



## SYSCILIA Newsletter 7 – September 2012

### Midterm Review

On September 20 & 21, 2012 the project's Midterm Review was performed by the European Commission in Heidelberg.

All partners were present and very well prepared providing the Commission all information needed to assess the project. Thanks to all of our efforts, the Commission, represented by Christina Kyriakopoulou and the external reviewer Prof. Milan Macek, expressed a very positive view on our project.



### Publications and Press releases

#### **EU funded studies on gene therapy and gene-based therapy for ciliopathies**

Gene therapy has been used to give mice born without a sense of smell the ability to sniff their surroundings, an international team of researchers say.

The mice had a genetic disease which affected microscopic hairs in their body - called cilia - which can detect chemicals in the air.

Cilia stick out from many cells in the body. Improper cilia development due to genetic defects can result in a range of disorders called ciliopathies. One symptom can be a lifetime without a sense of smell, called congenital anosmia.

The study, published in **Nature Medicine** looked at mice with a mutation in their *Ift88* gene, which meant they struggled to produce cilia and could not smell.

The group created a virus which was capable of infecting cells with a working version of the *Ift88* gene. This was injected into the nose on three consecutive days. This was able to restore the cilia and a sense of smell.

The international team of researchers, of which 3 groups are funded from the SYSCILIA project, part of the 'Health' Theme of the EU's Seventh Framework Programme (FP7), hope their findings will lead to treatments for diseased cilia, which can cause blindness, deafness and kidney disease in people.



Prof. Philip Beales from University College London, partner in the SYSCILIA project, was involved in the study and interviewed by the BBC (<http://www.bbc.co.uk/news/health-19409154>). He said: "It is a proof of concept that has shown we can get that gene back into these cells, produce the right protein, produce cilia and function as expected. He said the mice were then able to use their sense of smell to seek out food. However, it is hoped a similar approach could be used for other symptoms of the disorders.

Dr. James Battey, director of the US National Institute on Deafness and Other Communications Disorders said: "These results could lead to one of the first therapeutic options for treating people with congenital anosmia. They also set the stage for therapeutic approaches to treating diseases that involve cilia dysfunction in other organ systems, many of which can be fatal if left untreated."

Gene addition by viral vectors is a promising strategy for the treatment of hereditary disorders, including retinal diseases. However many genes are frequently alternatively spliced or their coding sequences are too large for any available viral delivery system.

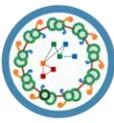
Human ciliopathies are often caused by nonsense mutations (30%) resulting in a premature termination codon. Aminoglycosides and PTC124 have tremendous therapeutic potential by promoting read-through of nonsense mutations and thereby generating full length-proteins. Molecular diagnostics allows selection of patients for application of mutation-specific therapies. Such a personalized therapy can be accomplished by administering drugs that induce the translational read-through of nonsense mutations.

The group of Prof Uwe Wolfrum, another partner in the SYSCILIA project, compared for the first time the ability of three different translational read-through inducing drugs, NB30, NB54 and PTC124, to induce translational read-through. The attention was focused on a mutation known to develop the most severe form of Usher syndrome, the most common form of inherited deaf-blindness. This mutation is a so-called nonsense mutation in the USH1C gene, which leads to the generation of a stop signal in a DNA base, resulting in premature termination of protein synthesis. The comparison, published in **EMBO Molecular Medicine**, emphasizes the potential of NB54 and PTC124 in treating nonsense mutation based retinal disorders.

### **EU funded studies link degenerative diseases that affect kidney, retina and brain to defective DNA damage repair.**

For reasons not well understood, chronic kidney disease is on the rise in developed countries. The biology of renal fibrosis, it's central feature, also remains a mystery.

Associate Professor Rachel Giles, PhD, from UMC Utrecht and her group participate in the FP7 SYSCILIA project, which partly funded the study that links degenerative diseases to defective DNA damage repair. SYSCILIA, part of the 'Health' Theme of the EU's Seventh Framework Programme (FP7), takes a systems biology approach to dissect cilia function and its disruption in human genetic disease.



Recently, together with colleagues from seven other countries, Giles described in **Nature Genetics** [44(8), 910-5, August 2012] new gene mutations that cause the very rare genetic kidney disorder KIN (karyomegalic interstitial nephritis). Children suffering from KIN suffer from prematurely ageing kidneys. Their kidneys look like organs from elderly persons.

Giles and colleagues found in 9 out of 10 examined families that mutations in the *FAN1* gene caused this rare disease. It fits with the function of the FAN1 protein, which is involved in DNA repair. Apparently, in KIN patients, kidney cells are unable to repair DNA damage, which accelerates the ageing process, specifically in the kidney. UMC Utrecht researchers confirmed the FAN1 impact on kidneys by altering the gene in zebrafish.

The health implications of the finding may seem limited. Prior to this publication only 15 families worldwide were known to suffer from KIN. But the link between cellular ageing and kidney disease is a new one, and suggests a whole new cause of kidney disease.

“We believe”, Giles says, “that this mechanism explains how factors like DNA damage cause kidney disease in the general public. It would for example explain why children with relatively ‘young’ organs sometimes exhibit kidney diseases typically associated with the ageing population.”

A paper in the prestigious journal **Cell** [150, 533-48, August 3, 2012] confirms the link between DNA damage and kidney disease. In this paper they link renal ciliopathies to DNA damage response signaling. An international team of researchers, of which 6 groups are funded from the SYSCILIA project, has identified by whole-exome resequencing disease causing mutations in 3 genes that function within the DNA damage response pathway.

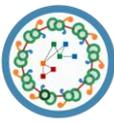
Nephronophthisis-related ciliopathies (NPHP-RC) are degenerative recessive diseases that affect kidney, retina, and brain. Genetic defects in *NPHP* gene products that localize to cilia and centrosomes defined them as “ciliopathies.” However, disease mechanisms remain poorly understood. Less than 50% of all cases with NPHP-RC have mutations in known NPHP-genes.

Some of the recently identified genetic causes of NPHP-RC are exceedingly rare which necessitates the ability to identify novel single-gene causes of NPHP-RC in single affected families. To achieve this goal, a strategy was developed that combines homozygosity mapping with whole-exome resequencing. Because this approach allows identification of multiple different causes of NPHP-RC within a short timeframe, it has the potential of delineating pathogenic pathways.

Using this approach, the study identified mutations in three NPHP-RC genes, *MRE11*, *ZNF423* and *CEP164*, which together suggest involvement of a DDR signaling pathway in NPHP-RC pathogenesis.

Based on their findings the researchers propose a pathogenic hypothesis for NPHP-RC that implicates DDR signaling as a relevant disease mechanism. Within this hypothesis, loss of function of NPHP-RC proteins with a dual role in DDR and centrosomal signaling, would cause disturbance of cell-cycle checkpoint control.

The link between degenerative diseases and DNA damage response signaling, causing impaired cell-cycle checkpoint control might provide a mechanism for the dual phenotypes of degeneration/dysplasia seen in NPHP-RC in kidney, eye, cerebellum and liver. The degenerative



phenotypes would be characterized as diseases of “organ-specific premature aging”, thereby pointing in new directions for the identification of small compounds for therapy.

For a complete overview of publications with SYSCILIA acknowledgement, please refer to our website: [syscilia.org/results](http://syscilia.org/results).

### Calendar 2012 / 2013

#### [7th French Meeting on Cilia, Flagella and Centrioles](#)

22-24 Oct, 2012; Calanque des Eaux Salées, 13620 Carry-le-Rouet, France

#### [American Society of Nephrology 2012](#)

30 Oct – 4 Nov 2012; San Diego, California, USA

#### [The American Society of Human Genetics, 62nd Annual meeting](#)

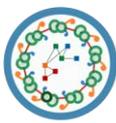
6 – 10 Nov 2012; San Francisco, USA

#### **2013 – Cross Component meeting SYSCILIA.**

16 – 18 January 2013; Heidelberg, Germany

#### [FASEB 2013 conference on the biology of Cilia and Flagella](#)

23-28 June 2013; Niagra Falls, New York, USA



### SYSCILIA participants

**Gabriella Wheway  
(LIMM)**



**Simone Dusseljee  
(RUNMC)**



### Who are you?

My name is Gabrielle Wheway, post-doc in the ciliopathy research group of Prof Colin Johnson at Leeds Institute of Molecular Medicine. I was born in Taunton, Somerset in 1985 and grew up in Burnham On Sea, a small seaside town in the West Country. I studied Natural Sciences at Emmanuel College, Cambridge from 2004 – 2007, completed my PhD with Colin in 2011 and am now working on the Syscilia project in my first post-doctoral position.

My name is Simone Dusseljee, project manager for SYSCILIA. I'm trained as research technician and have worked on cancer research projects for several years. First two years at the University Medical Center Leiden, then 6½ years at the Dutch Cancer Institute in Amsterdam (group of Jacques Neefjes). After working for a company for four years, Numico BV (now Danone) in Wageningen, I started in Nijmegen studying CRB1 function in retinal dystrophies combined with coordinating tasks like ordering, health and safety regulations, quality system set up and implementation. After effectuating a project aiming to improve and centralize sample reception for our department, I was asked to be project manager for SYSCILIA, which I happily accepted and still like to be.

### What have you learned about yourself over the past two years?

That I care more about my career in scientific research than I previously realized.

That I have more skills fit for the job than I anticipated but also that I'm susceptible for stress ....

### What dream do you want to come true in the coming year?

More security for my future.

To find the perfect balance between private and working life.

### What do you want to achieve next year with the project?

I am looking forward to completing the screen and getting to work on investigating the interesting, novel hits we identify. I am really looking forward to publishing our data. I also look forward to working with the other members of the Syscilia consortium some more. I feel very lucky to have met such nice people and such excellent scientists through being part of this project.

A smooth reporting period and establishing more collaborations and connections with external scientist and projects.



### What is your life motto?

Plan for the future but enjoy the present.

Don't dream your life, but live your dreams

### What trait would you like to change about yourself and what do you find a nice personal trait?

I wish I was more resilient to adversity and didn't worry so much. I like that I am honest and caring.

Change: to be able to let go.... I always want to be in control.

Nice trait: I'm organized and considerate.

### What helps you to relax in times of rush and stress?

Eating and drinking with my husband and my friends. Also, walking with my husband and our lovely Labrador.

Running, reading, cooking and jigsaw puzzles

### If you could choose another profession what would you choose and why?

Teaching. I really enjoy working with young people, and I value education very highly.

I chose to be a manager instead of technician. I'm very organized

### Who is your idol and why?

Within the realm of science I would have to say Phil Robinson, a colleague from our Section, who died recently. He was a truly inspirational scientist who did science in the right way and for the right reasons.

Nelson Mandela. I guess no further explanation needed, he's magic.

### Where do you become inspired by?

Places with interesting culture, such as London. Also, where I grew up in the West Country. I don't think I appreciated how calm and beautiful it is when I lived there. When I go back now I realize how lucky I was to spend my childhood there.

Highly motivated researchers inventing new ways to study scientific problems, like Roger Y.Tsien.

Do you have any news item that you would like to see announced in this Newsletter? Input can be send to: [s.dusseljee@gen.umcn.nl](mailto:s.dusseljee@gen.umcn.nl)

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