Each year over 10,000 Americans sustain spinal cord injury (SCI). Functional loss following SCI results from damage to axons, loss of neurons and glia, and demyelination. SCI pathology is determined not only by the initial mechanical insult, but also by secondary processes including ischemia, hypoxia and a complex inflammatory response that persist for hours and days post-injury. Resulting damage to proteins, lipids, nucleic acids and enzymes trigger apoptotic and necrotic pathways. Ultimately, a glial scar is formed at the lesion site encapsulating a necrotic cyst, inhibiting signal transduction and axonal re-growth. This pathophysiology, termed ‘secondary injury’, further eliminates the opportunity for functional recovery of patients suffering SCI. Meanwhile, preservation of even a small percentage of spinal cord tissue is associated with enhanced functional recovery, implying a therapeutic window for intervention. Although there have been encouraging reports of deficit reduction there is currently no practical treatment for SCI.

Recently, an implant modeled after the intact spinal cord consisting of a multicomponent polymer scaffold seeded with murine neural stem cells (mNSC) was developed in the Langer Lab. Implantation of the scaffold–mNSC unit into an adult rat hemisection model of SCI promoted long-term improvement in function relative to a lesion-control group. Histology and immunocytochemical analysis suggested that this recovery might be attributable partly to a reduction in tissue loss from secondary injury processes as well as in diminished glial scarring.

Therapeutic impact of human neural stem cells (hNSCs) for acute SCI has been limited by the rapid loss of donor cells. Inflammation is implicated as a possible cause. Therefore, the role of peroxynitrite formation and scavenging on the survival and cell death signaling of hNSCs in vitro using poly-lactic-co-glycolic acid (PLGA) polymer films embedded with manganese (III) tetrakis (4-benzoic acid) porphyrin (MnTBAP) or uric acid was tested. Films releasing the peroxynitrite scavenger MnTBAP were demonstrated to protect hNSCs in vivo in a model SCI in rodents.

Rodents may over-predict the efficacy of interventions given high rates of spontaneous recovery from induced spinal cord injury, even following profound lesions. The spinal cord anatomy and physiology of old world monkeys are more similar to humans, particularly with respect to the position and function of corticospinal tracts. A surgical model of acute SCI in the African green monkey (Chlorocebus sabaeus) was developed for the evaluation of biomaterial implants as a translational interval between rodent and clinical investigations. A lateral hemisection at level T9–T10 in the thoracic spine was created, designed to result in Brown-Séquard syndrome with minimal post-operative complications. Both neuromotor and histological outcome measures were evaluated to ascertain objective measures of the efficacy of potential therapeutic interventions.

Clinically available injectable hydrogels face technical challenges associated with swelling after injection and toxicity from unreacted constituents that impede their performance as surgical
biomaterials. To overcome these challenges, we developed a system where chemical gelation was controlled by a conjugate Michael addition between thiol and acrylate in aqueous media, with 97% monomer conversion and 6 wt.% sol fraction. The hydrogel exhibited syneresis on equilibration, reducing to 59.7% of its initial volume. It had mechanical properties similar to soft human tissue with an elastic modulus of 189.8 kPa. Furthermore, a mesh size of 6.9 nm resulted in sustained release of methylprednisolone sodium succinate with a loading efficiency of 2 mg/mL. Functionalization with 50 μg/mL of an oligolisine peptide resulted in attachment of freshly isolated murine mesenchymal stem cells. The rational design of the physical, chemical and biological properties of the hydrogel make it a potentially promising candidate for injectable applications.

In 1990 a high dose glucocorticoid, methylprednisolone, was adopted as a clinical treatment option for acute SCI, designed to suppress harmful inflammation. This treatment process has recently become controversial, due to adverse side effects (Infection-pneumonia and septic shock, diabetic complications, delayed wound healing) and dosage difficulties associated with a non-monotonic dose-response. Local drug administration using a polymeric delivery system could help address these issues through controlled release profiles and reduced systemic exposure. We performed a study to determine the feasibility and safety of injecting a hydrogel for sustained release of methylprednisolone into a clinically relevant contusion injury. This study involved a contusion (240 Kdynes) at T9 and either no treatment, intraparenchymal injection of a PEG-based hydrogel (15 μl, inject to the lesion site) 6 hours post injury or a PEG-based hydrogel (15 μl, inject to the lesion site at 3 μl/minute) plus methylprednisolone (15 μg) 6 hours post injury (n=10 per group, all rats in pain category). Rats were tested for BBB open field locomotor score one day and every week post injury for four weeks. The kinematics of the hip, knee, ankle and distal phalanges during treadmill locomotion at 13.5 and 21 cm/s were recorded and analyzed 1, 2, and 4 weeks post injury using SIMI. Four weeks post injury, all rats were perfused and the thoracic region encompassing 5 mm rostral and 5 mm caudal to the lesion site was serially sectioned for H&E, Silver staining, Solochrome staining, GFAP & Iba1 immunohistochemistry.