Chabner Colloquium: Answering the Big Questions in Cancer Research & 2016 STO Annual Meeting

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Liberty Ballroom
The Liberty Hotel
Boston, Massachusetts

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Day One

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S5 Financing Start-Ups (abstract 12)
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MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

TheOncologist.com
Abstract 1 – Epigenetic Mechanisms of Tumor Initiation and Evolution

BRADLEY E. BERNSTEIN, MASSACHUSETTS GENERAL HOSPITAL CANCER CENTER, HARVARD MEDICAL SCHOOL, BROAD INSTITUTE OF HARVARD AND MIT, BOSTON, MASSACHUSETTS, USA

The importance of epigenetic regulation in cancer is now well established by a convergence of data from cancer genome sequencing, epigenomics, and the transcriptional and molecular characterization of tumors and models. Our laboratory is focused on characterizing epigenetic mechanisms of tumor initiation as well as on understanding how epigenetic changes and intratumoral heterogeneity contribute to drug resistance and tumor relapse. We have focused in particular on brain tumors as clinically compelling models for investigating epigenetic mechanisms of tumorigenesis. I will present two ongoing projects in this area. The first project is focused on genetic mutations that affect epigenetic regulators and processes and are associated with gliomagenesis. Here I will discuss our progress toward delineating specific mechanisms, regulatory targets, and programs that explain the tumorigenicity of individual mutations. The second project is focused on epigenetic mechanisms that enable glioblastoma stem cells to adapt to environmental stressors or drug pressures. Here we have identified a specific role for histone demethylases in resetting the epigenetic landscapes of glioblastoma stem cells, thereby allowing them to transition to a more primitive and refractory state. These respective studies exemplify ongoing research in our laboratory as well as in the broader research community and have general relevance for cancer biology, diagnosis, and therapy.

Abstract 2 – New Approaches to Challenging Targets in Cancer

NATHANIEL GRAY, DANA-FARBER CANCER INSTITUTE, HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS, USA

More small molecule degraders, such as the imide class of drugs, will eventually enter clinical practice. Understanding the mechanistic underpinnings of these agents is important. This lecture will discuss new approaches to developing small molecule agents that can address challenging cancer targets. In particular, small molecules that can induce selective protein degradation by recruitment of E3 ligases will be discussed. The difference between small molecule degraders and inhibitors will be covered, as will intervention strategies involving degradation versus inhibition.

Abstract 3 – Development of Novel Anti-Ras Therapy

MICHAEL R. BOYD, ADT PHARMACEUTICALS, INC., ORANGE BEACH, ALABAMA, USA

Ras proteins serve ubiquitously within cells as molecular “on/off” switches, determining passage of extracellular signals to intracellular components regulating cell growth and survival. In about a third of all human cancers, Ras is abnormally “locked” in the “on” or activated state due to mutation in Ras itself or in an upstream partner, resulting in uncontrolled cell growth. Despite more than 3 decades of Ras-focused drug development research within industry and academia worldwide, no effective cancer therapy directly targeting constitutively activated Ras has been forthcoming. This presentation describes the discovery of a novel, small-molecule drug development candidate, DC070-547, that potently and selectively inhibits growth of cancer cells harboring constitutively activated Ras, independent of Ras isoform or mutational status. Convergent experimental data support a direct, noncovalent association of DC070-547 with Ras to disrupt its normal interactions with binding partners upstream and downstream. DC070-547 has favorable “drug-like” physicochemical properties and has shown robust antitumor efficacy in a murine xenograft model of Ras-driven cancer. INDA-directed preclinical development of DC070-547 is being initiated, aimed at proof-of-concept clinical investigation.
Abstract 4 – Optimal MAPK Inhibition as a Key Component of Therapeutic Strategies for KRAS Mutant Cancers

RYAN B. CORCORAN, MASSACHUSETTS GENERAL HOSPITAL CANCER CENTER, HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS, USA

KRAS is the most commonly mutated oncogene in human cancer, yet no effective therapeutic strategies currently exist for KRAS mutant cancers. Since KRAS has proven difficult to target directly with small molecules, an alternative approach has focused on inhibiting key downstream effector pathways. Promising therapeutic combination strategies are currently in clinical trials and will be reviewed. Since the MAPK pathway is one of the most important downstream effector pathways of KRAS, MEK inhibitors, which inhibit MAPK signaling, have become common components of targeted therapy combination strategies. However, we find that while MEK inhibitors lead to effective short-term inhibition of MAPK signaling, complex adaptive feedback mechanisms drive MAPK pathway reactivation, reducing the therapeutic efficacy of MEK inhibitors. This vulnerability may be a key factor underlying the recent lack of success of many MEK inhibitor-based combinations in KRAS mutant cancer trials. However, other classes of MAPK inhibitors, such as ERK inhibitors, are less susceptible to adaptive feedback reactivation and can produce more sustained MAPK inhibition and improved efficacy in KRAS mutant cancer cells. Exploration of ERK inhibitors or other approaches to achieve more optimal MAPK inhibition may be key to the development of future targeted therapy combination approaches for KRAS mutant cancers.

Abstract 5 – FLT3 Inhibitors in Acute Myeloid Leukemia

RICHARD M. STONE, DANA-FARBER CANCER INSTITUTE, HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS, USA

Acute myeloid leukemia (AML) is a diverse disease biologically; subtypes may be defined on the basis of patients’ blast-cell-specific mutational profile. FLT3 mutations, found in 30%–31% of AML, activate the transmembrane tyrosine kinase and cause it to be able to drive growth in a factor-independent fashion. There are two FLT3 mutation types: point mutation in the tyrosine kinase domain and the more common FLT3 ITD (internal tandem duplication) subtype associated with a higher relapse rate. Small molecule inhibitors of activated FLT3 have been developed. They differ in potency, specificity, and binding. Initial single-agent trials in patients with mutant FLT3 AML yield clear biological activity but few complete remissions. The remission rate with newer, more specific FLT3 inhibitors may be slightly higher, but hematopoietic recovery is rare. Nonetheless, there are two ongoing phase III trials comparing single agent FLT3 inhibitors (gilteritinib and quizartinib) with chemotherapy in advanced mutant FLT3 AML. A clear, bright spot was the result from the CALGB 106/RATIFY trial, which studied the addition of FLT3 inhibitor + multitargeted kinase inhibitor, midostaurin; it showed improved survival when added to chemotherapy in adults aged 18–60 years with FLT3 mutant AML.

Abstract 6 – Checkpoint Blockade in Lymphoma

PHILIPPE ARMAND, DANA-FARBER CANCER INSTITUTE, HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS, USA

Immune checkpoint blockade, especially using monoclonal antibodies against programmed cell death 1 (PD-1) or its ligand PD-L1, has proven to be an effective therapeutic strategy against a variety of solid tumors. More recently, PD-1 blockade has also been tried across a spectrum of hematologic malignancies. Among them, classic Hodgkin lymphoma (HL) was predicted, based on its genetics, to have a potentially unique vulnerability to PD-1 blockade, and clinical results so far have supported this hypothesis. The activity of PD-1 blockade in HL is likely to change the treatment paradigm for this disease but also may help to select other promising targets for PD-1 blockade. This presentation will summarize the possible roles of checkpoint blockade in lymphoma.
Abstract 7 – Dihydroorotate Dehydrogenase: An Unexpected Metabolic Vulnerability in Acute Myeloid Leukemia

DAVID B. SYKES, MASSACHUSETTS GENERAL HOSPITAL CANCER CENTER, HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS, USA

Acute myeloid leukemia (AML) is a disease characterized by differentiation arrest: the inability of self-renewing progenitors to undergo their normal process of maturation. These immature leukemic “blasts” accumulate in the bone marrow, resulting in the anemia, thrombocytopenia, and infections that ultimately bring patients to medical attention. Despite a growing understanding of the genetic underpinnings of the disease, patients diagnosed with AML have an overall survival rate of only 25%. Furthermore, advances in diagnosis have not been accompanied by advances in treatment, and the chemotherapy standard of care remains unchanged since 1973.

Our project sought to identify and to develop new differentiation therapy for the treatment of patients with AML. The ideal differentiation therapy would remove or overcome the blockade in maturation, and these mature cells would lose their leukemia stem cell activity. We established a new cellular model of differentiation arrest that permitted a high-throughput phenotypic screen of more than 330,000 small molecules. This led to the unexpected observation that inhibitors of the mitochondrial enzyme dihydroorotate dehydrogenase (DHODH) triggered myeloid differentiation.

DHODH inhibitors were active in murine and human models of AML in vitro. Brequinar, a potent inhibitor of DHODH, was active in vivo, leading to differentiation, to a reduction in leukemia cell burden, and to a loss of leukemia-initiating cell activity across multiple models of AML. In addition, brequinar was well-tolerated in mice and spared the function of normal hematopoietic stem cells. DHODH inhibition hopefully represents a much needed therapeutic avenue for the treatment of patients with AML.

Abstract 8 – Genomic Analysis of Mitochondria-Rich Tumors

RAJ GOPAL, MASSACHUSETTS GENERAL HOSPITAL, HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS, USA

An array of metabolic adaptations, from a preferential utilization of glycolysis to a striking upregulation of mitochondrial oxidative phosphorylation, can be seen in cancer. Integrative genomic analyses have revealed key pathways enabling such stereotyped metabolic shifts in tumor metabolism. While great attention has been paid to the “Warburg effect”—the tendency of cancer cells to rely on aerobic glycolysis—less is known about the role of mitochondrial metabolism in tumors. An opportunity for investigating this role exists with oncocytoma, an epithelial tumor of variable invasive potential made up of cells called oncocytes. Characterized by a hallmark granular eosinophilic cytoplasm due to a remarkable abundance of mitochondria, oncocytomas occur throughout the body, including the thyroid gland (known as Hurthle cell carcinomas, or HCC), salivary gland, and kidney (known as renal oncocytoma, or RO). To determine the molecular mechanism of mitochondrial accumulation and to delineate whether this contributes to tumor formation, our lab performed next generation sequencing of HCC and RO. We focused on simultaneous analysis of both mitochondrial DNA (mtDNA) and nuclear DNA (nuDNA) for somatic events that may contribute to oncogenic cellular change. Our results showed that somatic mtDNA mutations in complex I genes are enriched in both HCC and RO in the absence of recurrent nuclear events. Thus, impairment of complex I, the first step of the mitochondrial electron transport chain, via mtDNA mutation may play an important role in both the mitochondrial accumulation and abnormal cellular proliferation of these unique tumors.
Abstract 9 – Germline Defects Underlying Sporadic Cancers

MANISH K. GALA, MASSACHUSETTS GENERAL HOSPITAL, HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS, USA

Large scale genomic analyses of tumors have led to the identification of numerous putative somatic driver mutations, many of which are potentially targetable. However, tumor heterogeneity limits therapeutic efficacy of such strategies. Here, we discuss the analysis of the germlines of over 4,000 individuals with hereditary and sporadic cancer and demonstrate that current annotation and pathway analyses are often inadequate in the identification of host-derived driver mutations with therapeutic potential that are present in almost all tumor subclones. We further demonstrate that such germline driver mutations may be more common than anticipated. Finally, through organoid models, we demonstrate proof-of-principle for this therapeutic strategy in which a person's host genome plays an important role in selection of targeted therapies.

Abstract 10 – Platinum Chemotherapy: Genomic Markers of Vulnerability, Resistance, and Effects on Tumor Evolution in Muscle-Invasive Bladder Cancer

DAVID LIU, DANAFARBER CANCER INSTITUTE, MASSACHUSETTS GENERAL HOSPITAL, HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS, USA

While targeted therapy and immunotherapy are incredibly exciting and promising therapeutic developments in cancer treatment, chemotherapy remains a mainstay of therapy. Precision medicine in chemotherapy is important to better target susceptible tumors, avoid ineffective treatment in resistant tumors, and inform rational therapeutic combinations. Muscle-invasive bladder cancer (MIBC) is treated with neoadjuvant cisplatin-based chemotherapy (NACC), and a near-complete pathologic response at cystectomy is associated with improved progression-free and overall survival. This is an ideal setting in which to discover markers of NACC sensitivity and resistance and examine the effects of platinum chemotherapy on tumor evolution.

To accomplish these goals, we performed whole-exome sequencing on matched pre-NACC tumor biopsies and post-NACC cystectomies of 102 MIBC patients from 3 academic centers. Using established pipelines and novel analytical adaptations, we called mutations (single nucleotide alterations + indels), copy number alterations, neoantigens, estimated purity and ploidy, and inferred phylogenetic relationships between matched pre- and post-treatment samples. Integrating clinical with genomic data, we looked for markers of susceptibility (enriched in responders) and resistance (enriched in nonresponders) and performed functional validation on candidate genes. We also investigated the effect of platinum-based therapy on mutation load and neoantigen burden and whether a platinum-induced mutational "signature" could be found in post-NACC tumors.

In this presentation, we will highlight findings, discuss clinical and biological implications, and lay out future directions for investigation.

Abstract 11 – Generation of Models of Human Hematologic Malignancies Using CRISPR Genome Engineering

ZUZANA TOTHOVA, DANAFARBER CANCER INSTITUTE, HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS, USA

Hematologic malignancies are driven by combinations of genetic lesions that have been difficult to model in human cells. We used CRISPR/Cas9 genome engineering of primary human hematopoietic stem and progenitor cells, the cells of origin for myeloid malignancies, followed by transplantation into immunodeficient mice, to generate models of clonal hematopoiesis and malignancy. Human cells bearing mutations in combinations of genes observed in myeloid malignancies, including cohesin genes, generated neoplastic clones capable of long-term, multilineage reconstitution and serial transplantation. Employing these models to investigate therapeutic efficacy, we found that cohesin-mutated hematopoietic cells were sensitive to azacitidine treatment. These findings demonstrate the potential for generating genetically-defined models of hematologic malignancies that reflect human disease and are suitable for the examination of the biological consequences of somatic mutations and the testing of therapeutic agents.
**Abstract 12 – The Art of Investing in Science**

OLEG NODELMAN, EcoR1 Capital, LLC, San Francisco, California, USA

EcoR1 Capital, LLC, is a fundamental biotechnology-focused investment advisory firm. Based in San Francisco, EcoR1 evaluates and selects extraordinary biotechnology companies that are pursuing the highest quality science and demonstrate strong business fundamentals. Like the EcoR1 restriction enzyme that helped to transform the biomedical field, EcoR1 seeks to help move medical research forward through investments into compelling biotech companies that are developing promising new solutions for untreated diseases. The EcoR1 portfolio consists of investments in both public and private therapeutics companies and often resembles a mix between Tomorrowland and the Island of Misfit Toys.

The team looks for asymmetric opportunities, or those investments or companies that have a potential return that is exponentially greater in probability and absolute dollars than the potential loss. Typically, biotech investors find a molecule or technology that they think will “work” and “bet” on the various stages of clinical outcomes, terminology overheard as frequently in this sector as in Las Vegas. Biotech investors tend to travel in herds; they either love or hate companies with no room in between. Valuations follow suit, dramatically overshooting both for perceived successes and for failures. To add to the inefficiencies, many biotech companies are off limits to traditional funds due both to the long-time horizons between new data announcements and to market caps that are lower than institutional limits. This strategy of identifying and investing in asymmetric opportunities is important, because it makes investing in biotech less risky and more sustainable.

**Abstract 13 – T-Cell Therapy: Current Applications and Future Directions**

MARCELA V. MAUS, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, Massachusetts, USA

Genetically-modified T-cell immunotherapy has achieved unprecedented responses in hematologic B-cell malignancies, and T cells modified with chimeric antigen receptors have been granted Breakthrough Therapy designation by the Food and Drug Administration at multiple institutions. Despite having been developed in the academic setting, many T-cell therapies are now entering an industry setting to be developed into commercial therapies to treat cancer. We will discuss the components and technologies used in making a T-cell product, some of the factors considered to be important for efficacy, and recent results in hematologic malignancies and some solid tumors.

**Abstract 14 – Addressing Clonal Heterogeneity in Chronic Lymphocytic Leukemia: Developing Personalized Neoantigen-Based Cancer Vaccines**

CATHERINE J. WU, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts, USA

Clonal evolution is a key feature of cancer progression and relapse. Recent studies across cancers have demonstrated the extensive degree of intratumoral heterogeneity present within individual cancers. We hypothesized that evolutionary dynamics contribute to the variations in disease tempo and response to therapy that are highly characteristic of chronic lymphocytic leukemia (CLL). Indeed, our recent integrated studies of genetic and epigenetic heterogeneity in CLL have revealed the complex and diverse evolutionary trajectories of these cancer cells. Immunotherapy is exquisitely suited for specifically and simultaneously targeting multiple lesions. We have developed an approach that leverages whole-exome sequencing to systematically identify personal tumor mutations with immunogenic potential, which can be incorporated as antigen targets in multi-epitope personalized therapeutic vaccines. We are pioneering this approach in an ongoing trial in melanoma and will now expand this concept to address diverse malignancies. Our expectation is that the choice of tumor neoantigens for a vaccine bypasses thymic tolerance and thus generates highly specific and potent high-affinity T cell responses to eliminate tumors in any cancer, including both “trunk” and “branch” lesions.
Section Editors

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2016 STO Annual Meeting

Select presentations from this year's Colloquium will be available on the STO website early 2017.

Visit http://STO-Online.org/Chabner-Colloquia for new videos or watch the lectures from last year.

Featured Presentations and Summaries - 2015

The Changing Nature of Phase I Trials
Lillian L. Siu, MD
Princess Margaret Cancer Center, University of Toronto

Monitoring Cancer Through Circulating Tumor Cells
Daniel A. Haber, MD, PhD
Massachusetts General Hospital Cancer Center, Harvard Medical School

Oncology Drug Development in the Era of Precision Medicine: FDA Perspective
Gideon M. Blumenthal, MD
Office of Hematology and Oncology Products, Center for Drug Evaluation and Research, U.S. Food and Drug Administration (FDA)

Preferentially Targeting the Malignant Hematopoietic Clone in Myeloproliferative Neoplasms (MPN)
Ann Mullally, MD
Dana-Farber/Brigham and Women’s Cancer Center, Harvard Medical School

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