stress resistance and lifespan of *C. elegans*. It is currently unknown how checkpoint proteins mechanistically determine lifespan. Therefore, to further our understanding of this phenomenon we completed a *C. elegans* whole genome RNAi screen for checkpoint defects which returned 50 genes that cause resistance to the chemo therapeutic drug hydroxyurea when inactivated. A detailed analysis of these genes will help us understand how checkpoints determine lifespan. Importantly, by taking a comparative biology approach in our analysis we will be able to address how well these findings translate to higher organisms such as humans. Our group also uses *C. elegans* to study other age-related diseases such as Alzheimer's disease.

(A)



Rattan, S.I.S. Increased molecular damage and heterogeneity as the basis of aging. Biochemical Journal, 389: 267-272 (2008).
Berge, U., Kristensen, P. and Rattan, S.I.S. Hormetic modulation of differentiation of normal human epidermal keratinocytes undergoing replicative senescence *in vitro*. Experimental Gerontology, 43(7):658-62 (2008).
Rattan, S.I.S., Sejersen, H, Fernandes, R.A. and Luo, W. Stress mediated hormetic modulation of wound healing and angiogenesis in human cells. Annals of the New York Academy of Sciences, 1119: 112-121, (2007).
Kim Bak Jensen, Ole Nørregaard Jensen, Peter Ravn, Brian.F.C.Clark and Peter Kristensen. Identification of Keratinocyte Specific Markers using Phage Display and Mass Spectrometry. Molecular and Cellular Proteomics, 2, 61-69 (2003).
Jesper S. Pedersen, Daniel E. Otzen and Peter Kristensen. Directed evolution of barnase stability using proteolytic selection. Journal of Molecular Biology, 323, 115-123 (2002).
Olsen, A., Vantipalli, M. C., and Lithgow, G. L. . Checkpoint Proteins Regulate Survival of the Post-Mitotic Adult Soma in *Caenorhabditis elegans*. Science, 312(5778):1381-5 (2006).

(B) **(C)**



A. The Hayflick system of cellular ageing *in vitro*, which is used to test potential anti-ageing interventions. Pictures show young, middle-aged and senescent human skin fibroblasts.

B. (Top) Human endothelial cells forming tubes *in vitro* (blood vessels). Recombinant antibodies can be tested for the ability to inhibit tube formation – anti-angiogenic effect. (Bottom) subpopulation of blood cells recognised by antibodies (arrows point at red antigen staining, blue nuclear stain) generated using only one single cell as antigenic material – single cell analysis.

C. (Top) The soil nematode *C. elegans* is a powerful model organism for studying the genetics of ageing. (Bottom) Transgenic nematode showing localisation of the FOXO transcription factor fused to GFP.

Structural Biology

Professor Poul Nissen
Associate Professor Søren Skou Thirup
Associate Professor Morten Kjeldgaard
Associate Professor Charlotte Rohde Knudsen
Associate Professor Gregers Rom Andersen
Associate Professor Ditlev Egeskov Brodersen

Cartography of the molecules of life

In the visual culture of the 21st century, scientific imagery has become increasingly important in popularising and communicating scientific knowledge. Moreover, in analysing the structure and function of the large molecules of the cell at the atomic level visualisation becomes more than just a matter of communicating scientific insight, it is an integral part of the production of scientific knowledge in the field of structural biology.

At the Centre for Structural Biology we explore nature on the atomic level analysing the processes of decoding genetic information, cell to cell signalling, the immune system, and transport in and out of the cell.

The Centre for Structural Biology (www.bioxray.au.dk) was founded by Jens Nyborg and represents over 30 years of experience with structure determination of macromolecules. The Centre consists of eight independent but closely connected research groups at the Department of Molecular Biology, University of Aarhus. Common to the groups is the use of X-ray crystallography to elucidate the three-dimensional structure of biological macromolecules. In addition to the crystallographic analysis, a wide range of molecular biological, biochemical, biophysical, and analytical techniques are used at the Centre.

Ion pumps and ribosomes

The group of **Poul Nissen** studies ion pumps like Na+,K+-ATPase, Ca2+-ATPase and H+-ATPase. Ion pumps are key enzymes in cell biology, physiology and medicine. The pumps transform the chemical energy from ATP hyrolysis to the powersource of electrochemical gradients and voltage across biomembranes. They are fascinating examples of biological nanomachines. These studies are organised in the Center for Membrane Pumps in Cells and Disease (www.pumpkin.au.dk). The Na+,K+-ATPase maintains the steep Na+ and K+ gradients across the cell membrane that are critical for secondary transport schemes and the action potential used in neurotransmission (see figure 1a). The first structure of this pump was recently determined (Morth *et al.*). The pumps represent very promising targets for the development of new antibiotics, and drugs against cancer and cardiovascular diseases. Also, Ribosome complexes are being studied to elucidate the mechanisms of protein synthesis in eukaryotes. Complexes with the translation factor eEF2 have been studied by single-particle cryo-EM in a collaboration with a cryo-EM group. These studies showed large conformational changes on the ribosome to be associated with hydrolysis of GTP.

Neuroreceptors and mitochondrial translation

In **Søren Thirup**'s group the Vps10p family of receptors is the subject of structural studies. These receptors are primarily expressed in neuronal tissue and they have been shown to be involved in the signalling of neuronal cell death, alzheimers disease and type 2 diabetes. In sortilin the 680 amino acid Vps10p domain, the common denominator of the family, constitutes the entire extracellular part, whereas additional domains are found in the other four members; SorLA, SorCS1-3 (see figure 1b). The receptors have a single transmembrane helix and a short cytosolic C-terminal tail containing sequence motifs recognised by sorting adaptor proteins such as GGA1. The group has recently determined the crystal structure of the Vps10p domain of sortilin in complex with neurotensin (Quistgaard *et al.*). Also structures of fragments of the sortilin and SorLA cytoplasmic tails have been determined in complex with the VHS domain of GGA1. The group is also studying elements of mitochondrial protein synthesis, where the non-canonical structure of mitochondrial tRNA's are of special interest.

Structural bioinformatics and termination of translation

In the research group of **Morten Kjeldgaard** release factors involved in translation termination are studied. We have determined the structure of release factor

aRF1 from *Halobacterium sp.* to a resolution of 2.1Å. The structure is superficially similar to the human release factor eRF1, but with some important differences. For example, one domain which is not visible in the human factor is visible in the archeal structure, and the structure is generally more accurate. Another effort concerns the development of new methods in the processing of crystallographic diffraction data. Other projects focus on methods in structural bioinformatics, in particular of calcium ATPase membrane proteins. We have developed methods to determine flexible regions in these molecules, defining areas of significance in the conformational changes they undergo. We are involved in the development of a comprehensive database that will enable researchers to overview a wide range data on the calcium ATPase family of structures. Finally, a research area in development is focussed on molecular shape analysis.

Elongation factors in translation

The laboratory of **Charlotte R. Knudsen** studies the functionalities of translation elongation factors EF-Tu from *E. coli* and eEF1A from humans with special emphasis on the relationship between structure and function. These elongation factors belong to the family of guanine-nucleotide binding proteins and play a prominent role during the assembly of amino acids into proteins upon decoding of the genetic message. The multifunctionality of EF-Tu is scrutinized using a protein engineering protocol. Recently, the group has studied aspects of the guanine nucleotide exchange mechanism (Dahl *et al.*). In addition, studies of the dynamic nature of EF-Tu was initiated using a single-molecule approach. Another theme in the laboratory is the identification and analysis of novel interaction partners of eEF1A which shed new light on some of the noncanonical roles that have been ascribed to this factor including cytoskeletal organisation, apoptosis and signal transduction. Furthermore, the group focuses on the role of various eEF1A isoforms in cancer.

Eukaryotic translation and the complement system

The research group of **Gregers R. Andersen** studies protein synthesis in eukaryotes with crystallography, small angle scattering and cryo-EM in collaboration. In particular, the translation elongation factor eEF2 with its toxin sensitive diphthamide modification has been investigated. Also, the fungi specific translation factor eEF3 have been studied both in isolation and a variety of complexes revealing important features of tRNA translocation and release from ribosomes. Furthermore, the group has determined the structure of the mRNA associated exon junction complex (see figure 1c). This is deposited upstream of splice sites and provides a binding platform for a variety of peripheral proteins. The complex functions during mRNP export, cytoplasmatic localization and nonsense mediated decay of aberrant mRNA during translation (Andersen *et al.*). Finally, the research group is engaged in structural studies of complement system being part of the the innate immune defense. We have determined the structures of complement C3 and C5, which after proteolytic cleavage by specific convertases elicit the proximal and terminal complement response, respectively.

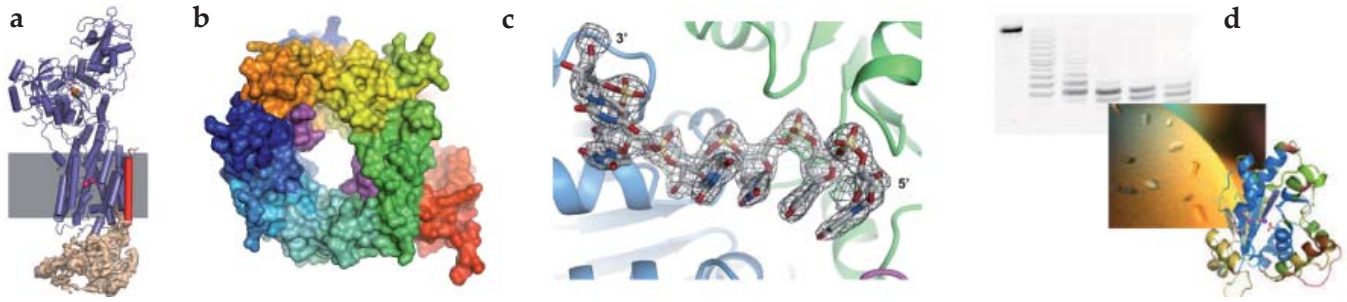


Figure 1. **a***: The crystal structure of the Na+,K+-ATPase showing the α (blue), β (gold) and γ (red) subunits and bound ions as spheres. The membrane is indicated as the grey box.* **b***: Surface representation of the neuroreceptor Sortilin with structural features indicated by different colours.* **c***: Electron density of RNA bound in the exon junction complex.* **d***: RNA degradation assay, crystals, and structure of the Schizosaccharomyces pombe Pop2p deadenylation subunit.*

RNA metabolism and decay

The laboratory of **Ditlev E. Brodersen** studies the controlled turnover of nuclear and cytoplasmic RNAs - fundamental processes which are essential for maintaining the quality and quantity of all transcripts. In the eukaryotic nucleus, elaborate quality control mechanisms are in place that guarantee that mRNAs exported to the cytoplasm for translation into proteins are intact and fully functional. Aberrant molecules are quickly intercepted and targeted for destruction via a large complex known as the RNA exosome. The group has determined the crystal structure of the nuclear 3′-5′ exonuclease Rrp6p responsible for this removal (Midtgaard *et al*.). The group also studies RNA turnover pathways in the cytosol, such as the removal of the poly-A tail found in the 3′ end of eukaryotic mRNAs (deadenylation). One of the active subunits of the mega-Dalton Ccr4-Not complex responsible for this process, Pop2p, has been characterised both biochemically and structurally (see figure 1d), detailing the specificity and activity of the enzyme (Jonstrup *et al*.).

Innate immunity

In the research group of **Rune Hartmann** the interferon cytokines (small hormone like proteins) are studied. These control the innate immune response to viral infections, and are popularly speaking the body's alarm system. If a cell is infected by a virus, the cell will start to produce interferon within one to two hours. The newly produced interferon will bind to receptor complexes found on the cell surface of neighbouring cells and activate this receptor. The activation of the receptor leads to activation of transcription factors which induce the synthesis of a number of antiviral genes. Thus, in effect interferon is warning the cell of the coming virus and initiates the defensive mechanism. Our prime interest is Type III Interferon's. We study how interferon binds to its receptor and induces signalling. Through determination of the crystal structure of interferon bound to the receptor we hope to gain novel insight in the receptor interaction. We are using the knowledge gained from structural biology to design *in vivo* experiments that can further illuminate the role of Type III interferon in the innate immune response.

Microbial symbiosis and pathogenesis

In the laboratory of **Thomas Boesen** research is centered around the interplay between host cells and microbes. Based on the wealth of genomic information available today a large family of LysM (Lysin Motif) containing proteins can be identified in bacteria, plants and mammals. The functions of these proteins are diverse. For bacterial LysM proteins the functions range from peptidoglycan degradation during division to involvement in pathogenesis. In higher eukaryotes the LysM proteins functions in signal perception pathways implicated in immune defence and development. We study the structural basis for the interaction between LysM proteins and carbohydrates and the implication on the function af these complexes in e.g. signalling process initiating symbiosis between legumes and rhizobia bacteria. Also, the group focuses on a range of bacterial toxins and their interaction with host cell receptors or substrates (Jørgensen *et al*.). The aim is to obtain an understanding of the molecular details and chemical basis for microbiol pathogenesis. This knowledge can be used for designing new, highly specific anti-microbial drugs.

Selected publications

Andersen CBF, Ballut L, Johansen JS, Chamieh H, Nielsen KH, Oliveira CLP, Pedersen JS, Seraphin B, Le Hir H, Andersen GR. (2006). Structure of the exon junction core complex with a trapped DEAD-box ATPase bound to RNA. Science 313: 1968-72.

Dahl LD, Wieden H-J, Rodnina M, Knudsen CR. (2006). The importance of P-loop and domain movements in EF-Tu for guanine nucleotide exchange. J Biol Chem 281: 21139-46.

Jonstrup AT, Andersen KR, Van LB, Brodersen DE. (2007). The 1.4 Å crystal structure of the S. pombe Pop2p deadenylase subunit unveils the configuration of an active enzyme. Nucleic Acids Res 35: 3153-64.

Jørgensen R, Merrill AR, Yates SP, Marquez VE, Schwan AL, Boesen T, Andersen GR. (2005). Exotoxin A-eEF2 complex structure indicates ADP-ribosylation by ribosome mimicry. Nature 18: 979-84.

Midtgaard SF, Assenholt J, Jonstrup AT, Van LB, Jensen TH, Brodersen DE. (2006). Structure of the nuclear exosome component Rrp6p reveals an interplay between the active site and the HRDC domain. Proc Natl Acad Sci USA, 103(32): 11898-903.

Morth JP, Pedersen BP, Toustrup-Jensen MS, Sørensen TL, Petersen J, Andersen JP, Vilsen B, Nissen P. (2007). Crystal structure of the sodium-potassium pump. Nature 450: 1111-4.

Quistgaard EM, Madsen P, Grøftehauge MK, Nissen P, Petersen CM, Thirup S. (2008). Ligands bind to Sortilin in the tunnel of a 10 bladed b-propeller domain. in prep.

PhD degrees

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Henrik Karring
Henrik Uffe Holst
Jeannette H.F. Justesen

2003
Kim Bak Jensen
Lars Aagaard
Mads Breum Larsen
Hanne Poulsen
Louise Vagner Laursen
Victor G. Stepanov
Karina Dalsgaard Sørensen
Trine Elkjær Larsen Crovato
Charlotte Georgi Jakobsen

2004
Vibeke Diness Jakobsen
Steen Günther Nielbo
Søren Vestergaard Rasmussen
Katrine Egelund Pedersen
Félicie F. Andersen
Shervin Bahrami
Esben Lorentzen
Brian Søgaard Laursen
Martin Larsen
Rolf Bo Andersen
Hans Peter Sørensen
Stig Uggerhøj Andersen
Signe E. Larsen
Anne Ahlmann Nielsen
Rikke Høegh Lorentsen

2005
Mai Marie Holm
Charlotte Harkjær Fynbo
Stefan Borre-Gude
Anette Thyssen Jonstrup
Rene Jørgensen
Camilla Skouboe
Søren Lykke-Andersen
Karen Colbjørn Larsen
Steffen Sinning
Morten Bjerring
Kasper Thorsen
Jens Raabjerg Olesen
Kristian B. Laursen
Tina Thorslund
Lisbeth S. Laursen
Astrid Colding Sivertsen
Vibe Hallundbæk Østergaard
Henning Bünsow Boldt
Rikke Christina Nielsen
Jens Preben Morth

2006
Mads Gravers Jeppesen
Jan Kristian Jensen
Esben Bjørn Madsen
Line Hummelshøj Mogensen
Lone Tjener Pallesen
Kim H. Hebelstrup
Kristian Wejse Sanggaard
Jesper Bøje Andersen
Ebbe S. Andersen
Christian B.F. Andersen
Morten Muhlig Nielsen
Marianne S. Hede
Rikke F. Hougaard

2007
Jesper Bertram Bramsen
Niels Høgslund Jørgensen
Claus Gyrup Nielsen
Julie Støve Bødker
Brian Christensen
Louise C.V. Rasmussen
Birgit K. Hougaard
Trine Kastrup Dalsgaard

2008 (until mid-September 2008)
Simon Glerup
Lotte Schack
Daniel M. Dupont
Søren Peter Jonstrup
Svend Haaning
Esben M.H. Quistgaard
Per Larsen
Henrik Hornshøj Jensen
Joachim Silber
Jesper Pallesen
Ulrik Lytt Rahbek

Privat milliongave til Molekylærbiologisk Institut

Molekylærbiologisk Institut på Aarhus Universitet har gjort sig godt bemærket – så godt, at det li-

Æresdoktorgrad

Brian F. C. Clark

selv har været syg. Tværtimod fordi

Kan vi påvirke tiden i fremtiden?

Nyt håb for folk med dårligt syn

Professor Poul Nissen har sammen med sit forskerhold som de første fået udgivet tre artikler i det samme nummer af tidsskriftet Nature. PR/Aarhus Universitet

Eksperter i det indre univers

Maria Diget Aamann, ph.d.-stud Universitet, har modtaget det presti Augustinus Fondet for at kunne forts of Health, Maryland, USA, i laborato barnebarn af Niels Bohr.

Vil knække kulhydraternes kode

Ny forskning i sund stress

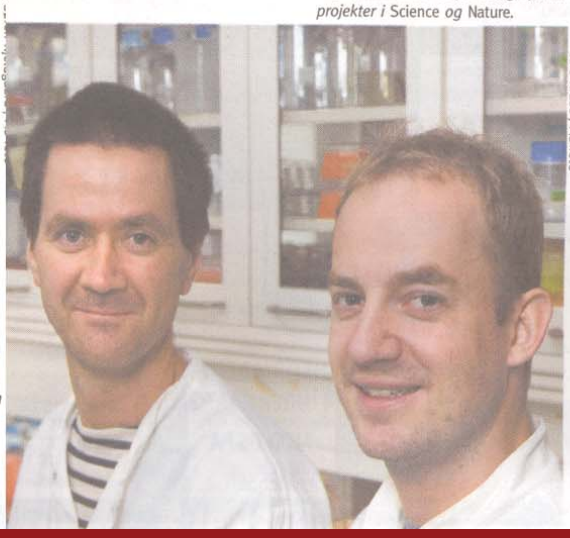
...f kulhydraters rolle i samspillet mellem ...hvre vanskeligt arbejdsområde. De ... komplekse end for eksempel protei... ...og ikke forskerne ved et af Aarhus U... centre, der de næste fem år skal arbe... af naturvidenskabens mest komplicerede felter.

Skræddersyet medicin

Ph.d.-studerende fik forskerdrømmen opfyldt

Christian har opnået,

Roistea Andersen, der inden for to dage publicerede to forskellige ph.d.-projekter i Science og Nature.



Lars Kruse / AU-foto

Debut med et brag

ÅRHUS PÅ FORSIDEN AF *nature*

Nobelpristagere på besøg

Staff and students at the Annual Meeting and 40th Anniversary Meeting of the Department of Molecular Biology - 4 June 2008