PRBB-CRG CONFERENCES

Conference Programme financed by the CRG and the PRBB

MICHAEL EISEN, Friday November 20. Eisen, from the Howard Hughes Medical Institute and the University of California at Berkeley in the US, studies how the genomic sequences that control gene expression function and evolve, with the aim to understand the molecular basis of organismal diversity. He uses genome-scale computational as well as experimental analysis of gene regulation in *Drosophila melanogaster* and *Saccharomyces cerevisiae* and closely related species. He has been invited by Roderic Guigó and Toni Gabaldón (CRG).

MICHAEL LEVITT, Monday November 23. Levitt, from Stanford School of Medicine at Stanford University, the US, focuses on three different but inter-related areas of research: prediction of protein folding with emphasis on how the hydrophobic forces affect the pathway; prediction of protein structure from sequence without regard for the process of folding; and mesoscale modeling of large macromolecular complexes. He has been invited by Josefa González (IBE).

KATERINA POLITI, Friday December 4. Politi, from Yale School of Medicine, US, studies lung cancer to answer the following questions: What are the alterations in cellular pathways that cause tumors to form? How can we interfere with these pathways to get tumors to regress? How do tumors become resistant to drugs? How can we detect tumors early when they are still curable? She focuses on one of the genes that is mutated in lung adenocarcinomas, the Epidermal Growth Factor Receptor (EGFR) gene. She has been invited by Michela Bertero (CRG).

JOHN MCGANN, Friday December 11. McGann, from the Psychology Department Rutgers at The State University of New Jersey, US, studies the olfactory system to explore how our brains understand the world around us and how they adapt to new environments and experiences. Using genetically engineered mice, he looks through a window implanted in the skull and watches neurons in the brain's olfactory bulb light up in characteristic patterns as the animal smells different odors. He also studies how the brain uses learned information to guide olfactory processing and perception. He has been invited by Mathieu Louis (CRG).

CAROLINE RELTON, Monday December 14. Relton, from the University of Bristol in the UK, works on epigenetic epidemiology, and she is involved in the Accessible Resource for Integrated Epigenomics Studies (ARIES), a BBSRC-funded resource to generate epigenomic information on a range of human tissues at multiple time points across the lifecourse. These data will be integrated with genetic and transcriptomic data and made available to the scientific community, with the facility to link data to both exposure and phenotypic data. She has been invited by Mariona Bustamante and Marine Vrijheid (CREAL).

ENTREVISTA CIENTÍFICA / SCIENTIFIC INTERVIEW

JOSE LUIS MOLINUEVO – FUNDACIÓ PASQUAL MARAGALL (FPM)

«EPAD proposa un innovador assaig clínic per a l'Alzheimer»

Maruxa Martínez-Campos

PERFIL / PROFILE

La iniciativa europea per a la prevenció de la demència associada a l'Alzheimer EPAD (European Prevention of Alzheimer's Dementia, www.ep-ad.org), de la qual formen part 35 institucions acadèmiques i laboratoris farmacèutics de tot Europa, va néixer el gener de 2015 i durarà cinc anys. EPAD es coordina a Espanya a través del Barcelonaβeta Brain Research Centre, centre de recerca de la Fundació Pasqual Maragall, i José Luis Molinuevo n'és el director científic, a més de colíder europeu.

The European initiative EPAD (European Prevention of Alzheimer's Dementia, www.ep-ad.org), was set up in 2015. It comprises 35 academic institutes and pharmaceutical companies from across Europe and will last for five years. In Spain, EPAD is coordinated by the Brain Barcelonaβeta Research Centre, part of the Pasqual Maragall Foundation. José Luis Molinuevo is its scientific director, as well as being the European co-leader.

Quins reptes suposa el projecte EPAD?

Fer assajos amb gent amb risc de desenvolupar demència associada a la malaltia de l'Alzheimer requereix implicar una població difícil de trobar, perquè no són malalts. Inclou des de gent completament sana des del punt de vista cognitiu fins a persones amb problemes de memòria, però que no han arribat a una fase de demència. És molt complicat trobar aquesta gent, per això la primera part del projecte consisteix a contactar diferents cohorts ja existents, com la nostra del projecte Alfa, i oferir a alguns dels participants que formin part d'EPAD, als quals s'inclourà en un registre de 24.000 persones. La idea és cobrir un ampli espectre de risc de patir demència, des de molt baix fins a molt alt —tenint en compte factors com ara tenir familiars amb la malaltia, el genotip ApoE, l'edat, biomarcadors d'Alzheimer, tests cognitius que han empitjorat amb el temps, etc.; això sí, sempre sense presentar demència. De les 24.000 persones del registre, 6.000 s'inclouran en una cohort observacional i 1.500 acabaran entrant a un assaig.

Així doncs, es pretén fer un assaig clínic amb gent sana?

De fet, no. La cohort és observacional; no fem cap intervenció, sinó que seguim en el temps els participants, que abracen tot l'espectre de risc, per estudiar com es desenvolupa la malaltia. En canvi, les 1.500 persones que participaran de l'assaig clínic i que rebran una intervenció totes estaran en la fase preclínica o prodròmica de la malaltia. És a dir, biològicament ja tindran la malaltia; per exemple, tindran marcadors d'Alzheimer al cervell, encara que no patiran demència.

Què és el que converteix aquesta iniciativa en diferent en la lluita contra l'Alzheimer?

El disseny de l'assaig és molt innovador, perquè és un assaig adaptatiu. Això vol dir que es començarà amb quatre branques en paral·lel, en cadascuna de les quals s'estudiarà un fàrmac diferent. Al cap de dos anys es comprovarà si el fàrmac està arribant a les seves dianes al cervell. Si tot va bé, es continuarà dos anys més i es pot passar a un assaig de fase III; si no, aquesta branca s'atura i es continua amb les altres, o es pot introduir una nova branca amb un nou fàrmac.

La població estudiada també és nova, perquè és gent que encara no té els símptomes de la malaltia, mentre que els assajos que han fracassat fins ara s'han fet amb malalts ja amb demència. La darrera novetat és la infraestructura, la gran cohort que es crearà i que esperem que sigui permanent.

Quan començarà l'assaig?

Està previst que d'aquí a sis o nou mesos comenci a entrar gent a la cohort i que cap al 2017 s'endegui l'assaig amb les 1.500 persones seleccionades.

Així doncs, podem esperar disposar d'un fàrmac que previngui l'Alzheimer d'aquí a uns anys?

Aspirem a trobar un fàrmac que retardi o previngui l'avenç de l'Alzheimer, però el dany que s'hagi fet al cervell en el moment que fem la intervenció ja és irreversible. Cal recordar que és una malaltia que comença a afectar el cervell entre 10 i 20 anys abans que apareguin els símptomes.

"EPAD proposes innovative clinical trial for Alzheimer's"

What challenges does the EPAD project face?

Carrying out trials on individuals at risk of developing the dementia associated with Alzheimer's means identifying a group of people that is difficult to find, because they are not sick. It includes individuals that are completely healthy from a cognitive point of view, to people with memory problems, but who have not yet reached the dementia stage. It is very difficult to find these people, so the first part of the project involves contacting various existing cohorts, like our own Alpha project, and inviting some of the participants to join EPAD. These people will be included on a register of 24,000 names. The idea is to cover a broad spectrum of dementia risk, from very low to very high, taking into account factors such as having family members with the disease, the ApoE genotype, age, Alzheimer's biomarkers, cognitive tests that have worsened over time, and so on. But always with no dementia being present. Of the 24,000 people on the register, 6000 will be included in an observational cohort and 1500 will become part of a trial.

So, the idea is to do a clinical trial with healthy people?

In fact, no. The cohort is observational, they will not have any treatment, but we will monitor the participants. They represent the full spectrum of risk, and over time we will see how the disease develops. On the other hand, the 1,500 people who are to take part in the clinical trial and receive treatment, will all be in the pre-clinical or prodromal phase of the disease. This means that at the biological level they already have it, for example they will have Alzheimer's markers in the brain, although they do not yet have dementia.

What is it that makes this initiative different in the fight against Alzheimer's?

The trial design is very innovative, because it is an adaptive test. This means that we will begin with four parallel branches, each looking at a different drug. In two years we will see whether the drug is reaching its targets in the brain. If all goes well, we will continue for two further years and move on to a phase III trial; if not, the branch will stop and we will continue with the others, or a new branch may enter with a new drug.

The study population is also new because it involves people who still have no symptoms of the disease; the trials that have failed up to now have been carried out on patients with dementia. The latest novelty is the infrastructure, the large cohort that will be created and which we hope will become permanent.

When is the trial going to start?

We plan to start getting people into the cohort within 6 or 9 months, and by 2017 we will begin the trial on the 1,500 selected individuals.

So, can we expect to have a drug that prevents Alzheimer's within a few years?

We are hoping to find a drug that delays or prevents the advance of Alzheimer's; but any damage to the brain occurring before we give the treatment is irreversible. We have to remember that this disease starts to affect the brain around 10 to 20 years before any symptoms become apparent ■