Strategic partnership between Ksilink and CECS/I-Stem

Joint drug discovery program for treating autism and myotonic dystrophy

Strasbourg, February 5th 2019. The public-private translational institute Ksilink and CECS (Centre d'Etude des Cellules Souches) of the Institute for Stem cell Therapy and Exploration of Monogenetic diseases (I-Stem) have entered into a strategic partnership. The two enterprises, based in Strasbourg and Corbeil-Essonnes respectively, aim to develop new active substances for treating muscular diseases and mental disorders. Last year they initiated two new drug discovery projects for identifying active substances that could treat autism and the neuromuscular disease known as 'myotonic dystrophy'. "In I-Stem, we have gained the ideal partner with whom we can head targetedly towards preclinical trials for these two indications," says the CEO of Ksilink, Dr. Ulf Nehrbass. "I-Stem has vast experience in the development of specific, patient-based cell culture models – and in proving their suitability for preclinical trials." The CEO of CECS/I-Stem, Raymond Zakhia, is similarly positive: "Ksilink will be using our cell culture models to test drug candidates from a large substance library of the pharmaceutical company Sanofi, automatically and with the aid of artificial intelligence. That is the very step we need to advance our research translationally, meaning towards the patient."

Ksilink and CECS/I-Stem's collaboration is based on cell culture models that I-Stem has obtained from tissue samples of patients with autism or myotonic dystrophy. The cells are first converted into so-called pluripotent stem cells in the laboratory. The researchers can then develop these into precisely the cell types implicated most strongly in each disease – neurons in the case of autism and muscle cells in the case of myotonic dystrophy.

What makes the partnership special is that, for both cases, CECS/I-Stem has access to cells from patients whose disease is triggered by a single mutation. "The cell models are therefore relatively simple and straightforward to handle in the laboratory," says Dr. Alexandra Benchoua, group head at CECS/I-Stem for neuroplasticity and therapeutics. Thanks to this simplicity, Benchoua and her team have already identified a first active substance using neurons of patients with a genetic form of autism spectrum disorders, and have even tested it directly in patients. This substance alleviates the symptoms of this type of autism that are due to a mutation of the Shank3 gene.

"It is a big advantage for us that I-Stem already has such immense experience in testing their cell cultures," says Dr. Mona Boyé, a business developer at Ksilink. "It means the team knows the strict requirements for preclinical research and we can very quickly get onto screening with the Sanofi substance library. Thus, we avoid technical or regulatory errors that could otherwise be made in the early stage in labs that don't have this experience."

As for Ksilink's advantage: only with fully automated high-throughput technology like that at the Strasbourg translation institute is it possible to work through giant substance libraries and achieve meaningful results. In order to obtain such results, large numbers of cell cultures are exposed to the substances from the Sanofi library and observed under high-resolution microscopes at Ksilink. Ksilink has imaging techniques for analysing cell cultures automatically and with the use of deep-learning algorithms, or in other words artificial intelligence (AI). The use of AI enables them to detect even very slight and heterogeneous structural changes in the cells when they are exposed to a potentially active substance.

There are also financial advantages. "Our institute has a unique investment programme that allows even small companies and academic partners to perform large-scale translational programmes in an

industrial environment in living cells to the successful conclusion of a proof of concept," says Mona Boyé.

This is evidenced as I-Stem already identified of a potentially active substance for Shank3 neurons. When Ksilink's microscopes observe cells shifting towards a healthy state under the influence of molecules from the Sanofi substance library – similarly as it was with the already identified active substance – then that is a good sign, as Boye says: "It points us towards potential drug candidates, which we then examine more closely and develop further here at the Institute."

The next step is then to clarify the mechanism of action: "Our approach is described as undirected," Boyé explains. "We don't focus on a specific target molecule or specific signal transduction path; rather we test the substances in the whole, complex cell system. There is a strong chance of identifying a novel active substance that represents a completely new class of active substances. The exact target molecule and mechanism of action will then be determined as a part of downstream drug development."

If these investigations are successful, i.e. if a substance exhibits the desired effect in the cell system and a relevant mechanism of action can be demonstrated, then the drug candidate will go into subsequent preclinical and clinical development. "The likelihood that this innovative approach for identifying new active substances will result in a drug is much higher than with classical approaches," Ksilink CEO Nehrbass says.

Raymond Zakhia, the CEO of CECS/I-Stem, expects so, too: "We hope that, through the collaboration with Ksilink, our research will be of benefit to sufferers of myotonic dystrophy and other neuromuscular disease. This is especially important to us given our very close ties with AFM-Téléthon, the French patients' association for muscular disease. AFM-Téléthon has been deeply dedicated to our line of research for many years. To be able to give a wealth of therapeutic perspectives in return would be a great success."

About **Ksilink** www.ksilink.com

Ksilink is a private-public translational institute for phenotypic drug discovery and preclinical development of novel drugs. Ksilink was founded in 2014 in Strasbourg, France, by seven German and French partners: Sanofi, Institut National de la Santé et Recherche Medicale (INSERM), University of Strasbourg, University of Heidelberg, the German Cancer Research Center (DKFZ), the industrial clusters BioPro Baden Württemberg and Alsace BioValley, and the major pharmaceutical company Sanofi. Together with industrial and academic partners, Ksilink enables collaborative translation programmes focusing on novel patient-based therapy development. Ksilink provides unique expertise in the fields of high-throughput screening (HTS / HCS), development of image analysis techniques using machine-learning algorithms, and preclinical drug development in highly industrial environments. Now with nine ongoing drug discovery programmes, Ksilink has developed over the past three years into a renowned, innovative translation institute.

About **CECS/I-Stem** www.istem.eu

CECS is a research and development centre dedicated to the development of treatments based on the potential offered by pluripotent stem cells and applicable to rare diseases of genetic origin. CECS is member of the Biotherapies Institute created and funded by the AFM-TELETHON. CECS is also a part of the Institute for Stem cell Therapy and Exploration of Monogenic diseases (I-Stem), created by the AFM-TELETHON and the INSERM on January 2005 and dedicated to the development of treatments based on the potentials offered by pluripotent stem cells and applicable to rare diseases of genetic origin. The field of activity of CECS and I-Stem extends from basic research to the pathological mechanisms and transfer of new therapies to clinical research. The programs of each of the research teams are devoted either to a set of genetic diseases or to the development of new technologies around the major instruments implemented in the Institute. Currently, the major pathological indications studied concern diseases of the muscle, motor neurons, skin, retina and those associated with abnormalities in the development of the central nervous system. The technology platform team is exploring and implementing the large tools of cell production, high throughput screening, automated cell imaging, next generation sequencing and technological innovations in cell biology.