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Engineering Regeneration Through the Bridge/Host Distal Interface

Abstract

One of the major experimental approaches to spinal cord repair is the development of cellular and / or biomaterial "bridges" that promote nerve regeneration through or around injured regions allowing the re-establishment of functional connections and restoration of movement and sensory perception. While regenerating nerve fibers have been shown to successfully enter a variety of bridges, in general substantially fewer fibers are able to exit the bridges and continue growth in the spinal tissue on the distal side of the injury. Despite this limitation, several bridging approaches have been able to achieve functional improvements in animal injury models, suggesting that once this challenge is overcome, bridging could be rapidly developed into a highly effective clinical treatment capable of providing significant functional recovery. Consistent with this aim, the first objective of this proposal is the development of a cell culture model replicating the interface between the bridge and the patient's spinal tissue where regenerating nerve fibers must exit the bridge and re-enter the native tissue. Such a model will provide a basis for studying the mechanisms of inhibition encountered at the boundary between implanted bridges and the patient's tissue and rapidly testing potential solutions. One possible reason that has been proposed for the difficulty regenerating nerves experience in exiting bridges and re-entering the patient's tissue is that many bridges contain high concentrations of growth-promoting stimuli relative to the surrounding tissue, creating an abrupt boundary that regenerating nerve fibers have difficulty crossing. To address this difficulty, the second objective of this proposal is the creation of "off-ramps" consisting of spatially defined biochemical gradients providing gradually changing concentrations of adhesive or stimulatory molecules involved in the development and regeneration of the spinal cord. The cell culture model developed will be used to test this concept and to rapidly optimize the concentration, steepness, and extent of the gradients in order to maximize the number of nerve fibers successfully crossing the model boundary from the "bridge" to "host" portions of the model. While this model will initially be created and tested in two-dimensions, the techniques developed for creating transitional "off-ramps" will be readily applicable to three-dimensional materials allowing rapid translation to testing in animal injury models. In addition, the proposed "ramp" concept is designed in such a manner that it can be readily incorporated into a variety of existing bridging strategies already under development.