Molecules made by IUPUI students may have potential to cure diseases

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By substituting different ingredients for R1and R2 in a chemical recipe, students can make thousands of variations of a potential drug. Credit: School of Science at IUPUI

Not many college students can say their efforts in the laboratory may lead to therapies for diseases that devastate millions of people worldwide, but chemistry students in the School of Science at Indiana University-Purdue University Indianapolis can. As they learn the science of chemistry they are actually synthesizing molecules that may someday be tested in human clinical trials as potential drug treatments or cures for such devastating diseases as malaria and tuberculosis.

Led by School of Science Department of Chemistry and Chemical Biology faculty members William Scott, Ph.D., and Martin O'Donnell, Ph.D., the students are an essential resource in a new low-cost strategy to accelerate the discovery of drugs to treat neglected diseases. Called Distributed Drug Discovery (D3), the goal of this effort is to identify, synthesize and ultimately test molecules that have not been previously considered for use as drugs to treat these deadly diseases. D3 does this through a distributed problem solving process that breaks large problems

into small pieces that are "distributed" to multiple, small, low-cost sites to obtain a solution.

Because of the need to make and test large numbers of molecules, D3 uses a distributed problem approach at each of the three key stages of drug discovery. The initial step identifies candidate drug molecules to be made. To do this the IUPUI researchers are soliciting the advice of computational experts in neglected diseases. Some of these experts will utilize the computational power of multiple personal computers around the world to analyze the large numbers of molecules that students could make to identify the smaller number of drug-candidate molecules they should actually focus on making. Scott and O'Donnell believe this is the most direct path to the selection, synthesis and eventual development of innovative and inexpensive drugs to treat these neglected but very common diseases.

The IUPUI chemistry students get involved at the second step of D3. As part of their training in synthetic chemistry, they make the molecules that have been computationally identified as potential candidates for drug discovery. Students learn and employ combinatorial chemistry, which uses a standard synthetic procedure and various combinations of chemical reagents to produce different molecules.

Scott uses the analogy of a fruit pie recipe to explain what the students are doing. "Everyone is using standard instructions. With this basic recipe, and under the guidance of a master chef (chemistry faculty member), different ingredients can be used at each stage of the process. At the "add berries" stage some of the novice cooks use blueberries, others use raspberries and yet others use blackberries. At the "add shortening" stage some use butter and others substitute oil or margarine. There may even be a choice of crusts, say traditional or graham cracker. By trying out all these possible variations at each step, many different pies can be made. A taste test can then identify which combination of

ingredients produced the best tasting pie."

This is actually very similar to how combinatorial chemistry works. The goal is to use many different chemicals at each stage of a synthetic recipe to create, in combination, large numbers of molecules that can then be tested to determine their potential as drugs.

"I am a hands-on person and working on D3 kept me engaged and definitely propelled me to a graduate program in organic chemistry. I learned so much," said Stephen Brown who graduated from IUPUI in 2010 and is a first-year graduate student at the University of Pennsylvania.

The final stage is evaluation of the molecules made by the students. Ninety-one molecules made by students at IUPUI and the University of Indianapolis (working under Lindsey Fischer, who recently received a master's degree from IUPUI) have been deposited at the National Institutes of Health Small Molecule Repository for potential screening to see if they merit further movement along the drug development pipeline. Scott has received word from the NIH that some of these molecules have shown biological activity and are being further evaluated.

"As far as we know, our molecules are the only ones made and contributed to the NIH repository by undergraduates. We are very excited about the potential of these molecules in the battle against some very devastating diseases, and that these molecules show the students that make them the importance of the work and skills they are learning. We also are very pleased that this project is teaching our students about drug development and the global, reproducible nature of science," said Scott.

The pharmaceutical industry has often been reluctant to get involved in developing treatments for diseases that occur primarily in low-income

countries. The low cost D3 approach, employing distributed global educational resources at the early stage of discovery, is even more attractive in this time of global economic downturn.

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