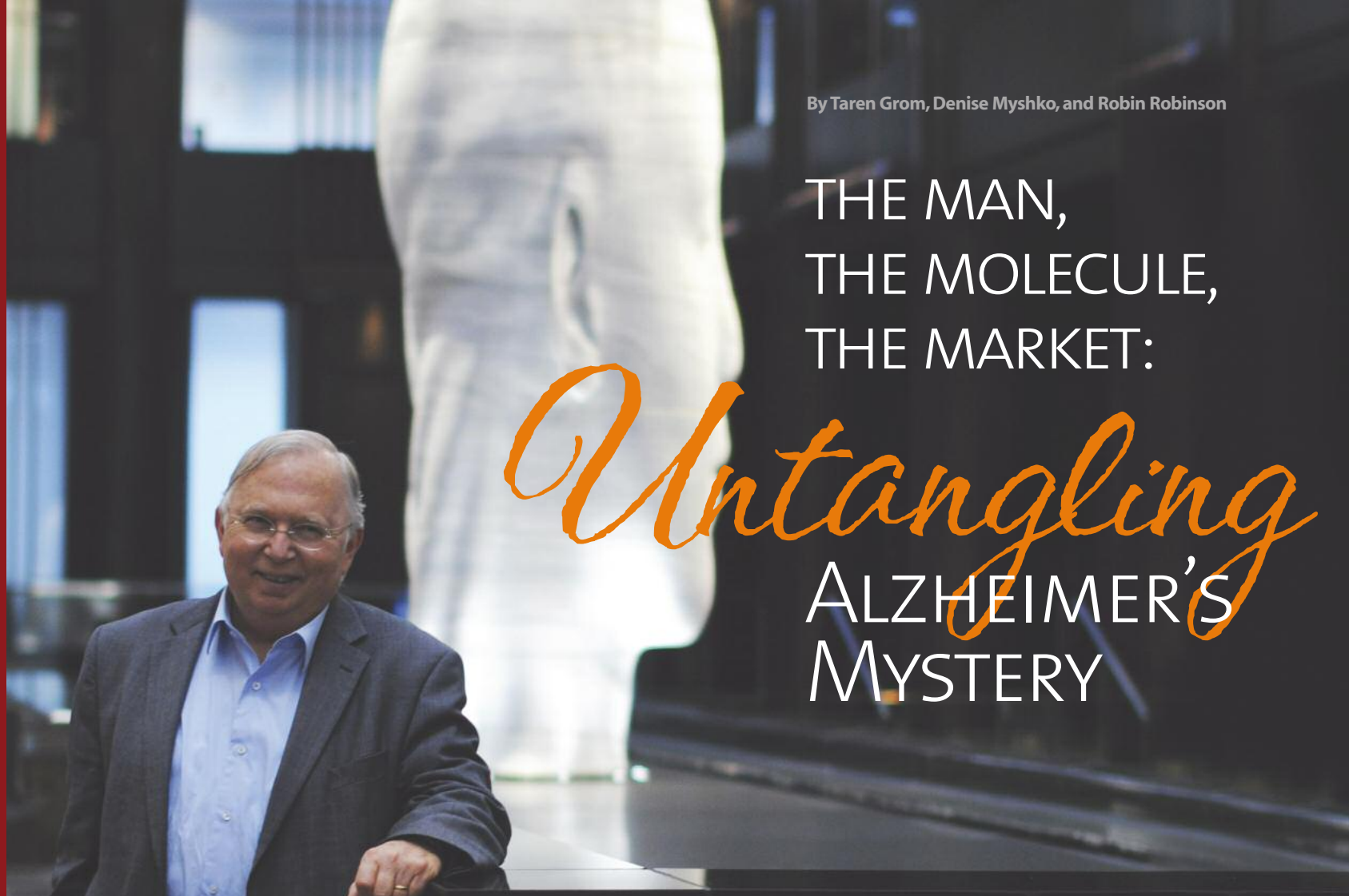


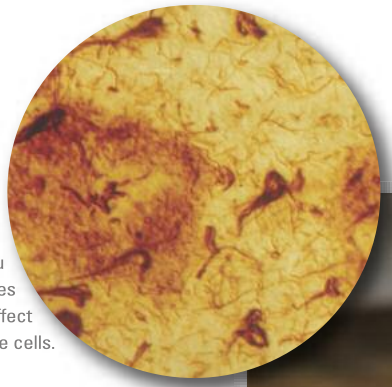
By Taren Grom, Denise Myshko, and Robin Robinson

THE MAN, THE MOLECULE, THE MARKET: *Untangling* ALZHEIMER'S MYSTERY

Alzheimer's disease is a progressive brain disorder that damages and eventually destroys brain cells, leading to loss of memory, thinking, and other brain functions. Alzheimer's is not a part of normal aging, but results from a complex pattern of abnormal changes. It usually develops slowly and gradually worsens as more brain cells wither and die. The underlying causes and processes involved in this harmful deterioration are still under debate within the scientific community.

This spotlight feature article takes a unique look at Alzheimer's disease. In an exclusive interview, Professor Claude Wischik, M.D., Ph.D., executive chairman and co-founder of TauRx Therapeutics and professor of Old Age Psychiatry at the University of Aberdeen, discusses his 30-year journey of tau research, the divergent scientific views on the role of beta amyloid and tau pathology in Alzheimer's, and what success from TauRx's upcoming Phase III clinical trials denotes for the market and patients.

Photography: Kristen Velit



A histological view of the tau protein indicates the "strangle" affect it has on nerve cells.

"WE PLACED OUR BET IN THE MID-1990S; I ACKNOWLEDGED I WAS WORKING AGAINST CONVENTIONAL THINKING IN THE ACADEMIC SCIENCE FIELD.

For more than 25 years, academics, pharmaceutical companies, patient groups, and government-funded researchers have pinned their hopes and their investment — upward of $15 billion — on a single path to treat Alzheimer's disease: beta amyloid. This is the protein found in the plaques that form in the brains of people with Alzheimer's, and has been considered by many experts to play a pivotal role in the development of the disease.

This singular focus on amyloid plaques overshadowed other hypotheses and other lines of research. Consequently, until now alternative research approaches focusing on tangles made up of abnormal tau protein in the brains of Alzheimer's patients have been largely overlooked. But, tau research is drawing renewed attention and could turn Alzheimer's research and the market on its head.

AMYLOID MAY WELL BE IRRELEVANT TO EXPLAIN WHY PEOPLE DEVELOP DEMENTIA.

Prof. Claude Wischik

In an era in which disruptive innovation is sorely needed and in an area where an effective disease-modifying therapy is needed even more, Professor Wischik is on the verge of becoming an overnight success — 30-plus years in the making — if the Phase III trials for LMTX, the second-generation tau aggregation inhibitor (TAI), prove to be as successful as the Phase II trials of its predecessor, rember.

Data released in 2008 from Phase II trials involving 321 patients with mild and moderate Alzheimer's disease revealed a 90% reduction in the rate of disease progression over two years in mild-moderate Alzheimer's patients at the 30 mg and 60 mg doses. While the results drew media attention at the time, they barely made a ripple in the Alzheimer's community. However, recent clinical failures with products addressing the beta amyloid pathway now have some believing that a tau-based product is industry's next best hope for a successful Alzheimer's treatment.

The implications are vast. This could be one of the biggest discoveries in modern history. Yet, still others think that a combination of the two approaches could provide the necessary silver bullet.

Prof. Wischik remains committed to pursuing the tau tangles and is confident that LMTX is the right way forward. If he is right, TauRx Therapeutics, as well as the Alzheimer's patient and caregiver community, will be the big winners.

At the same time, Prof. Wischik is quick to point out that in the end it's not about the money; it's about doing the right thing. And that right thing is bringing a treatment to market that halts or reverses the devastating affects of Alzheimer's.

When asked if he is discouraged by the lack of attention from investors, potential partners, and even the media to the tau approach, he says no.

"We're driven by the data, and our conclusions came from the experimental data," he says. "It doesn't matter how many experts line up, they can't fight data. We have been able to say through our years of research that amyloid is interesting but it may well be irrelevant to why people develop dementia."

THE MAN: The Road Less Taken

Prof. Wischik, working with a team of chemists, has spent 30-plus years investigating the structure and the role of tangles, which are found in the brains of Alzheimer's patients. In the mid-1980s he discovered that these tangles are made of an abnormal form of tau protein. He and his colleagues have implicated this tau protein in the progression of Alzheimer's.

Prof. Wischik's journey, which has become a life-long passion, began in the laboratory as a Ph.D. student.

Prof. Wischik's life, and potentially the lives of millions of patients and caregivers who may benefit from his research, changed with the mere exchange of a letter.

Prof. Wischik had just completed a medical internship and was working in the emergency admission unit of a local hospital in Adelaide, Australia, when at 3 a.m., he decided that he needed a change. With a background in medicine and arts, he decided that the combination of the two — psychiatry — would be an interesting area of research to pursue.

Prof. Wischik looked for the best psychiatrist doing the most interesting work at the time, and came upon Sir Martin Roth at Cambridge University.

"I sent him a letter and Sir Martin welcomed me," Prof. Wischik recalls. "On this

Alzheimer's Facts

- 5.4 million Americans are living with Alzheimer's disease.
- One in eight older Americans has Alzheimer's disease.
- Alzheimer's disease is the sixth-leading cause of death in the United States and the only cause of death among the top 10 in the United States that cannot be prevented, cured, or even slowed.
- More than 15 million Americans provide unpaid care valued at $210 billion for people with Alzheimer's and other dementias.
- Payments for care are estimated to be $200 billion in the United States in 2012, including $140 billion in costs to Medicare and Medicaid.
- The costs of Alzheimer's in 2050 are predicted to total $1.1 trillion (in today's dollars). Costs to Medicare and Medicaid will increase by almost 500%.

Source: Alzheimer's Association.
For more information, visit alz.org.

basis, I got a scholarship to go to Cambridge to do a Ph.D., so I went."

Sir Martin Roth, who became Prof. Wischik's long time mentor and friend, had in 1968 established the correlation between dementia and the tangles. This discovery represented the first time anyone had established a quantitative link between a psychiatric syndrome and measurable biological change in the brain. This eventually earned him a Fellowship of the Royal Society. His next quest was to determine the chemical structure of the tangles.

"Having done the fundamental work to map mental functioning and dementia, Sir Martin published papers that showed that tangles appear to explain the cognitive decline in Alzheimer's," Prof. Wischik says.

Working with Cambridge's Sir Aaron Klug, who had received the Nobel Prize the year before in chemistry for his development of crystallographic electron microscopy, Prof. Wischik's task was to look at the tangle and determine, first what its structure was, then what it was made of.

"The main results of my Ph.D. research were first to define the structure of the tangle filaments — paired helical filaments or PHFs — as being a de novo polymer, and then to identify tau protein as an integral constituent of the PHF," he says. "Before that, a large number of proteins had been identified in tangles on the basis of low-resolution antibody labeling of tangles. These included vimentin, neurofilament protein, and even beta amyloid, as well as two different microtubule associated proteins MAP-2 and tau. It was not possible to determine which of these was the actual building block of the new polymers that assemble to form the tangles and which proteins were just trapped by the tangle after it had formed. What my work showed for the first time was that tau is the only protein that is part of what the PHF is actually made of. At that time, we did not know whether there were other proteins inside the PHF, but we were sure for the first time that tau was one of them. It was only later that we were able to prove that tau protein accounts for at least 90% of the protein mass of the PHF."

IN MY PH.D. RESEARCH, I DISCOVERED THE TANGLE WAS MADE OF TAU PROTEIN.

Prof. Claude Wischik

Gaining an early understanding of the correlation between the tangles and mental functioning wasn't always easy, Prof. Wischik recalls.

"Sir Martin sent me to the salt mines to find out what the tangles were," he says. "The only way we could do this was to get brain tissues from people. So, there I was in the second year of my Ph.D. and we were going out in the middle of the night because 'Mrs. Smith' in the backwoods had just died and I needed to collect her brain tissue within eight hours of her death. The way to achieve this was to ask 'Mrs. Smith's' daughter whether she was willing for her mother's brain to be used in research.

"I went to these grieving families with my request, and the deceased's relatives responded with a purity of intention to help other people," he continues. "I found this fundamental generosity of spirit inspiring, and it has remained with me all along."

Prof. Wischik's Cambridge research team showed that at an early stage of the disease there was tangle-based destruction of nerve cells in the hippocampus of the brain, and that tau aggregation first appears in the brain about 20 years before the clinical impact on the person becomes evident.

Prof. Wischik recalls that at one point, Sir Martin said: "We must seize the tangle by the throat."

"Sir Martin was inspiring," Prof. Wischik says. "My professional career represents a continuation of his professional career. Where we are today in terms of tau research represents two generations of research."

About the same time Prof. Wischik and his team began researching ways to target the tau protein, the molecular structure of amyloid plaques was also discovered.

Molecular biology was all the rage among researchers in the 1990s. It was also at this time that a gene — amyloid precursor protein (APP) — was identified and linked to Alzheimer's disease.

"There was a strong sense that once the gene was in hand it could be expressed and this would somehow lead immediately to finding a way to cure the disease," Prof. Wischik says. "At the same time, biotech research, basic high-intensity sequencing, and the ability to express proteins using bacteria were just taking off."

In parallel, many papers were being published emphasising the relationship of amyloid beta to Alzheimer's disease and forgetting entirely about Alzheimer's tangles.

"Meanwhile, we were finding that there could be large quantities of amyloid in the brains of people who were completely normal cognitively," Prof. Wischik says. "In 1994, my colleague Charles Harrington published a paper based on biochemical measurement of amyloid load in the brain showing that the accumulation of amyloid did not appear to explain dementia. Although there were somewhat higher levels in Alzheimer's cases, there was a 76% overlap with the levels of amyloid found in normal elderly people."

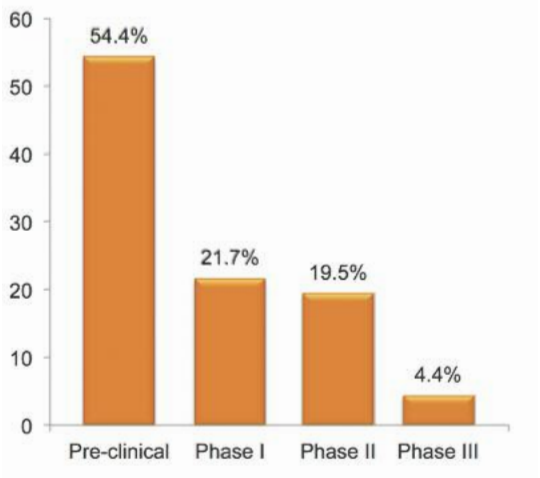
Much later in 2008, a paper published in Lancet Neurology by another team of researchers at the University of Southampton, U.K., also supported the theory that amyloid was not the driving force behind clinical dementia. These researchers found that although immunization with beta amyloid resulted in clearance of amyloid plaques in patients with Alzheimer's disease, this clearance did not prevent progressive neurodegeneration and progression of the tau pathology through its later stages.

THE JOURNEY CONTINUES

After many years at Cambridge, Prof. Wischik and his team moved to the University of Aberdeen in 1997, where work continued in the laboratories of the Institute of Medical Sciences. In 2000, Prof. Wischik and his team showed that the accumulation of abnormal aggregates of tau, again measured biochemically, is directly linked quantitatively to clinical dementia. Surprisingly, they also found that tau aggregates measured biochemically in the frontal and temporal lobes of the brain begin to appear long before the later-stage increase in beta-amyloid plaques seen in Alzheimer's. This was a crucial find-

Pipeline Analysis by Clinical Phase

Alzheimer's Disease Medication Market: Percent of Drug Candidates in Pipeline, Global 2012



Almost 54% of the drug candidates are in the preclinical phase of development with just 4.4% in Phase III. Furthermore, the mechanism of action for almost one-third of the compounds in the pipeline could not be exactly identified, which reflects the complexity of the disease pathology and underlying mechanisms.

Source: Frost & Sullivan. For more information, visit frost.com.

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"This is research that needs doing and it just so happens that we're the ones who ended up doing it. This is not about glory.

ing in thinking about the treatment of Alzheimer's.

"The University of Aberdeen took my entire team and funded our research for five years," he says. "That proved to be very important. That five years of funding, is what allowed me to build out the company. I had five years where I didn't have to write grants. It was during this time that we perfected the cell assays and developed the first transgenic animal models of tau pathology. We took a leap of faith.

"There's a very solid scientific Scottish infrastructure that's founded on solid medical education," he continues. "Many people don't know that the MRI was invented in Aberdeen. The imaging team at Aberdeen is excellent. And we have an incredible chemist group, which has been crucial in supporting the next phase in our development. So the fabric is all there and my role is to move the company forward down a clear path toward a treatment."

Prof. Wischik's research was so far removed from the prevailing amyloid view that even today, the closest competitor is seven to 10 years behind. Even though he was convinced he was on the right path, few others were equally as sure.

"We placed our bet back in the mid-1990s, and I acknowledged that I was working against conventional thinking in the academic science field," he says. "No matter how many papers I wrote, it didn't change the consensus. In the end, I knew this debate will only be settled when there is an effective treatment; the rest is all academic conjecture. Either the amyloid approach will work or it won't; and either a tau-based treatment will work or it won't."

Due to the amount of work that he, his team, and the company have already done, it's too late for another company to place that same bet today. Prof. Wischik says he and his team had to innovate every step of the way. They did research on Braak staging, i.e. the spread of tau pathology, in patients at the pre-dementia and early stages of Alzheimer's in the 1990s, they developed screening tools for drug discovery, and they developed their first tau transgenic animal models that showed the tau pathology for testing their drugs in 2002.

"We had to create the tools we needed out of nothing at every step of the way," Prof. Wischik says.

Prof. Wischik recalls a moment just after moving to Aberdeen when he and his close colleague — Charles Harrington, Ph.D., now chief scientific officer of TauRx — thought maybe, just maybe they shouldn't move forward.

"There was a time when we thought it was just too hard," he recalls. "Then Dr. Harrington, who put it very well, said nobody else is stupid enough to do this; we seem to be the only ones. The rationale to move forward was based on years of research and the likelihood

ALZHEIMER'S TIMELINE

1906

Dr. Alois Alzheimer at a meeting described for the first time a disease of the cerebral cortex of patient Auguste Deter, who had a type of dementia that would later bear Dr. Alzheimer's name

Dr. Alois Alzheimer publishes his lecture the following year

1910

Emil Kraepelin, Dr. Alzheimer's colleague in Munich, includes in the eighth edition of his book Psychiatrie Dr. Alzheimer's description of Auguste Deter's symptoms

1963

Paired helical filaments (tangles) and amyloid plagues are identified

1984

Researchers identify the protein beta amyloid in the plagues of Alzheimer's patients

1986

Researchers identify the tau protein in the nerve tangles of Alzheimer's patients

1987

Warner-Lambert's tacrine, the first drug specifically targeting symptoms of Alzheimer's disease, begins clinical trials

Researchers identify the mutation in the beta-amyloid precursor protein (APP) gene on chromosome 21

1988

MRC Laboratory of Molecular Biology in Cambridge (UK) identifies the tau protein in the nerve tangles

that a tau aggregation inhibitor could be a treatment. We reached the conclusion that, given what we knew and how this could potentially benefit people, it was actually our duty to carry on regardless of how hard it was or how much opposition there was to how we saw things.

"The implications are so large, that it actually doesn't matter what the pain is," he continues. "This is research that needs doing and it just so happens that we're the ones who ended up doing it. This is not about glory. We have a privileged view from our own experimental data about how things probably are. Given this knowledge and insight, there is nobody else who can carry this research forward, so it fell to us to carry on. I remember thinking that we have no right not to do this; this became my mantra."

THE NEXT LEG OF THE JOURNEY

In 2002, Prof. Wischik serendipitously met Dr. K M Seng, a gynecologist, surgeon, and venture capitalist. The two founded TauRx Therapeutics in Singapore with the mission to develop new treatments and diagnostics for a range of neurodegenerative diseases related to tau pathology.

The connection came through Damon, one of Prof. Wischik's three sons, who was going to the same private boarding school in Cambridge with Dr. Seng's son. Prof. Wischik's sons have played key roles in the company's evolution.

"The initial investors in the company came from Singapore. Dr. Seng was instrumental in bringing in Tay Siew Choon, who had a top management role in a major subsidiary of the Singapore sovereign wealth fund, Temasak, to join the board of TauRx," Prof. Wischik explains. "As of last December, we had raised $170 million from a variety of investors. We have 640 shareholders, many include Singapore doctors with additional monies from large investors."

Prof. Wischik had much better success going this route than through the traditional venture capitalist model, which he found to be disingenuous, unrealistic, and ultimately incapable of independent thought and analysis. He found that, they could not make independent venture judgments outside the main stream and were behaving just like big pharma.

As far as moving out of the lab and into the boardroom, Prof. Wischik is as pragmatic about running a company as he is about everything else. But he also has a sincere sense of responsibility, duty, and humility.

"I don't care about the fluff," he says. "That's a long way behind me. It's just about doing the business, the real business of what has to be done. For me, learning how to raise money, or how to calculate a net present value, or put together business plans is just like learning how to use the electron microscope or how to make monoclonal antibodies — it's all just technology. Business processes are just like different bits of technology that I've had to master."

Prof. Wischik is truly in the right place at the right time with the right skills to hopefully bring LMTX successfully to market.

"Being in a place where I can bring a clinical and business perspective to the table, as well as keeping an eye on the science, is the right place for me to be," he says. "I used to ask myself, would I have chosen me to do this? The answer is probably no, but as it turns out I actually do seem to have the necessary skill sets. The combination of being able to tell the tau story while being solidly rooted in science turns out to be very important. Real innovative science is extremely hard to do well; it's not just about cranking the technology, you don't know the answers beforehand."

The science may be hard, but Prof. Wischik says treating Alzheimer's should be relatively easy, from a patient's perspective as well as the resources needed for diagnosis, which brings the conversation back to the concept of disruptive innovation.

Clayton Christensen of Harvard Business School defines disruptive innovation as making it possible for simple, affordable, and accessible products to replace products that are complex, expensive, and inaccessible.

"This is exactly what we want to do," Prof. Wischik says. "We want to make accessible and affordable drugs that are necessary. When we do our financial projections about our drug, we don't say it's going to cost $30,000 per infusion; we made the decision that rember or LMTX will be a pill. If it works as we predict, enough people will take it and the

1993

COGNEX FIRST FDA APPROVED PRODUCT TO TREAT AD

FOUR DRUGS APPROVED IN NEXT 10 YEARS: ARICEPT (1996), EXELON (1997), NAMENDA (2003), RAZADYNE (2004)

APOE-E4 IDENTIFIED ON CHROMOSOME 19

AT U. OF PENN MICROTUBULE STABILIZERS IDENTIFIED AS SUBSTITUTE TO TAU FUNCTION

1995

LILLY PURCHASES AND RENOVATES DR. ALZHEIMER'S BIRTHPLACE IN MARKTBREIT AS A MUSEUM; IT OPENED ON THE 80TH ANNIVERSARY OF DR. ALZHEIMER'S DEATH

2000

PROF. WISCHIK'S TEAM SHOWS TAU IS DIRECTLY LINKED TO CLINICAL DEMENTIA

2002

PROF. WISCHIK AND DR. K M SENG COFOUND TAURX

2008

TAURX REPORTS ON PHASE II STUDIES THAT SHOW REMBER, AN ANTI-TAU THERAPY, REDUCES COGNITIVE DECLINE IN ALZHEIMER'S PATIENTS

LANCET PUBLISHES PAPER BY RESEARCHERS AT THE UNIVERSITY OF SOUTHAMPTON, UK, SHOWING THAT CLEARANCE OF AMYLOID PLAQUES DID NOT PREVENT NEURODEGENERATION

2012

BMS BEGINS PHASE IB TRIAL OF EPOTHILONE D, NOW KNOWN AS BMS-241027

SEVERAL HIGH-POTENTIAL PHASE IIII ANTI-BETA AMYLOID DRUGS FAIL TO MEET CLINICAL ENDPOINTS

TAURX BEGINS PHASE III TRIALS OF LMTX

AC IMMUNE/ GENENTECH BEGIN RESEARCH ON ANTI-TAU ANTIBODIES

2013

AC IMMUNE AND GENENTECH WILL BEGIN A STUDY OF THE ANTI-BETA AMYLOID CRENEZUMAB TO LOOK AT PREVENTION IN PATIENTS WITH A GENETIC MUTATION THAT RESULTS IN EARLY ONSET ALZHEIMER'S DISEASE

profits will follow. A company doesn't have to charge the moon for it."

THE MOLECULE: A DIVERGENT COURSE

There are two main pathological features found in the brains of Alzheimer's patients. One is the plaques that contain the protein beta amyloid and the other is the tangles that contain the tau protein. The debate about which of these plays a key role in progression of the disease has been ongoing since they were identified, as well as which causes cognitive decline in Alzheimer's patients.

Much attention has been paid to beta amyloid, mainly because mutations were found in the amyloid precurser protein gene (APP) in Alzheimer's patients. This led researchers to believe beta amyloid was the primary pathology in Alzheimer's and tau aggregation was a secondary feature.

Prior to that, research had centered around developing symptomatic treatments based on boosting or inhibiting neurotransmitters in the brain.

"A symptomatic treatment is one that offers temporary improvement in symptoms, but does not deal with the underlying disease process," Prof. Wischik explains. "These treatments produce a benefit that is measurable for about six months, but then the underlying disease takes over, and that benefit is lost."

The symptomatic approach has brought five products to the market: Eisai's Aricept, Shionogi's Cognex, Novartis' Exelon, Forest Laboratories' Namenda, and Janssen's Razadyne. (Editors' note: Cognex is no longer marketed in the United States.) At least 16 product candidates targeting beta amyloid have failed in trials or have been discontinued.

The most recent failure was a Phase III trial of bapineuzumab reported in July 2012. Elan, Pfizer, and Janssen announced that the co-primary clinical endpoints — change in cognitive and functional performance compared with placebo — were not met. Janssen Alzheimer Immunotherapy (AI) R&D led the Phase III trial of intravenous (IV) bapineuzumab in patients with mild-to-moderate Alzheimer's disease who carry the ApoE4 (apolipoprotein E epsilon 4) genotype. Pfizer and Janssen AI are partners in the Alzheimer's Immunotherapy Program (AIP).

At the same time, the companies had indicated that based on a comprehensive review of the data by the independent safety monitoring committee, all other ongoing Janssen AI and Pfizer bapineuzumab studies were continuing as planned. But just a few weeks later, the companies announced that all Phase III programs were being discontinued.

Lilly's potential Alzheimer's beta amyloid drug isn't faring much better. In August, the company announced that primary endpoints, both cognitive and functional, were not met in either of the two Phase III, double-blind, placebo-controlled solanezumab trials in patients with mild-to-moderate Alzheimer's disease. But company officials say a prespecified secondary analysis of pooled data across both trials showed statistically significant slowing of cognitive decline in the overall study population of patients with mild-to-moderate Alzheimer's disease. In addition, prespecified secondary subgroup analyses of pooled data across both studies showed a statistically significant slowing of cognitive decline in patients with mild Alzheimer's disease, but not in patients with moderate Alzheimer's disease.

> WE HAVE DEVELOPED PROPRIETARY TECHNOLOGY FOR DISTINGUISHING BETWEEN COMPOUNDS THAT SIT AT THE TAU PROTEIN AND ANOTHER ONE THAT 'BLOWS UP' THE AGGREGATE.
>
> Prof. Claude Wischik

THE TAU APPROACH

To change the consensus around Alzheimer's and beta amyloid, Prof. Wischik says he knew he had to be successful with a treatment based on tau.

The team at the University of Aberdeen has been working with TauRx 2002 and developed a therapy that targets the aggregation (clumping) of abnormal tau protein inside nerve cells in the brain. The tau protein normally functions inside nerve cells to stabilize nerve connection fibers. However, the abnormal tau aggregates, or tangles, accumulate in the neurons and destroy them. They first destroy nerve cells critical for memory and then destroy neurons in other parts of the brain as the disease progresses. To stop the spread of the tangles, Prof. Wischik's team developed a novel form of methylthioninium chloride (MTC), trademarked as rember.

"MTC was a complete accident," Prof. Wischik says. "It was a wrong experiment done for the wrong reason that produced the right result. It was complete serendipity. I was trying to isolate the paired helical filaments in the tangles. The only assay I could use was the electron microscope. There was a catch-22. We didn't have enough of the protein to make a monoclonal antibody to use the antibody to fish out the protein. By then, we'd had a collaboration with ICI and a researcher there suggested another molecule that does the same thing. It was a variant of MTC, and it made the filaments disappear. Then it took me about a year to understand that the filaments were being destroyed by this molecule."

Prof. Wischik then went looking for other variants of MTC.

"I found one that had already been used in psychiatry, in fact, for the treatment of manic depressive psychosis," he says. "This turned out to be MTC. In my test tube, I was able to dissolve the tangle filaments, which until then had proved to be extremely intractible. So I realized I had the combination of a drug that could get into the brain and dissolve the tangle filaments. From there, it took a lot of work to develop the cell-based assays, the in vitro assays, the screening platform, and the transgenic animal models to prove what was, originally, a very simple observation."

Along the way the company has filed and received patents on the assays and the animal models it has developed, as well as rember and later follow-on molecules.

In 2008, TauRx released the results of a Phase II study of rember that involved 321 patients with mild and moderate Alzheimer's disease in the United Kingdom and Singapore. Patients receiving the study treatment experienced an 80% to 90% reduction in cognitive decline over two years. The TauRx brain imaging data also showed that the drug had its biggest effect in the memory critical parts of the brain where the tangle density is highest. In the control group, there was a significant decline from the starting score in cognitive testing and on brain scans, but not in those receiving the drug at an adequate dose.

Since then, the company has developed a version of MTC to allow for better absorption, particularly at higher dosages, which could mean potentially greater clinical efficacy and fewer side effects. The company found that at the highest dose tested in the Phase II study, due to a problem with the encapsulation process of the gelatin capsule, MTC was not being absorbed in the stomach where it could become activated and therefore didn't have as good clinical effect. The company later found that even when the encapsulation problem was corrected, MTC was still not properly absorbed in the presence of food. But in the MTC form, it needed to be taken with food to

be tolerated by patients. LMTX, the next-generation drug based on rember overcomes both these problems and has a new chemical entity patent status with patent life to 2027.

The new drug, LMTX, will begin a Phase III study in late 2012 in more than 20 countries with 1,500 patients. A separate study will be conducted in patients with frontotemporal degeneration (FTD), also known as Pick's disease. Frontotemporal degeneration is characterized by progressive atrophy of several different areas of the brain, particularly the frontal and temporal lobes, the parts of the brain that control executive functions, such as decision-making, personality, social behavior, and language. Uniquely, it affects people as early as in their 40s.

Prof. Wischik points out that in discussions with the FDA, the agency agreed that based on the company's Phase II data with MTC, it did not have to repeat Phase II trials with LMTX.

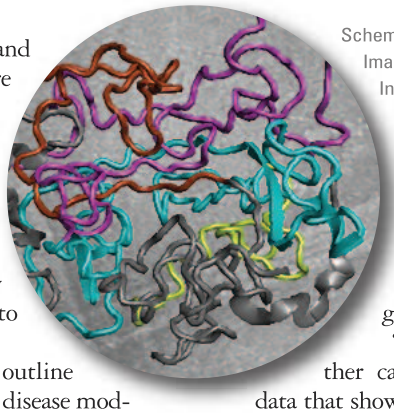
"At that time, we only had primate data in 2009," he says. "Later we were able to supplement this with data from elderly human volunteers. Essentially, data showed the same blood levels result whether MTC or LMTX is dosed in fasting subjects — that is the blood profile is identical and the mass spec is the same. The difference is that at higher doses, MTC is not properly obsorbed in the presence of food, but LMTX is. LMTX turns out to be much better tolerated with or without food, and we have so far achieved single doses of 800 mg in humans without this being the maximum tolerated dose."

Prof. Wischik says if all goes well, he expects a launch date that could be as early as 2016. And if the results of the Phase III trials follow the previous Phase II research, it is expected that this next-generation LMTX will lead to a new way of thinking and treating Alzheimer's disease.

In addition, TauRx Therapeutics is looking at LMTX for the treatment of other neurodegenerative diseases with pathology involving the aggregation of other proteins, such as Parkinson's disease. (Please see the digital edition for more information on TauRx's additional research projects.)

THE MARKET: UNTAPPED POTENTIAL

Every four seconds around the world, someone is diagnosed with dementia. According to Alzheimer's Disease International, there are 7.7 million new cases of dementia each year. If dementia care were a country, it would be the world's 18th largest economy, ranking between Turkey and Indonesia. If dementia care were a company, it would be the world's largest by annual revenue exceeding Wal-Mart at $414 billion. Already 58% of people with dementia live in developing countries, but by 2050 this number will rise to 71%.



Schematic view of the tau protein structure. Image courtesy of the Max Planck Institute for Biophysical Chemistry.

These figures not only outline the treatment value of a new disease modifying drug for Alzheimer's, but the worldwide economic need as well. Any therapy that can put a dent in the spiraling costs of the disease would, as the MasterCard commercials say, be priceless.

"Alzheimer's has the potential to bankrupt the healthcare system and ruin our economy," says William Thies, Ph.D., chief medical and scientific officer for the Alzheimer's Association. "Currently, any estimates on the potential market of a therapy for Alzheimer's disease is based on its prevalence."

"Any drug that can slow the progression of dementia in Alzheimer's disease, or even slow the conversion of mild cognitive impairment (MCI) patients to dementia, would be enormously valuable," says Daniel Chancellor, senior analyst at Datamonitor. "A successful disease-modifying drug targeting tau has a huge market potential."

Aiswariya Chidambaram, senior research analyst, healthcare, Frost & Sullivan, says given such unresolved controversies ongoing with beta-amyloid, researchers have begun to increasingly focus on the second key hallmark feature of Alzheimer's disease, namely the tau protein.

"With such high levels of associated complexities and high failure rate — almost 92% — of clinical compounds, it is crucial that pharmaceutical companies identify and develop drugs with strong scientific back-up and distinct features and benefits to patients," he says.

In addition to TauRx, several life-sciences companies have drug compounds that target tau protein in their pipeline, the key ones being Noscira SA and Allon Therapeutics.

"The core focus of R&D revolves around this class, which is expected to command premium pricing and fuel the growth of the Alzheimer's disease medication market," Ms. Chidambaram says. "However, I don't see much of a difference in the market value of drugs that target beta-amyloid and tau protein, as both are proposed to be the key hallmark features of Alzheimer's disease and the two signaling pathways are inter-connected."

However, until there are positive Phase III results to prove the therapies will work in humans, it is anyone's guess how much revenue a new therapy could generate — beyond a lot.

"What we don't have in either case is the definitive human data that show if we change the concentration of amyloid or tau in the brain of a person with the disease that it changes the course of the disease in that person," Dr. Thies says. "Until we have that, the market potential can only be guessed at, as we don't know if or who the drug will be effective for."

Dr. Thies suggests that if drugs targeting the two pathologies are successful, they may end up working together to combat the disease, much like treatments for hypertension that combine two or more drugs to accomplish successful management of blood pressure.

"The competition between tau- and amyloid-targetted drugs may not be how these therapies will best impact the treatment of the disease, but rather how can they be used together or sequentially to best manage Alzheimer's in a particular group of patients," he says.

MAJOR MARKET POTENTIAL

Ms. Chidambaram predicts that disease-modifying drugs will also enable the use of a combination/cocktail therapy with acetylcholinesterase inhibitors and memantine, thereby paving the way for additional revenue contribution from existing drugs as well.

"As tau pathology occurs later than beta amyloid accumulation, it may be that such a strategy wouldn't work in the earliest of Alzheimer's disease patients — those who are presymptomatic or have MCI," Mr. Chancellor says. "However, it may have greater potential than an amyloid treatment in those with moderate or severe dementia."

The ultimate goal would be to manage Alzheimer's disease so that it would become a chronic condition. New therapies are needed to realize this, together with lifestyle interventions and improved diagnostic tools, Mr. Chancellor says.

Research results show that Alzheimer's may be present long before the symptoms appear, so treating the disease early or even in a preventive manner may be beneficial. This would serve to increase the already monumental market base.

"It could turn out that either or both types of therapies will be more successful in prevention mode," Dr. Thies says. "Instead of treating people at stages of Alzheimer's who are symptomatic, they may instead be used to treat those at risk for the disease or who are in the earliest, pre-symptomatic stage. This is a much larger population than just those with established dementia. It's estimated that roughly half of people older than 65 will have dementia, and if for instance we roll that back to those who are 60, could half of those people be at risk? We don't know the answer to that yet, but it is a possibility. So, if we are looking at a market that includes half of everyone over 60, this is a pretty big market."

According to Frost & Sullivan, about 250 disease-modifying Alzheimer drug candidates exist in the pipeline, and amyloid synthesis inhibitors and amyloid plaque inhibitors together constitute 37.7% of the total drug candidates in pipeline. On the other hand, the mechanism of action of almost one-third of the compounds in the pipeline could not be exactly identified, which reflects the complexity of the disease pathology.

"R&D in Alzheimer's disease is fairly diverse already," Mr. Chancellor says. "There are a lot of different targets being explored and it isn't just beta amyloid. Nevertheless, I think many companies and researchers will have been heartened with the recent solanezumab data; there appears to be a glimmer of efficacy with the suggestion that the treatment is more effective the earlier on in the course of illness that a patient receives the drug. This validates much of the criticism against current trials of beta amyloid therapies, but also provides that vital proof-of-concept efficacy."

A lot of media attention has been given to the hypothesis of beta amyloid, especially since the failure of two monoclonal antibody drugs reported this summer. Dr. Thies suggests that the news media may be more familiar with the amyloid-based theory of Alzheimer's because it has been around longer.

"Mainstream news media tends to look at these trials as being the marker for success or failure," Dr. Thies says. "There's been more written in the general press about amyloid, but tau is coming along and will have its day."

Tau researchers, in general, may be five to 10 years behind amyloid on their timeline, but TauRx is getting ready to launch Phase III clinical trials. This is a good thing, Dr. Thies says.

"If any of these potential disease-modifying drugs are approved and launched by end of 2013, the Alzheimer's disease market could triple over the subsequent five years," Ms. Chidambaram says.

MARKET OVERVIEW

Valued at almost $6 billion in the seven major markets in 2011 (U.S., Japan, France, Germany, Italy, Spain, and the U.K.), the Alzheimer's disease drug market is forecast to experience double-digit growth until 2020,

ASSESSING COGNITIVE ASSESSMENT

No country, government, or healthcare system could afford — in terms of both financing and time spent — to perform a cognitive test on every person who might be at risk for or who is experiencing dementia as a result of Alzheimer's disease.

Following the same path of disruptive innovation that he has been on for for his lead Alzhehimer's drug LMTX, Professor Claude Wischik, cofounder and executive chairman of TauRx Pharmaceuticals and professor of Old Age Psychiatry at the University of Aberdeen, along with MediciGlobal, have developed a more efficient and less costly approach to accurately assess the cognitive abilities that are associated with the Braak staging of Alzheimer's, a method used to classify the degree of pathology in Alzheimer's.

"Conducting a serious screening process with meaningful intervention for every single patient is not viable anywhere, so we need a better way to screen," says Prof. Wischik.

MediciGlobal and Prof. Wischik developed a prescreener for a clinical trial that will have larger implications for collecting important data regarding Alzheimer's disease and cognitive tests.

"Our real objective is to collect the data and to gradually refine our standard set of questions," he says. "We are using the recruitment process to bootstrap our way into better and better tools and question sets that can be accessed by computers and hand held devices."

While brain scans and other cognitive tests are an effective method of assessing dementia, they are not cheap and they require highly skilled clinicians. Traditional assessment tests that require face-to-face interaction with several healthcare practitioners and psychiatrists are also too time-consuming considering the number of patients involved.

"For example, in the United Kingdom, in order to provide the 50,000 patients who need the traditional cognitive tests, we would need six times the number of psychiatric teams," Prof. Wischik says.

His proprietary tool, called TauAssess, is expected to be to dementia what the blood pressure cuff is to hypertension. One of the key goals was to develop a tool that can be used in the general practice setting.

The management of hypertension used to be solely in the hands of cardiologists, who performed the tests and did the prescribing; the GP was not involved. Now this condition is being managed in the primary-care setting and the cardiologist is called in for a cardiac event, or for a second opinion or review, but rarely is he or she the one prescribing the medications for lowering blood pressure and cholesterol.

"GPs need to be given the tools to be confident about achieving Braak stage ratings," Prof. Wischik says. "We developed a tool for handheld devices and we tested it with 4,000 patients in Scotland and London."

"These trials provided some positive results in identifying at-risk Alzheimer patients, and now we can expand it for broader applications," says Liz Moench, president and CEO, of MediciGlobal.

While there are several different cognitive assessment tools being used, Prof. Wischik's idea of providing the test to health professionals, caregivers, and patient themselves with the goal of improving Alzheimer diagnoses is a first, Ms. Moench says.

"The self-advocacy aspect of this tool makes it very innovative," she says.

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Datamonitor reports. Pfizer/Eisai's Aricept (donepezil) remained the highest-selling brand in 2011 with Forest/Lundbeck/Merz's Namenda (memantine) close behind. However, the two drugs are following differing growth trajectories: Namenda's sales will continue to rise while Aricept's revenue is being severely eroded by generic competition.

The catalysts for the overall market growth include an aging population, earlier and improved diagnosis, and the introduction of immunotherapies that will be prescribed in addition to existing treatments. The WHO estimates that about 36 million individuals are living with dementia, at an annual cost of $600 billion (greater than 1% of global GDP). Alzheimer's disease is the predominant cause of dementia, accounting for around two-thirds of cases.

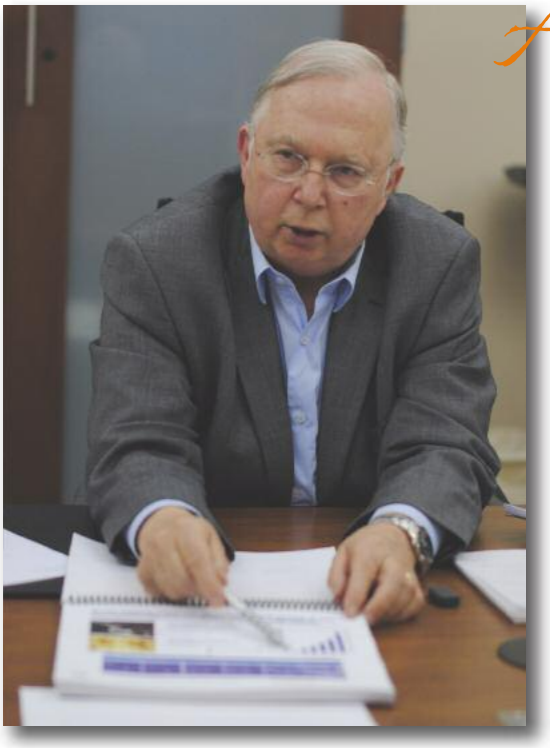
Datamonitor forecasts that about 600,000 patients with mild cognitive impairment or mild-to-moderate Alzheimer's disease will receive immunotherapies annually by 2020 in the seven major markets.

"We had produced fairly conservative forecasts for bapineuzumab — now discontinued — and solanezumab of $3.3 billion each in peak-year sales in the seven major markets," Mr. Chancellor says. "Now that bapineuzumab has been discontinued, and solanezumab appears ineffective in moderate Alzheimer's disease, we would forecast sales of around $4 billion for solanezumab."

New symptomatic drugs therapies will have a smaller market opportunity, such as GlaxoSmithKline and Lundbeck's 5-HT6 receptor antagonists. They would fail to address the biggest unmet need among Alzheimer's disease drugs and face competition from generic cholinesterase inhibitors and Namenda, Mr. Chancellor adds.

The number of products in development for Alzheimer's disease is greater than ever, despite the pipeline's inability to produce a new chemical entity since Namenda in 2002.

"The vast majority of products in clinical development are in either Phase I or Phase II, while just three drugs are in Phase III trials or pending approval and launch," Ms. Chidambaram says. "The huge disparity between the number of drugs in Phase II and Phase III highlights the problem in developing novel therapies for Alzheimer's disease."



As far as moving out of the lab and into the boardroom, Prof. Wischik is as pragmatic about running a company as he is about everything else. But he also has a sincere sense of responsibility, duty and humility.

THE MARKET BEYOND ALZHEIMER'S

Therapies that target tau may prove to be useful in the treatment of the dementia associated with Parkinson's disease. However, whether that would dramatically increase the market value of a drug is up for debate. Dr. Thies says the Parkinson's market is not as big as Alzheimer's, possibly 10% of the market size.

> I REMEMBER THINKING THAT WE HAVE NO RIGHT NOT TO DO THIS; THIS BECAME MY MANTRA.
>
> Prof. Claude Wischik

However, Mr. Chancellor says the added value to be gained from additional approval for Parkinson's disease dementia would be minimal. The only drug to be approved for Parkinson's disease dementia, Novartis's Exelon (rivastigmine), has a far smaller market share than donepezil and Namenda.

"The Alzheimer's disease population is far larger than that of Parkinson's disease," he says. "We estimate these at 6.9 million and 2.3 million in 2011 in the seven major markets, respectively, although only a quarter of these Parkinson's patients will suffer from dementia."

The theory behind targeting tau as a therapeutic strategy for Alzheimer's disease, and other related neurodegenerative diseases in which tau is implicated — the so-called tauopathies — is well established, Mr. Chancellor says.

The presence of neurofibrillary tangles correlates well with severity in Alzheimer's disease, which is not always the case with beta amyloid plaques.

"However, we have yet to see a proof-of-concept study in which a tau-targeted treatment unequivocally improves the symptoms of Alzheimer's disease patients," he says.

Dr. Thies believes researching tau as a therapeutic target in Alzheimer's is a solid path to follow, since tau tangles are one of the hallmark lesions identified in the disease.

Mr. Chancellor, like others at that time, was skeptical when the data from the rember Phase IIb study was released at the 2008 International Conference on Alzheimer's Disease (ICAD) Annual Meeting.

"It was announced with much fanfare in the press, although key opinion leaders were very skeptical," he says.

Dr. Thies says that even if tau-targeted drugs fail in Phase III trials, the research done so far will help provide answers down the road.

"We need answers, so the more trial paths taken to find those answers the better," he says. "I think it's really terrific that tau has gotten this far. To make it to Phase III, a treatment has to leap over a lot of barriers and it's pretty easy to trip on any of them along the way. That being said, we shouldn't confuse getting to Phase III with having what we really need to know: does this therapy benefit people?"

Dr. Thies adds that Alzheimer's clinical research "is not for the faint of heart."

"It's very expensive and fraught with technical difficulties," he says. "But it is one of the last great frontiers, and the first company in will have the leg up." PV

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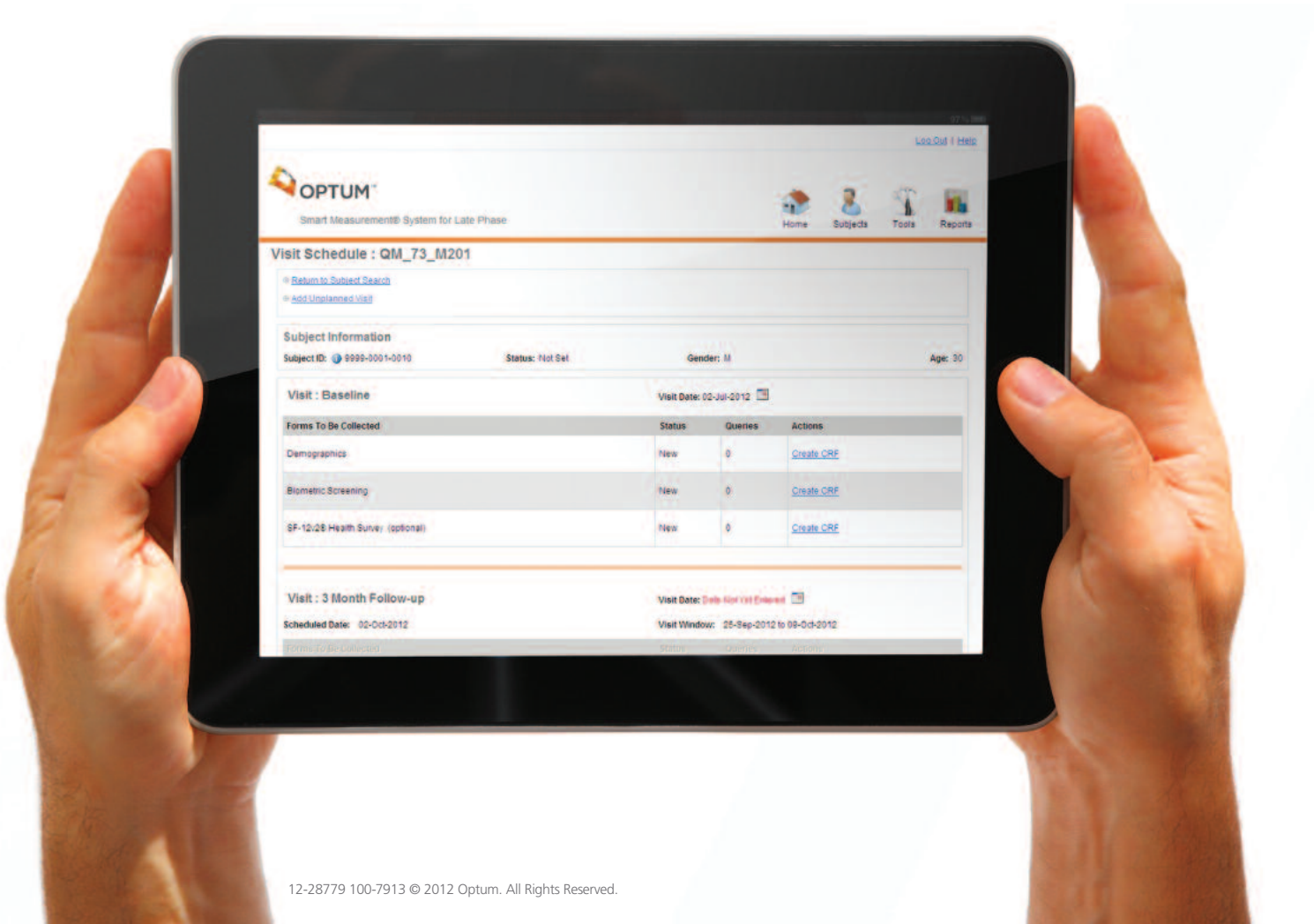


MAKING A CASE FOR Beta Amyloid

Beta amyloid proponents are not quite ready to give up on this path of Alzheimer's research. While beta amyloid appears not to play as big a role in cognitive impairment as initially thought, researchers still believe beta amyloid does play some role in disease development.

THE EVIDENCE REMAINS STRONG THAT THE BETA AMYLOID OR SOME FORM OF THE AMYLOID HAS A ROLE IN ALZHEIMER'S. THE BIGGEST FLAW WITH THESE STUDIES IS THAT THEY BEGIN IN PEOPLE WHO ALREADY HAVE ALZHEIMER'S DISEASE. MANY PEOPLE IN THE FIELD BELIEVE THIS MAY BE TOO LATE.

Dr. Kenneth Kosik
University of California, Santa Barbara

The recent failures of anti beta amyloid products may not address the question of whether beta amyloid plays a role in Alzheimer's, says Kenneth Kosik, M.D., Harriman Professor of Neuroscience Research, MCDB, co-director, Neuroscience Research Institute at the University of California Santa Barbara.

"The evidence remains strong that beta amyloid or some form of the amyloid has a key role in Alzheimer's," he says. "The biggest flaw with these studies is that they begin in people who already have Alzheimer's disease. And many people in the field believe this may be too late. There is already sufficient damage to neurons and to synapses that by simply reducing the amyloid burden at that stage may be too late to show efficacy."

The tau protein and beta amyloid may be linked, says Karen Duff, Ph.D., professor of pathology, Columbia University Medical Center.

"The tangle burden in the brain correlates much closer to a person having dementia than the amyloid load," she says. "It's possible that amyloid load can build up to a point that it provokes the tau into becoming abnormal and then it is the tau that is driving the dementia. Reducing amyloid at this point might not reverse the damage that abnormal tau causes, and can continue to cause even when amyloid is reduced. Alternatively, the two proteins might both contribute to dementia but tau is worse. Based on the results of the clinical trials completed so far, patients with Alzheimer's present to doctors at a stage at which using an anti-amyloid therapeutic drug is too late in their disease to be effective. The damage is already done.

"In the future, there will be therapeutic possibilities to stop the tangles from doing their worst damage," Dr. Duff concludes.

Dr. Kosik says in rare cases of Alzheimer's in which there is a mutation in the amyloid precurser protein, these mutations lead to textbook Alzheimer's.

"What we don't know is when a person has dementia, are the symptoms generated directly from the amyloid or is the amyloid inducing something else, such as the tangles," he says. "It's probably the later because we do know that people can walk around with a significant amount of amyloid in the brain and really be quite normal. But when the tangles

THE BETA AMYLOID FAILURES UNDERLINE ONCE AGAIN HOW CRITICAL IT IS FOR THE PHARMACEUTICAL INDUSTRY TO KEEP ON TRYING TO DEVELOP AN EFFECTIVE TREATMENT. MANY BIG PHARMA COMPANIES AND SMALL BIOTECHS WILL LEARN FROM SUCH FAILURES.

Dr. Andrea Pfeifer
AC Immune

WE HAVE TO OPEN UP MORE AVENUES OF RESEARCH FOR THERAPEUTIC TARGETS, AND TANGLES ARE AN OBVIOUS NEXT TARGET IF ANTI-BETA AMYLOID THERAPIES FAIL. BUT, WE MIGHT HAVE TO PROTECT THE BRAIN FROM DAMAGE CAUSED BY BOTH TAU AND BETA AMYLOID ACCUMULATION.

Dr. Karen Duff
Columbia University Medical Center

WE PROBABLY KNOW LESS THAN WE THINK WE KNOW ABOUT ALZHEIMER'S DISEASE AND WE SHOULDN'T FORECLOSE ON THE PURSUIT OF PLAUSIBLE AND PROMISING NEW DIRECTIONS FOR ALZHEIMER'S RESEARCH

Dr. John Trojanowski
Dr. Virginia Lee
Perelman School of Medicine at the University of Pennsylvania

emerge, patients seem to clinically deteriorate. That observation alone is not sufficient to prove this idea but it suggests that the dementia is caused by more than just the amyloid alone."

Dr. Kosik also points out that a mutation of the tau gene alone does not lead to Alzheimer's disease but to frontotemporal degeneration (FTD). Frontotemporal degeneration is characterized by progressive atrophy of the frontal and/or temporal lobes.

Dr. Duff also has done some research to look at the connection between tau and beta amyloid.

"The mouse models do not completely replicate the complex pathology of human Alzheimer's as amyloid mouse models don't form tangle pathology," she says. "But there are some alternations in the brain of Alzheimer's patients before there are lesions: abnormal tau and increased levels of beta-amyloid. And it might be that the mice are not capable of forming the plaque and tangle lesions unless more protein is provided, as is done with the transgenic mouse model. Humans and mice can respond very differently to the same protein. We have to be careful in assigning a cause and a function to something because a mouse doesn't show it."

RESEARCHERS SAY WORK NEEDS TO CONTINUE TO DETERMINE EXACTLY HOW TAU AND BETA AMYLOID LEAD TO ALZHEIMER'S DISEASE.

Researchers say work needs to continue to determine exactly how tau and beta amyloid lead to Alzheimer's disease.

Andrea Pfeifer, Ph.D., CEO of AC Immune, says recent failures underline how critical it is for the pharmaceutical industry to keep trying to develop an effective treatment for Alzheimer's disease.

"Big pharma companies and small biotechs such as AC Immune will learn from such failures as they continue to devote significant R&D resources to understanding this very complex disease," she says.

There are a lot of data implicating amyloid beta (abeta) in Alzheimer's diseases, but it may not be the driver of neurodegeneration, says John Trojanowski, M.D., Ph.D., professor of pathology and laboratory medicine at the Perelman School of Medicine at the University of Pennsylvania.

"The most fervent believers in the abeta cascade hypothesis say that abeta is necessary but not sufficient for neurodegeneration," he says. "I would say the failure of the beta bapineuzumab and others is a serious cautionary tale about whether that is the right drug target for people who clinically manifest disease."

But Dr. Pfeifer remains confident that the anti-beta amyloid route will result in a viable therapy, and she says these failures have no impact on AC Immune's collaboration with Genentech for an anti-beta amyloid. Crenezumab was discovered and humanized by AC Immune. It is currently being evaluated by Genentech in a Phase II trial in Alzheimer's patients with mild-to-moderate symptoms.

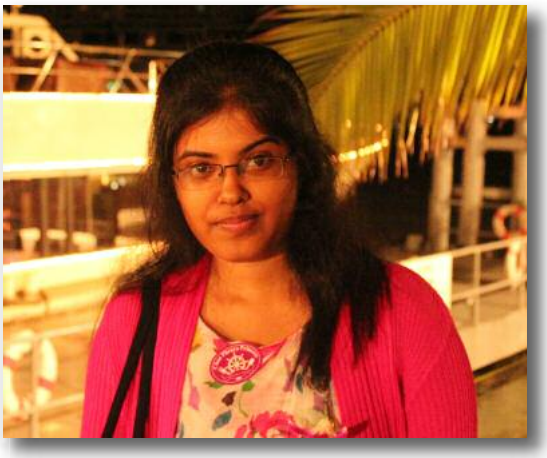
"Crenezumab is an antibody that targets a beta, the same protein targeted by Pfizer in its trial of bapineuzumab," Dr. Pfeifer says. "But there are significant differences. We recently published in the Journal of Neuroscience that crenezumab shows a different mode of action and has a much better safety profile, making it possible to administer much higher doses once a month resulting in a 10-100 fold increased antibody exposure in the brain."

Others researchers, however, point to the need for trials of beta amyloid earlier in the development of Alzheimer's disease as a possible preventive medication.

"I don't think it is wrong to go with abeta," says Virginia Lee, Ph.D., professor of pathology and laboratory medicine at the University of Pennsylvania School of Medicine. "The data that led us to studying the importance of abeta involved genetics. There are patients who have a mutation of the abeta precursor protein (APP) gene, the gene that produces abeta through its release from APP. These mutations are autosomal dominant and are inherited by offspring of a mother or father with the mutation, which means if the child inherits the mutation he or she will develop Alzheimer's and all of these patients accumulate deposits of abeta amyloid plaques and neurofibrillary gtau tangles. Perhaps overproduction of abeta deposition initiates the disease cascade familial Alzheimer's disease thereby leading to other Alzheimer brain ab-

THE AMYLOID HYPOTHESIS WAS FORMED FIRST AND IS A LITTLE AHEAD IN ITS TIMELINE AND TYPICALLY MAINSTREAM MEDIA TENDS TO LOOK AT THESE TRIALS AS BEING THE MARKER FOR SUCCESS OR FAILURE.

William Theis
Alzheimer's Association



normalities earlier in the disease. So, the thinking is, based on familial Alzheimer's disease, that abeta amyloid comes first, but it is not clear this is true in sporadic or non-familial Alzheimer's disease."

Dr. Lee says conducting trials based on the familial Alzheimer's diseases with anti-abeta therapies is a reasonable approach.

"As we know more about the progression of Alzheimer's disease, we realize that the disease starts much earlier," she says. "When there is cognitive impairment, the pathology is based on the plagues and the tangles. So knowing what we know about the progression of Alzheimer's disease in terms of cognitive impairment appearing so long after tangles and plaques begin to accumulate in the brain, perhaps we have to start earlier in terms of getting rid of abeta plaques in a prevention type of study before clinical onset of disease, and not an intervention study, i.e. when memory loss is severe enough to impair activities of daily living."

DR. LEE AND DR. TROJANOWSKI HAVE DISCOVERED A PRODUCT CANDIDATE THAT IS ABOUT TO ENTER HUMAN TRIALS.

Dr. Kosik is one researcher working on a trial of anti-beta amyloid for familial Alzheimer's. In 2013, he and his colleagues will begin a study of AC Immune/Genentech's crenezumab in 300 members of a family in Colombia with a genetic mutation that results in early onset Alzheimer's disease. The five-year, $100 million study will look to see if crenezumab can delay or even stop the onset of dementia.

"People who carry this mutation will get the disease," he says. "We know who is going to get Alzheimer's and we even know when they are going to get it because the mutation is like clock work. Symptom kick in by the mid 40s and patients have Alzheimer's by age 50."

ALZHEIMER'S AND TAU RESEARCH

While research continues on the role of beta amyloid in Alzheimer's, other researchers are looking at the tau protein in the neuron tangles in the brain.

Dr. Duff this year has introduced a new mouse model of Alzheimer's that puts the tau pathology in the region of the brain where it develops in humans.

"Tangles in Alzheimer's follow a path around the brain," she says. "They start in one area. They then show up in another area that appears to be linked through the anatomy of the brain to the first area. Then they impair a third area and they spread all over the brain. Interestingly, dementia only becomes obvious once the tau has moved to areas of the brain later in the disease, which gives a unique window of opportunity to prevent dementia, especially if imaging techniques can be developed to identify tangles when they are in the first area. We've set off the pathology in the one area and we're trying to stop it from going to the second and third areas to stop the spread of pathology through the brain. By stopping it from spreading from one area to another we might be able to stop the disease in its tracks."

Dr. Duff's team is interested in looking at an immunotherapy to target tau.

"Immunotherapy seems to have a lot of promise because it just might suck up the tau before it can move to another area of the brain," she says.

Dr. Kosik is looking at mutations in the tau gene.

"My work right now in the area of tau is to prepare pluripotent stem cells from patients who have mutations or polymorphisms in the tau gene and differentiate these cells to neurons so we can study the tau pathology in living neurons," he says. "We're preparing transcriptomes from those cell types, so we can assess patient-specific gene expression in neurons."

IF ANY OF THESE POTENTIAL DISEASE-MODIFYING DRUGS ARE APPROVED AND LAUNCHED BY END OF 2013, THE ALZHEIMER'S DISEASE MARKET COULD TRIPLE OVER THE SUBSEQUENT FIVE YEARS.

Aiswariya Chidambaram
Frost & Sullivan

PROGRESS IN DEVELOPMENT

Taking a different approach to Alzheimer's disease drug discovery that many doubted would work, Dr. Lee and Dr. Trojanowski lead their research team in studies conducted over the past decade years that have led to the discovery of natural products designed to target pathological tau for the treatment of Alzheimer's and one of these candidate compounds is entering human clinical trials. Drs. Lee and Trojanowski are a husband-and-wife team and are the founders of the University of Pennsylvania's Center for Neurodegenerative Disease Research (CNDR). They and their team at Perelman School of Medicine at the University of Pennsylvania have have been testing whether they can compensate for defective tau with microtubule-stabilizing molecules that are derived from natural products. Tau functions to stabilizes the microtubules critical for transporting molecules in neurons so their idea for treating Alzheimer's is to correct or offset the loss of tau function with small molecule microtubule stabilizers that enter the brain to exert their beneficial effects.

"One drug we tried was Taxol and it worked reasonably well but it didn't have good blood-brain barrier penetration so it isn't an attractive drug to carry forward," Dr. Trojanowski says. "We then identified epothilone D, which enters the brain much better and has a long half life or stays in the brain longer and while also having

a short half life in plasma so it won't cause some of the side effects typical of microtubule stabilizing drugs that are used to treat cancer."

Drs. Lee and Trojanowski were able to show efficacy in animal models of tau tangle pathology like that found in the brains of Alzheimer's patients. Since Bristol-Myers Squibb owns epothilone D, the company is now conducting a clinical trial of epothilone D — now known as BMS-241027 — to evaluate safety and the pharmacodynamic effects on cerebrospinal fluid (CSF) tau, magnetic resonance imaging (MRI), and cognitive tests in mild Alzheimer's disease.

"In 1993, we formulated the hypothesis that by substituting for the lost function of tau when it is trapped in tangles using microtubule stabilizers we could offset this loss of function and treat Alzheimer patinets," Dr. Lee says. "Our initial work was designed to identify a molecule that can get into the brain, have more efficacy in the brain than in the periphery, and thereby stabilize microtubules in the brains of Alzheimer patients without damaging the rest of the body. We think epothilone D is such a compound."

Dr. Trojanowski explains how epothilone D works using a train track analogy.

"We all have a nerve cell at the top of our skulls in the motor cortex of the brain that projects over a meter down to the lower spinal cord where its activation enables us to walk," he says. "That axon requires a transportation system because motor neurons have to fire just the right number of synaptic proteins. There has to be an exquisite transportation system to get these and other proteins delivered a meter away to the nerve terminal that triggers walking, and this transportation system has been well understood for years. It's based on microtubules. Those are analogous to the rails of a train track; so envision tau as the being the cross ties that keep the tracks straight and parallel. If the ties are removed, the rails will wobble and trains will run off the track."

Dr. Trojanowski says when tau proteins are trapped or sequestered into tangles the microtubules fall apart and the transportation system fails.

"We have shown in animal models when the transport fails tangles form an Alzheimer tau pathology," he says. "We have shown that with epothilone D we are able to restore the microtubules and when they are intact again, transport in nerve cells is restored. Our latest study shows that when mice had behavioral impairments because they had tangles, we were able to reverse the memory impairments and were able to eliminate the tangles and restore axonal transport. We believe this is because we are able to replace tau and get the microtubules stable again. In other words, we are able to get the train tracks stable again to keep cargoes moving in nerve cells despite the fact that they had developed tau tangles."

Dr. Trojanowski says he and Dr. Lee are working independently now to identify other natural products that are as good as epothilone D that can be taken orally, since Bristol-Myers Squibb's epothilone D requires an intravenous infusion.

"One area that needs exploring is to find other small molecules where synthesis is simple and develop compounds to do the same thing epothilone D does to stabilize microtubules and also have the desirable property of crossing the blood brain barrier after oral administration," Dr. Lee says. "We are working in that space right now. Some of our initial studies already show we may now have unique small molecules or compounds that can do just that. We are working with medicinal chemists at Penn, and we are a hopeful that by working together we will in the near future identify a number of these microtubule stabilizing drugs that would hopefully work for Alzheimer's disease."

ANTIBODY PROGRAMS

AC Immune is working on an antibody program that targets tau protein. In June 2012, the company teamed up with Genentech for the research, development, and commercialization of AC Immune's anti-tau antibodies for the potential treatment of Alzheimer's disease and other neurodegenerative diseases.

AC Immune is working in partnership with Genentech to identify and formulate several preclinical candidates. Genentech will have global responsibility for preclinical and

SETTING THE RECORD STRAIGHT

Dr. Alois Alzheimer was born in June 14, 1864, in Marktbreit, Germany, and studied medicine at the universities of Würburg and Berlin. Upon his graduation in 1887, Dr. Alzheimer worked as a medical officer at the state asylum in Frankfurt am Main. There he became a leading neurologist, publishing works on epilepsy, brain tumors, syphilis, and hardening of the arteries. He was known for correlating the clinical course of his patients with the changes to the brain observed when autopsies were performed after their deaths.

In 1903, Dr. Alzheimer moved to Munich to a new institute established by Emil Kraepelin, who wrote Compendium der Psychiatrie, to discover the causes of psychiatric illnesses. This group made some of the fundamental discoveries in neurodegenerative disorders and mapping of the structure of the neocortex.

When he move to Munich, Dr. Alzheimer met Auguste Deter, a 51-year-old woman who became his patient at the asylum. Her condition steadily deteriorated displaying memory loss, difficulty with speech, confusion, suspicion, agitation, wandering, and screaming when bedridden. She became incontinent and unaware of her surroundings.

After the autopsy in 1905, Dr. Alzheimer found her brain had shriveled and neurons had disappeared. It was at this time that he first discovered the "neurofibrillary tangles," which he thought were a characteristic feature of a new type of psychiatric disease. Up to that point, he had thought that the disease was caused by damage to blood vessels rather than to the nerve cells themselves. What struck him about the case of Deter was that the severe psychiatric disease he had seen during the patient's life had appeared without any evidence of atherosclerosis, stroke or inflammation.

Dr. Alzheimer presented his findings to a group of psychiatrists in 1906, the first public description of this new disease. When he made this discovery, Dr. Alzheimer was unaware that the disease would be named after him and would also become the most common form of dementia in older people.

The "senile plaques" had been described in 1892 by Dr. Paul Blocq and Georges Marinesco. Unlike the tangles, these were generally seen to be a feature of normal aging without the severe dementing syndrome Dr. Alzheimer had seen in Auguste Deter.

According to Prof. Claude Wischik of TauRx Therapeutics, neither Dr. Alzheimer nor Mr. Kraepelin considered the plaques as having any real psychiatric or pathological significance, and this was the position Mr. Kraepelin took in the next edition of his influential textbook.

THE ULTIMATE GOAL WOULD BE TO MANAGE ALZHEIMER'S DISEASE SO THAT IT WOULD BECOME A CHRONIC CONDITION. NEW THERAPIES ARE NEEDED TO REALIZE THIS, TOGETHER WITH LIFESTYLE INTERVENTIONS AND IMPROVED DIAGNOSTIC TOOLS.

Daniel Chancellor
Datamonitor

clinical development, manufacturing and commercialization of antibodies resulting from the collaboration.

The company's antibodies were discovered and humanized through AC Immune's proprietary SupraAntigen technology platform, which is designed to produce high affinity ligands and bind specifically and with high-affinity to proteins in "sick" conformations.

"One of the challenges of conformational diseases comes from the fact that the proteins that need to be targeted are 'self' proteins, coming from our own organism, and they do not elicit an immune reaction from the body," Dr. Pfeifer says. "Moreover, the difference between a 'good' and a 'bad' protein is typically only expressed by a conformational change in the protein structure. With our SupraAntigen platform we can discover both vaccines and antibodies that 'break' the pathological conformation of the 'sick' proteins by shifting the equilibrium via stabilization of the soluble form of the protein target and therefore render them harmless."

The company's program generated vaccines using in-house liposomal vaccine technology to mimic the aggregated forms of tau. By displaying multiple molecules of the antigen and adjuvant on one liposomal vaccine molecule, AC Immune can stimulate the immune system with a specific and high antibody response.

Dr. Pfeifer says the company's antibodies are designed as a passive immunotherapy against misfolded tau proteins. AC Immune will work in partnership with Genentech to identify and formulate several preclinical candidates.

"We are confident that this collaboration gives the anti-tau program the highest chance to reach the market," she says. "Moreover, antibodies arising from this program could also be used in a companion diagnostic or an in-vitro diagnostic. At the moment there is no effective diagnostic for this terrible disease, and therapy is usually given far too late." PV

ADDITIONAL TAURX RESEARCH

TauRx Therapuetics Alzheimer is looking at LMTX for the treatment of other neurodegenerative diseases, such as Parkinson's disease, with pathology involving the aggregation of other proteins. The investigational drug has shown activity on the synuclein fibers that accumulate in the brains of Parkinson's patients. The company has a Phase II protocol written, but needs to raise additional funds to take this indication into further trials. There was a recent independent report that LMTX could also work in the protein aggregates that do damage in Huntington's disease where the aggregates are composed of a different protein, Huntingtin. This is in addition to other diseases in which tau protein itself aggregates, such as Progressive Supranuclear Palsy and Corticobasal Degeneration. There was also an independent report showing that MTC stops the aggregation of a protein called TDP-43. This motivated the trial that the company is about to start in FTD, since about half the cases have aggregates of TDP-43 in their brains, and the other half have tau, although it is not possible to tell which during life. These are all severely disabling neurodegenerative diseases that could potentially benefit from treatment with LMTX.

"We also have five other follow-on compounds after LMTX that we have synthesized ourselves, and these have reached the assay stage," says Prof. Claude Wischik, co-founder and executive chairman of TauRx Therapeutics. "We know these molecules work in transgenic animals. We could take any one of these into Phase I trials, but our immediate focus is our Phase III trials."

In addition, Prof. Wischik says WisTa Laboratories, a sister company to TauRx, recently completed a screen of 2.8 million compounds.

"We have the technology for distinguishing between compounds that are potentially diagnostic and compounds that are potentially therapeutic," he says. "From this intial screen, we have a bank of about 200 good candidates after several rounds of testing using different assay systems. There is some further work we have to do to refine the hits to narrow them down even further."

On the diagnostic side, the company is working to identify compounds that bind to the tau protein, as well as the synuclein protein, to allow for the development of imaging agents known as diagnostic ligands.

"We have developed proprietary technology for distinguishing between compounds that bind to tau protein aggregates and others that bind and destroy the aggregate," Prof. Wischik says. "These are two parallel discovery streams."

Prof. Wischik adds that the company has an antibody that is selective for early tau aggregates.

"We are in the process of humanizing these antibodies," he says. "Tau amplifies itself like a virus within the nerve cell and then it bursts out to the next cell, where the process of aggregation is repeated, sucking normal tau into the toxic aggregates and spreading the infection further across the brain. LMTX attaches to the tau aggregates and destroys them releasing individual damaged tau molecules, which can be more readily cleared by the cell. The antibody we've developed captures the aggregates in the act of transmission and sequesters them so that they can't get to the next nerve cell. In other words, a nerve cell in which the process starts would be doomed to death but it wouldn't be able to propagate the damage to other neurons."

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