TSRI WINS GRANT FOR ARTIFICIAL IMMUNE SYSTEM

Project to build on earlier DNA work

By Bradley J. Fikes • U-T 5:06 a.m. Sept. 25, 2014

When scientists at The Scripps Research Institute announced in May that they had expanded the genetic code in a living organism by adding artificial DNA, the unprecedented feat was hailed as a potential boon for many consumer uses.

Experts in the thriving field of synthetic biology said the achievement could eventually lead to quicker and broader development of drugs, more-effective vaccines, a multitude of new nano-materials, better forensics work and even more precise ways to detect counterfeiting.

On Wednesday, Scripps Research said it had won a $7.9 million grant to pursue yet another possible application based in part on the earlier breakthrough — creating an artificial immune system to neutralize poisons, combat the effects of chemical warfare and fight diseases beyond what the body's naturally occurring antibodies can tackle.

At the institute's headquarters in La Jolla, professor Floyd Romesberg is leading one arm of the project. In Florida, where Scripps Research has a satellite campus, professor Tom Kodadek and assistant professor Brian Paegel are heading a complementary endeavor.

Their combined pursuits are being funded by the Defense Advanced Research Projects Agency, commonly known as DARPA.

While the concept of an artificial immune system will guide the scientists' efforts, the exact form of their technologies still needs to be determined.

Loosely speaking, Kodadek, Paegel and their fellow researchers in Florida plan to compile an inventory of molecules and tag them with DNA "barcodes" that indicate their distinctive chemical structures.

They also will tap highly sophisticated, automated methods for rapidly screening and synthesizing these molecular compounds.

"We hope to create chemical 'libraries' and screening platforms that are truly revolutionary in their capabilities," Kodadek said in a statement.

The so-called libraries will complement the group's development of ultraminiaturized equipment that can screen more than 200,000 compounds in a matter of hours.

Romesberg and his team will harness their colleagues' newly identified compounds to fashion DNA and RNA fragments — the universal building blocks of life — that possess immunity traits not found in nature.

In May, Romesberg and others had enlarged the four-letter DNA alphabet by adding two synthetic letters and then getting a bacterium to successfully replicate the lengthened DNA strand. Their accomplishment led to formation of the San Diego biotech company Synthorx, which is exploring ways to commercialize various products and technologies resulting from that discovery.

As part of the DARPA-financed project, Romesberg and his team will use the artificial letters to develop synthetic DNA and RNA fragments called oligonucleotides.

Then utilizing a novel approach established by Tingjian Chen, a postdoctoral fellow in Romesberg's lab, they will manipulate these oligonucleotides to make them more heat-resistant, more able to bind to specific parts of targeted molecules and more stable overall.

If the technology works, DNA and RNA could be crafted to precisely identify and neutralize a more-expansive catalog of hazardous microbes and deadly chemicals. Oligonucleotides could even be designed like microprocessors to gather data and analyze it — on a microscopic scale that the best electronic chips can't match.

A spectrum of DNA and RNA oligonucleotides is being made — each different from the others, Romesberg said. Then these fragments will be analyzed for whether they perform their intended functions, such as binding to a particular protein on the surface of a dangerous microbe.

Oligonucleotides deemed to be successful are isolated, modified further if necessary and subjected to another round of testing — a process analogous to natural selection in biological evolution. Romesberg's group has developed a method of molecular evolution that mimics what happens in nature, a process called Systematic Evolution of Ligands by Exponential Enrichment.

It could very well be that oligonucleotides can do things that antibodies can't, said Shane Crotty, a professor in the vaccine discovery division of the La Jolla Institute for Allergy & Immunology.

Antibodies are large molecules in the natural immune system. They can bind to unwanted molecules with accuracy, making them highly useful in creating medications to fight infection or neutralize abnormal cells.

But their size presents a limitation: Antibodies might be too big to access some key parts of a pathogen, for example.

Oligonucleotides are smaller than antibodies, so they can get into areas that antibodies can't reach, Crotty said.

"There could be a very wide spread of applications" for these experimental DNA and RNA fragments, he added.

Major technical obstacles need to be solved to make the overall idea workable, Crotty said. However, DARPA specializes in such "blue sky" projects.

"It's high-risk, but potentially high-reward," Crotty said.