



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

## An Overview of a Successful 2007 from the DSRTF Board Chair and CEO

### Dear DSRTF Friends & Supporters,

In 2007 DSRTF led the way to achieving a significant milestone in re-energizing Down syndrome cognition research. Dr. Roger Reeves of Johns Hopkins School of Medicine, and DSRTF SAB member, recently described the past year as a 'year of unprecedented progress for Down syndrome basic research' and the mood among those doing DS research as "more upbeat than I have seen in more than 20 years of working to understand the basis for DS."

DSRTF is pleased to have served as a major catalyst in this exciting progress. The optimism and energy within DSRTF and among our donors and volunteers is increasingly high, and has led to a more than 60% growth in donations enabling DSRTF's most significant progress:

- The year began with an important first for DSRTF—our inaugural Scientific Advisory Board meeting. The energy, focus and contributions of this distinguished and accomplished group have been impressive. These scientists, from both within and beyond the DS research community, validated the merit and progress of the ongoing DSRTF-funded research at Stanford University, identified critical new research areas and recommended a major new research grant initiative at Johns Hopkins School of Medicine. The DSRTF SAB will continue to play a key role in identifying promising research directions.
- The year continued with the publication of very exciting research results from Dr. Craig Garner's lab at Stanford, which showed the beneficial effects of a drug, PTZ, on cognition in a DS mouse model. DSRTF is continuing to fund Dr. Garner's research advances with PTZ.
- In June, we were fortunate to have Dr. Michael Harpold, board member and Chair of our Scientific Advisory Board, become DSRTF's new CEO. The combination of Michael's scientific research and biopharmaceutical operational expertise has already offered benefits to the organization in the ability to more proactively identify and target key research areas and programs most likely to accelerate development of new treatment opportunities.
- DSRTF's research grant award to Dr. Roger Reeves at Johns Hopkins - our most recent research news - is enabling a significant extension of his investigation of the effects of the drug compound SAG - which normalized the development of the cerebellum in a DS mouse model - to the hippocampus, another brain area directly involved in learning and memory.

This tremendous progress would not have been possible without the many volunteers from across the country leading and supporting fundraisers - from cocktail parties and golf tournaments to the NY Romp for Research and LA event at the Hollywood Bowl. This was a record year for involvement of parents, siblings, friends and individuals with Down syndrome—leading to a greater than 60% increase in year-to-year donations—and enabling DSRTF to award more than \$1 million in research grants. Together with the momentum of the 'unprecedented' successes in 2007 and your increasing contributions, DSRTF will be able to extend support to critical new research and bring the most promising advances even closer to creating new opportunities for all individuals with Down syndrome.

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!

Warm regards,  
Patty O'Brien White  
*Chair, Board of Directors*

Michael Harpold, Ph.D.  
*Chief Executive Officer*

## IN THIS ISSUE

THE DSRTF STRATEGY .....	PAGE 2
EARLY SUCCESS .....	PAGE 3
FINANCIAL HIGHLIGHTS....	PAGE 4
VOLUNTEER SPOTLIGHT....	PAGE 5
EVENT HIGHLIGHTS.....	PAGE 6

# THE DSRTF STRATEGY

In a very short time, DSRTF has established itself as a leader in the DS research arena.

Founded in 2004, DSRTF is the largest private source of funding for Down syndrome cognition research with an enviable track record for high-impact research results. DSRTF is building upon this early research success by following a focused strategy guided by our mission.

The three key aspects of the DSRTF's comprehensive, paradigm-shifting strategy are: 1) a focus on **cognition research**; 2) an **acceleration of an innovative, results-driven research process**; and, 3) the **development of effective new therapies**. These strategic objectives reflect the core of DSRTF's mission and our ultimate goal to improve memory, learning and speech for individuals living with Down syndrome.

**Cognition research** is a critical focus since most individuals with DS fall into the mild to moderate range of cognitive impairment. Even a relatively small improvement in cognitive functions could dramatically impact a broad range of opportunities for these individuals. Cognition research can also yield potential new therapies targeting further premature cognitive decline associated with the Alzheimer's disease pathology which occurs as early as age 40. Clearly, cognition research provides a significant path to creating new opportunities, including the potential for greater independence and achievement, for all individuals with DS.

**Acceleration** of an innovative, results-driven research process is critical since DS research has traditionally endured chronic underfunding and lack of awareness regarding its potential, which resulted in minimal progress. Importantly, recent advances in neuroscience, genetics, genomics, molecular cell biology and physiology, and drug discovery and development, including interdisciplinary applications, are opening the way to new approaches for a deeper understanding of cognitive impairments in DS and development of new therapies.

## THE 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

Accelerating and achieving research success requires establishing critical mass in *awareness, innovation, interdisciplinary collaborations, attraction of needed new expertise, coordination and targeting for research synergy, discovery of new underlying mechanisms, therapeutic targets and drug candidates, and crucially, increased R&D funding*. All of these aspects are integrated into DSRTF's proactive strategy—further enhanced by the comprehensive interdisciplinary expertise and networks of DSRTF's staff, board and SAB.

## Development of New Therapies

DSRTF's ultimate strategic goal is the development of formally validated, effective new therapies to ameliorate cognitive impairment in individuals with DS. Attaining this goal requires progression through the established multi-step drug R&D pipeline (see diagram below). While it is essential to accelerate and maintain a flow of new fundamental research discoveries into this pipeline—proactive, targeted funding of innovative translational and clinical research at key steps throughout the pipeline by DSRTF can further accelerate the process and eliminate critical obstacles to success—thus assuring even more rapid progress toward our ultimate goal. Such research initiatives are another critically important component of DSRTF's strategy.

In summary, DSRTF has uniquely integrated its mission, comprehensive proactive strategy and ability to leverage critical resources to accelerate the development of effective new therapies for cognitive impairment in individuals with DS. Of course, the true measure of success is determined by results; and importantly, DSRTF-funded research has already led to remarkable early success!

## 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.

# REMARKABLE EARLY SUCCESS

## DID YOU KNOW....

As recently as 2004 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 and development. After three years and over \$3 million generated by DSRTF for critically targeted new research, dramatic progress has been made. There are now three independent studies showing the promise for improving cognitive function in those with Down syndrome.

### THE APP GENE

*An Alzheimer's Disease-DS Connection*  
*Earlier DSRTF-supported studies established that the APP gene, found on human chromosome 21, is associated with impaired cognition in Down syndrome. The additional copy of the APP gene negatively impacts a transport mechanism necessary for the normal function and survival of a specific population of neurons communicating with the hippocampus (an area of the brain involved in learning and memory). The studies suggest that reducing levels of APP could have beneficial consequences in Down syndrome and applications to Alzheimer's disease.*

To extend their discovery that the over-expression of the specific APP gene, a gene also known to be associated with the pathology of Alzheimer's disease, is involved in cognitive impairment in a mouse model of Down syndrome, recent DSRTF-funded research by Dr. Mobley and his collaborators at Stanford is progressing to gain deeper insights into this impaired molecular mechanism as well as identify potential drug compounds that will reduce the level of APP expression. Together with physics Nobel Laureate Dr. Steven Chu, they recently developed a novel quantum-dot based technique to further define the APP-mediated impairment and with potential to provide a novel method to identify new drug candidates affecting the process. This mechanistic linkage between Down syndrome and Alzheimer's disease suggests that not only may individuals with Down

syndrome potentially benefit from the on-going research and development for new Alzheimer's disease drugs, but individuals with Alzheimer's disease may also benefit from DSRTF-supported Down syndrome research.

### GABAA INHIBITORS

*Another breakthrough study published this year, linked cognitive impairment of DS mouse models with an excitatory and inhibitory circuitry imbalance within the hippocampus. Results with administration of a specific drug, PTZ, suggest that inhibitors of GABAA receptors may reduce inhibitory circuit activity and show promise for improving cognition in DS.*

Building on earlier DSRTF-funded research by Dr. Mobley and collaborators, Dr. Garner and colleagues published exciting research results in April demonstrating that potential drug compounds which inhibit GABAA receptors, such as pentylentetrazole (PTZ), dramatically improve cognitive function in a DS mouse model. This DSRTF-supported research has advanced the field another promising step toward realizing an effective treatment to improve cognition in individuals with Down syndrome. Dr. Garner and his collaborators are continuing to test and evaluate the potential of these compounds for a new treatment strategy and gain further insight to how they produce effects on cognition. Further, while the trisomic gene(s) involved in the specific cognitive processes studied in this research remains unknown, their recently published studies sug-

gesting differences in the hippocampal pathology between two different mouse models of Down syndrome may help narrow the search for such genes.

### THE Shh PATHWAY

*A third breakthrough study demonstrated that a specific protein, Shh, a growth factor, is important in brain development and had a normalizing effect on the developmental process of the cerebellum in DS mouse models. DSRTF's most recent grant award is supporting investigation of whether Shh activators will produce analogous effects on the development of the hippocampus, and positively impact behaviors such as learning and memory in DS mouse models.*

At the end of September, based on the review and recommendations of the SAB, DSRTF awarded a \$250,000 research grant to Dr. Roger Reeves, Professor in the Department of Physiology and McKusick-Nathans Institute for Genetic Medicine at Johns Hopkins School of Medicine. Dr. Reeves' recent research discovered that a specific area of the brain, the cerebellum, is underdeveloped in a Down syndrome mouse model, analogous to observations in humans with Down syndrome. The studies by Dr. Reeves and colleagues

In describing promising research results, 'drug target' represents a specific gene, protein, or part of a cell pathway that interacts with a drug and results in amelioration of Down syndrome-associated effects on the brain and cognition.

# REMARKABLE EARLY SUCCESS

*continued*

*Con't from Page 3*

further led to the identification of a potential drug, a specific activator of the Shh (Sonic hedgehog) biological signaling pathway, which essentially normalized the development of the cerebellum in the mouse model. DSRTF funding for this new research program will significantly extend and accelerate Dr. Reeves' research to address two critical questions:

- *Does the potential drug compound, targeting the Shh pathway, correct the neurogenesis deficit in the Down syndrome hippocampus?*
- *Does the action of the potential drug compound acting through this pathway produce measurable positive effects on learning and memory?*

## NEW RESEARCH DIRECTIONS

### *Memory Function and Synapses*

Additional recently published DSRTF-funded research studies further define potential specific biological mechanisms underlying the cognitive impairment in Down syndrome. Dr. Dan Madison and his collaborators have discovered specific neuronal circuit abnormalities in a distinct area of the hippocampus, the CA3 region, in the Ts65Dn mouse model of Down syndrome which appear to result in "reduced-complexity networks" and may affect memory functions in Down syndrome. Interestingly, subsequent research in Dr. Madison's laboratory revealed parallel results relating to cognitive dysfunction in a mouse model for Fragile X syndrome. Dr. Mobley and colleagues also recently reported research studies analyzing genotype-phenotype relationships involving specific synaptic structural and functional alterations linked to cognitive dysfunction in two different DS

mouse models. Importantly, they also continue an intense pursuit to develop a more comprehensive model interrelating each of the identified dysfunctional mechanisms with cognitive impairment in Down syndrome. These studies are providing critical new experimental information with promise for identifying additional potential therapeutic targets.

## CONCLUSION

Recent research breakthroughs are serving as critical catalysts for new and expanded research that can yield the next critical advances. Significantly, this research has also focused attention, both in the public and biomedical communities, on the potential for innovative research strategies to yield effective new pharmaceutical interventions to ameliorate cognitive impairments in individuals with Down syndrome. Successful achievement of this goal will require coordination and increased research funding to sustain new discoveries and facilitate progression throughout the drug development pipeline – key thrusts in DSRTF's mission and strategy.

## DSRTF FY2007 Financial Highlights

>60% Revenue Growth

>80% of Expenditures  
Allocated to  
Research Programs

Grant Awards  
\$1,050,000



*Federal funding for DS research has steadily decreased and is currently estimated at \$13 million, or less than \$40 per individual. It is significantly under-funded compared to other conditions on a per capita basis:*

2008 FEDERAL FUNDING		
CONDITION	ESTIMATE	xDS
Cystic Fibrosis	\$2800	70x
Huntington's Disease	\$1565	38x
ALS	\$1480	37x
Multiple Sclerosis	\$280	7x
Down syndrome	\$40	1x

Source: NIH

## NEW JERSEY'S OWN JACK DEAN A DSRTF VOLUNTEER AND FUNDRAISER EXTRAORDINAIRE

Jack Dean, Executive Vice President of Power Battery in Paterson, NJ, has an adult son, Jarrett, with Down syndrome and continues to be a dedicated DSRTF volunteer spearheading informational and fundraising events in the NY/NJ area. Jack was recently interviewed by DSRTF:

*Q: How did you hear about and get involved with DSRTF?*

A: About 3 years ago, I started researching the link between Down syndrome and Alzheimer's disease and what I found scared me tremendously. I also stumbled upon some research being done at Duke by Dr. Priya Kishnani exploring Alzheimer's drugs to improve cognitive abilities in people with DS. I was really intrigued, so although I hadn't done something like this before, I called up Dr. Kishnani and asked if she would come up to New Jersey to give a presentation.

I started calling people I knew in the community and expected maybe 20 people to show up, but it ended up being closer to 100 people. What struck me was that no one knew there was any research going on for cognition in persons with DS. We were all just doing the regular therapies of PT, Speech, and OT, which are great and have certainly benefited my son. But for me there was this dark cloud of Alzheimer's looming out there, and I saw the effect happening on some of my adult son's friends and that's what made me spring into action. I kept researching and found out about DSRTF. I called (DSRTF Board members) Pat White and Patty O'Brien White from DSRTF and from them I learned about what Dr. Mobley was doing. I really liked that they had an

infrastructure with real goals -and I liked their focus.

*Q: Tell us about your recent fundraiser.*

A: After I met Pat White, I started to solicit groups for lunches to hear from her what Dr. Mobley was doing. I had a core group of people really interested in talking about DSRTF and I felt that now was the time to act on their enthusiasm. We set up a date for Dr. Mobley to come to New Jersey, sent invitations, called people, arranged for a donated very nice room and a caterer. Basically, I just made it up as I went along. We ended up raising over \$60,000 for DSRTF. My advice to other people is: a) Just jump in and do it, and b) Don't be heartbroken that not all the parents are falling all over you to give. And lastly, educate while you solicit funds from your friends and business associates as well as people in the DS community.

*Q: Tell us about your family and especially your adult son with Down syndrome.*

A: I have two sons: Jarrett who is 28 and has DS and Jonathan who is two years older. My sons are super, super close. Jonathan is very protective of his brother. They are both very athletic and Jonathan would always bring Jarrett along to basketball games. They have a special bond and see each other a lot. But Jarrett definitely has his own life!

Jarrett is very into Special Olympics, playing basketball, floor hockey, softball, and bowling. He is very outgoing, charming and has a stubborn streak. He's a fantastic dancer and usually the life of the party. He lives with my wife and me, downstairs in his own apart-



Jarrett Dean

ment. He works at my company, Power Battery, 5 days a week. He loves people and lives to be with them. He

is very close to the people he works with and they are like a second family to him. Jarrett definitely lives a full life every day.

*Q: Words of wisdom for other parents?*

A: I have a renewed interest in meeting younger families with children with Down syndrome because of DSRTF. I have been so inspired by their love and dedication as well as their enthusiasm. I would also love to see more parents of older children become involved with DSRTF.

There is a brighter future than there has ever been for children with DS. Not just with current research but also because of all the strides of the generation before. We have an obligation to bring the awareness of DS and what's possible to the next level. It doesn't take a lot to get involved. So, my words of wisdom are: get involved and don't wait for someone else to do it. And send money!



DONATE NOW  
*Be part of the breakthrough.*

[WWW.DSRTF.ORG](http://WWW.DSRTF.ORG)

# 2007 EVENT HIGHLIGHTS



## 2<sup>ND</sup> ANNUAL ROMP FOR RESEARCH WEEKEND

New York, New York

The weekend started on Friday evening with a reception and informational research presentation on Down Syndrome Cognition Research by special guest speaker Dr. William Mobley, Director of the Center for Research & Treatment of Down Syndrome at Stanford University. The reception was held at

Proskauer Rose LLP in downtown New York City and was open to professionals, parents, friends, relatives and supporters of people with Down syndrome. Following the Friday evening research presentation, friends and family were invited to join DSRTF, Anna's Amigos, and Troy's Boys and Girls for the 2nd Annual Romp for Research.

The New York Area Romp for Research is a festive, family-fun event that raises awareness and support for Down syndrome cognition research and the Down Syndrome Research and Treatment Foundation. On September 16, more than 700 participants at the 2007 Romp for Research enjoyed arts & crafts, non-competitive sporting activities, fire engines courtesy of the NYC Fire Department and dazzling basketball tricks performed by the famous Hood Wizard! DSRTF extends its thanks to all the participants and very special thanks to all our donors and corporate sponsors for making this year's event a spectacular success!

For more on the 2007 Romp for Research, including photos, donors and sponsors, and to find out how you can get involved in next year's 2008 Romp for Research, please visit [www.rompforresearch.com](http://www.rompforresearch.com).



*Na'eem Salaam, DSRTF Executive Director, Jane Leeves, Dr. Michael Harpold- DSRTF CEO*

## DSRTF AT THE FAMOUS HOLLYWOOD BOWL

On August 28, 2007, the famous Hollywood Bowl set the stage for the Down Syndrome Research and Treatment Foundation's Second Annual Southern California Event- One EXtra Reason to Live . . . Love . . . Hope. Located in Hollywood, CA this year's event was hosted by the lovely and talented actress Jane Leeves, well known for her work as "Daphne Moon" on the NBC hit sitcom *Frasier*. Jane welcomed over 120 guests who were eager to hear updates on the on the current state of Down syndrome-related cognition research by Dr. William Mobley, Director of the Stanford University Center for the Research and Treatment of Down Syndrome and supported by DSRTF.

The Down Syndrome Research and Treatment Foundation especially thanks Suzanne & Erik Lezotte, Steve Monarque, Jennifer Caras, Jen Burns, Martha Winterhalter, Susan Pickert, Kathy O'Connor, Lazaro Mesa, An Tran, and the rest of the Southern California DS Research Committee for their dedicated efforts in organizing such a fabulous event. DSRTF is also sincerely grateful to our corporate sponsors whose generosity turned the event into a magical evening- House of Blues, The Standard, Kodak, The American Society of Cinematographers, Ferrett Mobile, Deluxe, PanaVision, Sandals Resorts, and Alicats Winery.

Finally, DSRTF extends a very special thanks to our host for the evening, Jane Leeves. Jane truly did a marvelous job and is helping propel Down syndrome research to the next level of awareness and further advances. Not only did Jane host the event, but her two children, Isabella and Finn Coben, organized their own fundraising initiative by creating a lemonade stand to raise funds to support DSRTF's research efforts!

# 2007 EVENT HIGHLIGHTS

*continued*

## New Jersey Golf Tournament A Letter from Lisa Piserchio

On July 20, 2007, our 2nd Benefit Golf Outing took place at Shawnee Inn and Golf Resort in Shawnee, PA. With help from Bob Law, Kristen Zekunde, Jack Dean and many others, the event was a huge success! We doubled our hole sponsorships and had 98 golfers compared to 68 last year. I was so happy to have received such wonderful support from both friends and family! With the support from several companies and local businesses, we were able to raise over \$13,000 for DSRTF!

Spreading awareness about DSRTF has become such an important part of my life and it has given me the hope that one day it will not only make a difference in my own son's life but also in the lives of everyone living with Down syndrome. Once again, thanks to everyone who made this another wonderful outing!

- Lisa, Mark & Little Sal

## Bubblemania- Who loves Bubbles!!!

In April of this year, Markley Rizzi, her family, and a dedicated group of volunteers organized a special event, "BubbleMania" to entertain children and adults of all ages! The award winning bubble artist Casey Carle provided an evening of laughter, music, and amazement!

## The Diercksens' First Birthday Party!

Congratulations to the Diercksens who recently welcomed a beautiful new addition to their family. In honor of their son's first birthday, the Diercksens organized and hosted a "DSRTF birthday party" where in lieu of gifts, party goers donated to DSRTF!

## Annual DSRTF Boston Charitable Golf Tournament

On September 23, 2007 Board member Roger Kafker again hosted the 5th Annual DSRTF Boston-area Charitable Golf Tournament at the spectacular Stow Acres Country Club in Stow, MA. This year more than 70 players enjoyed a beautiful Fall day of golf followed a catered luncheon and lively auction. The auction included donated tickets with enviable VIP seating and experiences for World Series-winning Boston Red Sox, Boston Celtics, New England Patriots, and Boston Bruins games. The auction also included a football autographed by Doug Flutie and Gerard Phelan, of the 1984 Boston College "Hail Mary" pass fame, and tickets to the Boston College vs. Miami game at the end of November. DSRTF sincerely thanks all of the corporate sponsors, donors, players and participants for making this another truly successful and enjoyable DSRTF fundraising event!

## FUTURE DSRTF EVENTS HOW YOU CAN HELP

DSRTF is in the process of organizing and planning a multitude of new events and activities in 2008 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](mailto: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**

## 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!*



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

## DID YOU KNOW...

As recently as 2004 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 and development. After three years and over \$3 million generated by DSRTRF for critically targeted new research, dramatic progress has been made. There are now three independent studies showing the promise for improving cognitive function in those with Down syndrome.

