Biomarkers and clinical trials

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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)
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


  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 etanerept non responders
Overview of differentially expressed neutrophil genes, before and after IL-1 blockade

Computational modeling of selected genes using “IPA pathway designer” programme. IPA was also used to determine interactions between proteins. The genes are displayed in various shapes that represent the functional class of the gene product (see legend). In green are genes that are downregulated, red is upregulated. Blue represent genes identified by IPA to have direct or indirect interaction with some of the differentially expressed genes.
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

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