Jerome Lejeune FOUNDATION USA
Research Care Advocacy

JLF USA NEWSLETTER
Summer 2015

Committed to those with Down Syndrome and other genetic intellectual disabilities

HAPPY BIRTHDAY, JEROME LEJEUNE!

June 13, 1926 - April 3, 1994

June 13th would mark Dr. Jerome Lejeune's 89th birthday, so in honor of his life and legacy as the Father of Modern Genetics, we are dedicating this newsletter to a topic he was passionate about- research, and the hope it provides to people living with genetic intellectual disabilities.

When Jerome Lejeune counted the 47th chromosome in 1958 and identified the genetic cause of Down syndrome, he knew he had discovered an opportunity for researchers to investigate what he hoped would someday be a "cure." As time progressed into the late 1960s, a very real threat emerged. Amniocentesis was used in 1968 for the first time to diagnose Down syndrome in the womb. Just a couple of years later there was a push to legalize abortion in France, and babies prenatally diagnosed with Down syndrome became the first targets. Jerome Lejeune was heartbroken that his discovery could be used to selectively terminate a pregnancy prenatally diagnosed with Down syndrome, but he was confident that research would one day remove any reason a parent would feel compelled to make that drastic decision.

Dr. Lejeune's future as a physician and researcher was decided when a young patient ran into his examination room one day. Throwing his arms around him, he said, "You have to save us because they want to kill us." The young patient had seen a debate on television the evening before, debating what we now call disability selective abortion. Dr. Lejeune knew what he must do.

After Jerome Lejeune died in 1994, this same determination set the course for the Jerome Lejeune Foundation. The Jerome Lejeune Foundation is first and foremost a research foundation because for us, research can be a powerful tool for advocacy. It holds potential to improve lives, and to be an antidote to the problem of prenatal diagnosis and abortion.

Like Jerome Lejeune, the Foundation is narrowly focused on improving the lives of children and adults living with genetic intellectual disabilities through medical research into targeted treatments to improve cognition. We are also focused on advancing prenatal therapies that may one day soon offer families the real hope that after an early prenatal diagnosis, their child may develop typically in the womb and be born healthy and strong.

Without our philanthropic partners, this research would not be possible. By working together, we can secure a better future for children born with a genetic intellectual disability. Together, we can remove a parent's fear and uncertainty after a prenatal diagnosis. And, together, we can make Dr. Jerome Lejeune's dream for the future a reality!

Research as Advocacy

"If we don't cure them of their innocence, there will be another massacre of the innocents."

-Dr. Jerome Lejeune

In July 2013, headlines began to proclaim that a cure for Down syndrome had been discovered. Dr. Jeanne Lawrence at the University of Massachusetts, Worcester had discovered a way to completely silence the extra 21st chromosome in an induced pluripotent stem cell line generated from an individual with Down syndrome. Dr. Lawrence made clear that her discovery was in no way a "cure," but the headlines that followed the publication of her research incited some lively exchange among advocates regarding what a "cure" might mean for the Down syndrome community.

When we published our very first newsletter after opening the U.S. office of the Jerome Lejeune Foundation, we used a well-known phrase of Jerome Lejeune as our headline: "The only way to save them is to cure them." It was not long until we received a phone call from the director of a Down syndrome advocacy organization wanting to know what we meant by that phrase. He said that if the goal of the Jerome Lejeune Foundation was to "cure" Down syndrome, then we would not have their support. He said that self-advocates (Down syndrome advocates who themselves have Down syndrome) were happy with their lives and did not believe there was anything that needed "curing."

While some people living with Down syndrome share this view, it is not the opinion of everyone. In the documentary film *Crash Reel* about the life of Olympic half-pipe legend, Kevin Pearce, Kevin's brother, David, who has Down syndrome, is asked about his disability. He very powerfully says on camera:

I don't like it. I hate it. I want my disability to go away and not come back. I know that I have it. It's really hard to have it. Sometimes I feel stressed out about it and sometimes I feel anxiety about it too. I go to my room and hang out there and cry sometimes, and then I perk up, come downstairs and move on to a different day.

David Pearce is not alone in regretting that he has to live with Down syndrome, but often the voices of those who long for treatments that would improve their cognitive capacity are lost among the voices of advocates working to further acceptance and inclusion. Some parents and other advocates deny that Down syndrome is a genetic anomaly and insist it is a natural part of human variation. Some reject the efforts of research to improve cognition, claiming that it is a form of "positive eugenics." Others fear that a drug to improve their child's cognition will change their child's personality that they have come to love deeply.

The reasons why we might want to "cure" Down syndrome:

When the debates were active around what a cure would mean to the Down syndrome community, we spoke out in support of research with what we believe are three very good reasons of why we might want to "cure" Down syndrome. Those reasons were these:

1. **Down syndrome is a neurodegenerative disorder.** The metabolic imbalance caused by living with an entire extra copy of a chromosome is devastating over time. The beauty and simplicity we appreciate in children with Down syndrome gives way to more rapid aging than is experienced in the typical population, and often includes severe withdrawal, cognitive decline, and early dementia. **Researchers** are addressing this metabolic imbalance and are beginning to identify potential solutions to these problems.

2. **The majority of women who receive a prenatal diagnosis of Down syndrome choose to terminate their pregnancy.** Roughly 67% who choose to abort a child with Down syndrome in the U.S. are aborting an otherwise wanted child solely because of the result of a prenatal diagnosis, and because they fear what the future may bring. **Researchers** are working to identify prenatal therapies that have been shown to practically "normalize" the birth and early development of mouse pups that have been genetically designed to mimic Down syndrome. We may soon be able to offer the same treatment to humans, bringing to an end that agonizing decision so many fear.

[1] Positive eugenics is defined as a social philosophy that advocates for the improvement of human genetic traits by promoting higher reproduction among people who have desirable traits.

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Research as Advocacy Cont.

3. **Those living with Down syndrome are people too.** Perhaps most importantly, we cannot forget the humanity of people living with Down syndrome. They have the same hopes and dreams, the desire for autonomy, clear expression of their feelings and ideas, love, and companionship as everyone else. They deserve to be able to participate as fully as possible in their communities. **Researchers** believe that even the early round of therapies currently in, or approaching clinical trial, might improve cognition by 15-20%. In a population that is identified as having mild to moderate intellectual disability, that boost could make a HUGE difference in their quality of life.

Those living with Down syndrome are remarkable people who bring so many positive qualities to the lives of those who know them. While research to identify treatments to improve cognition may not be for everyone, there are many like David Pearce out there who long for the day when research will provide access to meaningful work, independence, better health, intimate relationships that do not depend on family for support, and a future that does not include the strong possibility of dementia or other complex neurological conditions.

Prenatal Diagnosis and Abortion

A New Paper Clarifies the Facts

When talking about Down syndrome and abortion, the statistic most commonly cited in the U.S. is 90%. However, a paper was recently published in the *American Journal of Medical Genetics* that shows that the actual number is considerably less.

The study, conducted by Gert de Graaf, Frank Buckley, and Brian Skotko, applies rigorous statistical modeling to diverse data sets in an attempt to provide the most accurate number possible, and for one primary reason: So we can determine - over time - the impact emerging noninvasive prenatal screening (NIPS) technologies will have on the termination rate after a prenatal diagnosis of Down syndrome.

So what is the number? For the most recent years (2006–2010), the researchers discovered that:

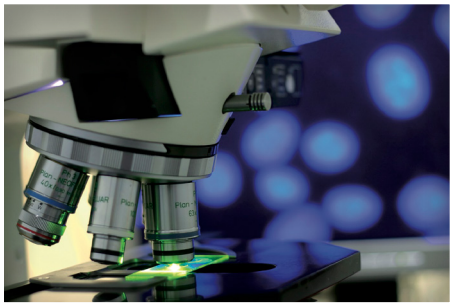
- The estimated live birth prevalence for DS was approximately 12.6 per 10,000, or a total of around 5,300 births each year;
- The number of pregnancy terminations following prenatal diagnosis is estimated at 3,100 each year;
- Taking natural losses into account (miscarriage), the authors estimate that there would have been 7,600 live births each year in the absence of prenatal diagnosis that resulted in abortion.

The authors have determined that the population of individuals living with Down syndrome is 30% lower than it would be if there was no prenatal diagnosis that results in abortion. This study validates an earlier 2012 study that claimed the abortion rate in the U.S. following prenatal diagnosis is around 67%.

So, where did the 90% number come from? From a 1999 European study that included little data drawn from the U.S. Since it is not an accurate representation of the situation in the U.S. it should no longer be used. In fact, continuing to use the 90% statistic could be counterproductive to the end that advocates desire. If families who receive a prenatal diagnosis hear that 90% of families decide to abort, the pressure on them to do the same is tremendous. Many might wonder who their child's peers would be, what support services might be available for such a small population, and if their family would be outcast in society for making such an unusual choice.

The Jerome Lejeune Foundation's goal is to use this new benchmark as a watershed point to show the success of our efforts and an increase in births over time, rather than a decrease. We firmly believe that can be accomplished through Down syndrome prenatal information laws that we are involved in promoting to not abort but to accept and love a child, and through research into prenatal therapeutic interventions that will provide hope and encouragement to families.

Research: Targeting Cognition in Down Syndrome



Researchers have identified certain genetic targets that they believe are responsible for intellectual disability in Down syndrome. Understanding research can be difficult, but we have tried to provide a simplified, brief explanation of three of those targets, including a short description of the research being done in each.

GABA

GABA is short for *gamma-Aminoburtrytic acid*. It is an inhibitory neurotransmitter, and its role is to suppress the excitability of neurons in the central nervous system. Normal neurotransmission relies on a balance between GABA and an excitatory neurotransmitter called glutamate. In simple terms, GABA helps put the brakes on the communication between neurons (the cells that transmit nerve impulses) so that neurologic processes flow smoothly. It has long been thought that individuals with Down syndrome have an imbalance in the GABAergic system, and therefore too much inhibition (slowness) in neurotransmission. However, recent research funded by the Jerome Lejeune Foundation has challenged that notion and suggests that GABA in those with DS may actually be excitatory, rather than inhibitory. (see *Breaking Developments* later in this newsletter)

Some researchers believe that rather than looking to specific genes to improve cognition, it would be better to focus on balancing the GABA system. To accomplish this, they are looking at drugs called inverse agonists, or antagonists, that will put the brakes on GABA to reduce its excessive inhibitory effect. Drugs currently being investigated in clinical trials by Roche and Balance Therapeutics are in this family of drugs.

DRK1A

Dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1a (isn't DRK1A much easier?) is a gene that resides on chromosome 21, and through mouse studies has been shown to contribute to cognitive disability in Down syndrome. The Jerome Lejeune Foundation is deeply involved in supporting research on DRK1A, and we have written about our supported projects in past newsletters. The Foundation has been supporting Drs. Mara Dierssen and Rafael de la Torre in a clinical trial on the use of EGCG (an antioxidant in green tea), and also the development of a new drug to regulate the gene through our partnership with ManRos Therapeutics.

In investigations on mice, resolving the overdosing of DRK1A to improve cognitive function is easy. As researchers say, you just "knock out" the extra copy of the gene by removing it through a breeding process. Of course, that is not possible in humans, so drug therapies that regulate DRK1A are the solution.

APP

The link between Down syndrome and Alzheimer's disease has become broadly discussed and is now closely investigated by researchers working in both areas. The way the body processes APP (*Amyloid precursor protein*) is known to be responsible for the accumulation of amyloid plaque and neurofibrillary tangles within the brain. Since APP is a gene on the 21st chromosome, those with Down syndrome have three copies of the gene rather than two; and therefore, the problem is exacerbated for these individuals. Researchers claim that all those living with Down syndrome will have the neurological features of Alzheimer's disease by the time they are 35 or 40 and some 80% will experience dementia later in life!

DRK1A may have a relationship to APP in that DRK1A is responsible for something called phosphorylation, a process that turns protein (like APP) on and off. Since DRK1A is over-expressed in those with DS, some believe its affect on APP may be the cause of the excessive accumulation of neurological plaques and tangles that occur in these people. Maybe if we can regulate DRK1A, we can re-balance APP too!

Targeting Cognition in Down Syndrome Cont.

The TRIAD program being funded by the Jerome Lejeune Foundation is developing a new drug that we believe will regulate DRK1A, and also impede the development of Alzheimer's disease in those with Down syndrome.

Transition Therapeutics (Elan Corp) completed a phase 2a study of their drug ELND005 on patients with Down syndrome in April 2014. ELND005, or scyllo-inositol, is thought to decrease the accumulation of amyloid.

Featured Researcher

Mara Dierssen, PhD, Center for Genomic Regulation in Barcelona, Spain

In our experience, medical researchers are passionate, engaging, and creative people who are wholly devoted to improving the lives of the people they serve. This is especially true in the fairly small Down syndrome research community, and could not be more descriptive of Dr. Mara Dierssen, head of the neurobehavioral analysis group at the Center for Genomic Regulation in Barcelona, Spain.

To say that Dr. Dierssen is lively and passionate about what she does would be an understatement. As proof of her commitment and diverse interests, Dr. Dierssen - in her free time - encourages young people in neuroscience research through programs in Barcelona, and performs with a rock band that has recorded a CD of music written by people with Down syndrome. Proceeds from her band's performances are often used to support research to improve intellectual disability.

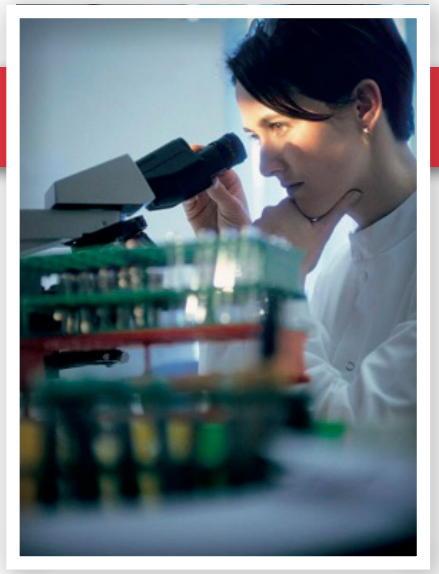
Dr. Dierssen's pioneering research into the use of a natural antioxidant in green tea called EGCG (Epigallocatechin gallate) is better known to the international community and to families in the United States. In 2010, the Sisley-Jerome Lejeune Prize was awarded to Dr. Dierssen for her ground-breaking contributions to the development of research in cognitive disability.

We have discussed elsewhere in this newsletter the DRK1A gene and its role in intellectual disability in Down syndrome. Initial research conducted by Dr. Jean Delabar confirmed DRK1A as a suspect, and it is he who first identified EGCG as a possible candidate for treatment use. Dr. Dierssen's work has built upon the initial investigations of Dr. Dalabar. With her colleague, Dr. Rafael de la Torre, they have taken EGCG to the clinic and ran a successful clinical trial funded largely by the Jerome Lejeune Foundation. In their initial trial, a group of 87 patients from 18 to 30 years old were enrolled and given EGCG in conjunction with a regimen of brain stimulating exercises. The first analysis of the data from this trial has been promising and a publication is pending. Meanwhile, plans are underway for a follow up trial that will include 2 groups of children- the first from 2 to 6, and the second from 6 to 12 years of age. The Jerome Lejeune Foundation will be supporting Dr. Dierssen once again in her pursuit of treatments to improve cognition in individuals living with Down syndrome.

Dr. Dierssen is appreciative of the support of the Jerome Lejeune Foundation and its confidence in her research. Likewise, the Foundation appreciates Dr. Dierssen's contributions to the field of research and her whole-hearted commitment to improving the lives of people living with genetic intellectual disabilities.

You can view a 2011 interview the Foundation conducted with Dr. Dierssen in which she discusses the focus of her research. https://youtu.be/LKVGSlcOuQE

Breaking Developments



A new study funded by the Jerome Lejeune Foundation calls into question the role of GABA in intellectual disability in Down syndrome.

Earlier in this newsletter we described GABA as one of the targets for researchers to improve cognition in individuals with Down syndrome. GABA has been thought by researchers to be excessively inhibitory in individuals with Down syndrome, but recent research funded by the Jerome Lejeune Foundation and published in the journal *Nature Medicine* has raised questions regarding that hypothesis and suggested that it may, in fact, work in the opposite way. It may be excitatory.

What does this mean for people living with Down syndrome? Well, potentially a lot! In the first place, it could have a considerable impact on the kinds of drugs being investigated that are targeting the GABA system. Another finding of the research team in Genoa is the most significant for people living with Down syndrome. They discovered that the use of a drug already approved by the FDA called bumetanide was effective in improving neurological activity, synaptic plasticity, and some types of memory in mouse models of Down syndrome. If that result could be translated safely into humans, the benefit could be considerable.

Of course, this research will need to be verified in other studies, and it will be interesting to see the results of drugs already in clinical trial whose purpose is to suppress GABA. If they are proven to be effective, then there will be many more questions about the role of GABA and future research into potential treatments.

To the Least of These...

A documentary film has been made to celebrate the 20th anniversary of the death of Dr. Jerome Lejeune. We were privileged to premier the film in Washington, DC on May 6th and the response was enthusiastic to say the least. It will have its second U.S. showing at the National Down Syndrome Congress in Phoenix at the end of June.

To the Least of These My Brothers and Sisters chronicles the life of Dr. Jerome Lejeune, the Father of Modern Genetics, and contains numerous interviews with former colleagues and parents whose lives were changed by knowing Jerome Lejeune. The film discusses the importance of his discovery of the genetic cause of Down syndrome, and presents the controversies that arose in France during his opposition to his discovery being used to selectively terminate Down syndrome pregnancies. Attorneys representing both parties in the Davis case in Maryville, TN, the first legal test of the person-hood of the human embryo, are interviewed, as are current researchers who reflect on the important legacy of Jerome Lejeune.

We would be happy to work with you to arrange a screening in your area. If interested, please contact us at 267-403-2910 or contact@lejeuneusa.org.

Ways YOU Can Help

Become a Donor
YOU are the Jerome Lejeune Foundation. Your gift supports our mission of research, care, and advocacy following the medical and ethical standards of Dr. Jerome Lejeune, the "father of modern genetics." Please make a tax-deductible contribution today.

Become a Volunteer
Contact us at contact@LejeuneUSA.org to join our network of volunteers and advocates.

Invite us to a Meeting
If you are a member of a local Down syndrome support group, we would love to learn more about your work and tell you about the work of the Foundation.

Spread the Word
Pass this newsletter on to families you know who might be interested in joining us in our exciting work.

Want to Learn More?
To learn more about the important research we fund, read stories about the care we provide and explore and join our network, visit our website at **www.LejeuneUSA.org**.

Giving to JLF USA
The Jerome Lejeune Foundation USA is a registered 501(c)(3) charitable organization. All contributions made to the Foundation in the U.S. are fully deductible from federal income tax.

YOU are the Jerome Lejeune Foundation. TOGETHER we can do amazing things!

Checks are welcomed at the address below, or you may go to the following link to contribute online: ***www.LejeuneUSA.org.***

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Pioneering Innovative Therapies

to improve the lives of those with genetic intellectual disabilities

Created in 1996 in Paris and in 2012 in the United States, the Jerome Lejeune Foundation is registered with the Internal Revenue Service as a 501(c)(3) nonprofit corporation serving those with genetic intellectual disabilities and their families...

Research in order to identify targeted treatments for patients affected by genetic intellectual disabilities. The Jerome Lejeune Foundation is the world's largest private funder of research on trisomy 21 (Down syndrome) and other disabilities. The Foundation funds projects in basic science, and also early clinical trials on drugs that offer hope that commercially available products will one day be available to improve the lives of those affected by genetic intellectual disabilities.

Care to provide specialized medical treatment and follow-up throughout the patient's life. The U.S. Foundation is involved in improving medical education and developing guidelines for care of individuals modeled after the work of the Lejeune Institute in Paris, a medical clinic which provides care to over 6,000 patients.

Advocacy for the fundamental human rights of persons with genetic intellectual disabilities. The Jerome Lejeune Foundation is committed to the inherent human dignity of all persons and the protection of life from conception to natural death.

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