Predicting outcome in IBD
by crossing the T’s

Dr James Lee
No financial disclosures
Patient 1. PC

- Male, 32 years
- 5 months:
  - Weight loss (2 stone)
  - Colicky RIF pain
  - Intermittent non-bloody diarrhoea – BO up to 10x/24h
  - Fatigue
- Grandfather has Crohn’s disease
- Non-smoker
- Bloods:
  - Raised inflammatory markers (ESR 45, CRP 22)
  - Monocytosis
  - Not anaemic
  - Albumin 35
Diagnosis: Ileocolonic Crohn’s disease
Patient 2. EG

- Female, 22 years, non-smoker
- Diarrhoea, abdo pain, weight loss, fatigue (6 months)
- CRP 47, ESR 81, Alb 27
- No FH

Diagnosis: Ileocolonic Crohn’s disease
**Patient 1. PC**
- Male, 32 years
- Newly diagnosed Ileocolonic CD
- No perianal involvement
- Non-smoker
- CRP 22 mg/l
- ESR 45 mm/hr
- Hb 14.5 g/dl
- Alb 35 g/l
- ASCA negative
- NOD2 wildtype
- No previous treatment

**Patient 2. EG**
- Female, 22 years
- Newly diagnosed Ileocolonic CD
- No perianal involvement
- Non-smoker
- CRP 47 mg/l
- ESR 81 mm/hr
- Hb 12.3 g/dl
- Alb 27 g/l
- ASCA negative
- NOD2 wildtype
- No previous treatment
Follow up

No further flares to end of follow up (475 days)
Disease course: variable and unpredictable

Quiescent disease

Persistent or flaring disease

A case for personalised medicine?

“The success of personalised medicine depends on having accurate diagnostic tests that identify patients who can benefit from targeted therapies.”

Quiescent disease
Protected from risks of unnecessary immunosuppression

Aggressive disease
Receive aggressive therapy as early as possible (ideally at diagnosis)

Dr Margaret Hamburg (Commissioner – FDA)
Dr Francis Collins (Director – NIH)
Hamburg and Collins. NEJM (2010)
The benefit of early aggressive therapy...

- Enhanced efficacy of early anti-TNF therapy vs late usage
  - Schreiber et al. NEJM (2007)

- Minimize progression to disease that requires surgery (strictures, fistulas)
... balanced against the risks of overtreating

- Tuberculosis
- Solid tumours
- Lymphoma
- Demyelination
- Other opportunistic infections
- etc...
"If people never tried anything new we wouldn't be living in caves."
Transcriptional (gene expression) profiling

- Used successfully in oncology – diagnostic and prognostic signatures described
- Less successful in auto-inflammatory disease – often confounded by the heterogeneity of the tissues examined
A CD8$^+$ T cell transcription signature predicts prognosis in autoimmune disease

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**Study design (prospective)**

- Recruit pts with active UC/CD; newly diagnosed or flaring on no treatment
- Separate CD8 and CD4 T cells from whole PBMC
- Assess whole genome gene expression by microarray
- Followed prospectively, managed conventionally in IBD clinics (blinded)
- 32 UC, 35 CD recruited; median follow-up 550 days
Are there any inherent patterns (subgroups) in the data?

CD4 T cells – no consistent subgroups identified

CD8 T cells:

True in both UC and CD

Lee et al. JCI 2011
The gene signatures in UC and CD were highly overlapping...

...to the extent where they could be used interchangeably to recreate the same subgroups – termed IBD1 and IBD2
Comparison with SLE/AAV signature

UC patients (by SLE/AAV signature)

CD patients (by SLE/AAV signature)

SLE/AAV vs CD overlap: $p < 1 \times 10^{-300}$
SLE/AAV vs UC overlap: $p < 1 \times 10^{-300}$

Lee et al. JCI 2011
No significant correlation with contemporaneous clinical/laboratory parameters:

- Gender
- Smoking
- Age
- Disease severity
  - CRP
  - ESR
  - Harvey Bradshaw Index / Walmsley Index
- Disease location
- Newly vs previously diagnosed
- Extra-intestinal manifestations
- ASCA serology
Quiescent vs. Aggressive

Common end-point:
- Immunomodulators
- Surgery
CD – requirement for escalation in treatment

Survival without need for treatment escalation (%)

Follow up (days)

Number at risk

IBD1 12 9 5 5 2 2 1 0
IBD2 23 19 17 14 11 8 5 1

p = 0.003

Lee et al. JCI 2011
**BUT** necessity for treatment escalation does not automatically indicate an aggressive/progressive disease course.

*Lee et al. JCI 2011*
Other methods of “disease prediction”

ASCA serology

Survival without need for treatment escalation (%)

Follow up (days)

ASCA -ve (n=17)
ASCA +ve (n=18)

Clinical parameters
(<40y, perianal disease, steroids)

Survival without need for treatment escalation (%)

Follow up (days)

Mild (n=15)
Severe (n=20)

Lee et al. JCI 2011
and UC....
Effect of stratifying by the IBD1/2 signature

Crohn’s disease

Ulcerative colitis
What biological differences cause this gene signature?

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Subgroup in which pathway is enriched</th>
<th>Nominal $P$ value (Primary cohort)</th>
<th>Nominal $P$ value (Replication cohort)</th>
<th>FDR $q$ value</th>
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<tr>
<td>IL-2 pathway</td>
<td>IBD1</td>
<td>0.0267</td>
<td>0.0020</td>
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<td>IL-7 pathway</td>
<td>IBD1</td>
<td>0.0102</td>
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<td>CD28 co-stimulation pathway</td>
<td>IBD1</td>
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<td>T-cell receptor pathway</td>
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<td>0.0185</td>
<td>0.1001</td>
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<td>IL-2 receptor beta pathway</td>
<td>IBD1</td>
<td>0.0183</td>
<td>0.0328</td>
<td>0.1654</td>
</tr>
</tbody>
</table>

Lee et al. JCI 2011
**CD8 T cell memory generation**

Activation and proliferation

Antigen-driven differentiation

Antigen-stimulated CD8+ T cell

Effector cells

TCR

CD28

IL-2

Memory cells

IL-7

More memory

↓

More able to respond to small amounts of re-encountered antigen (flare)

Kaech et al. Nat Rev Immunol 2002
Are CD8 T-cells from IBD1 patients more activated?

CD8 T cell activation signature

![Graph showing CD8 T cell activation signature with IBD1 (positively correlated) and IBD2 (positively correlated) on the x-axis and enrichment score on the y-axis. The graph shows a peak at P = 0.048.]

Lee et al. JCI 2011
Summary

- A gene signature, enriched for T cell activation genes, exists in peripheral CD8 T cells of patients with UC and CD at diagnosis.
- This divides all patients into two distinct groups that are otherwise clinically indistinguishable.
- In both diseases, patients enriched for this transcriptional signature experience significantly more aggressive disease behaviour characterised by frequently-relapsing/chronically active disease.
- This may enable personalised therapy to be initiated at diagnosis in the future – and will be tested in a UK-wide trial soon!
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