Indianapolis: Frontotemporal Dementia Research Comes of Age

1 November 2010. There was a feeling in the air at the 7th International Conference on Frontotemporal Dementias, held 6-8 October 2010 in Indianapolis, Indiana, and it wasn't that of fall in the Midwest. Quite the opposite—it was that the study of FTDs seems to have entered a season of growth. For many years, the frontotemporal dementias, also called frontotemporal lobar degeneration (FTLD), have languished in relative obscurity, overshadowed by the more common Alzheimer's disease. But rapid progress in discovering the molecular underpinnings of FTD has energized the research, and it is now moving with a distinct spring in its step.

Frontotemporal dementias are a set of devastating, progressive diseases. They attack the parts of the brain responsible for judgment, empathy, and social behavior. People with FTD often develop personality changes, make ruinous financial decisions, become sexually inappropriate, or engage in compulsive behavior. Some patients with AD exhibit some of those behaviors, too; however, with FTDs they are front and center. Some forms of FTD rob people of normal speech, while others impair movement, similar to Parkinson's disease and amyotrophic lateral sclerosis. FTD typically strikes at younger ages than does AD, often in a person's late forties or fifties. It involves less memory loss than AD, but much worse behavior problems. One woman described how her 53-year-old husband, a computer engineer, urinates in public unashamedly (see story at The Globe and Mail). He has to be reminded to chew his food and wipe his nose, once wandered into the staff room at the mall and started rooting through the fridge, and shows no emotion. Other patients, in early stages of FTD, cheat on their spouses and find absolutely nothing wrong with that; FTD patients often seem indifferent to what would be a mortifying situation for a healthy person.

The disease is particularly devastating to families, said Susan Dickinson, who heads the Association for Frontotemporal Dementias, because it often goes unrecognized or misdiagnosed. Families, therefore, have no recourse if a spouse with FTD blows all his or her money on a sports car, or makes advances to a neighbor, since the spouse is not recognized as ill. Friends may withdraw because of the rude or disturbing behavior of the person with FTD. "Living with these diseases is incredibly isolating," Dickinson said. "These families are losing their loved ones, and nobody will listen. We have a lot of people who get divorced." Earlier diagnosis of the disease would help families to understand and cope with what is happening, Dickinson said. "As soon as there is a medical diagnosis, a lot of people get right back together to care for their spouse."

FTDs are fairly rare. Scientists estimate as many as 20,000 Americans suffer from them, said **David Knopman** of the Mayo Clinic in Rochester, Minnesota, reviewing the findings of several recent papers. This is similar to the number of Americans with amyotrophic lateral sclerosis, but about 200-fold less than people with Alzheimer's disease. FTD most often hits between 45 and 64 years old, and people typically survive six to nine years after diagnosis, Knopman said, similar to Alzheimer's.

Frontotemporal dementia is an umbrella term that encompasses a large number of clinical syndromes and distinct pathologies. This includes a confusing lexicon of terms such as progressive supranuclear palsy (PSP), corticobasal degeneration (CBD),

primary progressive aphasia (PPA), behavioral variant FTD (bvFTD), and Pick's disease. The distinctions among these syndromes are often hazy, and diagnosis can only be reliably made after death by examining brain tissue changes. Until quite recently, the fundamental biology at the root of many of these syndromes was a mystery.

At the 5th FTD Conference, held in 2006 in San Francisco, California, however, scientists announced the discovery that TAR DNA binding protein 43 (TDP-43) is the major component of protein deposits in about half of FTD patients (see ARF related news story), as well as the finding that mutations in the progranulin gene are responsible for many of these cases (see ARF related news story). And in 2009, scientists discovered that the fused in sarcoma (FUS) protein accumulates in inclusions in another 10 percent or so of FTD cases (see ARF related news story).

At this year's conference, organized by **Bernardino Ghetti** of Indiana University, Indianapolis, an enthusiastic crowd of about 600 scientists from around the world showed each other the advances to which these discoveries have since led. These run the gamut from more accurate diagnosis and classification of FTD subtypes, to imaging news and the launch of a major biomarkers initiative and, finally, the creation of new animal models and deeper understanding of the molecular pathways involved in the disorder. At this meeting, but a handful of presenters discussed clinical trials or potential therapies. It's too early for experimental therapies to have grown out of the new basic research yet, but many scientists said they believe a boom in trials is close at hand. **Bruce Miller**, a leading FTD expert at the University of California at San Francisco, summed up the mood when he said, "This is the most exciting time I've seen in this field."

Clinically Diverse Tauopathies Present a Challenge for Diagnosis

One of the primary themes in Indianapolis was that a new understanding of the molecular basis of frontotemporal lobar degeneration will sharpen its diagnosis, which traditionally has been based on clinical symptoms. For example, about 40 percent of FTLD cases are characterized by tau pathology, but several subtypes exist, said **Dennis Dickson** of the Mayo Clinic in Jacksonville, Florida. In some variants of FTLD-tau, including most cases of progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD), the deposits consist of isoforms of tau with four microtubule binding repeats, Dickson said (see Dickson et al., 2010). In other tauopathies, such as Pick's disease, the deposits contain isoforms of tau with three microtubule repeats, whereas in Alzheimer's, both three-repeat and four-repeat tau are present in neurofibrillary tangles. Dickson pointed out, however, that the molecular nature of tau deposits carries less weight than where they form. The differing symptoms of PSP and CBD result from what brain areas and what cell types develop tau tangles, Dickson said. He emphasized that tauopathies form a disease spectrum with overlapping symptoms, and that current distinctions between these diseases may not help in the clinic. He said clinicians need a better classification system that will have greater prognostic and therapeutic significance.

Similarly, **Brad Boeve** of the Rochester Mayo Clinic showed that, for example, CBD underlies many different clinical diagnoses. The disorder often starts as a focal brain lesion in one hemisphere, Boeve said, and degeneration gradually spreads to surrounding regions, including the homologous region of the opposite hemisphere. As

the damage spreads, the clinical symptoms change, depending on what brain areas are affected. This results in frequent misdiagnoses.

This clinical heterogeneity highlights the need for reliable biomarkers, such as brain imaging or protein levels in body fluids, in order to discern the underlying disease pathology, Boeve suggested. Boeve's talk, and the FTD 2010 conference in general, showcased the well-known and knotty problem that clinical diagnoses of this group of diseases often match up poorly with subsequent postmortem pathological diagnosis. Thus far, classifying diseases by molecular genetic knowledge has not fully resolved the issue. For new imaging data to crack this nut, see Part 2.—Madolyn Bowman Rogers.

Indianapolis: Neuroimaging Opens Window to Disease, Better Diagnosis

2 November 2010. Frontotemporal dementias pose a challenge for diagnosis because numerous overlapping clinical syndromes are associated with the disease. Scientists at the 7th International Conference on Frontotemporal Dementias, held 6-8 October 2010 in Indianapolis, Indiana, held out hope that this situation will soon change, thanks to advances in neuroimaging and greater knowledge of fluid biomarkers. "The biggest change since our last [FTD] meeting has been the proliferation of rational imaging approaches to frontotemporal dementia," said **Bruce Miller** of the University of California in San Francisco. "I think we really are understanding these diseases from a circuit perspective."

For example, **William Seeley** of UCSF showed that neurodegenerative syndromes map onto specific brain networks (see ARF related news story). In behavioral variant FTD, he said, connectivity falters primarily in the salience network (see Zhou et al., 2010). Consisting of regions of the prefrontal cortex, anterior cingulate, insula, and striatum, the salience network is activated by events with emotional or survival significance, and so is dubbed the "here and now" network. In AD, by contrast, the default mode network sustains the most damage. This network includes regions of the medial temporal lobe, posterior cingulate, and inferior parietal cortex, and is active during daydreaming and in between a person's focus on a specific task, prompting Seeley to refer to this network as the "there and then" system. These two networks have opposing functions in the brain, and lesions in one system seem to increase connectivity in the other, Seeley said. Thus, people with AD tend to have overactive salience networks, whereas people with FTD have more connectivity in the default mode network than do healthy people. Because of these changes in brain circuits, AD patients are acutely emotionally sensitive, whereas bvFTD patients tend to be emotionally flat and more captivated by non-emotional stimuli in the outside world. The clinical potential of this finding, Seeley said, is that by comparing blood oxygen-level dependent (BOLD) magnetic resonance imaging signals from the two networks, research physicians can readily discriminate between behavioral variant FTD and AD.

On a larger scale, consider this: As scientists have grasped the importance of imaging for FTD diagnosis, they took a page from the AD book and established the FTLD Neuroimaging Initiative (see press release), announced study leader **Howard Rosen** of UCSF. Funded in late 2009 by the National Institute on Aging and the National Institute of Neurological Disorders and Stroke, the project is patterned after the

Alzheimer's Disease Neuroimaging Initiative. It will study 120 FTLD patients for 18 months using positron emission tomography (PET) and structural MRI, as well as diffusion tensor imaging, which measures axon integrity and connectivity. The study will also collect CSF, blood, and urine to look for molecular biomarkers in collaboration with the University of Pennsylvania in Philadelphia. UCSF is collaborating with the Mayo Clinic in Rochester, Minnesota, to enroll and test patients. The goal is to develop standardized, shared datasets, Rosen said. He noted that studies show that the use of imaging plus a fluid biomarker can provide a 100 times more sensitive diagnosis than can cognitive tests. This is the second large neuroimaging initiative ADNI has inspired for related neurodegenerative diseases, the other being the Parkinson's Progression Markers Initiative sponsored by the Michael J. Fox Foundation for Parkinson's Research (see ARF related news story).

Diagnosis Goes Modern

How will imaging advances affect diagnosis? **Murray Grossman** of the University of Pennsylvania in Philadelphia proposed that a two-stage diagnostic process for FTLDs would be most effective. First, the clinician could distinguish FTLD from AD using imaging techniques. For example, positron emission tomography with Pittsburgh compound B (PET-PIB) detects amyloid deposits, which are florid in AD but largely absent in FTD. Grossman said that the pattern of degeneration in FTLD involves frontal and anterior temporal lobes, whereas AD strikes the medial temporal and parietal lobes, but even so, the distinction between the two diseases is not always clear on the MRI of an individual patient. To increase diagnostic sensitivity, Grossman suggested combining structural MRI with diffusion tensor imaging. If the images are analyzed with support vector machines, a type of software that recognizes patterns, patients can be reliably diagnosed as having one disease or the other (see Grossman, 2010).

Rik Vandenberghe, of University Hospitals Leuven in Belgium, said that functional MRI imaging can distinguish between people with AD and people who have FTLD with primary progressive aphasia (PPA). In early-stage AD patients, connectivity in the language circuit is preserved, he said, in contrast to people with PPA, where those circuits disconnect.

Once FTLD has been diagnosed, Grossman said, biomarkers in blood and cerebrospinal fluid (CSF) generally are the most sensitive method for identifying subtypes. In this area, tau is fairly established and TDP-43 is a newcomer. Grossman showed that CSF levels of TDP-43 at present make a poor biomarker because patient and control levels overlap. However, several other proteins may prove useful, including adrenocorticotropic hormone, Agouti-related protein, Fas, Interleukin-17, and Eotaxin-3 (see Grossman, 2010). For tracking disease progression, current data suggest that imaging methods are more sensitive than fluid biomarkers, Grossman said, although some fluid markers show potential as well. Other scientists agreed with Grossman's findings. For example, **Keith Josephs** of the Rochester Mayo Clinic found no consistent differences in the patterns of atrophy between FTLD-tau and FTLD-TDP patients, suggesting that these disorders must be separated instead by fluid biomarkers.

Primary Progressive Aphasia

Primary progressive aphasia presents another diagnostic challenge. Scientists now

recognize three categories of PPA, which are distinguished by their most common underlying pathology. As described by **Marsel Mesulam** of Northwestern University in Chicago, Illinois, in an overview talk on the disease, the categories include agrammatic PPA (FTLD-tau), semantic PPA (FTLD-TDP), and logopenic PPA, found in Alzheimer's disease (see Bonner et al., 2010). Clinicians do not yet have reliable tests for sorting out these subtypes in living patients.

In agreement with Vandenberghe's findings, Mesulam suggested that impaired connectivity, rather than brain atrophy, may be the culprit in primary progressive aphasia. Mesulam found that atrophied language areas retain some activity and are still functional in some patients. Mesulam also discussed his findings that people with learning disabilities seem to be more vulnerable to developing PPA (see ARF related news story). He mentioned the IMPPACT website that seeks to register PPA patients from around the world for studies and clinical trials.

For his part, **Brad Dickerson**, of Brigham & Women's Hospital and Massachusetts General Hospital in Boston, described the development of a Progressive Aphasia Severity Scale (PASS) that uses both performance-based language tests and measures of cortical thickness to more accurately diagnose and track PPA. Initial results show that the scale is a valid and reliable tool, Dickerson said, and should be useful in clinical trials (see Sapolsky et al., 2010).

Behavioral Variant FTD

Continuing the theme of better diagnosis, **Katya Rascovsky** of the University of Pennsylvania in Philadelphia presented a report on proposed new diagnostic criteria for behavioral variant FTD. Rascovsky coordinates the International bvFTD Criteria Consortium (FTDC). The new criteria allow clinicians to distinguish between possible, probable, and definite bvFTD. They are expected to be more flexible and sensitive than the previous Neary criteria (see Neary et al., 1998). Patients need meet only three of six criteria to receive a diagnosis of possible bvFTD, as opposed to five of five features to meet the Neary standard. "The Neary criteria have served us well for many years," said consortium member Boeve, "but we increasingly appreciate that some patients who clearly have FTD didn't formally meet the Neary criteria." In one comparison, the proposed criteria were able to detect possible bvFTD with 85 percent sensitivity, as opposed to 52 percent with the Neary criteria, Rascovsky said. She added that the consortium is still in the process of evaluating just how reliable and specific the new criteria truly are. For news on animal models and molecular findings in FTD, see Part 3 of this series.—Madolyn Bowman Rogers.

Indianapolis: Dissecting the Pathways Behind Frontotemporal Dementia

3 November 2010. Recent discoveries of the molecular underpinnings of nearly all frontotemporal dementias (FTDs), as well as at least one genetic cause for each major subtype, have nudged open a door for researchers to begin to unravel disease pathways—a necessary step toward developing new therapeutic approaches. At the 7th International Conference on Frontotemporal Dementias, held 6-8 October 2010 in Indianapolis, Indiana, many scientists presented new molecular and genetic findings on disease mechanisms, and described recently developed animal models for different forms of FTD. The upshot from Indianapolis: It's too early for consensus pathways to

be anointed, but at least scientists now know where to look, and data are beginning to pour in.

Strange Bedfellows: ALS and FTD

In the last few years, researchers have found that the proteins TAR DNA binding protein 43 (TDP-43) and fused in sarcoma (FUS) form deposits in both FTD and in amyotrophic lateral sclerosis (ALS), suggesting these disorders have more in common than was once thought. The disorders can also occur together, said **Catherine Lomen-Hoerth** of the University of California in San Francisco; up to 30 percent of ALS patients develop dementia, and up to 15 percent of FTD patients get ALS. "The thing that was most interesting to me [at the conference] was to see how the ALS field has now sort of merged with the FTD field," said **Rosa Rademakers** of the Mayo Clinic in Jacksonville, Florida. One session of the meeting dealt especially with this FTD/ALS connection.

Teepu Siddique of Northwestern University in Chicago, Illinois, discussed evidence that TDP-43, FUS, and a third protein, optineurin, act in a common pathological pathway in both familial and sporadic ALS (see ARF related news story). Mutations in SOD1 cause many cases of familial ALS; however, aggregates of SOD1 protein do not include TDP-43 or FUS, Siddique said, and therefore SOD1 may represent a separate disease pathway. Recent work in the field suggests that SOD1 may have a role in sporadic ALS as well (see ARF related news story).

TDP-43 and FUS are both RNA/DNA binding proteins found predominantly in the nucleus, said **Christopher Shaw** of King's College London, U.K. He suggested that mislocalization of these proteins to the cytoplasm might drive the disease process (see Rogelj et al., 2010 and also ARF related news story on FUS localization). Shaw and colleagues expressed mutant FUS in cell lines, and confirmed that the protein accumulated in cytoplasm. However, only a tiny percentage of ALS cases have mutations in their genes for FUS or TDP-43, Shaw said. He speculated that defects in a person's nuclear import/export machinery might contribute to non-genetic forms of the disease, and is pursuing this possibility.

One of the most tantalizing genetic mysteries in this field at present is the association of a region on chromosome 9 with both FTD and ALS cases. It shows up in multiple linkage studies, but researchers have been maddeningly unable to pinpoint the gene hiding in there. The data are consistent with a single Scandinavian founder, said **John Hardy** of University College London, U.K. The locus covers three genes, and no one has yet reported a mutation that consistently segregates with the disease, although speakers discussed their efforts to find it.

More Evidence for Risk Factor TMEM106B

Several speakers, such as Hardy, **Andrew Singleton** of NIH in Bethesda, Maryland, and **Gerard Schellenberg** of the University of Pennsylvania in Philadelphia, talked about genomewide association studies (GWAS) that are underway to turn up risk factors for various forms of frontotemporal lobar degeneration (FTLD). These should provide further clues to the molecular mechanisms of the disorder. **Vivianna Van Deerlin** of the University of Pennsylvania discussed the previously reported identification of membrane protein TMEM106B as a risk factor for FTLD-TDP in an international GWAS (see ARF related news story). People who carry the high-risk

allele show higher TMEM106B expression, Van Deerlin said, and the allele associates with mutations in the progranulin gene.

Julie van der Zee of the University of Antwerp, Belgium, announced that her group replicated this finding in a Flanders-Belgian cohort, where two copies of the TMEM106B risk allele double the risk of FTLD-TDP. Van der Zee added, though, that in her study the RNA levels of TMEM106B and disease risk did not correlate. **NiCole Finch** of the Jacksonville Mayo Clinic provided some clues to the mechanism with her report that genetic variants of TMEM106B regulate plasma progranulin levels in people with mutations in the progranulin gene. The protective minor allele of TMEM106B leads to less TMEM106B expression, more progranulin expression, and a later age of onset of FTLD, Finch said.

Animal Models Galore

Ever since TDP-43 popped up in FTD research, scientists have raced to develop overexpression, knockout, and mutant transgenic animal models for the disease. For a fairly complete summary of sundry TDP-43 mouse models, as discussed at the International Conference on Alzheimer's Disease 2010, see ARF related news story. At FTD 2010, speakers put forth several more, reflecting a smorgasbord of approaches.

One strategy models FTLD-TDP by tinkering with the progranulin gene, the cause of many human cases of the disease. **Lauren Herl**, working with **Robert Farese** at UCSF, presented a mouse progranulin knockout. Both homozygous and heterozygous knockouts exhibited social deficits and impaired fear conditioning, suggesting they model features of FTD, Herl said. Both strains also lost more dopaminergic neurons and activated their microglia more potently after administration of a neurotoxin than wild-type mice did. The results suggest that progranulin could promote neuronal survival by suppressing inflammation, Herl said.

Philip Van Damme of the Catholic University of Leuven, Belgium, investigated the effects of progranulin in zebrafish. He used morpholinos, a form of antisense RNA, to knock down endogenous progranulin. In the fish with less progranulin, axons grew poorly. The same thing happened in zebrafish that overexpressed wild-type or mutant human TDP-43, Van Damme said. Injecting either of these models with human progranulin rescued axon growth, confirming progranulin's importance in the pathway (see Laird et al., 2010).

Continuing the model menagerie with flies, **Jane Wu** of Northwestern University described a series of *Drosophila* strains that express wild-type human TDP-43 in neuronal subpopulations and develop neurodegeneration (see Li et al., 2010). When the flies express mutant human TDP-43, their neurodegeneration is more severe (unpublished data). That even wild-type TDP-43 is toxic suggests to Wu that both overproduction or delayed clearance of TDP-43 could lead to disease.

Researchers in the laboratory of **Virginia Lee** of the University of Pennsylvania developed transgenic mice that overexpress wild-type human TDP-43 or mutant human TDP-43 with a defective localization signal. The mice develop rare TDP-43 deposits, but profound neuron loss and motor defects. Endogenous mouse TDP-43 was downregulated in these transgenics, Lee said, which suggests the mice may be

modeling a loss of function of TDP-43, rather than a toxic gain of function. The mice Lee described share many features with transgenic human TDP-43 mice made by **Leonard Petrucelli** of the Jacksonville Mayo Clinic (see ARF related news story). Petrucelli also discussed a *C. elegans* model that overexpresses human TDP-43 and has a motor defect (see Ash et al., 2010), as well as the expression of truncated TDP-43 in a cell culture model that lends support to a toxic gain-of-function mechanism (see ARF related news story).

Have the animal models available to date produced any overarching insights? "I think there's a consensus in the field that basically all the transgenic mouse models we've developed by overexpressing wild-type protein or mutant proteins lead to loss of function," Lee said. "In other words, the cells rapidly die. So the challenge for the future is, Can we produce animal models that develop pathology, in addition to the loss of function?" Although many of the mouse models develop TDP-43 deposits, Lee said, these deposits are quite rare and cannot account for the massive neuron loss. What might explain it? Lee summed up the current data: "If you overexpress TDP, you get neuron loss; if you knock down TDP, you get neuron loss, so that suggests that TDP-43 is very finely regulated." In support of the idea that regulation of TDP-43 levels is crucial for brain health, **Emanuele Buratti** of the International Center for Genetic Engineering and Biotechnology in Trieste, Italy, found that TDP-43 can regulate its own levels through a negative feedback loop. The protein's sequestration in aggregates may co-opt this self-regulation and result in its overproduction, Buratti speculated.

Rademakers said the value of these model organisms is they will allow scientists to begin to tease out the functions of TDP-43 and progranulin. "Now we can start doing very specific studies and hopefully find some new targets for therapy using these models," she said. Many researchers are already doing this. For example, **Philipp Kahle** of the University of Tubingen in Germany examines the physiologic role of TDP-43. In Indianapolis, he presented data to suggest that one of its targets is HDAC6, a histone deacetylase enzyme that is also a major mediator of toxic protein turnover in the cell. Higher levels of TDP-43 reduce HDAC6 levels and activity, Kahle said, which in turn leads to increased aggregation of toxic polyQ proteins, the hallmark of several neurodegenerative diseases, including Huntington's disease (see Fiesel et al., 2010).

Adrian Isaacs of University College London pointed out that several genes in the endosomal sorting pathway are mutated in human neurodegenerative diseases. He cited as examples the genes VCP, CHMP2B, Alsin, Rab7, Fig4, and Spastin, associated with a gamut of neurological conditions including FTDs, upper motor neuron disease, peripheral neuropathies, and paraplegia. A large body of evidence implicates sorting proteins such as SorL1, sortilin, and Vps35 in Alzheimer's disease (e.g., see ARF related news story and ARF news story). Isaacs suggested that defects in endosomal sorting and protein degradation might be a common disease mechanism in neurological disorders. Supporting this idea, Rademakers announced the discovery of yet another endosomal sorting gene as a regulator of plasma progranulin levels (paper in preparation—stay tuned).

Do Neurodegenerative Proteins Act Like Prions?

A repeated finding from imaging studies is that pathology can spread through brain

networks, but how that happens is unknown. **Michel Goedert** of the MRC Laboratory of Molecular Biology in Cambridge, U.K., presented his finding that tauopathies can be transmitted from cell to cell in a prion-like fashion. It is based on experiments in which brain extracts from diseased mice seeded tau aggregation in healthy mice overexpressing tau (see ARF related news story). Goedert also described new work in which extracts from human patients with various FTDs were injected into the tau-overexpressing mice, with disease-specific results. For example, mice that received extracts from people with a dementing tauopathy called argyrophilic grain disease developed grain-like structures that mirrored the human disorder. "It is fascinating that there is some sort of specificity in terms of the pathology," Lee said. "[Goedert] was able to show that the pathologies that developed in the mice recapitulated those of the human disease." Goedert's work adds evidence to the emerging idea that many pathological proteins, such as Aβ, huntingtin, and α-synuclein, can propagate themselves in a prion-like way by seeding misfolding and aggregation (see ARF Live Discussion).

Masato Hasegawa of the Tokyo Institute of Psychiatry, Japan, suggested that a similar process may happen in FTLD-TDP and ALS. He showed in cell culture that C-terminal fragments of TDP-43 can form inclusions that recruit full-length TDP-43 (see Arai et al., 2010). TDP fragments vary from patient to patient, but are indistinguishable between the brain regions of a given patient, Hasegawa said. This suggests that the pathology may propagate from cell to cell. Hasegawa referred to amyloid-like proteins in neurodegenerative diseases as "protein cancers," and speculated that they might be transmitted through synapses. The audience was intrigued by the hypothesis, but wanted to see more cases than the handful presented. For a discussion of possible FTD therapies and current clinical trials, see upcoming Part 4 of this series.—Madolyn Bowman Rogers.

Indianapolis: Clinical Trials a Ripple, Scientists Hope for a Wave

4 November 2010. Currently there are no treatments that slow the progression of frontotemporal dementia (FTD), and no new mechanism-based candidate drugs are being tested in clinical trials. Pharmaceutical treatment options for FTD are even sparser than for Alzheimer's disease, where acetylcholinesterase inhibitors and an NMDA receptor antagonist drug provide at least a small measure of relief to a large minority of patients who respond to these drugs. This dismal picture may change in the next decade. At the 7th International Conference on Frontotemporal Dementias, held in Indianapolis, Indiana, on 6-8 October 2010, many scientists said the progress in identifying the basic biology behind FTDs encouraged them to believe that this greater understanding will soon translate into new therapeutic targets. Many speakers echoed the theme that a wave of clinical trials is coming, and that advances in imaging and protein biomarkers will make these trials more effective than past efforts.

They tempered their optimism because they know that a wave of trials in neurodegenerative disease does not equal a wave of treatments. A large majority of drug trials in this area fail. And yet trials are the only way to treatments, so even just having trials in the pipeline represents tangible progress over the current situation. As some drugs fail, others will succeed. In particular, researchers are excited by the discovery that about half of FTDs are characterized by accumulations of TAR DNA

binding protein 43 (TDP-43). Because this finding is only four years old, however, clinical trials for this type of frontotemporal lobar degeneration (FTLD) are still some years off.

In contrast, scientists have known for many years that nearly one-half of FTDs are characterized by tau protein deposits. Tau tangles are also a major feature of Alzheimer's disease, implying that tauopathy treatments might be effective for both types of dementia. But tau has proven to be an elusive target, and despite efforts in academia and by drug companies, only a handful of potential treatments for tau diseases are in human trials, and no new ones from major pharmaceutical companies.

Michael Hutton of Eli Lilly in Windlesham, U.K., discussed some of the reasons for this. One of the major problems, Hutton said, is that, to date, scientists have not reached a consensus on how tau contributes to disease. It could be that tau aggregates (tangles) themselves are harmful, or it might be that tau detaching from microtubules destabilizes these neuronal highways to the point where the cell withers. Without knowing the primary pathogenic mechanism, pharmaceutical companies lack a specific pathway to target. Moreover, Hutton said, many of the proteins involved in tau processing have multiple biological roles, and efforts to target some of those proteins, for example, tau kinases, have led to undesirable side effects. In addition, tau-based disease models suitable for drug development have only recently become available. Despite these problems, Hutton said that the big pharmaceutical companies do have tau drug discovery programs and are doing preclinical work.

More tau therapies are likely to appear in the near future, Hutton predicted. For one, transgenic mouse models of tauopathy that allow treatment hypotheses to be tested are now available; for another, research programs such as the Alzheimer's Disease Neuroimaging Initiative are developing biomarkers of disease progression that will allow clinicians to assess treatment effects more easily.

Hutton suggested, as did other speakers, that the tau-based syndrome, progressive supranuclear palsy (PSP), might be an ideal first test case or proof of concept for tau-based therapies, because it is a pure tauopathy, with no amyloid or other pathologies to confound results. Because this disease progresses rapidly, Hutton said, it also has the potential to show a more dramatic treatment effect than more slowly progressing tauopathies such as Alzheimer's disease. PSP causes physical problems such as stiff gait, loss of balance, blurred vision, and slurred speech, as well as personality changes like depression, apathy, and irritability. Unlike Parkinson's disease, which has similar symptoms, PSP responds poorly to levodopa, leaving it without a good treatment. The Spanish biotech company Noscira has completed recruiting for a Phase 2 trial of a tau kinase inhibitor in PSP.

Despite the challenges of targeting tau, a few treatments are in development or in early pilot trials. On the academic front, **Kurt Brunden** of the University of Pennsylvania in Philadelphia described a test of microtubule-stabilizing agents in a mouse model of tauopathy (Tg(P301S)PS19). If part of the problem in tauopathies is the loss of microtubules, these drugs could slow disease progression. Microtubule-stabilizing agents are used to treat cancer, but these drugs often have serious side effects and many barely enter the brain. However, Brunden described a class of microtubule-stabilizing compounds, the epothilones, that do get in. These drugs leave

the bloodstream after 24 hours, but stay in the brain up to 10 days, suggesting that low doses could do some good in the brain while avoiding systemic side effects. In a study performed on three-month-old mice with tauopathy, one of these compounds, epothilone D, when given at the relatively low dose of 1 mg/kg body weight for three months, decreased axon degeneration and improved cognition in treated animals (see Brunden et al., 2010). Preliminary work on epothilones was discussed at the 2008 International Conference on Alzheimer's Disease (see ARF related news story). Brunden said he now plans to test the compound on older mice with more established degeneration, and to look at longer-term treatment. Brunden's drug discovery program has a research agreement with AstraZeneca, a pharmaceutical company that for years has tried to develop anti-tau drugs for neurodegeneration (see press release).

Einar Sigurdsson of New York University in New York City presented a different approach to treating tauopathies. He is trying to harness the immune system to clear tau tangles. Immunotherapies against Aβ in Alzheimer's disease have so far been rather disappointing, Sigurdsson acknowledged. Because tau pathology correlates more tightly with the degree of dementia than does amyloid load, he believes tau immunotherapy may stand a better chance for treating Alzheimer's, especially once disease is symptomatic. Tau immunotherapy has worked in two models with aggressive tau aggregation, the JNPL3 P301L mouse model of tauopathy and a new tau AD model generated by Allal Boutajangout in Sigurdsson's laboratory by crossing two available models, htau and PS1(M146L). Sigurdsson said immunotherapy reduces tau aggregates in both models. It also attenuates motor impairments in JNPL3 and prevents cognitive decline in htau/PS1 mice (see Sigurdsson 2009 and ARF related news story). "Tau immunotherapy is a promising approach," Sigurdsson concluded. He noted ongoing studies to identify the best candidate for a clinical trial, but no specific sponsor or date.

Finally, two talks featured small human trials for tau therapies. **Adam Boxer** of the University of California in San Francisco announced the results of a 12-week human safety study of the drug davunetide, derived from a neuronal growth factor called activity-dependent neurotrophic protein. Boxer conducted the trial for the biotechnology company Allon Therapeutics. Davunetide was previously shown to improve memory in a mouse model, and also to have a slight effect on working memory in humans with mild cognitive impairment, Boxer claimed (see trial results and ARF related news story from 2002, 2008, and 2009). In the new trial, eight people diagnosed with a tauopathy received the drug intranasally twice daily, and four received placebo. Participants had mild to moderate adverse effects such as headaches and congestion, Boxer said, but showed no evidence of cognitive benefit. He said that, based on the results of the safety study, they are preparing to enroll people with PSP for a pivotal Phase 2/3 trial.

A human trial described by **Gunter Höglinger** of Philipps University in Marburg, Germany, took a radically different approach to tauopathy treatment. In previous work, Höglinger and colleagues had found that inhibitors of mitochondrial complex I induced the redistribution of tau and increased neuron death (see Höllerhage et al., 2009). Moreover, mitochondrial function and energy metabolism appear to be damaged in people with progressive supranuclear palsy (see Stamelou et al., 2009), as has been found in numerous neurodegenerative diseases. Because coenzyme Q10 (CoQ10), which forms part of the electron acceptor chain in mitochondria, is known

to quench the toxicity of mitochondrial inhibitors, Höglinger and colleagues tested CoQ10's effects on people with tauopathies. In a six-week Phase 2a trial of 20 people with progressive supranuclear palsy, 10 people received 5 mg/kg per day of CoQ10, 10 received placebo. Several measures of energy metabolism showed improvement in people who got the drug, Höglinger said. Significantly, in those taking CoQ10, motor function and cognition improved, whereas these abilities deteriorated in participants who got placebo (see Stamelou et al., 2010). Höglinger said that further studies of CoQ10 are planned.

It will be one of a flurry of CoQ10 trials in the works for various neurodegenerative diseases. The Lahey Clinic in Burlington, Massachusetts, is currently enrolling 60 people with PSP for a Phase 2/3 trial, following a previous Phase 2/3 study on CoQ10's effects on people with PSP or corticobasal degeneration. Other CoQ10 trials now recruiting include a Phase 3 trial of 600 people with Parkinson's disease, a similar Phase 3 trial for Huntington's disease, as well as a smaller Phase 2 trial for people with preclinical Huntington's that will test CoQ10's value as a preventative. CoQ10 has also been tested in Alzheimer's patients. CoQ10 supplements are available in health food stores, and many people with diseases such as ALS and Parkinson's already self-medicate with it even though the jury is still out on how much benefit the drug truly provides. A short-term trial on Parkinson's patients did little to slow the progression of the disease (see ARF related news story); several current trials are designed to measure possible long-term effects.

Davunetide and CoQ10 have both been under investigation for some time, and neither was originally developed to target specific FTD disease mechanisms. The FTD 2010 conference presented no new therapeutic compounds that grew out of recent insights into the basic biology. Many scientists said, however, that they expect more mechanistic drugs to appear over the next few years, and predicted the current handful of FTD clinical trials are but a hint of what is to come. "Therapeutic trials in PSP are going to spill over nicely into the FTLD field," said **Brad Boeve** of the Mayo Clinic in Rochester, Minnesota. "We likely will have at least a couple of agents being tested in clinical trials over the next two years."

Other researchers agreed that therapeutic trials for the other major FTD pathology, marked by progranulin deficiency and TDP-43 deposits, are close behind. UCSF has established the Consortium for Frontotemporal Dementia Research with the goal of finding a cure for FTLD-TDP caused by progranulin mutations within 10 years. Consortium member **Bruce Miller** at UCSF said, "I believe strongly that the progranulin mutations may be treatable in the next few years."

Glenda Halliday, of the University of New South Wales in Randwick, Australia, summed up the overarching mood at the conference: "Understanding how proteins interact in the cells gives us a lot more capacity to change those interactions and to have targets that are actually going to be treatable."—Madolyn Bowman Rogers.