

Biomarkers and clinical trials

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UCL

Definitions

- Surrogate biomarker:

A laboratory or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful endpoint, e.g. Blood glucose, tumour size

- Nonsurrogate biomarkers:

adjunct to clinical measures, provide added value

Efficacy and safety of a drug in development

- All trials with placebo arm show a % of non-responders in the group receiving the drug, as well as 30-40% placebo response. *Reason? How to increase efficacy profile by using more homogeneous patient populations?*
- The side effect profiles and infusion reactions often can lead to withdrawal of a drug. *Pharmacogenomics and pharmacodynamics, drug metabolism*

Added value

- Increase understanding of a disease mechanism, thereby provide better choice of drug targets for the future

Towards “personalised treatment”:

- Reduction of failure rate of subsequent studies, as well as provide explanation of drug failure
- Provide rationale for adverse events and so increase safety profiles

New technology: molecular biomarkers

Why do we need molecular biomarkers in the conduct of clinical trials in JIA?

JIA is heterogeneous, and there are

1. definite clinical subpopulations (ILAR classifications);
2. Genetic differences between ILAR groups in candidate gene association studies (GWAS in progress)
3. Gene expression profiles showing different disease pathways (*Barnes et al. Arthritis Rheum. 2009 Jul;60(7):2102-12*)

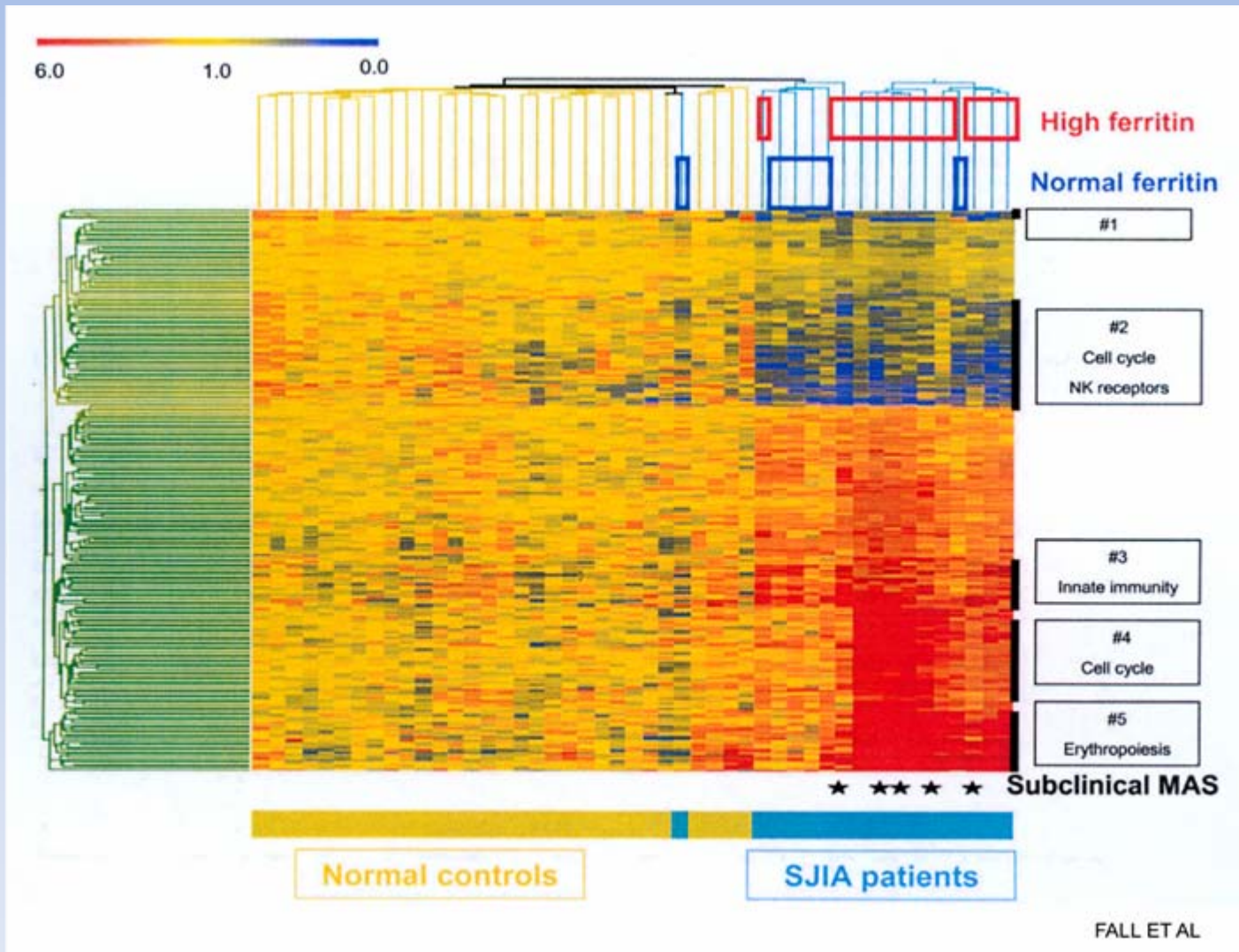
Gene expression signatures in disease

- Interferon Signature in SLE. *Pascual et al J. Exp. Med.* 197: 711-23
- IL-1 signature in sJIA and treatment with anakinra. *Allantaz et al. J.Exp. Med.* 2005□
- An integration of complementary strategies for gene-expression analysis to reveal novel therapeutic opportunities for breast cancer. *Bild et al. Breast Cancer Res.* 2009;11(4):R55.

Clinical trials of new drugs with such targets will need to include gene expression profiling to see if the pathway(s) affected is as expected or different from the initial rationale

Gene expression profile

Fall et al A&R 2007



Increase understanding of disease pathology

- Particularly important in clinical trials of immunomodulatory drugs e.g. TNF vs IL1 vs IL6 as targets in sJIA; T/B cell depletion
- Prospect of subdivision of a heterogeneous clinical population
- Which technology is most appropriate to use in drug development: genome wide scans? Gene expression profiling of RNA and proteins? Immune cell profiling?

Methotrexate studies

- Prediction of flare after withdrawal of MTX: S100 proteins as predictors *in progress*
- Pharmacogenetics identified so far genes in the folate, transporter and adenosine pathways. Hider, Bruce & Thomson Review *Rheumatology* 46:1520-4. 2007
Need for GWAS : in progress
- Gene expression profiling for gene prediction and genotype-phenotype matching: *in progress*

Autoinflammatory diseases

- Cryopyrin associated periodic fever Syndromes (CAPS) with NLRP3 mutations respond well to IL-1 blockade

BUT

- Tumour necrosis factor receptor associated periodic fevers (TRAPS) do not respond well to etanercept and worsen with infliximab, but respond to anakinra

Biomarkers needed in clinical trials for this group

Lessons so far from biologics trials in JIA

- Anti-TNF trials: etanercept has different efficacy in subtype: polyJIA vs sJIA
- Anakinra in sJIA: 2 populations of rapid responders and partial/non responders. Also canakinumab
- Tocilizumab in sJIA: 85% response in treatment group vs placebo of 24%
- Abatacept: similar response rate to etanercept, but some are etanercept non responders

Other relevant recent publications related to gene profiling in drug treatments

- Julia et al . Identification of candidate genes for rituximab response in RA patients by microarray gene expression profiling in blood cells. *Pharmacogenomics*, 10: 169701708, 2009
- Julia et al. An eight –gene blood expression profile predicts the response to infliximab in RA. *PLoS One*. 2009 Oct 22;4(10):e7556.

Reduction of failure rate

- Specially appropriate in phase II, also in phase III

Tools

- Serum biomarkers : biomarkers for efficacy from academic studies e.g. S100 proteins, SAA
- Pharmacodynamic markers
- Pharmacogenomics
- Cell profiling

Increase safety

- Particularly valuable in phase I/II drug development , but also in phase III

Tools

- PK, PD guide exposure to the drug at different doses and BMI
- Genetic differences in the metabolism of the drug to guide dosing schedules and explain toxicity (*e.g. Affy's drug metabolism enzymes and transporters panel*)
- Biomarkers for subpopulations of patients : for efficacy as well as toxicity e.g. Genetic markers, proteomic markers

