STORM Therapeutics
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Attacking diseases by inhibiting RNA modification

STORM Therapeutics is looking to harness the power of RNA epigenetics by honing in on the modulation of RNA-modifying enzymes.

The majority of drug targets are proteins, but more than 90% of the output of the human genome is RNA that does not encode proteins. Noncoding RNAs have been shown to regulate biological processes, including transcription, stability of mRNA and translation of protein-coding genes as well as the development of cancer. Not surprisingly, modification of RNA, one of the hottest areas in biology at the moment, is fuelling interest as a potential target for novel treatments.

Ground-breaking science focused on the role of noncoding RNAs, including microRNAs, in the pathology of cancer and other diseases, emerging from the laboratories of Tony Kouzarides and Eric Miska at the University of Cambridge's Gurdon Institute, is underpinning the biotech startup STORM Therapeutics. Spun out in 2016, STORM has, to date, raised £12 million in a series A venture round from Touchstone Innovations, Cambridge Innovation Capital, Merck Ventures and Pfizer Venture Investments.

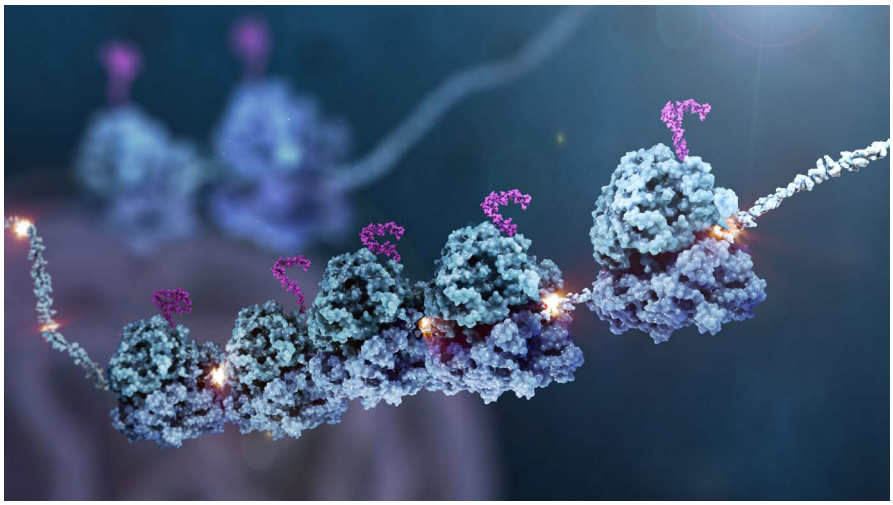

Figure 1: Messenger RNAs harbouring modifications. Modifications such as methylation (shown in gold) can enhance translation to protein and drive disease progression (including in cancer).

RNA-modifying enzymes

Kouzarides and Miska, and their research teams, have identified RNA-modifying enzymes that catalyze a diverse range of epigenetic modifications of RNA. "The founder labs have discovered a number of enzymes that modify RNA and linked them to human disease," explained co-founding scientist Miska (**Fig. 1**).

"There are a number of enzymes that are critical for RNA function, and that is why targeting RNA modification opens up, in an unprecedented way, the whole RNA space as a new drug discovery target. There are more than 100 different modifications in humans, and there are at least 100 RNA-modifying enzymes—1% of all coding genes in the human genome are dedicated to modifying RNA. This area is therapeutically completely untapped, and we are looking to identify small-molecule inhibitors and develop them into drug-like molecules," he added.

Key to achieving this goal is the creation of a toolbox in which the founding scientists with the team at STORM have many of the enzymes and corresponding assays at hand and are able to track the modifications using RNA mass spectrometry. "There are probably only three or four academic laboratories that can measure RNA modifications, so as a company, we have an amazing capability," he noted.

"We have assembled a toolbox that should be attractive to anyone who wants to get into the field of RNA-modifying enzymes from a drug discovery perspective," noted Keith Blundy, STORM's CEO. More importantly, the relationship between STORM and the founding scientists will continue to evolve and be crucial to the company's future development.

"We are working very closely with the two founder labs to discover new targets. There are regular meetings at multiple levels, there are materials exchanges, and joint experiments are planned. It is very interactive. We have all these enzymes and assays for them, but apart from our core portfolio of projects, we don't quite yet know a clear disease association, know exactly which RNA they are modifying and how that links to a particular disease phenotype. That is what Eric and Tony will help us with," Blundy added.

By modulating RNA, Blundy argued that STORM's approach places it closer to the top of the regulatory cascades than drugs that are targeting proteins that are at the end of the effect chain. The company is working on two undisclosed enzyme classes and have plans to develop expertise in a third one. While the company would expect to see stand-alone activity in defined tumor genotypes, it is likely that any resulting compounds would end up in combinations with immune checkpoint inhibitors or other agents.

Early partnering approach

"We are open to getting into partnerships with pharma and biotech as early as possible. We have got the ability to prosecute our own discovery programs but are willing to do so on a risk-sharing basis. I think the way to build a successful company is not just to sit there with your financing and do everything on your own—you have to build some core assets that you do not partner, but I would also rather have more shots on goal through partnering additional programs with other pharma and biotechs because there is a lot more opportunity in this space than we can handle on our own," Blundy explained.

Despite only being created last year, the company already has preclinical drug discovery programs ranging from assay development and high-throughput screening to early lead optimization. STORM has chemical matter that it is moving forward and expects to see cellular activity within the next nine months. "By then, we will have proved that RNA-modulating enzymes are chemically tractable to inhibition with small molecules," predicted Blundy.

In addition to cancer, which is the main focus area for STORM, there are also implications for other indications, including metabolic and neurodegenerative diseases. "There is a lot of this noncoding RNA that has been implicated in disease etiology. Unfortunately, the challenge, to date, has been how to target it, and that is why recognizing these RNA modifications is such an exciting new opportunity," noted Miska.

"We have an initial focus in oncology, but should one of these targets pop out and have a clear clinical association in other disease areas, we would try and find a way to progress that," added Blundy.

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