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ARRAKIS THERAPEUTICS

Targeting RNA with small-molecule drugs

By Ryan Cross

If you've only ever seen RNA pictured in an introductory biology textbook, you could be forgiven for thinking it would make a pretty bad target for small-molecule drugs. In contrast to structurally complex proteins, which feature nooks and crannies for drugs to bind, RNA is a floppy, noodlelike strand of genetic code that at first glance doesn't offer any stable structures for drug docking.

Yet if small molecules could target specific RNA strands, a vast new continent ripe for drug discovery would be opened. Of the over 20,000 human proteins, only about 15% are believed to be accessible by small molecules. Since messenger RNA (mRNA) is the chemical courier between a cell's DNA script and its protein actors, an mRNA-binding drug should be able to halt production of proteins, including the ones out of reach via traditional chemistries.

When Michael Gilman first heard about a biotech start-up pursuing this idea, he was dumbstruck. After shaking off his initial disbelief, he thought, "Wow, if you could figure out how to do that, it would be really great."

AT A GLANCE

Launched: 2015

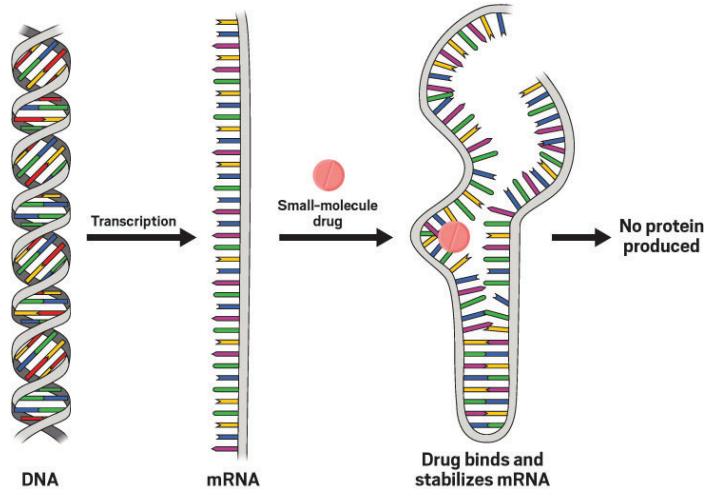
Headquarters: Waltham, Mass.

Focus: Drug discovery

Technology: Small-molecule drugs that bind RNA

Founder: Russell Petter

Funding or notable partners: $38 million from investors including Canaan Partners, Advent Life Sciences, Pfizer, and Celgene



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RNA smackdown

Most small-molecule drugs target proteins, but Arrakis is designing compounds that bind RNA molecules. Those that bind mRNA—the genetic precursor to proteins—could prevent cells from producing disease-causing proteins that are difficult to drug themselves.

Gilman is now CEO of that start-up, Waltham, Mass.-based Arrakis Therapeutics, which was founded in September 2015 by Russell Petter, former vice president of chemistry at Celgene and now chief scientific officer for Arrakis.

“It’s a bit like getting the band back together again,” says Gilman, who previously worked at Biogen along with Petter and Arrakis Chief Business Officer Daniel Koerwer in the late ’90s through mid-2000s.

Gilman has already helmed two successful start-ups: Stromedix, acquired by Biogen in 2012, and autoimmune-focused Padlock Therapeutics (**featured in C&EN’s 10 Start-Ups to Watch in 2015**), **acquired by Bristol-Myers Squibb** in 2016. This February, he helped rake in a **$38 million series A** funding round for Arrakis.

Many companies have tried targeting RNA in the past decade using techniques based on RNA interference, or RNAi, in which a strand of RNA binds to and helps eliminate a complementary strand in the body. It’s been difficult to get the technique to work well in humans, however, except for one recent success in treating liver disease.

Arrakis is attempting to block RNA with the same chemistries used in protein-binding drugs. Gilman thinks that’s possible because contrary to oversimplified illustrations, RNA is more intricate than a simple strand; it twists and folds around itself into structures that present promising binding spots for drugs. Gilman doesn’t expect all RNA molecules to selectively bind a drug, but he says that Arrakis wants to “find small molecules that stabilize one of these transient, dynamic structures of RNA and essentially lock it down.” The small molecule would thus prevent an mRNA from forming a protein or inhibit a noncoding RNA that controls gene expression.

“People will always ask, ‘Why haven’t we found selective RNA-binding compounds in the past?’ ” Petter says. “Well, you actually have to look.”

Koerwer says Arrakis hopes to make a name for itself by doing that searching. Arrakis has one disclosed program: targeting mRNA for huntingtin, which is the protein associated with Huntington’s disease. After that, Arrakis isn’t committing to any particular diseases. Instead, the company will “screen as many libraries as we can against hundreds and hundreds of targets, and then choose from that data set,” Koerwer says.

If Arrakis can find selective small molecules that bind RNA and demonstrate a biological effect, Petter anticipates the firm will run drug development and clinical trials just like any other pharma company. “Our ambition is for the drugs to be painfully boring” compounds that can be packaged in pills and easily reach their targets in the body, Petter says.

Still, Arrakis must first demonstrate that it can be done. “This is going to be hard,” Gilman says. “But hard doesn’t scare me; that was actually part of the attraction.”