Schwann cells (SC) in the corneal limbus, we hypothesize that SCs, via paracrine interaction with LSC, play a key role in corneal epithelial maintenance and healing.

In this study we wanted to (1) Define the role of SCs in corneal healing; (2) Determine the paracrine interaction between the limbal SCs and LSC.

METHODS: (1) Local corneal ablation of SCs was induced in a genetically modified mouse where the topical application of tamoxifen induced SCs apoptosis. The corneal epithelium was then removed with an Amoils brush under anesthesia and fluorescein was used to assess healing over 4 days. (2) We performed single-cell RNA expression analysis of 10,000 cells derived from dissociated rat limbus with droplet-based high throughput 10× Genomics to identify ~3000 genes. We used the data to predict possible ligand-receptor interactions between the limbal SCs and LSC.

RESULTS: (1) Ablation of SCs impaired corneal wound healing in mouse cornea, suggesting the involvement of SC in innervation-dependent corneal epithelial recovery. (2) Genomic analysis suggested the presence of paracrine crosstalk between SCs and LSCs, and relevant downstream intracellular signaling events in LSCs. The latter included activation of Notch signaling and VEGF-mediated cell migration and inhibition of apoptosis. Further expression analysis comparing the limbal region of healthy and wounded cornneas indicated significant changes in the expression of jag1, Pdgfa, Tgfb1, and Ptn genes by SCs. All of these genes could potentially play a role in corneal recovery.

CONCLUSIONS: Our findings (i) describe the presence of a high volume of SCs at the limbus, located in close spatial vicinity to LSCs, (ii) demonstrate the importance of the limbal SCs for corneal wound healing, and (iii) suggest the presence of paracrine SC-LSC interaction that may be responsible for the limbal nerve-mediated activation of LSCs during homeostasis or the epithelial wound healing after injury. These findings suggest new therapeutic targets for treating NK.

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Targeted Muscle Reinnervation Reduces Postoperative Opioid Requirements in Major Lower Extremity Amputation

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PURPOSE: Major amputations of the lower extremity are highly traumatic procedures, often requiring the use of opioids in the postoperative period. Major amputation patients are also at risk of chronic pain in the form of phantom limb pain or stump pain, increasing susceptibility to chronic opioid dependence. Preoperative opioid use is known to increase the risk of chronic postoperative opioid use; however, even opioid naïve patients carry a 20% chance of developing a need for chronic opioid use following major amputation. Given the many risks inherent to opioid use, perioperative narcotic-reduction strategies are critical. Our center instituted a protocol for major amputations that includes continuous regional anesthesia, for intraoperative and postoperative pain control, and targeted muscle reinnervation (TMR) nerve transfers, to reduce risk of chronic pain. The aim of this study was to analyze the impact of continuous regional anesthesia, TMR, and preoperative opioid use on early postoperative opioid requirements following major lower extremity amputation at our limb salvage center.

METHODS: We retrospectively reviewed our center’s below-knee and through-knee-amputations from 2017 to 2019 for utilization of regional pain catheters and TMR nerve transfers. Opioid usage as morphine milligram equivalents (MMEs) was tracked for the first seven postoperative days and then averaged into an average daily postoperative opioid use. Preoperative opioid use was defined as the documented opioid
dose used one day before amputation. Multivariate linear regression was performed to examine the association between postoperative opioid use and the main predictors—(1) TMR, (2) Regional pain catheters, and (3) Preoperative opioid use—in addition to several possible confounders, including age, sex, and Charlson Comorbidity Index (CCI).

RESULTS: An estimated 198 patients were reviewed. In total, 95 patients received perioperative regional anesthesia and 111 patients underwent TMR. Mean preoperative opioid use was 75.9 MME (standard deviation (SD) 166.9 MME) per day while mean postoperative opioid use was 98.4 MME (SD 192.0 MME) per day. Undergoing TMR significantly reduced daily postoperative use by 41.5 MME ($P < 0.05$, 95% confidence interval (CI) $-82.01$ to $-0.89$). Every 1 MME of preoperative opioid use significantly increased postoperative opioid daily use by 0.87 MME ($P < 0.001$, 95% CI $0.77–0.97$). Regional anesthesia, age, sex, and CCI were not found to have significant effects on postoperative opioid use.

CONCLUSIONS: Our results suggest TMR nerve transfers are independently effective in reducing postoperative opioid requirements following major lower extremity amputation. Regional anesthesia did not have an individual, statistically significant effect, although it may have amplified the opioid lowering effects of TMR. Minimizing baseline opioid use prior to amputation may also decrease postoperative opioid use. TMR nerve transfers can decrease reliance on postoperative pain control with opioids in lower extremity major amputation patients and may subsequently reduce rates of opioid dependence.

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A Markov Analysis of Surgical versus Medical Management of Chronic Migraines

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PURPOSE: Refractory chronic migraine (CM) is a common and debilitating neurological condition, affecting over 8 million people in the United States. It is associated with billions of dollars in lost productivity annually. Novel medical (anti-calcitonin gene-related peptide antibodies, or erenumab) and surgical treatment modalities have emerged for CM in recent years. Given the substantial economic burden of CM, it is not sufficient to simply understand clinical outcomes: it is also critical to study the cost-utility of CM treatment, especially in refractory cases. Although prior studies have demonstrated the cost-utility of migraine surgery over long-term onabotulinumtoxinA injections, no one has investigated the cost-utility of migraine surgery versus medical management of CM with erenumab. The current study examined the cost-utility of surgical versus medical management of refractory CM.

METHODS: This was a cost-utility analysis comparing surgical therapy to erenumab in adults with refractory CM. The primary model outcomes were the incremental cost-effectiveness ratio (ICER), which is represented in terms of cost per quality-adjusted life year (QALY) gained. Hybrid Monte Carlo patient simulation and Markov cohort modeling were used to study the cost-effectiveness from both societal (indirect costs—time lost from work, productivity lost, etc.) and payer perspectives (direct costs—costs of care, cost of medication, facility fees, etc.).

RESULTS: Migraine surgery was associated with a 0.2 increase in QALYs per patient when compared with erenumab. In terms of direct costs (ie, payer perspective), migraine surgery resulted in a decrease in cost of $19,337 when compared with erenumab. Thus, surgery was a dominant strategy compared with erenumab given that it reduced global costs and improved patient-reported outcomes. In terms of indirect costs (ie, societal perspective), migraine surgery resulted in a decrease in cost of $470 when compared with erenumab. Thus, surgery was again the dominant strategy as it reduced indirect costs and improved patient outcomes in comparison with erenumab. Multiple scenario analyses were completed to more-comprehensively evaluate cost-effectiveness. In one scenario, we extended the time horizon of the model, and we assumed that 12% of patients undergoing migraine surgery required revision surgery within five years of the initial procedure, based on published results by Guyuron et al. Even in this scenario, surgery remained the dominant strategy over erenumab, as global direct and indirect costs considering revision procedures were still less than costs associated with lifetime utilization of erenumab. Sensitivity analyses demonstrated that surgery was cost-effective compared with erenumab when patients required medical therapy for at least 1 year.