

## Kirk, to boldly go into synthetic biology

Synthetic biology company Intrexon Corp. led by Randal J. Kirk has been scooping up biotechs with a broad range of applications—from apples to art with microbes. In September the Germantown, Maryland-based company acquired genetically modified (GM) insect developer Oxitec, based in Milton Park, UK (*Nat. Biotechnol.* **33**, 792–793, 2015). Earlier this year Intrexon picked up GM nonbrowning apples (*Nature Biotechnology* **33**, 12–13, 2015) and another firm producing swine models for therapeutic research (Table 1). The sums paid for these companies are not large—usually in the tens of millions of dollars. But some of the purchases, such as the majority stake in GM salmon developer AquaBounty, of Maynard, Massachusetts, have left many people in the biotech business wondering where this unconventional company is headed.

Intrexon takes its direction from CEO and majority shareholder Randal J. Kirk, a billionaire. The country-lawyer-turned-entrepreneur made his fortune in part by running and then selling psychiatric drug makers New River Pharmaceuticals, which sold in 2007 for \$2.6 billion; and Clinical Data, which sold in 2011 for \$1.2 billion. Kirk's investment company, Third Security, has pumped about \$400 million since 2005 into Intrexon, which went public in 2013.

Emily Waltz talked with Kirk about his esoteric strategy for Intrexon.



Randal J. Kirk, Intrexon's chairman and CEO

**Aquabounty, the maker of GM salmon, is another curious choice for Intrexon. It is embroiled in public controversy, and approval of its salmon has been under scrutiny by the US Food and Drug Administration (FDA) for two decades. Intrexon saved them from collapse by buying a controlling stake. Why?**

Unlike row crops, salmon has never been engineered by humans, so the opportunities for productivity improvements are simply huge.

**What about the sociopolitical obstacles?**

I get the concerns that underlie anti-GMO activity. Humans have always been technophobic. In mythology, our fire bringer was derided by his peers as being a trouble maker for having brought us fire. That is because technology disrupts the status quo, which results in winners and losers. How do we overcome the concerns of biotech opponents? We overcome them through delivering genuine value to people in something that they recognize. I genuinely believe that the salmon will be approved by the FDA. Besides, intelligent adoption of technological answers to food issues is not optional. At

**Jim Cramer on CNBC's Mad Money recently described Intrexon as a divisive stock, meaning that investing in your company comes down to trust: those who are bullish believe in you, personally, whereas bears say this is a cult of personality built around your past successes. Is that a fair assessment?**

That's not how I view it. I think the odds of success for many fields involving the engineering of biology are one over one. Can Intrexon competently execute its industrial mission within this field of inevitability? I think the probability of that would be quite high. And that has nothing to do with me. It just has to do with the poignant moment in time that we're in.

**What do you consider the core of your business? I understand that you have a library of genetic elements—promoters, regulatory components—that you are assembling into gene constructs with the help of bioinformatics and algorithms.**

Yes, we have generated over a million genetic components, which we have divided into 40 component classes, of which 5 are effector and 35 are regulatory. We were founded on an appreciation that it should be possible to construct numerous species within each component class and to do so in a hierarchical way. This gave us the ability to generate a significant number of novel components and invent components that are not wild type, annotate their performance and in a variety of genomic contexts and variety of cells of interest. We're not just synthesizing DNA, we're synthesizing everything that contributes to engineered biology. And now we offer the whole package: computational biology systems, bioinformatics, whole genome engineering.

**Let's talk about your acquisitions. The scope of the technologies you have amassed this year alone is pretty broad. Is there a cohesive strategy here?**

The outside perception is that the scope is broad, but that is not how they are viewed internally. Our genome editing team—they don't really care whether they're working on an avocado or a primary human T cell. We run the company in a matrix-management structure, meaning we think of the operating units, such as the genome editing team, as divisions. Then trans-axial to that are the sectors—health, food, energy, consumer and environment—where our technologies are productized. Ultimately, our vision is to contribute to the industrialization of biology by bringing products to the market that improve the world.

**In August, you acquired Oxitec, which is genetically modifying agricultural pests and disease-carrying mosquitos. Where does it fit with Intrexon's strategy?**

The world clearly cries out for environmental solutions, and we view Oxitec as a tremendous opportunity to contribute in that way.

**Oxitec's technology is neat, but how is Intrexon equipped to move those insects from field trials through regulatory processes on different continents, and then through the logistics of commercialization?**

I would be an arrogant fool if I were to suggest to you that we have some sort of secret sauce that would address your question. We do not. So why try? Doing something no one has done before represents challenges but also sometimes provides enormous opportunities. With Oxitec, it's going to take real determination. We're going to have to invent some business models.

**Table 1** Intrexon (XON) acquisitions 2013 to present

Acquisition announcement	Company acquired	Technology	Application	Deal structure
August 10, 2015	Oxitec (Milton Park, UK)	Genetically modified (GM) autocidal agricultural pests and mosquitos aimed at reducing their wild counterpart populations that damage crops and transmit disease	Agriculture and insects	Oxitec shareholders received ~\$80 million in Intrexon stock and \$80 million in cash.
February 27, 2015	Okanagan Specialty Fruits (Summerland, British Columbia, Canada)	Apples modified to resist browning. Engineered with a transgene that produces RNAs to silence the expression of four polyphenol oxidase genes	Agriculture and food	Okanagan shareholders received \$31 million in Intrexon stock and \$10 million in cash.
February 13, 2015	ActoGeniX (Ghent, Belgium)	GM food-grade microbes to deliver therapeutics to the gastrointestinal tract. Clinical-stage candidates AGO13 delivers a therapeutic peptide for preventing and attenuating oral mucositis, and AGO14 secretes anti-TNF- $\alpha$ Fab to treat inflammatory bowel disease.	Microbes as delivery for human therapeutics	ActoGeniX stockholders received \$39.7 million in cash and \$40 million in Intrexon stock.
January 26, 2015	Exemplar Genetics (Sioux Center, Iowa)	Transgenic swine models of human disease for research in heart disease cancer, cystic fibrosis and other disorders	Animal models and human therapeutics	Exemplar Genetics is a majority-owned subsidiary of Trans Ova, which Intrexon acquired in 2014. Intrexon acquired the remaining stake in Exemplar for \$1.6 million in cash and \$12.5 million in Intrexon stock
July 1, 2014	Trans Ova Genetics (Sioux Center, Iowa)	Bovine reproductive technologies: supplies bovine embryos and conducts embryo transfer and <i>in vitro</i> fertilization in cows	Animal health and productivity	Trans Ova received \$63.6 million in cash, \$32.8 million in stock and \$20.1 million in deferred payments.
December 20, 2013	Medistem (San Diego)	Endometrial regenerative cells utilized as therapies for cancer, inflammation and orphan diseases	Human therapeutics	Medistem shareholders received \$19.4 million in Intrexon stock and \$4.9 million in cash.
October 2, 2013	Yonder Biology (Carlsbad, California)	"Living arts" products in the fields of fine and decorative arts, accessories, toys and novelties	Art	Intrexon acquired a 51% stake in Yonder Biology for \$1.3 million and renamed it Biological & Popular Culture (BioPop).
2012–2015	Aquabounty (Maynard, Massachusetts)	GM salmon with improved growth rates	Aquaculture and food	Intrexon paid ~\$23.9 million over the course of four transactions to acquire 63% of Aquabounty common shares.

the present rate of marine extraction, your children are going to know fish to be a luxury good, and their children will know them to be nonexistent.

**You have made a lot of people wealthy through your past successes, which include the sale of New River Pharmaceuticals and Clinical Data. People say a lot of investors follow you because they think you can do it again.**

I can't take any credit for the success of New River's Vyvanse [lisdexamfetamine]. Same with Clinical Data. I positioned it from 2004 on as a pharmacogenomics company, and we just got the timing wrong. ViiBryd [vilazodone]—a drug we led the development of—was supposed to be accompanied by a diagnostic, but it turned out we didn't need it for FDA approval. My point is that I don't deserve any credit for programs that have

succeeded in the past. But I may deserve some credibility by virtue of the fact that people know I'm going to be honest and candid.

**"We plan to start ten companies a year and take stock in each one."**

**Your collaborators often pay to access Intrexon's technologies with shares in their companies rather than cash. Why do you structure your deals that way?**

Originally because the only people who were intrepid enough to do business with us were tiny companies, and we wanted them to focus their cash on product development. When we started doing larger deals, those were structured often in cash. But then our team didn't really want to do the smaller

partnerships anymore. So we contracted with an investment bank to create a venture capital fund dedicated to these opportunities. Instead of dealing with each of these ten companies individually, our team can just deal with the fund managers until these companies become more significant. We plan to start ten companies a year and take stock in each one.

**What's up with the owl in the photograph?**

This Eurasian Eagle Owl was my all-time favorite bird and he died by poisoning when he consumed a wild rodent that we believe had eaten rodenticide. That demonstrated for me the importance of technologies such as that of Oxitec, and the need for targeted vector control that pesticides can't offer. Plus, I like falconry. It is thrilling to enjoy a relationship of mutual respect with a wild animal.

**Emily Waltz**