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PRODUCT R&D

RNA, MEET SMALL MOLECULES

By Lauren Martz, Senior Writer

Arrakis Therapeutics Inc.'s unveiling this week marks another notch for RNA, this time not as a modality to treat disease but as a route to expanding the world of druggable targets for small molecules by more than an order of magnitude. The company believes the goal of using small molecules to target RNA, once considered impossible by medicinal chemists, is now close enough in reach to create a viable platform and sustainable pipeline.

On Monday, Arrakis announced the closing of a \$38 million series A round led by [Canaan Partners](#), and the appointment of industry veteran Michael Gilman as its chairman and CEO. The company intends to develop therapies for cancer, CNS diseases and rare genetic conditions.

Most approaches to developing therapeutics against RNA employ antisense oligos or RNAi.

However Gilman, who previously founded [Padlock Therapeutics Inc.](#) and [Stromedix Inc.](#), believes RNA-binding small molecules represent a coveted therapeutic class that opens up a pantheon of new possibilities for traditional drug development.

"The infrastructure in our industry, physical and intellectual, has been relentlessly focused on targeting proteins with small molecules. That's what we do and we're really good at it, but we're starting to run out of targets because only certain kinds of proteins are readily targetable by small molecules," Gilman told BioCentury.

Proteins need well-defined binding sites like the catalytic domains of enzymes or the ligand binding domains of receptors to be good targets for small molecules. Gilman estimates that only about 3,000 proteins fall into that category, leaving behind about 20,000 others.

According to co-founder and CSO Russell Petter, those 20,000 correspond to up to 44,000 mRNA transcripts. However, the number of total RNA targets is much higher, because there are manifold other forms of RNA — such as long noncoding RNA (lncRNA), microRNA and other small noncoding RNAs (sncRNAs) — which put the universe of targets in the realm of 200,000.

Gilman sees the opportunity to redraw the boundary between what's druggable and what isn't by rethinking what

kinds of RNA structures can bind small molecules, rather than by turning to different modalities or new formulations.

A few small molecules are known to bind RNA; examples include antibiotics like tetracycline that bind ribosomal RNA and [SMN2](#) splice modulators that bind the gene's pre-mRNA

But according to Gilman, most were found by serendipity and RNA has been off the map for most drug developers because it doesn't follow the same behavior as proteins.

"This may seem like a pioneering idea today, but I have a feeling that five years from now, targeting RNA will be a big deal."

Michael Gilman, Arrakis

"I think people just haven't looked very hard because of the view that the structure of RNA is very different than the structure of proteins," said Gilman.

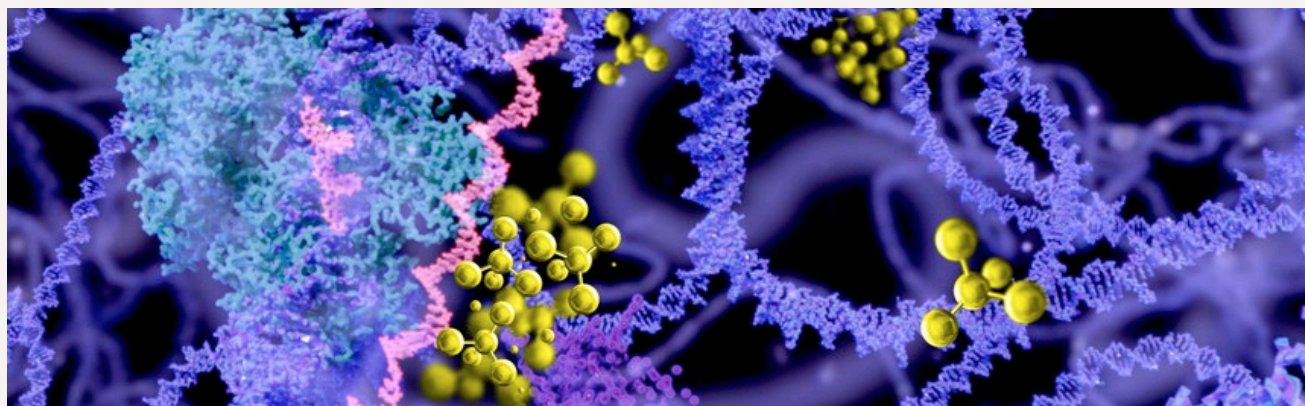
Compared with proteins, RNA has a highly dynamic and poorly defined structure at the tertiary level.

But while others view the dynamic structure as a challenge, Gilman and Petter think it is actually a feature drug developers can exploit.

"Our view is that RNA's dynamics are a feature rather than a bug. If dynamics are part of RNA's function, we need to figure out how to impact them to alter function," said Petter.

Arrakis believes it can alter those dynamics by using small molecules to lock mRNA in one of its many conformations.

"mRNA, which has a highly dynamic structure that changes configurations rapidly, does need to become linear at some point to allow the ribosome to read through. If you think of those different structures, you could trap the molecule into any one of the configurations, making it incompatible for



translation. If you can do that you've essentially inactivated the gene," said Gilman.

Conversely, small molecules could be designed to activate RNA by binding sites that stabilize the structure in such a way that prevents its degradation, for example.

"So for RNA, you don't have one active site, but you may have a zillion allosteric sites," he said.

Arrakis plans to build its pipeline by re-gearing a small molecule drug discovery platform to find RNA targets, using the company's TRYST and PEARL-seq platforms. TRYST uses bioinformatics to identify druggable structures from the primary sequence of RNA, whereas PEARL-seq contains chemical biology tools to validate that a hit binds the target of interest, without binding anywhere else.

TWEAKING THE TOOLKIT

Since founding the company in 2015, Petter has been training TRYST and PEARL-seq to "think" RNA instead of proteins.

Arrakis designed the platforms to address two principal differences between RNA and proteins: the types of druggable sites, and the requirements for specificity and selectivity.

TRYST is designed to identify possible sites within an RNA target for a small molecule to bind.

With information about "what druggable sites on RNA ought to look like and the best way to interfere at those sites," TRYST's algorithm picks out viable targets in RNA sequences, said Gilman.

That information can then be used to isolate small molecules from chemical libraries using screening systems already in place for protein-based discovery.

Gilman is confident that hits can be found within existing compound libraries, but expects the company will identify scaffolds frequently involved in RNA binding, from which it can build its own library.

The PEARL-seq system can then validate the lead molecules. "This platform allows us to take a compound, go into cells and fish out the RNAs that bind it. We can then deconvolute the RNA by deep sequencing everything that comes out," said Gilman.

"Selectivity is the great unknown here, and one that has dissuaded people from trying to develop these kinds of molecules before."

Michael Gilman, Arrakis

He told BioCentury that the purpose of this step is twofold: to be sure the molecule binds RNA within the cell in the same way that it binds in a test tube, and to map any off-target activity. He added that within the cell, different conditions exist and RNA may be complexed with binding proteins, which shifts its structure.

"Selectivity is the great unknown here, and one that has dissuaded people from trying to develop these kinds of molecules before." PEARL-seq helps answer the question of whether it is even possible to generate a molecule that hits

“Our view is that RNA’s dynamics are a feature rather than a bug. If dynamics are part of RNA’s function, we need to figure out how to impact them to alter function.”

Russell Petter, Arrakis

“one and only one RNA, and completely ignores the tens of thousands of others,” said Gilman.

Thus far, Arrakis has identified a few hits against an undisclosed target based on structural and functional information available in the literature. Although that screen was performed without TRYST, the company believes it provides important support for its concept.

“We’re excited about those hits because they validate our idea that RNA binders are out there in our existing libraries, we just have to go look for them,” said Gilman.

The company plans to develop clinical candidates based on the hits, but is not releasing any timelines.

TAPPING TARGETS

Arrakis’ founders selected the company’s therapeutic areas based on biology that lends itself logically to RNA targets, and on the competitive landscape for other modalities targeting RNA.

For cancer, Gilman pointed to [MYC](#) and Ras as examples of good targets because at a protein level they have been notoriously difficult to drug. “Those were nailed down as human oncogenes 30 years ago, yet we still can’t go after them. There are lots of ‘if only’ targets for these indications. ‘If only’ we could figure out how to target them, they’d have a great impact,” said Gilman.

For CNS disorders, triplet RNA repeats — found in diseases like amyotrophic lateral sclerosis, Huntington’s disease (HD) and myotonic dystrophy — make sense because the repeated triplet codons are themselves pathogenic, and the disease-specific RNA has a different structure from the

wild-type RNA. That could make them tractable targets for small molecules.

Finding where small molecules have advantages over other modalities is also a factor in choosing indications, said Gilman.

“It doesn’t make sense to go after targets in the liver where RNAi does a good job,” he said. But RNAi can’t easily access the brain, whereas small molecules often can. Similarly for cancer, small molecules can penetrate the tumor microenvironment more easily than large molecules.

YOUR MOVE

While Arrakis is one of the first companies to develop a small molecule platform for targeting RNAs, and Gilman hopes to capitalize on its first-mover advantage, he expects many others to move into the field in the near future.

Already, there are a few companies developing research methods to determine RNA structures, which could ultimately be used to develop small molecule binders.

However, Petter said that the competitors are pursuing RNA-oriented strategies, which he believes will be less successful than Arrakis’ approach of adapting a protein-oriented strategy to fit RNA.

“Other companies are technique-oriented. I don’t believe you need special techniques to screen RNA. I believe the existing technology will do just fine,” he told BioCentury.

For example, [Nymirum Inc.](#) is a nuclear magnetic resonance (NMR) company that offers a service to solve high-resolution 3-D structures of RNA. The company also offers a service that provides small molecules and scaffolds for RNA targets.

Ribometrix LLC was founded in 2014 based on the work of Kevin Weeks, a professor at the [University of North Carolina at Chapel Hill](#) who has been developing small molecules that target RNA. Ribometrix was unavailable for comment in time for publication.

Gilman told BioCentury that Arrakis received a lot of interest from pharmas when the company was raising funds. [Pfizer Inc.](#) and [Celgene Corp.](#) are among the company's new investors announced this week.

"This may seem like a pioneering idea today, but I have a feeling that five years from now, targeting RNA will be a big deal," said Gilman.

Arrakis has filed patent applications covering both platforms. █

COMPANIES AND INSTITUTIONS MENTIONED

Arrakis Therapeutics Inc., Waltham, Mass.

Celgene Corp. (NASDAQ:CELG), Summit, N.J.

Nymirum Inc., Ann Arbor, Mich.

Pfizer Inc. (NYSE:PFE), New York, N.Y.

Ribometrix LLC, Greenville, N.C.

University of North Carolina at Chapel Hill, Chapel Hill, N.C.

TARGETS AND COMPOUNDS

MYC (c-Myc) - v-myc myelocytomatosis viral oncogene homolog

SMN2 - Survival of motor neuron 2 centromeric

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