Rheumatology: Leading the molecular revolution in the 21st century?

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Director, Institute of Infection, Immunity and Inflammation,
University of Glasgow
Scotland, UK
A molecular revolution in clinical medicine - RA?

• Lessons from a decade of progress…?
  • Celebrating success
  • Embracing therapeutic failure
  • Unmet needs remaining

• Towards the future?
  • Pathogenesis lead interventions
  • Novel therapeutics
  • Enriching for success

• Systems or “the system”
Rheumatoid arthritis: recognition of a syndrome
Therapeutics in RA: impact across the syndrome

- Reduced signs and symptoms of inflammation
- Reduced erosive progression
- Favorably altered co-morbid features:
  - vascular surrogates risk profile
  - osteoporosis
  - cognitive function
- Improved employability
- Remission achievable for a proportion
- ...
A pre-molecular history of arthritis management...

Willow (Salix)  Johann Andreas Buchner

SALICIN

ACTH, MTX

NSAIDs  GC +DMARD

1829  1948  1994
Lessons from a decade: molecular hierarchies exist

Many vulnerable nodes in inflammatory cascade – cell receptors and their requisite signalling pathways?

Cytokine-targeting biologics

- Anti-IL-1s
  - IL-1
  - Extracellular
  - Intracellular
  - Blockade of TNF signalling pathways

- Anti-TNFs
  - TNF
  - Extracellular
  - Intracellular
  - Blockade of IL-6R classic and trans signalling pathways

- Tocilizumab
  - Extracellular
  - Intracellular
  - Abatacept
    - Blocks co-stimulatory signal

Cell-targeting biologics

- Abatacept
  - T-cell receptor
  - Inhibition of T-cell activation

- Rituximab
  - T cell
  - B cell
  - Depletion of B cells

Lessons from a decade:
Towards molecular taxonomy in inflammation medicine?

See for example: Smolen J et al *Lancet* 2008
McInnes IB et al *Lancet* 2015

AID, autoinflammatory disease including Still’s disease; CD, Crohn’s disease;
GCA, giant cell arteritis; IL, interleukin; JIA, juvenile idiopathic arthritis; RA, rheumatoid arthritis;
SpA, spondyloarthritis; TNF, tumor necrosis factor; UC, ulcerative colitis

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The impact of strategy can be dramatic: TICORA

<table>
<thead>
<tr>
<th></th>
<th>Intensive group (n=55)</th>
<th>Routine group (n=55)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EULAR good response</td>
<td>80%</td>
<td>44%</td>
<td>3.6 (1.5, 8.7)*</td>
</tr>
<tr>
<td>EULAR remission</td>
<td>65%</td>
<td>16%</td>
<td>9.6 (3.8, 24.3)*</td>
</tr>
<tr>
<td>ACR 20</td>
<td>89%</td>
<td>64%</td>
<td>4.0 (1.5, 10.5)*</td>
</tr>
<tr>
<td>ACR 50</td>
<td>82%</td>
<td>45%</td>
<td>4.9 (2.1, 11.4)*</td>
</tr>
<tr>
<td>ACR 70</td>
<td>70%</td>
<td>18%</td>
<td>9.5 (3.9, 23.0)*</td>
</tr>
</tbody>
</table>


*p<0.001
Lessons from a decade: strategies matter in chronic disease

‘Treat to target’… but ‘knowing when to stop?’


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Lessons from a decade: remission in chronic disease?

Remission will lead to:
- lower radiographic progression
- sustained physical function
- mortality
- employability (?)

![Graph showing treatment initiation and progression rates with and without delay.]

Lessons from a decade: remission in chronic disease?

Despite early and aggressive intervention…

• Remission rates remain low, however defined
• Drug therapeutics are required for such disease state
• Damage is progressive in a proportion of patients
• Socioeconomic decline is ongoing
• Morbidity and mortality remain significant

• Management is not pathogenesis driven!

RA: over time does the immune system ‘adapt’ to the new scenario – embracing chronicity?

Immune adaptation: recruitment of new pathways
- Implications for therapeutics and the move to prevention

Lessons from a decade: do chronic diseases require tissue adaptation?


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Key current concepts of RA pathogenesis – clinical relevance?

Genetics
- Clear evidence of immune function contribution
- Epigenetic abnormalities, e.g. methylation, microRNA, chromatin structure

Environmental components
- Smoking (and other pulmonary stimuli, e.g. silica)
- Microbiome – periodontal disease, gastrointestinal / pulmonary mucosa
- Obesity, alcohol, vitamin D...

Evidence for early immune and metabolic perturbation – pre-arthritis onset?
- Autoantibodies – glycosylation status
- Epitope spreading
- Cytokines & chemokines
- Dyslipidaemia, metabolic syndrome

GWAS, genome-wide association studies
Towards pathogenesis lead interventions?

- Sequential, varied interactions...
  - Best explained by a multi-hit model?
- Subserved by complex immunology...
  - Adaptive
  - Innate
  - Perpetual
- Evolving concept of ‘RA syndrome’

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Towards pathogenesis lead interventions?


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Areas of potential interest in current development in RA?

**Moieties, Pathways and Cells...**

- DAMPs / PAMPs and other innate receptors
- *Chemokines / cytokines*
  - “me too” sarilumab, sarukumab...
  - e.g. CCR1, GM-CSFR, IL-17, IL-20, IL-21, BLyS...
- *Small molecule inhibitors* e.g. JAK, BTK, PI3K, epigenetic targets...
- Post translatational modification – PADI4
- Autoreactivity e.g. T cell, B cell, dendritic cells, MSC....
- Neuroendocrine pathways
  - e.g. vagal drive
  - GnRH antagonists

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Learning from success and failures: Targeted therapy based on interfering with (which?) critical immune cells and cytokines

Synovial histopathology

- Fibroblast
  - OSM, IL-11, IL-17, IL-18, IFN, IL-19, IL-20, IL-22, TGFβ

- Myeloid
  - Macrophage, dendritic cell
  - IL-11, IL-10, IL-12, IL-27, IL-32, OSM, GM-CSF, M-CSF, IFN, PDGF, RANKL, TGFβ

- Lymphoid
  - T cell, B cell
  - IL-2, IL-4, IL-7, IL-9, IL-10, IL-12, IL-13, IL-15, IL-21, IL-23, IL-27, IFN, TGFβ

Cytokine interplay

Synoviocyte

Bone and cartilage

GM-CSF = granulocyte macrophage colony-stimulating factor, IFN = interferon; M-CSF = macrophage colony-stimulating factor; OSM = oncostatin M; PDGF = platelet-derived growth factor; RANKL = receptor activator of nuclear factor-κB ligand; TGF = transforming growth factor

Learning from success and failures: Targeted therapy within the cell to target cytokines?

TNF, IL-1

FcR, BCR

FcR, Cytokine R

GPCRs e.g. chemokines

TNF, IL-1

Various Cytokines

BTK

PI3K

Syk

PI3K

Kinases

ERK

JNK

p38

Second messengers

Lipid messengers

Gas

AC

PDE4

PKA

JAK

JAK

Signal transduction

Gene transcription

Nucleus


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Enriching for response:
Developing biomarkers in chronic inflammation

Adapted from:

**Descriptive Biomarkers**
- Imaging-based biomarkers (X-ray, CT, MRI, DEXA)
- Acute-phase reactants (e.g., ESR, CRP, SAA)

**Mechanistic Biomarkers**
- Autoantibodies
- Gene-expression signatures
- Cytokines
- Immune-cell types
- Genotype

- Diagnosis of symptomatic disease
- Assessment of disease activity
- Assessment of drug-related toxicity

**Breach of tolerance**
- Genetic susceptibility
- Epigenetic modification
- Environmental factors

**Transition event**
- Autoreactivity
  - ACPA
  - RF
- Synovitis
- Structural damage
- Comorbidity

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Do we really need a personalised medicine based approach?

Consider:

• Responses post TNFi are equivalent regardless of treatment modality
• Combinatorial biologic approaches increase AEs but not efficacy

therefore…

Forget personalised medicine and focus on abating disease activity

Josef S Smolen,¹,² Daniel Aletaha¹


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Do we really need a personalised medicine based approach: lessons from the real world?
Do we really need a personalised medicine based approach: lessons from the real world?

<table>
<thead>
<tr>
<th></th>
<th>TNFi-first</th>
<th>Rituximab-first</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Medicines, infusions, clinics</td>
<td>£10,356</td>
<td>£8,391</td>
<td>&lt;0.001*</td>
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<tr>
<td>Primary care</td>
<td>£370</td>
<td>£366</td>
<td>0.92</td>
</tr>
<tr>
<td>Blood tests, Xray</td>
<td>£163</td>
<td>£141</td>
<td>0.51</td>
</tr>
<tr>
<td>Total</td>
<td>£11,523</td>
<td>£9,405</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

Bootstrap estimated mean cost difference (95% CI) = £1,999 (£2,755, £1440)

Quality-Adjusted Life Years (1-EQ-5D AUC)

<table>
<thead>
<tr>
<th></th>
<th>QALYs</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>QALYs</td>
<td>0.481</td>
<td>0.454</td>
<td>p=0.25</td>
</tr>
</tbody>
</table>

Bootstrap estimated mean QALY difference (95% CI) = 0.028 (-0.041, 0.094)

* Wilcoxon
The promise of personalised medicine

Disease population -> One size fits all treatment
Mixed responders, mixed outcomes

Disease population -> Stratification tools -> Disease cohorts -> Matched treatments
More responders, better outcomes
The promise of personalised medicine
Profiling the circulating CCS signature in early RA

- SERA - >1000 patients
- 123 genetic loci
- *in silico* prediction of high-confidence CCS candidates
  - 13,322 CCS probes
  - 99 ± 64 CCS per loci
  - Tested in quadruplicate

Carini C, Goodyear C et al McInnes IB (submitted 2016)
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The critical challenge in biomarker development in chronic inflammatory diseases?

"There is something fascinating about science. One gets such wholesale returns of conjecture out of such a trifling investment of fact."

Mark Twain from Life on the Mississippi
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• Systems or “the system”
The current translational model?

GA FitzGerald,

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Does our translational model work...

Genomic responses in mouse models poorly mimic human inflammatory diseases

Junhee Seok1,*, H. Shaw Warren1,*, Alex G. Cuenca1,*, Michael N. Mindrinos1,*, Henry V. Baker1,*, Weihong Xu1,*, Daniel K. Richards1,*, Grace P. McDonald-Smith1,*, Hong Gao1,*, Laura Hennessy1,*, Celeste C. Finnerty1,*, Cecilia M. Lopez1,*, Shari Honari1,*, Ernest E. Moore1,*, Joseph P. Minei1,*, Joseph Cusciere1,*, Paul E. Bankay1,*, Jeffrey L. Johnson1,*, Jason Sperry1,*, Avery B. Nathens1,*, Timothy R. Billiar1,*, Michael A. West1,*, Marc G. Jeschke1,*, Matthew B. Kleir1,*, Richard L. Gamelli1,*, Nicole S. Gibran1,*, Bernard H. Brownstein1,*, Carol Miller-Graziano1,*, Steve E. Calvano1,*, Philip H. Mason1,*, J. Perren Cobb1,*, Laurence G. Rahme1,*, Stephen F. Lowry1,*, Ronald V. Maier1,*, Lyle L. Moldawer1,*, David N. Herndon1,*, Ronald W. Davis1,*, Wenhong Xiao1,*, Ronald G. Tompkins1,*, and the Inflammation and Host Response to Injury, Large Scale Collaborative Research Program

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Contributed by Ronald W. Davis, January 7, 2013 (sent for review December 6, 2012)

Perhaps not....!
Does our translational model work...
What is Systems Medicine?
How could systems medicine help?

- Improved molecular resolution of key cellular / molecular players.
  - *e.g. the true IgG repertoire in healthy individuals or in response to infectious disease.*

- Improved methods for stratifying patient subgroups in heterogeneous diseases
  - leading to improved diagnostics and therapeutic regimes.

- Insight into the systemic effects of medications.
  - *Lipid metabolism, hepatic toxicity*....

- Insight into the disease process for new therapies
  - drug design, drug repurposing and best practice.

http://genome.cshlp.org/content/19/10/1817 – Robert Holt T-cell receptor beta chain sequencing. 

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The systems “conundrum”

• More data should lead to more insight
• Which cell, which parameter, which platform?
  – not all information will be informative, reproducible or insightful
  – no formula for working this out.
• Becomes a computational/statistical question
  – how do we bring biology or clinic back into the picture?
The data “conundrum”
The three principals for making sense of Systems-scale data

– **Modularity**: finding networks and pathways
– **Emergence**: gaining insight from layers of data.
– **Robustness**: understanding network properties

In practical terms, we must resource:

1/ generation of quality data
2/ tools for visualization, integration and sharing of data
3/ collaboration between bioinformatics, biostatistics and biologists to mine the data
or…. “How do we choose new biomarkers & targets in a rational way?”

- **Linear models**
  - TNF is predominant

- **Parallel models**
  - TNF and IL-6 sit in parallel but can be dominant

- **Network theory**
  - Complex networks of cytokines exist in functional modules
  - Predicated on their role in host defense
or…. “How do we choose new biomarkers & targets in a rational way?”

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Feldmann M et al *Cell* 1996 85;307
Cytokines and RA – embracing complexity

Adaptive immunity
- Ectopic lymphoid structure
- T cells / DC
- B cells

Lining layer
- FLS
- Macrophages

Interstitium
- Mast cells
- Macrophages
- Neuroreceptors

Trafficking
- Angiogenesis
- Lymphangiogenesis
Cytokines and RA
– embracing complexity

Adaptive immunity
- Ectopic lymphoid structure
- T cells / DC
- B cells

Interstitium
- mast cells
- macrophages
- neuroreceptors

TNF, IL-1, GM-CSF
IL-6, IL-15, IL-17
IL-18, IL-20, IL-23, IL-32...
Inflammatory chemokines

Lining layer
- FLS
- macrophages

Trafficking
- angiogenesis
- lymphangiogenesis

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Evolving models for cytokine hierarchies in synovitis?

- **Linear models**
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- **Parallel models**
  - TNF and IL-6 sit in parallel but can be dominant

- **Network theory**
  - Complex networks of cytokines exist in functional modules
  - Predicated on their role in host defense
RA: can we define functional modules of inflammatory moieties within biologic networks?

RA: can we define functional modules of inflammatory moieties within biologic networks?


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Empowering clinical rheumatologists to navigate data to find useful patterns

Traditionally

- Biology-group generates data
- Black Box
- Bioinformatician analyses data

3iiiformatics.org approach

- Biology-driven question
- Clinical Researcher
- Bioinformatician
- Data application

Direct and intuitive interaction with your own data

Collaborative environments that enable biology
...drives clinical insight
...as well as facilitates computational outcomes

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Rheumatology – leading the molecular revolution?

Plausible, enticing therapeutics are emerging in RA and are required…
• Unmet needs remain…
• Capitalizing on ‘new’ immunopathology going forward

Encouraging efficacy, but…
• Strategically ill-defined?
• Biomarkers to revolutionize the approach?
• Integrating systems versus minimalist science

Towards a molecular taxonomy…
• Define clinical endotypes
• Towards preventative therapeutics
• Can we repair those already damaged?