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Systems pharmacology modelers accelerate drug discovery in Alzheimer's

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An InSysBio scientific group led by Tatiana Karelina has developed a quantitative system pharmacology model of Alzheimer's disease. The first part has been published in CPT Pharmacometrics & Systems Pharmacology, and shows how to design initial phases of clinical trials of new drugs and to interpret the data.

Alzheimer's is a chronic neurodegenerative disease that leads to senile cognitive impairment and memory loss affecting one out of three people over 70. Such changes are caused by functional disorders and the subsequent death of neurons. However, the causes of brain cell death remain unknown, and there is no effective therapy for Alzheimer's disease.

At the moment, the most common hypothesis is a theory of the toxic effect of the beta-amyloid protein, which accumulates in the brain with age, aggregating into insoluble amyloid plaques. The presence of these plaques in the brain is the main marker of Alzheimer's disease (unfortunately, often found postmortem). Soluble forms of the protein that do not aggregate into plaques are also considered to be toxic.

All modern Alzheimer's therapies act in one of the three ways: They can block production of soluble beta-amyloid, they destroy the protein before transformation into the insoluble form, or they stimulate plaque degradation. "Clinical trials for Alzheimer's therapies have got one significant feature—their short duration. They last for no more than five years, whereas the disease can progress for decades. And early Phase I-II

tests last for only few weeks. With such experiment designs, research can affect only the processes of distribution and degradation of the soluble beta-amyloid forms. Therefore, we developed this part of our model to analyze and predict the dynamics of the new generation of drugs, for instance, the inhibitors of amyloid production," says Tatiana Karelina, the head of the neurodegenerative disease modeling group InSysBio LLC.

The first difficulty encountered by drug developers is the interpretation of the results obtained in animal tests. In general, most studies of the distribution of amyloid are carried out on mice. Scientists inject a labeled protein into the mouse brain and observe the distribution of the radioactive label. Alternatively, researchers study the dynamics of amyloid in the presence of drugs. Based on the data obtained, researchers can calculate the therapeutic window for the medication—a range of doses from the minimum effective to the maximum nontoxic dose. Then doses for humans or monkeys are calculated by using mass or volume scaling.

The project team collected the data from the literature and derived a system of equations that fully describe the existing results. First, the model was calibrated (i.e. the missing parameters were estimated) for the mouse, and then for the human and monkey. It turned out that the scaling method to transfer results from rodents to primates was not useful. The deduced mathematical equations have shown that not only the rate of beta amyloid production was different, but that the blood-brain barrier is different in rodents and higher primates. At the same time, there was no significant difference between humans and monkeys, and the standard scaling could be used to translate predictions between them.

The next big question in Alzheimer's clinical trials is how to understand if the drug affects a specific target in the short term. It is impossible to

observe the processes that occur in the human brain directly. Usually, a cerebrospinal fluid probe is used to determine the change in the concentration of beta-amyloid. Actually, these data strongly differ from the values of amyloid concentration in the brain, since the cerebrospinal fluid is strongly influenced by the processes taking place in the blood plasma, and amyloid demonstrates another dynamic.

"A structural model calibrated on this large amount of data can easily match the results of cerebrospinal fluid sample analysis with the real processes in the patient's brain. This will greatly accelerate the development of new drugs and improve the accuracy of the therapy selection," explains Tatiana Karelina.

Scientists report that their model predicts how these new drugs must be administered. Total daily dose can be reduced, but should be split over several doses during the day, providing optimal brain efficacy. The InSysBio team is confident that their systems-pharmacological modeling can greatly improve the development of drugs for Alzheimer's disease and are already negotiating the introduction of technology with their partners in the pharmaceutical industry.

More information: Tatiana Karelina et al, A translational systems pharmacology model for Aβ kinetics in mouse, monkey, and human, *CPT: Pharmacometrics & Systems Pharmacology* (2017). DOI: 10.1002/psp4.12211

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