Conference on Immigrant Entrepreneurship

November 17, 2010

Babson College, Wellesley, Massachusetts
Summary

- In 1998 the FDA licensed the use Remicade®/infliximab for the treatment of Crohn’s disease, marking the first approval of a new class of therapeutic agents that act by blocking the action of tumor necrosis factor (TNF).

- Approval of Remicade® was followed by the approval of Enbrel®/etanercept, later of Humira®/adalimumab, and, most recently, Cimzia®/certolizumab pegol and Simponi®/golimumab.

- Together, TNF inhibitors are now approved for the treatment of seven different chronic inflammatory disorders (rheumatoid arthritis, Crohn’s disease, ulcerative colitis, ankylosing spondylitis, psoriasis, psoriatic arthritis, juvenile arthritis).

- To date, approximately 5 million patients have been treated with TNF inhibitors.

- Current world-wide sales of TNF inhibitors have reached approximately $20 billion.
TNF 1975-1985

1975: Presence of “Tumor Necrosis Factor” was reported in the blood of some infected mice. TNF was postulated to play a role in resistance to certain malignant tumors.

1984-85: Human TNF protein was purified and TNF gene sequenced.
Useful Roles for TNF in the Body of Humans and Other Animals

• TNF helps the body fight some infections

• TNF plays a role in the development of certain cells and tissues of the immune system
Early Evidence That TNF Can Contribute to the Development or Severity of Diseases

- Malaria (1981)
- Bacterial sepsis (1985)
- Graft-vs-host disease (1987)
- Lung fibrosis (1989)
- Rheumatoid arthritis (1991)
The Centocor/NYU License Agreement

- In 1984 Centocor and NYU signed a License Agreement covering monoclonal antibodies against TNF and other cytokines developed in the Vilcek lab at NYU.

- NYU granted Centocor an exclusive, royalty-bearing license to inventions developed by NYU (or developed jointly by NYU and Centocor) in the course of research covered by this license agreement.
Diagram of cA2 chimeric antibody against TNF
Some years later...

• cA2 became the first TNF-neutralizing agent to be successfully used in humans

• cA2 = Remicade® (infliximab)
Remicade®/Infliximab Milestones

1988-89: Murine anti-TNF Ab (A2) generated at NYU
1990-91: Generation of chimeric Ab (cA2) in collaboration with Centocor; preclinical testing
1991-92: Clinical trial of cA2 in sepsis showed no significant benefit
1992: cA2 used successfully in rheumatoid arthritis patients (M. Feldmann, R. Maini et al.)
1993: cA2 used successfully in Crohn’s disease patients (S. van Deventer et al.)
1998: FDA approval for Crohn’s disease
1999: FDA approval for rheumatoid arthritis
2004: FDA approval for ankylosing spondylitis
2005: FDA approval for psoriatic arthritis
2005: FDA approval for ulcerative colitis
2006: FDA approval for severe plaque psoriasis
2010: Over 1.2 million patients have been treated with Remicade®/infliximab
Uncertainties Faced upon FDA Approval of Remicade®/Infliximab for Crohn’s Disease and Rheumatoid Arthritis in the late 1990s

• Is long-term anti-TNF therapy feasible?

• Will the equilibrium of the immune system be too severely disturbed?

• Will anti-microbial or anti-tumor defenses be too severely compromised?

• Will the body’s immune response against the anti-TNF agent preclude long-term administration?
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2006: FDA approval for severe plaque psoriasis
2010: Over 1.5 million patients have been treated with Remicade®/infliximab
<table>
<thead>
<tr>
<th>Agent</th>
<th>Nature</th>
<th>Approved for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enbrel®/etanercept</td>
<td>Soluble p75 TNF-R/IgGfusion protein</td>
<td>RA, Juvenile idiopathic arthritis, Ankylosing spondylitis, Psoriatic arthritis, Plaque psoriasis</td>
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<tr>
<td>Humira®/adalimumab</td>
<td>Human MAb</td>
<td>RA, Juvenile idiopathic arthritis, Ankylosing spondylitis, Psoriatic arthritis, Plaque psoriasis, Crohn’s disease</td>
</tr>
<tr>
<td>Cimzia®/certolizumabpegol</td>
<td>Humanized Fab' fragment (pegylated)</td>
<td>RA, Crohn’s disease</td>
</tr>
<tr>
<td>Simponi®/golimumab</td>
<td>Human MAb</td>
<td>RA, Psoriatic arthritis, Ankylosing spondylitis</td>
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Some Problems Associated with the Use of Anti-TNF Agents

- Not all patients respond to therapy.
- Even though treatments are generally well tolerated, some patients develop side effects (increased susceptibility to some infections).
- After successful therapy patients may cease responding.
- Treatments are generally very costly.
Factors Responsible for Successful Development of Remicade®

• Right “chemistry” between academic scientists at NYU and investigators at Centocor
• Expertise of the clinical investigators and skilled planning of key trials that formed the basis for regulatory approval
• Dramatic clinical efficacy with manageable side effects
No one should come to New York to live unless he is willing to be lucky

E. B. White
Co-inventors on Remicade® Patents

NYU

JunmingLe*
Jan Vilcek*

Centocor

John Ghrayeb*
Scott Siegel
David Shealy
David Knight
Peter Daddona

* Immigrants