Public Summary

Investigational Drug Steering Committee (IDSC)

Tuesday-Wednesday, October 6-7th (2009)

1. **Call to Order, Announcements, and Review of Minutes**
    a. **New IDSC N01 co-chair:** Dan Sullivan (Moffitt) has been elected as the new IDSC N01 co-chair. He will begin his term on January 1, 2010 replacing Charles Erlichman.
    b. **Cancer Therapy Evaluation Program (CTEP) update:** James Zwiebel (Investigational Drug Branch (IDB) Head) presented an LOI summary (October 2008-present), number of Career Development LOIs (CRDLs), and upcoming agents for potential IDSC review in 2009/2010.
    c. **The Immunotherapy Task Force and potential new members:** The IDSC approved Jedd Wolchok, MSKCC; Patrick Hwu, MDA; Madhav Dhodapkar, Yale; and Robert Vonderheide, UPenn as potential new members.

2. **Chemical Biology Consortium (CBC)**
    a. The National Cancer Institute (NCI) Chemical Biology Consortium (CBC) will facilitate the discovery and development of new agents to treat cancer. This effort will be managed by the NCI's Experimental Therapeutics Program (NExT) through SAIC-Frederick. It is envisioned that initiation of this consortium will provide cutting-edge chemical tools for probing complex signaling pathways and will serve as the starting point for the elaboration of first-in-class targeted therapies. The **mission of the CBC** is to increase the flow of early stage drug candidates into NCI's drug development pipeline. The CBC will be an integrated research consortium at the interface of chemical biology and molecular oncology that will, working with various programs within the NCI's Division of Cancer Treatment and Diagnosis (DCTD) and the Center for Cancer Research (CCR), establish an iterative cancer drug discovery group on the scale of a small biotechnology concern.
    b. By establishing a network of chemical biologists and molecular oncologists from government, industry and academia, these CBC associate organizations and the NCI (collectively "Participants") can further address the unmet needs in therapeutic oncology focusing on areas such as "undruggable" targets and under-represented malignancies e.g. pediatric tumors and natural products. Through the CBC and the interactions among the various Participants, the NCI's drug discovery and development pipeline can be enabled from target identification through proof-of-concept (POC) clinical trials. It is expected and understood that NCI will have the option to clinically develop successful compounds (NMEs) created by the CBC. The long-term vision of the CBC is to bridge the gap between basic scientific investigation and clinical research supported by the NCI. This integrated process will allow NCI to maximize the

return on its investment in molecular oncology over the past decade by making the following world-class resources available to CBC Participants:

i. Molecular and small animal imaging.
ii. Animal modeling of targeted therapies, including pre-clinical, pharmacokinetics and pharmacodynamics.
iii. Development and validation of pharmacodynamic assays to confirm drug effect on molecular target in preclinical studies and clinical trials conducted under an exploratory investigational new drug (IND) or in a traditional Phase I/II setting.
iv. High throughput screening of compound libraries, including natural products.
v. A network of medicinal chemists and chemistry intellectual thought leaders.
vi. A fully functional and experienced drug development program.

3. **CTEP Drug Development Plan - cMet**
   a. CTEP is considering three c-Met inhibitors (MK-8033, ARQ-197, and SCH900105) for its portfolio (*further information is confidential*).
   b. Signal Transduction TF recommendations were presented to the IDSC.

4. **PI3K/Akt/mTOR (PAM) Task Force**
   a. A refined gap analysis of mTOR inhibitors and evidence-based pros/cons of adding Rapamycin to the CTEP portfolio were discussed. A recommendation was made not to bring Rapamycin into the CTEP portfolio per IDSC vote.

5. **New IDSC Working Group:** A motion was approved by the IDSC to establish an LOI Review Working Group. The goal of the WG is to improve the efficiency of the LOI submission and review process.

6. **Metrics Working Group:**
   a. IDSC surveys from January 2008 and June 2009 were compared by the Metrics WG and results discussed.
   b. Members are generally satisfied that the IDSC is providing important input into the NCI drug development process.
   c. Members noted that IDSC brings a broad scope of drug development expertise to development of the NCI portfolio, adds transparency, and facilitates integration of CTEP's plans into U01, N01, cooperative group and cancer center approaches for specific diseases

7. **Division of Cancer Therapy and Diagnosis (DCTD) Pharmacodynamic (PD) – Biomarker Update:**
   a. Joe Tomaszewski presented the status of the DCTD PD – Biomarker portfolio to IDSC members. More information can be found at this website: http://dctd.cancer.gov/ResearchResources/ResearchResources-biomarkers.htm

8. CTEP Drug Development Plan – AT13387 (HSP90)

a. Alice Chen (IDB drug monitor) discussed the AT13387 drug development plan and then the Signal Transduction Task Force provided recommendations (*further information is confidential*).

9. Angiogenesis Task Force:

a. The hypertension (HTN) manuscript (Michael Maitland leader) has been accepted (with revisions) as a commentary to the JNCI.
b. Manuscript project # 2 involving recommendations for the initial assessment, surveillance, and management of hypertension and cardiac toxicity in patients receiving VEGF Signaling pathway (VSP) inhibitors draft is almost completed.
c. The Task Force will review an Ang 1 and 2 inhibitor on October 9th for potential presentation to IDSC.

10. Biomarker Task Force

a. **Biomarker educational session - Spring 2010 Early Drug Development (EDD) meeting: Topic**: Issues in Development of Companion Diagnostics for Novel Therapeutics
b. The Biomarker Task Force manuscript will be submitted to Clinical Cancer Research (CCR) in November 2009.

11. DNA Repair and Programmed Cell Death (RAD) Task Force:

a. Poly Adenosine Dinucleotide Phosphate Ribose Polymerase (PARP) educational session held at the CTEP Fall EDD meeting on October 5th
b. Autophagy session will be held at the CTEP Spring EDD meeting on March 23rd 2010.
c. Face to face TF meeting on PARP inhibitors will be held during the Spring 2010 CTEP/IDSC meeting on Monday, March 22nd in the evening. Disease-specific Steering Committees will be invited to nominate a representative to this meeting.

12. Future Calls/Meetings/Plans

a. IDSC Winter 2010 meeting: Friday, January 15th (Chicago, IL)
b. EDD/IDSC Spring 2010 meeting: Tuesday-Wednesday, March 22-24 2010 (Bethesda, MD)

TABLE 1: 13 investigational agents reviewed by the Investigational Drug Steering Committee

Agent Name	Inhibits	IDSC Review	Mass Solicitation Status?
IMC-A12	IGF-1R	September 2006	Issued
IL-12	immune regulation	July 2008	Issued
SCH727965	cdk	February 2008	Issued
GDC-0449	sonic hedgehog	November 2008	Issued
RO4929097	notch	January 2009	Issued
OSI-906	IGF-1R	March 2009	Pending
MK-2206	akt	March 2009	Issued
ABT-263	bcl2, BH3 mimetic	April 2009	Issued
AZD8055	mTOR	May 2009	Pending
ARQ-197	cMet	October 2009	Pending
SCH900105	cMet	October 2009	Pending
MK-8033	cMet	October 2009	Pending
AT13387	HSP90	October 2009	Pending