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Rheumatology Therapeutic Clinical Trials Centre

Timaru

Therapeutic Advances in Rheumatology - Main Session (Workshop options scheduled)

Sunday, 18 August 2013 Start 8:30am Duration: 25mins Plenary

Therapeutic Advances in Rheumatology

GP CME Meeting, Dunedin, 18.08.2013

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Disclosures

- Advisory Boards and speaker at meetings: Abbott/Abbvie, Roche, Pfizer/Wyeth, MSD, Novartis, Quintiles CRO and Janssen.

- Investigator in clinical trials for: Boehringer Ingelheim, MSD, UCB, Medi-Immune, Centocor, Roche, Abbott, Pfizer, Celgene, Lilly, Sanofi and Galapagos.

Take Home Message 1:

Ankylosing Spondylitis Action Pathway

Patients with persistent low back over three months and onset under 45 years plus:

1. Morning stiffness >30 minutes
2. Improvement with exercise but not rest
3. Awakening in the 2nd half of the night with pain
4. Alternating buttock pain

- 0-1 symptoms – consider mechanical LBP
- 3-4 symptoms – refer to rheumatology
- 2 symptoms – check other factors:
  - Family history of spondyloarthropathy
  - Extra-articular features such as uveitis, psoriasis, enthesitis, inflammatory bowel disease and peripheral joint involvement
  - Respond to NSAIDs within 48 hours

- If only two symptoms and no factors – mechanical low back pain
- One factor – test for HLA-B27. If positive refer to rheumatology. If negative consider mechanical LBP
- 2-3 factors – refer to rheumatology

Take Home Message 2:

Rapid referral to a Rheumatologist of all inflammatory arthritis or when RA is suspected is crucial to the prognosis of the patient.

This may be supported by the presence of any of the following:

- $\geq$ 3 swollen joints
- MTP/MCP involvement
- morning stiffness of $\geq$ 30 minutes.

P Emery et al. ARD 2002;61:290-7

NB: No blood tests in the alarm signals for early referral for potential RA

- Don't delay referral because of test results:

	% of negative tests
X-rays of hands and feet	80
CRP	50
RF and anti-CCP antibodies	40

Why early referral?

- Window of opportunity of up to six months to reset immunology of RA so Rheumatologists need to see patients within 12 weeks of onset of arthritis

- If achieved clinical remission within six months of onset of disease, can stop treatment in up to 80% of undifferentiated inflammatory arthritis

The Treat-to-Target initiative

- An international initiative to define treatment targets in RA (similar to glycated haemoglobin targets in diabetes or BP in hypertension)
- Target is clinical remission

Definition of clinical remission ACR/EULAR criteria

Annals of Rheumatic Diseases 2011; 70:404-13

- Boolean definition:
  - Tender joint count ≤1
  - Swollen joint count ≤1
  - CRP ≤1mg/dl
  - Patient global assessment ≤1 on a 10 point scale

Other definitions of clinical remission

1. A DAS 28 score of
   <3.2 = low disease activity.
   <2.6 = remission

2. SDAI (Simple Disease Activity Index). Remission is a score of ≤3.3
   - 28 tender joint count
   - 28 swollen joint count
   - Patient global assessment
   - Physician global assessment (no inflammatory indices done)

To achieve remission:

(i) Initiation of treatment early in disease process

(ii) Vigilant monitoring with prompt adjustment of therapy for flares ("tight control") and for medication toxicity

(iii) Combination DMARDs

(iv) Biologics

(v) SMEs (Small Molecule Immunomodulators)

Historic milestones in therapy of RA

- Pre-historic — Opium for pain/rheumatism
- 1763 — Willow bark for rheumatism
- 1876 — Salicylic acid
- 1897 — Synthetic aspirin
- 1929 — Gold salts
- 1941 — Recognition of RA as a distinct entity by American Rheumatism Association
- 1949 — First Glucocorticoid used in arthritis
- 1955 — Prednisone for RA (Nobel Prize for Phillip Hench)

- 1960s NSAIDs, Chloroquine/hydroxychloroquine
- 1980s DMARDs: Sulphasalazine, oral gold Azathioprine, cyclosporine, penicillamine, methotrexate
- 1998 Leflunomide, etanercept
- 1999 COX-2 inhibitors, infliximab
- 2001 Anakinra
- 2002 Adalimumab
- 2005 Abatacept
- 2006 Rituximab
- 2009 Tocilizumab, Certolizumab, Golimumab
- 2012 Tofacitinib

Tumour Necrosis Factor Alpha

- Major mediator of immune responses and inflammatory reactions
- Functions as a soluble messenger protein to act on target cells
- Involved in the pathogenesis of many human diseases, including autoimmune diseases, such as RA

Key Actions Attributed to TNF-alpha

Macrophages	↑pro-inflammatory cytokines ↑chemokines →	Increased inflammation
Endothelium	↑adhesion molecules →	Increased cell infiltration
	↑vascular endothelial growth factor (VEGF) →	Increased angiogenesis
Hepatocytes	↑acute phase response →	Increased CRP in serum
Synoviocytes	↑metalloproteinase synthesis →	Articular cartilage degradation

TNF-alpha Inhibitors

5 Commercially Available:

- Infliximab (Remicade) - IV
- Etanercept (Enbrel) - SC
- Adalimumab (Humira) - SC
- Certolizumab Pegol (Cimzia) - SC
- Golimumab, humanized form of Infliximab (Simponi) - SC and IV

PHARMAC'S 7 Criteria for TNF Inhibitors (Adalimumab or Etanercept)

1. Severe and active erosive RA for $\geq$ 6 months.
2. Adjunct to Methotrexate or monotherapy if intolerant to Methotrexate.
3. No response to at least three months of 20mg weekly of Methotrexate or maximum tolerated dose.
4. No response to at least three months of Methotrexate in combination with Sulphasalazine and Hydrochloroquine (at maximum tolerated doses).

5. No response to at least three months of Methotrexate with maximum tolerated dose of Cyclosporin or IM Gold or Leflunomide.
6. Either persistent symptoms of poorly controlled and active disease in at least 20 active, swollen joints or at least four active joints from the following: wrist, elbow, knee, ankle and either shoulder or hip.
7. Either CRP $\geq$ 15 mg/l measured no more than 1/12 prior to application or CRP not measured as patient is receiving Prednisone >5 mg/day and has done so for >three months.

Switching to a different TNF inhibitor

1. If patient has an initial Special Authority approval for Adalimumab (or Etanercept) for RA.
2. Patient has experienced intolerable adverse effects or patient has received insufficient benefit to meet renewal criteria.

Renewal criteria

1. Applicant is a Rheumatologist or a practitioner with evidence that a Rheumatologist has confirmed continuing treatment with Adalimumab
2. Adjunct to Methotrexate or monotherapy where use of Methotrexate is limited by toxicity or intolerance
3. Following 4 months of initial treatment, 50% decrease in active joint count from baseline and clinically significant response in the opinion of the physician OR subsequent reapplications patient demonstrates at least 30% improvement in active joint count from baseline and clinically significant response in the opinion of physician
4. No greater than 40 mg every 14 days OR can't take MTX and requires Adalimumab > 40mg every 14 days

Rituximab (MabThera)

1. Results in depletion of CD20 surface antigen positive B cells.
2. B cells are believed to play a central role in the pathogenesis of RA.
3. B cells implicated in a number of roles in the autoimmune/inflammatory process including:
   - Cytokine production
   - Autoantibody production
   - Antigen presentation leading to T cell activation

Administration

- IV Infusion of 1000mg two weeks apart (lasting 4-6 hours).
- Prophylactic IV Methylprednisolone 125mg stat, Paracetamol and Antihistamine half an hour prior to Rituximab infusion.
- Repeated every 6 months but usually much longer intervals with more cycles.

Initiation for RA – prior TNF inhibitor use

1. Patient had an initial Special Authority for ADM and/or ETC for RA and;

   either patient has intolerable adverse effects

   or following a 4-month trial, patient did not meet renewal criteria

2. Rituximab to be used as an adjunct to Methotrexate or Leflunomide

   or MTX and LEF are contraindicated, requiring Rituximab monotherapy

3. Maximum of two 1000mg infusions of Rituximab given two weeks apart

Initiation for RA – TNF inhibitors contraindicated

1. Treatment with a TNF inhibitor is contraindicated and the 7 criteria required for a TNF inhibitor met

8. Rituximab to be used as an adjunct to MTX or LEF or MTX or LEF contraindicated requiring Rituximab monotherapy

9. Maximum of two 1000mg infusions of RIX given two weeks apart.

Continuation for RA re-treatment in partial responders to RIX

1. At 4 months following initial course of RIX, patient had 30-50% decrease in active joint count and a significant response in the opinion of the physician.

   OR at 4 months following second course of RIX patient had at least 50% decrease in active joint count and a clinically significant response in the opinion of the physician

   OR at 4 months following the third and subsequent courses of RIX the patient demonstrates at least 30% improvement in active joint count and a clinically significant response to treatment

2. RIX re-treatment not to be given within 6 months of previous course

3. RIX either to be used as an adjunct to Methotrexate or Leflunomide

   or MTX and LEF are contraindicated, requiring Rituximab monotherapy

4. Maximum of two 1000mg infusions of RIX given two weeks apart

Continuation for RA re-treatment for responders to RIX

1. At 5 months following initial course patient had a 50% decrease in active joint count from baseline and clinically significant response according to physician

   or at 4 months following the second and subsequent RIX infusions, patient demonstrated at least a continuing 30% improvement in active joint count and a clinically significant response

   and RIX re-treatment not to be given within 6 months of the previous course of treatment

3. RIX either to be used as an adjunct to Methotrexate or Leflunomide or MTX and LEF are contraindicated, requiring Rituximab monotherapy

4. Maximum of two 1000mg infusions of RIX given two weeks apart

RIX Infusions

- If patients respond, the more cycles they have, the less frequently they seem to need RIX.
- Some studies suggest 500mg of RIX is as good as 1000mg in third and subsequent cycles.
- Overall, a lower incidence of serious infections than patients on TNF inhibitors.
- Complete vaccinations at least four weeks prior to treatment (pneumococcal and flu vaccinations now recommended on all rheumatology patients on immunosuppressives).

Tocilizumab (Actemra), a humanised monoclonal antibody against Interleukin-6 receptor

- Given IV for an hour monthly (subcutaneous weekly injections now available).
- Systemic juvenile idiopathic arthritis
  1. Patient diagnosed with systemic JIA and
  2. No response to a reasonable trial of the following, either alone or in combination: MTX, NSAIDs and systemic corticosteroids

Continuation for JIA

- Reassessment required after six months.

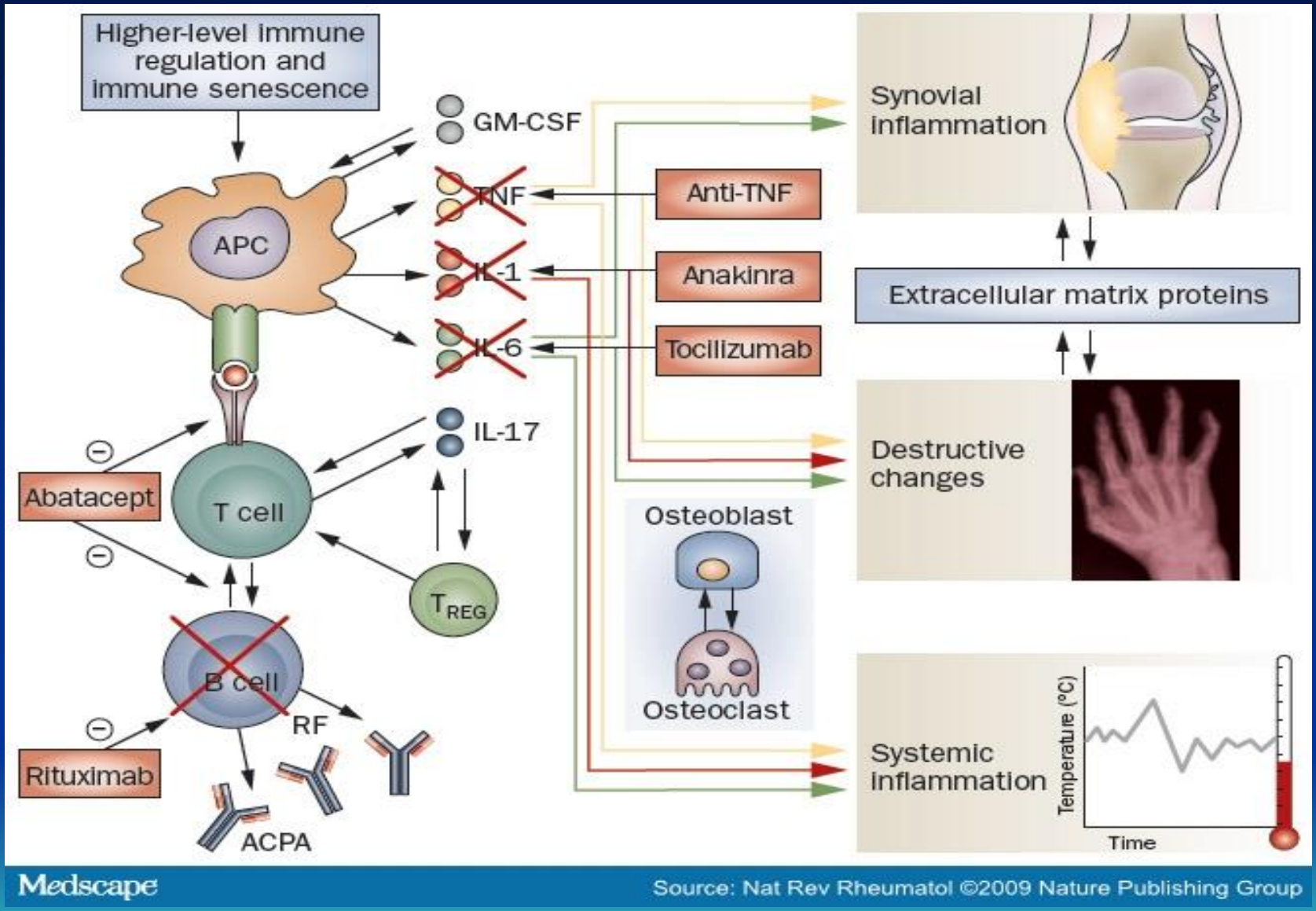
- Either patient had achieved ACR Pediatric 30% improvement criteria (ACR Pedi 30) response from baseline or on subsequent application patients demonstrate at least a continuing ACR response from baseline

Adverse effects

- Serious infections as in all patients on biologics (latent TB needs to be excluded).
- Transient neutropenia, less commonly anaemia, thrombocytopenia and pancytopenia.
- Abnormal LFTs.
- Increase in cholesterol level.

Funding from Pharmac sought for:

1. TNF inhibitors in Behcet's disease (medium priority status).
2. Tocilizumab in RA.
3. Tocilizumab for adult-onset Stills' disease (low priority status).
4. Rituximab for SLE.
5. Rituximab for ANCA-associated vasculitis (low priority status).


Higher-level immune regulation and immune senescence
GM-CSF
TNF
IL-1
IL-6
APC
IL-17
Abatacept
T cell
T_{REG}
B cell
RF
Rituximab
ACPA
Anti-TNF
Anakinra
Tocilizumab
Osteoblast
Osteoclast
Synovial inflammation
Extracellular matrix proteins
Destructive changes
Systemic inflammation
Temperature (°C)
Time
Medscape
Source: Nat Rev Rheumatol ©2009 Nature Publishing Group

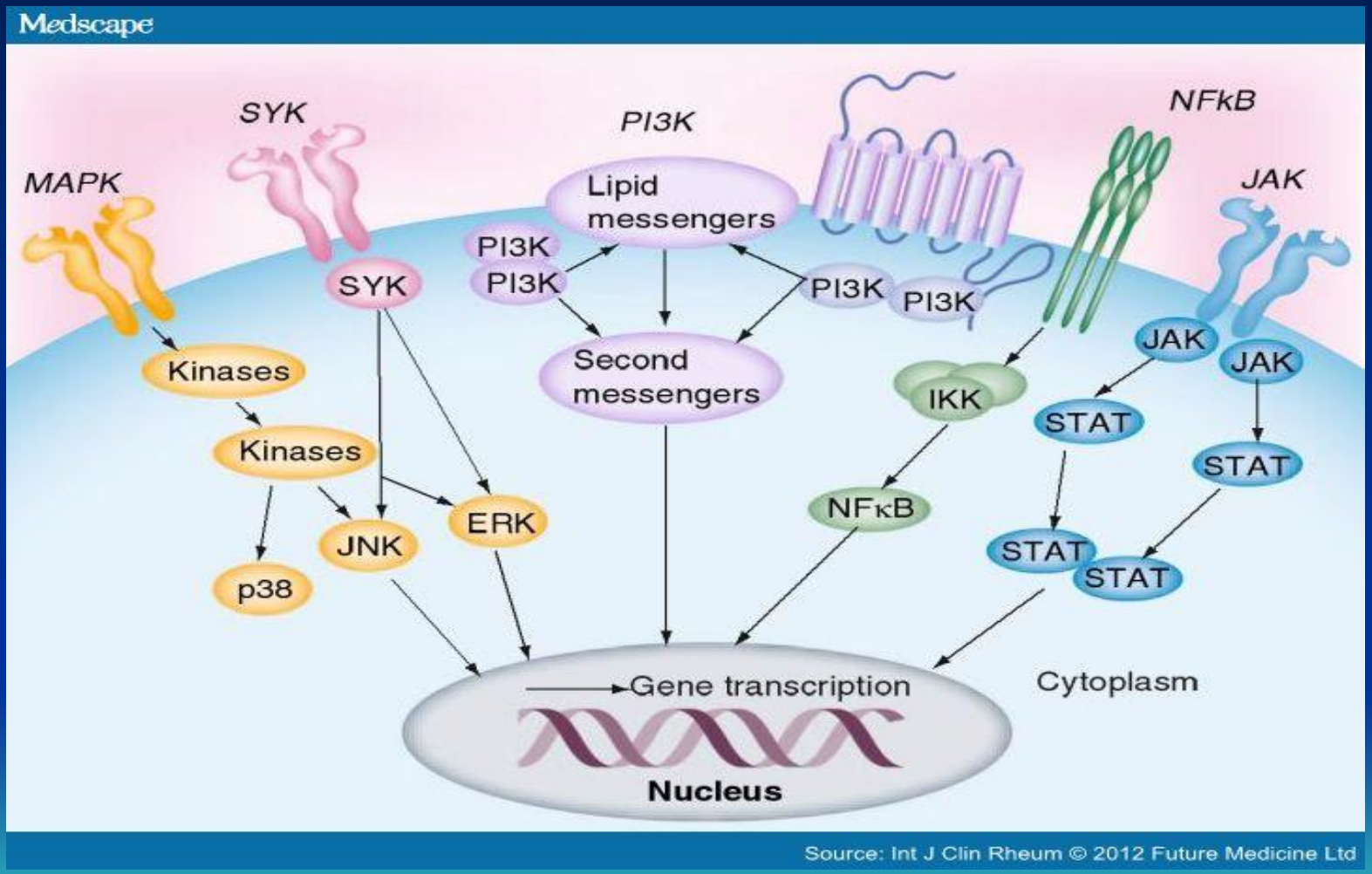
The Unmet Need in RA Therapy 2013

- Many patients are partial responders
- True remission is achieved by only a minority
- 'Cure' remains an elusive goal
- Toxicities and adverse effects
- Destructive process cannot be halted in all patients
- Repair of previous damage remains elusive

A new chapter in RA therapeutics - Small Molecule Immunomodulators (SMEs)

Discovery of a small group of four closely related intracellular enzymes in the transduction that occurs after the binding of cell surface receptors for a range of cytokines, chemokines, growth factors and hormones. These four intracellular enzymes are called JAK1, JAK2, JAK3 and TYK2.

Significant pathways involved in proinflammatory cytokine production after receptor/ligand binding



Tofacitinib (Xeljanz)

- Is the first of the SMEs and is a JAK1 and 3 inhibitor with weak affinity for JAK2.
- Tofacitinib 5 (or 10mg) b.d. approved by FDA on 06.11.2012.
- Efficacy: Rapid onset, within two weeks and as efficacious as TNF inhibitors and Interleukin-6 inhibitors with the usual 60% achieving ACR 20 response, 40% achieving ACR 50 response and 20% achieving ACR 70 response.

Possible adverse effects of Tofacitinib

- Cytopenia, most commonly neutropenia and also anaemia and thrombocytopenia.
- Abnormal LFTs.
- Increased risk of infections.
- Increase in LDL and HDL cholesterol.

Cost of Tofacitinib

Approximately $US2000.00 per month.

BUT a number of competitors coming and generics in the far future.

RA Landscape

Key products and Stakeholders

[1]TNF [2]IL-6 [3]PDE4 [4]CD4 [5]CD80 [6]CCR1 [7]JAK [8]CD19 [9]CTLA [10]Steroid [11]Syk [12]GM-CSF [13]S1PL [14]AP-1 [15]CD3 [16]CD20 [17]FMS [18]VLA [19]LTa [20]IL-20 [21]C5aR [22]IL-21 [23]NKG2A [24]IL-23 [25]IL-17 [26]A3 [27]IL-10 [28]c-Kit [29]PI3K [30]H4 [31]BAFF [32] DHODH

Biologics

Phase 1	Phase 2	Phase 3	Marketed
ASP2408[9] Astellas	ALX-0061[2] Ablynx	Tregalizumab[4] Abbvie	PDA001 Celgene	Sarilumab[2] Regeneron/Sanofi	Humira Abbvie
ATN-192[1] Ablynx					
SAN-300[18] Santarus					
PF-04236921[2] Pfizer	Mavrilimumab[12] AstraZeneca	Ofatumumab[20] GSK	Clazakizumab[2] BMS	Secukinumab[25] Novartis	Kineret Sobi
SA237[2] Roche					(Ro)Actemra Roche
Otelixizumab[15] GSK					
NN-8209[21] Novo	Ozoralizumab[1] Ablynx	Cx611 TiGenix	Olokizumab[2] UCB		Enbrel Amgen/Pfizer
NN-8210[21] Novo					Cimzia UCB
NN-8765[23] Novo					
MT203[12] Nycomed	NN-8226[20] Novo	MPC[32] Mesoblast	NN-8828[22] Novo	Veltuzumab[16] Takeda	Sirukumab[2] J&J/GSK	Simponi(sc*) J&J/Merck
MEDI5117[2] AstraZeneca						Remicade J&J/Merck
Dekavil[27] Philogen						
PRTX-100 Protalex	XmAb5871[8] Xencor	ISIS-CRP$_{Rx}$[34] ISIS	MP-435[21] Mitsubishi	TNFα kinoid[1] Neovacs	Remsima (Infliximab) Celltrion	Rituxan BI/Roche
AME-133v[16] MENTRIK						Orencia BMS
BI 655064 Boehringer	MOR-103[12] Morphosys	CNTO 1959[24] Janssen		Ustekinumab[24] Janssen	BI-695500 (Rituximab) Boehringer	

*iv sNDA filed; sMAA withdrawn

BI-695501 Boehringer
MK-8808 Merck
GP2013 Sandoz
Biosimilars Tracker
TL011 Teva
PF-05280586 Pfizer
CT-P10 Celltrion

MTX Products

Otrexup Antares | Metoject Medec | Methotrexate Generic

Orals

Phase 1	Phase 2	Phase 3	Marketed
PRT-062607[11] Biogen-Idec	Apremilast[3] Celgene	LX-2931[13] Lexicon	INCB039110[7] Incyte	IPI-145[29] Infinity	
PLX-5622[17] Plexxicon	CF-101[26] Can-Fite	JNJ-3851818[30] J&J	JNJ-40346527[17] J&J	ASP015K[7] Astellas	
HE-3286[10] Harbor	RhuDex[5] Medigene	T-5224[14] Toyama	PF-04171327[10] Pfizer	Masitinib[28] AB Science	Neoral Novartis
ASLAN003 Aslan					Tofacitinib[7] Pfizer
ABT-494 Abbvie	BMS-817399[6] BMS	CCX-354[6] GSK	MK-8457[11] Merck	Baricitinib[7] Lilly	Iguratimod Eisai (Just Japan)
HM71224[33] Hanmi	GLPG-0634[7] Galapagos	Aminopterin Syntrix	VX-509[7] Vertex	Fostamatinib[11] AstraZeneca	

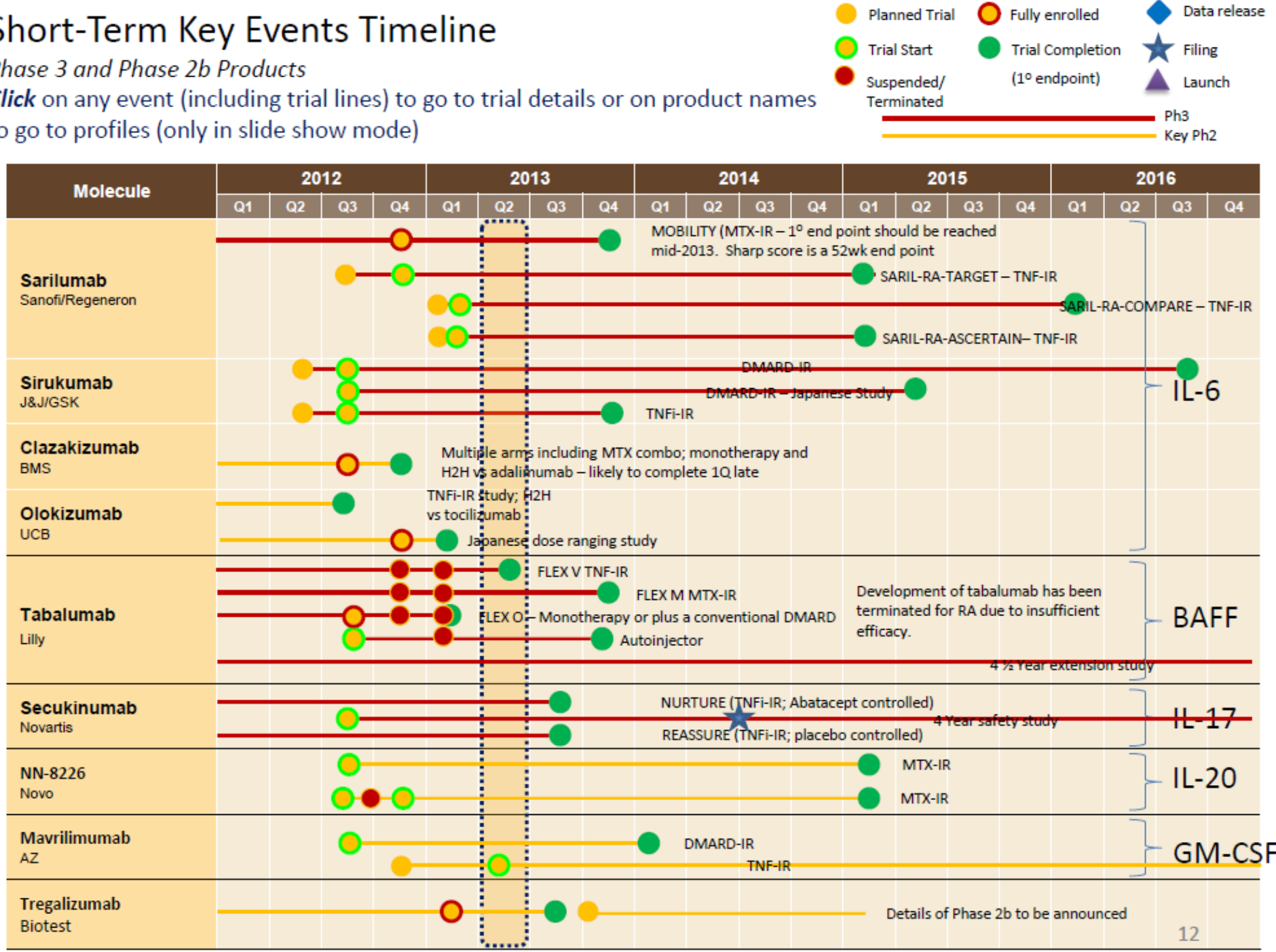
Linked molecules reflect those with significant new information

All identified products cross checked with company websites. Excluding analgesics; steroids; cell therapies

Short-Term Key Events Timeline

Phase 3 and Phase 2b Products

Click on any event (including trial lines) to go to trial details or on product names to go to profiles (only in slide show mode)



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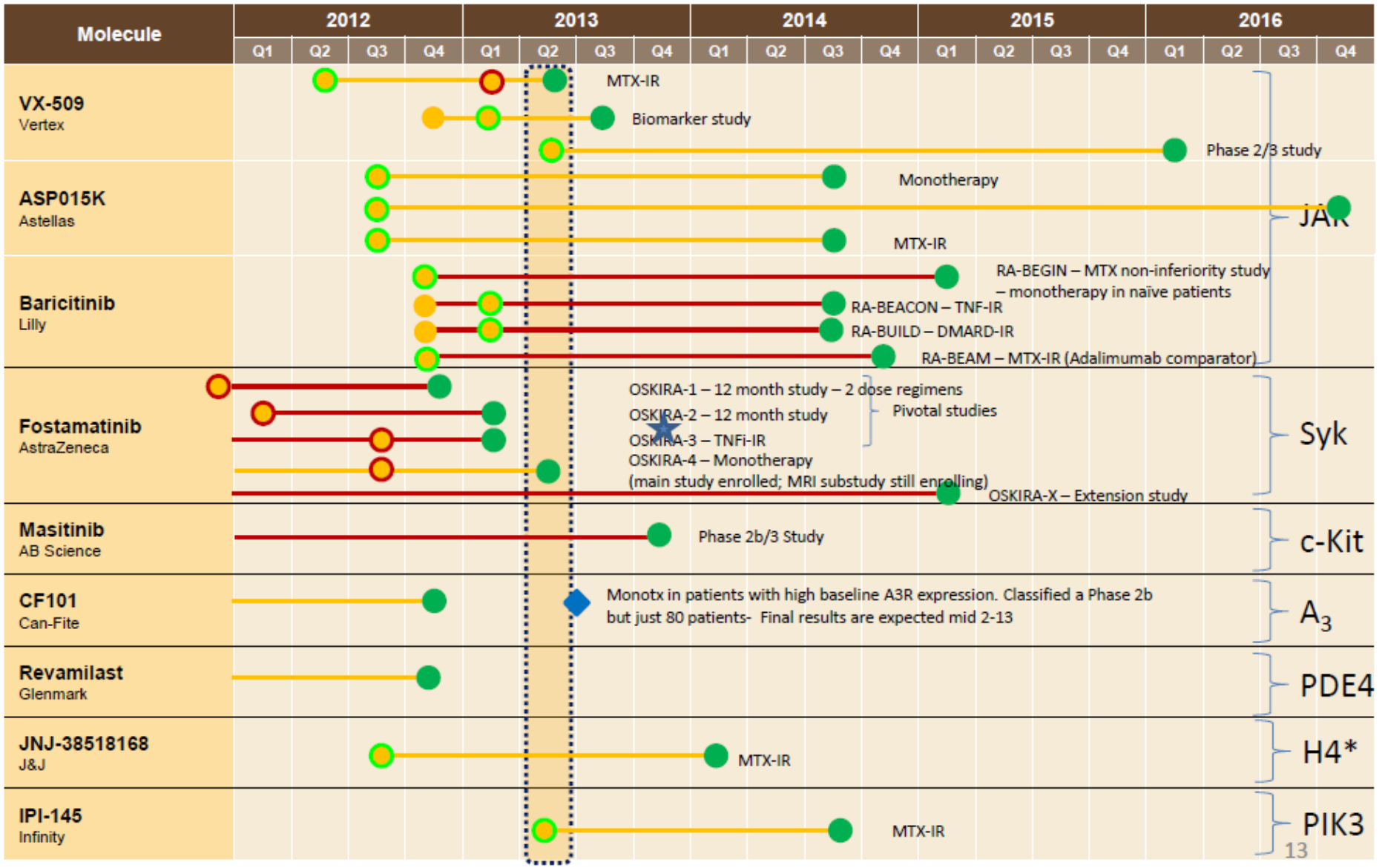


*To be confirmed

Dr J Goldhill

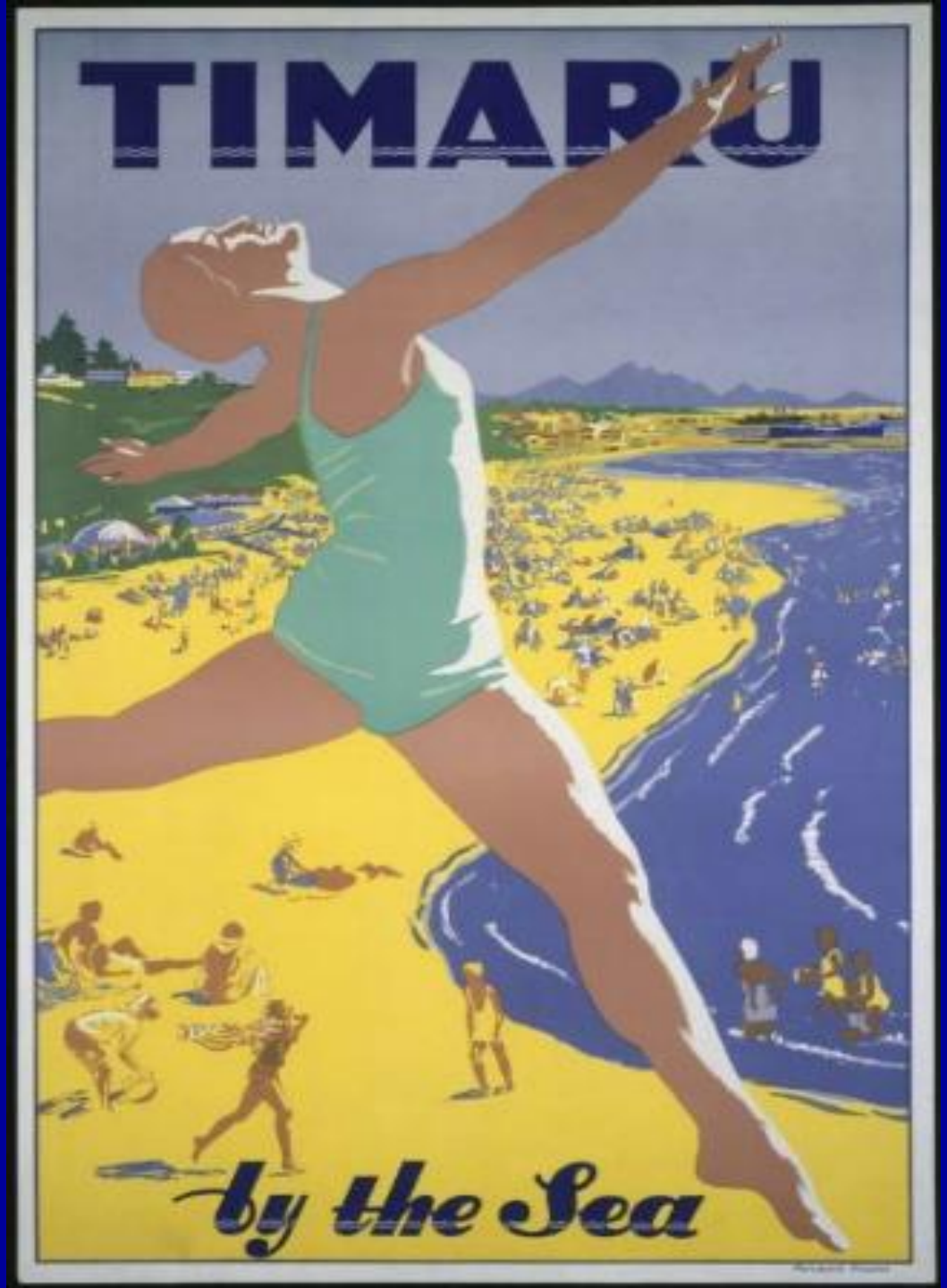
CEO of
UpdatesPlus – Rheumatoid Arthritis

Future therapy for polymyalgia rheumatica and giant cell arteritis

- Current steroid-sparing agents
  - Methotrexate
  - Azathioprine
  - Leflunomide (recent case series)
- Likely future therapy
  - Interleukin-6 inhibitor: investigator-initiated trial using Tocilizumab about to start

Possible FDA approved new therapy for psoriatic athritis and psoriasis in 2013/2014

Apremilast, a Phosphodiesterase type 4 (PDE4) enzyme inhibitor, given orally 20 or 30mg b.d.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by the Sea