Discovery & Development of Humira™
The Patients Perspective

At Last, Enjoying My Life

By Richard Shirley, Rheumatoid Arthritis Patient

The last two years of my life have been sensational. My wife and I have traveled to New Zealand, visited the rainforest in Trinidad & Tobago and flown in a hot air balloon.

What's more, I've taken up new hobbies and even started to ballroom dance again.
CAT in early 1990’s….

- Antibody start-up in rural Cambridgeshire
- Antibodies deeply unfashionable
- No way to make human Mabs
- Phage display fresh out of the box
- Intellectually simple but technically challenging
BASF deal 1992/3

- Bob Kamen (BASF) & Dave Chiswell (CAT) former ICRF
- MAK195 in phase II/III for sepsis
- Early phase II data for Enbrel & Remicade in RA
- Aim to produce fast follower fully human anti-TNFα
Humira- if you did it now.. (..ish)

libraries of $10^{11}$ human scFv

→ Selection on BLyS

Panel of anti-BLyS scFv (>1200)

DNA sequencing (HGS) → Ligand binding assay

Cell based assay

Lead anti-BLyS neutralising scFvs

→ HT Reformat

Fully human IgG1 mAb (Benlysta)
Humira Program

*Enforced technical innovation*
Innovation 1

- Humanisation by chain shuffling
- Use of MAK 195 as a template
- Preservation of epitope & activity
- Potency >10,000-fold down (and stayed there)
Innovation 2

BIACore

RU

MAK 195

CAT antibody

time
Innovation 3

- Site directed mutagenesis of CDRs
- Ability to combine multiple mutations
- D2E7 (aka ‘Eric’) was VH D2 and VL E7
- Later given brand name ‘Humira’ (human, RA)
Innovation 4

- The ‘Bonus Effect’
- Multimeric targets
- Conversion to IgG 1-1000x inc. potency
- >10x in D2E7
Clinical Development

- Controlled by BASF
- Straightforward development path
- First into man still tense (weeks after CAT IPO)
- Acquisition by Abbott
Stock Market Listing

- London Stock Exchange - main market
- 25 March 1997
- Net raised - £41 million
- Explicitly to build a therapeutic product pipeline
- Market cap £100M (@ £5 per share, March 1997)
## Equity Raised

<table>
<thead>
<tr>
<th>Year</th>
<th>Amount</th>
<th>Share Price</th>
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<tbody>
<tr>
<td>1990</td>
<td>£0.75m</td>
<td>£0.12</td>
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<tr>
<td>1993</td>
<td>£3.0m</td>
<td>£3.00 (notional)</td>
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<td>1995/6</td>
<td>£12.75m</td>
<td>£2.50 - £3.00</td>
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<td>1997</td>
<td>£41.0m (IPO)</td>
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<td>2000</td>
<td>£93m</td>
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Outside Influences

- London Stock Exchange open to Biotech in 1997
- LSE closed to biotech from May 1997- early 2000
- Antibodies beginning comeback in late 90s
- Genomics revolution -> vast numbers of targets
- Significant US competition
67% premium looks like a good deal…

AstraZeneca to buy CAT for £702m

The two companies have been in partnership to develop drugs since 2004. Anglo-Swedish drug giant AstraZeneca has confirmed that it is to buy biotechnology firm Cambridge Antibody Technology (CAT) for £702m ($1.32bn).

AstraZeneca said it aims to "establish a major international presence in the research and development of biological therapeutics" in a statement.
...But wasn’t

AstraZeneca to buy CAT for £702m

• AZ sold Humira royalty for £400m
• CAT had £200m cash
• Net is £100m for technology, programs & infrastructure
• (PanGenetics sold one early stage program to Abbott for £100m a few weeks ago)
Lessons learned

- It doesn’t stop with the initial idea
- Chaos favours the adaptable
- Pretty much everything comes down to people
- Alignment of interests
- Surviving long enough to get lucky