BRUSSELS – 10th November 2015

PIONEERING ANTI-TNF THERAPY: DO LESSONS LEARNED POINT PATH TO FUTURE PROGRESS?

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UNIVERSITY OF OXFORD

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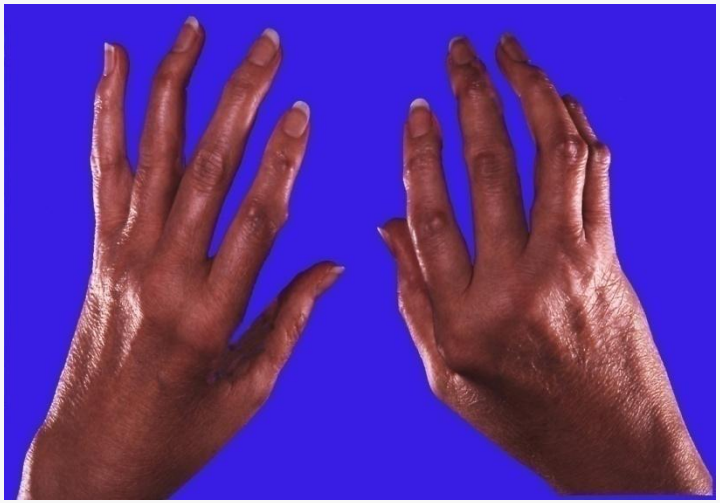
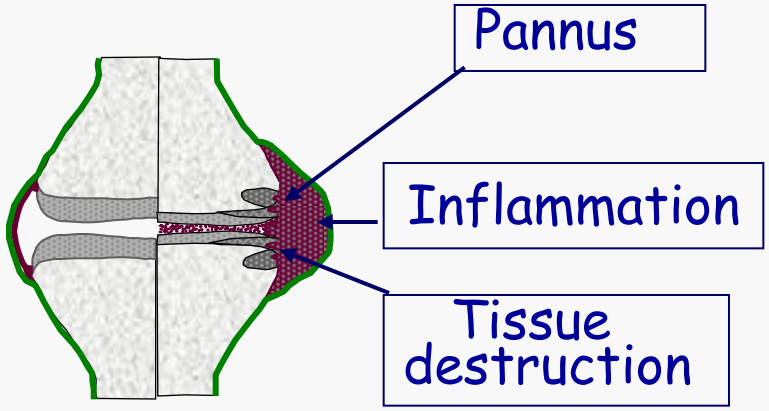
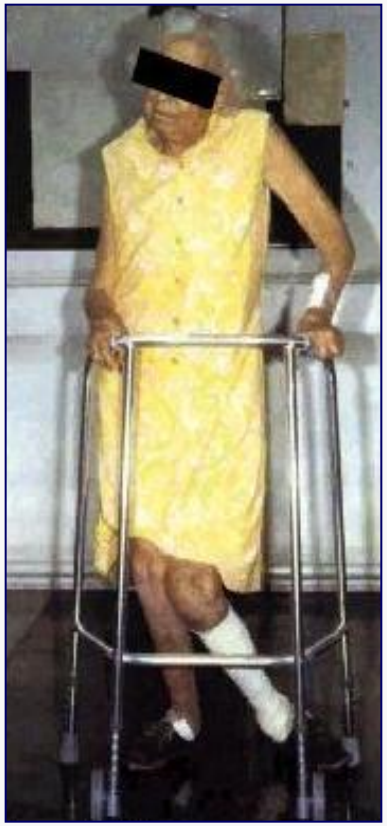
RHEUMATOID ARTHRITIS (RA)





- **Chronic immune inflammatory disease**
- **Sex : F:M 3:1, ~1%**
- **Progressive joint damage & disability, reduced quality of life. Shortened lifespan**
- **Structural damage early & progressive**
- **50% severely impaired by 10 yrs (not working)**
- **Pathology: leucocyte recruitment inflammation, tissue destruction and repair**



PLAN OF TALK

1. TNF is a good therapeutic target

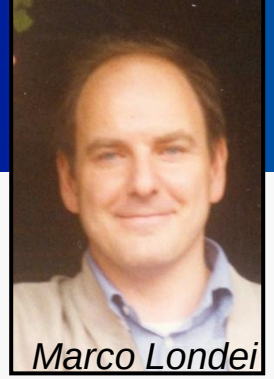
2. Optimal use of TNF blockade is with Methotrexate

3. Unexpected: a therapeutic revolution

4. Limitations of anti-TNF: need to get closer to a cure

5. Approaches to get closer to a cure

1983: A NEW HYPOTHESIS FOR AUTOIMMUNITY


Marco Londei

VIRUSES

Upregulation of HLA class II and antigen presentation

CYTOKINES & INTERFERONS

T

APC

CYTOKINES

Londei et al., 1984, Nature
Epithelial cells expressing aberrant MHC class II determinants can present antigen to cloned human T cells.

T

Non tolerant autoantigen reactive T cells

B

TISSUE DAMAGE

Pujol-Borrell et al., 1987, Nature
HLA class II induction in human islet cells by interferon-g plus TNF or lymphotoxin

CYTOKINES

Autoantibodies and tissue damage

Bottazzo, and Feldmann, 1983, Lancet Hypothesis: Role of aberrant HLA-DR expression and antigen presentation in the induction of endocrine autoimmunity.

Londei et al., 1985, Science
Human T-cell clones from autoimmune thyroid glands: specific recognition of autologous thyroid cells.

ANALYSIS OF CYTOKINE REGULATION
REVEALED IMPORTANCE OF TUMOUR NECROSIS FACTOR

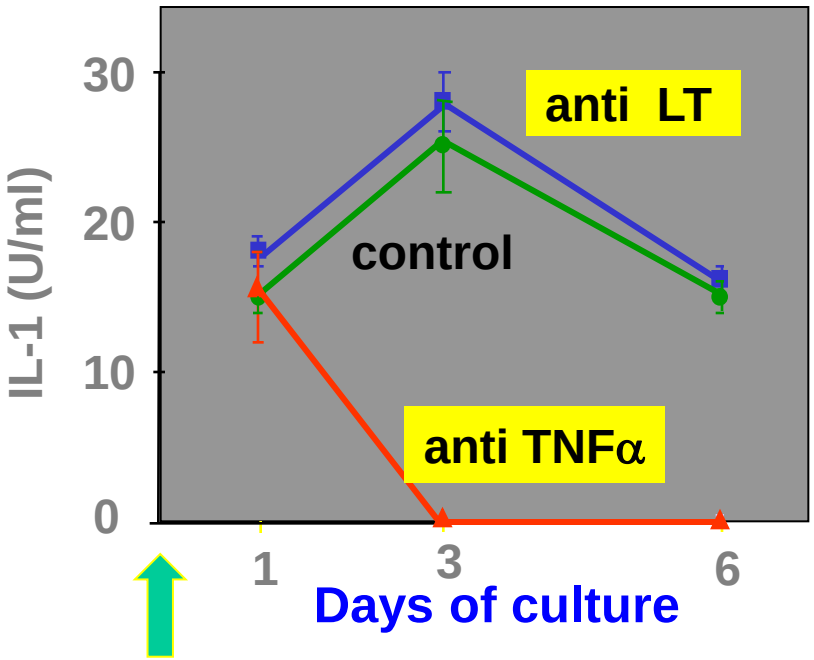
APPROACH Operative sample synovium, active RA cells isolated, placed in 'tissue culture'

OBSERVATION Spontaneous production of many mediators of disease - cytokines, enzymes etc.

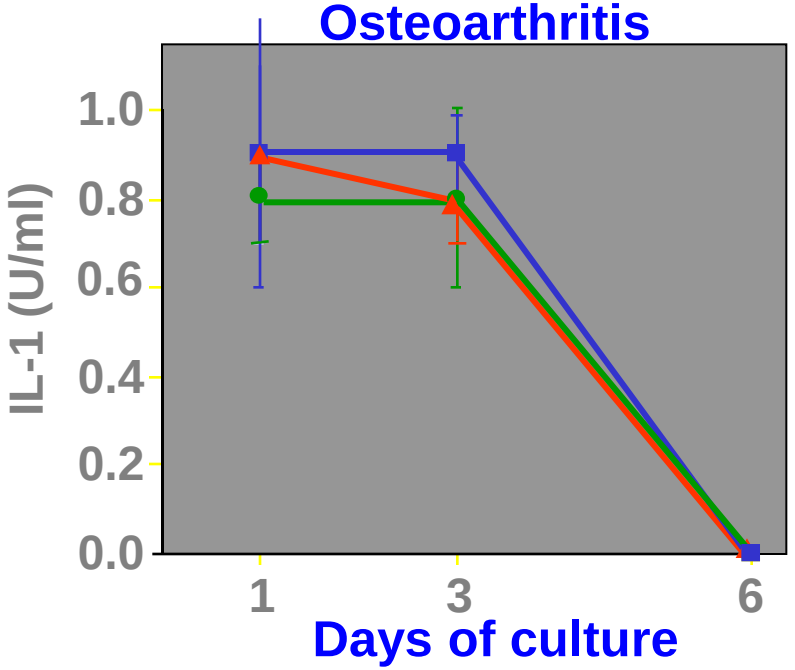
EXPERIMENT Antibody to TNF inhibits production of other pro-inflammatory cytokines

Fionula Brennan

Rheumatoid Arthritis

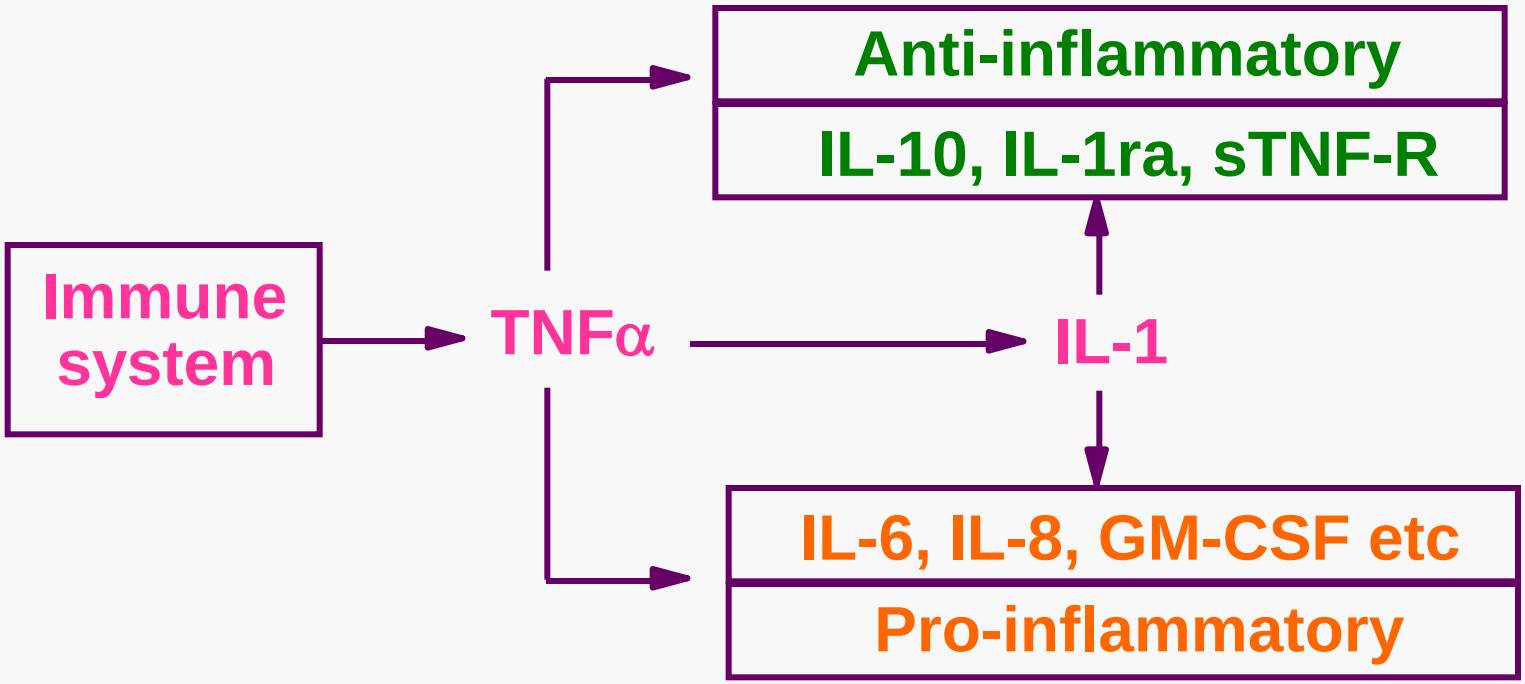


Osteoarthritis



Brennan et al (1989) Lancet ii 244-247

TNF DEPENDENT CYTOKINE CASCADE IN RHEUMATOID ARTHRITIS



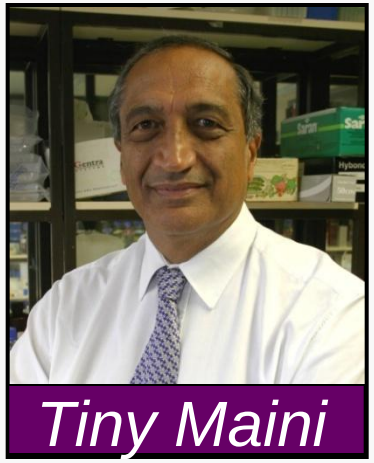
Feldmann, Brennan and Maini (1996) Cell, 85: 307

RATIONALE FOR ANTI-TNFα THERAPY IN RHEUMATOID ARTHRITIS

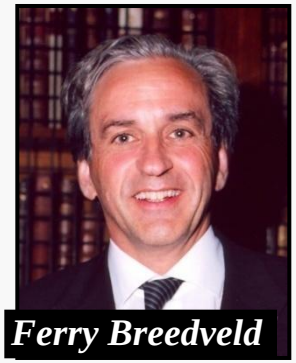
1. **Disregulated cytokine network in RA synovium is dependent on TNFα**

2. **TNFα/TNF-Receptor upregulated in synovium**

3. **Animal model of RA responds very well to anti TNFα administered after disease onset.**



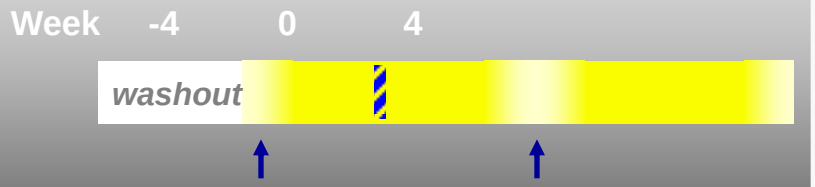
FORMAL PROOF:
RANDOMISED, PLACEBO-CONTROLLED TRIAL OF INFLIXIMAB IN RHEUMATOID ARTHRITIS


Ferry Breedveld


Jochen Kalden


Josef Smolen

Design



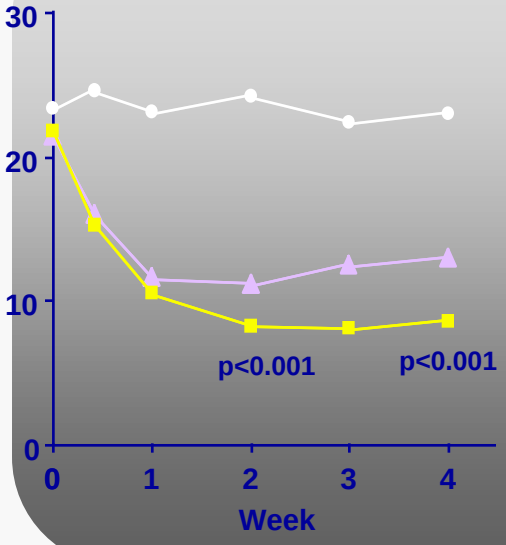
cA2: 1 or 10 mg/kg or HSA — 3, 10 or 20 mg/kg

Results

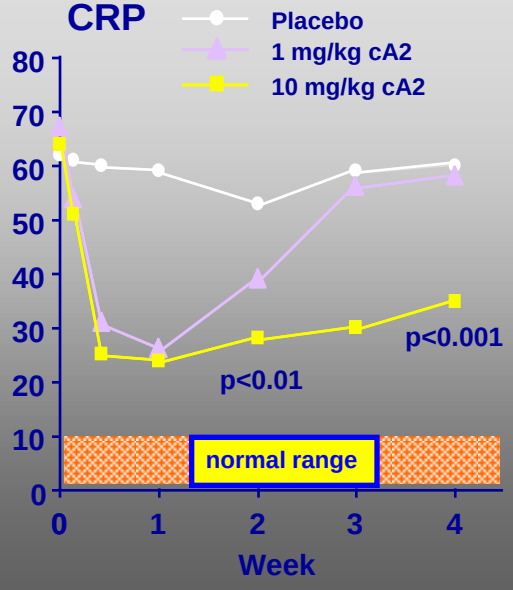
well-tolerated
good clinical responses
dose-response


Sir Ravinder Maini

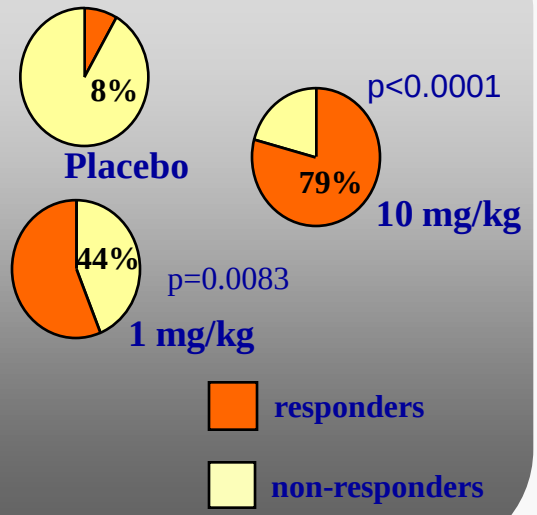
Swollen Joint Count



CRP

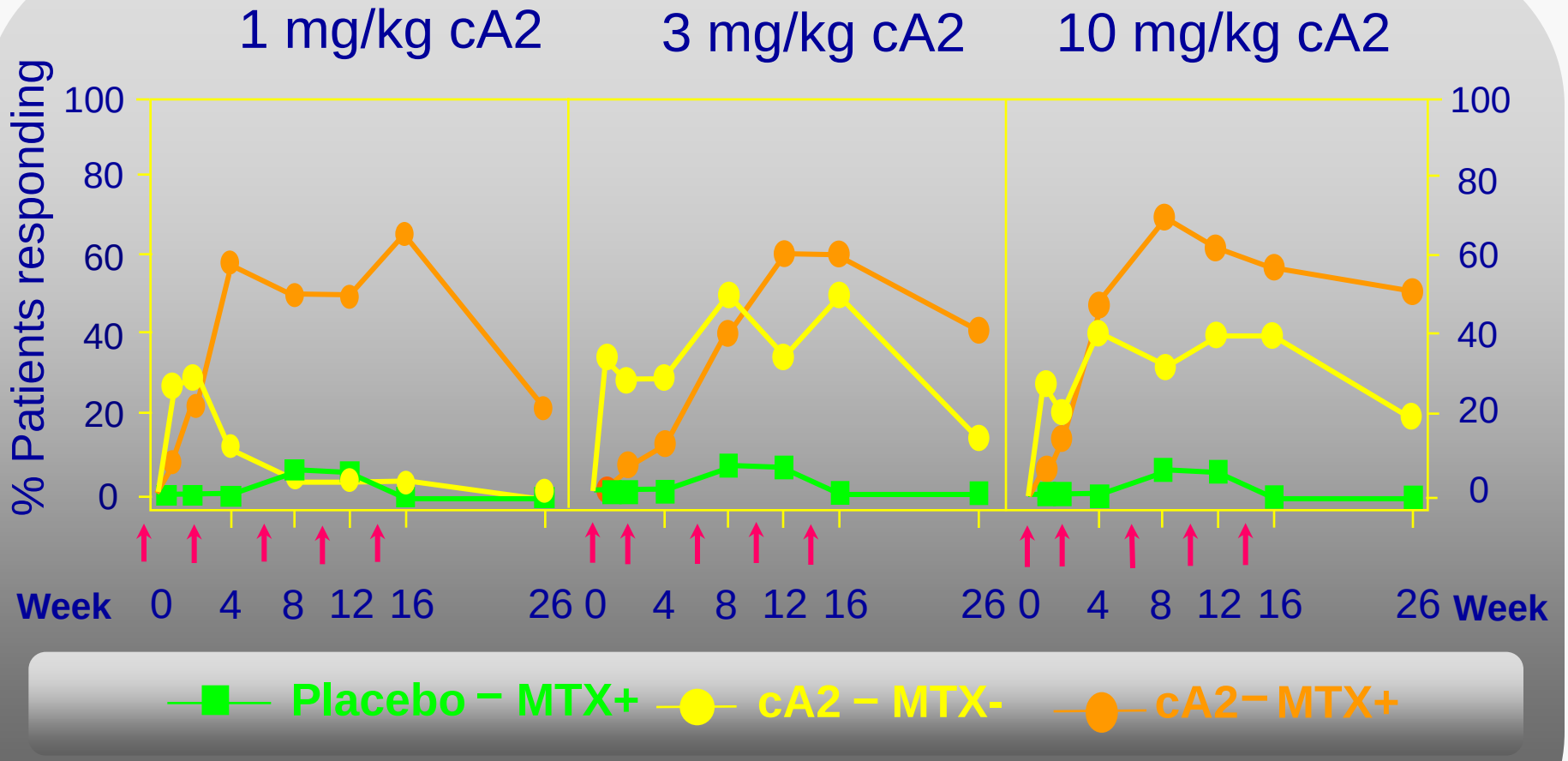


Paulus 20% responses at week 4



Elliott, Maini, Feldmann et al, Lancet 1994; 344: 1105-10

FILLING AN UNMET NEED: EFFICACY OF ANTI-TNF WITH METHOTREXATE: ACR 50



Used in >70% patients

Kennedy Institute gets royalties on USE patent

Maini RN et al. (1998) Arthritis Rheum.; 41:1552-1563.

SUCCESS OF ANTI-TNF THERAPY IN RHEUMATOID ARTHRITIS

1. **CONTROL OF SYMPTOMS: pain, stiffness, fatigue**
2. **CONTROL OF SIGNS: swelling, tenderness**
3. **CONTROL OF JOINT DESTRUCTION**
4. **INITIATION OF JOINT REPAIR:**
   reduced Sharp Score
5. **IMPROVEMENT IN HEALTH (HAQ)**
6. **> 5 x 10^6 treated patients**
7. **Long term benefit > 10 years**

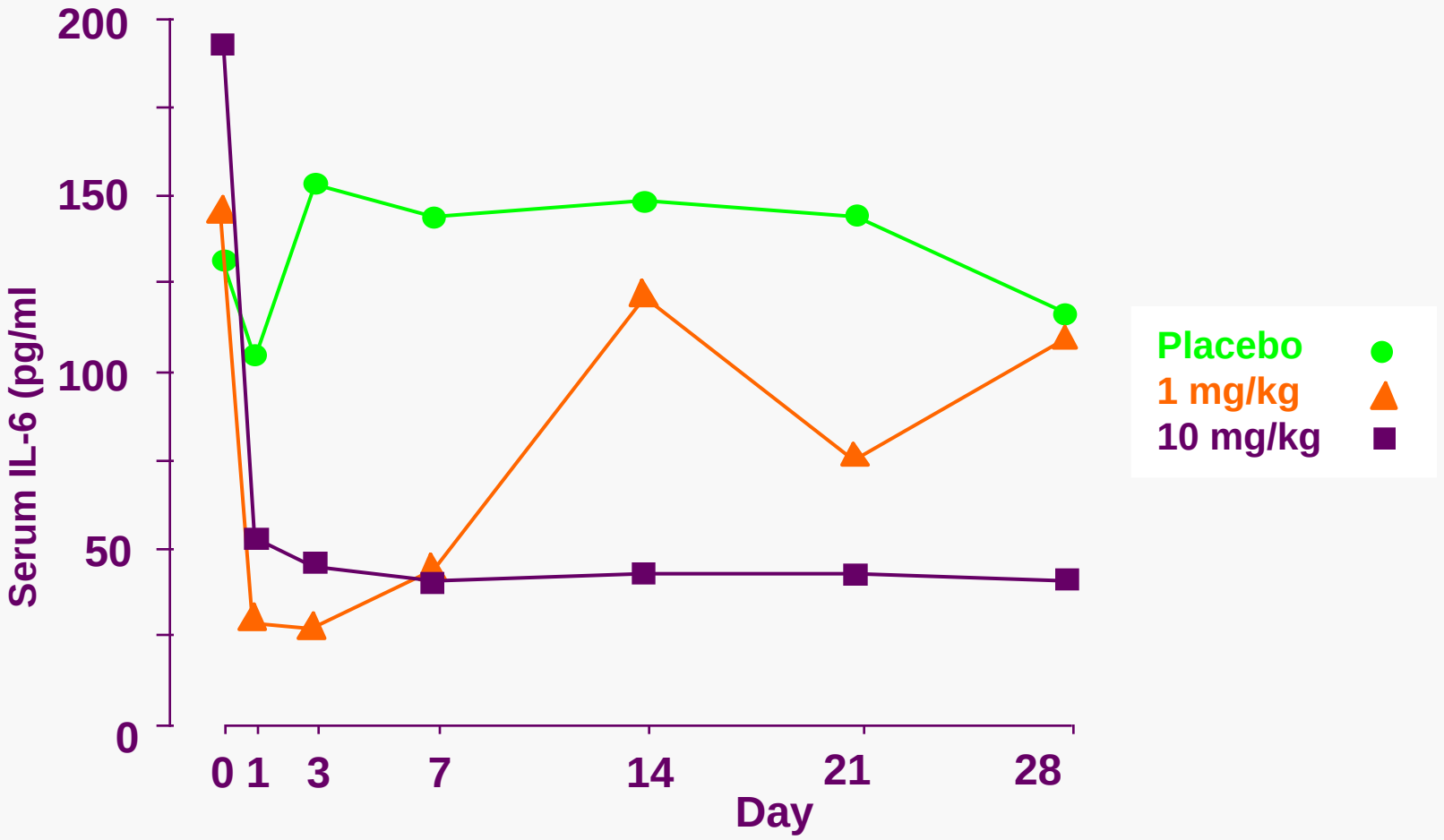
SAFETY ISSUES

TNF blockade interferes with host defence:
Risk becoming clearer with post-marketing registries

1. **All cause mortality and cancer not increased (BSR register)**
2. **Serious infection risk 60/1000 Pt Years: skin - same as other DMARD (BSR register)**
3. **Reduced risk of cardiovascular events? 14/1000 PtY cf 35/1000 PtY**
   (Jacobsson et al., 2005, J Rheum. 32: 1213)
4. **Reduced risk heart failure**
   (Wolfe, 2004, Am J Med. 116: 305)
5. **No increased risk lymphoma**
   (Askling et al., 2005, Am Rheum Dis. 64: 1414)
6. **Demyelination**

OVERALL: SAFER THAN PREVIOUS THERAPY

MECHANISM OF ACTION:
TNFα DEPENDENT CYTOKINE CASCADE IS OPERATIVE *IN VIVO*

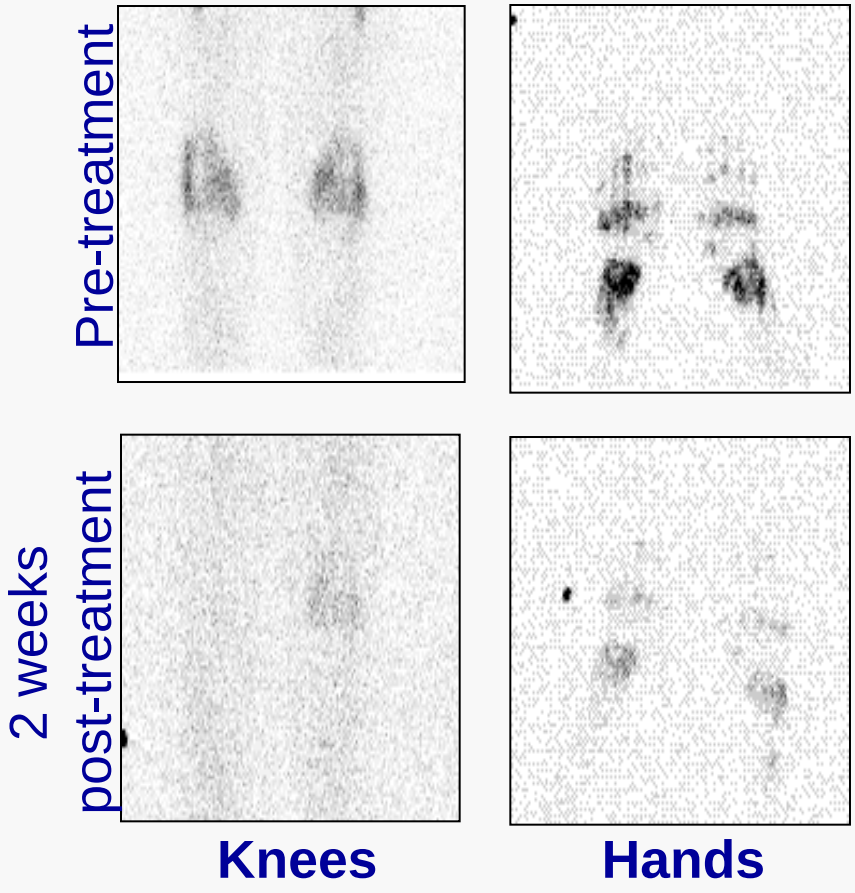


Also IL-1, GM-CSF, IL-8, VEGF etc

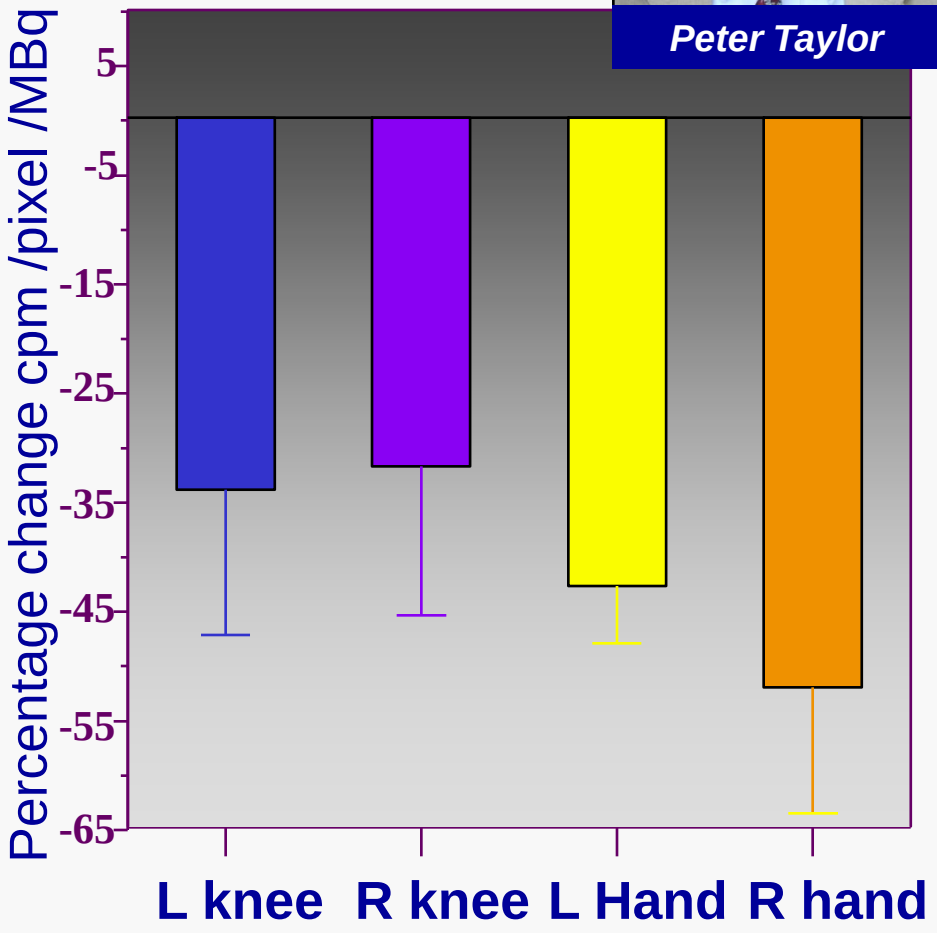
Charles et al (1999) J Immunol; 163: 1521-28

REDUCED LEUCOCYTE TRAFFICKING AFTER INFLIXIMAB THERAPY EXPLAINS EFFICACY IN MANY LOCAL DISEASES

Peter Taylor



^{111} Indium labelled polymorphs



Taylor et al (2000)Arthritis Rheum 43:38-47

UNEXPECTED: ACCELERATING A THERAPEUTIC REVOLUTION

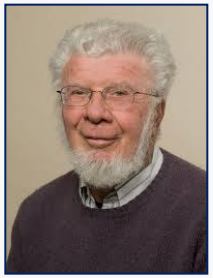
1977 Kohler and Milstein:
mouse Mab by fusion
- problem immunogenicity

1980's Molecular engineering
Chimeric Ab
- Infliximab, Rituximab
approved 1999/2002

1990's Humanization & Human
Antibodies - Adalimumab
Phage Display, Engineered Mice


Georges Köhler


Cesar Milstein


Len Herzenberg


Greg Winter

SALES OF MONOCLONAL ANTIBODIES

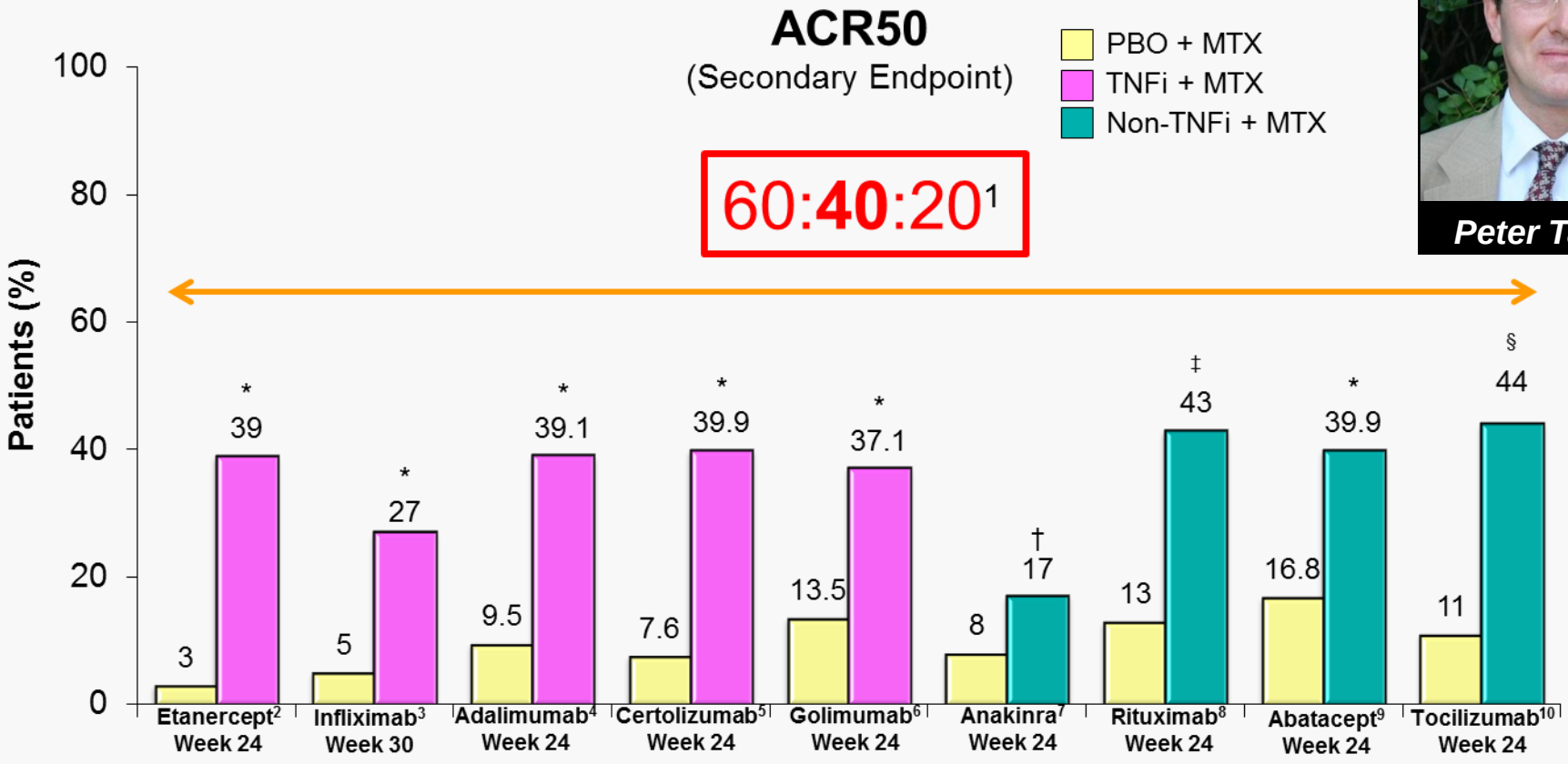
2012 5 of top 10 drugs Mabs
anti-TNF biggest drug class
Mab revolution driven by
- anti TNFs - $30bn in 2014
- anti cancer - >$20bn Herceptin, Avastin, Rituxan

CURRENT PROBLEMS OF ANTI-TNF THERAPY

1. Not all patients respond
2. Degree of response inadequate
3. Side effect profile
4. Cost of therapy ($30 K)

CURRENT ANTIBODIES INDUCE PARTIAL RESPONSE

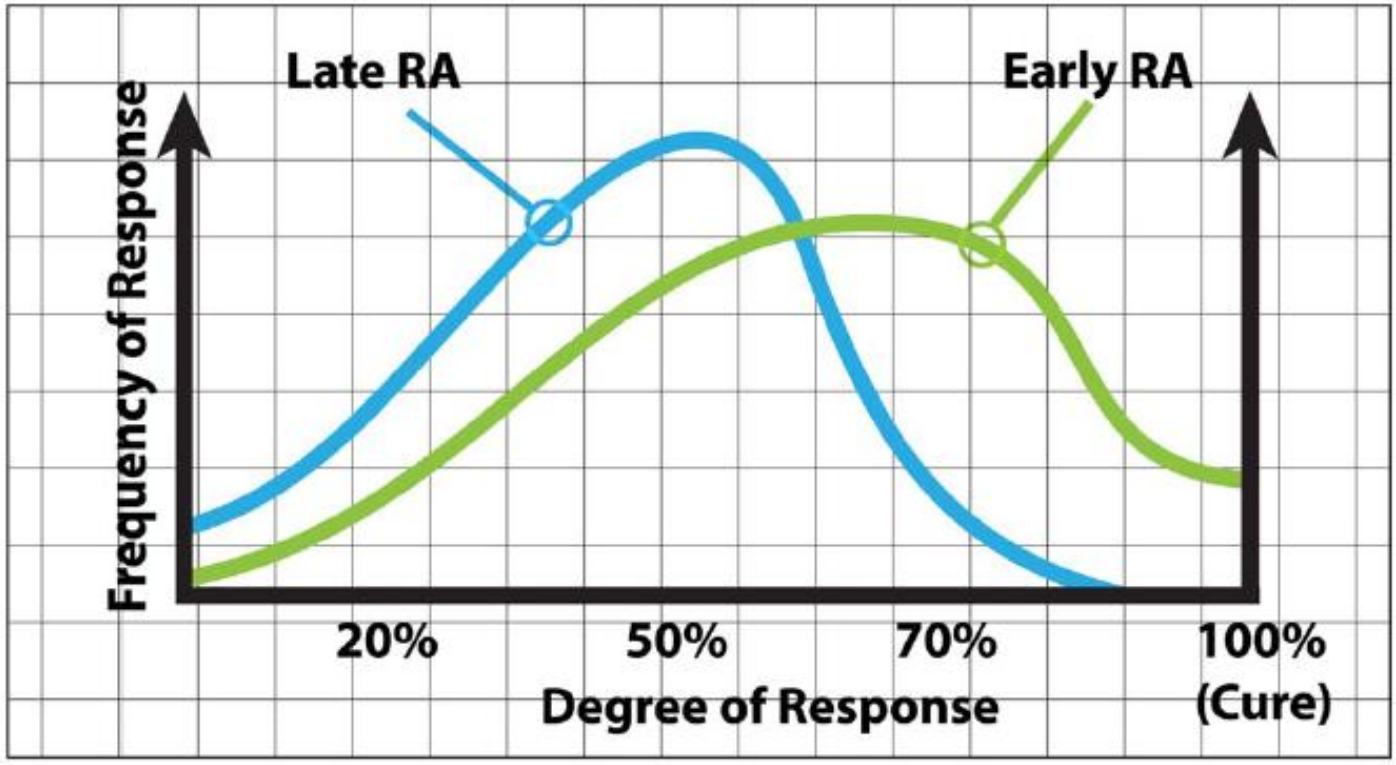
NOT HEAD TO HEAD



Courtesy of Professor Peter C. Taylor

NO PROGRESS THIS CENTURY

RESPONSE TO ANTI-TNF IN EARLY OR LATE STAGE RA



Glass more than half empty!

But no wheelchairs, walking frames, little joint surgery

Feldmann & Maini, A&R (2015) 67: 2283

ANTI-TNF THERAPY: WHY DON'T ALL RA PATIENTS RESPOND?

1. **Non Responsiveness variable**
   - non responders can respond in future

2. **Possible Mechanisms**
   - Immunogenicity of therapeutic antibody
   - Other pathways involved in disease persistence

HOW TO GET CLOSER TO A CURE FOR A MULTIGENIC/MULTIFACTORIAL DISEASE ?

DISEASE: Failure to compensate for multiple abnormal pathways

1. BIGGEST SUCCESSES	Combination therapy	HIV Leukaemia
2. RISKS OF COMBINATION	INFECTION Examples: anti TNF + anti IL-1 or CTLA4Ig	
3. BUT POSSIBLE	Anti TNF + MTX	
4. THE FUTURE	Combinations with anti-TNF+MTX as bedrock ADD Inhibitors of different pathways and processes	
CHALLENGES	Regulatory Authorities Legal issues Costs of combination How to predict responders? How to monitor immune function to reduce infection risk Human Immune monitoring to reduce risk	

CURRENT FOCUS:
WAYS OF GETTING CLOSER TO A CURE

antiTNF + MTX PLUS

A. **REDUCE INFLAMMATION/IMMUNITY IN RATIONAL COMBINATION**
   eg anti-TNF plus anti IL-17/23 *(Williams)*

B. **RESTORE ABNORMAL HOMEOSTASIS**
   eg Activate regulatory receptors – PD-1, CD200R *(Davis & Williams)*
   Upregulate Treg and FoxP3 *(Brennan)*

C. **REDUCE ANTIGEN LOAD**
   eg reduce PAD enzymes *(Venables)*

D. **EMPIRICAL**
   eg determine what signalling pathways are dominant
   Challenging: serial biopsies and CytoF *(Taylor)*

E. **INHIBITING ANGIOGENESIS**

F. **INHIBITING STROMA : FIBROBLAST LIKE SYNOVIOCYTES (FLS):**
   eg antiMMP14, antiCAD11

COULD TARGETING ANTI-TNF PLUS FLS LEAD TO SAFE AND EFFECTIVE THERAPY?

HOW COULD FLS BE TARGETED?

Wnt pathway
CAD-11 ***(M. Brenner)***
Cytokines IL-33, IL-32 etc
Epigenetics ***(S. Gay)***
MMP14


Michael Brenner


Steffen Gay

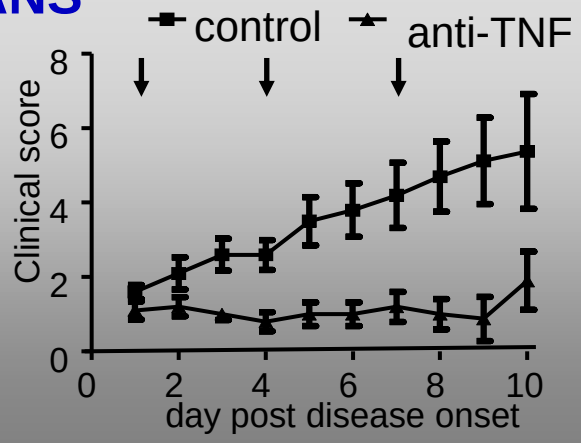
COMBINATION OF FLS INHIBITION PLUS IMMUNE INHIBITION?

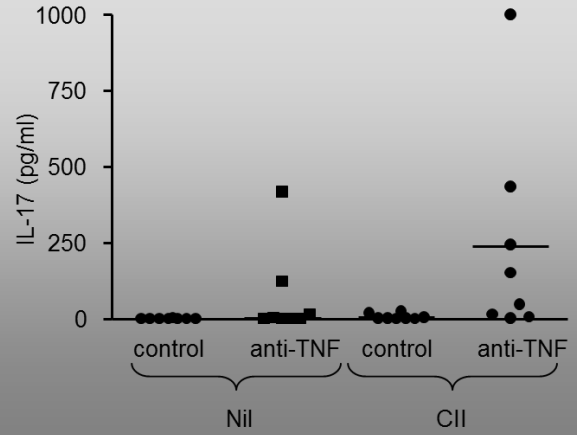
GETTING CLOSER TO A CURE:

REDUCING RESIDUAL INFLAMMATION VIA TARGETING IL-17 PATHWAY

ANTI-TNF THERAPY INCREASES IL-17 PRODUCTION IN MICE AND HUMANS

αTNF

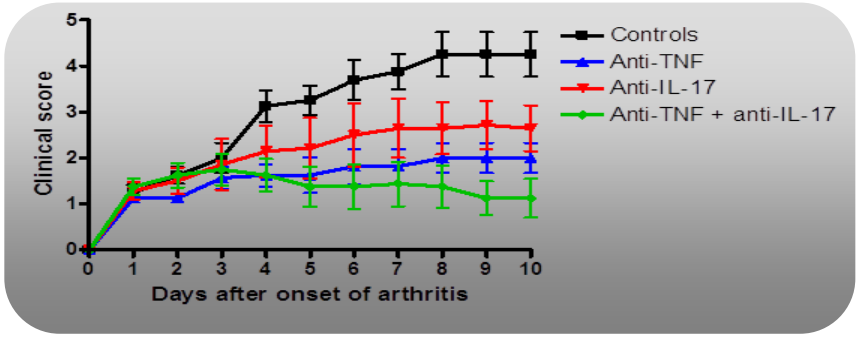


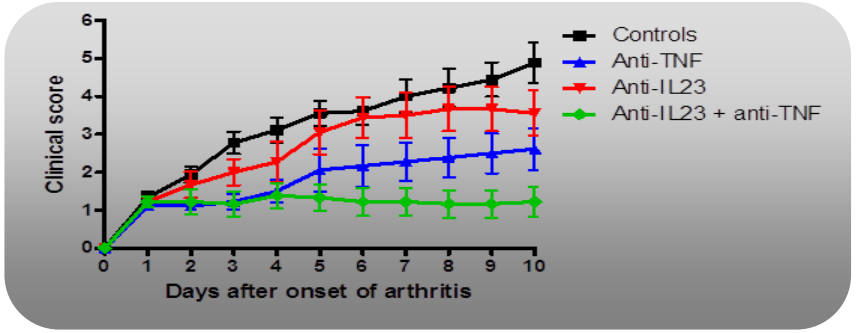


IL-17

POTENTIAL SYNERGISTIC THERAPY

Anti-TNF plus p40 (IL-12 and IL-23) or Pp19, IL-23 specific



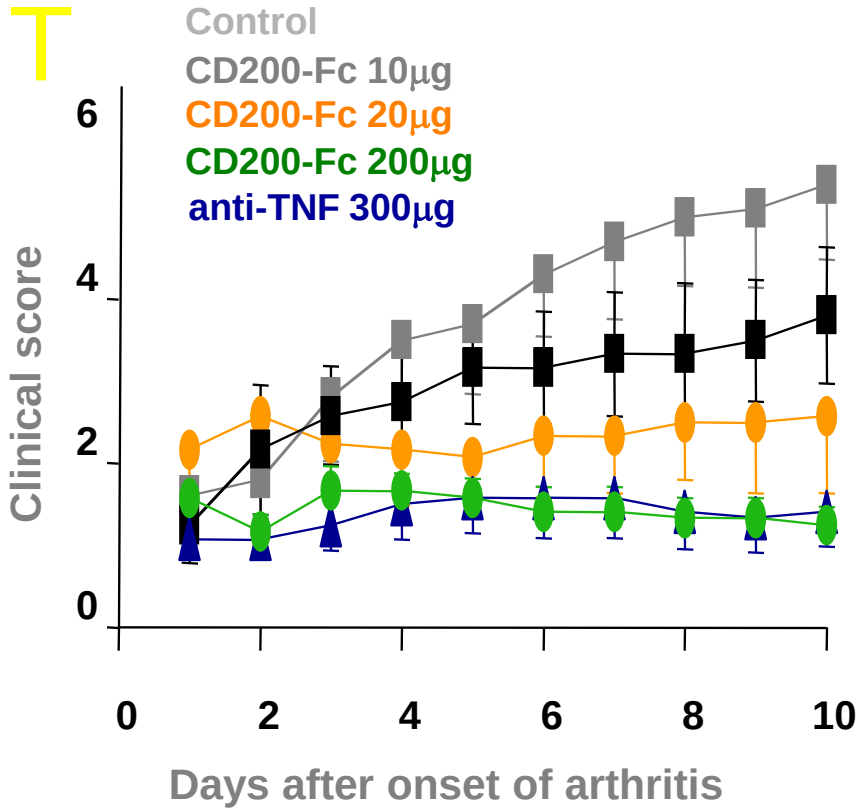


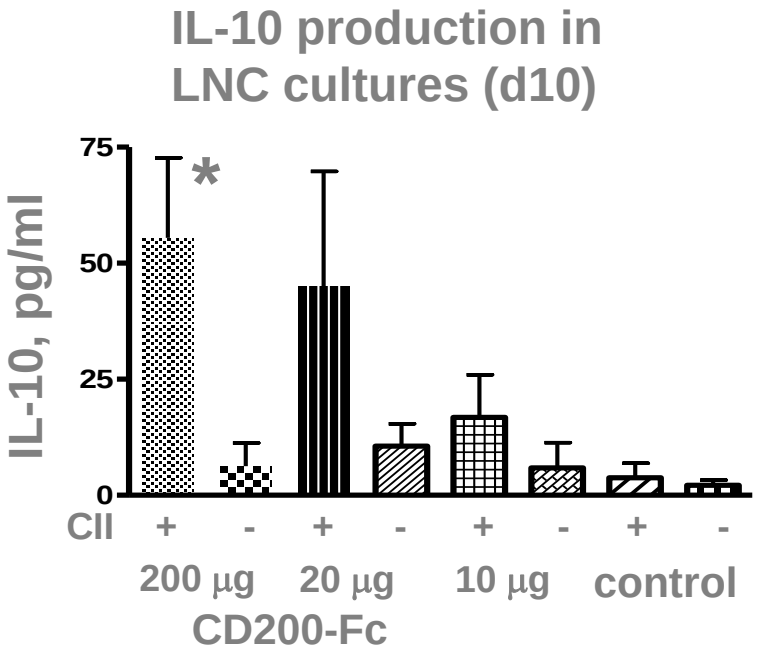
HUMANS: RISK OF INFECTION COULD BE MITIGATED BY REDUCING DOSE ANTI-TNF OR INTERMITTENT THERAPY

GETTING CLOSER TO A CURE:
B. RESTORING ABNORMAL HOMEOSTASIS


Richard Williams

Activate endogenous regulatory receptors
e.g. CD200R activated by CD200Fc





Simelyte, Feldmann & Williams, A&R, 2008

GETTING CLOSER TO A CURE:
C. REDUCING ANTIGEN LOAD

Citrullinated proteins key autoantigens in RA

Cit autoantigens: Enolase (discovered Patrick Venables)
Vimentin
Fibrinogen
Collagen II

Autoantibodies to Cit Protein Antigens = ACPA

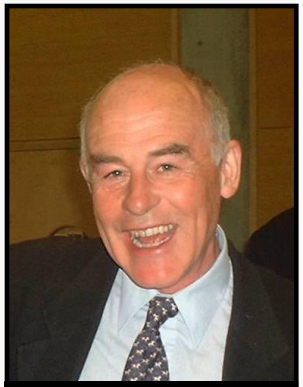
ACPA influence disease

- Antibody directly e.g. osteoclasts
- Immune complexes via TLR4

HYPOTHESIS: Reducing Cit Antigens will reduce autoimmunity

HOW: Inhibiting Peptidyl Arginase Deiminases (PAD)
P.Gingivalis PAD? Antibodies? Vaccines

Walter van Venrooij



Patrick Venables

REMOVING ROAD BLOCKS: BETTER DIAGNOSTICS

KEY ISSUES FOR GETTING CLOSER TO A CURE FOR RA

1. Which patients to treat?
2. How to minimise risk of infection?

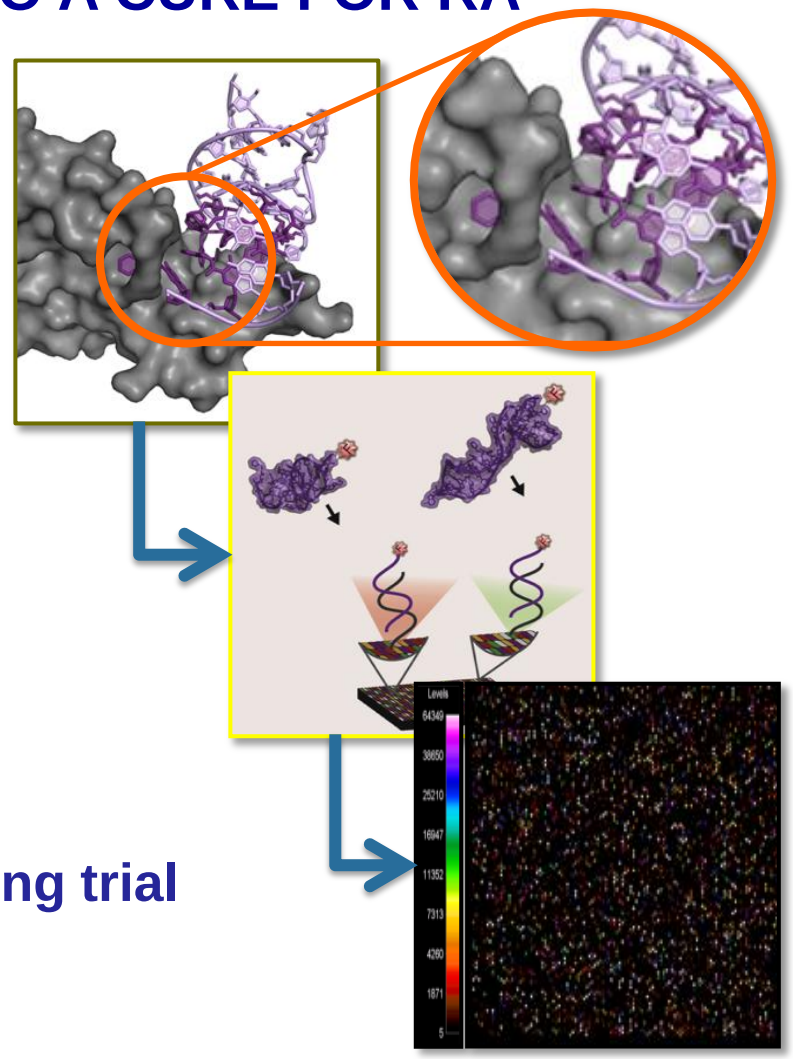
APPROACH: BETTER DIAGNOSTICS

The SOMAscan Assay:

1. Multiplex of modified aptamers
2. Monitors ~4000 proteins in 100µl

UTILITY

1. Can characterize patients before trials to profile likely 'Responders'
2. Potential to monitor immune status during trial



CONCLUSION

1. Understanding pathogenesis of RA
   permits effective therapy

2. Getting closer to a cure is challenging
   but is possible

3. **MULTIPLE THERAPEUTIC TARGETS NEEDED**

to get closer to a cure: antiTNF + MTX

AND
- restoring homeostasis T cells
- removing antigen (PAD esp PPAD)
- activating inhibitory receptors
- Inhibiting Fibroblasts

DO WE HAVE THE AMBITION TO AIM TO CURE?

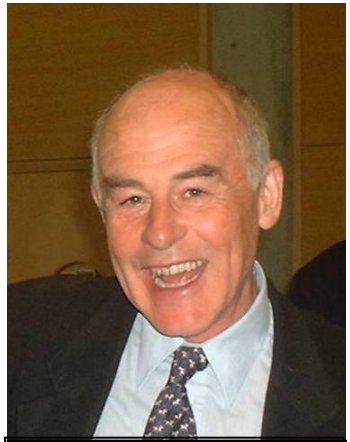
ACKNOWLEDGEMENTS

Sir Ravinder Maini

Fionula Brennan

Peter Taylor

Richard Williams



Patrick Venables

FUNDING: arc, KIR Trustees, MRC, Wellcome Trust, Centocor, Inc., Nuffield Foundation, etc