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Narrative of Final Report.

During the years of my work at the Keck Center for Collaborative Neuroscience and the Department of Cell Biology and Neuroscience at Rutgers, The State University of New Jersey, we have been able to gain more insights into the functional roles of neural cell adhesion molecules of the immunoglobulin superfamily, and in particular of L1, the molecule that was discovered in the mouse in my laboratory at the time at the University of Heidelberg, Germany. The main achievements can be summarized in the bullet points, which show the bandwidth of the multifunctionality of this multidomain molecule.

We could show that L1 can be applied to lesioned spinal cord of the mouse and enhance locomotor recovery in several modes:

- We could show that L1 can be infused into the lesioned rodent spinal cord to promote recovery, but also applied via expression by adeno-associated virus, by implantation of L1 overexpressing neural stem cells that not only synthesize full length L1, but also as the secreted soluble trimer that can interact in a function triggering homophilic manner with the transmembrane full length form of neuronal L1.

- We also discovered that L1 is not only beneficial for recovery in the acutely injured spinal cord, but also when applied 3 weeks after injury in the mouse and that a combination with ChaseABC enhances recovery.

- Furthermore, L1 is not only beneficial for recovery after spinal cord lesion, but also in ameliorating the deficits in mouse models of Parkinson's and Huntingtons's diseases. Particularly exciting for me is that L1 can ameliorate deposition of plaques in a mouse model of Alzheimer's disease. First insight into the mechanism of action derive from our observation that L1 binds to Abeta (to the more pathogenic form 42 more than to 40), but not to functionally important amyloid precursor protein from the Abeta fragments arise. An important control for the specificity was that that CHL1, the close homolog of L1 (CHL1) does not bind to the Abetas.

- We have also validated function triggering antibodies against mouse and now also human L1, which not only promotes neuritogenesis and synapse formation in vitro, but also myelination as we could show both in the peripheral and central nervous system of mice. We have also generated a transgenic mouse that overexpresses full length L1 in peripheral and central nervous system neurons (under the control the neuron-specific Thy-1 promoter). These mice do not show better locomotor recovery after femoral nerve lesion – which may be attributed to the ample expression of L1 in the mammalian peripheral nervous system – but myelination/remyelination is more extensive than in their wild type control littermates. The function triggering antibodies in mouse has improved functional and histological regeneration in the mouse model.

- The function triggering antibodies to human L1 react also with tissue from monkey peripheral nerves and is now being tested for locomotor recovery as

we did successfully for evaluating the effects of the HNK-1 glycomimetic peptide in the monkey femoral nerve lesion model.

- A gratifying finding was that L1 is not only important in promoting functional recovery in mammals, but it is also used by fish which possess the amazing capacity to regenerate almost fully six weeks after complete transection of the spinal cord. This could be shown by inhibiting the production of the L1 protein by treatment of the lesioned fish with a stable anti-sense oligonucleotide (morpholino). This finding showed us that zebrafish with their well studied genetics and the availability of mutants have considerable potential in finding molecules that promote regeneration.

- We have started to screen libraries of small organic compounds from synthetic chemistry and natural compounds from traditional Chinese medicine encompassing from herbs and marine organisms. And using a competition ELISA with a functionalized L1 fragment – which we identified to locate between the 2nd and 3rd fibronectin type III homologous domain – and the L1 function triggering antibodies to mouse and human L1. First hits look very hopeful in biochemical assays, but will need to be validated for L1-specific functions in vitro. If the in vitro results should turn out to be positive, they will have to be probed for in vivo in spinal cord lesion paradigms, hopefully with colleagues that are experts in spinal cord lesion in this non-human primate. In case of a positive outcome, venues will have to be thought to apply these compounds sustainably in a large nervous system in the hope to contribute to a first step in translational medicine.

I have been able to establish fruitful collaborations not only within the Keck Center and the Department of Cell Biology, but even more vital collaborations with colleagues in the Centers for Biomaterials and Biomedical Engineering in peripheral nerve regeneration. These interactions have led to the awards of RO1 and R21 grants. Finally, thanks to my continued activities at Rutgers I have been made a member of the German Academy of Sciences (Leopoldina). My Hirsch-factor (an indicator of visibility in the scientific community) was 113 in January 2013, and I am among the 10% most cited neuroscientists worldwide. One of my publications has now been cited more than 900 times. I am very grateful to the New Jersey Commission for Spinal Cord Research for making me the New Jersey Professor of Spinal Cord Research and their generous funding of this chair.