Spinal muscular atrophy: from gene and modifiers to therapy

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Proximal spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder that represents the leading genetic cause of death in childhood. Homozygous mutation of the *survival motor neuron* gene *1* (*SMN1*) causes SMA, while the number of nearly identical *SMN2* copies determines disease severity. *SMN1* almost exclusively produces full-length (FL) transcripts. Due to a silent mutation, *SMN2* undergoes alternative splicing and generates only 10% of FL-*SMN2* transcripts but 90% of transcripts lacking exon 7 (Δ7-*SMN2*). The latter encode a biochemically defective, truncated protein. However overexpression of the splicing factor Htra2-beta1 that binds to an ESE in exon 7 restores the correct splicing to almost 80%. Therefore, activation of the *SMN2* transcription or modulation of its splicing pattern is likely to be clinically beneficial (1).

Several inhibitors of histone deacetylases (HDACs) have been identified as potential drugs for SMA treatment (2). Valproic acid (VPA), a short-chain fatty acid and histone deacetylase inhibitor, is able to significantly increase the protein level of SMN2 in fibroblast cell lines from SMA patients as well as in neuronal tissue, such as cultured rat and human hippocampus brain slices (3). Since VPA is an FDA approved drug and used since more than three decades in long-term epilepsy treatments, a first clinical trial in parents of SMA patients was carried out in order to verify the finding *in vivo*. Ten SMA carriers with 1 *SMN1* and 1-3 *SMN2* copies were enrolled in a VPA pilot trial. Drug treatment revealed increased FL-*SMN* mRNA/protein levels in blood from 7/10 probands. In a subsequent investigation of peripheral whole blood from 20 SMA type I-III patients treated with VPA in individual experimental curative approaches, FL-*SMN2* mRNA levels were found to be increased in 7 patients, whereas 13 presented unchanged or decreased transcript levels (4). This provided a first proof of principle of an *in-vivo* activation of SMN2 by VPA in SMA. Individual therapies of type I-III SMA patients with VPA/L-carnitin showed an improvement of the clinical picture or stabilization after 5-6 months of treatment in about half of these patients. However, systematic placebo-controlled multicenter clinical trials with VPA were mandatory and are in progress in the USA and Europe.

Finally, we identified a first fully protective modifying gene for SMA, plastin 3, that when overexpressed fully protects individuals carrying homozygous deletion of SMN1. Overexpression of plastin 3 rescues the detrimental effect of reduced SMN levels on axonal growth and development as we have shown in zebrafish and motor neurons derived from SMA mice (5).

1. Wirth, B., Brichta, L. and Hahnen, E. (2006) Spinal muscular atrophy: from gene to therapy. *Semin Pediatr Neurol,* **13,** 121-31.
2. Wirth, B., Riessland, M. and Hahnen, E. (2007) Drug Discovery for Spinal Muscular Atrophy. *Expert Opin Drug Discov,* **2 (4),** 437-451.
3. Brichta, L., Hofmann, Y., Hahnen, E., Siebzehnrubl, F.A., Raschke, H., Blumcke, I., Eyupoglu, I.Y. and Wirth, B. (2003) Valproic acid increases the SMN2 protein level: a well-known drug as a potential therapy for spinal muscular atrophy. *Hum Mol Genet,* **12,** 2481-9.
4. Brichta, L., Holker, I., Haug, K., Klockgether, T. and Wirth, B. (2006) In vivo activation of SMN in spinal muscular atrophy carriers and patients treated with valproate. *Ann Neurol,* **59,** 970-5.
5. Oprea, G.E., Krober, S., McWhorter, M.L., Rossoll, W., Muller, S., Krawczak, M., Bassell, G.J., Beattie, C.E. and Wirth, B. (2008) Plastin 3 is a protective modifier of autosomal recessive spinal muscular atrophy. *Science,* **320,** 524-7.