THE FSMA/AURORA PROJECT

Historical Summary

In January 2000 Families of SMA (FSMA) funded researchers announced findings that Spinal Muscular Atrophy (SMA) can be corrected in SMA mouse models through increasing the amount of the SMN2 gene (Monani et al., 2000). This study would predict that early activation of the SMN2 gene could correct SMA before symptoms are seen. It may also be that by elevating SMN2 gene expression in patients that have SMA, it will help preserve motor neuron function.

In March 2000, FSMA entered into a $2.6 million collaboration agreement with Aurora Biosciences Corporation (Aurora) to screen over 500,000 compounds on 2 separate mechanism-based assays (a promoter assay and a splicing assay) for use in high-throughput screening for drug leads. The strategy behind both of the high-throughput compound screens was to identify agents that increase the total amount of functional SMN messenger RNA (mRNA) and protein in motor neuron cells. Approximately 1.16 unique compounds have been tested using the 2 assays. This effort has resulted in identification of 16 compounds with confirmed biological activity. These 16 compounds fall into ten different structural families. Secondary testing was then done on SMA patient-derived cell lines. To date, 4 compound classes clearly increase the level of normal SMN2 mRNA by 2- to 5-fold in patient cells. This first phase of this high-throughput screening process was completed in March 2002.

Project Proposal

The second phase of the Aurora project is to take the compounds that were found in the high throughput screening process that are within the necessary therapeutic range for increasing SMN expression but too low for testing in animal models and develop them further. There are 2 objectives within the second phase: 1) to conduct a limited chemistry effort on the most promising compound classes identified in the drug screens to better understand the chemical properties required for beneficial biological activity and 2) demonstrate that the compounds showing positive biologic activity in the initial assays also clearly increase SMN protein levels in SMA patient cells. Aurora will devote an additional 1.5 full-time chemists and 2.5 full-time biologists to this project. The estimated time to complete will be 6 months from the date of the contract was signed, April 15. The total cost of this phase is $650,000.

Method of Evaluation

The completion of the second phase will guide the decision to initiate the "hit-to-lead" program and determine which compounds will be included in this effort. This determination will be made by the FSMA Steering Committee Members and the FSMA Scientific Advisory Board.

The FSMA Steering Committee Members include:

Arthur Burghes, Ph.D. Dr. Burghes is a Professor at Ohio State University and the lead developer of the SMA Mouse model and principal investigator of the insertion of the SMN gene in mouse models.