Determination of the Neuroprotective Index for Neuroprotective Treatments Based on a Mouse Model of Retinitis Pigmentosa

W.Raffelsberger[1], R.Reddy[1], F.Chalmel[1], N.Wicker[1], A.Legrand[1], N.Chadderton[2], P.Humphries[2], J.Sahel[3], T.Leveillard[3], O.Poch[1]. [1]RetNet Team VI, Department of Structural Biology, IGBMC, Illkirch, France; [2]RetNet Team II, Trinity College,Department of Genetics, Smurfit Institute, Dublin, Ireland; [3]RetNet Team V, INSERM-U592, Institut de la Vision, Paris, France.

Keywords:
525 gene microarray, 468 computational modeling, 672 retinal degenerations: hereditary

Purpose: Retinitis Pigmentosa (RP) is an inheritable degeneration of photoreceptors though two subsequent steps characterized by i) the loss of rods in a cell autonomous manner which is followed by ii) loss of cones in a non cell autonomous manner, leading to complete blindness. The *rd1* mouse serves as animal model for RP as both stages can be observed during retinal degenration. We investigated the neuroprotective index of neuroprotective substances in the mouse transcriptome during the first phase of RP in *rd1* mice.

Methods: The neuroprotective agents GDNF, CNTF and Dialtiazem as well as mock-controls were injected to *rd1* mice at 15 days postnatal and RNA was isolated from mouse retina 48 h later. Duplicate samples were subjected to Affymetrix transcription profiling experiments and that were analyzed using a novel bioinformatics protocol based on the assessment of a quality indexes. The degree of homogeneity for the probes defining each microarray's probe set and the agreement of the biological duplicates were analyzed by an automated protocol measuring each gene's apparent quality assessment index. These indexes were then considerated in the subsequent clustering analysis based on the Density of Points Clustering (DPS) algorithm to characterize regulated genes representing the molecular targets of RP and measuring the neuroprotective index.

Results: This procedure allowed to significantly reduce the amount of false positives among the genes reported, which is especially important for low level expressed genes as they are typically subject to less precise measurements. These results were further examined for enrichment of functional ontologies and signalling cascades. Finally, we defined and determined the neuroprotective index considering for each i) treatments and ii) all transcripts.

Conclusions: The determination of a neuroprotective index across genes and neuroprotective agents combined with a very low risk of false positives was made achieved through clustering of transcription profiles while considering the apparent quality assessment index.

This project was supported though the European Retinal Research Training Network 'RETNET', MRTN-CT-2003-504003.

Commercial Relationship:
W. Raffelsberger, None; **R. Reddy**, None; **F. Chalmel**, None; **N. Wicker**, None; **A. Legrand**, None; **N. Chadderton**, None; **P. Humphries**, None; **J. Sahel**, None; **T. Leveillard**, None; **O. Poch**, None.

Support:
MRTN-CT-2003-504003