

# Executive Summary

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## BACKGROUND AND SIGNIFICANCE

This conference was designed to generate innovative ideas that will ultimately lead to enhanced understanding of mucosal injury and strategically improved therapies for cancer patients.

There has been an impressive recent history relative to publications about and funding directed toward mucosal injury in cancer patients. In addition, professional organizations, including the International Society for Oral Oncology and the Multinational Association of Supportive Care in Cancer, have targeted mucositis as a major toxicity of cancer treatment for which new research and standards of care are needed. In this context, conference participants critically evaluated the current status of science relative to mucosal injury in cancer patients and delineated future research directions that could ultimately lead to new management strategies.

The conference format consisted of a lecture series, multiple workgroup discussions, and a summary plenary session. The research directions that emerged are summarized below. Successful pursuit of these research themes could lead to clinically important advances in the amelioration of cancer therapy-associated mucositis as well as to enhanced quality of life (QOL) for patients. The research could also potentially permit use of new, more aggressive cytoreductive cancer therapy that results in more durable remissions and improved long-term patient survival rates.

## FUTURE RESEARCH DIRECTIONS

The following two principles were identified as the foundation for establishing new research directions:

- 1) The etiology, progression, and resolution of cancer therapy-associated mucositis are multifactorial in nature.
- 2) The best research model is ultimately the human model.

Specific research themes follow.

### Models for the Study of Mucosal Biology, Injury, and Repair

Mucositis is an important model for the study of mucosal biology, injury, and repair. The discovery of potent agents that might protect or promote healing of the mucosal lining could lead to therapeutic, curative approaches rather than to palliation in cancer patients. Most therapeutic molecules identified to date are cytokines that affect epithelial proliferation. Basic, translational, and applied research involving the most promising molecules should be pursued.

In addition to cytokines, there is a critical need to identify and characterize other molecular interventions with similar effects. For example, current research supports the concept that significant reductions in mucositis can be achieved by appropriate manipulation of stem cell sensitivity by use of growth factors. With the identification of regulatory factors specific for the gastrointestinal tract, it is possible that the stem cells also might be more effectively regulated. New studies are required to assess

the most efficacious doses and delivery protocols, including combined and sequential use of different cellular and molecular factors.

Immune-mediated mucosal injury and repair can be investigated in substantial detail with use of *in vivo* model systems that control for antigen expression and the immune response directed toward that antigen. The following are examples:

- 1) Use of transgenic and gene-targeted mice will continue to define important mechanisms of mucosal injury, including analysis of the stages of epithelial cell damage and repair. These studies thus provide logical and relevant targets for future pharmacologic intervention. New studies are needed to further elucidate basic mechanisms of mucosal cell growth and differentiation. This research should translate these findings into patient-oriented research for treatment of inflammatory bowel disease, in addition to mucositis and other gastrointestinal complications of cancer therapies.
- 2) Mediators of cell death produced by CD8 T cells that act on intraepithelial lymphocytes can be evaluated via gene knock-out mice and blocking antibodies. Moreover, mechanisms by which tolerance versus autoimmunity is induced are readily testable in this well-defined and tissue-specific system. Future studies should focus on interaction of CD4 T cells with intraepithelial cell-expressed antigen so that new mechanisms relative to mucosal tolerance and immunity can be defined.
- 3) The gene knockout murine model also presents a unique system in which factors influencing mucosal repair can be studied. This research could directly influence the understanding of repair of epithelial damage inherent to cancer therapy. Intraepithelial cell damage can be selectively induced in enterocytes and is regulated by antigen levels and perhaps other factors such as T-cell number and viral dose. Thus, the system may be manipulated to examine the factors, immune or otherwise, involved in the repair of mucosal tissue. A further level of control can be attained by using other mucosal-specific promoters with distinct expression patterns.

Relationships between oral and gastrointestinal mucositis should be further defined, including the potential role of surrogate markers and the patient-related risk factors, including the possible role of genomics in defining risk profiles for mucositis.

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## Infection and Mucosal Injury

Intact mucosa is an important host defense against systemic infection in neutropenic patients. Conversely, mucosal injury is a significant and identifiable risk factor for localized and systemic infections, including those lesions caused by bacteria and fungi. Distinguishing between infectious-related versus regimen-related tissue damage is crucial to maintaining optimal delivery of cytoreductive cancer therapy. These principles collectively provide a basis for future research directed to several concepts, including the following:

- 1) Understanding the early steps in pathogenesis of infection at damaged mucosal sites could lead to improvements of overall outcome of cancer patients by reducing morbidity and mortality associated with both mucositis and infection.
- 2) No molecular intervention has yet been definitively proven to be effective for either prevention or treatment of mucosal injury secondary to cytotoxic cancer therapy. Furthermore, the specific mechanisms by which colonizing pathogens may amplify the severity of pre-existing mucosal damage require further study. It may be possible to bridge these scientific gaps by delineating novel, anti-infective approaches that reduce overall severity of mucosal toxicity in cancer patients by inhibiting deleterious effects of pathogenic flora at localized mucosal sites.

## Mucosal Pain

Basic and clinical studies are needed to characterize the biology of pain associated with mucosal injury. Studies might include the following:

- 1) Detailed epidemiologic trials to determine patterns and severity of acute and chronic pain, as well as related side effects associated with various stomatotoxic chemotherapy and radiotherapy regimens.
- 2) Characterization of types of pain that result from oral mucosal injury as well as mucosa at other gastrointestinal tract sites.
- 3) Development of new animal models that permit evaluation of the anatomy and physiology of nociceptive processes in both normal and inflamed mucosal tissues. Emphasis should be placed on determining which inflammatory mediators activate and sensitize primary afferent nociceptors during mucosal injury.
- 4) Delineation of new clinical assessment tools for mucosal pain, including pain arising from nonoral intestinal injury.

Knowledge collectively gained from these innovative approaches can be used to develop novel therapies to decrease significant clinical problems associated with pain and its sequelae in cancer patients.

## Mucosal Drug Delivery

A major challenge in formulating topical agents for the oral cavity is the need for both adhesion to moist mucosal surfaces and the maintenance of resistance to physical removal by saliva. Strategies to eliminate these research barriers should be pursued, since maximizing drug retention time at localized mucosal sites is important for improving clinical effectiveness. Use of a bioadhesive gel, for example, may reduce the frequency of application and amount of drug administered; thus, patient compliance is enhanced. In addition, lubrication and physical

protection by the bioadhesive gel often lead to reduced discomfort associated with mucositis.

Scientific findings currently exist regarding the effectiveness of transport machinery in facilitating absorption of a diverse array of therapeutic molecules into intestinal epithelial cells. In contrast, further research is needed to understand better the capacity of comparable transport processes in oral epithelial cells that are altered because of oral mucositis. Study of how best to use chemoprotective drugs to mitigate this subcellular injury is also important.

The profound effect of selected cytokines on cell proliferation requires that they be delivered locally to mucosa so as to not promote tumor growth in the patient receiving cytoreductive cancer therapy. To exert a mucoprotective effect after topical application, such compounds must transit a surface permeability barrier to reach the proliferative compartment of the epithelium. New research is needed relative to (1) preservation of high local concentrations at the mucosal surface so as to maintain a concentration gradient and (2) use of permeabilizers to ensure penetration of large molecules across the epithelial permeability barrier.

## QOL and Economic Outcomes

Understanding of the effect of mucositis on QOL would be enhanced by a prospective, comprehensive, and longitudinal evaluation of mucositis severity and symptoms in relation to global and specific QOL outcomes. Such research would permit exploration of the potentially complex relationships between physician-graded mucosal injury, patient-reported specific symptom severity, and the multiple domains of QOL.

Evaluation of patient preferences for the potentially different acute and long-term consequences of increasingly aggressive cancer treatment protocols is necessary. Precise explanation of QOL implications of different therapeutic regimens may enhance treatment decision making by the patient, family, and health professionals. This may be particularly valid when there is an absence of clear survival advantage associated with the various treatment modalities under consideration.

Systematic, prospective evaluation of economic costs associated with management of mucositis is important. Cost-effectiveness and cost-benefit analyses could be conducted on the basis of the knowledge of true costs of mucositis management in relation to costs and efficacy of the preventive and therapeutic agents.

## NEXT STEPS

It is essential that ongoing communication occur across relevant groups to strategically advance this research agenda. In addition to this *Journal of the National Cancer Institute* publication, specific next steps, include the following:

- 1) Posting of conference material on the Web site of the National Cancer Institute with links to the National Institute of Dental and Craniofacial Research through its National Oral Health Information Clearinghouse as well as Web sites for other relevant National Institutes of Health agencies.
- 2) Coordination of conference outcomes with the January 2002 clinical consensus conference being developed by the Mul-

tinal Association of Supportive Care in Cancer and the International Society for Oral Oncology.

3) Development of a listserve of conference participants.

Continued efforts should be directed to health professional groups and patients to clarify the nomenclature for mucositis across health professional groups. This is essential for the determination of precise outcomes.

Effective integration of objective and patient-oriented outcomes of interventional clinical trials relative to federal regulatory mandates is critical. It is important to coordinate this relationship among various user groups, including academic health center investigators, clinicians, industry representatives, government officials (including those from the Food and Drug Administration and the National Institutes of Health), and patient advocate groups.