Gene editing therapy for human cancers driven by FUSION GENES (FUGE) and ONCOGENE AMPLIFICATIONS (AMP)

CNIO

Dr. Sandra Rodríguez-Perales

PROFILE

cnio stop cancer

Within CNIO, the main interest of the *Molecular Cytogenetic and Gene Editing* (**MC&GE Unit**) is the study of how the fusion of two different genes—a class of oncogenes that provide immense diagnostic and therapeutic advantages because of their tumour-specific expression—and the amplification of (onco)genes can cause cancer. In addition, the group is developing new genome editing tools as therapeutic approaches to treat human cancer. Dr. Rodríguez-Perales is working on translational projects with an innovative edge trying to develop and valorised products that can tackle unmet medical needs.

SPEAKER

Dr Sandra Rodriguez is a geneticist with a robust knowledge of the fields of Molecular Cytogenetic and Gene Editing (MC&GE) in cancer. She is currently the Head of the MC&GE Core Unit at the CNIO. After her PhD training she focused on the discovery and study of new chromosomal rearrangements in cancer, she carried out postdoctoral work on modifications of the mouse genome to reproduce cancer chromosome translocations. In 2014, she developed the first genome engineering approach able to reproduce cancer translocations in human cells (Nature Commun, 2014). She has contributed to the field with more than 50 publications in international scientific journals and is an inventor on 2 patents.

srodriguezp@cnio.es

PRODUCT

Gene editing therapy for human cancers driven by fusion genes (FuGe) and oncogene amplifications

MECHANISM OF ACTION

Chromosome rearrangement plays a causal role in tumorigenesis mainly by contributing to the generation of novel fusion oncogenes or oncogene amplification. Fusion oncogenes (FOs) are chimeric genes resulting from in-frame fusions of the coding sequences of two genes involved in a chromosomal rearrangement and are common in many cancer types being powerful drivers of tumour development.

Because their expression is exclusive to cancer cells and their elimination induces cell apoptosis in FO-driven cancers, FOs are attractive therapeutic targets. Gene amplification is a relatively frequent event in cancer genomes and overexpression is a requisite for amplified genes to function as driver alterations. We have developed a gene editing strategy for the treatment of tumours driven by FOs and gene amplifications.

Based on the use of an innovative CRISPR-based gene editing approach, we have developed a feasible, efficient and non-patient-specific strategy based on gene editing that specifically targets FOs and gene amplifications only in cancer cells.

Through targeting two locus in both genes involved in these gene rearrangements we accomplished a robust disruption of the FO and amplified genes specifically in cancer cells while sparing wild-type gene expression in non-cancer cells.

TARGET INDICATIONS

Gene editing technique can potentially treat all tumours driven by fusion or amplified (onco)genes, including leukaemia, sarcoma and many epithelial cancers including prostate, colorectal, breast or melanoma. In particular, we are developing a strategy against high-risk neuroblastoma.

CURRENT STATUS

- Concept tests show how the treatment of tumors bearing these fusion genes with our new CRISPR-based approach leads to tumor cell death in culture and to a decrease in tumor size and mortality in mice xenografted with human sarcoma or leukemia cells (in press at Nat. Comm.).
- Although the approach has proven successful in vitro and in mouse models, the process remains complex, and several techniques need further development. The technical challenges identified so far include increasing the efficiency, specificity and safety of the system. To address this, different molecular "vectors", such as adeno and adeno-associated virus, nanocages and virus capsids, will be tested to deliver our CRISPR-based approach to cancer cells. These vectors will have to efficiently release our system to overcome any immune-related barrier and be produced in a feasible manner for clinical use.

INNOVATIVE ASPECTS

- The product is based on a novel engineered Gene Editing Cassette (CnioGEC) capable of removing the gene fusions, and thereby inducing cell death specifically in the tumour cells. The ability to precisely manipulating cancer cell genomes to correct or eliminate cancer-causing aberrations by highly efficient CRISPR/Cas9 genome editing has provided us new possibilities to develop FO- and oncogene amplification-targeted options to eliminate cancer cells.
- FOs and gene amplifications are attractive targets for directed therapy; however, therapeutic targeting of specific FOs and amplified genes has remained challenging. The reasons include both difficulties in specifically recognizing and targeting the resultant chimeric protein and the nature of FO products, which are intracellular, necessitating effective approaches for delivery of therapeutic molecules targeting the chimeric transcripts/proteins inside the cell.
- Likewise, the development of genome editing approaches offers new possibilities to directly and specifically targeting and modifying the genomic sequence of cancer cells.

IPR

There is a patent application with patent publication number WO2020/079243 A1 with priority number EP18382746.8 and international application number PCT/EP2019/078408. The priority date is 18-10-2018. The patent will enter in national phases in 2021 and the institution will likely enter examination in the major markets (USA, Europe with wide country coverage, Japan and Canada).

PARTNERING OPPORTUNITIES

Our current strategic approach with industry will be to establish a co-development collaboration so we can continue leveraging our know-how or the system and the indication and use in parallel the capabilities of industry to develop a delivery system for our CRISPR-based technology to start defining a clinical-grade product for further testing in both small animal system and in future clinical trials.