The 6th International Cystinosis Conference was held on 23–26 September in Lignano, Italy. The event was organised by the Italian Cystinosis Foundation and the Cystinosis Foundation USA. The event was attended by over 200 people and was very well supported by clinicians and researchers along with Cystinotics and their families. The programme of events was very full and covered all aspects of Cystinosis, including both research and family orientated sessions. On the Friday morning we had an initial presentation from Dr Jerry Schneider on “50 years of Cystinosis”.

Dr Schneider first became involved with Cystinosis in 1965. He reminded us that at this time there was no treatment, no way of measuring Cystine levels in the body and only a vague understanding of what caused Cystinosis to occur. Dr Schneider was not only involved in patient treatment and research, but also pivotal in setting up the first foundation in 1982 with Jean Hotz in the USA. His historical review included key events, such as the introduction of Cystagon in the 1980s, and offered hope for the future with new medicines and, through stem cell research, a potential cure, although there is still a long way to go. Dr Schneider is retiring and will be sorely missed in the Cystinotic community. A gala dinner was held on the Sunday evening to mark this event.

A couple of items of interest that came out on that first morning were the European Cystinotics Registry and the Cure Cystinosis International Registry.

The Cure Cystinosis International Registry (www.cystinosisregistry.org) has the aim of having every patient with Cystinosis entering their details onto a database. Access will then be given to approved professionals to allow them to spot trends and generally assist their research. All information is presented anonymously and such databases have helped greatly in the advancement of other medical conditions. The Cystinosis Foundation UK is an advocate of this project and we encourage every Cystinotic to register.

The European Cystinotic Registry is a similar database, but with a different aim, in that it is to be completed by doctors, as opposed to patients. Again, the UK Foundation encourages patients to have their doctors complete the registration form for this database, and the information can be used to supplement medical records. Other exciting updates were received from Dr Ranjan Dohil who is involved with the Raptor Pharmaceuticals work into the enteric coated Cysteamine that would only need to be administered every 12 hours, rather than the current 6 hours for Cystagon. This is currently undergoing trials in the USA and Europe. Current estimates predict this treatment to be generally available in two years time.

Dr Stephanie Cherqui presented on the developments in gene therapy and bone marrow transplantation. This work is exciting as it presents a possible “cure” for Cystinosis in the longer term. The research seems to be well advanced to producing something that will work. However, timescales are unknown at this time and there is substantial work required to understand the long term effects of such treatment.

Along with other sessions on the Saturday, a poster session was held and researchers had the opportunity to display their recent work and discuss it with others. Our funding of Sunderland University into developing a pro drug was presented by Lisa Frost and Prof Roz Anderson. Furthermore, work by the Robert Gordon University, whom we are also funding, was presented by Barbara Buchan and Prof Don Cairns. Particular interest was shown in both these projects from other researchers and Cystinotic support groups.

In addition to the various research presentations, there were several sessions dedicated to families. Some of these were open forums with a panel of experts, where families could ask specific questions. Other were more focused, such as the “children only” sessions with doctors, enabling the children to speak freely to the doctors, without the presence of parents or other adults. Again, Dr William Van’t Hoff, from Great Ormond Street Hospital, was in attendance at these sessions. In addition, Dr Van’t Hoff gave a presentation on a Cystinosis information booklet aimed at children that he is currently working on. We hope to hear about this project in the future.
On the Sunday morning, the W.L. and Sophie Hobbs Award was presented to Dr Alexey Tsygin and Mikhail Kagan for their work on Cystinosis in Russia. They gave a report on the current state of knowledge and the difficulties they faced such as acquiring medication within Russia.

A small delegation from the Cystinosis Foundation UK was in attendance and several families from the UK had made the journey over too. We are pleased you were able to come, and we appreciate the effort this involved. The conference was a great opportunity to meet people, put faces to names, and to make new contacts with other Cystinotic support organisations from around the world.

Finally, a special mention must go to Valerie Hotz of the Cystinosis Foundation USA who played a pivotal part in this event and really went over and above the call of duty to assist with running it – Valerie just seemed to be everywhere!

Roy Forsyth, Chairman
Cystinosis Foundation UK

Research Summary

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. 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, 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.
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.

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.

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.

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. 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, 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.
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, 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 \textit{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 and anecdotal evidence during family sessions.

\textbf{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.

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 (\url{www.cystinosisregistry.org}). Data can only be accessed by approved professionals and all data is anonymous to these professionals.

\textbf{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 (\url{www.cystinosisregistry.org}), and a common theme through many presentations and patient sessions was \textit{“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.

\textit{Matt Blackham}

\textit{Cystinosis Foundation UK Volunteer, Uncle to a Cystinotic.}

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.