BANBURY CENTER REPORTS

Rhabdomyosarcoma: A critical review of research and implications for developing therapies

Banbury Center, Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, USA
May 13-16, 2014

Organizers:
Charles Keller, Oregon Health & Science University, Portland, Oregon, USA
Amy Wagers, Harvard University, Boston, Massachusetts, USA

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BACKGROUND

Rhabdomyosarcoma is the most common soft tissue sarcoma of childhood, but despite four decades of advances in chemotherapy, radiation and surgery, the outcome for metastatic or relapsed disease is particularly poor. Why is this? What are the biological characteristics of these recurring tumors? Can these characteristics be exploited for new therapies?

New approaches, catalyzed by partnerships across science, medicine and engineering, in both the public and private sectors, are greatly needed to drive research. This is an auspicious time to ask these questions. Recent changes to the NCI Cancer Therapy Evaluation Program and the Children's Oncology Clinical trial process, in conjunction with FDA incentives, are facilitating moving basic science discoveries from bench to clinical trial.

Some of the key topics that to be examined at the Banbury Center meeting were:

- why does the Pax3:Foxo1a fusion oncogene reduce long term survival by up to 50% in alveolar rhabdomyosarcoma?
- how can microscopic residual disease at the tumor bed be addressed by molecular therapy?
- what aspects of metastasis are cell autonomous, and what aspects can be attributed to the microenvironement/extracellular matrix?
- is differentiation therapy possible for rhabdomyosarcoma, as it is in neuroblastoma and promyelocytic leukemia?

DETAIL

The conference brought together more than two dozen international clinical and research experts on rhabdomyosarcoma, as well as engineers, community advocacy groups, muscle biologists, and research & development representative from the pharmaceutical industry. Key clinical issues included metastasis, local disease failure and chemotherapy & radiation resistance. Driving biological problems for basic science investigation included a renewed interest in the tumor microenvironment, an increased emphasis on targeted the Pax3:Foxo1 transcription factor, and a more uniform standard for preclinical research.

Discussed also were the necessary resources for validating potential drug targets (live tissue for generation of new cell cultures and patient-derived xenograft models) – and ever-present need to address rhabdomyosarcoma as a multiple-target, multiple-drug disease.

A highlight of the meeting was a newly emerged community advocacy group, FocusOnRhabdo.org, which is coordinating communication and resource sharing of patient family, scientific and clinical stakeholders. Plans were set forth for strategic collaborations amongst more than 50 percent of attendees.

In summary, this was a very productive meeting, interchange of clinical and basic research findings in this exciting new area that holds tremendous promise for a new era of rapid acting, efficacious and safe antidepressant agents.

MEETING SESSIONS

Session 1

Charles Keller (Oregon Health & Science University, Portland)
Amy Wagers (Harvard University, Boston, Massachusetts)
Introduction to the meeting

Leonard H. Wexler, Memorial Sloan-Kettering Cancer Center, New York, New York:
Sleepong Beauty, The Sequel – The Search for Prince Charming

Javed Khan, National Cancer Institute, Bethesda, Maryland:
The application of Omics to identify novel targets and treatments for rhabdomyosarcoma

Peter Houghton, Nationwide Children's Research Institute, Columbus, Ohio:
Exploiting the IGF-mTOR pathway for treatment of rhabdomyosarcoma

Charles Keller, Oregon Health & Science University, Portland, Oregon:
Three novel target-therapy pairs for potential clinical trials within 18 months

Session 2

Terence A. Partridge, Children's National Medical Center, Washington DC:
A model of reversible context-dependent rhabdomyosarcoma in the dystrophic mouse

Beat Schaefer, University Children's Hospital, Zurich, Switzerland:
Cancer stem cells in RMS: fact or fiction

Lee Helman, National Cancer Institute, Bethesda, Maryland
Development of novel combination targeted therapies for rhabdomyosarcoma

Janet Shipley, Institute of Cancer Research, Sutton, United Kingdom:
Histone methylation status and differentiation therapy

Dawn Cornelison, University of Missouri, Columbia, Missouri:
Comparative medicine-Eph/eprin expression profiles in RMS samples from canine & human patients

Session 3

Amy Wagers, Harvard University, Boston, Massachusetts;
A translant-based model for rhabdomyosarcoma in mice.

Frederic Barr, National Cancer Institute, Bethesda, Maryland
The molecular correlates of fusion status in rhabdomyosarcoma

Denis C. Guttridge, Ohio State University, Columbus Ohio :
Regulation and Function of NF-kB in Rhabdomyosarcoma

Corinne M. Linardic, Duke University, Durham, North Carolina:
Hippo pathway signaling in ARMS

Session 4

Ranadip Pal, Texas Tech University, Lubbock, Texas:
Predictive Modeling of Drug Sensitivity

Simone Hettmer, Charite-Universitaets-Medizin Berlin, Berlin, Germany:
Asparagine homeostasis and its contributions to rhabdomyosarcoma growth

Grace Pavlath, Emory University, Atlanta, Georgia:
Nuclear transport receptors and myogenesis

Rossella Rota, Ospedale Pediatrico Bambino Gesu, Rome, Italy:
Notch3 signaling, EZH2, non-coding RNAs in rhabdomyosarcoma

Alan R. Ehrlich, Focus on Rhabdomyo:
An ad hoc framework for community - scientific collaboration for rhabdomyosarcoma survivability

Session 5

David Langenau, Massachusetts Hospital, Charlestown, Massachusetts:
Self-renewal mechanisms in embryonal rhabdomyosarcomas.

Andrea Hayes-Jordan, MD Anderson Cancer Center, Houston, Texas:
The Potential Role of TOX-4 in Rhabdomyosarcoma: Implications for Metastatic Disease

Zhizhong Li, Genomics Institute of Novartis Research Foundation, San Diego, California:
Study and screen rhabdomyosarcoma in NIBR

Summary and Closing Discussion: Charting Future Research

- what are the key areas for research that will advance our understanding of rhabdomyosarcoma?
- what can be done to ensure funding for research?
- how can we fund the development of promising laboratory findings into drugs for clinical trials?

MEETING PARTICIPANTS

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