Targeting brain chemistry to beat disease

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Thanks to advances in big data and medicinal chemistry, scientists can screen thousands of molecules in the search for protein structures leading to new drugs for brain diseases.

Researchers participating in a COST network have filed a patent on one potential treatment and plan to move forward with a view to clinical development. They also collaborated on a technique enabling them to monitor changes in dopamine and serotonin levels, opening the door to a deeper understanding of the brain.

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For many brain diseases, including Alzheimer's disease and epilepsy, there are no medicines, or existing therapies do not work for all patients.

Proteins that affect neurotransmitters such as dopamine and serotonin could hold the key to finding new treatments. Thanks to advances in big data and medicinal chemistry, scientists can screen thousands of molecules in the search for promising new drug candidates.

"Computational chemistry offers an opportunity to look for untapped potential by searching for protein structures that might play a role in the brain," says Professor Rona Ramsay, University of St. Andrews. "This is the payoff for decades of crystallography work on molecular structures. Machine learning also allows for the repurposing of existing drugs which

have not been tested for certain neurological diseases."

Professor Ramsay chaired COST Action CM1103, which brought together chemists and biologists to focus on brain diseases where new therapies are needed. One of the areas she has been exploring is the potential of "dirty drugs" – molecules that interact with several targets in the brain.

"We can now design drugs to hit specific targets. In Alzheimer's, for example, we are developing drugs to keep acetylcholine, dopamine and serotonin in the synapses for longer; add an anti-oxidant to prevent damage caused by dying brain cells; then add a metal to 'mop up' oxidants which would otherwise cause problems," explains Professor Ramsay.

To achieve this, multidisciplinary networks have to design molecular structures and test them in brain cells and animal models. Participants in the network have filed a patent on one potential treatment and plan to move forward with a view to clinical development.

Other participating groups have collaborated on a technique which enables them to measure electrical firing in the brain and monitor changes in the levels of neurotransmitters – opening the door to a deeper understanding of the brain. The network also led to new strategies for treating epilepsy, a novel way to assess new compounds in animals, and an original theory on how dopamine neurotransmitters are oxidised.

The biggest value of this COST Action, according to Professor Ramsay, arose from partnerships between academics and the valuable exposure to other disciplines that it offered younger researchers.

This is echoed by Dr Katrina Nikolic, University of Belgrade, Serbia, who uses computer programs to design new compounds. "Our

collaboration with organic chemists in Spain, Germany and the UK allowed us to test compounds which could become drugs for Alzheimer's disease," she said. "This is very important for labs like ours and a big step forward for my career."

Almost half of participants were from COST Inclusiveness Target Countries, which Professor Ramsay describes as a particularly "enriching" aspect of the network. "I'm also very proud that 50% of our network was female at the outset – not many Actions in chemistry can say that!"

The network is currently finalising an e-book of its research results and many of its members continue to collaborate. Members in Spain, the UK and Germany are developing a three-in-one compound that can target three brain receptors linked to Alzheimer's disease in a single drug. Members from Italy and Turkey are running an EU-funded project training 12 PhD students in neuroscience research, focusing on neurodegeneration, neurotherapeutics development and neurorepair. Each student also receives 3-5 months training on cutting-edge technology within a company from the industry.

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