



Funding research to improve learning, memory and speech in individuals with Down syndrome.

Dear DSRTF Friends and Supporters,

Throughout 2008 and into the start of 2009, DSRTF continues to build on its leadership as the largest non-governmental source of funding that has led to unprecedented advances in evidence-based biomedical research for cognition in children and adults with Down syndrome.

With dramatic research results achieved at such a rapid pace, effective new therapies and greater independence are now within reach for people with Down syndrome. Galvanizing an unprecedented optimism and energy within DSRTF and among the Foundation's donors, volunteers and supporters, has enabled even more progress and successful validation of DSRTF's paradigm-shifting strategy:

- As recently as 2004, when DSRTF was founded, there were no defined biological mechanisms known to have a direct correlation with cognitive impairment in DS – and as a result, no drug targets suitable for drug discovery R&D.
- Today, with over \$4 million generated by DSRTF for critically targeted new research - including more than \$1.49 million in DSRTF grant funding to Stanford University School of Medicine, Johns Hopkins University School of Medicine and the University of Arizona since late 2007 – there are now five new potential therapeutic drug targets that have been identified and are currently being pursued to ameliorate the intellectual disabilities associated with Down syndrome. Significantly, DSRTF grant funding is also now targeting the advancement of potential drugs through the preclinical stage and clinical trials to

further accelerate progress toward the approval and availability of new therapies.

All of the remarkable progress and successful validation of DSRTF's strategy would not be possible without the dedication of the many donors, event organizers, volunteers and supporters from across the country and internationally to our shared mission. This has been another record year with increasing involvement of parents, siblings, family members, and friends of individuals with Down syndrome, many becoming key DSRTF ambassadors in their local communities.

DSRTF events this past year included continuing the very successful Romp for Research in New York to the newest Romp for Research in Shreveport, LA as well as tremendous events in New Jersey, Illinois, California, Arizona, Florida and Texas among many others. DSRTF also is extremely grateful to have been invited once again to present at the recent Affiliates in Action conference held February 25-28, 2009 in Washington DC, which provided the opportunity to meet with leaders and expand the awareness about our mission and accomplishments among more than 85 local groups in the Down syndrome community and across the country.

We are dedicated to continuing to extend our hand in partnership to all individuals and groups within the Down syndrome community to leverage funds and resources together, to further accelerate the discovery and development of effective new therapies and new opportunities for all individuals with DS. We remain extremely proud of DSRTF's stewardship and efficiency – with > 86% of all FY 2008 expenditures allocated to DSRTF research programs and >\$1.2 million to DSRTF grants.

On behalf of DSRTF, we extend our sincerest thanks to you for continuing to support and enable the exciting progress in Down syndrome cognition research and working to get others involved. Together we can be part of the breakthrough!

Warm regards,

Patricia White Flatley, MD
Chair, Board of Directors

Michael Harpold, Ph.D.
Chief Executive Officer

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RESEARCH UPDATE: DSRTF UNCOVERS AT LEAST 5 NEW POTENTIAL DRUG TARGETS

DSRTF'S MISSION IS TO IDENTIFY TREATMENTS THAT WILL IMPROVE COGNITION IN THOSE WITH DOWN SYNDROME. Our research strategy is to fund activities in multiple places along the R&D pipeline in order to streamline, thus ultimately speeding up the time it will take to have a therapeutic available in the market. (See graphic: R&D Pipeline).

The lion's share of our research dollars continue to fund the most promising areas of basic research with the goal of identifying specific differences in the way the brain of an individual with Down syndrome processes information. We have enjoyed unprecedented success, uncovering at least five new 'mechanisms of action' or 'potential drug targets.' Four of these findings have come from research that DSRTF has funded at the Stanford Center for DS Research and Treatment.

The first body of work from Stanford has to do with modulating neural circuits involved in learning and memory. It is known that circuit actions are influenced by both excitatory and inhibitory inputs. In the mouse model of DS there is excess inhibition in brain areas critical to cognition, a change that appears to reduce the ability of circuits to change or to "learn". Two potential targets for treatment have been identified based on this knowledge.

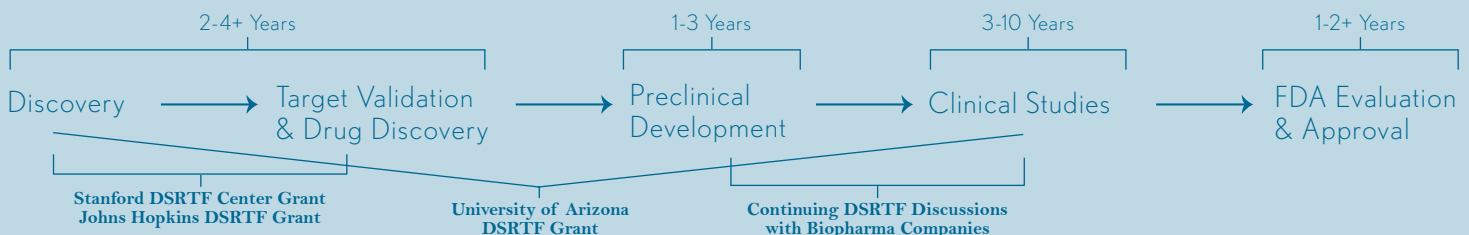
The first is a specific receptor for a small neurotransmitter molecule called GABA, which is responsible for inhibiting neurons within neural circuits. The name of the receptor is the GABA-A receptor (the first of the five identified potential targets). By blocking this receptor, it has been possible, using slices of brain in the laboratory, to restore the ability to "learn" in a very important circuit

in a brain region called the hippocampus. These studies, carried out in the Mobley laboratory, were a stimulus to Craig Garner and his colleague Fabian Fernandez at Stanford to study the actions of compounds that block the GABA-A receptor in mice. They found that they could restore the ability of the mice to learn certain tasks. Taken together, these studies point to the possibility of using existing compounds to enhance learning in people with DS. However, it is far too early to claim that such compounds will work in people. DSRTF believes strongly that carefully controlled preclinical research and clinical trials will be needed to test these ideas.

A second, different receptor for GABA is the GABA-B receptor (the second potential target). This receptor is also involved in modulating neural circuits. Interestingly, it interacts with another protein called GIRK2 (a third potential target) which is produced by a gene on chromosome 21. The Mobley lab tested the idea that, working together, the GABA-B receptor and GIRK2 could also be responsible for the increased inhibition in the hippocampus in mouse models of DS. They found that blocking this receptor with a compound that is being evaluated for other indications in human trials restored "learning" in slices of mouse hippocampus in the laboratory and are now actively testing the ability of this blocker in studies on the mice. The results so far are quite encouraging. If the findings can be confirmed, this would be a second treatment approach to turning down inhibition in the brain to restore learning in people with DS.

The next body of work may have implications for Alzheimer's disease (AD). It is known that the brains of people with DS show the changes associated with AD during aging. During the past year significant progress was made towards curtailing these changes.

THE RESEARCH AND DEVELOPMENT PIPELINE



DSRTF's unique approach emphasizes results-oriented, targeted-funding aimed at stimulating all steps in the discovery and development pipeline. This comprehensive approach enables DSRTF to focus on identifying and

removing obstacles at each step along the pipeline, resulting in scientific breakthroughs and a streamlined path to therapies that will improve cognitive abilities for people with Down syndrome.

The APP protein (the 4th of five potential drug targets), which is made by a gene on chromosome 21, plays an important role in the degeneration of neurons that use acetylcholine to communicate with other neurons. Normally these neurons are important for learning, memory and attention. The degeneration of the neurons that make acetylcholine is a very important and characteristic feature of both AD and adults with DS, and likely contributes to cognitive deficits. This year the Mobley laboratory tested the idea that a small molecule called Posiphen would act to reduce the level of the APP protein in a mouse model of DS. The hypothesis is that by reducing APP it might be possible to prevent or reduce degeneration of these neurons. The lab showed that Posiphen did reduce APP protein levels and it is now engaged in testing whether or not this results in protection of acetylcholine producing neurons and to preventing cognitive deficits in mouse models of DS.

This past year the Stanford researchers further explored the other groups of neurons whose degeneration is seen in DS. One particularly important group of neurons make the neurotransmitter norepinephrine, which also acts to support learning and memory. The researchers found that these cells did degenerate with aging in mouse models of DS and have now begun to try to define the genes responsible. Even before finding the gene, it is possible to attempt to treat the defect by increasing the brain level of norepinephrine. Early results suggest that it may be possible to rescue certain aspects of memory in mice that model DS by administering a drug that increases norepinephrine levels and that has been used safely in people with another specific medical condition.

Complementary work is taking place at John Hopkins University Medical Center where researchers have been focused on a different pathway in a different part of the brain. The Reeves lab has identified that a certain neural pathway is compromised due to a decreased response to the SHH protein (the 5th potential drug target). By identifying and substituting a compound similar to SHH in brains of mouse models of DS Reeves was able to normalize the operation of that pathway. This work is currently developing in two important directions. First, the mice are now being tested to see if the normalized pathway will have the expected behavioral implications, which would result in improved learning and memory. Secondly, studies are now taking place to see if the SHH-like compound will

have similar effects on the hippocampus as it did in the cerebellum, the area of the brain in which the studies were initiated.

As was the case at Stanford, interest in DS cognition work seems to be contagious. Drs. Worley and Smith-Hicks, research colleagues of Reeves, have identified yet another pathway involved in neuroplasticity. Early studies of this pathway indicate that there may be a relationship to earlier APP findings and to some cognitive deficits in fragile X syndrome.



DSRTF AWARDS GRANT TO THE UNIVERSITY OF ARIZONA IN ANTICIPATION OF FDA APPROVAL PROCESS

The third institution to receive a grant from DSRTF is the University of Arizona. There Drs. Lynn Nadel and Jamie Edgin are developing a battery of standardized cognitive tests that can be used to more accurately identify and measure specific cognitive impairment in people with Down syndrome and, ultimately, assess the efficacy of drug compounds like the ones identified by the scientists at Stanford and Johns Hopkins. These behavioral tests are designed specifically for individuals with Down syndrome and are able to evaluate the effect of drug compounds on cognitive functions mediated by specific parts of the brain. Having a generally accepted standardized test of the efficacy of potential therapeutics for improving cognitive abilities in individuals with Down syndrome will be critical for the preclinical research and clinical phases of the FDA approval process. Identifying such tests before they are needed is a prime example of DSRTF's interest and strategy to streamline the FDA approval process. (see graphic: R&D Pipeline)

FINANCIAL HIGHLIGHTS

RESULTS AND FINANCIAL HIGHLIGHTS

Fundraising Success: Over \$4 million generated in research funding since 2004; FY2008 donations to DSRTF exceeded \$1.9 million

Research Grants: Over \$1.49 million in research grant awarded since September, 2007

Operational Efficiency: 86 cents of every dollar donated to DSRTF is allocated to DSRTF research programs

Current DSRTF-Supported Research

- DSRTF Research Center Grant
Stanford University School of Medicine-
Four Principal Investigators: Drs. Mobley, Garner, Madison & Graef
\$880,000 for 2007-09
>\$3 million since 2004
- DSRTF Innovation Research Grant
Johns Hopkins University School of Medicine-
Principal Investigator: Dr. Roger Reeves
\$250,000 for 2008-09
\$500,000 since 2007
- DSRTF Innovation Research Grant
University of Arizona- Principal Investigators:
Drs. Lynn Nadel & Jamie Edgin
\$113,719 for 2008-09

THE FUNDING REALITY

Federal funding for DS research from the NIH has **decreased** over the past decade and is currently at **\$42 per capita**. It is **significantly under-funded** compared to other conditions on a per capita basis:

2008 FEDERAL FUNDING		
CONDITION	ESTIMATE \$	xDS
CYSTIC FIBROSIS	\$3,000	71x
HUNTINGTON'S	\$1,700	40x
FRAGILE X	\$1,529	36x
ALS	\$1,433	34x
DUCHENNE MD	\$485	11.5x
MULTIPLE SCLEROSIS	\$422	10x
CROHN'S DISEASE	\$128	3x
PARKINSON'S	\$101	2.5x
DOWN SYNDROME	\$42	1X

Source: NIH

ANNUAL SCIENTIFIC ADVISORY BOARD MEETING, FEBRUARY 2009

Gathering on February 1-2, 2009, in San Francisco, the DSRTF Scientific Advisory Board (SAB), whose members are among the most highly accomplished researchers in Down syndrome research and critically related biomedical research, further intensified their focus on evaluating ongoing DSRTF-supported research programs and identifying and continuing to develop results-driven strategies to accelerate the development of new effective therapies. Through the interactive advisory discussions with the current DSRTF-funded researchers and the wider research community, the DSRTF SAB continues to be extremely impressed by the high quality and rapid pace of the DSRTF-supported research. The SAB also specifically noted the increased emergence of a wide array of important new research ideas and projects that could lead to additional significant advances, and the continuing challenges associated with having more such promising research projects than available DSRTF funds to quickly initiate many of these projects.

DOWN SYNDROME AND ALZHEIMER'S DISEASE

The awareness of the link between Alzheimer's disease and Down syndrome has recently received increased attention. Since it's founding DSRTF has supported research to determine the relationship between these two conditions recognizing that not only may individuals with Down syndrome potentially benefit from the ongoing research and development for new Alzheimer's disease drugs, but individuals with Alzheimer's disease may also benefit from Down syndrome cognition research and new drugs resulting from this research.

Children with DS can begin developing the pathology of Alzheimer's as early as 8 years old and by the age of 40, virtually all individuals with Down syndrome have the plaques and tangles that are a physical hallmark of Alzheimer's disease. While it is common for these individuals to eventually develop the dementia associated with AD (50-70% of individuals with DS will develop dementia by the time they reach 60-70 years of age), recent studies have shown that it is not inevitable.

THE APP GENE

In 2006 DSRTF-funded researchers at Stanford University determined that the extra copy of the APP gene, found on the 21st chromosome, may be associated with impaired cognition in Down syndrome. Previously it had been determined that over-expression of APP is related to deposits of amyloid in the brain and is critical to the development of AD and its associated plaques and tangles. The 2006 research finding also recognized that the increased dose of APP affected the functioning of a brain growth factor, NGF, resulting in neurodegeneration of neural circuits believed to be involved in cognitive dysfunction in both DS and AD. Evidence of this impaired mechanism is the first step towards identifying a treatment that would benefit both DS and AD.

AD DRUGS FOR THE DS POPULATION

The current drug treatments approved for clinical use in AD have the function of blocking an enzyme with the end result of maintaining and allowing for better communications between brain cells. Because DS exhibits some of the same neuronal communication issues as AD, there is a belief that AD treatments may have some benefits for those with DS. To date there have been a handful of pilot studies that show promising results.

The first placebo-controlled study is currently taking place and results of the study are yet to be published.

DSRTF'S ROLE

DSRTF funding was instrumental in the determination of the APP link between DS and AD and the identification of new a drug development target. DSRTF continues to support this research. New donations will make it possible for DSRTF to support and target research to evaluate potential new drugs which currently only target AD or cognitive issues in other disorders. In addition, with further work on known mechanisms and additional studies identifying new mechanisms associated with impaired cognition, DSRTF-funded work offers promise of benefits beyond the DS population.

DR WILLIAM I. COHEN:

*A Remembrance of a Friend, Colleague
and DSRTF Scientific Advisory Board Member*

William I. Cohen, MD, great friend, colleague, and very active and highly supportive inaugural member of the DSRTF Scientific Advisory Board, passed away on February 6, 2009. Bill will be greatly missed by the Foundation and each of his colleagues on the Scientific Advisory Board.

Bill Cohen has been widely recognized for his deep compassion and contributions to the medical care of children with Down syndrome, and his unwavering commitment to, and support of, the entire Down syndrome community. His energy, joy for all of life, and enthusiastic excitement for the potential of the most rigorous new evidence-based biomedical research for creating new opportunities for all people with Down syndrome has been inspiring to researchers, physicians, as well as all in the Down syndrome community and beyond.

On behalf of everyone involved with DSRTF, we extend our deepest and most sincere sympathies to Bill's family, friends and colleagues.

STEPHEN LAZARE CO-CHAIR NYC ROMP FOR RESEARCH



Q: Tell us about your daughter.

What can I say? Anna is the best thing that ever happened to me -- to all of us. When Anna was born, all but one of the attending doctors, acted as though we should be in mourning. Three days after Anna's birth, a pediatrician in the NICU, who we met once and have not seen since, told us "she's beautiful....congratulations." That was the first time anybody had said something positive. He explained that he had patients with Down syndrome, any one of which he would be proud to have as his own child. Our outlook changed immediately. Anna is an amazing and inspiring kid. All kids with DS have different strengths and challenges. Anna, while she has some physical delays, has been an avid reader since age four, loves horseback riding, enjoys making fun of her dad's baldness, and does not forget a thing. She has been in a typical nursery school since age 2. She is a big inspiration to her teenage siblings, Libby and Alex. They are like an extra set of parents; to say that my two older kids have developed perspective, an appreciation for differences, and the ability to look past disability -- would be an understatement. They are well beyond their years in this regard. I am very proud of both of them. I can't imagine what it is going to be like for all three of them once the older ones

are off to college; the three of them are very close. It would not surprise me to see Alex end up in a career devoted to working with people like his sister.

Q: What do you envision for your daughter's future?

I am confident she will be happy and bring joy to those around her. We are careful not to define her by the DS and will not assume any limits. Our goal for her is the same as it is for her siblings -- a happy and fulfilling life. That should be everyone's goal.

Q: Tell us about the Romp for Research and your event co-chair Anthony Providenti.

Our close friendship with the Providentis is yet another one of the "meant-to-be" fateful things that can be traced to Anna. Troy, their son, is an amazing, wonderful and loving kid. I had a nice chat with him just the other day over a piece of pizza. Anthony is a force -- his energy and vision is boundless. The idea of a Romp -- a family-fun way to raise funds and awareness for DSRTF (a break from the conference room cocktail events) -- came to us over a cup of coffee at cafe in Pleasantville (where we live, as do Troy's grandparents). Anthony said "let's do it" and has not looked down since. He is unflappable and has a way of making things happen. Without Anthony, there is no Romp -- not even close. I should say, that's equally true for my wife, Mary. For her, the Romp becomes almost a full time job starting in July. Our house becomes filled with goodie bags, arts and crafts, stomp rockets, face paint, etc. -- it is the staging area. This year we had nearly 1000 attendees, and now there are Romps in the south and on the west coast. I hope this is just the start.

Q: What advice do you have for other parents?

Take a break from all of the challenges DS brings and enjoy your child. Five years ago, I never would have thought that having a child with DS would be anything other than a hardship. I was very wrong. Like I said, there are challenges and it would be a mistake and disservice to our kids to turn our heads to that. At the same time, these are -- first and foremost -- our kids. Like they say, they are more like us than they are different. When I find myself telling stories about Anna, they never seem to have anything to do with DS; they are always about some "typical-kid" like moment - much like all the fond memories we have of raising our two older kids. She is, in so many ways, really just a "typical kid" and we are all so much better off because of her.

THE DSRTF MISSION

DSRTF will stimulate bio-medical research that will accelerate the development of treatments to significantly improve cognition, including memory, learning and speech for children and adults with Down syndrome in order that they can:

- Participate more successfully in schools
- Lead more independent lives
- Avoid early cognitive decline

2008 EVENT HIGHLIGHTS: OVER 50 EVENTS AND COUNTING...

DSRTF has realized tremendous momentum over the last few years with respect to fundraising events. To date our volunteers have held over 50 events in over 20 states from New York to North Carolina to California; including cities like Washington D.C., Shreveport, Louisiana, Los Angeles, Chicago and Mesa, Arizona. In 2008 the number of events nearly doubled over the number held in 2007. Events have varied in size and theme, from family-centered events like the New York Romp for Research to cocktail parties and golf events. Some have even turned their family birthday parties into an opportunity to raise funds for DSRTF.

We owe the success of these events to those of you who have joined us to “Be a Part of the Breakthrough.” Please help us continue this success by organizing an event in your area. Call us at 650.468.1668 to learn more. Following are some highlights of upcoming events. For more information about these and other events in your area go to www.dsrtf.org/events.



1ST ANNUAL BAY AREA ROMP FOR RESEARCH

*Shoreline Lake, Mountain View,
California / May 16, 2009*

Come out for a festive, fun-filled Family Event to raise awareness and support for Down syndrome cognition research!!! Bring your family and friends for WATER ACTIVITIES including paddleboats, GAMES including a bounce house, dunk tank, volleyball, frisbee, football toss, ARTS & CRAFTS like face painting, jewelry making, cupcake icing, balloon animals, and more.



2ND ANNUAL SALVATORE PISERCHIO GOLF OUTING

Washington, NJ / April 20, 2009

Last year, Lisa Pischerio's team organized the 1st Annual Salvatore Pischerio Golf Event to support DSRTF and Down syndrome cognition research. This year's event will take place at the Hawk Pointe Golf Club in Washington, NJ, and it promises to be even bigger and better than the first.

WASHINGTON STATE DS COGNITION RESEARCH PRESENTATION

Tukwila, Washington / April 18, 2009

Join DSRTF and the Down Syndrome Community in Washington State in welcoming leading researchers in the area of Down syndrome cognition research to give a presentation to interested parents, caregivers and professionals about the current state of Down syndrome-related cognition research.



2ND ANNUAL HAYES

MECHANICAL GOLF EVENT

Chicago, Illinois / June 23, 2009

Come out and join the Hayes Mechanical team as they sponsor their 2nd Annual Hayes Mechanical Golf Event to support DSRTF and Down syndrome cognition research.

DOWN SYNDROME CRUISE FOR A CAUSE 3 Night Baja Cruise / June 5, 2009

Join DSNetwork for this 3 Night Baja Mexico Cruise aboard the Carnival Paradise departing from Long Beach, CA on June 5, 2009! This amazing experience includes shipboard accommodations, ocean transportation, fabulous entertainment, daily activities, onboard meals, port charges and more! And best of all, a portion of your fare will go to support DSRTF!



WWW.DSRTF.ORG
Palo Alto, California 94304
755 Page Mill Road, Suite A200
DSRTF
Down Syndrome Research
and Treatment Foundation

THANK YOU!!

Your past support, has enabled DSRTF to make significant strides in a short period of time. Continued support will help keep the research moving at this exciting pace. You can also help by telling others about DSRTF's mission and success.

Be part of the breakthrough!

FUTURE DSRTF EVENTS HOW YOU CAN HELP

DSRTF is in the process of organizing and planning a multitude of new events and activities in 2009 focused on raising awareness and support for Down syndrome research all across the country! If you are interested in helping DSRTF organize an event in your area, contact us now at (650)468-1668, or via email at dsrtf@dsrtf.org !!!



THE DOWN SYNDROME RESEARCH
AND TREATMENT FOUNDATION
755 Page Mill Road, Suite A200
Palo Alto, CA 94304
tel. (650) 468.1668 and online at
WWW.DSRTF.ORG