Symposium and Workshop on Autotherapies: Enhancing Our Innate Healing Capacity  
January 25-26, 2018  
NIH Campus  

**Symposium**  
January 25, 2018

**Introduction**

Autotherapies are treatments based on the body’s natural ability to heal and protect itself. In the dental, oral, and craniofacial region, autotherapies could be used to selectively signal the body to repair and regenerate tissue, resolve inflammation, trigger immune responses to overcome diseases, and restore a natural microbial balance. These strategies might also help to heal damaged or diseased tissues in other parts of the body.

**Welcome**  
**Martha Somerman, DDS, PhD**  
Director, National Institute of Dental and Craniofacial Research

Dr. Somerman welcomed attendees and explained that this is the first symposium to be held as a result of [NIDCR 2030](https://www.nidcr.nih.gov/Research/NIDCR-2030), an initiative that was launched less than a year ago to encourage discussion about the future of dental, oral, and craniofacial research and to strategically plan for the future. Five goals for 2030 were established, one of which is advancing the development of autotherapies. Dr. Somerman outlined the goals of the symposium: to identify areas of progress, gaps in knowledge, and opportunities where additional investment would significantly advance autotherapy strategies and accelerate translation to the clinic.

**Opening Remarks and Overview**  
**Lawrence Tabak, DDS, PhD**  
Principal Deputy Director, National Institutes of Health

Autotherapies can be framed within two broad themes that are now central to the NIH: the elucidation of endogenous tissue regenerative and reparative responses, and the modulation of the immune system. Dr. Tabak shared several examples of current research supported by NIH related to the development of autotherapies and stated that we will see many more examples of this area of research going forward. He emphasized that achieving the translation of autotherapies to the clinic will require widening the focus of research to evaluate patients across disease conditions in an interdisciplinary way. He predicted that electronic medical records of the future will contain not just a few parameters—such as heart rate and blood pressure—but will also include our genomic and microbiomic profiles. Achieving this goal will require the development of strategies and technologies to analyze and synthesize data in real time.
Successful treatments using stem cells have yet to materialize. There are still difficulties optimizing their potency, current clinical trials are poorly designed, and significant placebo effects exist. In most studies, clinicians obtain cells from a patient, manipulate them outside the body, and inject them back into the patient. Dr. Karp described his team’s alternative but still experimental approach to modify stem cells from intestinal epithelium using small molecule biopharmaceuticals and other non-stem cell types present in the gut.

Intestinal stem cells are also being tested as candidates for reversing noise-induced hearing loss caused by the death of sensory hair cells in the cochlea. The results from Dr. Karp’s group suggest that specific small molecule biopharmaceuticals that target intestinal stem cell signaling can induce generation of new sensory cells from intestinal stem cells in vitro and in vivo.

Children have much better rates of bone regeneration than adults, for example, there is 100 percent regeneration in a child’s rib after six months, but at 20 years of age, there is a significant decrease in regrowth rate. Following this lead, Dr. Lee and her team have explored why bone regeneration appears to decrease with age. She investigated differences in bone marrow-derived stem cells (BMSCs) in young versus older hosts and noticed that a bone morphogenetic protein, BMP6 (which plays a role in the mature skeletal system), is expressed at higher levels in older BSMCs. Dr. Lee and her team have begun to examine how BMP6 paracrine expression affects bone regeneration.

Dr. Lee showed case studies demonstrating the need for non-invasive, non-surgical procedures to correct craniofacial deformities and showed promising data from another
team of scientists who are using a pharmacological approach to repair cleft palate in a mouse model. Using a Pax9-/+ mouse model of cleft palate, this group was able to correct the palatal part of the defect in fetuses using a small molecule drug that activates the Wnt pathway.

Biomaterials to Re-engineer Immune Response and Enhance Regenerative Capacity of Musculoskeletal Tissues
Edward Botchwey, PhD
Associate Professor, Wallace H. Coulter Department of Biomedical Engineering at Georgia Tech and Emory University
Director, Laboratory for Immuno-Regenerative Engineering, Parker H. Petit Institute for Bioengineering and Bioscience at Georgia Tech

Finding ways to measure the potency and quality of biomanufactured mesenchymal stem cells (MSC) remains a challenge for the field. Dr. Botchwey’s group has developed a method, as yet unpublished, which uses information about the composition of cellular membrane lipids as an indicator of the quality and potency of biomanufactured MSCs. The approach consists of extracting lipids from the MSC samples, analyzing composition and structural variation of the lipid fraction, and correlating this information with MSC quality and potency in biological assays.

Dr. Botchwey also discussed his group’s work investigating how cells interact with their microenvironments, and how to use this information to induce desired cell responses. Within this line of investigation, Dr. Botchwey’s team is using specialized, engineered bioscaffolds called hydrogels to measure and modify functional immune responses in vivo. Using these hydrogels, they introduce enzymes normally present in placenta and embryos into the microenvironment of immune cells to modify their phenotype. Dr. Botchwey and his colleagues are using advanced bioinformatics to analyze changes in immune responses as a result of these manipulations.

Mechanisms of Response and Resistance to Cancer Immunotherapy
Robert Ferris, MD, PhD
Hillman Professor of Oncology and Director of the Hillman Cancer Center University of Pittsburgh Medical Center

Immune checkpoint inhibitors targeting CTLA-4 and the PD-1/PD-L1 axis have shown unprecedented clinical activity in several types of cancer, including head and neck squamous cell carcinoma (HNSCC), and are rapidly transforming the practice of medical oncology. The challenges ahead are to discover why immunotherapy treatments work so dramatically in some cancers and patients, while not at all in others, as well as how some treatment-responsive tumors subsequently acquire resistance. Dr. Ferris, a tumor immunologist who specializes in head and neck cancer (HNC) research, discussed the importance of better understanding the mechanisms limiting cancer immunotherapy in order to broaden the clinical applicability of these treatments.

Dr. Ferris and his team have studied the role of human papilloma virus (HPV) in HNSCC, and particularly host response in the tumor microenvironment and its therapeutic implications. He also leads several prospective phase I, II, and III trials on HPV+/- HNSCC and antiviral
immunity, with HPV therapeutic vaccines and anti-PD-1 monoclonal antibody immunotherapy. Although the rates of HNC due to tobacco use or other toxic exposures are declining, the rate of HNC caused by HPV is rising. Researchers continue to search for effective treatments to eradicate tumors, as well as to understand differences between HPV+ and HPV- HNC.

In his presentation, Dr. Ferris described the critical interactions between the immune system and cancer cells. Cancer growth and progression, from the initial establishment of a cancer cell to the development of metastatic disease, is dependent on immune evasion. While HNSCC is a favorable disease for immunotherapy, only a minority of patients derive benefit from single-agent immunotherapies. In this regard, Dr. Ferris also discussed the future and potential benefits of combinatorial immunotherapy as an alternative strategy that might increase the number of patients who respond to immunotherapy.

***Workshop Sessions***

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Morgan O’Hayre, PhD, project lead for NIDCR 2030, opened the workshop by stating that the main goals of the meeting were to evaluate the current state of autotherapies research, to identify significant gaps in knowledge and pinpoint areas that are sufficiently advanced to benefit from further development in the near future.

**Session I: Cells and Microenvironment**

Three 20-minute presentations explored issues related to manipulating cells and their microenvironments to promote regeneration.

*Mimicking Cellular and Hormonal Mechanisms for Tissue and Bone Repair*

**Laurie McCauley, DDS, PhD**  
The William K and Mary Anne Najjar Professor, Department of Periodontics and Oral Medicine, University of Michigan School of Dentistry  
Dean, University of Michigan School of Dentistry

Dr. McCauley discussed approaches to harness endocrine mediators to enhance endogenous mechanisms of bone healing and regeneration. She also highlighted strategies for reducing inflammation and pain, and encouraging bone regeneration, using endogenous, specialized pro-resolving mediators such as resolvins, protectins, and maresins. Further, Dr. McCauley described her group’s work on stimulating bone production by homing osteal macrophages to the site of tissue injury. These macrophages serve multiple functions, including removing dead cells and secreting soluble biomolecules that enhance tissue healing and regeneration. Last, she discussed the potential for directing tissue regeneration by using specialized engineered microspheres that incorporate small molecule drugs that are activated once the microspheres are engulfed by macrophages.

*Mechanical Forces and Regeneration*

**David Mooney, PhD**  
Robert P. Pinkas Family Professor of Bioengineering, Harvard University
Dr. Mooney described studies from his group that examined how mechanical forces from the microenvironment are sensed by cells. Because researchers have established that mechanical forces play an important role in tissue development, morphogenesis, and cell fate determination, Dr. Mooney hypothesized that mechanical forces might also promote tissue regeneration. To this end, his group is developing hydrogel scaffolds that when injected in vivo, can exert defined mechanical forces on the embedded cells. Dr. Mooney emphasized that achieving spatiotemporal control of the mechanical properties of in vivo tissue microenvironments is an important goal for achieving effective tissue regeneration. His group is beginning to explore this avenue of research using soft robotic devices that can exert controlled mechanical forces on tissues.

**Strategies for Autologous Tissue Regeneration**  
**William Murphy, PhD**  
Harvey D. Spangler Professor and H. I. Romnes Faculty Fellow, University of Wisconsin

Dr. Murphy stressed that improvement in combinatorial and spatiotemporal in vivo delivery and release of multiple bioactive molecules such as growth factors, cytokines, and small pharmaceuticals will be central to the success of autotherapies. It is also important to consider biological stability and unique interactions between biomolecules in the in vivo microenvironment, which can significantly differ from those in vitro. Dr. Murphy’s group is developing specialized polymer microspheres and other types of bioscaffolds that can exert precise control over stability of biomolecules bound to them.

**Session II: Immunity and Infections**

Three 20-minute presentations explored issues related to harnessing immune system function to combat diseases including cancers and autoimmune disorders and to influence wound healing and regeneration.

**T-reg Cells: Targets for Autotherapeutic Manipulation**  
**Ethan M. Shevach, MD**  
Chief, Cellular Immunology Section, Division of Extramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health

T-reg cells are immune function regulatory cells that could be successfully targeted by autotherapies because they work to suppress T cell responses. Removing these cells from mouse models usually causes immune system-related disease. Transcription factor FOXP3 is a marker for the T-reg cell population. Depletion of FOXP3+ cells from adult mice results in catastrophic autoimmunity. Depletion of regulatory T-cells in germ free mice also results in death. Autoimmune disease is thought to be due to T-reg dysfunction in one of the suppressive pathways. T-regs have been used with interesting therapeutic results. An immunotherapy using polyclonal T-reg cells has been tested as a treatment for type 1 diabetes. Another treatment application could be for cancers, where carefully timed
depletion of T-regs was shown to counteract low immune response to highly immunogenic and even poorly immunogenic tumors in mice.

According to Dr. Shevach, potential T-reg clinical applications include:

- Cellular biotherapy in autoimmunity/inflammation/transplantation;
- augmentation of function or numbers with small molecules or monoclonal antibodies; and
- reversal of suppressor function or deletion in cancer.

**Immunoeescape Mechanisms, Immunosurveillance, and immunotherapy**

Soldano Ferrone, MD, PhD
Professor of Surgery, Harvard Medical School, Massachusetts General Hospital

Cancer immunologists’ efforts to show that innate and adaptive immune cells recognize tumor cells and reject tumors in experimental animal models have paved the way for cancer immunotherapies in humans. However, tumor antigen-specific T- and B-cell immune responses often do not correlate with improved clinical outcome. This discrepancy between immune and clinical responses underlines the need to better dissect the molecular and cellular events leading to immune-mediated tumor rejection in humans. Dr. Ferrone’s presentation explored the different mechanisms used by tumor cells to escape recognition by immune system cells.

One approach to overcome tumor immune evasion, Dr. Ferrone explained, is to correct defects in HLA class I antigen-processing machinery (APM) component expression and/or function. It has become increasingly evident that defects within the APM pathways are associated with malignant transformation of cells. Understanding the role of the host immune system and evasion strategies—in this instance the role of the altered APM and antigen presentation—could provide essential insights and reveal targets for new immunotherapies based on generating tumor-specific antigens and eliciting effective T-cell response.

**Immunity at the Oral Mucosal Barrier**

Niki Moutsopoulos, DDS, PhD
Clinical Investigator, Oral Immunity and Infection Unit, Division of Intramural Research, National Institute of Dental and Craniofacial Research, National Institutes of Health

Many oral diseases are associated with pathogenic microbes, an altered microbiome, and immune dysfunction. These include dental caries, Sjögren’s syndrome, periodontal disease, oral cancer, and oral mucositis as a consequence of chemotherapy/radiation. Dr. Moutsopoulos pointed out that when immune dysregulation leads to a disease, it can be difficult to pinpoint initiating factors, or to identify critical mechanisms of pathogenesis.

In humans, T cells are important to barrier function, especially in the oral mucosa. T cell dysfunction is associated with specific diseases:

- TH17 is associated with antifungal immunity;
- neutrophils are associated with periodontal immunity; and
- T cells and natural killer cells are associated with antiviral immunity.
The oral cavity is home to a diverse microbial community, and it is a place of minimal infection, with regulated inflammatory responses and optimal wound healing. It could be possible to use mechanisms that drive oral mucosal immunity to inform autotherapies, but there are still outstanding questions about functions, such as:

- Local triggers: how they shape protective immune response;
- key immunologic mechanisms;
- key mechanisms ensuring tolerance; and
- local priming of immune responses.

To balance the body’s potential toward health and away from disease, future research goals should include studies to better understand the mechanisms of homeostatic immune regulation surveillance at the oral mucosal barrier, and to identify key microenvironmental triggers that stimulate beneficial immunity in the oral cavity.

Session III: Tools and Technologies

Three 20-minute presentations explored issues related to the development of new tools and technologies to advance autotherapies.

*Engineering Molecules to Engineer Tissues*

**Jeffrey Hubbell, PhD**

Barry L. MacLean Professor of Molecular Engineering Innovation and Enterprise, Institute for Molecular Engineering, University of Chicago
Professor, Committee on Immunology, University of Chicago

Dr. Hubbell and his group are exploring how interactions between extracellular matrices (ECM) and growth factors can be optimized for productive tissue regeneration. He emphasized that chronic inflammation at the site of disease or tissue injury detrimentally affects growth factor-ECM interactions. To address this challenge, his group is engineering ECM-like molecules and growth factors with optimized mutual binding affinities. Dr. Hubbell’s laboratory is also developing novel approaches for reducing potential side effects of cancer immunotherapies. These efforts entail engineering ECM-like molecules that have high binding affinity to immunotherapy drugs to allow better retention of these drugs at the tumor site and to reduce systemic drug concentration, thereby lowering overall drug toxicity.

*Cancer Peptide Vaccines*

**Esteban Celis MD, PhD**

GRA/Cecil Whitaker Jr., MD Eminent Scholar in Cancer Immunology
Leader, Cancer Immunology Inflammation and Tolerance Program, Georgia Cancer Center
Professor of Medicine, Augusta University

A major challenge for cancer immunotherapies is the need to develop agents that are consistently effective in a majority of patients and cancer types. Immunotherapies that use immune checkpoint inhibitors (e.g. anti-CTLA4, -PD-1 and -PDL1) and adaptive cell therapies that rely on the infusion of T cells (e.g. purified, genetically modified T cell receptors, modified to express T cell receptors or chimeric antigen receptors) to recognize, target, and
destroy tumor cells can be efficacious, but the numbers of responders and types of cancers that can be treated are limited. Both are expensive treatments and can have toxicity problems when used long term. Alternative strategies such as cancer vaccines to elicit cytotoxic T cell responses are cost-effective and have shown promising results in the lab, but the results of most therapeutic cancer vaccine trials that target tumor-associated antigens have been unsatisfactory. However, there is renewed interest in further developing therapeutic cancer vaccines based on the growing evidence that immune response is best achieved when immune cells are presented with neoantigens—proteins encoded by tumor-specific mutated genes. Dr. Celis discussed engineering peptide vaccines using synthetic peptides to duplicate a portion of tumor-specific antigen to mimic a systemic viral infection as an attractive alternative strategy to induce highly targeted immune responses with few side effects.

**CRISPR Delivered Therapies**

Farshid Guilak, PhD
Professor, Department of Orthopaedics, Washington University

Chronic inflammatory conditions are perpetuated by overproduction of inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1). Pharmacological anti-TNF-α/IL-1 therapies are often effective in arresting excessive chronic inflammation, but they have significant side effects because of high systemic exposure to the drugs. Dr. Guilak and his group are engineering self-regulatory, feedback-controlled, cell-based systems that use gene-editing technologies to re-wire the inflammatory circuits of diseased tissues. These systems produce the exact amounts of TNF-α/IL-1 antagonists to curtail inflammation while avoiding side effects of the drugs. Dr. Guilak emphasized that such self-regulating feedback-controlled systems could find broad utility in treatment of many inflammatory diseases and conditions, and could serve as a valuable tools for achieving the goals of autotherapies.

**Session IV: Recommendations and Prioritizations**

Lillian Shum, PhD, director of the Division of Extramural Research at NIDCR, summarized the concepts and areas of interest that emerged from the symposium and workshop sessions. Subsequent discussion highlighted areas of significant interest for moving the field forward.

There is a need to study both the healthy state and the disease state, especially at their extremes, such as super-healthy centenarians or those with rare diseases. In healthy states, knowing more about resistance to degeneration could inform tactics to promote regeneration. Further, understanding immunoescape can inform immunotherapy for cancers, as well as autoimmune diseases. In disease states, rare disease studies could provide large effect size to make it easier to identify molecules and cells that are critically important for understanding the etiology of disease or restoration of homeostasis.

Manipulation of the cellular microenvironment to promote tissue regeneration is an area of research that offers much potential. There are a number of approaches to modify the endogenous microenvironment, ranging from chemical cues, to genome engineering techniques (such as CRISPR), and mechanical forces, delivered with tissue-specific, spatial
and temporal precision. Several workshop presentations shed light on new tools that allow exquisite control of the microenvironment. Equally significant is manipulation of cellular fate at the single cell level that utilizes state-of-the-art technologies in microfluidics and genetic programming. The field would also benefit from faithful models of disease that could present local cellular microenvironment for manipulation as well as sensing and measurements of physiological variables and outcomes.

The recent clinical successes of immunotherapies for cancers, presented by several investigators, pointed to a pathway for studies that could prove fruitful in other immune disease states. Immunotherapies use checkpoint inhibitors, adoptive cell therapies, and peptide vaccines to reverse the immunoescape tricks of cancer cells. This approach offers a model of immune engineering that could be tried with other diseases and disorders, including autoimmune diseases. Combination therapies could enhance/optimize current single therapy to increase efficacy and decrease toxicity. Precision medicine approaches could include identifying genetic predisposition that can stratify patients and predict individual responses to treatment, and characterizing individual’s microbiome that could modulate treatment responses.

And, finally, developing a pipeline that brings together the fields of developmental biology, immunology and stem cell biology with tools and technologies that are ready for implementation could be used to more rapidly advance translational research.

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A video of the symposium is available for viewing. Articles about the symposium are in The NIH Record and The NIH Catalyst.