NEW KNOWLEDGE
NEW MEDICINES

PROFILE / CUTTING-EDGE KNOWLEDGE IS THE KEY TO DEVELOPING SUCCESSFUL MEDICINES OF THE FUTURE
Through our excellent research at the University of Copenhagen, we are helping to create new knowledge on medicines and thereby contributing to a solid foundation for the development of effective drugs.

This magazine provides insight into how the development of new medicines requires complex interdisciplinary research from molecular level to patients. Leading researchers are working closely together within genetics, bioinformatics, biophysics, medicinal chemistry, pharmacology, drug delivery, nanotechnology, clinical research and other fields. In essence, deeper understanding of both healthy and diseased states will improve our scientific basis for developing new medicines.

The many close collaborations between the university, hospitals and industry are instrumental in maintaining a global position in the pharmaceutical industry. The stakeholders’ geographical proximity in Greater Copenhagen is causing a positive spiral, with research and innovation enriching each other and promoting growth and knowledge. For example, approximately 60 per cent of the graduates from our pharmaceutical education programmes choose jobs in the pharmaceutical or biotech industries.

We would like to strengthen this collaboration further to maintain and develop our strong region with front-line international research in order to retain and create attractive workplaces. This requires trust, dialogue, an international mindset and investments in both basic research and interdisciplinary projects. The new Pharma Science Building on our North Campus is a prime example of an investment in state-of-the-art laboratory facilities that will contribute significantly towards strengthening our pharmaceutical research – to benefit both patients and society.

We are looking forward to more value-creating collaborations.
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Highly specialised researchers at the University of Copenhagen and Johns Hopkins University, working with other specialists, have created a cytotoxin based on a natural substance that, like a ‘heat-seeking’ hand grenade sent into the body, is only released when it hits the cancer cells. The drug is now undergoing clinical trials.
It was not obvious that a toxic weed would lead to a medicine that seems able to kill cancer cells selectively.

“At least not obvious to me,” says Søren Brøgger Christensen, professor of pharmacognosy (chemistry relating to drugs of natural origin) at the Department of Drug Design and Pharmacology, Faculty of Health and Medical Sciences at the University of Copenhagen.

In the 1970s, he immersed himself in identifying and isolating the toxins from *Thapsia garganica*, an umbellifer that grows wild in Mediterranean countries. Today – forty years later – based on the toxin thapsigargin from the plant, and in collaboration with US researchers, he has designed a promising ‘heat-seeking’ cytotoxin. Both in the cell cultures, in animal models and in early clinical trials in humans, the toxin has proved to be a tough adversary for cancer tumours. Notably, without the adverse effects we know from the other toxic substances currently used for chemotherapy. The treatment has no effect on the immune system and causes no hair loss.

**THE RIDDLE OF THE ‘DEATH CARROT’**

Plenty of natural substances were waiting to be isolated and have their structures clarified, and it was relatively coincidental that Søren Brøgger Christensen began investigating *Thapsia garganica* years ago. The plant commonly referred to as the ‘death carrot’ has been known for centuries. It was also general knowledge that if the juice came into contact with the skin, it caused serious itching and skin irritation but no one knew why.

Søren Brøgger Christensen and his team managed to isolate the dominant toxin in the plant, which was called thapsigargin, and clarify the structure of the substance. Meanwhile, pharmacological investigations revealed that the substance not only provokes the release of histamine, which causes serious skin irritation, it also activates myocytes and all the other cells in the immune system. Such a dramatic effect simply had to be investigated.

**THE CELLS COMMIT SUICIDE**

It was already known that disturbances in the calcium balance in a cell prompt the release of histamine, so Brøgger Christensen and his colleagues asked cell biologist Ole Thastrup, now Head of Department at the Department of Drug Design and Pharmacology, to conduct a series of measurements to determine whether thapsigargin altered the calcium balance.

Ole Thastrup mobilised an international team of highly specialised researchers who discovered that thapsigargin penetrates the cell and blocks a calcium pump that had the
function of maintaining the intracellular calcium balance. This block causes the cell to commit suicide via programmed cell death. The technical term for this mechanism is apoptosis.

The discovery, which was published in 1990, was groundbreaking. It meant that thapsigargin became an important tool for biochemists and pharmacologists aspiring to study and understand other functions in the cell. Thapsigargin as a medicine? No!

“The substance itself was completely useless because the calcium pump is present in all cells. Thapsigargin would kill all the cells in the body. As far as we were concerned, this was purely basic scientific research that could help enable other disciplines to develop,” says Søren Brøgger Christensen.

AN EXPLOSIVE IDEA

Then one day he received a call from the US.

That was in 1992. The call came from Professor of Oncology John T. Isaacs from the Johns Hopkins School of Medicine, Johns Hopkins University in Baltimore.

He suggested a research cooperation to develop a cytotoxin that would move through the body like a ‘heat-seeking’ hand grenade and only be activated when it hit cancer tumours. Selectivity was achieved through taking advantage of a unique enzyme that is expressed exclusively in prostate and neovascular tumour tissue.

This enzyme was first discovered in the prostate gland and is therefore called the prostate-specific membrane antigen (PSMA) – however it has also now been identified in tumours related to liver cancer, ovarian cancer, kidney cancer and breast cancer.

The enzyme only cleaves certain peptides. Isaacs therefore proposed that for his part he should develop some peptides that the enzyme could divide, and that Søren Brøgger Christensen could modify thapsigargin to bind with the peptide, thereby making it harmless. When PSMA divided the peptide, it would be like pulling the pin on a hand grenade. The toxin would be released, destroying the blood vessel and starving the cancer tumour of oxygen and nutrients.

“A telephone call like that, which provides the opportunity for cross-disciplinary collaboration at the highest scientific level, must be any researcher’s dream. Anyone trained in pharmaceuticals would want to develop a drug one day – knowing full well that it probably happens for fewer than one in every thousand of us,” he says.

REady For Clinical Trials

Seven years later, the research team succeeded in creating a prodrug, or inactive drug, that would not be transformed into a medicine until it was activated by an enzyme or other substance in the body. In this case, by the enzyme PSMA in the cancer cells. Before the researchers reached the clinical trials in humans, they demonstrated that the prodrug is not released in healthy animals but is simply excreted in the urine. In other words, just as desired, the potential medicine works selectively on cancer tumours.

In the meantime, Isaacs had obtained the keen interest of Craig A. Dionne, an American with many years of experience in bringing promising cancer treatments to the clinic. Dionne established the company GenSpera and is in charge of the clinical studies and applications to the US health authorities for permission to conduct them.

Promising Results

The prodrug, Mipsagargin, has undergone Phase I and II trials in patients with liver cancer, and Phase III is expected to start soon. This also applies to Phase II in patients with glioblastoma (an aggressive brain cancer).

Only a small number of cancer patients have been involved in these early phases but the results are promising: their tumours have shrunk and many months passed before the tumours began growing once more.

“We have not yet managed to make the patients’ symptoms disappear, but the trials have been conducted on very sick and weak patients who have failed to respond to other treatments. It is hoped that when our ‘heat-seeking’ grenade is launched early in the cancer process, it will fight the cancer cells with considerable force,” Søren Brøgger Christensen says.

He emphasises that the drug remains at an experimental stage and is not available for treating patients outside the clinics where the trials are being conducted.
One challenge involving the use of natural substances is that creating sustainable production is arduous. One kilo of plant material from a ‘death carrot’ produces ten grams of medicine. The researchers are therefore investigating alternative supply routes. One of them is to modify other organisms, mainly moss, to produce thapsigargin. Henrik Toft Simonsen, associate professor of plant biochemistry, the Department of Plant and Environmental Sciences, is striving to develop this method.

Søren Brøgger Christensen has also applied for a patent for a new synthetic method based on a more easily accessible natural substance.

The story of Mipsagargin in the words of Søren Brøgger Christensen “a tale of professionals who are so highly specialised in their respective fields that they can see when a mechanism of action is so new and surprising that they have to team up to investigate it more closely”.

However, it also involves opportunities for building bridges between research and business:

“As university researchers, our primary aim is to make discoveries that can enhance our understanding of the world. Yet this process also shows the importance of patenting inventions so that they can subsequently be commercialised,” Søren Brøgger Christensen says.

PRODUCTION OF THAPSIGARGIN

One challenge involving the use of natural substances is that creating sustainable production is arduous. One kilo of plant material from a ‘death carrot’ produces ten grams of medicine.

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Major benefits from close links between the university and industry

A strong academic environment that exchanges knowledge and candidates with the industry is the best guarantee that research will create value for society. The potential benefits of interaction between independent research and industrial innovation is far from exhausted.

The Øresund region is providing the site for one of Europe’s most important medical clusters, Medicon Valley. The region, which covers Greater Copenhagen, Zealand and Skåne, houses up to 300 pharmaceutical and biopharmaceutical companies, with the University of Copenhagen at its heart. See page 18.

The tradition of close collaboration between researchers at the university and the pharmaceutical companies spans many years. These close links have opened up a powerful flow of knowledge, insight and innovation between the two environments. However, what do these close links mean specifically for pharmaceutical research and the design of new drugs?

What value does the interaction create for the rest of society?

We have asked two of the key representatives of the industry and university, respectively: CEO of the Innovation Fund Denmark, Peter Høngaard Andersen (PHA) and Professor and Vice Dean Sven Frøkjær (SF).

SOCIETY IS BASED ON STRONG UNIVERSITIES

How does research at UCPH benefit the development of new drugs in the Danish pharmaceutical industry?

SF: We contribute broad basic biological, molecular biological, systems biological, pharmacological and pharmaceutical research. The deeper our understanding of both healthy and diseased states, the better the experimental platform we create for designing new drugs. We are also strong within translational research, through which preclinical research is transferred to the clinic via our colleagues at the university hospitals. It is also absolutely central that we provide the industry with high-calibre candidates and PhD students and graduates.
How important is Danish pharmaceutical research and the production of researchers at UCPH for the industry? Surely, the industry can simply obtain knowledge and candidates from the global market?

**PHA:** Proximity is vital! Our modern society is based on strong universities creating the foundation on which the industry is built; that applies unilaterally – not only within the biotechnological and pharmaceutical areas. If the industry does not experience that the university environment is strong, it will disappear. **Unless Denmark continues to invest heavily on the university and research front, I believe we will lose both a lot of industry and many attractive workplaces.**

**THE INDUSTRY SHOPS GLOBALLY**

**PHA:** It is vitally important that UCPH engages in demanding, independent basic research that affords individual researchers the scope to conduct investigations – fuelled by their own curiosity. At the same time, the university must take care to link it to the needs of the customers – often the industry, in the final analysis.

As a customer, you shop where the frontline research is at an extremely high level and globally competitive.

**How does UCPH ensure that the industry selects you?**

**SF:** By engaging in research at the very highest level. We have high-profile researchers and conduct top-calibre research in many, many areas. We must continue this while strengthening the research. We already have both Danish and foreign companies dropping in with their shopping baskets and commenting that the products on our shelves are interesting and competitive.
To what degree does the university target its research at the industry?

SF: As a rule of thumb, our researchers should not as such serve the pharmaceutical companies. We must have our platform, our basic knowledge, at the highest international level. That will ensure that we are interesting business partners for the global industry. That is the best way we can educate qualified candidates who can perform jobs in the pharmaceutical industry.

The researchers must cultivate their special research interests and exploit their special strengths; the university’s task is then to ensure the research is presented worldwide, and we are well on our way to achieving that. For example, we have strategic cooperation agreements with some of the major players among the pharmaceutical companies.

IDEAS MUST BE SUPPORTED AND MATURED
Is there the required flow of knowledge and innovation from the university to the industry?

PHA: The flow is strong and steady but it could become even stronger. Part of my job is to make sure the flow is unrestricted and even smoother – via support and various incentive structures.

A researcher receives credit for publishing work, and the higher the Journal’s impact factor, the better it looks on paper. However, that does not always coincide with what is required to mature an idea until it is attractive to the industry. We must therefore join forces with the universities to set up some structures that facilitate both aspects, so that the ideas are matured just a touch more than would otherwise normally be the case.

Are you referring, for example, to the ideas that form the basis for the researcher’s own companies – with support from the Innovation Fund Denmark, for example?

PHA: Absolutely. Consider it an ecosystem. Spin-outs or small start-ups are extremely important as a food chain of upcoming new ideas. The large companies typically follow them for some years and at one point or another, perhaps want to acquire them and make sure the ideas are fully matured and reach the market.

OPENNESS GENERATES RESEARCH THAT HITS THE GROUND RUNNING

SF: The researchers must also be willing to bring their knowledge and ideas out into the industry. On the one hand, the university world still tends to see cooperation with the industry as odious. On the other hand, we now have quite considerable external activities that we are still striving to develop.

PHA: The University of Copenhagen is making good progress, but I believe that with even greater openness, much more value can be obtained from the research being conducted.

Recently, I had lunch with three people from different foreign companies. All three of them had academic collaborations here in Denmark. One explained that he can clearly see that over the past 15 years, Denmark has invested a great deal in university research and that the quality is high. ‘There is really something worth pursuing here,’ he said, adding, ‘but when it comes to using your research on something that hits the ground running and creates value, many researchers do not really want to participate.’

This conversation strengthened my impression that UCPH could deliver even more value to society if there was more willingness to take risks and more backing for e.g. creating your own adventure in spin-outs and small start-ups.

SF: I agree. That is why our university strategy plan has a special focus on the area of innovation. We need a change of culture in the direction of more openness, and this process is certainly well under way. For example, it became clear evident what openness can achieve when we joined NEXT, a Danish National Experimental Therapy Partnership funded by the Innovation Fund Denmark.

NEXT includes four faculties of health and medical sciences that, together with the regions and the industry, are striving to strengthen Denmark as a preferred country for early clinical research. As soon as we announced the partnership, Danish subsidiaries in foreign groups began locating more trials in Denmark. That is a major source of income for society.

PRIVILEGED ACCESS

How could UCPH implement a specific initiative to make it even more attractive to the private sector?

PHA: During my time in the industry, we found MIT’s Industrial Liaison Program very useful. In return for a modest USD 5,000 we were invited to three or four meetings a year where we could see what research was underway before it became official. In other words, we “were let into the supermarket” before all the other customers gained access. This generated a first-mover benefit. UCPH could perhaps copy a scheme like this. The model was employed successfully at various locations worldwide.
FOCUS ON NEW MEDICINES

The Innovation Fund Denmark will strengthen research and innovative solutions to drive growth and employment in Denmark. In 2015, the Fund distributed grants of almost DKK 1.6 billion. One of the Innovation Fund Denmark’s six broad action areas is “Biotech, medico and health”, which also covers the development of new medicines.

The University of Copenhagen has defined nine interdisciplinary areas of strength. One of them is “New medicines”. The research is being conducted across professional disciplines and in interaction between biomedical basic scientific research, natural science and engineering as well as clinical research at the university hospitals.

INVESTING IN RESEARCH

PHA: NEXT is an excellent growth initiative. I believe this trend will continue. It is no secret that I have had visits from two multinational companies that are planning to establish R&D centres in Denmark based on our strong academic environments.

So progress is already being made…

PHA: The first step was to raise the level, and I believe we have achieved that. However, I think the area deserves greater political acknowledgement. If public-sector research investments rose from 1 per cent to 1.5 or even 2 per cent of GNP, I think we would see more international companies basing their research centres here.

It is almost unique for such a small country to have three very large international pharmaceutical companies. Unfortunately, in some circles there is a tendency to say they are so large that they can be self-sufficient. However, if you tone down the investments in the public system, I predict that the companies will calmly and quietly begin to leave the country.

SF: Also bear in mind that UCPH not only focuses on delivering high quality in terms of Drug Discovery but also production – e.g. Development, Quality and not least Regulatory Affairs. Within the regulatory area, the industry has a great need for candidates who can join in a qualified and scientific dialogue with authorities and researchers. We have therefore recently established the new Center for Regulatory Science (see page 12). If we could not meet that need, the major pharmaceutical companies would soon be forced to look for candidates elsewhere. UCPH’s research, also in the supporting disciplines, is extremely crucial for retaining the industry here in Denmark.

“ Our modern society is based on strong universities creating the foundation on which the industry is built. 

CEO Peter Høngaard Andersen
Improving patient involvement in the development of new medicinal products

Research and training in Regulatory Affairs comprise the focal point for a new interdisciplinary centre at the University of Copenhagen that aims to lead the field in Europe. Its research will include determining how to improve patient involvement.

No newly designed pharmaceutical is released onto the market until it has been very thoroughly investigated, analysed and pronounced safe by the authorities. There are countless safety and quality requirements, and pharmaceutical companies have large Regulatory Affairs departments closely monitoring whether all the rules are being met.

“However, do we have the rules we need? Can we regulate in a more efficient way? Our researchers must ask questions like that,” says former Project Manager Karin Friis Bach, who was the anchor for developing and building up UCPH’s brand new Copenhagen Center for Regulatory Science (CORS). Science must be in focus because through researcher and master’s programmes, the centre is to help ensure that Regulatory Affairs has research-based knowledge on which to draw to benefit the industry, authorities and patients.

“The regulatory area has become vast and complex. The industry and authorities are calling for staff with in-depth legislative insight who can also adopt a critical approach to problems that arise. In the long term, CORS will therefore offer master’s programmes covering competencies that are in demand, while building up completely new knowledge in the field through a wide range of research projects,” Karin Friis Bach says.

PATIENTS SHOULD HAVE INFLUENCE

The centre is unlikely to run out of research topics. Over the years, more and stricter rules have appeared, and as personalised medicine, based on genetic testing, is gaining favour, Regulatory Affairs should not simply be adapted to suit new forms of treatment. It should also include assessing diagnostic methods. In addition, at European level, patient involvement in the development and approval of new pharmaceuticals has also been added to the agenda.

“After all, the patients will be using the medicine, and they might not necessarily rate the benefits and adverse effects in the same way as the doctors and pharmaceutical companies. If the patients will not use the medicine, the companies will be unable to sell it, so it is also in the companies’ interests to involve patients. The only question is how. We already have good contact with EUPATI, the European consortium working to engage and train patients in drug development,” Karin Friis Bach says, adding:

“It would also be sensible to study how Danish and European legislation on clinical trials affects the companies’ and Denmark’s ability to attract research projects. And we will investigate whether randomised double-blind trials...
are always the most ethically acceptable research method."

**AN INTERDISCIPLINARY APPROACH ADDS STRENGTH**

CORS became a reality in spring 2015 and in terms of organisation, it is based at and refers to the Department of Pharmacy at the Faculty of Health and Medical Sciences. Other departments at the Faculty of Health and Medical Sciences, and departments at the faculties of social science, law and humanities, are also partners and contribute lecturers and researchers. This means that health economics, patent rights and dissemination of knowledge etc. can be incorporated in both teaching and research.

The ambition is for CORS to make the University of Copenhagen the strongest academic university within regulatory research in Europe.

"USA has two or three universities with similar centres but in most European countries, the research initiatives have been very sporadic. It is a clear strength for the University of Copenhagen that CORS has been established and is based on an interdisciplinary approach," Karin Friis Bach says.

**FACTS ABOUT CORS**

CORS was founded in the spring of 2015 and is run by the University of Copenhagen. The departments from four different faculties are partners at the centre. Other external partners include the Danish Health and Medicines Authority as well as major pharmaceutical companies such as Novo Nordisk, Lundbeck, Ferring Pharmaceuticals and LeoPharma.

The centre expects to obtain research funding from the industry, patient organisations and foundations. To date, support from the industry has enabled the establishment of five or six PhD programmes and one postdoc programme. CORS also offers courses and has applied for accreditation of a master’s programme.

*Read more at pharmacy.ku.dk/cors*
Nanomedicine is one way of assuring that drugs are delivered safely in the body and work at their intended destinations. With a new joint professorship in drug delivery and nanomedicine, the University of Copenhagen and the University of British Columbia have significantly boosted this area of research.

Since 2004, Urs Hafeli PhD has been employed at the Faculty of Pharmaceutical Sciences at the University of British Columbia in Vancouver, Canada as a professor of Drug Delivery and Nanomedicine.

His professional competencies are strongly rooted in chemistry. The research covers synthesis and radioactive marking of new molecules, production of medicine transporters in the form of nanoparticles, microspheres, antibodies and polymers, evaluation of drug delivery systems in in vitro models and in toxicological experiments as well as efficacy testing in in vivo models using diagnostic imaging modalities (SPECT, PET, CT, MR, optical imaging).

His research is aimed mainly at fighting cancer with radioactive pharmaceuticals and developing diagnostic imaging agents in various nuclear medicine procedures. Another of his research interests involves magnetic nanoparticles as transporters of anticancer drugs as well as arrays of hollow microneedles that penetrate the skin without pain and deliver vaccines more effectively.

Read more about Urs Hafeli’s research at magneticmicrosphere.com/hafeli_lab.
Enthusiasm on both sides of the Atlantic reflects the great shared expectations surrounding the innovative step of creating a joint professorship.

Since 2010, the Faculty of Health and Medical Sciences (SUND in Danish) at UCPH and the University of British Columbia (UBC) in Vancouver, Canada, have run a joint Pharmaceutical Sciences PhD programme. Now they have taken their collaboration a step further. With support from the Lundbeck Foundation, they have set up a joint five-year international professorship in one of the most important areas of current research: drug delivery and nanomedicine.

Both parties already hold strong positions in this field of research, “however it is a vast area, and we have complementary competencies. By cementing the existing good collaboration and combining our expertise and resources, we can conduct joint projects that allow us to draw even more on each other’s competencies, attract more funding and create results that can ultimately contribute to the development of better and more effective drugs,” says Flemming Madsen, Head of the Department of Pharmacy, where the Danish part of the professorship is anchored.

INTERNATIONAL CAPACITY

Swiss-born internationally renowned researcher Urs Hafeli has been selected to lead The UBC-SUND Lundbeck Foundation Professorship, and will therefore spend equal amounts of time at SUND and UBC.

“The Lundbeck grant and collaboration with SUND open up a wide range of exciting new research opportunities. I am looking forward, among other things, to being able to train at least four PhD students in this important area,” Urs Hafeli says.

NANOPARTICLES CAN BE GUIDED TO THE TARGET

Research into drug delivery involves finding ways to transport the drug intact and directly to the site in the body where it is to be effective – without producing adverse effects. The active drug must be formulated or ‘encapsulated’, so that it fulfils a long list of criteria. It must not succumb to degradation while being transported in the body. It must not be released until it reaches the correct destination. It must be released in the
correct volumes and at the correct rate. It must be soluble and able to pass the barriers with which the body is equipped to exclude foreign materials.

Not many existing pills and injection fluids meet all these criteria. For example, few drugs work selectively, which is a major problem with chemotherapy, among other things. An effective drug delivery system is therefore as important as an effective drug.

A vital part of the answer could be nanomedicine – the overall term for working with nano-sized materials and systems in the development of new drugs. The research involves aspects such as encapsulating drugs in nanoparticles produced from biodegradable materials, which can be designed to transport the drugs to the targeted diseased cells.

**DEVELOPING RADIOACTIVE DRUGS**

Nanomedicine research can also involve designing radioactive drugs for both treatment and diagnostic imaging. This is one of Urs Hafeli’s specialities, and his work is aimed particularly at fighting cancer. In his laboratory at UBC, he and his research team are producing microspheres (tiny spheres of biodegradable polymers) that contain anticancer medicine. By radiomarking the microspheres, it is possible to investigate how they are distributed in the body.

“We can track them and see, from the outside, if they actually reach a tumour or end up elsewhere in the body where they can cause harm,” Urs Hafeli says.

“At UBC, we have the equipment and imaging expertise, and we have chemists who can create radioactively marked drugs. I believe this will be one of the areas where we can contribute an extra dimension to the research in Copenhagen,” he says.

Flemming Madsen agrees:

“Urs’ approach to drug delivery and nanomedicine is a very important supplement to our research.”

**HIGH-CALIBRE DANISH LABORATORIES**

Similarly, the Department of Pharmacy is an attractive partner for Urs Hafeli and UBC. This is due partly to the Department’s high international research standards within drug formulation and analysis.

The research aims to achieve increasingly in-depth understanding of the physicochemical properties of drug substances – including their interaction with the biological transport systems and other components of a drug delivery system e.g. the additives that bind the pill together or transport the drugs in the body.

“In Copenhagen, they are very skilled at analysing, for example, how microspheres should be encapsulated to prevent damage to the drug, and so that it is released at the correct rate,” says Urs Hafeli.

He visited SUND for the first time in the spring of 2015.

“It was fantastic to experience the activity. Even the students were in full swing in the laboratories. In one, at least 20 people were conducting HPLC analyses, each of them on their own equipment, measuring how fast a drug was released in a solution. Our students at UBC do not spend very much time working in the laboratories. After graduating, most of them are employed at pharmacies or as clinical pharmacists at hospitals. Only one student out of a whole year joins the industry. At SUND, about 60 per cent of the students end up working in the industry,” he says.

**COLLABORATION CREATES A RIPPLE EFFECT**

Both the Department of Pharmacy at SUND and the Faculty of Pharmaceutical Sciences at UBC engage in multi-disciplinary cooperation with research teams at other universities, but a joint professorship is a new collaboration concept for them both.

“With a joint professorship, we will have the professional capacity to channel knowledge and insight both one way and the other. Every time Urs engages in a cooperation project, it will create ripple effects that others can pursue,” Flemming Madsen says.

“We already enjoy good collaboration with UBC, and as the mind-set and culture in Vancouver closely resemble those in Europe, the cultural barriers are insignificant.”

He adds that SUND’s and UBC’s pharmaceutical departments are very alike both in terms of size and international research ranking.

**TWO OF THE BEST CITIES IN THE WORLD**

As a ‘joint professor’ Urs Hafeli will be dividing his time between the two institutions. This means he will spend a month or two at SUND several times a year, and when he is at UBC, he will spend one day a week in contact with researchers and students at SUND, e.g. via Skype.

“Naturally, this means I will have to reorganise some aspects of my life, but as my wife finds Copenhagen quite interesting, I am counting on and hoping that on most occasions she will accompany me,” Urs Hafeli says.

“You know the lists where they name the best cities in the world? Both Vancouver and Copenhagen are always near the top. They are expensive cities to live in, but both are excellent places to be.”

Read more about the research at the Department of Pharmacy here: pharmacy.ku.dk
The joint professorship has become a reality thanks to a DKK 10 million donation from the Lundbeck Foundation.

“We hope this research project can create new knowledge in the drug delivery field, and we look forward to following its progress. The grant brings together two of the main objectives of the research funding we grant. On the one hand, to promote and further enhance the qualifications of the excellent Danish health science research environments and, on the other hand, to strengthen the internationalisation of Danish health science research,” Director of Research Anne-Marie Engel, the Lundbeck Foundation explains about the donation.
A cohesive pharma region

A STRONG BUSINESS CLUSTER
The region’s Medicon Valley is one of Europe’s three largest business clusters within biotechnology medicines and medical technology.

The cluster includes approximately 300 companies, most with their own R&D and/or production in the region. Among the leading pharma companies in the region are Novo Nordisk, Lundbeck, Leo Pharma, Ferring Pharmaceuticals, GlaxoSmithKline, MSD and Symphogen.

HOSPITALS
Copenhagen University Hospital is the framework for the university-based collaboration between the University of Copenhagen and the health-care system in the Capital Region of Denmark and Region Zealand.

Rigshospitalet has the status of a highly specialised hospital; accompanied by a number of major acute hospitals with activities spanning several addresses in the region.

Skåne University Hospital, one of Sweden’s seven regional hospitals, is an alliance of the university hospitals in Lund and Malmö.

UNIVERSITIES
The University of Copenhagen and four other universities in the region are contributing research and education of relevance in the field of medicine and the pharmaceutical industry.

LEADING GLOBAL RESEARCH FACILITY
The European Spallation Source (ESS) will be the world’s most powerful source of neutrons for research into substances – from biomembranes and molecules to magnetic materials and superconductors as well as research into all types of surfaces. ESS is also expected to have significant importance for basic research in the field of medicines.

The MAX IV X-ray light source is a facility for producing synchrotron light from extremely intense X-rays. The facility will produce almost 100 times more intensity than other existing synchrotron facilities worldwide. MAX IV is expected to be a major asset for both the universities and the companies working with research and development within medicines etc.

The research facility itself will be based in Lund whereas the datacentre will be based in Copenhagen.
With an extensive business cluster in biotech and pharma, as well as strong research environments around the university and university hospitals, Greater Copenhagen is a natural hotspot for collaboration on developing new medicines.
In the future, pharmaceuticals based on peptides and proteins will be developed through an innovative combination of chemical and biological methods. The Center for Biopharmaceuticals has built up a unique international research environment in this field.
Advanced research attracts international talents

The human body’s own molecules are an ingenious starting point for pharmaceuticals. Not least peptides and proteins, as they can be precisely targeted and thereby cause fewer adverse effects. However, peptides and proteins are difficult to work with. As they are typically large and unstable, it is difficult to develop peptide- and protein-based drugs that are effectively absorbed in the body.

The Faculty of Health and Medical Sciences’ Center for Biopharmaceuticals is a clear front-runner and pioneer of basic research that will facilitate overcoming these obstacles and will lay the foundation for developing peptides and proteins with entirely new properties. The recipe is an innovative combination of chemical and biological methods.

UNIQUE RESEARCH ENVIRONMENT

We now have basically two types of pharmaceuticals. Firstly, small molecule pharmaceuticals, such as painkilling pills, based on a wide range of input, which are ultimately chemically synthesised drugs. Secondly, biological pharmaceuticals that are more extensively based on the body’s own raw materials, typically peptides and proteins that are almost exclusively genetically engineered and are produced in living cells such as yeast cells. Insulin for diabetes treatment is a familiar example of a therapeutic protein.

The researchers at the Center for Biopharmaceuticals work with technologies that combine chemical principles and tools with processes from living organisms.

“We are not unique in combining chemistry and biology, but the range of technologies we have gathered in one and the same research environment is unique. This has, for example, helped us to attract talented researchers from both Denmark and abroad,” says Professor of Chemical Biology, Kristian Strømgaard, Director of the Center for Biopharmaceuticals.
MODIFIED PROTEINS
A key part of the centre’s research involves introducing artificial protein modifications. Consequently, the researchers started with amino acids – the building blocks that comprise proteins. Every protein consists of up to 20 different amino acids. Kristian Strømgaard calls them ‘the genetic alphabet of proteins’. Like strings of pearls forming long chains, they intertwine, creating a three-dimensional structure.

By removing, inserting and exchanging the amino acids and then observing the biological effect of the changes, the researchers gain insight into the correlations between the structure and function of the protein.

DESIGNING A NEW ALPHABET OF PROTEINS
To expand the scope of the variations, the researchers employ methods to customise brand new amino acids and peptides. This can provide even deeper understanding of the proteins’ basic mechanisms. This insight is also key for designing proteins with optimal properties and therefore new and better protein-based pharmaceuticals.

However, the purpose of the Center for Biopharmaceuticals is not to develop the drugs.

“We conduct all the preliminary work. Hopefully, we are laying the foundations that, in the long term, will enable the design of stable and selective medicines formulated with letters differing from the 20 in the existing genetic alphabet,” Kristian Strømgaard says.

Hopefully, we are laying the foundations that, in the long term, will enable the design of stable and selective medicines formulated with letters differing from the 20 in the existing genetic alphabet.

Professor Kristian Strømgaard
A NUMBER OF MEDICINES for treating depression work by inhibiting the transporter, SERT, that transports the signal substance serotonin in the brain. The picture shows a model of the spatial structure of SERT, to which the new antidepressant vortioxetine (marked in yellow) is bound. By inserting artificial amino acids in SERT, the researchers at the Strømgaard Lab have gained insight into the molecular details relating to how vortioxetine inhibits SERT.

CENTER FOR BIOPHARMACEUTICALS

Established in 2014, the centre is anchored in the Faculty of Health and Medical Sciences’ two pharmaceutical departments, the Department of Drug Design and Pharmacology and the Department of Pharmacy. Over the next year, the centre will receive DKK 35 million from the University of Copenhagen as well as support from a number of funds. The centre has approximately 35 employees – one third are post-docs and one third are PhD students.

The centre has three rising stars at its helm, each in charge of his own laboratory:

Professor Christian Adam Olsen, specialist in chemistry and chemical biology.

Based on chemical synthesis, the laboratory studies the functions of peptides and their effect in biological systems in particular. For example, the team is striving to map the fundamental function of a range of proteins of relevance for cancer treatment. This includes both the synthesis of new drugs and use of chemistry-based methods for understanding the function of these proteins.

Professor Kristian Strømgaard, specialist in chemical biology.

Work at the laboratory includes combining biological and chemical methods to create semisynthetic proteins and subsequently observing their functions. The semisynthetic proteins are formed from biologically expressed proteins that are ‘glued’ together with peptides that are built up, amino acid by amino acid, using a chemical technique.

Associate Professor Stephan Pless, specialist in biology.

The laboratory is working on e.g. advanced methods for inserting synthetic amino acids in the membrane proteins of cells, the so-called ion channels. This also facilitates studying the molecular and pharmacological functions of the ion channels that play an important role in the development of a number of diseases.

Read more at biopharmaceuticals.ku.dk.
Two researchers from the Center for Biopharmaceuticals have developed a new concept for acute medical treatment of strokes. The drug they have produced is so promising that they have set up their own company, Avilex Pharma, and received a prestigious grant from one of the largest foundations in the world.

**STROKES**

WHO estimates that every year, about 15 million people suffer either a blood clot (thrombus) or haemorrhage in the brain. The general term for this is a stroke or apoplexy. Blood clots in the brain cause 85 per cent of these cases and are treated acutely with medicine that dissolves the blood clot. Brain haemorrhages cause 15 per cent of these cases.

Currently, no medicine is available that can slow down cell death after a stroke. Avilex Pharma is founded on the discovery of an entirely new drug that works via a new strategy for treating strokes both safely and effectively.
On 28 January 2015, Kristian Strømgaard was on cloud nine in more sense than one. Just before his flight from London to Copenhagen took off, he noticed a missed call on his phone from one of the largest foundations for biomedical research in the world, the London-based Wellcome Trust.

Kristian Strømgaard is a professor of chemical biology and Director of the Center for Biopharmaceuticals. He is also CEO of his own biotech company, Avilex Pharma, and it was in this capacity that he was returning from London. He had been overseas to support an application for DKK 18 million to conduct preclinical studies on a promising drug for acute treatment of strokes.

As soon as he landed, he returned the contact person’s call. Wellcome Trust had decided to approve the application.

“It was time to break out the champagne!”

A TOTAL OF DKK 28 MILLION RAISED

According to Kristian Strømgaard it is the first time the Wellcome Trust has granted a so-called ‘Translational Award’ to a Scandinavian company. The award for Avilex Pharma is also unusual in that the trust is supporting the development of a drug that can protect the brain against cell death after a stroke.

“Countless people have tried to develop medical products that limit the damage in the brain following a stroke but so far none have succeeded. Potential investors are therefore sceptical about the new drugs in this area,” Kristian Strømgaard says.

Nevertheless, Avilex Pharma has successfully raised a total of DKK 28 million to test its drug. DKK 18 million from the Wellcome Trust and the remainder from Novo Seeds, which is part of Novo A/S.

Avilex Pharma has managed to dispel the scepticism as its potential medicine has produced promising results based on an innovative concept.
Kristian Strømgaard and Anders Bach still spend most of their time at the University of Copenhagen, where the fact that their research has led to a business spin-out company has brought an extremely positive response.

“Strømgaard and Bach are outstanding examples of what we would like to show our young PhD students and postdocs, that the Department’s research environment can offer a solid scientific education and an academic career that also opens up for the opportunity to establish their own companies,” says Head of the Department of Drug Design and Pharmacology, Ole Thastrup.

“In my experience – also in an international context – there is a perfect correlation between solid research and innovation. The two are inseparable. People who are innovative also have scientific strengths and publish in the prestigious international scientific journals. Science and innovation go hand in hand,” he says.

“You can easily be an extremely skilled scientist without necessarily establishing a spin-out company. We do not force innovation on people. But we like nothing better than to spar with researchers who are blessed with an innovative approach and who enjoy translating their ideas and research into developing specific products. We advise them on e.g. practical aspects such as raising capital, cooperation agreements, planning tasks and laboratory facilities,” Ole Thastrup explains, adding:

“The academic environment is exceptional in that sense. It provides the scope and freedom to create.”
FROM EXTERNAL TO INTERNAL

Traditional drugs target proteins in the cell membrane and act on receptors for signalling substances (neurotransmitters). When brain damage occurs, the receptors in the nerve cells are overactivated by the signalling substances. Typically, attempts have been made to develop medicines that protect the receptors by blocking them. However, in doing so, they also blocked the receptor’s other vitally important functions – which produces unacceptable adverse effects.

In recent years, interest in an alternative approach called protein-protein interactions has increased. Rather than having a direct effect on the receptor from the outside, attempts are being made to influence and alter the interaction between the receptor and proteins inside the cell.

Academic curiosity about this strategy led Strømgaard and Bach to begin this research in the mid-2000s, which resulted in their breakthrough.

DELAYED THE RELEASE OF TOXINS

At that time, Anders Bach was a PhD student and his supervisor Kristian Strømgaard was already a successful researcher who, at an early age, was appointed professor in charge of what was then a new research area termed chemical biology.

Kristian Strømgaard’s attention was attracted by the PSD-95 protein, which is found in brain cells. The protein was assumed to play a role when the so-called NMDA receptors in the nerve cells were overactivated.

It was assumed that PSD-95 comprised a biological bridge between the NMDA receptor and the nNOS enzyme, which produces nitrogen oxide. In large volumes, nitrogen oxide is extremely toxic for the cell. The reasoning was that when the receptor was overactivated, the nNOS was also overactivated – via PSD-95. By combining chemical and biological methods, Strømgaard and Bach produced a peptide that could not only penetrate the brain’s protective blood-brain barrier but, among other things, could also bind with PSD-95 in an entirely new way. The bridge was destroyed and this limited the release of the toxic nitrogen oxide.

“I can clearly recall when Anders came and showed me the results in 2008. It was amazing,” Kristian Strømgaard says.

FOUNDED THEIR OWN COMPANY

In the years to followed, they further developed their research and in 2012 could demonstrate that one of the drugs they had optimised had a significant effect on strokes in animal models. They applied for capital to continue their development research but it was an uphill struggle because the potential investors had encountered bad experience with drug candidates aimed at limiting stroke-induced damage. Despite this, they finally succeeded in obtaining a seed investment from Novo Seeds that helped Strømgaard and Bach to establish their own company, Avilex Pharma, which became a reality on 27 December 2012.

BOTH RESEARCH AND BUSINESS

It has been quite challenging for Strømgaard to become CEO of his own biotech company and learn to navigate in an entirely different environment to the academic world – while performing his job as a full-time researcher at the university.

“But it has also been extremely interesting, and naturally, now it is tremendously exciting,” says Kristian Strømgaard, who is counting on soon relinquishing the role of CEO. Avilex Pharma is currently scouting for a professional director to enable Kristian Strømgaard to focus on the role of chief scientific officer for the company.

Read more at avilexpharma.com
Biobanks are a treasure trove for research

Access to blood samples from thousands of people is a valuable resource for researchers exploring the importance of genetics in diseases. Research results can pave the way for improved diagnostics, more effective prevention and personalised medicine.

Every year, thousands of patients at hospitals in the Capital Region of Denmark provide blood samples for diagnostic purposes. Before 2012, surplus blood samples were usually discarded when analyses were completed. Today, they are stored for research purposes at the Capital Region of Denmark’s Biobank.

“We have therefore compiled a resource that, compared with data in registers covering e.g. demography, disease and medicine consumption, represents vast research potential for both the industry’s and the university’s researchers,” Henrik Ullum says. He is a specialist in clinical immunology at Rigshospitalet, Professor at the University of Copenhagen and head of the Capital Region of Denmark’s Biobank, which became a reality largely on his initiative.

“The many blood samples facilitate the study of genetic variations in large groups of patients and show the importance of those variations for their diseases. The knowledge we gain could be the key to designing personalised medicine, i.e. treatment targeted at patients’ individual needs and adapted to suit the patient’s genetic heritage,” he says.
DANISH BIOBANKS

Denmark has a wide range of biobanks of different sizes that store blood samples for research purposes.

One of them is the Capital Region of Denmark’s Biobank, which comprises blood samples from patients, and another is the Danish Blood Donor Study’s biobank, which comprises blood samples from healthy donors.

There are also e.g. cancer biobanks, a diabetes biobank, an HIV biobank and the Danish National Biobank, which collects e.g. blood samples from the heels of all new-born babies.

The Danish National Biobank Register provides all researchers from Denmark and abroad with online access to determine which samples are available for a given diagnosis. Altogether, searches can be conducted among more than 16 million biological samples from five million Danes.

The many biological samples in Danish biobanks are stored in refrigerators at –80°C. There are more than 2,000 of them throughout Denmark.

Read more about the Danish National Biobank Register at biobankdenmark.dk
EFFECTIVE VERIFICATION OF HYPOTHESES

In 2009, Henrik Ullum prompted the storing of surplus patient blood samples at Rigshospitalet, and, in 2012, all the hospitals in the capital region followed suit. That generates about 70,000 surplus samples a year, and the bank now comprises about 250,000 samples.

“This means that researchers can find a vast number of samples for almost any disease and can rapidly verify a theory on a correlation between a particular genetic factor and the progress of a certain disease,” Henrik Ullum says.

For example, one team of researchers hypothesised that a genetically determined damaged mucous membrane could increase the risk of cervical cancer. The biobank contained 800 surplus blood samples from women with cervical cancer. Based on the extensive material available, the researchers could reject the hypothesis after just a few months.

RESEARCH COLLABORATIONS

Although the biobank facilitates contact between the clinics and the external researchers, it is neither a business nor simply a service unit.

“The public authorities and pharmaceutical and medico-technical industry agree that all access to biobank samples should be available via collaboration with Danish researchers in the public system,” Henrik Ullum says, adding:

“We are not a commercial enterprise but prefer to retain a scientific involvement in the research projects that are launched. For instance, we recently completed an extremely extensive project with a private research institution and expect a explosive increase in scientific articles,” Henrik Ullum says.

Read more about the Capital Region of Denmark’s Biobank at regionh.dk/english
TERMS OF USE FOR BLOOD SAMPLES

The Capital Region of Denmark’s Biobank is subject to the Danish Health Care Act, which stipulates that blood samples donated for diagnostic purposes are the legal property of the hospital. They may be used for research purposes unless the patient concerned is personally registered with the register for tissue use at the Danish Health and Medicines Authority.

A health science research project must always be reported to the Danish Data Protection Agency and approved by the National Committee on Health Research Ethics. Projects aspiring to utilise blood samples from the Capital Region of Denmark’s Biobank must also be approved by the associated committee, which ensures that no material is distributed without the acceptance of the clinics where the patients were treated.

“Researchers can find a vast number of samples for almost any disease and can rapidly verify a theory on a correlation between a particular genetic factor and the progress of a certain disease.

Professor Henrik Ullum
With approximately 100,000 participants, the Danish Blood Donor Study (DBDS) is one of the largest population studies in the world. It provides the opportunity to study biomarkers for subsequent disease occurrence.

In 2009, at about the same time that Henrik Ullum had the idea of establishing the Capital Region of Denmark’s Biobank, the idea was conceived to create a national research resource based on blood from Danish blood donors.

“Blood donors are healthy, and generally enjoy better health than the rest of the population. Studies based on blood samples from the donors can give us important information about preventing disease,” he says.

Henrik Ullum contacted the association Bloddonorerne i Danmark (blood donors in Denmark), which welcomed participation in the research project due to its potential importance for public health. In 2010, the Danish Blood Donor Study (DBDS) was established in cooperation between the association and researchers from both Aarhus University/Aarhus University Hospital and the University of Copenhagen/Rigshospitalet.

WIDESPREAD PARTICIPATION
Approximately 100,000 blood donors from throughout Denmark have agreed to participate, making DBDS one of the most extensive population studies in the world. It covers a wide range of research projects, all aimed at discovering the reason why Danish blood donors are healthier than the Danish population as a whole. For example, one project intends to determine the importance of iron levels in the blood. Another is focusing on revealing the degree to which blood donors differ from non-donors in terms of lifestyle factors, self-assessed health and demography.

BENEFITING FUTURE PATIENTS
Other research projects aim to identify biomarkers that can predict disease. For although blood donors are generally healthy, some of them subsequently develop diseases, and this provides scope for studying whether there are markers that could have predicted the disease – e.g. depression.

“We know that blood donors receive fewer prescriptions for psychotropic medicines than the background population, and our research has also revealed that activation of the immune defence system is associated with depression. We are therefore now investigating whether we can identify infection markers that can predict depression, and whether there is a correlation with specific infections and genetic susceptibilities. Other researchers are attempting to identify early markers for lymphomas, leukaemia and colon cancer, respectively, and similarly, we are studying whether there is a correlation between obesity and infections,” Henrik Ullum says.

“The opportunity for identifying early disease markers is an important strength for DBDS. It provides us with valuable knowledge that we can use to improve the prevention and treatment of diseases – to benefit patients in the future,” he says.

Read more about DBDS at dbds.dk
Donor blood contains valuable information

"Studies based on blood samples from the donors can give us important information about preventing disease."

Professor Henrik Ullum
Facts about the School of Pharmaceutical Sciences

- **DRUGS** are the focus for all the educational programmes at the School of Pharmaceutical Sciences.

- The school offers a selection of broad-based natural and health science programmes – at BACHELOR’S AND MASTER’S LEVELS as well as further and continuing education programmes.

- A total of 1,400 STUDENTS attend the school on an everyday basis. The majority of them train to be pharmacists, and 230 new pharmacy students are enrolled every year.

- 60% of the pharmaceutical MSc graduates are employed in the medicinal/biotech industry. That is a far stronger industrial profile than in most other countries. Approximately 25 % are employed in the public sector (university, hospitals etc.), 15 % in pharmacies.

- The programmes are developed in continuous INTERACTION WITH THE INDUSTRY, pharmacies and other employers. Cooperation includes curricula, courses, theses and research projects etc.

- The School of Pharmaceutical Sciences offers two INTERNATIONAL MASTER’S PROGRAMMES in pharmaceutical sciences, two continuing education master’s programmes and a range of individual further and continuing education courses.

- The LECTURERS are mainly from the Department of Drug Design and Pharmacology and Department of Pharmacy. This ensures that the programmes are based on the most recent research.

- A total of 160 PHD STUDENTS are enrolled at the two departments. The majority of these are associated with the interdisciplinary Drug Research Academy graduate school programme.

- The School of Pharmaceutical Sciences is based close to THE CENTRE OF COPENHAGEN where, with the rest of the Faculty of Health and Medical Sciences, it forms part of Copenhagen Science City.

Read more at pharmschool.ku.dk/english.
A step towards the industry

SILVIA BARBATESKOVIC is working on her thesis while studying for a master’s degree in pharmacy at the School of Pharmaceutical Sciences. She is writing her thesis, on the configuration, structure and function of proteins, in cooperation with the Protein Structure research department at Novo Nordisk.

“One of the benefits of a thesis collaboration with the industry is that I get to know how a research unit functions in a leading pharmaceutical company. I find working with professionals whose competencies differ to mine particularly rewarding. It is also especially motivating to know that my academic insight can be useful for their product development and will create value for others in the long term,” says Silvia, who is setting her sights on a career in the pharmaceutical industry.

THE NEW cutting-edge laboratories in the Pharma Science Building will strengthen both the on-site pharmaceutical research and the students’ profiles. In total, the pharmaceutical research and education facilities cover approximately 46,000 square metres.
NEW KNOWLEDGE
NEW MEDICINES

PROFILE / EXCELLENT RESEARCH ACROSS SCIENTIFIC DISCIPLINES. A CLEARER FOCUS ON TRANSLATIONAL RESEARCH. STRONG SYNERGY BETWEEN THE UNIVERSITY AND THE REGION'S PHARMA AND BIOTECH INDUSTRY. THESE ARE THREE KEY INGREDIENTS THAT THE UNIVERSITY OF COPENHAGEN CONTRIBUTES TO THE DEVELOPMENT OF MEDICINES OF TOMORROW.

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