HOW ANTI-TNF THERAPY WAS DISCOVERED BY A PUBLIC-PRIVATE PARTNERSHIP

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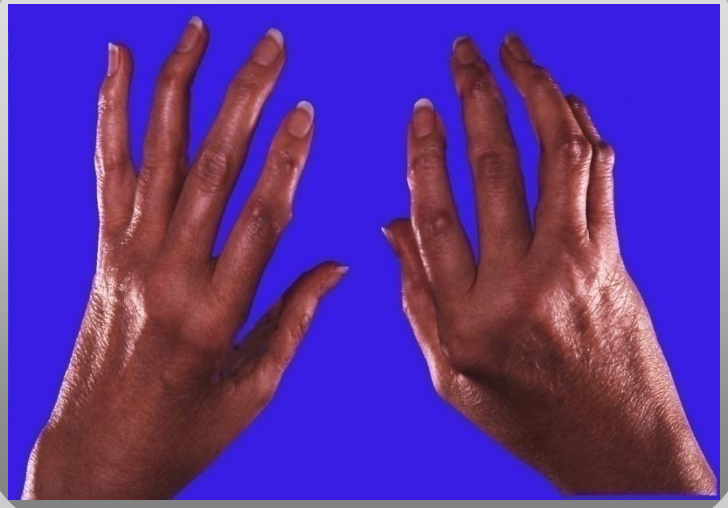
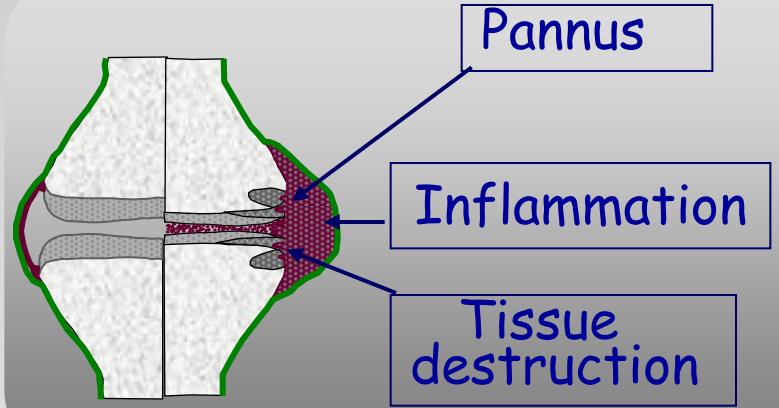
Supported by
Arthritis Research UK

RHEUMATOID ARTHRITIS (RA)





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

PLAN OF TALK

A. IDENTIFYING & VALIDATING TNF AS A THERAPEUTIC TARGET

B. TRANSLATING INTO CLINICAL PRACTICE

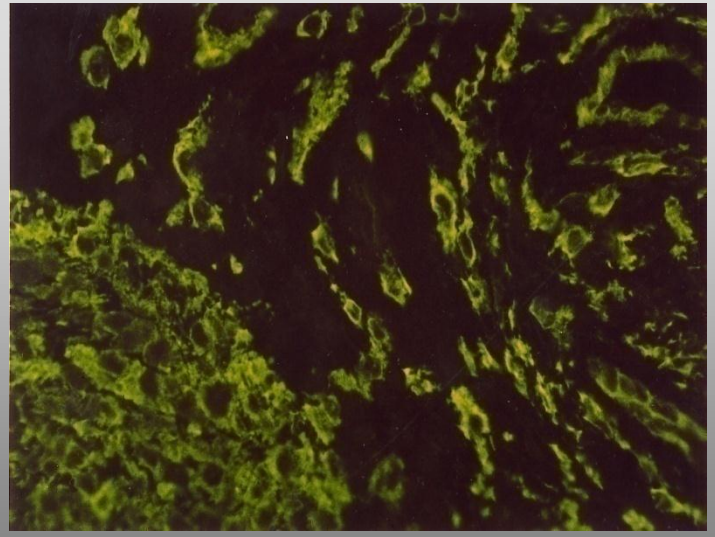
C. HOW WAS ANTI-TNF DISCOVERY A PUBLIC-PRIVATE PARTNERSHIP?

D. FUTURE OF PUBLIC-PRIVATE PARTNERS
e.g. STRUCTURAL GENOMICS CONSORTIUM

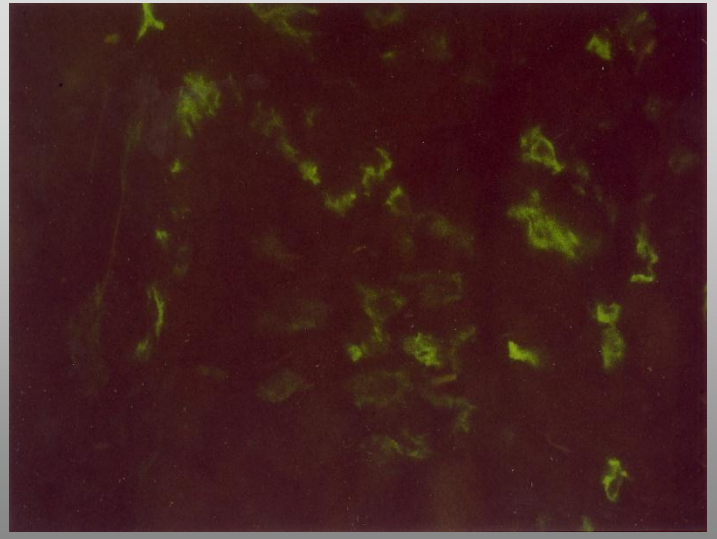
WHY LOOK FOR CYTOKINES IN RHEUMATOID ARTHRITIS?

Upregulation of HLA-DR in rheumatoid synovium

(Klareskog, Wigzell, Panayi, Janossy etc. 1981/82)



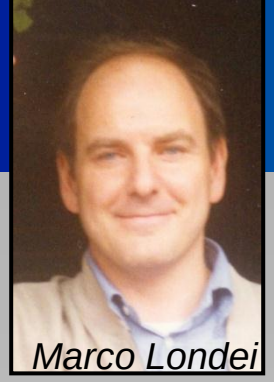
Rheumatoid Arthritis



Osteoarthritis

Expression of HLA-DR on cells usually negative indicates presence of inducers = cytokines

1983: A NEW HYPOTHESIS FOR AUTOIMMUNITY


Marco Londei

VIRUSES

Upregulation of HLA class II and antigen presentation

CYTOKINES & INTERFERONS

T

CYTOKINES

APC

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

TISSUE DAMAGE

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

B

CYTOKINES

Autoantibodies and tissue damage

Bottazzo et al, 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.

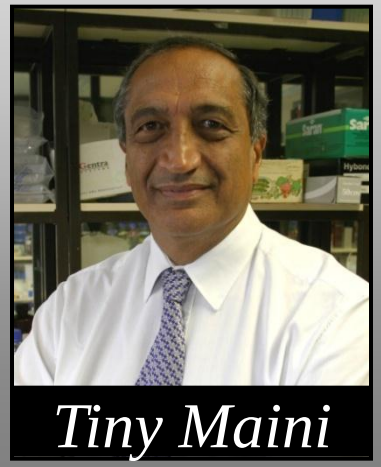
MANY CYTOKINES ARE PRODUCED IN RHEUMATOID SYNOVIUM

Pro-inflammatory
e.g. IL-1, IL-6, TNFα, IL-12, IL-15, IL-17, IL-18, IFNγ, IL-2, OncoM, GM-CSF

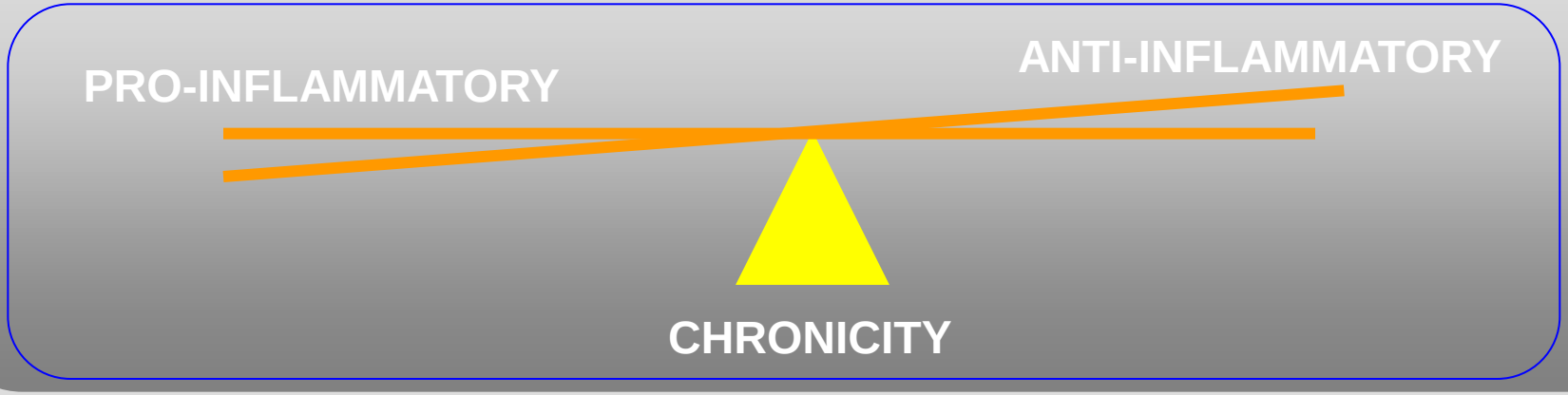
Anti-inflammatory
e.g. IL-10, IL-1Ra, TGFβ, IL-11, IL-13

Chemokines
e.g. IL-8, MIP-1α, MCP-1, RANTES, ENA-78, GROα

Growth Factors
e.g. VEGF, PDGF, FGF



ARE ANY THERAPEUTIC TARGETS?



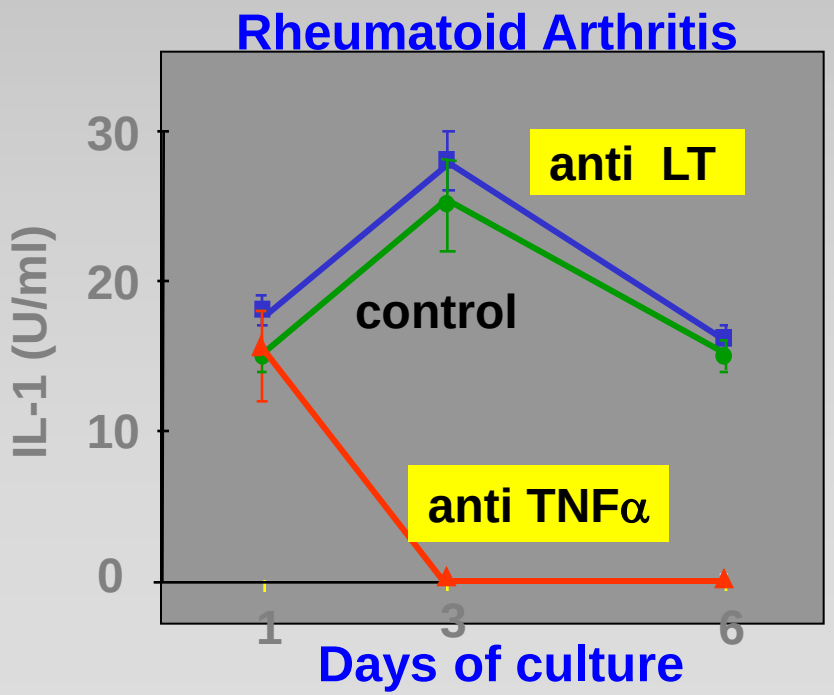
ANALYSIS OF CYTOKINE REGULATION
REVEALED IMPORTANCE OF TUMOUR NECROSIS FACTOR

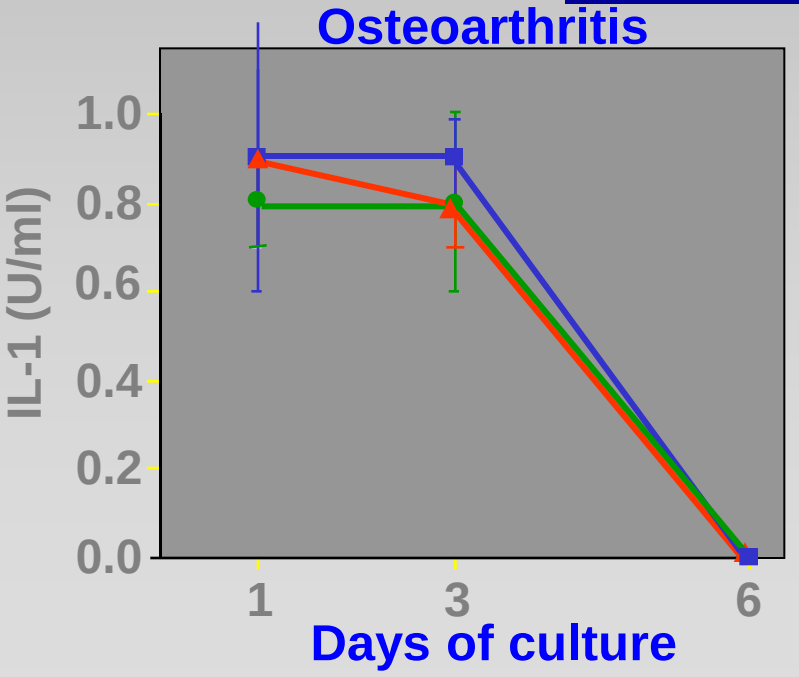
APPROACH Operative sample RA synovium, cells placed in 'tissue culture'

OBSERVATION Spontaneous production of cytokines etc

EXPERIMENT Antibody to TNF

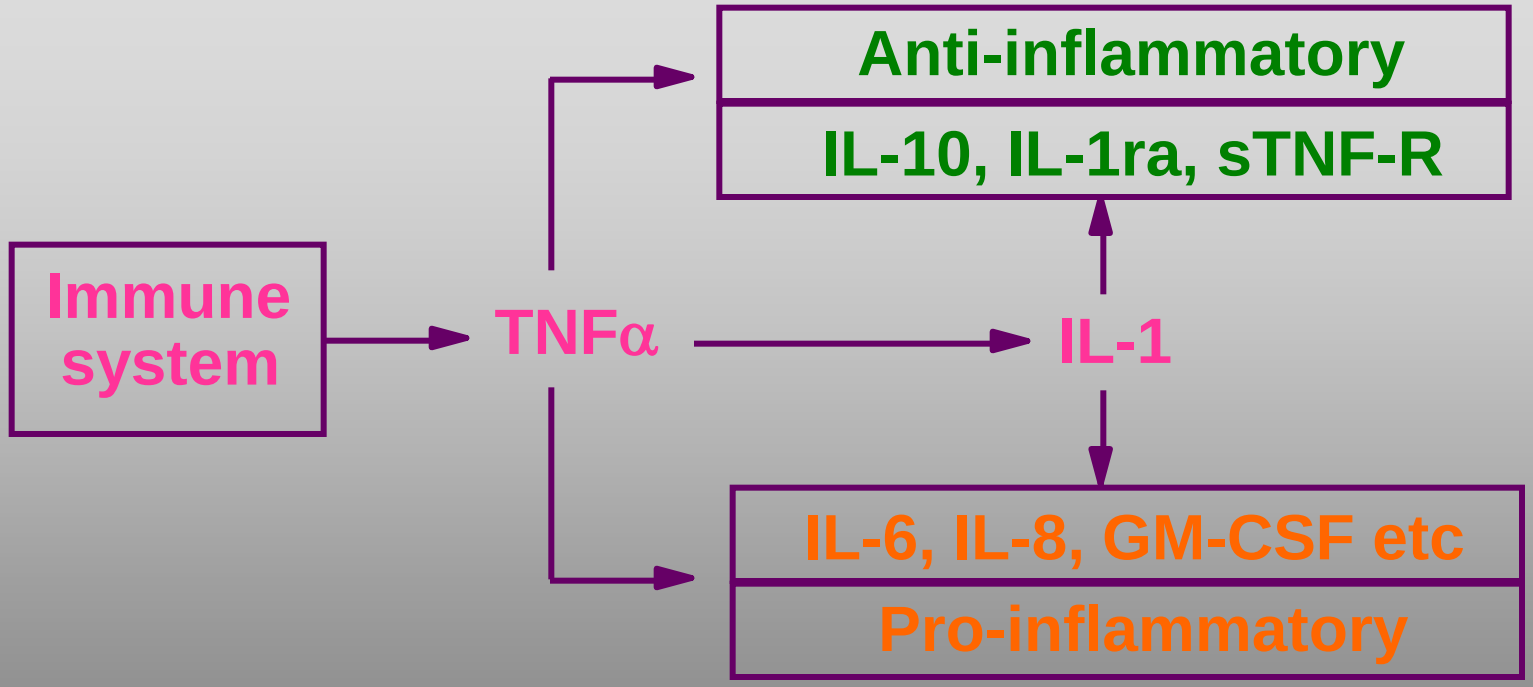
Fionula Brennan





Brennan et al (1989) Lancet ii 244-247

TNF DEPENDENT CYTOKINE CASCADE IN RHEUMATOID ARTHRITIS



A USEFUL OVERSIMPLIFICATION….

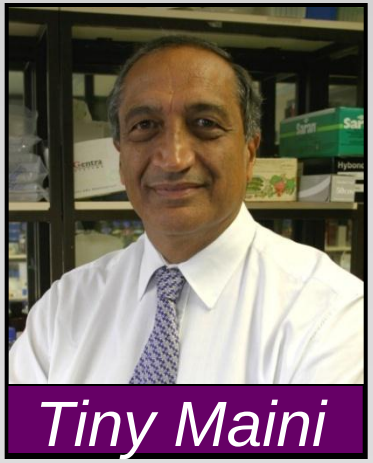
Feldmann, Brennan and Maini (1996) Cell, 85: 307

RATIONALE FOR ANTI-TNFα THERAPY IN RHEUMATOID ARTHRITIS

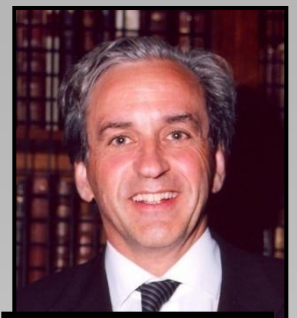
1. Disregulated cytokine network in RA synovium is dependent on TNFα

2. TNFα/TNF-Receptor upregulated in synovium

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



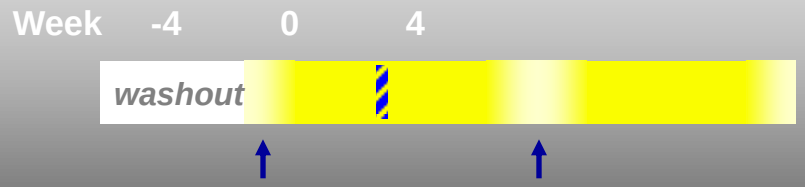
FORMAL PROOF:
RANDOMISED, PLACEBO-CONTROLLED TRIAL OF INFLIXIMAB IN RHEUMATOID ARTHRITIS


Ferry Breedveld


Jochen Kalden

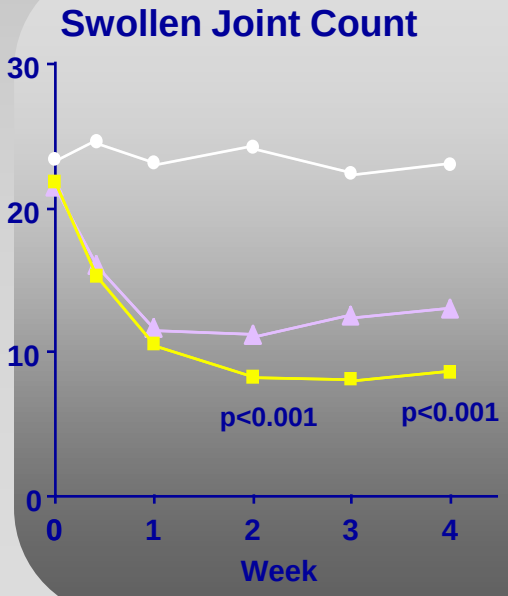

Josef Smolen

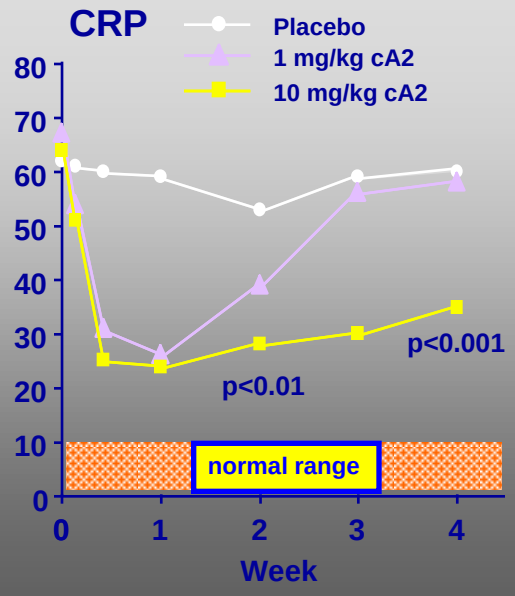
Design

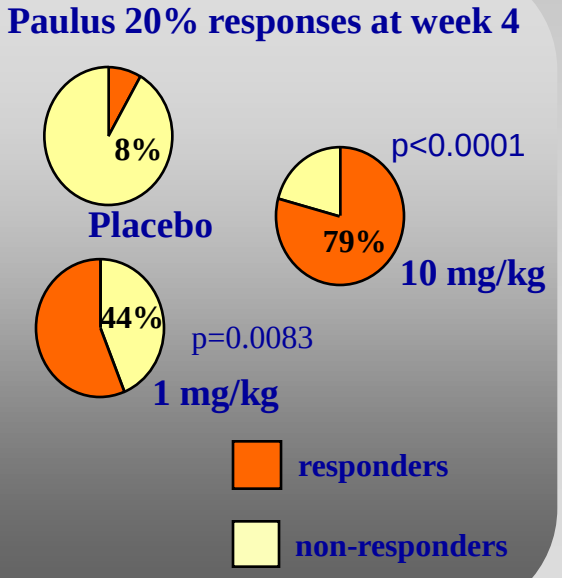


Results

- well-tolerated
- good clinical responses in cA2 groups
- dose-response relationship

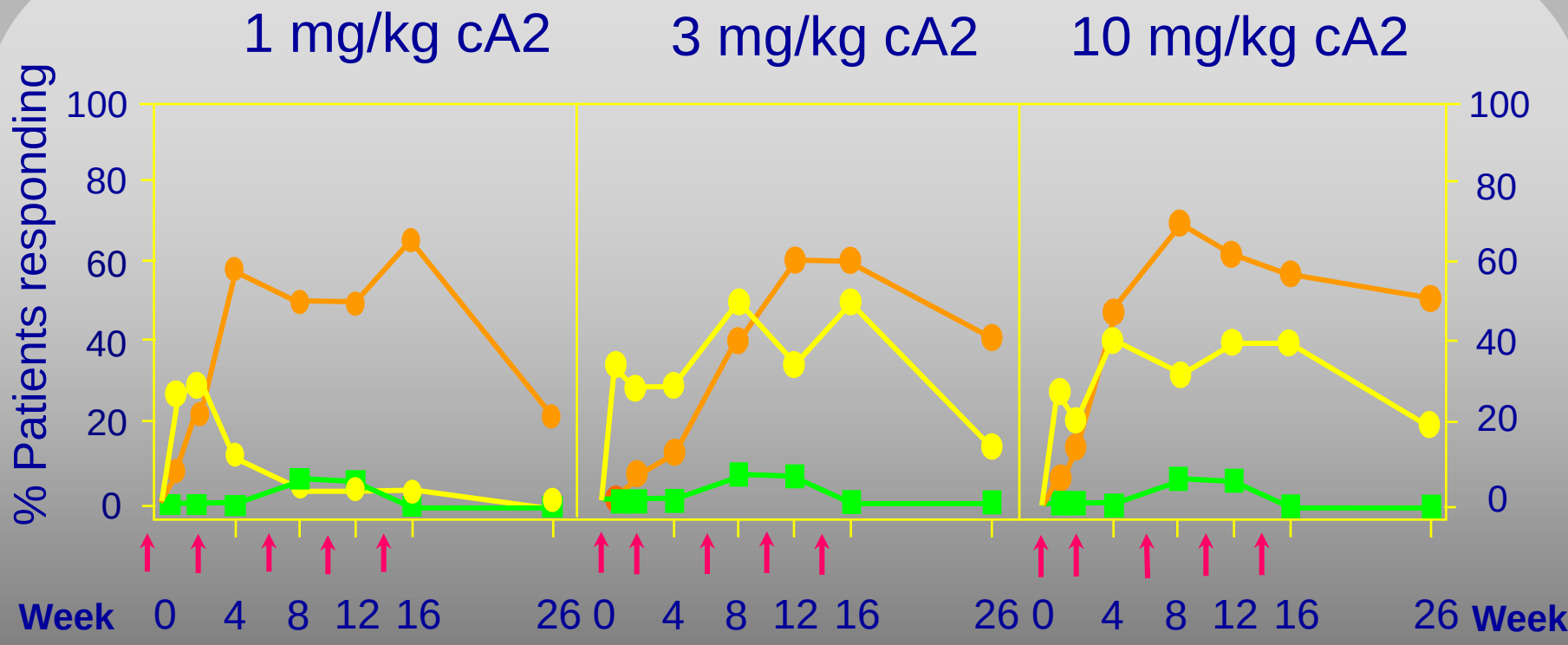






Elliott, Maini, Feldmann et al, Lancet 1994; 344: 1105-10

ENHANCED EFFICACY OF ANTI-TNF WITH METHOTREXATE: ACR 50 *(50% Paulus response)*

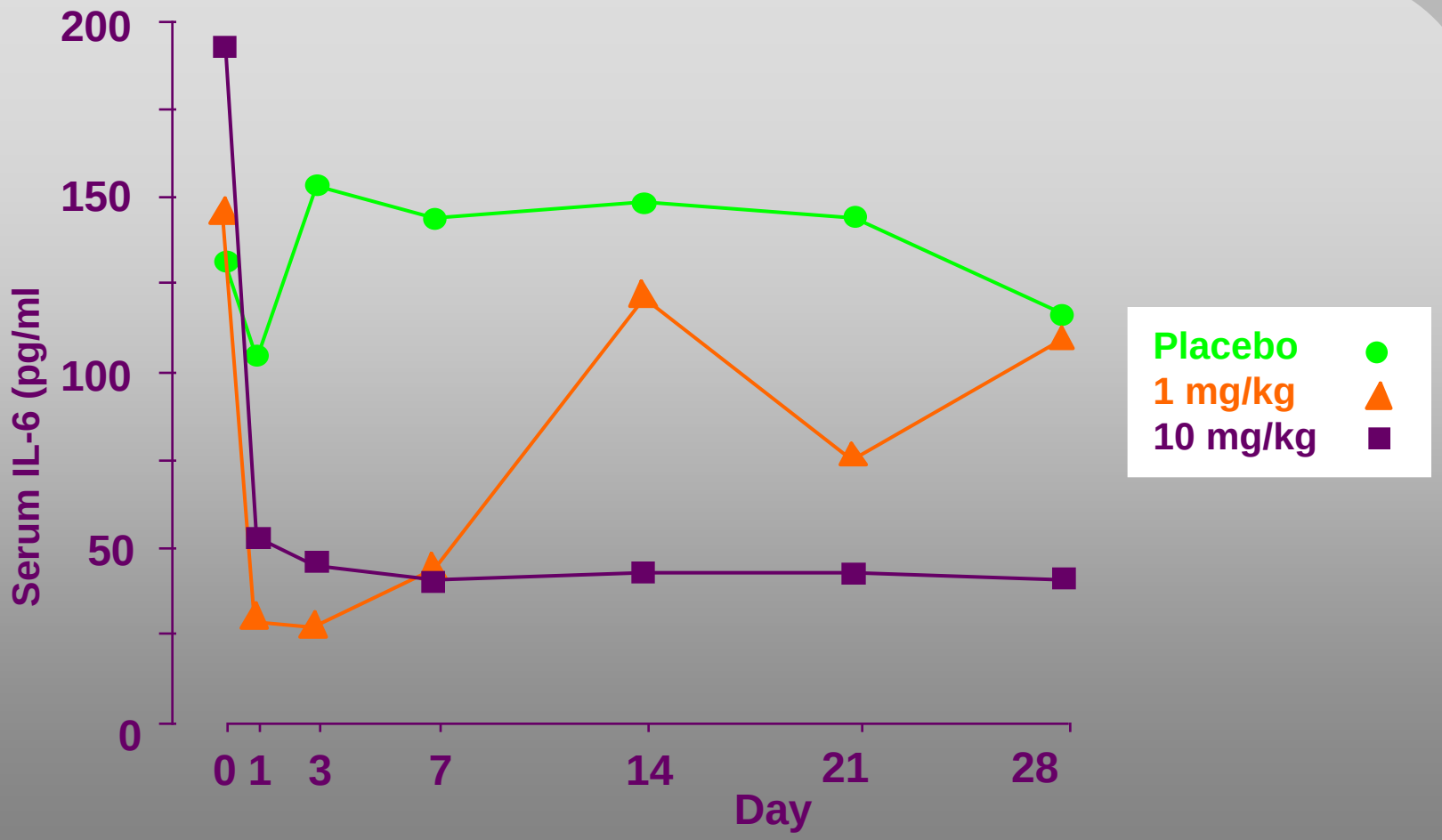


Used in >70% patients

Kennedy Institute gets royalties on USE patent

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

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

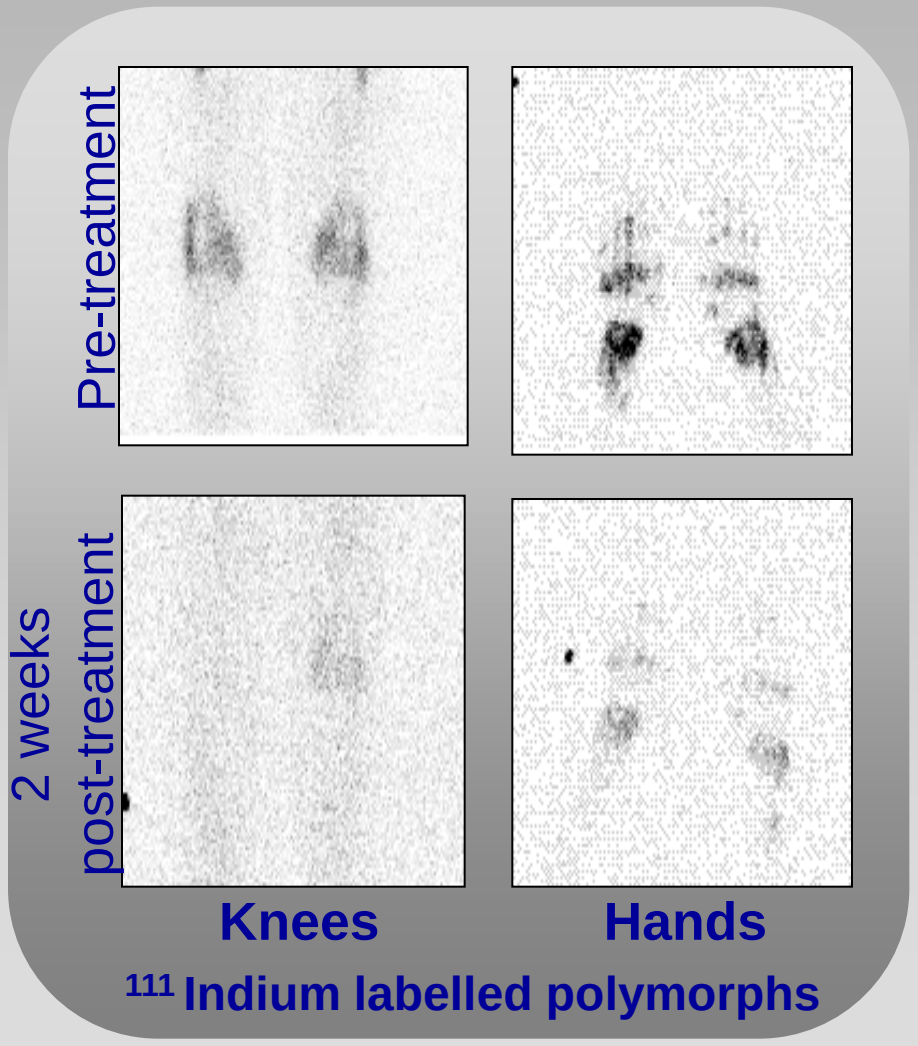


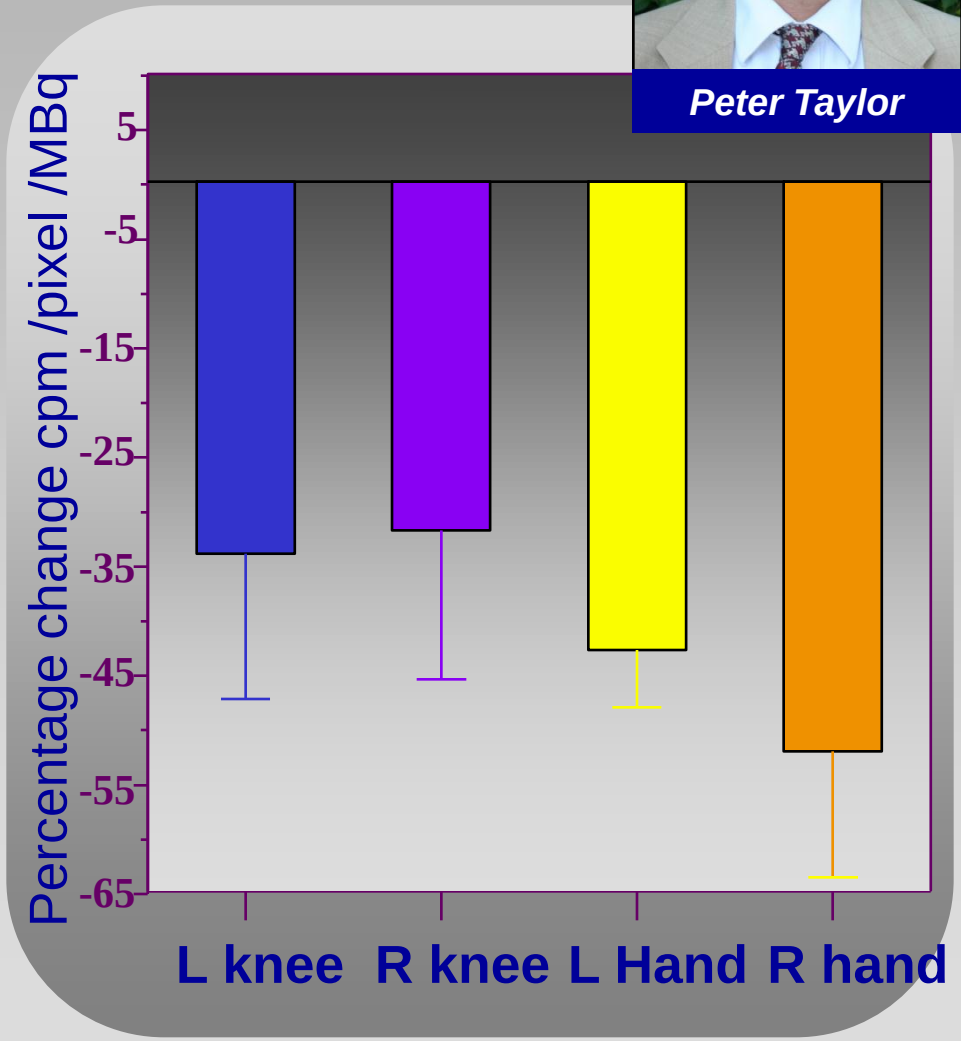
Also IL-1, GM-CSF, IL-8, VEGF etc

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

MECHANISM OF ACTION:
REDUCED LEUCOCYTE TRAFFICKING AFTER INFLIXIMAB THERAPY

Peter Taylor





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

TNF BLOCKADE IN OTHER DISEASE:

1. CLINICAL STUDIES IN MANY DISEASES

2. APPROVAL ALSO IN:
   - Juvenile RA
   - Ankylosing spondylitis
   - Psoriatic arthritis
   - Psoriasis
   - Crohn's disease
   - Ulcerative colitis

3. ROUTINE USE IN:
   - Behcet's
   - Amyloidosis
   - etc

4. FUTURE USE:
   - Fibrosis-Dupuytren's
   - Post-Operative Cognitive Decline

CURRENT PROBLEMS OF ANTI-TNF THERAPY

1. Not all patients respond
2. Degree of response inadequate
3. Side effect profile ● Infection
4. Cost of therapy ($20-30K)

UNEXPECTED: ACCELERATING A THERAPEUTIC REVOLUTION


Georges Köhler


Cesar Milstein

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

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


Greg Winter

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

SALES OF MONOCLONAL ANTIBODIES

2012 5 of top 10 drugs Mabs
anti-TNF biggest drug class
Mab revolution driven by
- anti TNFs - $25bn
- anti cancer - >$20bn

ANTI-TNF THERAPY: PRIME EXAMPLE OF BENEFIT OF OPEN RESEARCH

1. **Hypothesis** ➡ **Rationale** ➡ **Proof of Principle 1983-1992**

2. **Public Disclosure** - **Sept 1992**
   - **Publication Dec 1993**

- **Grant by Centocor did not prevent early disclosure for common good**
- **Other companies joined fray post hearing of clinical success e.g. Celltech, Roche, Immunex, BASF (Abbott)**

Public disclosure is a fundamental principle of science:

credit for discovery depends on disclosure

- **first to disclose is discoverer (Royal Society 1660's)**
- **reproducibility is key to science**

TIMELINE: DISCOVERY AND DEVELOPMENT OF ANTI-TNF THERAPY

ACADEMIC

1983	Hypothesis
1985-90's	Cytokine analysis in RA and Joints
1989	TNF dependent cytokine cascade (Brennan)
1991	Anti-TNF ameliorates mouse arthritis (Williams)
1992	Proof-of-Principle open trial London } GRANT
1992/3	Re-treatment }
SEPT 1992	DISCLOSURE IN ARAD, ISRAEL
DEC 1993	PUBLICATION

COMMERCIAL

1993	Randomized, placebo-controlled
1994-5	Dose ranging and combination
1996	Mechanism Action
1997-8	Phase III

1998/9	Registration Etanercept/Infiliximab
2002	Approval NICE
2003-	Safety by patient registers

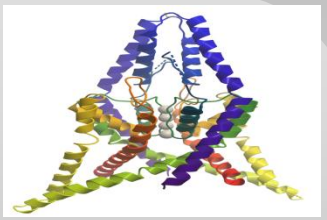
2002 ONWARDS Commercial and Patent Disputes

PUBLIC-PRIVATE PARTNERSHIPS

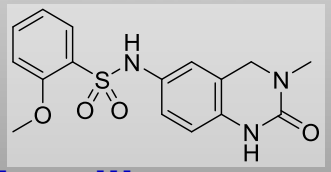
example in Toronto/Oxford - Structural Genomics Consortium

SGC-Oxford: human proteins/ structures to facilitate therapeutics development

- **World leader in human protein structural biology**
  - Nearly 700 novel structures
  - 8% of all structures solved per annum



- **Generating freely available novel epigenetic inhibitors**
  - 10 so far
  - 5 more per annum
  - In partnership with 8 companies (GSK, Pfizer, Novartis, Lilly, Abbvie, Boehringer-Ingelheim, Janssen, Takeda)

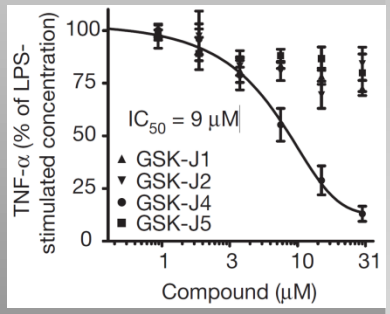


- **Now working closely with Kennedy Institute, to help discover a cure for RA**

SGC

FUTURE: EVOLUTION OF SGC

- Working closely with Kennedy Institute to develop new therapeutics on new targets
  e.g. DDR1
  CCR4-CAF1
- Use of human disease cells to improve target validation
  - increase throughput
- Taking new targets and drugs into proof-of-principle clinical trials



KEY POINTS

- Academic researchers far outnumber Industrial
- Certain specialized skills only in academia due to restricted resources e.g. human blood/tissue
- Avoiding needless duplication reduces costs, improves quality
- i.p. on targets difficult to sustain
- Commerical use of targets leads to new drugs with solid i.p.

SGC

CONCLUSIONS

- **Private-Public partnerships are a very efficient way of conducting research with major human impact**

ACKNOWLEDGEMENTS

Fionula Brennan

Peter Taylor

Sir Ravinder Maini

Richard Williams

Claudia Monaco

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