“Dispelling the Myths About Pharmaceutical R&D”

ISPE
San Diego
November 10, 2009
Does Chlamydia Pneumoniae Cause Coronary Artery Disease?

Evidence in 1990’s

- analysis of heart disease patients showed evidence of prior Chlamydia pneumoniae infection
- organism present in atherosclerotic plaque
- animal studies showed infection with Chlamydia pneumoniae accelerated the development of atherosclerosis

Farfetched?

- Helicobacter pylori shown by Marshall to cause ulcers
Clinical Trial to Test Theory

- **WIZARD (Weekly Intervention with Zithromax for Atherosclerosis and its Related Disorders)**
  - 7747 patients with previous MI
  - Randomized to placebo or azithromycin
  - Dosed for 12 weeks
  - Monitored for one year

- **ACES (The Azithromycin and Coronary Events Study)**
  - 4012 patients with previous MI
  - Patients dosed 12 months with placebo or azithromycin
  - Followed for 3.5 years

No Benefit Seen
The Research Based Pharmaceutical Industry

Our Work Validates or Disproves Medical Hypotheses
Myth: *The Industry Is Not Innovative*
“Innovative research is done mainly by taxpayer funded research – government and universities funded by the NIH usually in universities and government labs and now in smaller biotech companies and then they license those to big drug companies.”

– Dr. Marsha Angell
“The Today Show”
September 2, 2004
JAK3 (Janus Kinase 3) Inhibition for Autoimmune Diseases
Janus Kinases (JAKs)

- Named after Janus, the two-faced Roman God of gates and doors

- JAK family of kinases
  - JAK1: IL2, IFNg signaling
  - JAK2: Epo receptor signaling; plays a central role in RBC homeostasis
  - JAK3: T and B cell activation/proliferation
  - Tyk2: IFN signaling Innate immunity

- Pfizer’s interest
  - JAK3 inhibition for inhibiting organ transplant rejection

http://www.pantheon.org/articles/j/janus.html?esc
Dr. John O’Shea (NIH):

– JAK3 controls signaling for growth factor that produces T-lymphocytes, the cells responsible for kidney transplant rejection

– Ultimately, it was shown that a genetic defect that prevented the production of JAK3 is the cause of Severe Combined Immunodeficiency Disease (“Bubble Boy Syndrome”)

Dr. Paul Changelian (Pfizer):

– Could an inhibitor of JAK3 modulate the immune system in people with autoimmune disease?
Screening Strategy

- Cell-free assays (enzyme)
- Cell (functional) assay
- Cell specificity assays & in vitro PK
- In vivo PK & Kinase selectivity screening
- Murine heart transplant
Med Chem Summary: Key Molecules

CP-352,664
Lead compound

CP-690,550
Improved potency
Improved metabolic stability
Other favorable properties

CP-599,083
10x Improved potency

CP-537,555
Improved cell potency
Reduced lipophilicity

CP-634,558
Defined stereochemistry
Improved potency
CP-690,550 in Monkey Transplant Rejection Studies

Renal Allograft Biopsy

PLACEBO

Destructive T Cells
Allograft Rejection

CYCLOSPORINE

Normal Renal Tissue

CP-690,550
**Phase I Study of CP-690,550**

*Given twice daily at a dose of 30mg in volunteers with psoriasis*
Week 6 ACR Response Rates

- ACR 20: 29% Placebo, 70% 5 mg, 81% 15 mg, 33% 30 mg
- ACR 50: 6% Placebo, 22% 5 mg, 54% 15 mg, 3% 30 mg
- ACR 70: 3% Placebo, 28% 5 mg, 51% 15 mg, 13% 30 mg

Full analysis set (LOCF).
“The story began when my second son was in utero. He is now a 15 year old high school freshman. If everything goes well, by the time he goes to his senior prom, 18 years after I went to a scientific meeting in the woods of Vermont, CP-690,500 might make it to pharmacy shelves and to patients who need it.

Or it might not. It is a tough game – but always worth playing.”

– Dr. Paul Changelian
Pfizer Scientist
Innovation in the Pharmaceutical Industry is Being Spurred by Genomics
AIDS – The Global Health Crisis

Within the next 25 years, AIDS will join heart disease and stroke as one of the top three leading causes of death Worldwide.*

*Medicine, Public Library of Science, November, 2006
Why is it that some who are exposed to HIV do not contract AIDS?

- Scientists studied these patients’ genetic profiles

- People who were missing a certain gene did not become infected with HIV
# Results of Genetic Studies*

<table>
<thead>
<tr>
<th>Genetic Profile</th>
<th>Impact</th>
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<tbody>
<tr>
<td>2 copies of normal gene</td>
<td>HIV susceptible</td>
</tr>
<tr>
<td>1 copy normal gene</td>
<td>Can be infected with HIV but disease progression is delayed</td>
</tr>
<tr>
<td>1 copy abnormal gene</td>
<td>Remarkably resistant to HIV</td>
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*First time any gene was implicated to play a role in infectious disease*
How HIV Invades A Cell

- The virus enters a cell via a gateway also known as a receptor

- The receptor that most strains of HIV use to enter a cell is called CCR5

- Resistance to AIDS has its origins in Bubonic Plague survival in Medieval Europe
HIV attempting to enter an immune cell

Immune-cell surface
By using this knowledge, can we create a drug to prevent HIV from entering a cell?
Pfizer’s Sandwich Labs Begin A Program To Find a CCR5 Antagonist

- **1996**: Conduct screens of Pfizer’s massive compound library -- up to 1,000,000 compounds -- looking for a compound that blocks the gateways (CCR5 Receptor)

- **1997**: 60 – 70 compounds show activity; 5 chosen for further refinement

- **2000**: One candidate is singled out for further development: UK-427,857

- **2001**: Compound is tested in Phase I, healthy volunteers
Maraviroc
Compelling Preclinical Profile

- Selective, reversible binding to the CCR-5 receptor
- Animal models showed good safety profile
Maraviroc
Clinically Effective in Early Patient Studies

Reduction in Viral Load

HIV Cell Entry Inhibition

Data Are Mean Values From Studies in 8 Separate Patients

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“Maraviroc (Selzentry™) is a really remarkable development in the field (of HIV therapies)”

- John Mellors
University of Pennsylvania Researcher
Myth: The Industry Invents Diseases
“There’s a lot of money to be made from telling healthy people they’re sick. Some form of medicalising ordinary life may now be better described as disease mongering: widening the boundaries of treatable illness in order to expand markets for those who sell and deliver treatments.”

Disease Mongering

- Is “bone thinning” a disease?

  No. However, if you are a petite woman of Asian or Northern European descent, bone-thinning is the first sign of osteoporosis.

- Is “hypercholesterolemia” a disease?

  No. But if you are an overweight male, with high LDL cholesterol and a family history of heart disease, you must get your LDL levels to < 100 mg/dl.
Drug Approval For A Unrecognized Disease Is Difficult

- Global regulatory agencies must recognize such a condition merits treatment
- Drug-sponsor must agree to criteria established by Regulatory Agencies for potential drug approval
- Clinical trials required to demonstrate safety and efficacy
- Physicians must believe the disease is serious enough to be willing to prescribe the medicine
- Payers must believe the condition is serious enough to warrant reimbursement
- Patients must be sufficiently concerned about their illness, pain or discomfort to be willing to seek treatment
Diagnostic Criteria for PTSD*

A person must have been exposed to a traumatic event.
The event involved a perceived or actual threat to the person’s own life or physical integrity or that of another, such as a physical or sexual assault, rape, a serious accident, a natural disaster, combat, being taken hostage, torture, displacement as a refugee, sudden unexpected death of a loved one, and witnessing a traumatic event.
The person’s response to the event involved fear, helplessness, or horror.
The person persistently experiences the event in at least one of several ways:
The person has intrusive recollections of the event.
The person has nightmares.
The person has flashbacks, which are particularly vivid memories that occur while he or she is awake and make him or her act or feel as though the event was recurring.
The person has intense psychological distress in response to reminders of the traumatic event.
The person has intense physiological reactions in response to reminders of the event (including palpitations, sweating, difficulty breathing, and other panic responses).
The person avoids reminders of the event and has generalized numbness of feeling, as indicated by the presence of at least three of the following:
The person actively avoids pursuits, people, and places that remind him or her of the event.
The person avoids thinking of or talking about the event.
The person is unable to recall aspects of the event.
The person has lost interest in or participates less in activities.
The person has felt detached or estranged from other people since the event.
The person has a restricted range of emotions or a feeling of numbness.
The person feels as though his or her life has been foreshortened or as though there is no need to plan for the future, with respect to his or her career, getting married, or having children.
The person has symptoms of increased arousal, as evidenced by the presence of at least two of the following:
The person has difficulty falling or staying asleep (sometimes related to fear of having nightmares).
The person is irritable and has feelings or outbursts of anger.
The person has difficulty concentrating.
The person has become more vigilant and concerned about safety.
The person has exaggerated startle reactions in response to sounds or movements.
The three types of symptoms must be present together for at least one month.
The disorder must cause clinically significant distress or impairment in social, occupations, or other areas of functioning.

*There are three subtypes of PTSD. Acute PTSD refers to symptoms that last less than three months. Chronic PTSD refers to symptoms that last three months or longer. Delayed-onset PTSD refers to symptoms that begin at least six months after a traumatic event.

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Zoloft For Post-Traumatic Stress Syndrome

- Anecdotal clinical evidence suggested activity

- In consultation with the FDA, clinical trials were designed:
  - patients with PTSD for \( \geq \) six months
  - dosed with Zoloft or placebo for 12 weeks
  - trials assessed symptomatic, psychosocial and quality of life outcomes

- Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Zoloft</th>
<th>Placebo</th>
</tr>
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<tbody>
<tr>
<td>#1</td>
<td>60%</td>
<td>38%</td>
</tr>
<tr>
<td>#2</td>
<td>53%</td>
<td>32%</td>
</tr>
</tbody>
</table>

- Zoloft approved for PTSD in December 1999
Fibromyalgia

- Clinical descriptions first appeared in the 1850s
  - widespread pain of unknown etiology
  - associated with poor sleep pain and stiffness
  - believed to result from neurological changes in how patients perceive pain

- Lyrica had already been approved for neuropathic pain
  - Would it work in fibromyalgia?
Results from a 14-week, randomized, double-blind, placebo controlled study of 745 patients to evaluate the efficacy and safety of LYRICA in Fibromyalgia. Criterion for entry into the double-blind phase was absence of a high placebo response (>30% decrease on the pain VAS) during the 1-week run-in phase. Patients received: LYRICA 300 mg/day (150 mg twice daily), 450 mg/day (225 mg twice daily), 600 mg/day (300 mg twice daily), or placebo. The primary efficacy measure was symptomatic relief of pain associated with Fibromyalgia.
“I couldn’t spend time with my kids and do the things that I wanted to do with them. You know, I went from being able to hike and bike and walk around and go shopping and go to the movies and hang out with my friends. I could not even get off the sofa for three days at a time. Within two weeks after reaching my dosage level, I started having a life again. I got to go out with my family. I got to have lunch with friends. I went to a movie, which was something I had not been able to do because it hurt so bad to sit in a theater chair.”
Myth: *The Industry Doesn’t Care About Diseases of the Developing World*
“Drug companies spend more on advertising and marketing than research, more on research on lifestyle drugs than on life saving drugs, and almost nothing on diseases that affect developing countries only.”

– J. E. Stiglitz

Diseases of the Developing World
- A Complicated Problem

Involves:

- Poverty and Disease
- Access to Medicines
- R&D in Neglected Diseases
Pharmaceutical Industry and Philanthropy

The top corporate donors in 2006 according to The Chronicle of Philanthropy

1. Pfizer $1.7 billion
2. Merck $826 million
3. J&J $545 million
4. BMS $528 million
5. Microsoft $436 million
Partnerships to Build Healthier Societies In the Developing World
Examples of some key education initiatives:

GSK African Malarial Partnership
- Implementing behavioral change programs in vulnerable communities

Novartis Foundation ACCESS Project
- Informing Tanzanians about malaria prevention
- Improving malaria diagnosis
- Increasing access to medicines

AstraZeneca-Red Cross TB Partnership
- Increasing awareness and diagnosis of TB
- Improving treatment compliance
- Providing ongoing care
Access to Medicines

Every major pharmaceutical company has programs which provide free medicines to the developing world.

**Bayer:** provided the WHO 2.5 million doses of Lampit to fight Chagas disease

**Sanofi-Aventis:** gave the WHO one million injectable doses of pentamidine / melarsoprol / effornithine (plus $25 million to support its distribution) to fight African typanosomiasis

**Merck:** in 2007 donated $125 million worth of medicines and vaccines to fight diseases in the third world

**Pfizer:** Diflucan Partnership has provided more than $500 million worth of this medicine to treat fungal infections associated with HIV/AIDS in more than 80 countries in need
PhRMA’s Commitment of Talent & Expertise

- **Research Institutes Established**
  - *Astra Zeneca*  
    - Bangalore unit focused on TB
  - *GSK*  
    - Spain unit focused on TB and malaria
  - *Novartis Institute*  
    - Based in Singapore and focused on malaria and Dengue fever

- **WHO’s Special Program for Research and Training in Tropical Diseases**
  - Provides research expertise and resources for target ID and HTS
  - Advises on clinical trial design
  - Aids in dossier preparation
  - Shares manufacturing skills and formulation development
  - Provides medical training

- **Eradication of Disease**
  - *Merck*  
    - Ivermectin program to eliminate onchocerciasis (river blindness)
  - *Pfizer*  
    - Azithromycin program to wipe out trachoma

On track to eradicate the top two causes of preventable blindness by 2020!
Myth: *Big Pharma’s Day Has Passed*
Innovation in Cancer Therapy
Future Treatments
New Cancer Drugs

• Nixon’s “War on Cancer”
  • signed National Cancer Act on December 23, 1971
  • committed $100 million additional funds to NCI
  • since 1971 $50 BILLION has been spent on cancer research
    with 80% of these funds used to understand disease processes

• Investments Just Now Paying Off
  • more than 750 new cancer drugs now in development
**Strategies To Attack Cancer**

- Block Growth of Tumor Blood Vessels
  - Angiogenesis Inhibition

- Reawaken Immune System
  - Immunotherapy

- Inhibit Aberrant Signals in Cancer Cells
  - Signal transduction inhibitors
Sutent
VEGFR Plus Inhibitor

Multi-Targeted Kinase Inhibitor

Inhibits Tumor Vascularization

Disrupts Tumor Survival
Sutent
Gastrointestinal Stromal Tumor and Renal Cell Carcinoma

Strong Efficacy in Refractory GIST

Source: Demetri, ASCO Virtual Meeting, 2003
**Sutent**

**Significant Efficacy In Advanced Metastatic Renal Cell Carcinoma (mRCC), First And Second Line**

- *Sutent “Is The New Reference Standard For The First-line Treatment Of mRCC And Demonstrates Exceptional Antitumor Activity And Durable Clinical Benefit In mRCC.”*

* R Mozer ASCO 2006 Plenary Session

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**Tremelimumab – Anti-CTLA4 Antibody**

Release ‘Brake’ to T Cell Expansion

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**Releasing the Brake**

Diagram illustrating the interaction between MHC, B7, Peptide, CTLA4, CD3, CD28, and the regulation of transcription factors in T cells.
Tremelimumab
Single Agent in Metastatic Melanoma

Results Are Representative Of One Patient Only And Results May Differ For Other Patients.
IGF-1R As A Cancer Therapy Target

- IGF-1R plays a critical role in the regulation of cell growth
- Enhanced IGF-1R signalling promotes tumor growth and survival
- High IGF-1 & 2 serum levels correlate with increased cancer risk (Breast, Colon, Prostate, Lung, Cervix)
An Optimal Response With Figitumumab In Sarcoma

Baseline

24 weeks on CP-751,871

D. Olmos, J Clin Oncol 26: 2008 (May 20 suppl; abstr 10501)
“There is a wonderful story to be told here about what we do at Pfizer, why we do it, and what it means to be a colleague. It would be an honor and a privilege to tell this story to any and all who’ll listen.

In my nine years at Pfizer, I have always taken comfort in knowing that I was contributing to something greater than myself. At no other time has this fact been driven home more profoundly and personally.

We like to say here at Pfizer that “the patient is waiting”. Little did I know that it would be my father.

With Thanksgiving around the corner, there certainly is a lot to be thankful for.

I am thankful that my children get to visit their “Grandpa Bobby”.

I am thankful that my Mom gets to keep the love of her life.

I am thankful that I get to argue with my Dad about politics and the NY Mets’ starting line-up.

Lastly, I am thankful and truly proud that I can be part of what we do here at Pfizer.”

David P. Leventhal