

Hereditary Disease Foundation
Workshop on Drug Discovery for Huntington's Disease
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Executive Summary

Thirty-three scientists pursuing a wide range of research interests convened for a two-day workshop sponsored by the Hereditary Disease Foundation (HDF). The purpose of the workshop was to focus current research efforts in Huntington's Disease (HD) on discovering and developing drug treatments for HD. Currently, no drugs are available that treat the cause of HD – mutations in the huntingtin gene that result in CAG repeats of varying lengths. Assays have been developed to test the effects of compounds at various stages of the purported HD pathological pathway. "Hits" (promising compounds) have begun to emerge from these assays. The main goals of the workshop were to identify criteria for selecting compounds for further testing and to determine the best procedure to follow once primary hits are identified. Speed and thoroughness are both important at this stage.

Several criteria for identifying lead compounds were discussed. However, it was generally agreed that it was too soon to choose criteria for all to follow. Participants agreed that all assays should continue in parallel, until some patterns begin to emerge. Mechanistic and phenominological assays should be developed for HD. Screens should begin with FDA2000 libraries of at least 1,000 compounds and move to larger libraries. Investigators must develop counterscreens for their assays, with potential deselection criteria including toxicity and suppression of expression from CMV or another promoter. An efficacy level of 10mM was proposed. Compounds effective in the nM range should be tested in mice. However, it was agreed that no hits should be discarded, because analogues might be more efficacious. Potency should be maximized before pharmacokinetics or *in vivo* efficacy studies.

Limiting factors were discussed, including costs, funding, research interests of investigators and chemists, availability of libraries, screening speed, and intellectual property issues. Creation of a centralized facility for high-throughput screening was proposed, perhaps through the NINDS. Potential resources for assisting in moving compounds into the clinical trial stage include the NINDS epilepsy drug discovery program. Many participants expressed interest in a common database of hits, allowing individuals to make private arrangements for sharing and partnership. Hits might be sent out blind, with negative controls, and with several assays performed on the same set of compounds. The HDF might speed this process by facilitating it. It was also proposed that the HDF maintain an updated model of HD pathological pathways. The HDF might play a facilitating role in other ways, for example by funding of visits to the NIH for training. Several participants commented on the willingness of other participants to share

information, and expressed the hope that intellectual property issues could be handled so that some of that openness might continue.

The following topics were covered:

1. Criteria for selecting compounds to move forward into animal and clinical trials
2. Other compound screening models
3. Current understanding of pathways of HD pathologies
4. Research updates from the participants' laboratories
5. The current state of compound libraries and plans for further library developments
6. The NINDS/NIH funding process, and how it applies to HD research

Day One

Introduction

Allan Tobin began the meeting with a comment from Milton Wexler: "If you get a small number of people together in a room, they will freely associate and exchange information freely." He and Nancy Wexler expressed the hope that, although a relatively large number of participants were at this workshop, all would feel they were part of one family, speaking freely.

The Foundation started when Wexler's mother, who studied *Drosophila*, developed Huntington's Disease (HD). Her mother's three brothers and their father died of HD. In Venezuela, 11 of 13 children have it. It's a prevalent, yet hidden, disease. Their family talks about it openly and publicly, which helped them to fight it better. But most families aren't as lucky. There's a huge stigma, as with HIV, but there's no treatment, except for depression treatment. "That's why we're looking to you" for help.

Ethan Signer said primary screens are beginning and would come up with compounds – probably more than are easily handled. He noted the need for a rational way to choose compounds for further screening. The Foundation is considering whether to set up a committee to choose compounds for further screening.

Carl Johnson said the primary question is which primary screens should be pushed forward, which compounds, and where those primary screens are going to be done. He said an aim of this workshop would be to come up with some consensus on these questions – with the expectation that the consensus would be of a high standard. Then a system could be established to fulfill the agreed-upon goals.

Compound Selection Criteria

Tobin posed the questions, which assays are most important: yeast primary cells, *in vitro* assays, worm assays, fly assays, etc? Which is the most relevant? Should we look for compounds that are successful in all or only some of those assays? Christopher Henderson recommended multiple solutions for the moment, with the hope of seeing a compound work in multiple assays. Tobin and others noted that all compounds would eventually have to be funneled into clinical trials, and that the first "constriction point" would be the mouse model. One mouse trial (for example, with minocycline) costs

\$25,000, using mice that develop symptoms early. It's unrealistic to think of testing 100 compounds, Signer said.

Wexler emphasized that the process to be used once hits are found should be discussed now. She noted that, before the HD marker was found in 1983, the HDF organized a workshop on what to do when the marker was found. Many people thought that workshop would be premature, but the marker was found just before the workshop.

Brian Pollok said that hits from primary screens may not be efficacious enough to work in animal models, even if they cross the blood-brain barrier. Finding compounds that work at a micromolar level will require costly chemistry. Within the next 12-18 months, the Foundation will have to determine what the most promising compounds look like and how many they can afford to take into chemistry. Some may be of sufficient potency to take directly into animals. But there will need to be oversight of validated hits that warrant chemistry. Pollok recommended the following steps:

- Validate that hits have specific activity. Ensure potency – single-digit micromolar - that can be translated into animals.
- Engage chemists as well as biologists now.
- Determine chemical tractability, pharmacokinetics (expensive) of the compound. It's unlikely that "big pharma" will take this task on, even for the lead compounds. Some companies will do contract work. It depends on which company would be suitable for the given compound's backbone.

The possibility of finding a compound that is a candidate for other neurodegenerative diseases was discussed. Cynthia Bamdad suggested such compounds might simply be toxic, and not target the specific disease process underlying HD. Pollok said that counter-screens during validation would show whether there was induction of cellular apoptosis or another toxic effect. He recommended looking for specific effects on the Huntingtin protein. J. Paul Taylor added that, in cancer research, specificity isn't crucial. However unlike for cancer, drug administration for HD will have to be chronic, so low toxicity is more important. Ingram said that efficaciousness in more than one disease would depend on the cause of the overlap. For example, the common denominator might be beta sheet formation or a stable non-beta intermediate. Jochen Knolle said that, in the absence of a clear understanding of the pathology, it is important to have an idea of the relevant *in vitro* screens and to prioritize those screens. It will be important to look early into whether the compound crosses the blood-brain barrier and whether it is taken up selectively in damaged versus healthy neurons. There is a formulation problem: if we talk about an antibody, transition will be faster. You see uptake of antibodies into neurons. It's important to look at a class of compounds, and make sure the pharmacokinetics, pharmacodynamic, toxicity are acceptable.

Johnson estimated the number of compounds that would result from primary screens would be between 10 and 100, based on a screen of 1 million leading to a 1% hit rate, which could be further narrowed down to about 50. Alex Kazantsev noted that poor screens might produce irrelevant hits. Pollok added that an orally active compound needs 50 nM affinity. Sherman and Tobin identified three groups of primary screens:

aggregation, toxicity, and dysfunction. Sherman said it's unknown whether aggregation is good or bad, so the two require different funnels, with different sets of criteria.

Screening Models

The National Cancer Institute drug screening and selection model was discussed. Other screening models besides the NCI model include those for Parkinson's disease (which tend to be phenomenological), Alzheimer's disease (not very successful), and AIDS (very successful). Johnson noted the difference between the biochemist's approach - working from compound that works, backward to the reason it worked - and the geneticist's approach, working forward from gene to disease. Neither is necessarily better. The interactive process of discovery between the different approaches is apparent in HD. Tobin noted that the R6/2 mice may have led to too much focus on aggregates, which may be irrelevant. But Wexler noted that those mice were the reason for looking for, and finding, aggregates in humans.

Tentative Huntington's Disease Pathway

Kravitz suggested that the Foundation should make widely available a model of HD pathologies, periodically updated to reflect current understanding. Subsequent discussion listed a number of pathological events, with the caveat that the order of the individual pathological processes is still unclear.

1. **Protein cleavage.** There may be many cleavage products, resulting from different proteins acting at different cleavage points. Whether cleavage is required for pathogenesis, and if and when it occurs, remain unclear. Kazantsev noted evidence that cleavage may depend on polyQ length. Signer noted that cleavage may not be essential for transport into the nucleus. Ivelisse Sanchez noted that the assumed path after cleavage and the path for degeneration might not be the same. It's unknown whether the full-length Htt^{ex} (expanded, pathogenic huntingtin protein) is itself toxic.
2. **Nuclear localization.** Most researchers have found Htt^{wt} (wild-type huntingtin) in cytoplasm only, but Htt^{ex} in the nucleus as well. Most groups have found cleaved Htt^{ex} in the nucleus; one group found uncleaved Htt^{ex} in the nucleus.
3. **Caspase induction** (caspases 8 and 3). It's unclear which ones are induced, which ones matter in pathogenesis, or whether their activation produces apoptosis.
4. **Mitochondrial effects.** Energy metabolism is compromised in late-stage HD. Whether it is part of the disease pathogenesis or just a cell's "last gasp" is unknown. If mitochondria are compromised, mitochondria may be lost with time. There are changes in complex 2 and complex 4 compromise, as well as alterations in small molecules in the electron transport chain.
5. **Calcium homeostasis** (in YAC mice). It is unclear whether this is an early and causative process or a late-stage, nonspecific phenomenon.
6. **Selectivity.** Striatal neurons are lost during the disease process, but this loss may be a late-stage event. There is some evidence for earlier loss of cortical and hippocampal cells.
7. **Aggregation events.** It is unclear whether aggregation is pathogenic or protective.

8. **Transcription events.** It is possible that 90% of polyglutamine (polyQ)-containing proteins are involved in transcription, and so could be involved in HD. There are too many scientifically plausible pathways, and we don't know how to test to distinguish which are important.
9. **Murder or suicide** – which is it?
10. **Function of normal Htt.** Is Htt needed in the adult brain? If so, we must knock out mutant, not Htt^{wt}.
11. **Proteasome function.** Htt^{ex} may “clog” or somehow modify the ability of proteasomes to degrade damaged cellular proteins.

Shuttle Peptides

Shuttle peptides have some toxic effects, but are highly efficient at getting into cells. Two classes of peptide penetration are possible: nonpolar and positively charged. Cellgate's (R6) hexa-arginine is among the most efficient and could help transport single-chain antibodies. Other peptides are derived from Antennapedia, VP22, and TAT (from HIV).

Next Generation of Libraries

Valery Folkin said that as many compounds as possible should be screened against primary assays, if easily modified compounds are available. Using the “click chemistry” developed at Scripps, analogs of compounds are relatively easy to make once hits are made: Hits from this library can be synthesized and modified in large amounts.

Scripps has openly available, large random libraries of small, non-peptide-based SPONCH compounds with molecular weight less than 1000. There are 7000 compounds in 96-well plates and 25,000-30,000 compounds in mixtures. They can eliminate DMSO if necessary (currently the compounds are in 20-50 mM DMSO). They also have some compounds in solid form, molecular weight (MW) 400-800, more hydrophilic than hydrophobic. The representation of their compounds in 3D space is nontraditional, with nonmetabolizable backbones. There are as many as 10^{61} small molecules with MW under 1000, but only 10^8 are likely to be biologically meaningful. Standard combinatorial libraries now have about 10^6 compounds. Pollok noted Lipinski's rule for pharmacologically active compounds – what a drug-like molecule should look like.

Knolle said that most drugs in the pharmacopoeia have a MW less than 300. The most efficacious are more hydrophobic than hydrophilic; peptides are a good starting place. Brent Stockwell noted that the 300 MW of current drugs may reflect the bias of what chemicals could be synthesized 50 years ago. Most were discovered by random screen. There are now 20,000 compounds from Congenics; 2000 from NCI and 2000 with known mechanisms and known target compounds; 1,536 FDA-approved drugs, 20,000 FDA-approved products.

Hughes noted that natural products have more biologically relevant diversity, even with smaller numbers. Stockwell noted the small amount of natural products available, and the need for a renewable source. NCI has many, but they aren't easily used for high-throughput screens.

Pollok said there are four vendors of FDA-approved compounds (with no appreciable differences between them): Contact Services, Congenics, Chembridge, and RBI (Lopac).

Day Two

The Government Funding Process

Funding issues include the need for private funding at some point, and the value of government databases. Robert Baughman described different ways in which the NIH solicits proposals:

RFAs - Requests For Applications for grants. Typically, all applications are reviewed at once, with a few million dollars set aside for these projects. Out of 12 applications for HD, for example, 4 or 5 would be taken.

RFPs – Requests For Proposals for contracts. RFPs are similar to the RFA, but are reviewed by the technology review committee. The NINDS funds few contracts compared to grants.

RFIs – Requests For Information. RFIs apply only to contracts. They are sometimes put out, about 6 to 9 months before RFPs, to explore whether the request is reasonable based on people's capabilities. About 90 percent of RFIs lead to RFPs. There is now an RFI out for a high-throughput screening facility for neurodegenerative disease (NS-01-005). The purpose is to translate decent screening ideas from the lab bench to a high-throughput format.

Research Organization Issues

Research organization issues include whose libraries should be used, who should do the work, and whether there should be a centralized facility for certain aspects such as high-throughput screening.

Five separate issues were identified:

1. Libraries
2. Assay Development
3. Screening facility
4. Database for results
5. Toxicity, pharmacokinetics, pharmacodynamics

Funding and division of labor

Ethan Signer said that the NINDS focus on the front end, because industry is more likely to fund later stages. The critical component is the library, which is usually beyond the budget of individual labs. Of the many libraries available, it's impossible to tell which are the best. One way to test them would be to develop a panel of known enzymes and get together the best minds to develop a diverse library. Government-sponsored libraries might be developed on the study/peer review basis. Baughman said no such proposals

have been sent to the NINDS, but one could be generated from within. Goodman said the smaller labs might be encouraged (funded) to focus on library development.

Pollok said Tripos has a standardized system that works well according to chemists. He noted that there would be a problem translating assays from labs to a central facility, which would mostly have to start over again. One would want to limit the formats used in the facility. Bamdad said standardized formats might not suit a particular need. Signer said that once an investigator puts together a proposal, he or she might meet with researchers from the screening facility to develop an assay.

There was some disagreement about whether small laboratories had the interest in doing the repetitive work involved in screening, versus whether larger facilities were specialized enough for the needs of HD researchers. Sanchez noted that planning the automation would be critical.

Ross noted the Center for Inherited Disease Research (CIDR) model, which will do genome screening if an assembled pedigree is available, though it may take time (perhaps 1.5 years) to get on the list. In its drug discovery program, the Huntington's Disease Society of America (HDSA) will ask academic investigators to screen the FDA2000 library for proof of concept. Signer suggested the NIH or a contractor could train people on a short-term basis. For biochemical assays, screening against 100,000 compounds a day is possible.

Pollok liked the idea of assays against a small set of compounds; 100 screens a year are possible. One set of scientists should develop screens, another perform them, and a third "cherry pick" compounds, he said.

Wexler was concerned that a central facility would become overloaded. Schechtel noted that government initiation, at the right time, might attract the "best minds." Signer noted that government is focused on small science, but HD research now needs big science. Knolle said that because the technology is evolving rapidly, a library should be developed and then contracted out (lots of companies are appearing), without creating a government facility. Bamdad said some assays are generalizable, so why not have several parallel paths?

Baughman said the government's creation of libraries and laboratories would likely be by contract, as a pilot. He said the genome projects showed the government process is inherently fairer, but slow. However, the government's involvement might increase industry interest. The genome projects involved data sharing, but issues of sharing remain. Ross noted the genome was a one-time project, while the HD effort will be ongoing. Housman said that a public domain library would have the largest impact, because creating such a library is too large a project for an academic lab, and big pharmaceutical companies already have proprietary libraries. (SBIR funding constitutes 2.5% of the total NIH extramural budget.) Library creation might best be done in an SBIR format.

Signer said the best way to proceed might be to start an entity that would do only high-throughput screening for HD. Problems to surmount would include equipment procurement, training, and management. Housman echoed Bamdad's point that most assays are inappropriate because they are designed for high-throughput. The more standard H-T assay is biochemical or cell-based.

Ingram said his peptides are about 5 micromolar; AD compounds are <10 micromolar; Wanker's best compounds are <10 micromolar.; Sherman's are 10s of micromolar in a cell-based assay.

Information exchange was discussed. Ross noted that the previously discussed exchange of compounds was completely voluntary. Thompson noted that people are naturally curious, so truly blinded testing may not be possible, though it would be possible to avoid sharing that information. Hughes has some hits with FDA2000; Gullans (or Hughes) has interest in characterizing compounds, himself, which NCE says he can share only as coded compounds. Johnson said participants in sharing compounds could file a disclosure, agree not to violate by determining the structures. Signer noted that universities wouldn't agree to the Foundation administering patents.

Heemskerk said the NINDS is now considering an RFA for low-throughput screens of FDA-approved compounds (for which there's no secrecy problem), working through an administrative supplement mechanism. This could quickly identify a set of assays for late-onset neurodegenerative diseases. NINDS might provide investigators with standardized kits, pure collections of compounds, including favorite compounds such as minocycline. Investigators would report compounds and range of efficacies to the NINDS. After about 6 months, participants could convene to see what worked at 1 mM or less. The concept has been approved, but there are IP issues for both individuals and universities, though the government has ways around that issue (by demanding control of the data). Compounds must be patent-protected (or be potential candidates for a new indication) to motivate companies.

Kazantsev said Massachusetts General Hospital might be a good centralized facility. There is a Partners-wide facility (Robolab). Anne Young has a smaller version that can interact with it (CAGN). There's an effort at Whitehead as well. Heemskerk said all are eligible for an RFI described contract.

Wexler asked which of the FDA-approved libraries is best - Gullans, MS Discovery, or Prestwick Chemical (DC, Kitty Clarence-Smith). These libraries were designed with clinical trials in mind, from identifying hits to 700 nonredundant compounds with chemical diversity. The compounds can be screened in a low-throughput manner, and the company can provide more of the same compounds in a 96-well format. MS Discovery has made everything available and also has natural product libraries. There are also nutraceuticals, including controlled substances, which are promising because they get into the nervous system. These companies provide CDs with data; they will test any hits against other compounds in that class. Another library from New Chemical Entities,

recently acquired by Albany Chemical, was mentioned. Called Chemifocus, it is chemically diverse and has about 800 unique plant and microbial compounds.

Tobin suggested that the Foundation do only one library at a time. A “drug czar” could help coordinate reporting back to the NINDS. Heemskerk said the NINDS might identify a set of diverse compounds for which it would run screens and provide information on structure-function relationships. Kasantzev noted the need to act now, before the field goes “out of fashion.” Mice need to be ready when the compounds are ready.

Priorities

- The group discussed whether to set up criteria for lead compounds, but many felt it was too early to do so. Signer said all assays should be run for initial screens, using the quickest tests first, and working in parallel in cells, flies, and worms.
- Screens should start with FDA2000 libraries and move to bigger libraries (e.g., from Scripps, or Whitehead). Individual investigators should do about 1000 or so compounds in FDA2000.
- Developing a counterscreen is the responsibility of each investigator. Potential deselection criteria include toxicity. Sensitivity is assay-specific – compounds must not affect reporter molecules. If the readout is cell survival, a counterscreen might be to test against other chemical insults. Compounds that work in several assays can be considered validated (Tobin). Ten micromolar might be considered a hit. Compounds must not suppress expression from CMV or another promoter (Henderson). (This assay might be worth soliciting. A measurement might be a luciferase assay with the same promoter.)
- Anything in the nM range is ready for humans and mice.(Heemskerk)
- Don't throw out hits, because analogues may be far more efficacious. Look for cell toxicity first. (Bamdad) The example of Congo red was discussed: it works in aggregation assays, but is toxic if fed to mice. Congo red is nontoxic if delivered by pump ICV or IP (effective at 45 mg for 48 hours).
- A common database of hits from a given screen might be set up, allowing individuals to make confidential arrangements. Hits might be sent out blind, with negative controls.
- It's best to have different assays on the same set of compounds. If the Foundation coordinates this, everyone's work will go faster. (Pollok)
- Focus on increasing potency before doing pharmacokinetics (pre-screen) or *in vivo* efficacy studies. Official FDA toxicity studies are expensive and should come later - \$ 1 million per compound in rats, when good manufacturing practice (GMP) is followed.
- Do predictive toxicology. In the mouse model, it's important to know that the compound gets in at the right concentration, so if it doesn't work, it's not because it doesn't get in. First, the compound must not be toxic to cells. (Pollok). If it's toxic in mice, that's a negative screen(Signer).
- Mechanistic and phenomenological assays should be developed for HD. (Tobin). Screen libraries of at least 1,000 compounds. Then share compounds to determine if hits should go into mice. Most investigators don't want to screen 100, 000 hits; we need a special laboratory for this.
- The Foundation can catalyze the exchange of information, for example by paying for visits.

Final Comments/Wish Lists

Participants were asked for comments on the workshop and for “wish lists” for the near future. Most participants noted the generosity of other participants with their information and willingness to cooperate, as far as their institutions’ requirements regarding intellectual property rights permit. Experiments participants wish to conduct or have the NIH conduct include:

Ingram plans to develop pentapeptides, improve by modifying side chains; test these in aggregation assays and look at cell-based assays for death and for dysfunction, specifically at Ca^{2+} homeostasis. Ingram would like others to test compounds found to be efficacious at 1-10 mM in animal models, even without animal toxicity studies.

Bamdad is looking for constructs that will drive Htt expression in *E. coli* with 47, 27, and 103Q. There is a danger of targeting just the polyQ, which may interfere with TATA-binding protein and other polyQ-containing transcription factors. Signer noted many reagents are available via the HDF website www.hdfoundation.org.

vanBeuzekom noted that hits from a proprietary library must be treated differently from hits from nonproprietary libraries.

Kazantsev noted the lack of diversity of assays. Sharing of compounds, and screening efforts (perhaps with five assays) might be done under HDF supervision. Candidates should be tested in mice immediately. Some won’t pass toxicity, but we should start right away.

Ko Ferrigno wanted 10-12 impartial assays for 100 frozen compounds, by either a centralized facility or a network or a dozen labs. Compounds could be sent out in mammalian expression vectors. A restricted website might be useful for exchanging information when laboratories have compounds they want tested.

Hughes would like others to retest his compounds; he will similarly test others’ compounds in a blinded manner. If IP issues can be settled, an impartial medicinal chemist should analyze those data once compound exchange becomes formalized.

Sanchez will retest compounds to those who request via email using her cell-based assay. More diverse libraries would be useful.

Thompson’s short-term goal is to screen 5-10 compounds per month in flies. She is speaking with Union Biometrical about their \$100-200,000 machine for high-throughput assays.

Ross sees much basic science left to do. For example, cleavage must be understood better in order to assay effects on cleavage. He would like to set up cell-based assay for medium throughput, and could test others’ initial hits.

Gusella expects to have compounds soon that will inhibit aggregation and that can therefore be used to address the role of aggregation in HD pathogenesis. He is less certain

of whether other kinds of compounds will be found. Transcriptional and translational assays need more attention, as do the differences between Htt^{wt} and Htt^{ex} at the physiological level.

Neri wants to develop secondary assay for more compounds.

Knolle would like to keep data on compounds in nM to mM range in a central databank. Data from the FDA200 library should be made available soon. The best of each class should be tested in primary cells.

Signer was encouraged by the lack of debate over strategy. He noted that the work is moving from academia to the marketplace, where more input from industry is needed.

Krobitsch would like a centralized library. Hits in yeast must be exchanged among people using the yeast assays.

Berthelier has an *in vitro* assay and can screen about 160 compounds a day.

Taylor wishes for good candidate hits from the FDA-approved library. Finding good candidates would accelerate the move to clinical trials. In the next year, assays should be prioritized. Which are best at turning up effective compounds in mice? Bamdad noted that when a compound is tested in mice it should be tested in all the assays.

Goodman is interested in creating a website to handle IP issues.

Stockwell emphasized the importance of a central repository of immortalized cell lines.

Johnson said those who develop an assay should test about 1000 compounds, not 100,000. He will try to establish a central facility for dispensing liquid compounds in wells, providing sets of about 10,000 compounds to individual labs.

Henderson said Trophos wants to participate in the drug discovery process, and is in discussions with pharmaceutical companies. He is interested in speaking with those who have interesting primary screen hits.

Sherman reiterated the need for basic science. He said there are no good targets besides polyQ itself. HDF might support a scheme of screens and a scheme for genes involved in the process. Who would do medicinal chemistry? Pollok noted that IP issues get tricky here: HDF must select one or two counselors to discuss strategies for synthetic program, and bring them in at the appropriate time, perhaps in a year. He also thinks an *in vivo* pharmacologist should get involved. Chemistry can't reasonably be moved along by workshops. It will become a "jump ball" situation: Everyone will have their own composition of matter, and it will be difficult to share chemistry information.

Nancy Wexler asked how the HDF could assist the field to develop promising compounds with their own IP. Pollok said the only way is to have preferred commercial

partners. Stockwell said an alternative is to use an academic organic chemist. Folkin said it would be difficult to find academic chemists interested only in making analogs.

Heemskerk said the many lead compounds would soon have to be prioritized. We will need to develop the capacity to handle the next step – validating compounds and testing toxicity in animals. The NINDS epilepsy drug discovery program might be refocused on neurodegeneration. That program took lead compounds from several sources, starting with the European approved compounds, and helped them through FDA approval. The program can be expanded into pilot trials.

Pollok noted there are many assay choices, but a good distance from these to mice. It's important to get an HD model in retina, such as the SCA7 model. Assessment of retinal signs would allow the longitudinal monitoring of pathology in single animals.

Fokin noted the need for a centralized facility to assist in compound exchange. The ease and expense of chemical development depend on the complexity of the molecules. Medicinal chemistry is expensive, so it would help to evaluate the libraries for diversity and ease of synthesis. For example, large pharmaceutical companies often reject efficacious compounds that are difficult to make. The Scripps group has thought about these issues, and it has compounds available, as well as an automation lab. Provisional patent applications might be filed now. But the real IP issue is with analogs of compounds. One strategy would be to use FDA-approved compounds and to apply for patents for second medical uses. A generic way to handle these issues might be useful. Johnson noted the need to settle the scientific issues first.

The meeting closed with an agreement to meet again in six months, perhaps with people from both academia and industry.

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