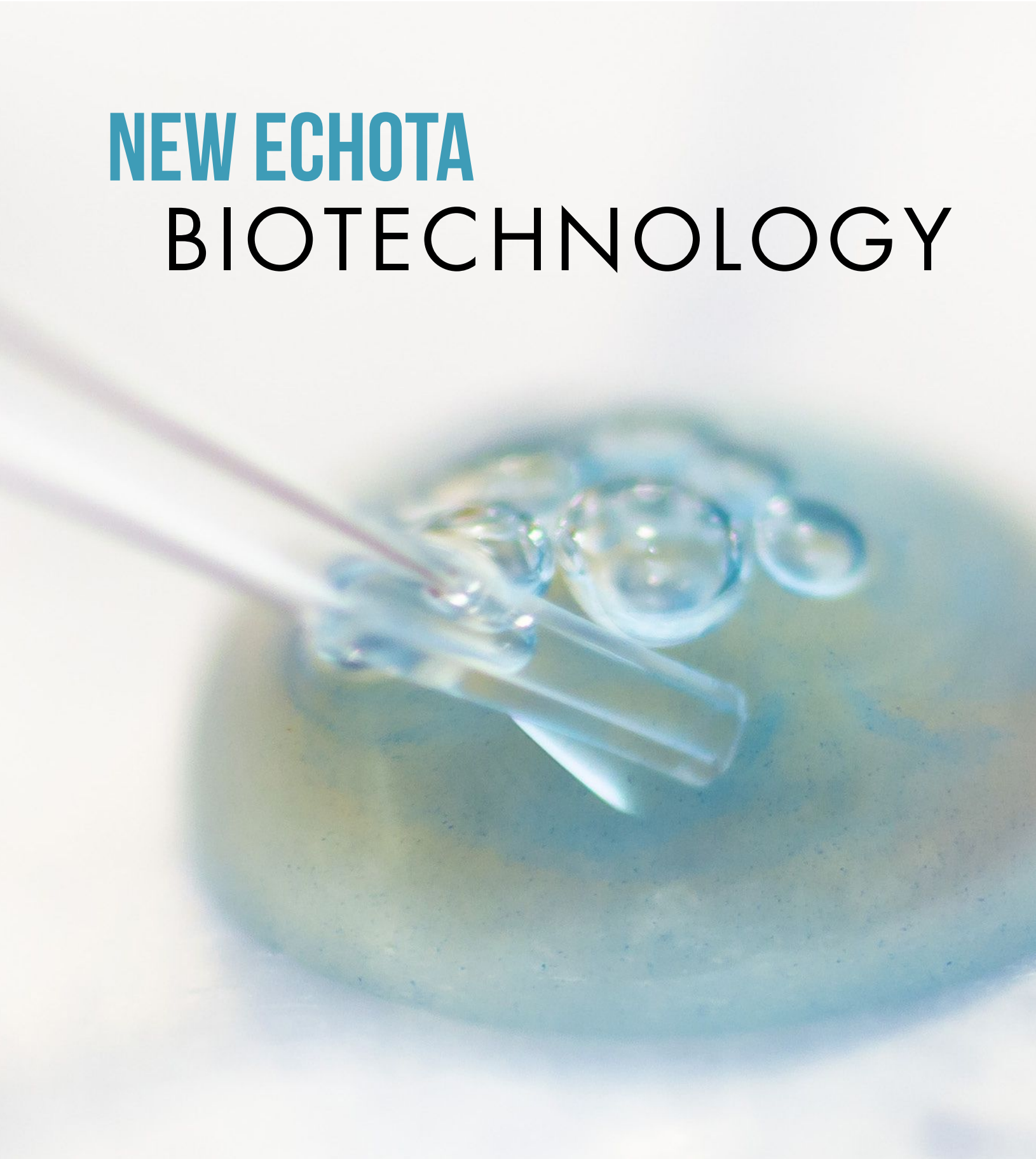
NEW ECHOTA BIOTECHNOLOGY



Paving the way to deliver therapeutics to living cells

By Joëlle Walls

What happened when biophysicist John Salerno and biochemist Jonathan McMurry joined forces at Kennesaw State University to confront challenges associated with combatting cancer and genetic diseases? They founded New Echota Biotechnology, KSU's first incubator company, which is paving the way to deliver edited proteins more effectively into living cells that could rewrite the code in suppressing the propagation of cancer cells or repairing a mutated gene that causes a genetic disease.

McMurry, also associate vice president for research at KSU, recalled how Salerno's impromptu visit to his lab in 2006 shaped the future course of his scientific career. At that time, McMurry had recently been hired as assistant professor in biochemistry, while Salerno, already a veteran researcher, joined KSU as the Neel Distinguished Chair in Biotechnology.

"While setting up my research program, John walked into my lab one day, introduced himself and from that moment on, we started collaborating," said McMurry. "John brought a quantitative focus to my research, and I became an expert on optical biosensing, which is a technique that helped him develop some research he was conducting. We published quite a few papers together as colleagues, but mostly with him in the mentor role."

Another impromptu visit by Salerno, this time to McMurry's office in 2013, put into motion the beginnings of New Echota Biotechnology. McMurry said Salerno's original idea involved manufacturing specialty proteins for other companies that can be difficult to make since they both had experience purifying proteins in their academic labs.

"We had this business model in which we could sell enough of these proteins to generate revenue that would not only benefit the university, but support the development of intellectual property based on one of John's ideas," explained McMurry. "We have yet to sell our first protein, but we have been able to develop the core technology of John's idea – the cell-penetrating peptide adaptor protein."

The name of the company is derived from New Echota, the capital of the Cherokee Nation that was established in 1825 at the headwaters of the Oostanaula River. The logo for the company shows the confluence of the Coosawattee and Conasauga rivers that meet to form the Oostanaula River.

"The confluence of the two rivers also looked like a messenger RNA being translated into a nascent protein chain to John and I to reflect the company's original purpose of protein manufacturing," added McMurry.

While the company's staff scientist worked on potential sales of the specialty protein, McMurry and Salerno focused on writing proposals for Small Business Innovation Research (SBIR) grants, one of the largest sources of federal funding for early-stage capital for technology commercialization in the U.S.

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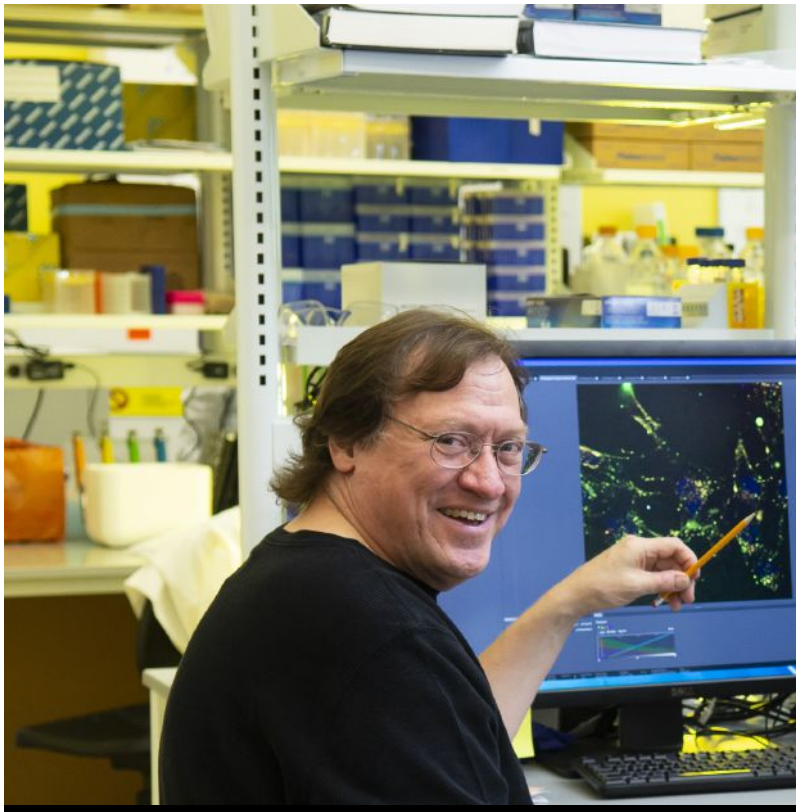


Daniel Morris (left) and Jonathan McMurry are currently licensing the CPP-mediated technology from KSU to develop other ideas.

In 2015, New Echota received its big break – $227,000 from the National Institutes of Health SBIR grant program to develop the novel technologies of intracellular manipulation for research, diagnostic and eventually therapeutic outputs. The Georgia Research Alliance also supported the company through the GRA Ventures program, Georgia's only non-profit catalyst for seeding and shaping companies around research at multiple universities.

Until then, technology delivering cell-penetrating peptides (CPPs) to the inner sanctum of targeted cells was not always successful. The CPPs are short chains of amino acids responsible for facilitating cellular uptake of various molecules such as large fragments of DNA or therapeutic proteins to fight infection. McMurry said the molecular cargoes transported would get trapped with the CPPs in undesired locations of the cell.

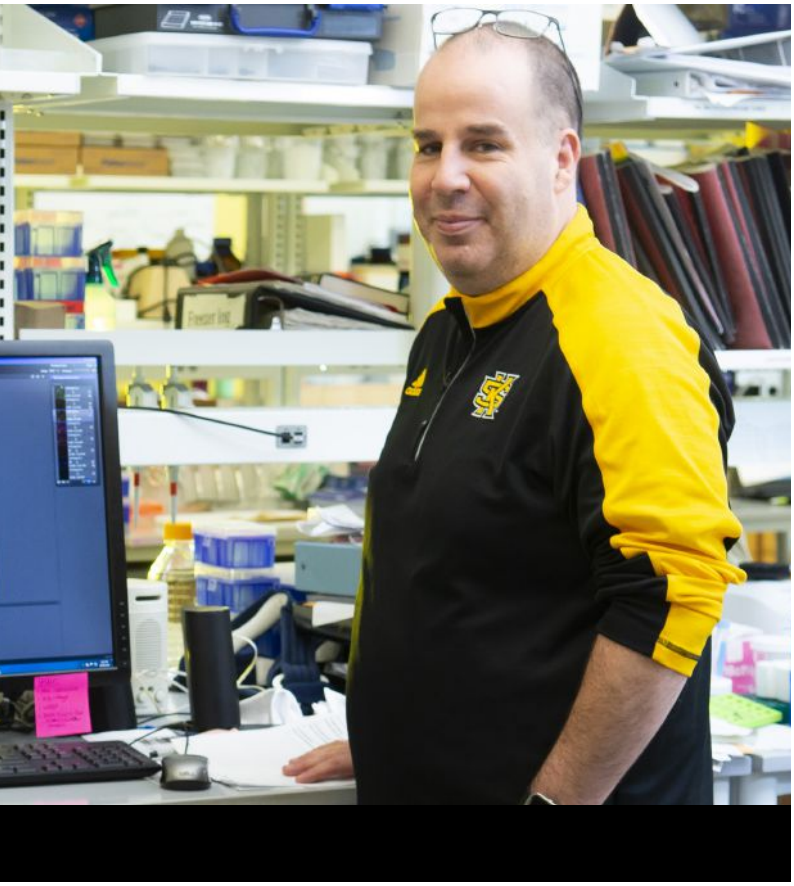
However, Salerno's idea focused on using a CPP adaptor protein which would ensure that the targeted cargo would get delivered to a living cell's core. Unfortunately, before he could see the fruits of his idea become a reality, Salerno passed away in December of 2015.

"We had the grant for about two months before John's passing and so essentially the face of the company became me as CEO and John's estate as co-owner and two employees, a staff scientist and a technician," said McMurry. "In John's memory, we continued to pursue the aims of the grant and were very successful in developing the technology, showing that it works and can be generalizable for other purposes."

"This is the first business I have been a part of, and I still do not know everything about running a business," he said. "I think the stunning difference between academia and industry is that more ideas are acceptable for academic research, while one idea is all you need in industry because to bring a single drug to market now costs about $3 billion."

With McMurry leading a team of KSU faculty and students, including biologist Scott Nowak and chemist Carol Chrestensen, he said that the issue of "getting into a cell but not getting out into a cell" was solved with the novel CPP adaptor protein. McMurry explained that instead of attaching the molecular cargo to a CPP, the cargo would be attached to a CPP adaptor protein created by mixing a viral protein fragment with the human protein Calmodulin.

This CPP adaptor protein, called TAT-CaM, would get taken up by the cell and also be trapped in an undesired location of the cell. However, TAT-CaM would release its cargo of DNA or therapeutic proteins upon entering the cell membrane. Thus the cargo would be efficiently delivered to the requisite location



– the cell's inner core such as the nucleus.

"The Kennesaw State University Research and Service Foundation has supported our patent applications for this technology and others in the works," said McMurry, whose team is currently licensing the CPP-mediated technology from the University to develop other ideas.

One of those ideas is improving the CRISPR/Cas system, a very rudimentary bacterial immune system which allows the bacteria to recognize an invading virus, saving a piece of the viral genome to use in future detection of infections, thereby forming acquired immunity.

"If you purify the system from bacteria and put it in a mammalian cell, you can specifically edit the DNA of a mammalian cell," said McMurry. "Rather than treat diseases such as cystic fibrosis with therapeutics or ameliorating the symptoms, delivering genome editing capabilities using our novel CPP technologies would in fact repair the mutated gene causing cystic fibrosis."

McMurry, along with current employees Daniel Morris, senior research scientist, and Stephane Hill, research associate, are conducting proof of concept experiments to improve gene editing efficiencies using CRISPR/Cas technology. They received another NIH SBIR grant in early August last year to fund this recent project, to include hiring undergraduate students to assist in the research.

"If we can get CPPs to consistently deliver cargo proteins, DNA and RNA, to the correct compartments, essentially all of cellular biology is open to our approach," said Morris. "Indeed, medicine's inability to deliver large macromolecules to the cytoplasm and organelles within cells has been called the major problem in the biomedical sciences. I really enjoy the fact that I am a central element in New Echota Biotechnology's success and not a cog in an enormous pharmaceutical machine."

Morris, also an associate research professor of biology in KSU's Department of Molecular and Cellular Biology, is conducting independent research on the idea thanks to a recent three-year NIH grant. With a Ph.D. in biochemistry and enzymology, he joined New Echota Biotechnology and KSU in 2016.

"With Dan also having a basic science research grant from the NIH fits in well synergistically with what the company is trying to do and what the academic lab is trying to do," said McMurry. "We hope to get a mouse model, which is the typical mammalian model system used, to show our technology works in a living organism, hopefully by the end of the year."

Hill, who started working at New Echota Biotechnology last July, knows McMurry from her KSU days as an undergraduate researcher in his lab. She started out as a chemistry major, but after career advice from McMurry, she changed her field of study and graduated with a bachelor's degree in biochemistry in 2013.

"Working for a small company alongside my undergraduate mentor has been an amazing experience," she said. "I am helping build the company from the ground up and looking forward to watching it grow."

"I am happy that for the rest of my career, I am going to be able to come up with ideas and turn them into reality which is what you do in science – you want to make a discovery," added McMurry. "I love getting up every day and going to the lab and maybe have a one in 10,000 chance of curing cancer, but that is the sort of odds you follow up on in science."