

AutoCurious

A newsletter from AutoCure • JUNE 2009

Gaining more and more knowledge on early diagnosis and early treatment of RA

AutoCure has now passed its three year anniversary, and many programs are in their most active phase, and will remain so during the coming two years.

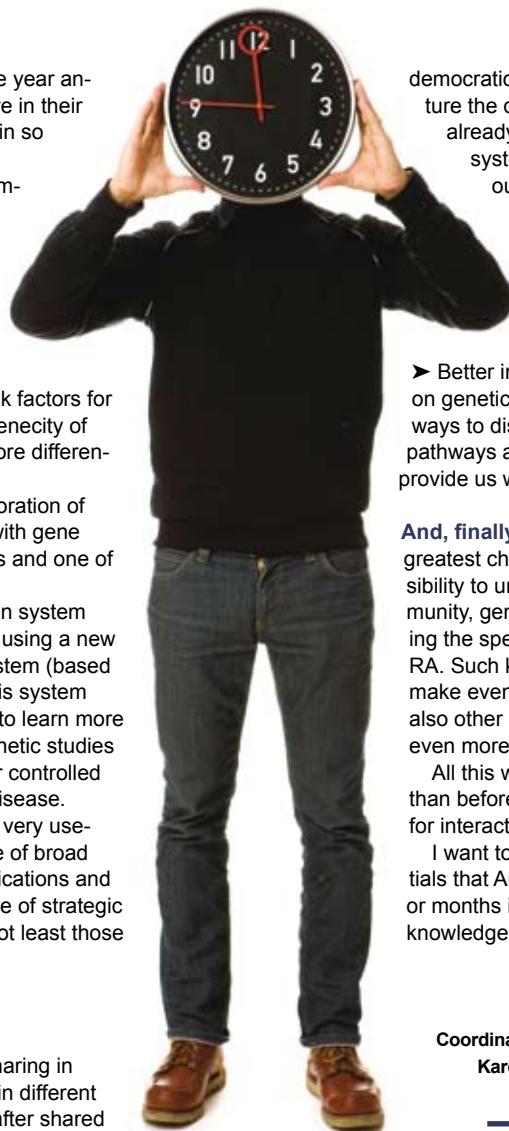
Looking both on what has been accomplished and even more on what can be achieved in the remaining time, I want to highlight a few accomplishments as well as a few urgent needs.

So far we have accomplished:

- ▶ Use of the many longitudinal cohorts of RA to describe a new pattern of risk factors for RA, which demonstrates the heterogeneity of the disease, and the potentials for more differentiated and early treatment
- ▶ Establishment of a very active collaboration of new techniques for treating arthritis with gene therapy, where both academic groups and one of our SME:s (Arthrogen) are involved.
- ▶ Establishment of a new pan-European system for long term surveillance of myositis using a new web-based and generic database system (based on the Danish DanBio programs). This system will provide a totally new opportunity to learn more about etiology for myositis via the genetic studies under way, and also pave the way for controlled clinical studies in this rare (orphan) disease.
- ▶ Our bioethics program has produced very useful information and arguments for use of broad consent strategies in our ethical applications and patient information sheets. This will be of strategic importance for many of our studies, not least those that involve genetics.

What has not yet been accomplished and what is needed includes:

- ▶ A better European system for data sharing in arthritis where data can be captured in different existing or novel systems, and thereafter shared



MICKE LUNDSTRÖM

democratically between the partners which capture the data. The building of such systems has already begun at several places. Data sharing systems enable the most efficient use of our clinical databases and biobanks and gives us fantastic new opportunities to study etiology and individualised therapies.

- ▶ A better coordination of the biobanks and the generated data (genetic, biomarkers etc)
- ▶ Better integration between the animal work on genetic and genetically determined pathways to disease, and studies on whether similar pathways are used in humans. Such work should provide us with better predictive models of arthritis.

And, finally: In my eyes, we have one of the greatest challenges just in front of us, i.e. the possibility to understand how innate and adaptive immunity, genes and environment interact in shaping the specific immune reactions that can cause RA. Such knowledge may indeed allow us both to make even more early diagnosis of arthritis (see also other interviews in this issue) and to develop even more specific immunotherapies.

All this will be so much more efficiently done than before using our consortium and our options for interactions and exchange.

I want to encourage you all to use the potentials that AutoCure provide to spend days, weeks or months in other AutoCure units, gaining new knowledge as well as new friends. □

Professor Lars Klareskog,
Coordinator for the AutoCure-project,
Karolinska Institutet, Stockholm,
Sweden



AutoCure
- curing autoimmune diseases

AutoCure is an FP6 EU-funded integrated research project, with a translational approach to autoimmune diseases in the postgenomic era, using inflammatory arthritis and myositis as prototypes and learning examples.

 THE BIRMINGHAM EARLY TREATMENT RECIPE

Unique chance to study the early mechanisms of RA

Catch RA-patients very early, treat them aggressively and do thorough regular follow ups with ultrasound. That's the treatment recipe currently being developed by the Rheumatology Research Group (RRG) at Birmingham University.

Thanks to a very effective collaboration with the GPs, the Early arthritis clinic, set up in 2000 by Dr Karim Raza, usually sees the patients within a few weeks after their first symptoms.

— This gives us the possibility to gain knowledge of the early and very specific mechanisms of the disease and perhaps find the answer to why 50 percent of such early patients never actually develop RA, says Professor Chris Buckley. Professor Buckley is a member of the AutoCure management group, and head of a group of 25 people, a dynamic mix of basic researchers and clinicians. Four out of the six teams in the Birmingham RRG are part of the AutoCure project.

— I am a big fan of this modern way to do research. By combining skills and collaborating with other research groups you have a much better chance of getting good results. Even with some healthy competition between the AutoCure groups it's a win-win situation. The partnership with AutoCure has facilitated our work in Birmingham, not least by funding one of



Professor Chris Buckley



The Medical School in Birmingham.

our excellent technicians, and new funding for a much needed research nurse. We also collaborate closely with our partners in Amsterdam, Leiden, Switzerland, Sweden and Austria. So far six of the lab staff have visited colleagues at the AMC in Amsterdam and one in Zurich, says Professor Buckley, who is a perfect example of translational research himself, having a dual role as clinician and research scientist.

A significant part of the research in our group is based on two fundamental questions "Why does RA persist and why does it have a predilection for the synovium?"

— We know that more than half of our patients with early symptoms like stiffness and pain in the joints will get better without any treatment after six months. But the other half WILL develop RA or some other inflammatory disease. We want to find out why. Our best bet is that it is the stromal cells, the soil in which the white blood cells grow, which seems to be abnormal, says Professor Buckley.

Thanks to a seminal study on a cohort of patients with early disease the RRG

team discovered that patients with a certain cytokine-profile are much more likely to develop RA than others.

— This has only been known for about five years but now we are exploring whether patients with this particular cytokine-pattern should be treated with an aggressive therapy right from the start, says Professor Buckley and refers to Dr Karim Raza who is leading this part of the work.

— The key is to catch and identify patients by taking blood and tissue-samples at a very early stage of the disease. Thanks to the extensive network that we have built with a wide range of primary care physicians, people are sent to our clinic as soon as they present to primary care with RA-symptoms.

— This makes it possible for us to do unique follow-ups, comparing those who develop RA and those who get well. Because we have samples from the onset of the disease we have a unique chance to study and gain knowledge of the underlying mechanisms in the inflammatory process. □

THE PATIENT'S STORY

No pain and hardly any symptoms

One year ago her hands suddenly became stiff and swollen and her shoulder started to ache.

— I thought it had to do with the menopause but as the pain got worse I made an appointment with my GP who thankfully immediately referred me to Dr Karim Raza's Early arthritis clinic, says 52-year old Zoë Langfield from Birmingham.

Zoë Langfield, who works as a Town Planner for the Birmingham City Council, seldom sees her doctor, but this time the unusual and inexplicable pain was bothering her a lot.

— I knew nothing at all about arthritis and it never occurred to me that I could have the disease. But the blood test clearly showed an RA-factor and thanks to the NHS rapid electronic referral system I got an appointment with Dr Raza within two weeks.

At first she wasn't really too concerned about her diagnosis.

— But when I came home and started

to read about RA on the internet I almost scared myself to death. I had no idea how serious this disease is and I started to ask myself what I had done to cause it. There seems to be no genetic history at all in my case, says Mrs Langfield who is married and has two grown up children.

Soon after her steroid treatment started the pain disappeared almost completely and today she has virtually no symptoms at all.

— I come here for monitoring once a month and it makes me feel very calm and assured to be in such good hands.

— My disease doesn't prevent me from doing things but I decided early on to try and stress less at work and to take better care of myself in every way. More exercise, a bit of yoga and maybe only two hours of gardening instead of all day...I try to keep a very positive attitude and to live here and now, she continues and adds that she willingly participates in several of the studies



CATHERINE SHUTTLEWORTH

— I am very grateful that I was referred to Dr Razas clinic so rapidly, says Zoe Langfield.

conducted at the treatment center.

— I like to help others so giving blood and tissue samples is a completely natural thing for me to do. Studies like these can probably help us all in the future. □

CATHERINE SHUTTLEWORTH



To catch patients early dr's Andrew Filer (responsible for ultrasound- imaging) and Karim Raza who work together at the Early Arthritis clinic have developed a successful collaboration with the primary care. Thanks to this rapid system patient Zoe Langfield got an appointment here two weeks after her first visit to the GP.

The rapid access team is convinced:

It really "pays off" to see a doctor as soon as possible

Many people don't take symptoms like stiff fingers in the morning or swollen joints seriously. Instead of seeing a doctor they take painkillers and just hope that the problems will go away. But many studies show that it is of great importance to treat RA as early as possible for good results.

To be able to find patients with early symptoms Dr Karim Raza set up a rapid access clinic where he usually sees patients just a few weeks after their first visit to the GP. He is also looking into the reasons for why people delay in seeking medical help for rheumatoid symptoms.

Recognising the importance of studying patients within the first few months of the onset of symptoms, dr Karim Raza set up the rapid access early synovitis clinic in 2000 and now runs this with dr Andrew Filer.

His research, stemming from this clinic, led to him being awarded the British Society for Rheumatology's prestigious Michael Mason prize in 2009.

Karim Raza and his colleagues realized that the key to recruiting patients with early symptoms was to work closely with primary care physicians and build a network for efficient referral to secondary care.

Today dr Raza usually sees patients

within two weeks of their first visit to the GP and if synovitis is present, invites them to participate in research studies (several of which are AutoCure-related).

— Our work here suggests that early RA is, in many ways, different from established RA which is why we really need to find the patients as soon as the first symptoms start. Indeed findings from others, that early aggressive therapy may switch off the disease, supports this idea.

But the problem is that it often takes several months before these patients show up in the clinic. To understand the determinants of delayed presentation to Rheumatologists, Karim Raza carried out a study which showed that the majority of the delay lay at the level of the patient seeking medical advice in the first place

— People wait a median of three months after the first symptoms before they call the GP.

To understand the reasons for this Dr Raza and colleagues conducted a qualitative study involving face to face interviews with patients; the results of this were illuminating but depressing.

—Very few patients knew anything about rheumatoid arthritis when they first developed their symptoms; they were certainly not aware that it was a serious condition for which highly effective treatments were available and that early treatment was important. Many patients were under the impression that the only

Ultrasound is an excellent detection tool

What exactly is happening in the joint?

The Birmingham team is using ultrasound imaging to find out.

— Ultrasound is less invasive than tissue samples and it gives us a lot of useful information about the inflammatory status in the joints, says senior lecturer Andrew Filer.

It is too early to tell if ultrasound will be used as a screening method, but after three years practice with the machine Andrew Filer is quite optimistic.

— I think ultrasound is an excellent tool for scanning the joints. You can easily detect ongoing inflammation early on in the disease process and you can rapidly see if the treatment works. Patients who have seen the inflamed tissue within their joints using the ultrasound machine are usually very happy to give tissue samples for research, says Andrew Filer who has visited AutoCure partner professor Paul Peter Tak in Amsterdam to share knowledge on how to work with arthroscopic techniques.

— We do it in different ways but it was very interesting to learn more about their method. One of the great advantages with AutoCure is that it's so easy to get in touch with research colleagues all over Europe. □

treatments available for musculoskeletal symptoms were analgesics and anti-inflammatory drugs and so often self-medicated for prolonged periods before seeking help.

— Interestingly, there appears to be cultural differences in patients behaviour patterns with patients of South Asian origin for example delaying for longer than patients of white British origin and ongoing work is addressing the reasons for this.

As an extension of this work, AutoCure-partners are now collaborating in an audit to look at the extents of delay in the patient journey between symptom onset assessment by a Rheumatologist.

The results will allow comparisons of delays at different levels within different healthcare systems in the EU.

— An audit like this will allow us to determine whether patient delay is the principle reason for delay in assessment by Rheumatologists in other EU countries. The problem of patient delay can only really be addressed with a public health campaign and it may be that the AutoCure consortium could play a role in this in the future. It would be of great value if AutoCure could help in informing the European public about the first symptoms of RA and let them know that it really pays to see a doctor as soon as possible, says Karim Raza who foresees even more fruitful cooperation in the consortium in the years to come. □

Early treatment standard in Vienna



ROLF ADLERCREUTZ

AKV, The Vienna General Hospital is one of Europe's largest hospitals with more than 2000 beds.

Early treatment is not a new concept at the Vienna General Hospital (AKV) in Austria. AutoCure partner professor Josef Smolen was among the first rheumatologists in Europe to open an early arthritis clinic 15 years ago. Many studies on outcome of RA have provided his research group with convincing evidence that early and aggressive treatment is successful – more than 25 percent of the patients treated here are in full remission.

Professor Josef Smolen, who was the president of EULAR 2003–2004, started his career as a basic researcher but gradually switched over more and more to clinical work.

— I still see patients twice a week and

it gives me great pleasure. Everyone in our group is a combined researcher and clinician, and we inspire each other by looking at the diseases from different angles.

Every year about one thousand

patients from Vienna and surroundings are treated here at the clinic, which is a kind of emergency ward or early diagnosis clinic for patients with rheumatoid symptoms.

— Before we started this the patients normally had to wait for around six months before they could see a rheumatology specialist. With our system we usually see them within a day from their first visit to a GP.

— We have educated almost all the GP:s in and around Vienna, so that they can do a rapid preclinical diagnosis, including relevant blood tests etc, before sending the patient to us. But many patients also come straight to the clinic

ROLF ADLERCREUTZ



Occupational therapist Alexa Binder.

“We have started to ask the patients why they waited to see a doctor”

Occupational therapist Alexa Binder is doing a Master degree in occupational therapy and has worked at the Department of Rheumatology for one year. She asks the patients to fill in a questionnaire where they evaluate their symptoms and she examines their joints on several systematic follow up-controls during 3-4 months.

— In cooperation with our colleagues in Birmingham we have recently started to ask the patients why they waited to see a doctor, says Alexa Binder who also makes sure that blood samples are taken and delivered to the biobank. □



ROLF ADLERCREUTZ

ROLF ADLERCREUTZ



After 15 years pioneer – work with the early treatment – concept Professor Josef Smolen can show very good results.

because we are rather wellknown by now.

— Since we only have trained specialists at the clinic we are able to diagnose the patients very rapidly through interview and inspection and immediately give them adequate treatment. We see 15 to 20 patients every day thanks to this quick expert screening which saves a lot of time.

As long as the disease is active the patients come to the clinic for controls every 3–4 months.

The key to successful therapy is to intervene before the eroding process of the joints has started.

— In our experimental models we have seen that it's important to interfere as soon as you see the first hints of nibbling at the bones. This inflammatory process in the joints can be detected even before the patient has developed RA, explains professor Smolen, who also recently has started to use ultrasound imaging at the clinic, like AutoCure partners in Birmingham.

Studies conducted in his group have shown that it in some cases could be a waste of time to start the treatment mildly.

— We have seen that it's often more effective to give the patients an aggressive therapy as soon as possible after the onset of the disease. This method can prevent permanent bone destruction and is therefore a question of longterm saving, says professor Smolen, who can present impressive statistics:

— More than 25 percent of our pa-

tients are in full remission and almost fifty percent are in a low disease-state, that is with only one swollen joint.

The Vienna group is collaborating closely with AutoCure-partners in Amsterdam, Birmingham and Montpellier, just to mention a few.

— There was a rather extensive rheu-

matology research collaboration even before AutoCure started, but the AutoCure consortium has succeeded in making the network stronger and more solid. This way of working together on an international level, with joint access to large patient cohorts, will have a great impact on European research in the future. □

THE PATIENT'S STORY

"It didn't even cross my mind that it could be anything serious"

One day last summer Dieter Kocian, a 35-year old make-up artist at the Vienna Opera house, woke up with pain in his right hand.

— After a few weeks both my hands and knees were swollen and I had no idea why, I thought maybe it had to do with my training at the gym but it turned out to be polyarthritis. But thanks to the rapid treatment I got I am now without symptoms.

Nobody in Dieter Kocian's family has rheumatism and he had no idea that his symptoms could have anything to do with a disease.

— It didn't even cross my mind that it could be anything serious, but after a few weeks I went to see an orthopedist. He took bloodtests but as they showed no sign of a RA-factor he just gave me some painkillers. It was my sister who advised me to go to the Akutambulanz -

the Rheumatology emergency unit at the AKH, the main hospital here in Vienna.

He was thoroughly examined by the specialists at the clinic and got his diagnosis in one day. The tests showed that he had polyarthritis and he was immediately treated with steroids.

— When I got home I started to read about my disease and look at photos. That really scared me. Sometimes it's maybe better not to know too much, he adds.

— Shortly after my first visit they asked me if I wanted to participate in a double blind study with biological treatment and I didn't hesitate at all. I have no idea if I only got the placebo infusions, all that matters to me is that all my symptoms are gone now. I feel optimistic about the future and I live as I did before, with the exception that I don't really dare to go back to the gym... □

THE VIENNA EARLY TREATMENT RECIPE

It only takes them five minutes to identify a patient

Assistant professors Kurt Redlich and Clemens Scheinecker divide their working hours between basic research and clinical work at the Early Arthritis Clinic at the Vienna General Hospital.

They see around 20 patients every day and it usually only takes them five minutes to identify if the patient suffers from some kind of rheumatoid disease and should be treated at the clinic.

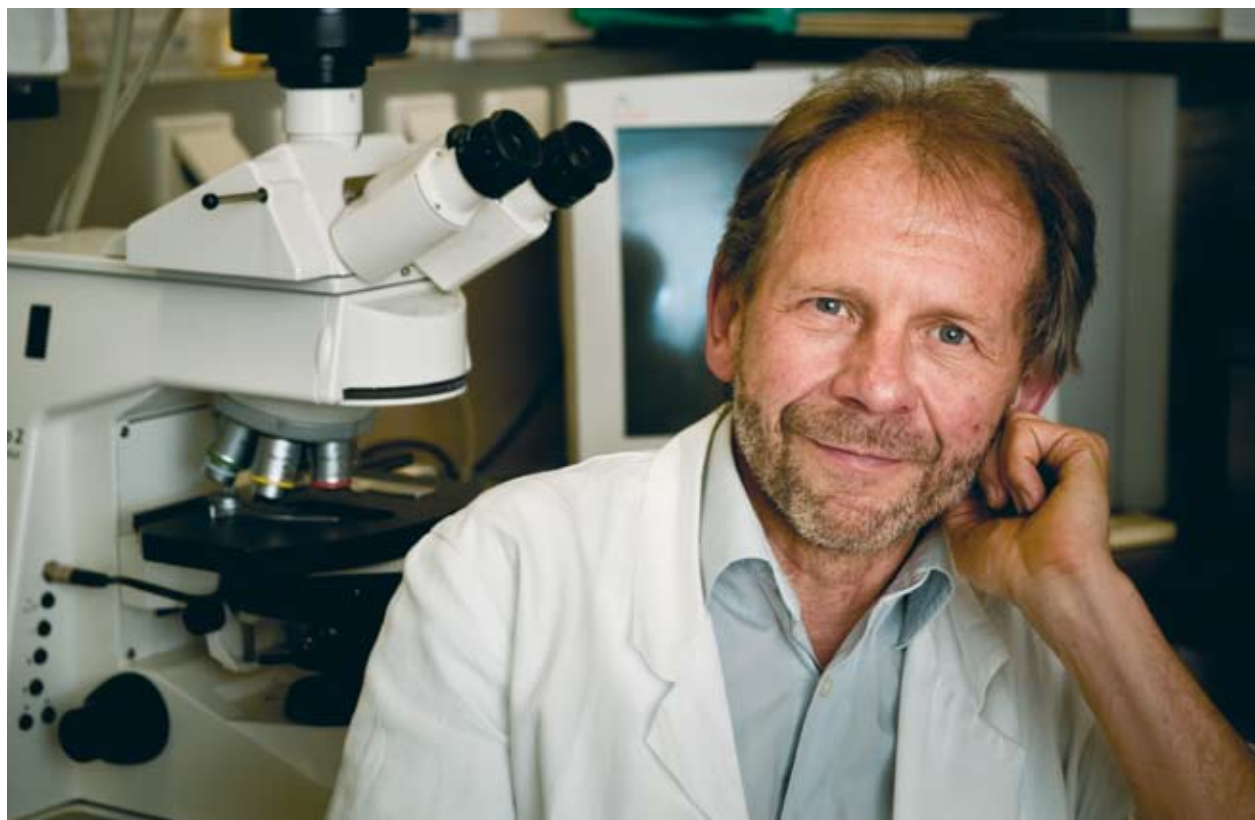
— We use a very efficient method, we only treat the ones who really need specialist care, says Kurt Redlich who in his current research is busy finding out why inflammation is able to use the same mechanisms to destroy and to build up bones.

— We have started to use ultrasound imaging now too, it is a very helpful diagnostic tool, says colleague Scheinecker who is focusing on T-cells in Lupus patients in his research. □



Assistant professor Kurt Redlich and Clemens Scheinecker.

ROLF ADLERCREUTZ



Together with other AutoCure-partners assistant professor Günter Steiner is on his way to identify new autoantigens.

ROLF ADLERCREUTZ

Possible new treatment concept for early RA

Associate professor of biochemistry Günter Steiner is the only group leader in professor Josef Smolens research team who is a 100 percent basic science researcher.

Günter Steiner and Josef Smolen have collaborated successfully since 1989 when they discovered a new autoantigen together.

In numerous studies they and other researchers have showed that there are many more autoantibodies involved in Rheumatoid Arthritis than just the rheumatoid factor.

— We worked together in a network before but AutoCure certainly has provided us with a platform where we have to do European – not national – thinking, says Günter Steiner who thinks highly of this new way to collaborate over the borders.

His main research focus is on nuclear autoantigens and he has many ongoing research projects with several AutoCure partners, for example with professor Rikard Holmdahl at Karolinska Institutet in Stockholm, PI Florence Apparailly at Inserm in Montpellier and PI Margriet Vervoordeldonk at the AMC in Amsterdam.

— We induce arthritis in rats by injecting pristane oil subcutaneously which

allows us to study the development of disease from the beginning and we have seen some amazing patterns in the very first stages of the inflammatory process.

— It's all still in the lab of course but many things point to the fact that we are on our way to identify some novel autoantigens that also apply for humans. If our joint experiments turn out well we might be able to soon develop new therapeutic concepts for treating the disease effectively in its early stages and maybe be able to stop the deleterious processes, says Günter Steiner and adds that a result like that would be a very good proof of the fruitful work in the AutoCure consortium. □

Regular exercise can reduce inflammation

New studies now confirm that moderate regular exercise is very beneficial for Myositis-patients – and most likely also for other inflammatory diseases. In the near future exercise could be made a common prescription "drug".

— Exercise strengthens the muscles and seems to reduce the inflammation. Training could even be introduced as early treatment, says professor Ingrid Lundberg at Karolinska Institutet.

Not so long ago it was a firm belief that exercise was harmful for people suffering from RA or myositis.

— Patients were recommended to avoid physical training because it could make the inflammation worse. But for the past ten years many clinical studies have showed that it is the other way around. Light or moderate regular training actually seems to have a significant anti-inflammatory effect, says professor Lundberg who is about to publish an AutoCure-led study on a small cohort of myositis-patients who trained with intensive resistance exercise for seven weeks.

— Our patients were ordained up to one hour of intensive resistance exercise, including stretching, situps and gym

machines, three days out of five in a week. The clinical effects were obvious. Biopsies showed a decrease in the inflammatory process.

—A training program with moderate intensity has



ISTOCKPHOTO

Moderate physical training has been proved to be very beneficial for myositis-patients.

been undertaken in newly diagnosed myositis patients likewise without any sings of increased inflammation It could be important to start the training as soon as possible after the diagnosis, since cortisone treatment affects the muscles negatively.

The clear clinical results in these and other studies could lead to new treatment models.

— We need to find an effective combination of immunosuppressive drugs and

exercise, continues professor Lundberg who thinks that its most likely that exercise will be a normal part of the doctors prescription in the near future.

— It is necessary to design a good standardised training programme for myositis-patients. This, as well as other studies on the benefits of physical training, could hopefully be done within the AutoCure-network who has access to the world largest cohort of myositis-patients. □

ROLF ADLERCREUTZ



Professor Ingrid Lundberg

AutoCure management site visit – Heraklion, Crete

AutoCure coordinator Lars Klareskog, Administrative Project manager Susanne Karlfeldt and Myositis representative Ingrid Lundberg, visited AutoCure partner number 28 – IMBB-FORTH in Heraklion, Crete during a few days in Mid May.

Principal Investigator at FORTH, Professor Dimitrios Boumpas, had organised a very intense programme where both junior and senior scientists got the opportunity to discuss and present their research.

Lars Klareskog gave a research seminar on Evolving concepts in rheumatoid arthritis: The interplay of environmental and genetic factors for researchers and students at the Medical School.

Ingrid Lundberg gave a seminar, more directed to the clinical fellows, on inflam-



AutoCure in Heraklion.



The home of IMBB-FORTH in Heraklion.

matory myopathies. Both seminars were very much appreciated and well attended.

Following the seminars, there was a press conference with representatives from the patient organization, news papers and national and local TV-stations. The focus was to high-light the problems that come with rheumatic diseases, the great impact that smoking has on the risk of developing rheumatoid arthritis and also AutoCure's role as a very important network for new and larger collaborations, leading to more efficient research leading to new ways of preventing and treating rheumatic diseases.

The very fruitful site visit ended with a dinner, during which the local television evening news showed interviews with Professors Boumpas and Klareskog. □



AutoCure is an FP6 EU-funded integrated research project, with a translational approach to autoimmune diseases in the postgenomic era, using inflammatory arthritis and myositis as prototypes and learning examples.

Objectives

To transform knowledge obtained from molecular research particularly within genomics, into a cure in an increasing number of patients suffering from inflammatory rheumatic diseases. Rheumatoid arthritis (RA) is used as a prototype since this disease offers unique opportunities to define and evaluate new therapies.

Work plan

- Potential key molecular mechanisms determining the course of RA and myositis are defined from genetic studies in humans, from relevant animal models and from basic cell and molecular biology.
- Predictors of disease development and therapeutic responses, enabling future individualised therapies, are developed with the help of our unique large patient cohorts and, biobanks.
- Development and evaluation of new therapies is performed using combinations of novel molecular tools and precise definition of disease phenotypes.

FRONTER – for internal communication

Fronter is the internal web site for AutoCure colleagues. The site can be reached via a link at www.autocure.org. In Fronter we put guidelines, programs and protocols for meetings, publications published or submitted, project scientific tools etc. You can also find contact information to all participants in the project. Files and documents that are downloaded can be protected so that only a minor group can have access to it.

For more information on Fronter, please contact Susanne Karlfeldt, susanne.karlfeldt@karolinska.se.

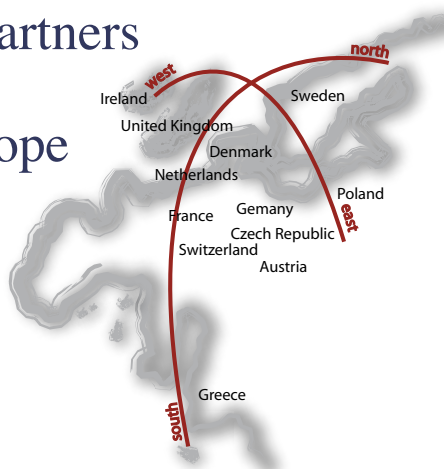
Action plans /Gender and Leadership

The work on Gender and Leadership in the academic world continues within AutoCure. At the gender work shop at the annual meeting in Potsdam the following new action plans were taken:

- To develop a mentor program within AutoCure
- To send out a survey to AutoCure members with the aim to map out the present situation and define career obstacles
- To advertise a part-time post-doc position, funded by AutoCure, in gender and leadership research
- To arrange a new work shop on gender issues during 2009

AutoCure-partners are located all over Europe

- Austria
- Czech Republic
- Denmark
- France
- Germany
- Greece
- Ireland
- Netherlands
- Poland
- Sweden
- Switzerland
- UK



AutoCurious

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