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Big Performers
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where next?
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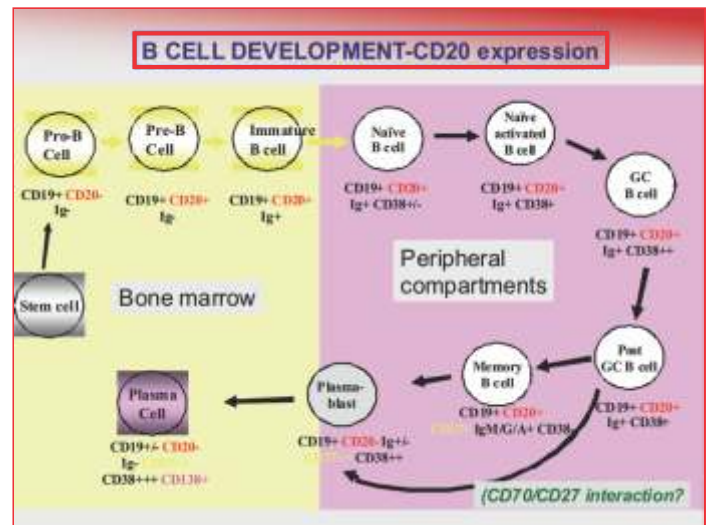
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Flight Path from T-Cell centric to B-Cell depletion Therapy *A story of Persuasion, Persistence, Perseverance, Performance - David A Isenberg*

In the 1990s it was widely believed that rheumatoid arthritis was a disease of T-cells and cytokine abnormalities. The B-cell was generally disregarded as an important player in the origins of this serious and widespread condition. My, now retired, colleague Professor Jo Edwards believed however, very strongly, that B-cells played a far bigger role in the development of rheumatoid than was generally believed. As evidence he pointed out the existence of foci of B-cells in synovial tissue and in a variety of other organs associated with clinical features of RA, lungs, skin.

In November 1997 the Federal Drug Administration approved the use of Rituximab for the treatment of non-Hodgkin's lymphoma. This biologic drug was known to bind the CD20 molecule present on many although not all B-lymphocytes. It seemed to Jo Edwards that if he was correct, B-cell depletion should be a very effective therapy for patients with rheumatoid arthritis. He went to speak to Roche to explain his ideas and to ask for sufficient doses of the drug to treat a small number of patients as part of an investigator-led study.(continued on Page 6)



Happy New Year!

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Incoming APLAR President Kazuhiko Yamamoto

After the APLAR 2016 in Shanghai, I succeeded Professor Kevin Pile as the President of APLAR for the upcoming 2 years. As you know, we have recently celebrated the 50th anniversary of APLAR, which has experienced enormous growth. However, it is important to recognize the heterogeneity of several aspects of rheumatology in APLAR. In fact, we have different histories, ethnicities, religions, and social systems amongst the APLAR membership. The medical environments are also diverse. Nevertheless, we believe that rheumatology in our APLAR region is now expanding. The scientific meeting of APLAR has been held every year. In this regard, we should be aware that each annual scientific meeting has been rather independently organized by each national organizing committee.(continued on Page 3)



Small Molecules ... Big Performers Presidential Address by Kevin Pile

Janus kinases are a small group of intra-cytoplasmic enzymes that modulate the effect of a range of interleukins, interferons, and growth factors after they bind to their membrane receptors and in doing so modulate downstream effects in the inflammatory cascade. We are becoming increasingly familiar with Janus kinase inhibitors in the treatment of RA, and we will now see an eruption of inhibitors into a diverse range of disorders and I aim to identify but a few.

Discovered in the mid 1980's by Andrew Wilks in Melbourne when he was searching for colony stimulating receptors, they were originally put low on his research priority as "just another kinase" which he labelled JAK1 and JAK2.(continued on Page 2)



Unwilling to publish using this nomenclature he chose Janus kinase to reflect the two kinase-like domains similar to the two faced Roman deity, Janus. Contemporaneous to this Tyrosine kinase 2 was cloned, and we ended with 4 Janus kinases (JAKs) with mixed nomenclature of JAK1, JAK2, JAK3 and TYK2. While JAK1, JAK2, and TYK2 are ubiquitously expressed, and JAK3 is expressed in haemopoietic, myeloid and lymphoid cells.

JAKs bind in pairs to the intracytoplasmic tails of the transmembrane receptor and catalyse the transfer of

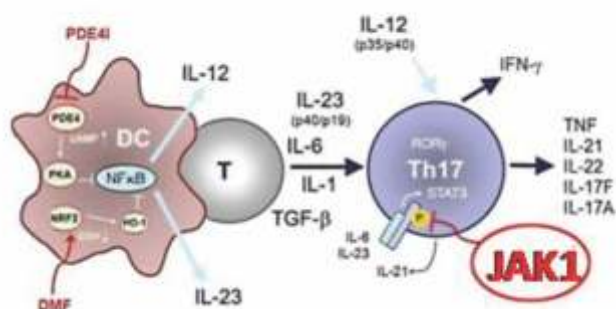


Fig Jakin(h)ibs: small molecule intra-cytoplasmic modulators of surface receptor to nucleus messaging

a phosphoryl group from ATP to a tyrosine residue within the protein. As can be seen in the diagrams cytokine-receptor binding first phosphorylates trans-phosphorylates two sites of the adjacent paired JAK molecule. A conformational change ensues, leading to cis-phosphorylation of the cytokine receptor tail, with a STAT (signal transducer and activator of transcription) monomer binding around this site. The JAK in turn phosphorylates the STAT molecules which are released into the cytoplasm as dimers, crossing into the nucleus as transcription inducers. As noted the JAK molecules function in pairs, either as homodimers eg JAK 2/2, or heterodimers JAK 1/3. Up to 10 combinations are possible and the Table shows those identified and the cytokines, hormone, or growth factor mediated by the dimer pair. A quick glance at this list reveals mediators that are implicated in a range of diseases, particularly IL-2, 6, 12, and 23 for rheumatic diseases. Only one of the pair needs to be inhibited to effectively block the action of the cytokine mediated by that pairing. JAK inhibitors, Jakin(h)ibs are small molecules that can be readily produced using standard pharmaceutical/chemical methodologies, with the potential to design them according to the desired binding attributes within the catalytic site of the enzyme target. An individual cytokine may be blocked by the inhibition of several JAKs eg Il-6 and a single JAK inhibition may modulate many cytokines eg JAK 3 modulation of the common gamma chain cytokines. To date over a dozen jakinibs have been described, and their theoretical impact can be derived from a knowledge of cytokines

modulated. The Table suggests that JAK2 inhibition may be haematologically deleterious due to its blockage of erythropoietin and thrombopoietin.

In the coming months, much discussion will focus on whether inhibition of a single JAK is more desirable than a dual or pan JAK inhibitor, the relative specificity for inhibition of one JAK over another (who can recall the COX1/COX2) which will also rely on different assay methods. Much is still to be learnt about the tissue distribution and intracellular concentrations of these inhibitors as even within the same cell line the 50% inhibitory concentration for a particular JAK can vary dependent on the cytokine stimuli, and also varies when the stimuli is kept constant but different cells are used. Researchers are investigating the impact of the duration and periodicity of JAK inhibition, and I suspect much will be made of this in the marketing of new agents.

Th17 cells and IL-23 have become prime therapeutic targets in spondyloarthritis with jakinibs disrupting the signalling cascades of IL-6, 21 and 23 and the activation of pathogenetic TH17 cells. The Oral Psoriasis Trials (OPT) used the Psoriasis Area Severity Index (PASI) as an outcome with a 75% reduction being an outcome measure that occurs with a placebo rate of 6-11%. Tofacitinib (a pan-JAK inhibitor) achieves a PASI75 of 40+% at 5mg bd, increasing to over 60% with 10mg bd. This higher dose achieving similar results

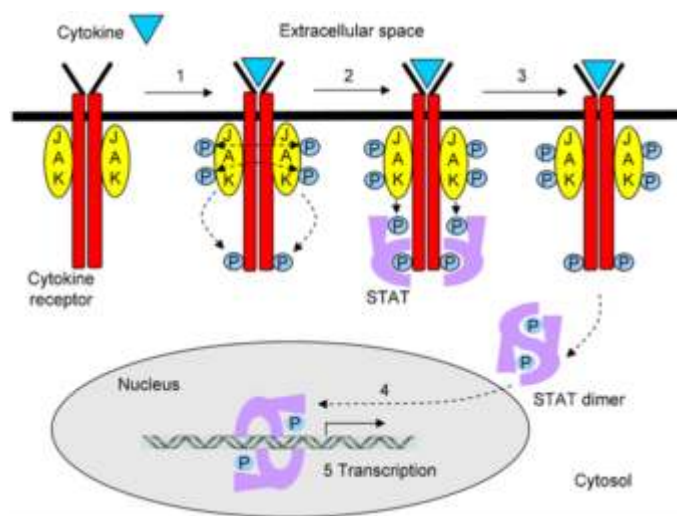


Fig Transduce extra-cellular signals from cytokines, growth factors, and hormones -

and being non-inferior to that obtained with etanercept 50mg twice weekly. Baricitinib (JAK 1/2 inhibitor) in a dose escalation study achieves PASI75 in the mid-50's at higher dose, and the "pure" JAK3 inhibitor similarly achieved almost 60% at the higher dose of 100mg bd. To date very little information is in the public domain for psoriatic arthritis, although positive press releases have been made to the share market, and it is expected trial results will be presented at ACR in 2016.

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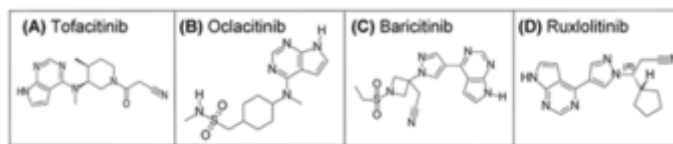
JAK dimer	Receptor mediation and potential inhibition
JAK 3, 1	IL-2, 4, 7, 9, 15, 21 – the common γ chain cytokines
JAK 2, 2	Erythropoietin, thrombopoietin, GM-CSF, growth hormone, IL-3, 5
JAK 1, Tyk 2 JAK 2, Tyk 2	IL-6
JAK 2, Tyk 2	IL-12, 23
JAK 1, Tyk 2	Type 1 interferon α , β
JAK 1, 2	Type 2 interferon γ

Table of JAKS

In a small subset of Japanese patients treated for psoriasis, very impressive ACR20/50/70 results were reported, but the patient sample was small and it was not placebo controlled. The results of a trial of tofacitinib in ankylosing spondylitis is available on the clinicaltrials.gov website, reporting significant ASAS20 results at week 12, being 60% plus with both 5mg and 10mg bd.

Furumoto demonstrated that tofacitinib ameliorates murine lupus when used both preventatively and therapeutically. The preventative strategy having the greater impact on autoantibody production, renal histology scores and immune deposition. Therapeutically a reduction in dsDNA but not ANA was seen, along side a reduction in proteinuria. Finally cytokines from the above Table have been implicated in alopecia areata universalis, a chronic immune mediated disorder that can result in total body hair loss. In grafted mice both topical and systemic JAK inhibition reversed the alopecia, and there have been case reports in humans. We were caring for a 40 year old woman with psoriatic arthritis and severe alopecia universalis that had been present for several years and resistant to all manipulations we trialed. Emboldened by the information on JAK inhibition we commenced tofacitinib 5mg bd and within months she had regained profound hair regrowth. Several similar reports exist, and the challenge appears to be maintaining the hair growth and control of the underlying disease. In our case both seemed to have been achieved but it is very early days.

In finishing, biologically derived cytokine and cytokine receptor antibodies and antagonists will continue to have a major role in therapeutics, but we will experience a resurgence in synthetic small molecule enzyme inhibitors. Much has been made of the production cost of bDMARDs, and with jakinibs having simpler production methodology and the avoidance of cold storage and cold-chain transport we should see a significant

Fig JAK and disease- K Yamaoka. *Curr Opin Chem Biol* 2016;32:29-33

lessening of price and hence access to these agents. The sheer number of jakinibs in trial and production is daunting, and the challenge to us as clinicians will be determining optimal choice for a specific indication or disease pattern and at the same time reducing adverse events.

*Author:

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VoA
welcomes YOUR
articles, letters, views and news

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Incoming APLAR President - Kazuhiko Yamamoto

These meetings have been very successful. In contrast, it has not been easy to create sustainable scientific interactions among rheumatologists from APLAR members in various countries and fields of rheumatology.

Thus, the APLAR executive committee has started to improve our system. For example, we established Special Interest Groups (SIGs). The initial SIGs included the following fields: SLE, RA, OA, vasculitis, SpA, and genetics. Importantly, we will not limit the fields. If the initial SIGs work well, we would like to expand the fields. We also started the nomination of the Center of Excellence in 2016. The initial five centers were excellent, and several other centers will soon be nominated every year. These centers will serve as cores to facilitate the science of rheumatology and increase the skills of rheumatologist, and as communication hubs of rheumatology in the APLAR regions.

Together with these new activities, the Community-oriented Program for Control of Rheumatic Diseases (COPCORD), which was launched by the WHO-International League of Associations for Rheumatology (ILAR) is one of the important programs in our region. Continuous educational activities for young rheumatologists, or even general physicians, are also important in several countries.

The executive committee of APLAR, together with several committees, will do our best to manage and encourage the activities of APLAR.



From the Editor's Desk



E-in-C

PAIN

VOICE OF APLAR wishes All of YOU a very HAPPY NEW YEAR !

VOA was launched at a glittering ceremony witnessed

by around 2,600 delegates at APLAR Congress Shanghai, September 26, 2016. Its scientific programme predictably had a surfeit of lectures and papers on Biologicals ... as indeed at any Rheumatology conference anywhere be it mammoth or tiny anywhere. In the process are we forgetting the basic, crying needs of our patients? After all nearly every patient comes with a presenting cardinal

Relief : How good are we? Triumphs & Failures

NSAIDs: Pain killers or 'Plain killers'?

- *Relieve pain*, reduce swelling
- GI toxicity
- Cardiovascular events
- Analgesic nephropathy
- *Rise and fall of NSAIDs leading to*
- Overuse of glucocorticoids
- Opioids resurgence : in desperation ??
- Emergence of PAIN CLINICS
- Failure of Rheumatologists to *relieve pain*?

Aspirin is an analgesic. At ten times the dose (3 – 6 gms per day), it is an anti-inflammatory. No wonder it became a household remedy that every 300 mg tablet could induce 0.3 ml of fecal blood didn't seem to matter, gastritis did.

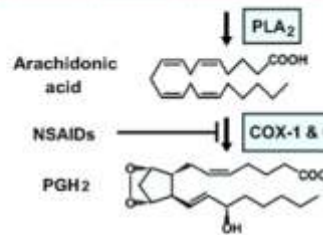
Post-war, better substitutes were invented, notably phenylbutazone, oxyphenbutazone, indomethacin, and later ibuprofen, naproxen

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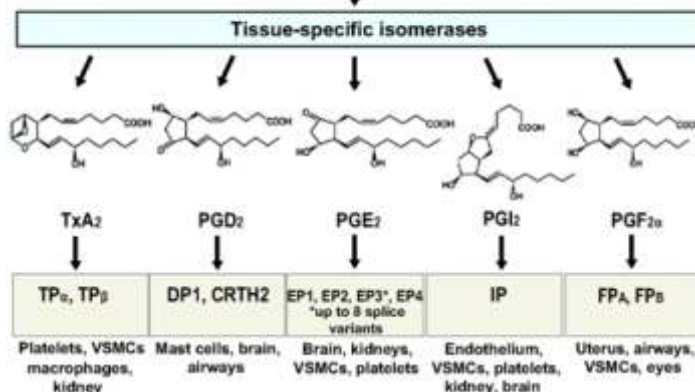
symptom PAIN, isn't it ? Over centuries bizarre remedies were attempted from witchcraft to blood letting, branding, acupuncture, music therapy, sleep therapy, outright quackery, what have you. Surely the landmark proven pain reliever was the extract of willow bark. In 1920s Felix Von Hoffman a 28 year old chemist in Germany could not bear the sight of his father suffering from rheumatoid arthritis and intolerable pain drinking a litre or two of extracts of willow bark. It led him to identify the chemical, its structure and synthesis : molecular weight a mere 270, its name ? You got it right, ASPIRIN. He first administered it to the fish in his pond and then gave it to his father. What followed was a success story : Bayer's bestseller ASPIRIN (inset).

At 300 – 600 mg (one to two tablets)

Membrane phospholipids



Sir John Vane Nobel Laureate



in 1969 a young man from India dared to present his first international paper at a Pharmacology conference in Basle. His Chairman was Professor John Vane (London) who was working on mechanism of action of Aspirin and other NSAIDs. The young man later was involved in researching Ibuprofen clinically. The two of them at times exchanged notes and met again in 1980s in Geneva. By then John Vane was a Nobel Laureate and was Knighted by the Queen. By then the young man had become a Rheumatologist. His name, Prakash Pispati.

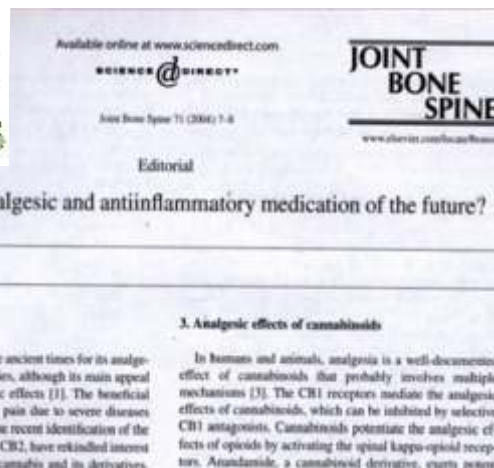
What made John Vane a 'Sir' and a Nobel Laureate? His elucidation of mechanism of action of Aspirin, via pathway of prostaglandin, prostacycline which lead to invention of better NSAIDs including COX-1 and COX-2 inhibitors eg. ibuprofen, ketoprofen, naproxen, etoricoxib, celecoxib. Aspirin receded as an anti-rheumatic but became a must to minimize and prevent pathogenic platelet aggregation. (inset).

In the 70s and 80s NSAIDs seemed the saving grace of Rheumatology practice at least to relieve pain and to reduce joint swelling. Their frequent over usage led to accumulated ARAMIS data on GI and cardiovascular adverse effects. Simultaneously was the uprise of methotrexate and other DMARD usage for RA. A few cynics termed NSAIDs not pain killers, but 'plain killers'.

Such harsh critics alas had *no options to offer* to relieve pain, the presenting symptom of rheumatic patients. Their tirade against NSAIDs caused their decline. This may have led to the epiphenomenon of further unwarranted overuse, misuse and abuse of glucocorticoids with worse side-effects; besides growing popularity of acupuncture, acupressure, alternative medicines of doubtful efficacy advertised to tall claims eg. magnetotherapy, electrotherapy, megavitaminotherapy, ozone therapy, music therapy, sleep therapy bordering on outright quackery. Alongside massage clinics and fancy spas understandably more pleasurable than cold clinical colourless Rheumatology clinics dishing out boring 'lifelong treatment' perceived by many patients as "side-effect drugs".



Boil this Himalayan herb with milk, honey and rose petals, drink it ten times daily for a year. If this doesn't cure simply take a couple of **ASPIRINS**



Discerning Rheumatologists must have noticed this hiatus so took recourse to revive even addictive opioid derivatives such as morphine, codeine, dehydrocodeine ... and by JO, even the alarming psychedelic cannabis indica (LSD25) popular in drug dens (inset). To justify, some Rheumatologists now seem to underplay their dangerous addictive abuse giving a label of 'analgesics' respectability by prescriptions to legitimize these. 'I hope that drug mafia is not subtly taking over Medicine via backdoor' quipped a brash wag.

If Aspirin was a distinct triumph for a long time in Rheumatology clinics, isn't pain management in recent years our shortcoming, our failure? Are our patients frequenting expensive 'pain clinics' and falling prey to heavily advertised pseudo-clinics to capture gullible patients? Are we unwittingly, unduly obsessed with the routine of DMARDs and the glamour of Biologicals? Are we overwhelmed by the not-yet all promising 'hi-fi' elitist therapeutics to combat complications in a mere 9% to 10% of all rheumatic patients?

Mind you, am all for this search and research for the new science of 'RheumaNology'. Am a confessed, fearless advocate for timely intervention, induction therapy with Biologicals to prevent deformities and systemic complications as feasible. But let us not forget altogether our hugely unmet need for superior, simple analgesics. Stated simply, this is a priority plea for far better ASPIRINS, and refined NSAIDs. *Who is at it?*

Dr Prakash Pispati, M.D., F.R.S.M.(Lon), M.Sc.(Med.)

Editor-in-Chief, **VOA**
Past President, APLAR, IRA. Master, Hon. Member
Director of Rheumatology, Jaslok, Saifee Hospitals,
Mumbai, India.



Recommended reading:

1. Rainsford KD. Aspirin and salicylates. London: Butterworth & Company; 1984
2. Brune K. The early history of non-opioid Analgesics. *Acute Pain* 1997; 1:33-40
3. Brune K, Hinz B. The Discovery and Development of Anti-inflammatory Drugs. *Arthritis & Rheumatism* 2004; Vol.50:8, pp 2391-2399.
4. Vane JR. Introduction: Mechanism of action of NSAIDs. *British Journal of Rheumatology* 1996; 35 (Suppl.1):1-3
5. Fries James F, et al. The Rise and Decline of Nonsteroidal Antiinflammatory Drug-Associated Gastropathy in Rheumatoid Arthritis. *Arthritis & Rheumatism* 2004; Vol.50:8, pp 2433 - 2440.
6. Bret S. Stetka, MD. Opioids for Chronic Pain: Yes or No? *Medscape Rheumatology*. In *Medscape Medical News from the American College of Rheumatology (ACR) 2015 Annual Meeting*.

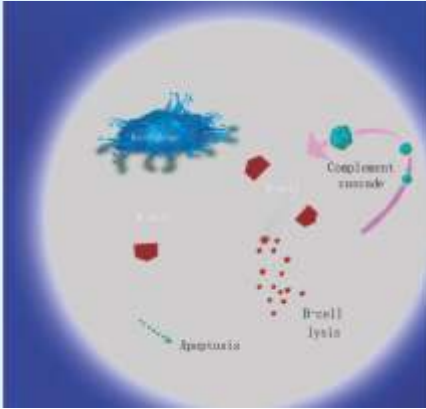
The company being focused on the treatment of non-Hodgkin's lymphoma was not interested, but persistence won the day! On the fourth attempt the company was persuaded to give him a sufficient amount of the drug to treat five rheumatoid patients. Remarkably he showed that four of them achieved an ACR 70 and one an ACR 50 after six months.

RITUXIMAB : MECHANISM OF ACTION (3)

- Rituximab initiates complement-mediated B-cell lysis
- Rituximab initiates cell-mediated cytotoxicity via macrophages and natural killer cells
- Rituximab induces apoptosis

CD20
Rituximab

(Clynes et al, 2000; Reff et al, 1994)



remove B-cells. The initial combination of 1g of Rituximab x 2, two weeks apart with Cyclophosphamide of 500-750mg IV and Methylprednisolone up to 250mg IV to accompany the Rituximab was used by me until 2004 when, for these hard-to-treat patients, I felt able to cut the Cyclophosphamide to a single dose. My practice has always been in these patients who have been treated with major immunosuppression for many years to stop the concomitant immunosuppression until such time as the B-cells return (median time is six months) or even until the clinical features return which may be several years. I have also tried hard to reduce the steroids that are being used orally after B-cell depletion as my principal concern is about infection.

RESULTS

Clinical outcome at 6 months: BILAG

Full Remission	n= 19 (42%)
Partial remission	n=21 (47%)
No improvement	n=5 (11%)

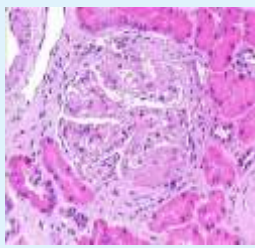
These data were shared with the company who, less grudgingly, made additional drug available. Jo presented the work at the American College of Rheumatology meeting in Philadelphia in 2000 and it caused quite a sensation. Jo took the view (although I did not share it) that Rituximab might even cure rheumatoid arthritis patients and his use of the word "cure" led to something approaching pandemonium in our secretarial office in the Centre for Rheumatology at University College London. By the time Jo returned home from the meeting, literally thousands of people from around the world had attempted to contact his secretary with requests, or even demands, that they be given this new cure for their disease. We were in fact so overwhelmed that Jo in the end hired his sister for six months to help sort out the backlog of requests!

AFTER B-CELL DEPLETION

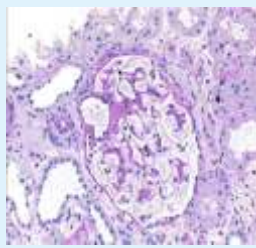
Antibody levels that fall	Antibody levels that do NOT fall
Anti-DNA	Anti-Ro
Anti-nucleosome	Anti-La
Anti-C1q	Anti-Sm
Anti-cardiolipin	Anti-RNP
	Anti-measles
	Anti-tetanus toxoid

I took the view that whereas the role of B-cells in the development of rheumatoid arthritis was more contentious, it was widely agreed to be integral to the development of systemic lupus erythematosus. Following the same "flight path" that Jo had established, I approached Use of Medicines Committee at the hospital and made a plea that patients with lupus who had failed conventional drugs and were still active might be given B-cell depletion.

RENAL BIOPSY APPEARANCE



Before



After

Rituximab

With thanks to Professor Ronald Van Vollenhoven

The committee approved this request and in 2000 I too began to treat patients (with SLE) with B-cell depletion. Three drugs used initially by Jo for rheumatoid and by myself for lupus ie steroids, Cyclophosphamide and Rituximab were the then currently available drug to

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Now, sixteen years later, I have treated over 140 patients with lupus at our hospital and, following the initial suggestion of Professor Liz Lightstone at the Hammersmith Hospital we have been offering Rituximab (also with the approval of the Use of Medicines committee) to newly diagnosed patients with the stated aim of trying to avoid the use of any oral steroids. Given that oral steroids had been used to treat lupus nephritis since 1950 this is really quite a major development and is encouraged by a study published by Professor Lightstone showing that after two years of treating fifty patients with lupus nephritis (at or close to the time of diagnosis) only two have required regular oral steroids.

There is however a strange paradox here in the UK. Rituximab, frustratingly, in spite of over twenty reports from around the world describing its successful use in virtually every type of lupus, did not meet its primary endpoints in two clinical trials (although close examination of the data indicates that it clearly was having some clinical and serological benefit). It is therefore not approved by the FDA, by the European Medicines Agency or by NICE and yet virtually everybody who has ever used it agrees that while it is not a cure for lupus it can be very helpful for hard-to-treat SLE.

In contrast Benlysta, the anti-BAFF antibody did meet its endpoints in two clinical trials (admittedly only

just!) and is therefore approved by the FDA, the European Medicines Agency and, very recently, by NICE. Yet I have treated over 140 lupus patients with Rituximab and just one with Benlysta! How have I “got away with it”? Several years after starting the use of Rituximab I was approached by a senior official within the hospital who “wagged a finger” at me and asked me to confirm if it was true that I was using Rituximab to treat SLE. I said that I was indeed doing that. He asked how many patients I was treating per annum. I said “oh about ten a year”. “Ten a year!” he repeated and then smiled “oh that's OK – that haematologists and oncologists are treating about ten a week. Carry on!”. In other words my use of Rituximab has in effect “gone under the radar” and the total cost of Rituximab for lupus is clearly a very small fraction of the cost of its use in the treatment of haematological malignancies and other haematological indications. I plan to carry on using it though I anticipate that in the near future we will see the introduction of Rituximab biosimilar, and I hope, a fully-humanised anti CD20 which should reduce the frequency with which we see allergic responses.

by David A Isenberg MD FRCP FAMS,
ARC Diamond Jubilee Professor of Rheumatology
at University College London



Prof. David Isenberg with E-in-C, VOA at National Seminar hosted at NIZAM Institute, Hyderabad, India (Aug.2016). His lecture chaired by Prof. G. Narsimulu

RISK OF SERIOUS INFECTIONS IN LUPUS BIOLOGIC TRIALS n (%)

	n =	Placebo	Low Dose	High Dose
Atacicept (Flare Prevention)	455	7 (4.5)	6 (3.8)	10 (6.9)
Tabalumab Illuminate 1	1164	17 (4.4)	19 (4.9)	20 (5.2)
Tabalumab Illuminate 2	1124	25 (6.6)	22 (5.9)	16 (4.3)
Belimumab BLISS-52	865	17 (6)	22 (8)	13 (4)
Belimumab BLISS-76	819	16 (5.8)	19 (7.0)	20 (7.3)
Sifalimumab P2	431	8 (7.4)	9 (8.3)	8 (7.5)



Snippet ... tongue in cheek !

A 26 year old bright, beautiful MBA was across my table with fever, rash, alopecia, mouth ulcers, and joint pain.

She: “Doctor what is wrong with me?”

Me: “Systemic Lupus Erythematosus”

She was speechless for a few moments. It took me next ten minutes to explain what that meant. To clarify, I wrote in my illegible handwriting those terrifying words which precisely consume 26 letters of the alphabet, hard to pronounce, prone to spelling mistakes. To be practical why not simply standardize ‘Lupus’? (5 letters!) At least it sounds patient friendly even if the disease is not! Academic purists, pundits and ‘lupologists’ may specify subsets such as neurological lupus, systemic lupus, nephritis lupus, or ‘lupus lupus’ proclaimed by a young ‘Lupologist’!!

by Prakash Pispati, E-in-C, VOA

The Rheumatologist Volume 6 No 10 Oct 2012 p10
Confusion or Clarity ?

Nomenclature, Semantics, Jargon, lingo, eponyms, etymology, and terminology in rheumatology

by Prakash Pispati



Rheumatoid arthritis therapeutics, where next? ... Beyond Biologicals ...

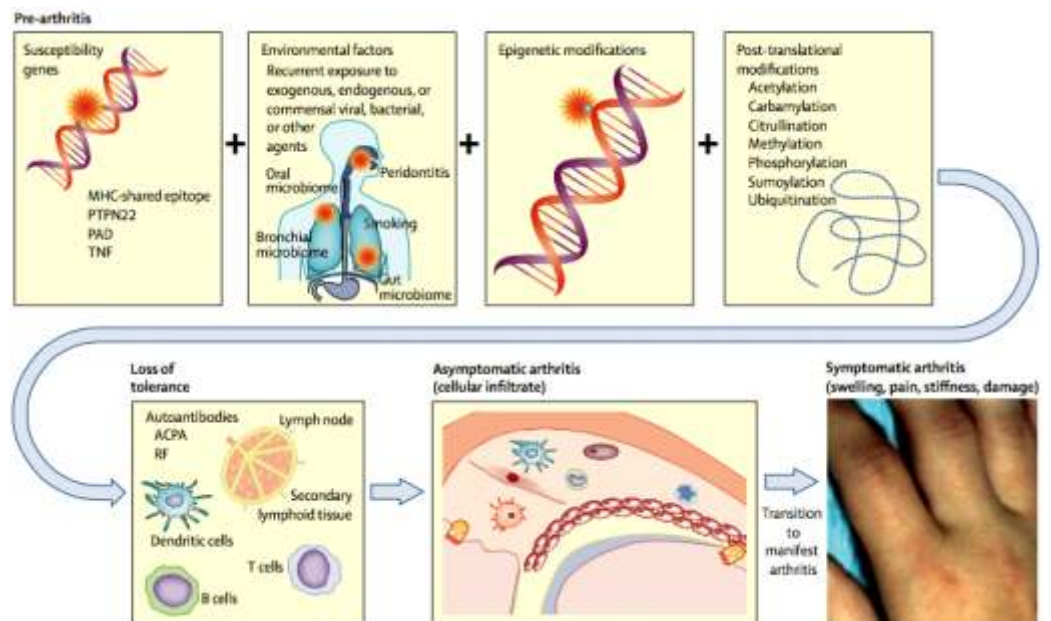
Final plenary lecture at APLAR Congress, Shanghai, September 2016



Prof Iain B McInnes, UK

During a recent plenary lecture at the APLAR meeting in Shanghai, it was a pleasure to consider the next steps in rheumatoid arthritis therapeutics. Looking first to the past I consider it vital to learn of those factors that have most driven our progress. Thus we have learned much from the advent of biologic therapies. In particular, we have learned that there are vulnerable nodes within the *inflammatory cascade* such as *TNF*, *IL-6 receptor*, *CD28* and indeed *CD20* bearing B-cells that when blocked lead to a 'collapse' of the *inflammatory lesion* to the benefit of patients. We have learned that therapeutics strategies are at least as important, not least when one treats to a *given target*. Starting with TICORA we now have a plethora of evidence to support treatment within a logical escalation driven by some measure of disease activity. We have learned that over time the efficacy of drugs across a range of modes of action reduces and the reasons for this are quite unclear. This may reflect accumulating tissue damage, Perhaps *epigenetic changes* are implicated? It is possible that this is a function of *immunological adaptation*, itself a necessary part of evolutionary imperative on the immune system to adapt to chronic infectious challenge. Finally we have learned that the *pre-arthritis* phase is associated with *immunological abnormality* predating clinically evident illness and that may offer therapeutic opportunity in future.

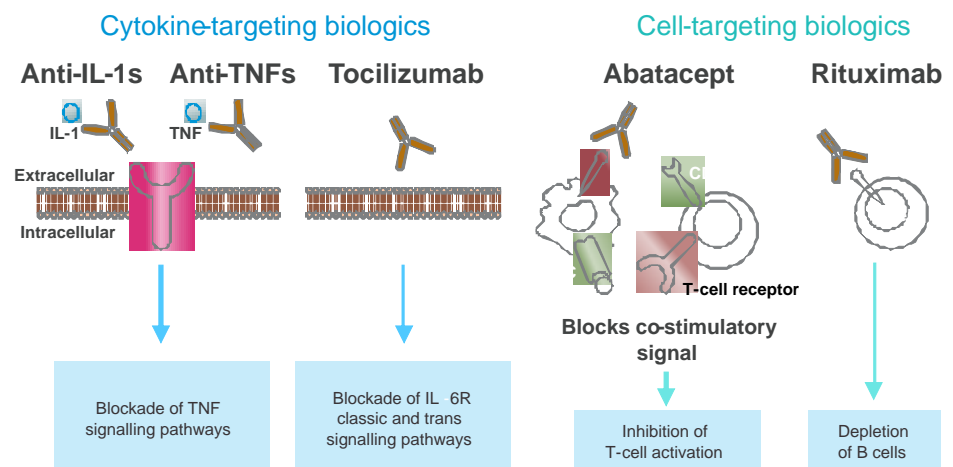
Towards pathogenesis lead interventions?



Smolen J, Aletaha D & McInnes IB *Lancet* (2016) in press

Lessons about key targets?

Many vulnerable nodes in inflammatory cascade – cell receptors and their requisite signalling pathways?



Choy EH, et al. *Nat Rev Rheumatol* 2013; 9:154–163; McInnes IB & Schett G. *N Engl J Med* 2011; 365:2205–2219. Emery P & Dörner T. *Ann Rheum Dis* 2011; 70:2063–2070; Edwards JC, et al. *Curr Dir Autoimmun* 2005; 8:175–192; Ko HJ, et al. *J Autoimmun* 2010; 34:111–120; Woodrick RS & Ruderman EM. *Nat Rev Rheumatol* 2011; 7:639–652.

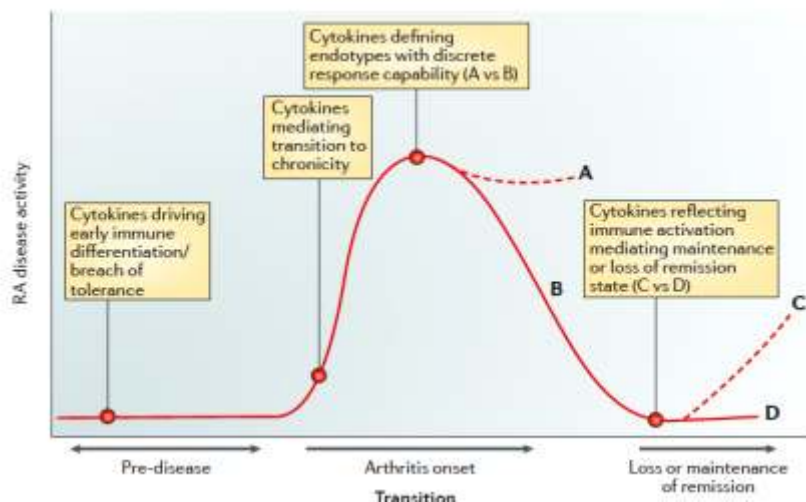
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Current therapeutics are by and large derived from the conventional translational model whereby plausible biological targets are tested in pre-clinical in vitro and amino systems and thereafter in progressive phase 1 through 4 development protocols. A variety of approaches are currently being taken in pursuit of new agents. In particular, there are therapeutics aimed at targeting damage associated and other innate pattern receptors. New entities are being created that targets cytokines both biosimilar and particularly new approaches to targeting the *IL-6* and *GM-CSF* cytokine pathways. A number of small molecule inhibitors are in current development including those targeting the members of the *JAK* family, *BTK* and *PI3kinase* families. There is also increasing interest in the pathways that may allow us to alter epigenetic changes and thus address the fundamentals of chronicity, which we believe are a major problem for our patients. There are also intriguing ideas thinking outside the box. For example, there are preliminary data suggesting that *gonadotropin releasing hormone* may offer a therapeutic opportunity. Similarly *vagal nerve stimulation* has been proposed as an alternate route to generating anti-inflammatory pathways.

To maintain therapeutic progress it will be necessary to take a more systematic approach to the treatment and accordingly the identification of new possibilities in rheumatoid arthritis. As such there is renewed interest in the very high quality data science capabilities available to physicians as we go forward. This taken together with the remarkable advances in *polyomic medicine* should open up new opportunities. Whereas such efforts to generate a *biomarker driven approach* have not been so far successful, the prediction is that the appropriate

RA: over time does the immune system 'adapts' to the new scenario – therapeutic utility?



McInnes IB et al Nature Rev Rheum 2016 Smolen & Aletaha Ann Rheum Dis 2013;72:3–6. doi:10.1136/annrheumdis-2012-202361.

application of these methodologies to large a cohorts with sufficient refinement of *clinical phenotyping*, will bring about developments in due course. These taken together with sophisticated systems medicine approaches will start to unlock the doors to a new therapeutic horizon for our patients with rheumatoid arthritis.

Pivotal to all of the above will be continued recognition of the unmet needs of people with RA. Careful attention to their challenges, and to the health economic limitations surrounding their care will be even more critical. That said with application of the new science of large data the future should and could be rather bright.

Author

Prof. Iain B McInnes PhD, FRCP
Muirhead Professor of Medicine,
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Systemic Sclerosis (SSc) - A Worthy Therapeutic Challenge

(Summary of Lecture Delivered At Inaugural Annual Scientific Sessions of Sri Lanka College of Specialists In Rheumatology & rehabilitation) ... by Chula Rajapakse

Inflammatory oedema in the deeper layers of the skin and subcutaneous tissue gives rise to the diffuse puffiness in hands seen in early active scleroderma. This process of inflammatory oedema being replaced by fibrous tissue probably forms the basic pathogenesis of internal organ involvement too in Scleroderma. Targeted treatment of autoimmune driven inflammatory process & a vasculopathic process that eventually leads to fibrosis has led to a significantly improved in outcome of Scleroderma over the last decade or two. The next tier of management is directed at the end organ consequences of scleroderma.

Methotrexate (for skin and joints),
Mycophenolate Mofetil/Oral or IV

Cyclophosphamide (skin and lung), cautious use of low dose oral Prednisone (for skin-acute oedematous phase, joints and muscles) involvement and higher doses for internal organ involvement, and Autologous Haemopoietic Stem Cell Transplantation (benefitting skin and lung but not the Kidney), form the modalities that have successfully targeted the auto immune inflammatory process in SSc.

Author:

Dr. Chula Rajapakse, MNZM, FRCP/FRACP...
Sr. Consultant Rheumatologist,
Hutt Hospital, Wellington, New Zealand.



Turning point: Two years in Harvard - Reflections of a fellow - By Dr. Yue Yang

“Every profession has an apprenticeship, and the apprenticeship in medicine is called residency”. An unexpected offer letter from the Ragon Institute, Massachusetts General Hospital (MGH), Boston, United States changed all my plans and became a turning point of my life. Our laboratory was located in Charlestown Navy Yard, a historical landmark established over 200 years ago with the beautiful view of Boston Skyline and the quiet Charles river.

I worked with Professor Xu Yu, whose laboratory focused on cellular and molecular mechanisms involved in immune control of human immunodeficiency virus (HIV)-1. A major area of our investigations was the role of dendritic cells and their immunoregulatory functions during HIV-1 infection. These studies focused on the leukocyte immunoglobulin-like receptors (LILRs), a group of immunomodulatory receptors that interact with HLA-I molecules and in this way influence HIV-1 disease outcomes.

Although rheumatology is a relatively new field in China, it is one of the most rapidly developing specialties. In the past 10 years, more than 160 million RMB (equivalent to ~US\$26 million) from government and private funding was granted to rheumatology research in China. Young rheumatologists are now receiving increased support from overseas as well, including from Asia Pacific League of Associations for Rheumatology (APLAR) and International League Against Rheumatism (ILAR) grants. With these enormous supports and resources, basic research investigating immunological mechanisms in the pathogenesis of autoimmune



diseases is flourishing.

Since coming back to China, under the supervision of Professor Zhan-guo Li, my collaborators and I are investigating the role of LILRs in the pathogenesis of several rheumatic diseases including rheumatoid arthritis (RA), Sjögren syndrome (SS) and systemic lupus erythematosus (SLE). These are early days yet, but our findings are promising and have found place in renowned journals.

In the words of Marcel Proust, "The voyage of discovery is not in seeking new landscapes but in having new eyes". I believe that the postdoc experience in Harvard not only helped me prepare for a faculty position in one of the top teaching hospitals in China but also changed the way my mind integrates the scientific findings of basic research into clinical practice.

Author

Dr. Yue Yang, Attending Physician, Department of Rheumatology, Peking University People's Hospital, Beijing, China



The 5th Scientific Meeting of the Asian Federation of Osteoporosis Societies 2017

Theme: *Best Practices, Future Directions.*

Date : **6th – 8th October 2017** | Venue: **Hilton Kuala Lumpur, Malaysia**

IMPORTANT DATE

Registration & Abstract submission opening in
1st January 2017.

Abstract will be published in AFOS
Journal Osteoporosis & Sacropenia.

www.afos2017malaysia.com | Email: secretariat@afos2017malaysia.com

India's premier Immunology - Rheumatology teaching Institute, Lucknow - By Amita Aggarwal* and R.N. Mishra**

Sanjay Gandhi Post Graduate Institute of Medical Sciences (SGPGI) was established in 1987 with a generous support from Japan via IICA grant. SGPGI is a well equipped tertiary care hospital with a sprawling residential complex in 550 acre land.

The Department of Clinical Immunology was the first of its kind in India and was based on ethos of having a crosstalk between clinicians and basic scientists. The training program (DM, Clinical Immunology) trains the internist in Rheumatology, basic Immunology and Lab immunology thus providing a comprehensive knowledge of the subject. Interaction with fellow PhD students further provided a boost to understanding of basic biology. The course is recognised by Medical Council of India.

The first DM student passed out in 1991 and the course was soon recognised by peers and medical postgraduates in the country and abroad. Initially annual intake was 2 but in 2010 was increased to 4. Nearly 50 postgraduate students compete for the 4 seats every year making it a highly competitive and much sought after course. So far 47 DM students have



graduated and of these nearly half are in practice. Some of them have established Departments of Rheumatology or Clinical Immunology in leading medical institutions of the country. Both PhD and DM students working in USA and UK have achieved accolade for their work.

In addition to regular courses the department also accepts short term trainees (1-3 months) from India and abroad. We have had trainees from Arthritis Research Council, UK, University of Ohio, USA etc besides a host of faculty members from different medical schools in India. The department also conducts regular autoantibody and US/MRI workshop to enhance skills of persons practising Rheumatology.

We have the honour to host IRACON 2017, November 30 to 3 December 2017 at Lucknow, India.

(*Dr Amita Aggarwal, President, Indian Rheumatology Association (IRA). Professor Clinical Immunology

**Dr R.N. Mishra, Past President, Indian Rheumatology Association (IRA). Dean, SGPGI Lucknow, India)

Inaugurated: College of Specialists in Rheumatology and Rehabilitation - Sri Lanka.

It all started in April 1994 when Sri Lankan Association of Rheumatology and Medical Rehabilitation was formed at the initiative of Dr. Prakash Pispati, then an active Executive Committee member of APLAR. The Association flourished, a few budding Rheumatologists received APLAR fellowships, several academic meetings organized. Now, the Association proudly has transformed itself into College of Specialists in Rheumatology and Rehabilitation with a grand inaugural ceremony on 22nd October, 2016 (see pics) and day long academic sessions on 23rd October: presentations by Sri Lankan rheumatologists senior and juniors, free papers by enthused trainees. The international



faculty comprised Dr. Adrian Pace, Consultant Rheumatologist, National Health Service, U.K., Dr. Chula Rajapakse, Consultant Physician, Rheumatology & Internal Medicine, New Zealand and Dr. Prakash Pispati from India the Chief Guest. Nearly 200 delegates from all over Sri Lanka participated actively invigorating the rheumatology scenario in enchanting Sri Lanka, the Pearl in blue waters of Indian ocean.

Sent by

Dr. Nihal Gunatillake, President
Dr. Duminda Abeysinghe, Secretary
Dr. Gunendrika Kasthuriratne, Treasurer,
Event/Program Co-ordinator.

In the pics:

Top: PKP with President Dr. Gunatillake.
Below: Dr. Rajapakse, NZ, President Dr. Gunatillake, PKP, Dr. Pace, UK



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Key dates

Abstract submission deadline

Monday, April 3, 2017

Early fee deadline

Wednesday, June 28, 2017

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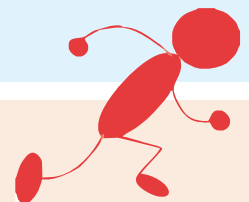
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