Outline

- Goals of IDSC
- Activities of IDSC and Task Forces
- Achievements of IDSC
- Future directions
IDSC Goals

- Provide **external** strategic input into the prioritization of phase I and II trials for new agents with NCI CTEP
- Increase **transparency** of prioritization process
- Optimize clinical trial designs to improve effectiveness of early phase therapeutics
- Increase the predictive value of early phase trials, resulting in the design of more successful phase III trials
- Develop a new forum for interaction among grant and contract holders and with CTEP
IDSC: Membership

- PI’s of all NCI Phase I U01 grants and Phase II N01 contracts
- Representatives from Cooperative Groups
- Liaisons with other Steering Committees
- Subject area experts:
  - Biostatistics, Industry, Imaging, Radiation Oncology, Clinical and Pre-clinical Pharmacology, Patient Advocates, NCI Staff
- 40+ members working through Task Forces or Working Groups
Scientific Meeting Planning Working Group

- Work with CTEP to develop the educational sessions for the semi-annual Early Drug Development (EDD) Meetings
  - cMET inhibitors
  - PI3K inhibitors
  - Cancer stem cells and targets
  - PIM kinase inhibitors
  - JAK/STAT inhibitors
  - Autophagy
Biomarker Task Force

- Use of biomarkers in early drug development
  - Proof of mechanism and proof of principle

- Questions
  - Should biomarkers be part of all early drug trials?
  - If biomarkers are to be used what level of technical and clinical validation is necessary?

- Recommendations developed to guide both CTEP and investigators
  - A manuscript is almost completed
Clinical Trial Design Task Force

- Focus is phase I and phase 2 designs
- Phase I workshop held July 2008
  - manuscript will be developed
- A series of opinion papers in press in Clinical Cancer Research
  - Introduction on Phase 2 Trial Designs
  - Imaging Endpoints
  - Randomized Phase 2 Designs
  - Biomarkers in Phase 2
  - Predictive Analysis of Alternative Endpoints
Clinical Trial Design Task Force

Future directions

- Tumor measurement analyses using Waterfall Plots and Tumor Burden
- Phase 2 simulation trial comparing Adaptive Design and Frequentist Approaches
- Phase 2 Historical Controls Database
- Novel ways of incorporating imaging data in early phase trials
Angiogenesis Task Force

- Identified need and developed guidance to manage hypertension related to antiangiogenic agents
  - Recommendations will be presented by Dr. Maitland
  - For 2009: ventricular dysfunction and myocardial ischemia

- Reviewed CTEP portfolio of anti-angiogenic agents to identify gaps and opportunities

- For 2009: evaluate use of angiogenesis biomarkers in CTEP Drug Development Plans

- Review imaging methods to assess angiogenesis in cancer
Signal Transduction Task Force

- Worked with CTEP on the development plan for IGF-1R antibody (IMC-A12), CDK2 inhibitor (SCH 727965), and cMET inhibitor

- Reviewed PI3K inhibitors

- For 2009: JAK/STAT inhibitors, proteosome inhibitors, and PIM inhibitors
PI3K/Akt/mTOR Task Force

- **Subgroup 1**: Review CTEP’s ongoing plan for mTOR inhibitors (including but not limited to deferolimus, everolimus, sirolimus and temsirolimus)

- **Subgroup 2**: Assess biomarkers and imaging in the development of PAM targeting agents

- **Subgroup 3**: Toxicity management (hyperglycemia – hyperlipidemia)

- **Subgroup 4**: Identify new agents/targets to add to portfolio
Immunotherapy Task Force

- Provide input to CTEP on novel immunomodulators
- Review CTEP’s current portfolio of agents
  - IL-12 development plan
- Recommend new immunotherapeutic strategies
  - MPL, CpG, IL15, IDO, CCL21 adenovirus, 1MT, IL7, IL21, TGF-beta antibody
Cancer Stem Cell Task Force

- Newly formed
  - Embryonic pathways signaling in CSCs
  - Identification of therapeutics that inhibit pathway signaling horizontal, vertical, parallel
    - Hh
    - Notch
    - Wnt
- Biomarkers for
  - CSCs, CTCs, TICs, TPCs
  - Proteins in signaling cascades
  - Genomic/proteomic analysis
- Hedgehog
  - GDC-0449 drug development plan was devised with significant involvement of this taskforce
- Notch
  - Gamma secretase inhibitor development is most recent input
### Example of TF/WG Grid

**INVESTIGATIONAL DRUG STEERING COMMITTEE STRATEGIC INITIATIVES FOR FY09**

The Strategic Initiatives represent specific projects planned in support of the IDSC Mission and Vision.

<table>
<thead>
<tr>
<th>Time Frame for Completion</th>
<th>Signal Transduction Task Force</th>
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<tbody>
<tr>
<td></td>
<td>1. Review new IGF-1R small molecule inhibitors; discussion of OSI-906; update on IMC-A12</td>
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<tr>
<td>Q4 2008</td>
<td>T T * T T T T T</td>
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<td>2. Review current status of STAT3 and JAK2 inhibitors with invited experts</td>
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<tr>
<td>Q3 2008</td>
<td>T T * T T T T T T</td>
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<td>3. Review STAT/JAK Inhibitors from pharmaceutical companies and arrange an educational session on STAT/JAK inhibitors for spring IDSC meeting</td>
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<tr>
<td>Mar-09</td>
<td>* T T T T T T</td>
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<td>4. Review Pim kinase inhibitors with invited experts</td>
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<tr>
<td>Q1 2009</td>
<td>T * T T T * T</td>
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<td>5. Review proteosome inhibitors with invited experts</td>
</tr>
<tr>
<td>Q1 2009</td>
<td>* T T T * T T T</td>
</tr>
<tr>
<td></td>
<td>6. Other</td>
</tr>
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* Designates Project Leader(s) / T Designates Team Member
Accomplishments

<table>
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<tr>
<th>Date</th>
<th>Development Plan for</th>
<th>Class</th>
<th>Task Force</th>
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<tbody>
<tr>
<td>November 2006</td>
<td>IMC-A12</td>
<td>IGF-1R Inhibitor</td>
<td>Signal Transduction</td>
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<tr>
<td>September 2007</td>
<td>Career Development LOI</td>
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<td>IDSC</td>
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<tr>
<td>February 2008</td>
<td>SCH 727965</td>
<td>CDK Inhibitor</td>
<td>Signal Transduction</td>
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<td>October 2008</td>
<td>IL-12</td>
<td>Immunomodulator</td>
<td>Immunotherapy</td>
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<tr>
<td>November 2008</td>
<td>GDC-0449</td>
<td>Hedgehog Inhibitor</td>
<td>Cancer Stem Cell</td>
</tr>
<tr>
<td>January 2009</td>
<td>RO4929097</td>
<td>Notch Inhibitor</td>
<td>Cancer Stem Cell</td>
</tr>
</tbody>
</table>
Accomplishments

- Reviewed 8 potential agents since inception
- Eight manuscripts in preparation
  - Clinical Trial Design has 4 FOCUS articles being published in CCR (March 2009, based on Phase 2 meeting) and are working on a Phase 1 meeting manuscript.
  - The Angiogenesis TF Cardiovascular Toxicities Panel subcommittee has a blood pressure manuscript completed and a second under development involving ventricular dysfunction.
  - The Biomarker TF has a Phase I and II recommendations manuscript completed.
Accomplishments

- Defined a mechanism for review of CTEP Drug Development Plans
- Defined productivity metrics
- Assisted with educational sessions at CTEP Early Drug Development (EDD) meetings
- Developed a newsletter for distribution
- IDSC’s interaction with Disease-based Steering Committees (IDSC and GUSC)
Example of SC Collaboration

- IDSC and Prostate Cancer Task Force/GU Steering Committee Members in common:
  - Wilding, Carducci, DiPaola
- Review possible new agents for CTEP portfolio
  - CYP17 inhibitors
  - Steroid sulfatase inhibitors
  - Androgen receptor antagonists
  - Cancer vaccines
- Provide input to CTEP regarding
  - Translational markers
  - Preclinical characterization
  - Combinations with other targeted agents
Challenges

- New agents in the portfolio
  - Convincing Pharma of the value-added and complementation that CTEP can bring
- Increase coordination and interaction with other Steering Committees, Cooperative Groups and SPORES
Future Directions

- Increase novel agents in CTEP portfolio
  - IGF-1R small molecule inhibitor
  - Akt inhibitor
  - Chk1 inhibitor
- Increase trials opportunities with agents already in CTEP portfolio
- Work with NCI to address biomarker development
  - CLIA related issues
  - DCTD PD Biomarker Development Program to coordinate the assay development with the CTEP portfolio
- Develop an effective communication effort in collaboration with disease steering committees to inform them of early drug development
Many Thanks

- All members of IDSC for giving of their time AND opinions
- Task force members
- IDB staff for their engagement
- CCCT
  - LeeAnn Jensen
- EMMES
  - Amy Gravell
Organizational Chart

CTAC & NCI

IDSC-CT

IDSC

Core Processes

Developmental Processes

Biological Processes

Pathways
IDSC Core Processes

COI Working Group
- WG chair: Joseph Sparano
- WG co-chair: Sherry Ansher

Gap Analysis Working Group
- WG chair: Donald Kufe
- WG co-chair: Edward Sausville
  NCI: James Zwiebel

Scientific Meeting Planning Working Group
- WG chair: John Wright
- WG co-chair: Michael Carducci

Metrics Working Group
- WG chair: Deborah Collyar
- WG co-chair: Anthony Murgo
  NCI: James Zwiebel
COI Working Group

Charge: Develop conflict of interest policy, process, and documents to identify potential significant financial conflicts of interest related to providing input to CTEP on clinical development plans

- IDSC COI policy
- IDSC COI financial disclosure questionnaire
- LOI review procedures
Metrics Working Group

A small ad hoc Working Group to develop metrics to evaluate the IDSCs activities

Goal: help the IDSC work as productively as possible

Each Taskforce was asked to set goals

“Who is responsible for what by when and how are we going to get there”
IDSC Developmental Processes

Developmental Processes

Biomarker Task Force
TF chair: Janet Dancey
TF co-chair: Walter Stadler
NCI: Kim Jessup

Clinical Trial Design Task Force
TF chair: Lesley Seymour
TF co-chair: Don Berry
NCI: Percy Ivy

Pharmacology Task Force
TF chair: Edward Newman
TF co-chair: Merrill Egorin
NCI: Jerry Collins
IDSC Biological Processes

Angiogenesis Task Force
- TF chair: George Wilding
- TF co-chair: Roy Herbst
- NCI: Helen Chen

DNA Repair and Programmed Cell Death Task Force
- TF chair: Robert DiPaola
- TF co-chair: Miguel Villalona
- NCI: Naoko Takebe

Immunotherapy Task Force
- TF chair: Mario Sznol
- TF co-chair: Tom Gajewski
- NCI: Howard Streicher
IDSC Pathways

Pathways

Cancer Stem Cell Therapeutics Task Force
- TF chair: Pat LoRusso
- TF co-chairs: Lucio Miele, Bill Matsui
- NCI: Percy Ivy

PI3k/Akt/mTOR Task Force
- TF chair: Afshin Dowlati
- TF co-chair: Lillian Siu
- NCI: Austin Doyle

Signal Transduction Task Force
- TF chair: Razelle Kurzrock
- TF co-chair: Dan Sullivan
- NCI: John Wright
Process for assessing CTEP Drug Development Plans

- CTEP identifies new agent for their portfolio
- Agent is assigned to appropriate taskforce
- A drug development team (DDT) is established
  - Includes members of clinical trial design, biomarker and pharmacology task forces
  - Provides input to CTEP Drug Development Plan
- Drug Development Plan is brought to full IDSC for final review and comment
Potential Strategies to Increase IDSC Interaction with Disease SCs

- Liaisons on each committee
- Circulating newsletter
- Disease SC members attend EDD meetings
- Notification of SC and SPORE chairs of new developments from IDSC by e-mail with posting on accessible website
- Specific workshops of U01/N01 holders with SPORE and Disease SC leaders at NCI translates meeting