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Small steps towards treatment of incurable neurodegenerative diseases

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Drug Discovery in Neurodegenerative Disease symposium
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At the *Drug Discovery in Neurodegenerative Disease symposium*, held 2–5 December at Cold Spring Harbor Laboratory, NY, USA various neurodegenerative diseases, including Alzheimer's (AD) disease, Parkinson's disease (PD) and polyglutamine disorders such as Huntington's disease (HD), Amyotrophic Lateral Sclerosis (ALS), Spinal Muscular Atrophy (SMA) and prion disease, were discussed with the purpose of elaborating on common therapeutic approaches, such as inhibition of fibrillization or neuroprotection. There was about an equal attendance from industry and academia and the objective of the meeting was to provide a progress update on translational medicinal science in CNS neurodegenerative diseases.

The NIH Molecular Libraries Roadmap Initiative (Christopher Austin, NIH, Rockville, USA) is focused on performing HTS on assays submitted by the research community, optimizing confirmed hits into *in vitro* chemical probes, and making all data and probes available to the community. In so doing, the Initiative hopes to encourage academic labs to screen less-precedented targets, for example, those relevant to neurodegenerative diseases that are less attractive to big pharmaceutical companies. This project has been empowered by the availability of chemical libraries and medicinal support from the NIH (http://nihroadmap.nih.gov/index.asp). An interesting case in point is the project on FDA-approved agents, a library of 1040 molecules that are currently on the market, which are tested in 29 neurodegeneration-related assays in 26 laboratories. Compounds from that library with a proof-of-principle activity in appropriate animal models can then be developed clinically much faster because an extensive clinical experience is available as they have been on the market for so long. This is an ideal solution for diseases with a much smaller incidence, such as ALS, Huntington, SMA and prion disease. In addition, the NIH provides support for follow-up critical resources in drug development such as production, bulk supply, GMP manufacturing, formulation, development of an assay suitable for pharmacokinetic testing and animal toxicology.

Well before the NIH Roadmap initiative started, the Laboratory for Drug Discovery in Neurodegenerative Disease (LDDN), Harvard Medical School (Boston, USA) was running a program to transform basic science insights into opportunities for drug discovery (http://www.hcnr.med.harvard.edu/programs/drugDisc.php). Greg Cuny presented the organization of the laboratory with, as an example, a project addressing the inhibition of neuronal cell death in a stroke model with an explicit application of the drug (LDN-53064) six hours post-occlusion.

Innovative chemistry

Many neurodegenerative diseases are characterized by the malignant aggregation of amyloidic proteins, such as β-amyloid and tau in Alzheimer's disease, tau in frontotemporal dementias and tauopathies, huntingtin proteins in Huntington's disease, α-synuclein in Parkinson's disease, and prion proteins in Creutzfeld Jacob's disease. There are common themes in this self-aggregation process, as evidenced by the oligomer-specific antibody that recognizes amyloidic oligomers, but not monomers or fibrils, irrespective of their primary sequence [1]. This opens the possibility to use similar or identical therapeutic agents, such as 4,5 dianilinophthalimide DAPH [2] as suggested by Vernon Ingram (MIT, Boston, USA) and James Shorter (Whitehead Institute, Boston, USA). Both speakers explored more kinetic details and similarities of the interaction between this compound and Aβ and yeast prion protein, respectively.

A 'Trojan horse' strategy uses a chemical trick to increase the molecular weight of small molecule inhibitors of protein–protein interactions. This approach makes use of bifunctional compounds consisting of a targeting moiety, which specifically binds to β-amyloid, and a recruitment moiety, which binds to the endogenous chaperone FK506 Binding Protein (FKBP). The resulting drug/FKBP complex substantially increases the steric bulk of the small molecule [3] and thus improves the potency of small molecule inhibitors of amyloid aggregation to yield nanomolar inhibitors of

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β-amyloid aggregation (Isabella Graef, Stanford Medical School, California, USA).

New organizational models for screening

One novel functional approach to drug discovery in neurodegenerative diseases was illustrated by Rebecca Pruss (Trophos, Marseille France), where functional assays based on primary cultures of specific brain neurons (e.g. trophic factor-deprived motoneurons for ALS and SMA, or genetically modified striatal medium spiny neurons for Huntington's disease) have been applied to high-throughput imaging screening (http://www.agl.univ-mrs.fr/trophos.asp). Once a hit is identified and lead optimization is performed, the target is subsequently investigated on a parallel track with the toxicity and PK aspects. This substantially shortens the time in drug discovery as target identification and validation comes in a parallel way rather than a sequential approach. The approach has identified compounds that are active in animal models and one compound, TRO19622, is now in Phase 1 clinical trials for SMA and ALS.

Automated screening of human disease in *Drosophila* models can also accelerate the discovery time (Chris Cummings, Envivo Pharma, Boston, USA) because of the simplicity to develop transgenics, the short *Drosophila* lifespan, the strong conservation of genes between flies and humans and the advantage of whole-organism phenotypic screening (http://www.envivopharma.com/). An example of a discovery process in a model of Huntington's disease was given using an automated industrialized phenotype profiling (one compound every 10 seconds).

Another novel approach for increasing the throughput of *in vivo* pharmacology is based on the advances in automatization and the use of bioinformatics to increase statistical power (http://www.psychogenics.com/), in addition to clever optimization analysis that can reduce the number of animals by designing successive phases of screening and prioritization while still preserving the necessary power to detect beneficial effects (Dani Brunner, Psychogenics, NY, USA).

Advances in Alzheimer's disease

Eckhardt Mandelkow reviewed the extensive work of the Max-Planck lab in Hamburg on tau protein. Using tools ranging from electron microscopy to molecular biology to transgenic animals, they identified key parts of the tau protein necessary for PHF formation. A number of small compounds (anthroquinones-like daunorubycin) were found to prevent PHF formation and disassemble preformed PHF in an *in vitro* cell system. They are now planning to test these compounds in a Dox-inducible ΔK280 tau transgenic animal.

Advances in ALS and SMA

As an example of a successful drug identified from the FDA approved library, a beta-lactam antibiotic, ceftriaxone, was found to increase the expression and the function of glutamate transporter protein *in vitro* and *in vivo*. This protein was also neuroprotective in three other *in vitro* screening assays based on mutant superoxide dismutase (SOD1) toxicity and glutamate toxicity. Furthermore, the drug-induced overexpression of the transporter was neuroprotective *in vitro*, in models of ischemic injury and in glutamate-mediated motor neuron degeneration. In the G93A SOD1 transgenic animal model of ALS, the drug delayed loss of grip strength, delayed loss of motor neurons, and increased survival (Jeff Rothstein, Johns Hopkins, Baltimore, USA). This compound is scheduled to enter clinical trials in 2005.

Patients with SMA have a missing or a dysfunctional survival motor neuron gene 1 (*SMN1*) gene, and low levels of the SMN protein. Funded by the Families of Spinal Muscular Atrophy, a drug discovery program aimed at increasing the amount of full SMN protein starting from the functional SMN2 gene has yielded a compound with a quinazoline scaffold. This compound is metabolically stable in dogs and humans and will be tested in appropriate animal models (Mark Gurney, deCode, Illinois, USA).

The patient in perspective : translational medicine

Three clinical trials were presented on disease-modifying agents. Francine Gervais (Neurochem, Montreal, Canada) gave an update on the clinical status of Alzhemed, a GAG mimetic, currently starting two pivotal Phase III trials. The compound had its biggest effect in mild AD cases, both in terms of lowering Cerebro Spinal Fluid (CSF) Aβ42/40 ratio and in cognitive stabilization. As an example, nine out of 13 mild AD patients in the open-label extension did not deteriorate in the ADAS-Cog over a period of 20 months.

Larry Sparks (Sun Health Research Institute, Arizona, USA) presented the results of a small (63 evaluable subjects) double-blind placebo-controlled one-year study with atorvastatin, added to standard care (AchE-I). This was based on his long-time research into the relationship between cholesterol and Aβ metabolism. Atorvastatin-treated patients showed in the Alzheimer Disease Assessment Scale Cognitive subscale (ADAS-Cog), a 4-point superiority to placebo at the end of one year and unexpectedly a significant improvement on the Geriatric Depression scale and a trend for benefit on the Neuropsychiatry Index. Interestingly, atorvastatin had been documented not to cross the blood–brain barrier.

John Collinge (Medical Research Center, London, UK) presented an overview of the ongoing preclinical and clinical activities in the area of vCJD, including the design of the recently started PRION-1 study, using quinacrine. The particular nature of the disease precludes the use of a double-blind placebo-controlled approach, so the patients were offered three possibilities, as follows: (i) 16 patients enrolled in the open-label non-random quinacrine treatment arm; (ii) 15 selected to be followed for the natural history; and (iii) none opted for the randomized immediate versus six-month delay quinacrine treatment.

Computational neuropharmacology (Hugo Geerts, In Silico Biosciences, Philadelphia, USA) is an innovative approach for supporting the design of clinical trials in CNS disorders, and addressed the possible problem of polypharmacy with neuroleptics and antidepressants in these patient populations. Indeed, G-Protein Coupled Receptors, which are the target of psychoactive drugs, have been shown to interfere with intracellular pathways typically associated with disease-modifying approaches and vice-versa. For example, using computer simulation of the documented interaction between different subcortical basal ganglia areas, a much better prediction of the extra-pyramidal

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symptomatology with existing neuroleptics has been achieved, thus potentially increasing the predictability of the clinical outcome with novel therapeutic agents (http://www.in-silico-biosciences.com).

Concluding remarks

The conference addressed a number of scientific and pharmaceutical issues, but did not neglect the contextual and ethical aspects of drug development for many neurodegenerative diseases, which are not well covered by the efforts of the private pharmaceutical companies. This area has benefited much from genetic manipulation of various species, such as mouse, *Caenorhabditis elegans*, zebrafish and *Drosophila*, with a positive impact on the development of functional assays for the drug discovery process. The NIH Roadmap Initiative has provided an incentive and a support framework for many academic centers to capitalize their biological expertise in the discovery of new drugs, while the pioneering work form the UK Prion group has provided an ethical approach to the design of clinical trials in these incurable devastating diseases.

This conference has presented some concrete progress in the translational science of neurodegeneration, both in diseases with a large societal impact and in more rare diseases with a small incidence. No doubt we will know in the next few years which one of the scientific projects will provide clinical benefit for the patients.

References

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