Computational Institute for Health and Environmental Research

Scientific Research Team

For over 20 years, this team was the National Cancer Institute (NCI), Developmental Therapeutics Program's (DTP) Computational Drug Development Group (CDDG). Located at the Frederick National Laboratory for Cancer Research (FNLCR), the CDDG was a grant-based, competitively funded group conducting research on NCI and Department of Defense (DoD)/Department of Homeland Security (DHS) priorities. From 2000-2012, the CDDG managed the chemistry component of the famous National Cancer Institute-US Army Medical Research Institute for Infectious Diseases-Interagency Agreement (NCI-USAMRIID IAA). The NCI-USAMRIID IAA was publicized as the model program for the National Interagency Biodefense Campus, as it was the first Department of Defense (DoD) and Department of Health and Human Services (DHHS) small molecule research partnership to demonstrate success at the FNLCR. From 2000-2021, the CDDG also worked in three operating committees in DTP while investigating links between cancers and infectious disease targets through the NCI-USAMRIID IAA. CDDG success resulted in their funding being expanded twice out of four DoD grant review cycles, attaining a peak budget of $2.5 million per year. At that time, the CDDG was composed of 12 members that supported four international collaborations. The CDDG's success in the DTP Rapid Access to New Discovery Resources program (RAND), secured the funding for the Chemical Biology Consortium in 2003. In 2004, the DTP stopped filing Investigational New Drugs (IND), despite their average filing of four INDs per year with the FDA. Even with a track record of 42 drugs, in 2015, the DTP operational committees were closed. As a result, part of the CIFHER mission includes promoting the development of drug candidates that were ignored by NCI leadership. This is especially true for Natural Products that may treat orphan cancers. CIFHER scientific staff uniquely combines technologies from detailed molecular modeling to the application of broad-scaled informatic methods. The CIFHER research team has also expanded their mission as a unique resource to promote personal and environmental health for the prevention of cancers through research and education.

Dr. Jim Burnett, Chemistry, Computational Chemistry, Synthetic Organic Chemistry, X-ray Crystallography, Protein NMR, Analytical Chemistry and Spectroscopy, Protein Modeling, Structure-based modeling techniques, Molecular Docking and Structure-based Design, Grant Management, Process Chemistry, and Pharmacokinetics.

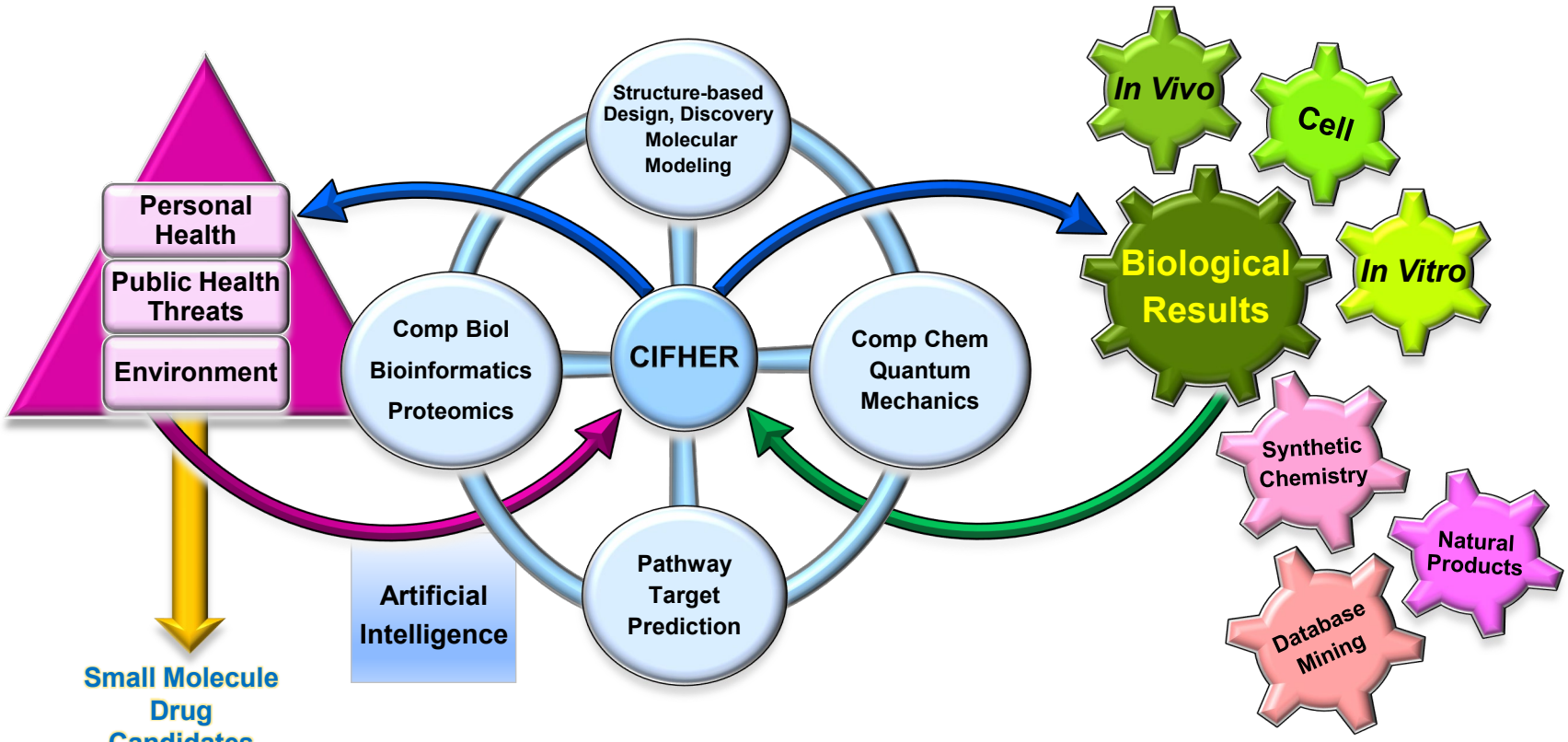
Dr. Rick Gussio, Pharmaceutical Sciences, Physical Organic Chemistry, Applied Statistics, Computational Chemistry, Quantum Mechanics, Structure-based design & discovery, QSAR, Molecular docking, Precision molecular modelling, Pharmacophore development, the molecular modeling of Natural Products, small molecule target interfaces, protein structure and function

Dr. Ann Hermone, Computational Chemistry, Quantum Mechanics (DFT, *ab initio*, transition states, molecular orbital properties), 3D pharmacophore query development & virtual discovery (>30% discovery in most targets), Chemo-informatics and specialized database development for discovery. Her interests also include the chemistry of environmental toxins, and ecology.

Dr. Connor McGrath, Bioinformatics, Computational Biology, Protein Modeling, Applied Mathematics, Neural networks & AI, Algorithm development, Specialized database development, (Pipeline Pilot, MATLAB, SQL, etc.), Molecular dynamics (MD) simulations & analysis, Data modeling, MD Trajectory analysis. An experienced educator, his interests also include agricultural toxicology.

Computational Institute for Health and Environmental Research (CIFHER.ORG)

Scientific Approach and Capabilities



Computational modeling: *from electrons to biochemical pathways*

NCI-USAMRIID Inter Agency Agreement Successes

Cancer Targets

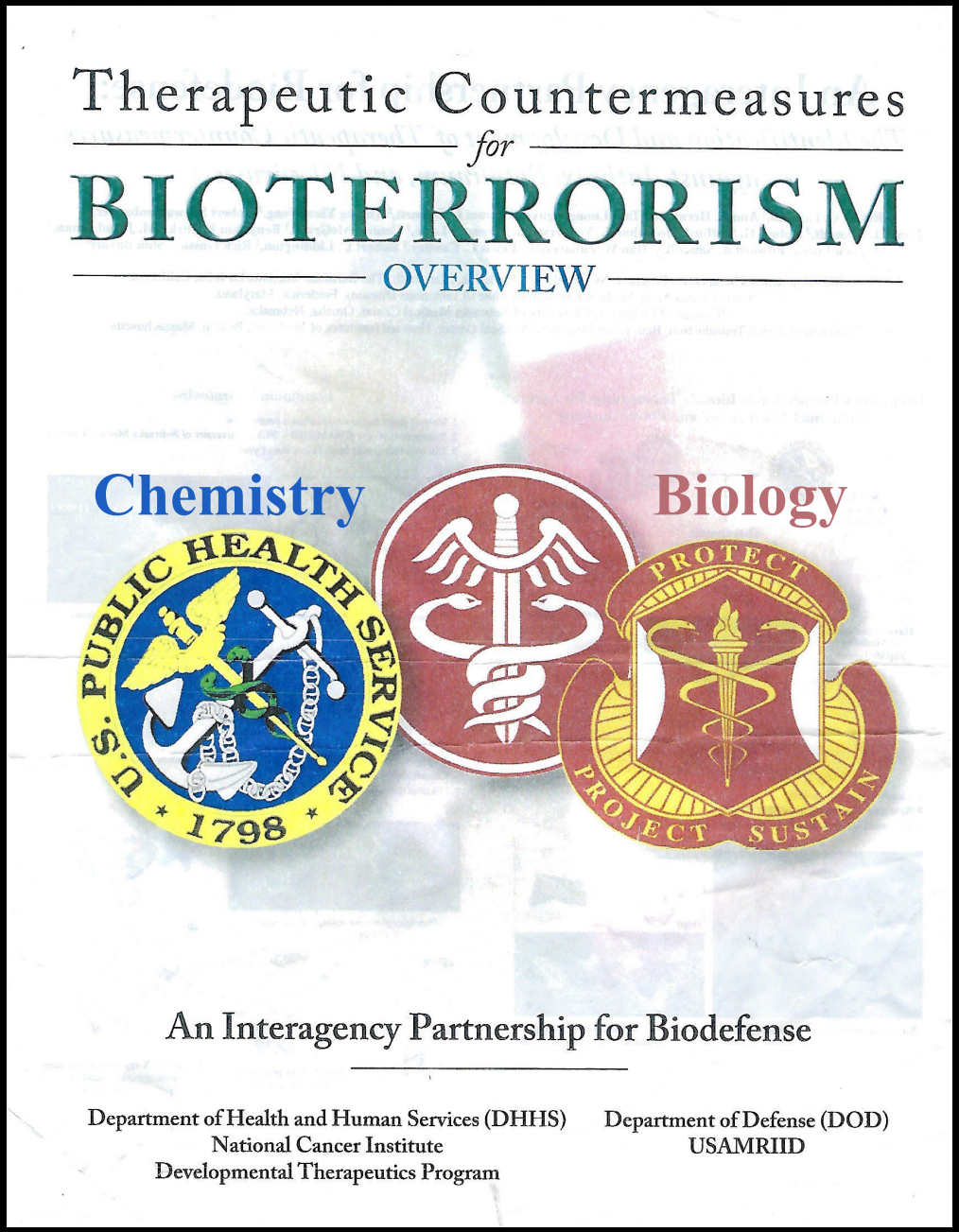
Cyclin Dep. Kinases
SRC Kinase
RSK2 Kinase
CD45 Phosphatase
Taspase
7 Tubulin Sites
P97
Phosphatases
KDM5
Artemis

NCI-DTP Drug Development Operations
(defunct since 2015)

RAND Program

Biological **E**valuation **C**ommittee

Data **R**eview **C**ommittee



Class A Biothreat Agents

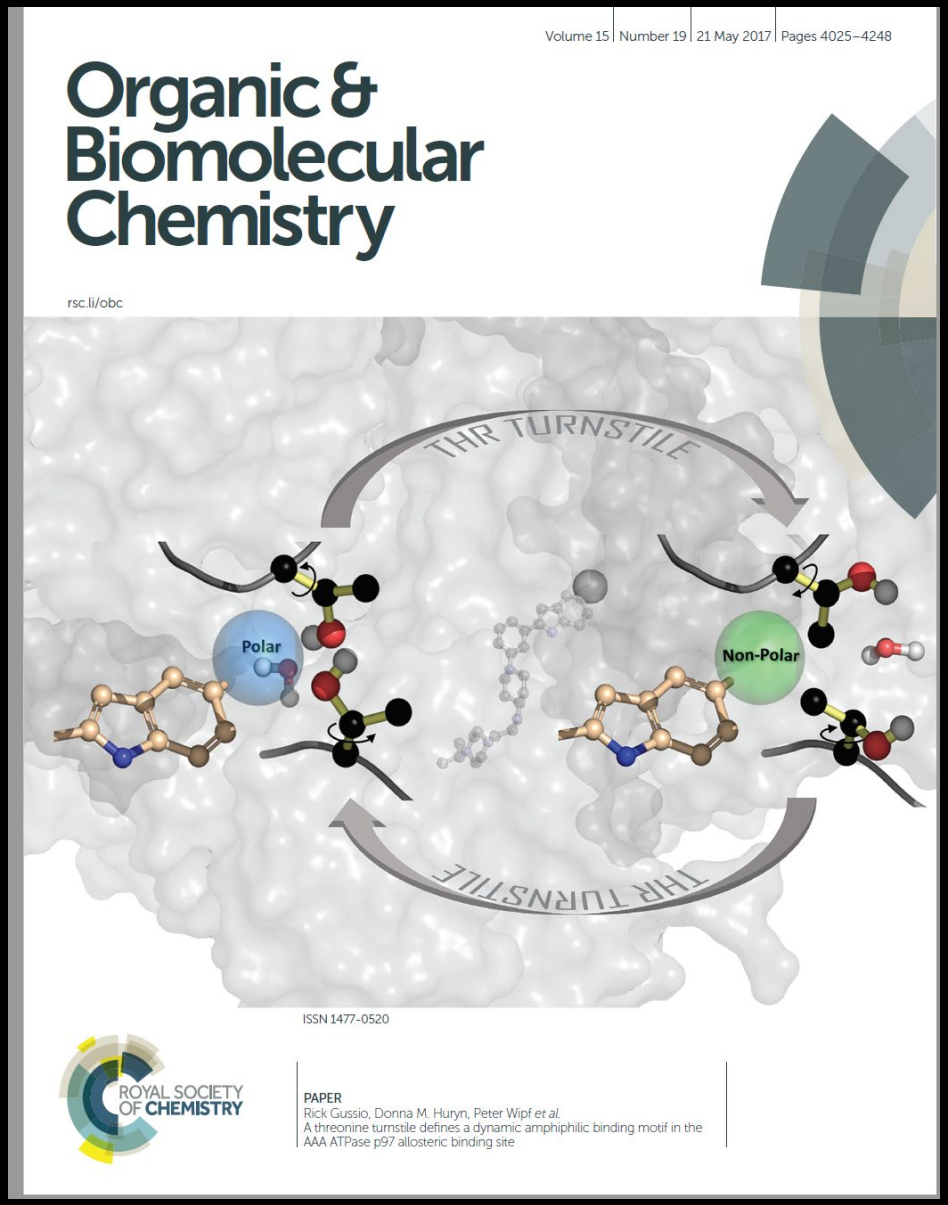
Anthrax
Botulism
Ebola
Marburg

Infectious Disease Drug Discoveries

HIV-1 RT
Mers
Sars Cov-1
Sars Cov-2
Zika
EEE
VEE
West Nile

Discovery of a new biochemical structural motif using P97 SAR

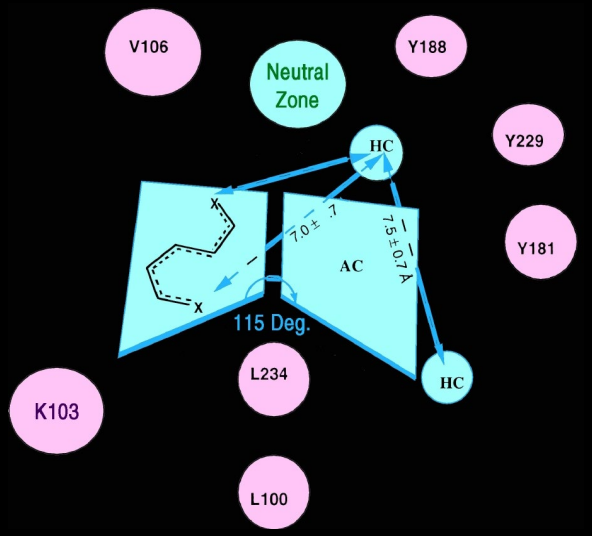
Bis-Threonine Turnstile



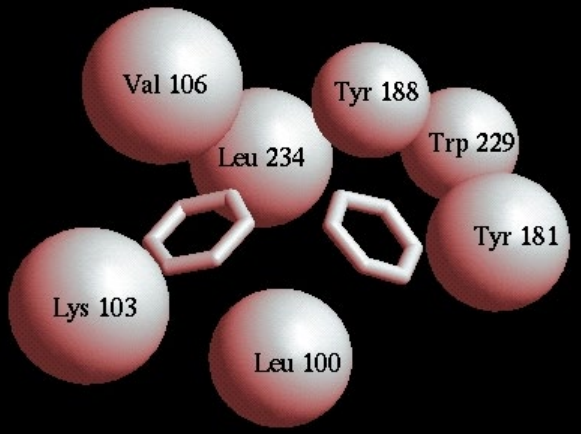
P97 Unfoldase

(Burnett, J.C. et al. *Organic Biomolecular Chemistry*. 2017, 15(19): 4025-4248)

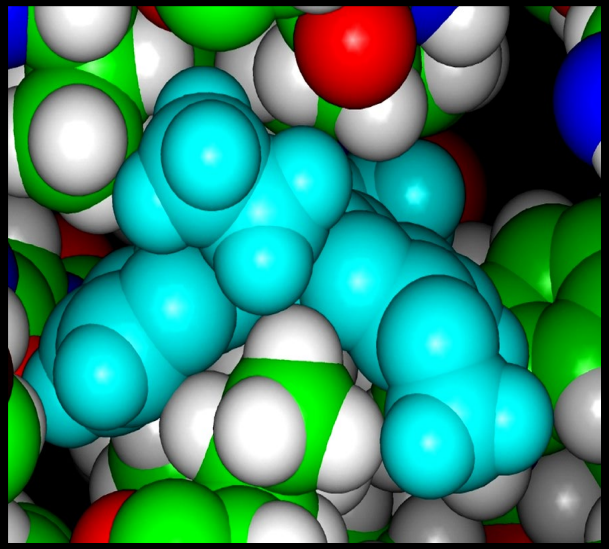
Target Structure-Based Discovery & Virtual Screening



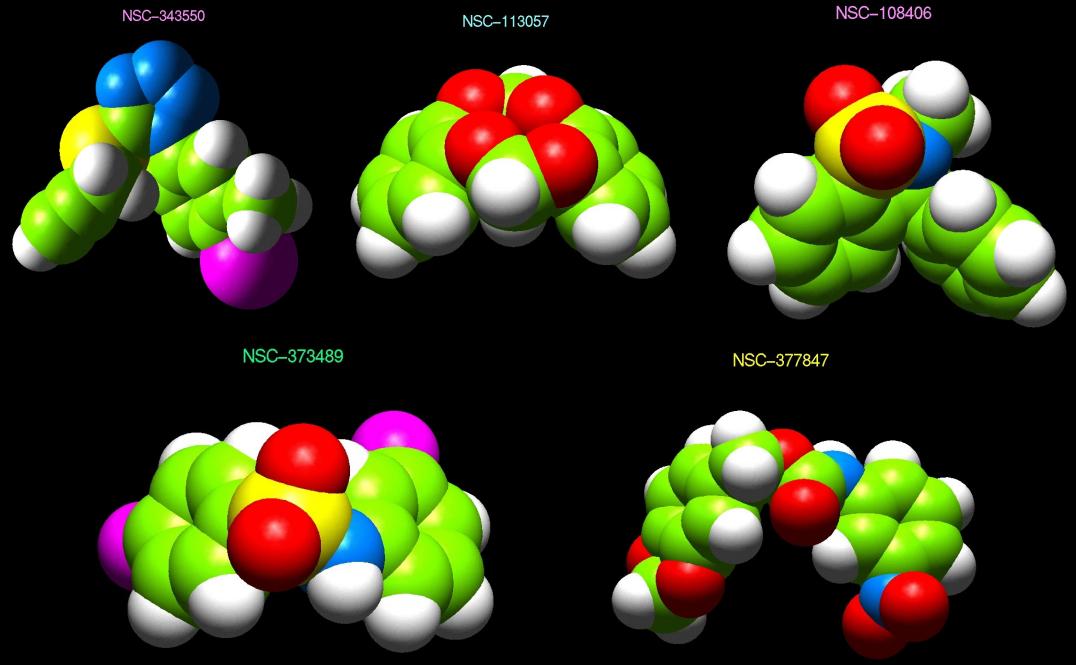
1. Generate structure-based pharmacophores



2. Form 3D search queries



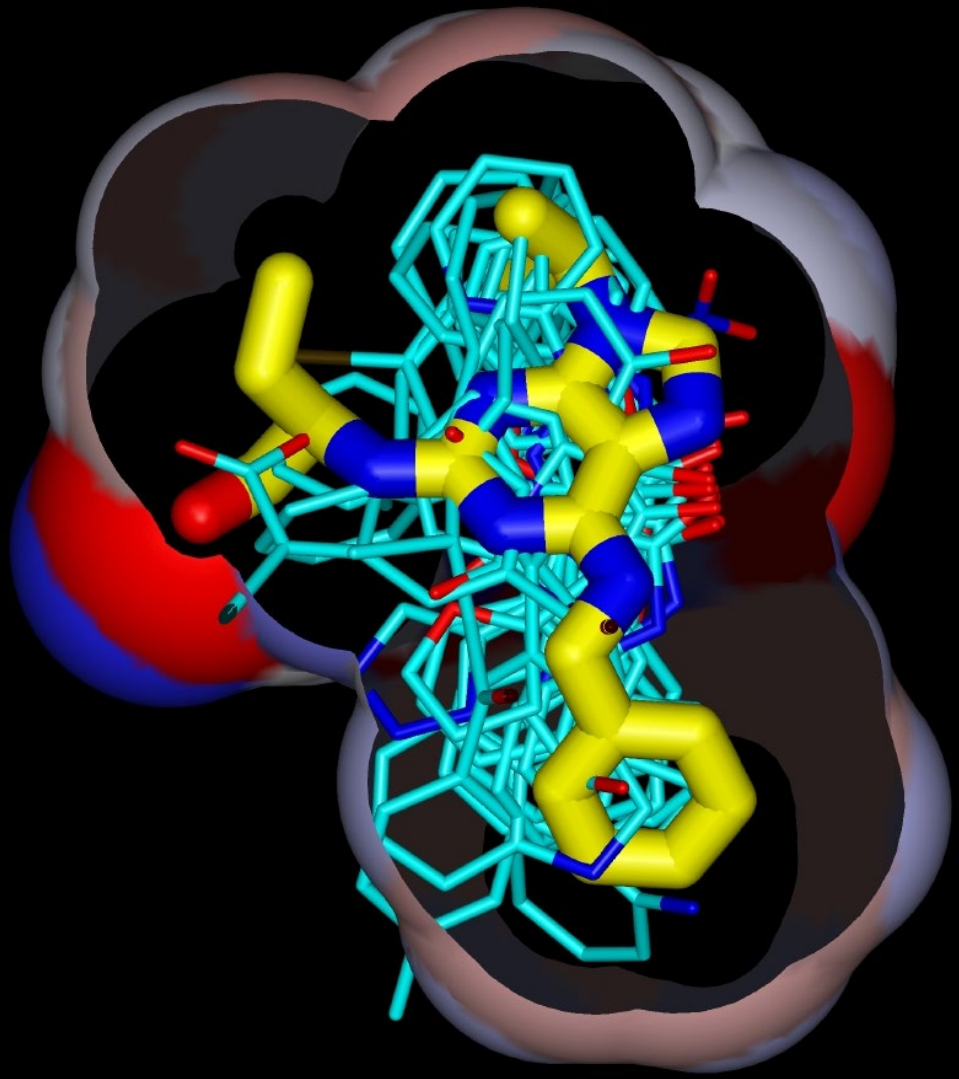
3. Evaluation of hits by molecular docking



4. Verify in biological testing assays

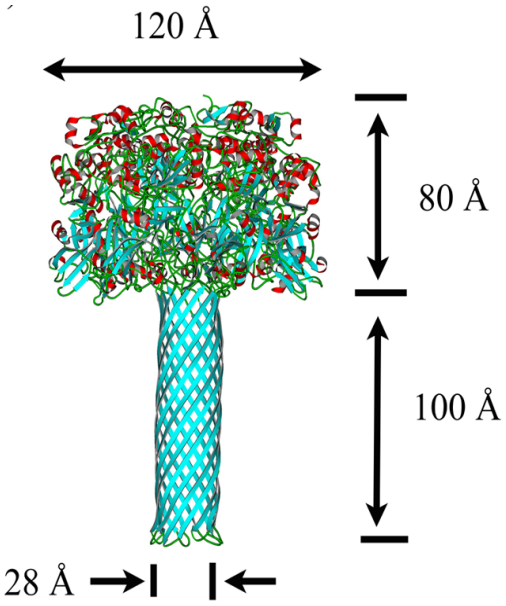
(Gussio et al., *J Med Chem*. 1996 Apr 12;39(8):255-63.)

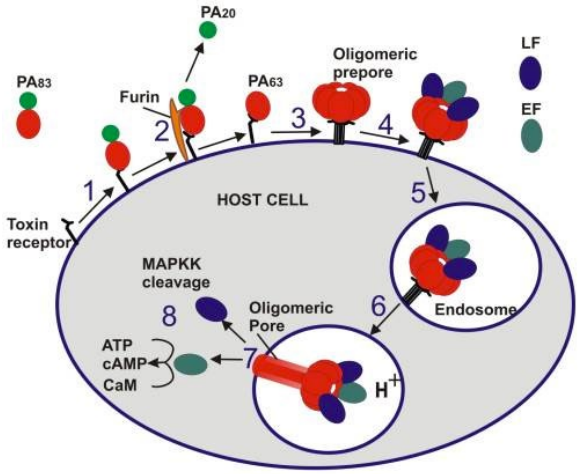
Probing for New CDK Binding Space Using a QSAR Lead Discovery Approach



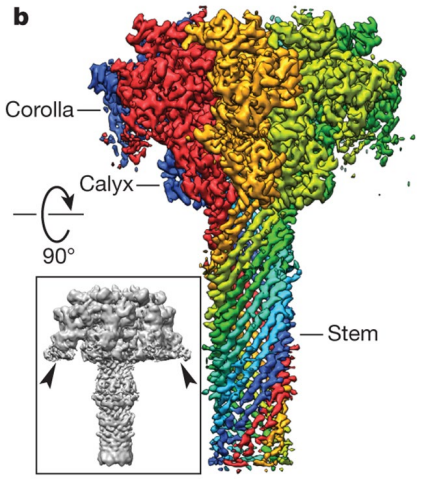
(Gussio et al., *Methods*. 1998 Mar;14(3):255-63.)

10 Years Ahead: Modeling complex Anthrax Protective Antigen pore based on biophysical data





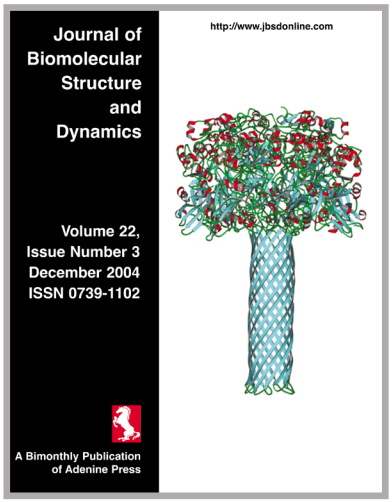
Anthrax Toxin cell entry mechanism



In 2004, PA pore model (PDB 1V36)

Nguyen, T. L., Three-dimensional model of the pore form of anthrax protective antigen. Structure and biological implications. *Journal of biomolecular structure & dynamics* **2004,** *22* (3), 253-65.

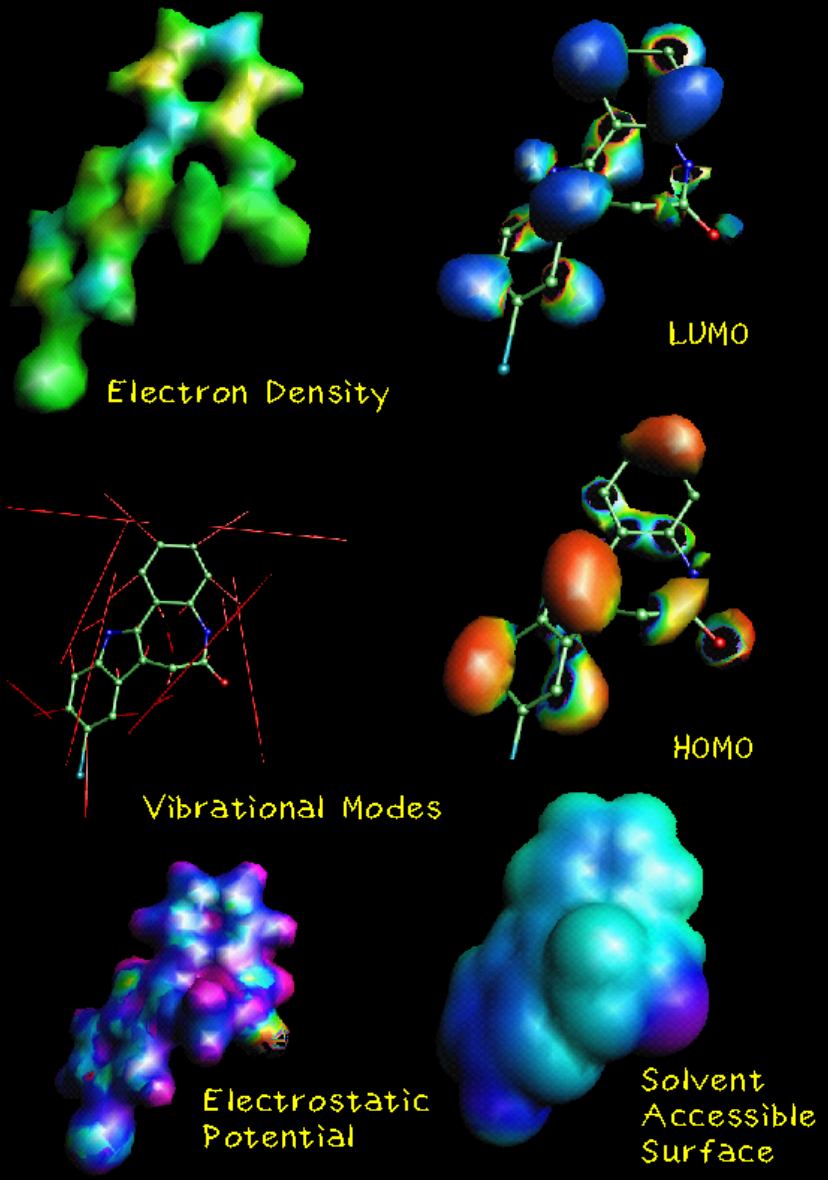
Work by former CDDG Member Dr. TL Nguyen



In 2015, CryoEM Reconstruction

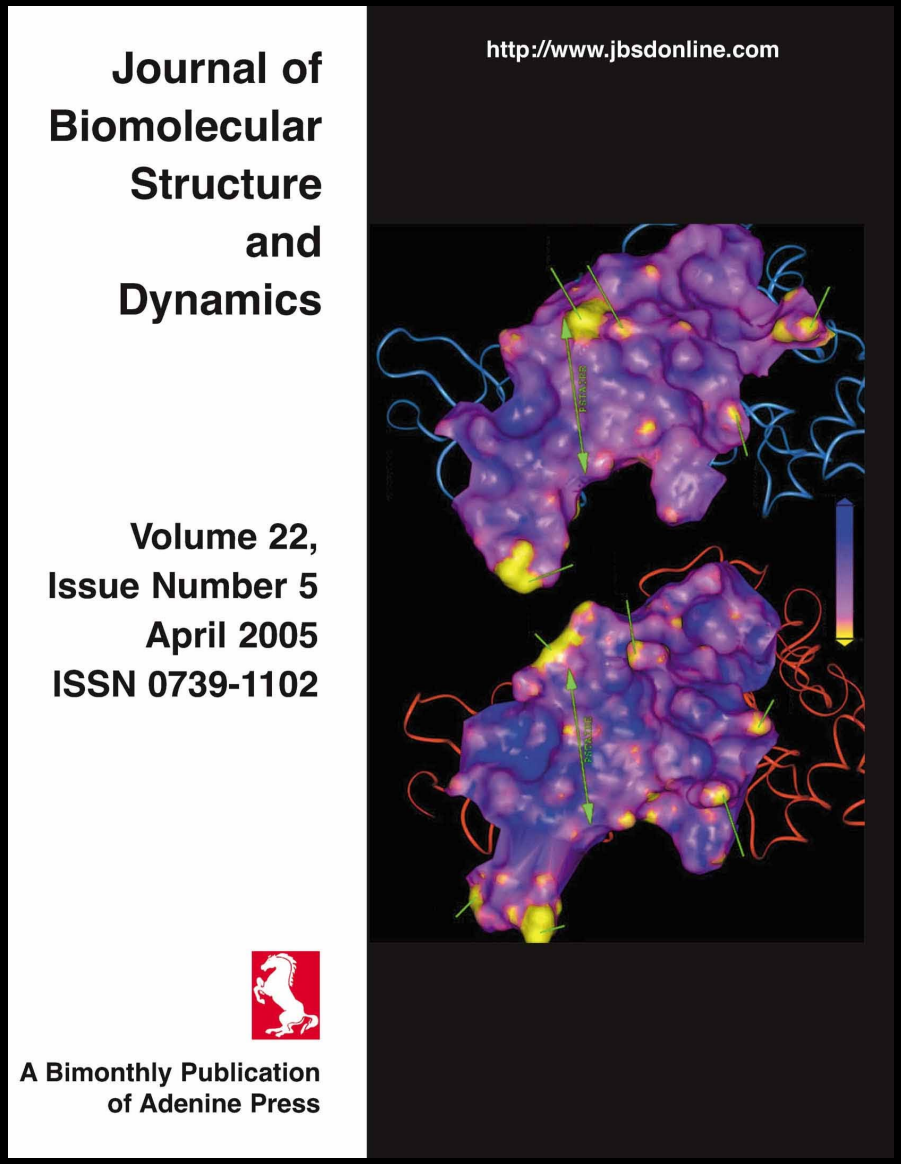
Jiang, J., Pentelute, B., Collier, R. *et al.* Atomic structure of anthrax protective antigen pore elucidates toxin translocation. *Nature* **521,** 545–549 (2015). https://doi.org/10.1038/nature14247

Using Quantum Mechanics in Stereo-electronic Design



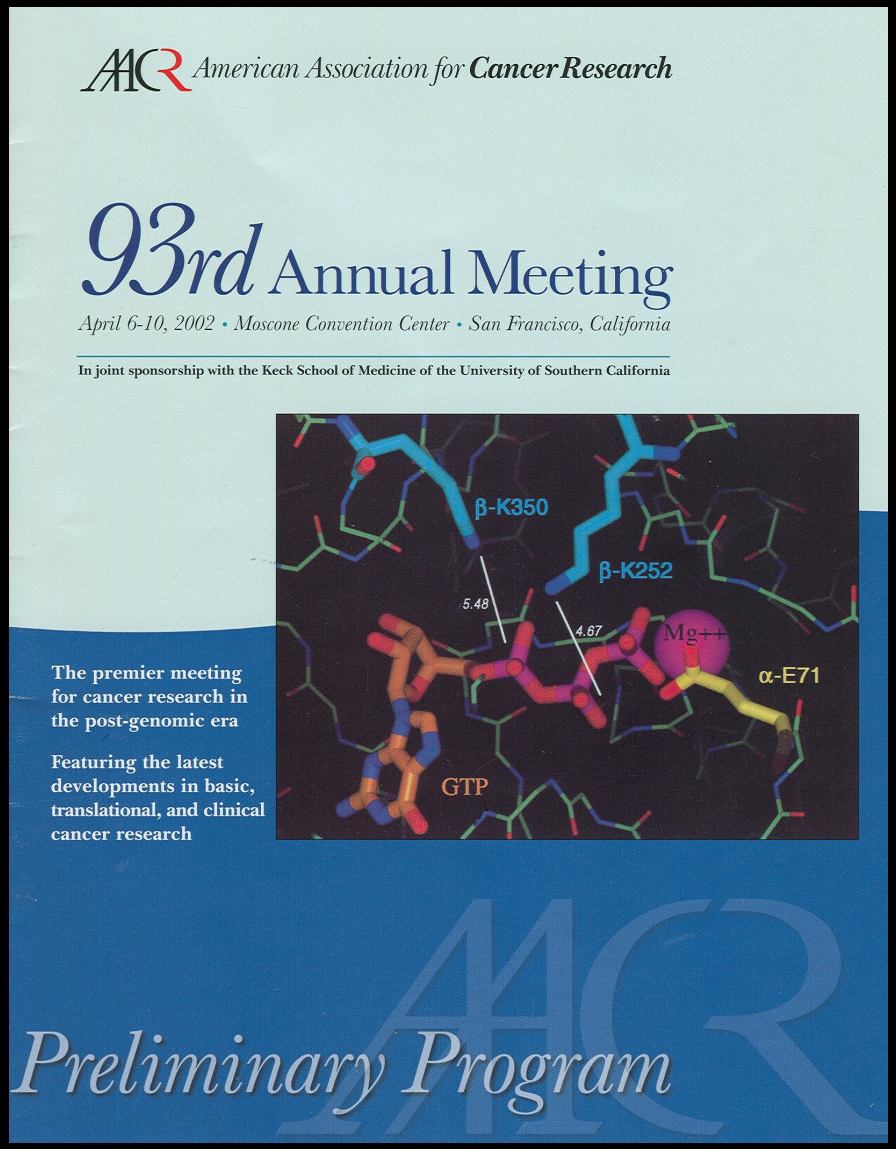
(Gussio et al., *Anticancer Drug Des.* 2000, (1):53-66)

CDK1 SAR-Based Generation of the Cyclin B1-CDK1 Interface



(McGrath CF, et al., *J Biomol Struct Dyn*. 2005 Apr;22(5):493-502.)

Protein Modeling of Primary Drug Resistance by Site Directed Mutagenesis & SAR



(Hua et al., *Cancer Research*. 2001 Oct 1;61(19):7248-54)

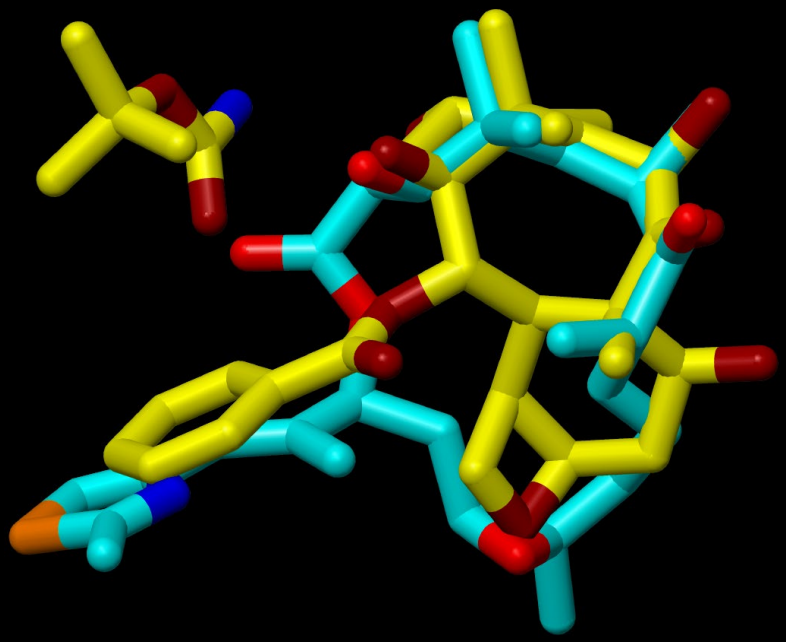
Characterization of Macromolecular Response Surfaces

Electrostatic
Potential
Response Surfaces

IL2

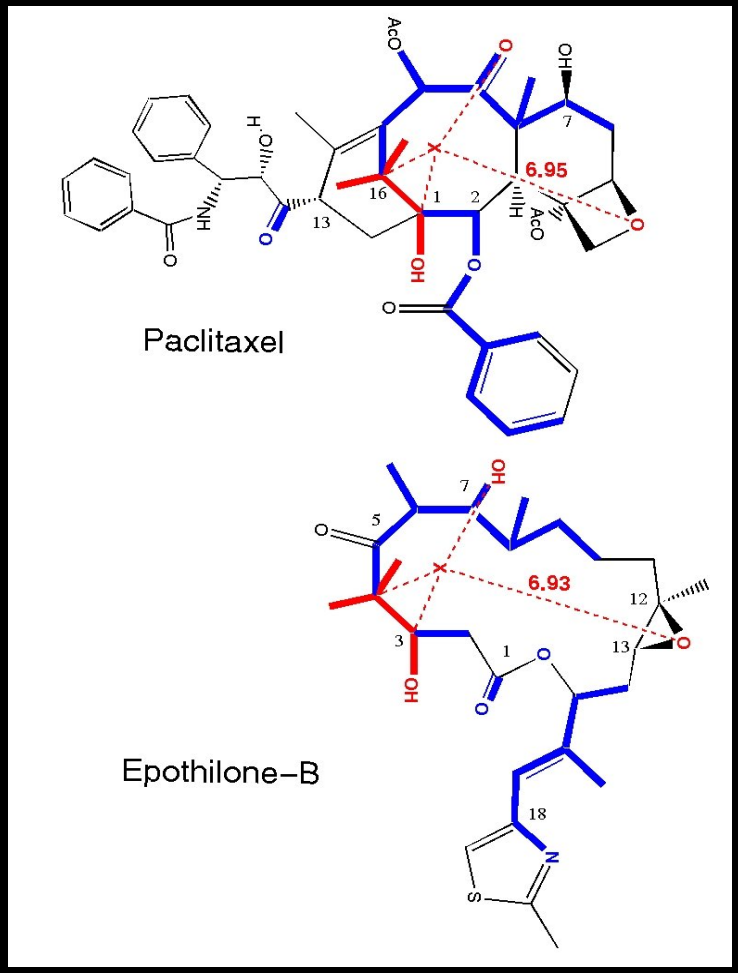
IL4

Determine Binding Modes and Pharmacophores of Natural Products



Taxotere

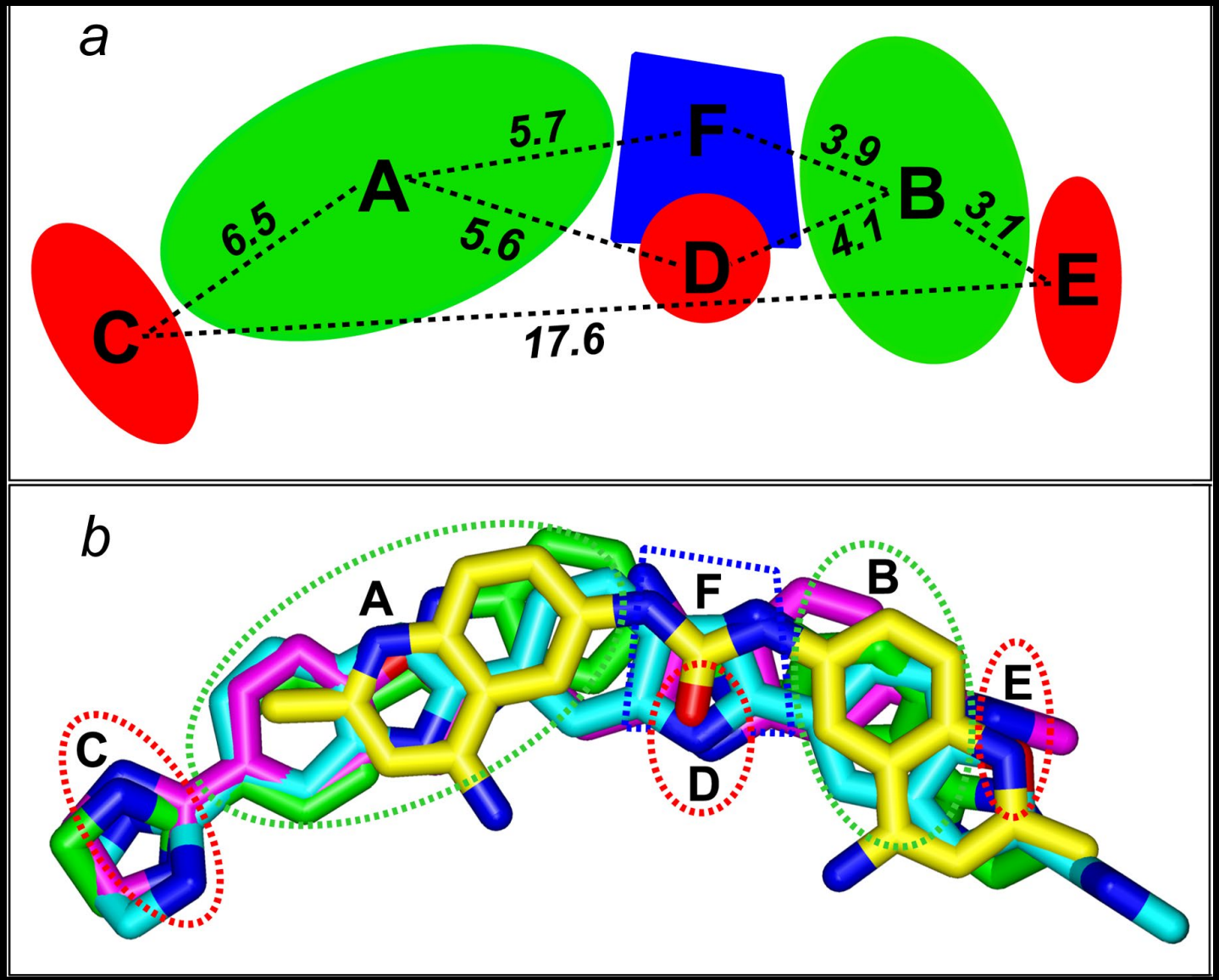
Epothilone-b



(Giannakakou et al., *Proc Natl Acad Sci U S A*. 2000, 97(6):2904-9)

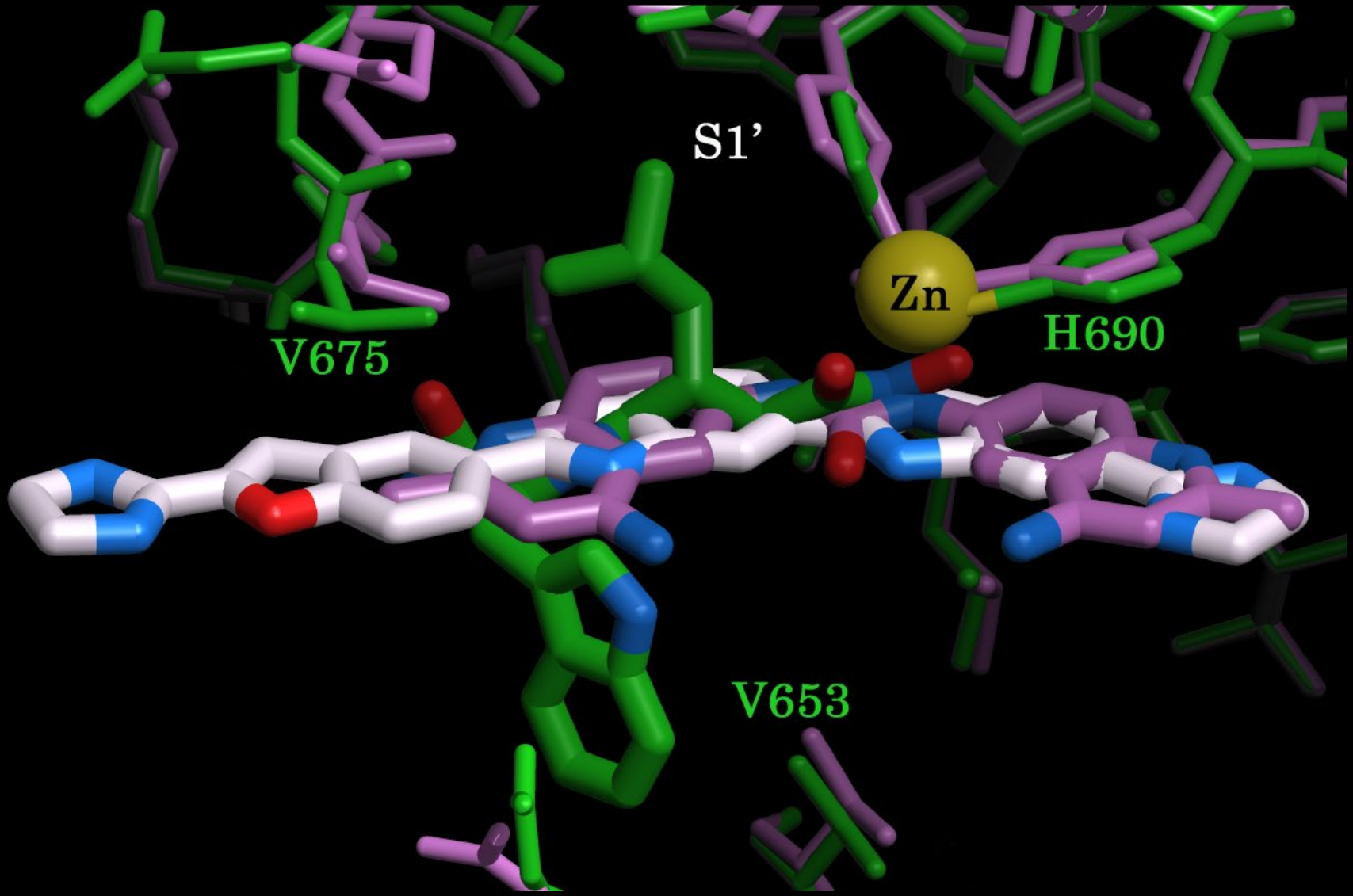
(Gussio R, Fojo T, Giannakakou P. *TIPS*: 2000 Sep;21(9):323-4.)

Gas Phase Pharmacophore to Structure-based Refinement



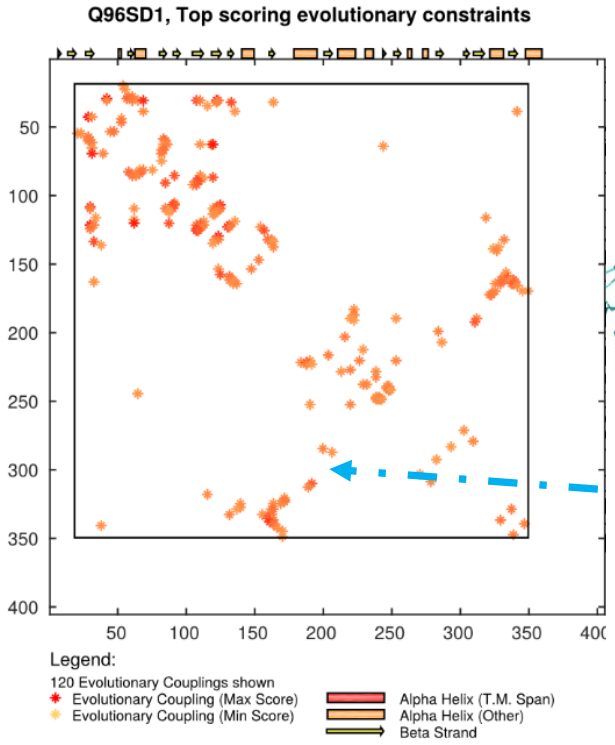
(Panchal et al., *Nat Struct Mol Biol.* 2004 Jan;11(1):67-72.)

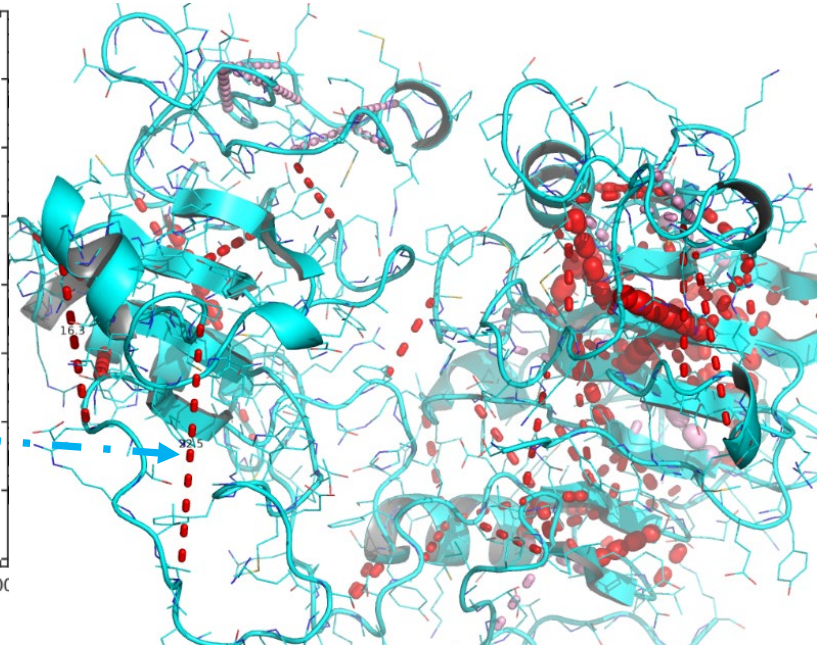
Structure-based discovery and pharmacophoric classification

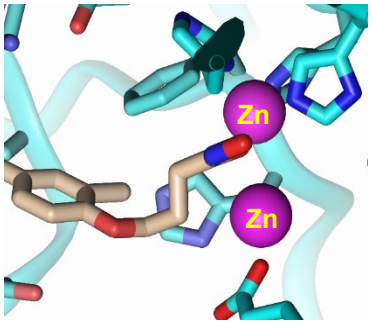


(Hermone et al., *ChemMedChem.* . 2008 Dec;3(12):1905-12)

Using Evolutionary Coupling to Refine Protein Structure with Molecular Dynamics to Form Predictive Designs for Artemis



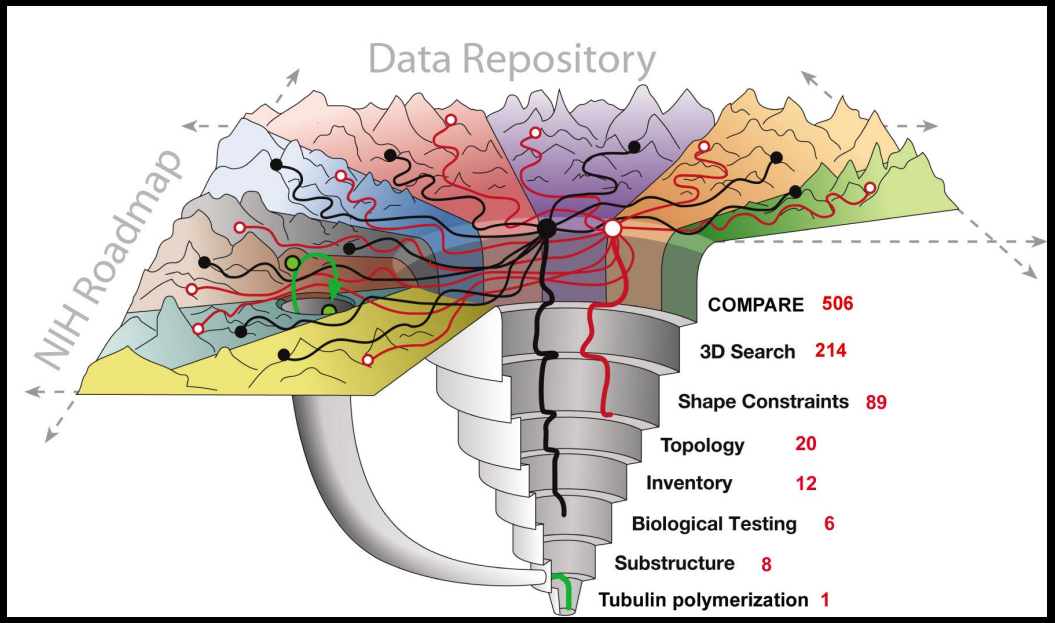


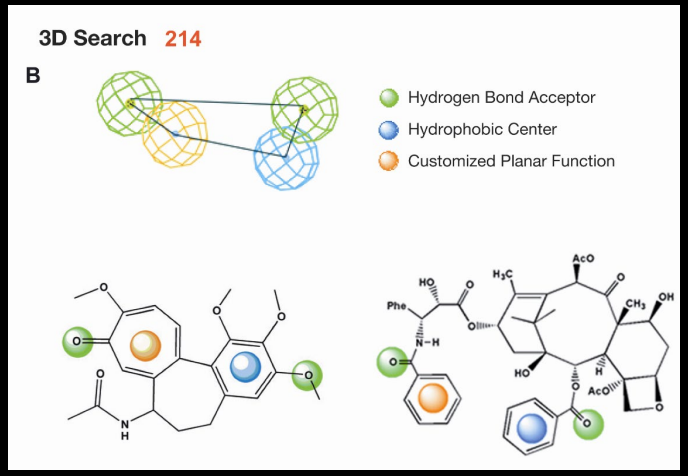


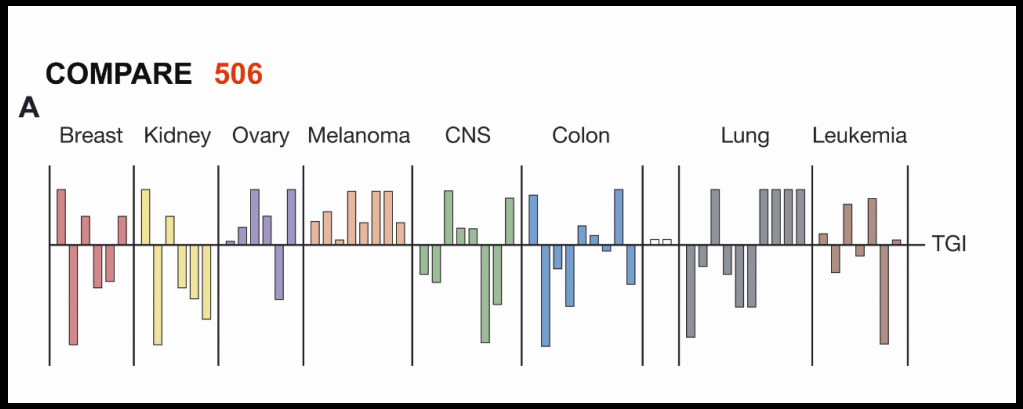
Evolutionary Coupling → Distance constraints in MD simulated annealing → Predictive Designs

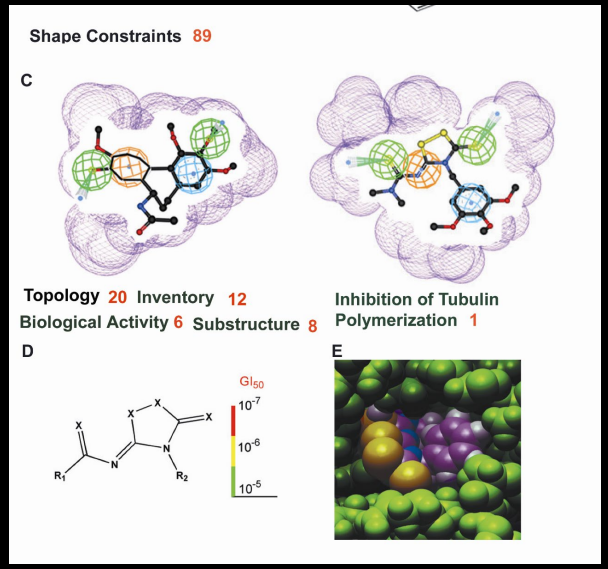
Work includes former NCI's Computational Drug Development Group (CDDG) member Dr. Brian Peyser

Integration of Bioinformatic Response Surfaces with Structure Based Methods

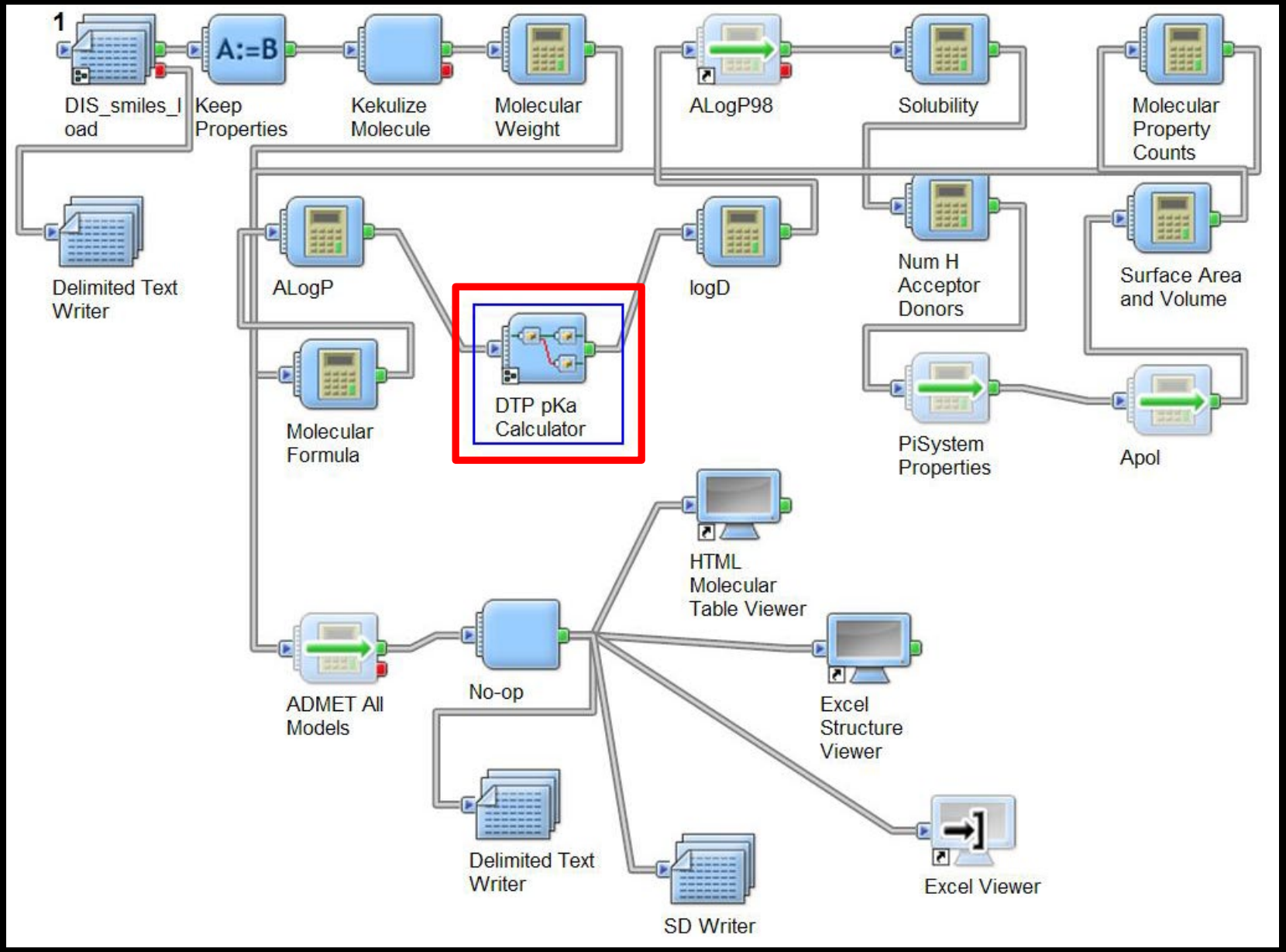




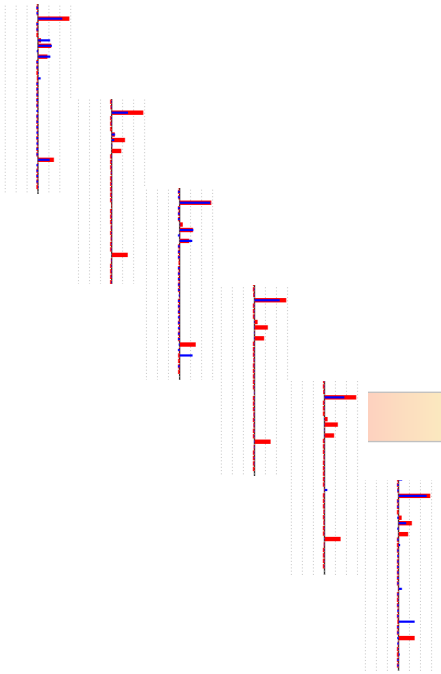


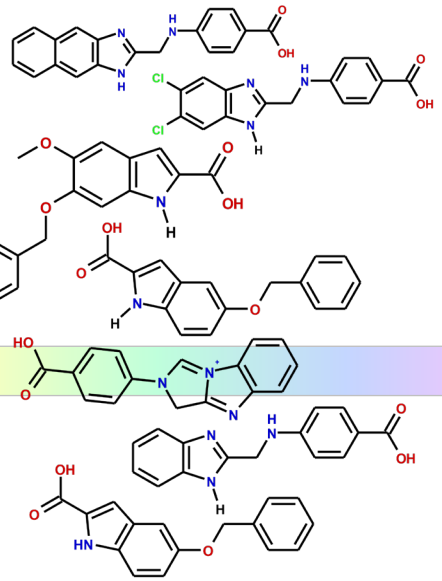


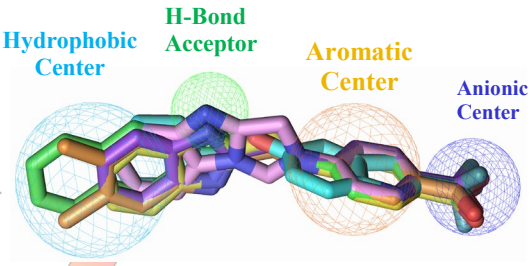
Development of Custom CDDG Informatic Tools in the Pipeline Pilot Platform



CDDG online tool for new drug discovery efforts: PRISM



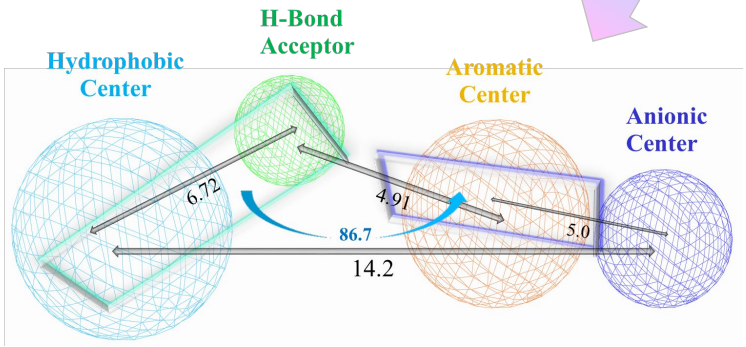




Biological Patterns

Chemical Structures

3D Pharmacophore



Find new substances

Virtual Target Discovery

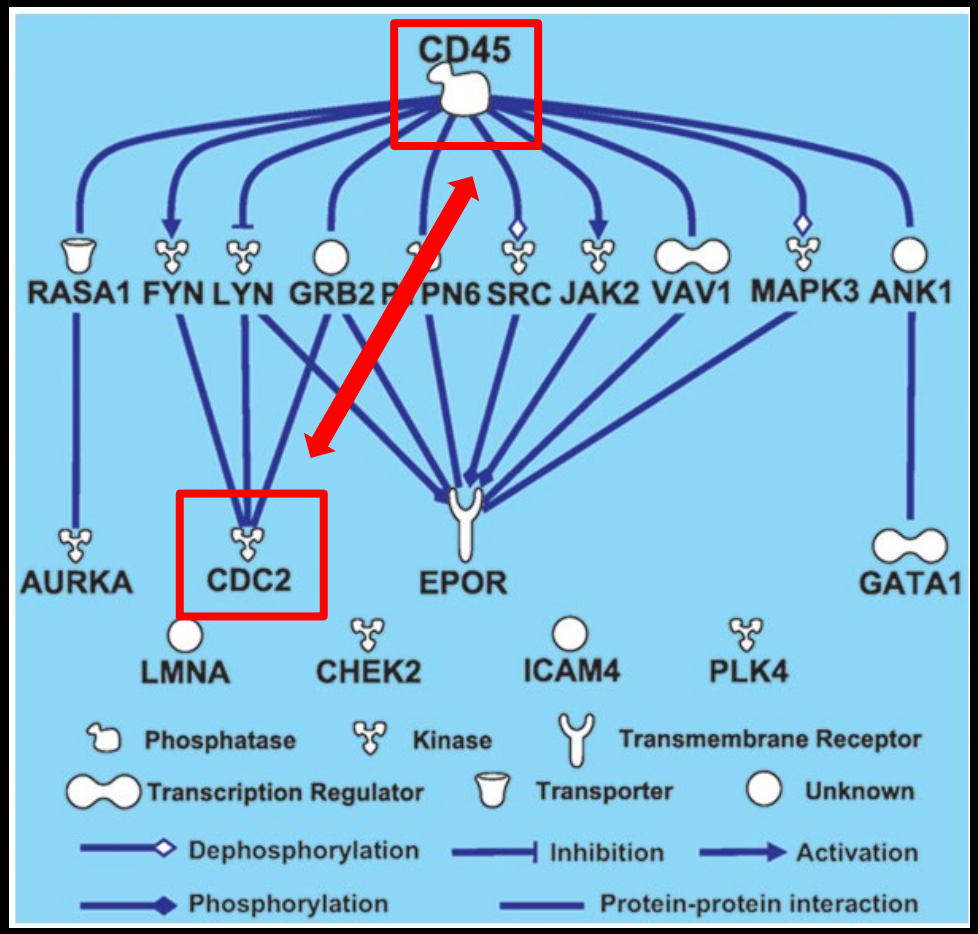
SIGMA-ALDRICH

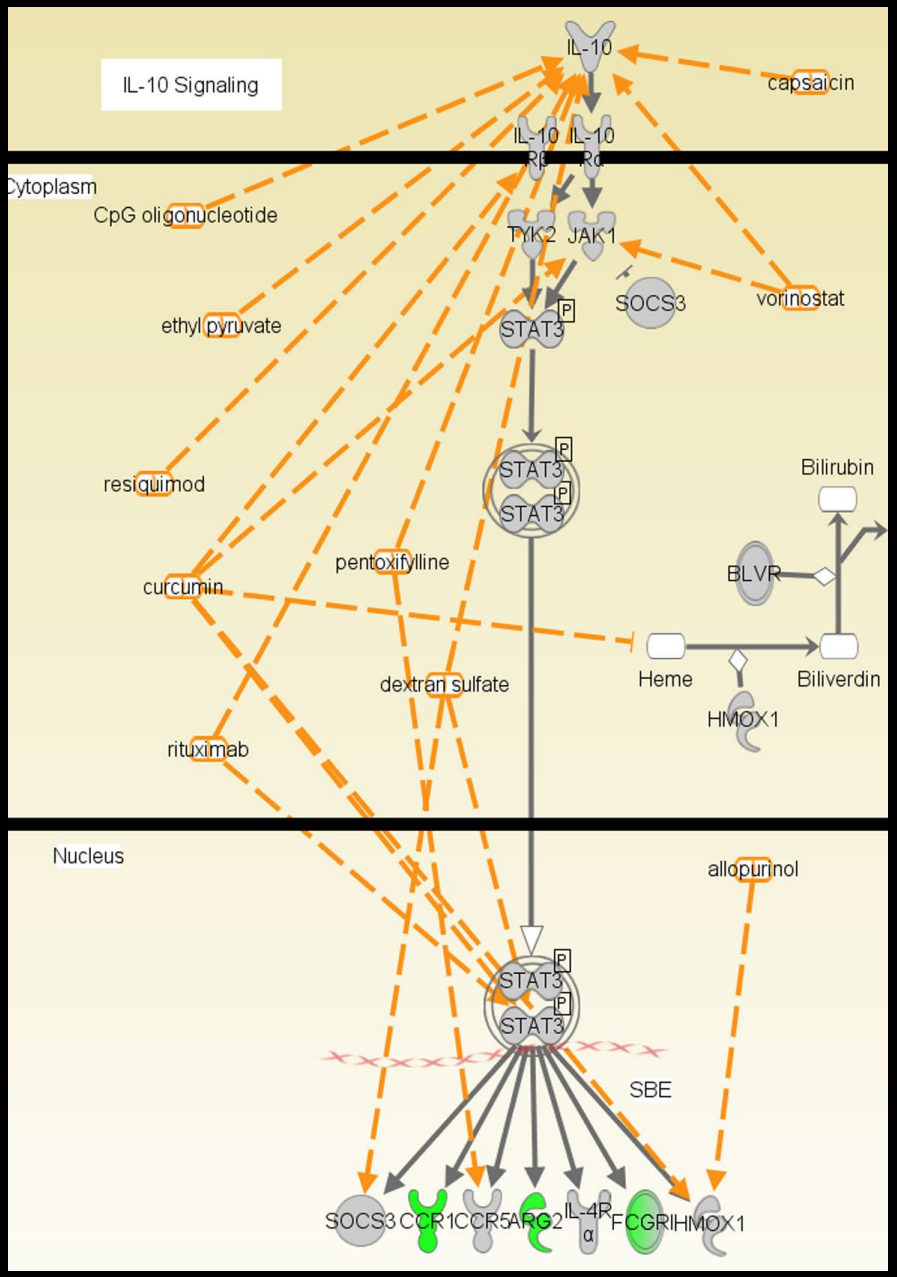
RCSB PDB PROTEIN DATA BANK

NIH NATIONAL CANCER INSTITUTE

Work includes former CDDG Member Dr. Brian Peyser

Protein-Drug Interaction Pathway Generation





Work includes former CDDG Member Dr. Brian Peyser