



## **Collaborative Drug Discovery**

### **Community Users Meeting**

Monday, March 5th, 2007

J. David Gladstone Institute Auditorium

UCSF Mission Bay Campus, San Francisco, CA



## Acknowledgements

Douglas Crawford, Ph.D., QB3  
Millo Mau Pasquini, QB3

Bruce Conklin, M.D., J. David Gladstone Institute

Where available, speaker presentations will be provided on the  
CDD website after the event at:

[http://www.collaboratedrug.org/community\\_mtg07](http://www.collaboratedrug.org/community_mtg07)

*No food or drink in the auditorium  
Please turn off phones*

## Schedule

10:30-11:30 pm Software training at QB3 with Kellan Gregory

12:30 pm Coffee and registration, poster viewing in Lobby and Rooms A & B

1:00 – 1:10 Welcome from QB3 and CDD

1:10 – 1:40 James McKerrow, MD, PhD, UC San Francisco

1:40 – 2:10 Matt Bogyo, PhD, Stanford University

2:10 – 2:40 Anang Shelat, PhD, St. Jude Children's Research Hospital

2:40 – 3:10: Break and poster viewing in Lobby and Rooms A & B

3:10 – 3:40: Andrej Sali, PhD, UC San Francisco

3:40 – 4:40: Panel, Technical community roadmap for open collaborations and global health  
(Moderator: Barry A. Bunin, PhD Panelists: Bernard Munos, PhD, MBA, Eli Lilly; Robert Damoiseaux, PhD, UCLA; Jim McKerrow, MD, PhD, UCSF; Chris Lipinski, PhD ex-Pfizer)

4:40 – 4:50: The future collaborative roadmap (Peter Cohan, The Second Derivative)

4:50 – 5:00 Break

5:00 – 6:00: Christopher Lipinski, PhD, Pfizer (retired), Melior Discovery

6:00 – 7:00: Wine and cheese reception, poster viewing and prizes in Lobby and Rooms A & B  
(Raffle and Best Poster Announcements)

## Speaker Biographies and Abstracts

### **Matthew Bogyo, Ph.D.**

Assistant Professor, Department of Pathology, Stanford University

<http://bogyolab.stanford.edu/index.html>

#### **Mining small molecule probes of malaria proteases from libraries of covalent inhibitors**

##### **Bio**

Dr. Bogyo received his Ph.D. in Chemistry from the Massachusetts Institute of Technology in 1997. After completion of his degree he was appointed as a Faculty Fellow in the Department of Biochemistry and Biophysics at the University of California, San Francisco. Dr. Bogyo served as the Head of Chemical Proteomics at Celera Genomics from 2001 to 2003 while maintaining an Adjunct Faculty appointment at UCSF. In 2003, Dr. Bogyo joined the Department of Pathology at Stanford Medical School and was appointed as a faculty member in the Department of Microbiology and Immunology in 2004. His interests are focused on the use of chemistry to study the role of proteases in human disease. In particular, his laboratory is currently working on understanding the role of cysteine proteases in tumorigenesis and in the life cycle of the human parasites, *Plasmodium falciparum* and *Toxoplasma gondii*. Dr. Bogyo, is the Faculty Co-Director of the Stanford Proteomics and Integrative Research Facility and currently serves on the Editorial Board of Biochemical Journal, Chemistry and Biology. Molecular and Cellular Proteomics and Drug Discovery Today: Technologies. Dr. Bogyo is a consultant for several biotechnology and pharmaceutical companies in the Bay Area.

##### **Abstract**

Malaria, a disease caused by the human protozoan parasite *Plasmodium falciparum*, affects 300-500 million people annually and is the cause of approximately 2 million deaths per year, many of which are children. This obligate intracellular parasite is a member of the phylum Apicomplexa that consists of several important pathogens including *Cryptosporidium*, *Babesia* and *Toxoplasma*. Disease pathology is associated with the parasite-mediated lytic destruction of infected host cells. Therefore, a significant effort has been made to understand the biochemical processes used by the parasite to invade, colonize and eventually rupture host cells. Multiple classes of proteases have been shown to play important roles in each of these pathways yet a detailed understanding of the primary players and their mechanisms of action is lacking. This gap in our understanding is due largely to a lack of tools and reagents for the study of proteases. We are currently carrying out forward and reverse chemical genetic screens in a blood-stage culture model of parasite infection in order to begin to map out the primary protease pathways used by the parasite to survive inside the host. We have begun by assembling a large library of diverse, covalent serine and cysteine proteases inhibitors from our own in-house collection of compounds and from large pools of compounds that we have collected from other medicinal chemistry laboratories throughout the country. This library has been organized into a structure searchable database using the Collaborative Drug Design web platform. This allows us to link data from multiple screens and assays to specific compounds and to make this information available for sharing with collaborators through a simple web interface. We have recently completed screening more than 2,000 compounds using several FACS based screens that allow us to monitor the progression of the parasite life cycle inside host red blood cells. These initial

efforts have identified a significant number of both serine and cysteine protease inhibitors that block the process of parasite mediated rupture of host cells. We have used several of these hits to identify both serine and cysteine proteases that play important roles in this process. We are currently using biochemical and cell biological assays combined with our inhibitors to gain mechanistic insight into how these proteases regulate the process of host cell rupture.

### **Robert Damoiseaux, Ph.D.**

Molecular Screening Shared Resource (MSSR), UCLA  
<http://mssr.pharmacology.ucla.edu/>

#### **Bio**

After having earned a M.S. in classical organic synthesis and molecular biology in Bochum, Germany, and a Ph.D. degree in Lausanne, Switzerland he joined the Novartis Institute for Functional Genomics in La Jolla, CA, as a postdoctoral fellow. There he became interested in assay design and novel assay platforms and developed microarray based assays for proteolytic enzymes. He joined UCLA in 2004 as the Technical Director of the Molecular Shared Screening Resources (MSSR) and oversees the operations of all drug discovery projects (over 50 so far) at the MSSR. His main interests are at the interface of chemistry, biology and engineering and include the development of new assay technology platforms, assay automation, high throughput screening, high content screening and directed molecular evolution.

### **Chris A. Lipinski, Ph.D.**

Pfizer (retired) and Scientific Advisor, Melior Discovery

#### **Academic drug discovery: the chemistry challenges of target choice and screening library selection**

#### **Bio**

Dr. Christopher Lipinski was Adjunct Senior Research Fellow at the Pfizer Global R&D Groton CT Laboratories following his retirement in June 2002 and is now a Scientific Advisor to Melior Discovery, a drug repurposing startup. He is a member of the American Chemical Society (ACS), AAPS, Society of Biomolecular Sciences (SBS) and EUFEPS. A consultant on drug-like properties he serves on numerous scientific advisory and journal editorial boards. He is the author of the “rule of five” a widely used filter to select for acceptable drug oral absorption. In 2006, he received an honorary law degree from the University of Dundee and is the 2006 Society for Biomolecular Sciences Achievement Award winner. In 2005, he was the American Chemical Society winner of the E. B. Hershberg Award for Important Discoveries in Medicinally Active Substances and in 2004 the winner of the Division of Medicinal Chemistry Award of the ACS Division of Medicinal Chemistry. Since 1984, he has been an adjunct faculty member at Connecticut College in New London CT, and has over 225 publications and invited presentations and 17 issued US patents.

#### **Abstract**

Academic chemical biology is well established and stable. By contrast academic drug discovery is much newer and is undergoing an explosion of effort. To succeed in academic drug discovery one has to understand the chemical differences between tools and probes on the one hand and real drug discovery starting points on the other. Typically, the weakest link in academic drug discovery is the poor access to competent medicinal chemistry, which I define as 10-15 years biomedical chemistry pattern recognition superimposed on a solid synthetic chemistry background. The degree of the medicinal chemistry challenge depends on the academic drug discovery business model. Access to adequate chemistry is easier if the planned handoff to a commercial partner is at “hit to lead” exit and is much more difficult if the handoff is at phase I exit. Paralleling the need for medicinal chemistry is the need for affordable chemistry data access, data sharing and data analysis (chemoinformatics). All of these are now undergoing a revolution. Academic drug discovery efforts cannot compare in screening library size with those of big pharma so the target choice has to be different and smarter and the screening library design has to be more focused. My ideas on screening libraries are likely very different from those of many academic biologists. Screening a truly diverse library is the worst way to discover a drug. Rather, rational clustering about chemical motifs with a previous history of biological activity is the way to go. For academics, a smart target choice is one where useful results can be expected from screening 50,000 or fewer compounds. To make the smart target choice requires affordable batch mode chemoinformatic data access. It is striking to me that so many existing biomedical data web sites either have no computer retrievable chemistry structures linked to the biological data or the chemistry structure data retrieval is clunky and awkward. These limitations led to my interest in CDD.

### **James McKerrow, M.D., Ph.D.**

Director, Sandler Center for Basic Research in Parasitic Diseases, QB3  
Robert E. Smith Endowed Chair in Experimental Pathology, UCSF  
<http://www.ucsf.edu/mckerrow/>

#### **Developing Drugs for Parasitic Diseases in an Academic Incubator**

##### **Bio**

Dr. James McKerrow holds the Robert E. Smith Endowed Chair in Experimental Pathology, at UCSF, is Director of the Tropical Disease Research Unit, and Director of the Sandler Center of Basic Research in Parasitic Diseases. His research interests are in the biochemistry and molecular biology of parasitic diseases. We work on tropical parasites like *Schistosoma mansoni* (bilharzia, blood fluke), *Entamoeba histolytica* (amebiasis), *Onchocerca volvulus* (the agent of African River Blindness), and *Trypanosoma cruzi* (Chagas' disease). Our major research themes are molecular mechanisms of host invasion and virulence, gene regulation during parasite development, and structural analysis of parasite enzymes. Dr. McKerrow earned a PhD in Biology from UC San Diego, and his MD at University of New York, Stony Brook. He did his medical residency and postdoctoral work at UCSF.

##### **Abstract**

Perhaps the greatest challenge to the development of new therapy for parasitic diseases is the relative lack of interest in the pharmaceutical industry in addressing this issue. To circumvent this obstacle, we have taken advantage of a culture of interdisciplinary science, coupled with a willingness to recruit scientists from industry into academia, to fashion a consortium of core laboratories that carry out preclinical drug development in an academic institution. This effort was further facilitated by the commitment of the University of California to provide space, and philanthropic investment in the type of equipment and technical personnel normally found in the pharmaceutical industry. Following launch of this Center, we have taken two approaches to the identification and development of new drugs for Chagas' disease, African trypanosomiasis, leishmaniasis, malaria, and schistosomiasis. In the first, exemplified by human African trypanosomiasis, we have utilized high throughput screening to identify drugs already approved for use in other clinical settings that are trypanocidal. Up to 40 promising hits were found, and are posted on an open source website. The second approach follows standard target discovery, lead optimization, and identification of drug candidates using parasite proteases or kinases as the primary targets. Both computational facilitated drug design and optimization of existing chemical scaffolds were strategies pursued. Drug candidates for Chagas' disease, schistosomiasis, and cryptosporidiosis are currently in the final stages of lead optimization or manufacture for clinical trials.

### **Bernard Munos, MBA, Ph.D.**

Eli Lilly and Company

#### **Bio**

Bernard Munos is an advisor in corporate strategy at Eli Lilly and Co. Bernard's research interests center on disruptive innovation and the radical redesign of the pharmaceutical business model. He received his MBA from Stanford University and holds other degrees in economics and animal science from the University of California at Davis and the Institut National Agronomique in Paris, France.

### **Andrej Sali, Ph.D.**

Professor and Vice Chair, Department of Biopharmaceutical Sciences

Department of Pharmaceutical Chemistry, QB3, UCSF

Web <http://salilab.org>

### **Tropical Disease Initiative**

#### **Bio**

Andrej Sali received his BSc degree in chemistry from the University of Ljubljana, Slovenia, in 1987. He was awarded the Research Council of Slovenia Scholarship, the Overseas Research Students Award, and the Merck Sharpe & Dohm Academic Scholarship at Birkbeck College, University of London, where he received his PhD in biophysics in 1991, under the supervision of Prof. Tom L. Blundell. He focused on development of methods for comparative modeling of protein three-dimensional structure and their implementation in the program MODELLER. He

then went to the Department of Chemistry at Harvard University as a Jane Coffin Childs Memorial Fund post-doctoral fellow with Prof. Martin Karplus, where he continued to develop comparative modeling methods and also studied simple lattice Monte Carlo models of protein folding. From 1995 to 2002, Dr. Sali was first an Assistant Professor and then an Associate Professor at The Rockefeller University. In 2003, he moved to UC San Francisco as Professor of Computational Biology in the Departments of Biopharmaceutical Sciences and Pharmaceutical Chemistry, and California Institute for Quantitative Biomedical Research. He was a Sinsheimer Scholar, an Alfred P. Sloan Research Fellow, and an Irma T. Hirschl Trust Career Scientist. Dr. Sali is an Editor of *Structure* and a Founder of Prospect Genomix, now Structural Genomix. He is interested in using computation grounded in the laws of physics and the theory of evolution to study the structure and function of proteins. He is aiming to improve and apply methods for (i) predicting the structures of proteins; (ii) determining the structures of macromolecular assemblies; and (iii) annotating the functions of proteins using their structures.

**Abstract:**

Dr. Sali will discuss his lab's efforts on behalf of the Tropical Disease Initiative (<http://tropicaldisease.org>): (i) the construction of a web site with a number of resources to facilitate the initiative; (ii) large-scale comparative protein structure modeling of proteins in 10 parasite genomes to facilitate protein target selection; and (iii) identification of human-pathogen protein interactions that may provide hints about the mechanisms of infection as well as targets for drug discovery.

**Anang Shelat, Ph.D.**

Saint Jude Children's Research Hospital

<http://www.stjuderesearch.org/guy/>

**Charting the Past and Proposing the Future Course of Antimalarial  
Discovery in Chemical Space**

**Bio**

Anang graduated from Harvard University in 2000 with a B.A. in the Biochemical Sciences. He received his PhD in 2005 from the Chemistry and Chemical Biology program at the University of California, San Francisco. As a joint student in the Guy and Kuntz groups, Anang had the unique opportunity to approach biological problems from the perspectives of both synthetic organic and computational chemistry, but soon realized his talents were more amenable to "virtual" experiments. He devised novel chemical library design and quantitative-structure activity relationship (QSAR) algorithms aimed at identifying small molecule therapeutics for Cystic Fibrosis as part of a collaboration among academic groups from UCSF, UCD, and the Giannina Gaslini Institute in Italy. He also spearheaded efforts to automate the acquisition and analysis of high-throughput screening data for the Bay Area Screening Center. Upon graduation, Anang became the Cheminformatics group leader for the Chemical Biology and Therapeutics Department at St. Jude Children's Research Hospital. Anang's research is focused on three areas: (a) the robust investigation of screening experiments using novel statistical tools and visualization techniques, (b) the development of computational learning algorithms for QSAR/QSPR, and (c) the application of chemical space concepts and graph theory towards

chemical library design. Anang was awarded the Long Award for Excellence in Teaching (2005), the Burroughs Wellcome Fellowship (2004), and the National Defense Science and Engineering Fellowship (2001).

### **Abstract**

The success of biological screening endeavors is highly dependent on the composition of the chemical library assayed. Indeed, Oprea, Hopkins, and others have shown that compounds targeting certain activity classes often occupy narrow regions of “chemical space”, or subsets of the joint distribution of physicochemical properties. This is problematic, as certain therapeutic agents, such as antineoplastics or anti-infectives, often possess rare chemotypes derived from natural products, and/or violate medicinal chemistry rubrics such as the “Rule of Five”. These compounds are unlikely to be found in commercially-available, small molecule screening collections. Here, we examine the distribution of antimalarial molecules in one representation of chemical space. Working with Collaborative Drug Discovery (CDD), we extracted data from the Army Malaria Screening Collection, a repository of ~13000 compounds annotated with *in vivo* screening data dating back to the 1940s. Together with knowledge garnered from bioactive databases and our own high-throughput screening, we chart the past and propose the future course of antimalarial drug discovery efforts. This type of exploration is particularly suited to the CDD paradigm.

## Posters

### **New Potent Inhibitors of *Trypanosoma cruzi* Sterol C14 Demethylase Based on a Substituted 2-quinolinone (R115777)**

Frederick Buckner<sup>1</sup>, Michael Gelb<sup>2</sup>, James Kraus<sup>2</sup>, Christophe Verlinde<sup>3</sup>, Mandana Karimi<sup>1</sup>, Pravin Kumar<sup>2</sup>, Srinivas Olepu<sup>2</sup>, and Jan Schoepe<sup>3</sup>

<sup>1</sup>Dept. of Medicine, <sup>2</sup>Dept. of Chemistry, and <sup>3</sup>Dept. of Biochemistry University of Washington, Seattle, WA

The primary goal of this project is to produce new chemotherapeutic agents for treatment of Chagas disease. Current drugs are toxic and have low cure rates for persons chronically infected with *Trypanosoma cruzi*. Based on extensive evidence that antifungal drugs (i.e. azoles) have moderate activity against *T. cruzi*, we are pursuing new compounds that are better optimized for inhibition of the target, sterol C14-demethylase. The starting point is a class of compounds based on R115777 (tipifarnib), a human protein farnesyltransferase (PFT) inhibitor developed by Johnson & Johnson, which is in Phase III clinical trials as an anti cancer drug. This compound has oral bioavailability, a good pharmacokinetic profile, and is fairly well tolerated in cancer patients. Earlier work by our group demonstrated that R115777 is very potent against *T. cruzi* grown in 3T3 fibroblasts (ED<sub>50</sub> = 5-10 nM). Follow up investigations demonstrated that R115777 appears to mediate its toxic effects on *T. cruzi* by inhibiting sterol C14-demethylase rather than by inhibiting *T. cruzi* PFT. Using structural models of the *T. cruzi* sterol C14-demethylase and the mammalian PFT, we are making modifications to R115777 in order to optimize binding to sterol C14-demethylase while removing activity against mammalian PFT. The purpose will be to minimize any toxicity of the drug that may be mediated through inhibition of mammalian PFT. Simple changes to R115777 have led to a ~400-fold increase in IC<sub>50</sub> against the mammalian PFT with a small change in anti-*T. cruzi* activity. Our goal is to design a potent anti-trypanosomal agent that can be taken orally for an extended period with minimal toxicity.

### **A metallopeptide mimic of the coiled coil domain of Class 1 viruses is a useful target for antiviral drugs**

Lifeng Cai<sup>1</sup> and Miriam Gochin<sup>1,2</sup>

<sup>1</sup>Department of Basic Sciences, Touro University – California, Vallejo, CA 94592

<sup>2</sup>Department of Pharmaceutical Chemistry, University of California San Francisco CA 94143

We have been working on a metallopeptide construct of the coiled coil domain of HIV-1 gp41, for use as a receptor to detect entry inhibitors through high throughput fluorescence screening. A metal coordination complex holds together three component peptides from the trimeric coiled coil and quenches fluorescently labeled peptide from a viral domain that binds to the coiled coil. This binding event precipitates the fusion process in the intact virus. Small molecules able to prevent the binding can act as fusion inhibitors and can be detected by an increase in fluorescence in a ternary system, which contains the metallopeptide, the fluorescent peptide and the small molecule inhibitor. We have carried out studies to confirm that the metallopeptide is

representative of the intact viral protein, including the ability of the assay system to specifically and sensitively detect known gp41 fusion inhibitors. We will demonstrate a novel class of peptidomimetic fusion inhibitors that we have detected using this system. Although these only inhibit in the micromolar range, they are relatively small and amenable to modification, so that they may be developed into more potent fusion inhibitors. The fluorescence assay is robust, quantitative and easily automated for high throughput screening. A similar fusion process occurs with other class 1 viruses including paramyxoviruses (RSV, Mumps, Measles, Sendai Virus), orthomyxoviruses (Influenza A), coronavirus (SARS), retroviruses (HIV, HTLV) and filovirus (Ebola), so that broader application of the method is expected.

### **Simple spectroscopic monitoring of liquid surface curvature changes in thin wells**

Lifeng Cai<sup>1</sup> and Miriam Gochin<sup>1,2</sup>

<sup>1</sup>Department of Basic Sciences, Touro University – California, Vallejo, CA 94592

<sup>2</sup>Department of Pharmaceutical Chemistry, University of California San Francisco CA 94143

The boundary between liquid and solid is often characterized by a curved liquid surface in thin tubes or in small liquid drops on a solid surface. The surface curvature is a manifestation of the equilibrium between solid surface tension, liquid surface tension, solid-liquid interface tension and gravity. Knowledge of these forces is important in many technological processes, including surfactant development in drug delivery formulation and physiology, micro- or nano-manufacturing, microfluidics and surface fabrication. Classical liquid surface tension measurements are very precise, but require complex preparation and expertise in sample handling. Few simple and high-throughput (HT) methods are currently available to study liquid-solid-surface interactions. Here we report a simple fluorescence method to study liquid surface curvature changes in thin-well plates, with a dynamic range of 60% and a relative sensitivity of 2%. It exploits the effect of total internal reflection on fluorescence emission through a curved liquid surface. Application of the effect is demonstrated by a method for rapid and universal determination of surfactant critical micelle concentration (CMC) and by a simple assay for promiscuous inhibitors resulting from micelle formation. Plate-based measurement of surface curvature is an efficient method for investigating systems where colloidal properties, surface tension or interfacial tension are paramount.

### **Reduction in pathology and parasitologic cure of mice infected with *Schistosoma mansoni* using a peptidomimetic cysteine protease inhibitor**

C.R. Caffrey, M. Abdulla, K.C. Lim, M. Sajid, and J.H. McKerrow.

Sandler Center for Basic Research in Parasitic Diseases, California Institute for Quantitative Biomedical Research, Box 2550, University of California, San Francisco, San Francisco, CA 94143

Small-molecule inhibitors of Clan CA cysteine proteases are in pre-clinical development for treatment of a number of diseases caused by parasitic protozoa, including *Falciparum* malaria, African Sleeping Sickness and Chagas' disease. Similar research for parasitic helminth diseases

lags behind, but given the well-documented central functions of Clan CA proteases in such parasites, a similar therapeutic strategy may prove beneficial. Schistosomiasis is second only to malaria in numbers infected and, in the absence of a vaccine, just one drug is recommended for chemotherapy with the continual concern of the emergence of resistance. We tested the efficacy of the peptidomimetic vinyl sulfone inhibitor, K11777, in the murine model of Schistosomiasis mansoni. Disease parameters measured were worm and egg burdens, and organ pathology, including hepato- and splenomegaly, presence of parasite egg-induced granulomas in the liver and levels of circulating alanine aminotransferase activity as a marker of hepatocellular function. K11777 (25mg/kg *BID*), administered intra-peritoneally at the time of parasite migration through the skin and lungs (days 1 – 14 post-infection), resulted in parasitologic cure (elimination of parasite eggs) in 70% of infections and a resolution of other disease parameters. K11777 (50mg/kg *BID*), administered at the commencement of egg-laying by mature parasites (days 30 – 37 post-infection), reduced worm and egg burdens and ameliorated organ pathology. Using protease class-specific substrates and active site-labeling, one molecular target of K11777 was identified as a cathepsin B cysteine protease associated with the parasite gut. K11777 has completed pre-clinical tests for the treatment of Chagas' disease and the inhibitor is non-toxic and non-mutagenic with an acceptable pharmacokinetic profile. The pronounced ameliorative impact on parasite burden and pathology demonstrated here for K11777 suggests that a similar therapeutic strategy may prove valuable in the treatment of human schistosomiasis.

### **The *Trypanosoma cruzi* protease cruzain mediates immune evasion**

Patricia S. Doyle, Juan C. Engel, Yuan M. Zhou, Ivy Hsieh, Pn'g Loke, Doron Greenbaum, and James H. McKerrow

Tropical Disease Research Unit, and Sandler Center, Department of Pathology, University of California, San Francisco, CA 94121

The biological role for the *Trypanosoma cruzi* cysteine protease cruzain in immune evasion was elucidated in a comparative study of parental wild type-parasites and parasites resistant to the cysteine protease inhibitor N-Pip-F-hF-Vs $\phi$  that results in protease-deficiency. Wild type *T. cruzi* does not activate the host macrophage following infection. Cruzain and the signaling factor NF- $\kappa$ B P65 co-localize to the cell surface of intracellular parasites. P65 is proteolytically cleaved. No significant IL-12 expression occurs in macrophages infected with wild type parasites and subsequently activated with LPS confirming macrophage unresponsiveness. In contrast, cysteine protease inhibitor-resistant, and cruzain-deficient parasites induce macrophage activation and nuclear NF- $\kappa$ B P65 localization. Thus, cruzain hinders macrophage activation allowing *T. cruzi* survival and replication, and expansion of infection in Chagas' disease.

## **A Cysteine Protease Inhibitor Cures Chagas' disease in an Immunodeficient Murine Model of Infection**

Patricia S. Doyle, Juan C. Engel, Yuan M. Zhou, and James H. McKerrow  
Tropical Disease Research Unit, and Sandler Research Institute, Department of Pathology,  
University of California, San Francisco, CA 94121

Chagas' disease remains the leading cause of heart disease in Latin America with 12 to 16 million people estimated to be infected, and over 90 million at risk. Chagas' disease is caused by the protozoan parasite *Trypanosoma cruzi* that infects the human host most commonly through an insect vector or blood transfusion. Classic clinical manifestations derive from parasite infection of cardiac muscle, leading to progressive cardiomyopathy. Some patients develop megacolon or megaesophagus due to infection of plexus nerve ganglia. A very aggressive clinical course including fulminant meningoencephalitis has been reported in patients who contract Chagas' disease in the background of immunodeficiency. This includes patients with HIV infection as well as patients receiving immunosuppressive therapy for cardiac transplant. Currently, only two drugs are approved for the treatment of Chagas' disease, Nifurtimox and Benznidazole. Both have significant limitations due to common and serious side effects, as well as limited availability. One promising group of new drug leads for Chagas' disease is cysteine protease inhibitors targeting cruzain, the major protease of *Trypanosoma cruzi*. At least one of these inhibitors is in late-stage preclinical development. Cruzain plays a number of roles during the lifecycle of *T. cruzi*, including a role in immune evasion. Therefore, the question arises whether protease inhibitors targeting cruzain would have efficacy in Chagas' disease, occurring in the background of immunodeficiency. To address this question, we studied the course of infection in recombinase deficient (Rag1 knockout) mice infected with *T. cruzi*. We show that a vinyl sulfone protease inhibitor administered at a daily dose of 100mg/kg weight can cure animals even in the absence of a functioning adaptive immune response.

## **Docking based discovery of non covalent cruzain inhibitors**

Rafaela S. Ferreira, Alan P. Graves, Brian K. Shoichet, James H. McKerrow  
Department of Pharmaceutical Chemistry and Department of Pathology, University of California  
San Francisco, CA 94158

Cruzain, the major cysteine protease of *Trypanosoma cruzi*, is an essential enzyme for this parasite and a therapeutic target for Chagas' disease. Different classes of cruzain inhibitors have been developed, and in several cases co-crystallized with the enzyme, providing a platform to structure-based drug design. Current cruzain inhibitors are mostly peptidic compounds which bind irreversibly to the enzyme. In an attempt to find new classes of inhibitor with better pharmacological properties, we used DOCK to search for reversible, non-covalent cruzain inhibitors. The lead-like subset of the ZINC database (~about 450,000 compounds), was docked and the top 500 scoring molecules were inspected. 17 compounds were purchased and tested for inhibition of cruzain activity. 2 compounds were shown to be competitive inhibitors with  $K_i$  values of 64  $\mu\text{M}$  (compound 1) and 125  $\mu\text{M}$ . A series of commercially available analogs of compound 1 was purchased and tested against cruzain, providing information about the

pharmacophore and insights for structure-based design of new inhibitors.

## **Archiving and Mining Neglected-Infectious-Disease Screening Data for Web-based Collaborative Drug Discovery**

E. Hansell<sup>1</sup>, K. Gregory<sup>2</sup>, B. Bunin<sup>2</sup>, P. Doyle<sup>1</sup>, D. Ruelas<sup>1</sup>, M. Abdulla<sup>1</sup>, N. Tucker<sup>1</sup>, Z. Mackey<sup>1</sup>, C. Caffrey<sup>1</sup>, and J. McKerrow<sup>1</sup>.

<sup>1</sup>Department of Pathology, Sandler Center for Basic Research in Parasitic Diseases, University of California, San Francisco CA 94158

<sup>2</sup>Collaborative Drug Discovery (CDD, Inc., [www.collaborativedrug.com](http://www.collaborativedrug.com)) 1818 Gilbreth Road, Suite 220, Burlingame, CA 94010

The Sandler Center for Basic Research in Parasitic Diseases at UCSF has been using a new type of web-based database to study neglected-infectious diseases such as Malaria, Chagas Disease, Leishmaniasis, African Sleeping Sickness and Schistosomiasis. This web-based database has been created by Collaborative Drug Discovery (CDD) to help scientists more effectively develop new drug candidates for commercial and humanitarian markets. This database can be used to archive, mine, and collaborate around drug discovery data. The CDD technology uses automated data "mappers and slurpers" to upload the assay data that researchers typically have in Excel and sd file formats. This technology is designed to provide gated access for private versus public groups at the individual experimental data level. The data can be "mined" at the molecular level, using keywords or structural elements. It can also be mined at the assay level, by selecting all or a subset of assays, with the option of setting cut-off limits for viewing. These elements can be combined to mine a subset of structures. Data reports can be exported for local use. Additional tools are being developed for viewing structure assay relationships, and improving ease of use. The Sandler Center has successfully used the CDD database to accumulate information on 8000 molecular structures from more than 20 collaborators (academic and industrial), and assay data from enzyme, cell, and animal assays.

## **The ZINC database of commercially available compounds for virtual screening**

John J Irwin and Brian K Shoichet

Department of Pharmaceutical Chemistry, University of California, San Francisco CA 94158

An important problem in virtual screening is the quality of the database being screened. Careful database creation and curation are ongoing problems for experts in the field and barriers to entry for non-experts. This has led us to create ZINC, a free database of commercially available compounds for virtual screening, on the web at <http://zinc.docking.org>. ZINC includes multiple representations of molecules which attempt to capture the physiologically relevant protonation state, tautomeric, regio- and stereo-isomeric forms. ZINC is available in pH-range-specific subsets, so as to be able to cope with both low charge sites as well as more extreme charge situations as found in metalloenzymes, for example. ZINC has been broadly sub-categorized into several libraries, such as 'drug like', 'lead-like' and 'fragment-like' molecules, for different applications that we and our colleagues find useful. Our quest to create biologically relevant

representations has led us to prepare a database of high energy intermediates for substrate discovery. Experimentally tested prospective substrate will be described.

### **Community-based approach to research on infectious diseases of the developing world and global health**

Rita Stanikunaite, Arnas Palaima, Barry A. Bunin

Collaborative Drug Discovery (CDD, Inc.), 1818 Gilbreth Road, Suite 220, Burlingame, CA 94010

Currently, infectious diseases of the developing world (e.g., malaria, tuberculosis) represent a global health challenge of the 21<sup>st</sup> century and require new approaches that would allow scientists to do research more effectively. As a result of the development of web-database technologies, recently a community-based approach to research on infectious diseases of the developing world and global health has emerged. The major components of effective scientific community include: (1) unifying goal, or focus on common therapeutic areas/diseases; (2) multiple research areas/expertise; (3) uniform database platform that allows effective data accumulation and management; (4) easy access and sharing of information; (5) potential for unlimited growth. The Collaborative Drug Discovery (CDD) database built by utilizing community-based web technologies currently provides a platform that allows scientists to archive, mine, and share research data with a focus on infectious diseases of the developing world. This new collaborative technology allows researchers to build up networks of technical experts around therapeutic or target areas thus facilitating discovery of new drug candidates. It allows scientists to speed up the research by sharing unpublished data providing new hope in the race to overcome drug resistance. An example illustrating how potential chemosensitizers to address chloroquine resistance could be identified by using the CDD database platform is presented.

# Sponsors



**Collaborative Drug Discovery (CDD)** enables scientists to develop new drug candidates for commercial and humanitarian markets more effectively. CDD has developed a customizable, web-based database to **archive, mine, and collaborate** around pre-clinical drug discovery chemical and biological data.

This is a new type of web-database to help scientists more effectively develop new drug candidates from commercial and humanitarian academic drug discovery research. The default for all data is to be private, secure, user name and password protected. ~80% of the Community data is private by default, however about 20% of the data is being made openly available for the community to use, including the following data sets from the following leading researchers:

- 1. Dr. Christopher Lipinski**
  - Chemoinformatics data on FDA and Orphan approved drugs
- 2. Prof. Roos (U. Penn)**
  - Modern Malaria literature data linked to genes
- 3. Prof. Gelb (University of Washington)**
  - Modern Malaria literature data linked to assays
- 4. Prof. Guy (St. Jude Children's Research Hospital):**
  - >15,000 Army Malaria screening data dating back to WW-II after escrow period
- 5. Prof. McKerrow (UCSF):**
  - "Open-Content" Drug discovery – T. Brucei, T. Cruzi, S. Mansoni, Leishmania, P. falciparum

Community-based technologies are currently being used to help develop new treatments especially for infectious diseases afflicting poor people in developing countries including Malaria, Chagas Disease, and African Sleeping Sickness. Community case studies range from early stage HTS screening to lead optimization and GMP scale-up for clinical trials entirely in academic laboratories. The current CDD Community includes collaborations with leading researchers at UCSF, UC Berkeley, Stanford, UCLA, U. Penn, Burnham Institute, Univ. Washington, St. Jude Children's Research Hospital, as well as international scientists in Australia and Africa who are using CDD technologies to archive, mine, and (selectively) collaborate around their drug discovery data. The novel functionality is the web-based collaborative environment for heterogeneous drug data. Heterogeneous low-throughput and high-throughput enzyme, cell, and animal data can be *selectively* shared among colleagues or even openly shared on the internet if desired. After providing direct collaborations with the top ~100 researchers studying infectious disease, broader community-generating strategies will be organically nurtured in other therapeutic areas. For more information, contact [info@collaborativedrug.com](mailto:info@collaborativedrug.com).

## QB3



The California Institute for Quantitative Biomedical Research (QB3), a cooperative effort among three campuses of the University of California and private industry, harnesses the application of the quantitative sciences - mathematics, physics, chemistry and engineering - to biomedical research. This long-sought integration allows scientists to attack problems that have been unapproachable before; thus setting the stage for fundamental new discoveries, new products and new technologies for the benefit of human health. Furthermore, QB3 has been tasked by the State to ensure that its innovations reach patients and the marketplace as quickly as possible. Consequently, QB3 is dedicated to promoting translational research, establishing effective partnerships with industry, and helping its faculty explore commercial opportunities for their discoveries. QB3 also provides state-of-the-art core research facilities to its investigators and the local biotech community, including the Small Molecule Discovery Center, the UCSF Nikon Imaging Center, and high-field human magnetic resonance imaging.

## **J.D. Gladstone Institute**



### **GLADSTONE CENTER FOR TRANSLATIONAL RESEARCH**

Gladstone is composed of three institutes. The Gladstone Institute of Cardiovascular Disease, which opened in 1979, focuses on atherosclerosis and its complications. In 1992, the Gladstone Institute of Virology and Immunology was established to study HIV, the causative agent of AIDS. The 1993 discovery that apolipoprotein E—long studied at the Gladstone Institute of Cardiovascular Disease for its role in heart disease—plays a role in Alzheimer's disease as well led to the establishment of the Gladstone Institute of Neurological Disease in 1998.

The three institutes are located at Gladstone's new research facility adjacent to the Mission Bay campus of UCSF. While independent, Gladstone is formally affiliated with UCSF, and Gladstone investigators hold university appointments and participate in many university activities, including the teaching and training of graduate students.

Primary research efforts at the J. David Gladstone Institutes focus on three of the most important clinical problems of modern times: cardiovascular disease, AIDS, and neurodegenerative disorders. Cardiovascular disease, the nation's leading killer, claims the lives of over one million Americans each year. Despite more effective treatments, AIDS remains a leading cause of death in the United States. Worldwide, more than 40 million people are living with HIV/AIDS, and more than 21 million have died as a direct result of HIV infection. Alzheimer's disease, the most recent focus of investigation by Gladstone scientists, is the fourth leading cause of death in adults, affecting four million Americans. The realization of the impact of these diseases on world health infuses Gladstone scientists with a sense of purpose and urgency.

Although autonomous in their areas of specialization, the institutes share a common approach. Each institute is organized around research units consisting of scientists, postdoctoral researchers, research associates, and students. This structure is designed to accommodate small groups of scientists who work together closely but who also benefit from collegial interactions with other research groups. Collaborations among staff members with various areas of expertise create a stimulating environment that fortifies the scientific lifeblood of the organization.

## **Evaluation Questionnaire**

*Turn in your questionnaire for a chance to win a \$100 Amazon gift certificate!  
Drawing will be made at the reception*

What did you find most useful about today's meeting?

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What did find most useful about the morning training session, if you attended?

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Do you currently engage in collaborative drug discovery? Please Circle: **Yes** **No**

If Yes, what kinds of data would you most like to share with your collaborators? (eg. chemical structures, cell-based assays, biochemical assays, etc) \_\_\_\_\_

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How many collaborators would you share data with? \_\_\_\_\_

Please provide names of any scientists that you think may be interested in the CDD community.

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What are your therapeutic area(s) and targets of greatest interest? \_\_\_\_\_

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Do you use CDD software now? Please Circle: **Yes** **No**

If not, are you interested in a demo or trial? \_\_\_\_\_

### **Future Meetings:**

Would you like to participate in future meetings? Please Circle: **Yes** **No**

Any suggestions for papers, presentations, or changes?

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Would you like to serve on the Steering Committee? Please Circle: **Yes** **No**

*Please turn page to complete the questionnaire.*

**Poster Competition:**

Which did you think was the best poster? (please provide 1st Author name):\_\_\_\_\_

**Drawing:**

If you would like to participate in the drawing, please provide your name and email below

Name:\_\_\_\_\_

Email:\_\_\_\_\_