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

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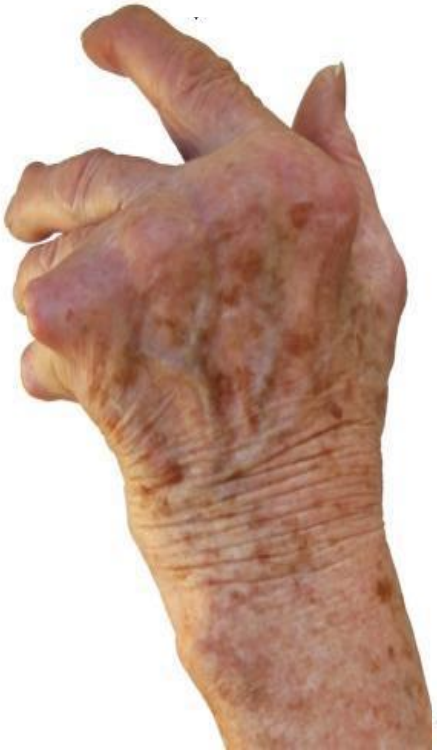
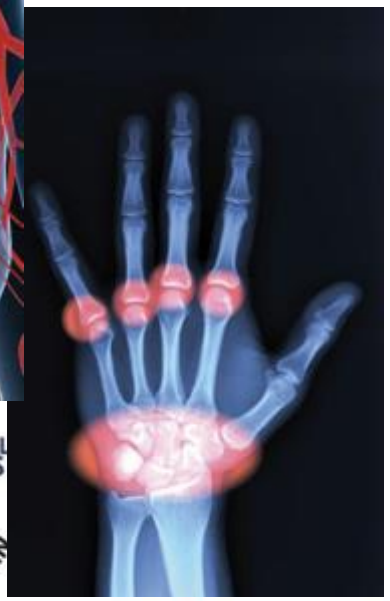
AJS McFadzean Distinguished Lecture 2016

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



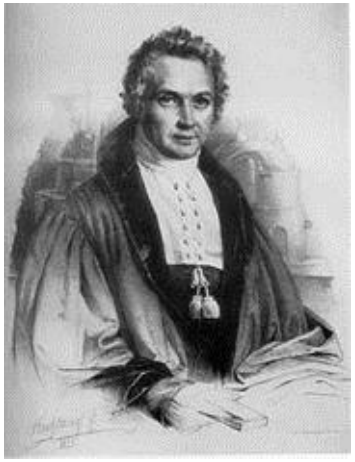


Therapeutics in RA: impact across the syndrome

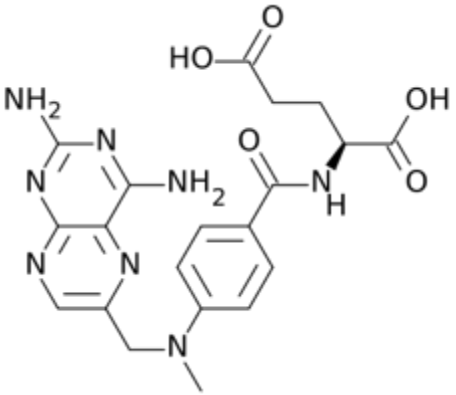
- **Reduced signs and symptoms of inflammation**
- **Reduced erosive progression**
- **Favorably altered co-morbid features:**
  - **vascular surrogates risk profile**
  - **osteoporosis**
  - **cognitive function**
- **Improved employability**
- **Remission achievable for a proportion**
- **…**

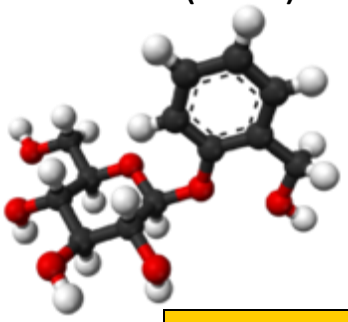
A pre-molecular history of arthritis management...

Willow (Salix)

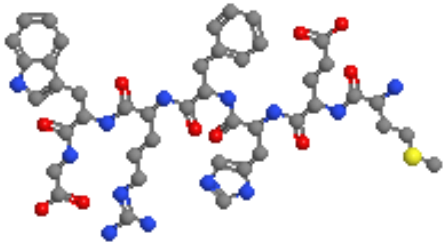


Johann Andreas Buchner

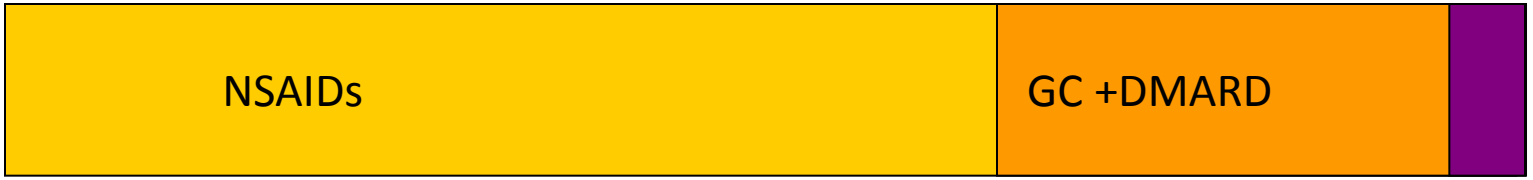




SALICIN



ACTH, MTX



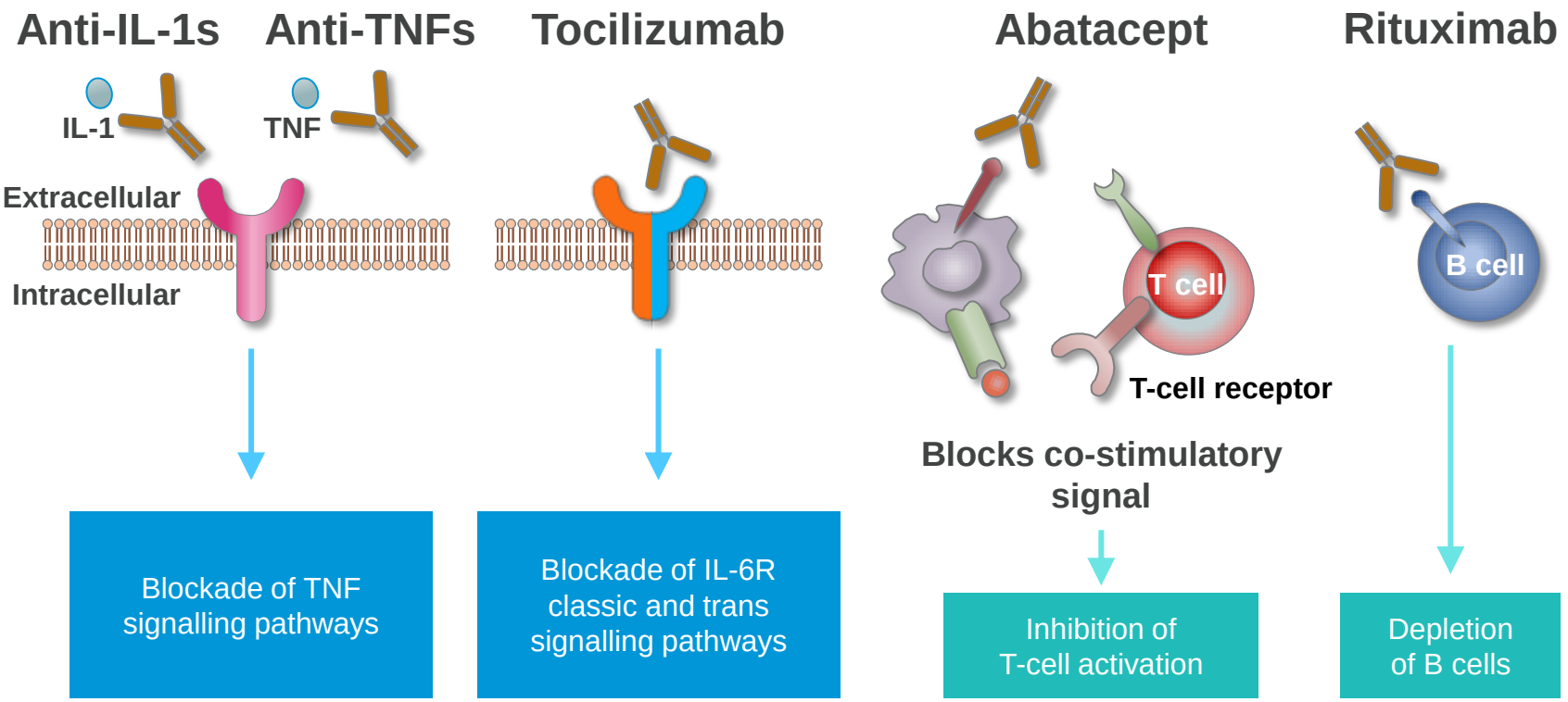
1829 1948 1994

Lessons from a decade: molecular hierarchies exist

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

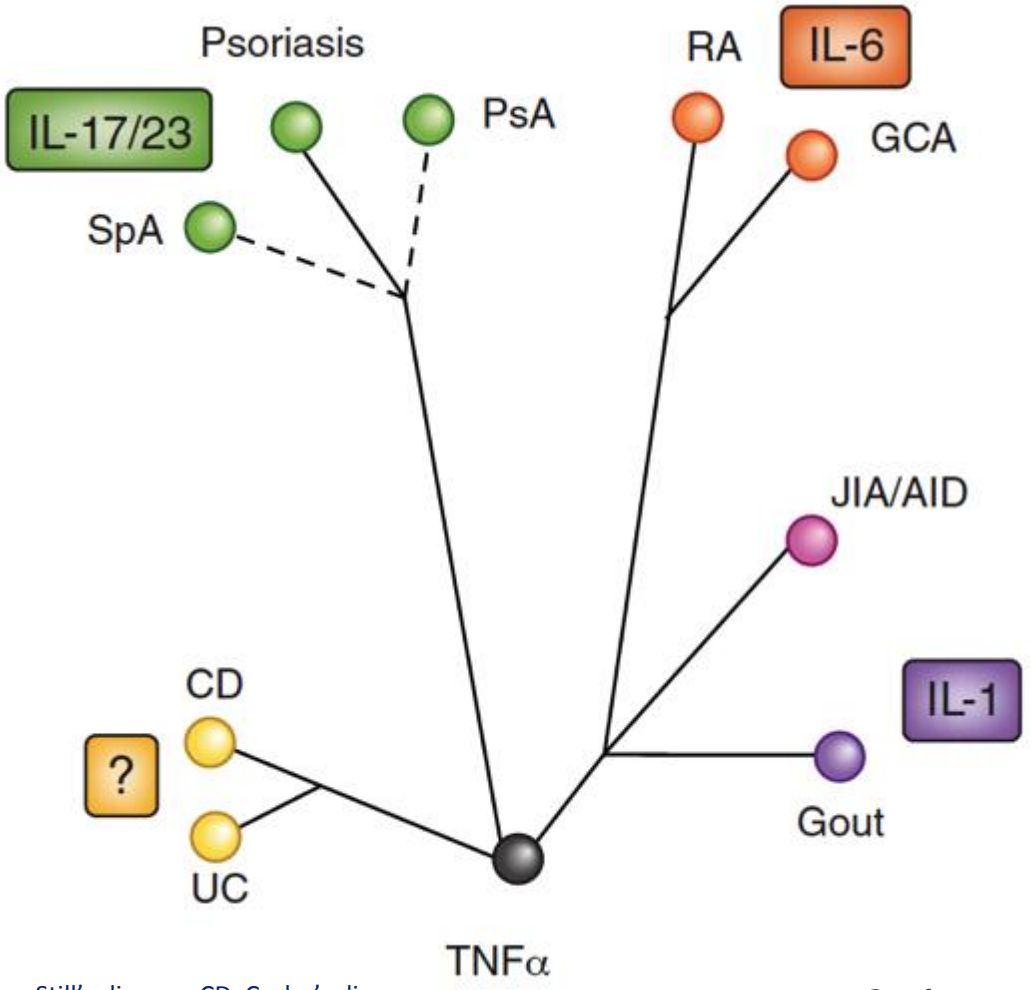
Cytokine-targeting biologics

Cell-targeting biologics



Choy EH, *et al. Nat Rev Rheumatol* 2013; **9**:154–163.; McInnes IB & Schett G. *N Engl J Med* 2011; **365**:2205–2219. Emery P & Dörner T. *Ann Rheum Dis* 2011; **70**:2063–2070.; Edwards JC, et al. *Curr Dir Autoimmun* 2005; **8**:175–192.; Ko HJ, *et al. J Autoimmun* 2010; **34**:111–120.; Woodrick RS & Ruderman EM. *Nat Rev Rheumatol* 2011; **7**:639–652.

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



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

See for example: Smolen J et al *Lancet* 2008

Schett G, McInnes IB et al. *Nature Med* 2013

McInnes IB et al *Lancet* 2015

The impact of strategy can be dramatic: TICORA

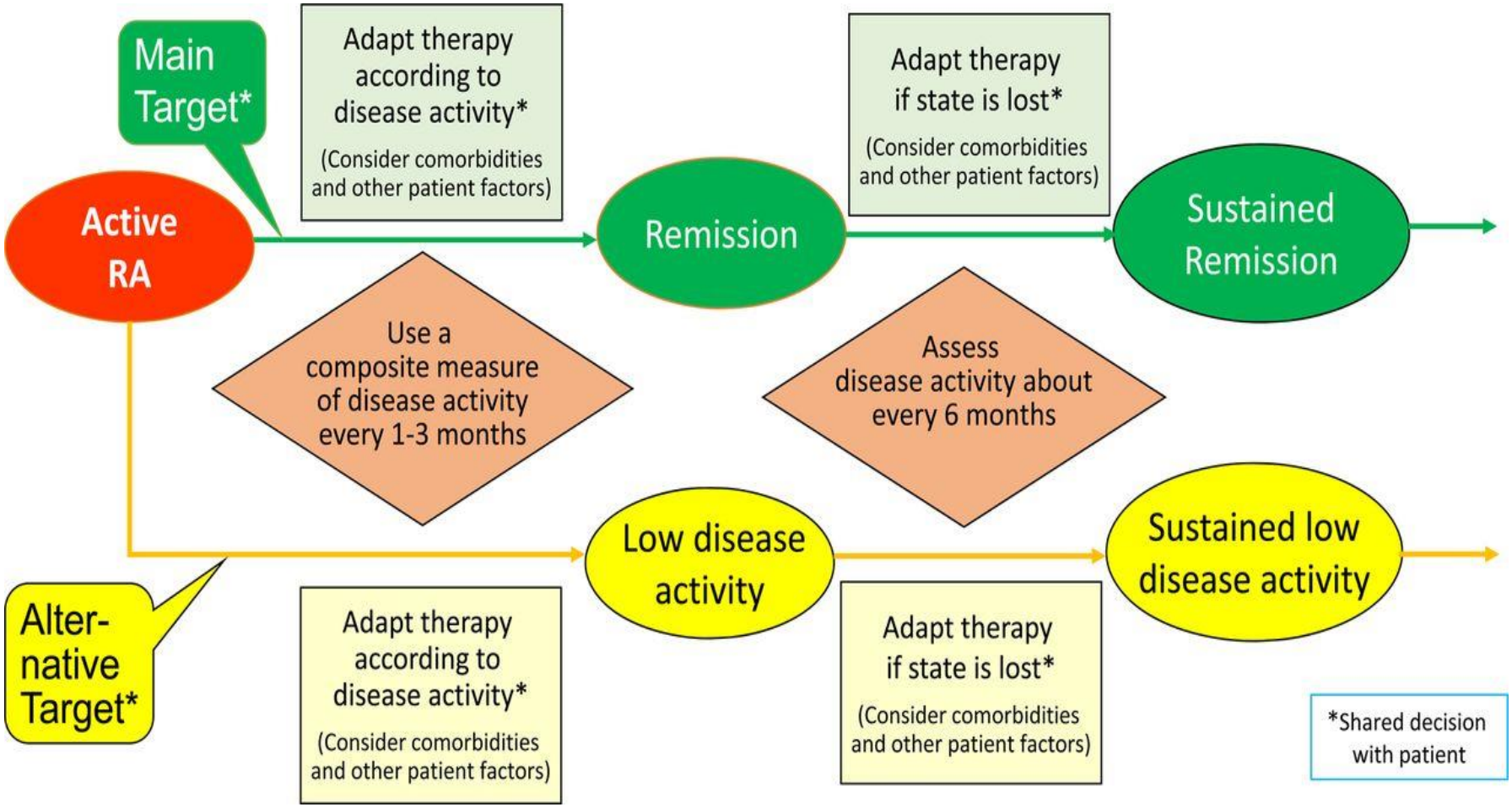
	Intensive group n=55	Routine group n=55	Odds ratio (95% CI)
EULAR good response	80%	44%	3.6 (1.5, 8.7)*
EULAR remission	65%	16%	9.6 (3.8, 24.3)*
ACR 20	89%	64%	4.0 (1.5,10.5)*
ACR 50	82%	45%	4.9 (2.1,11.4)*
ACR 70	70%	18%	9.5 (3.9,23.0)*

Grigor et al. *Lancet* 2004; 364:263-69

*p<0.001

Lessons from a decade: strategies matter in chronic disease

'Treat to target'… but 'knowing when to stop?'

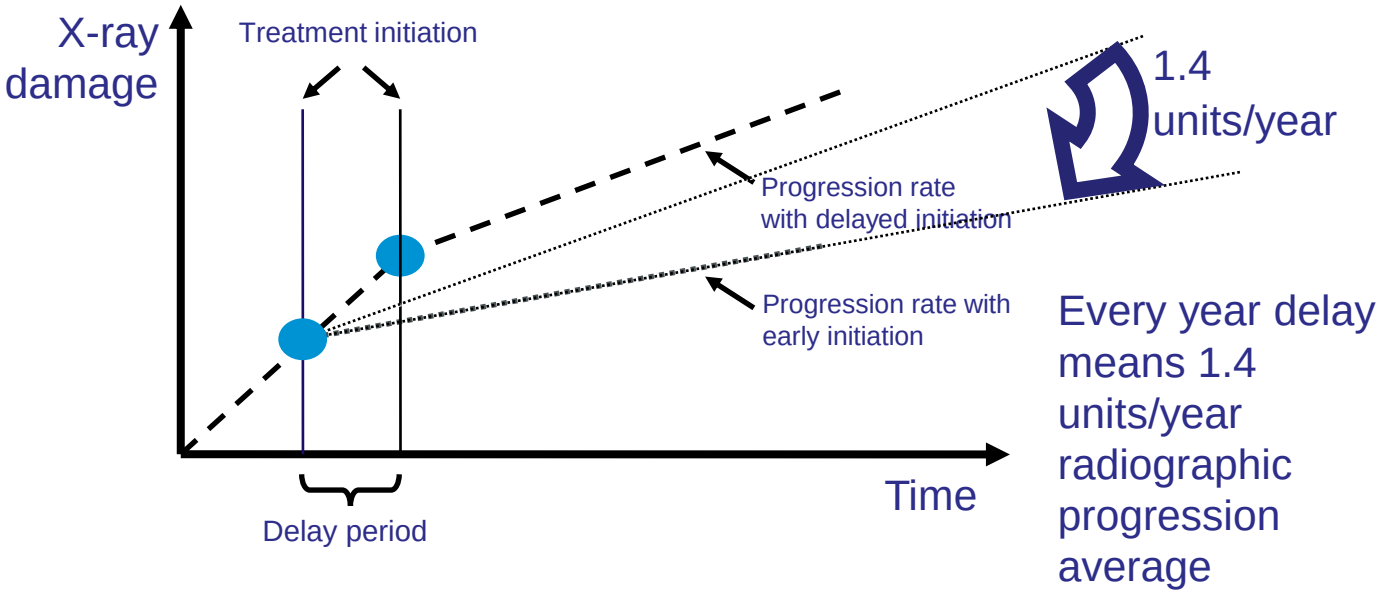


Adapted from Smolen JS et al (2015) Ann Rheum Dis doi:10.1136/annrheumdis-2015-207524

Lessons from a decade: remission in chronic disease?

Remission will lead to:

- lower radiographic progression
- sustained physical function
- mortality
- employability (?)



Finckh A, et al. ***Arthritis Rheum.*** 2006;55:864-872; van der Heijde D. ***Nature Clin Pract Rheumatol.*** 2007;3:258-259

Lessons from a decade: remission in chronic disease?

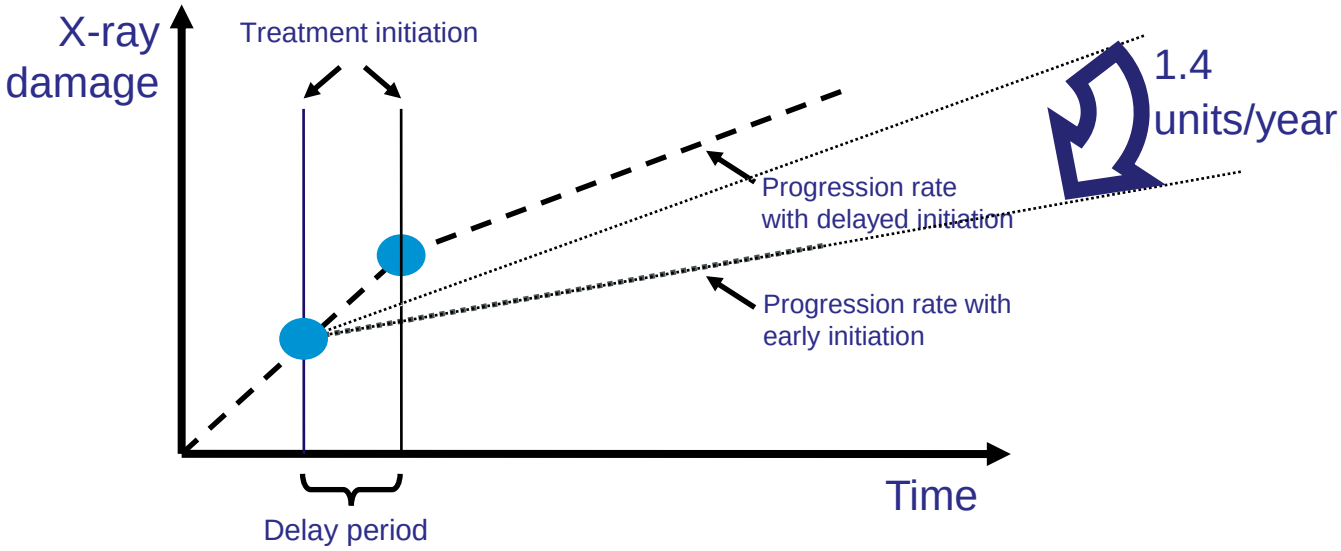
Despite early and aggressive intervention…

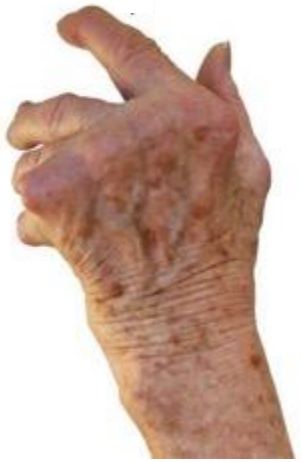
- Remission rates remain low, however defined
- Drug therapeutics are required for such disease state
- Damage is progressive in a proportion of patients
- Socioeconomic decline is ongoing
- Morbidity and mortality remain significant

- Management is not pathogenesis driven!

Finckh A, et al. ***Arthritis Rheum.*** 2006;55:864-872; van der Heijde D. ***Nature Clin Pract Rheumatol.*** 2007;3:258-259

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



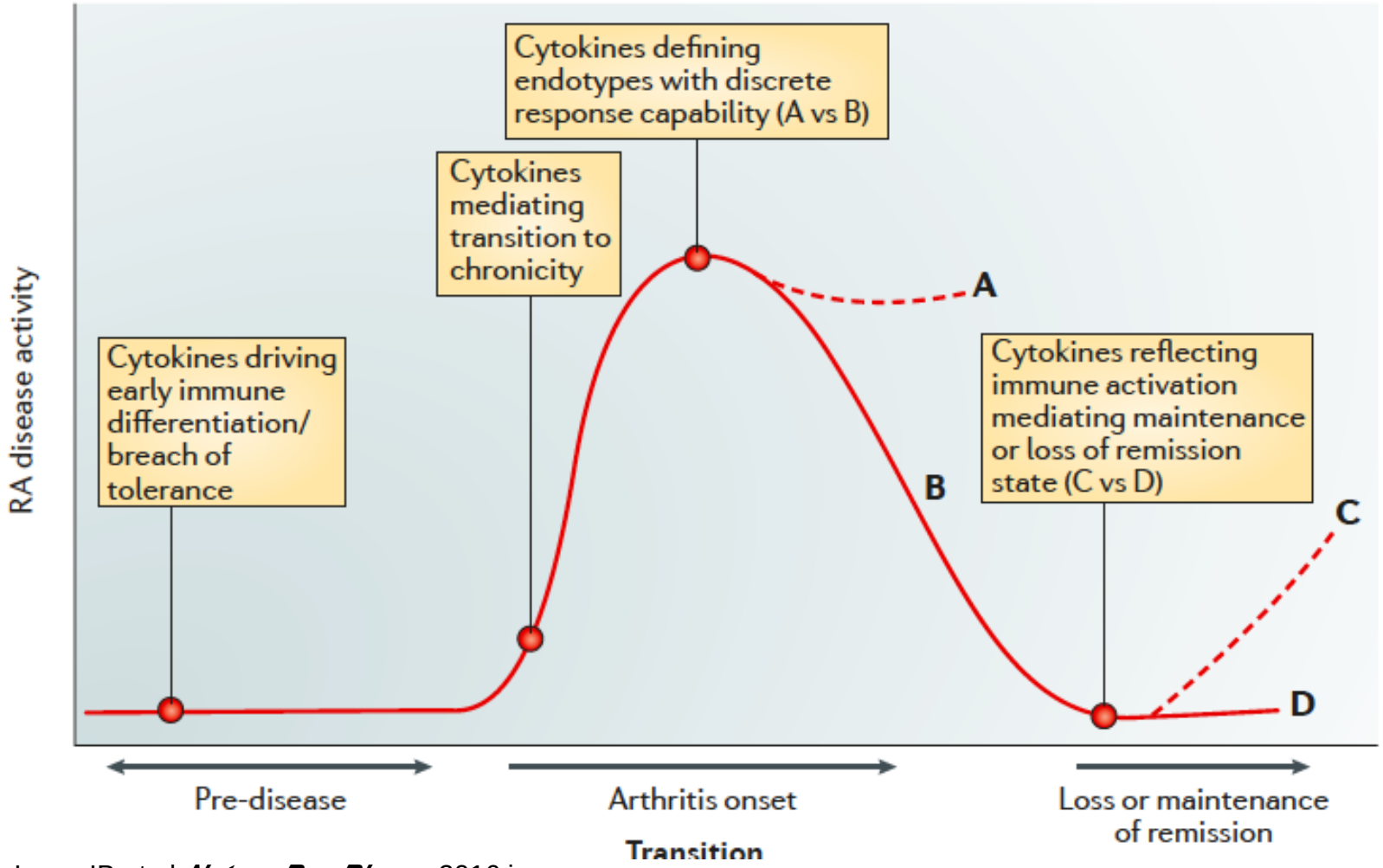


Immune adaptation: recruitment of new pathways

- Implications for therapeutics and the move to prevention

Finckh A, et al. ***Arthritis Rheum.*** 2006;55:864-872; van der Heijde D. ***Nature Clin Pract Rheumatol.*** 2007;3:258-259

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



McInnes IB et al ***Nature Rev Rheum*** 2016 in press

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- Towards the future?
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- Systems or “the system”

Key current concepts of RA pathogenesis – clinical relevance?

Genetics

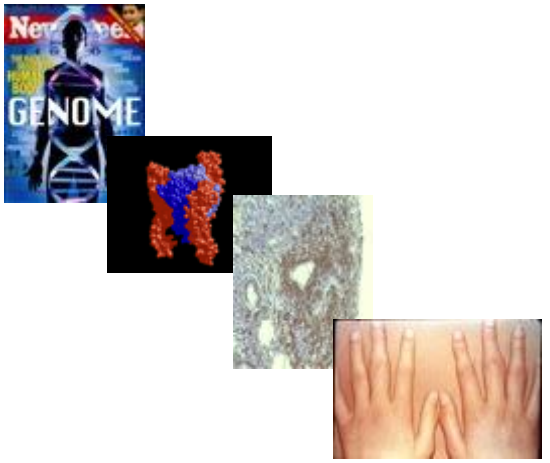
- Clear evidence of immune function contribution
- Epigenetic abnormalities, e.g. methylation, microRNA, chromatin structure

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

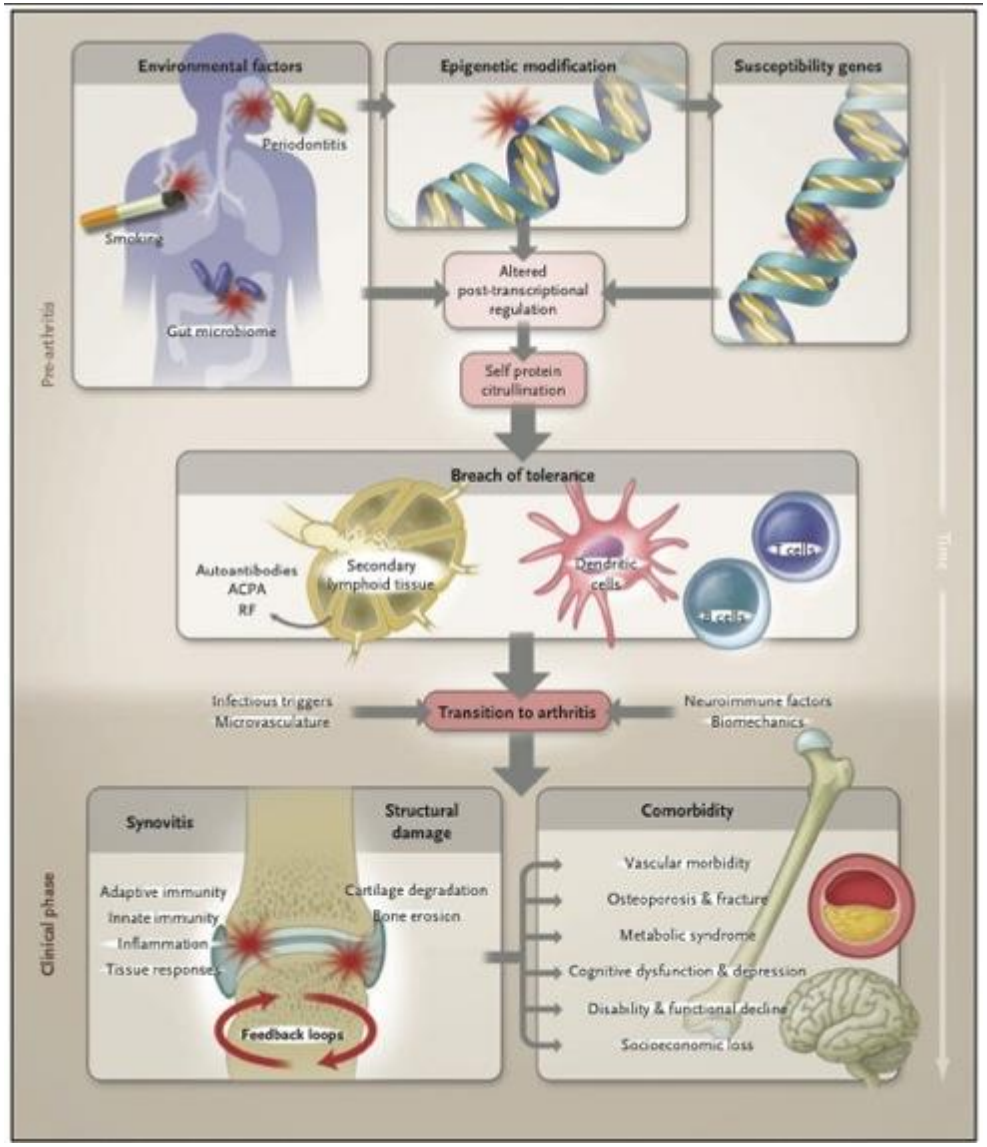


GWAS, genome-wide association studies

McInnes IB & Schett G. *N Eng J Med.* 2011;365:2205-2219.

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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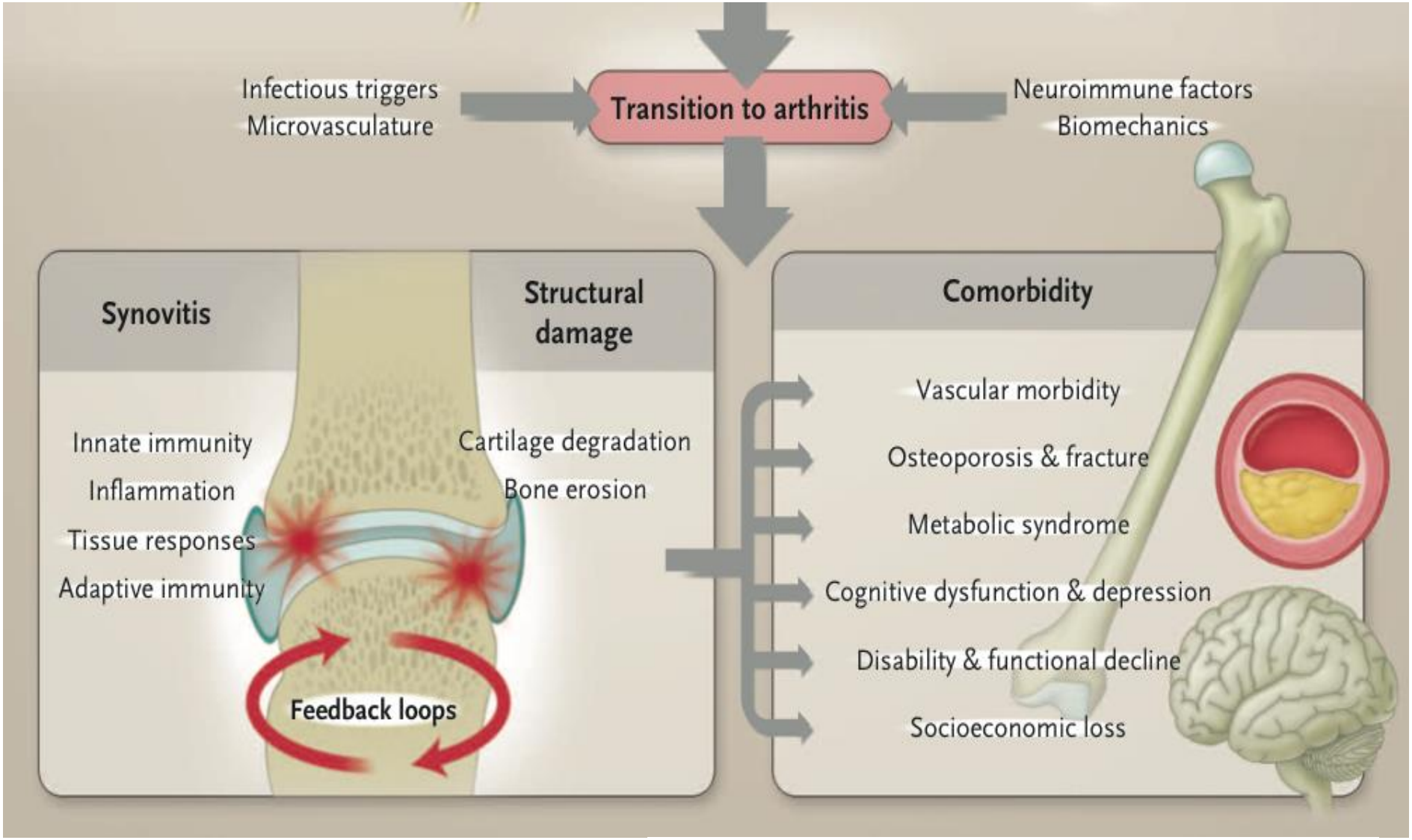


McInnes IB and Schett G. *N Eng J Med* 2011;365(23):2205–2219.

Areas of potential interest in current development in RA?

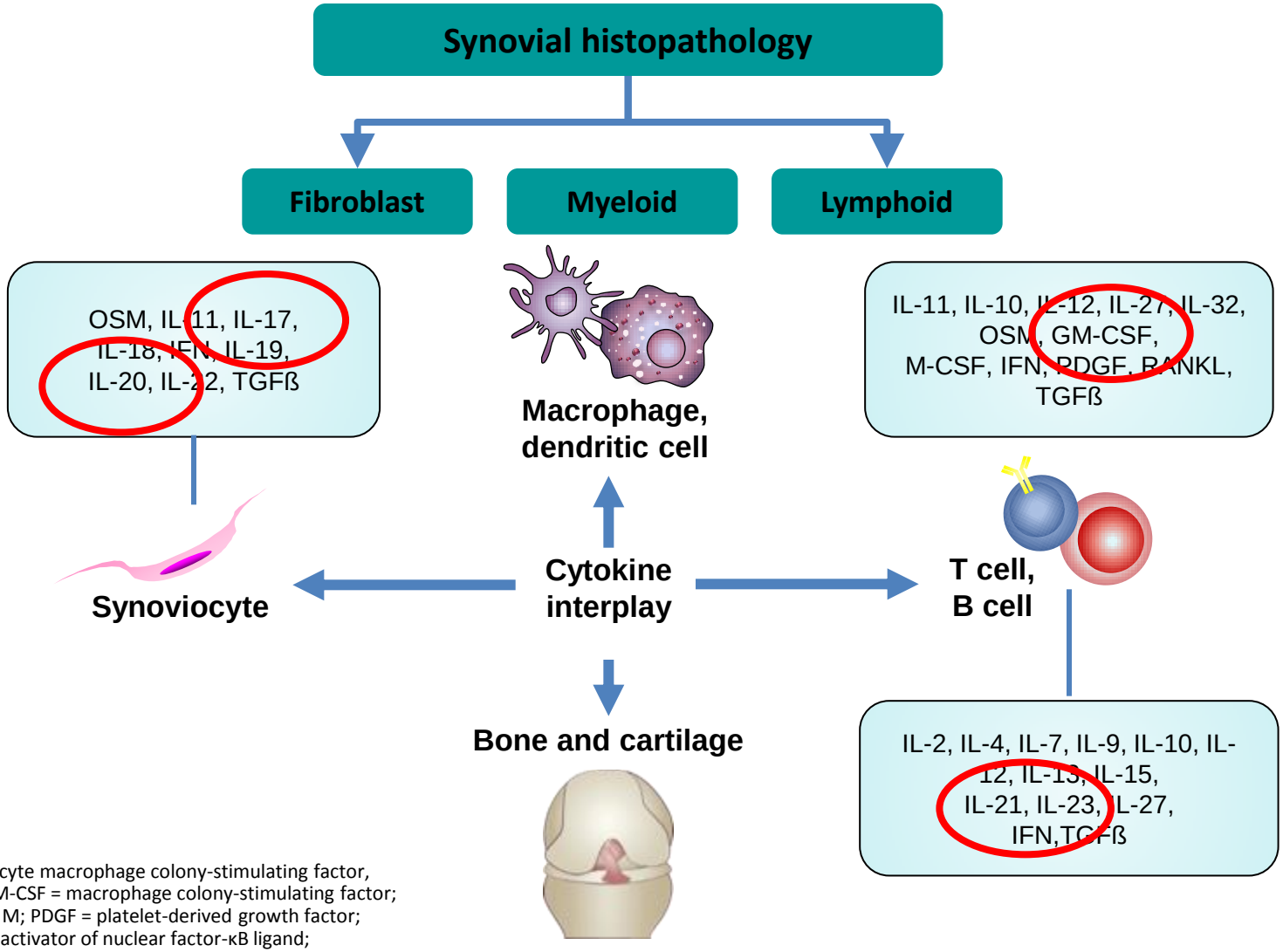
Moieties, Pathways and Cells…

- 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 translational modification – PADI4
- Autoreactivity e.g. T cell, B cell, dendritic cells, MSC….
- Neuroendocrine pathways
  - e.g. vagal drive
  - GnRH antagonists

Innate

Adaptive

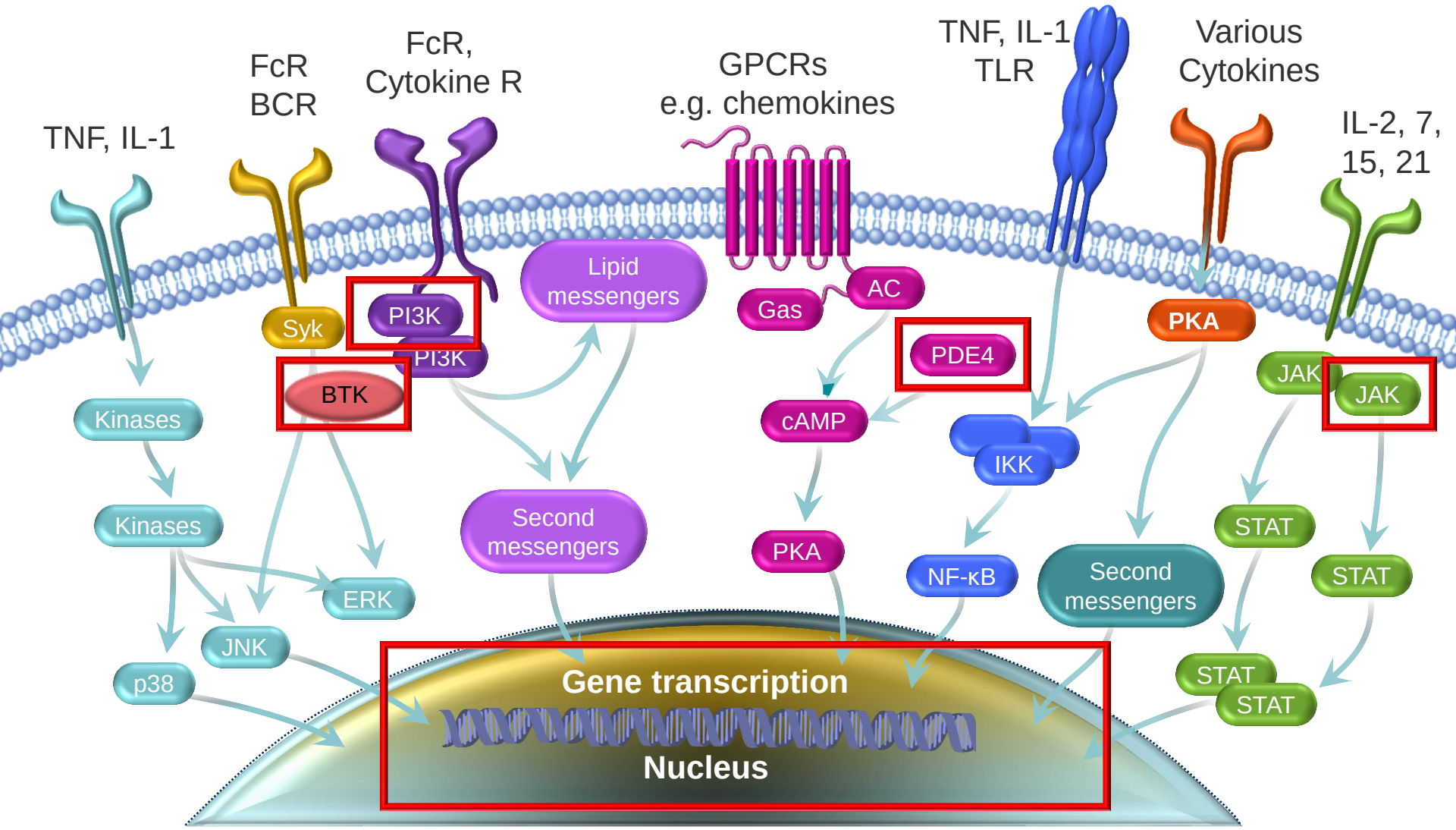
Learning from success and failures: Targeted therapy based on interfering with (which?) critical immune cells and cytokines



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

Choy E, *et al. Nat Rev Rheumatol* 2013; **9**:154–163.

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



Tas SW, et al. *Curr Pharm Design*. 2005;11:581-611; Schafer P. *Biochem Pharmacol*. 2012;83: 1583–1590.

Enriching for response:

Developing biomarkers in chronic inflammation

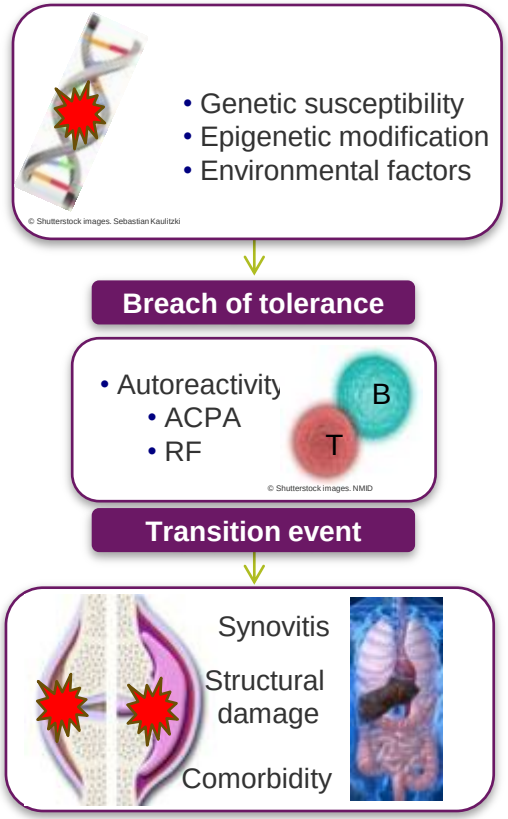
Descriptive Biomarkers

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

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

Mechanistic Biomarkers

- Autoantibodies
- Gene-expression signatures
- Cytokines
- Immune-cell types
- Genotype



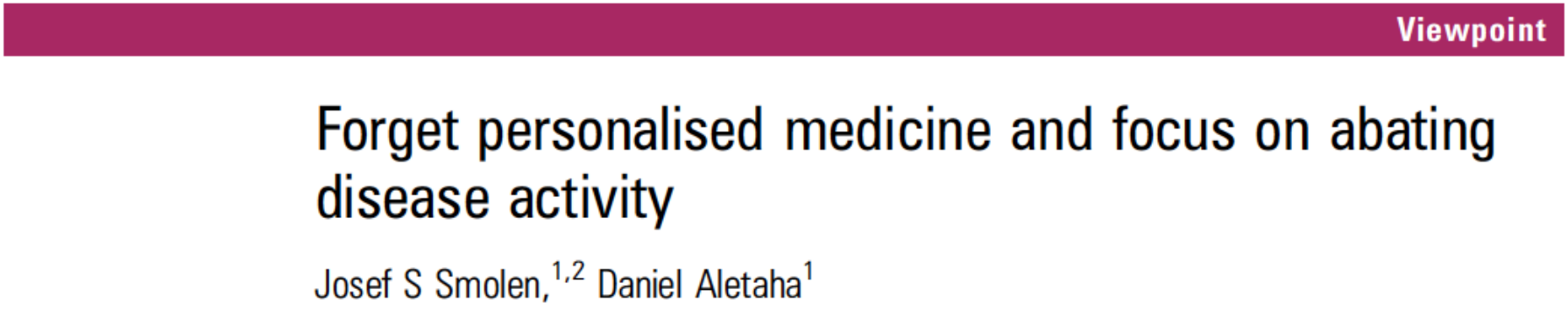
Adapted from:
Robinson WH et a *Nature Reviews Rheum* (2013)l 9; 267
McInnes IB & Schett G *New Eng J Med* (2011)

Do we really need a personalised medicine based approach?

Consider :

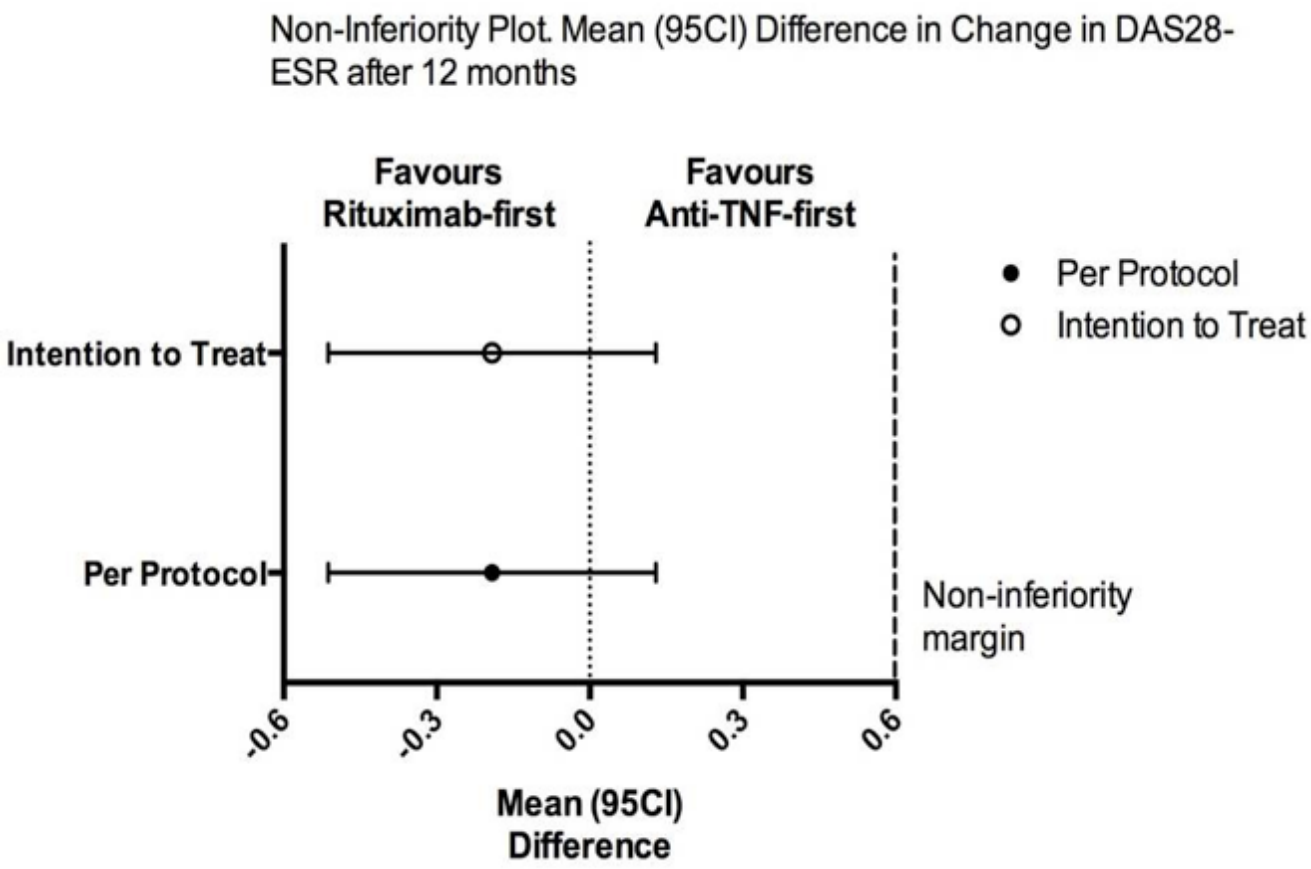
- Responses post TNFi are equivalent regardless of treatment modality
- Combinatorial biologic approaches increase AEs but not efficacy

therefore…



Smolen & Aletaha *Ann Rheum Dis* 2013;72:3–6. doi:10.1136/annrheumdis-2012-202361.

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



Porter D et *Lancet* 2016 in press

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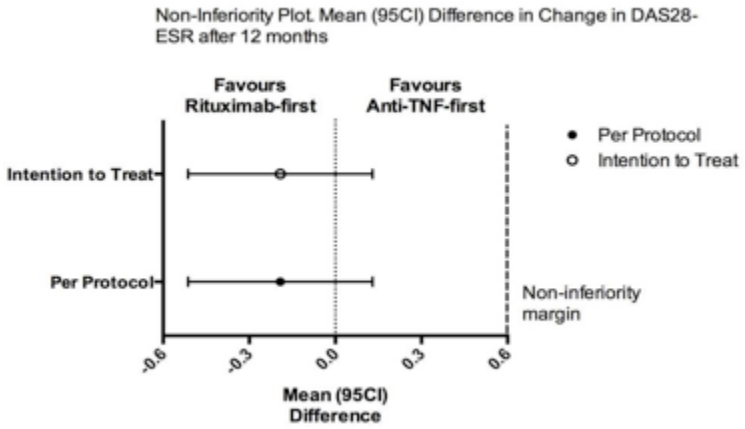


	TNFi-first	Rituximab-first	
Medicines, infusions, clinics	£10,356	£8,391	p<0.001*
Primary care	£370	£366	p=0.92
Blood tests, Xray	£163	£141	p=0.51
Total	£11,523	£9,405	p<0.001*

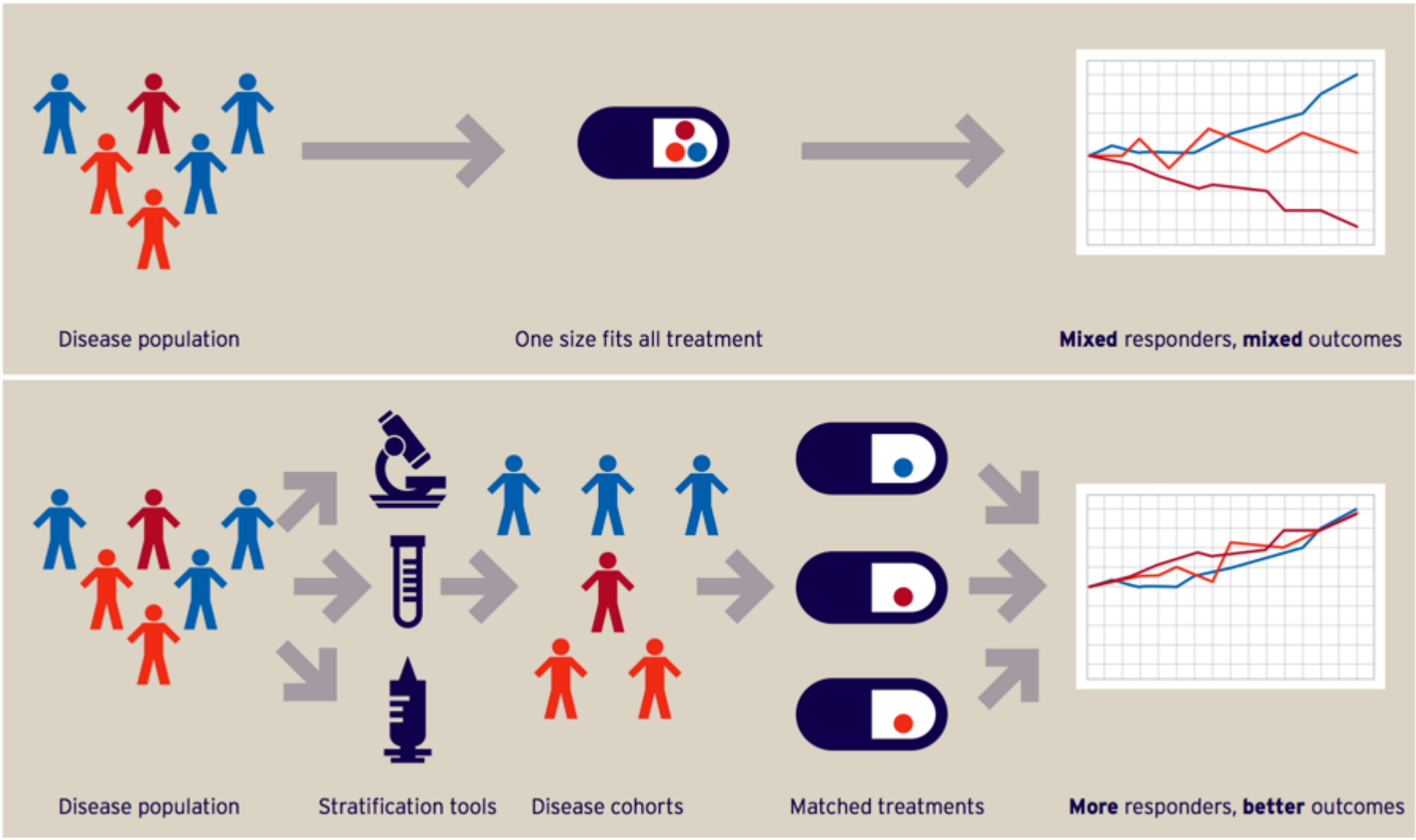
Bootstrap estimated mean cost difference (95% CI) = £1,999 (£2,755, £1440)

Quality-Adjusted Life Years (1-EQ-5D AUC)			
QALYs	0.481	0.454	p=0.25

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

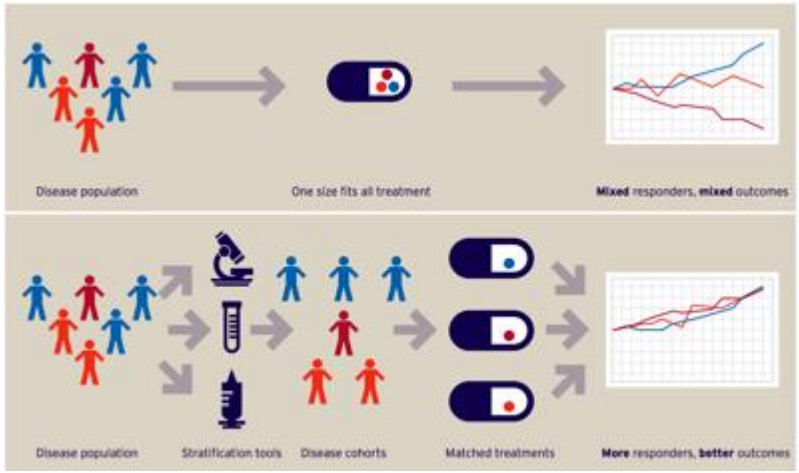
* Wilcoxon

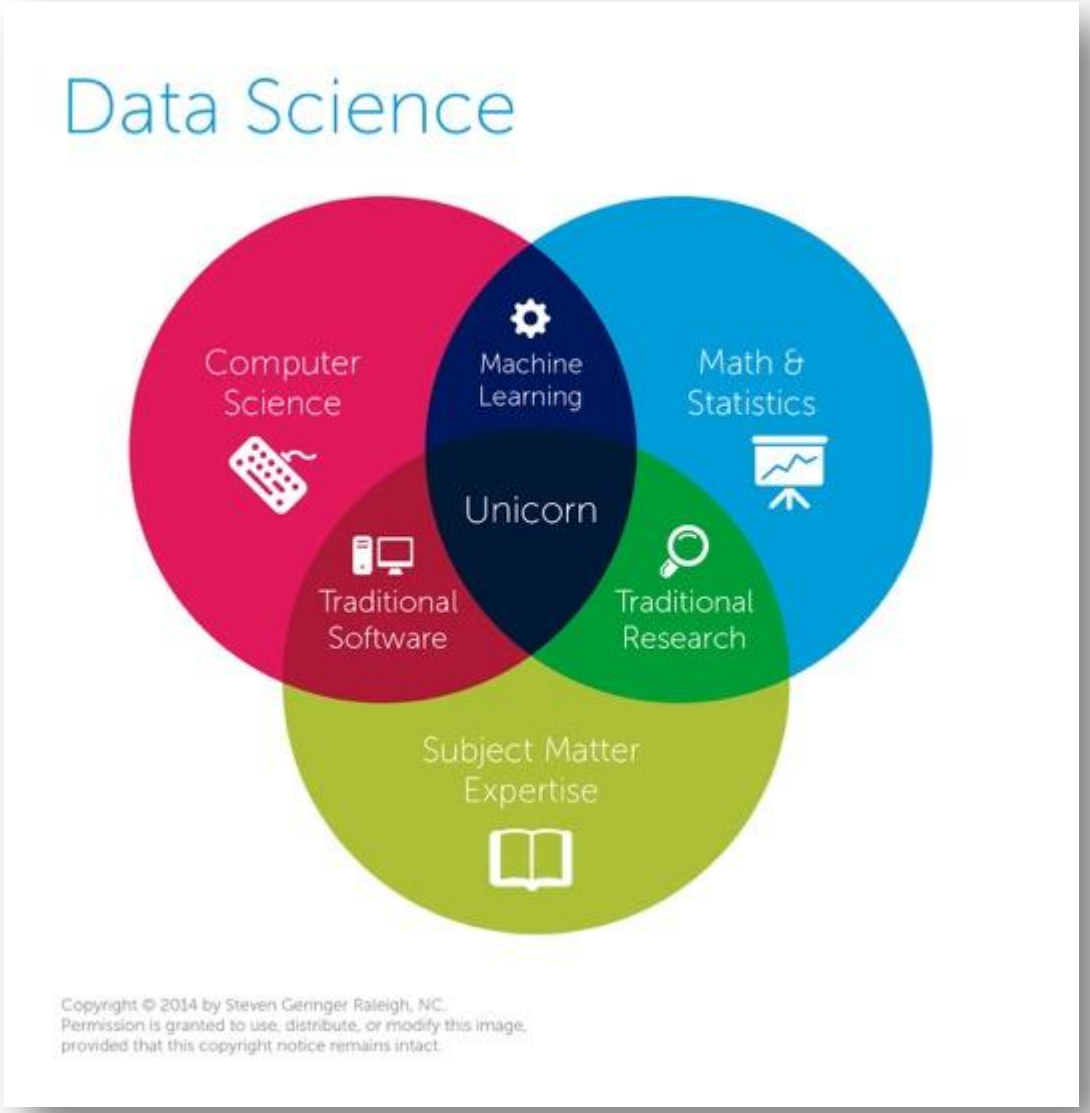
The promise of personalised medicine



UKTI 2013. Unlock Your Global Business Potential UK Stratified Medicine

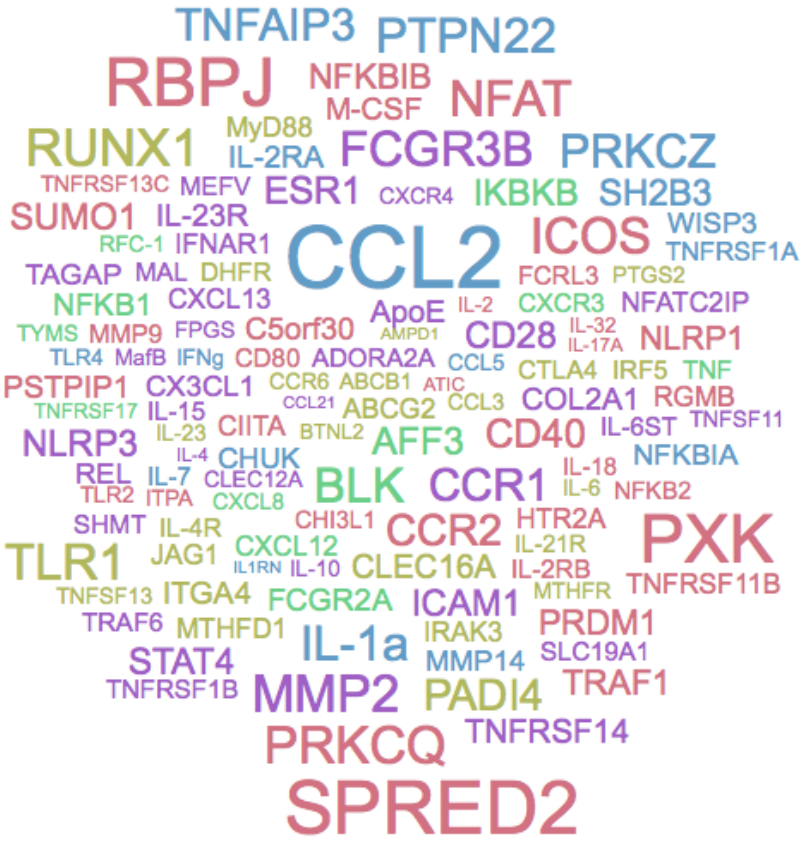
The promise of personalised medicine



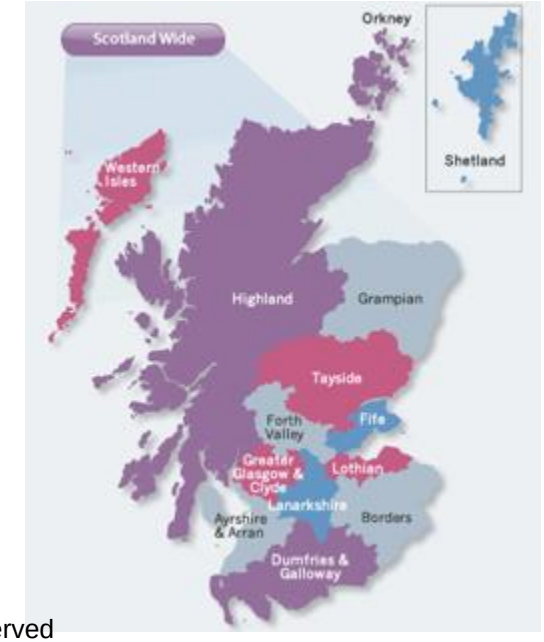


UKTI 2013. Unlock Your Global Business Potential UK Stratified Medicine

Profiling the circulating CCS signature in early RA



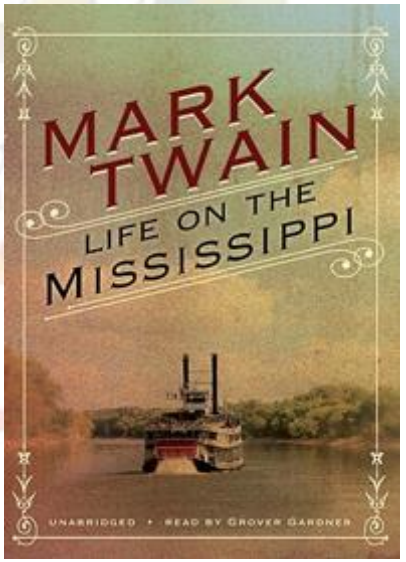
- SERA - >1000 patients
- 123 genetic loci
- *in silico* prediction of high-confidence CCS candidates
  - 13,322 CCS probes
  - 99±64 CCS per loci
  - Tested in quadruplicate



Carini C, Goodyear C et al McInnes IB (submitted 2016)

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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The current translational model?

PERSPECTIVES

OPINION

Anticipating change in drug development: the emerging era of translational medicine and therapeutics

Garret A. FitzGerald

the emergence of low-cost competitors to create a 'Southwest Airlines Moment' for the pharmaceutical industry.

How can the industry and, indeed, the US economy respond to this challenge? Expenditure on research and development in the US by the pharmaceutical industry, which provides employment to almost 200,000 individuals, was estimated at US$25.7 billion in 2002[1]. Reductions in drug pricing have already hastened the migration of research

OPINION

Anticipating change in drug development: the emerging era translational medicine and the

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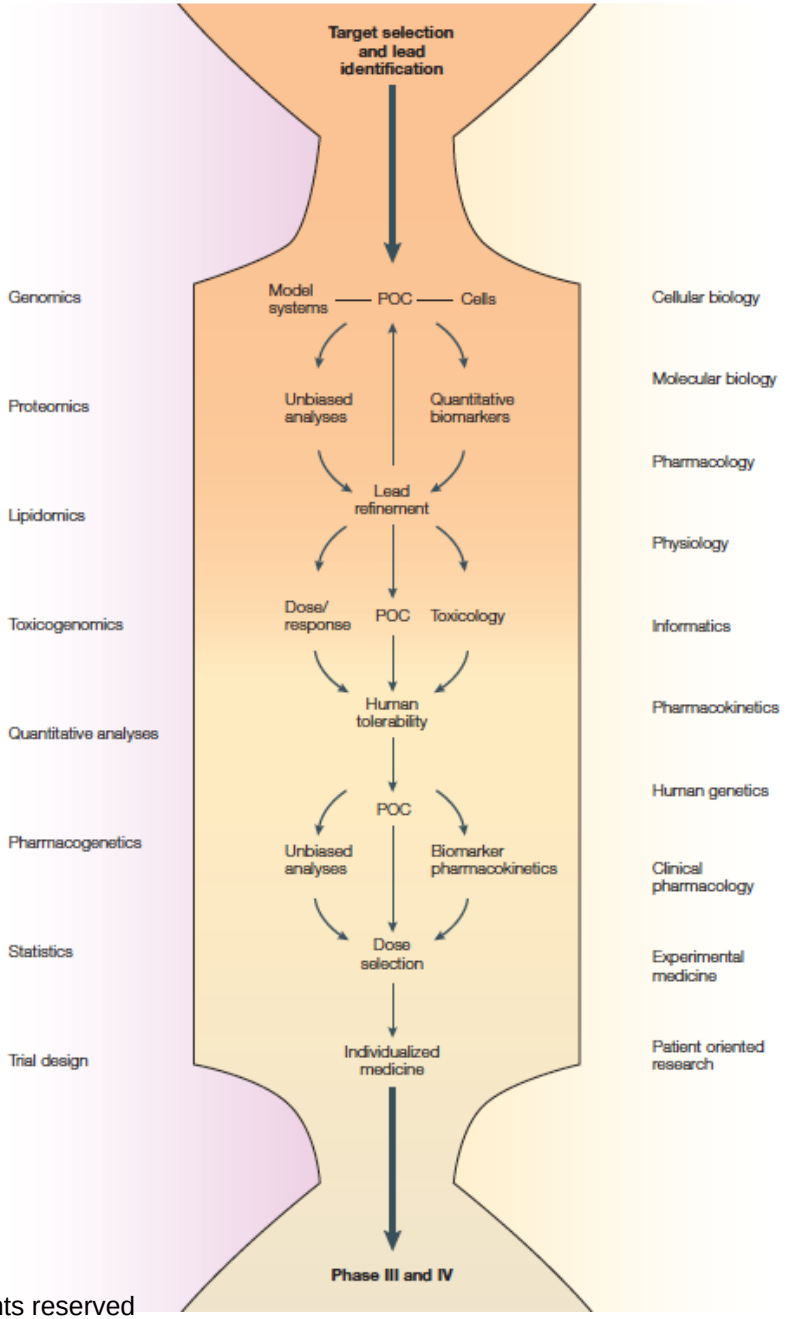
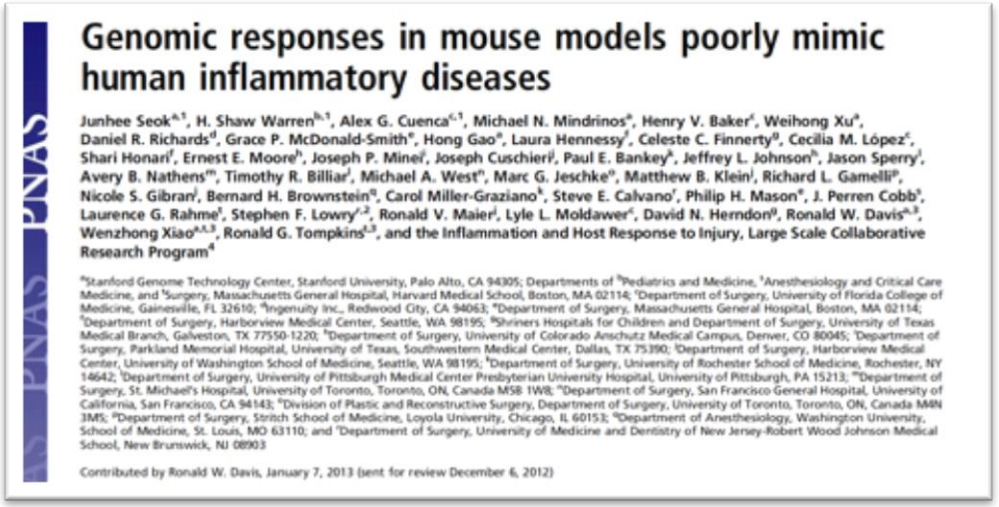


GA FitzGerald,
***Nature Rev Drug Discovery* (2005) 4;815**

Does our translational model work…



Genomic responses in mouse models poorly mimic human inflammatory diseases

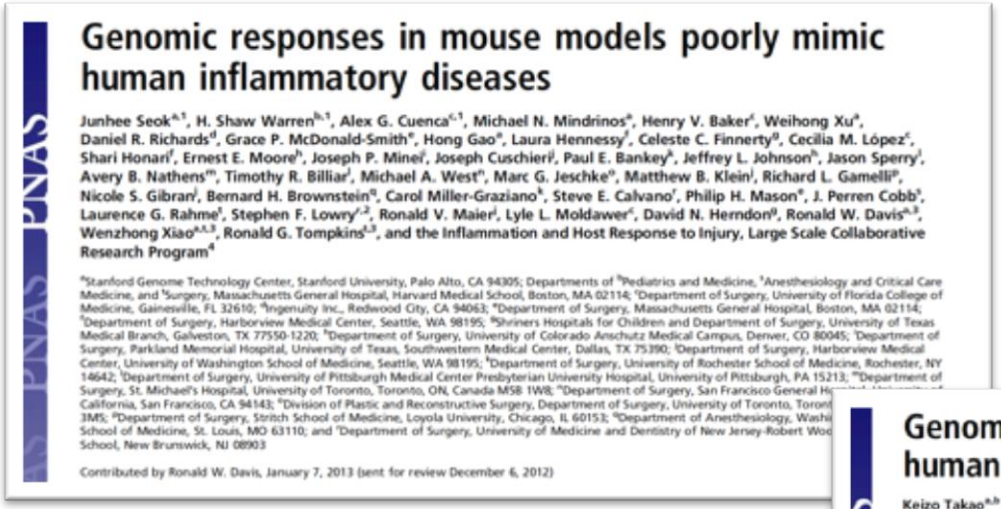
Junhee Seok[a,1], H. Shaw Warren[b,1], Alex G. Cuenca[c,1], Michael N. Mindrinos[a], Henry V. Baker[c], Weihong Xu[a], Daniel R. Richards[d], Grace P. McDonald-Smith[e], Hong Gao[a], Laura Hennessy[f], Celeste C. Finnerty[g], Cecilia M. López[c], Shari Honari[f], Ernest E. Moore[h], Joseph P. Minei[i], Joseph Cuschieri[j], Paul E. Bankey[k], Jeffrey L. Johnson[h], Jason Sperry[l], Avery B. Nathens[m], Timothy R. Billiar[l], Michael A. West[n], Marc G. Jeschke[o], Matthew B. Klein[l], Richard L. Gamelli[p], Nicole S. Gibran[j], Bernard H. Brownstein[q], Carol Miller-Graziano[k], Steve E. Calvano[r], Philip H. Mason[e], J. Perren Cobb[s], Laurence G. Rahme[t], Stephen F. Lowry[r,2], Ronald V. Maier[j], Lyle L. Moldawer[c], David N. Herndon[g], Ronald W. Davis[a,3], Wenzhong Xiao[a,t,3], Ronald G. Tompkins[s,3], and the Inflammation and Host Response to Injury, Large Scale Collaborative Research Program[4]

[a]Stanford Genome Technology Center, Stanford University, Palo Alto, CA 94305; Departments of [b]Pediatrics and Medicine, [c]Anesthesiology and Critical Care Medicine, and [s]Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114; [d]Department of Surgery, University of Florida College of Medicine, Gainesville, FL 32610; [e]Ingenuity Inc., Redwood City, CA 94063; [f]Department of Surgery, Massachusetts General Hospital, Boston, MA 02114; [g]Department of Surgery, Harborview Medical Center, Seattle, WA 98195; [h]Shriners Hospitals for Children and Department of Surgery, University of Texas Medical Branch, Galveston, TX 77550-1220; [i]Department of Surgery, University of Colorado Anschutz Medical Campus, Denver, CO 80045; [j]Department of Surgery, Parkland Memorial Hospital, University of Texas, Southwestern Medical Center, Dallas, TX 75390; [k]Department of Surgery, Harborview Medical Center, University of Washington School of Medicine, Seattle, WA 98195; [l]Department of Surgery, University of Rochester School of Medicine, Rochester, NY 14642; [m]Department of Surgery, University of Pittsburgh Medical Center Presbyterian University Hospital, University of Pittsburgh, PA 15213; [n]Department of Surgery, St. Michael's Hospital, University of Toronto, Toronto, ON, Canada M5B 1W8; [o]Department of Surgery, San Francisco General Hospital, University of California, San Francisco, CA 94143; [p]Division of Plastic and Reconstructive Surgery, Department of Surgery, University of Toronto, Toronto, ON, Canada M4N 3M5; [q]Department of Surgery, Stritch School of Medicine, Loyola University, Chicago, IL 60153; [r]Department of Anesthesiology, Washington University, School of Medicine, St. Louis, MO 63110; and [t]Department of Surgery, University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School, New Brunswick, NJ 08903

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

Perhaps not….!

Does our translational model work…



Genomic responses in mouse models poorly mimic human inflammatory diseases

Junhee Seok[a,1], H. Shaw Warren[b,1], Alex G. Cuenca[c,1], Michael N. Mindrinos[a], Henry V. Baker[c], Weihong Xu[a], Daniel R. Richards[d], Grace P. McDonald-Smith[e], Hong Gao[a], Laura Hennessy[f], Celeste C. Finnerty[g], Cecilia M. López[c], Shari Honari[f], Ernest E. Moore[h], Joseph P. Minei[i], Joseph Cuschieri[j], Paul E. Bankey[k], Jeffrey L. Johnson[h], Jason Sperry[l], Avery B. Nathens[m], Timothy R. Billiar[l], Michael A. West[n], Marc G. Jeschke[o], Matthew B. Klein[j], Richard L. Gamelli[p], Nicole S. Gibran[j], Bernard H. Brownstein[q], Carol Miller-Graziano[k], Steve E. Calvano[r], Philip H. Mason[e], J. Perren Cobb[s], Laurence G. Rahme[t], Stephen F. Lowry[r,2], Ronald V. Maier[i], Lyle L. Moldawer[c], David N. Herndon[g], Ronald W. Davis[a,3], Wenzhong Xiao[a,t,3], Ronald G. Tompkins[s,3], and the Inflammation and Host Response to Injury, Large Scale Collaborative Research Program[4]

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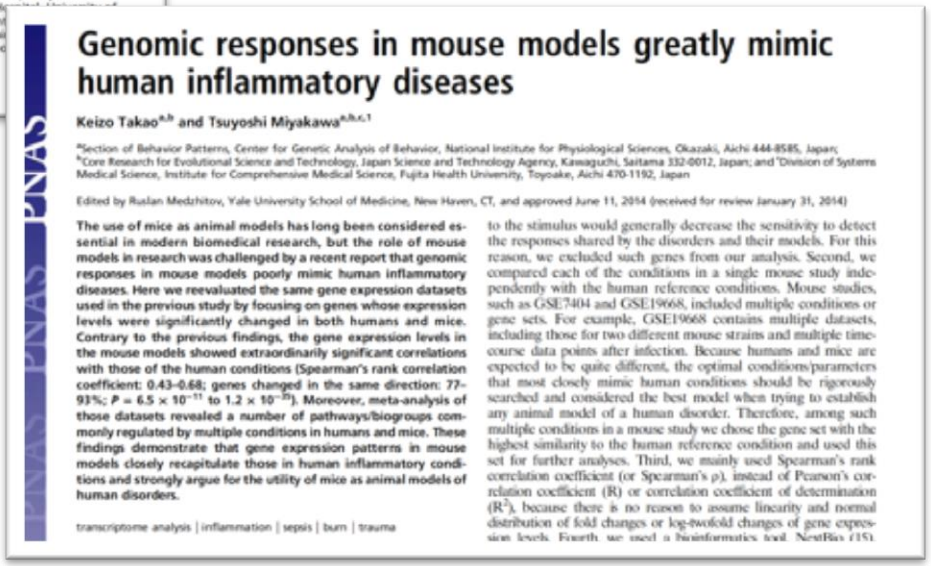
Contributed by Ronald W. Davis, January 7, 2013 (sent for review December 6, 2012)



Genomic responses in mouse models greatly mimic human inflammatory diseases

Keizo Takao[a,b] and Tsuyoshi Miyakawa[a,b,c,1]

[a]Section of Behavior Patterns, Center for Genetic Analysis of Behavior, National Institute for Physiological Sciences, Okazaki, Aichi 444-8585, Japan; [b]Core Research for Evolutional Science and Technology, Japan Science and Technology Agency, Kawaguchi, Saitama 332-0012, Japan; and [c]Division of Systems Medical Science, Institute for Comprehensive Medical Science, Fujita Health University, Toyoake, Aichi 470-1192, Japan

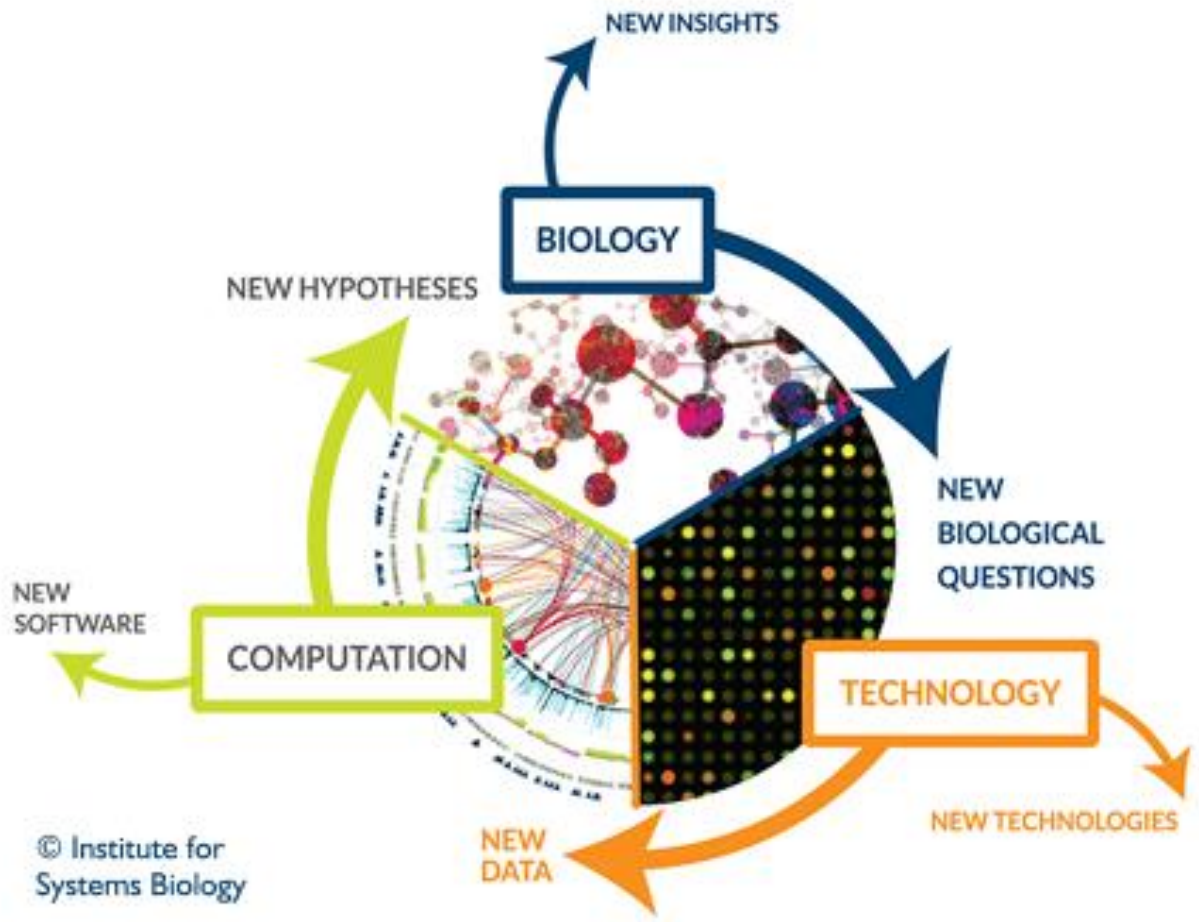
Edited by Ruslan Medzhitov, Yale University School of Medicine, New Haven, CT, and approved June 11, 2014 (received for review January 31, 2014)

The use of mice as animal models has long been considered essential in modern biomedical research, but the role of mouse models in research was challenged by a recent report that genomic responses in mouse models poorly mimic human inflammatory diseases. Here we reevaluated the same gene expression datasets used in the previous study by focusing on genes whose expression levels were significantly changed in both humans and mice. Contrary to the previous findings, the gene expression levels in the mouse models showed extraordinarily significant correlations with those of the human conditions (Spearman's rank correlation coefficient: 0.43–0.68; genes changed in the same direction: 77–93%; $P = 6.5 \times 10^{-11}$ to 1.2×10^{-85}). Moreover, meta-analysis of those datasets revealed a number of pathways/biogroups commonly regulated by multiple conditions in humans and mice. These findings demonstrate that gene expression patterns in mouse models closely recapitulate those in human inflammatory conditions and strongly argue for the utility of mice as animal models of human disorders.

transcriptome analysis | inflammation | sepsis | burn | trauma

to the stimulus would generally decrease the sensitivity to detect the responses shared by the disorders and their models. For this reason, we excluded such genes from our analysis. Second, we compared each of the conditions in a single mouse study independently with the human reference conditions. Mouse studies, such as GSE7404 and GSE19668, included multiple conditions or gene sets. For example, GSE19668 contains multiple datasets, including those for two different mouse strains and multiple time-course data points after infection. Because humans and mice are expected to be quite different, the optimal conditions/parameters that most closely mimic human conditions should be rigorously searched and considered the best model when trying to establish any animal model of a human disorder. Therefore, among such multiple conditions in a mouse study we chose the gene set with the highest similarity to the human reference condition and used this set for further analyses. Third, we mainly used Spearman's rank correlation coefficient (or Spearman's ρ), instead of Pearson's correlation coefficient (R) or correlation coefficient of determination (R^2), because there is no reason to assume linearity and normal distribution of fold changes or log-twofold changes of gene expression levels. Fourth, we used a bioinformatics tool, NetBox (15),

What is Systems Medicine?



https://www.systemsbiology.org/

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.

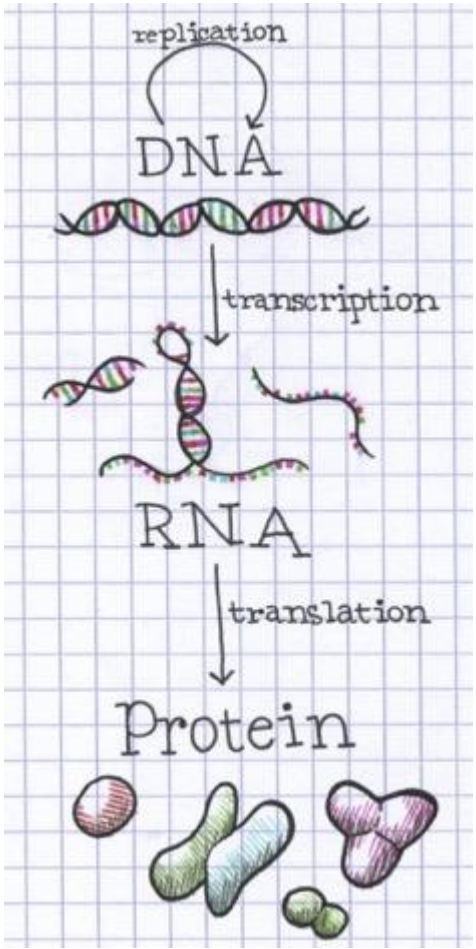
http://www.sciencedirect.com/science/article/pii/S1931312814002984 – IgG repertoire to HIV infection
http://genome.cshlp.org/content/19/10/1817 – Robert Holt T-cell receptor beta chain sequencing.
Charles-Schoeman et al Arthritis Rheumatol. 2014 Dec 2. doi: 10.1002/art.38974.

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”

Epigenomics



Genomics

Transcriptomics

Proteomics

Metabolomics

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:

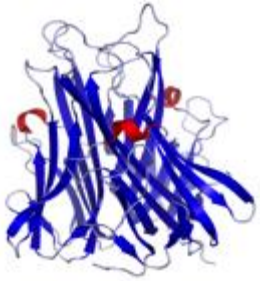
1/ generation of quality data

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



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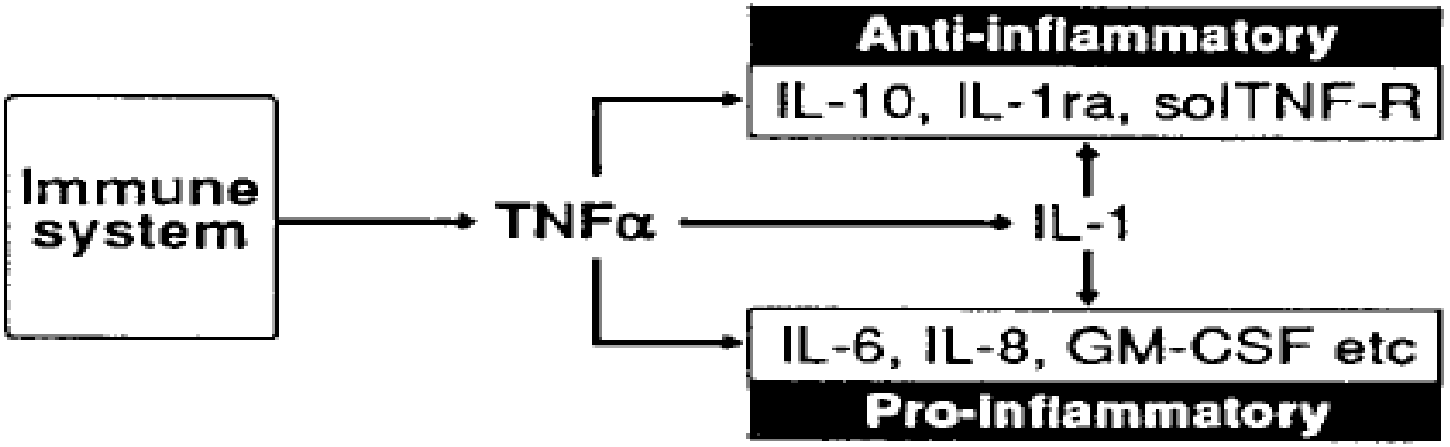
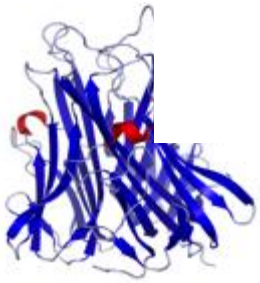
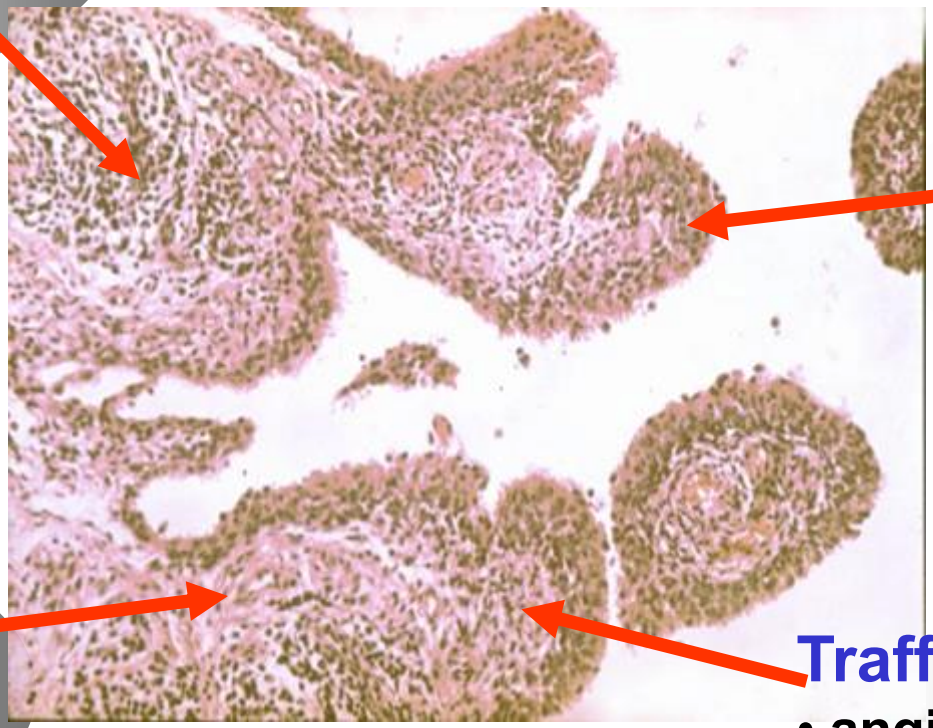




Feldmann M et al *Cell* 1996 **85**;307

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

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

IL-10, IFN, IL-35

Lining layer
- FLS
- macrophages

Interstitium
- mast cells
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- neuroreceptors

Trafficking
- angiogenesis
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Evolving models for cytokine hierarchies in synovitis?

- Linear models
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- Network theory
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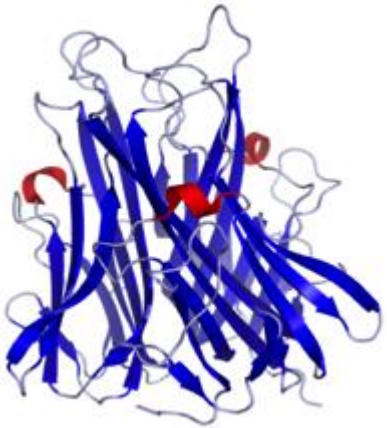
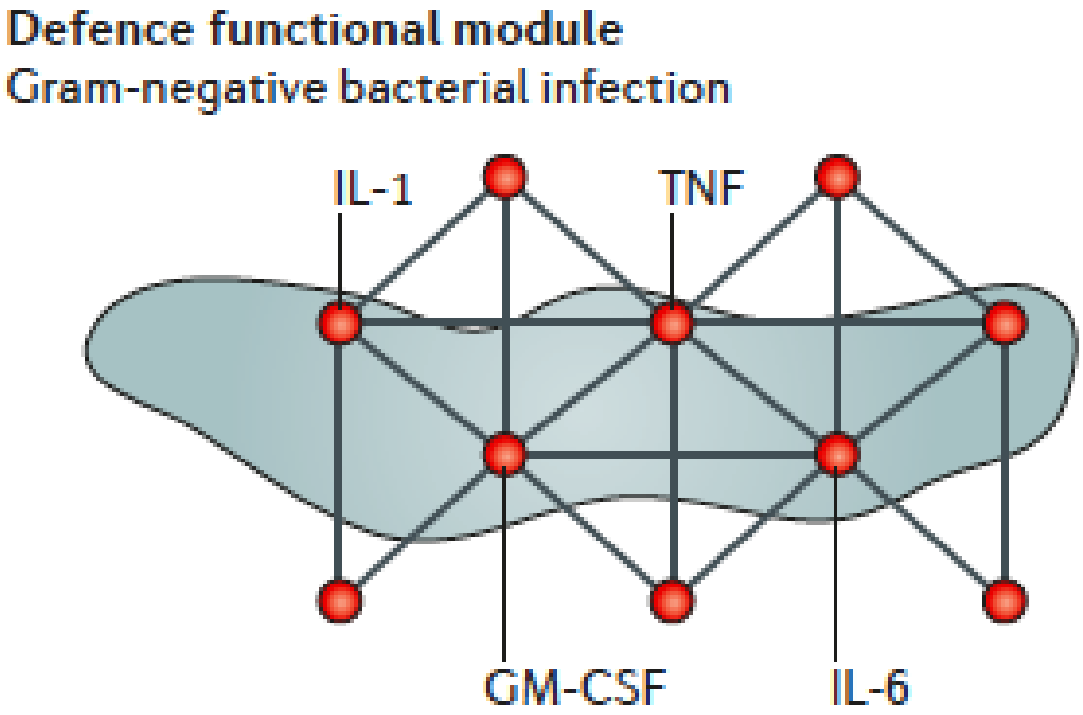


RA: can we define functional modules of inflammatory moieties within biologic networks?



McInnes IB et al ***Nature Rev Rheum*** 2016 in press; see also Barabasi AL et al *Nature Rev Genetics* 2011: 12:56-67

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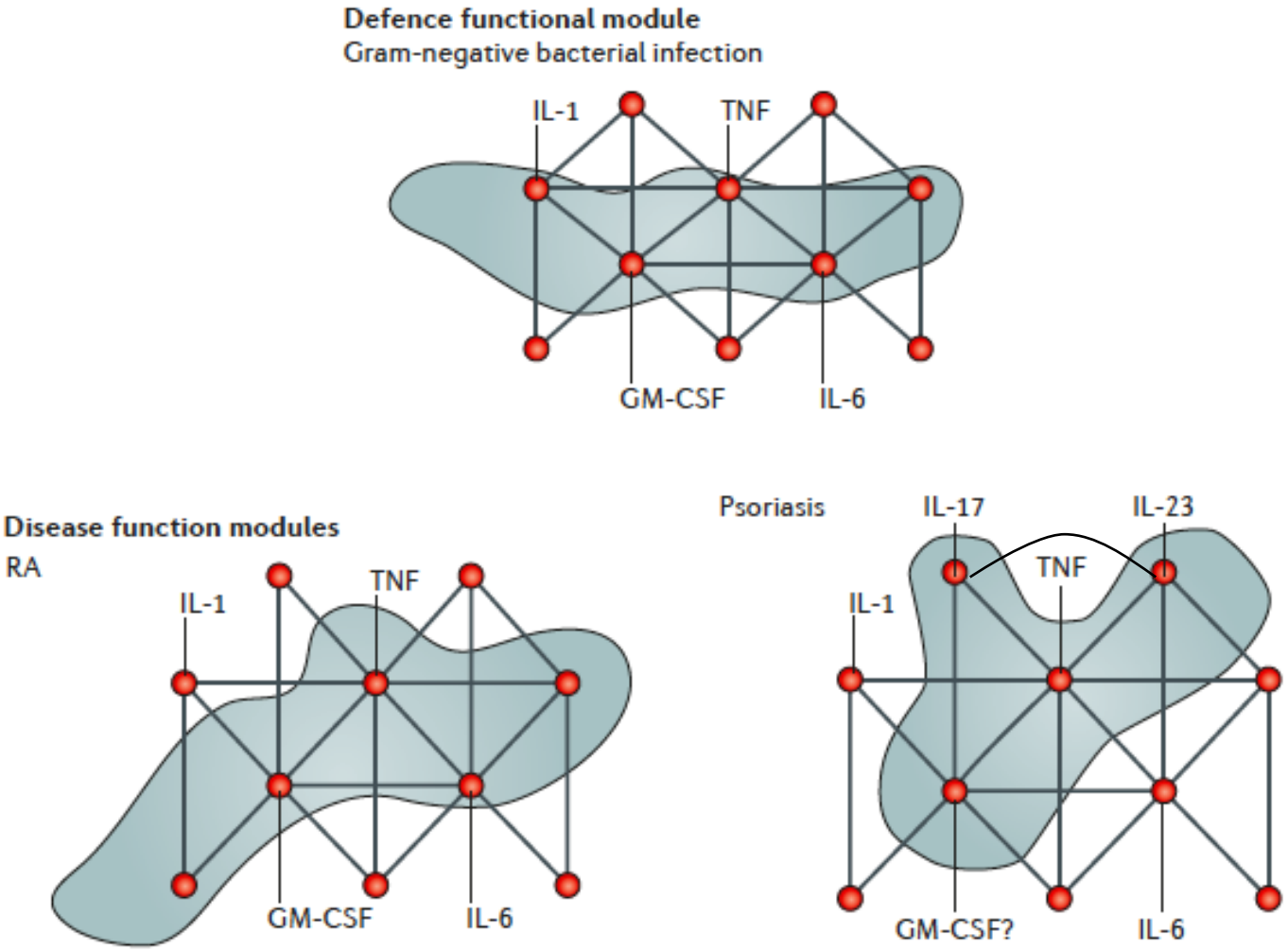

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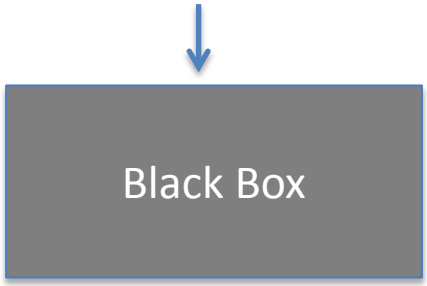
Empowering clinical rheumatologists to navigate data to find useful patterns

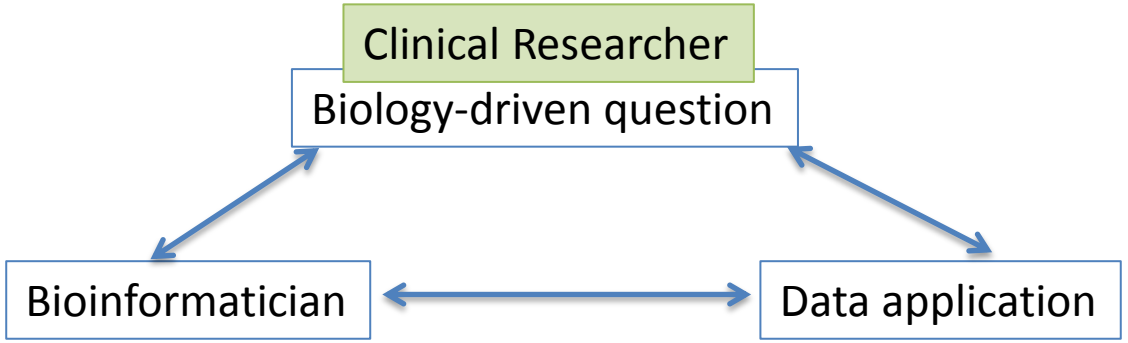
Traditionally

Biology-group generates data



Bioinformatician analyses data

3iiiformatics.org approach



Direct and intuitive interaction with your own data

Collaborative environments that enables biology
…drives clinical insight
…as well as facilitates computational outcomes

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?