New method to study key targets in Alzheimer's disease and prostate cancer

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When designing a drug against a disease, chemists often used detailed plans of the proteins affected and against which the drugs must act. However, about a third of the proteins of our bodies have not yet been "photographed" because they generally vary in form, are in constant movements and have very little structure.

This lack of "photographs" hinders the design of drugs against diseases involving proteins that are structurally "evasive", such as those in Alzheimer's disease and in prostate cancer that does not respond to conventional drugs. The group headed by Xavier Salvatella, ICREA researcher with the Chemistry and Molecular Pharmacology Programme at the Institute for Research in Biomedicine (IRB Barcelona/Spain), has developed a method to obtain structural information about intrinsically disordered proteins. The study appears in this week's Journal of the American Chemical Society, one of the most important journals in this field.

Proteins are combinations of amino acids that fold in tri-dimensional forms that determine their function. The particularity of intrinsically disordered proteins is that because they are so dynamic and have little folded structure it is almost impossible to determine the variety of shapes that they adopt and consequently the functions they exert. Classical techniques, such as crystallography and nuclear magnetic resonance, do not work with these proteins. The researcher Xavier Salvatella, who left Cambridge to join IRB Barcelona a little over a year ago, develops methods to study the movements of proteins through

combining laboratory experiments and computational predictions, an approach used by very few groups in the world. The researchers have simultaneously used a thousand processors of the supercomputer MareNostrum to study a single protein model and develop a new programme for structural calculation, named ERIDU. They then checked that the calculated structures agreed with lab data measured independently. The researchers will make ERIDU available to the international scientific community.

Objective: Alzheimer's disease and prostate cancer

With this new methodology, the group at IRB Barcelona, in collaboration with the University of Cambridge, will study why beta-amyloid plaques develop in Alzheimer's disease. They will examine the variety of forms that this protein adopts before and during accumulation. In another project, Salvatella will address the androgen receptor, the target protein in Kennedy's disease, a rare neurodegenerative disorder that causes muscular atrophy, as well in prostate cancer. "Oncologists are calling for new strategies to stop the growth of prostate tumours", explains Salvatella. The drugs currently available inhibit a part of the androgen receptor that is well known but in later stages of the disease these drugs can stop working. This protein has another important part that is intrinsically disordered and about which there is no structural information. "If our method is as reliable as we think, we could start to decipher the variety of structural forms that this other active part adopts in order to design drugs in the future".

In only ten years intrinsically disordered proteins have become one of the most interesting fields of research for biomedicine. "We have seen that the greater the complexity of the organism, the more proteins of this kind it has; however, although these proteins are highly relevant we still know very little about them because, among other things, it is very difficult to study their structures", comments Salvatella. Next October,

IRB Barcelona, jointly with the BBVA Foundation, is organising a Barcelona BioMed Conference on intrinsically disordered proteins. This event will bring together experts in this field to discuss the most relevant breakthroughs made in pioneering labs worldwide.

Provided by Institute for Research in Biomedicine (IRB Barcelona)