Photos courtesy of University of Windsor

Left to right: Dr. Sarfraz Ahmad, Dr. Abd Al-Aziz Abu-Saleh, Daniel Meister, Dr. John F.Trant, Dr. Farsheed Shahbazi, Dr. Muhammad Usman Mirza, Dr. Purshotam Sharma, Saeed Velayati

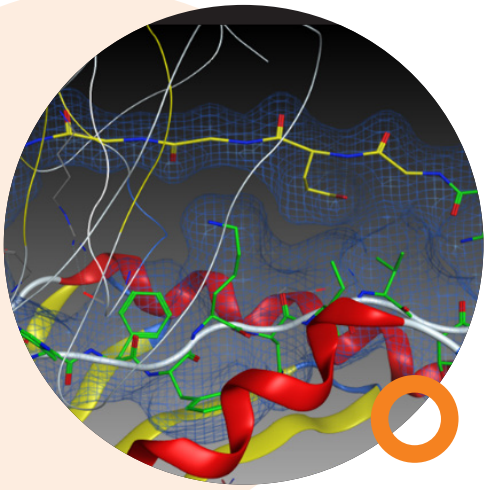
RESEARCH IMPACT

DESIGNING UNNATURAL MOLECULES TO CURE DISEASE

Dr. John Trant, an associate professor at the University of Windsor, works on the cutting edge of medicinal chemistry by designing, making, and testing new drugs. Integral to all of his team's work is computational chemistry, a discipline that, by definition, depends on access to Digital Research Infrastructure (DRI). The Trant Team uses computer simulations to design and test molecules with the goal of solving a diverse array of problems in biomedicine, from investigating the potential therapeutic properties of cannabinoids to attempting to cure celiac disease.

In celiac and other auto-immune diseases, the immune system targets and destroys one of the body's own cells as if it were a virus or bacteria. At the molecular level, this involves an immune receptor binding to a protein. For example, in rheumatoid arthritis, immune receptors bind to a part of the collagen protein, resulting in damage to the fluid that protects the joints. At present, the only way to prevent this is to shut down immune system activity altogether. While this helps to reduce damage to organs and joints, it also greatly increases the patient's risk of serious infection.

Clearly, a targeted approach would be preferable. Scientists are looking for a way to shut down the immune receptors involved in the disease without impacting other receptors in the body. They seek to build a protein-like molecule that would accomplish this goal and effectively cure the disease. The foremost challenge to this strategy is the complex structure of immune receptors which have multiple binding sites of various shapes. This complex structure enables our very few (8 – 12) types of immune receptors to defend us against the thousands of different viruses, bacteria and fungi we might encounter in our day to day lives. Designing a new molecule that can fully bind all sites on an immune receptor is a tall order. To complicate the situation further, some auto-immune diseases can involve as many as 4 or 5 different types of immune receptors. Given the time and expense required to build and test even one new molecule in a lab, it's understandable that progress has been slow.



By contrast, the computational approach is fast and inexpensive. The Trant Team has taken off-the-shelf software and customized it to enable computerized molecule design. Using computer simulations, the team can quickly test hundreds of thousands of molecule designs to weed out the ones that will not work and identify the promising candidates. The team can then make and test a small number of molecules in vitro and in humanized mice (mice whose immune system has been removed and replaced with a human analog), with a greater likelihood of success.

"This would have been impossible even as recently as ten years ago," says Dr. Trant. "Computing speed was too slow, algorithms weren't optimized." Even now, he says, "you could not do this research with a couple of computing clusters on campus." The Trant Team annually uses nearly 4,000 CPU-years of processing power and 1.4 petabytes of storage provided largely by SHARCNET, a consortium of 19 universities and colleges. SHARCNET runs one of the largest high-performance clusters in Canada: Graham, located at the University of Waterloo.