

# Nicole Gibran, M.D.

- Burn Wound Repair
- Cytokine Response to Thermal Injury
- Neuroinflammatory Response to Wound Repair



## FUNDING

### National Institutes of Health

- National Institute of General Medicine Sciences
- National Institute of Diabetes, Digestive and Kidney Diseases

### WA State Association of Fire Fighters Burn Foundation

Wound repair constitutes an essential component of every surgical subspecialty. The health care system spends millions of dollars annually to apply the latest goo-du-jour onto wounds. But in spite of all we know about response to injury, we still do not offer good solutions to patients with chronic non-healing wounds or with hypertrophic scars and keloids. Our collective efforts have been focused on understanding the response to cutaneous injury for wounds with either insufficient or exuberant responses.

### Burn Wound Repair

With increased patient survival following burn injuries, rehabilitation and problems associated with scarring such as hypertrophy and itching become important. Since early civilization, we have been adapting topical treatments for wounds. While the growth factors that we apply to wounds today are more sophisticated than the honey, wine, oil or resins that were used in ancient medical practices, we still do not know what the growth factors do or when they should be applied.

Valuable studies over the past 30 years have augmented our understanding of the progression of repair from an acute injury through coagulation, inflammation, blood vessel formation, fibrogenesis and epithelialization, and finally to remodeling. Nevertheless, we still do not fully understand normal wound repair and thus, how to therapeutically modulate repair in compromised wounds.

We designed our basic science efforts to define cellular and extracellular inflammatory processes in normal burns. Our aim has been to better understand what deviations result in non-healing wounds or in abnormal scars in order to know when to perturb the healing process with a repair accelerant.

We have studied the temporal and spatial localization of dermal inflammatory cells, basic fibroblast growth factor, macrophage chemoattractant protein-1, and collagenase during repair. Collectively, our data support the theory that the skin itself is a component of the immune system and that non-inflammatory cells may contribute to the initiation and maintenance of the inflammation at the wound site. Furthermore, these studies have accentuated the notion that inflammatory mediators at the wound site are present at specific phases in the repair process, and that interventions with exogenous mediators must be timely.

### Cytokine Response to Thermal Injury

Our latest therapeutic approach to the acute care management of patients with thermal injury has been to reintroduce plasmapheresis into the care plan of patients with large burns that are failing resuscitation. With advances in wound closure we are able to treat patients effectively if we can help them to survive the initial resuscitative phase — or 48 hours after injury. Over the past year we have had favorable experience using plasmapheresis on selective patients with large

---

*These findings are important because itching, which is mediated by neuropeptides, is a major complaint of patients with thermal injuries.*

---

burns. Since these patients represent anecdotal evidence that plasmapheresis may have a role in the management of patients with large burns, we are pursuing an in depth clinical and basic science study of the effect of plasmapheresis. We are looking at cytokine levels in the plasma of the patients before and after their plasmapheresis has been completed to determine which mediators are elevated during the inflammatory response to injury. We are correlating these results with the clinical course of patients that undergo plasmapheresis compared with control subjects matched in age and burn size.

### Neuroinflammatory Response to Wound Repair

Our lab has been dedicated to defining the neuroinflammatory response to wound repair. The sensory nerves in skin regulate not only pain transmission, but also a local inflammatory response within the wound bed. We have identified the normal temporal and spatial distribution of pain fibers in human burn wounds.

Following injury, sensory nerves are absent within the injury site. With time there appears to be a transient abnormal increase in neuroinflammatory mediator within the wound that eventually approaches normal. These findings are important because itching, which is mediated by neuropeptides, is a major complaint of patients with thermal injuries.

We have demonstrated that patients with sensory deficits due to both spinal cord injury and diabetes mellitus have a dramatic reduction in cutaneous sensory nerves, especially in the wound beds. We have also recently determined that activity levels of neutral endo-

peptidase, a membrane bound enzyme that degrades substance P, is elevated in the wounds and skin of patients and mice with diabetes. Therefore, it was not a surprise to us that exogenous substance P shortens time to healing in a model of delayed wound repair in diabetic mice. We have also observed increased levels of the enzyme neutral endopeptidase in skin and wounds from diabetic mice. We have shown that increased glucose and fatty acids increases neutral endopeptidase levels in cultured endothelial cells. Most interestingly, this increase can be inhibited with antioxidant treatment.

Our lab is focused on determining the endothelial cell derived signals that govern nerve cell differentiation. Sensory nerve-derived neuropeptides stimulate endothelial cells following injury to round up, proliferate and synthesize adhesion molecules and cytokines. These studies are currently focused on intracellular signaling pathways that mediate substance P mediated changes to the endothelial cell.

Activated endothelial cells stimulate reinnervation of the injury site. We have defined this process to be a neuro-endothelial axis and believe that it may contribute to the pathophysiology of hypertrophic scar formation. Our latest effort has been to determine the mechanism by which substance P upregulates an inflammatory response. We have evidence that change in substance P-induced cell shape with the accompanying reorganization of the cytoskeleton may be an intermediary step. Most recently we have focused on the role of nitric oxide synthase and the EGFR as means of mediating substance P activity. These studies have been funded by the NIH.

---

**RELATED PUBLICATIONS**

1. Cole J; Tsou R; Wallace K, et al. Early gene expression profile of human skin to injury using high-density cDNA microarrays. *Wound Repair Regen*, 2001; 9(5):360-70.
2. Matsumura H; Engrav LH; Gibran NS, et al. Cones of skin occur where hypertrophic scar occurs. *Wound Repair Regen*, 2001; 9(4):269-77.
3. Tsou R; Cole JK; Nathens AB, et al. Analysis of hypertrophic and normal scar gene expression with cDNA microarrays. *J Burn Care Rehabil*, 2000; 21(6):541-50.
4. Spenny M; Maungman P; Olerud J, et al. Neutral endopeptidase inhibition improves wound repair in diabetic mice (abstract). *J Invest Dermatol*, 2001; 117:441.
5. Underwood RA; Gibran NS; Muffley LA, et al., Color subtractive-computer-assisted image analysis for quantification of cutaneous nerves in a diabetic mouse model. *J Histochem Cytochem*, 2001; 49(10):1285-91.
6. Antezana M; Sullivan S; Usui M, et al. Neutral endopeptidase activity is increased in the skin of subjects with diabetic ulcers. *J Invest Dermatol*, 2002; 119(6):1400-4.
7. Gibran NS; Jang YC; Isik FF, et al. Diminished neuropeptide levels contribute to the impaired cutaneous healing response associated with diabetes mellitus. *J Surg Res*, 2002; 108(1):122-8.
8. Spenny ML; Muangman P; Sullivan SR, et al. Neutral endopeptidase inhibition in diabetic wound repair. *Wound Repair Regen*, 2002; 10(5):295-301.
9. Muangman P; Spenny ML; Tamura RN, et al. Fatty acids and glucose increase neutral endopeptidase activity in human microvascular endothelial cells. *Shock*, 2003; 19(6):508-12.
10. Gibran NS; Tamura R; Tsou R, et al. Human dermal microvascular endothelial cells produce nerve growth factor: Implications for wound repair. *Shock*, 2003, 19(2):127-30.

---

**DEPARTMENT CO-INVESTIGATORS**

**Eileen Bulger, M.D. / Loren H. Engrav, M.D. / David M. Heimbach, M.D. / F. Frank Isik, M.D. / Ronald Maier, M.D.**

**OTHER CO-INVESTIGATORS**

**John E. Olerud, M.D.;** UW Department of Medicine

---