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R&D
REPORT

Gonna Have a Revolution

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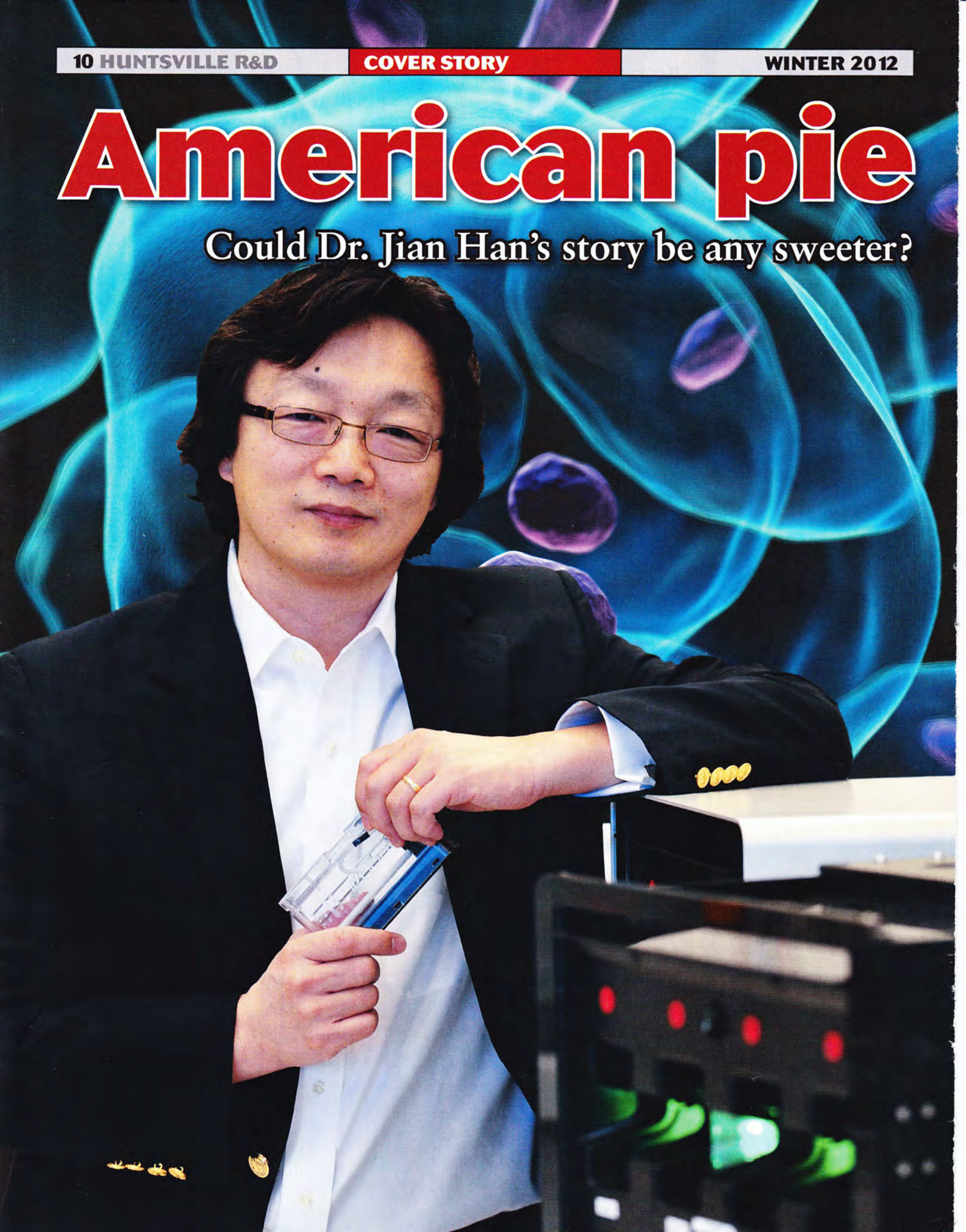
American pie

Could Dr. Jian Han's story be any sweeter?



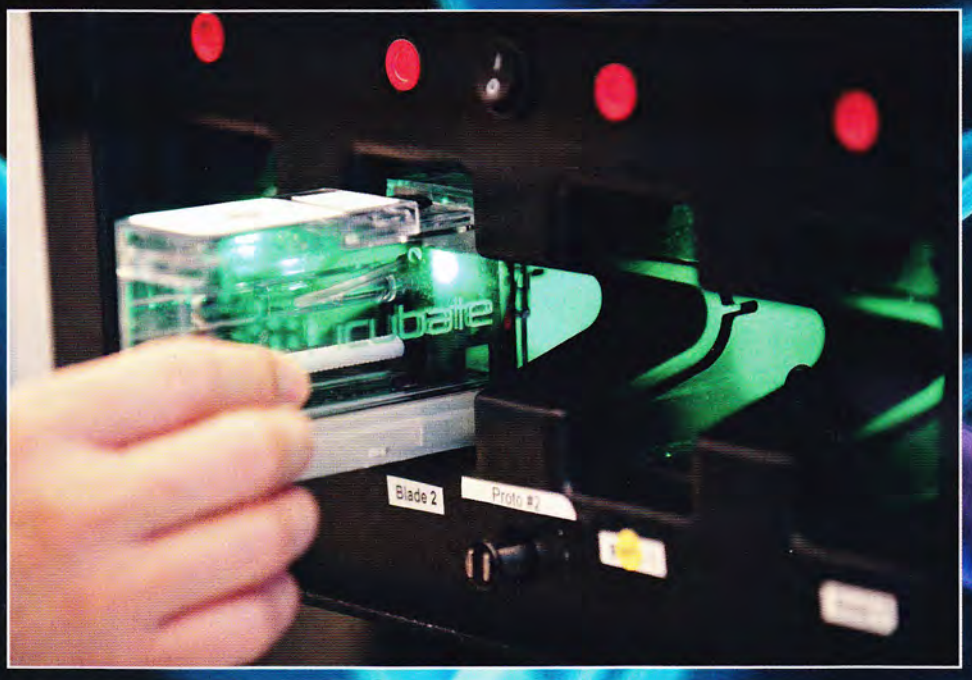
He arrived here with $100 and determination. He took a bite from Job's Apple. He's changing the biological testing paradigm.

By Diana LaChance

Dr. Jian Han, faculty investigator at the HudsonAlpha Institute for Biotechnology, has transformed a labor-intensive, training-reliant and potentially risky research process into a faster, more-efficient system that can be overseen by a single technician. Further, he plans to revolutionize the field of biotechnology Apple-style by opening up future innovations in his new system to researchers worldwide via his for-profit spin-off company. Not bad for a young Chinese man who came to the United States as a college student with just $100 in his pocket.

Han's new iCubate offers researchers a closed, automated system that uses amplicon-rescued multiplex polymerase chain reaction (arm-PCR) technology to make molecular differential diagnoses of infectious diseases. If that sounds complicated, it is. So to understand the iCubate system and how it works, it helps to understand just what PCR is. "Each disease-causing pathogen has its own genetic code, or signal," explains Han. "But trying to find it in a sample is like looking for a needle in a haystack." For example, says Han, imagine a patient with sepsis. To diagnose it on his own, a technician must be able to identify some 20 copies of the pathogen (in this case, a bacteria) among the 20 million other cells in one cubic centimeter of blood. That's no easy feat, so what PCR does is amplify that signal. Han says the technology "Xeroxes it" so that it can be more easily identified by a technician.

However, in the past scientists were only able amplify one unique signal at a time, a process known as singleplex PCR, which made for a tedious diagnostic process at best. "If the test for that one pathogen came back negative, then you had to repeat it to keep looking for answers," says Han. So he began



working on a next-generation multiplex PCR (mPCR), that he called target-enriched multiplex PCR (tem-PCR), to expand the number of targets to between 10 and 30. That increase ended up being especially critical during the SARS outbreak of 2003/2004, when Han was able to develop a respiratory panel to group 20 common bacteria and viruses together to be detected with one test. "It was time-saving, lifesaving and money-saving," says Han. First, it allowed researchers to test for more diseases at one time, rather than "testing for one at a time and then waiting three hours to see the results before testing for the next one." Second, it allowed researchers to diagnose and treat co-infections, which are cases in which a patient has multiple infectious diseases. And third, it allowed researchers to save money, both by reducing the cost per pathogen tested and by avoiding the isolation and quarantine costs associated with an outbreak.

Now consider arm-PCR, the current iteration of mPCR technology and the foundation of the iCubate system. With it, researchers have the ability to amplify a quarter million unique signals in one reaction. But with that advance in capability comes a significant downside: those hundreds of thousands of copies increase the chance for contamination. "If one 'Xeroxed' signal falls into the next patient sample, it can cause a false positive," says Han. To resolve that, "hospitals have to have different rooms for the different steps in the process – amplification in one room, analysis in another, etc. In all, four rooms would be required to do molecular analysis." That's where the iCubate system comes in. It's a closed, automated system that prevents contamination and reduces the amount of time needed to complete the process.

At the system's center is what Han refers to as a cassette. "The cassette is an automated and closed system," says Han. "So to develop something in our cassette means everything can be done in one room, with no special training required and no contamination." He says "the hands-on time needed is one minute to load sample," compared to the current system wherein "the technician has to babysit the sample from the beginning to the end, which could be up to two hours." Once the sample is loaded into the cassette, it in turn is loaded into the iC-Processor, which performs the automated processing of the cassette. After that, the iC-Reader carries out automated data collection from the cassettes and the iC-Report software performs automated data analysis and generates individual reports for each cassette.

That the entire system runs on an Apple iMac computer using an iTunes-like interface is no coincidence, says Han. "Steve Jobs inspired me to care about details, to think about what our customers want even before they know it. That's why our goal was to develop an instrument that wasn't intimidating, but that was easy to use and that 'just worked.'" And like Steve Jobs, Han's vision encompassed not just turning the technology into a product, but also turning the product into a company, the for-profit spin-off iCubate. "I think what we learned from Apple is not just how to care about our customers and develop insanely great products – which is what we hope the iCubate system is – but how to develop also smart business models," says Han.

OPEN PLATFORM

That smart business model, in Han's case, is iCubate 2.0, an on-line open platform more commonly seen in the information technology world. "What iCubate 2.0 is trying to do is to mimic Web 2.0, with user-generated content and an online store," says Han, explaining that while music or application software is the content for the IT industry, diagnostic assays are the content for the biotechnology industry. But as smart as it is, the model is also quite revolutionary for the field, wherein "content in biotechnology is extremely lacking due to the biotechnology tradition of keeping the platform technology closed to one company." So opening it up with iCubate 2.0 is not easy, says Han. "Not only do we need to change practice, we need to have a different

mindset and also solve many technological challenges."

To face this uphill battle, Han looks to business models like those at Google and Facebook. "These companies often give out 'free' products and services to attract users, knowing that once a sizable customer base is established, the company may figure out a way to make money," he says. Thus, with iCubate 2.0, he says, "we want to make things inexpensive and even free – iCubate's iC-Architect software is free, and our R&D cassette is inexpensive – and we don't want to charge up-front licensing fees or back-end royalties, which are biotech industry standard." The same applies to iCubate 2.0's online store, the iC-Store. "Our online store will help distribute content, in the form of assays, that is developed by third-party developers," he says. "And once the content is sold, the developer would get 70 percent of sales," which Han says is also based on the Apple formula.

Han ultimately hopes this open model will bring content and end-users together more quickly and more directly, much like apps have done for iPhone users; that's also uncommon in the biotechnology industry given the amount of time it typically takes for a product in the field to get FDA approval. "The FDA requires a longer lead process, but with the open platform, researchers can work on content now, using our equipment, for purposes that don't need FDA approval," says Han. As an example, he points to a local professor who used the technology to identify plant DNA and ended up getting a grant from USDA to detect invasive plants at ports of entry. "And you can do the same thing with food safety or bioterrorism – with many things other than diseases," says Han. "Any group of genes that need to be detected for any reason, this is a platform that can be used."

Indeed, Han himself is already using the platform for yet another ambitious endeavor; he recently started another for-profit spin-off company called iRepertoire. "iRepertoire uses the same arm-PCR technology, but focuses on the immune system," he says. "It will enable us to us to look into a person's immune system to see if a specific disease is already present and, if so, to detect it early." That process of sequencing the immune repertoire goes hand-in-hand with a project that is close to Han's heart, R10K, an international non-profit collaboration to sequence the immune repertoire of 10,000 samples representing 100 diseases. "We will provide the technology to researchers worldwide and they amplify the immune repertoire on their side," says Han. "Then they will send us the amplified DNA sample so that we can sequence the immune repertoire using HudsonAlpha's high-throughput sequencing lab." The results of the project, he says, will allow doctors to "read into a patient's 'log book' of what diseases they had before, what they have now, and what drugs can be used to improve their outcome."

It's the type of revolutionary, long-range vision of which Steve Jobs would be proud. But unlike Steve Jobs, who was sometimes seen as egocentric and not much of a team player, Han acknowledges the considerable support he's received along the way, particularly from HudsonAlpha founder Jim Hudson. "Jim really taught me a lot about how to start a business and about how to run a business," Han says, recalling Hudson's investment in his first company, Genaco. Hudson was also instrumental in Han joining HudsonAlpha after Genaco's acquisition, and in encouraging Han to focus on meeting user needs via the end product rather than becoming bogged down in writing and publishing basic research. "From the beginning," says Han, "we were instructed as investigators to do product development, to collaborate, and to file patents so that we could speed up the process and develop something that could be used quickly." By bringing the iCubate system to researchers across the globe, Han has done so. ■