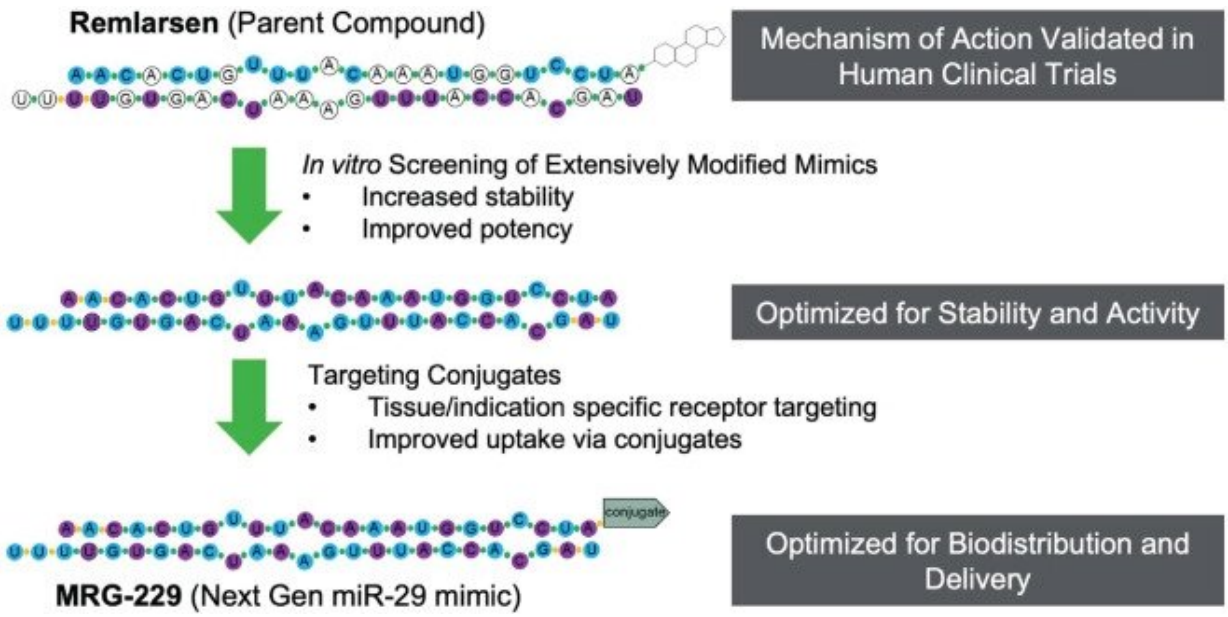
Newly designed molecule could help treat deadly lung condition

October 31 2022, by Isabella Backman



Overview of modifications differentiating second-geneneration miR-29 from first gen MRG-201/Remlarsen. Top, first-gen MRG-201, the parent compound, bottom, MRG-229 (Next generation miR-29 mimic), the second-gen compound. DNA bases: white circles = unmodified base, blue circles = 2'OMe, purple circles = 2'F, linkages: green circles = phosphorodiester linkage, orange circles = phosphorothioate (PS) linkage. NH2 terminus modification: MRG-201/Remlarsen = cholesterol, BiPPB = platelet-derived growth factor beta receptor (PDGFβR)-binding peptide (BiPPB). Credit: *eBioMedicine* (2022). DOI: 10.1016/j.ebiom.2022.104304

Idiopathic pulmonary fibrosis (IPF) is a deadly condition. The only available therapies can slow disease progression, but they are not a cure and often cause intolerable side effects. Patients diagnosed with the disease will die within three to five years of diagnosis. "It is more lethal than most cancers," says Naftali Kaminski, MD, Boehringer Ingelheim Pharmaceuticals, Inc. Endowed Professor of Medicine (Pulmonary) at Yale School of Medicine.

A team led by Kaminski used a newly designed molecule, called MRG-229, with potential therapeutic implications for IPF. The study is one of the first to use a microRNA mimic as a viable therapeutic in the lungs. The group published its findings October 17 in *eBioMedicine*.

"I feel so lucky to have contributed to this work because it could lead to a treatment for such a devastating disease," says Maurizio Chioccioli, Ph.D., instructor at Yale School of Medicine and first author. "I got to touch with my hands something that could be a big hope for many people."

MicroRNA molecule miR-29 is linked to fibrosis

Patients suffering from IPF experience scarring in lung tissue that can cause difficulty breathing. Nearly a decade ago, Kaminski's team discovered that the accumulation of scar tissue in the lungs was linked to a decrease in a microRNA molecule called miR-29. Other studies documented that scarring in other organs was also related to a decline in this microRNA. This sparked the team's interest in creating a miR-29-like molecule that could be given to patients with a goal of reversing this scarring.

In 2014, Kaminski's team published its work on a first-generation miR-29 mimic, Remlarsen/MRG-201, which showed that high doses of the miR-29 mimic could reduce fibrosis. The dosage used in the study

was much too high to give to human patients, but the work was promising evidence for Yale and miRagen Therapeutics (now Viridian Therapeutics) to establish an NIH-NHLBI–funded collaboration to develop microRNA mimics as IPF therapeutics.

MicroRNA mimic reduces fibrosis in various settings

In their latest study, the team created their new and improved MRG-229 molecule. They chemically modified the molecule to make it more stable and added a peptide that allowed for more targeted delivery.

Using multiple models, the team then studied their latest microRNA mimic's ability to reduce fibrosis. First, they showed that MRG-229 decreased fibrosis in cultured human lung fibroblasts. Next, they tested the molecule in mouse models. These models revealed that not only did MRG-229 show anti-fibrotic activity but could also be administered at a dose barely one tenth the strength of the original MRG-201. They also found that in addition to being delivered intravenously, MRG-229 could be administered subcutaneously [under the skin], which is less risky for patients, and that it could be given effectively at a lower frequency that MRG-201. "With this model, we started to see MRG-229 as a viable option for trials in humans," says Kaminski.

Finally, they tested their molecule in human lung segments to better understand its efficacy in human tissue. "We took human lungs, cut them very thinly, cultured them, and then caused scarring in them," says Kaminski. Once again, MRG-229 was successful in reducing fibrosis. "We proved in multiple models—in vivo, ex vivo, and in vitro—that through using a microRNA mimic we could reverse fibrosis," he says.

After finding promising results across several models, the team next ran several toxicological studies in rats and non-human primates to assess the molecule's safety as a potential therapeutic. They found that MRG-229

was well-tolerated and did not create any adverse effects.

Furthermore, they studied two cohorts of IPF patients to determine the best candidates for a new therapeutic. In collaboration with Gisli Jenkins (National Heart and Lung Institute, Imperial College London, London, U.K.) and Jose Herazo (University of South Florida, Tampa, FL, U.S.) they tested blood levels of miR-29 and found that low levels of miR-29 were correlated with an increased risk of mortality. "This finding is important for guiding researchers to patients who should get this drug in the future," says Kaminski.

A promising new therapeutic for IPF

Kaminski feels that his team's work is powerful evidence in support of MRG-229 as a therapeutic. "Our study is unique because we incorporate the concept of triangulation, in which we tested three models—in vitro, ex vivo, and in vivo," he says. "We do a lot of exciting research where we discover a lot of things, but rarely do we make something in a way that would be attractive for someone to actually do the next step and test it in humans."

Today, treatment options for IPF are scarce. "One of the problems with many of the drugs that we give is that they're supposed to work in the lung, but they actually hit every cell in the body," he says. "It makes patients feel sick, and many stop taking the drug because they never feel better. So, although current therapies improve the lung, they don't improve a patient's well-being." Because MRG-229 is designed with a targeting receptor to limit its impact outside the lung and was shown to be safe and effective in animals, the team is hopeful that the molecule will be tolerable in human patients.

MRG-229 is approaching the end of the preclinical stage of drug development. It will need to be formulated for humans, and then tested

extensively first for safety and then for efficacy in human clinical trials before it can be approved for use in patients, says Rusty Montgomery, Ph.D., a co-corresponding author on the paper and one of the original developers of the drug. "We hope that the publication of our work will reawaken interest in the potential clinical development of miR-29 as a therapy in the lungs and possibly other organs" he says.

Kaminski adds, "I would think that with the recent success of RNA therapeutics, such as the COVID19 vaccines, and the desperate unmet need for new therapies in IPF, and out results, the clinical research community and industry should be excited to try to bring miR-29 mimicry to humans—I really hope it happens."

More information: Maurizio Chioccioli et al, A lung targeted miR-29 mimic as a therapy for pulmonary fibrosis, *eBioMedicine* (2022). DOI: 10.1016/j.ebiom.2022.104304

Provided by Yale University