The Centre for Drug Research and Development (CDRD)

Transforming Discovery into Opportunity

Allergen NCE: Planning for Research Success Series

Knowing Your Customer

December 1st, 2015

Jonathon Jafari
Who Are Your Customers?

- BioPharma
- Regulators
- Researchers
- Patient
- Healthcare Systems
- Caregiver
- Investors

CDRD
Transforming Discovery into Opportunity
Product Market Assessment

- Market assessment of a new technology
  - What is the mechanism?
  - What diseases does this pathway effect?
  - If you inhibit or stimulate this pathway how would it change the disease?
  - The number of patients who may benefit
  - Unmet need
  - Competitive landscape
  - Pricing
  - Regulatory Pathway
  - Health Economics
  - Payor Assessment
Asthma Unmet Needs

- The majority of patients respond to steroids and β-agonists, but ~10% of patients with severe asthma could use improved treatments.
- Asthma is a heterogeneous disease but researchers have identified potential targets for patients with severe asthma based on the drivers of the immune response:
  - Xolair: anti IgE antibody (Genentech/Roche 2003)
  - Nucala: anti IL-5 antibody (GSK 2015)
  - Benralizumab: anti IL-5 (PHIII positive results 2016)
Asthma Market

- Asthma market estimated to be in the range of $18 to $20 Billion per year
- Largely generic but branded products available for severe asthma
  - Xolair sales over $2B (~$600M in Asthma) per year through Novartis and Roche
- New products to treat severe eosinophilic asthma from AZ, Teva, and GSK

http://www.pmlive.com/pharma_news/teva_set_for_fda_verdict_on_reslizumab_early_next_year_758467
Patient Populations

Xolair, Lebrikizumab: Moderate to Severe Asthma

2015 estimates for number of patients (000)

- Diagnosed Asthmatics (12+): 20,231
- Treated Asthmatics: 11,524
- Moderate and Severe: 5,551
- Uncontrolled: 2,075

Source: Roche/Genentech
Reimbursement: Ontario Exceptional Access Program Asthma

<table>
<thead>
<tr>
<th>DRUG NAME</th>
<th>BRANDS REIMBURSED</th>
<th>DOSAGE FORM/STRENGTH</th>
<th>REIMBURSEMENT CRITERIA</th>
<th>STANDARD APPROVAL DURATION</th>
</tr>
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<tbody>
<tr>
<td>Leukotriene Receptor Antagonists</td>
<td></td>
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<tr>
<td>Zafirlukast</td>
<td>Accolate</td>
<td>20 mg tablet</td>
<td><em>For the treatment of asthma patients who cannot manage the use of an inhalation device despite assistance with a spacer (e.g., physically or mentally disabled patients or pediatric patients).</em>&lt;br&gt;<strong>OR</strong>&lt;br&gt;<em>For the treatment of asthma in children and adolescents whose asthma cannot be controlled on ICS alone and where the condition remains uncontrolled despite using full doses of ICS with addition of LABA, and with assurance of good adherence and inhaler technique.</em>&lt;br&gt;&lt;br&gt;<em>Renewal</em> of requests that meet the above criteria will be provided where the following apply:&lt;br&gt;- Current medications and dosages must be clearly specified;&lt;br&gt;- Objective evidence of positive response from treatment (spirometry OR decrease in health care utilization) must be provided.&lt;br&gt;&lt;br&gt;Initial: 5 years&lt;br&gt;Renewal: 5 years</td>
<td></td>
</tr>
<tr>
<td>Montelukast</td>
<td>Singulair</td>
<td>5 mg, 10 mg tablet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omalizumab</td>
<td>Xolair</td>
<td>150 mg/ vial</td>
<td><em>For the treatment of severe uncontrolled asthma in patients who meet the following criteria:</em>&lt;br&gt;- Has required hospitalization for asthma within the past 12 months; OR&lt;br&gt;- Has required two or more urgent visits for asthma to a physician or an emergency department within the past 12 months; OR</td>
<td>Initial: 1 Year</td>
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Pricing/Reimbursement

What $250 of Advair looks like:

United States
1 inhaler

France
7 inhalers

Source: IHS. The comparisons are based on the manufacturer’s suggested retail price. Insurance companies may negotiate lower prices.

Potential Targeted Treatments

IL-17 Ab from Medimmune
Anti-TNF-α trial in asthmatics had modest results
IL-18 Ab in Dev for IBD & T2DM (GSK)
IL-13 Ab for TH2 Asthma from Roche & Medimmune
IL-5 Ab (multiple) for eosinophilic asthma
IL-9 Ab from Medimmune
The increasingly granular umbrella for Type 2 cytokine-associated asthma molecular phenotypes, all of which encompass some Type 2 inflammatory biomarkers.

**Type 2-Molecular Phenotypes**

- **Type-2 Asthma**
  - **Eosinophilia**
  - **Periostin**
  - **FeNO**

- Mild CS naive/CS responsive early onset asthma (IL-4/13)
- Moderate-Severe Early onset CS treated atopic asthma (persistent IL-4/13)
- Late onset eosinophilic (IL-5, ?13)
- Type-2 +Very severe, autoimmunity, eosinophils, neutrophils IL-4, 5, 13 and Type 1 factors

Medimmune/AZ Targeting Severe Asthma

![Venn Diagram]

- **MEDI9929** (TSLP)
- **AZD5069** (CXCR2)
- **brodalumab** (IL-17R)
- **tralokinumab** (IL-13)
- **TH2-driven**
- **Neutrophil-high**
- **EOS-dominant**
- **IgE-high**
- **benralizumab** (IL-5Rα)

**Personalized Healthcare Approach: Targeting Different Segments of the Severe Asthma Population**

http://biotuesdays.com/2014/01/07/in-conversation-with-bing-yao/
Rationale for Targeting IL-13

Asthma: Identification of asthma patients likely to benefit from anti-IL-13 (Lebrikizumab) therapy

IL13 induced genes in lung epithelial brushings

- asthmatics
- asthmatics & controls

Responsive to α-IL-13? Non-responsive to α-IL-13?

Blood periostin levels in asthmatics

- Plasma periostin (ng/ml)
- Th2-LOW N=7
- Th2-HIGH N=6
- bronchial epithelial Th2 signature
- p=0.03

- Peripheral blood periostin may serve as a non-invasive surrogate for IL-13 related asthma
- A predictive diagnostic marker (periostin) may predict improved clinical responses to Lebrikizumab

Internal data
Rationale for Targeting IL-13

Asthma: Relative change in FEV1 from baseline in asthma patients treated with Lebrikizumab

<table>
<thead>
<tr>
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<th>Total ITT population</th>
<th>Periostin High</th>
<th>Periostin Low</th>
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</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>4.3%</td>
<td>5.8%</td>
<td>3.5%</td>
</tr>
<tr>
<td>Lebrikizumab</td>
<td>9.8%</td>
<td>14.0%</td>
<td>5.1%</td>
</tr>
<tr>
<td>Difference</td>
<td>5.5% (p=0.02)</td>
<td>8.2% (p=0.03)</td>
<td>1.6% (p=0.61)</td>
</tr>
</tbody>
</table>

Corren et al. NEJM, 2011

cobas e 601
Periostin assay

92
Project Example: GTPases in Targeting Neutrophils

- ARHGAP15 knockout affects RAC1
- Neutrophils in ARGAP15-/- show decreased circulating neutrophil and macrophages
  - Increased motility
  - Increased phagocytosis
  - Increased ROS generation
  - Increased Bacterial Killing
- Animals were protected from induced sepsis
  - Reduced secretion of cytokines

These Studies Suggest That There May Be Utility in Targeting Specific GTPases
Figure 1. Schematic representation of potential phenotype switching of neutrophils during airway mucosal inflammation in severe asthma. Under homeostatic conditions, neutrophils are present in the circulation predominantly in a mature (neu-2) phenotype. Upon immunologic stress, 2 additional phenotypes mobilize in large numbers: banded (neu-1) and hypersegmented cells (neu-3). In contrast, in neutrophilic asthma, particularly during an exacerbation, there may be a shift in the phenotypes resulting in differential neutrophils homing toward the airway tissue as a consequence of epithelial-derived mediators (e.g., LTB₄, IL-8, IL-1β, IL-17A). These neutrophil-active factors could not only extend neutrophil life span to increase their proinflammatory potential but also affect their potential transformation into other repopulating cells, such as neutrophil-APC hybrid cells that may interact with T cells to precipitate mucosal neutrophilic inflammation.
Neutrophils in Disease

- Strategies to inhibit RAC may have significant potential in Neutrophil mediated diseases
- Significant market potential but highly competitive markets
  - High throughput screening for small molecules
    - Cell based assays to further clarify RAC inhibition on Neutrophil activities compared to other products in development
    - High unmet need in many indications
  - Potential for inhaled formulation for COPD/Asthma
    - COPD and Asthma preclinical studies
    - Need to identify KOL's for asthma in Canada
    - Small molecule approach may allow for decreased costs compared to biological therapy
Role of Neutrophils in Inflammatory Lung Disorders

- Neutrophils have been found to have a role in various inflammatory pulmonary disorders including Asthma, COPD, Cystic Fibrosis, and Acute Lung Injury
- Due to heterogeneous nature of these disorders, researchers have looked to identify different disease phenotypes including the role of neutrophils
- Researchers have recently applied concepts from oncology in order to target subsets of patients in order to improve effectiveness in these difficult to treat populations
  - Anti IL-5 for eosinophilic, Anti IL-13 for TH2 Asthma
Role of Neutrophils in Asthma

- Neutrophils are commonly found in the sputum of asthmatics, especially in severe asthma
  - The number of neutrophils has been found to be correlated with the severity of the disease
  - Patients with high levels of neutrophils have been shown to be resistant to inhaled corticosteroid therapy
    - Eosinophilic (Mild/Moderate) asthma responds better to inhaled corticosteroid therapy
    - Recent data from GSK for their anti IL-5 antibody for eosinophilic subtype is a good example of the benefit of testing Asthma subtypes
Potential Benefits of RAC Inhibition

- Various MOA’s have targeted Neutrophil activity with limited success
- RAC2 Inhibition may have advantages compared to other MOA’s
  - GTPase affects many functions of neutrophil function including signaling to other cells, chemotaxis, and reactive oxygen release
  - Other strategies such as IL-8 Inh may only affect chemotaxis which may not sufficient to impact disease progression
# Neutrophil Inhibitors Potential Inflammatory Lung Disease Patient Populations in Major Markets

<table>
<thead>
<tr>
<th>Disease</th>
<th>Big 7 Market Prevalence (US, EU5, JPN)</th>
<th>WW Pharma Sales</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma*</td>
<td>67M</td>
<td>$16B</td>
<td>Severe Neutrophilic Asthma is estimated to be ~5 to 10% or ~3 to 7M</td>
</tr>
<tr>
<td>COPD*</td>
<td>41M</td>
<td>$10.5B</td>
<td>Unclear what % would be neutrophilic</td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>80K WW</td>
<td>$1.1B</td>
<td>New Vertex drug will Increase Market</td>
</tr>
</tbody>
</table>

*It may be interesting to look at Bronchitis (GSK doing this with Mepolizumab) mediated by Neutrophils as a separate sub-population
# Deal-making in Pulmonary Inflammation

<table>
<thead>
<tr>
<th>Partners</th>
<th>Program</th>
<th>Upfront</th>
<th>Milestones</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amgen/Astra Zeneca (2012)</td>
<td>Multiple (5) Clinical Molecules</td>
<td>$50M</td>
<td>&gt;$500M</td>
<td>Pulmonary Inflammation &amp; Other Disorders Anti IL-17 is late stage</td>
</tr>
<tr>
<td>Reata/Abbott Labs (2011)</td>
<td>Antioxidant Inflammation Modulators</td>
<td>?</td>
<td>$400M</td>
<td>2nd partnership between companies Nrf2 Activation</td>
</tr>
<tr>
<td>Portola/Biogen Idec (2011)</td>
<td>Oral Syk Inh.</td>
<td>$45M</td>
<td>$553.5M</td>
<td>Asthma, Lupus, Cancers, RA</td>
</tr>
</tbody>
</table>

*Note there are many more deals in Inflammation Which May Target Pulmonary Disorders but therapeutic area was not disclosed (Medtrack)*
Conclusions

- Market assessment of new opportunities is driven by both scientific and business information
- At CDRD we look at market data from providers such as Evaluate Pharma (pipeline, market data) and Recap (deals data) along with presentations from pharmaceutical and biotech players in the space and solicit feedback from our Innovation partners
- Freedom to operate analysis is also critical
- Health economics important but difficult to assess at the early stage of a program
Sources

1. Amulic et al. Neutrophil Function From Mechanisms To Disease Annual Reviews of Immunology 2012. 30:459-89
4. Summers et al. Neutrophil Kinetics in Health and Disease Trends in Immunology V31 No. 8
5. FDA Guidance for Industry: Chronic Obstructive Pulmonary Disease Developing Drugs for Treatment
8. Daxas (Roflumilast) Tablets: Pulmonary-Allergy Drugs Advisory Meeting Presentation Forest Labs 2010
9. FDA Presentation: Pulmonary-Allergy Advisory Meeting April 2010
Sources

13. Cockayne et al. Systemic Biomarkers of Neutrophilic Inflammation, Tissue Injury and Repair in COPD Patients with Differing Levels of Disease Severity PLOSone June 12, 2012
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20. Videos of the Assays and Methods: [http://bloodjournal.hematologylibrary.org/content/118/4/1099/suppl/DC1](http://bloodjournal.hematologylibrary.org/content/118/4/1099/suppl/DC1)
22. Kolanus Neutrophils Bridled by GAPS Blood July 28 2011 832-34