Undergrad researchers lay groundwork for drug addiction remedy

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Sarah Steele and Langtian "Ren" Yuan were both self-admittedly inexperienced Duke freshmen in the spring of 2006. But then they followed helpful directions of an assistant chemistry professor, added their own patience and ingenuity, and ended up identifying compounds that might allay the powerful cravings of methamphetamine and cocaine addiction.

The two women, now seniors, have since moved on to other things. But their earlier accomplishment was recently celebrated by a research paper in a British journal. It also helped bring the professor, Jiyong Hong, a $390,000 stimulus grant from the National Institutes of Health and the American Recovery and Investment Act to do follow-up research.

"I think this is a kind of showcase for something that Duke is very strong in -- undergraduate research," Hong said. "And, socioeconomically, it deals with drugs of abuse that are huge problems."

Hong, whose research group investigates the synthesis of natural products for drug design as well as small molecules' roles in biological processes, got interested in finding small molecules that could inhibit the good feelings induced by meth and coke after reading a 2006 paper in the journal *Science*.

That study implicated a derivative of an enzyme called protein kinase C zeta (abbreviated PKCzeta) in brain chemistry changes involved in memory and learning.

"When people take methamphetamines and cocaine, that gets engraved in their memories," Hong said. "So the hypothesis was that by inhibiting a specific enzyme, in this case PKCzeta, we might be able to delete those memories."

The problem was that researchers had never identified a PKCzeta inhibitor, he added. "PKCzeta is one of the least studied members of the PKC family." In other words, his quest would be like searching for needles in a haystack.

Enter the two undergraduates. Steele, an intended biology major, showed up in Hong's lab to do an independent study tied to a freshman chemistry research seminar class. "I hadn't taken organic chemistry, but he explained everything to me so I was sure of what I was doing," she said.

Following Hong's elaborate instructions, Steele began the task of canvassing about 1,200 different small molecules looking for candidate PKCzeta blockers. "It was repetitive work, but once we learned the concept it was easy to continue," she recalled.

The work involved placing each candidate inhibitor into one of 96 tiny wells on a sample plate, along with PKCzeta and an energy-providing chemical called adenosine triphosphate (ATP), plus a light-emitting enzyme called luciferase.

If a candidate compound was ineffectual, then the ATP in the well would be used by PKCzeta's activity. But if a compound did interfere with the PKCzeta, then the energy of the ATP would instead cause the luciferase to light up. The better the blocking action, the brighter the glow.

Yuan, originally a premed student planning to triple major in biomedical engineering, economics and public policy, had also approached Hong

seeking freshman work as a lab assistant, though not as part of a class.

"Originally I was asked to try to find an inhibitor for something other than PKCzeta," she said. But when Steele entered a different summer research program after the spring semester, "I kind of picked up where Sarah stopped.

"I was doing similar things as she, but really trying to pinpoint which specific compounds worked as inhibitors," Yuan recalled. "We were almost out of molecules to test by then. But, in the last batch, there were a series that were similar that all lit up really well."

The work required lots of transferring chemicals with the aid of a pipette, and then incubating them at different temperatures and at different concentrations. "That was a lot of hours," she said. "I was working almost full time during the summer. But I'm glad it paid off."

Other researchers from Duke's Chemistry Department and Medical Center, as well as a separate group from Korea, filled in gaps in the research. Their results were published online on May 8, 2009 in *Molecular Biosystems,* a journal of the Royal Society of Chemistry. That paper identified several promising PKCzeta blockers for further follow-ups that are now underway.

"I didn't expect to have anything come out of it," said Steele, who was listed as a coauthor. "But it's nice that something good did." Yuan was listed as the paper's first author. "Honestly, I think I got too much credit," she said. "But it was exciting."

Support for the study came from the National Institutes of Health, Duke and Korea's Ministry of Education, Science and Technology.

After her spring with Hong's lab, Steele went on to join another Duke

research program that has been probing the relationship between nerve cells and immunity in roundworms, which led to her co-authoring a paper in the October 17, 2008 issue of the journal *Science*. She followed that up with summer cancer research in her native Tampa, Fla., and is now applying to medical schools.

Meanwhile, Yuan went on another pathway. After creating an experimental computer animation to help psychiatric patients take their medications on time, she dropped her premed plans, her major in biomedical engineering and her minor in political science to concentrate on economics and public policy.

"I would have kept up with all my majors and minors but it was just too stressful," she said. "I was overloading everything, staying up until 3 a.m. every single night." Her parents were "shocked," she acknowledged. "My dad's a doctor, my mom's a nurse and my aunts are all doctors too. It was the biggest decision of my life."

But now she is expecting to be first author on a paper from her public policy internship, "Managing Climate's Impact on Health: Common Ground for U.S. China Collaboration." Yuan has also discovered a liking for economics. With her fluency in Mandarin Chinese, French and English, she's hoping to work as a consultant, perhaps at a think tank.

Source: Duke University (news : web)