

## **AFM – spinal amyotrophy**

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### **PRESS RELEASE**

#### **Gene surgery in spinal amyotrophy**

#### **Reduction of disease symptoms in the animal**

**Using a gene surgery technique, a team of Swiss researchers led by Prof Daniel Schümperli of the University of Berne has succeeded in restoring production of the SMN (Survival MotoNeuron) protein in mouse models of spinal amyotrophy, one of the most frequent neuromuscular diseases in children. To obtain this result they used antisense U7 RNAs which specifically recognise one part of the gene (the exon), thus avoiding its “elimination” by the cell machinery. Disease symptoms were considerably improved in the treated mice and – for a number of them – even disappeared.**

**This work was in part financed by the AFM thanks to Téléthon donations and has been published in *Human Molecular Genetics*. It can be consulted online on the Internet site of the review.**

The human genome contains about 25 000 genes, from which several hundreds of thousands of different proteins can be produced through a process known as “alternative splicing.” During the process of protein manufacture, splicing is the stage when the gene copy becomes messenger RNA, in other words it deletes what is known as its “non-coding” parts to keep only its “coding” parts, exons. In function of the protein that the cell wants to produce, it does not assemble all the same exons (a particular exon can be skipped or included) – this is alternative splicing, which is the normal process for about 70% of human genes. In the case of genetic diseases this complex process becomes disordered – the splicing does not take place correctly due to mutated or absent exons. For many years Daniel

Schümperli's laboratory at the University of Berne has been studying splicing mechanisms in order to develop therapeutic strategies to inhibit or – on the contrary – promote their expression. It's this latter approach that was implemented for spinal amyotrophy.

In this neuromuscular disease the gene involved, *SMN1*, carried by chromosome 5 is either absent (in more than 95% of cases) or mutated. Thus it can no longer ensure the production of SMN protein.<sup>1</sup> The total absence of the SMN protein is incompatible with life and, in cases where the *SMN1* gene is non-functional its production is taken over by a similar gene called *SMN2*, also carried by chromosome 5. However, the *SMN2* gene cannot wholly replace the *SMN1* gene – a sporadic variation of its sequence induces incorrect splicing of the RNA excluding exon 7, which leads to the production of a mainly truncated and only partially (25%) functional protein. Insofar as all spinal amyotrophy patients possess at least one copy of *SMN2*, it should be possible to restore a normal level of SMN protein by strategies aimed at re-establishing exon 7 inclusion in *SMN2*, which would lead to the production of a completely functional SMN protein.

This is what Daniel Schümperli's team has succeeded in doing by bringing the U7 gene to the cell. This produces antisense RNA which allows the cell machinery to recognise exon 7. The results published today demonstrate the therapeutic potential of this technique in mouse models of spinal amyotrophy, which die prematurely during the first week after birth. The Swiss researchers were able to observe an increase in the quantity of SMN protein in the cells of the animals, correlated to an increase in their life expectancy and – for some of them – normal muscle function and the possibility of reproduction for the females.

With these results, the development of gene therapy for spinal amyotrophy begins to look more hopeful. However, for the time being researchers must succeed in introducing the U7 gene into the majority of motor neurons in the mouse spinal cord, and then into human patients. If this challenge can be

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<sup>1</sup> This protein is expressed in all tissue and its involvement in the specific degeneration of spinal amyotrophy motoneurons still remains largely misunderstood.

successfully met over the next few years, the first clinical trials on humans will be conceivable.

**This result confirms the therapeutic potential of the gene surgery techniques being developed to repair defective parts of the gene itself. Some of these techniques are already being tried on humans, such as exon skipping in Duchenne myopathy. They foreshadow the medicine of the future, a medicine “à la carte” (i.e. in function of the genetic anomaly of each patient) for both rare as well as more frequent diseases.**

### **ZOOM on spinal amyotrophy**

Spinal amyotrophies are hereditary neuromuscular diseases with autosomal recessive transmission. Their prevalence is estimated at 1 birth out of between 6 and 10 thousand. They are due to the degeneration of certain nerve cells (motoneurons) of the spinal cord: the motor nerves of the muscles are damaged and die, recruitment orders are no longer carried to the muscles. Being inactive, these weaken, atrophy and retract. The disease is expressed by weakness (paralysis) and early-onset atrophy of the pelvis, shoulder, trunk, arm and leg muscles. Movement of these muscles is difficult, even impossible. Depending on the age of onset (from birth or during the first months) the first motor difficulties can be expressed by an inability to reach a seated posture, to walk, to hold the head up etc. In more severe cases the intercostal muscles are affected, necessitating assisted breathing.

**For further information:**

**Rescue of a severe mouse model for Spinal Muscular Atrophy by U7 snRNA-mediated splicing modulation** – Kathrin Meyer, Julien Marquis, Judith Trüb, Rachel Nlend, Sonia Verp, Marc-David Ruepp, Hans Imboden, Isabelle Barde, Didier Trono and Daniel Schümperli. ***Human Molecular Genetics***. Advanced Access published on November 13, 2008, DOI 10.1093/hmg/ddn382.

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