IMMUNOTHERAPY AS THE SPRINGBOARD TOWARDS A CURE FOR RHEUMATOID ARTHRITIS

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THE BEGINNINGS OF IMMUNOLOGY

1908 NOBEL PRIZE: Eli Metchnikoff and Paul Ehrlich
Recognition of Immunology as a Scientific Discipline

Eli Metchnikoff
Founder of “Innate Immunity”, Inflammation, Phagocytosis etc

Paul Ehrlich
Founder of “Adaptive Immunity”
Predicted Autoimmunity

Illustrations from S. Kaufmann, Nat. Immunol. 2008
AUTOIMMUNITY = IMMUNE DEFENCE SYSTEM AWRY

ATTACKS SELF

Paul Ehrlich
‘Horror Autoxicus’ concept proposed 1900’s

Evidence in 1950’s
Sir Frank McFarlane Burnet (Melbourne)

Many Autoimmune Diseases
e.g. Juvenile Diabetes
Multiple Sclerosis
Rheumatoid arthritis

Genetic Control of Immunity:
Hugh McDevitt (Stanford) 1970s
HLA genes control immunity
Major genetic risk factor in autoimmunity

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

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

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.

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

Hypothesis: Role of aberrant HLA-DR expression and antigen presentation in the induction of endocrine autoimmunity.

Autoantibodies and tissue damage

Non tolerant autoreactive T cells

B

APC

Marco Londei

CytoKines

CytoKines & Interferons

CytoKines

Viruses

Tissue Damage

CytoKines
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

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**TNF DEPENDENT CYTOKINE CASCADE IN RHEUMATOID ARTHRITIS**

**Immune system** → **TNFα** → **IL-1** → **IL-6, IL-8, GM-CSF etc** (Pro-inflammatory)

**Anti-inflammatory**
IL-10, IL-1ra, sTNF-R

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.

PIONEERS OF ANTIBODY THERAPY

Emil von Behring
Nobel Prize 1901

Georges Köhler
Cesar Milstein
Nobel Prize 1984
Monoclonal antibody technology

Von Behring and Ehrlich collaborated from 1893 on diphtheria antitoxin therapy
FORMAL PROOF:  
RANDOMISED, PLACEBO-CONTROLLED TRIAL 
of INFLIXIMAB IN RHEUMATOID ARTHRITIS

**Design**

Week -4 0 4  
washout

ca2:  1 or 10 mg/kg 
or HSA

3, 10 or 20 mg/kg

**Results**

well-tolerated

good clinical responses
dose-response

**Swollen Joint Count**

Week 0 1 2 3 4

CRP

Week 0 1 2 3 4

p<0.001  
p<0.01

3, 10 or 20 mg/kg

1 or 10 mg/kg 
or HSA

Paulus 20% responses at week 4

Week -4 0 4

washout

ca2:  44%

Placebo 8%

10 mg/kg 79%

responders

non-responders

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

% Patients responding

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

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

Placebo – MTX+  
ca2 – MTX+  
ca2 – MTX+

Used in >70% patients

Kennedy Institute gets royalties on USE patent

FDA APPROVALS OF ANTIBODY THERAPEUTICS

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 10⁶ 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
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

![Graph showing serum IL-6 levels over time for different treatments.](image)

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

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


111 Indium labelled polymorphs

L knee R knee L Hand R hand

Percentage change cpm / pixel / MBq

Peter Taylor

UNEXPECTED: ACCELERATING A THERAPEUTIC REVOLUTION

1977 Kohler and Milstein: mouse Mab by fusion
- problem of 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, $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

PLenty of scope for improvement
But no wheelchairs, walking frames, little joint surgery

Glass more than half empty!

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. RISK COMBINATION
   - Toxicity: 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**

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

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

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

![Graph showing clinical score and IL-10 production](image)


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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 (SomaLogic):
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?

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