TARGETING DISEASE *with* "Designer" Drugs

Finding and understanding how proteins bind to one another to initiate disease processes has been one of the most critical tasks performed in recent years by high-performance computing and algorithms to speed those discoveries. The work is fundamental to drug discovery and what has become commonly referred to as "drug design."

Igor Tsigelny, a research scientist at SDSC, has been using SDSC computational resources to help experts search for new insights into a cross-section of medically challenging conditions, from heart disease to cancer to mental disorders.

During the past year, for example, Tsigelny worked with other researchers at UC San Diego and the Institut Pasteur in Paris to identify coherent-gene-groups (CGGs) responsible for brain development which can be affected for the treatment of developmental and mental disorders such as autism-spectrum disorders (ASD) and schizophrenia. In a paper published in the journal *Gene, Brain and Behavior*, the researchers identified the hierarchical tree of CGG-transcription factor (TF) networks that determine the patterns of genes expressed during brain development, and found that some "master transcription factors" at the top of the hierarchy regulated the expression of a significant number of gene groups.

Using samples taken from three different regions of the brains of rats, the researchers used *Gordon* and SDSC's BiologicalNetworks server to conduct numerous levels of analyses, starting with processing of microarray and SOM (self-organizing maps) clustering, before determining which gene zones were associated with significant developmental changes and brain disorders.

Said Tsigelny, also a researcher with UC San Diego Moores Cancer Center and the Department of Neurosciences: "We have proposed a novel, though still hypothetical, strategy of drug design based on this hierarchical network of TFs that could pave the way for a new category of pharmacological agents that could be used to block a pathway at a critical time during brain development as an effective way to treat and prevent mental disorders such as ASD and schizophrenia. On a broader scale, these findings have the potential to change the paradigm of drug discovery."

Tsigelny's collaborators included Valentina L. Kouznetsova (SDSC and Moores); Michael Baitaluk (SDSC); and Jean-Pierre Changeux, with the Institut Pasteur, a distinguished visiting professor in pharmacology at UC San Diego (2008) and member of the foreign faculty at UC San Diego's Kavli Institute for Brain and Mind.

In 2013, Tsigelny was a part of a team of UC San Diego researchers that designed new compounds that mimic those naturally used by the body to regulate blood pressure. The most promising of them may literally be the key to controlling hypertension, switching off the signaling pathways that lead to this condition.

Published in the online version of *Bioorganic & Medicinal Chemistry*, the scientists studied the properties of the peptide called catestatin that binds nicotinic acetylcholine receptors found in the nervous system, and developed a pharmacophore model of its active centers. They next screened a library of compounds for molecules that might match this 3D "fingerprint". The scientists then took their *in-silico* findings and applied them to lab experiments, uncovering compounds that successfully lowered hypertension.

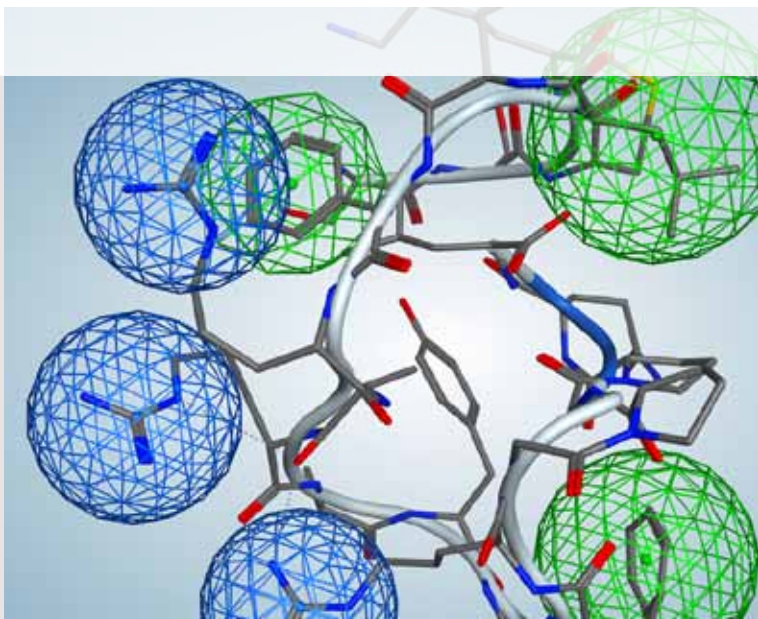
The research may lead to a new class of treatments for hypertension, a disease which affects about 76 million people, or about one in three adults, in the United States, according to the American Heart Association.

"Our results suggest that analogs can be designed to match the action of catestatin, which the body uses to regulate blood pressure," said Daniel T. O'Connor, a professor at the UC San Diego School of Medicine and senior author of the study.

"This approach demonstrates the effectiveness of rational design of novel drug candidates," added Tsigelny.

Other authors included Kouznetsova, Nilima Biswas and Sushil K. Mahata, of UC San Diego's Departments of Medicine and Pharmacology.

Igor Tsigelny, SDSC research scientist (above)



Catestatin-mimic pharmacophore model developed by researchers to help in the fight against hypertension. Image: Valentina Kouznetsova, UC San Diego (right)