Press Release

Engineered bacteria with the ability to produce hundreds of millions of different molecules and perform rapid and efficient discovery of new drugs against diseases caused by protein misfolding

A new study by the research group of Dr. Georgios Skretas at the Institute of Chemical Biology of the National Hellenic Research Foundation (ICB-NHRF) published in the scientific journal ***Science Advances*** describes the development of engineered bacteria with the ability to:

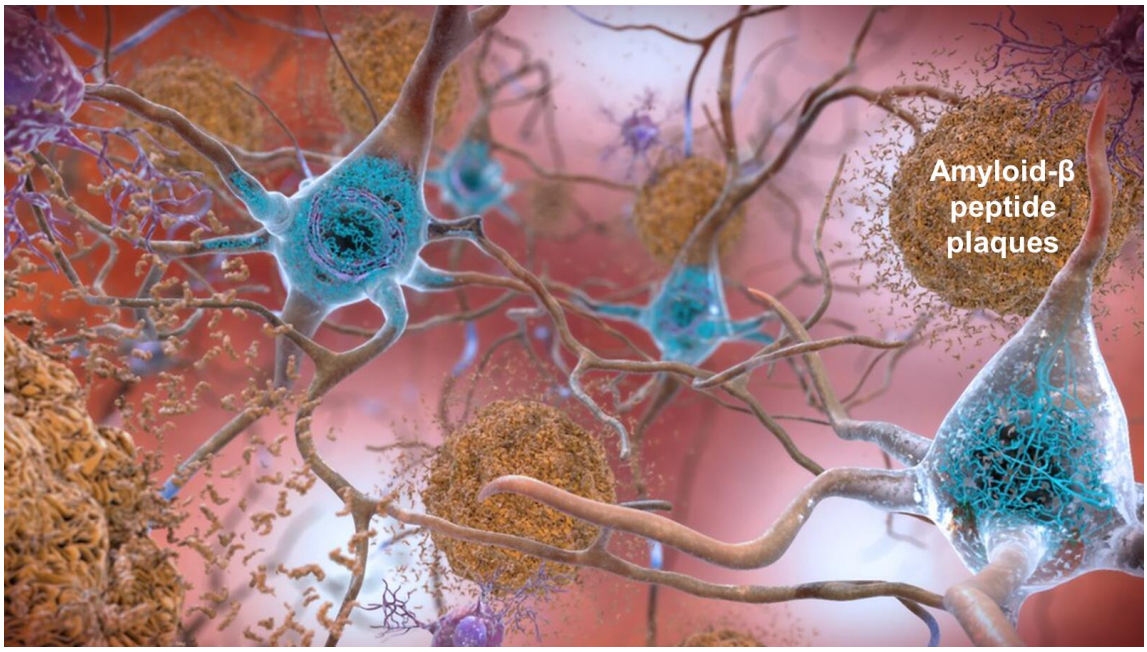
- produce hundreds of millions of different molecules and
- discover potentially therapeutic compounds against diseases caused by "crumpled" proteins, such as Alzheimer's disease, rapidly, easily and effectively.

According to recent studies, more than 50 human diseases, such as Alzheimer's disease, Parkinson's disease, type 2 diabetes, certain forms of cancer etc., share a common molecular origin: the problematic folding of specific proteins and accumulation of pathogenic oligomers/aggregates of these proteins. Due to their enormous socio-economic impact, the research community has invested heavily in the discovery of new drugs against these diseases. However, the vast majority of them remain incurable. Furthermore, the established methodologies for discovering new bioactive compounds are particularly time-consuming and costly.

In order to accelerate the discovery process for new drugs against these diseases, a team of scientists led by Dr. Georgios Skretas at ICB-NHRF have developed engineered bacteria that allow for the production of a remarkably large number of test molecules, as well as their simultaneous evaluation for their ability to repair problematic protein folding and to prevent protein aggregation. As a result, this dual new property of the modified bacteria enables the rapid discovery of new bioactive compounds against the target diseases.

In their study now published in the scientific journal ***Science Advances***, the research group of Dr. Skretas -in collaboration with the groups of Dr. Niki Chondrogianni from the ICB-NHRF and of Prof. Michele Vendruscolo from the University of Cambridge, UK- present for the first time the production of a collection -a combinatorial library as it is commonly referred to- of about 200 million different molecules and their simultaneous evaluation for the identification of bioactive molecules against the pathogenic misfolding of the β-amyloid peptide associated with Alzheimer's disease.

This led to the identification of more than 400 new bioactive molecules with the ability to inhibit the pathogenic aggregation of the β-amyloid peptide, both at the level of the isolated protein, as well as in small-animal models of Alzheimer's disease in the nematode *Caenorhabditis elegans*.



In addition, this study describes how this bacterial platform can be combined with next-generation DNA sequencing techniques to quickly and easily identify the elements of the resulting bioactive molecules that are responsible for their beneficial properties and which are essential for their optimal activity. This knowledge is particularly important in order to rapidly transition from the original hit compounds to lead compounds and – eventually- to new therapeutics.

Dr. Skretas and coworkers have already filed a patent application and have begun studying these molecules at a preclinical level aiming at their future entry into clinical trials against Alzheimer's disease.

At present, the research team of Dr. Skretas is also applying this innovative technology against additional target proteins in order to discover new potentially therapeutic compounds against a wide range of serious illnesses, such as amyotrophic lateral sclerosis, Huntington's disease and systemic amyloidosis.

Reference:

"Bacterial production and direct functional screening of expanded molecular libraries for discovering inhibitors of protein aggregation"

Dafni C. Delivoria, Sean Chia, Johnny Habchi, Michele Perni, Ilias Matis, Nikoletta Papaevgeniou, Martin Reczko, Niki Chondrogianni, Christopher M. Dobson, Michele Vendruscolo and Georgios Skretas*

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