https://doi.org/10.1038/s41587-024-02423-9

EDITOR'S PICK: SWITCH THERAPEUTICS

Each year, *Nature Biotechnology* highlights companies that have received sizeable early-stage funding in the previous year. Switch Therapeutics is rethinking cell-type specificity, building precision RNAi therapeutics for the brain. **By Iris Marchal**

Small interfering RNA (siRNA) drugs, which trigger RNA interference (RNAi), have emerged as a promising class of medicine capable of silencing the expression of a disease-related gene inside a cell. Getting them into the right cells, however, has proven challenging, limiting their use to treating diseases of specific organs. This has left a vast space of potential targets unexplored, with most efforts to reach these targets focused on developing new delivery systems to help siRNA drugs reach the right organs. Switch Therapeutics wants to open new target space via a different approach, by building a molecular 'switch' into siRNA drugs such that they can turn on their activity after delivery and only in desired cells.

Dee Datta, CEO and co-founder, Switch Therapeutics.

Limiting gene silencing to specific cells, such as only those affected by a disease, could reduce the risk of off-target effects and improve therapeutic outcomes. It took years of collaborative research between Switch's co-founders at Caltech, City of Hope and Harvard to develop their initial idea into a technology. Dee Datta, CEO and co-founder of Switch Therapeutics, says, "Ultimately, these three institutes generated convincing data around this platform, and it was time to think about how to take this to the next level." Switch Therapeutics emerged from stealth in early 2023 with $52 million in series A financing.

The company is working with a programmable siRNA molecule, named CASi (conditionally activated siRNA). CASi combines the features of single- and double-stranded RNAs into a three-stranded molecule. Two of the strands are the siRNA itself. The third strand is a single-stranded molecular 'switch' that the siRNA docks into. This third strand — also called the sensor strand — is what makes Switch's approach different. First, the sensor strand has single-stranded regions and can be chemically modified, with ligands added so that the CASi molecule can target specific types of cells. This circumvents the need for delivery agents such as lipid nanoparticles or adeno-associated viral vectors. Once inside the cell, the sensor strand causes steric hindrance that prevents RNAi activity, but when the sensor strand base-pairs with an intracellular RNA target, it unzips from the CASi molecule and releases the siRNA. By designing the sensor strand to base pair with RNA present in specific cells, the siRNA can be activated only in certain cell types or tissues.

Switch's platform can change the way we think about cell-specific RNAi therapeutics. Targeted delivery platforms rely on natural ligands or receptors on cell surfaces, which may not always be available. The CASi construct can use any expressed RNA as a marker to activate RNAi activity. "We look at the transcriptome data [for each cell]. Pretty much every cell type has some unique RNA [sequences]; that's what we take advantage of," Datta says.

The CASi molecule was initially tested in cardiomyocytes[1], but the company has since shifted its focus to developing drug candidates for central nervous system (CNS) diseases. "We wanted to build our pipeline by taking advantage of the [specific properties] of the CASi molecule while also opening up more target space for patients," Datta explains. Existing oligonucleotide therapies that target the CNS are usually delivered through spinal cord injections, which can be burdensome for patients. "[In such cases], you want to make sure that these molecules are good in terms of distributing to all regions of the brain, showing deep [and durable] knockdown," says Datta, who is confident that the CASi molecule can deliver on these attributes.

Datta thinks that cell-selective targeting will be particularly valuable in CNS indications. "Whether it is astrocytes, microglia, even different types of neurons, [specific cell types] play important roles depending on the disease." The team is currently testing the performance of CASi in the CNS of rodents and non-human primates. "We're seeing deep knockdown from a single dose, even up to three months," says Datta, describing unpublished data. She hopes to achieve a dosing frequency of once every six months, or less, in patients.

Gene Yeo, director of the Center for RNA Technologies and Therapeutics at the University of California, San Diego and chief scientist of the Sanford Laboratories for Innovative Medicines, whose work focuses on RNA biology and therapeutics and who is not connected to Switch Therapeutics, is excited about Switch's approach. He thinks a strength of the CASi platform is its potential to avoid liver toxicity, which is important for certain CNS targets. In neurodegenerative and CNS diseases, many pathways are dysregulated, and targeting them with conventional siRNA drugs can cause unwanted silencing in other organs. For example, apolipoprotein E (APOE) could be silenced in the CNS to lower the burden of Alzheimer's disease, but it is also highly expressed in the liver. Even when an siRNA is administered through spinal cord injections, unwanted silencing of APOE in the liver could have detrimental effects on cholesterol homeostasis. "Switch's platform may be able to [prevent this] through cell-type-specific knock down, which would be very good," Yeo says.

The company has not disclosed full details of its pipeline but plans to announce two development candidates for neurodegenerative indications this year. According to Datta,

CREDIT: SWITCH THERAPEUTICS

there are many areas this technology can enter, such as the peripheral nervous system and systemic indications.

For systemic indications, Yeo expects that the construct would benefit from optimization to reach the right organs, through adding a ligand to the third strand. Datta says that, although Switch is not primarily focused on tackling the delivery challenge, any new therapy must of course reach the right tissues. She notes that different formats of CASi molecules can be designed to optimize delivery to specific organs, adding that many companies are developing new delivery platforms and CASi could be combined with any of those.

Yeo is curious to see how versatile the platform can be in terms of sensor strand design. "Let's say you want to target a disease in a specific population of neurons, or neurons and astrocytes. You have to find the correct RNA that allows activation in two different cell types but not the liver. That will be challenging to figure out." Datta points out that, once a sensor strand has been designed to a specific RNA target, it can be combined with any payload. So far, Switch has mostly developed CASi molecules with siRNA as the payload, but the docking site of the sensor strand can likely accommodate other short RNA therapeutics as well, including microRNAs and small activating RNAs. As the company is still in its early stages, the Switch team will have many options for how to take this technology forward. "Exciting science always comes with its own challenges," says Datta. "It's a unique platform, and there has been a lot of learning. I am very proud of the team and our focus to do the right thing."

Iris Marchal
Associate Editor, Nature Biotechnology.

Published online: 14 October 2024

References

1. Han, S.-p et al. *Mol. Ther. Nucleic Acids* **27**, 797–809 (2022).