

Highlights of Clinician/Scientist Translational Discussion Session

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Discussion topic: Bridging the basic understanding of wound healing to clinical applications and therapeutic development. How can we bridge the gap to the clinic? What are some of the obstacles to progress and how can we approach and overcome them?

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The last session of the 54th Annual Montagna Symposium on the Biology of Skin consisted of breakout discussion sessions to highlight the areas of wound healing that could make the transition between the laboratory bench and the bedside, and to highlight areas that need more research. The discussion leaders set the topics for discussion:

GROUP 1. IS THE INFLAMMATORY RESPONSE NECESSARY?

Inflammation exists to protect and defend wounds against bacterial invasion. In the real world, wounds can become contaminated. However, in the laboratory setting, most wound models are sterile. Thus, to address this question, we will need more natural wound models. We would never suggest in the clinic to deplete all the inflammatory cells. One thing upon which we can all agree is that chronic inflammation is not going to help. Persistent inflammation kills. We could apply antibiotic to kill all the bacteria in a child in the hospital but how can we apply this to a chronic wound. An essential point is the underlying disease. Young and/or healthy people do not get chronic wounds. Chronic wounds occur with underlying disease. What about some chronic wounds that do not exhibit acute inflammation or blood vessels? Should we infect our laboratory models to make them more realistic?

Timing is essential. Evolutionarily, tissues need a fast inflammatory response to survive, but this response needs to be turned down for healing. Inflammation may be critical in determining the healing capacity of wounds. In chronic wounds, the amount of bacteria is critical; too much or too little may lead to chronic wound failure. What cells bring in the inflammatory cells: fibroblasts, epithelial cells? Alternatively, we do not need a cell, as matrix fragments act as chemoattractants. Every cell can be proinflammatory. Damaged cells, leakiness, and factors such as IL-1 attract leukocytes. By the same token, all cells can engulf debris.

In the clinic, we cannot eliminate inflammation, but we could target inflammatory cells and tell them to leave or to shut down, selectively depleting immune cells or inflammatory molecules, for example, V-cam. This specific targeting could aid in healing chronic wounds, if we knew which molecules to target and when to target them.

GROUP 2. CAN TRANSPLANTATION OF STEM CELLS HELP TO HEAL CHRONIC WOUNDS?

The primary goal is to choose the most appropriate model. Most models use punch biopsies, which yield a large round wound, whereas clinically, most wounds are incisional. Delivery of stem cells to punch wounds may be problematic because the center of the wound contains too many proteases. A matrix holding the cells could be used to deliver the cells and other wound-healing factors. Delivery of growth factors and cytokines in the correct amount and order could be sufficient to heal the wounds, but may not prevent recurrence. Does use of stem cells help prevent recurrence of the wound? It may be that delivery of sequential growth factors/cytokines will be required to assist survival of the stem cells. The last point is the model. Current mouse models do not recapitulate chronic wounds. Thus, chronic wound *in vitro* models may need to be developed.

GROUP 3. WHAT PREVENTS RE-EPITHELIALIZATION AND MODULATION OF WOUNDS?

In general, when wounds do not re-epithelialize, the edge of the wound is bulbous, but contains proliferative keratinocytes. Re-epithelialization does not need inflammatory cells. In the lung, there is healing without inflammation. Thus, lack of wound closure is likely owing to underlying matrix/wound bed factors, such as proteases. Clinically, these wounds must be debrided to rid the wound of denatured collagen and fibronectin. It is believed that too much inflammatory response is the main problem. However, there must be some response to activate release of metalloproteinases, which are needed for cell migration.

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It may be that each individual wound is unique. If so, we will need to design a therapy to address each condition. For example, large wounds could be covered by a matrix with the appropriate growth and migration factors. This would allow the epithelial cells to close the wound.

GROUP 4. WHAT IS NECESSARY FOR EXTRACELLULAR MATRIX REMODELING AND SCAR PREVENTION?

The differences in scarring between the skin and the oral mucosa need to be explored. Why does the oral mucosa not scar? It may be temporal in nature. The oral mucosal cells proliferate and migrate more rapidly than skin cells. It may be the orientation of collagen fibrils and how fibroblasts align these. Also, differences in aging effects between skin and oral mucosa are unknown. We need to ensure that during wound closure, both collagen types I and III are placed appropriately in the wound. Scars are primarily collagen type I only. There is also a need to understand how anti-scarring agents, such as IL-10/tubuloglomerular feedback- β , work. Critical is expand-

ing research to different types of scarring (hypertrophic, keloid) and defining which animal models are most informative for each (scarring in mouse *versus* "red dog" pig models; lack of scarring in fetal and mucosal wound models).

A critical obstacle perceived in the progress to the clinic is the restriction of end points currently recognized by the Food and Drug Administration for testing new drugs. Expanding those end points could lead to progress. Such end points include improving the quality of granulation tissue, or reducing scarring, and partial wound closure rather than full wound closure. Some end points may not have good animal models, and approval for clinical biopsies may be appropriate and should be considered. In the real world, we will need to deal with issues of protocols for multiple drug application and wound care nursing. Particularly challenging in this regard are the prospects that treatments will be different for each day of acute wound care and that chronic wound treatment occurs for the most part without nursing care.