Research, Development & Innovation at Aché

Cristiano Guimarães

March 2016

Research, Development & (Open) Innovation at Aché

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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?

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

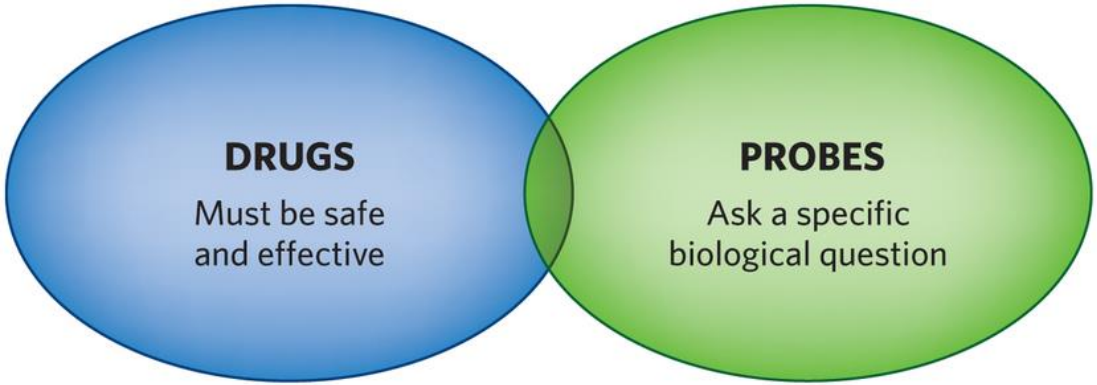
:: Open Innovation with the Structural Genomics Consortium

Open 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

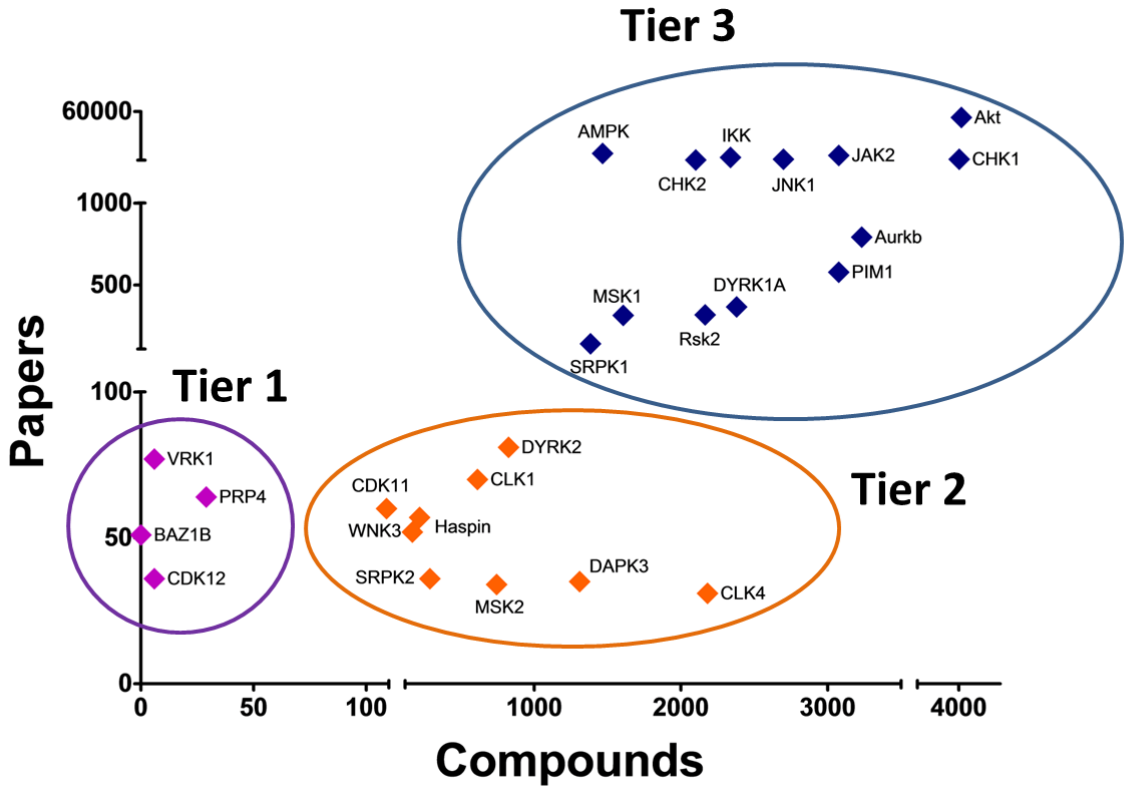
:: Drugs vs Probes



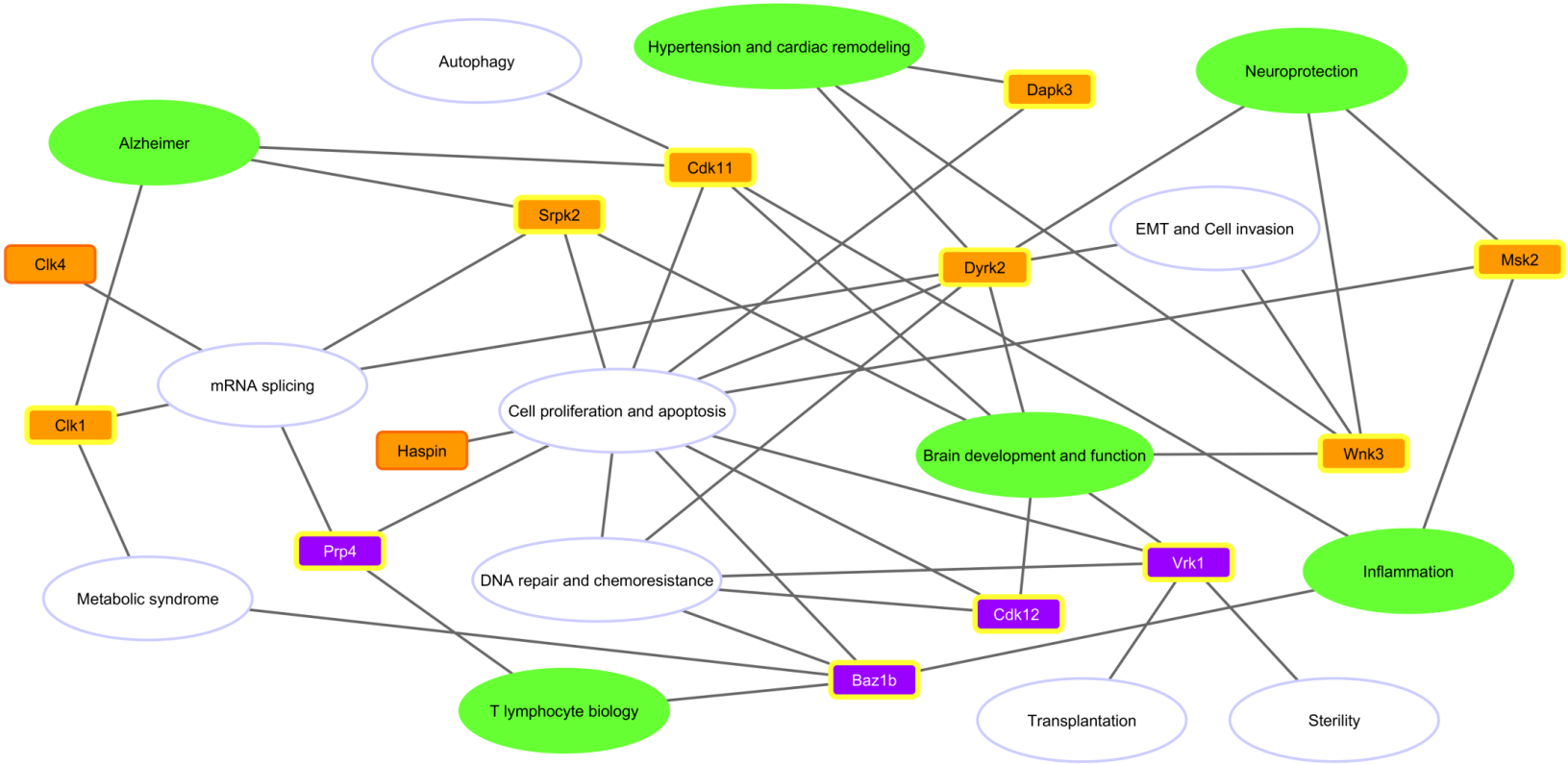
- May have undefined MoA
- IP restrictions; limited availability
- Must have human bioavailability
- High bar for physicochemical (guidelines for MW, lipophilicity, etc.) and pharmaceutic properties (stability, reasonable and economic synthesis, defined crystallization form, etc.)

- 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



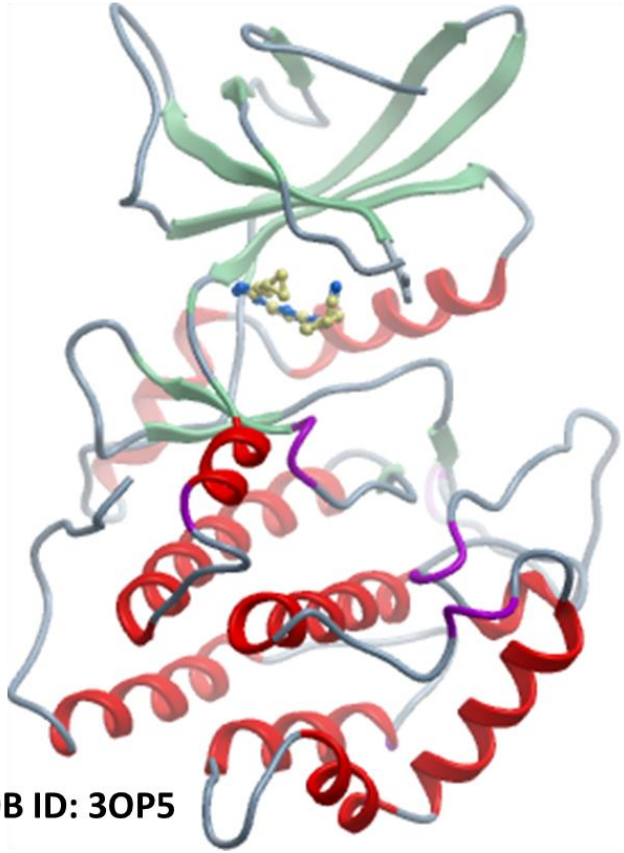
:: Potential Indications



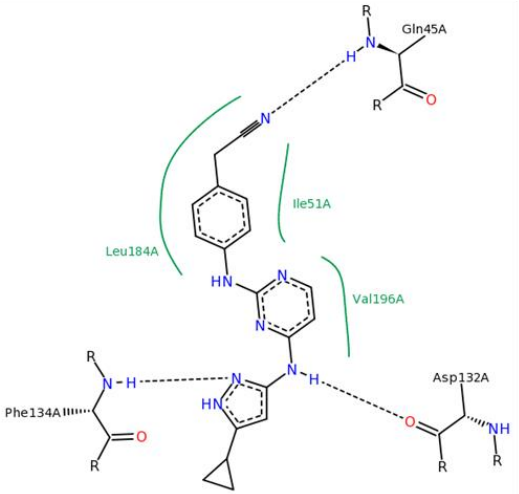
:: VRK1: Vaccinia-related kinase 1

- 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)

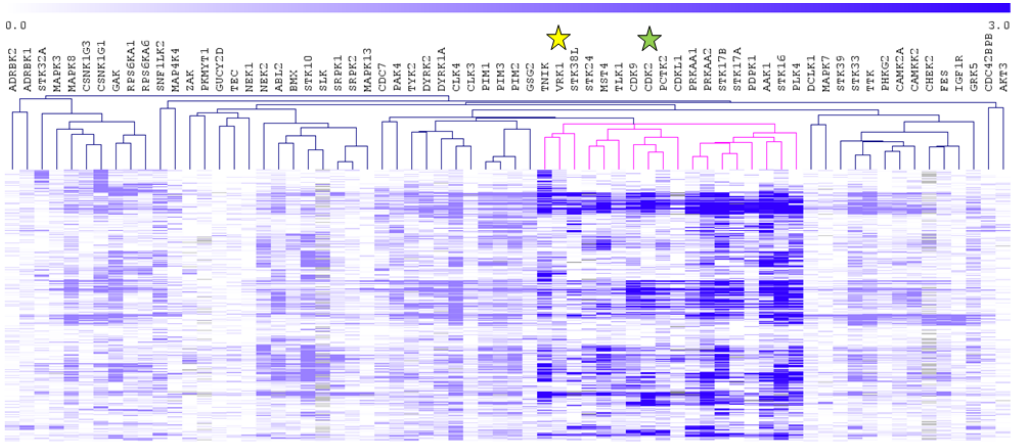
:: VRK1 Crystal Structure (Literature)



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



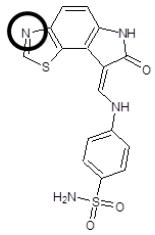
:: PKIS Screening



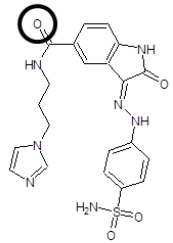
CDK2 series active in VRK1

Compound	VRK1 ΔTm	CDK2 ΔTm	CDK2 IC_{50}
GW297361X	9.7	13.0	2 nM
GW290597X	6.0	8.0	25 nM
GW305178X	4.7	13.9	3 nM
GW280670X	2.1	9.8	43 nM
GW275944X	0.5	8.9	46 nM
GW396574X	0.1	13.5	2 nM

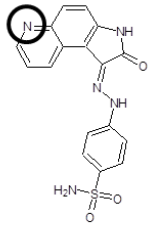
GW297361X



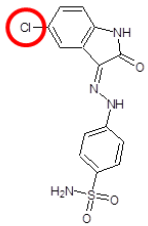
GW290597X



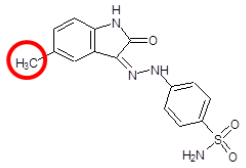
GW305178X



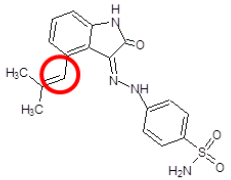
GW280670X



GW275944X



GW396574X

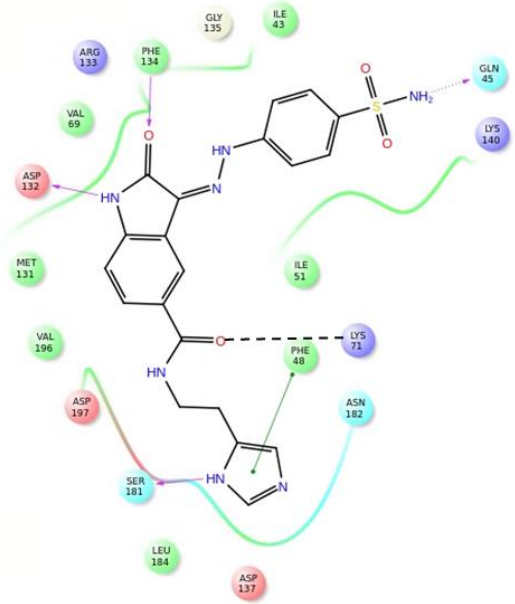


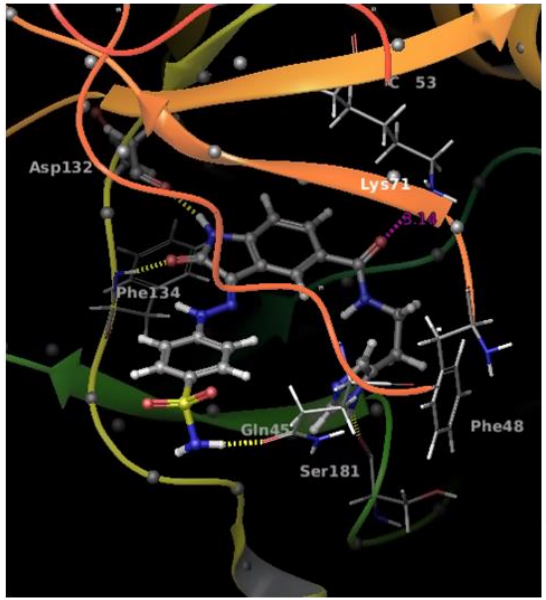
- HB aceptor seems important for VRK1 activity but not CDK2
- Inibitors likely rely on other interactions for CDK2 activity as the series has been optimized for this kinase

:: Docking Studies

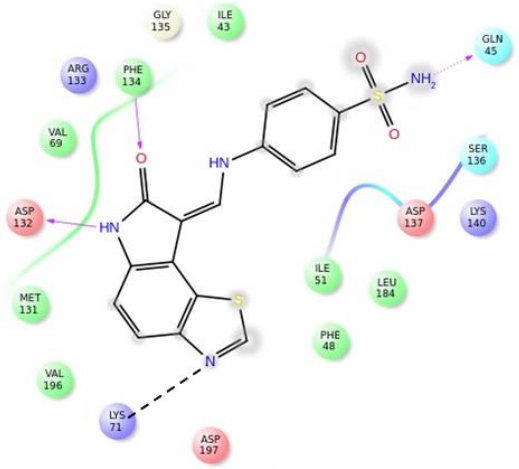
- Putative binding mode in VRK1 typical of kinases
- Docking suggests interaction between HB acceptor and Lys71 (catalytic Lys)
- In theory, good for potency, but bad for selectivity as it is a conserved residue

GW30660X (ΔT_m = 4.8° C)

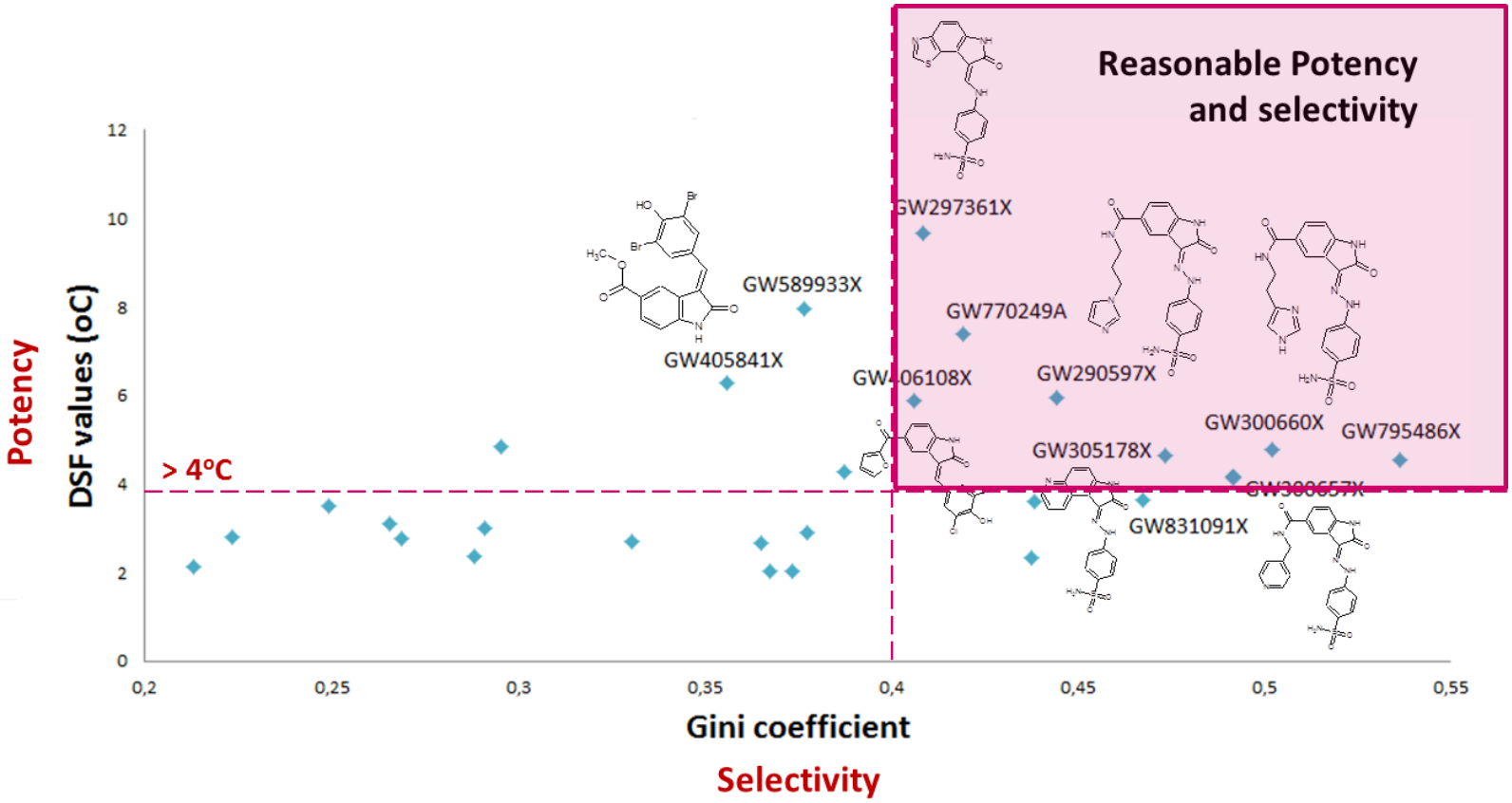




GW297361X (ΔT_m = 9.7° C)

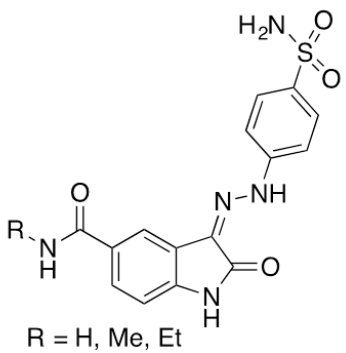


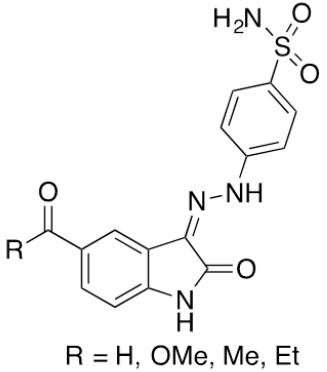
:: VRK1 Potency vs Selectivity

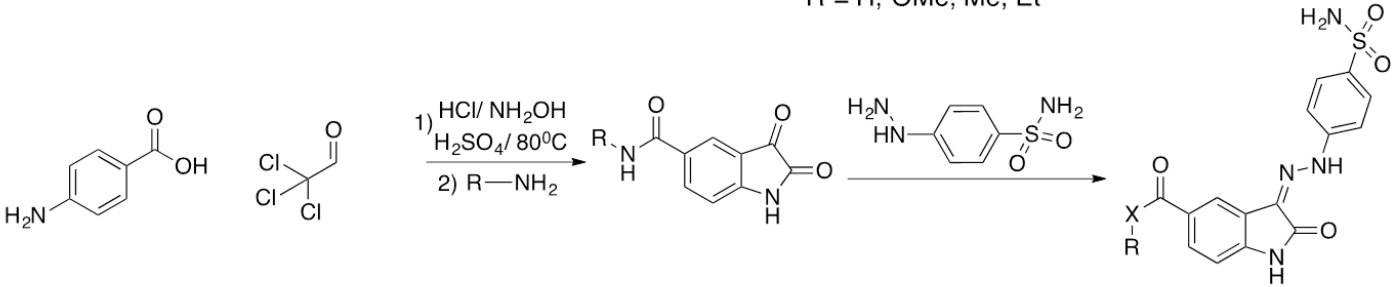


:: Design Strategy

- 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







:: Additional Chemical Matter

Kinase SARfari

Kinases more similar to VRK1 (based on residues in the binding site)

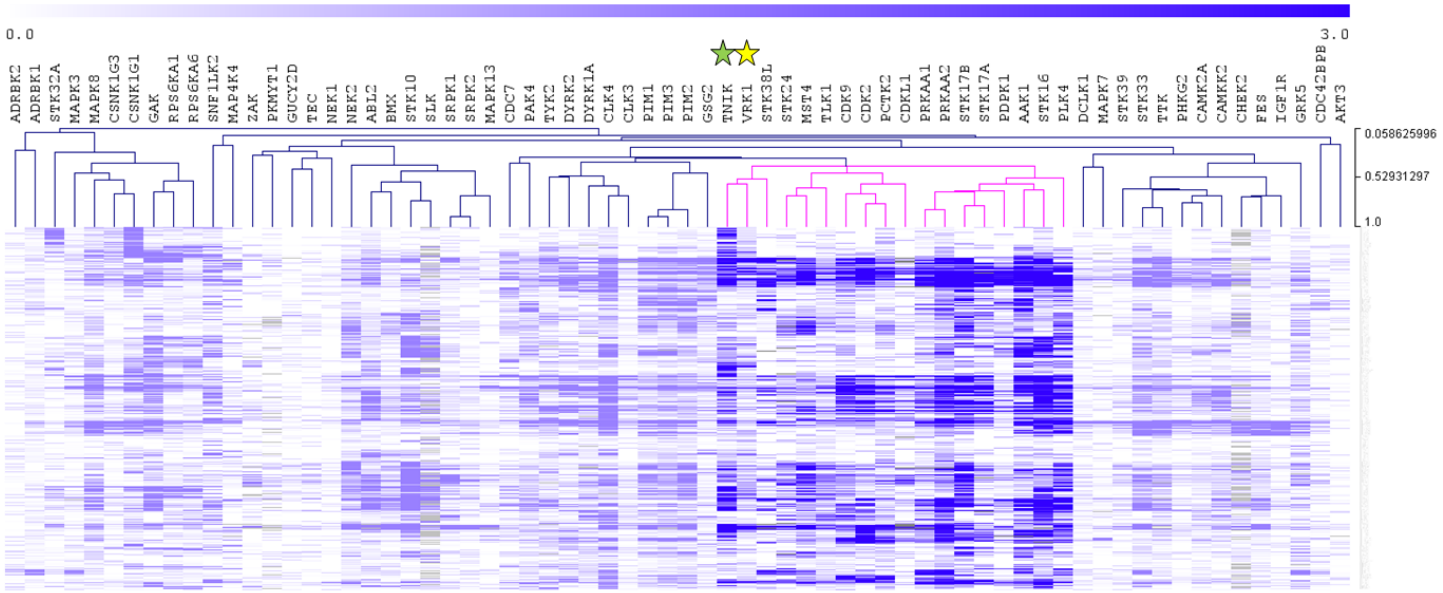
VRK2, ERK1, ERK2, CDK2, NLK, ERK5, CDK3, CDK10, MKK4, MAP2K4

Name	Organism	Level 2	Level 3	Level 4	Drugs	Bioactivities	Compounds	Distance
VRK2	Human	CK1	VRK	VRK	0	0	0	1.60
ERK1	mouse	CMGC	MAPK	ERK1	0	7	5	3.02
ERK1	rat	CMGC	MAPK	ERK1	0	8	7	3.02
ERK1	Human	CMGC	MAPK	ERK1	0	659	560	3.02
ERK1	Human	CMGC	MAPK	ERK1	0	0	0	3.02
ERK1	Human	CMGC	MAPK	ERK1	0	0	0	3.02
ERK1	Human	CMGC	MAPK	ERK1	0	1068	14417	3.03
ERK1	Human	CMGC	MAPK	ERK1	0	0	0	3.03
ERK2	xenopus	CMGC	MAPK	ERK1	0	5	5	3.03
CDK2	Human	CMGC	CDK	CDC2	0	0	0	3.12
NLK	Human	CMGC	MAPK	nmo	0	99	85	3.18
ERK5	Human	CMGC	MAPK	ERK5	0	100	76	3.25
CDK3	Human	CMGC	CDK	CDC2	0	146	140	3.26
CDK2	Human	CMGC	CDK	CDC2	0	4940	4076	3.31
CDK2	Human	CMGC	CDK	CDC2	0	0	0	3.33
CDK10	Human	CMGC	CDK	CDK10	0	0	0	3.34
MKK4	Human	STE	STE7	MEK4	0	109	106	3.41
MKK4	Human	STE	STE7	MEK4	0	0	0	3.41
MAP2K4	mouse	STE	STE7	MEK4	0	17	18	3.41

- 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

Understanding the Impact of the P-loop Conformation on Kinase Selectivity

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J. Chem. Inf. Model., **2011**, *51* (6), pp 1199–1204
DOI: 10.1021/ci200153c
Publication Date (Web): May 13, 2011
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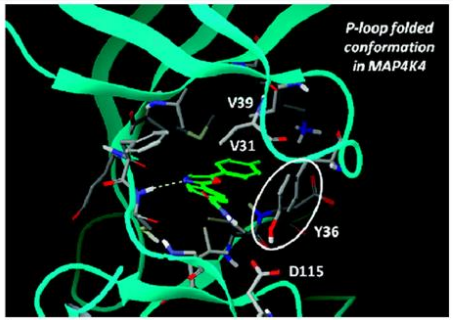
Abstract



Discovery of an *in Vivo* Tool to Establish Proof-of-Concept for MAP4K4-Based Antidiabetic Treatment

Mark Ammirati†, Scott W. Bagley†, Samit K. Bhattacharya*†, Leonard Buckbinder‡, Anthony A. Carlo§, Rebecca Conrad‡, Christian Cortes‡, Robert L. Dow†, Matthew S. Dowling†, Ayman El-Kattan⊥, Kristen Ford∥, Cristiano R. W. Guimarães†, David Hepworth†, Wenhua Jiao†, Jennifer LaPerle⊥, Shenping Liu†, Allyn Londregan†, Paula M. Loria∥, Alan M. Mathiowetz†, Michael Munchhof†, Suvi T. M. Orr†, Donna N. Petersen∥, David A. Price†, Athanasia Skoura‡, Aaron C. Smith†, and Jian Wang†

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ACS Med. Chem. Lett., **2015**, *6* (11), pp 1128–1133
DOI: 10.1021/acsmedchemlett.5b00215
Publication Date (Web): October 6, 2015
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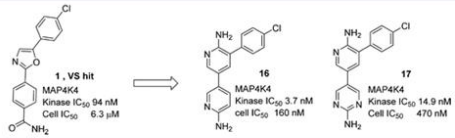
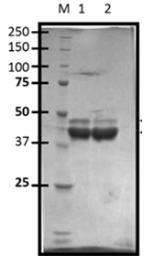
Abstract

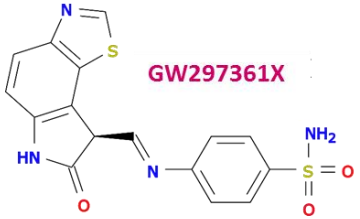


:: Crystallization Efforts at SGC-UNICAMP

Protein production at SGC-UNICAMP

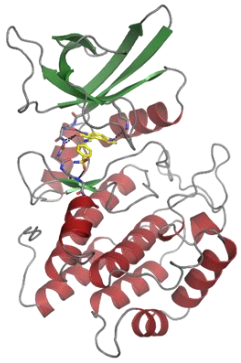


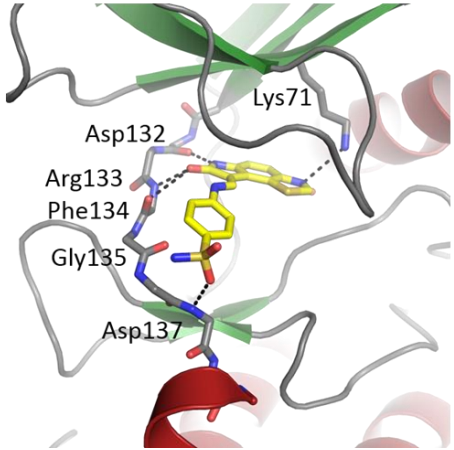
Starting compound from SGC-UNC



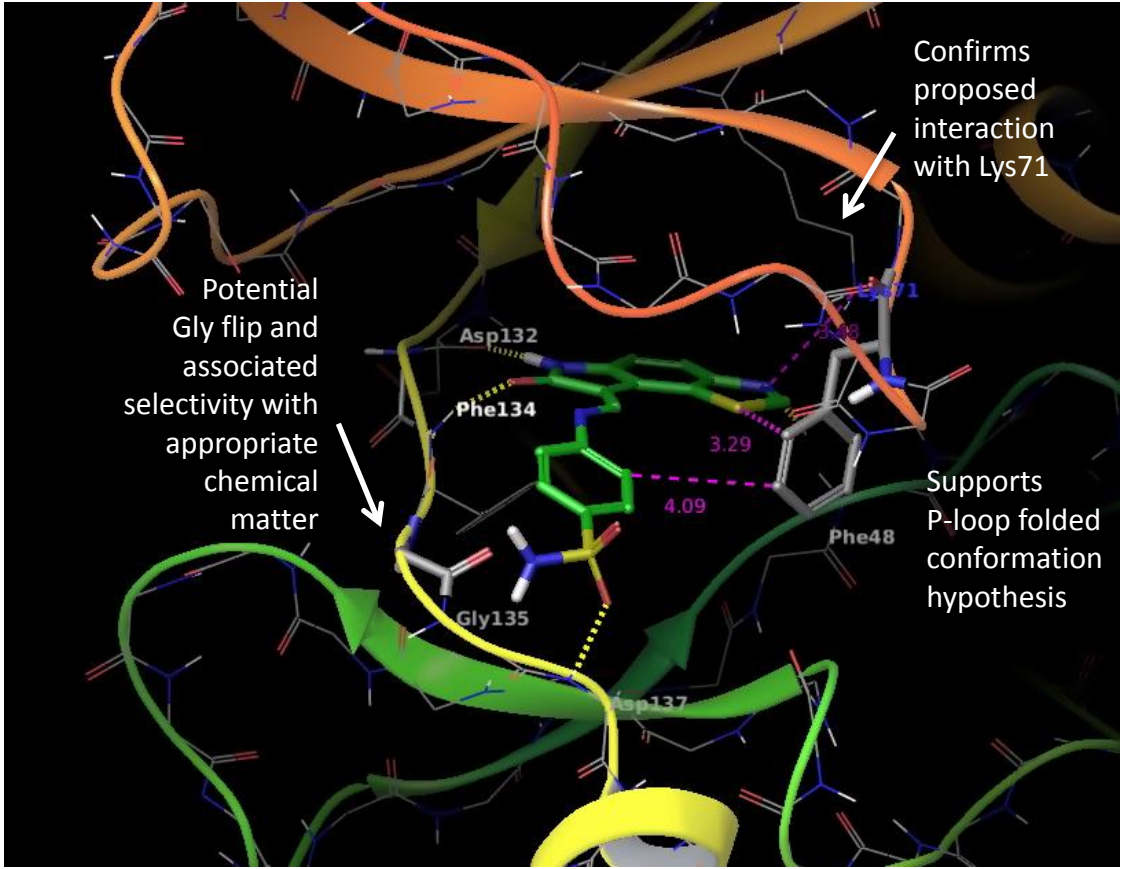
Co-crystallization at SGC-UNICAMP

Co-crystal structure solved at SGC-UNICAMP





:: Crystal Structure at a Glance



:: Perspectives – High Risk, High Reward, High Expectations

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!

Aché
Hatylas Azevedo
Alessandra Mascarello
Eloísa Ishikawa
Fernando Gama
Marcos Ferreira Jr
Natanael Segretti

SGC-Unicamp
Paulo Arruda
Opher Gileadi
Rafael Couñago
Anita Salmazzo
Carina Gileadi
Katlin Massirer
Marcella Reis
Natalia Verza
Nathalia Zocal
Paulo Godoi
Roberta Ruela-de-Souza

SGC-UNC
Bill Zuercher
Alison Axtman
Carrow Wells
Harold Drewry
Tim Wilson

SGC-Oxford
Wenhua Lee

SGC-Toronto
Aled Edwards