What We Know About the Science Behind
Alzheimer's Disease

and Cure Alzheimer's Fund's Approach to Slowing, Stopping or Reversing It

Cure Alzheimer's FUND
targeting breakthrough research

Alzheimer's Disease in America

Alzheimer's disease, the most common type of dementia, was "discovered" one hundred years ago in Bavaria by Dr. Alois Alzheimer. It is a progressive and fatal disease. Alzheimer's destroys brain cells, causing problems with memory, thinking and behavior severe enough to affect work, lifelong hobbies and one's social life. The cause of the disease is not known.
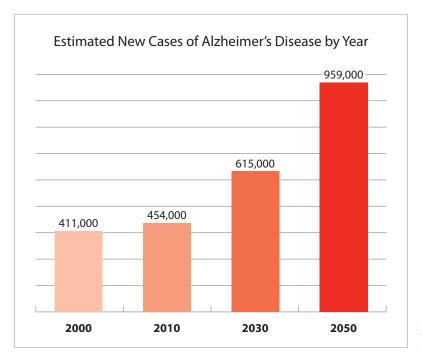
There are more than 5 million documented patients according to best estimates, with some experts suggesting that may be only 20% of the total number actually affected. The number of new cases grows by more than 10% per year.

Alzheimer's current and growing devastation

Alzheimer's disease is the seventh leading cause of death for people of all ages, the fifth leading cause of death in people age 65 and older, and is the only one of the major diseases (heart disease, breast and prostate cancer and stroke) to be *increasing* in mortality; up almost 33% from 2002 to 2004.

Medicare expenditures for Alzheimer's and other dementias in 2005 were $91 *billion*; this total is projected to increase to $160 billion by 2010. State and federal Medicaid spending for nursing home care for people with Alzheimer's and other dementias was estimated at $21 billion in 2005, and is projected to increase to $24 billion by 2010.
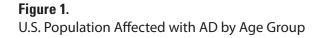
Given these estimates and no significant containment or decrease in Alzheimer's, Medicaid and Medicare expenses for Alzheimer's and related dementias will be approximately $184 billion by 2010, or approximately 27% of the entire combined anticipated expenditure for Medicare and Medicaid in 2010!

Estimated New Cases of Alzheimer's Disease by Year

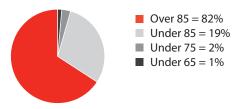| Year	New Cases
2000	411,000
2010	454,000
2030	615,000
2050	959,000

From a report by the Alzheimer's Association released in March of 2007

Alzheimer's disease is not a normal part of the aging process. It is a progressive disease and the leading cause of dementia. Risk factors are multifold and complex.
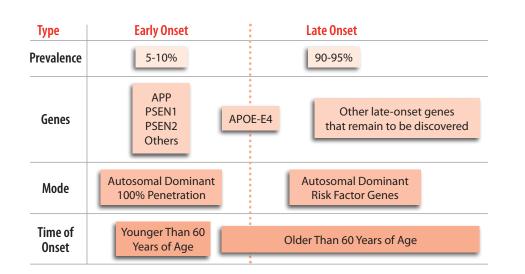
What We Know About Alzheimer's Disease:
Risk Factors

1. *Age* is the most predictive risk factor. The current breakout of the percent of the U.S. population affected with AD by age group:

Figure 1.
U.S. Population Affected with AD by Age Group

- Over 85 = 82%
- Under 85 = 19%
- Under 75 = 2%
- Under 65 = 1%

2. *Family History.* Studies of families affected by Alzheimer's disease show a strong genetic component. A much-quoted study of more than 14,000 identical twins in Sweden showed that of pairs of twins in which one was affected with Alzheimer's disease, the other twin also had the disease roughly 80% of the time.

Figure 2 shows the power and complexity of the genetic factor in Alzheimer's disease. Researchers now agree on four key genes, three of which (APP, PSEN1, PSEN2) can carry mutations that cause early-onset AD and account for five to ten percent of AD cases. A particular variant (E4) of another gene called APOE increases risk for roughly half of the late-onset cases of AD, which account for the other 90 to 95% of AD cases. Since the APOE-E4 variant does not guarantee onset of AD, other genes and environmental factors likely work together with this genetic variant »

Figure 2. Alzheimer's Disease Genetics:
Distribution of Disease Types and Genetic Factors

Type	Early Onset		Late Onset
Prevalence	5-10%		90-95%
Genes	APP PSEN1 PSEN2 Others	APOE-E4	Other late-onset genes that remain to be discovered
Mode	Autosomal Dominant 100% Penetration		Autosomal Dominant Risk Factor Genes
Time of Onset	Younger Than 60 Years of Age		Older Than 60 Years of Age

30%
of AD genetics known

70%
remain to be discovered

to bring on the disease. All told, the three early-onset genes and APOE account for about 30% of the genetic activity contributing to AD. Thus, 70% of the genetic activity in AD is yet to be determined, and almost certainly will hold critical clues about the root causes of the disease and how to stop it. In a highly complex genetic disease, it is absolutely imperative to know which genes are contributing to risk for the disease and how they are operating to gain a sufficient understanding to treat and prevent the disease.

3. *Gender:* After adjusting for lifespan, women are more affected with AD than men.

4. *Environment or "Life Factors:"* Certain environmental factors either trigger or exacerbate the progression of Alzheimer's disease. Researchers have been able to isolate and rank the leading "environmental" factors as follows:

- Head trauma or stroke is the leading environmental factor. At least as early as 1999, there was good evidence of the linking of head trauma to Alzheimer's disease. Further study has been done that shows the mechanism for "causing" or accelerating Alzheimer's from head trauma or Traumatic Brain Injury (TBI) is the same as that resulting from stroke. Dr. Giusseppina Tesco of Massachusetts General Hospital recently published a paper in *Neuron* that documents the linkage of enzymes responsible for increasing the levels of a particular peptide (A-beta 42, about which more detail is presented below), during or after stroke, to the downstream effects of Alzheimer's disease. These findings are particularly important as more attention is given to TBI in general as a result of the high occurrence of this kind of injury incurred by the military in Iraq, and by the growing number of head injuries in sports at all levels.

- High cholesterol and high homocysteine (an amino acid naturally occurring in the body) levels also are linked to increased risk for Alzheimer's disease. Both are associated with higher risk for heart disease, heart attack, diabetes and other circulatory problems. Controlling the levels of both of these substances helps to reduce risk for Alzheimer's. Why that is the case is not yet known.

- Lack of physical and mental exercise. Experiments published in the journal *Cell* showed that mice who already had Alzheimer's pathology that were kept in an environment enriched with opportunities for physical exercise showed much slower and less advance of the disease than those that had the same pathology but no opportunity for exercise. At least the anecdotal conclusion from observations about cholesterol, homocysteine and exercise is that "what is good for the heart is good for the brain." Some claim that intellectual stimulation—crossword puzzles, watching "Jeopardy," etc.—have beneficial effects. This may be the case, but the literature so far shows more evidence from the benefits of physical exercise than from intellectual activity.

- Lack of social interaction. Care givers and elder care workers report that those people who stay active socially take longer to develop patterns of dementia.

What We Know About
Alzheimer's Disease:
The Pathogenetic Story

While we do not know the exact cause of Alzheimer's disease (AD), most researchers have agreed on a few of the key actors and how they arise in the brain.
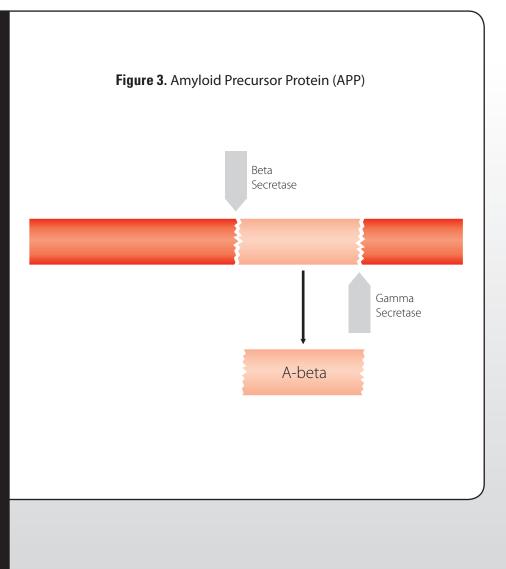
1. The accumulation in the brain of a peptide (small protein) called the amyloid beta peptide (A-beta), and especially the form of it that consists of 42 amino acids (A-beta 42). More specifically, the ratio between A-beta 42 and the more common form, A-beta 40, appears to be increased in the AD brain. The more out of balance they are, the more likely that A-beta 42 will accumulate at pathological levels in the brain, increasing the likelihood of AD pathology.
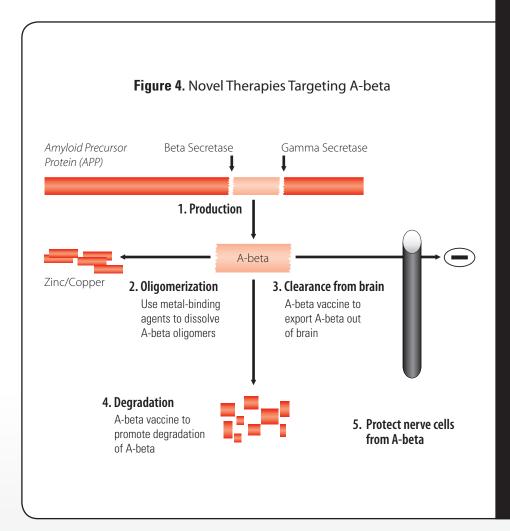
2. A-beta 42 has dominated AD research. It is central in the creation of beta-amyloid deposits that are found in "senile plaques," which accumulate outside of nerve cells, and in clumps on brain

Origins of A-beta

Amyloid beta (Aß or A-beta) is a peptide (small protein), composed of amino acids, that is the main constituent of plaques and tangles in the brains of Alzheimer's disease patients. A-beta 42, the form of A-beta with 42 amino acids, is widely believed to be a key contributor to Alzheimer's pathology.

Most AD researchers think that the role of A-beta in Alzheimer's pathology is best expressed through the Amyloid Cascade Hypothesis. That hypothesis has evolved from the theory that the mis-folding of A-beta molecules to create fibrils in the brain was the primary cause of the disease. Most AD researchers now think the pathology originates when single molecules of A-beta 42 combine to form "oligomers" (A-beta 42 molecules combined in different configurations) which interfere with or are toxic to neural synaptic activity in the brain.

Figure 3. Amyloid Precursor Protein (APP)

Beta
Secretase

Gamma
Secretase

A-beta

Figure 4. Novel Therapies Targeting A-beta

Amyloid Precursor Protein (APP)

Beta Secretase

Gamma Secretase

1. Production

A-beta

Zinc/Copper

2. Oligomerization
Use metal-binding agents to dissolve A-beta oligomers

3. Clearance from brain
A-beta vaccine to export A-beta out of brain

4. Degradation
A-beta vaccine to promote degradation of A-beta

5. Protect nerve cells from A-beta

Targeting A-beta

1. Stop or slow down A-beta 42 production.

2. Stop or slow down the aggregation of A-beta into oligomers, and specifically those oligomer configurations that seem to be the most toxic.

3. Clear A-beta from the body, and most particularly from the brain, before it has a chance to form oligomers or to build up beyond the normal, healthy "carrying capacity" of the brain.

4. Dissolve or break down the toxic A-beta oligomers in the brain.

5. Protect nerve cells and their synapses from the toxic A-beta oligomers.

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blood vessels. Beta-amyloid drives the formation of "tangles" inside of nerve cells leading to their breakdown. While we still do not understand precisely how A-beta leads to tangles and nerve cell death, we do know that:

- The ratio of A-beta 42:A-beta 40 is determined by how certain enzymes (beta-secretase and gama-secretase) clip the amyloid precursor protein (APP), which is produced by one of the early-onset AD genes (Figure 3).

- While A-beta mainly accumulates in the brain, it can be shuttled out of the brain into the bloodstream. The balance of A-beta production in the brain versus clearance out of the brain determines just how much accumulates and can form the toxic beta-amyloid deposits.

- The gene APOE appears to play a key role in the clearance and breakdown of A-beta in the brain. If A-beta (and particularly A-beta 42) accumulates to a high level in the brain, it can aggregate into clusters called "oligomers" prior to being deposited into senile plaques.

- It now appears, thanks in part to research sponsored by Cure Alzheimer's Fund, that certain configurations of A-beta oligomers are more toxic than others. The nature of these oligomers and how they are held together is critical to the pathological process underlying AD.

- Certain A-beta oligomers, e.g., dimers (two A-beta's stuck together and bonded by zinc and copper) can disrupt neuronal activity by short-circuiting the communication between nerve cells at "synapses." As nerve cell-to-nerve cell communication breaks down, so does the neural network of the brain, leading to cognitive impairment and ultimately nerve cell death in key "message centers" of the brain; first, in the short-term memory sections, and then on to other brain regions, e.g., those involved in long-term memory.

- Assuming this model (Figure 4) of the pathogenesis of Alzheimer's disease, it follows that there are several ways to arrest its development. They are outlined in the figure above.

Challenges to the Development of Effective Therapuetic Interventions

➤ *Not all Alzheimer's disease (AD) genes are known.* AD is a genetically complex and heterogeneous disease. To date, researchers agree on only four genes that cause or confer increased risk for AD. These four genes explain 30% of the inheritance of AD. Three of them cause early-onset familial AD. *The information gained from studies of these three genes is currently driving approximately 95% of all drug discovery and development for AD. Our greatest hope for making significant progress toward a real cure cannot be made until all genes that contribute to risk have been identified and, most importantly, it is known how they confer risk for the disease. Every new gene identified provides a novel shot on goal for drug discovery.*

➤ *Lack of definitive, clinical, biologically based tests.* Diagnosis of AD currently is carried out by psychological testing. Since the only way to confirm AD is through autopsy, all diagnoses of AD are considered dementia-probable AD. While there are genetic tests based on the early-onset familial AD genes that can confirm AD, the only established late-onset gene, APOE4, cannot be used to confirm AD—its presence in a patient with dementia only serves to increase the probability of a correct diagnosis of AD. Considerable research has gone into the development of "biomarkers," biologically identifiable signs of presence of the disease that will allow clinicians to better diagnose and predict AD. *Ultimately, the combination of the identification of all AD genes and the development of sensitive and specific biomarkers will serve to better diagnose and predict AD. But, much work remains to be done.*

➤ *The blood-brain barrier keeps >99% of molecules in the blood from entering the brain.* Thus, it is challenging to design a drug that will traverse safely and efficiently into the brain. This is why many pharmaceutical programs concentrate on drugs called "small molecules" that have a chance of getting into the brain.

➤ *Little understanding of the normal physiological role of A-beta and its various forms, A-beta 40, A-beta 42, etc.* Most research has focused on A-beta's pathological roles in AD. However, we have only limited knowledge of the normal (positive) roles of A-beta. Since most AD therapeutics are aimed at reducing the accumulation of A-beta in the brain, it is critical that we understand its normal functional role first. The identification of novel AD genes that interact with A-beta can greatly help this process.

➤ *Absence of definitive agreement of a "cause" for AD.* There are multiple competing theories about how the disease starts and progresses. While a broad spectrum of basic or "foundational" research is certainly warranted to leave no causative stone unturned, such lack of research focus strains or even dissipates human and financial resources that might otherwise be focused on the most plausible theories of causation.

Cure Alzheimer's Fund Research Strategy

Cure Alzheimer's Fund and the researchers it supports believe that the key to developing effective therapeutic interventions to slow, stop or even reverse the effects of Alzheimer's disease is to first determine its fundamental biological causes with certainty. Given that Alzheimer's is a complex and heterogeneous genetic disease, we think that identifying all genes that contribute to risk for the disease is critical to fully understanding its causes. Armed with this knowledge, we should be able to dramatically accelerate our understanding of the exact biochemical pathways that are involved in AD. This understanding, in turn, ultimately should lead to the discovery and development of effective therapeutic interventions.

Therefore, the approach to developing a cure for Alzheimer's championed by Cure Alzheimer's Fund is to:

1. Identify all genes that contribute to risk for AD;

2. Facilitate research into how those genes serve to confer risk or protection for AD; and

3. Find the best, most accessible and least harmful points for therapeutic intervention in the most relevant biochemical pathways driving AD pathology.

Meanwhile, Cure Alzheimer's Fund will, with the advice of its Research Consortium and Scientific Advisory Board, support other research initiatives that are based on sound science. This will accelerate development of effective strategies for preventing and treating the root causes and progression of AD, and not just its symptoms, like current drugs.

Research Roadmap

Cure Alzheimer's Fund has laid out a "Research Roadmap" to develop a rational, focused research strategy leading to "*early detection and early prevention*," based on what most researchers agree is the best science available and the most plausible current theories. Cure Alzheimer's Fund's objective is simply to get to a cure as quickly as possible.

Part 1: Foundational Building Block	Part 2: Translational Analysis	Part 3: Crossover Research	Part 4: Facilitative Research
Identify all of the remaining AD genes.	Understand how identified AD genes work at the molecular and biochemical levels in order to elucidate biological pathways that are impacted and determine points where pharmacological intervention would be possible.	Integrate results from foundational and trans-lational research studies integrated into studies aimed at discovering effective therapeutics. Search for drugs (existing, approved and unap-proved) and compounds for the ability to intervene at appropriate steps.	Maximize the speed to market for candidate AD drugs, using medicinal chemistry, high-through-put organic synthesis. Advance promising com-pounds to mouse model testing and for the most promising initiate human trials working with phar-maceutical companies.
FUNDED RESEARCH:	**FUNDED RESEARCH:**	**FUNDED RESEARCH:**	**FUNDED RESEARCH:**
Alzheimer's Genome Project™ Initiative:	ACAT Inhibitor – Dora Kovacs	To be determined	To be determined
1. Alzheimer's Genome Map – Rudy Tanzi	Cure Alzheimer's Fund Oligomer Collaboration – Paul Greengard, Sam Gandy, Charles Glabe, David Holtzman, Tae Wan Kim, Virginia Lee, Robert Moir, Sam Sisodia, Rudy Tanzi		
2. Genetics and Molecular Imaging Study – Deborah Blacker	Facility for Microdialysis Drug Discovery Program – David Holtzman		
3. Alzheimer's Brain Genetic Study – Bradley Hyman	Alzheimer's Disease Neuroimaging Initiative – Leslie Shaw and John Trojanowski		
4. AlzGene Database and Website – Lars Bertram			
Alzheimer's Gene Characterization Project – Rudy Tanzi			

Parts 2, 3 and 4 of the Roadmap deal with the challenge of understanding the functioning of AD genes, finding cures and bringing those cures to the public.

Report on Funded Research
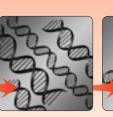
1. Basic "Foundational" Research

Dr. Rudy Tanzi

■ The Alzheimer's Genome Project (AGP)™ initiative.

Research Objective: Find all the genes that affect risk for Alzheimer's disease (AD), beginning with those that confer the greatest risk. With the genetic component of the disease so strong and only four significantly contributing genes identified and confirmed so far, three of which relate to the very small proportion of the AD population with early-onset Alzheimer's, it is extremely important to identify *all* genes that affect risk, both positively and negatively, for the disease. Every new AD gene identified provides another window into the cause of AD and a novel target for drug discovery. Cure Alzheimer's Fund has exclusively supported the Alzheimer's Genome Project (AGP) initiative, based at Massachusetts General Hospital under the direction of **Dr. Rudy Tanzi**, who has been involved in the identification of all four of the currently known genes. The AGP is a three-year, approximately $3 million effort that is scheduled to have first round results of the entire Alzheimer's genome by the summer of 2008. This will be the first comprehensive, unbiased whole genome association for Alzheimer's disease. This effort would not be possible without the mapping of the entire human genome several years ago. That true scientific breakthrough enables Alzheimer's researchers to compare the genome of Alzheimer's patients against the putatively "normal" human genome to identify those genes that are different in the Alzheimer's samples. This process requires the newest technology (Figure 5. Microarray "Chips," for example), sophisticated statistical skill, large family samples for DNA and a profound understanding of genetics. Because of the human genome project and the newly developed technologies to take advantage of it, researchers can move much more quickly and accurately now than as recently as two or three years ago.

Figure 5. How a DNA Microarray Chip Works for the Alzheimer's Genome Project

DNA is taken from the blood of individuals (some with and some without Alzheimer's disease) in a family sample.

Billions of duplicates of DNA are made.

DNA is chopped up into pieces that contain one SNP (single nucleotide polymorphism).

The DNA is put onto a microarray (chip) and, using fluorescent dye and a laser light, variants are "lit up," revealing a pattern.

A computer scans each SNP pattern and then geneticists conduct statistical analysis of the differences in patterns between those with Alzheimer's and those without. This process identifies suspect SNPs that reside within or alongside genes that could be involved in Alzheimer's disease.

Once researchers have identified potential target genes, the candidate gene is thoroughly examined in cell and animal studies to explore its potential role in the disease and to what extent it may affect risk.

Researchers evaluate the candidate genes that look most promising for therapeutic intervention.

More importantly, these whole genome scans produce "unbiased" genetic results. Before this technology was available, researchers essentially had to guess about where in the human genome to look for Alzheimer's-related genes. Those guesses might be very well informed, but no amount of that kind of knowledge could address comprehensively and accurately the roughly 3 billion genes in the human genome. The whole genome scan technology and statistical reading technique employed to determine the results *can* address those issues much faster and with a much higher degree of accuracy. Therefore, the genes that are identified and confirmed as being related to Alzheimer's disease through this process have a very high probability of contributing risk to the disease in some way.

Two separate but related studies also are underway in this first, "foundational" part of the Roadmap as part of the AGP. **Dr. Brad Hyman** of Massachusetts General Hospital is analyzing the pathological features of brains to understand the differences between Alzheimer's and "normal" brains. Dr. Tanzi then will implement those findings into his genetic studies to determine which gene defects are associated with specific pathological characteristics of AD. With funding from Cure Alzheimer's Fund, Dr. Hyman is building on and contributing to the genetic findings of Dr. Tanzi and his colleagues.

Dr. Deborah Blacker, also of Massachusetts General Hospital, is analyzing DNA from live individuals along the spectrum of "Benign Forgetfulness" to "Mild Cognitive Impairment" to full-blown AD. Her group is using cognitive testing and brain imaging to monitor the progression from one stage of cognitive impairment to the next. Dr. Tanzi then will implement those findings into his genetic studies to determine which gene defects are associated with specific clinical characteristics of AD.

The AGP has a fourth component, funded entirely by Cure Alzheimer's Fund. The AlzGene website (**www.alzgene.org**) is now the largest and most trusted interactive database of weekly updated information about Alzheimer's-related genes in the research community.

AlzGene.org, developed by **Dr. Lars Bertram** and Dr. Rudy Tanzi and their group at Massachusetts General Hospital and Harvard Medical School, is an online interactive database that provides a comprehensive and continuously updated encyclopedia of genetic risk factor data published in the field of AD. Its core constituent is an analysis engine that allows to quantitatively summarize these published data for each gene and genetic variant (or: polymorphism, mutation) using a statistical method called meta-analysis. With more than 1,000 scientific papers published in AD genetics over the past two decades, it has become impracticable for AD researchers to regularly track and evaluate the multitude of—many times conflicting—findings in the field in a systematic manner, making it impossible to tease out the potentially most important risk factors for AD. AlzGene closes this gap and provides weekly updated meta-analyses of all published studies, prominently displaying the most promising ("top") results on its homepage.

What have we learned? The AGP will ultimately provide the first complete catalog of genes conferring risk or protection for AD. The anticipation is that at least two or three dozen "new" genes will be identified, some of them related to biological systems that may or may not have been suspected of being implicated in Alzheimer's pathology.

As of January 1, 2008, two of our genetic "hits" are already in the "Crossover" block of the Roadmap; that is, being used for new studies in drug discovery programs. Several other newly identified genes are now in the "Translational" stage. This stage will determine how they work at the molecular and biochemical level in order to elucidate biological pathways that lead to AD and show where pharmacological intervention into those pathways can be most effective. Providing the broader research community with information about these newly identified genes will, we think, dramatically accelerate the development of effective therapeutic interventions.

In addition to providing information to other researchers about genes heretofore unknown to have any relationship to Alzheimer's disease, the technical and statistical process of

Dr. Brad Hyman

Dr. Deborah Becker

Dr. Lars Bertrum

developing this whole genome scan will set new standards and guide the establishment of new protocols for analysis for genome-wide association studies of complex and heterogeneous diseases like AD. The first paper describing the strongest results of the AGP currently is under review for publication.

Understanding what genes are implicated in Alzheimer's pathology will help immensely to accelerate progress toward establishing solid biological targets to guide the development of novel therapeutics for AD. This ground breaking research also will lead to earlier detection and prediction of AD through carefully developed genetic tests, supported by skilled genetic and psychological counseling to help people determine their risk profile for Alzheimer's before symptoms present. In this way, we hope someday to treat AD before it starts with "early prediction-early intervention."

2. "Translational" Research

■ The ACAT Project

Research Objective: Determine the ability of an existing drug to clear or significantly reduce A-beta from the system. Under the direction of **Dr. Dora Kovacs** at Massachusetts General Hospital, tremendous progress has been made in identifying a particular drug previously developed for anti-cholesterol use that has demonstrable A-beta clearing properties in mice. The data, although unpublished as of January 1, 2008, is strong enough already to have interested at least one large drug company in the possibility of clinical trials. This project addresses both the issue of A-beta production and clearance and will be critical to early prevention and treatment of AD, if proven effective.

What have we learned? We have learned that there is a class of existing drugs, already tested in human beings, that is able to very effectively clear A-beta from the brains of transgenic AD mice. The data are sufficiently striking to have already provoked interest by big pharma to begin considering clinical trials in AD patients.

■ Cure Alzheimer's Fund Oligomer Collaboration

Research Objective: (1) Determine which configurations of A-beta oligomers are most toxic to neurons and their synapses, leading most quickly to AD pathology. (2) Determine the process by which neurotoxic A-beta oligomers form to guide effective pharmacological intervention.

Cure Alzheimer's Fund is supporting complementary oligomer research with nine scientists across the country; seven from the Cure Alzheimer's Fund Research Consortium, one member of the Cure Alzheimer's Fund Scientific Advisory Board and one invited researcher. A-beta oligomers are such an important and insufficiently understood part of the AD pathology story that the members of the Research Consortium decided to put a "full court press" on the issue to see what could be learned through collaborative research.

Interest in oligomers arose with the recognition that the accumulation of the longer fibrils of A-beta found in senile plaques do not correlate well with the degree of dementia in AD patients. **Dr. Charles Glabe** describes "Some cognitively normal individuals were found to have the same amount of insoluble amyloid deposits as AD patients, indicating that these deposits are not always associated with the disease. Similarly, other AD patients have been observed with relatively little of the insoluble amyloid deposits. These observations refocused research away from the insoluble amyloid deposits to other types of amyloid aggregates known as 'oligomers'."

Another attractive aspect of focusing on oligomers for research is that they are amenable to targeting by vaccines. **Dr. David Holtzman** of the Cure Alzheimer's Research Consortium provided this background on the development of vaccines:

> *In 1999, it was shown if mice that develop amyloid buildup in the brain were actively immunized with the amyloid-beta protein itself (amyloid-beta was injected under the skin of the mice), they developed antibodies against*

Dr. Dora Kovacs

Dr. Charles Glabe

Dr. David Holtzman

amyloid-beta and had much less buildup in their brain. It was later shown, if one directly infused antibodies against amyloid-beta (called passive immunization) into mice, this would also decrease the buildup of amyloid-beta and in some cases, improve the cognitive deficits seen in the animals.

Dr. Holtzman goes on to describe, and Dr. Glabe reiterates, that despite these promising findings, the vaccines developed from these experiments were toxic to humans, producing undesirable inflammatory side effects. However, Dr. Glabe describes how "vaccines that specifically target the misfolded conformation (of protein fibrils) specific to amyloid oligomers may eliminate oligomers or block their toxicity (to humans) and block their side effects." If the research team can (1) identify the configuration(s) of A-beta oligomers that are the most directly related to Alzheimer's pathology; *and* (2) develop or find antibodies that are specific to those oligomers, there is every reason to think that development of a successful vaccine to promote the clearance of the most toxic A-beta oligomers from the brain is feasible in humans.

What have we learned? Early findings suggest that the species of oligomer that seems to be most directly involved in causing the disease are the smaller configurations: two and three A-beta peptides stuck together as "dimers" and "trimers," respectively. Earlier theories postulated that it was the bigger configurations, and one in particular (12 A-beta's stuck together), that was the primary culprit; but this as-of-yet unpublished research suggests the smaller dimer and trimer versions are the primary targets. If that is the case, *and* if the Collaborative researchers also identify antibodies that are specific to those oligomers, more productive work on "safe" and "effective" vaccines can proceed for earlier prevention and treatment of the disease.

■ Alzheimer's Disease Neuroimaging Initiative (ADNI)

Research Objective: Determine biological "markers" of Alzheimer's disease much earlier than the disease manifests itself to (1) assist and confirm diagnosis in living AD candidates; and (2) help prevent the disease from evolving as quickly as it might otherwise if appropriate therapeutic intervention can be developed.

Cure Alzheimer's Fund has joined with several other organizations in supporting a project with the National Institute for Aging that is investigating the presence or lack thereof of A-beta in the central nervous system as a reliable "biomarker" for Alzheimer's disease.

What have we learned? The data submitted in the proposal for the project is compelling, but as of January 2008, it is too early to predict results.

3. Translational/Crossover Research

■ Facility for Microdialysis Drug Discovery Program

Research Objective: Make available to the Alzheimer's research community a "novel method that allows one to measure the concentration of A-beta dynamically (in real time) in the brains of living mouse models that develop pathological features of AD, including buildup of A-beta in the brain due to the introduction of human AD gene mutations (transgenic AD mice). We can now begin to screen for drugs that lower A-beta directly in the brain in a relatively high throughput fashion (roughly 400 compounds a year)." Dr. David Holtzman's laboratory at Washington University at St. Louis has developed this "core facility" with funding from Cure Alzheimer's Fund and an anonymous foundation to provide this "in vivo" drug screening ability for researchers in the field. This will help to prove out potential drug applications or dismiss them much more quickly than previous methods, and therefore could accelerate progress on the development of drugs for inhibiting the production of or increasing the clearance of A-beta.

What have we learned? The screening process already has been well developed and proven on a small scale by researchers at Washington University at St. Louis. The program now is funded on a scale large enough to allow these researchers to build the "production" scale facility.

High priority research
to be supported by
Cure Alzheimer's Fund
in 2008 approaches
$6 million.

The Future

Goal for 2008: Accelerate the pace of discovery for a cure.

1. Focus on those genes identified through the Alzheimer's Genome Project™ (AGP) initiative that are most likely to advance our understanding of Alzheimer's and lead to substantive therapeutic intervention into the origin and progress of the disease.

2. Clarify the role of specific oligomeric assemblies of A-beta in the causes of Alzheimer's disease in order to disrupt their formation.

3. Push to Phase II trials a repositioned drug shown in animal studies to be effective at lowering A-beta levels in the brain and thereby significantly reducing risk for the disease.

4. Aggressively pursue the relationships among stoke, Traumatic Brain Injury (TBI) and Alzheimer's disease to develop new possibilities for effective treatment and prevention.

5. Promote truly breakthrough research by creating a financial reserve for plausible "wild card," paradigm-changing discovery emerging from recent findings.

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