

Conference Report

“Wound Healing: Oxygen and Emerging Therapeutics” Columbus, Ohio, September 12–15, 2002

Sponsored by the National Institutes of Health (R13AR049171), International Union of Biochemistry and Molecular Biology, and UNESCO–Global Network of Molecular and Cell Biology. Conference co-chairs: Chandan K. Sen, The Ohio State University Medical Center, and Thomas K. Hunt, University of California-San Francisco.

FAILURE TO HEAL, wound infections, and excess scarring have a significant negative impact on the quality of life of the many millions of affected individuals and occur at a great cost to society. The cost of caring for chronic wounds alone exceeds \$1 billion dollars annually in the United States. Oxygen therapy is widely used clinically to promote wound healing under certain circumstances. Although some of oxygen's effects on wound healing are well established, it is clear that far more remains to be discovered. Therapeutic modalities such as hyperbaric and topical oxygen seem to provide beneficial results on chronic or slowly healing wounds. Although the available controlled scientific data are generally supportive, these therapies suffer from a general lack of acceptance. Thousands of patients all over the world receive these treatments, yet understanding of the underlying scientific mechanisms is clearly limited.

In the wound site with disrupted vasculature, oxygen availability is a key rate-limiting step in early wound repair. Molecular oxygen serves as a nutrient to provide the increased energy demand of regenerating tissues. In addition, derivatives of oxygen commonly referred to as reactive oxygen species appear to promote wound repair as well. Recently, it has been proposed that, at low concentrations, reactive oxygen species may serve as cellular messengers that regulate a variety of events tightly linked to wound repair, such as cell proliferation, angiogenesis, and extracellular matrix synthesis. The objective of this conference was to facilitate greater discussion, promulgation, and development of these new results.

In 1967, the first conference focusing on Oxygen and Wound Healing was held with 15 delegates in attendance at Turku, Finland, hosted by Dr. Juha Niinikoski. Dr. Niinikoski is currently the Professor and Chair of Surgery at Turku University and attended the current meeting as an invited speaker. The 2002 Conference on Wound Healing was hosted by the Department of Surgery and the Davis Heart and Lung Research Institute of the Ohio State University Medical Center. It was attended by 226 registered participants from 14 different countries. Participants included basic and clinical scientists, clinical residents, wound care professionals, and wound care product manufacturers. Fifteen leading companies exhibited their products at the conference. Twenty-six

continuing medical education credit hours were offered. The conference was covered by the *Columbus Dispatch* news daily and by Paul Harvey on ABC news radio.

On September 12, 2002, the inaugural session of the conference started in the Davis Heart and Lung Research Institute. Welcome addresses were delivered by the university and city authorities. Columbus Mayor Michael Coleman greeted the conference with a citation of recognition from the city. The opening lecture was presented by Dr. Gregg L. Semenza of Johns Hopkins University. Dr. Semenza discussed the molecular mechanisms implicated in oxygen homeostasis with special reference to the hypoxia-inducible factor. Although this lecture was primarily focused on molecular mechanisms, the following lecture focused on the overall impact of oxygen on wound healing. Dr. Thomas Mustoe of Northwestern Medical School presented data from a variety of experimental wound models. He concluded that combining oxygen therapy with other agents that regulate signal transduction pathways offers considerable promise for the future. Next, Dr. Angelo Azzi from the University of Berne in Switzerland discussed the signal transduction regulatory properties of α -tocopherol. Based on current results, it was speculated that vitamin E enrichment in the skin may interfere with dermal wound healing. Dr. Pascal Goldschmidt-Clermont of Duke University followed with a lecture focusing on the role of oxidants as mitogens. The small G protein Rac and its role in regulating cell proliferation were discussed. The therapeutic value of stem cells in the treatment of vascular disorders was discussed in the context of new findings. Dr. Adrian Barbul of Johns Hopkins University presented a series of results from his laboratory describing the significance of nitric oxide in wound healing. In the final lecture of this inaugural session, Dr. Irshad Chaudry of the University of Alabama at Birmingham addressed the burning issue of gender dimorphism in responses to trauma and sepsis. These lectures were followed by the welcome reception and a tour of the Davis Heart and Lung Research Institute.

Scientific sessions on the remaining days of the conference were held in the Columbus Hilton located in the Easton Town Center. The first two lectures of the second session focused on oxidant imaging and tissue oxymetry. These were presented by

Dr. Jay Zweier of the Ohio State University and by Dr. Harold Swartz from Dartmouth Medical School. Dr. Zweier presented evidence of high-resolution free radical imaging which could be applied to study clinical wounds. Next, Dr. Aron Fisher from the University of Pennsylvania described how reactive oxygen species play a role in mechano-transduction responsive signaling. Dr. Dipak Das from the University of Connecticut discussed redox signaling in response to reoxygenation of the heart. After a brief break, Dr. Junji Yodoi of Kyoto University presented a series of studies from his laboratory highlighting the significance of thioredoxin in redox signaling. The possibility that oxidants may actually serve as a survival factor in monocytes was described by Dr. Clay Marsh of the Ohio State University Medical Center. Next, Dr. Bernard Babior from the Scripps Institute presented evidence showing that neutrophils generate considerable amounts of ozone. The chemical basis of this synthesis was discussed. The second session concluded with an exciting audiovisual presentation by Dr. Scott Melvin, an expert in robotic surgery at the Ohio State University. Dr. Melvin demonstrated the emerging power of robotic surgery and discussed its significance in the context of wound healing.

The third session focused on the role of oxidants in supporting wound repair. Dr. Thomas K. Hunt of the University of California at San Francisco provided a historical perspective on the role of oxygen in wound healing. He summarized over three decades of work in his laboratory focusing on key related variables such as temperature, humidity, and lactate. Dr. Chandan Sen of the Ohio State University Medical Center specifically addressed the significance of oxidants in wound healing. He reported that at low concentration oxidants support the healing process. Specifically, Dr. Sen described the transcriptional mechanisms involved in peroxide-induced vascular endothelial growth factor expression. In addition, he presented evidence showing that Rac1 gene transfer facilitates closure of dermal wound. Next, Dr. Marcos Rojkind of the Walter Reed Army Medical Center discussed the role of excessive oxidants in hepatic fibrogenesis. Dr. Zamir Hussain of the University of California at San Francisco presented the final talk of this third session. He described the role of lactate and oxidants in wound repair.

The final session of the second day addressed issues related to oxygen sensing and detection. Dr. Nanduri Prabhakar of the Case Western Reserve University discussed mechanisms and significance of intermittent hypoxia. Next, Dr. Paul Schumacker of the University of Chicago described the role of mitochondria and oxidants in signaling for hypoxia. Dr. Sashwati Roy of the Ohio State University Medical Center presented new evidence characterizing how changes in partial pressure of oxygen are sensed by primary cardiac fibroblasts. The next two lectures were directed toward the physical estimation of oxygen level in tissues. Drs. Donald Buerk and David Wilson of the University of Pennsylvania presented the final lectures of the day, describing the various approaches available for tissue oxymetry, including advantages and limitations of each approach.

The third day started with the fifth session addressing oxygen therapy in wound healing. Dr. Juha Niinikoski of the University of Turku in Finland presented his long experience with clinical hyperbaric oxygen therapy. Next, Dr. Harriet

Hopf of the University of California at San Francisco discussed the significance of oxygen in resisting wound infection. Dr. Finn Gottrup from the Copenhagen Wound Healing Center, one of the world's largest centers practicing oxygen therapy, followed with his studies and experience with oxygen therapy. The session continued after a short break with a series of brief presentations. Drs. Yoshimasa Ishii of the Japanese National Institute of Advanced Industrial Science and Technology, Mark Iafrafi of New England Medical Center, and Gayle Gordillo of the Ohio State University presented their experience with topical oxygen therapy, concluding that systemic hyperbaric oxygen therapy poses significant risk to humans that may be avoided with topical oxygen therapy. They also concluded that current experimental data from studies using topical oxygen are highly limited. Finally, Dr. Claude Piantadosi of Duke University presented a detailed lecture explaining the risks of systemic hyperoxia. This session was followed by the poster session.

After lunch on the third day, the seventh session was a panel discussion of practical issues related to oxygen therapy and wound healing. The session was chaired by Drs. Thomas Hunt and Luisa DiPietro of Loyola University Medical Center and Richard Schlanger of the Wound Healing Clinic at the Ohio State University Medical Center. Panelists included basic science and clinical experts in wound healing. Several issues of outstanding practical significance were discussed during this session. After a brief break, the eighth session resumed with a lecture by Dr. John Engelhardt of the Center for Gene Therapy of Cystic Fibrosis and Other Genetic Diseases, University of Iowa. Dr. Engelhardt presented an hour-long lecture describing the fundamentals of gene therapy. The potential of gene therapy to treat wound was discussed. This lecture was followed by a poster presentation session. The conference banquet was hosted in the Columbus Hilton later. At the banquet, four junior investigators and four students were recognized for their outstanding abstracts. Blinded abstracts were judged by Drs. Thomas Hunt, Bernard Babior, Charles Orosz, and Clay Marsh. The awardees in the junior investigator category were Drs. Oren Tirosh, Savita Khanna, William Wallace, and Mustafa Atalay. The awardees in the student category were Cynthia Head, Praveen Gajendrarreddy, Li Zuo, and Jani Lappalainen. Each winner received a certificate of recognition and a cash award.

The final day started with the tenth session focusing on wound immunity. Dr. Jorge Albina of Rhode Island Hospital lectured on the role of neutrophils and macrophages in the wound. He proposed that the role of neutrophils in wound healing and inflammation goes beyond infection control and involves the regulation of macrophage phenotype. Next, Dr. Luisa DiPietro explained why wounds in the aged heal more slowly compared with those in younger models. Dr. John Sheridan of the Ohio State University showed that social stress is a key factor that impairs wound healing. He presented new experimental models to study the effects of social stress on wound healing. He also commented on some clinical studies, conducted by Dr. Phillip Marucha of the Ohio State University, which tested the effects of social stress on wound healing.

The eleventh and final session included a series of brief presentations of outstanding interest. Dr. Scott Hansen from

the University of California at San Francisco reported that homeobox gene HOXD3 accelerates diabetic wound repair in db/db mice. Dr. Francisco Laurindo from the University of Sao Paulo discussed the issue of oxidative stress in impairing wound healing. Next, Dr. Hakan Nygren presented a very interesting analytical approach for the subcellular localization of membrane lipids with a 100-nm spatial resolution, based on secondary ion mass spectrometry imaging. Dr. William Ennis of Advocate Christ Medical Center discussed the use of laser Doppler image analysis in studying wound microcirculation. The effects of homocysteine and its effect on vascular smooth muscle cells were discussed by Dr. Nesrin Ozer of Marmara University in Turkey. Dr. Gail Besner of the Ohio

State University discussed the antioxidant functions of heparin-binding epidermal growth factor, including experiments related to intestinal cytoprotection. The conference concluded with the final oral presentation by Dr. Naoki Yahagi of the University of Tokyo, who presented preliminary data describing the effects of electrolyzed water on wound healing.

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