SCIENTIFIC ABSTRACT

APPLICANT NAME	DATE SUBMITTED
d'Ydewalle, Constantin	1/30/2015 1:54:32 PM

TITLE OF PROJECT *(Titles exceeding 81 characters, including spaces and punctuation, will be truncated.)*

LncRNA as therapeutic target for SMA

This Scientific Abstract will become public information; therefore, do not include proprietary/confidential information.

Spinal muscular atrophy is the leading inherited cause of infant mortality and is caused by mutation of survival motor neuron 1 (SMN1) gene, retention of a highly homologous SMN2 gene, and reduced levels of SMN protein. Hence, SMA treatments currently under development aim to increase SMN protein expression.

In spinal cords of both humans and mice, SMN expression is high in embryonic stages, but SMN levels drop in late gestational stages and remain low in postnatal life. Several studies that reduce SMN levels in mice or conversely that rescue the phenotype of SMA mice all have indicated that there is an early temporal requirement for SMN. The mechanism that regulates SMN expression is however not clear to date.

Several studies from our laboratory and from others have indicated that histone acetylation is an epigenetic change in the SMN2 promoter that regulates, at least in part, SMN2 promoter activity. Hence, histone deacetylase inhibitors have shown to increase SMN expression in SMA mice. In clinicals trial however, HDAC inhibitors have shown limited efficacy, suggesting that there are other epigenetic changes underlie regulation of SMN2 promoter activity.

We have identified a long non-coding RNA that arises from the opposite strand in a a central region of intron-1 of the SMN genes. Preliminary work has indicated that this SMN-associated natural antisense transcript (SMN-NAT) is a separate transcript from SMN mRNA. In non-neuronal cells, we have shown that SMN-NAT regulates SMN expression at the transcriptional level. SMN-NAT recruits the Polycomb repressive complex-2 (PRC2) to the SMN2 promoter and inhibits expression of SMN by methylating histon-3 at Lysine-27 (H3K27Me3). Antisense technology has demonstrated that knockdown of SMN-NAT increases SMN expression in non-neuronal cells.

Based on these observations, we postulate that SMN-NAT also regulates SMN expression in neurons through the same mechanism. To test our hypothesis, we will determine expression levels as well as the intracellular distribution of SMN-NAT in cultured primary neurons at different times post-plating as well as in neuronal tissue of SMA mice at different ages and different ages during development. We will also evaluate whether targeting SMN-NAT either embryonically or postnatally in mice rescues the SMA phenotype.

Our long-term goal is to understand how SMN expression is regulated during neuronal development. Finally, our experiments proposed in this project will determine whether SMN-NAT is a new and promising therapeutic target for SMA.