Gateway

News from Huntington's New South Wales

Volume 20 No 3 **Spring 2017**

Saturday 18th November 2017, 12noon
A very important date!

- **We are changing our name to Huntington's NSW & ACT Inc.**

  We have been serving families in the ACT since our organisation was founded in 1975. For more than twenty five years our telemarketing program has been conducted in the ACT and in more recent times we have held three Walks 4 Hope there. It's time to include and acknowledge the important role our families in the ACT play and it will allow us to advocate on their behalf regarding issues that are unique to them.

- **We are adopting a new Constitution.**

  In order to change our name, we need to change our Constitution. This is a good opportunity to update the Constitution and bring it in line with changes to the Incorporations Law under which we operate.

- **We are holding our Annual General Meeting.**

  As an incorporated organisation we must hold an AGM each year—we cannot exist if we don't. The AGM provides an opportunity to hear about the Association's achievements over the past twelve months. We will also elect our Board Members for the coming year.

- **We are farewelling Fiona Richards.**

  After thirty five years working with Huntington's families, Fiona Richards is retiring. Fiona's commitment and professionalism are to be applauded and so we want to acknowledge and thank her for her dedication over so many years.


Fiona Richards (right) with Robyn Kapp at the 2010 AGM

- **We are having a delicious BBQ lunch.**

  Following the formal part of the meeting there'll be sizzling sausages and hamburgers, onions (of course) and tasty salads, culminating with delicious desserts. A donation of $5 per person would be appreciated. For catering purposes it would be appreciated if you would let us know if you're coming by telephoning 9874 9777 or emailing info@huntingtonsnsw.org.au.

Everyone is most welcome — we do hope you can make it!

Annual General Meeting

Our AGM will be held on Saturday 18th November 2017 at 21 Chatham Road West Ryde at 12 noon.

The Business of the Meeting is to
1. To accept the Minutes of the 2016 AGM
2. To accept the Annual Report of the Association
3. To accepted the audited Annual Financial Statements of the Association
4. To appoint the Auditor for 2017/2018
8. To elect the Office Bearers and Board Members
9. To accept the Special Resolutions

Nomination forms for the Office Bearers and Board elections are available upon request. Please contact the office if you would like one sent to you. Completed forms should be returned to Huntington's NSW no later than Friday 10th November 2017.
Nominations may also be made at the meeting.

Note: You need to be a financial member to be able to nominate or vote. However non-members are very welcome to attend.

Membership Renewal

Thank you to everyone who has renewed their membership for 2017/2018. We are also very grateful for the many donations we have received to date.

It is now possible to renew your membership, join the Association and give donations on-line by visiting our website www.huntingtonsnsw.org.au

If you still prefer to fill out a membership form and post it with your payment, you can either download one from the website or contact us on 9874 9777 and we will send one out to you.

The membership fee is still only $22 (incl GST) per annum.

A strong membership will ensure that the Association continues to be representative of, and relevant to, people affected by HD in NSW and the ACT. So why not encourage another family member or friend to join?

Westmead Hospital Phone Numbers Change

All Westmead Hospital phone numbers now start with 8890.

For example, if the Westmead Hospital number you are currently dialling is 9845 5555, the new number will now be 8890 5555.

The 8890 numbers are now live, so please update your contacts now!

Please note, this phone upgrade does not affect
The Children's Hospital at Westmead.

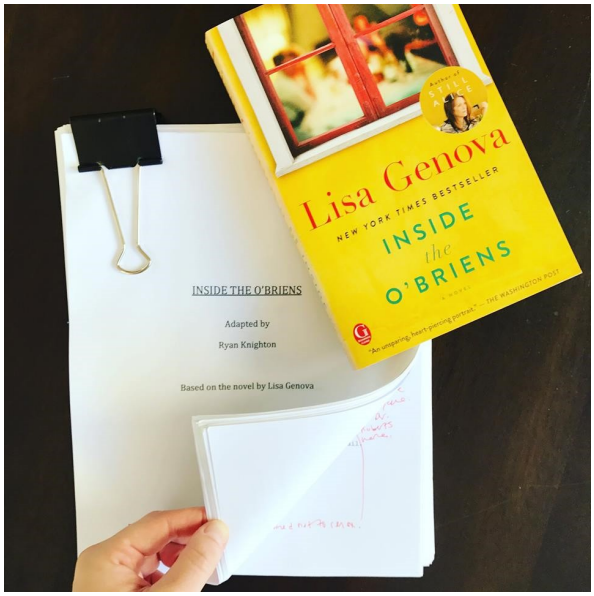
Meet Jasmin

Jasmin who is a year 6 student at the International Grammar School asked the question "what is Huntington's disease and what effects does it have?" for her Independent Research Task. Jasmin involved her school community in raising over $1,000 for Huntington's NSW and she also completed a 21 page report on HD which has affected her family through a much loved uncle and aunt.

She also constructed a model which represented some of the various characteristics of HD and wrote a song. Congratulations Jasmin and thank you for all your hard work. You are a very motivated and inspirational young woman.

Inside the O'Briens - Movie

Lisa Genova has announced on her Facebook page that a movie is to be made of her best selling novel, "Inside the O'Briens", which tells the story of a Boston family impacted by Huntington's disease. More details to follow soon!



$20,000 Grant Received

We have received a grant for $20,000 from the NSW Department of Family and Community Services to develop an NDIS Participant Readiness Resource for people with Huntington's disease and their families and carers.

Concerns were raised regarding the issues experienced by people with degenerative neurological conditions such as HD, neuromuscular conditions, complex physical disabilities, acquired brain injury and younger onset dementia transitioning to the NDIS. Some of these issues have resulted in people with disability not receiving the supports they need in a timely manner.

The Community Support Program – NDIS Participant Readiness Resources Project has been initiated to support participants to address some of these issues through the development of NDIS readiness resources. The resources developed as part of the project will guide people through preparing documents and ensuring the inclusion of all supports required are properly recognised in the NDIS assessment and planning phase.

It is hoped that our resource, developed specifically for people with HD, will be completed before the end of November. It will be available on-line, from your key work at the HD Service at Westmead Hospital or by post from the Association.

Precision huntingtin-lowering drug trials target the mutant protein

WAVE Life Sciences launches PRECISION clinical trial to suppress the mutant Huntington's disease protein By Dr Michael Flower and Edited by Dr Tamara Maiuri, 25th August 2017

A new exciting chapter in Huntington's disease (HD) treatment is just beginning – WAVE Life Sciences have announced PRECISION-HD1 and 2, clinical trials of two new drugs that lower the mutant Huntington's disease protein. We're excited about this novel approach to huntingtin lowering therapies, but these are early days and we've got a long way to go to show they're safe and effective in people.

Why are we trying to lower the amount of huntingtin protein?

If genes are the instruction manual that our cells use to make our body, then DNA is the language that the manual is written in. Each chapter makes a different protein, and it's these thousands of different proteins that make up all the cells of our body. Officially, the HD gene is called *HTT* and the protein whose instructions it contains is called huntingtin.

Humans have two copies of the *HTT* gene, HD happens when a mutation makes one copy too big. The expanded protein made from this mutant copy of the gene is toxic to our cells, particularly those in the brain. We know that lowering the level of mutant huntingtin protein in HD mouse models significantly improves symptoms reminiscent of HD, providing hope that similar treatments in people may be effective.

What is huntingtin lowering?

In the same way we've done with many antibiotics and cancer drugs, we can take advantage of one of nature's natural processes in order to suppress the huntingtin protein. In this case it's a means by which cells maintain and copy their own DNA.

The DNA found inside of our cells is usually made of two intertwined strands of DNA, curled around each other in the well-known *double helix* form. These paired strands allow the cell to *replicate* or copy their DNA by pulling apart each strand and using it as a template for a new copy. At various points in this process, cells use RNA as a sort of scaffold to help replicate DNA. When the copying is done these scaffolds need to be removed, so cells have gotten really efficient at degrading bits of RNA and DNA bound together.

The WAVE ASO acts like a drone that wants to shoot down the bad HD gene, or kite, but can't tell the difference between the good and bad kites. However, it can recognise the different coloured ribbons in the tail. Shooting at the ribbon instead of the kite is good enough to take down the whole thing. Image credit: Mike Flower

Cells use RNA for another purpose, which is carrying genetic messages throughout cells. When a cell needs a specific protein - say, the Huntingtin protein - to carry out their function, a request is sent to cells DNA managers. DNA is precious - if we screw up our DNA we end up with cancer, or dead - so the cellular managers of the DNA make a copy of the requested gene. The copy is made not in DNA, but in the language of RNA. This RNA message - called *mRNA* - is used by the cells manufacturing plants to create more huntingtin protein.

This intermediate mRNA shuttling information between DNA and protein-making machinery is the target of *huntintin lowering* drugs. The goal of these drugs is to, in various ways, destroy this message, denying the protein making machinery of the cell the instructions for making a specific protein.

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What does this have to do with HD?

Enter antisense oligonucleotides, or 'ASOs'. ASOs don't occur naturally, but are made by scientists to trick the cell into destroying a specific messenger RNA molecule. Essentially, ASOs resemble short stretches of DNA that have been modified to be able to enter cells. Once in, the ASO sticks to one specific sequence, found only in the messenger RNAof the HD gene.

Remember the scaffolds for copying DNA and how they're cleaned up? When cells see a stretch of DNA (the ASO, in this case) stuck to a piece of RNA (the HD message), they think it's a bit of scaffolding left over and destroy it. Voila, we've tricked a cell into destroying just one of the many tens of thousands of RNA molecules found inside that cell.

A major challenge is getting these manufactured ASOs into the brain because they can't get across the walls of the blood vessels in our brains. We've been able to get around this by injecting them directly into the cerebrospinal fluid (CSF), the fluid surrounding and cushioning the brain and spinal cord. From there, the ASOs get taken up into brain cells where they continue to suppress their target protein for a month or so, after which time more needs to be injected.

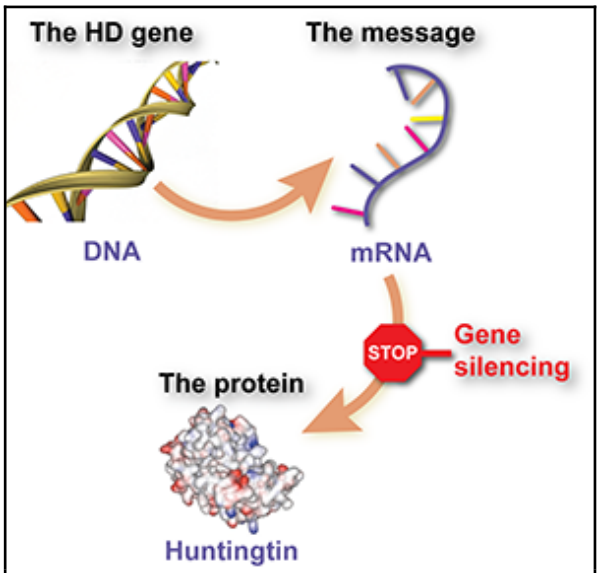
How is this different than the ongoing ASO trial?

Ionis pharmaceuticals are currently nearing the end of an exciting clinical trial using an ASO that targets the huntingtin RNA. The Ionis ASO doesn't distinguish between RNA coming from the normal and mutant copy of the gene, so it lowers the amount of both the normal and mutant protein. This is one of the reasons we're moving forward so carefully with this treatment – lowering the amount of normal protein may well be safe, but could also potentially be harmful in the long term. We know having the normal protein is really important for a baby's development. However, studies in several animals have shown that partially suppressing both normal and mutant versions by about 50% in adults is safe and improves symptoms.

What WAVE has done might get around these issues because their two drugs specifically target the mutant gene, leaving the normal copy alone. They do this by aiming for little genetic differences in DNA called single nucleotide polymorphisms, or 'SNPs' (pronounced 'snips').

Think of these SNPs as different coloured ribbons hanging from a kite. Everyone with HD is flying two kites – a 'good' one and a 'bad' one. Imagine the ASO as a drone that wants to shoot down the bad kite. Unfortunately, the drone can't tell the difference between the kites themselves. However, it can recognize the different coloured ribbons in the tail and shooting at the ribbon instead of the kite is just as good in terms of taking down the whole thing.

WAVE designed ASOs that target two SNPs in the HTT gene, which is why they're launching two separate clinical trials. These SNPs were chosen because their sequences tend to be different in the normal and mutant HTT gene: the ribbons at that point in the good and bad kites' tails tend to be a different colour, distinguishable by the drone. At the location of the first SNP, which in scientific language is called 'rs362307', half of HD patients have different coloured ribbons in their good and bad kites. For the second SNP, 'rs362331', there are different coloured ribbons in 40% of HD patients.



We know that lowering the level of mutant huntingtin protein in HD mouse models significantly improves symptoms reminiscent of HD, providing hope that similar treatments in people may be effective.

Overall, at least two thirds of people with HD in Europe and the US should have different ribbons that allow one of these drugs to shoot down the bad kite.

Unfortunately, that means that about one third of people have the same ribbons at these points on both the good and bad kites, so these drugs wouldn't specifically target the mutant HTT gene. However, should the drugs work in people, there would be a strong incentive to look into

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developing new ASOs targeting other ribbons.

What's the evidence that these drugs will work?

These trials from WAVE are slightly unique, because the company has not conducted studies in HD animal models with their specific drugs. Mice, and other animals loved by researchers, also have two copies of the HD gene. However, there's a lot more genetic variation between humans and mice than there is amongst humans. This means the SNP variations targeted by WAVE's ASOs aren't shared with mice, and so can't be tested in them.

What has WAVE done? The specific drugs designed by WAVE have been tested in cells in a petri dish, where they successfully lowered the mutant protein whilst leaving the normal version relatively untouched. Researchers at WAVE reason that - for HD - the case for lowering the HD gene is so clear that additional animal studies would be a waste of time.

This doesn't mean these trials aren't safe - before any drug is administered to people, even experimentally, it must be thoroughly tested in animals to ensure it is not toxic. WAVE haven't publicly detailed the work they've done in animals to prove these drugs are nontoxic, but rest assured that the regulatory agencies in charge of letting these trials go forward will have seen the results of such experiments.

How are the trials organized?

The WAVE trials are officially called phase 1b/2a trials. A phase 1 study is one in which the primary goal of the study is to understand whether the drug is safe in a small number of volunteers. Normally, a phase 2 study is conducted in a slightly larger number of people, with the goal of collecting a little bit of evidence that the drug may work. In this case, because everyone wants to move as quickly as possible, WAVE have structured the trial to combine aspects of a phase 1 and 2 trial. This means that they'll test to see if the drug is toxic (phase 1), but also if it has an impact on various important symptoms of HD (phase 2).

Similar to the ongoing Ionis trial, WAVE's drug will be injected into the CSF by lumbar puncture. This allows researchers to collect a little bit of the spinal fluid that surrounds the brain and spinal cord, in which we can now measure levels of the harmful huntingtin protein. We hope this will allow WAVE to actually measure what they're trying to do, which is to reduce the levels of the mutant huntingtin protein in the brain.

How can someone get into the trial?

WAVE aims to recruit 50 people with HD worldwide onto each of the two trials. That's a small number, but if the drug is safe they'll move on to bigger trials with more people to look at whether it's actually working. The current study will start in Canada, then will enrol patients in Europe and the US. To be considered, you have to be an adult over the age of 18, and must have started developing symptoms. There's no way to tell what colour the ribbons in your DNA are just by looking at you, so eligible people will have a genetic test and if they have either of the two SNPs they'll be included in the trial. The best way to get involved is to express your interest in research to your clinical team.

What does this mean for HD?

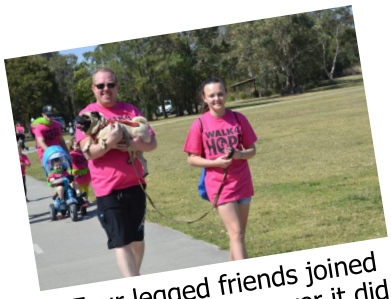
We're all hopeful that the Ionis ASO will be the first drug to slow down or stop HD. However, it's important to realise that this is the first time these drugs have been used in people. Though they made mice much better, humans are a very different species. Even if they do lower protein level in adults, they may not be effective because damage done earlier in life is irreparable. They could also have side effects in humans that didn't happen in mice. Whilst WAVE's drugs shouldn't affect the level of the normal protein, they might react with other RNAs causing their protein levels to be reduced. However, we're excited and optimistic about huntingtin lowering treatments, and WAVE's latest refinement looks like it could be a an exciting advance.

Acknowledgement: https://en.hdbuzz.net/

A Super Successful September
$80,000 raised and lots of awareness

September this year was a fabulous month for awareness and raising funds for Huntington's NSW. We had many events throughout the month including:

- Walk4Hope — Croudace Bay
- Walk4Hope — Canberra
- Walk4Hope — Orange
- Walk4Hope — Parramatta
- High Tea — Orange
- The Lady Hampshire Trivia Night — Camperdown
- Redhead World Record Attempt — Orange
- Settlers Tavern Social Golf Club Day — Gosford
- "The Inheritance" screening — Port Macquarie
- "The Inheritance" screening — Orange
- HD Stall — Westmead Hospital
- HD Stall — St Joseph's Hospital, Auburn



Four legged friends joined in the walks, however it did prove a little tiring for one family pooch

It was a magnificent day by Lake Burley Griffin for our Canberra walk

A bitterly cold day in Orange didn't deter our walkers

Some well known faces at the Redhed World Record attempt in Orange

Michelle Hanna, Julie Leto & Rachael Brooking at the screening of "The Inheritance" in Orange

The winners for guessing the correct number of lollies in the jar with Board Member, Therese Alting, at Parramatta

A very special thank you to everyone who helped in any way to make September such an amazing month for Huntington's NSW. We couldn't have done it without you!

It was a picture perfect pink day at Croudace Bay

Huntington's New South Wales

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Huntington's NSW
The Australian Huntington's Disease Association (NSW) Inc, trading as Huntington's NSW, is a not-for-profit organisation established in 1975.

Our Mission
The energies and resources of the Australian Huntington's Disease Association (NSW) Inc are directed towards satisfying the needs of people with or at risk for Huntington's Disease and their families in NSW and the ACT by providing and/or facilitating delivery of a range of quality services.

Our Philosophy
People with Huntington's Disease and their families are individuals with equal value to all other members of Australian society, with the right to treatment and care by knowledgeable professionals and care givers, the right to appropriate support services and the right to have the best quality of life possible.

Our Services
These include education and information; advocacy; counselling and referral; holiday programs; family support; rural outreach and client services.

Our Board
President: Brian Rumbold
Vice President: Deb Cockrell
Treasurer: Stephen Guthrie
Secretary: Therese Alting
Members: Richard Bobbitt
Katy Clymo

Association and Other Useful Contacts

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Dr Therese Alting
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0438 604 719 (Mon & Thur)

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Outpatients Department
Westmead Hospital
(02) 8890 6544

Huntington's Unit St Joseph's Hospital

(02) 9749 0215

Hunter HD Service

John Conaghan
Social Worker
John Hunter Hospital
(02) 4922 3076

Predictive Testing

Find your nearest Genetics Clinic at
Genetic Services