Docket #: S21-398

A Method of Enhancing Nerve Regeneration and Repair Using a Small Molecule Smoothened Agonist Applied Directly to Sites of Nerve Repair or Surgery

Peripheral nerve injury is widespread, with U.S. estimates of over 200,000 cases per year and worldwide estimates as high as 1 million cases per year. Although in cases of minor injury, peripheral nerves can regenerate, for more severe injuries, direct microsurgical nerve repair is the preferred treatment. surgery often improves neurologic function in cases of severe peripheral nerve injury, but complete recovery of function is unfortunately quite rare. Surgical repair may fail to restore normal function as seen in approximately 40-60% of cases. There are currently no pharmacologic treatments available to patients that can accelerate nerve regeneration after injury and observation, direct surgical repair, or nerve graft repair. Given the high failure rate of complex nerve reconstruction, more effective methods of reconstruction are necessary.

Stanford researchers have found that a low dose of a small-molecule, systemic pathway agonist, SAG21k, improves nerve regeneration after injury and increases expression of injury-responsive genes within Schwann cells in the injured nerve. SAG21k is a potent hedgehog signaling pathway agonist that targets Smoothened, the key pathway effector protein. Administration is also feasible during surgery and may reduce the risk of systemic side effects.

Stage of Development

In vivo mouse models: researchers have found that the Smo agonist SAG21k improves nerve regeneration after injury in a mouse model. Current work entails translating this to a topical treatment that can be applied during surgery along with

commonly used nerve sealants (ie, fibrin hydrogel or fibrin nerve wraps) that may limit potential systemic toxicity of the small molecule being administered systemically.

Applications

- Surgical nerve repair
- Any peripheral or cranial nerve

Advantages

- First drug that contains a biologically active compound to facilitate nerve regeneration after injury
- Can be used in conjunction with commonly used nerve sealants (e.g. fibrin hydrogels)
- Increases chance of surgical nerve repair

Publications

- Faniku, C., Kong, W., et al. (2021). Hedgehog signaling promotes endoneurial fibroblast migration and Vegf-A expression following facial nerve injury. Brain research, 1751, 147204.
- Dogaru, G. L. B., Juneja, et al. (2018). The role of Hedgehog-responsive fibroblasts in facial nerve regeneration. Experimental Neurology, 303, 72-79.

Patents

- Published Application: WO2024173529

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