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

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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
- 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)

Expression of HLA-DR on cells usually negative indicates presence of inducers = cytokines
1983: A NEW HYPOTHESIS FOR AUTOIMMUNITY

Upregulation of HLA class II and antigen presentation

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

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.

Non tolerant autoantigen reactive T cells

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

HLA class II induction in human islet cells by interferon-g plus TNF or lymphotoxin

- Pujol-Borrell et al., 1987, Nature

VIRUSES

- CYTOKINES & INTERFERONS

TISSUE DAMAGE

- CYTOKINES
MANY CYTOKINES ARE PRODUCED IN RHEUMATOID SYNOVIOUM

**Pro-inflammatory**
e.g. IL-1, IL-6, TNF$_\alpha$, IL-12, IL-15, IL-17, IL-18, IFN$_\gamma$, IL-2, OncoM, GM-CSF

**Anti-inflammatory**
e.g. IL-10, IL-1Ra, TGF$_\beta$, IL-11, IL-13

**Chemokines**
e.g. IL-8, MIP-1$_\alpha$, MCP-1, RANTES, ENA-78, GRO$_\alpha$

**Growth Factors**
e.g. VEGF, PDGF, FGF

ARE ANY THERAPEUTIC TARGETS?

PRO-INFLAMMATORY

ANTI-INFLAMMATORY

CHRONICITY
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

Brennan et al (1989) Lancet ii 244-247
TNF DEPENDENT CYTOKINE CASCADE IN RHEUMATOID ARTHRITIS

Immune system

TNFα

Anti-inflammatory

IL-10, IL-1ra, sTNF-R

IL-1

IL-6, IL-8, GM-CSF etc

Pro-inflammatory

A USEFUL OVERSIMPLIFICATION….

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

Design
- Placebo
- 1 mg/kg cA2
- 10 mg/kg cA2
- 4, 3, 2, 1, 0 mg/kg or HSA
- Washout

Week -4 0 4

Results
- Well-tolerated
- Good clinical responses in cA2 groups
- Dose-response relationship

Swollen Joint Count
- p<0.001
- p<0.001

CRP
- Placebo
- 1 mg/kg cA2
- 10 mg/kg cA2
- p<0.001
- p<0.01

Paulus 20% responses at week 4
- 8%
- 79%
- 44%
- p<0.0001
- p=0.0083

responders
non-responders

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

- 1 mg/kg cA2
- 3 mg/kg cA2
- 10 mg/kg cA2

% Patients responding

Week 0 4 8 12 16 26 0 4 8 12 16 26 0 4 8 12 16 26

- Placebo – MTX-
- cA2 – MTX-
- cA2 – MTX+

Used in >70% patients

Kennedy Institute gets royalties on USE patent

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

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

MECHANISM OF ACTION:
REDUCED LEUCOCYTE TRAFFICKING
AFTER INFLIXIMAB THERAPY


Knees
Hands

Pre-treatment

2 weeks
post-treatment

\(^{111}\) Indium labelled polymorphs

Percentage change cpm / pixel / MBq

L knee  R knee  L Hand  R hand

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)
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

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


- 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

<table>
<thead>
<tr>
<th>Year</th>
<th>Event/Outcome</th>
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<tbody>
<tr>
<td>1983</td>
<td>Hypothesis</td>
</tr>
<tr>
<td>1985-90’s</td>
<td>Cytokine analysis in RA and Joints</td>
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<tr>
<td>1989</td>
<td>TNF dependent cytokine cascade (Brennan)</td>
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<td>1991</td>
<td>Anti-TNF ameliorates mouse arthritis (Williams)</td>
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<td>1992/3</td>
<td>Re-treatment</td>
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<td>SEPT 1992</td>
<td>DISCLOSURE IN ARAD, ISRAEL</td>
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<tr>
<td>DEC 1993</td>
<td>PUBLICATION</td>
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### COMMERCIAL

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<th>Year</th>
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<tr>
<td>1993</td>
<td>Randomized, placebo-controlled</td>
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<tr>
<td>1994-5</td>
<td>Dose ranging and combination</td>
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<td>1996</td>
<td>Mechanism Action</td>
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<tr>
<td>1997-8</td>
<td>Phase III</td>
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<tr>
<td>1998/9</td>
<td>Registration Etanercept/Infliximab</td>
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<td>2002</td>
<td>Approval NICE</td>
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<tr>
<td>2003-</td>
<td>Safety by patient registers</td>
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<tr>
<td>2002 ONWARDS</td>
<td>Commercial and Patent Disputes</td>
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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
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
• Commercial use of targets leads to new drugs with solid i.p.
CONCLUSIONS

• Private-Public partnerships are a very efficient way of conducting research with major human impact
FUNDING: ARUK, KTRR, MRC, Wellcome Trust, Centocor, Inc., Nuffield Foundation, etc