
Investigational Drug Steering Committee Update

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Co-chairs

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, proteasome 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

FINAL (Version 09-15-2008)

INVESTIGATIONAL DRUG STEERING COMMITTEE STRATEGIC INITIATIVES FOR FY09

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

	Time Frame for Completion	Dr. Dan Sullivan (Co-chair)	Dr. Razelle Kurzrock (Co-chair)	Dr. John Wright (NCI Liaison)	Dr. Adam Dicker	Dr. Robert Ferry	Dr. David Gandara	Dr. Steve Grant	Dr. Mark Levis	Dr. Wells Messersmith	Dr. John Perentesis	Dr. Gary Schwartz	Dr. Said Sebti	Dr. Joe Sparano
Signal Transduction Task Force														
1. Review new IGF-1R small molecule inhibitors; discussion of OSI-906; update on IMC-A12	Q4 2008	T	T	*			T	T						T
2. Review current status of STAT3 and JAK2 inhibitors with invited experts	Q3 2008	T	T	*	T	T	T				T	T	T	
3. Review STAT/JAK Inhibitors from pharmaceutical companies and arrange an educational session on STAT/JAK inhibitors for spring IDSC meeting	Mar-09	*	T	T			T	T					T	T
4. Review Pim kinase inhibitors with invited experts	Q1 2009	T	*	T				T	*	T				
5. Review proteasome inhibitors with invited experts	Q1 2009	*	T	T			T	*	T		T		T	
6. Other														
** Designates Project Leader(s) / * Designates Team Member														

Accomplishments

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

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

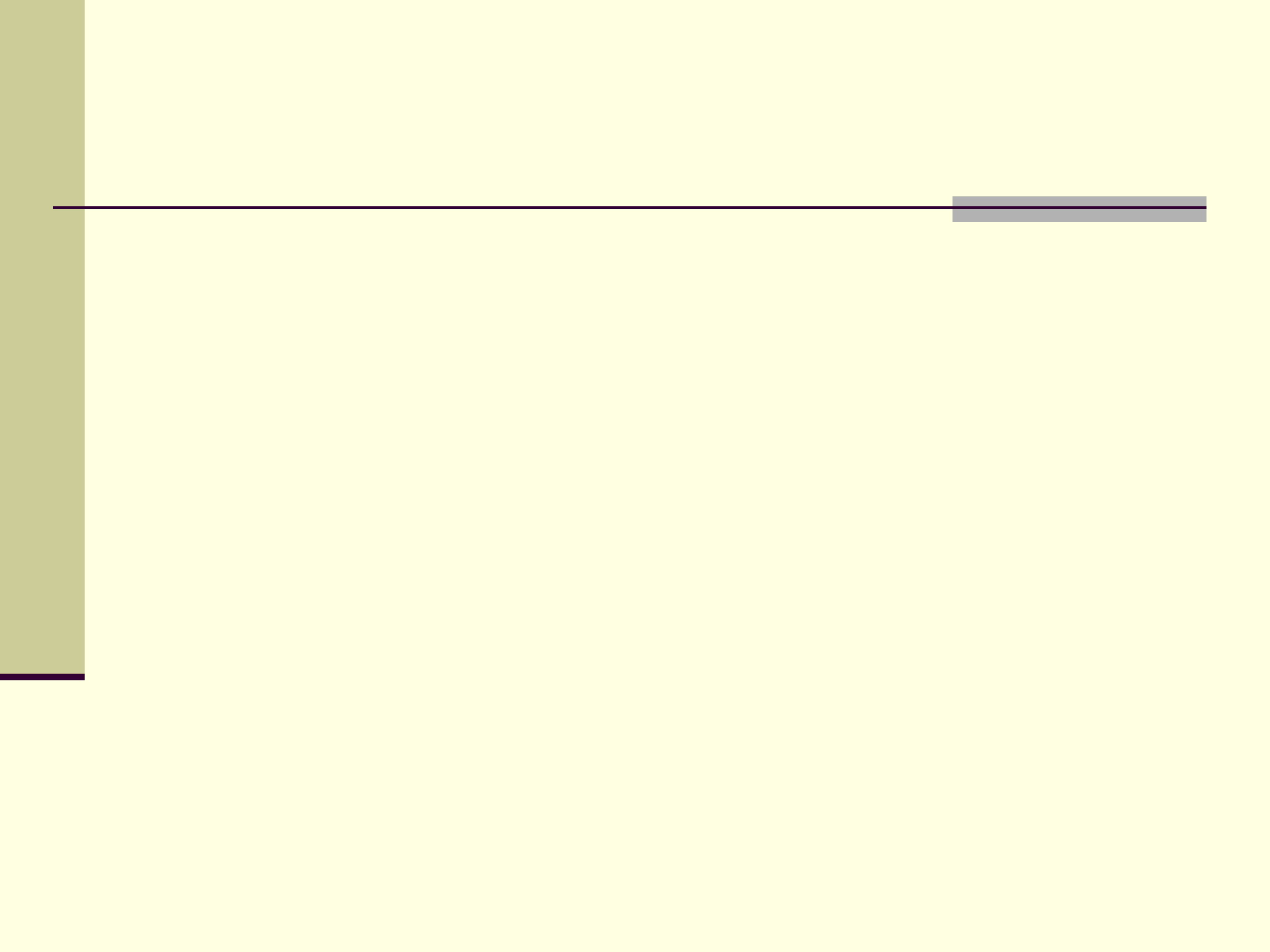
- New agents in the portfolio
 - Convincing Pharma of the value-added and complementation that CTEP can bring
- Increase coordination and interaction with other Steering Committees, Cooperative Groups and SPORES

Future Directions

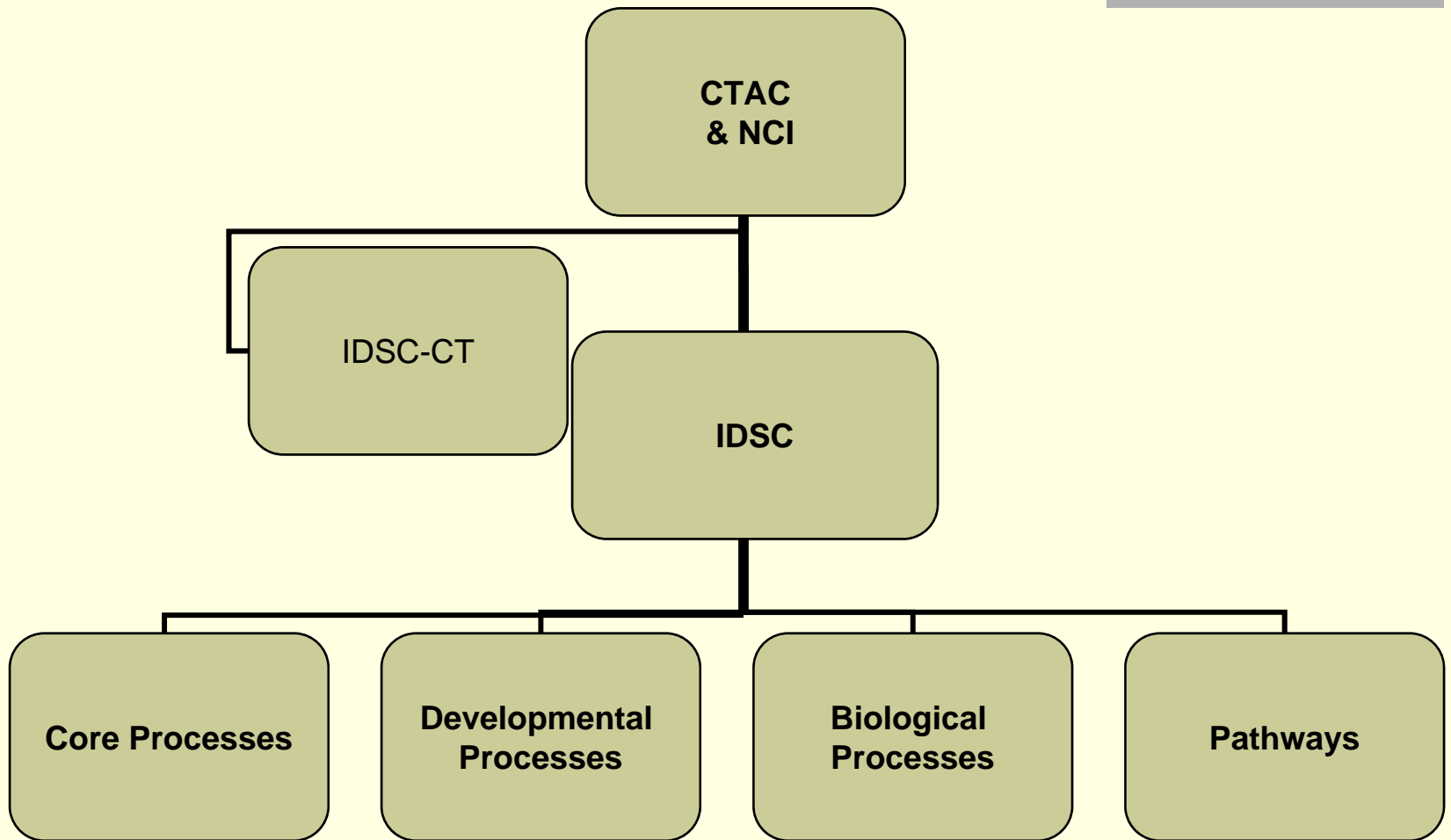
- Increase novel agents in CTEP portfolio
 - IGF-1R small molecule inhibitor
 - Akt inhibitor
 - Chk1 inhibitor
- Increase trials opportunities with agents already in CTEP portfolio
- Work with NCI to address biomarker development
 - CLIA related issues
 - DCTD PD Biomarker Development Program to coordinate 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

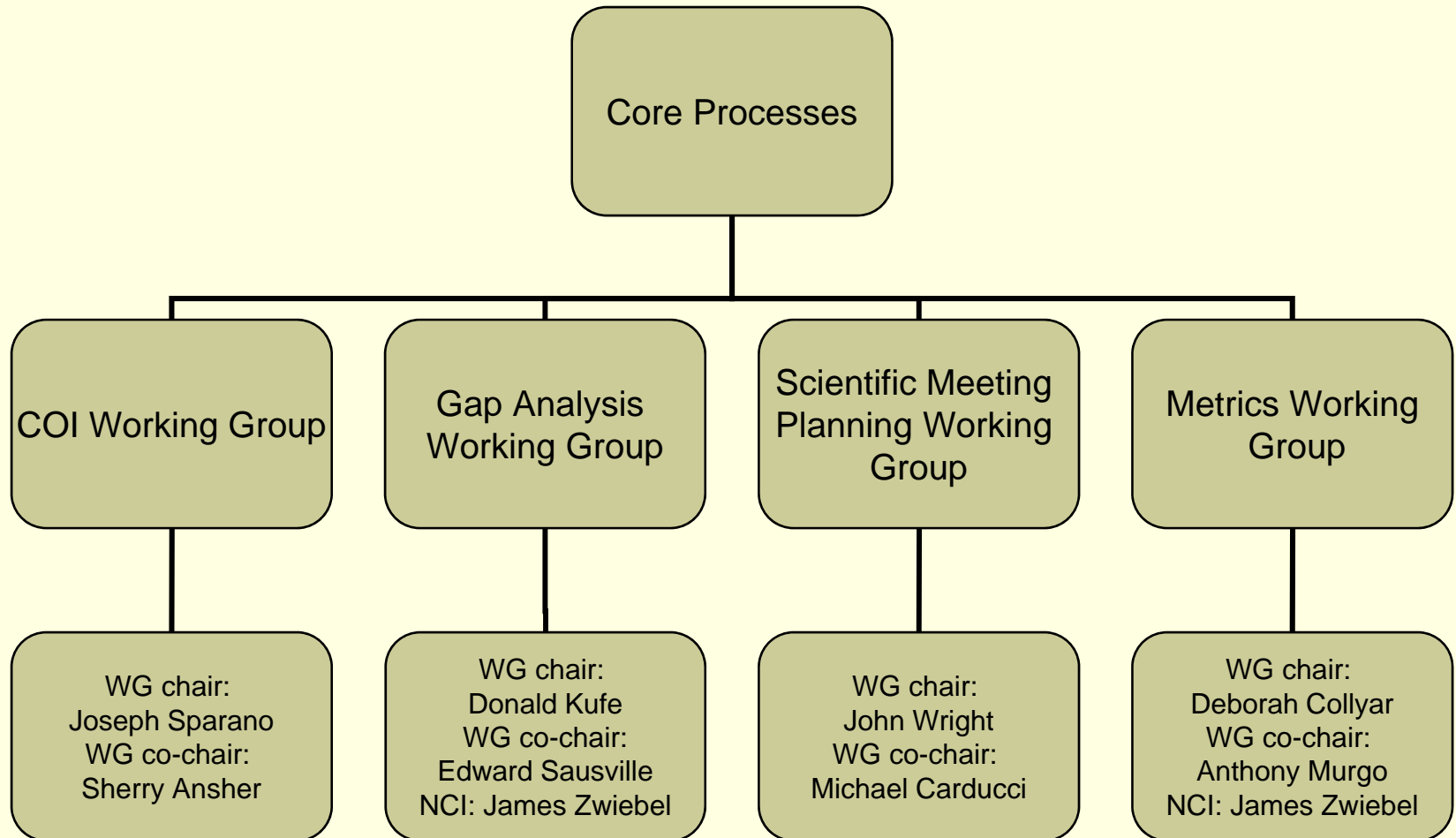
- All members of IDSC for giving of their time AND opinions
- Task force members
- IDB staff for their engagement
- CCCT
 - LeeAnn Jensen
- EMMES
 - Amy Gravell



Organizational Chart



IDSC Core Processes



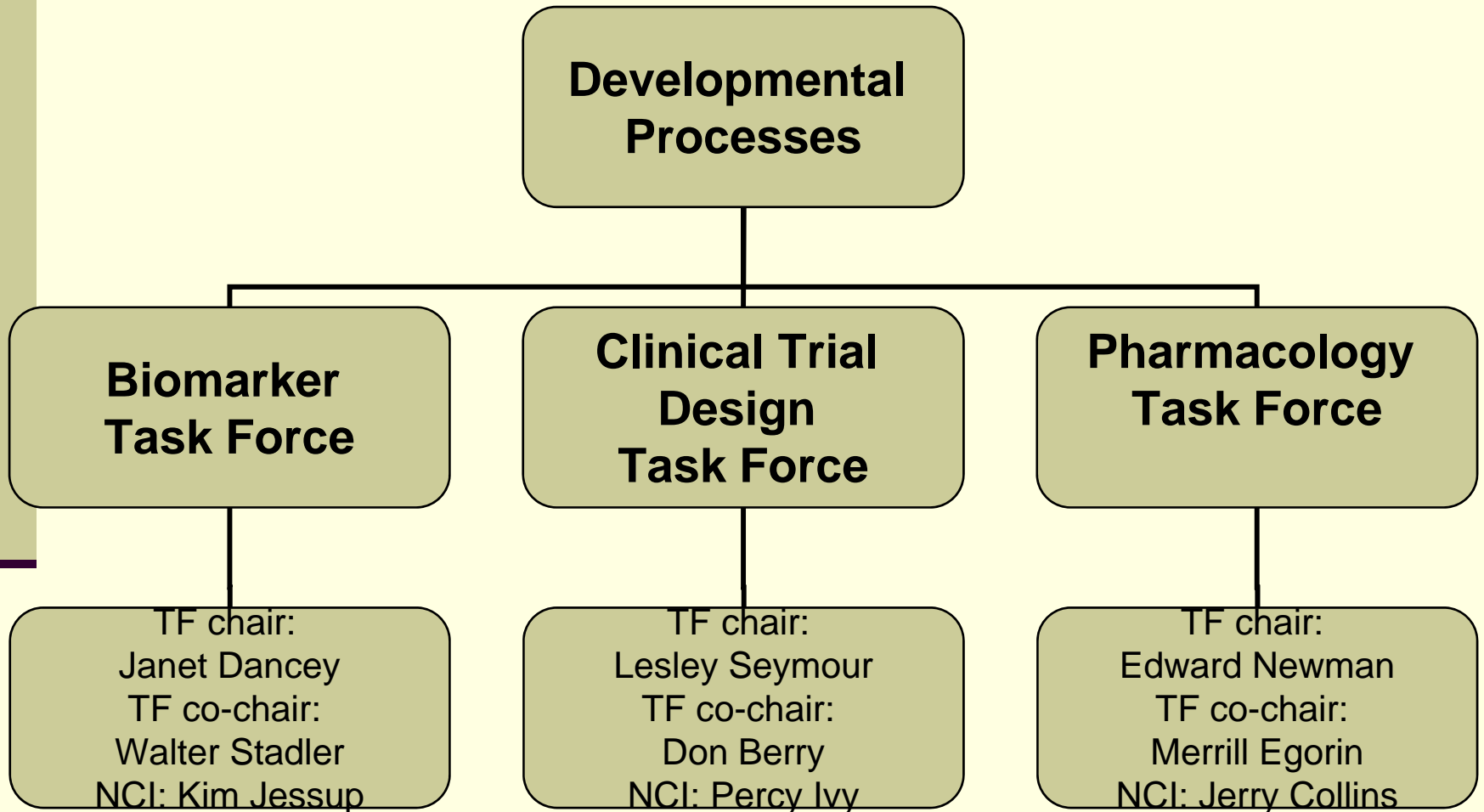
COI Working Group

- 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

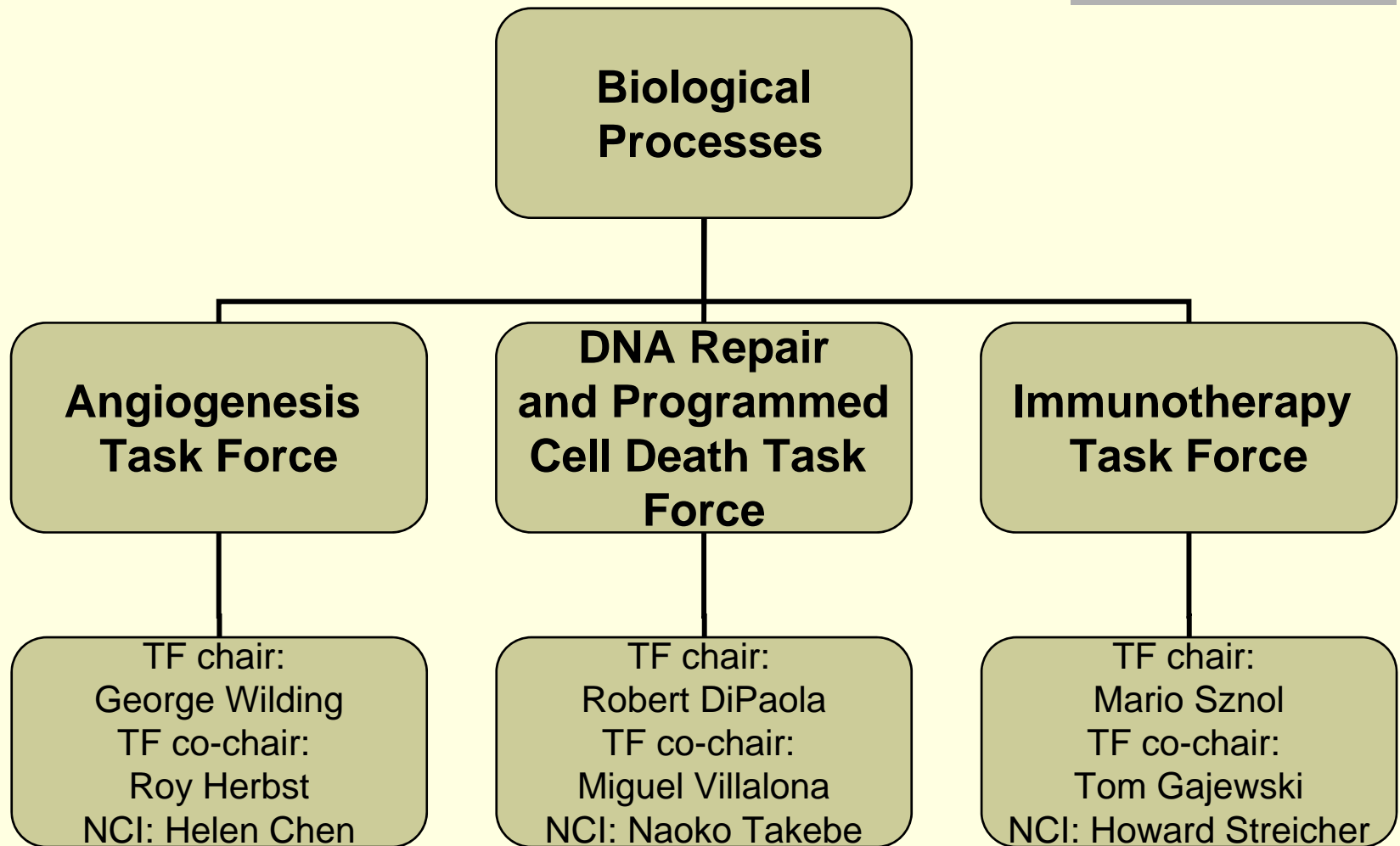
Metrics Working Group

- 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”

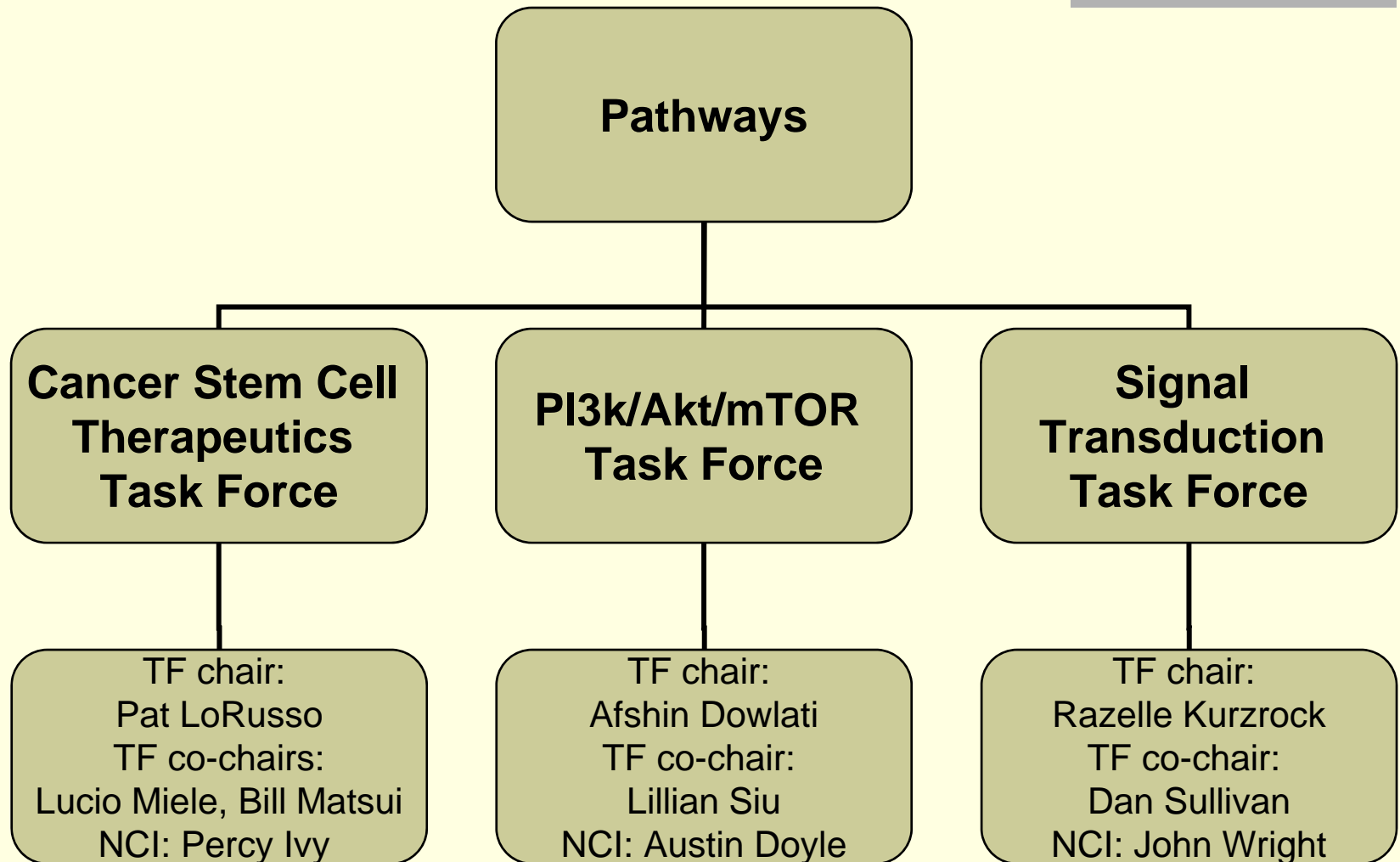
IDSC Developmental Processes



IDSC Biological Processes



IDSC Pathways



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