Research, Development & Innovation at Aché

Cristiano Guimarães

March 2016
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Exploring understudied Kinases with the Structural Genomics Consortium

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:: Some Facts about Aché

- Privately owned company, 100% Brazilian, founded in 1966 by three families (Baptista, Siaulys, Depieri)
- Branded and non-branded generics in a portfolio of 303 brands in 747 SKUs
- 20+ medical specialties, 130 therapeutic classes
- 176 programs in development
- 5 BUs: Prescription, OTC, Dermocosmetics, Specialty Care, Generics
- Multiple channels: wholesalers, pharmacies, hospitals, and government
- Leader in prescription in Brazil for the 8th consecutive year
- 4,500 employees (largest salesforce in Brazil)
- Net revenues of R$ 2.4 Billion
### Why Innovate?

<table>
<thead>
<tr>
<th>SCENARIO</th>
<th>INNOVATION VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Competition for price reductions and market share among generics;</td>
<td>• IP generation as a barrier to competitors;</td>
</tr>
<tr>
<td>• Unfavorable IP for the development of generics and branded generics:</td>
<td>• Greater life cycle of innovative products;</td>
</tr>
<tr>
<td>Evergreening of patents, art. 40;</td>
<td>• Sustainable growth of the company (greater than organic growth);</td>
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<tr>
<td>• Big pharma crisis: prohibitive cost to develop a blockbuster, FDA</td>
<td>• Generation of out-licensing and co-development opportunities: faster</td>
</tr>
<tr>
<td>hurdles, patent cliff;</td>
<td>return on investment;</td>
</tr>
<tr>
<td>• Big pharma is focused on few TAs: opportunity in deprioritized TAs;</td>
<td>• Generation/Addition of know-how and complexity to the processes of the</td>
</tr>
<tr>
<td>• Risk and return sharing: partnership opportunities with big pharma;</td>
<td>company;</td>
</tr>
<tr>
<td>• R&amp;D decentralization: CROs with expertise in different stages of</td>
<td>• Foster the development of capabilities/expertise in Brazil;</td>
</tr>
<tr>
<td>development;</td>
<td>• Increase in company’s intangible assets.</td>
</tr>
<tr>
<td>• Government funding available for innovation.</td>
<td></td>
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</tbody>
</table>
Open Innovation with the Structural Genomics Consortium

Open Phase

- Probe library
- Screening
- Hit identification and co-crystal structure
- Probe Optimization (Potency and Selectivity)
- Target exploration in biological studies

Closed Phase

Unicamp Kinases

- **Tier 1**: few compounds and poorly studied targets
- **Tier 2**: many compounds allow the study of targets
- **Tier 3**: many compounds and well studied targets
:: Drugs vs Probes

**DRUGS**
Must be safe and effective

- May have undefined MoA
- IP restrictions; limited availability
- Must have human bioavailability
- High bar for physicochemical (guidelines for MW, lipophilicity, etc.) and pharmaceutic properties (stability, reasonable and economic synthesis, defined crystallization form, etc.)

**PROBES**
Ask a specific biological question

- Defined MoA is required
- Needs selectivity
- Freely available (both the physical compound itself and activity data)
- Drug-like properties, such as bioavailability, not necessarily required
- Value is markedly enhanced by use of structurally related inactive and structurally unrelated active compounds
:: Unicamp Kinases
:: Potential Indications

- Alzheimer
- Autophagy
- Hypertension and cardiac remodeling
- Depk3
- Neuroprotection
- EMT and Cell Invasion
- Msk2
- Cdk11
- Srpk2
- Dyrk2
- Brain development and function
- Wnk3
- mRNA splicing
- Cdk4
- Cell proliferation and apoptosis
- Haspin
- Metabolic syndrome
- Cdk1
- Ptp4
- DNA repair and chemoresistance
- Vak1
- Cdk12
- T lymphocyte biology
- Baz1b
- Transplantation
- Sterility
:: VRK1: Vaccinia-related kinase 1

- Cellular proliferation, cell cycle regulation, and carcinogenesis (Valbuena et al, 2011)

- Confers resistance to DNA-damaging agents in human breast cancer (Salzano et al, 2014)

- VRK1 expression increases after allograft heart transplantation (Qian et al, 2014)

- Plays a role in germ cell development, and its deficiency results in sterility (Choi et al, 2010; Wiebe et al, 2010)

- Spinal muscular atrophy-associated gene that regulates neuronal migration (Wee et al, 2010; Vinograd-Byk et al, 2015)
:: VRK1 Crystal Structure (Literature)

- Resolution: 2.4 Å
- Crystal structure: 4 identical chains with one ligand in each chain
- Ligand has key interactions with Phe134, Asp132 and Gln45
:: PKIS Screening

CDK2 series active in VRK1

<table>
<thead>
<tr>
<th>Compound</th>
<th>VRK1 ΔTm</th>
<th>CDK2 ΔTm</th>
<th>CDK2 IC₅₀</th>
</tr>
</thead>
<tbody>
<tr>
<td>GW297361X</td>
<td>9.7</td>
<td>13.0</td>
<td>2 nM</td>
</tr>
<tr>
<td>GW290597X</td>
<td>6.0</td>
<td>8.0</td>
<td>25 nM</td>
</tr>
<tr>
<td>GW305178X</td>
<td>4.7</td>
<td>13.9</td>
<td>3 nM</td>
</tr>
<tr>
<td>GW280670X</td>
<td>2.1</td>
<td>9.8</td>
<td>43 nM</td>
</tr>
<tr>
<td>GW275944X</td>
<td>0.5</td>
<td>8.9</td>
<td>46 nM</td>
</tr>
<tr>
<td>GW396574X</td>
<td>0.1</td>
<td>13.5</td>
<td>2 nM</td>
</tr>
</tbody>
</table>

- HB acceptor seems important for VRK1 activity but not CDK2
- Inhibitors likely rely on other interactions for CDK2 activity as the series has been optimized for this kinase
:: Docking Studies

- Putative binding mode in VRK1 typical of kinases
- Docking suggests interaction between HB acceptor and Lys71 (catalytic Lys)
- In theory, good for potency, but bad for selectivity as it is a conserved residue

GW30660X ($\Delta T_m = 4.8^\circ C$)

GW297361X ($\Delta T_m = 9.7^\circ C$)
:: VRK1 Potency vs Selectivity

Reasonable Potency
and selectivity

> 4°C
:: Design Strategy

- Keep HB with Lys71, which seems important for VRK1 potency
- Explore potency and selectivity using amides, ketones, and esters – chemistry that is library enabled and allow rapid SAR exploration
Match between PKIS screening results and computational method suggest screening of additional CDK2 chemical matter (beyond PKIS) as well as of other similar kinases to VRK1.
:: Additional Chemical Matter

- Hierarchical clustering analysis of the kinase set based on inhibitors bioactivity profiles
- VRK1 Cluster: Similarity between VRK1 and TNIK bioactivity profiles
:: Additional Chemical Matter

- VRK1 Cluster: Similarity between VRK1 and TNIK (same family as MAP4K4 and MINK)
- MAP4K4 crystal structures display unusual folded conformation for the P-loop - selectivity hook as it binds favorably very small molecules, weak for kinases unable to adopt such conformation
- Is VRK1 also able to adopt the P-loop folded conformation?
- Searched ZINC database for commercially available TNIK/MAP4K4/MINK inhibitors as well as similar scaffolds to TNIK/MAP4K4/MINK chemical matter
:: Crystallization Efforts at SGC-UNICAMP

Protein production at SGC-UNICAMP

Starting compound from SGC-UNC

Co-crystallization at SGC-UNICAMP

Co-crystal structure solved at SGC-UNICAMP
:: Crystal Structure at a Glance

Confirms proposed interaction with Lys71

Potential Gly flip and associated selectivity with appropriate chemical matter

Supports P-loop folded conformation hypothesis
1. OPEN PHASE:
   a) Innovative Biology: access to novel, potentially hot targets
   b) Networking: development of scientific relationships, collaborations
   c) Develop people: interaction with high caliber scientists worldwide, publish in high impact journals
   d) Brand equity: attract/retain talents, attract scientific/commercial partners

2. CLOSED PHASE:
   a) Competitive edge: knowledge and relationships generated during open phase provide competitive edge during closed phase
   b) The Lottery Ticket: really innovative drug discovery program if a novel target becomes hot
Obrigado!

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