



Gateway

News from Huntington's New South Wales

Volume 17 No 2

Winter 2014

Young Khyra's Mission to Make a Difference

Hi, my name is Khyra, I'm 8 years old and I am a Huntington's Disease (HD) fundraiser.

Some of my Pop's brothers have pretty bad HD and when I see them I feel devastated for them as they cannot walk and talk the same as me. I really wanted to do something where I could collect money to help make their life better.

So this is what I decided to do....

One day I was shopping with Mum and saw some loom bands the same colours as the HD charity. I asked Mum if I could buy them so I could make some bands to sell and give money to the HD charity.

Mum did and in our spare time my brother and I made some bands. That afternoon, my friends and I took the bands and knocked on the doors of our neighbours' homes. We showed them a letter explaining what we were doing (written by Mum) and asked them if they could help us raise money for HD by buying a band. And they happily did. That afternoon we collected \$72.20.

The next day I made more bands and took them to my brother's soccer and raised more money.

Later that week, my Nan and Pop were going on a wine tour and asked me to make some HD bands for the people on the bus. I made 40 bands, and a short video asking the people to buy a band to help me get from \$72.20 to \$150 for HD. I also told my Nan "Not to come home until all the bands were all

sold". She did sell them all (thanks Nan) and handed me a HEAVY bag of money to count. It was exciting to find out I had actually passed my fundraising goal.

At our next HD support group meeting I was lucky enough to personally handover \$231.10 to Robyn

Kapp, the EO of HNSW. I also meet my local federal member of parliament, Lucy Wicks.

I now want to keep raising money for the HD charity by selling my HD bands; my tally is now at \$241.10.

If you'd like your own HD band please email me your address details to



huntingtons.centralcoastnsw@gmail.com.

You'll be advised where to send your \$5 HD donation and then I'll post you your own HD band.

Now, I want to ask a question to the kids in our HD community. Will you raise money for HD with me too? I challenge you to make HD coloured loom bands like me or create something HD, of your own, and ask people in your local area to buy it to help you raise money for HD.

Let's see how much we can raise together by the end of the year.

PS don't forget to email Robyn your idea and let her know how you're doing so we can see our tally growing.

Membership Renewal!!

Thank you to everyone who has renewed their membership for this year. We are also very grateful to those who were able to make a donation—your generosity is much appreciated.

For those who haven't yet renewed, it's not too late. 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.

A membership form can be downloaded from our website www.huntingtonsnsw.org.au. Donations are always appreciated and are also tax deductible.



National Huntington's Conference 2014

"Embracing Opportunities with HD"

Perth, Western Australia 11th - 12th September

University of Western Australia, UWA Club

Huntington's WA invites you to the National Huntington's Conference in Perth, bringing together family members, researchers, allied health professionals, care workers and members and supporters of all Huntington's Disease Associations across Australia.

An exciting line up of keynote speakers includes

- Richard Faull (New Zealand)
- Nellie Georgiou-Karistianis (Victoria)
- Tony Mims (Victoria)

as well as presentations around living well with HD, sharing best practice and translational research, engaging youth and exploring new boundaries.

Full program and registration including links to accommodation and popular tourist activities are available at www.huntingtonswa.org.au.



Annual General Meeting

8th November 2014

Camp Breakaway, San Remo

Our Annual General Meeting this year will be held on Saturday 8th November at Camp Breakaway, San Remo, which has been the venue for our Holiday Camps since 2002.

We are planning a day for the whole family –

- Fun and games for the kids
- Activities for people with HD
- Guest speaker
- BBQ lunch

So put the date in your diary now and we will send out further information closer to the day.

Save the Date!!



Making Huntington's their Cause

Golf Day

A very successful Golf Day was held by the Rotary Club of Concord at Concord Golf Club last month. At the dinner our President, Brian Rumbold, accepted a cheque for \$6,000.

Sincere thanks to our member, Margaret Bain-Smith; our Secretary, Don Ayres; Concord Rotary Club and Concord Golf Club.

Hunter Valley Wine Tour

Friends and relatives of the Central Coast Support Group had a very enjoyable day touring the vineyards of the Hunter Valley. They raised \$1,345 for HNSW. We are most grateful for making Huntington's their cause.

City2Surf

Rebecca Walker is competing for the 3rd consecutive year in the City2Surf to raise funds for Huntington's NSW. This year, she will be completing the 14km journey with her husband, Ryan, their 3 month old son and Ryan's parents, Tracy and Jeff. If you would like to support Rebecca and her team you can do so by going to <https://city2surf2014.everydayhero.com/au/fighting-hd>

Thank you so very much Rebecca and good luck !!



From the Executive Officer

Dear Friends

I do hope you enjoyed reading about Khyra and her wonderful fundraising effort for Huntington's NSW. It was an absolute delight to meet Khyra and she was so excited about handing over the money she raised from making her loom bands.

One way we could all help fundraise is to text or email a photo of any Dick Smith product in your pantry to charity@dicksmithfoods.com.au.

The charities with the most votes will share in the second round of \$500,000 in December (\$510,000 was donated to 38 charities on 8th July). So get all your friends and family on board and see how many votes we can get.

For further details go to www.dicksmithfoods.com.au. I trust you'll find the other articles in this edition of "Gateway" both interesting and informative.

*In friendship
Robyn Kapp*

you decide where it goes!
**\$1 MILLION
TO CHARITY**

\$6 million donated so far ...

Dick Smith Foods Foundation will donate at least \$1 million to charity this year.

Why not be part of the decision making process?

Simply **text or email a photograph** of any Dick Smith Foods product in your pantry to: charity@dicksmithfoods.com.au as well as the name of the charity you would like money to go to*. The charities with the most votes will share in \$1 million.

What could be simpler?

See our website www.dicksmithfoods.com.au

**DICK SMITH FOODS
FOUNDATION**
Keeping jobs in Australia

*For a list of charities that are eligible and details of how the voting and decision making takes place, please go to our website.



Jumping genes: Huntington's disease protein invades brain transplants

Huntington's disease is caused by the malfunctioning and early death of brain cells. Replacing those dead and dying cells with stem cells has long been a goal of some HD scientists. A new study investigates the long-term health of some of the earliest cell transplants into HD patient brains — and finds a surprising result.

Filling in the gaps in the HD brain

Huntington's disease, and other 'neurodegenerative' diseases like it, happen when specific cells in the brain die. Unfortunately for people carrying the HD mutation, these critical brain cells are mostly only made during our early development. After we're born, most areas of the brain don't grow many new brain cells to replace those that are inevitably lost, even during normal aging.

What if we could take tissue from a developing brain and use it to fill in the gaps in a degenerating HD brain?

Though there's a pretty high 'ick-factor', it's technically possible to dissect brain regions from human embryos and transplant them into the degenerating regions of HD patient brains.

Cell replacement therapy

In fact, this 'cell replacement' idea has a long history in HD. In the mid-1980s, a series of animals studies showed that it was possible to fix brain damage caused by toxins, by transplanting embryonic brain cells into the damaged area. Subsequent work, in more sophisticated animal models, supported the idea that this approach might be beneficial.

Based on this animal work, and the progression of similar trials in Parkinson's disease, a small number of HD patients received grafts of embryonic brain tissue starting more than 15 years ago. Disappointingly, none of the patients receiving transplants showed much, if any, sustained improvement in their HD symptoms after receiving these transplants.

One patient who received a fetal tissue transplant died about 18 months after surgery,

due to unrelated causes (heart disease). While sad for the patient and their family, this enabled scientists to study the transplanted tissue and see how it was doing in the brain. One possible explanation for why the patients didn't get much better is that the transplants may not have survived, or might not have made the right kind of connections in the host brain.

In fact, this early study showed that the fetal tissue did survive in the brain of the HD patient, and the cells in the graft seemed to make the kinds of connections they should have made with other cells in the brain. This is good news, because it means this kind of transplant is technically possible, but bad news, because it means we don't know why it didn't make the patient better.

New cells, old problems

After more time had passed, scientists were able to study a larger number of brains from Huntington's disease patients who had ultimately died of HD, years after receiving grafts of fetal tissue. This analysis pointed to a more disappointing reason for the failure of the grafted tissue to help HD patients: the new cells seemed to be dying, much like the old cells around them.

This was unexpected! Remember, the cells grafted into the brains of HD patients were from human embryos, and so were very young. Nevertheless, something about being inside of an HD brain made these brand new cells sick, and in fact lead them to die like the cells they're supposed to be replacing.

Similar disappointing results were observed in Parkinson's disease patients who'd received fetal tissue grafts, suggesting that this might be a general problem with the whole idea of cell replacement therapy. It could be that the brains of patients with neurodegeneration are just too inhospitable for new cells to be of much help.

There goes the neighborhood

But how could this be? If the donor cells don't

have an HD mutation, why do they get sick just like those cells that do? We don't know the answer to this question yet, but an emerging body of work suggests brain cells in people with neurodegeneration may actually make each other sick.

In many neurodegenerative diseases, brain cells are found to be full of clumped up garbage. These clumps are called 'aggregates' in HD, 'Lewy bodies' in Parkinson's and 'amyloid plaques' in Alzheimer's disease. In each case, cells in certain areas of the brain seem unable to take out the cellular trash, which might contribute to them getting sick and dying.

When fetal grafts were implanted into the brains of patients with Parkinson's disease, the cells in the graft were discovered to contain Lewy bodies, just like the sick cells around them. This was very surprising - these are healthy young cells, and it normally takes decades for Parkinson's disease to develop.

New HD work

Could something similar be happening in Huntington's disease grafts? A recent study from a group of scientists led by Francesca Cicchetti, Université Laval, suggests something funny might be going on. Cicchetti examined the brains of 3 HD patients who died about 10 years after receiving grafts of fetal tissue.

To understand their findings, we have to remember a few things about how HD works. Every HD patient has inherited a mutant copy of the HD gene, which causes their cells to make a mutant HD protein. It's this mutant HD protein that causes damage in the HD brain. In fact, most of those clumps of garbage found in HD brain cells (the 'aggregates') are made of the mutant HD protein.

Cicchetti's team noticed something strange about the grafted fetal tissue in HD patient brains — it contained aggregates! That's very surprising, because this grafted tissue doesn't have a mutant HD gene, and so shouldn't have any mutant HD protein in it. *What's going on?*

To be clear: the clumps of mutant HD protein aren't inside the cells of the graft, but rather stuck outside the cells like litter that

shouldn't be there. The explanation for this surprising result isn't clear, but figuring out where these clumps come from and whether they contribute to the failure of these grafts is going to be an important area of work. But at least now we know that they're there.

So, now what?

The results of this study, as well as the other studies in other neurodegenerative diseases, suggest that we need to be very cautious about simply replacing dead cells in the degenerating brain. If the underlying sickness is still present, the new cells we put in the brain may simply become ill as well.

This is somewhat disappointing news, in terms of accomplishing cell replacement therapy for HD. But great strides are being made in stem cell science in labs around the world, so this story is not the end of this particularly road. Finally, though cell replacement is an attractive idea, work to boost the survival of brain cells, rather than replacing them when they die, is rapidly developing and continues full speed.

Glossary

Parkinson's Disease A neurodegenerative disease that, like HD, involves motor coordination problems

neurodegenerative A disease caused by progressive malfunctioning and death of brain cells (neurons)

aggregate Lumps of protein that form inside cells in Huntington's disease and some other degenerative diseases

stem cells Cells that can divide into cells of different types

amyloid The main protein that builds up in the brains of Alzheimer's disease patients

embryo the earliest stage during the development of a baby, when it consists of just a few cells

Acknowledgement: Written by Dr Jeff Carroll, edited by Dr Ed Wild, May 26, 2014
HD Buzz: www.hdbuzz.net



Searching for therapies, one step at a time

Bernhard Landwehrmeyer, Chair, Executive Committee, European Huntington's Disease Network (EHDN)

At the EHDN plenary meeting in Barcelona in September, Bernhard Landwehrmeyer will stand down as chair of the Executive Committee. Though he will remain on the EC and very active in the network, we asked him to look back on a productive career and 10 years at the helm of a unique organisation.



Bernhard Landwehrmeyer and Nancy Wexler at the 2008 EHDN plenary meeting in Lisbon, Portugal

My first real exposure to Huntington's disease as it is lived by patients was in 1994, when I had the opportunity to accompany Nancy Wexler and Anne Young to Lake Maracaibo in Venezuela. I was struck by the tremendous impact the disease had on these people who had hard lives anyway. They were fishermen, simple people. Many of them lived in shacks, and this deadly disease imposed a terrible additional burden on them that they carried with great bravery.

There was one incident I will never forget. We visited an old lady whom we found starving and emaciated. She hadn't eaten for two days. Her 16-year-old grand-daughter was supposed to be looking after her, but this young girl also had to look after her younger siblings since one of her parents had HD, and the only way she could support them all was by prostituting herself. She appeared while we were with her grandmother, and apologised for not having come earlier, but as she explained, she simply wasn't able to be everywhere she had to be, while also earning the money she needed to feed her family.

That visit left a powerful impression on me, and I found it extremely motivating. The previous year, 1993, I had gone to work as a postdoc in Anne Young's lab at Massachusetts General Hospital in Boston. By then, in my career as a neurologist, I had reached the point where I wanted to study the pathological mechanism from first principles, so to speak, and so I had become interested in monogenic diseases. Anne's interest was in HD, which is why I applied to work in her lab. Serendipitously, in March of that year, Jim Gusella, Marcy MacDonald and others identified the huntingtin gene and mutation, and I became involved in efforts to visualise the distribution of huntingtin mRNA in brain tissue, using a technique called in situ hybridisation histochemistry. Those were exciting times!

After three years in the US, I returned to Germany, to Freiburg where I set up an HD clinic, and in 1999 I was recruited by Ulm University where I still work today. My first task in Ulm was to set up a trial of a drug called riluzole that, it was felt, could potentially modify the disease process in HD. It had to be a long trial, lasting three years, and it had to recruit a large number of patients, over 500, which meant that we required the participation of a number of sites in different European countries.

This posed something of a logistical challenge, but we pulled it off. The trial was called the European Huntington's Disease Initiative, and while it was still underway I and others began to think that it would be a waste to let the infrastructure we had created wither away after the trial had ended. How could we maintain that infrastructure to support future clinical trials? we asked ourselves. In 2003, I happened to meet Robi Blumenstein of CHDI at a Gordon Research Conference in Tuscany. We talked, the talks carried on after the conference had ended, and the result was the CHDI-funded European Huntington's Disease Network.

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Enduring Powers of Attorney

As a carer you may have to make legal, financial, medical or lifestyle decisions on behalf of the person you care for. Appointing a power of attorney can make difficult choices easier for you, the person you care for and the rest of your family.

Appointing a Power of Attorney or having guardianship provisions in place can help prepare you and your family for sudden changes in circumstance. It helps if everybody in your family knows who has been nominated to make important decisions when somebody is no longer able to decide for themselves. It is also useful to know what they might have wanted in a range of common situations.

Enduring powers

Enduring powers are legal documents that let a person choose someone they trust (an 'agent') to act on their behalf if they become unable to make decisions for themselves.

Power of Attorney

Power of Attorney gives someone the ability to act on someone else's behalf in financial matters such as paying bills and managing money if for any reason they are unable to manage financial matters themselves. For example, a daughter may be caring for her frail mother who has mobility difficulties and can no longer go to the bank to pay her bills. Her daughter, with a power of attorney, can pay her mother's bills on her behalf.

A power of attorney does not allow the attorney to continue to act on your behalf after you have lost capacity.

Capacity is the ability to make decisions and understand the effects of those decisions. A person is said to have capacity when the person can understand the information and choices presented, weighing up the information to make a decision and then communicating that decision. A person who can't follow this process and communicate decisions is said to lack capacity.

Enduring Power of Attorney

Enduring Power of Attorney becomes effective only after the person has lost capacity and can no longer make decisions. A person must appoint

their enduring power of attorney before they lose capacity. An enduring Power of Attorney cannot make lifestyle, accommodation or medical decisions and is limited to overseeing finances or property; only an enduring Guardian can make lifestyle decisions on someone else's behalf. The appointment of an enduring Guardian comes into effect when the person loses capacity to make personal or lifestyle decisions.

Enduring powers need to be prepared in a particular way and you should consult a solicitor. Printed Power of Attorney forms are available from newsagents. You can cancel ('revoke') an enduring power at any time provided you are still competent.

Who can appoint enduring powers?

To appoint enduring powers, you must have capacity, be competent and able to understand what you are doing. You cannot appoint enduring powers for another person only for yourself.

Under some circumstances, a Guardian or Administrator can be appointed by the Guardianship Tribunal to protect the interests of somebody who is not competent to make decisions for themselves. This usually happens when there is concern about their rights.

Choosing your agent

Your agent can be any competent adult who is able and willing to act on your behalf.

Choose someone that you trust to act in your best interests and carry out your wishes. He or she should also understand your views about the decisions they might be asked to make for you and know you well enough to make the kind of choices you would make for yourself.

Making your wishes known

If you have clear views about particular medical and legal situations that might affect you, write them down. This is sometimes called an 'advance directive'. Ask your doctor or lawyer to help you to work out what you would like to do in a range of common situations.

Discuss your views with close family members

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Rather, we took the view that it was necessary to approach the disease rationally, advancing step-by-step along a path of learning that would involve from many different disciplines working in parallel and collaboratively. Patients understandably feel frustrated sometimes, when they see our approach, because for them time is running out, but I believe that this is the best way we can help them in the long run.

We've come a long way. We can already suppress mutant huntingtin in the brains of transgenic mice very effectively. A mouse brain is much smaller than a human brain, however, and delivering these therapies will be our next big challenge. Our goal for the next 10 years, with that of our colleagues beyond Europe, should be to translate our successes to date into effective therapies for patients. That, in my view, will mean combining some of the approaches that are currently working so well in mice. It's a big ask, but with the help of the network we have put in place, I think we can do it.

Acknowledgement: EHDN News July 2014, Issue 22

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and friends and give them copies of your advance directives. Letting people know in advance what you want in a particular situation can help prevent distress or conflict if different people have different views about what should be done.

Find out more

The NSW Trustee and Guardian (www.tag.nsw.gov.au) has more information on wills and powers of attorney. The website of the Public Guardian (www.publicguardian.lawlink.nsw.gov.au/publicguardian) also has information and factsheets on enduring guardianship. A book on advanced care directives and making health decisions, *My Health, My Future, My Choice*, is available from the Advanced Care Directive Association (www.advancedcaredirectives.org.au)

*Acknowledgement: Carers NSW
www.carersnsw.org.au*

Carer Support Groups

Our West Ryde Carers Support Group meets on **Wednesdays** each month at **10.30am**, at the Association's office,
21 Chatham Rd West Ryde,

*It's a great time to get together with other carers who, like yourself, are caring for a partner,
a family member or a friend with HD.
The group is facilitated by Jet Aserios and Cecelia Lincoln from the HD Service.*

Come along and join us as we share our chatter, laughter, tears and experiences.

Remaining 2014 Sessions

13th August	24th September
15th October	12th November

Our Penrith group meets on **Wednesday afternoons** at **2pm** at the **South Penrith Neighbourhood Centre**
3 Trent St, South Penrith.

The dates for these sessions are
23rd July 27th August
1st October 5th November

To RSVP for either group and for further information, please contact:
Jet Aserios or Cecelia Lincoln 9845 6699,
Social Work Department, Westmead Hospital or
Robyn Kapp, Huntington's NSW, 9874 9777

A combined Christmas Dinner will be held on either Friday 5th or 12th December (tbc).

Do you have a Story to Share?

If you have a contribution that you wish to make to the Newsletter please send it to us at the Association office (see details on the back page) or by email to Robyn at robyn.kapp@huntingtonsnsw.org.au

Fresh Air and Exercise

High atop Dundas Peak, Robert "Schelly" Shellenberg has a chance to catch his breath and take in the view of his hometown of Dundas, Ontario, (Canada) nestled far below. The craggy lookout is just one of the 73-year-old's favourite stops during the two-hour walk he takes each morning along the Niagara Escarpment.

There is more to Schelly's daily constitutionals than keeping the pounds off. Ever since his wife Lenita was diagnosed with HD in 1994, staying active also helps both his mind and body stay fit to handle the everyday challenges he faces as a caregiver. "It gives you a feeling that everything is going to be all right, that you can deal with living again," he says.

Schelly can feel the difference the moment he steps outside his door. "The first thing I notice walking is the air hitting my face," he says. "You get happier right away." Schelly winds his way along Spencer Creek and the Bruce Trail, taking in the sights and sounds around him: the ripples in the water, the chirping birds, the chatter of chipmunks, the wind in the top of the trees. These outings are a chance for Schelly to recharge his batteries, clear his head and rejuvenate his spirits. "Being a caregiver is a very difficult endeavour," he says. "If I didn't have the walking, it would be a terrible time."

According to award winning scientist and author, Diana Beresford-Kroeger, the forests around Schelly's home may be doing more than just buoying his spirits, however. Diana is an expert in something called forest bathing: a practice that involves spending time in mature forests to breathe in and absorb healing compounds that are released from certain trees. Advocates of forest bathing believe these compounds have curative properties that help boost the immune system, improve heart flow and strengthen the nervous system.

Whether you are a caregiver, someone with HD, or someone at-risk, Diana believes forest bathing can bring benefits across the continent. For best results, she recommends walking slowly through a mature pine or cedar forest during a warm, sunny day, taking the time to breathe deeply and physically handle the sticks and other tree material you come across. While the jury is still out on the health merits, it is hard to argue with

the price tag. "What I am talking about is not a strict science," Diana says. "But it is something that can be tried for next to nothing."

Just down the road from Schelly's house, Dr. Tamara Maiuri is hard at work at Dr. Ray Truant's HD lab at McMaster University. As a contributor to HD Buzz, Tamara has seen mounting evidence supporting the idea that active lifestyles are beneficial to patients with Huntington disease. Recent studies out of Norway and Australia show that patients engaged in programs that promote physical, mental and social stimulation saw a noticeable improvement in symptoms.

Participants in the studies did not have to go on hikes, like Schelly, each day to see results. The regular exercise they were getting had a positive effect on things like balance, walking ability and physical quality of life, underscoring an age-old truth: exercise is good for you.

Another study involving gardening activities highlighted some of the psychological benefits of getting off the couch. "People reported that they got a lot from being outside," says Tamara. "The gardening aspect of it really gave them a sense of achievement." Interesting, yes, but Tamara is quick to point out that the sample sizes of these studies were very small and that more research needs to happen before any concrete conclusions can be made.

Still, she says, finding an activity you can safely enjoy that keeps your body and mind stimulated is never a bad thing. "If something improves your quality of life, then do it," Tamara suggests.

You do not have to tell Schelly twice. Back in Greensville, he is lacing up his hiking shoes for another trek up to Dundas Peak. Maybe today he will see his favourite kingfisher. As far as he is concerned, a breath of fresh air and the sun on his face are the best kinds of medicine out there. "It is kind of like a happy pill," he says.

Acknowledgement: By Josh Martin, "Horizon", No 143, Spring 2014, Huntington Society of Canada.



Enjoying the fresh air on our Holiday Camp earlier this year.

Illuminating the progression of Huntington's disease

Huntington's disease (HD) progression is a long process in which the first changes in the brain happen well before we even see symptoms in patients. It makes sense to focus our efforts on treating the earliest changes, to nip the problem in the bud. But what are these changes and how can we target them? A recent study has literally shed some light on this question. By creating HD mice with glowing brain cells, researchers at the University of Nottingham Medical School and the Babraham Institute in the UK have found that some of the earliest changes happen before these cells start to die, in a region of the brain where HD researchers have never before thought to look.

Turn on the magic of colored light

The mice in question have but a small percentage of brain cells, called neurons, lit up, and for good reason. Neurons can be thought of as miniature information processors that receive incoming signals at input structures called "dendrites", process the information in the cell body or "soma", and transmit the signal down a long thin wire called the "axon".

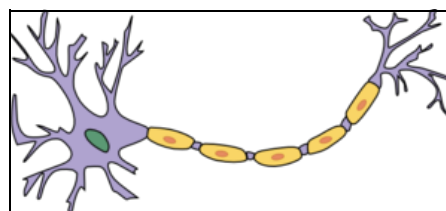
The information is relayed to the next neuron's dendrites to propagate messages throughout a vastly complex network — messages that coordinate our every thought, action, and bodily function. This complexity means that neurons are densely packed in amongst all kinds of other cells and material in the brain. So, much like the nostalgic Lite-Brite toy, illuminating a small subset of neurons and leaving the rest dark allows a clear picture to emerge.

Another reason neurons are difficult to study in the brain is that a neuron's "output wire", or axon, can run long distances. The neurons that control your body's movements, for example, have their soma in the cortex, but send their axons all the way down to the spinal cord. That's a long trip for a tiny cell!

Lighting up one entire cell allows investigators to trace an individual neuron from its dendritic input points, through the soma, all along the axon to its final destination in another brain area. This means they can ask whether abnormalities in an axon are associated with changes in the rest of the cell to which that specific axon belongs. Knowing which part of the neuron gets sick first

could help scientists understand what processes go wrong earliest in HD.

The neurons of two different HD mouse models were illuminated in this way: one "transgenic" model and another "knock-in" model. The specific transgenic mouse they



In this cartoon, the "dendrites" of the neuron are the fine projections on the left. The "soma" of the neuron is the main body of the cell (in purple here). The long wire projecting out to the right is the "axon" of the neuron. Image credit: Quasar Jarosz

used has been engineered to carry a small chunk of the mutant HD gene. The knock-in mouse, on the other hand, has the HD-causing expansion "knocked-in" to its natural mouse version of the huntingtin gene.

The major difference between these two mouse models is the speed and severity with which they get sick. The transgenic model progresses much faster (showing symptoms at 12 weeks versus 12 months), which can be advantageous, for example to get quicker answers about potential drug compounds. The knock-in model takes much longer to get sick and has less drastic (sometimes more difficult-to-measure) symptoms, but more closely resembles what happens with HD patients, making it a more accurate model. Often in research, there's a trade-off between accuracy and speed, and that's the case with these two different models.

Bulges in the wire

While HD is a brain disease, the problems found in HD are not evenly distributed throughout the brain. Cells in certain brain regions are known to get sick and die earlier than others. A small region deep within the brain called the "striatum" is the most vulnerable part of the brain in HD, almost disappearing during the course of disease.

To study this brain area in HD mice, the research team compared the glowing neurons in each

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model at their respective early and late stages of disease. Surprisingly, in the transgenic mice, neurons of the striatum were found to be normal and healthy, despite the fact that the mice had a number of symptoms. This suggests that other factors, besides the obvious death or dysfunction of neurons in the striatum, must cause the HD-like symptoms seen in these mice.

As for the knock-in model, while the early-stage mice had normal, healthy-looking brain cells in their striatum, the late-stage mice showed regions of bulgy swelling in their axons. Axons, remember, are the transmitting wire of the neuron, carrying its message out to other cells in the brain.

Axonal swelling happens naturally during aging and in some brain diseases, but it happened earlier and more often in knock-in HD mice. Each axon's corresponding soma (cell body) and dendrites (input structures), meanwhile, still looked healthy. This is very interesting, because it suggests that in this accurate mouse model, changes in the axon are the first to be seen.

If we assume that this mild mouse model represents an early stage of what goes wrong in the HD brain, these results might help us focus our energy on studying the right part of the neuron, particularly the axon. There is significant evidence of problems in axons in HD, and these results add support to the idea that these problems are worth understanding in HD.

The researchers weren't content to study only changes in the striatum, however, they looked widely at other brain regions in hopes of identifying other early changes in the HD brain. Surprisingly, the region with the most axonal swelling was a structure near the striatum called the stria terminalis, which is involved in anxiety-related behavior.

Axons in the stria terminalis showed swelling even at the early stages of disease progression, and it got worse at late stages. Once again, each affected axon could be traced back to its soma (in yet another brain region called the amygdala), and these cell bodies were still healthy. This suggests that this brain region is also worthy of additional attention in HD.

A gramme in time saves nine

We never get tired of saying that even

genetically modified mice are not HD patients, and no mouse model will be able to tell us everything about what's happening in the HD brain. But the results of this study tell us that, at least in a model more similar to HD, axons show degeneration

before the other

neuron bits do. We need to think about which parts of the cell are sick before we can think about how to treat them, and while the knock-in mouse model has its limitations, it's a good place to study axon

degeneration during HD.



Much like the nostalgic Lite-Brite toy, illuminating a subset of neurons and leaving the rest dark allows a picture to emerge

This work also tells us that the first site of decline in the HD brain may not be the striatum after all. To be sure, we may be missing some important information since not all of the neurons of the striatum were made visible by the glowing trick. But we certainly have a new brain region to explore, and if turns out to be the opening scene for degeneration, then it will make an attractive target for therapies that can stop the damage before it starts.

Glossary

transgenic an organism that has had an extra 'foreign' gene or genes inserted into its DNA.

knock-in an organism that has had one of its genes altered, for example by adding a long CAG repeat into the huntingtin gene.

Amygdala A small brain area, in the temporal lobe, important for emotions and response to fear.

neuron Brain cells that store and transmit information

axon long extensions of neurons, that act like electrical wires to carry signals in the nervous system.

soma the main cell body of a neuron, which contains the cell nucleus where genes (DNA) are located.

*Acknowledgement: Written by Dr Tamara Maiuri, edited by Dr Jeff Carroll, June 25 2014
HD Buzz www.hdbuzz.net*



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AHDA (NSW) Inc

The Australian Huntington's Disease Association (NSW) Inc 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.

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