

New Drugs for an Old Disease



Donna Huryn, PhD
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The discovery and development of new drugs, once the exclusive domain of the pharmaceutical industry, is increasingly taking place in academia. The career of Donna Huryn, PhD, who spoke at our March meeting about drug discovery for Alzheimer's disease and her industry-to-academia trajectory, reflects this new trend.

Dr. Huryn had early connections to the University of Pennsylvania, the venue for tonight's meeting, receiving her PhD in Chemistry here before moving directly to a position at Hoffmann-La Roche. She was later head of the CNS chemistry department at Wyeth, where she had the chance to work on projects relating to depression, stroke and Alzheimer's disease. However, Dr. Huryn described how her successful career at Wyeth actually led to her spending more and more time on things she didn't enjoy, like performance reviews, budgeting and extensive travel, and less time on the science that she loved. It was this realization that prompted a bold move; she quit her position at Wyeth and moved into academia. A position at the University of Pittsburgh, where she was able to bring valuable medicinal chemistry expertise, was followed by an additional appointment at Penn, where she is part of the Synthetic Chemistry Core at the Penn Center for Molecular Discovery. Dr. Huryn's move into academia was well-timed, as the NIH was becoming more interested in drug discovery, and had started funding academic centers like the one at Penn designed to carry out this kind of research.

'New drugs for an old disease' was the title of Dr. Huryn's presentation, in which she shared with us two projects she had worked on to develop drugs to treat Alzheimer's disease, the first while at Wyeth and the second during her time at Penn. Some numbers from the Alzheimer's Association put the problem in perspective: in the US, 5.4 million people are living with Alzheimer's, and it is the 6th most common cause of death. There are 15 million caregivers who contribute 17 billion hours of unpaid care

every year. In total, Alzheimer's costs the US \$183 billion each year; worldwide, the cost is \$600 billion. Fifty percent of people over the age of 85 have Alzheimer's, so with a growing older population, the 'epidemic' is only set to get worse.

Some challenges in developing drugs for Alzheimer's are the difficulty in diagnosing it (since the molecular changes in the brain can only be observed on autopsy) and in measuring such subjective symptoms as loss of memory; there are no effective biomarkers. There is a lack of good animal models, and clinical studies are confounded by the variability of the disease and the likelihood of other conditions being present in the patient population. Additionally, any drug developed for Alzheimer's would need to be safe for long-term use, and be able to cross the blood-brain barrier.

The two characteristic features of a brain affected by Alzheimer's are extracellular β -amyloid peptide (BAP) plaques and intracellular neurofibrillary tangles made of tau, a protein that regulates microtubules. Thus, those researchers who believe that the β -amyloid plaques are the most relevant aspect of the pathology are known as 'BAP-tists' while those who feel that tau tangles are more important are known as 'tau-ists'.

Dr. Huryn started out as a 'BAP-tist' at Wyeth, where she worked on developing an inhibitor for γ -secretase, one of the enzymes responsible for processing the amyloid precursor protein (APP) into the plaque-forming BAP. High-throughput screening of 5000 compounds yielded two closely related hits, and investigation of their structure-activity relationship (SAR) revealed two changes in the chemical structure that each increased the potency of the drug 10-fold. In a rare stroke of medicinal chemistry luck, combining the two chemical changes produced an overall 100-fold increase in activity. The new molecule had good 'drug-like' properties and was able to reduce plaques in a mouse model that overexpresses BAP. However, it had a half-life of only a few minutes. Further adjustments of the chemical structure improved the half-life to over 90 minutes and significantly reduced the dose needed in the mouse model. The final compound, begacestat, is currently in Phase II clinical trials.

On moving to Penn, Dr. Huryn was converted to 'tau-ism'. There has been a recent resurgence of interest in tau after it was discovered that tau mutations lead to FTDP-17, a rare form of dementia. The function of tau is to stabilize microtubules, and hence axons. In Alzheimer's, where tau is caught up in tangles, other microtubule-stabilizing agents could potentially protect axons from degeneration. Natural microtubule stabilizers are known, for example taxol (paclitaxol), which is used as an anti-cancer drug. However, taxol does not penetrate the brain, so it can't be used for Alzheimer's. The team at Penn started with a taxol analogue, Tx-67, and worked on structural alterations to improve its properties. The final molecule, CNDR3, represented the best compromise between desirable attributes, having good cell membrane permeability, plasma stability, brain penetration and microtubule-stabilizing activity. Other issues with taxol analogues meant that this class of compounds were not pursued further, but the project provided an important validation of microtubule stabilization as a target for Alzheimer's disease. Other microtubule-stabilizing agents are currently under investigation.

Ending on a note of optimism, Dr. Huryn mentioned the National Alzheimer's Project Act recently signed into law by President Obama, as well as new research into vaccinations for Alzheimer's and imaging agents that can allow visualization of plaques in living brains, giving huge potential for both diagnosis and outcome measurement in clinical trials. There is clearly hope that, with the efforts of both industry and academia, we may yet stave off the epidemic of Alzheimer's disease.

Photo of Dr. Huryn courtesy of Sherri Meyer, PhD

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