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Sisaf to move siRNA program for bone growth disorder into the clinic in 2022

By Cormac Sheridan

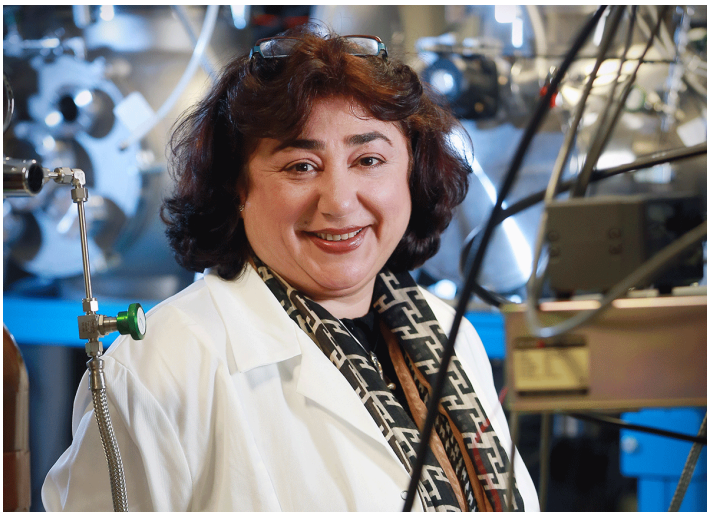
DUBLIN – Sisaf Ltd. has exercised an option on an Italian preclinical program to treat a rare bone disorder, autosomal dominant osteopetrosis type 2 (ADO2), with an siRNA molecule, which it will deliver with its in-house Bio-courier technology. The Guildford, U.K.-based company is now gearing up for a phase I study, which will be conducted next year under the leadership of Michael Econs, of Indiana State University Medical School.

The agreement follows 12 months of preclinical research, which established that a siRNA designed to knock down expression of a disease-associated *CLNC7* allele rescued the phenotype of an ADO2 mouse model. The therapeutic approach, developed by Anna Maria Teti, of the University of L'Aquila, and her team, restored bone mass and bone quality to near-normal levels. "It was so good we exercised our option," Sisaf founder and CEO Suzanne Saffie-Siebert told *BioWorld*. The effects were maintained across different injection routes and formulations. "That was extremely exciting for us," she said. They included clearance of bone debris as well as improved growth.

CLNC7 encodes a chloride channel 7 (ClC7), the loss of which impairs bone resorption and leads to dense, fragile bones that are prone to frequent fractures. ClC7 is involved in maintaining the charge balance in the extracellular space between the osteoclasts, the multinucleated cells that break down old bone, and the bone matrix. Heterozygous dominant negative mutations in *CLNC7* cause a milder form of osteopetrosis than homozygous loss-of-function mutations, but the condition remains highly debilitating. Patients are at risk of developing osteomyelitis or bone infection, which can cause permanent damage. Vision loss and anemia are further complications arising from the condition. There are no approved therapies for ADO2.

Econs previously led a small-scale, open-label trial in ADO2 of Actimmune (interferon gamma-1b), which is already approved for delaying progression in patients with severe, malignant osteopetrosis, a related but more severe condition that emerges during infancy. In ADO2, however, Econs and colleagues reported, it failed to demonstrate any significant effects on markers of bone resorption, while it was also poorly tolerated.

That mechanism was indirect, and apparently inadequate, whereas the therapy Sisaf has in-licensed, SiS-101-ADO2, addresses the genetic cause of ADO2 directly. It targets the most prevalent dominant mutation, without affecting expression of the wild-type allele that patients also possess. The hope is that a successful therapy would transform patients into a condition that Teti and colleagues have described as "pseudo-haplosufficiency", in which a single healthy allele will give rise to enough activity to restore bone resorption to adequate levels.



Suzanne Saffie-Siebert, founder and CEO, Sisaf Ltd.

The upcoming trial will, therefore, provide early insights on whether the preclinical findings are likely to translate into patients, although the main focus will be on safety.

The trial will also be among the early tests of Sisaf's Bio-courier hybrid silicon-lipid nanoparticle technology, which is designed to combine the most desirable features of both lipid nanoparticles and inorganic or metalloid approaches to drug delivery.

Lipid nanoparticle technology has become highly prominent, because of its use in the delivery of mRNA COVID-19 vaccines. However, its shortcomings have also been laid bare. The instability of mRNA vaccines, which necessitates freezing for long-term storage and cold-chain distribution, is not solely a function of mRNA itself. "Lipid nanoparticles are not stable," Saffie-Siebert said. "Physics goes against them."

In contrast, gold-based or silicon-based nanoparticles are highly stable, but they have other shortcomings. "The issue with them is safety," Saffie-Siebert said. They need to be biodegradable, biocompatible and bioabsorbable.

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Sisaf has developed a technology that incorporates elements of both. By functionalizing a silicon surface, using solvents to eliminate an oxidized layer, it can generate electrostatic interactions between the silicon, the lipid nanoparticle and the active pharmaceutical ingredient it is carrying. "The key to success is to stabilize the complex," Saffie-Siebert said. "You stabilize the lipids and remove the requirement for ultra-cold chain." The process generates orthosilic acid (Si(OH)4), a species that is actually beneficial for human health, and avoids the formation of silicon-based polymers which are problematic. Manufacturing is not overly complex. "It's actually a beautifully easy scale-up," she said.

In addition, it is possible to tune parameters, such as particle size and surface charge, to tailor the hybrid particles for particle settings. Receptor specificity can also be engineered into the particles, as is the case with lipid nanoparticles. During the ADO2 preclinical research, delivery was about twice as efficient as compared with conventional lipid nanoparticles.

The ADO2 program will not represent the first clinical trial to involve the Bio-courier technology. An unnamed partner is employing the technology with an existing drug already approved for alopecia, and it recently received approval from the U.K.'s Medicines and Healthcare Products Regulatory Agency to conduct a clinical trial in the U.K. under the equivalent of the FDA's 505(b)(2) pathway.

The company's in-house pipeline also includes SIS-201-CD, another siRNA-based program which is currently undergoing IND-enabling studies prior to entering clinical development in patients with type II (or Avellino) corneal dystrophy. Delivered topically, it targets mutated forms of transforming growth factor beta I (TGF-beta I). An earlier-stage program, SIS-201-CDC, is designed to accomplish the same goal by topically delivering a CRISPR-Cas9 payload.

Sisaf began life in Belfast, Northern Ireland, more than a decade ago, where Saffie-Siebert was then located. This time last year, it raised $13.2 million in a first tranche of a series B funding round led by Vickers Ventures. "We do need to raise more cash," Saffie-Siebert said. "The lead investors are backing the company and following their money."