Time Is Ripe for Clinical Trials in Frontotemporal Degeneration

27 December 2011. As trialists are retooling in the face of disappointing results in Alzheimer's disease (AD), researchers in frontotemporal degeneration (FTD) are learning from AD woes and gearing up to take a seat in the front row. This year's 4th International Conference on Clinical Trials in Alzheimer's Disease, (CTAD), held 3-5 November 2011 in San Diego, California, included a session on preparing for treatment trials in FTD. Presenters made the case that trials in FTD may stand a better chance of succeeding than those in AD. As research has uncovered many molecular pathways common to FTD and related disorders ranging from the common (AD) to the rare amyotrophic lateral sclerosis (ALS), any treatments developed for FTD may have broad applications and energize the field of neurodegeneration as a whole.

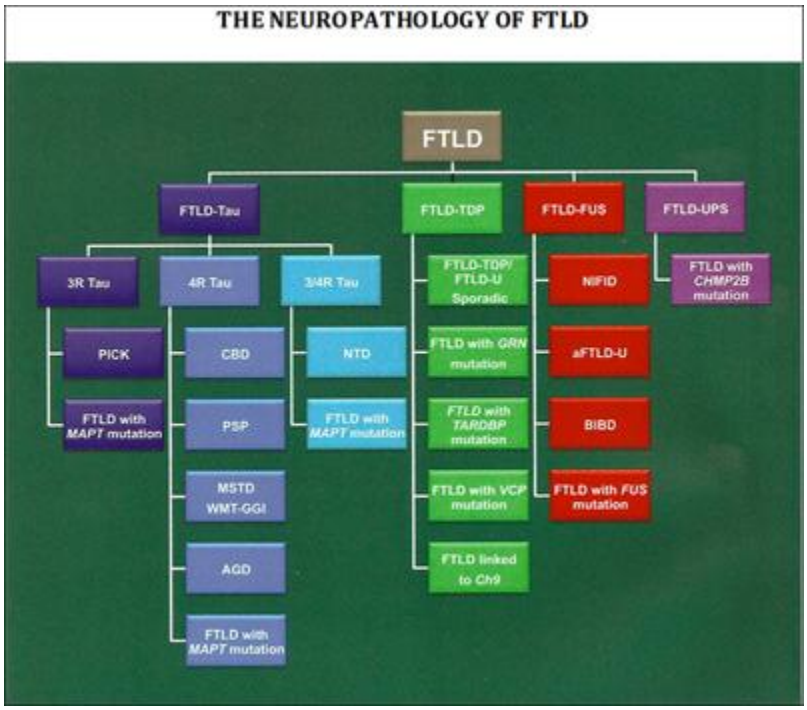
The session at CTAD represented the third meeting of the fledging FTD Treatment Study Group (FTSG). Since its inception in 2010 the group has been trying to drum up interest from pharmaceutical companies in conducting FTD trials (see ARF related news story). The reason for holding the meeting at CTAD was to catch a "broader audience who might not be involved in the FTD field at the moment," said **David Knopman** of the Mayo Clinic in Rochester, Minnesota. "We wanted to see if we could attract clinical trialists from other areas and pique their interest by highlighting some of the new developments in FTD."

The meeting also marked the beginning of FTSG's formal association with the Association for Frontotemporal Degeneration (AFTD), a not-for-profit advocacy group that will serve as FTSG's home, at least initially. "Being adopted by AFTD will allow us to grow and raise funds to help foster FTD drug development," said **Adam Boxer**, University of California, San Francisco, who leads the FTSG. The funds will be used, for example, to encourage companies to share compounds that they might have otherwise abandoned so that they can be tested in FTD animal models. The funds will also help educate regulatory agencies about FTD-specific issues, further develop clinical trial methods, and create a patient registry, explained Boxer.

One of the main developments in the FTD field is that the molecular biology of the disease has been cracked open. "When I started to work in this area six years ago, we just knew about tau, but there have been such advances in our knowledge since then. As far as the genetic basis of disease, I think we virtually solved it. There are still many questions about how the different genes and proteins interact and how they lead to neurodegeneration, but we know who the main players are," said **Ian Mackenzie** of the University of British Columbia in Vancouver, Canada.

In the "old" days, FTD—which is actually a group of diseases—was defined according to clinical criteria. Most people with FTD have behavioral variant FTD (or bvFTD), which degrades a person's social skills and emotions. The next major category is semantic dementia, which hollows out their language; people can speak but no longer know the meaning of words. On the other hand, people with progressive non-fluent aphasia (PNFA) cannot speak fluently even though they know the meaning of the words they are trying to say. Finally, corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP) are characterized by muscle weakness, rigidity, and/or parkinsonian symptoms.

More recently, researchers have adopted a classification of FTD based on the types of proteins that aggregate in cells (Mackenzie et al., 2009; Cairns et al., 2007; see also ARF related news story). The proteins involved are thought to play a role in the disease process, and are thus obvious targets for therapies.



Researchers have uncovered many of the genes and proteins that play a role in FTD, leading to a new classification of disease based on its molecular pathology. *Image credit: Nigel Cairns* View larger image.

About 40 percent of FTD patients have intracellular accumulations of an abnormal form of the protein tau. This group of conditions, known as frontotemporal lobar degeneration (FTLD)-tau, includes most cases of PSP and CBD, as well as Pick's disease. For PSP and CBD, the deposits consist almost exclusively of isoforms of tau with four microtubule-binding repeats (4R tau; Dickson et al., 2010), whereas in Pick's disease, deposits contain 3R tau. Both 3R and 4R tau accumulate in neurofibrillary tangles in AD. In about 50 percent of FTD patients, including most who develop the disease in combination with ALS, the protein that accumulates is the TAR DNA binding protein 43 (TDP-43) (see ARF related news story). These patients fall into the FTLD-TDP-43 disease category. In 2009, investigators identified that the final subset of FTD patients (about 10 percent) have accumulation of the ALS-linked protein fused-in-sarcoma (FUS).

How do the clinical and protein-based classifications match up against one another? In the most common form of FTD, the behavioral variant, there is no clear correlation between clinical and molecular subtypes, which presents a challenge for selecting patients for trials. But with other subtypes, the relationship is clearer. Patients with the clinical symptoms of PSP and CBD almost

always have pure tau pathology. As a result, patients with these conditions have been selected for early trials of tau-based therapies.

Why not test those therapies in Alzheimer's patients first? After all, neurofibrillary tangles have been a defining pathology of AD for a century. In reality, only a minority of AD patients have pure amyloid and tau pathology; most also have concurrent vascular or Lewy body disease. These other pathologies could mask any beneficial effects of drugs that target tau in those patients. "Clinical trials in FTD could be used for de-risking tau-related approaches to AD. A win here would rejuvenate the entire industry," said **Jeffrey Cummings**, Cleveland Clinic, Nevada, at the meeting.

Another advantage of conducting trials in FTD is that in about 10 percent of patients, the disease is caused by a genetic mutation inherited in an autosomal-dominant manner (see ARF related news story). "We are taking about mutations that have a substantial impact on disease," said **Howard Feldman** of Bristol-Myers Squibb, Wallingford, Connecticut, and the University of British Columbia in Vancouver. In his presentation at CTAD, Feldman suggested that genetic patients are obvious candidates for FTD trials. For years, AD trials focused on sporadic disease and excluded people with autosomal-dominant disease, but now some researchers are rethinking that strategy (see ARF related news story and ARF news story). "In FTD we have learned from the AD experience, and we are planning trials in at least one autosomal-dominant diagnosis, that is, FTD caused by progranulin haploinsufficiency," Boxer told ARF. "Since the molecular defect is clear in this form of FTD, we may be able to hit an early home run that will help pave the way for wins in more common forms of FTD." But others caution that this strategy is less straightforward than it sounds. "I agree that it needs to be done. But it will be challenging because the number of patients is so small," Knopman told Alzforum.

Six genes have been associated with autosomal-dominant FTD. They are the MAPT gene on chromosome 17, which codes for tau; the PGRN gene, also on chromosome 17, which encodes the growth factor progranulin (see ARF related news story); the TARDBP gene on chromosome 1, which produces TDP-43; the VCP gene on chromosome 9, which codes for valosin-containing protein; the CHMP2B gene on chromosome 3, which expresses charged multivesicular body protein 2B (aka chromatin modifying protein 2B); and rare cases of FTLD are associated with mutations in the FUS gene (Van Langenhove et al., 2010 and Cairns and Ghoshal, 2010). Most recently, researchers identified an expanded GGGGCC hexanucleotide repeat in the noncoding region C9ORF72 as the cause of both chromosome 9p-linked FTD and ALS (see ARF related news story on Dejesus-Hernandez et al., 2011 and Renton et al., 2011).

These advances in genetics have highlighted the many similarities between FTD and ALS, and a number of researchers now view these two as opposite ends of a disease spectrum (see ARF related news story). But the overlap does not end there. FTD also shares common molecular pathways with Alzheimer's. Beyond tau, FTD and AD may share molecular pathways that involve TDP-43 and progranulin, according to Mackenzie.

TDP-43 pathology is detected at postmortem in 25 to 50 percent of people with AD, and one study suggests that polymorphic variants in the gene, although they do not cause AD, increase the risk for AD; however, other studies have not found this association (see AlzGene). For its

part, progranulin is an antagonist of the tumor necrosis factor α receptor, and has potent anti-inflammatory effects in animal models of arthritis (Tang et al., 2011). At CTAD, Mackenzie presented a model whereby progranulin may be involved in protecting the brain against damage. "It could be that reduced levels of progranulin put you at increased risk for neurodegeneration in general," he told Alzforum. According to his model, FTD patients with progranulin mutations cannot protect their brain from age-related stress and damage, which eventually lead to FTD. AD patients have other primary mechanisms of toxicity, but having less progranulin leads to a worsening of symptoms in them, too. "The model is that if you develop AD and have reduced levels of progranulin, you will have increased neurodegeneration," said Mackenzie. Although he acknowledged the proposal is highly speculative, he believes it is possible that progranulin-based therapies will work in both FTD and AD, as well as in inflammatory diseases.

In addition to these recent advances in understanding the molecular pathology of FTD, this past year has seen the development of clinical guidelines for the disease and the creation of two imaging projects à la ADNI. "All the pieces are falling into place for clinical trials in FTD. We now need to convince industry to share promising drugs," said Boxer.

Pieces Move Into Place to Stage Frontotemporal Trials

There are no treatments for frontotemporal degeneration (FTD), a common form of dementia in people younger than 65 years of age. That is one reason why speakers at a session titled "Clinical Trials in Frontotemporal Degeneration and Related Disorders" wanted to bring this somewhat neglected condition to the attention of the pharmaceutical industry and trialists working in Alzheimer's disease (AD). The session was part of the 4th International Conference on Clinical Trials in Alzheimer's Disease (CTAD) held 3-5 November 2011 in San Diego, California.

In his presentation, **Edward (Ted) Huey** of Columbia University in New York City summarized the current state of affairs of FTD treatments. The few trials that have tested the approved therapies for AD in FTD patients have had disappointing results. "It appears that some of the patients who respond to cholinesterase inhibitors are those with AD pathology," he said at the meeting. Memantine, too, has been tested in a small number of FTD trials. "So far it has been well tolerated in patients, but has not yet been shown to be efficacious," said Huey. The results of the largest trial of memantine in FTD to date, conducted by **Adam Boxer**, University of California, San Francisco, will come out in 2012. "It should provide an answer," said Huey.

Aside from therapies borrowed from AD, two FTD trials are testing compounds that target tau—a protein that accumulates both in some forms of FTD and in AD. Allon Therapeutics, headquartered in Vancouver, Canada, is sponsoring a Phase 2/3 randomized double-blind, placebo-controlled study to evaluate the safety and efficacy of davunetide in a type of FTD called progressive supranuclear palsy (PSP). Davunetide is an eight-amino acid peptide derived from a neuroprotective protein. It acts by maintaining and stabilizing the microtubular network (Divinski et al., 2004 and Divinski et al., 2006). Tau binds to microtubules and destabilizes them; davunetide presumably counteracts this effect, though its mechanism of action is not entirely clear. In PSP, the primary protein that accumulates in cells is a pathogenic isoform of tau, four-repeat tau. "There is little amyloid or other pathology, which makes the disease very attractive for a trial," said Boxer, who is the study director (see ARF related news story).

Another company, Noscira, based in Madrid, Spain, is testing a different tau-busting agent in PSP. On 18 October 2011, the company announced that the last patient completed treatment in the yearlong Phase 2 efficacy trial of tideglusib, an inhibitor of glycogen synthase kinase 3-β (GSK-3β), one of the enzymes that phosphorylates tau. The trial tested two different doses of tideglusib (600 mg and 800 mg, taken orally once a day) versus a placebo in 146 patients with possible or probable mild to moderate PSP for 52 weeks at 24 sites in Europe and the U.S. "If these two trials demonstrate success with a tau-based drug in a pure tauopathy, this may help predict success in AD," said Boxer.

Several presenters thought that targeting progranulin was a logical next step for FTD trials. Mutations in the progranulin gene may be the most frequent mutations among patients with autosomal-dominant FTD. The mutations lead to reduced levels of progranulin in blood and almost always produce TDP-43 inclusions in cells. Measuring progranulin blood levels in patients treated with a compound that boosts progranulin production may provide a way to monitor treatment effects (see ARF related news story). "A number of drugs that raise progranulin levels have been identified in high-throughput screens and tested in cell culture, and some have moved toward testing in animal models," Boxer told ARF. "We hope that we will see clinical trials with some of these compounds next year."

At the CTAD meeting, **Michael Gold** of Allon Therapeutics, which is sponsoring the davunetide trial, pointed out some of the regulatory advantages of conducting trials for orphan medications. Those are intended for the treatment of rare diseases that affect fewer than 200,000 people in the U.S., or that affect more but are not expected to recover the costs of developing and marketing a drug. (According to the presentation by **David Knopman** of the Mayo Clinic in Rochester, Minnesota, 20 people for every 100,000 aged 45 to 65 have FTD, and FTD has orphan disease designation.) "The FDA has indicated that drug approval based on a single trial is possible for many conditions that qualify for orphan indication," Gold said at the meeting. According to the Orphan Drug Act, the sponsor of a clinical trial on an orphan disease can readily obtain guidance from the FDA along the way and market exclusivity for the drug being tested can be extended. Other advantages of conducting trials in FTD are that patients are younger and more enthusiastic to participate in trials than AD patients, Gold said. In addition, FTD patients' symptoms are not complicated by changes due to aging, and the more rapid progression of disease makes trials shorter and requires fewer patients.

On the other hand, one challenge of conducting a trial with PSP patients is that the total number of patients with the disease is small, requiring that a given trial engages many different clinical sites, each of which recruits but a few patients. In the past, more sites have at times meant more sources for variability and error. "The FDA is responding to this problem and has released guidance on remote trial monitoring that may relieve that burden," Gold said in his presentation. The draft guidance was released on 1 September 2011.

In addition to a favorable regulatory environment, new clinical diagnostic criteria for FTD, released earlier this year, may make trials easier to carry out. "Having clinical diagnostic criteria is critical to conducting clinical trials. If there is significant disagreement, as there is in the field of vascular dementia, for example, that scares away regulators," said **David Knopman** of the Mayo Clinic in Rochester, Minnesota. "Although refinements are needed, there is broad

agreement that the new criteria are good and valid, and people are comfortable using them." One set of criteria is for behavioral variant FTD (bvFTD), the largest clinical subgroup of the disease (Rascovsky, et al., 2011). The second set of criteria is for the primary progressive aphasia (PPA) subtype of FTD (Gorno-Tempini, et al., 2011).

Another advance in the field has been the development of outcome measures that are appropriate for FTD. "We have to think outside the ADAS-Cog box," **Joel Kramer** of the University of California, San Francisco, told Alzforum. "Up until recently, all available instruments were very memory focused, but those are not helpful for many types of FTD." In his CTAD presentation, Kramer discussed tools his group has developed for measuring changes in executive function. One measure dubbed EXAMINER, for EXecutive Abilities: Measures and Instruments for Neurobehavioral Evaluation and Research, consists of a modular battery of tests that takes 30 to 40 minutes to administer and yields a composite score. Such tests may also be helpful in AD, Kramer believes. In the earliest stages of AD, memory is not sufficiently impaired for most current tests to capture changes, whereas it may be possible to detect shifts in executive function. His group has also made headway in developing measures for social behavior and emotion.

"The first step is to get pharmaceutical companies excited to conduct trials in FTD," Kramer told ARF. "Once we have enough trials, we can build a consensus for outcome measures. Traditionally, the measures that are used in the first five to six trials become the gold standard."

Another outcome measure that will be useful for FTD trials consists of changes in brain volume and function obtained through imaging. Taking the example of the landmark Alzheimer's Disease Neuroimaging Initiative (ADNI; see ARF related news story and ARF news story), two FTD-focused imaging studies have gotten off the ground. **Howard Rosen** of the University of California, San Francisco, described preliminary results from the FTLD Neuroimaging Initiative (FTLDNI). Funded in late 2009 by the National Institute on Aging and the National Institute of Neurological Disorders and Stroke, the project is following 120 FTLD patients with bvFTD, semantic dementia, and progressive non-fluent aphasia (PNFA), plus 75 controls. They are being examined at baseline, and then at six, 12, and 18 months using positron emission tomography (PET) and structural magnetic resonance imaging (MRI), as well as diffusion tensor imaging (see ARF related news story). "The changes we see in FTD are different from changes we see in Alzheimer's," Rosen said at CTAD. "And different variants of FTD are associated with different types of changes." He presented data from one patient who showed a visible decline volume in both left and right lobes as detected by MRIs taken six months apart. "We will have easier time than ADNI in delineating changes because disease progression is faster," said Rosen.

The second imaging initiative, headed by Boxer, is the Four Repeat Tauopathy Neuroimaging Initiative (4RTNI). Taking advantage of the FTLDNI infrastructure already in place at UCSF, this study will recruit 40 corticobasal degeneration (CBD) and 40 PSP patients, and study each for a year using a combination of clinical measurements, biomarkers, and 3T MRI scans. Both imaging projects have adopted standards developed by ADNI to enable comparisons.

One reason for conducting these studies is to find biomarkers specific for FTD. "One thing that is really missing is a biomarker approach that would enable clinicians to subdivide bvFTD into different entities according to molecular pathology," said Knopman. It is not surprising that

current trials are being conducted in patients with PSP, a type of FTD that is relatively uniform in terms of molecular pathology.

"It is difficult to tell the underlying pathology of FTD based on the clinical group, except for rare disorders," said **William Hu** of Emory University, Atlanta, Georgia, speaking at CTAD. "The clinical syndrome is useful for tracking progression of disease, but it is hard to say who has FTLD-TDP-43 and who has FTLD-Tau based on clinical criteria." To that end, his group is looking for sets of analytes that can differentiate between the two groups of pathologies.

With the molecular biology delineated, diagnostic guidelines and outcome measures developed, and longitudinal imaging studies underway, biomarkers are the last piece of the puzzle for a broad-based effort in FTD clinical trials. But even without such biomarkers, conducting clinical trials in certain types of FTD is already feasible. "The disease is not that rare, and there are enough patients out there who should make [the investment] worthwhile for pharmaceutical companies," said Kramer. "Plus, there are incredible applications for AD and other diseases."—Laura Bonetta.