**Top Priority Idea**

**Inflammation Science**

**What is the connection between inflammation and chronic disease?**

Inflammation is broadly defined as the body's reaction to harmful changes or events. It is a defensive response to any threat to homeostasis, including infection and tissue damage. Inflammatory response is governed primarily by the immune systems and serves to eliminate the harmful agents and restore homeostasis. Over the past 20 years, inflammation has emerged as a key factor in the diseases that comprise the top causes of death in the United States: cardiovascular disease, cancer, respiratory diseases, stroke, Alzheimer's disease, obesity, diabetes, kidney diseases, and a variety of infectious diseases including HIV/AIDS. While runaway inflammation is a major driver of these illnesses, a precise and thorough understanding of inflammation science has yet to emerge. Despite volumes of research, the full extent of the interplay among inflammation, organ systems, the immune system, environmental factors, the microbiota (the community of microorganisms that reside within the body) and genetics remains unknown. Establishing a foundation in inflammation science is therefore one of the most exciting scientific and health frontiers of today.

Acute inflammation occurs in response to injury or infection, when the immune system dispatches white blood cells to the affected site, resulting in redness and swelling or symptoms such as fever. However, the concept of inflammation extends far beyond acute responses to infection and injury. Inflammation can become chronic or systemic over time – as in responses to stressors such as environmental toxins, an unhealthy diet, excess fat, autoimmune reactions, aging, and persistent acute inflammation – resulting in chronic disease. The purpose of the inflammatory response is to remove or sequester the source of the disturbance, to adapt to the abnormal conditions and, ultimately, to restore tissue functionality. It has recently become clear that inflammation is fundamentally involved in all aspects of medicine.

Harmful effects arise as a result of chronic inflammation in excess of what can be handled by the body's intrinsic stabilizing and protective processes. Recent evidence also suggests that the progression of, and susceptibility to, many diseases are modulated by shared molecular and cellular mechanisms that are profoundly affected by extrinsic factors such as diet, genes, and the microbiota. Taken together, this provides both a challenge and a remarkable opportunity. Identifying the core shared rules and specific roles of these essential factors, the mechanisms by which they work and their interdependence will lead to new paradigms in human biology and leaps in our understanding and treatment of disease.

The picture that emerges from the current understanding of inflammation is that it is not just a specialized defense reaction, but rather it is a fundamental biological process that affects every aspect of human physiology. Each organ system can operate in either a normal (homeostatic) or an inflammatory mode, the latter providing the defense against, and adaptation to, the challenges that elicited the inflammatory response. Just as the endocrine and the autonomic nervous systems coordinate the homeostatic functions, the immune system orchestrates the inflammatory mode of function of every organ system. This new perspective departs from the traditional view of inflammation as a specialized defense reaction to infection and injury. Instead, inflammation is a fundamental mode of function of physiological systems, which is an alternative to the homeostatic mode of function. Because the two states of physiological systems are largely incompatible, inflammation has the potential to drive pathological states.

This perspective provides a framework for investigating these associations, and it calls for an integrated new scientific domain that combines currently disconnected biological disciplines. The goal of this initiative would be to develop this new interdisciplinary approach to inflammation and human diseases -
combining studies of gene regulation, cell communication and tissue organization, neuroendocrine control and systemic homeostasis and stress adaptations on cellular, tissue, and organismal levels. It will address the fundamental pathophysiological processes underlying aging and chronic diseases, including cancer, neurodegeneration, cardiovascular and metabolic diseases. Research in this area will include:

- Basic biology of inflammation as revealed by underlying gene regulation and cellular and tissue architecture
- Physiology of inflammation and its effects on neuroendocrine control and systemic homeostasis
- Host-microbe interactions, from infectious disease to commensal microbes
- Relationships between inflammation and age-associated illnesses, including cancer and neurodegeneration
- Inflammatory processes that lead to chronic diseases such as cardiovascular diseases, obesity and metabolic syndrome

Substantial progress in our understanding of inflammation will require a research structure focused on the breadth and interdisciplinary nature of the challenge. The overarching model for inflammation science spans components of immunobiology, cell biology, pathology, physiology and structural and molecular biology, and integrates aspects of diverse fields such as systems biology, biochemistry, computer science, bioengineering, neuroscience, and microbiology. Dissecting inflammation's complex effects on tissues requires knowledge of neurobiology, cardiology, cancer biology, metabolism, and digestive diseases. Work to understand the unique profile of inflammatory factors in autoimmune diseases will be crucial, as will expertise in human genetics—to identify contributing genetic variations. Ultimately, understanding the fundamental mechanisms involved in inflammation will provide new targets for therapeutic and improved patient care.

Why Yale? Strength in Immunobiology

Yale already has unmatched strength, position, intellectual capital, and potential for impact in this area. Our comparative advantages include broad expertise and clear leadership in inflammation and immunobiology. In 1988, Yale was one of the first universities in the country to create a Department of Immunobiology devoted specifically to the study of the immune system. It is now the top-ranked immunology department in the country. In 2006, the Human and Translational Immunology Program was founded to accelerate the application of discoveries in the field of immunology to the study of the human immune system and the treatment of diseases. Yale researchers have made unique seminal contributions to the molecular, cellular, and genetic underpinnings of immune system function and development, and their translation to human health. Breakthrough discoveries at Yale include:

- Discovery of the innate immune system
- Creation of innovative mouse models for human disease, including reconstitution of mice with a functional human immune system
- New vaccine strategies based on tissue-resident memory T-cells
- New understanding of human autoimmune diseases, based on their underlying genetic architecture and immune regulatory networks
- Implementation of immune check-point inhibitors for cancer therapy
With its community of scholars who are renowned for working collaboratively, Yale is now poised to transform research on some of the most devastating diseases of our day. It is the best place to create a research team dedicated to the study of inflammation. Yale has a unique opportunity to leverage these strengths toward understanding the underlying cause of a broad range of human diseases.

Inflammation sits at the intersection of a number of traditional academic disciplines and several independent departments and units. The establishment of a Yale Inflammation Science Institute would position us as a leader in research on inflammation and inflammatory diseases, a field that is ripe for transformative discovery. The Institute would boast a carefully selected faculty representing the most creative and original scientists in specific relevant fields, along with associate members, fellows, visiting scientists, and access to professionally managed research support facilities. Yale has an unparalleled opportunity to redefine the concept of inflammation itself and will be poised to transform research on some of the most devastating diseases of our day.

To advance University-wide efforts in Inflammation Sciences, we offer the following recommendations:

- **Organizational Structure**: Establish an interdisciplinary Yale Inflammation Science Institute dedicated to studying the fundamental principles of inflammation and its roles in a broad range of human diseases.

- **Faculty and Students**: The Institute would be organized around several major research themes, led by about 12 principal faculty members who represent the most creative and original scientists in the relevant field, and who would be engaged in close collaborations with Associate Faculty members.
  
  - Institute Faculty would be drawn from both those already at Yale and new hires to the University. Appointment in the Institute will be driven by the scientific need for specific fields and/or approaches, targeting the outstanding scientists with a demonstrated record of constructive interactivity.
  
  - Associate Faculty members. The Institute should also serve as an organizing center for multiple Associate Faculty, who will retain research space within their primary academic departments. Associate Faculty will conduct basic or clinical research in fields related to the Institute's core mission, such as cancer, metabolic disorders, neurodegenerative diseases, and cardiovascular diseases.
  
  - Visiting scientists. The Institute should provide a venue for visiting scientists (with terms of visit ranging from one week to a full sabbatical year) who are involved in collaborative studies and who will enrich the intellectual diversity of the Institute.
  
  - As faculty are added, there should be a commensurate increase in the number of graduate students in the relevant host departments.

- **Space**: Physical co-location of key faculty and resources. The physical co-location of the Institute's personnel and scientific resources will be essential to promoting collaboration and ensuring access. The proposed Institute will require the identification of suitable space most likely within YSM.

- **Core facilities**: The Institute will have access to technology platforms (see Core Facilities recommendation above) including imaging, genomics, proteomics, computational science, mass spectrometry, and bioinformatics.

- **Education**: The Institute will create a unique, multi-departmental advanced course in Inflammation Science to provide key interdisciplinary student training in this field.