Research Summary[1]

The 6th International Cystinosis Conference, Lignano, Italy

23–26 September 2010

During the 3 days of the 6th International Cystinosis Conference a wide range of presentations, discussions and social activities were arranged for a diverse audience. However, a large proportion of the conference is devoted to the medical and research community, allowing professionals to communicate their recent learning in the field of Cystinosis and how best to treat patients.

This article summarises some of the key work that was reported at the conference, but is not a comprehensive review of all the sessions – such an undertaking is impossible in only a few pages of text!

The theme of the previous 2008 conference, in Dublin, was "Dreams to Reality". At this year's conference it was hugely encouraging to see the progress that has been made in so many projects, as well as seeing awareness of Cystinosis growing around the world, particularly in Russia through the work of Alexey Tsygin and Mikhail Kagan.

In terms of the research there were two standout presentations that give great hope for the future – Enteric Coated Cysteamine by Dr Dohil and Stem Cell Research by Dr Stephanie Cherqui.

Enteric Coated Cysteamine (A Twice Daily Cysteamine Treatment?)

Dr Dohil and his team's work, in conjunction with Raptor Pharmaceuticals, involves the development of enteric coated Cysteamine. The application of such a coating helps Cysteamine avoid destruction in the stomach and reach the small intestine, where their research has shown it is better absorbed by the body.

> **What Is Enteric Coating?**
> An enteric coating is a barrier applied to oral medications (such as aspirin) that stops the medicine being absorbed before it reaches the small intestine.

Dr Dohil's team have been working on this coating since 2004 and they are now well into the trial phases of the treatment, with results to date being very encouraging. The last series of trials involved patients taking a lower dosage (two-thirds of the norm) twice a day. The results showed a trend for a greater reduction of cystine levels for a longer period in comparison to normal dosages of Cystagon taken 4 times a day.

This enteric-coated Cysteamine was administered in a capsule form similar in size to Cystagon, but g-tube and powdered versions are also believed to be possible.

This work has now reached Phase 3 trials in the USA and Europe and, although reports vary as to when it will be available, Dr Dohil suggested it may be 2 years before this product hits the market.

Stem Cell Research (Towards A Cure)

The second stand-out presentation was by Dr Stephanie Cherqui of Scripps Research Institute, San Diego, USA, reviewing the work performed into stem cell research.

Previous research, as presented by Dr Antignac of Paris University,[2] has already established the genes responsible for causing the different forms Cystinosis. This has helped in the creation of a Cystinotic mouse, which has proven crucial for the testing of new Cystinosis therapies. Genes act like an instruction set for the body, specifying how it should develop and maintain itself. It is well understood how the "Cystinosis gene" causes the cystine transporter not to function, leading to a build up of cystine in cells that then results in further complications. There is nothing wrong with the gene itself; it just contains the wrong instructions, building cells with this fault. Dr Cherqui's work has been concerned with methods for providing the body with stem cells that have modified genes containing "corrected" instructions.

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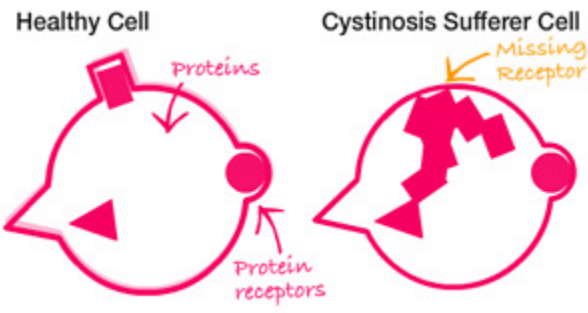
[1] This article is a summary of the research presented at the 6th International Cystinosis Conference as observed by a non-medical person. It does not constitute medical advice and therefore should not be treated as such.

[2] "Genetic Basis Of Cystinosis" – Dr C. Antignac.



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Using Cystinotic mice, they have been able to transplant bone marrow and haematopoietic stem cells containing functional Cystinosis genes and observe the growth of "corrected" cells within some organs such as the kidney, liver, eye and brain. In addition, cystine levels were observed as being lower in these organs – down 60% after 4 months.

These are just preliminary findings and there is still much work to be done. Rather than using donor cells as in the above approach, their longer term strategy is to isolate stems cells from the bone marrow of younger Cystinotics and modify them to introduce a corrected functioning version of the defective Cystinosis gene. The modified stem cells would then be re-planted back into the patient's body. A key advantage of using the patients own cells, as opposed to those from a donor, is that there is a reduced risk of rejection since the body is less likely to consider these modified cells as a foreign invader. However, it is not without risks. The modification vector (i.e. the design changes made to the stem cells) must be accurate and precise. Any additional, unintended changes could lead to corruption of other gene instructions, with side effects such as leukaemia being a possibility. Hence the next steps for the Scripts Institute team are many more tests for efficiency and safety via use of the mice.

However, if such a treatment could be perfected and approved for general use, it would be a one-off treatment, expected to last the life-time of the patient.

What Are Stem Cells?

In adult organisms, stem cells act as a repair system for the body, but also ensure the normal re-growth of regenerative organs, such as blood and skin.

Cystinosis Foundation UK Funded Research

The Cystinosis Foundation UK is primarily supporting two research groups – Roz Anderson's team at Sunderland University and Don Cairn's team at the Robert Gordon University in Aberdeen.

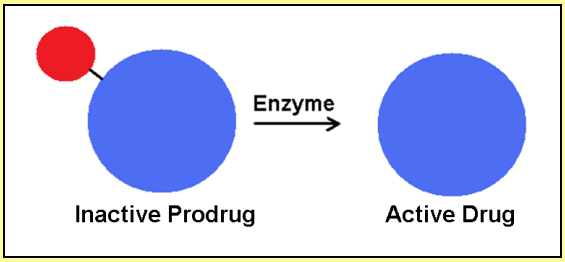
The research at Sunderland University has been focused on Prodrug research in order to improve the effectiveness of current Cysteamine treatments. Much of the Cysteamine administered is lost in excretion and is not efficiently absorbed in key areas. A successful Prodrug would initially disguise the Cysteamine and allow it to be transported around the body, where it is then better absorbed. This may lead to reduced, less frequent dosages and negate some side effects such as bad breath and vomiting.

The Sunderland team have been testing various compounds (around 15) for their effectiveness at delivering Cysteamine and have successfully identified compounds showing the desired behaviour. They are currently undertaking further testing of these preferred compounds, with clinical trials being the next stage.

The Cystinosis Foundation UK has been supporting Sunderland University by purchasing equipment and funding PHD student Lisa Frost, who is undertaking much of the practical research.

What Is A Prodrug?

A Prodrug is an inactive form of a parent drug which is only activated once inside the body, usually by an enzyme. This delayed release helps target the parent drug effectively. Prodrugs can help to overcome many problems, including inefficient delivery, poor absorption, poor bioavailability, noxious taste and smell.



Reproduced Courtesy of L. Frost, Sunderland University

Meanwhile, the group at the Robert Gordon University has been experimenting with different delivery mechanisms for Cysteamine, again with the aim of improving absorption to lower the dosage and frequency of administration, as well reducing other side effects. Their proposed delivery mechanisms in the past have included inhalers (as used to treat asthma) to deliver Cysteamine to the blood stream via the lungs. However, their current focus is the use of eye gels containing Cysteamine. The existing treatment, a water-soluble Cysteamine salt, quickly drains from the eye, leading to the need for frequent application (15 times a day in some cases). However, a gel exhibiting pseudo plastic behaviour would be able to remain in the eye for longer and have a greater effect.

Pseudo Plastic Behaviour

Materials that exhibit behaviour called *shear thinning*. Such materials are thick when at rest, but have lower viscosity when a force is applied.

Ketchup is such a material – it can be squeezed out of the bottle like a liquid, but retains its shape on your plate!

Long Term Considerations/Other Research

There were several sessions over the 3 days that related to long term outcomes of Cystinosis, in terms of physiological and psychological development, as well as side-effects due to long term use of Cystagon.

Dr Elena Levtchenko outlined her discoveries in "Update On Cysteamine Treatment And Adverse Events". Her studies of a group of 5 to 15-year-old Cystinotics, between 2004 and 2008, showed that in a small number of patients high dosages of Cysteamine resulted in lesions, bone pain and muscle weakness. These results challenge the strategy of taking as high a dosage of Cysteamine as is tolerable for managing cystine levels.[3] However, it should be noted these symptoms were only apparent in a small number of patients (a small subset of European patients) and more understanding of these effects is required.

Other sessions included research into muscle atrophy starting in late adolescence of some Cystinotics,[4] initially affecting the hands, but also leading to problems with swallowing and speech. Mitochondrial dysfunction is thought to play a role and low carnitine has also been found. It is unclear if Cysteamine will prevent these issues, or if exercise will help, but more research is felt to be necessary.

What are Mitochondria?

These are special parts of a cell responsible for converting nutrients to energy. If they don't work, your cells lack the energy to do their job.

As well as the physiological effects of Cystinosis, there are psychological considerations, ranging from reactions to a strict medical regime to simply being considered "different" from peers in the playground. Studies have been conducted in these areas,[5] as well as there being discussions in the family sessions. Furthermore, Dr Trauner of the University of California presented a session on "Cognitive Performance In Nephrophatic Cystinosis", highlighting issues with visual spatial, visual memory and visual motor performance. Dr Trauner has kindly made some of her publications on physiological and psychological effects of Cystinosis available to the Cystinosis Foundation UK, which we will be making available on our website in the near future.

Throughout the sessions a common noted theme was *keep taking your medications regularly*. There were many examples of improved growth and general health through frequent and sustained administration of medicines from various studies[6] and anecdotal evidence during family sessions.

Patient Databases

A key component of research is access to data to support research results and help identify trends (or anomalies) in order to reach accurate conclusions. Two new projects have recently been created aiming to provide this data.

[3] Note: the current Orphan Europe recommended dosage is 1.3g/m2 for under 12 years old and 2g/m2 for children over 12 years or over 50Kg in weight.

[4] "Muscle Wasting In Cystinosis" – Dr D. Trauner.

[5] "Psychological Aspects And Medication Compliance" – M. Ostermann.

[6] "Long-Term Outcome In Cystinosis" – Dr W. Gahl.

In Europe, with support from various organisations, a new patient database has been created that can be completed by medical practitioners. The data provided may also be used to supplement medical records, providing a clearer picture for local GPs.

The new Cure Cystinosis International Registry has been created, in conjunction with the Cystinosis Foundation USA and the Cystinosis Research Network. The key difference with this project is that it is patients who enter their details and, as advocates of this project, we encourage everyone to do so (www.cystinosisregistry.org). Data can only be accessed by approved professionals and all data is anonymous to these professionals.

Conclusions

Some truly exciting developments were presented at this conference. Cystagon is the main treatment for Cystinosis and its side effects and limitations are well known. However, with the new enteric coated Cysteamine treatment reaching later trial phases, there is future potential for a step-change in terms of quality of life. Furthermore, the results from stem cells research are showing that a cure is feasible, even if much more work is still required.

More generally, progress is being shown in many projects around the world. This is progress with which you can help by participating in the new database programmes (www.cystinosisregistry.org), and a common theme through many presentations and patient sessions was ***"keep taking your meds, and take them regularly"***.

Finally, as well as acting as an opportunity for professionals to present their work, the conference allows the exchange of ideas. Although not mentioned explicitly during presentations, "collaboration" and "sharing" were words mentioned more than once during conversations I had with individuals. "Dreams To Reality" was the theme of 2008 and now in 2010 we hope we are a step closer to that reality.

Matt Blackham

November 2010

Cystinosis Foundation UK Volunteer, Uncle to a Cystinotic.

