Editorial

Alzheimer's Disease Drug Discovery: Aβ and Beyond

Alzheimer's disease (AD) drug discovery researchers face immense challenges in developing drugs that get into the brain, are safe and ultimately produce clinically meaningful results. Perhaps even more challenging is determining at what point in the disease cascade is best to intervene. We know that many different pathways initiate or exacerbate disease progression [1]. Amyloid-β (Aβ), the main component of amyloid plaques, has long been considered the leading target for AD intervention programs even though the amyloid cascade hypothesis remains controversial to this day [2, 3]. Innovative approaches to target Aβ are being developed and may be the best way to treat the disease at its earliest stages. Yet, as we learn more about the disease, it is becoming increasingly clear that alternative approaches may also be necessary to diversify the AD drug discovery portfolio. Increasing "shots on goal" will bring new ideas and novel targets into the pipeline, accelerating treatment development for AD.

In the spirit of these objectives, the Alzheimer's Drug Discovery Foundation (ADDF) hosted the *10th International Conference on Alzheimer's Drug Discovery* on September 14-15, 2009 in Jersey City, NJ. At the conference, attendees were treated not only to the breathtaking skyline view of New York City, but also to two days of diverse research aimed at AD drug discovery. The conference drew attendants from academia, industry and government. Sessions focused on Neuroprotection Strategies (chaired by Frank Longo, Stanford University), Anti-Amyloid and Protein Misfolding (chaired by Michael Wolf, Harvard Medical School), Anti-Tangles and Frontotemporal Dementia (chaired by Jeff Kuret, Ohio State University), and Alternative Strategies: New Targets for AD Therapy (chaired by Diana Shineman, ADDF). A comprehensive summary of the conference can be found on the conference web site (http://www.worldeventsforum.com/addf/10th/html/summary.html) . The proceedings in this special issue highlight a few of exciting programs presented at this conference. This year's conference built upon previous efforts and focused more heavily on alternative targets for therapeutic development [4-6].

The ultimate goal for AD drug discovery, regardless of the molecular target, is to protect neurons and their processes so that memory and function can be maintained. There are many ways to target neuroprotection and strengthen neuronal defenses against the toxic insults of AD. For example, Karin Yurko-Mauro from Martek Biosciences presents an overview of clinical data on the health benefits of Docosahexaenoic acid (DHA), the main component of omega-3 fatty acids (Yurko-Mauro, page 190-196). Her paper notes that DHA supplementation resulted in a cardiovascular benefit (decreased heart rate, blood pressure and triglycerides) as well as some cognitive benefit in older individuals with memory complaints, specifically in the paired associated learning test. Still, further studies are needed to determine if DHA substantially impacts AD progression.

It is easy to lose sight of the big picture when the field is often focused narrowly on specific molecular targets. In this issue, Michela Gallagher (Johns Hopkins University) reminds us that AD is a disease of neuronal systems, underlined by synaptic failure that begins very early in the disease process (Gallagher *et al.,* page 197-199). This paper shows evidence that hyperactivity in the CA3 region of the hippocampus, the brain region critical for proper memory function, precedes memory deficits in animal models as well as in humans. Therapeutic development efforts are focused on inhibiting this hyperactivity to hopefully prevent downstream synaptic degeneration, memory loss and pathology seen in later stages of AD.

Echoing the sentiments of Dr. Gallagher, James Malter (University of Wisconsin) also looks at AD as a systems-based disease and presents work on the Fragile X Mental Retardation Protein (FMRP), which has recently been shown to regulate the dendritic translation of APP downstream of mGluR5 activation (Malter *et al.,* page 200-206). mGluR5 antagonists can decrease Amyloid Precursor Protein (APP) translation and reduce Aβ40 in brain lysate. Work is ongoing to expand on these findings.

While Dr. Malter's program targets upstream of Aβ generation at the level of APP, Michael Wolfe (Harvard Medical School), Philip Williams (University of Hawaii) and Michael Sierks (Arizona State University) are all focused on intervening directly at the level Aβ generation using very different approaches. In these proceedings, Dr. Wolfe presents a summary of the discovery and development of inhibitors of γ-secretase that block Aβ generation while sparing Notch to prevent the side effects seen with pan γ-secretase inhibition (Augelli-Szafran *et al.,* page 207-209). He is currently testing these compounds for drug-like properties and is further developing them to meet the criteria of a clinical candidate. Next, Philip Williams provides a summary of work targeting the β-secretase cleavage of APP to prevent Aβ generation (Williams *et al.,* page 210-213). He is tapping the resources around him in Hawaii to screen for new BACE1 inhibitors using marine organism extracts, an innovative BACE1 inhibitor assay and cell-based screen. He then plans to use the novel methods he has developed to isolate the specific active components from these extracts. Alternatively, Michael Sierks presents an overview of his approach to block Aβ generation using engineered antibody fragments (Kasturirangan *et al.,* page 214-222). An antibody fragment (or nanobody) would inhibit BACE cleavage by specifically binding to the β-secreatase cleavage site on APP. This nanobody would be conjugated to a proteolytic antibody that cleaves at the α-secretase site, driving APP processing away from pathological Aβ generation towards the α-secretase pathway.

On the other side of the Aβ story is Aβ clearance, removing Aβ from the brain so that it cannot accumulate and cause dysfunction. Here, Robert Marr (Rosalind Franklin University of Medicine and Science) presents an overview of work validating a novel Aβ degrading enzyme with very high ho-

mology to the well-know Aβ enzyme neprilysin (NEP) (Marr and Spencer, page 223-229). This new enzyme, NEP2, looks to be playing a significant role in Aβ degradation. NEP2 knockout mice have an increase in Aβ levels across many brain regions. While there may be other endopeptidases that play a role in Aβ degradation and more needs to be understood about its mechanism of degradation, NEP2 looks to be an important and interesting target.

Even though amyloid plaques are known to accumulate early in disease, plaques do not correlate well with disease state and cognitive decline. Tangles, on the other hand, correlate very well with these clinical symptoms [7, 8]. Jeff Kuret is working on developing imaging agents that would specifically bind to tangles and not other amyloid aggregates, like amyloid plaques (Kim *et al.*, page 230-234). Since tangles are more closely associated with disease progression than amyloid plaques, such an agent could be used for early diagnosis and to monitor changes in disease progression. Achieving specificity for tangles is quite challenging, as is developing agents that are able to enter the cell to bind tangles. Through the use of pharmacokinetic modeling methods, Dr. Kuret has been able to develop agents that specifically bind tangles over α-synuclein deposits, but has yet to develop agents with specificity over Aβ deposits.

In addition to developing agents that bind tau tangles for biomarker studies, agents that can bind and also disrupt tangle formation could be used therapeutically. Karen Duff (Columbia University) presented work at the conference on developing a brain slice model for higher-throughput testing of compounds that disrupt tau aggregation. Here, she discusses initial results on some of the cyanine dye derived compounds that cause tau disaggregation (Duff *et al.*, page 235-240). Unfortunately, higher doses of these compounds seem to accelerate tau aggregation. Nevertheless, these results are exciting as modifications can be made to these compounds to increase their potency without the negative pro-aggregating effects.

Focusing on a relatively new pathology only recently being studied in AD, James Bamburg (Colorado State University) presents interesting work on targeting cofilin pathology in this issue (Bamburg *et al.*, page 241-250). Cofilin is a major regulator of actin dynamics and plays an important role in cell division, chromatin structure, transcription and membrane lipid metabolism. Cofilin can bundle with actin, forming abnormal actin/cofilin rods which accumulate in neuronal processes. These rods are found in AD brain and could block axonal transport of valuable cargo. It is possible that these rods could alter microtubule function and could even be the first step in the tau pathogenic cascade. Dr. Bamburg is working to develop ways to block this cofilin/actin rod formation through the use of peptides and peptidomimetic compounds.

Finally, to accelerate the development of new drugs, Graham Jones (Northeastern University) presents work on developing new methods for producing drugs for SPECT and PET imaging of AD (Kallmerten and Jones, page 251-254). These new techniques allow for much easier production of these agents. The agents can be produced in house on the order of days (rather than months at a separate facility) through the use of microwave energy and modern catalysts to accelerate synthesis, thus reducing time and cost. These techniques can be applied to many compounds and could, for example, allow for monitoring of drug distribution in the brain.

In summary, this special issue on the proceedings from the *10th International Conference on Alzheimer's Drug Discovery* conference highlights the diversity and the complexity of on-going drug discovery research for AD. The ADDF continues to support novel programs in academia and biotechnology companies, often considered too risky by other funding sources. By nurturing these novel ideas and helping catalyze research programs into drug discovery, we come closer to reaching the ultimate goal we all strive for – to preserve memory and cognitive function.

In closing, we would like to thank our sponsors of *the 10th International Conference on Alzheimer's Drug Discovery*: Pfizer Inc., Elan Pharmaceuticals, Martek Biosciences Corporation, Schering-Plough, Allon Therapeutics, Inc., JSW Lifesciences, Abbott, The American Journal of Geriatric Pharmacotherapy, Apredica, Intra-Cellular Therapies, Inc., and Rhenovia Pharma.

REFERENCES

[1] Small SA, Duff K. (2008). Linking Aβ and tau in late-onset Alzheimer's disease: a dual pathway hypothesis. Neuron. 60: 534-542.

[2] Pimplikar SW. (2009). Reassessing the amyloid cascade hypothesis of Alzheimer's disease. Int.J.Biochem.Cell Biol. 41: 1261-1268.

[3] Hardy J. (2009). The amyloid hypothesis for Alzheimer's disease: a critical reappraisal. J.Neurochem. 110: 1129-1134.

[4] Refolo LM, Fillit HM. (2006). Partnerships between philanthropy, government and industry are needed to advance drug discovery for neurodegenerative diseases. Curr.Alzheimer Res. 3: 175-176.

[5] Shineman DW, Fillit HM. (2009). A multi-targeted approach for a complex multifaceted disease. Curr.Alzheimer Res. 6: 407-408.

[6] Horton AR, Fillit HM. (2007). Drug discovery for Alzheimer's disease: filling the pipeline. Curr.Alzheimer Res. 4: 501-502.

[7] Braak H, Braak E. (1991). Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol. 82: 239-259.

[8] Ghoshal N, Garcia-Sierra F, Wuu J, Leurgans S, Bennett DA, Berry RW, Binder LI. (2002). Tau conformational changes correspond to impairments of episodic memory in mild cognitive impairment and Alzheimer's disease. Exp.Neurol. 177: 475-493.

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