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Meeting Report

Teaching old drugs new tricks

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Meeting of the Neurodegeneration Drug Screening Consortium, held on 7–8 April 2002, Washington, DC, USA.

At a precedent-setting meeting of the Neurodegeneration Drug Screening Consortium, investigators from 26 academic laboratories joined forces to speed the search for treatments for neurodegenerative diseases. The researchers reported preliminary results from their testing of 1040 drugs, most of which had been US Food and

Drug Authority (FDA) approved. The testing formed part of a novel program co-sponsored by the National Institute of Neurological Disorders and Stroke (NINDS), the Huntington's Disease Society of America (HDSA), the Amyotrophic Lateral Sclerosis Association (ALSA) and the Hereditary Disease Foundation (HDF). Collaboration, rather than competition, energized the participants as they considered clues that could lead to effective treatments for devastating neurological diseases.

Treasure-hunting in the pharmacopoeia
The idea underlying the program was to tap into the treasure trove of potential therapeutics in the pharmacopoeia, trying to find new uses for known drugs. The 26 investigators each carried out 'blind' tests on the same set of 1040 compounds, which had been selected in association with MicroSource Discovery Systems (Gaylordsville, CT, USA). Their mission was to screen for compounds that interfere with neurodegeneration in simple experimental models (Table 1).

In an effort to focus on the most potent (and therefore, the most clinically promising) drugs, the screens used concentrations likely to be achievable in humans. The collection was enriched for compounds known to cross the blood–brain barrier, and included FDA-approved drugs, controlled substances and natural products. Because the toxicological profiles of most of the drugs are known, active compounds will face a shorter path to clinical trials than would novel drugs.

By joining the consortium, participants agreed to share and compare results. At the April workshop, each investigator outlined his or her strategy, described the particular assay or assays they had been using and summarized their results. Because all the consortium members tested the same set of drugs, the project has the capacity to provide insights into pathogenic mechanisms common to several diseases.

The 29 assays each emulated some aspect of neurodegeneration. For example, eight assays targeted protein aggregation, which is thought to contribute to pathogenesis in amyotrophic lateral sclerosis (ALS), Parkinson's disease, and polyglutamine diseases. Other assays tested effects on excitotoxicity, caspase activation and mitochondrial dysfunction – processes implicated in many neurodegenerative diseases. Other assays were more phenomenological, looking for agents that blocked the cytotoxicity of disease-causing proteins without making assumptions about disease mechanism. The proteins tested included mutant superoxide dismutase (SOD; an enzyme altered in familial ALS) and several polyglutamine-containing proteins implicated in Huntington's disease (HD), spinocerebellar ataxias and Kennedy's disease. Regardless of rationale, all the assays addressed neurodegeneration processes.

Before the meeting, each participant listed the compounds with the greatest activity in their assay(s). The 29 screens yielded 294 different 'hits' – compounds with activity in one or more assays. From this preliminary list, 82 compounds showed activity in more than one assay, with 17 compounds active in three or more assays.

These overlaps are intriguing. Given the distinctiveness of each assay, some participants had not expected many

Table 1. Neurodegeneration Consortium assays^a

Target disease	Type of assay	Model system
Polyglutamine diseases	Polyglutamine cytotoxicity	Cell culture, <i>C.elegans</i> (2), <i>Drosophila</i>
	Polyglutamine caspase activation	Cell culture
	Polyglutamine aggregation	Cell-free (3), cell culture (2), yeast (3)
Amyotrophic lateral sclerosis	Polyglutamine turnover	Cell culture
	SOD toxicity	Cell culture (3)
	SOD aggregation	Cell culture
Parkinson's disease	α -Synuclein toxicity	Yeast
Familial dysautonomia	RNA splicing	Cell culture
Spinal muscular atrophy	RNA splicing	Cell culture
Neurodegeneration (general)	Excitotoxicity	Cell culture (3), slice culture
	Mitochondrial function	Isolated mitochondria (2)
	Apoptotic protein association	Cell-free

^aNumbers in brackets indicate the number of assays performed. Abbreviation: SOD, superoxide dismutase.

overlaps; others were surprised at their paucity. It was suggested that further examination of the effects of each compound (e.g. at higher concentrations), might reveal more about shared pathogenic pathways.

Finding compounds with potent activity in more than one assay generated enthusiasm, curiosity and the promise of more experiments. For example, eight compounds overlapped in two or more assays of polyglutamine toxicity, including tests in cells, flies and worms. Similarly, seven overlaps were found in assays related to ALS, based both on mutant SOD toxicity and on excitotoxicity. Overlapping compounds could work on shared pathways, although the data need further evaluation. With cautious optimism, the group is now developing strategies to validate initial hits and to analyze the data more extensively, to look for further commonalities. If detailed examination supports cross-disease overlaps, the consortium will have provided strong support for the notion of

mechanistic commonalities among neurodegenerative diseases.

Mining the data

One of the most important outcomes of the meeting was the resolution to examine all data with greater rigor, with the goal of identifying the most promising drugs from the long list. Participants formulated plans to establish a shared database, to apply common statistical methods and to search for common chemical features. Because many compounds in the pharmacopoeia are chemically related, this detailed analysis might reveal features that are consistently associated with activity. With so many disparate assays, standardizing the format for data entry will be especially tricky – but this task is crucial to permit rigorous analysis of the degree of shared activities. The standardization and compilation of data from so many different assays is unprecedented outside the pharmaceutical industry and no such data set currently exists in the public

Key conference outcomes

- In a precedent-setting project, 26 laboratories joined forces to speed the search for treatments against neurodegenerative diseases, including Huntington's disease and related polyglutamine diseases, amyotrophic lateral sclerosis (ALS), Parkinson's disease and spinal muscular atrophy.
- All investigators performed blinded screens of 1040 compounds, mostly US Food and Drug Authority (FDA)-approved drugs.
- Investigators presented results from 29 different assays designed to emulate multiple processes involved in neurodegeneration.
- Of the 294 active compounds found, 82 were active in more than one assay and 17 were active in three or more assays.
- Eight compounds overlapped assays of polyglutamine toxicity and seven compounds overlapped in ALS-related assays.
- A database has been established for statistical analysis to analyze overlap, uncover common chemical and structural features of active compounds, and identify new chemical activities and mechanisms.

domain. Public access to the data will await peer-reviewed publication, anticipated in early 2003.

In addition to the possibility of identifying clinical candidates, one outcome of the program is certain to be the discovery of new biological activities of known drugs. This will inform new attempts to dissect pathogenic mechanisms and identify sub-cellular and molecular players. Further, even if none of the 1040 compounds is immediately useful for humans, the information about their unexpected actions should provide valuable leads to the development of related drugs.

Cautions

Most of the tested drugs are currently available to doctors and, thus, to patients. All consortium participants were

concerned about the premature release of potentially misleading preliminary data. Both the participants and the sponsors of the consortium are naturally eager to move potential treatments quickly from bench to bedside. With this goal in mind, all agreed to expedite careful statistical analysis and to publish as quickly as possible. All also agreed on the desirability of extending the experiment further, to the rapid testing of candidate compounds in animal models of neurodegeneration.

Conclusions

Although the scientific impact of this unusual collaboration is still unknown, the results of the cooperative experience are clearly positive. Investigators from 26 independent academic laboratories exchanged unpublished data, formulated shared goals and devised a plan to achieve

them. Whether or not a new treatment immediately emerges from this effort, this consortium has already defined a new method for joining forces to speed drug discovery in academia.

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Exploring brain connectivity: a new frontier in systems neuroscience

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Functional Brain Connectivity, held on 4–6 April 2002, Dusseldorf, Germany.

The organization of the primate brain is based upon two complementary principles. The first is that of 'modularity' – specialization of function within different regions of the brain, with local assemblies of neurons in each area performing their own unique operations on their inputs. The second is that functions are emergent properties of interacting brain areas within networks. This dichotomy lends itself to two corresponding approaches to explaining function. One is 'functional segregation', in which the aim is to localize functions to specific brain areas – this has been the dominant approach. The other is 'functional integration', in which function is explained in terms of the flow of information between brain areas. Until recently, there has been little focus on the distributed nature of information processing in the brain. However, lessons from traditional neuroanatomy and neurophysiology tell us that the application of functional segregation on its own will not explain brain function:

the brain is a massively parallel structure. It is composed of numerous networks of interconnected areas, and information is transferred and transformed within these. The challenge now is to understand brain function in terms of the dynamic flow of information in neuronal networks across the brain. Recently there has been a rapid expansion of interest in this issue in several different disciplines. Each has made significant contributions and has generated its own perspective on the issue, but this level of diversity makes integration between disciplines difficult. To redress this, Rolf Kotter (C & O Vogt Brain Research Institute, Dusseldorf, Germany) and Karl Friston (Wellcome Dept of Imaging Neuroscience, London, UK) organized a multi-disciplinary workshop on Functional Brain Connectivity. The conference brought together researchers from several disciplines whose common interest was to develop a better understanding of how the principle of functional integration is implemented in the brain. It is beyond the scope of this report to cover the events in the workshop

comprehensively. Rather, we have focused on four themes that emerged as key areas of interest and controversy.

Conceptual and theoretical frameworks for studying connectivity

One of the emergent themes at the workshop was the realization that the widely used terms 'functional' and 'effective' connectivity have had different meanings depending on the scientific background of the researcher. General discussion resulted in a degree of convergence. Studies of functional connectivity look for temporal correlations between neurophysiological events, regardless of the anatomical routes through which such influences are exerted. However, studies of effective connectivity look for the influence that one neural system exerts over another in the context of a particular anatomical model that specifies such routes a priori. The characterization of brain activity in terms of functional connectivity is therefore 'model-free', whereas the characterization of brain activity in terms of effective connectivity requires a 'causal