Additional Priority Idea

Conquering Cancer

How can we harness the “omics” revolutions to conquer cancer?

Cancer is one of the greatest challenges of our time. 40% of Americans will be diagnosed with cancer in their lifetime, and cancer remains a leading cause of death in the United States. With recent exponential progress in targeted therapies, in harnessing the body’s own immune system to kill cancer cells, and in understanding genetic predisposition to cancer, there are now unique opportunities to discover new approaches for conquering cancer.

Although our ability to describe cancer is now quite advanced, conquering this complex disease requires an understanding at multiple levels and scales – from molecules to communities. We need to understand differences between cancers at different sites, in different patients, and in different societies. Only then will it be possible to reduce cancer incidence and suffering through interventions at the population, familial, individual patient, sub-tumor, single cell, and molecular levels.

Unfortunately, most current cancer therapeutics are relatively blunt tools. Surgery removes what can be seen (and accessed) of a patient’s tumor. Chemotherapy and radiation therapy kill rapidly dividing cells with some selectivity – but with substantial side-effects and toxicity. New targeted therapies – although specific – have limited application and inevitably meet with resistance. Similarly, the new class of immunoncology agents (checkpoint inhibitors) that are now transforming cancer care only benefit a minority of cancer patients who cannot currently be identified prior to treatment.

The grandest challenges in cancer research are to develop new stables of patient-specific therapeutics so that all patients can be cured, and to match patients to these therapeutics. Advances in these directions will require progress with emerging and new technologies that allow cancers (and cancer patients) to be assessed simultaneously at molecular, cellular, immunological, physiological, genetic, microbiotic, and behavioral levels. Systematic acquisition of very large quantities of molecular, cellular, and patient care data – and its integration to establish biological interpretation and clinical action – will then be needed to drive new understanding and developments in cancer care and treatment.

Harnessing world class basic cancer research from molecules to man

Basic and clinical scientists at Yale are at the vanguard of understanding genetic, epigenetic, immunological, and biochemical changes that drive (or allow) cancer formation and progression – areas that will dominate cancer research in the coming years. Comprehending and engaging with these changes will illuminate paths to developing new analytical tools and technologies, new data resources, and new animal and “disease-in-a-dish” models of cancer that will spawn hitherto unimagined genetically- and molecularly-driven therapeutic approaches and diagnostic tests. So too, Yale is home to world-leading molecule designers and builders who make chemotherapeutic intervention possible. Harnessing these discoveries and inventions will require development and refinement of new cutting-edge technologies, and development of key core facilities to integrate them into cancer research and clinical trials.

- New CRISPR-based approaches to genome editing are revolutionizing cancer research, allowing rapid generation of specific somatic genetic changes in cells and advancing our ability to make complex experimental animal models of cancer.
- New technologies for studying tumors cell-by-cell (rather than as cell populations) are transforming our understanding of tumor heterogeneity, make-up, and evolution as well as the immune microenvironment of tumors. The ability to study the individual cells that make up a tumor (and its
microenvironment) – and how they differ in treatment response – is revolutionizing models of tumor initiation, development, and progression.

- The influence on cancer development of our microbiota is only now being realized, alongside startling revelations about how the composition of the microbiota affects response to treatment, metabolism of drugs, and metabolism (or production) of carcinogens.

- Cancer immunotherapy has shown great potential, but current therapies represent only the tip of the iceberg. Yale has a unique combination of strengths in immunology and clinical cancer research that can be leveraged to further advance this field – in which Yale already plays a leading role.

- Tremendous gaps between available data and biological interpretation and clinical action are being exposed as quantities of molecular and patient care information increase – including routine bioinformatic analyses of patient samples and collection of increasingly complex and informative clinical data available in electronic medical records. Closing this ever-increasing gap, and exploiting the burgeoning data to drive new science and medicine, will require complex and advanced computational and theoretical approaches.

Cancer Research at Yale

Yale has a history of firsts in all areas of cancer research – in basic science and its translation to the clinic. It was the birthplace of cancer chemotherapy, still the mainstay of cancer treatment. Yale established the first tumor registry – a core resource for clinical, epidemiological and laboratory investigations in cancer. Yale investigators developed the first genetically modified mice for studies of human disease. The first genetic diagnosis based on human DNA sequencing was also made at Yale, and Yale investigators pioneered the science and clinical application of immune checkpoint inhibition in cancer therapy. With a superlative record of high-impact research, the Yale Cancer Center (YCC), which unites research across 30 University departments and 286 Yale faculty with a vast range of expertise and interests, brings together outstanding faculty in immuno-oncology, cancer biology, signal transduction, cell biology, genetics, immunology, and dedicated disease experts who cross disciplines for clinical impact.

We endorse the ongoing investments into the interdisciplinary and translational efforts of the YCC and the creation of the Cancer Biology Institute on the West Campus. We also recommend further investment in a suite of core facilities (see Core Facilities above) that are needed to leverage recent developments in biological research for conquering cancer.
Additional Priority Idea

Precision Medicine

How can we exploit clinical and genomic “big data” to predict and individually improve each person’s health trajectory?

Medicine is entering a new era in which the acquisition and interpretation of vast quantities of data from human populations is not only beginning to enable individually-tailored clinical care, but is also opening previously inaccessible avenues for understanding the biology of health and disease. Electronic medical records give access to high quality phenotypic data, including medical history, family history, environmental exposures, and medication use. DNA sequence data give access to the underlying genetic information that encodes and influences phenotypes. This integration of clinical and genetic information promises to transform our understanding of human biology, and to boost discovery for diagnosis, individualized treatment, predictive medicine, and disease prevention.

Historically, personalized medicine began with blood transfusion, involving the assignment and matching of blood groups between donors and recipient patients. Now, the most visible recent development is individualized cancer therapy. For example, if a non-small cell lung cancer tumor is positive for the PD-L1 protein, it can be treatable with specific antibodies, known as checkpoint inhibitors, which enable the immune system to eliminate the cancer. Underscoring the broader significance of this approach to medicine, in 2016 the NIH announced initial funding “to inform efforts to accelerate the understanding of individual differences that play a role in health, with the goal of informing better prevention and treatment strategies tailored for each person.” Although there has been a remarkable pace of medical progress along these lines, there remains vast unexplored territory in understanding human biology and disease. For example, of the ~20,000 genes of the human genome, genetic variants in only 57 genes are currently considered to be “medically actionable,” that is, potentially targetable by therapeutics. Therefore, the grand challenge ahead is to comprehensively identify and functionally explain all individual genetic variants that correlate with human health and disease. These discoveries will have major scientific, medical, and economic impact.

There is a need for scalable, automated, and predictive algorithms for Precision Medicine. A top priority toward linking genetic data with human biology and disease is the need for generating algorithms that will derive novel insights from the vast amounts of multidimensional data entailed in the Precision Medicine enterprise. This will require intellectual expertise and innovation in data science and full participation of experts in this rapidly evolving field. Clearly, assistance will come from Machine Learning, Artificial Intelligence, and mathematical models, and the contributions of leading investigators in those areas will be essential (See Data Science above). At the same time, patient privacy and data security will remain paramount. Thus, a growing need for collaborative teams of big data scientists will confront biologists and clinicians engaging in the Precision Medicine enterprise.

Personalized Medicine at Yale

In 2009, Yale investigators developed exome sequencing, the small subset of the genome that encodes for protein function, selectively capturing and sequencing the exomes of expressed genes at high efficiency and low cost. The utility of this technology was demonstrated by performing the first genetic whole exome diagnosis of a chronically ill infant, identifying a homozygous defect in a bicarbonate/chloride exchanger of the kidney. In other studies, family pedigrees with the highest and lowest values of blood pressure were studied by exome sequencing, identifying a variety of kidney channels and transporters implicated in renal salt processing, thus establishing salt handling as a primary element responsible for blood pressure variation.