UNIVERSIDADE DE SÃO PAULO - USP

Instituto de Química de São Carlos - IQSC

Grupo de Química Medicinal do IQSC/USP

NEQUIMED10.
10 YEARS OF IQSC/USP MEDCHEM.

Carlos Montanari & Andrei Leitão

(Carlos.Montanari@usp.br, andleitao@iqsc.usp.br)

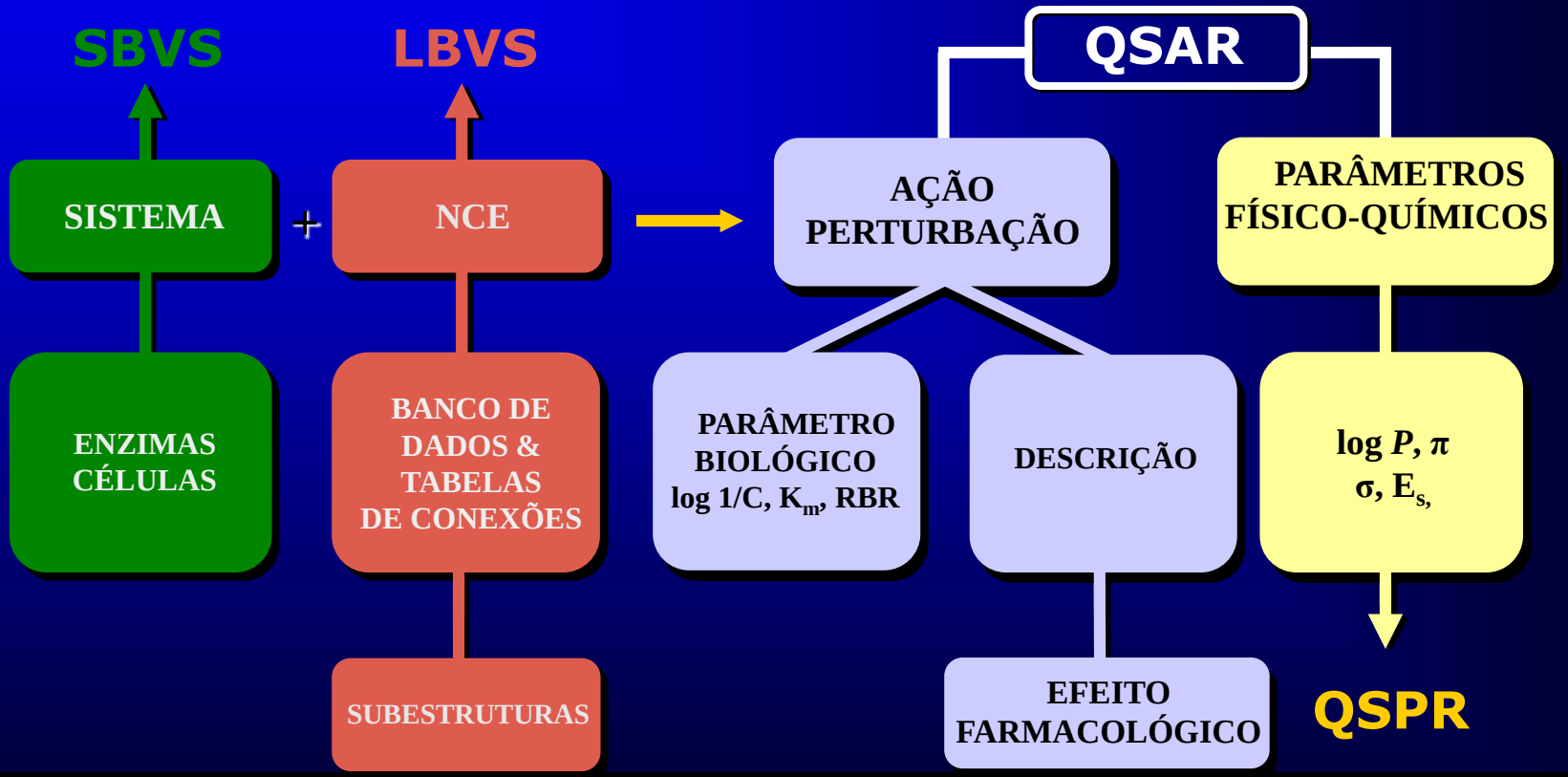
O problema combinatório da síntese de moléculas pequenas

O Universo químico. Chemical Abstract: > 50.10^6

10^{40}-10^{120} SUBSTÂNCIAS COM C, H, N, P, S, F, CL, Br, I e MM < 500 Da

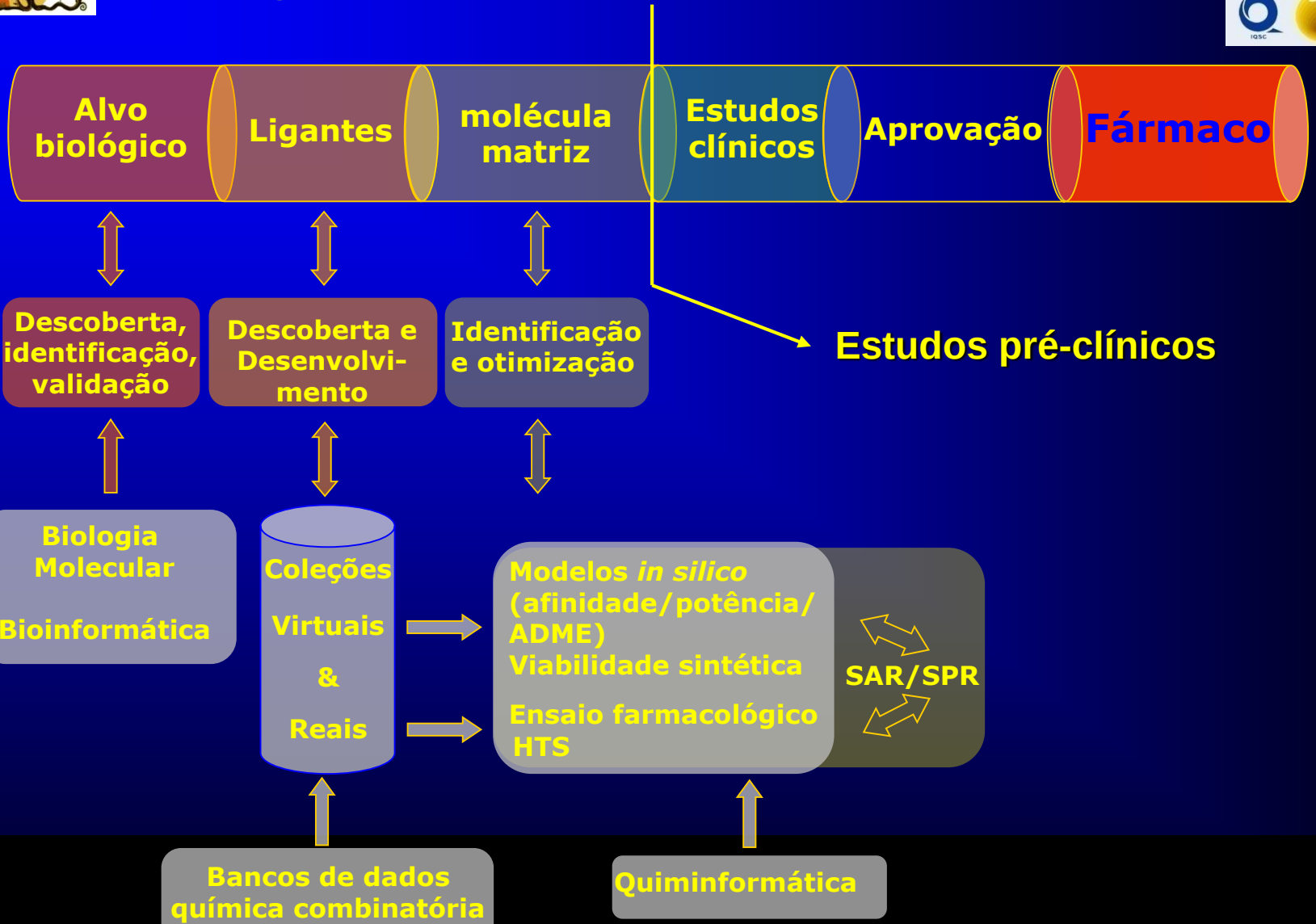
(www.kuninyi.de)

Química Medicinal:
o desafio de identificar novas entidades químicas bioativas (NCE) com propriedades qualificadas



(**Montanari *et al.*** *Quim. Nova* **1995**; *Anal. Chim. Acta* **2000**; *J. Chromatogr. A* **2006;** *Chem. Bio.* **2006;** Andricopulo **e Montanari** *Mini-Rev. Med. Chem.* **2005**)

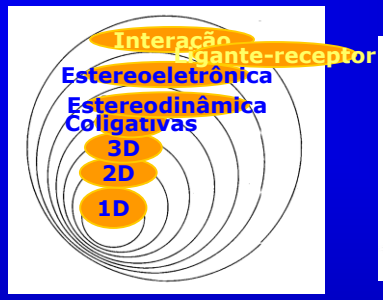
Química Medicinal: Integração com a quiminformática



(**Montanari *et al.*** *Quim. Nova* **2002;** *Anal. Chim. Acta* **2005**)

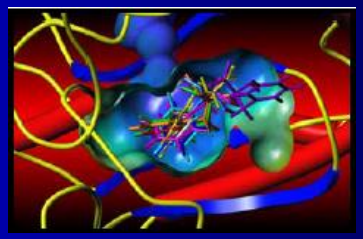
Integração de Tecnologias

Bancos de dados

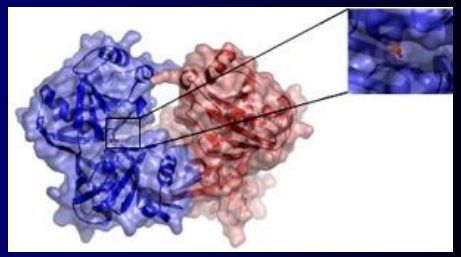


Moléculas sociais

Navegação do espaço químico

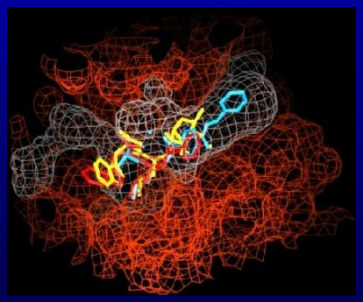


Ensaio virtual

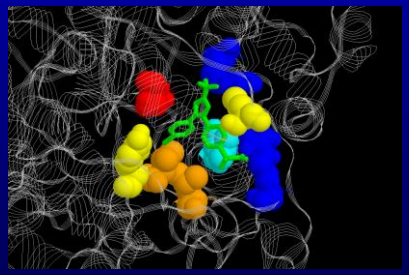


Raios X (PDB)

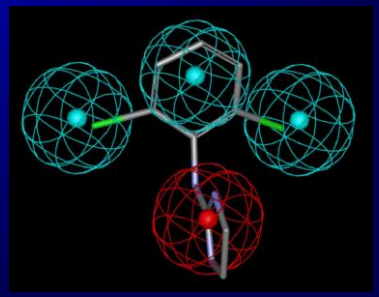
Clonagem, Expressão, Isolamento, Purificação



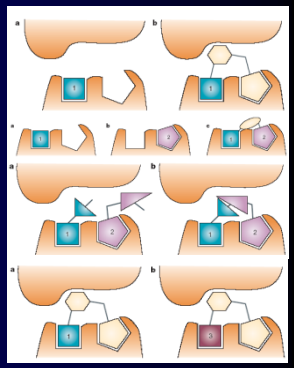
Docagem



Mapeamento do receptor



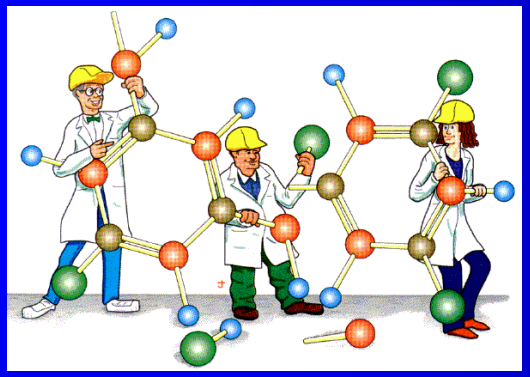
Hipótese farmacofórica



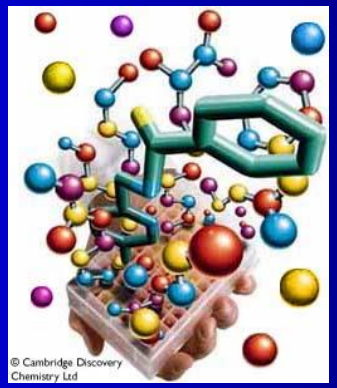
Ro3

(**Montanari** *et al. Eur. J. Med. Chem.* **2008**)

(Gaudio **e Montanari** *J. Comput.-Aided Mol. Des.* **2002**
Montanari *et al. Bioorg. Med. Chem.* **2008**)



MM



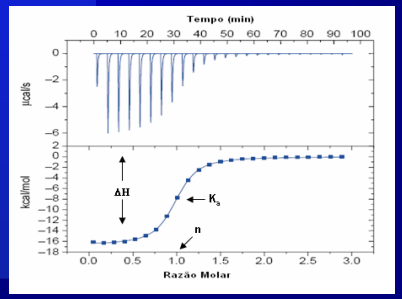
SAR

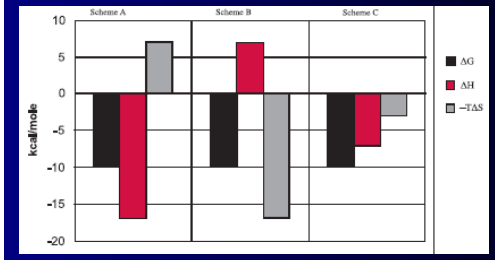
QSAR 2D e 3D

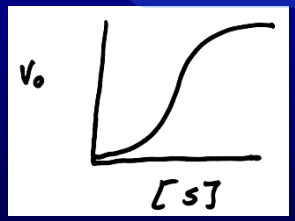
Síntese/ Isolamento

Validação do alvo → Ligantes → Matrizes → Pesquisa Clínica → Aprovação → Fármaco

Ensaio Calorimétrico (MOA/Assinatura TD)

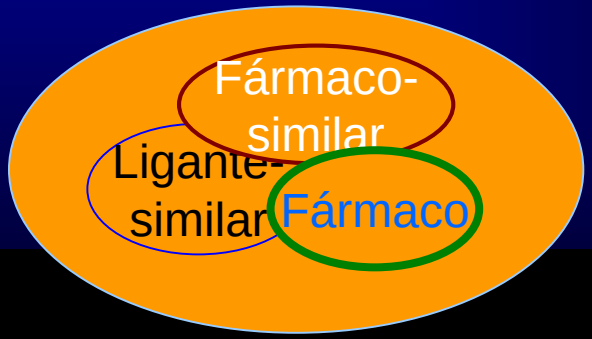






Cinética Enzimática (MOA)

Termodinâmica (MOB)



Espaço químico-biológico.

PD & PK otimizadas

(**Montanari, *et al.*** *J. Med. Chem.* **2000**; Andricopulo, Polikarpov, **Montanari**, Burger's MedChem **2010**)

Descoberta de novos agentes quimioterápicos por integração de tecnologias

Coleção de substâncias

ZINC®, Produtos Naturais (*in-home* DB)

Filter

1. MM
2. Lig.-H
3. Rotação
4. NHOH
5. ClogP

Inibidores conhecidos

Banco de dados filtrado

Omega

1. 2D ⇒ 3D
2. Ad H/Carga
3. Conformeros

Conformeros

Fred

Docagem de corpo rígido

Seletivi-dade

30-60% melhores pontuados

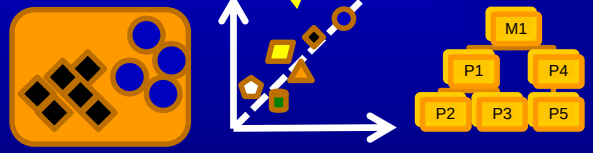
30-60% melhores pontuados

FLEx-X

Alvo 3D (Glide)

A-dock

Análise pós-docagem



Ensaio Bioquímico

Ensaio Celular

Candidatos a fármacos

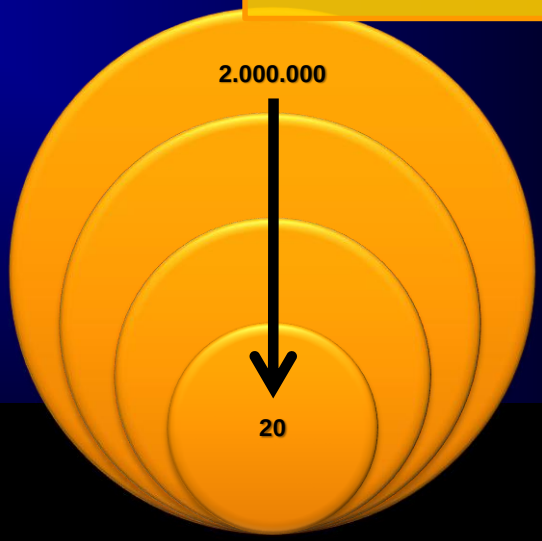
SELEÇÃO (nosso sistema)

- Coleção de substâncias
- (DOCAGEM, PCA, SIMCA, ANN, RANDOM FOREST)
- Agrupamento (SIMILARIDADE, HCA)
- Modelos DMPK: Solubilidade, Absorção, Metabolismo, BBB, Toxidez (GRID/VolSurf)
- QSAR 2D e 3D (CoMFA/CoMSIA/HQSAR/ROCS)
- Assinatura molecular

Fragmento-similar

Ligante-similar

Fármaco-similar



Eficiência do ligante ao nível atômico-molecular

Past funding sources

FAPESP

Optimization of tripanosomatide agents by integrating in silico, biocalorimetric and cell-based assays (2011-2013).

In silico and cell-based assays to identify new therapeutic alternatives to the prostate cancer (2011-2013).

Development of a bioproduc with high affinity for the Trypanosoma cruzi GAPDH (2009-2011).

Design of new trypanosomicide compounds (2005-2009).

CNPq
Conselho Nacional de Desenvolvimento Científico e Tecnológico

INCT: Pharmaceutical Innovation (2008-2013).

Current funding sources

FAPESP

Thematic project - Molecular design, synthesis and trypanocidal activity of cruzain reversible covalent inhibitors.

CAPES

Molecular Design, Synthesis, Structural Biology, and Biological Evaluation of Reversible Covalent Inhibitors for the treatment of Visceral Leishmaniasis.

CNPq
Conselho Nacional de Desenvolvimento Científico e Tecnológico

Molecular Design of Cruzain Reversible Covalent Inhi bitors

In silico and in vitro assays to identify new cathepsins inhibitors with anticancer activity.

INFRASTRUCTURE

IQSC

UNIVERSIDADE DE SÃO PAULO
SCIENTIA VINCES

FAPESP

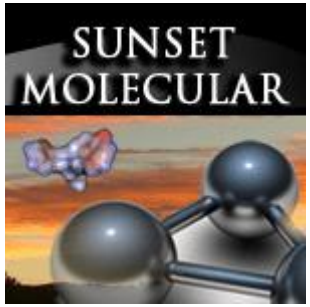
CNPq
Conselho Nacional de Desenvolvimento Científico e Tecnológico

inct-if
INSTITUTO NACIONAL de CIÊNCIA e TECNOLOGIA para INOVAÇÃO FARMACÊUTICA

CAPES

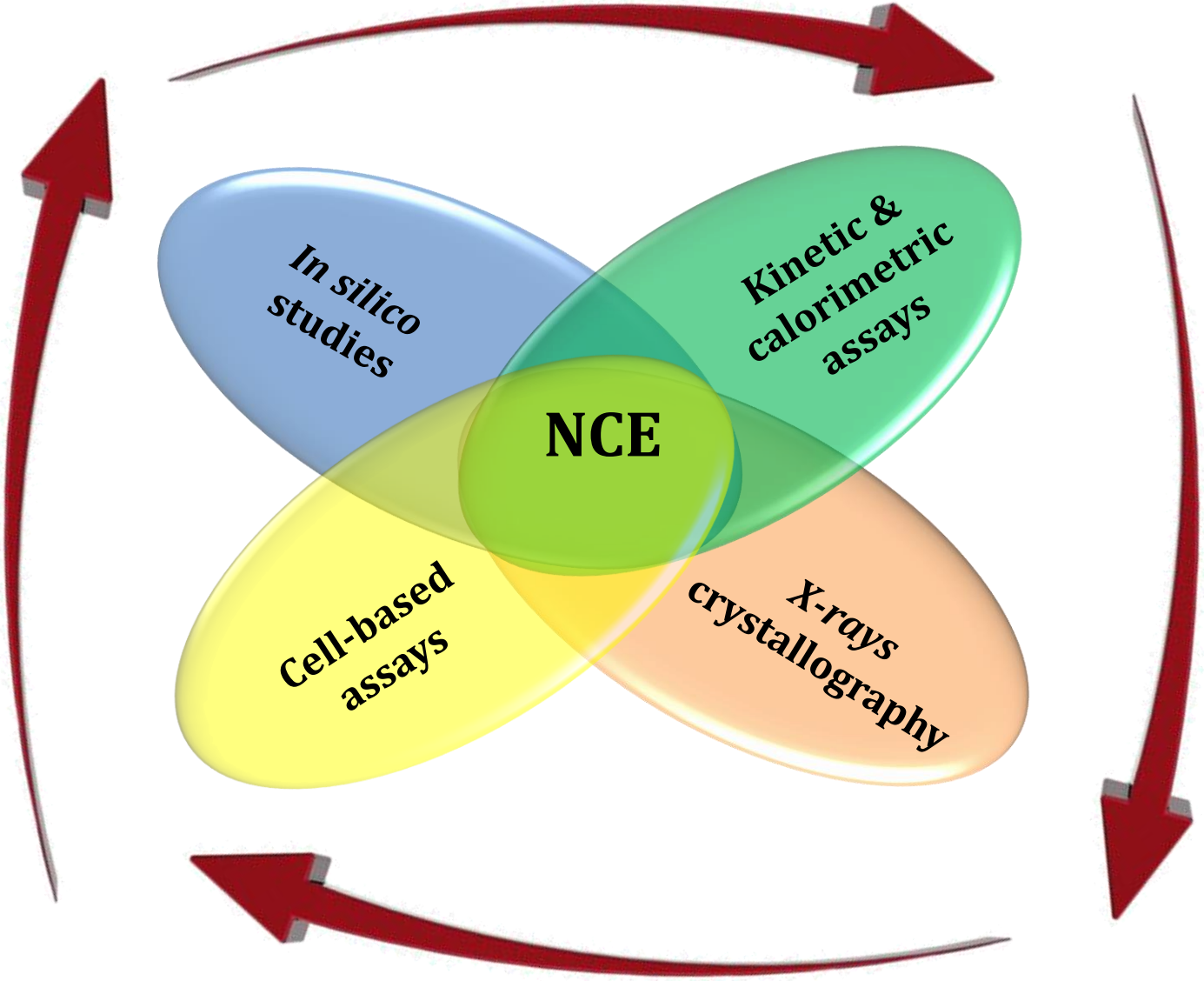
OpenEye Scientific Software — Shaping the industry.

SCHRÖDINGER.



ChemAxon

Modular structure of NEQUIMED

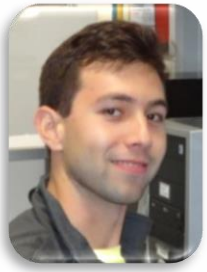


PEOPLE

Fabiana Rosini
Técnica

Dr. Josmar Rocha
Posdoc

Cristhian Camilo
Aluno de doutorado



Willian Fernades
Aluno de doutorado

Daniel Gedder
Aluno de doutorado

Erika Meñaca
Aluna de doutorado

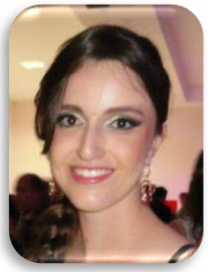
Igor Prokopczyk
Aluno de doutorado

Jean Ribeiro
Aluno de doutorado

Geraldo Sartori
Aluno de doutorado

José Carlos Quilles Júnior
Aluno de doutorado

Elisa Castañeda
Aluna de mestrado



Karen Rangel
Aluna de mestrado

Marta Saidel
Aluna de mestrado

Daiane Tesuka
Aluna de mestrado

Lucas Trevelin
Aluno de mestrado

Aluna de Doutorado Visitante UnB
Nádia Melo

Alunos de Graduação
Carlos H. Kruk, Letícia Martinelli, Júlio C. S. Filho

PEOPLE. Past!

Rosivaldo Borges
Pos-doc

Maria Goretti
Pos-doc

Fábio Molfetta
Pos-doc

Renato Ferreira de Freitas
Aluno de doutorado

Helton Wiggers
Aluno de doutorado

Leandro Avelar
Aluno de mestrado

Renato Bauab
Aluno de mestrado

Emanuella Fonseca
Aluna de mestrado

Ricardo Goulart
Mestrado

Cesar A. Kurohane
Aluno de mestrado

Anderson Zottis
Pos-doc

Juliana Cheleski
Doutorado

Fabyana Aparecida Soares
Mestrado

Karen Santos
Doutorado

Irwin Alexander Patiño Linares
Mestrado

Adriana Santoro
Mestrado

Elisangela Costa
Doutorado Sanduíche Universidade do Porto

PEOPLE. Collaborators.

Peter Kenny
Pesquisador visitante

Conceicao (Ciça) Minetti

David P. Remeta

Collaborators

PEOPLE. Past Collaborators.

Hugo Kubinyi
Pesquisador visitante

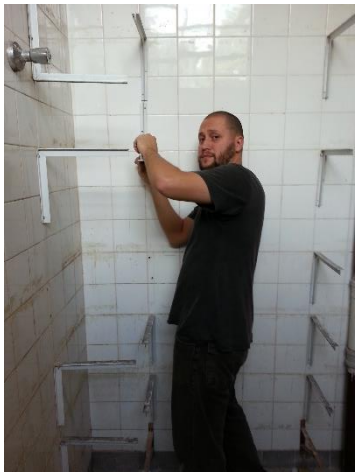
Tony Beezer
Pesquisador visitante

John Ladbury
Pesquisador visitante

Barry Sharpless
Pesquisador visitante

PEOPLE. Other activities.






PEOPLE. Other activities.

PEOPLE. Other activities.

MONTANARI & ANDREI

PEOPLE.
FAPESP Thematic Project.

Antonio Burtoloso
FCFRP/USP

Sérgio de Albuquerque
FCFRP/USP

João Santana da Silva
FMRP/USP

James Mckerrow
UCSD

PEOPLE.

CNPq AND CAPES PROJECTS.

Charles Laughton
University of Nottingham

Barrie Kellam
University of Nottingham

Jonas Emsley
University of Nottingham

Brasil

Prof. Adriano Andricopulo
LAQMED/CBME/IF/USP-São Carlos
Prof. Anderson C. Gaudio
UFES
Prof. Glaucius Oliva
CBME/IF/USP-São Carlos
Prof. Igor Polikarpov
IF/USP-São Carlos
Profa. Izabel Jardim
UNICAMP
Profa. Maria C. Nonato
FF/USP-RP
UNICAMP
Profa. Maria Fátima G.F.da Silva
DQ/UFSCar
Profa. Mônica Puppo
FF-USP/RP
Prof. Paulo C. Vieira
DQ/UFSCar
Profa. Quezia Cass
UFSCar
Prof. Pedro Volpe
UNICAMP
Prof. Roy Bruns
UNICAMP
Dra. Solange Castro
Fiocruz-RJ
Profa. Vanderlan Bolzani
UNESP
Prof. Vitor F. Ferreira
IQ/UFF

Dr. Peter Goodford
University of Oxford

US
Dr. Tudor Oprea
University of New Mexico

Arábia Saudita
Prof. H. Y. Aboul-Enein
King Faisal
Specialist Hospital

Itália
Dr. Gabrielle Cruciani
University of Perugia

48 papers published
9 book chapters

54° JABUTI
PRÊMIO 2012

CBL Câmara Brasileira do Livro

Química Medicinal: Métodos e Fundamentos em Planejamento de Fármacos - Edusp

2010: TEN YEARS OF BRAZMEDCHEM MEMORIALIZES A CENTURY OF CHAGAS' DISEASE

WHAT HAVE WE DONE SO FAR?

(BEYOND ALL OF THAT, OF COURSE)

Most promising NEQUIMED/IQSC/USP compounds exhibit characteristics of leads that can be optimized for drug candidates:

T. cruzi $pIC_{50} > 5$
with SI > 50 (SI ratio = IC_{50}(cyto)/IC_{50}(*T. cruzi*));
PFI < 8;
Ar rings < 5 and
MW 500 < Da.

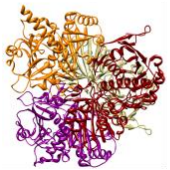
#Preclinical phase drug candidates: 7


QUÍMICA MEDICINAL:
um desafio para o Brasil

In 10 years time?

'DISCOVERY CONSISTS IN SEEING WHAT EVERYONE ELSE HAS SEEN AND THINKING WHAT NO ONE ELSE HAS THOUGHT!'

ALBERT SZENT-GYÖRGI



Portinari

MUITO OBRIGADO

CARLOS.MONTANARI@USP.BR