Advances in Molecular and Clinical Rheumatology – 2012

Budapest, 4th October, 2012

P R O G R A M M E

PROGRAMME OUTLINE

4th October, 2012	
09.00–09.30	**Welcome addresses**
09.30–09.45	**Inauguration of the new honorary members of the Hungarian Association of Rheumatologists: Roger Sturrock and Ronald van Vollenhoven**
09.45–10.00	Coffee break
10.00–11.10	**Background of rheumatic diseases (S1–S3)**
11.10–11.25	Coffee break
11.25–12.55	**TNFα blockade in inflammatory rheumatic diseases (S4–S7)**
12.55–14.15	Lunch
14.15–15.25	**Interleukin inhibitors and novel biologics in rheumatology (S8–S10)**
15.25–16.35	**New non biological therapies in different rheumatic disorders (S11–S13)**
16.35–16.50	Coffee break
16.50–18.00	**New approaches in the management of osteoporosis (S14–S16)**
18.00–	**Closing of the symposium**
19.00–	**Evening program**

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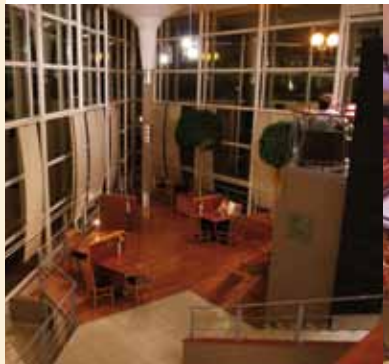
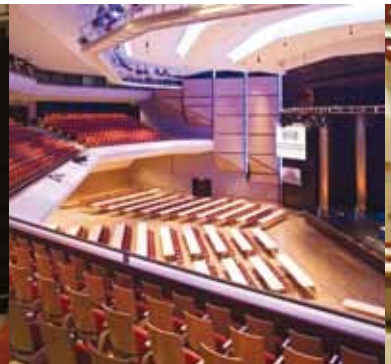
Budapest, 4th October

Hotel Novotel Budapest Congress
H-1123 Budapest, Alkotás u. 63–67.





Welcome

Dear Guests and Colleagues,

You are most cordially welcome to the international scientific symposium "Advances in Molecular and Clinical Rheumatology – 2012" organized by the Hungarian Association of Rheumatologists (HAR). Due to outstanding development of rheumatology and related areas achieved in the field of research and education the meeting is co-organized by the Hungarian Academy of Sciences and the Semmelweis University, Budapest.

Following 2008, when we celebrated the 80th anniversary of the HAR with the first similar symposium in Budapest, currently we intend to overview the most important therapeutic results born in the last five years. In order to cover hot topics opinion leaders from different parts of Europe, overseas and from Hungary have been invited to deliver exciting state of the art lectures. In the frame of the programme the honorary diploma of the HAR will be handed over to our new members: Professors Roger Sturrock and Ronald van Vollenhoven.

Rheumatic diseases have a major and increasing impact on the quality of life of patients and the financial burden is a considerable determinant of healthcare budgets. Many efforts have been made against these conditions worldwide and in Hungary and hopefully this meeting will promote the understanding of the underlying pathologic mechanisms and the usage of innovative therapies in the daily clinical practice.

Many thanks the speakers and the major sponsors for supporting our aims and activity. We wish you a nice and useful symposium Budapest.

On behalf of the organizers

With best personal regards

Budapest, 4th October, 2012.

Prof. Dr. Poór Gyula
Chairman of the symposium
President, HAR

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General Information

Organizer
Hungarian Association of Rheumatologists (HAR)

Co-organizer
Hungarian Academy of Sciences; Semmelweis University, Budapest

Patron
József Pálinkás,
President of the Hungarian Academy of Sciences

Chairman of the symposium
Prof. Dr. Gyula Poór,
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Scientific committee
Daniel Aletaha (Vienna), Maxime Dougados (Paris), László Czirják (Pécs), Steffen Gay (Zurich), Pál Géher (Budapest), Peter Gergely (Basel), Boulos Haraoui (Montreal), Emese Kiss (Budapest) Péter Lakatos (Budapest) Péter Mandl (Budapest) Imre Pávó (Vienna), Gyula Poór (Budapest), Monica Reuss-Borst (Bad Kissingen), Christian Roux (Paris), Roger Sturrock (Glasgow), Zoltán Szekanecz (Debrecen), Ronald van Vollenhoven (Stockholm)

Organizing committee
Gyula Poór, György Hittner, Csilla Várszegi, and the Board of the Association

Organizing office of accommodation and catering

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H-1014 Budapest, Országház u. 2.
Tel.: +36 1 213 6222
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Venue of the symposium

Novotel Budapest Congress
H-1123 Budapest, Alkotás u. 63–67.
Tel.: +36 1 372 5400
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Accommodation for the faculty

Hotel Novotel Budapest Congress (www.novotel-bud-congress.hu)

Note

Attendance at the symposium and at the evening reception to be held in Buda Castle are included in the registration fee of the HAR congress, October 4–6. Insurances are not provided for the attendees during the meeting. The organizers cannot be held responsible in case of loss, theft or damage of any personal things. The organizers kindly ask all participants not to use mobile phones in the lecture hall.

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Scientific Programme

4th October, Thursday

09.00–09.30 **Welcome addresses**

Gyula Poór
President, Hungarian Association of Rheumatologists

Maxime Dougados
President, European League Against Rheumatism (EULAR)

Valéria Csépe
Deputy General Secretary, Hungarian Academy of Sciences

Ágoston Szél
Rector, Semmelweis University

09.30–09.45 **Inauguration of the new honorary members of the Hungarian Association of Rheumatologists: Roger Sturrock and Ronald van Vollenhoven**

09.45–10.00 Coffee break

10.00–11.10 **Background of rheumatic diseases**
Chairmen: Steffen Gay and Péter Gergely

10.00–10.20 S1 What does genetics tell us about rheumatic diseases?
Roger Sturrock, Glasgow, United Kingdom

10.20–10.40 S2 Epigenetics in rheumatoid arthritis
Steffen Gay, Zurich, Switzerland

10.40–11.00 S3 Advances in translational rheumatology
Péter Gergely, Basel, Switzerland

11.00–11.10 Discussion

11.10–11.25 Coffee break

11.25–12.55 **TNFα blockade in inflammatory rheumatic diseases**
Chairmen: Maxime Dougados and Gyula Poór

11.25–11.45 S4 Penetration and impact of biological therapy in rheumatoid arthritis in Europe
Gyula Poór, Budapest, Hungary

11.45–12.05 S5 Strategies to tackle rheumatoid arthritis disease activity
Daniel Aletaha, Vienna, Austria

12.05–12.25 S6 Importance of fast response in rheumatoid arthritis treatment
László Czirják, Pécs, Hungary

12.25–12.45 S7 Recent advances in spondyloarthritis
Maxime Dougados, Paris, France

12.45–12.55 Discussion

12.55–14.15 Lunch

14.15–15.25 **Interleukin inhibitors and novel biologics in rheumatology**
Chairmen: Ronald van Vollenhoven and László Czirják

14.15–14.35 S8 Update on IL-6 targeting therapy in rheumatoid arthritis: Focus on monotherapy
Ronald van Vollenhoven, Stockholm, Sweden

14.35–14.55 S9 Biologics in pediatric rheumatology
Emese Virág Kiss, Budapest, Hungary

14.55–15.15 S10 Other novel biological targets in rheumatic diseases
Péter Mandl, Budapest, Hungary/Vienna, Austria

15.15–15.25 Discussion

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15.25–16.35 **New non biological therapies in different rheumatic disorders**
Chairmen: Boulos Haraoui and Zoltán Szekanecz

15.25–15.45 S11 Intracellular signalling pathways as novel targets in the management of rheumatoid arthritis
Boulos Haraoui, Montreal, Canada

15.45–16.05 S12 Gout: Diagnosis and new treatment options of an old disease
Monica Reuss-Borst, Bad Kissingen, Germany

16.05–16.25 S13 New perspectives of structure modification in osteoarthritis
Zoltán Szekanecz, Debrecen, Hungary

16.25–16.35 Discussion

16.35–16.50 Coffee break

16.50–18.00 **New approaches in the management of osteoporosis**
Chairmen: Christian Roux and Péter Lakatos

16.50–17.10 S14 Role of cortical bone in skeletal fragility
Christian Roux, Paris, France

17.10–17.30 S15 Teriparatide, the path of PTH from an initiator to a therapeutic tool of osteoporosis
Imre Pávó, Vienna, Austria

17.30–17.50 S16 Novel antiosteoporotic drugs
Péter Lakatos, Budapest, Hungary

17.50–18.00 Discussion

18.00– **Closing of the symposium**

19.00– Buses leave from the conference venue for the evening reception that starts at 19.30 in the Buda Castle (Budapesti Történeti Múzeum, Barokk Csarnok, Budavári Palota, E épület)

Abstracts

Abstracts are listed in the order of the lectures presented.

S 1

What does genetics tell us about rheumatic diseases?

Roger Sturrock
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In Human Biology there is a great debate regarding the influence of Nature and Nurture on the development of characteristics such as intelligence, sexuality and even criminal tendencies.
A similar debate is relevant to Rheumatic diseases and the factors that influence their genesis, prevalence and severity. The discipline of genetics has done much to inform our understanding of the pathogenesis of disorders such as Rheumatoid Arthritis, Osteoarthritis and the Spondyloarthropathies, however the Human Genome project and its application to chronic rheumatic diseases has raised more questions regarding their aetiopathogenesis than answers.
I will use the model of Ankylosing Spondylitis to illustrate both the importance of family studies and genetic markers in shedding light on the precise roles of nature and nurture in this disease and as a paradigm for other common chronic rheumatic diseases.

S 2

Epigenetics in rheumatoid arthritis

Steffen Gay
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After completing the human genome project, it is still unsolved when and for how long individual genes are expressed during development as well as in health and disease. At this point regulatory mechanisms are mediated by epigenetics involving biological processes including acetylation, methylation, sumoylation and miRNAs.
Our laboratory has addressed epigenetic modulations in inflammatory conditions over the past decade. In this regard we have shown that the synovial cells reside in an acetylated environment favoring the expression of inflammatory cytokines. We could further demonstrate that synovial cells appear hypomethylated keeping the aggressive behavior of these cells imprinted. In addition, a full array of dysregulated miRNAs induces various signaling cascades contributing to joint destruction and systemic inflammation. Thereby novel therapeutic targets appear on the horizon.

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S 3

Advances in translational rheumatology

Péter Gergely
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After decades of reliance on largely empiric approaches in the therapy of most rheumatic diseases, the introduction of TNF-alpha blocking agents in the late 90`s revolutionized the therapy of rheumatoid arthritis and other immune-mediated diseases. Further therapies targeting B cells, T cell costimulation or cytokines have since emerged out of improved understanding of the immunopathogenesis. Moreover, orally administered small molecules targeting specific pathways are also likely to play important roles in the therapeutic armamentarium of rheumatic diseases. The era of targeted therapies in rheumatology came about as a consequence of a number of concurrent advances such as the identification of pathogenic cytokines and other key players in autoimmune diseases as well as new methodologies in protein engineering to allow production of biologicals and engineered derivatives. Overall, the successful translation of preclinical findings to human disease pathology has contributed significantly to these advances. The presentation highlights the advances and challenges in translational rheumatology.

S 4

Penetration and impact of biological therapy in rheumatoid arthritis in Europe

Gyula Poór
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The overall prevalence of rheumatoid arthritis (RA) for Europe (EU27+3 countries) has been estimated at 0,49%, the total estimated number of RA patients amounts to 1,9-2 million. The overall number of approximately 250000 treated RA patients with biological agents means an average of 12,5% in Europe in 2011, naturally with the predominance of large Western European markets, followed by the small Western, the Nordic and the Central/Eastern European markets. However, the

proportion of RA patients was not the highest in the large Western countries (10-15%) but in the Nordic and the small Western countries (Norway, Ireland, Sweden over 30%). Hungary (7%) by far exceeded the Central/Eastern European average usage of 3-4%. Determinants of access to biological therapy include economic, medical and additional conditions, setup of arthritis/biological centres can promote its penetration.
Sufficient data have been generated on the impact of biological treatment in reducing disease activity and slowing the progression of the disease but not in cost effectiveness and sustaining work capacity. Factors influencing work capacity in RA include not only disease severity and access to adequate innovative therapy but also other determinants, like legal regulations, employers and employees attitudes, therefore much broader approach is needed to advance on this issue.

S 5

Strategies to tackle rheumatoid arthritis disease activity

Daniel Aletaha
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Rheumatoid arthritis (RA) is characterized by its chronicity and its propensity to destruct bone, cartilage, and whole joints. As a systemic inflammatory disease, RA has potential consequences for many organs outside the musculoskeletal system, and leads to impaired function and quality of life, and to increased mortality. All this has been known for years, but only in the past decade new treatment strategies and new therapeutics have made RA a less dangerous and less devastating disease. Although new drugs are necessary to have a large armament for therapy, it is particularly the new strategies that even the path to success. These include the definition of a clear treatment target, which is remission, and to modify treatment as long as the goal has not been achieved. It is essential to have tools that allow adequate and reliable assessment of disease activity (and its absences, remission). These tools will likely be indices of several disease activity measures, and have to include measures of formal joint assessment.
The hierarchy of drug application on the way to the target has also been laid out more clearly in the recent past. While methotrexate is the standard starting point, an evaluation of risk factors may guide the choice of subsequent treatment in individuals, who fail to respond to methotrexate: in the presence of higher levels of disease activity, early or rapid progressing structural damage or seropositivity, the next choice would be a biological compound, typically a TNF-inhibitor. In mild cases, other traditional DMARDs may be used before that step. Once the initial biological drug fails, any of the available four biological modes of action is an option

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for subsequent treatment, including B-cell depletion, inhibition of co-stimulation, IL6-blockade, or, yet another TNF-inhibitor.
With these strategies in place, and all the therapeutic compound to help follow these strategies effectively, the doom of RA may be history, and patients with RA may not show any evidence of damage or disability anymore in the future.

S 6

Importance of fast response in rheumatoid arthritis treatment

László Czirják
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Over the last decade, the introduction of biologics in the treatment of rheumatoid arthritis (RA), the use of high sensitive imaging technics for RA diagnosis, the recognition of the need of more frequent patient monitoring have revolutionized therapeutic approaches in RA. According to the current evidence-based therapeutic recommendations (*EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs, J. Smolen 2012*) early and intensive treatment is recommended with tight control of disease activity. The primary target of RA treatment is clinical remission or low disease activity especially in patient with long standing disease activity. Drug therapy should be adjusted until individual treatment target is not achieved. Early and fast response for a medication supports tight control of the disease and it has also favorable impact on long term clinical outcomes. According to a post hoc analysis of RAPID1 clinical trial, fast response to certolizumab pegol treatment was associated with better improvements in clinical outcomes, physical function and relief of pain and fatigue at 1 year in patients with active RA treatment. Besides the better long term outcomes, fast response to RA treatment may also ensure physicians and patients about the optimal treatment choice.

S 7

Recent advances in spondyloarthritis

Maxime Dougados
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The most important new information in this area of rheumatology is the name of the disease (e.g. spondyloarthritis). It has been recognized that the term spondyloarthritis preceded by both the main clinical presentation of the disease (e.g. axial versus peripheral) and for both presentation by the presence or not of radiologi-

cal structural damage (the current proposal is to use the term “radiographic” in case of demonstration of sacroiliac structural changes [e.g. sub-chondral bone osteosclerosis, joint erosions or fusion] for the axial presentation and the term of “erosive” in case of peripheral presentation).
Therefore, in 2012, for example, axial radiographic spondyloarthritis should replace the non appropriate one of “ankylosing spondylitis”.
Several advances have been achieved recently in the field of spondyloarthritis in terms of either recognition of the disease, physiopathology or treatment.
The recently proposed ASAS criteria for both the axial and peripheral presentation of the disease have been evaluated in different sets of patients. All these studies have confirmed the relevance of such sets of criteria and, in particular, have emphasized the relative high frequency of non-radiographic axial spondyloarthritis mainly at an early stage of the disease despite the fact that, at this stage, the burden of the disease is at a similar magnitude than in patients with radiographic axial spondyloarthritis.
In terms of physiopathology, improvement has been achieved in a better knowledge of the role of environmental factors not only in terms of microbial environment but also in terms of smoking habits. The still remaining question is whether ossification is a phenomenon resulting from inflammation or whether inflammation and ossification are two independent processes observed in this disease.
In terms of therapy, there is the debate of the exact role of physiotherapy (which one? Which “route of administration” [e.g. home exercises versus groups of patients supervised by a physiotherapist…]). There is also the debate of the mode of administration of NSAID (e.g. on demand) based on the level of the patients symptoms versus continuously whatever the level of patients’ symptoms. In case of active disease despite optimal NSAID therapy, TNF blockers have confirmed their short term and long term utility. The possibility to taper or discontinue a TNF blocker in case of persistent remission of the disease is still debated.
Finally, drugs with a different mechanism of action (e.g. bisphosphonates, IL-6 inhibitors) have failed to demonstrate their utility. At variance, the drugs such as IL-17 inhibitors are very promising.
In conclusion, dramatic improvements have been achieved in the field of spondyloarthritis coming from the recognition of the disease, the physiopathology to the management of the diseases.

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S 8

Update on IL-6 targeting therapy in rheumatoid arthritis: focus on monotherapy

Ronald F. van Vollenhoven
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IL-6 is a pleiotropic cytokine with a central role in the inflammatory pathway. Multiple large clinical trials have amply demonstrated the clinical efficacy of blocking the IL-6 pathway using tocilizumab, a monoclonal antibody against the IL-6-receptor. Most of these trials utilized the combination with methotrexate (MTX), but the AMBITION trial demonstrated already several years ago that excellent efficacy could also be achieved without MTX. In that trial, tocilizumab as monotherapy was superior to MTX as monotherapy (in MTX naïve patients). In addition, data from the ACT-RAY trial showed that tocilizumab as monotherapy was as effective as tocilizumab plus MTX. Several anti-TNF biologics are approved as monotherapy. It was therefore of interest to perform a direct “head-to-head” comparison of tocilizumab with one such anti-TNF, adalimumab, when both are given as monotherapy. This trial, name ADACTA, was recently completed and the results presented at the EULAR 2012 annual congress. The primary outcome, defined prospectively as the improvement in DAS28 by 24 weeks, was shown to be significantly greater for tocilizumab than for adalimumab, and several secondary outcomes also supported the superiority for the IL-6 targeting molecule. These data provide rheumatologist with strong evidence to apply in the clinical situation where monotherapy is needed or desirable, such as in patients who are intolerant to MTX.

S 9

Biologics in pediatric rheumatology

Emese Virág Kiss
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Biologics have revolutionarised survival and the quality of life of pediatric patients with inflammatory rheumatic diseases. The most frequent inflammatory rheumatic condition in childhood is juvenile idiopathic arthritis (JIA), which is a heterogeneous group of diseases including seven subgroups with different clinical phenotypes. The efficacy and safety of tumor necrosis factor alpha inhibitor etanercept, adalimumab and also infliximab in polyarticular course JIA have been evidenced

by several randomised controlled trials. Abatacept, the CTLA-4 Ig has recently been authorised in this condition. All these drugs have no effect in the most severe – i.e. systemic onset – form of the disease (sJIA). Phagocytes are the principal activated cells during the early disease course. High IL-6 levels were measured in the serum and synovial fluid of sJIA patients. The major pathogenic role of IL-6 has been confirmed by the marked efficacy of tocilizumab, a monoclonal antibody targeting the IL-6 receptor that has been licences more recently with sJIA indication. It is known that activated monocytes from sJIA patients secreted high amounts of IL-1β, a potent pleiotrop inflammatory cytokine. Several open label studies reported clinical efficacy of the recombinant IL-1 antagonist anakinra in sJIA. As a new concept, sJIA is considered as an autoinflammatory diseas. Autoinflammatory dieases are a group of rare, but rather severe inflammatory conditions associated with abnormal regulation of innate immunity. A number of monogenic and multifactorial disorders have been identified or reclassified as autoinflammatory in aetiology. The molecular pathogenesis remains elusive, however the central role of the IL-1 is a common feature. Although there are only few randomised controlled trials and observational studies, not surprisingly these indicated the efficacy of IL-1 antagonism with anakinra or both with canakinumab and rilonacept. The Eurofever study, an international registry on autoinflammatory diseases, may help to collect enough number of patients and sufficient information for better understanding of these diseases.

S 10

Other novel biological targets in rheumatic diseases

Péter Mandl
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Division of Rheumatology, Medical University, Vienna, Austria,
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Over the last two decades, the therapeutic armament available to rheumatologists for the treatment of rheumatoid arthritis has expanded considerably. Moreover, these pharmacotheraputic advancements have enriched our understanding of the pathophysiological processes which play key roles in rheumatoid arthritis. The first group of novel therapeutic targets have emerged from these efforts, included TNF, major proinflammatory cytokines IL-6 and IL-1, costimulatory molecules CD80/CD86 and the B cell marker CD20. In recent years several additional targets have emerged including other cytokines (IL12/23, IL-17, IL-21, GMCSF etc.), adipokines, chemokines, cell adhesion molecules, cell-depleting cellular targets including BLyS/BAFF and APRIL, as well as subcellular pathway components, such as mitogen-activated protein kinases and Janus kinases. This overview will elaborate

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on promising targets and potentially emerging biological agents in various stages of development that are as of yet not used in clinical practice.

S 11

Intracellular signalling pathways as novel targets in the managment of rheumatoid arthritis

Boulos Haraoui
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Pro-inflammatory cytokines play a major role in the pathogenesis of rheumatoid arthritis (RA). Several drugs that selectively target specific cytokines, namely the biologics such as the anti-TNF, anti-IL-6, anti-IL-1, have shown great efficacy and a good safety profile and have been widely used in the last decade.
Cytokines exert their role by interacting with cell surface receptors which trigger a cascade of intra-cellular events leading to the activation of the specific cell and the production of inflammatory mediators. Several intracellular pathways exist and one of them is the Janus Kinase (JAK) pathway which is used by several cytokines. The JAK family consists of 4 members: JAK 1, JAK 2, JAK 3 and TYK 2 (Tyrosine Kinase 2). Other signalling pathways are the MAPK (mitogen activated protein kinase), Syk (Spleen thyrosine kinase), NF-kB (Nuclear factor light chain enhancer of activated B cells) and the PI-3K (Phosphoinositide 3-kinase). Therefore, one way of blocking the effects of the different cytokines responsible for the RA inflammatory and destructive processes is to block the intra-cellular pathways by interfering with the JAK activation.
Tofacitinib a selective JAK inhibitor have shown great efficacy in phase II and III clinical trials with an acceptable safety profile.

S 12

Gout: Diagnosis and new treatment options of an old disease

Monica Reuss-Borst
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Gout is an inflammatory arthritis associated with hyperuricemia that is triggered by the deposition of monosodium urate (MSU) crystals in synovial fluid and other tissues. It affects 1-2% of the population, and its prevalence is still increasing due to changes in diet behavior and the ageing of the population. Major advances in understanding of the pathogenesis have been made in the past decade.

A typical clinical presentation with rapid onset of acute monarthritis, mainly in the first metatarsophangeal joint is strongly suggestive for diagnosis. The diagnostic standard remains synovial fluid or tophus aspiration with identification of MSU crystals under polarizing microscopy. However, ultrasound imaging as well as DECT (dual energy CT) may in future be new diagnostic tools in atypical or chronic progressive cases.
The main aim of therapy of acute gout is rapid relief of pain. The long-term purpose of lowering sUA levels is to prevent flares and the development of gout and chronic arthritis. Allopurinol has been the "gold standard" of urate-lowering therapy for many years. Although moderately effective, it is not well tolerated. Recent trials have confirmed that febuxostat, a non-purine selective inhibitor of xanthin oxidase is highly effective in lowering hyperuricemia. In these clinical trials, 80 and 120 mg a day of febuxostat reduced urate levels more effectively than allopurinol. Febuxostat is a valuable therapy option in patients who cannot tolerate allopurinol, have mild to moderate renal impairment and do not reach the UA (uric acid) target level of 6 mg/dl with allopurinol treatment.

S 13

New perspectives of structure modification in osteoarthritis

Zoltán Szekanecz
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Osteoarthritis (OA) may lead to chronic pain, joint destruction and often disability. Current treatment modalities including pain killers and NSAIDs confer symptomatic relief only. Chondroprotection may exert some disease-modifying action, however, recent study results have been controversial. There is an immense need for structure modifiers in OA.
Strontium ranelate (SrRan) has been registered for the treatment of postmenopausal osteoporosis. Recent data suggested that SrRan might have beneficial effects on cartilage degradation in OA. SrRan had been shown to reduce radiographic spinal OA progression and back pain in osteoporotic women with prevalent spinal OA.
In a recent double-blind, placebo-controlled, randomised, international 3-year study, 1683 patients with symptomatic primary knee OA were randomly allocated to receive SrRan 1 or 2g/day, or placebo. Treatment with SrRan was associated with less progression of cartilage degradation: decrease in joint space width was –0.23±0.56 mm with 1 g/day;–0.27±0.63 mm with 2 g/day and –0.37±0.59 mm with placebo. SrRan 2 g/day significantly reduced total WOMAC score (p=0.045) and pain subscore (p=0.028). SrRan was well tolerated.

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SrRan 1 and 2g/day demonstrated potential structure-modifying effects in knee OA accompanied by symptom improvement at 2 g/day. At present, OA may be used off-label in knee OA.

S 14

Role of cortical bone in skeletal fragility

Christian Roux
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The consequences of osteoporotic fractures are increasingly recognized, and non vertebral fractures are responsible for a large proportion of the morbidity, mortality and cost attributable to osteoporosis. Major non vertebral fractures at cortical sites, as hip, humerus and pelvis are associated with an increased risk of mortality. These epidemiological data are in parallel to the role of cortical bone in skeleton strength, as it represents 80% of the total amount of bone, with an increased rate of loss after age 60 years. Bone remodelling occurs is endocortical compartment, with trabecularization, and porosity increases in the cortex itself. Such changes are now assessable through non invasive imaging technique, as peripheral quantitative CT. Some studies suggest that therapeutics can decrease cortical thinning; they are expected to decrease the risk of cortical fractures.

S 15

Teriparatide, the path of PTH from an initiator to a therapeutic tool of osteoporosis

Imre Pávó
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In 1932, János Selye determined that parathyroid extract from Eli Lilly and Company stimulated osteoblast formation in rats and increased bone apposition. In 1974, Niall et al determined the active sequence used today as teriparatide, recombinant hPTH(1-34). In 1980, Reeve et al. administered hPTH(1-34) to patients with osteoporosis when iliac trabecular bone volume was increased by 70%. The mechanisms of action by which antiresorptive drugs confer protection against fractures differ fundamentally from the mechanism of fracture protection due to teriparatide. In contrast, to antiresorptive drugs, which suppress bone remodeling, teriparatide directly stimulates bone formation. New bone is formed on surfaces that have not undergone a prior phase of bone resorption as well as at sites where remodeling is taking place. The resulting effect is an increase in trabecular number and thickness, cortical thickness and improvement in trabecular connectivity. In the last fifteen years in a serious of large clinical

studies, teriparatide increased bone formation, bone mineral density and volume, improved various indices of bone quality including microarchitecture and decreased fracture incidence across a broad range of age and disease severity both in postmenopausal women and in men. Teriparatide is indicated for the treatment of osteoporosis in postmenopausal women and in men at increased risk of fracture and for the treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at increased risk for fracture. The use of teriparatide as anabolic agent differs from the use of antiresorptives.

S 16

Novel antiosteoporotic drugs

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Osteoporosis is a significant health care problem, and its treatment is of major interest. Despite of the wide spectrum of therapeutical modalities, the effective cure for all forms of this condition has not yet been developed. Recently, the focus is on the development of new pharmacological approaches. The RANK/RANKL/OPG system discovered one and a half decades ago provides a tool for the neutralization of the osteoclast-stimulating RANKL by the use of monoclonal antibodies. Catepsin-K inhibitors offer another pathway for the inhibition of bone degradation without interacting with the cellular players of bone metabolism. Anti-sclerostin and anti-Dkk-1 antibodies as well as the inhibition of GSK3β may stimulate bone formation by the release of Wnt signal transduction system. The application of activin AII receptor fusion protein may facilitate osteoblastogenesis, thus bone formation. Calcium sensor antagonist might elicit anabolic effect through the stimulation of cyclic PTH secretion. Glucagon-like peptide-2 could be the prototype of a novel anti-resorptive agent. Oral, transdermal or nasal administration of PTH analogs, new generations of selective estrogen receptor modulators and antibodies against vitronectin receptors as well as new genes as potential drug targets will enable us to fight bone loss more efficiently in the near future.

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Faculty

The received CV-s of the faculty members are listed in alphabetical order.

Dr. Daniel Aletaha

Daniel Aletaha is a consultant rheumatologist and Associate Professor at the Medical University of Vienna. He has spent two and a half years in the USA on a research fellowship at the National Institutes of Health in Bethesda, Maryland, and has graduated as Master of Clinical Health Sciences from Duke University in Durham, North Carolina, in 2006.
Dr. Aletaha's major research interests are outcomes research, clinical trials, and translational research in rheumatoid arthritis and other inflammatory rheumatic diseases. He has been involved in several International Task Forces, including the development of the 2010 Classification Criteria for RA. He is currently chairman of the EULAR Standing Committee on Clinical Affairs (ESCCA), and editorial board member of a number of rheumatology specialty journals.

Prof. Dr. László Czirják

László Czirják is the head of the Department of Immunology and Rheumatology in the University of Pécs. He is involved in teaching of rheumatology and clinical immunology for medical students (in Hungarian and English), and also a regular speaker in postgraduate courses in clinical immunology, internal medicine, and rheumatology. Several years ago, as a board member of the EUSTAR (EULAR Scleroderma Trials and Research Group), he organized the first EULAR/EUSTAR educational course on scleroderma in Budapest. Between 2007 and 2011 he worked as general secretary of the EULAR. He is a member of the Editorial Board of Annals of Rheumatic Diseases and Clinical Experimental Rheumatology.
He is the member of the Hungarian National Board of Rheumatology. He is predominantly interested is the investigation of the clinical and immunological aspects of connective tissue diseases. His research group performs studies on the survival, disease activity and other clinical-epidemiological aspects of systemic sclerosis. He is a participant and organizer of several international multicenter clinical studies.

Prof. Dr. Maxime Dougados

Positions in scientific societies and EULAR
Member of the Societé Française de Rhumatologie, since 1983; American College of Rheumatology , since 1989; Executive Board Member of Osteoarthritis Research Society, since 1993; Morocco Society of Rheumatology (Honor Member), since 2003.
Chairman of the EULAR standing committee for clinical studies including therapeutic trials (ECSISIT), 2003–2007; EULAR-ACR Officer liaison, since 2007; Vice-President of ASAS (ASsessment of Ankylosing Spondylitis), 2003–2010; EULAR President, since 211;
Editorial boards of sientific journals
Advisory editor past or present: Acta Reumatologica Portuguesa, Arthritis and Rheumatism, British Journal of Rheumatology, Clinical Experimental Rheumatology, EULAR Journal (Annals of Rheumatic Diseases), Journal of Rheumatology, Osteoarthritis and Cartilage, Revue du Rhumatisme, Scandinavian Journal of Rheumatology, International Journal of Advances in Rheumatology.
Key points of clinical activities and research
Chief of the Department of Rheumatology, Cochin Hospital;
Fields of research: Outcome measures in rheumatic diseases (osteoarthritis, bone diseases, inflammatory rheumatic disease); Classification criteria and prognostic factors of rheumatic diseases

Prof. Dr. Steffen Gay

Professor Steffen Gay has graduated from the Medical School at the University in Leipzig. Holding office from 1976-1996 at the Department of Medicine at the University of Alabama in Birmingham AL, he served there as Professor of Medicine from 1984-1996. Since 1996 he is Professor of Experimental Rheumatology at the University Hospital of Zurich. The center has been recognized as a EULAR Center of Excellence in Rheumatology from 2005-2015.
Steffen Gay has published largely related to the molecular and cellular basis of rheumatic diseases, including 64 book chapters and over 350 peer-reviewed scientific papers. He is among the most cited scientists in Clinical Medicine (ISI) with over 16,000 citations and a h-index of 72. He is a Honorary Member of the American Association of Physicians (AAP) and the Alpha Omega Alpha Honor Medical Society. He became the Spinoza Professor for 2002 at University of Amsterdam and a member of the Deutsche Akademie der Naturforscher Leopoldina in 2004. In 2008 he received the Kussmaul-Medal from the German

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Society of Rheumatology and in 2011 he became Honorary Member of EULAR. Current interest focuses on the epigenetic regulation of gene expression by acetylation, methylation, sumoylation and microRNAs in health and diseases.

Dr. Péter Gergely

Dr. Péter Gergely earned his medical degree in 1995 and his Ph.D. in 2004 at the Semmelweis University, Budapest, Hungary. As a Rheumatology Research Fellow, he was conducting biomedical research at the State University of New York, Upstate Medical University, Syracuse, NY, US from 1998 to 2001. He has Medical Board Certification in Rheumatology as well as in Clinical Immunology and Allergology.
Dr. Gergely worked as an Attending Rheumatologist and Head of Molecular Biology at the National Institute of Rheumatology and Physiotherapy, Budapest. Since 2008 dr. Gergely has been working as a Translational Medicine Expert in Autoimmunity for Novartis Institutes for BioMedical Research, Basel, Switzerland where he currently holds a Director position. He has been a Senior Lecturer at the Semmelweis University and he is an invited external speaker at the Trinity College, Dublin on a regular basis.
Dr. Gergely's main interest includes the pathophysiological, clinical and translational aspects of autoimmune rheumatic diseases. He has primary authorship in papers published in leading peer-reviewed journals such as J Immunolology, Arthritis&Rheumatism, Clinical Immunology, Rheumatology, Autoimmunity Reviews or British J Pharmacology. Overall, the research work by Dr. Gergely has produced 47 scientific papers and reviews and 8 book chapters to date. He has received numerous awards such as the Fogarty Fellowship Award from the National Institutes of Health, US, the Bolyai Janos Scholarship from the Hungarian Academy of Sciences or the Exceptional Contributing Award by Novartis.

Dr. Boulos Haraoui

He is a Clinical Associate Professor of Medicine at the Université de Montréal and head of the Clinical Research Unit in Rheumatology at the Centre Hospitalier de l'Université de Montréal (CHUM, Hôpital Notre-Dame).
Dr. Haraoui received his medical degree from St. Joseph University in Beirut, Lebanon. Following his postgraduate training in Internal Medicine and Rheumatology at the University of Montreal, he completed a research fellowship at the Arthritis Branch of the National Institute of Health in Bethesda,

Maryland. He is on staff in the department of Rheumatology at Hôpital Notre-Dame du CHUM since 1984.
Doctor Haraoui is the past-chairman of the Scientific Committee of the Canadian Rheumatology Association. He is currently the chair of CIORA, the Canadian Initiative for Outcomes in Rheumatologic Care.
He is a founding member and the vice-chairman of the Canadian Rheumatology Research Consortium. He is also a past- president of the Laurentian Conference of Rheumatology.
His main fields of expertise and research are the management of inflammatory arthritis and the optimal use of biologic agents. Doctor Haraoui sits on several national and international educational and scientific committees and advisory boards.

Dr. Emese Kiss

She was born in 1960 in Debrecen, Hungary. Educated at the Medical University, Debrecen from 1979 until 1985. Performed research work at the Students Scientific Society. Defended 3 theses about the pathogenesis of gluten-sensitive enteropathy. Received grant from the Hungarian Republic between 1983 -1985. Graduated in 1985. Worked at the 3rd Department of Internal Medicine, Medical and Health Sciences Centre, University of Debrecen between 1985–2007. Passed board certification exams on internal medicine in 1990, allergology and clinical immunology in 1998, and rheumatology in 2005. Defended her PhD thesis on the importance of complement receptor 1 expressed on lupus erythrocytes in 1998. Passed „habilitation" exam in 2004 entitled „Chronic organ damages and co-morbidities in systemic lupus erythematosus. Since 2004 she has been accredited as an examiner, reviewer and consultant for PhD theses and has worked as an associate professor. In 2007, she has been invited to the National Institute of Rheumatology and Physiotherapy, Budapest. Became the head of the Clinical Immunology Department of the Institute. Reorganised outpatient care and hospital treatment of patients with systemic autoimmune disorders. In 2009 she got an associate professor assignment at the 3rd Department of Internal Medicine, Semmelweis University, Budapest. Headed the Dept. of Clinical Immunology, Adult and Paediatric Rheumatology since 2010. Has continuously been participating actively in the gradual and post-gradual education. Research activity is indicated by 38 book chapters, 156 full text articles, 193.4 impact factors, 456 citations and 14 grants. Member of the editorial board in two national medical journals. Main secretary of the Hungarian Reproductive Immunology Society, and treasurer in the Hungarian Association of Rheumatologists. Possesses GCP certificate, has practice in performing clinical trials.

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Prof. Dr. Péter Lakatos

After studies in biology and chemistry, Dr. Peter Lakatos finished medical school at the Semmelweis University, Budapest, in 1981. He started his medical career at the 1st Department of Medicine, Semmelweis University. Between 1989 and 1992 he worked with Prof. Paula Stern at the Department of Pharmacology, Northwestern University, Chicago, studying intracellular signal transduction in bone cells. In 1993, he returned to the Semmelweis University but remained a faculty member at the Northwestern University until 1998. Currently, he is a full professor of medicine and endocrinology, as well as head of the Clinical Research Laboratory, at the Semmelweis University.
Dr. Lakatos and his research group have actively participated in the development and introduction of biochemical and densitometric methods in the management and research of osteoporosis. In the 80's, he was among first to develop an osteocalcin radioimmunoassay. He directs basic and clinical research programs in the field of metabolic bone diseases with a special interest in osteoporosis and thyroid hormone-stimulated bone loss. During the last decade, his major interest has been in the genetic background of metabolic bone diseases. Dr. Lakatos also conducts drug development studies. He has authored more than 345 full length scientific articles and book chapters. Amongst other posts, Dr. Lakatos has acted as the President of the Hungarian Society for Osteoporosis and Osteoarthrology (1999–2005) and was a board member of the European Society for Calcified Tissues (1997–2007).

Dr. Péter Mandl

Dr. Péter Mandl graduated from Semmelweis University Medical School, Budapest in 2001. He thereafter continued his studies at the Institute of Experimental Medicine, Budapest and the Nathan Kline Institute for Neuroscience in Orangeburg, New York and obtained a PhD degree in functional neuroscience from Semmelweis University in 2007. Dr. Mandl completed his training as a clinical rheumatologist at the National Institute of Rheumatology and Physiotherapy in Budapest and became a board-certified rheumatologist in 2009. He is currently working as a research fellow at the Division of Rheumatology at the Medical University of Vienna, where he has previously worked as an Articulum fellow. His research interests include the neural regulation of immune function and bone homeostasis and musculoskeletal ultrasonography, on which topics he has published numerous papers and book chapters. Dr. Mandl has organized and participated at several national and international musculoskeletal ultrasound

training courses, and has been a member of the faculty of EULAR Musculoskeletal Ultrasound Courses since 2009. In addition Dr. Mandl is a member of the EULAR/OMERACT Ultrasound Group and has served as the OMERACT Fellow for Group in 2010. He is the current chairman of EMEUNET (EMerging EUlar NETwork), the organization representing young rheumatologists within EULAR.

Dr. Imre Pávó

Imre Pávó, M.D, PhD, DSci is senior medical director and leader for endocrinology and diabetes research in Europe for Eli Lilly and Company. He received medical degree, completed postgraduate trainings in internal medicine, endocrinology and his Ph.D. thesis in research on somatostatin analogues at University of Szeged, Hungary. He performed postdoctoral research on vasopressin receptors at Max Planck Institute in Frankfurt and University of Münster, Germany. In 1993, he joined the Lilly Area Medical Center in Vienna, as clinical research physician. After completing an assignment as leader of international regulatory affairs in Indianapolis, Dr. Pávó is in charge for clinical drug development in osteoporosis, diabetes. Among others, he contributed to clinical development of raloxifene, pioglitazone and teriparatide. In addition, his interest is focused on osteoporosis and cardiovascular clinical research. Dr. Pávó has published more than sixty papers on the fields of biochemistry, pharmacology, experimental and clinical endocrinology.

Prof. Dr. Gyula Poór

Dr. Gyula Poór MD, PhD, DSc graduated from the Semmelweis University, Budapest in 1977. He started his medical career at the National Institute of Rheumatology and Physiotherapy, currently he works as the director general of the Institute.
He was conducting research on osteoporosis with L. Joseph Melton at the Mayo Clinic, Rochester, MN between 1992-1993. After returning home he launched the National Osteoporosis Programme in Hungary, along with others. Between 2001 and 2006 he was invited to join the World Osteoporosis Programme of the WHO, as rapparteur.
He is full professor of rheumatology at the Semmelweis University and the leader of the Postgraduate Rheumatology and Musculoskeletal Chair of the Medical University, Targu Mures, Romania, functioning in Budapest. He acted as the president of Hungarian Society for Osteoporosis and Osteoarthrology between 1993-1999, at present he works as the president of Hungarian Association of

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Rheumatologists and as the editor-in-chief of the journal Hungarian Rheumatology. He serves in three boards for the Hungarian Academy of Sciences.
His major interest lies in the research of metabolic and inflammatory rheumatic disorders. His molecular research group published a lot of papers on the genetic background of these conditions and won several international and national grants. Dr. Poór authored more than 300 scientific articles, book chapters and books and was honoured with several professional awards.

Prof. Dr. Monika Reuss-Borst

Professor Reuss-Borst is Director of the Clinic for Rheumatology and Oncology in Bad Kissingen. Prior to this position she was professor in rheumatology at the Georg-August University at Göttingen, Germany. Professor Reuss-Borst was scholar of the German National Scholarship Foundation and received her medical degree from the University of Würzburg, Germany. She trained in internal medicine, rheumatology and hematology/oncology in the US (UCSF San Francisco and Boston) and at the University of Tübingen, Germany. She has long-standing clinical experience in rheumatology and oncology, has been involved in various clinical studies and recently published several articles on gout and hyperuricemia.

Prof. Dr. Christian Roux

Christian Roux is professor of Rheumatology and Head of Bone Unit at Cochin Hospital, Paris Descartes University, Paris, France.
He received his medical training at the University of Paris, and his PhD at the University of Compiègne, for his data on bone assessment by ultrasounds. He has published works in the areas of primary and secondary osteoporosis, malignant bone diseases, and Paget's disease. He is author and co-author of 250 original papers, and chapters of books. He is past President of GRIO, the French Society of Osteoporosis. He is a member of the Editorial Board of Osteoporosis International.

Prof. Dr. Roger Davidson Sturrock

Education
Llanelli Boys' Grammar School; Queen Mary's School, Basingstoke; University of London;
University of Glasgow.
Degrees: MB BS 1969 – University of London (Kings College & Westminster Medical School); MD 1977 – University of London; B.D. (Distinction) University of Glasgow 2010
Diplomas: AKC – 1969 (King's College) Credit in Theology; MRCS LRCP – 1969 (Conjoint Diploma Examining Boards in England); MRCP (UK) – 1971 FRCP (Glasgow) – 1984; FRCP (London) – 1985.
Awards
1975 – Alessandro Robecchi International Prize in Rheumatology (shared) for work on HLA Antigens in ankylosing spondylitis (Awarded by European League Against Rheumatism;
1984 – Arthritis and Rheumatism Council Anglo-US Travelling Fellowship to the USA
Last previous posts
1979–1990: Senior Lecturer and Consultant in administrative charge, Centre For Rheumatic Diseases, University Department of Medicine, Glasgow Royal Infirmary;
As from 1990: McLeod/ARC Professor of Rheumatology, Centre for Rheumatic Diseases/University Department of Medicine, Glasgow Royal Infirmary/University NHS Trust;
2008 – Emeritus Professor of Rheumatology and Hon. Senior Research Fellow University of Glasgow;
2010 – Hon. Professor of Rheumatology, University of Aberdeen
Membership of Committees
College: Previous Member of the Joint Specialist Liaison Committee of the Royal College of Physicians in London; Previous secretary and Chair of the SAC in Rheumatology.
Specialist societies: Previous Secretary of the British Society for Rheumatology; Previous Chairman of the Heberden Committee of the British Society for Rheumatology; Past President – British Society for Rheumatology; Former Council Member, Rheumatology & Rehabilitation Section, Royal Society of Medicine; Past member of Executive Committee, Scottish Society of Rehabilitation Medicine; Past member of Executive Committee, Scottish Society of Physicians; Previous member of the British Society for Rheumatology, Clinical Affairs Committee.
Arthritis Research Campaign: Member of the Scientific Co-ordinating Committee – Arthritis & Rheumatism Council; Past member of the Standing Committee for Academic Development of Rheumatology of the Arthritis & Rheumatism Council; Previous Member of the Research Subcommittee of the Arthritis & Rheumatism

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Council; Previous Member of Education Committee of the Arthritis and Rheumatism Council; Previous Chairman, Board of Trustees Arthritis Research Campaign.
Medical Research Council: Previously on the general advisory board of the MRC.
Europe: Chairman of the Organising Committee for the European Congress of Rheumatology held in Glasgow, 1999; Previous member of the European Board of Rheumatology and of the Monospecialties of Rheumatology of the UEMS; Member of the European Spondyloarthropathy Advisory Group; Joint President of the International Spondyloarthropathy Congress 2010.
Government: Previous Chair – Silicone Gel Breast Implant Review Board commissioned by the Chief Medical Officer and Baroness Jay of the Department of Health; Former Advisor to the Committee of Safety of Medicines.
NHS: Previously member of the Postgraduate Medical Education Committee for the West of Scotland; Former Specialty advisor to the CMO Scotland.
University**:** Former Associate Dean for Student Welfare; Former Deputy head of the division of Immunology, Infection and Inflammation; Previous member of the New Curriculum Review Group for the Faculty of Medicine
Publications: More than 250 publications in peer reviewed journals.

Prof. Dr. Zoltán Szekanecz

Zoltán Szekanecz, M.D., Ph.D., D.Sc. is a Professor of Medicine, Immunology and Rheumatology. He is the head of Department of Rheumatology at the University of Debrecen Medical and Health Sciences Center (UDMHSC), Debrecen, Hungary. He received his MD degree in 1988. He specialized in internal medicine, immunology and rheumatology. He received his PhD degree in 1995 and his DSc degree in 2001. His main research fields are targeted therapies, vascular immunology, rheumatoid arthritis, osteoporosis, angiogenesis, genetics and molecular medicine. Dr. Szekanecz has authored 245 peer-reviewed papers, 60 book chapters and edited 8 books. His cumulative impact factor is 445, with 2500 citations. He is a member of 12 societies including the European League Against Rheumatism (EULAR) Education Committee (ESCET) and Clinical Trials Committee (ESCCA), as well as the American College of Rheumatology. Dr. Szekanecz is the vice-president of the Hungarian Society of Rheumatology and member of the steering committee of European Association of Clinical Pharmacology (EACPT). He is editorial board member at Joint Bone Spine and a reviewer for 16 journals. He has been principal investigator of more than 25 phase I-I-III clinical trials in the field of arthritis and autoimmune diseases. In patient care, Dr. Szekanecz has specialized in treating arthritis and autoimmune patients. He has been involved in graduate and postgraduate medical education since 1988.

Prof. Dr. Ronald F. van Vollenhoven

Professor Ronald F van Vollenhoven is Chief of the Unit for Clinical Therapy Research, Inflammatory Diseases (ClinTRID) at the Karolinska Institute, and of the Clinical Trials Unit Rheumatology at the Karolinska University Hospital.
He received his MD and PhD degrees from the University of Leiden in The Netherlands. After graduating in 1984 he pursued immunology research at Cornell Medical College in New York, followed by residency (specialty training) in Internal Medicine at the State University of New York at Stony Brook, and a fellowship in Rheumatology at Stanford University in Palo Alto following which he received American Board of Internal Medicine certification in both Internal Medicine and Rheumatology.
From 1993 to 1998 Dr van Vollenhoven held a faculty appointment as Assistant Professor of Medicine in the Division of Immunology and Rheumatology at Stanford University, and from 1995 he was the Medical Services Chief and Fellowship Director in that division.
In 1998 Dr van Vollenhoven moved to Stockholm, Sweden, where he worked as a Senior Physician and Chief of the Clinical Trials Unit in the Department of Rheumatology at the Karolinska University Hospital and Associate Professor of Rheumatology; and in 2010, he was appointed in his current position as Professor and Unit Chief at the Karolinska Institute.
Dr. van Vollenhoven's research interests focus around the development and systematic evaluation of biological and immunomodulatory treatments for the rheumatic diseases. With his co-workers, he has established the Stockholm registry for biological therapies (the STURE database) for this purpose, which has supported research projects relating to clinical efficacy, pharmacology, outcomes and pharmacoeconomics. He has been principal investigator in many clinical trials of novel therapies in rheumatic diseases and has contributed to a number of important investigator-initiated trials including the recently published SWEFOT trial. He has published over 150 original papers, book chapters and reviews, and is editor of the textbook Targeted Treatment of the Rheumatic Diseases. In 2004, Dr van Vollenhoven was awarded the Scandinavian Research Foundation Prize for excellence in clinical research in rheumatology. He is the Editor-in-Chief of European Musculoskeletal Review, member of several editorial boards and the EULAR scientific programme committee, chair of the Swedish health economics working group HeraS, and co-founder of the IRBIS registry for biologics in SLE and of the NORD-STAR collaboration for Nordic trials in the rheumatic diseases. Prof. van Vollenhoven lives just north of Stockholm with his wife and two children aged 16 and 13; in his spare time, he plays classical piano.

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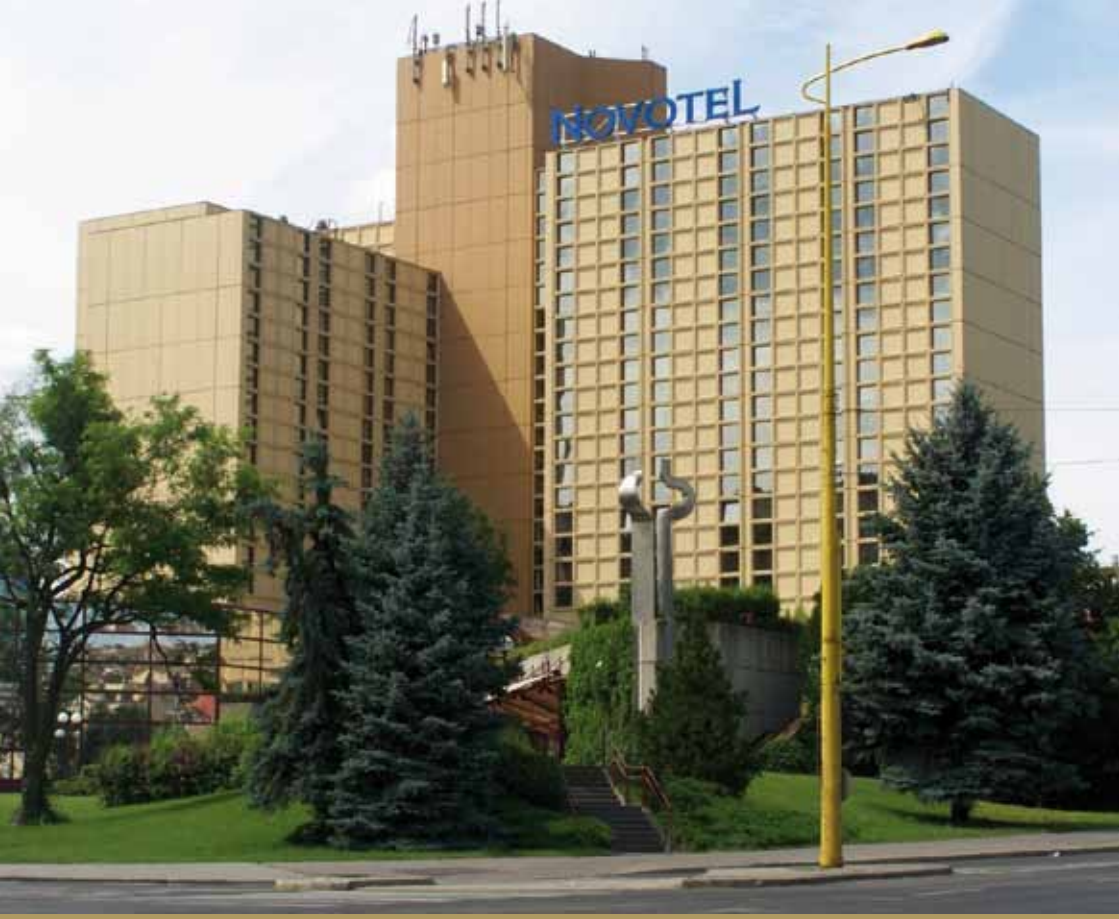

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