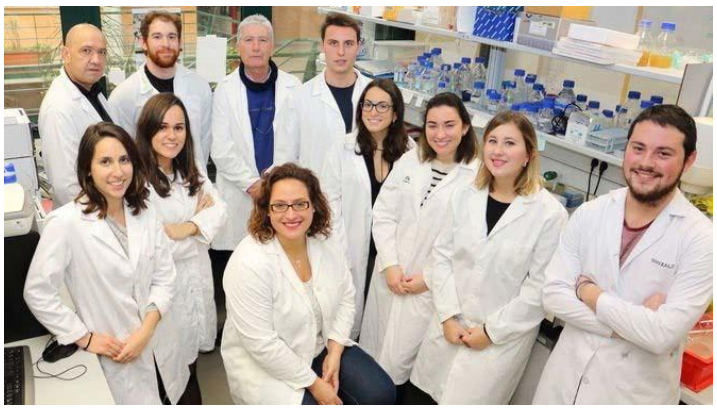
STATUS REPORT OF THE RESEARCH PROJECT: BRAINCURE.

1st UPDATE.



The team of Dr. José Antonio Sánchez Alcázar of the Andalusian Center for Developmental Biology (CABD) of the Pablo de Olavide University in Seville

April 7, 2018. In 3years from the beginning of Braincure, led by Dr. José Antonio Sánchez Alcázar, Andalusian Center for Developmental Biology (CABD) of the University Pablo de Olavide in Seville, the research project is reaching its target and is even opening new perspectives on the mechanisms that give rise to the most prevalent subtypes of ENACH.

BACKGROUND

In 2014, ENACH Association commissioned Dr. Sanchez Alcázar, Principal Investigator of the BRAINCURE Project, to try to find commercial drugs that individually or in combination with other drugs could be a therapeutic option for ENACH.

There were several reasons that guided BRAINCURE in this direction:

-Developing a new drug takes years and has an unattainable cost for a small association that had been formed just 1 year earlier.

- The process from the time the new drug is developed until it is available on the market can reach up to 10 years (European Medicines Agency authorizations, clinical trials, etc.). Our patients could not wait all that time.

-There were several groups worldwide working on different lines of research but we did not see that in the short-medium term, they could put on the table some specific therapeutic options.

-There was a biotech company that was finalizing the development of a drug for the conduct of a clinical trial in PKAN. This test is planned for the next few months but only PKAN is addressed and ENACH are a group of 11 diseases. We wanted to try to find a formula that could cover as many subtypes ENACH.

Finally, inspired by how was therapeutically managed the AIDS crisis in the early 90s: Combined treatment, known as cocktail of drugs (ARVs) all existing ones. Patients who received those combined treatments showed remarkable improvement from the outset. To this day, AIDS is not cured but, it has managed to chronify.

The project started and had before it a first major challenge, **finding a system that would detect whether the drugs to** be **tested in cells (fibroblasts) from patients were working at** the **cellular level.** To do this, BRAINCURE, developed a method using a staining system called "Prussian blue" that allows to detect if the samples of the patients accumulated iron. If the goal was to massively test drugs that could reduce or eliminate the accumulation of iron in the cells, it was necessary to have a tool that could tell if a drug worked or not. After several months of work, the tool, the screening, was set up and **patented.**

In parallel to the development of the screening system, ENACH was deepened in knowledge and started with PKAN (50% of ENACH cases).

The step before the beginning of drug screening was to study the pathophysiology (alterations) that showed the cells of the patients, being able to identify 3 biomarkers or pathological characteristics that allowed the running of the screening system.

In a few weeks a great milestone occurred: A drug, UPO001, was identified that, in certain concentrations, was able to restore the cells of the first patients to normal levels (in the 3 biomarkers).

In addition, the most prevalent ENACH subtype, PLAN / INAD (30% of cases) was started. In this subtype, 2 drugs were positive, UPO002 and UPO003.

The biobank of patient samples was growing and that led to BRAINCURE to one conclusion: The identified drugs that worked in the first patient samples did not work or worse in other patient samples. Depending on the type of mutation and where it was found, there was little or no response to the drugs tested. This led to approach the project in a personalized manner, patient to patient.

In recent months, it has also started with a subtype called BPAN with results very similar to those obtained in PKAN and PLAN / INAD

CURRENT SITUATION

To date this writing, have already been identified more drugs, either alone
or in combination, they have given excellent response in cells, restoring them as a normal patient levels:

-PKAN: 13 drugs
-PLAN: 12 drugs
-BPAN: 3 drugs

Also, the project is progressing in several directions simultaneously:

1º.- The fibroblasts of PKAN and PLAN / INAD patients have already been reprogrammed to neurons.

The purpose is to validate the results obtained in this other cellular model.

2º.- The first pilot studies carried out with patients have come to indicate that the drugs which have proved positive in the laboratory, have to be adjusted quantity, different combinations and consider routes of administration therefore currently is working in the "logistics" of delivering drugs in adequate to the place where it is required concentrations. This in next pilot studies will lead in the coming months with more patients.

3 .- A high level of knowledge about the disease and its mechanisms is being acquired, which is leading us to findings not previously described in the literature and which have already been sent to scientific journals for publication.

From the clinical point of view, to the date of this report, under observational study, there are:

-5 PKAN patients in treatment with **very positive results**.
-3 PKAN patients with an improved cocktail who have just started treatment.
-1 PLAN patient who has been in treatment for 2 months and is being observed.

Signed: The Board of Directors.