Coins for Alzheimer's Research Trust

The CART Fund

A joint project of Districts 6900, 6910, 6920, 7670, 7680, 7690, 7710, 7720, 7730, 7750, and 7770

The C.A.R.T. Fund

P. O. Box 1916

Sumter, South Carolina 29150

July, 2013

The C.A.R.T. Fund

Finding the cause of Alzheimer's disease, and then a cure.

Alzheimer's disease is claiming more and more victims worldwide every day. Over 5.2 million Americans are now victims; and medical scientists predict that, unless a prevention/cure is found, that the number of American victims will grow to 16 million within the next 20 to 25 years. Further, it is believed that without a cure, one out of every 10 living Americans will ultimately become victims. In addition, it is estimated that 75 percent of the world's victims live outside of the United States.

The CART Fund - Rotarians in 13 Rotary Districts in North Carolina, South Carolina, Georgia, Tennessee, and Virginia contribute small amounts weekly to fund research that can bring an end to this terrible disease.

The CART Fund was developed with the idea of accomplishing its goals without Rotary clubs having to conduct special fund raisers and without interfering with other projects of our various Rotary clubs. In order to do this, the concept was developed of asking Rotarians to voluntarily empty their pockets of change or whatever amount they wanted to donate when they attend their weekly Rotary Club meetings. (It is estimated that on any given day in America, $8.25 billion in loose change passes among our citizens.) This process provides a very simple, painless and effective way to raise much-needed funds for Alzheimer's research.

The effectiveness of donated change can be illustrated by considering that in the 13 Rotary districts of the Carolinas and Georgia (including one District in Tennessee and one District in Virginia), there are approximately 42,000 Rotarians. Assuming 85 percent attendance, 48 meetings a year and an average donation of just 55 cents a week, we could raise nearly $1,000,000 for research annually. For information on how your Rotary Club or you as an individual can join the fight against Alzheimer's disease, contact the CART Board by email at info@cartfund.org.

How can my club participate in C.A.R.T.?

1. First, adopt C.A.R.T. as on on-going service project for your club. Present the C.A.R.T. program to your club (and/or to your club's Board of Directors), and ask the club to adopt it.

2. Second, find a "Champion" for C.A.R.T. in your club – someone who believes in the object of the program (finding the cause of, and a cure for Alzheimer's disease) and who will agree to "take charge" of this project.

3. Third, ask the club "Champion" to serve as the coordinator of the C.A.R.T. program within the club (serve as the club's C.A.R.T. Fund Committee Chairperson).

4. Fourth, recruit/appoint a C.A.R.T. Fund Committee within your club, with the following duties/responsibilities:

    a) Place, or pass, the blue C.A.R.T buckets at the tables at each Rotary Club weekly meeting.

    b) Collect the contributions from the blue C.A.R.T. buckets at the end of each weekly meeting.

    c) Count the contributions each week, record the amount of the contributions, and give the contributions to the Club Treasurer to deposit.

    d) At the club meeting each week, remind the members (or have the club president/presiding officer remind the members) to "be sure to toss your pocket change into the blue C.A.R.T. buckets" (The club members will have to be reminded each week, or they will tend to ignore or forget to do this.)

Instructions for remitting your Rotary Club's CART Contributions

1. Have your club Treasurer establish a C.A.R.T. account (either a bookkeeping account, or a separate deposit/checking account).

2. Deposit the weekly collections/contributions to your club's account,

3. And then, write a check **at least quarterly** payable to: "***The C.A.R.T. Fund, Inc***." – and **mail the check to:**

4. Your Rotary District's C.A.R.T. Chairperson.

5. For Rotary District 7670 – Your C.A.R.T. Fund Representative (and C.A.R.T. Fund Board Member) is:

PDG Bill Parker
PO Box 1051
Blowing Rock, NC 28605

(Each of the 13 participating District's C.A.R.T. Fund Board Member has bank deposit slips for the C.A.R.T. fund's deposit account in Sumter, SC; and will deposit all Rotary club's checks/contributions received from clubs in their Rotary District once each month.)

Be sure your check indicates your club's name, so that your club is properly credited for your contribution. [If you send in a personal check written by a club member or someone else; be sure to write your club name somewhere on the check, so that your club gets credit.]

Please make your club's check payable to: **The C.A.R.T. Fund, Inc**. [*Do **not** make your check payable to PDG Parker; or to District 7670.][Also, do not make your check payable to the "District 7670 CART Fund". There is no District 7670 CART Fund.]*

For your information - The C.A.R.T. Fund Treasurer is:

ANGUS McDUFFIE
From SUMTER, SC

However, please do NOT mail your club's checks to Angus. [There are over 500 clubs participating in CART; and Angus has no way of knowing which Rotary District many of those clubs belong to – and therefore cannot correctly credit your club and District.]

Frequently Asked Questions

Q. How much actually goes to research?

A. Contributions are conservatively invested until grants are awarded. All (100%) of your original donation goes to Alzheimer's research. The small amount of expenses incurred (which is less than $25,000 in total administrative expenses since inception in 1999- through 2013) is paid out of the interest income. That amount is less than 25% of the total interest income to date.

Q. How can I find out more about Alzheimer's disease?

A. Numerous web sites have volumes of information on the disease. Try www.ahaf.org, the web site of the American Health Assistance Foundation.

Q. Our club is in one of the 13 Rotary Districts participating in C.A.R.T., but we have not been participating. What can we do to get started?

*A. While the thirteen Districts have agreed to participate, the word is slow filtering down to some clubs. Getting started is **EASY**. Explain the CART program to the club. In most areas, a CART spokesman can give a kickoff program. Pass a collection plate through the club meeting. (We will be glad to send you CART buckets to pass). Quarterly, have the club treasurer mail a check for the collected funds to the District's CART Board Member (list of Board members is located at the end of this manual).*

Q. This is a great project. Can Rotary Clubs not in one of the project's 13 districts participate?

A. Of course (like a Rotary project would turn down a donation?). In fact, several clubs in Florida, Kentucky, Illinois, Idaho, New York, California, Maryland and Texas have participated in the past. Send your collected funds to: CART Treasurer, P.O. Box 1916, Sumter, SC 29150.

Q. I'm not a Rotarian but this is something in which I would like to participate. Can I?

A. Of course! Send your donation to: CART Treasurer, P.O. Box 1916, Sumter, SC 29150. If you would like to become a Rotarian, visit www.rotary.org.

Q. Does a donation to CART help me become a Rotary Paul Harris Fellow?

A. Unfortunately, no; at least not yet. It is our dream to see CART adopted someday by Rotary International as a worldwide project.

CART Board Contact Information

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The History of the C.A.R.T. Fund

In October 1995, the Sumter, South Carolina (USA), Rotary Club initiated the effort to prove CART works by conducting an eight month testing program, which was highly successful.

In July of 1996 Rotary District 7770 in South Carolina adopted CART as a project.

In early January 1999, the American Federation for Aging Research (AFAR) very generously agreed to provide their expertise in assisting with the grant evaluation and selection process. Their valued assistance has continued with all twenty grants to date - primarily by recruiting some of the nation's top scientists in Alzheimer's disease research to serve as a peer advisory group to review all grant applications.

In April of 1999, the first grant of $100,000.00 was made to Emory University's Alzheimer's Research Center (under the leadership of Dr. Allan Levey, M.D., Ph.D).

In the 18 months from January 1999 until June 2000, 10 additional Rotary districts in the Carolinas and Georgia adopted CART as a project. The first Board of Directors meeting was held in November 2000, bylaws were adopted and PDG Bill Clark of D-7750 was elected the first president of the Board.

In May of 2001, a $250,000 grant was made to Case Western Reserve University's Alzheimer's Research Department (Dr. Karl Herrup, Ph.D and Dr. Gary Landreth,Ph.D), a two-year grant.

In April of 2002, Johns Hopkins School of Medicine (Dr. Philip C. Wong, Ph.D) received the third grant in the amount of $250,000.

In April of 2003, CART's fourth grant in the amount of $250,000 was awarded to the University of Pennsylvania School of Medicine (Dr. John Trojanowski, M.D., Ph.D).

In July of 2003, CART Treasurer Roger Ackerman announced that the Fund had exceeded $1 million in receipts.

I**n May of 2004**, The University of Connecticut Health Center (Dr. Robert Reenan,Ph.D) was announced as the recipient of the fifth grant, in the amount of $250,000.

In May of 2005, The University of California at Los Angeles (UCLA) (Dr. Gary Small, M.D.) was awarded the sixth grant, also in the amount of $250,000.

In May of 2006, The University of Texas, Medical Branch (Dr. Claudio Soto, Ph.D), was awarded the seventh grant, for $250,000.

In May of 2007, The Mayo Clinic College of Medicine – Jacksonville (Dr. Todd E. Golde, M.D., Ph.D), was awarded the eighth grant, for $250,000.

In May of 2007, CART Treasurer Roger Ackerman announced that the Fund had exceeded $2 million in receipts.

In May of 2008, The Cleveland Clinic (Dr. Sanjay Pimplikar, Ph.D) was awarded the ninth grant, for $250,000.

In May of 2008, The University of Alabama – Birmingham (UAB) (Dr. David Sweatt, Ph.D), was awarded the tenth grant, for $200,000. This marked the first time that a second grant was awarded in the same year.

In May of 2009, The Mayo Clinic – Jacksonville (Dr. Malcom Leissring, Ph.D), was awarded the eleventh grant, for $200,000.

In May of 2009, The University of Kentucky (Dr. Harry LeVine, Ph.D) was awarded the twelfth grant for 2009, for $250,000.

In April, 2010, The CART Fund Assistant Treasurer, Roger Ackerman, announced that total contributions to CART to date have exceeded $3,000,000.

In May of 2010, contributions to The CART Fund were down, due to the recession; but for the first time three (but smaller) grants were awarded. The University of Kentucky (Dr. Paul Murphy, M.D.) was awarded the thirteenth grant, for $200,000.

In May of 2010, The University of Wisconsin-Madison (Dr. Luigi Puglieli, M.D., Ph.D) was awarded the fourteenth grant, for $150,000.

In May of 2010, The University of Pennsylvania (Dr. Kurt Brunden, Ph.D.) was awarded the fifteenth grant, for $50,000 (a one-year pilot grant)

In May of 2011, The University of Pennsylvania (Dr. Kurt Brunden, Ph.D.) was awarded the sixteenth grant, for $250,000 (after the previous year's pilot grant produced promising results).

In May of 2011, Case Western Reserve University (Cleveland, OH) (Dr. Gary Landreth, Ph.D) was awarded the seventeenth grant, for $150,000. (Dr. Landreth was the recipient of the 2nd CART grant in 2001. He is the first research scientist to receive a second full grant.)

In May of 2011, Massachusetts General Hospital (Harvard Medical School) (Dr. Brad Hyman, M.D., Ph.D) was awarded the eighteenth grant – a $50,000 one-year pilot grant.

In May of 2012, Cedars-Sinai Medical Center, Los Angeles (Dr. Maya Koronyo-Hamaoui, Ph.D) was awarded the nineteenth grant, for $250,000.

In May of 2012, The University of Washington, Seattle (Dr. Valerie Daggett, Ph.D) was awarded the twentieth grant, for $150,000.

In May of 2013, The Children's Hospital, Harvard Medical School (Dr. Beth Stevens, Ph.D) was awarded the twenty first grant, for $250,000.

In May of 2013, The Learner Research Institute, Cleveland Clinic Foundation (Dr. Bruce Lamb, Ph.D) was awarded the twenty second grant, for $100,000.

A total of $4,250,000 awarded

[Twenty Two Grants through May of 2013]

The CART Grants Process –

Soliciting Applications, and Awarding the Grants

The CART grants committee and the CART Treasurer recruit a Selection Committee composed of three nationally recognized researchers in AD (Alzheimer's disease) who serve as a peer review committee for the LOI's.

The grant(s) availability is announced through the **American Federation for Aging Research (AFAR)** via their website; and also via a mailing to about 50 of the most prominent Aging/Alzheimer's Research Centers in the USA.

Interested researchers are invited to submit a Letter of Intent (LOI) for their proposed research project (LOI's are limited to 3 pages in length, and must be submitted electronically).

The LOI's are collected on a CD and sent to the three researchers on the selection committee. Each member of the committee independently selects five proposals for the final list for consideration. The Grants Coordinator notifies all applicants of the actions of the selection committee (notice is given of who is selected as a finalist, and who is not).

The finalists (up to 15) are sent a full proposal form to complete and return (4 hard copies are required to be submitted). The full proposal form may be up to 20 pages in length.

Each of the three members of the selection committee receives and reviews the full applications. They then confer by phone to select the top three finalists, in order.

A phone conference is then held with the three selection committee members and the Executive Committee of the Board of Trustees of The CART Fund, Inc. at which time the committee recommendations are given. The Executive Committee then acts upon the selection committee's recommendations and selects the final (generally one or two, depending on the available funds) grant recipients.

All applicants are then notified of the Board's actions; and the grant recipients are invited to attend the Annual CART Board Meeting, to make a presentation about their research project, and to receive their grant.

INFORMATION ON SELECTED PAST C.A.R.T. FUND GRANTS

1999 Investigator: Allan Levey, MD, Ph.D – Emory University

Project: Validation of a Novel Diagnostic Test for Alzheimer's Disease
Award: $100,000

This research project was designed to develop a diagnostic blood test to be sufficiently specific and sensitive for the diagnosis of Alzheimer's Disease (AD). The final results of the study proved to be inadequate enough to overcome the technical problems and cost of the test itself. This is basic research, which does not always produce the desired results. Nevertheless, a secondary finding was a difference in the function of a certain blood cell in patients with AD that may help the body's defense against infection. A $50,000 piece of equipment that was acquired for the grant continues to be used for many and various laboratory tests in other fields of aging research.

2001 Investigator: Karl Herrup, Ph.D & Gary Landreth, Ph.D – Case Western Reserve University

Project: Inflammatory Mechanisms in Alzheimer's Disease
Award: $250,000

This project was to locate genes that are regulated by exposure to amyloid plaques and inflammatory stimuli, and to examine the role of this inflammatory process in neuronal cell death. Deposits of amyloid activate the inflammatory process that stimulates neurons to begin cell division that then leads to cell death and clinical Alzheimer's Disease (AD). Investigators are now studying a specific protein that inhibits these neurons from dividing. They then can investigate genes that are "turned-on" by amyloid or "turned-off' by anti-inflammatory drugs; e.g. ibuprofen. Next will be an investigation of a new class of anti-inflammatory drugs using the above technology. They have had five (5) journal publications, with reference of support received from C.A.R.T. funds. Two members of our C.A.R.T. Board were briefed on this project during a site visit to their laboratory in July, 2003.

2002 Investigator: Philip Wong, Ph.D – Johns Hopkins University

Project: Nicastrin and gamma-Secretase in Alzheimer's Disease
Award: $250,000

The normal activities of certain enzymes are required for neuron function. In this project, a mouse model was engineered with a controlled set of genes that actively developed until given a "knock-out" substance that caused a specific deficiency of an enzyme that led to amyloid plaques. This information can now direct a course to find a mechanism-based therapy for AD, none of which are now available. As a result of a subsequent overlap grant funded by the National Institute of Health, our contract with Johns Hopkins required them to return $187,000 of this award. Dr. Wong had had one (1) journal publication with reference to support by C.A.R.T. Funds.

2003 Investigator: Dr. Philip C. Wong, Ph.D -

Project: Development of a Conditional BACE1 Transgenic Mouse Model
Award: $187,000

This investigator initiated efforts to study whether the amyloid plaques in the AD brain are dependent upon a continuous supply of amyloid and whether these plaques can be cleared by inhibiting a specific enzyme. Given the current state of knowledge, new compounds that directly impact this enzyme will be developed and tested in animal models, and if successful then brought to clinical trials in an effort to prevent or cure AD.

Note: Money returned from a previous grant was approved by the review of the peer committee to be awarded for this project. Dr. Wong has had two (2) journal publications with reference of support by C.A.R.T. funds.

2003 Investigator: Domenico Pratico, MD and John Trojanowski, MD, Ph.D – University of Pennsylvania School of Medicine

Project: Novel Therapeutics for Alzheimer's Disease Amyloidosis
Award: $250,000

This project was to determine if the accumulation of "fats" from metabolic oxidation in the central nervous system could cause amyloid plaques. They have then blocked this effect through a genetic chemical receptor and to date have found a significant reduction in the early phase of amyloid deposition.

Dr. Trojanowski has had one (1) journal publication with reference of support by C.A.R.T. funds.

2004 Investigator: Robert Reenan, Ph.D – University of Connecticut Health Center

Project: Testing the Amyloid Hypothesis in Drosophila
Award: $250,000

This project was started by engineering flies (Drosophila) that are either amyloid secreting or non-secreting types of flies. This gene expression is silent until they cross them with a stock of flies that activates their brains. They then can compare any tissue abnormalities and behavioral changes in the two types of flies. This could lead to developing specific medications for AD.

2005 Investigator: Gary Small, MD – UCLA Neuropsychiatric Institute

Project: Amyloid Plaque and Tangle Imaging in Mild Cognitive Impairment
Award: $250,000

This investigator has developed a clinical marker that enables him to see Alzheimer's plaques and tangles with a brain scan in a living patient. This could differentiate between mild cognitive impairment (MCI) and cognitively intact controls, predicting early detection and prevention of AD. This was the first screening device developed which could detect Alzheimer's disease in the brains of living patients.

2006 Investigator: Claudio Soto, MD – University of Texas, Medical Branch

Project: The Deletion of Misfolded Ab Oligomers for the Early Detection of Alzheimer's Disease. Award: $250,000

This project involves efforts at the early diagnosis of Alzheimer's Disease. At the time that the clinical symptoms of AD appear, the extent of damage from amyloid-b plaques has already occurred in the brain. The major goal of this project is to develop a biochemical assay to detect the early stages of these protein alterations that are characteristic of AD.

Dr. Soto's hypothesis is that small amyloid aggregates start many years before the onset of clinical symptoms with some of the structures circulating in blood and cerebral spinal fluid. His objective is to identify minute quantities of these aggregates and assess their utility for the pre-clinical diagnosis of AD.

2008 Investigator (2nd Grant that year): Dr. David Sweatt – Chairman of the Department of Neurobiology; and Director of the McKnight Brain Institute – The University of Alabama-Birmingham (UAB)

Project: Memory Formation in genetically-engineered mice and its potential for Alzheimer's drugs

CART funding will be critical for my laboratory to be able to aggressively pursue a new drug development opportunity that we have, that hopefully will lead to a new type of treatment for Alzheimer's disease. My lab has discovered that long-term memory formation involves changes in the chemical and three-dimensional structure of DNA. We have capitalized on this discovery to develop a new line of drug treatments that improve memory formation in laboratory animals. CART funding will allow us to test these new drugs in genetically-engineered animal models of AD – we will use mice that are genetically-engineered to have a mutated human AD gene in them, which have memory deficits similar to AD patients. If the new drugs work to improve memory in these animals that mimic human AD, the stage will be set for us to move into human clinic patient trials very soon.

CART announces the 2004 grant

University of Connecticut Health Center receives $250,000 award

May 4, 2004 -- At the annual meeting of the CART Board of Directors in Columbia, SC, the University of Connecticut Health Center was announced as the recipient of its fifth grant in the amount of $250,000.00 for research that will take place over the next two years.

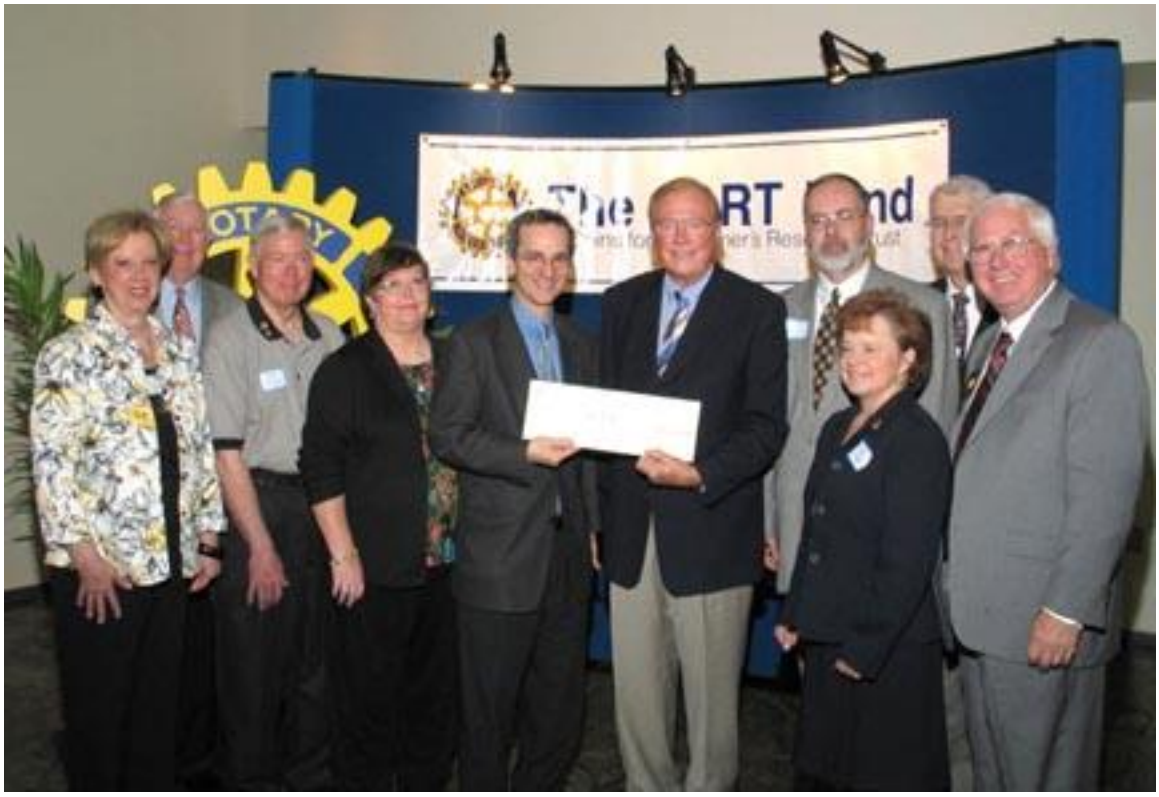
Above - left to right are: 2003-2004 CART President Von Starkey, Dr. Robert Reenan, Dr. Jack Bass, Grants Chairman, CART Secretary Karen Shore, Past District Governor Jim Puryear, CART Treasurer Roger Ackerman, and Past District Governor Bruce Baker.

Dr. Robert Reenan, principal Investigator of this research, was on hand to receive the award and check.

The University of Connecticut was the unanimous choice of the scientists who reviewed

all of the applications and reported their findings in a conference call with the CART Grants Committee, chaired by Dr. Jack Bass of the Hilton Head Rotary Club. Initially there were 34 research centers who applied by submitting a synopsis of their proposal. The advisory group of scientists chaired by Dr. Sam Gandy selected 12 of the 34 institutions – based on their proposed lines of inquiry/research - to receive invitations to apply and from these Connecticut was the clear choice. Dr. Gandy stated that all of the applications were outstanding.

CART Fund presents the 2005 grant to UCLA



Above, Rotarians from District 6920 join CART grants chairman Dr. Jack Bass in presenting Dr. Small with UCLA's check.

In May of 2005, the sixth grant made by the CART Fund was presented to Dr. Gary Small and his research team from UCLA. They received a check for $250,000. UCLA was selected ahead of 70 other applicants from research centers in over 40 states. This makes the total CART grants $1,350,000.00.

The UCLA scientists are the first to develop technology that will provide a direct measure of plaque and tangle density in the living patient. The plaque and tangles are commonly found in all Alzheimer's patients. Using only human volunteers, their project will be the first ever to detail the use of this technology in people at risk for Alzheimer's. This research hopefully will result in a major breakthrough in early detection and even prevention of the disease.

CART Fund presents 2006 grant to the University of Texas

Pictured left to right are CART Secretary PDG Dean Kanipe D-7670, Vice President Karen Shore D-7680, Dr. Soto, President Bruce Baker D-7750, Treasurer Roger Ackerman D-7770, and Vice President Jack Bass D-7770.

On May 3, 2006 at the annual meeting of the CART Board of Directors held in Columbia, SC, Dr. Claudio Soto of the University of Texas Medical Branch was awarded the seventh CART Fund grant, in the amount of $250,000 - for research into Alzheimer's disease.

The CART Board of Directors meets in Columbia, SC

CART Fund presents the 2007 Grant to the Mayo Clinic – Jacksonville

Pictured above, from left to right are: Karen Shore, President 2007-2008, Jim Miller (the first C.A.R.T. Fund Board member and representative from District 7670), Dr. Todd Golde, grant recipient for 2007, PDG Dean Kanipe (immediate past C.A.R.T. Fund Board member and representative from District 7670), DGE (2007-2008) Bill Shillito, and PDG Chuck Troutman (2007-2008 C.A.R.T. Fund Board member and representative for District 7670)

In May of 2007, the eighth C.A.R.T. Grant, in the amount of $250,000, was awarded to Dr. Todd Golde, M.D., Ph.D.., of the Mayo Clinic College of Medicine – Jacksonville, FL, at the annual C.A.R.T. Board meeting in Columbia, SC.

Dr. Golde's research project will involve the role of amyloidal beta peptides, in particular beta 40 and beta 42, in the onset of AD. Dr. Golde indicated that, in the past, the National Institute of Health – NIH – approved about 20-25% of all grant applications; but that it now only approves about 7-8% of applications for research grants. He stated that there is a dire need now for dollars for funding "high risk" research, and that the C.A.R.T. grant is an invaluable source of sorely-needed funding. He stated that research aimed at "re-directing" existing drugs to new purposes (such as treatment for Alzheimer's Disease) is vital, and needs funding – but that the drug companies will not do this – that their (the drug companies) profit is in ***new*** drugs. He noted that formal drug trials often cost $200-$300 million, and the drug companies will not spend this kind of money on trials for new uses of existing drugs.

2008 CART GRANTS (2)

Cleveland Clinic Hospital $250,000 grant. Investigator: Dr Sanjay Pimplikar.

Purpose: To screen for drugs that will prevent neurofiber tangles (tau) from massing together inside affected brain cells.

Background: While most of the A.D. research efforts have focused on the A-beta part of the amyloid protein as the culprit behind this disease (this is the 'plaque' that forms outside affected brain cells), these efforts have largely failed. Dr. Pimplikar's research has shown that part of the amyloid protein called AICD causes tau to aggregate. And it appears to precede the forming of plaque.

Dr. Pimplikar has the only mice with altered genes to test the AICD hypothesis. He hopes to prove that AICD activates tau and contributes to the accumulation of tau tangles. Our grant will allow him to find out if known drugs and even new ones will prevent the massing of tangles and lead to an eventual cure of this disease.

University of Alabama at Birmingham $200,000 grant. Investigator: Dr. David Sweatt.

Purpose: To aggressively develop new drugs that will lead to a new type of treatment for A.D.

Background: Dr. Sweatt has discovered that long-term memory formation involves changes in the chemical and structure of DNA. A new line of drug treatments will be tested on mice with a mutated human AD gene with memory defects similar to AD patients.

If the new drugs improve memory in these mice, Dr. Sweatt will begin human clinical trials with AD patients. With success, it is hoped that patients will experience less dementia, and that this research will lead to new treatment options and avenues for drug development.

Gary Landreth: CART Update 2009 (Dr. Landreth and Dr. Karl Herrup, of Case Western Reserve University, received the 2001 CART Grant)

My laboratory received a grant from CART in 2001 to support work on a then novel class of drugs for the treatment of Alzheimer's disease (AD). These drugs were originally developed for the treatment of diabetes. We were the first to recognize that this class of drug might affect AD.

The CART funds were absolutely critical to our success, as they allowed us to pursue experiments investigating the mechanism of drug action, for which we had no other means of financial support. We thought that these drugs would slow disease progression through their ability to inhibit the inflammatory response that occurs in the AD as a result of the deposition of amyloid plaques.

With the CART funds we identified a number of genes which participate in this anti-inflammatory effect. We published a number of papers in high impact journals as a result of the CART funding. Importantly, we were able to generate new preliminary data to support an application to the NIH (National Institute of Health) for grant support. We received a new grant, thus the CART funding was leveraged into a larger and more comprehensive research program. Over the intervening years, we have come to appreciate that this class of drugs have other disease-relevant actions.

GlaxoSmithKline tested, in a phase II trial in over 500 AD patients and found that 6 months of treatment improved memory and cognition. This has led to the initiation of three large Phase III trials, the last stage of clinical testing, involving over 3,400 AD patients and costing in excess of $200M. The first of these trials, involving 6 months of drug treatment, was completed in the fall of 2008 and the outcome will be reported in late 2009. The other two trials comprised studies of one year in length and were completed in the summer of 2009. We are anxiously awaiting the outcome of these pivotal trials.

The CART fund played an important role in the development of these new therapeutics. The provision of new financial resources for high risk projects is critical, as it allow the investigators to carry out projects that are too preliminary to garner financial support from federal agencies.

Roger Ackerman, CART Fund Secretary/Assistant Treasurer (and originator of The CART Fund) comments:

After reading his report I then summarized it as follows: Dr. Landreth told us in 2001 and repeats here that the CART Fund was their last resort for providing the "seed" money" for this cutting edge research. Their ultimate goal was to develop a specific anti-inflammatory drug to combat AD, which is an inflammation of the brain. They were so successful that at the end of two years research, they reapplied to NIH for a grant and received a million dollars or more to continue their research. The results were such that they patented their findings and negotiated with GlaxoSmithKline; who has committed in excess of $200 million dollars to complete the research. It is reasonable to assume that

no firm would commit that kind of money unless they felt they had an excellent opportunity for success.

Progress Report on 2007 CART research grant to Dr. Todd Golde, M.D. PhD – Mayo Clinic College of Medicine - Jacksonville
March 05, 2008

Executive summary:

- We have continued to make excellent progress towards completing the aims of our CART proposal. The overall goal of this proposal was to synthesize or identify new compounds that we have termed substrate targeting γ-secretase modulators (stGSMs) and evaluate their ability to lower Aβ42 and inhibit Aβ aggregation *in vitro* and i*n vivo*.
- We are now nearing the end of our in house in vitro screening and have nominated ~10 compounds for which we will assess their ability to acutely lower Aβ in vivo.
- In addition, we are currently synthesizing 5 "lead" GSMs that have been publically disclosed by industry. These GSMs are from Merck, Eisai, Cellzome, Torrey Pines, and Chiesi. This work is being done to determine if these compounds are working through the same mechanism, substrate-targeting, as our in house GSMs, and to enable us to compare our compounds for efficacy in vivo. This effort is extremely important as it will enable us for the first time to determine if all GSMs work the same way and if differences in mechanism of action influence in vivo activity.
- We have actively been breeding both APP Tg2576 and BRI-Aβ42 mice and will have a cohort of mice at appropriate ages to begin long term in vivo studies that will address whether the compounds work to reduce Aβ deposition by acting as GSMs or aggregation inhibitors these studies should be launched early next year.

Background

A great deal of evidence supports the hypothesis that Aβ42 is the initiating molecule in Alzheimer's disease (AD). Aβ42 preferentially accumulates in the AD brain, is selectively elevated by the vast majority of AD-causing mutations, and is required for deposition of Aβ in animal models. In addition, recent data from our laboratory and others show that Aβ40 inhibits Aβ42 deposition. Thus, selective lowering of Aβ42 has emerged as a leading therapeutic modality for the treatment or prevention of AD. An optimized safe Aβ42 lowering agent might prevent AD, if given years or decades before symptoms; however, lowering Aβ42 may not be sufficient to provide maximal benefit in patients with AD. Thus, we propose to evaluate novel Aβ42 lowering agents with several mechanisms of action as "magic shotguns" for the treatment of AD. We have recently identified three additional distinct structural classes of Aβ42 lowering agents that appear to bind Aβ and can in some instances inhibit Aβ42 aggregation. These three classes can be grouped into compounds that are steroid-like, isoflavone-like, and styrylbenzene-like. These compounds have not been previously shown to be Aβ42 modulating agents. Two of these compound classes, isoflavones and steroids, are compounds known to possess a rich pharmacology making them unattractive as "magic bullets" but possibly attractive as "magic shotguns". Although controversial, estrogenic activity has been purported to be protective in AD. Antioxidant activity such as that found in isoflavones, is thought to be generally beneficial and is of particular interest in AD where it is clear that oxidative stress contributes to the neurodegenerative disease process. Thus, it is possible these novel compounds besides targeting Aβ may have other interactions that could mediate beneficial effects. We will establish

structure activity relationships of i) readily available analogs of these novel Aβ42 altering and ii) novel compounds synthesized by the Mayo Chemistry Core facility with respect to the compounds ability to alter Aβ42 production and Aβ42 aggregation. We will subsequently perform proof of concept studies in mice that will enable us to determine if optimal compounds in terms of in vitro effects are acting to alter the AD like phenotype, by inhibiting Aβ42 production, decreasing Aβ42 aggregation or both. These later studies will take advantage of the BRI-Aβ42 transgenic model that we have developed (McGowan et al, Neuron 2005). In this model, Aβ production is independent of γ-secretase cleavage; therefore, production of Aβ42 is not altered by Aβ42 modulating compounds. By testing compounds in both BRI-Aβ42 and mutant APP mice we should be able to gain insight into whether compounds work by lowering Aβ42, inhibiting Aβ aggregation or both.

Progress

The narrative progress report follows the experimental outline as proposed in the original grant. The additional progress that we have made since the last report is included below.

As noted in the previous report the screen of the steroid "library is done, some of the follow up screening data are shown in Figure 1. Surprisingly our initial "hit" 5-β cholanic acid remains among the most potent Aβ42 lowering GSM we have identified in this series. Notably a very similar compound Chenodeoxcholic acid is also very potent, and is a compound used to treat humans with gallstones. Our first short term dosing study with these compounds did not show Aβ42 lowering in vivo, but we are concerned that their insolubility creates problems for delivery via oral gavage. We are therefore evaluating alternate delivery systems to see if oral dosing can lower Aβ42 acutely and if the compound does get in the brain. Though challenging studies they are highly important as positive results will provide data that will enable us to propose studies of the compound for its ability to lower plasma Aβ42 in humans. These human studies are certainly beyond the scope of the CART grant, but the studies that we are currently carrying out are essential. If we can't show biologic activity in an animal model, it is unlikely the human study will be approved. Notably Chenodeoxycholic acid is a very benign agent. In fact it is normally produced in bile; thus we are simply increasing endogenous levels to determine if it can influence Aβ production.

We have also generated another set of compounds not in the original proposal. These compounds, series FT-x have all been generated at Mayo by Dr. Fauq. Notably several of these compounds are very interesting. FT9-benzopheoneone 2 is a reasonably potent GSM and will be tested in vivo (Figure 2). Other compounds such as FT-9 hydroxyamine and FT9-benzopheone 1 are interesting because they appear to be acting as γ-secretase inhibitors rather then modulators. Again we are conducting further studies to try and understand why these small modifications shift the activity so dramatically. These compounds will also be tested in vivo.

Finally we have generated a handful of new X-34 derivatives and several of these are proving to be of interest. In particular two X-34 dehydroxy derivatives appear to show dramatic increases in potency (Figure 3A, 3B).

Plans.

1. Test ~10 of Mayo lead compounds in acute dosing studies in vivo (Timeline completion by December 2008)
2. Benchmark Mayo GSMs against other commercial GSMs (Timeline complete by January 2009)
3. Begin long term in vivo dosing studies with 2-Mayo Leads (launch in January 2009)

Publications:

Kukar, T. & Golde, T.E. Possible mechanisms of action of NSAIDs and related compounds that modulate gamma-secretase cleavage. *Curr Top Med Chem* 8, 47-53 (2008).

Kukar TL, Ladd TB, Bann MA, Fraering PC, Narlawar R, Maharvi GM, Healy B, Chapman R, Welzel AT, Price RW, Moore B, Rangachari V, Cusack B, Eriksen J, Jansen-West K, Verbeeck C, Yager D, Eckman C, Ye W, Sagi S, Cottrell BA, Torpey J, Rosenberry TL, Fauq A, Wolfe MS, Schmidt B, Walsh DM, Koo EH, Golde TE (2008) Substrate-targeting gamma-secretase modulators. Nature 453:925-929.

Progress Report on 2011 CART research grant to Dr. Gary Landreth, Ph.D – Case Western Reserve University, Cleveland, OH
November 30, 2012

Progress Report
Coins for Alzheimer's Research Trust Grant (CART)

Report Due Date: 11/30/2012

Case Western Reserve University
Gary Landreth, Dept. of Neurosciences, Case Western Reserve University School of Medicine, Cleveland, OH

Title of Research Project: Therapeutic efficacy of RXR activation in murine models of Alzheimer's disease"

Dates of Research Project: Beginning: 5/1/2011, Ending: 4/30/2013. Report for (dates): 3/31/2012 to 11/30/2012

Objectives of Research Project: The specific aims of the project are:

1. **To establish if bexarotene-mediated chronic elevation of brain ApoE levels will suppress soluble A levels and prevent amyloid deposition and the development of behavioral deficits.** *These experiments will establish the utility of drug treatment before the appearance of amyloid-induced behavioral deficits or pathology.*
2. **To determine if age and disease status affect the rate of bexarotene-stimulated amyloid plaque dissolution and reformation.** We wish to determine the rate of plaque reformation after first clearing plaques from the brain of 6 month old APP/PS1 mice with bexarotene treatment.

Progress toward completing proposed research
We have made significant progress since the initiation of the grant in May, 2011, and last reported on our progress in March 2012. The first year of the grant was focused on completion of experiments requested by the reviewers of our paper that was eventually published in Science in February 2012. This work documented the efficiency of the RXR agonist bexarotene in reducing the levels of soluble amyloid in the brain and rapidly clearing amyloid plaques. Importantly, drug treatment immediately reversed the defective neural network function in the brain and improved a broad range of behaviors that are impaired in three different mouse models of AD. CART was acknowledged for their support of our work in the published paper.

We found that we could clear about 80% of plaques from 6 month old APP/PS1 mice and we proposed to discontinue drug treatment and determine if and how fast the plaques returned. However, in an experiment in which we administered bexarotene daily for 90 days, we found that the drug-treated animals had plaque burdens that were the same as vehicle-treated mice. Importantly, ApoE levels remained elevated, soluble A levels were reduced and the mice still

exhibited improved behaviors in two different tests. We have treated 6 month old APP/PS1 mice with bexarotene for 14 days, and then discontinued drug treatment. In our initial studies we have evaluated the behavior of these mice found that, as expected, bexarotene reversed the amyloid-induced impairment in olfactory habituation behavior. However, this effect was lost and the mice were impaired in this behavior between 5 and 10 days following withdrawal of drug. We are now investigating how fast the plaques return with or without drug treatment.

In the past 6 months we have made several new and important observations. In collaboration with Dr. John Cirrito we have now been able to demonstrate that the levels of ApoE in the interstitial fluid are very rapidly induced. Using a new microdialysis procedure we found that ISF ApoE levels were increased within 6-8 hours of a single dose of bexarotene and increased linearly for 36 hrs. Importantly, using this new technology we found that ApoE was rapidly lipidated and incorporated into large HDL particles. Significantly, bexarotene treatment increases the average HDL particle size. Previous work has demonstrated that following a single dose of bexarotene ApoE levels remain elevated for 72-84 hours, reflecting the lifetime of the HDL particles.

We have new data that demonstrates that chronic treatment of mice with the FDA approved dose of bexarotene (100 mg/kg/day) daily for 30 days results in accelerated drug metabolism. This is important as it indicates that the drug becomes less effective at high dosages after long treatment intervals. Pilot studies have shown that a dose of 20 mg/kg/day is maximally effective. This finding, together with the observation that HDL levels are elevated for as long as 3 days following a single drug dose, suggests that it is both possible and prudent to lower the overall drug exposure by either lowering the dose and/or administering the drug at less frequent intervals.

Publications:

Cramer, PE., Cirrito, JR., Wesson, DW, Lee, C, Karlo, JC, Zinn, AE., Casali, BT, Restivo, JL, Goebel, WD ,. James, MJ, Brunden, KR, Wilson, DA and Landreth, GE. ApoE-directed Therapeutics Rapidly Clear β-amyloid and Reverse Deficits in AD Mouse Models. Science, 335:1503-1506, 2012.

OBSERVATIONS ON C.A.R.T – FUNDED RESEARCH

C.A.R.T. grants fund basic research. At the present time, there is no way to conclusively diagnose AD before a post-mortem autopsy; and there is certainly no known cure for this debilitating disease at this time.

It is difficult to procure evidence of what the impact of C.A.R.T. – funded research is to date, or any other research for that matter, after the initial project period. The item below, however, is a recent success story that reflects our Alzheimer's Disease research program:

Earlier this year, the daily media recognized a certain medical research center for the discovery of a new human gene that plays a significant role in the development of Alzheimer's Disease. This gene is called LR11; but it is also known as sorLA and sorLI.

It is only fair to state that Emory University's research group that includes Doctors Allan Levey (recipient of the first C.A.R.T. grant) and James Lah identified this particular gene in a 1999 study that was funded in part by C.A.R.T. This gene was more specifically acknowledged by publication in the August 2004 Archives of Neurology. It is envisioned that this discovery will immensely enhance future Alzheimer's Research.

Drs. Levey and Lah received the very first C.A.R.T. grant with the aim of developing a blood test that would be able to detect Alzheimer's Disease (AD) at its earliest stage. While they were not successful in obtaining results that would be as accurate as needed, they have told us numerous times that their research led to other findings that they continue to work on in their labs.

In the process of working on the above research, they found a protein in the brain that they had never seen before. They sent this information on to Toronto to scientists who specialize in this area of the brain. Toronto, in turn, shared this information with Columbia University and Wake Forest University scientists and together, after seven years, they were able to discover an unknown gene that holds great potential for helping to find a prevention/cure for AD.

In December, 2006, the national news networks featured these findings on two consecutive days.

This information illustrates two things:

1. Alzheimer's scientists are very supportive of each other and share their findings, unlike pharmaceutical houses.
2. Several scientists have told us that our C.A.R.T. grants allow them more flexibility that other (government) grants. For example: If in the course of their research, they are able to make some unexpected findings, they are allowed to pursue these findings under our grant. National Institute of Health (NIH) grants, on the other hand, require them to only use their funds for the specific research approved.

C.A.R.T. is recognized as one of the major private financial contributors to innovative, high-impact scientific research in Alzheimer's Disease. Nine publications from our other grant awards have occurred since 1999.

Thirty-three (33) investigators submitted letters-of-intent (initial applications) for the 2007 C.A.R.T award of $250,000. These included **Drexel, Yale, Duke, Mount Sinai, Johns Hopkins, Tufts, Columbia, California-Irvine, UCLA, Washington, Cleveland Clinic, Emory, Florida, Harvard, Michigan, and North Carolina –** a very prestigious group of institutions!. Using a peer review committee, our grants committee selects from these "letters-of-intent" lines of investigation which offer the most current promise, and invites those selected to submit a more formal, detailed, application which fully delineates their proposed line of research inquiry. The peer review committee then selects that year's grant recipient from those submissions/applications.

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Below is a lay review of a recent publication by Dr. Gary Small, UCLA that relates to our C.A.R.T. award for 2005.

New Imaging Method Identifies People At-Risk for Alzheimer's Disease

UCLA researchers used innovative brain scan technology to show that the abnormal brain protein deposits that define Alzheimer's Disease can be detected in mild cognitive impairment – a condition that increases the risk for developing Alzheimer's Disease and which effects 15 to 20 million Americans. The study was published in the December 21, 2006 issue of The New England Journal of Medicine.

The researchers used positron emission tomography (PET) imaging with a small molecule (FDDNP) invented at UCLA that binds to the abnormal proteins – amyloid plaques and tangles – that may cause the disease. Previously, only an autopsy could determine these deposits and confirm a diagnosis. The PET imaging showed that the more advanced the disease, the higher the FDDNP concentration in areas where the abnormal protein deposits typically accumulate – in the temporal, parietal and frontal brain regions. Patients with Alzheimer's Disease showed the most FDDNP binding, indicating a higher level of plaques and tangles than other subjects. "The study suggest that we may now have a new diagnostic tool for detecting pre-Alzheimer's conditions to help us identify those at risk, perhaps years before symptoms become obvious," said Dr. Small, lead study author at UCLA. "This imaging technology may also allow us to test novel drug therapies and manage disease progression over time, possibly protecting the brain before damage occurs".

The study was funded by the National Institute of Health, The Department of Energy-General Clinical Research Centers Program**, the Rotary C.A.R.T. Fund**, the Fran and Ray Stark Foundation Fund For Alzheimer's Disease Research, the Ahmanson Foundation, the Larry L. Hillblom Foundation, the Lovelace Foundation, the Judith Olenick Elgart Fund for Research on Brain Aging, the John D French Foundation for Alzheimer's Research; and the Tamkin Foundation.