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1. Global MND Clinical Trials

Overall, there are more new therapeutic approaches to MND than ever before, increasing the likeihood that new therapies will soon be available that provide a meaningful impact on the lives of MND patients.

Multidisciplinary clinics (MDTs) are the biggest advance – **patients in MDTs live on average a year longer**.

However: Progress in ALS therapeutic development has been slow. Multiple failed trials between riluzole and edaravone. People with MND have very few therapeutic disease-modifying options. Why is this?

- high disease variability - MND is an infinitely complicated disorder
- lack of relevant sporadic MND models
- lack of human models
- incomplete understanding of ALS triggers and cascade
- experimental designs that are inefficient
- insensitivity of outcome measures in clinical trials
- clinical trial process begins well after system begins dysfunctioning

The clinical hetergeneity (variety) of MND means it is very easy to include people in trial control or drug group that have different disease (genetic factors, environmental factors, progression rate and pattern) to the others. If we ignore these design points in clinical trials we will come to the wrong conclusions. How can we improve clinical trials for greater success?

- better define target populations to get a more homogeneous group
- find better biomarkers to measure the effectiveness of any treatment
- improve patient selection
- use markers of disease progression so trials are more sensitive
- develop better endpoints (the measurements which indicate whether an intervention has been effective in a trial) related to disease progression
- make clinical trials cheaper by reducing sample sizes by having patients self-measure daily
- earlier diagnosis = earlier enrollment in clinical trials

Only 375 new patients diagnosed with ALS in Australia each year, but many clinical studies. Should probably be thinking about sequential studies. And including New Zealanders!

Evidence-based medicine = include people with different genetic, environmental and progression courses in one trial.

Precision-based medicine = stratification, screening (biomarkers), understanding disease mechanism, individualised response to treatment – complementary to evidence-based medicine.

We urgently need biomarkers that reflect the underlying biology of MND, to guide more targeted clinical trials. Biomarkers could stratify people into fast and slow progressors, predict regional spread, save clinical trail $$$ and lead to better results.

See video presentation:
Why Haven't We Found a Cure Yet, Prof Kevin Talbot: https://youtu.be/WzneGfPaoPQ

Global Clinical Trials Update

Prof Jeremy Shefner
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- An impossible task to give a full global update on clinical trials.
- Although we have not cured MND, we have progressed in last ten years – and there are a number of medications we now use for symptom relief and quality of life. 'Neudexta' significant advance in treating emotional lability.
    - Sialorrhoea: Hyoscyamine; Scopolamine; Botulinum
    - Emotional lability: Neudexta
    - Cramps: Baclofen, Mexiletine
    - (List not exhaustive to treatment options and/or preferred drugs in NZ.)
- MDT clinics are the biggest advance – **patients in MDTs live on average a year longer**.
- Edaravone: introduction met with a bit of skepticism, similar to that which met riluzole. Reminder that **advances are meaningful and incremental**. Patients early on in disease with diffuse fast-moving disease – showed a 33% reduction in rate of progression. Represents a significant advance in ALS care. Lot of work yet to be done to made it easier to administer (currently multiple IV infusions).
- "While we wait for clinical trials to be successful, and we are closer than ever before to that happening, it's important that we continue to treat patients with the disease."

There are many ways we are approaching the ultimate treatment of ALS:

Therapies for selected populations

- eg SOD1, C9ORF72, UNC13A
- "Many of us are very excited about these selected populations being treated better than they are now."
- **Antisense oligonucleotide (ASOs)** approach to treatment scheduled for clinical trials in 2018.

Immune system

- Evidence for immune system role: very specific aspects of immune function are altered in ALS. Patients who progress more quickly have highly inflammatory markers (CRP). Clinical trials are looking at anti-inflammatory drugs, eg masitinib.
- **Masitinib** – interim analysis showed significant effect. Not published as some odd things about data. Is still an important drug to investigate further.

Muscle function

- **Tirasemtiv** – improves skeletal muscle function. Phase 3 study slowed progression by two-thirds. Unfortunately, drug proved very hard to tolerate. 34% of patients felt unwell, unable to continue to

take the drug. However, in the patients who continued, there was preservation of vital capacity – dropped about one-third slower on the drug.
- Second generation version of tirasemtiv has been developed – CK-107. Increases force in muscles. Currently being testing in phase two study.

Stem cell studies
- Brainstorm BCT-001-US (**NurOwn**) clinical trial, stem cell treatment injected into spinal fluid.
- Had some difficulty with tolerability but no severe adverse events.
- Data encouraging but tentative. At two weeks and 4 weeks reduction in slope of progression of ALSFRS. Neurotrophic factors increased in spinal fluid.
- Promising; further clinical trial in progress.

Other studies
- AMX0035 – looks at oxidative cell death of neurons. In a phase two trial.
- Acetyl-L-Carnitine (ALC) important in mitochondrial function, shown to be protective against variety of insults. Met primary outcome in 2013, now others are trying to reproduce results.
- Actermra
- retigabine, mexiletine
- mRNAs
- tecfidera (immunoregulation)

Clinical Trials Design for ALS trials

- Clinical trials should be a worldwide effort.
- Progress in ALS therapeutic development has been slow. Multiple failed trials between riluzole and edaravone.
- Main barriers:
    - incomplete understanding of ALS triggers and cascade (insufficient animal models)
    - experimental designs that are inefficient and insensitive
- Design issues we can change.
- We can **better define target populations** to get a more homogeneous group.
- We can **find better biomarkers**.
- Prof Shefner describes some failed clinical studies (telempanel, cefriaxone, dexpramipexole) and why they failed. “This is the depressing part of the presentation.”
- Why aren’t our phase 2 studies predicting these poor phase 3 results? Prof Shefner thinks they are predicting this.
- "The big challenge is going from Phase 2 to Phase 3 trials" which can be addressed **by improving patient selection & using markers of disease progression so that our trials are more sensitive**
- To improve: **develop better endpoints** (the measurements which indicate whether an intervention has been effective in a trial) related to disease progression for functional analysis in phase 2.
- Patients measuring themselves every day give accurate results because of volume of measurements, offer the chance of being able to significantly reduce sample sizes. Some potentially useful endpoints are:
    - electrical impedance myography (painless, non-invasive test of tissue resistance in muscle);
    - hand held dynameter (measure force in muscles)
- Combination therapy – The effect of edaravone is only known in conjunction with riluzole. If edaravone was a pill, all new studies will be in combination of riluzole + edaravone. We have to **add an investigatory agent on top of a known therapy**.
- Staging system – shows how long patients spend in a particular stage and predicts how long until they enter the next stage. This can also show when a treatment may be useful (eg riluzole). As an outcome measure in clinical trials – need to move toward a more precise outcome measure. Just

four outcomes (the stages) risks losing outcome sensitivity. Timing to a particular stage could be an outcome measure.

- Cognitive measures – we increasingly recognise that cognitive change in an important and intrinsic part of the disease in a sub-set of patients. 'ECAS' (Edinborough scale) includes behavioural and cognitive component. Longitudinal studies show cognitive change increases as disease progresses (up to 50% show some small affects by end of disease).
- Why are people with PEGs so often excluded from clinical trial? If medicine if a pill it is for practical reasons. It also gathers a more homogeneous population, to help demonstrate efficacy.

Modelling early phase pathogensis in MND

Prof Kevin Talbot
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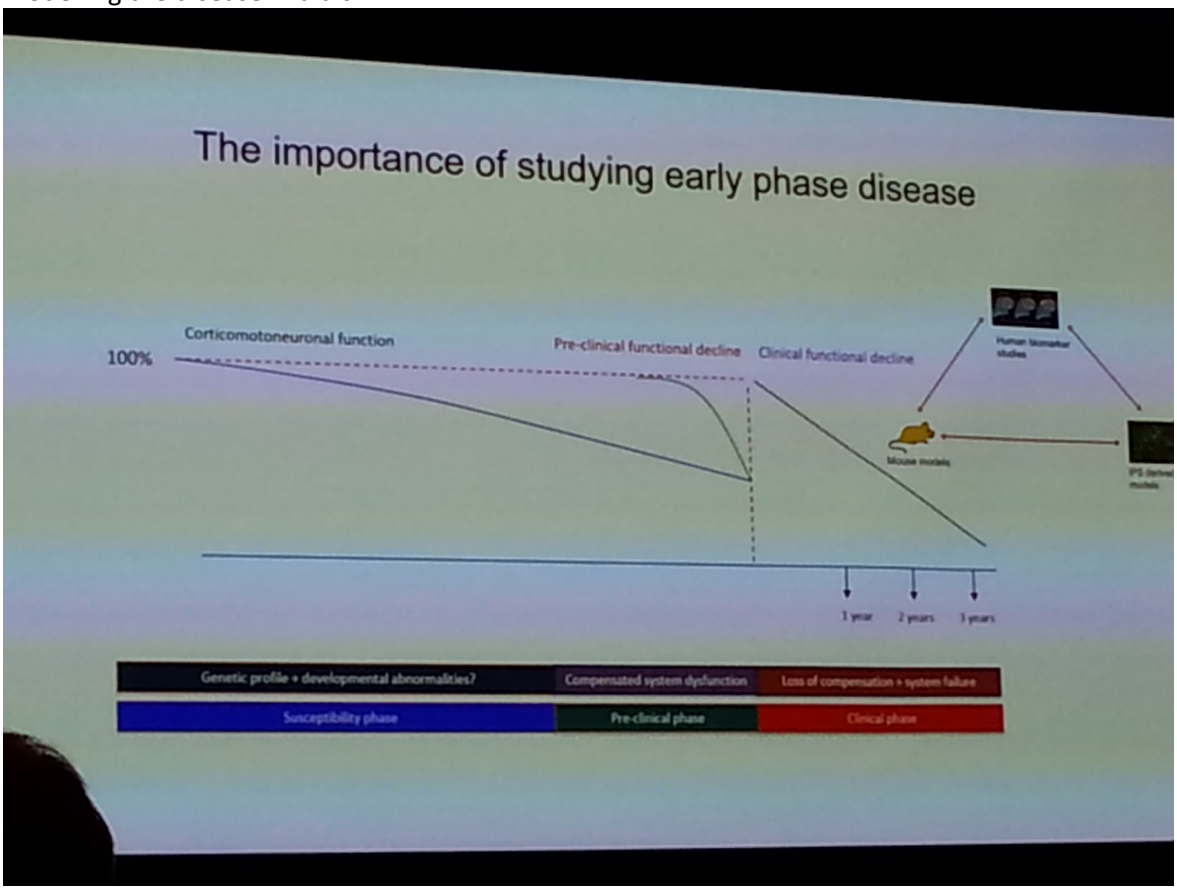
Kevin Talbot studies what's happening in the early stages of using neurons derived from stem cells, modelling the disease in a dish.



- When does ALS begin? Susceptibility based on genetic profile lasts decades. **Unknown period of time where system in a state of dysfunction but patient is compensating**. Begin to see patients when compensation is breaking down and symptoms beginning.
- The **clinical trial process therefore begins well after system begins dysfunctioning**. This suggests clinical trials are too late.
- "MND is a loss of tolerance for cell mutations."
- Talbot's research focussed on the earliest phases of ALS and FTD. **"We know TDP-43 over-expression is highly toxic."** It is a stress response reaction during times of cellular stress.
- Other key molecular discovery is ALS/FTD connection. The most common mutation in ALS, the repeat expansion in the chromosome C9orf72, explains 40% of ALS/FTD.

Making sense of big data

Prof Naomi Wray
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- Big data is important because of precision medicine initiatives – tailoring medicine to the individual. Big data can help separate patients into groups.
- Is big data overhyped? Results from machines are only as good as the data that go in. Need to maximise the number of people in the data. "Every person counts"
- Salsa Systems Genomics Consortium was awarded a grant after the Ice Bucket Challenge in 2015. Now launched in sites all over Australia. Collects hundreds of biological samples in 3 labs working to consistent protocols. Soon to start screening for known genetic mutations. About to launch environmental questionnaire (linked to European studies and census data). This will build up multiple layers of data for the same people.
- It's only if we have many risk factors to our genomic profile that we are at risk of disease.
- When we understand more genes associated with MND, they can be correlated. This lead to last year's paper showing a correlation between MND and schizophrenia. You can also start mapping which specific cells are involved in disease.

2. Australian Clinical Trials

DRUG SCREENING

Introducing the Fight MND Drug Screening Program
Associate Professor Brad Turner
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Objective: Rapid drug screening for sporadic MND using stem cells from pwMND.

- $5 million programme funded by Victoria State Government, Fight MND and Balcon Group.
- Take skin biopsy from forearm, culture skin cells (fibroblasts), turn into iPS stem cells, reprogram into motor neurons. **End up with 'MND in a dish'**. Takes 3-4 months to create.
- Funded to collect 150 pw sporadic and familial MND and 30 healthy controls.
- Use robots, automation, a live cell microscope to test existing drug libraries and hopefully identify drug hits.
- Just ordered first drug library: 4,500 prescription meds.
- By July 2018 will be into serious high throughput drug screening.
- Programme originally focused on Victoria, but **people have flown interstate to be part of the programme**. Early onset disease is model patient because responds well in the petri dish.
- Patient recruitment is ongoing. **Register at Fight MND website, click 'drug screening platform'**.

COPPER

Phase 1 study of CuATSM in MND
Craig Rosenfeld, CEO, Collaborative Medicinal Development, USA
CraigR@ColMedDev.com

- The drug CuATSM delivers copper to motor neurons. Anterior horn of brain in pwMND is copper deficient. CuATSM crosses the BBB in ALS patients.
- It extended lifespan in 4 out of 4 mouse models (SOD1). **First time in 15 years that ALS-TDI confirmed efficacy of an ALS treatment previously published by others.**
- Objectives of clinical trial: evaluate safety and tolerability of single and repeated oral dosage. Secondary objective to assess changes over 6 months. Open-label study (no placebo).

Results:

- Safety data collected for four dose levels, efficacy data collected for three dose levels.
- Mean decrease in ALSRFS of 4.7 points over 6 months.
- **Disease stabilisation of 4 patients.**
- Mean increase in ECAS (cognitive) scores of 8 points over 6 months (14 out of 15 showed improvement).
- 144mg cohort clinical trial is ongoing – recommended to be dose for phase 2.
- Phase 1 study should fully complete by end of 2018.

ANTIRETROVIRAL STUDIES

Phase 2 study of antiretroviral therapy, Triumeq, in MND – The Lighthouse Project
Professor Julian Gold, Sydney Medical School, Australia
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Objective: Repurpose HIV antiretroviral drug Triumeq to see if useful for MND.
Hypothesis: HERV-K activation is a casual mechanism in ALS, and prevention of HERV-K expression using antiretroviral drugs could be an effective treatment.

- The Lighthouse Project is a clinical trial to test whether MND is caused or triggered by human endogenous retroviruses (HERVs). HERVs are mostly inactive in adults, but have affected humans for all generations. 8% of our genome is composed of viral DNA that has been integrated into mammal DNA over <40 million years.
- We know of 5 retroviruses that are infecting humans now. HIV is a retrovirus that took 40 million lives.
- HERV-K is a human endogenous retrovirus associated with MND, incorporated into our DNA 100,000+ years ago. This gene virus can be upregulated and turned on. When turned on, it can infect other cells. People with ALS have very statisitical significant increase in HERV-K.
- In 2016 USA National Institute of Health took proteins from HERV-K, injected it into mice, and the mice developed ALS.
- Can antiretroviral drugs impact HERV replication? Developed for people with HIV, used for 15 years, turned HIV from a universally fatal disease to a manageable chronic illness. People who take this medication are expected to live a normal life span. Can we re-purpose these drugs for MND?

Results: 40 patients from Sydney and Melbourne, 6 months of open-label treatment (no control group) with Triumeq (combination of three antiretroviral drugs in once a day tablet, taken by around 250,000 people with HIV). Primary outcome achieved with Triumeq shown to be safe and well tolerated in patients with ALS. No interactions with Riluzole. **Some people 'responders', others 'non-responders'**. Statistically five people should have died over the time, but no one died during the study. The study will continue.

PK enhancement of retroviral therapy in HERV-K in ALS-FTD
Dr Ton Blunt
CEO, Izumi Biosciences, USA

- About half pwMND seem to have reverse transcriptase enzyme (retrovirus) in blood – 5 studies replicate these findings.

- In 1980s some young HIV patients developed ALS. Partial, transient response to antiretroviral therapy.
- The blood-brain barrier (BBB) protects the central nervous system (CNS), only 2% of FDA approved small molecule drugs cross the BBB. In MND, **early stage blood/spinal cord barrier (BSCB) breakdown/leakage could precede motor neuron death.**
- Dose of drug into CNS like hose into swimming pool. Drain/pumps in back could drain pool in seconds. 'Pumps' overexpressed in pwMND. In principal, if we block the 'pumps' we can keep drugs in brain and spinal cord.
- The PK enhancer Elacridar maintains therapeutic drug levels in pump-protected 'sanctuary' parts of brain. If combine PK enhancer with FDA approved drugs, you enhance therapeutic drug levels in brain.
- Compounds that can normally only be given via IV, now become orally available.
- Suggest: Start with patients who have HERV-K in blood. Use PK-enhancer to drive ARVT drugs into brain.

NB: This speaker was heavily criticised: ARVT already cross BBB and are able to suppress HIV in the brain indefinitely if you continue to take them.

INFLAMMATION STUDIES

Phase 1b study of anti-CD14 (IC14) in MND
Prof Robert Henderson, Royal Brisbane & Women's Hospital, University of Queensland
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- Whatever causes MND results in misfolded proteins, which triggers an immune response, which causes inflammation, which causes damage to functional cells. Cell stress leads to motor neuron death leads to motor function loss.
- Inflammation and microglial activation is common in neurodegenerative diseases. In MND, destructive microglial activation is accompanied by expression of pathogen-association molecular patterns and multiple damage-associated molecular patterns.
- The drug **IC14 is a master regulator of immune function** and inflammatory response. Has an extensive clinical history and good safety profile.
- Believe that immunotherapy has great promise for MND.
- People in this study were more than happy to have a lumbar puncture, which shows how keen pwMND are to participate in research.

Results: All patients completed the study, will be complete by April 18. IC14 well tolerated, no adverse events or withdrawals. Biomarker data may suggest modulated inflammatory response. Planning underway for phase 3 study in rapidly progressing MND.

Phase 2 study of Tecfidera in ALS (TEALS)
Prof Steve Vucic
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- Reduced regulatory T cells (T-regs) in ALS patients are associated with a rapid disease prognosis. Those with higher rates have slower rate of progression of MND.
- Tecfidera is safe and effective at increasing a person's T-reg numbers. Has an antioxidant response and anti-inflammatory response. Significantly improves responsiveness of T cells for immunoregulation by T-regs.
- Tecfidera has been shown to reduce cortical hyperexcitability, modulate microglial activity (inflammation) and has anti-oxidant effects.

Results: Has not yet started. TEALS study: will screen 150 pw sporadic ALS. Recruit 120. Will be **largest phase 2 study in Australia**. Hopes to reduce ALSFRS scores by five points over 9 months. Should have results by early 2019.

Phase 3: Clinical development of oral formulation of edaravone (TW001)
Inez de Greef-van der Sandt, CEO Treeway (Netherlands)
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- TW001 is an oral form of Edaravone which aims to delay disease progression by targeting oxidative stress.
- TW001 is designed to be a daily single dose that requires no drug holiday unlike the intravenous delivery of Radicut and Radicava. An oral version will be more patient-friendly, can give every day in a home setting. If can give it daily, efficacy may also be higher.
- TW001 has bioavailability of 70-80%. With continuous daily dosing, monthly exposure to drug is 2.8-fold increase over Radicava.
- Have done 4 x Phase 1 studies. Proven safe and tolerable.

Results: Upcoming phase 3 trial designed for Europe and Australia. 5th clinical study, 300 pwMND, 40 week trial but continue dosing til 72 weeks. Hope to have drug product available by end of 2018.

Audience question: What isn't Treeway dose-finding in current study? Because want phase 3 with highest chance of success. Maybe afterward will test other dosing schemes.

CANNABIS

Phase 2 study of cannabis based medicine extract (CBME) in ALS – EMERALD trial
Associate Professor Arman Sabat
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Objective: Trial high CBD, low THC cannabidiol (CBD) in pwMND to study the efficacy extending ALS survival and alleviating symptoms such as spasticity, pain, weight loss and assess quality of life.

- Animal MND models – review of 7 studies demonstrate **cannabinoids significantly prolonged survival time.**
- Cannabis has over 400 complex compounds. THC is the most active compound producing psychoactive effects. Next is CBD which is a protects against inflammation, oxidative stress and the proposed mechanism of ALS – glutamate excitotoxicity.
- Our body has endocannabinoid system (ECS) found in all vertebrates. Two types of cannabinoid receptors, CB1 and CB2. CB1 receptors are predominant in the brain, CB2 receptors are found in the immune system.

Results: About to start at Gold Coast Hospital. 30 pwMND, 6-month trial. Using CannTrust CBD oil (1:17 THC:CBD) in capsule form. Efficacy is the primary objective. Secondary objective is to evaluate safety, tolerability, effects on pain management.

Aidoence question: What do you tell patients who see clinical drug cannabis being tested, why not access cannabis through other sources? Decision to be made by the patient. Tell them there's really no data. Studies are to start providing information for patients.
Recommended further reading: Current Therapeutic Cannabis Controversies and Clinical Trial Design Issues, Ethan Russo

3. Disease Biomarkers

Discovery and Use of Biomarkers for MND/ALS
Prof Robert Bowser
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- In 2005 early profile of cerebrospinal fluid looked for biomarkers for ALS – probably the first use of these types of technologies.
- Oncology is always ahead of MND research, this approach had been used for cancer for a decade already.
- Now bio samples from well over 3000 subjects in different studies can be used to identify biomarkers.
- Neurofilament proteins are a known biomarker for MND – a prognostic marker too, that may help predict survival. Levels are higher in people with familial C9orf72 ALS.
- Neurofilament protein-based tests are now being commercialised and used in clinical trials. Testing will be available in the US this year, and is already available in Europe.
- We also need other types of biomarkers to reflect the different mechanisms of MND eg for neuro-inflammation.
- He described **biomarkers as a toolkit that will allow us to track biochemical changes in disease progression, guide patient enrollment in clinical trials & monitor drug efficacy**.
- Analysis of cerebrospinal fluid from people with fast and slow progressing MND found that the groups had different levels of the biomarker chitinase.
- Biomarkers can be used to identify changes to specific cells types in MND, which could be used to choose the patients who will best fit clinical trials. In future biomarkers will be used to define patients that will best respond to a particular treatment.
- Artificial intelligence can now be used to find biomarkers, combine datasets and clinical information to create a precision medicine approach.

The role of biomarkers in therapy development
Prof Michael Benatar
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- There is a plethora of candidate biomarkers. It's important to develop only those that are fit for purpose.
- It's important to **establish the intended clinical use of any biomarker and conduct large population studies similar to clinical trials**. This is the next step for p75 and Neurofilament protein biomarker development.
- For future development of biomarkers, need to have a heavy focus on what the potential future application will be.
- There are four purposes for biomarkers: diagnostic, prognostic, predictive, pharamacodynamic.
  1. **Diagnostic biomarkers:** Tests with high sensitivity are needed. We need to test the biomarkers in populations where a diagnosis of MND is unknown. We really need to get people to a neurologist as quickly as possible if MND is suspected.
  2. **Predictive biomarkers** are mostly restricted to genetic markers so far. We urgently need biomarkers that reflect the underlying biology of MND, to guide more targeted clinical trials.
  3. **Prognostic biomarkers** need to add value to what we can already tell.
  4. **Pharmacodynamic biomarkers** indicate a biological response to drugs or disease progression. Need to fully understand what things look like without treatment, to truly see the impact of a treatment.

Validation of urinary biomarker p75

Mary-Louise Rogers
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- Major barrier to successful clinical trial is the insensitivity of outcome measures. We need markers to measure the effectiveness of any treatment.
- p75 is a neurotrophin receptor that is expressed following nerve injury. It has long been known to be found in MND. Injured nerves shed p75, then it appears in urine.
- **Urinary p75 is significantly higher in people with MND**. It's also easy to measure and not invasive to collect.
- p75 is also raised in cerebrospinal fluid in people with MND and may also be raised in blood serum. This shows that it must be present in the fluid that bathes the spinal cord as the motor neurons are degenerating.
- Research then looked at whether levels of urinary p75 changed over time and therefore could mark disease progression and prognosis.
- Urinary p75 levels did increase in each patient as disease progressed, as motor function declined. There was a correlation between p75 and the ALSFRS (which is a more subjective measure currently used to measure progression in clinical trials).
- p75 is also a predictor of survival: high baseline p75 is a predictor of worse survival.
- Now being used in some clinical trials. It's an opportunity to get further validation of the use of p75 in clinical trials.

Whole blood transcriptome analyses

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- The search for a diagnostic and predictive biomarker in the Netherlands.
- Blood is drawn at first visit (pre-diagnosis). They looked at the genes that were deferentially expressed in people with MND compared to healthy controls.
- More work needs to be done to make sure results are more specific for MND. They are uploading their data to make it available to other researchers around the world.
- *(It's great to see this sharing of data and IP to advance research into MND!)*