This meeting was opened by Tore Saxne who reminded the audience of the untimely death of Dick Heinegård on 1. May one week after treatment for an acute MI. Dick was approaching his 71st birthday, he was just back from the Osteoarthritis World congress in Philadelphia and as active as ever. It was thanks to Dick’s wisdom, insight and worldwide network that the annual Cutting Edge attained and could keep its quality and freshness over the last 15 years. The program for 2013 was finalised in April and sadly it was to become the last which he was able to co-organise. It will be a daunting task to continue in Dicks spirit. Tore and I decided to ask one of Dick’s friends and close collaborators from the 1970’s, Vincent Hascall to come to Lund and highlight some of Dick’s many outstanding achievements, and we are deeply grateful that he immediately agreed to undertake this task. We were honoured in that Dick’s wife Lean attended parts of the meeting. I dedicate this report to the legendary wife of a legendary man.

Tore emphasised that the aims of this meeting is to cover areas of recent advances relevant to rheumatology, to introduce new faces from the international field, and to foster contacts between basic science and clinicians. Eight speakers are invited, one from Lund and the rest from “the world minus Sweden”. A speaker can as a rule only be invited once. There is no registration fee and meals during the day are provided at no charge. The meeting received support from the Kåre Berglund Foundation, from the Rune Grubb lecture fund and the industrial sponsors were Abbvie Scandinavia and Pfizer AB Sweden. Some 150 delegates participated, mainly rheumatologists from all over Sweden and basic scientists from the area. The invited speakers this year came from Germany, The Netherlands, United Kingdom and USA.
In 1967 when Dick Heinegård started research in the laboratory of Sven Gardell in Lund cartilage was considered a rather dull inert tissue containing chondrocytes, collagen fibres and “glucosaminoglycans”. Dick started working on the characterization of this terra incognita and published a few papers on "proteoglycan". In 1971 Dick presented early results at a Gordon conference on cartilage, where he met Vincent Hascall, a young Ph.D. from the Rockefeller Institute now working at the University of Michigan. Vincent recognised Dick’s eminent investigative mind and invited him to Michigan. Dick declined however and suggested that Vince should come to Lund instead. This actually materialised and Vince spent 1972-3 as post doc in Sven Gardell’s group. This was the start of 4 decades of scientific interaction and deep friendship. They published 4 seminal publications (1,2,3,4) on cartilage proteoglycan. These were included in Dick’s thesis in 1974. In the same year, based on its aggregating features with hyaluronan, the name was changed to aggrecan. Meanwhile Vince had moved to NIH where Dick was to spend a fruitful post doc period. The collaboration lead to important new knowledge regarding the structure and function of the hyaluronan-aggrecan molecular organisation in cartilage (5,6,7,8).

In 1979 Dick described a new 148 kDa protein (9) and over the years an ever more complex picture of cartilage matrix emerged containing a number of newly identified macromolecules. The most current picture was actually presented by Dick at a meeting at the Cleveland clinic where Vince is working now (fig 3). A fine example of Dick’s wisdom is the discovery of matrilin. He told the young student Mats Paulson in 1977 that there must be a protein connecting the proteoglycan aggregates to the collagen collagen network: “Go and find the glue”. This lead to the discovery in 1979 of the mentioned cartilage matrix protein, initially named 148 kD protein or cartilage matrix protein, CMP (9). Mats became professor of biochemistry in Cologne and continued to study this and similar related proteins which in 1997 was named the matrilin family. CMP is therefore named matrilin-1 Dick and his team discovered several new cartilage proteins i.e.PREL, chondroadherin, asporin and CILP and fibromodulin(10).
Dick’s contributions to matrix research were not confined to cartilage. He also described new constituents in bone, osteopontin and osteoadherin. Always keen to understand biologic functions a recent discovery concerned the regulation of complement activity by matrix proteins (11). Vincent Hascall also mentioned another recent breakthrough involving CHAD, chondroadherin, in the intervertebral disc, distinguishing degeneration from normal aging (12).

Dicks and Tore Saxnes collaboration over more than 3 decades had development of relevant prognostic biomarkers as a mainstream theme. This work is still far from completed, but recent promising results indicate the usefulness of sequential measurements of serum COMP as predictor of joint erosions at 2- and 5-year follow up (13).

Dick was a leader based on his eminent competence as an experimental biochemist combined with deep insight into clinical problems, by an exceptional dedication to his students, an ability to select the best collaborators, and a truly worldwide network. His competence was utilised in advisory boards by prestigious institutions in several countries. The loss to the scientific community is as immense as it is to his family.

References

**Dendritic cell subsets in the regulation of adaptive immune responses: lessons from the gut**

**Catharina Svanborg**, a previous speaker at Cutting Edge and expert in urinary tract microbial pathogenesis, introduced **William Agace**, Lund, a leading investigator of immune cells in the gut and homing of T-cells (1). The microbiota containing 10 times more bacteria than the total number of eukaryotic cells in the body are key players in regulating the balance between immune response and tolerance. Whereas lymphocytes can be characterised into functional subsets by a number of cell surface markers, it has been more difficult to distinguish classical dendritic cells, cDCs, and macrophages, MΦ, due overlapping staining with CD11c, CD11b, and MHC class II surface markers. Dendritic cells...
are found in most tissues and their function is to sample self and foreign antigens, migrate to draining lymph nodes and interact with T-lymphocytes (2). In the gut cDCs are found in the lamina propria, LP. cDCs can now be distinguished by their lack of FcγR1 and CD64. CD64 positive MΦs on the other hand do not express the integrin α chain CD103. A more complex picture of intestinal mononuclear phagocytes now emerges where CD64+ MΦs can be distinguished from CD64- cDCs. Furthermore the cDCs can be subdivided into CD103+/CD11b+, CD103+/CD11b- DCs, and a more recently identified CD103-/CD11b+ subset. These are now considered “bona fide DCs” and the former two subsets are essential intermediates between gut antigens and gut wall lymphocytes. The function of the last subset remains to be elucidated. Importantly there is now evidence that in addition to the established tolerogenic functions of DCs, other DCs are in contrast stimulatory and driving a proinflammatory IL17 expression, fig 4. CDc may become therapeutic targets, provided the right specific regulatory agents can be produced. Indeed work is in progress developing monoclonal antibodies aiming at reducing IL-6 production in models of IBD.

Lars Klareskog raised the question regarding possible influences of salt load on IL-17 expression and Catharina Svanborg was curious about possible inducers of the transcription factors involved in DC subset generation. These are among questions for future work.

References
The role of NETs - from infection to autoimmunity

Our next topic was the neutrophile leucocyte, discovered at the Charité in Berlin by a postdoc Paul Ehrlich, 26 years old. Ehrlich had in his doctoral thesis in Leipzig in 1878 introduced staining techniques for blood cells and discovered the mast cell. In Berlin two years later he also described the eosinophiles and neutrophiles (1). Anders Bengtsson introduced Arturo Zychlinsky, director of the Max Planck institute for infection biology at the same place, The Charité in Berlin. Zychlinsky who discovered neutrophile extracellular traps or NETs in 1997 while still working in New York (2) delivered a brief overview of the origin and short lifespan of the neutrophile and also mentioned Metchnikow’s contribution to phagocytosis (3). The name neutrophile refers to the affinity of the cells with their granule for neutral dyes. The lifespan from leaving the circulation and entering to sites of injury is only one day and neutrophils cannot be cloned or cultured, they are difficult to catch while in action. Their capacity to phagocytose and degrade foreign material has been known for long. Zychlinsky observed while studying interaction with Shigella bacteria that the neutrophiles could also attack the bacteria by forming large extracellular structures, containing various noxious substances (2). After forming NETs the cells die in what was named NETosis, to distinguish it from necrosis and apoptosis. Several pathogenic bacteria have been shown to stimulate NETosis. It turns out that this defence mechanism may also be harmful to the host and contribute to the pathogenesis of autoimmune conditions. This appears to be the case in SLE where impaired NET removal is present and relate to renal disease and disease activity(4,5). This may be due to anti-DNA and anti-DNAase autoantibodies. Zychlinsky showed movies of NET formation and described their content of elastase, calprotectin and other neutrophile proteins and also of reactive oxygen and chromatine. NETs can activate adaptive immune cells possibly mediated by the chromatine they contain. They may participate in the pathogenesis of several diseases in addition to SLE, e.g. preeclampsia, cystic fibrosis, sepsis thrombosis, RA and malignancy. A detailed methodology and movie showing how to generate and visualise NETs is available in Pubmed (6). A safe prediction is that we will learn more of NETs in coming years.

Zychlinsky was a most qualified Rune Grubb Lecturer.

One immediate question from Karin Lundberg in the audience was whether different classes of NETs could be identified. This very adequate question remains to be studied.
Fig 6. NETosis visualised. Upon stimulation NET formation starts within minutes. The cell nucleus is rounded and controlled cell death occurs. From Fuchs et al. J Cell Biol. 2007 Jan 15;176(2):231-41

References

Cellular immunopathology of spondyloarthritis

Lennart Jacobsson, Gothenburg, introduced the next speaker, Dominique Baeten, Amsterdam. Dominique delivered a superb overview of the newest insight in pathogenetic roles of both HLA-B27 and non-HLA gene associations, the role of TNF and hints of novel therapy in non-responders derived from this. Although the vast majority of patients with spondyloarthritis, SP, carry HLA-B27 the striking clinical diversity of phenotypes points to other modifying genetic or environmental factors.
Circulating levels of TNF are elevated in SP but not as much as in RA. Genomewide screening has identified up regulation of TNFR1A, TRADD and TNFST15, all related to TNF signalling (1,2). The effect of anti-TNF therapy is not only well documented but often prompt and dramatic. In contrast, the radiologic effects are less impressive. This indicates different mechanisms of action in comparison with RA. One unknown factor is which cells are overproducing TNF in SP. An enigmatic question is why some patients do not respond. The therapy does not cure the disease, and flares occur early even in patients which went into complete remission and also in patients with only peripheral arthritis (3). Baeten works on a better understanding on the mechanisms of anti-TNF therapy in animal models. One clue seems to be that osteoproliferation, destruction and inflammation are in part independent manifestations (4). The evidence in mice transgenic for membrane-bound TNF generated by Georges Kollias in Athens of male dominance is puzzling and unexplained. Also different biologic functions may be mediated by membrane-bound and circulating TNF, where the former signals local inflammation and bone proliferation whereas soluble TNF is mediating systemic inflammation and destruction. (5).

Fig 9, Pathways of soluble and membrane bound TNF. From ref (5)
The disease process may also be controlled through other pathways, e.g. prostaglandins and other cytokines. The work by Wandres et al showed an ameliorating effect on radiologic progression in users of NSAID and supports the former (6). Other data implicate IL-1, IL-6 and IL-22. Recent interest focuses on the cytokine IL-17A as an alternative driving factor and consequently putative target for treatment. GWAS has generated replicated evidence for the association with polymorphism leading to activation of the IL-23/IL-17 pathway and a recent phase II trial showed efficacy of anti-IL-17A (7).

Returning to HLA-B27, one can now recognise 3 possible ways of influence in SP:

- arthritogenic self peptides presented to Th8+ T-cells by properly folded HLA-B27/β2m dimers;
- naturally occurring HLA-B27 dimers could be recognised by killer immunoglobulin receptors resulting in activation of effector CD4+ T-cells;
- intracellular misfolding HLA-B27 monomeres leading to endoplasmic reticulum stress

The complex picture of how these mechanisms interact in time and in which cells remains to be sorted out (8)

References

Shifting paradigms in osteoarthritis

The topic of osteoarthritis, OA was close to Dick’s heart as investigator over the decades, and he was himself affected by hand OA. It was Dick who suggested the next speaker, Tonia Vincent from The Kennedy Institute in Oxford. Her talk was for the best of reasons designated as the first Dick Heinegård lecture. Contributions on OA have appeared frequently at this meeting over the years, with speakers such as Steffen Gay, Reinhardt Fässler, Wim van den Berg, Sergio Jimenez, Stefan Lohmander, Thomas Aigner, Björn Olsen, Gerard Karsenty, John Loughlin, Steven Goldring, Frank Barry, Francois Berenbaum, Farshid Guilak, and several others on the program. Dick and my co-chair Tore Saxne have devoted large parts of their research to OA related problems. I mention this only because the invited chairman of the session did not seem to be fully aware of these facts. Tonia shared some misconceptions regarding cartilage that she had been exposed to. Her favourite was “Cartilage is like rubber. It wears down with age”. Some others are

- “Cartilage is an inert tissue protecting the surrounding bone.” And interestingly
- “Cartilage lacks nerve supply and thus cannot signal pain”. Also
- “Cartilage cannot heal”.
- “Analgesia is bad for the joint cartilage”.

Vincent set out to examine these dogmas and could show that most of them were not true. A major advance in cartilage research was the observation by her teacher Jerry Saklavala that cartilage breakdown was engineered by a factor released from synovial cells and a substance he named catabolin which later turned out to be a cytokin called IL-1 and released from lymphocytes (1). Cartilage degradation turned out to be an extremely active process executed by environmental factors but also by the living cartilage itself. With time ADAMTS 4/5 and collagenase-13 have been identified as dominating enzymes. In 2002
while studying cartilage reaction to injury it was discovered that cutting intact cartilage resulted in activation of the extracellularly regulated kinase (ERK). By massspectrography the factor turned out to be basic fibroblast growth factor 2, FGF2. Originally this factor seemed to be a protective inhibitor of matrix degrading enzymes but later opposite catabolic effects have been described. The explanation is that the contrary effects are due to different receptors. FGF2 signalling through FGFR3 is anabolic whereas signalling through FGFR1 is catabolic. In OA unfortunately FGFR1 dominates and expression of FGFR3 is decreased (2).

Protease expression is mechanosensitive and this may have therapeutic implications. After injury it was shown that immobilisation prevents joint damage in mice (3). In humans promising results have been achieved by treatment with joint distraction. Several mediators including IL-6 and Cox2 were suppressed by immobilisation (4). As I commented in the discussion this may explain the popularity of tibial wedge resections as treatment of knee OA with varus deformity in the pre-total joint era. Promising signs of cartilage healing have also been observed.

One effect of FGF2 is induction of nerve growth factor, NGF, in chondrocytes. A widely used murine OA model of surgically induced instability of a hind leg resulted in pain and release of NGF. NGF blockade by a soluble receptor, TrkAd5 relieved pain and normalised the mobility of the animals. In this model one could distinguish between early inflammatory pain and late non-inflammatory pain. TrkAd5 was beneficial in both phases whereas anti-TNF only helped during the early pain phase (5). These results stimulated the synthesis of monoclonal anti-NGF reagents for use in human OA. Promising results were obtained in studies with the humanised product Tanezumab, but the trials were (temporarily ?) halted by FDA due to reports of rapid progression of OA in a few patients (6).

After this excellent presentation one could conclude that cartilage is a highly dynamic tissue, which under pathologic conditions can signal pain. It can also undergo healing, and at least induction of analgesia is not harmful to the joint at least in a murine model of OA.

Fig. 11. Electron microscopy of a chondrocyte and its pericellular and territorial surrounding. The pericellular matrix contains no thick type II collagen but thin type VI. The red dots are FGF2 bound to perlecan. From ref. (7)
References

Genetics and clinical variability of autoimmune disease

Fig 12. Lars Klareskog, Peter Gregersen and Catharina Svanborg

Lars Klareskog introduced his friend and collaborator Peter Gregersen Manhasset NY, the co-discoverer of “The shared epitope” in 1987 and the PTPN22 association with RA in 2004
and later with several other autoimmune diseases. In 1999 he wrote in a review paper “The completion of the human genome project, along with advances in informatics, will be required to reach a deeper understanding of RA. It is likely that this will involve an iterative and interactive process between several different scientific disciplines” (1). Peter has mastered the establishment of global collaborations examining huge patient cohorts and one has now been able to identify some 100 associations with polymorphic SNPs. And yet he started his presentation by stating that now it was not really interesting to find more genetic associations. The problem was what to do with them, or in other words, to learn more about mechanisms and how to interpret the associations. Different autoimmune diseases share susceptibility SNPs, PTPN22 being a good example. This indicates that the conditions share pathogenetic pathways. An important source of complexity is that different cell types are active in different diseases, for instance CD4+ T-cells in RA but dendritic cells in Crohn’s. Another general statement is that only 7% of the polymorphisms affect coding regions. Thus the bulk of the associations relate to regulatory pathways.

Epigenetic markers do help to towards identifying functionally important genes. An important recent advance is the discovery of histone marks, knots on the nucleosomes indicating chromatin marks helping in the fine mapping of complex trait variants to the critical cell types (2). The focus now shifts to defining endophenotypes, a task where the collaboration with careful clinical examination is absolutely essential. Bedside medicine is far from obsolete in the age of explosive technical advances.

So called rare variants, that is SNP polymorphism only found in a minority of individuals in a population can now be identified in large numbers thanks to increased capacity and decreased cost of genome wide screening (3). These variants may not themselves be disease associated but can reveal association with disease (4) and perhaps more importantly to endophenotypes. An example is a polymorphism of the OXO3 gene where the rare G variant is associated with severe disease in malaria but with mild disease in RA patients. This can be explained by its dampening influence on activation of immune responses (5).

As Gregersen so clearly demonstrated we are only in the infancy of understanding genetic mechanisms in causing disease. Or as Rune Grubb would have concluded “If you are not confused, your are not informed”. However some reasonably understandable conclusions of current knowledge have just been published by Peter Gregersen in the NEJM (6).

Does Peter Gregersen have time for any hobbies? He is an accomplished musician and enjoyed attending a chamber music concert with baroque music while in Lund (as did Constance and Arturo Zychlinsky). Peter has also published a paper on absolute pitch (7) and very recently on its overlap with synesthesia, that is the automatic association of certain colours with individual figures. (8). I happen to suffer from synesthesia but am fortunately not affected with absolute pitch.

References
The role of ACPA in the pathogenesis of rheumatoid arthritis

Karin Lundberg, Stockholm worked in Patrick Venables laboratory for 4 years and was a natural choice to chair his lecture. Walter van Venroij in Amsterdam and Guy Serre in Toulouse elucidated the identity of anti-keratin antibodies and antiperinuclear factor of RA patients and citrullination as the key feature of the autoantigen. This gave rise to the development of the diagnostic test with generic synthethised cyclic citrullinated peptides, which is in general use, called CCP2. Venables pointed out that CCPs do not cause disease. He is interested in understanding how the patients ACPAs are driving synovial cells in the pathogenesis of RA. More precisely he asked 3 fundamental questions: Which are the true autoantigens in patients. These have nothing to do with the generic CCP antigens. Reproduced candidates are instead fibrinogen, vimentin, enolase, and collagen. How do ACPAs arise in the first place. Which environmental factors except smoking can be identified and how do they interact? (1). Others have worked on animal models and are proposing posttranslational modifications involving citrullination and glycosylation of type II collagen as mediators of arthritis (2). Citrullinated forms of the 4 mentioned proteins have been found in joint tissue in both humans and animals. The Kennedy workers have studied α-enolase in great detail and identified the Epitope CEP-1 as a major autoantigen, Fig 15. The crystallographic localisation of CEP-1 is shown in fig. 16.
Parodontitis association with arthritis was studied further in collaboration with Jan Potemka in Krakow. It could be shown that infection with a pathogenic strain of \textit{Porphyromonas gingivalis} caused exacerbation of collagen induced arthritis (3). It seems very likely that the PPAD mediates this effect.

Fig 15. Percentage of serum immunoblotting positivity towards citrullinated and non-citrullinated antigens in 50 RA patients vs. 45 healthy controls. ALD= aldolase. Fbg= fibrinogen, His= histone, MBP= myeline basic protein, Eno= $\alpha$-enolase. From ref (1).

Fig 16. Molecular presentation of the human $\alpha$-enolase dimer with the CEP-1 epitope marked in red and its arginins in yellow. A is a ribbon diagram of the dimer, B a molecular surface model and C a monomer model with the CEP-1 looking onto the dimer interface. From ref (1).

In collaboration with a Belgian group lung tissue from patients with COPD and with pulmonary carcinomas was studied for presence of citrullinated proteins. It was found that COPD had increased presence and that the increase was more pronounced in smokers. However vimentin and not $\alpha$-enolase was dominating.

In a recent study of patients with parodontitis without joint disease RA related autoantibodies were explored. No increased levels of anti-CCP were found, but 12% of the patients had antiCEP-1 and 16% had anti-noncitrulinated $\alpha$-enolase. The reason for this is unclear (4). Epitope spreading is coinciding with disease onset in RA and suggested to contribute to the initiation of the manifest disease. Clearly many unknowns remain to be uncovered.
Smoking is not the only triggering factor. It has been shown that non-smoking women in Africa and Malaysia develop ACPA. Lars Klareskog suggested that inhaled dust could cause this. Also the effects of passive smoking remains to be explored. A further unexplored field is whether effective pharmacotherapy can reduce pathogenic ACPAs.

References


Pain mechanisms in arthritis

Fig 17. James O’Dell, and Hans-Georg Schaible. Fig 18. Lennart Jacobsson and Carl Turesson

Stefan Bergman, Spenshult, introduced Hans-Georg Schaible, Jena. Schaible started by emphasising the high prevalence of joint pain documented in 16 European countries (1). 19% of over 46,000 responding individuals reported chronic pain lasting over 6 months. Although the responder rate was only 45% we know that chronic pain is a very common and important health problem. Schaible started by giving a well needed overview of the nociceptive system and its regulation. Nociceptors react upon noxious stimuli by a complex assembly of mediators and ion channels, see fig 19, (2). One consequence of the multiple second messengers potentially released from the nociceptors in the joints and other tissues is that it can lead to peripheral sensitisation via changed activity of the ion channels and...
release of neuropeptides and prostaglandins. Other nociceptors are also activated and all this leads to peripheral sensitisation. Afferent nerve fibres go to the dorsal horns. From the dorsal horn other nerves signal to the CNS where pain becomes conscious. One can distinguish between discriminatory and affective experience of pain and between mechanical and thermal pain and the different categories have in part different mediators.

Figure 18. Schematic drawing of nociceptors complexity. From ref (2)

Technical advances in brain imaging, PET scanning and functional MRI, have revolutionised knowledge regarding the network of pain in the brain and defined several cortical and subcortical brain regions involved in processing of pain. Commonly activated areas are the primary and secondary somatosensory cortex (S1 and S2), the anterior cingulate cortex (ACC), insular cortex (IC) prefrontal cortex (PPF), thalamus, basal ganglia, and cerebellum, see fig. 20, (3). The functional understanding of how they interconnect and change in chronic pain is complex and under continued investigation. One important feature of chronic pain is a decreased pain threshold.

Chronic pain leads to thinning of cortical regions of the brain in patients with chronic back pain caused by ankylosing spondyloarthritis (4). The pain threshold remains unchanged but mechanical and cold sensitivity decreases. In the human joint the synovium normally contains a dense network of neural fibres, but in OA knees one can observe a disappearance of the nerves correlated to presence of inflammation. It is therefore unlikely that the synovium is a significant source of pain signalling in longstanding synovitis (5).

Modulation of pain can be achieved by reducing attention or by influencing the mood. Interestingly modulation of attention that is distracting the subject, influences the intensity of pain whereas mood modulation for instance provoking laughing influences mostly the unpleasantness of pain. The modulating influences signal via different pathways to different parts of the brain, fig. 29 (4).

The second part of the talk dealt with the roles of cytokines and other modulators of pain and the influence of biologics (6). TNF is a prominent mediator of signals which augment pain and anti-TNF therapy leads to a normalisation of lowered pain threshold. Blocking TNF in the spine normalises pain threshold and general pain (7). TNF is also involved in
both mechanical and thermal pain generation. IL-6 and IL-17 are more linked to mechanical pain (8,9), whereas IL-1 mostly signals thermal pain (10).

Prostaglandin E2 is a well established mediator of pain by engaging the receptors EP2 and EP4. Schaible’s group has recently made the interesting observation that PgE2 can also engage EP3, which signals analgesia. This creates an interest in developing agonists with specificity for EP3. Interestingly EP3 seems to mediate analgesia only during chronic pain situations and not in healthy conditions (11).

References
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**The role of synthetic DMARDs in modern treatment of rheumatoid arthritis**

It is always refreshing to listen to speakers who challenge current dogma. Carl Turesson had the honour to introduce this year’s Kåre Berglund lecture, given by James O’Dell, Omaha, NE. The selection was most fitting – Kåre Berglund was indeed not a conformist! The past president of the American College of Rheumatology has put Omaha on the map of rheumatologists by his NEJM paper on triple therapy for patients with RA (1). In this relatively small study 24 of 31 patients who started on either methotrexate in monotherapy or in combination with hydroxychloroquine and sulfasalazine remained in what then was considered remission after 24 months, compared to only 12 of 36 after methotrexate monotherapy (1). At the time combination therapies were uncommon. The paper received immediate attention. James was invited to write an editorial in the EULAR journal (2) and a number of attempts were made to replicate the results. The advent of biologics soon put the spotlight on inhibition of TNF α and later also on other cytokines, but some rheumatologists did not loose interest in development of new strategies with DMARDs. However time has now come to compare the combination of “conventional” DMARDs with other approaches, and we were fortunate to hear of two recent investigator initiated studies, in which the speaker has been actively involved. These the US TEAR study and the RACAT study which have been published recently (3,4). The 48 weeks 3-armed TEAR study examined in a blinded fashion starting methotrexate monotherapy with initial methotrexate plus ethanacept or methotrexate plus hydroxychloroquine and sulfasalazine in early poor
prognosis RA (3). Patients in the monotherapy arm could step-up therapy at 24 weeks if necessary. The results showed that 30% of the randomised patients did well on monotherapy after 48 weeks, and that a step-up strategy did not seem to be a disadvantage compared with the patients randomised to immediate combination therapy. The strength of this study is that it was randomised and involved more than 700 patients. No clinical differences were observed after 48 weeks. At 102 weeks there was still no clinical differences measured with DAS28-ESR ≤ 3.2, but radiology favoured the etanacept arm. Also at 24 weeks patients in the immediate combination arms showed a greater improvement than the patients in the monotherapy arm. (4).

The RACAT study examined 355 established RA patients who had not responded to methotrexate monotherapy within 24 weeks. They were then randomised to either triple DMARDs or etanercept and followed until week 102. There was an option for blinded switch in non-responders. The results showed similar clinical results after 48 weeks of blinded randomisation. 27% of patients in each arm switched and responded better after the switch. Although this study showed a non-inferiority of the triple arm there was a small difference in radiologic progression favouring etanercept.

These recent studies have been analysed in an editorial (6) which also compared them to the Swedish SWEFOT study. Despite methodological differences the results are in close agreement. However there are possible confounders. One is that prevalence of smoking was not assessed, the other that the arms were not balanced for use of glucocorticoids.

An important message may be that hydroxychloroquine is currently underused by many rheumatologists.

References


Lessons of the day
Lars Klareskog managed again to catch the attention of the audience at the end of the meeting by alluding to his own carrier from investigator in basic immunology to experimental rheumatology to clinical rheumatology. It is an understatement to say that he performed superbly in all roles. He then highlighted the breakthrough advances in research on arthritis by mentioning previous winners of the Crafoord prize in arthritis. Finally he highlighted some pearls from the presentations of the day, such as "Different cells make different things", as exemplified in Peter Gregersen’s genetic talk. He acknowledged that he now new much more about the nature of OA and that he had a clearer view on the differences between RA and AS. He also reiterated that the antigen used in anti-CCP tests do not identify causes of RA. The synergy between anti-DNA antibodies and NETosis in the pathogenesis of SLE was mentioned. The intriguing connections between cell type specific histone marks and disease heterogeneity was his last point (1), before mentioning Svante Pääbo’s work on the genome of the Neanderthals, who not only share similarities with us the living, but also show a mixture of influences from their contemporarians. Lars is indeed an essential ingredient in the Cutting Edge in Rheumatology meetings.

References

To conclude
Tore and I were gratified to receive many comments stating that this was perhaps the best Cutting Edge Rheumatology they had attended. If that is true, the honour belongs to all speakers and to the wisdom of Dick Heinegård. We hope that these meetings can continue in the same spirit. It would be a worthy tribute to our co-founder and friend Dick.

Acknowledgement. I am indebted to Tore Saxne and Magnhild Sandberg for valuable comments.