From the Disease Tissue to the Whole Patient
The role of pathobiology in patient stratification

Centre for Experimental Medicine & Rheumatology

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Disclosures

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The Promise of Stratified Medicine

Can we identify these groups prior to starting therapy 
& early in the disease course?

• More Effective, Safer & Cheaper Therapy
• Give the right drug to the right patient first time
Continuing using Biologics on a “trial an error” basis is not sustainable

£10K/pt/yr x 5000 new pt/yr

The Impact of Rheumatoid Arthritis

Equivalent data for the Newer Anti-TNFs & Abatacept, Tocilizumab and Rituximab
The Promise of Stratified Medicine

Can Molecular Pathology of the Disease Tissue Help to Stratify Medicines in RA?
Molecular Pathology to Stratify Medicine

Tissue Biomarkers in Management of Breast Cancer

a Prognostic value

Molecular signatures: Oncotype DX, MammaPrint, Theros, Rotterdam, Genomic Grade Index

- High HER2 (IHC, FISH)
- Ki67
- uPA PA-1
- TOP2A alteration
- BRCA1 mutation
- PTEN loss
- PIK3CA mutation

Biomarkers associated with:

- Good prognosis (strong evidence)
- Sensitivity to therapy (strong evidence)
- Good prognosis (value still discussed)
- Sensitivity to therapy (value still discussed)
- Poor prognosis (strong evidence)
- Resistance to therapy (strong evidence)
- Poor prognosis (value still discussed)
- Resistance to therapy (value still discussed)

b Predictive value

Conventional cytotoxics

-ER
- PR
- High HER2
- TOP2A alteration
- BRCA1 mutation
- PTEN loss
- PIK3CA mutation

Aromatase inhibitors

-ER
- PR
- uPA PA-1
- Ki67
- Oncotype DX

Tamoxifen

-ER
- PR
- Oncotype DX
- PTEN loss

Trastuzumab

- p95HER2
- IGF-1R
- High HER2 (IHC, FISH)

Multi-Omic Phenotyping in Personal and Public Healthcare

Rapid diagnosis and staging of colorectal cancer via High-Resolution Magic Angle Spinning Nuclear Magnetic Resonance (HR-MAS NMR) Spectroscopy of intact tissue biopsies


Distinct HR-MAS NMR spectroscopy–based metabolic phenotypes according to T-stage.
[Image showing the pathogenesis of RA synovitis and joint damage]

Pathogenesis of RA Synovitis and Joint Damage

- Bone damage occurs proportionally to the level of synovitis but not in its absence.


Does gene expression analysis inform us in rheumatoid arthritis?

T Häupl,1 B Stuhlmüller,1 A Grützkau,2 A Radbruch,2 G-R Burmester1


Figure 1 Differential gene expression in rheumatoid arthritis (RA) patients compared with normal donors (ND) in different types of samples. Compared with tissue, the number of probesets with increased expression in RA is much lower in whole blood or different cell types separated from blood. This difference was determined for a fraction of pairwise comparisons with increased expression in RA ranging from 50% to 100%.
New learnings on the pathophysiology of RA from synovial biopsies

Costantino Pitzalis, Stephen Kelly, and Frances Humby

RA Synovitis is Characterised by Highly Heterogeneous Histological & Molecular Patterns
Synovial Tissue Subsets have different Tissue cellularity

Training cohort of long term active RA synovial tissue (U. Michigan Ann Arbor, n=49)

Fibroid subset has fibroplasia but little inflammatory infiltrate

Dennis et al. *Arthritis Research & Therapy* in press
Agglomerative clustering of variable microarray probes reveals molecular subsets of RA synovitis

Training cohort of long term active RA synovial tissue (U. Michigan Ann Arbor, n=49)

Dennis et al. Arthritis Research & Therapy in press
New learnings on the pathophysiology of RA from synovial biopsies

Question?

Whether different synovial cellular & molecular signatures (pathotypes) can be informative of:

- Diverse Clinical phenotypes
  - Joint damage
  - Disease outcomes

&

Response to treatment

Costantino Pitzalis, Stephen Kelly, and Frances Humby

Biopsy

Synovial pathotypes (Gene expression, clinical covariates)

Identify systemic biomarker correlates
Integrated Pathobiology-Driven Patient Stratification Programme

A) MRC-Funded Pathobiology of Early Arthritis Cohort (PEAC)
   - DMARD Naive
     - Synovial Bx
       - DMARD Therapy

B) MRC/ARUK-Funded MATURA
   - Stratification of Therapy for RA by Pathobiology (STRAP)
     - DMARD Inadequate Response
       - Synovial Bx
         - Rituximab
         - Anti-TNF
         - Tocilizumab

C) NIHR/EME-Funded Mechanisms for Response-Relapse-Resistance to Rituximab in RA (R4-RA)
   - 1st Biologic Failure (Anti-TNF IR)
     - Synovial Bx
       - Rituximab
       - Tocilizumab

- TNF Blockade + other mAb
- Mac
- IL-6
- Tocilizumab
- IL-17
- B cell
- CD20

- Treg
- T-helper cell
- Neutrophil
- Dendritic cell
- T cell
- NK cell
- Lymphoid
- Myeloid

- MRC Medical Research Council
- Arthritis Research UK
- National Institute for Health Research
**Integrated Pathobiology-Driven Patient Stratification Programme**

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**C)**
- **NIHR/EME-Funded**
  - Mechanisms for Response-Relapse-Resistance to Rituximab in RA (R4-RA)
  - 1st Biologic Failure (Anti-TNF IR)
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Mechanisms for Response-Relapse-Resistance to Rituximab in RA (R4-RA)

Pre-defined treatment protocol
0 months 6 months 12 months

- Biopsy
- Biopsy

? General Population → Undifferentiated Arthritis (UA) → RA

Slowly Destructive
Rapidly Destructive

The goal of PEAC is to create a unique resource:

- 300 DMARD naïve patients (symptoms < 1 year)
- Detailed clinical phenotyping including state of the art 3D US imaging with time integrated synovitis and PDU scores to complement conventional clinical assessment tools (DAS 28 – HAQ) and x-ray scores at 12 months
- US-guided synovial biopsy at 0 and 6 months

Leading science for better health

PEAC Recruitment - 325 patients  (Total No. of Bx samples – n=414)
(Total No. Blood samples (+/- Bx) – n=432)

Biopsy Summary - QMUL

- **225pts.** recruited (Total No. Bx samples – n=348)
  (Total No. Blood samples (+/- Bx) – n=364)

- **217pts.** with 1st Bx* (- 131pts. with matching 2nd Bx**)  
  - 116pts. (59.5%) - Rheumatoid (RA)
  - 52pts. (26.5%) - Non-Rheumatoid (Non-RA)
  - 19pts. (11%) - Psoriatic (PsA)
  - 2pts. (1%) - diagnosis to be confirmed (TBC)

Diagnosis/Joint Stratification  (n=189)

- RA: n=127
  Knee: 23 (18%)
  Wrist: 83 (65%)
  MCP/PIP: 20 (16%)
  Elbow: 1 (1%)

- Non-RA: n=67
  Knee: 12 (18%)
  Wrist: 45 (67%)
  MCP/MTP: 9 (13.5%)
  MBT: 1 (1.5%)

- PsA: n=21
  Knee: 6 (28.5%)
  Wrist: 6 (28.5%)
  MCP/PIP: 9 (43%)

- TBC: n=2
  Wrist: 2 (100%)

* 8pts – no 1st Bx (bloods only)
** 7pts – no 2nd Bx (bloods only) & 1 pt. withdrawn (no 2nd Bx)

http://www.peac-mrc.mds.qmul.ac.uk
150 DMARDs-naïve patients with Early Inflammatory Arthritis (<12 months, at least 1 swollen joint) recruited at Barts and The London Hospitals.

Patients underwent US guided synovial biopsy of an active joint prior to commencing therapy.

Follow up every 3 months (clinical and ultrasound assessment); treatment adjusted according to T2T strategy aiming at DAS28<2.6.

All 150 patients analysed at baseline; a sub-analysis of 65 RA patients with a complete clinical, histological an US data-set will be shown, including association between synovial pathotype and clinical and US outcomes at 6mo.
Patient Research Cohorts Initiative Call
Leading science for better health

http://www.peac-mrc.mds.qmul.ac.uk
Patient Research Cohorts Initiative Call
Leading science for better health

http://www.peac-mrc.mds.qmul.ac.uk
Local anaesthetic injected into the soft tissues up to the joint capsule, visualized under US guidance.

Quick-Core® Biopsy Needle 16/14G is then placed within the synovium.

A minimum of 6 samples required.
Tissue Quality and Reliability of Ultrasound-Guided Synovial Biopsy

**Excellent**: >50% of all biopsy tissue can be scored, minimal adipose and necrotic tissue.

**Good**: >25-50% of all biopsy tissue can be scored, no more than 75% sub-lining/adipose/fibrous/necrotic tissue.

**Moderate**: ≤25% of all biopsy tissue can be scored, no more than 75% adipose and necrotic tissue.

**Poor**: No biopsy tissue can be scored (ungraded), no visible cell lining layer. Comprises of sub-lining/fibrous/adipose/necrotic tissues.
Patient Research Cohorts Initiative Call

Leading science for better health

Pathobiology of Early Arthritis Cohort (PEAC)

PEAC Matched Histology and RNA Quality Assessment
Results

Lymphocytic aggregates are found in approximately 28% of patients

RA, rheumatoid arthritis; UA, undifferentiated arthritis; SpA, spondyloarthritis,

χ² test, p = 0.23
## Results

Lymphocyte aggregates are associated with higher ESR, CRP and DAS28 as well as RF + and CCP +

<table>
<thead>
<tr>
<th></th>
<th>N = 150</th>
<th>Diff = 108 (72%)</th>
<th>Agg = 42 (28%)</th>
<th>p val</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR</td>
<td>32 ± 27</td>
<td>27 ± 25</td>
<td>42 ± 28</td>
<td>0.003</td>
</tr>
<tr>
<td>CRP</td>
<td>16 ± 27</td>
<td>14 ± 29</td>
<td>19 ± 21</td>
<td>0.008</td>
</tr>
<tr>
<td>TJ</td>
<td>9 ± 7</td>
<td>8 ± 7</td>
<td>9 ± 7</td>
<td>0.41</td>
</tr>
<tr>
<td>SJ</td>
<td>6 ± 5</td>
<td>5 ± 5</td>
<td>6 ± 5</td>
<td>0.18</td>
</tr>
<tr>
<td>DAS28</td>
<td>5 ± 1.7</td>
<td>4.8 ± 1.6</td>
<td>5.5 ± 1.7</td>
<td>0.01</td>
</tr>
<tr>
<td>RF +, %</td>
<td>41</td>
<td>35</td>
<td>57</td>
<td>0.02</td>
</tr>
<tr>
<td>CCP +, %</td>
<td>42</td>
<td>37</td>
<td>56</td>
<td>0.03</td>
</tr>
<tr>
<td>Erosive, %</td>
<td>11</td>
<td>9</td>
<td>20</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Values expressed as mean ± SD, unless specified otherwise. Mann Whitney or Chi-Square test, as appropriate.
Results

Presence of synovial aggregates is a predictor of response to DMARD in early RA patients

A. 

B. 

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>p val</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.960</td>
<td>0.919 - 1.002</td>
<td>0.062</td>
</tr>
<tr>
<td>CRP</td>
<td>0.974</td>
<td>0.947 - 1.002</td>
<td>0.073</td>
</tr>
<tr>
<td>Anti-CCP</td>
<td>0.997</td>
<td>0.994 - 1.000</td>
<td>0.058</td>
</tr>
<tr>
<td>Agg</td>
<td>11.978</td>
<td>1.607 - 89.298</td>
<td>0.015</td>
</tr>
<tr>
<td>STUS</td>
<td>1.089</td>
<td>1.016 - 1.167</td>
<td>0.016</td>
</tr>
</tbody>
</table>
Integrated Pathobiology-Driven Patient Stratification Programme

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C) NIHR/EME-Funded Mechanisms for Response-Relapse-Resistance to Rituximab in RA (R4-RA)

Pre-defined treatment protocol
0  6  12
months

Biopsy  Biopsy

→ Multi Omic Investigations
Approximately 1/3 of early RA synovium dominated by fibroid gene expression

These patients lack synovial aggregates, but continue to have active disease
Integrated Pathobiology-Driven Patient Stratification Programme

- RA disease taxonomy
- Therapeutic Response
- Clinical Phenotype
- Peripheral tissue
- Disease tissue
- Proteome
- mRNA & miRNA
- Epigenome
- Variation
- Genome

TranSMART Intersections

- e.g. biologic responders / non-responders

RA Life-course
Drug Response Stratification

AI disease Pathotypes
Biomarker ID
Causal gene ID

PaTaxRA Studies
Public AI Studies

Subjects
Time (life course)
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Overview of MATURA Consortium

Pathobiology-driven Stratification: Comparative Synovial tissue/blood analyses in RCT

- Methotrexate
- Anti-TNF
- Rituximab
- Tocilizumab

Large scale, blood-based screening from observational studies

- Genetic studies
- Epigenetic studies
- Expression profiling
- Pilot next generation sequencing
- Proteomic studies
- Deep immunological phenotyping

Pathobiology / Imaging Data

Biomarkers for stratified medicine

Work Stream 1

Statistics / Health Economics

Work Stream 2
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Agglomerative clustering of variable microarray probes reveals molecular subsets of RA synovitis

Training cohort of long term active RA synovial tissue (U. Michigan Ann Arbor, n=49)
Circulating Biomarker Derivation: ICAM1 and CXCL13 are expressed at highest levels in the myeloid (M) and lymphoid (L) phenotypes respectively.

Synovial gene expression

Serum biomarkers (RA patients vs. normal control, NC)

Dennis et al. Arthritis Research & Therapy in press
ADACTA: Phase IV, multicentre, randomised, double-blind study of anti-IL6R (Tocilizumab TCZ) vs anti-TNFα (Adalimumab, ADA) in RA
Orthogonal baseline serum biomarkers associate with differential clinical benefit to anti-TNFα vs. anti-IL6R

- sICAM1 contributes to anti-TNFα response
- CXCL13 contributes to anti-IL6R response

Dennis et al. Arthritis Research & Therapy in press
## Summary of Week 24 Response Rates in biomarker-defined subpopulations in the ADACTA Trial

<table>
<thead>
<tr>
<th>Biomarker Subset (n)</th>
<th>ADA ACR20 (%)</th>
<th>ADA ACR50 (%)</th>
<th>ADA ACR70 (%)</th>
<th>ADA DAS28-ESR (±SE)</th>
<th>ACR50 Odds Ratio (ADA vs TCZ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>sICAM^{high}/CXCL13 ^low (26)</td>
<td>73</td>
<td>42</td>
<td>23</td>
<td>-2.3 (±0.37)</td>
<td>2.93</td>
</tr>
<tr>
<td>sICAM^{low}/CXCL13 ^high (15)</td>
<td>27</td>
<td>13</td>
<td>7</td>
<td>-1.1 (±0.33)</td>
<td>0.07</td>
</tr>
<tr>
<td>sICAM^{high}/CXCL13 ^high (32)</td>
<td>50</td>
<td>28</td>
<td>19</td>
<td>-2.1 (±0.31)</td>
<td>0.53</td>
</tr>
<tr>
<td>sICAM^{low}/CXCL13 ^low (33)</td>
<td>52</td>
<td>24</td>
<td>18</td>
<td>-2.1 (±0.32)</td>
<td>0.41</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Biomarker Subset (n)</th>
<th>TCZ ACR20 (%)</th>
<th>TCZ ACR50 (%)</th>
<th>TCZ ACR70 (%)</th>
<th>TCZ DAS28-ESR (±SE)</th>
<th>ACR50 Odds Ratio (TCZ vs ADA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>sICAM^{high}/CXCL13 ^low (15)</td>
<td>60</td>
<td>20</td>
<td>7</td>
<td>-3.2 (±0.37)</td>
<td>0.34</td>
</tr>
<tr>
<td>sICAM^{low}/CXCL13 ^high (26)</td>
<td>81</td>
<td>69</td>
<td>50</td>
<td>-3.6 (±0.32)</td>
<td>14.6</td>
</tr>
<tr>
<td>sICAM^{high}/CXCL13 ^low (26)</td>
<td>58</td>
<td>42</td>
<td>31</td>
<td>-3.2 (±0.37)</td>
<td>1.9</td>
</tr>
<tr>
<td>sICAM^{low}/CXCL13 ^low (25)</td>
<td>60</td>
<td>44</td>
<td>24</td>
<td>-2.9 (±0.36)</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Dennis et al. *Arthritis Research & Therapy* in press
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Mechanisms for Response-Relapse-Resistance to Rituximab in RA (R4-RA)

Patient demographics of total study population (n=27)

<table>
<thead>
<tr>
<th></th>
<th>No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>21 (77)</td>
</tr>
<tr>
<td>Rheumatoid factor +ve</td>
<td>24 (88)</td>
</tr>
<tr>
<td>CCP +ve</td>
<td>25 (97)</td>
</tr>
<tr>
<td>Erosive</td>
<td>25 (97%)</td>
</tr>
<tr>
<td>Mean +/- St Dev</td>
<td>59.1 (+/-14.1)</td>
</tr>
<tr>
<td>Age</td>
<td>6.1 (+/-1.6)</td>
</tr>
</tbody>
</table>

Clinical Response to Rituximab

<table>
<thead>
<tr>
<th></th>
<th>Synovial Histomorphological pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low B cell score – n patients (%)</td>
</tr>
<tr>
<td>Responder</td>
<td>3 (20)</td>
</tr>
<tr>
<td>Non Responder</td>
<td>12 (80)</td>
</tr>
</tbody>
</table>

CD20+ B cell aggregational score

- Score 0
- Score 1
- Score 2
- Score 3
Integrated Pathobiology-Driven Patient Stratification Programme

A) MRC-Funded Pathobiology of Early Arthritis Cohort (PEAC)
   - DMARD Naive
   - Biopsy
   - Synovial pathotypes (Gene expression, clinical covariates)
   - Identify systemic biomarker correlates
   - B Cell Depletion | Anti-TNF | Costimulation Blockade | IL-6 Blockade

B) MRC/ARUK-Funded MATURA
   - Stratification of Therapy for RA by Pathobiology (STRAP)
   - DMARD Inadequate Response
   - Costimulation Blockade

C) NIHR/EME-Funded
   - Mechanisms for Response-Relapse-Resistance to Rituximab in RA (R4-RA)
   - 1st Biologic Failure (Anti-TNF IR)

QUESTION?

- Clinical Utility
- Feasibility
- Safety
- Tolerability
- Acceptability
Patients asked to complete questionnaire following procedure – typically 1-2 days post procedure

Data collected on
1. Patients perception of biopsy (pain / discomfort etc)
2. Change in joint disease activity following procedure (pain / stiffness / swelling)
3. Consideration of another biopsy
4. Complications e.g. infection / haemarthrosis etc.
Ultrasound-guided synovial biopsy: a safe, well-tolerated and reliable technique for obtaining high-quality synovial tissue from both large and small joints in early arthritis patients

S Kelly, F Humby, A Filer, N Ng, M Di Cicco, R E Hands, V Rocher, M Bombardieri, M A D'Agostino, I B McInnes, C D Buckley, P C Taylor, C Pitzalis

1. Patient reported discomfort during procedure

2. Joint discomfort following biopsy
Ultrasound-guided synovial biopsy: a safe, well-tolerated and reliable technique for obtaining high-quality synovial tissue from both large and small joints in early arthritis patients

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Pre and Post Procedure pain, stiffness and swelling as measured by visual analogue score

Would you have another Biopsy?

79% of patients likely or very likely to have another biopsy

In practice, when asked 3-6 months later 96% agreed to a 2nd biopsy
Ultrasound-guided synovial biopsy: a safe, well-tolerated and reliable technique for obtaining high-quality synovial tissue from both large and small joints in early arthritis patients

S Kelly, F Humby, A Filer, N Ng, M Di Cicco, R E Hands, V Rocher, M Bombardieri, M A D’Agostino, I B McInnes, C D Buckley, P C Taylor, C Pitzalis

### Safety and Tolerability of Ultrasound-Guided versus Arthroscopic Synovial Biopsy

<table>
<thead>
<tr>
<th>Ultrasound-Guided</th>
<th>Arthroscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appropriate for large and small joints in the hands of rheumatologists</td>
<td>Mostly appropriate only for large joints in the hands of rheumatologists</td>
</tr>
<tr>
<td>Good yield of tissue not under direct vision but US + PDU assessment</td>
<td>Good yield of tissue, under direct vision with possible macroscopic assessment</td>
</tr>
<tr>
<td>Minimally invasive, low rate of complications: Infection, DVT, Bleed</td>
<td>Fairly invasive, low rate of complications: Infection, DVT, Bleed</td>
</tr>
<tr>
<td>Short procedure (20-30 min)</td>
<td>Quite a long procedure</td>
</tr>
<tr>
<td>Acceptable to patients (majority happy to have the procedure repeated)</td>
<td>Acceptable to patients, but inconvenient and scary</td>
</tr>
</tbody>
</table>
Can Synovial Pathobiology Inform Disease Outcome and Response to Therapy?

Lots of work still remains to be done to demonstrate clinical utility for routine management!

Can it be done?

- Advances in US & minimally invasive Bx methodologies enable the biopsy of most joints in most patients
- Advances in high throughput molecular techniques facilitate analysis and validation

What can be achieved?

- Better understanding disease prognosis
- Better understanding Response/Resistance to therapy
- Patient Stratification into responsive therapeutic categories
Identification of Cellular Patient Strata

Identification of Molecular Patient Strata

Disease network reconstruction

mRNA-seq and miRNA-seq data analysis

TIQUA generate phosphoproteomic heat-map

Patients Benefits

Patients Stratification

Validation & Commercialisation

Disease Biomarkers

DMARD naive 6/12 DMARDs T0 PEAC (MRC) Biopsy

Fibroblast-rich 1
Lymphoid-rich
Myeloid-rich
B cells

M Townsend, F Martin, JG Monroe - Genentech RED
Stratify your patients with RA

http://www.vectrada.com
Systems diagnostics: anticipating the next generation of diagnostic tests based on mechanistic insight into disease

David A. Fryburg, dfryburg@elsevier.com, Diane H. Song, Daphna Laffenfeld and David de Graaf
Acknowledgements

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