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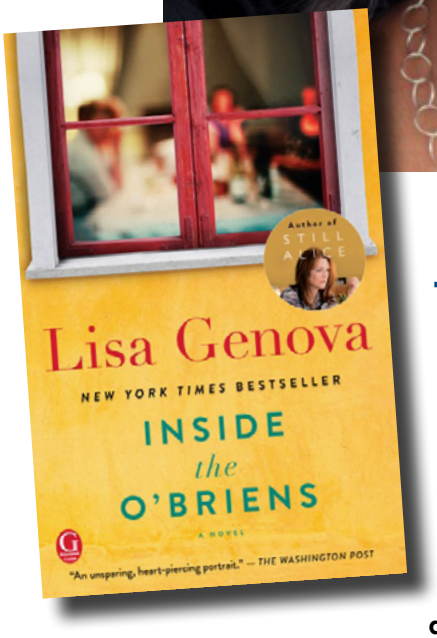
EHDN News

EUROPEAN **HUNTINGTON'S DISEASE** NETWORK



The power of fiction

In a piece written exclusively for this newsletter, American neuroscientist and author Lisa Genova talks about why she uses fiction to explore the subject of neurological disease. Her first novel, the bestselling *Still Alice*, dealt with Alzheimer's disease and was made into an award-winning film starring Julianne Moore. Lisa's latest novel, another bestseller called *Inside the O'Briens* (Gallery Books, 2015), tells the story of a family, the O'Briens, affected by Huntington's disease.

My first year out of college, I worked as a lab technician in a neurobiology lab researching drug addiction. I was 22 years old in February 1993 when the scientists down the hall began celebrating. They had just isolated the genetic mutation that causes HD. I remember getting very still, the goose-bumps on my arms, knowing I was witnessing a historic moment in all of neuroscience. Only one thing causes HD, and these scientists had just discovered it. Surely, there would be a cure for HD. We are now 23 years later, and we still don't have a treatment or cure.

Calling all HD researchers… use our data!

The EHDN is soliciting data mining proposals for 2016.

See page 2 for details.

CONTENT — Click the Page

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I've found that fiction is a powerful way in. Stories are accessible. Unless you're a geeky neuroscientist like me, you're probably not going to read the *Journal of Neuroscience* to learn about Huntington's disease. But you might read a novel called *Inside the O'Briens* (and I hope you do!). My role is to tell the truth under the imagined circumstances of my novels, to write informed fiction, to give the reader real medical information, but to package it in an accessible, human story that we can all relate to. I wrote *Inside the O'Briens* to hopefully create some much-needed awareness about a disease most people know little about.

And I've found that awareness and conversation are critically necessary steps in the march toward treatments and survivors. Historically, we've seen this with cancer and HIV. Awareness, open conversation, lifting the shame, secrecy, and stigma, acknowledging that the disease exists, are essential to developing treatments that lead to survivors. It's impossible to cure something that seemingly doesn't exist. A sense of urgency is needed. We're seeing this urgency happen with Alzheimer's, a disease we've all been terrified to openly talk about. *Still Alice* is playing a role in this, acting as a vehicle for conversation, for breaking down isolation and fear.

Inside the O'Briens is about Huntington's, but it's also about what's inside us and what gets passed down through the generations—not just our DNA, but also our faith, humour, resilience, love, gratitude. It's about how to find hope in a situation that appears hopeless. It's about finding courage when you're completely vulnerable. It's about learning to live in the moment. The future is a fantasy—only the present moment is real.

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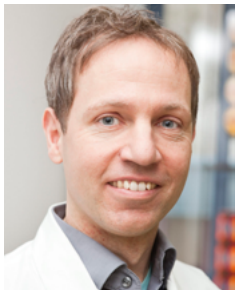


Calling all HD researchers... use our data!

Patrick Weydt, Chair,
EHDN Scientific and Bioethics Advisory Committee

The EHDN is soliciting data mining proposals for 2016. Through its Europe-wide network of HD centres, EHDN has generated a rich set of clinical data and biomaterial from HD patients. Longitudinal data collected from thousands of participants over the past 10 years, first in the context of the Registry observational study and then in its successor Enroll-HD, have been curated extensively by trained monitors and the network's Central Coordination (CC). This unique dataset is available to EHDN centres and the broader scientific community for investigator-initiated research, and data mining projects are a mechanism within the EHDN platform that offers them the possibility of accessing and analysing it.

The active participation of researchers is essential if the full potential of the network to benefit HD families is to be realised, and we encourage them to make use of this mechanism. The formal requirements for application are kept to a minimum and there are no deadlines. Efficient review by the Scientific and Bioethics Advisory Committee and Executive Committee insures that ethical and scientific standards are maintained without impairing a proposal's momentum. Details of how to apply can be found here, and CC representatives Christine Capper-Loup (christine.capper-loup@euro-hd.net) and Michael Orth (michael.orth@uni-ulm.de) are available to guide investigators through the process from application to data analysis.

European HD Youth Camp 2016

HUNTINGTON'S DISEASE YOUTH ORGANIZATION

The HD Youth Organisation (HDYO) and its European HD association partners are excited to announce the European HD Youth Camp for 2016. The goal of the camp is to offer young people aged 15 to 25 the chance to meet others of their age affected by HD, to learn about the disease through educational workshops, to share their experiences and to have fun participating in the many on-site activities, including ropes courses, archery and more. The camp will be held at Grosvenor Hall in Kent, UK, from 7 to 13 August, and the language spoken will be English. Camp, food and travel costs will be covered for those whose applications are successful. More information and details of how to apply can be found here.

Photo: ARTIFOX, Gabriele Stautner

Update: clinical trials

Jenny Townhill and Tim McLean,
Central Coordination

The business of finding novel treatments for HD continues apace. A precautionary dose modification and a name change are among the latest developments.

LEGATO-HD: On 4 January 2016, Teva Pharmaceuticals announced the discontinuation of testing of the highest doses of laquinimod in two ongoing studies of the drug for multiple sclerosis (MS). This was in the wake of the reporting of cardiovascular events, none of them fatal, in eight patients receiving 1.2mg and 1.5mg doses in those trials (no such events occurred in the 0.6mg or placebo groups). The mechanism of these cardiovascular events is so far unknown. Duration of exposure to laquinimod does not seem to have played a role, although cardiovascular risk factors and demographics may have. In LEGATO-HD, a Teva-sponsored, phase 2 safety and efficacy study of the same drug for HD, no cardiovascular events had been reported at any dose as of 10 January 2016. However, as a pro-active safety measure for patients participating in the study, the company has modified the trial design to discontinue the highest of the three dose arms (1.5mg/day) while maintaining the other two (0.5 and 1mg/day). All participants in the high-dose group have been informed and have stopped taking the study medication, though they have been invited to continue to attend follow-up safety visits. Additional safety measures and enhanced safety monitoring will be added to the study for the protection of patients who continue to participate.

Pride-HD: The end of 2015 saw intense activity in this phase 2 dose-finding and safety study of pridopidine, also sponsored by Teva, as six months' worth of trial data were cleaned and signed off ahead of a database lock. The target date was met thanks to the hard work of everyone involved, and data analysis has been underway since January. We hope to be able to report preliminary findings in the next edition of the newsletter. The open-label extension trial of pridopidine, **Open Pride**, is now enrolling and will run until at least 2017 (depending on the preliminary findings from Pride-HD). Nearly all participants in Pride-HD have expressed a desire to continue in the open-label phase.

Amaryllis: This trial of a PDE10 inhibitor sponsored by Pfizer is on target to complete recruitment this spring. A 12-month, open-label extension study is underway and will be completed in 2017.

IONIS (formerly ISIS): four participants have been randomised to the antisense drug IONIS-HTT_{Rx} or placebo groups, in this phase 1/2a trial of a potentially disease-modifying treatment, and no safety issues have been reported. Recruitment for the second cohort began early in 2016, following a review of safety data. The company sponsoring the trial, Ionis Pharmaceuticals, recently changed its name to avoid distraction from its goal of developing potentially life-saving therapies.

PEARL-HD: Analysis of the final patient cohort, in this CHDI-sponsored PET imaging study of levels of the PDE10A enzyme in the brain, is planned for completion early this spring. The **LONGPDE10** follow-up study has started recruitment and will continue into 2017.

For more information about these clinical trials, please visit: http://clinicaltrials.gov

Update: Enroll-HD

Olivia Handley, Global Project Manager, Enroll-HD

In the last newsletter we announced that two platform study proposals had been approved by the Enroll-HD scientific planning committee—a cerebrospinal fluid collection study called HDClarity, and a study evaluating the impact of choosing, or not, to have predictive testing for HD. Both studies have now been carried forward for implementation.

Platform studies make use of the Enroll-HD network and database—the "platform"—and facilitating them represents one of Enroll-HD's key aims. As Enroll-HD comes close to recruiting its 10,000th participant, any platform study that is approved has the unique advantage of being able to capitalise on a formidable research infrastructure that serves the global HD research community.

HDClarity will recruit up to 600 HD participants at different disease stages, and control participants, from roughly 30 sites around the globe. Since many of the core assessment data it requires have already been collected within Enroll-HD, those data are already available to it. In addition, data and samples collected specifically for HDClarity will be integrated to the electronic data capture (EDC) system used by Enroll-HD, which means that any site taking part in both studies will be in a position to recruit eligible Enroll-HD participants to HDClarity as well.

An important caveat to this streamlining of the two studies is that any site joining HDClarity must go through start-up as it would for a brand new study. This means, for example, that ethical review and approval must be obtained independently of Enroll-HD, that HDClarity-specific site contracts must be in place, and that site training and initiation will be coordinated by HDClarity's central coordination team, which is based at University College London in the UK. Any prospective recruit to HDClarity must already be a participant in Enroll-HD, and importantly, he or she is asked to provide separate, full informed consent ahead of joining the study.

Making HDClarity operational within the Enroll-HD platform has required considerable collaborative effort. The two study teams have worked closely together to develop the EDC system so that sites can recruit participants to HDClarity with ease and efficiency. This system is currently undergoing internal review to ensure that it is functioning optimally by HDClarity's "go live" date in the spring of 2016.

The second approved platform study, entitled "Why at-risk individuals choose to have or not to have predictive testing for HD", is also in the planning stage. This study, which is led by Martin Delatycki and Andrew Churchyard, both of whom are based in Australia, will require individuals who have undergone testing (either confirmed mutation expansion carriers or non-mutation expansion carriers), along with individuals at risk of developing HD, to complete a questionnaire. The goal is to identify the individual factors that drive choosing, or not, to have predictive testing. Efforts are underway to build the study into the EDC and it is expected to be launched in the second half of 2016.

Roundup: funding news

Fionnuala Margreiter, Grant Manager

News

- Emma Yhnell, Anne Rosser, Monica Busse and Claudia Metzler-Baddeley of Cardiff University in the UK have been awarded research funding by the Jacques and Gloria Gossweiler Foundation to investigate cognitive training in people with HD. Their project will explore the feasibility and acceptability of using computer games that focus on attention to "train the brain".

- EHDN and the European Huntington Association are participating in the setting up of a new European Reference Network on rare neurological diseases. The idea behind these networks is to bring together Europe's top specialists to tackle complex or rare medical conditions that require highly specialised healthcare and a concentration of knowledge and resources.

- The Polish Huntington's Disease Association has received a small grant of EUR4,800 from the Bratislava-based Visegrad Fund. This will finance a workshop on the contribution to be made by Visegrad countries (the Czech Republic, Hungary, Poland and Slovakia) to the new European Reference Network on rare neurological disorders.

- Are you interested in getting involved in an EU Horizon 2020 project, perhaps initially as a partner to gain experience? If so, then get networking! Develop your contacts across disciplines, present at conferences, attend Horizon 2020 events in your country. Take a look at the conferences advertised at the end of this newsletter: have you submitted an abstract?

Follow me on Twitter **@EHDN_GRANTM** for the latest news on EU funding and events and policy developments in the domain of rare diseases.

Funding opportunities

- The Huntington's Disease Society of America (HDSA), along with the Berman and Topper families, are offering three-year grants of up to USD80,000 a year to young scientists from around the world who are embarking on a career in HD research. The next deadline for applications is soon, **14 March 2016**, so hurry!

- The European Molecular Biology Organization (EMBO) awards short-term fellowships for exchanges between two laboratories in different countries. There is no deadline for applications, but it is recommended to apply **three months before** the proposed starting date. Other funding opportunities are also available (see EMBO website for details).

- The Ireland Funds offer small grants to Irish researchers. The next deadline is **4 April 2016**.

- The international Visegrad Fund offers small (less than EUR6,000) and standard (more than EUR6,001) grants to support a common workshop/seminar or a project. There are four **annual deadlines** for applications for small grants, and two for standard grants.

- The Human Frontier Science Program (HFSP)'s guidelines for its 2017 Program and Young Investigator applications are available. Applications are made via the HFSP extranet website which is now opera-

tional. You must register and obtain a 2017 reference number via the website by **21 March 2016**. The deadline for submission of letters of intent is **31 March 2016**.

- The Rosetrees Trust in the UK supports research into all aspects of biomedical science. It provides small grants of, typically, between GBP5,000 and GBP20,000 per year for up to three years, and is mainly though not exclusively targeted at research conducted in the UK. Applications are accepted **any time**; the review committee meets every two months.

- Up to CHF30,000 is available to Swiss researchers who want to organise a 2-5 day international exploratory workshop in Switzerland, with colleagues who work in their field abroad. The next deadline for applications is **1 June 2016**.

- The Thyssen Foundation supports German researchers pursuing projects on molecular causes in the development of illnesses. The next deadline is **30 September 2016**.

IMPORTANT: support available to EHDN researchers!

To discuss your project idea, find out about funding calls, request assistance with your application or scope out opportunities for collaboration, please contact Fionnuala Margreiter: fionnuala.margreiter@euro-hd.net

Paola Bellosta

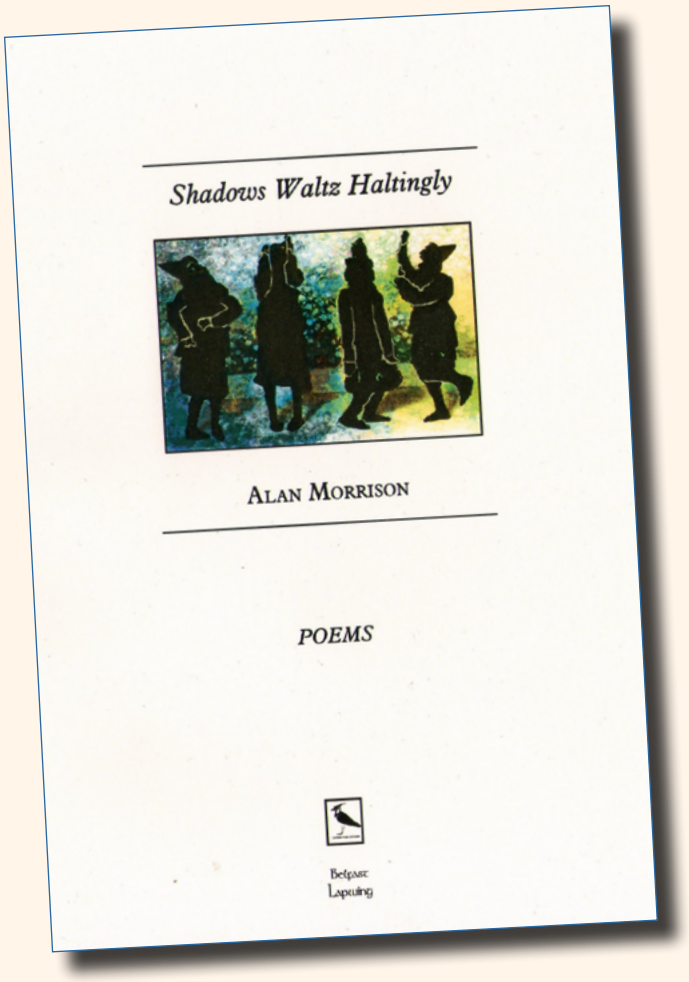
Rosanna Parlato

Falk Schradt

Three new seed grants awarded

Glutamate is essential for communication between neurons, but it can also kill them, and in HD this cell death results in involuntary movements, dementia, and ultimately, the death of the patient. Paola Bellosta of the University of Milan, Italy, has been awarded a seed grant to identify small molecules with a similar structure to that of glutamate, that facilitate neuronal communication without causing cell death, in a fruit fly model of HD. Meanwhile, Rosanna Parlato of the University of Ulm in Germany has been granted an award to investigate a putative metabolic biomarker of HD in the form of changes in ribosomal DNA. These are potential early signs of the transcriptional dysregulation that is associated with the mutant huntingtin (mHTT) protein. If validated, the marker could be used to assess experimental therapies that aim to lower mHTT levels in certain cells. Last but not least, a project led by Falk Schradt and Christina Lang, also of the University of Ulm, has been awarded a seed grant. This group will investigate the frequency, onset and progression of the swallowing difficulties that are associated with HD, that worsen as the disease progresses, and that can lead to bronchopulmonary infections and death.

Seed funds are intended to support pilot studies that will eventually kickstart larger projects. The next deadline for applications is 1 November 2016. More information about the programme and how to apply can be found here.



Japanese Gardens

If I could take you
to those Japanese gardens

throw your worries
to the orange blossoms

I'd lead you back
up those humbling stones

that stooped your head
till it drooped like a lily...

We'd drop bad thoughts
in the lotus well,

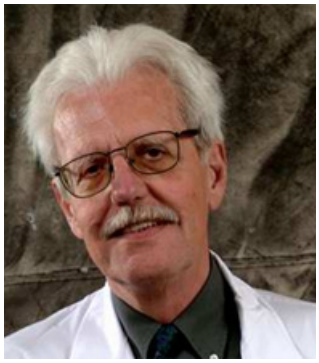
catch the koi fish
of your wishes back,

the splash of your last
laughter... *if*...

stones... the orange blossoms...
laughter... splashing ... throw...

no *if*... I would... I'd
follow you in....

A poem by Alan Morrison, from his collection *Shadows Waltz Haltingly* (Lapwing Publications, 2015). *Japanese Gardens* was one of many poems inspired by Alan's experience of living with HD, which affected both his mother and his grandfather. It is reproduced here with the kind permission of the poet himself, and his publisher Dennis Grieg.



All photos kindly provided by Caterina Mariotti

Obituary: Stefano Di Donato

A member of EHDN's first Executive Committee and the man who led Italy's research efforts in HD for many years, Stefano Di Donato passed away on 12 November 2015. His friend and colleague Caterina Mariotti pays tribute to him.

Stefano Di Donato died last November after a short but difficult battle with cancer. He was an exceptional scientist, a talented neurologist, an extremely kind and generous person and a very good friend. It is still difficult for me and for all those colleagues and friends who knew him to accept his loss.

I had the privilege of knowing and working with Dr Di Donato since 1991. During the last year of my residency in neurology, I heard him lecture on the subject of neurogenetic disorders. At that time, he was directing the biochemistry and genetics unit at the Carlo Besta National Neurological Institute in Milan. I was so impressed by the depth of his knowledge and his enthusiasm that I applied for a postdoctoral position in his lab.

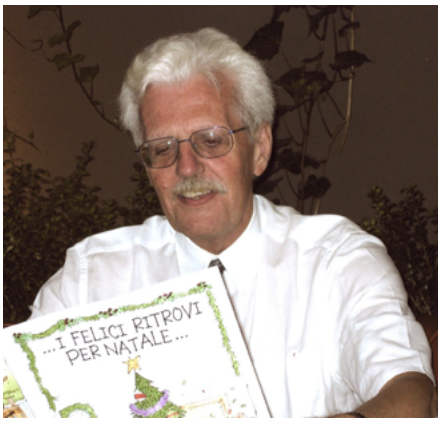
Stefano Di Donato began his professional career at the Carlo Besta Institute in 1969, at the age of 29. During his academic studies at the University of Milan's International Medical School, he had become interested in the biochemical and metabolic aspects of neuromuscular disorders, and after brief training in cell biology and biochemistry at the University of Milan and then at the University of Bern, Switzerland, he set up Carlo Besta's first biochemical laboratory. He would go on to become a pioneer in modern neurology.

In his lab in Milan, he initiated the study of the enzymes involved in ganglioside catabolism, carnitine metabolism, fatty acid beta-oxidation and brain lysosomes—all essential components of brain metabolism. He was intrigued by cellular metabolism and by the biochemical and molecular pathways that are implicated in mitochondrial disease and hereditary neurological disorders, particularly those associated with triplet expansions. Over the years, in line with his expanding scientific interests and endless curiosity, his lab grew exponentially. By the time I joined, it comprised more than 40 people, including biologists, neurologists, neuro-paediatricians, postdocs, technicians and students.

In 1995, Dr Di Donato took up the post of Scientific Director of the Carlo Besta Institute, and between 2002 and 2007 he also directed the institute's Department of Research and Diagnostic Technologies. In 2004 he began collaborating with EHDN to establish the first Italian HD network, which he coordinated until 2014. He always encouraged clinicians and families to participate in clinical trials and research projects that focused on HD biomarkers and disease pathogenesis.

Over the course of his career, he served as President of the Italian Society of Inborn Errors of Metabolism, President of the Italian Federation of Societies for the Study of Genetic Diseases, member of the National Committee of the Italian Minister of Health for the Study and Cure of Genetic and Metabolic Diseases,

member of the scientific committee of the European Genetic Foundation, and President-elect of the European Neurological Society (2000). He was honoured with the "Milano Medicina 1984" research award, the award of the Italian Association for Research and Prevention of Handicap (1993), and the Ludwig Schaefer Award given by the College of Physicians and Surgeons of Columbia University, New York.



His many achievements and honours speak to his undeniable strengths as a clinician and scientist, but on a personal level what was most striking and unique about him was his modesty, his simplicity, and the unfailing attention he paid to people and relationships. He was always willing to listen to problems or proposals, and always ready to lend support to patients and their families, while providing opportunities to researchers for developing new projects and ideas.

Stefano Di Donato believed that strong research sprang from the sharing of ideas and scientific collaboration, and this belief guided him throughout his career. He was tireless in his search for potential new scientific partners and in cultivating bonds that would generate fruitful collaborations and lasting friendships on an international level. He threw his considerable energy into the development of a number of international networks for hereditary neurological disorders, but in the last years of his life his particular focus was Huntington's disease. His goal was to find relief and a cure for patients, and to support the activities of families and patient associations. We will miss his wisdom, his teaching and guidance, his friendship and his kindness. Ciao Stefano!

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The Hague, The Netherlands

Dates for your diary

Save the dates for

- "Genome editing and neurosciences", organised by the Ipsen Foundation, Paris, France, 22 April 2016
- 8th European Conference on Rare Diseases & Orphan Products—ECRD, Edinburgh, UK, 26-28 May 2016
- 20th International Congress of Parkinson's Disease and Movement Disorders, Berlin, Germany, 19-23 June 2016
- 10th Federation of European Neuroscience Societies (FENS) Forum of Neuroscience, Copenhagen, Denmark, 2-6 July 2016
- 9th EHDN plenary meeting, The Hague, The Netherlands, 16-18 September 2016. Online registration will open later in the spring.
- World Orphan Drug Congress, Brussels, Belgium, 15-17 November 2016