National Cancer Institute

NCI Perspectives on Developing Radiopharmaceuticals and Imaging Biomarkers

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CANCER IMAGING PROGRAM

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Disclaimer

I have no financial conflicts of interest

I will not be discussing any unapproved drugs

I will not be discussing the off label use of any drug

The opinions expressed should not be interpreted as the official position of NCI, NIH, HHS or the Federal Government

Challenges and Responses

- Imaging Drug Development
- Imaging as a Biomarker
- Imaging in Therapy Development

Imaging Drug Development

Challenge

A Difficult Business Model

- **High Development Risk (Cost)**
  - **Academic discovery**
  - **Limited development skill and resources**
  - **Underestimation of regulatory requirements**
- **Limited Potential Benefit (Gain)**
  - **Compromised IP (onset generic)**
  - **Approval dilemma**
  - **Limited market**

Imaging Drug Development

NCI/CIP Response

- Risk Management/Reduction
  - Scale up
  - Perform pre/non clinical development
  - Assist with/File and hold INDs
  - Enable production and distribution for research
  - Fund and perform enabling clinical trials
  - File NDAs and enable ANDAs

Development of Clinical Imaging Drugs & Enhancers (DCIDE)

Imaging Drug Development

NCI/CIP Response

Development of Clinical Imaging Drugs & Enhancers (DCIDE)

DCIDE is no longer taking applications, as of August 2009. Imaging drug development resources should be requested through the new NExT/CBC program which has its own application and review process. See NCI Experimental Therapeutics Program (NExT) There are 4 review dates per year, instead of the previous DCIDE submission and review process.

Imaging Drug Development

NCI/CIP Response

Dr. Paula Jacobs – Deputy Associate Director
DCTD/CIP

Imaging as a Biomarker

Challenge

Pragmatist definition of a *clinical* biomarker –

A reproducible relevant measure of a biologic process that is routinely and widely used in decision making.

Imaging is NOT a Biomarker!

Imaging is a method of *in vivo* measurement of a relevant biomarker

Imaging as a method for *in vivo* measurement (assay)

Challenges

- **Inadequate standardization (acquisition, analysis, reporting)**
- **Lack of analytical standards (controls)**
- **Poor understanding of the biologic system**
- **Poor control of the measurement environment**
- **Poor range matching (serendipity)**

Imaging as an *in vivo* Assay

Challenges

- **Missing Elements of an Assay**
  - **Knowledge of system variation**
  - **Standard process for measurement**
  - **Reference standards**
  - **Knowledge of biomarker**

Imaging as an *in vivo* Assay

NCI/CIP Response

- **Development of reference phantoms**
- **Study of system measurement variation**
- **Longitudinal reference studies in phantoms and patients**
- **Standard imaging protocols in clinical trials**
- **Response measurement standards**
- **Advanced imaging qualification implementation for clinical research trials**

Imaging as an *in vivo* Assay

NCI/CIP Response

Diffusion-Weighted Magnetic Resonance Imaging as a Cancer Biomarker: Consensus and Recommendations

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Abstract

On May 3, 2008, a National Cancer Institute (NCI)–sponsored open consensus conference was held in Toronto, Ontario, Canada, during the 2008 International Society for Magnetic Resonance in Medicine Meeting. Approximately 100 experts and stakeholders summarized the current understanding of diffusion-weighted magnetic resonance imaging (DW-MRI) and reached consensus on the use of DW-MRI as a cancer imaging biomarker. DW-MRI should be tested as an imaging biomarker in the context of well-defined clinical trials, by adding DW-MRI to existing NCI-sponsored trials, particularly those with tissue sampling or survival indicators. Where possible, DW-MRI

Imaging as an *in vivo* Assay

NCI/CIP Response

April 9, 2010

News Note: NCI Launches Centers of Quantitative Imaging Excellence Program

NCI is launching a new program to qualify existing NCI designated Cancer Centers with an added attribute -- as Centers of Quantitative Imaging Excellence. This program will significantly decrease potential variability in image procedures done while a patient is undergoing treatment as part of a NCI-sponsored clinical trial. Advanced imaging plays a pivotal role in cancer care by providing the ability to detect tumors early and to guide therapy as well as subsequent disease monitoring and surveillance. **The American College of Radiology Imaging Network (ACRIN) and the American College of Radiology will coordinate this program for NCI.**

CMS APPROVES THREE NATIONAL ORGANIZATIONS TO ACCREDIT SUPPLIERS OF ADVANCED IMAGING SERVICES

MRI, CT AND PET SCANS AMONG SERVICES TO BE AFFECTED

National Cancer Institute

Imaging assay of Biomarkers

Challenge

Ultimate Challenge – relevance

We often do not know which biologic process will be predictive of response or how the process will be modulated by tumor or therapy

Imaging in Therapy Development

Challenges

- **Poor understanding of the target or process to be measured**
- **Absence of a clinically ready imaging option that is relevant to the target or drug**
- **Inadequate understanding of the link between target modulation and desired outcome**
- **Absence of an effective therapy option as a positive control**
- **Default – try something and validate as you go – "see if it sticks and justify"**

Imaging in Therapy Development

Working Premise

Successful development of an imaging assay of a biomarker must occur in parallel with *ex vivo* assay development and serve as a concurrent part of the biomarker strategy in the development and translation of new drugs and new therapeutic options including combination therapy.

Imaging in Therapy Development

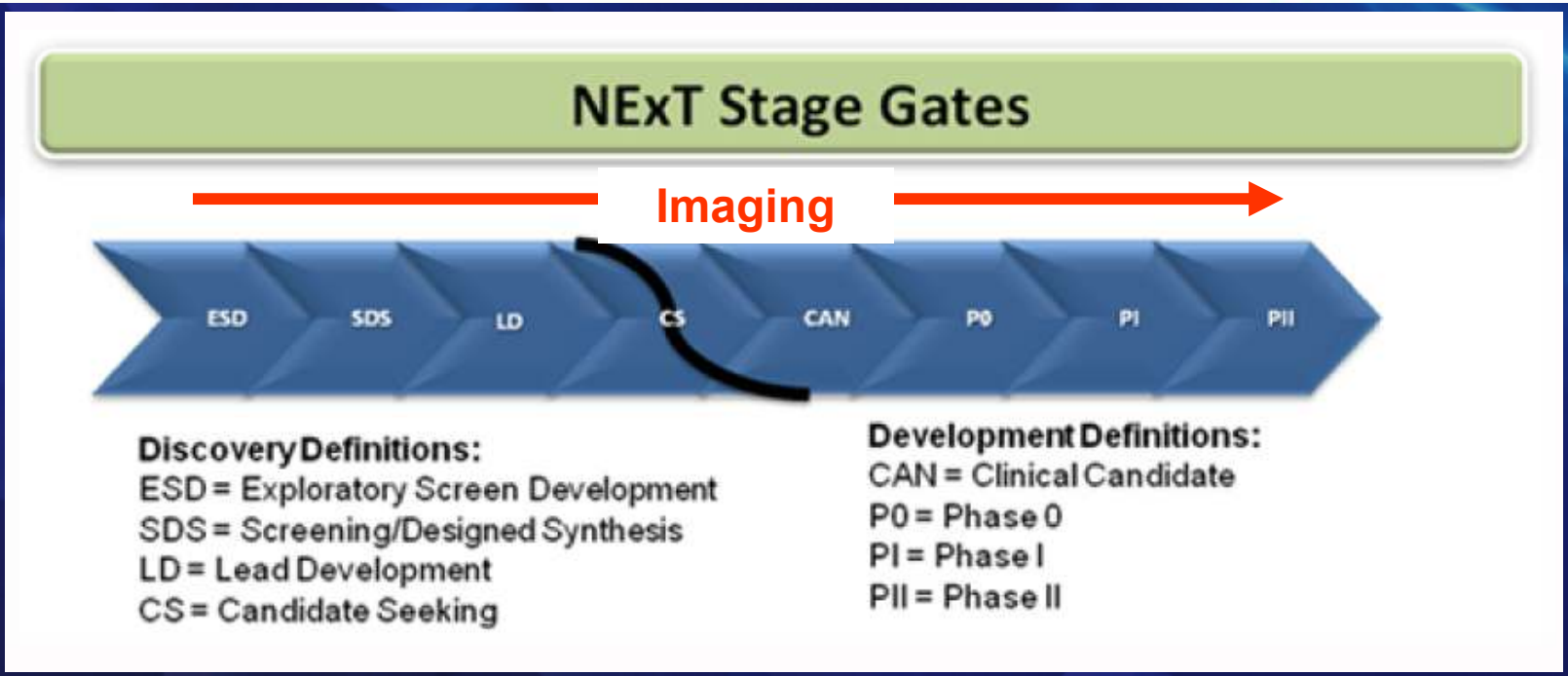
NCI Response

MISSION

The mission of the NExT Program is to advance clinical practice and bring improved therapies to patients with cancer by supporting the most promising new drug discovery and development projects. The NExT Program is not a grant mechanism; applications with exceptional science cannot be accepted without a clear path to the clinic or potential benefit to patients. Awardees will not necessarily receive direct funding; rather, the NCI may allocate various contract and grant resources toward the implementation and development of submitted projects. The NCI will partner with successful applicants to facilitate the milestone-driven progression of new anticancer drugs (small molecules, biologics) and **imaging agents** towards clinical evaluation and registration.

Imaging in Therapy Development

NCI Response



Imaging in Therapy Development

NCI Response

Concurrent **molecular imaging and/or pharmacodynamic assay development** provided by the **Cancer Imaging Program (CIP)** , **National Clinical Target Validation Laboratory (NCTVL)**, and **CCR** will allow early assessment of potential clinical biomarkers. These coordinated and focused R&D processes enable continued incorporation of new data and disease insights into every step of the discovery and development process, thereby increasing the potential for successful clinical evaluation of agents.

Imaging Assays of Biomarkers Summary

1. **Fund research that applies imaging to better understand target biology and network/ systems interactions fundamental to cancer therapy**
2. **Continue to support development of promising imaging drugs through NExT program and CIP regulatory affairs activities**
3. **Enable parallel development of imaging to allow *in vivo* measurement of relevant *ex vivo* biomarkers**
4. **Develop imaging strategies using translatable or available imaging techniques while therapeutic drug is in pre-clinical stage**

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