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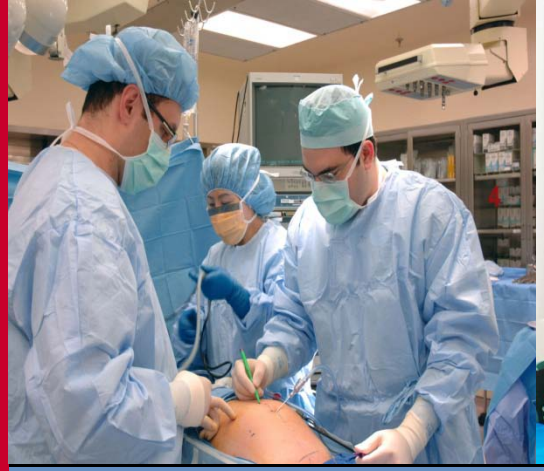
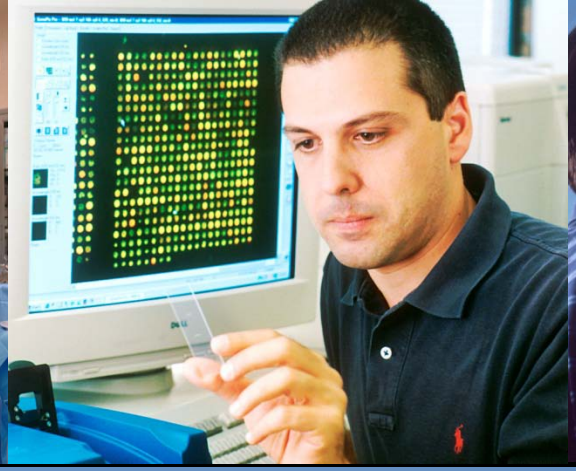


Re-inventing NCI-Supported Early Phase Clinical Trials

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Clinical Trials & Translational Research Advisory Committee

Bethesda, MD
March 7, 2012

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

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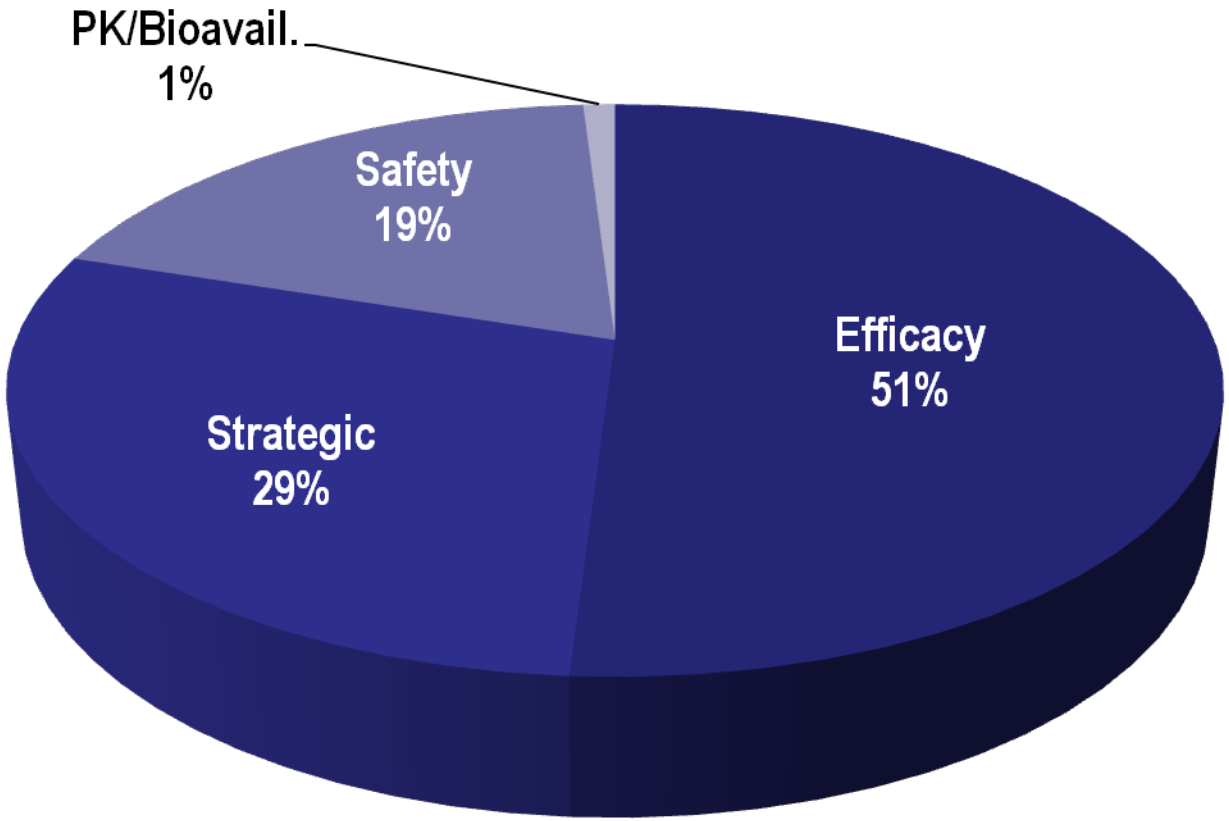
Causes of Phase II Failures: 2008-2010



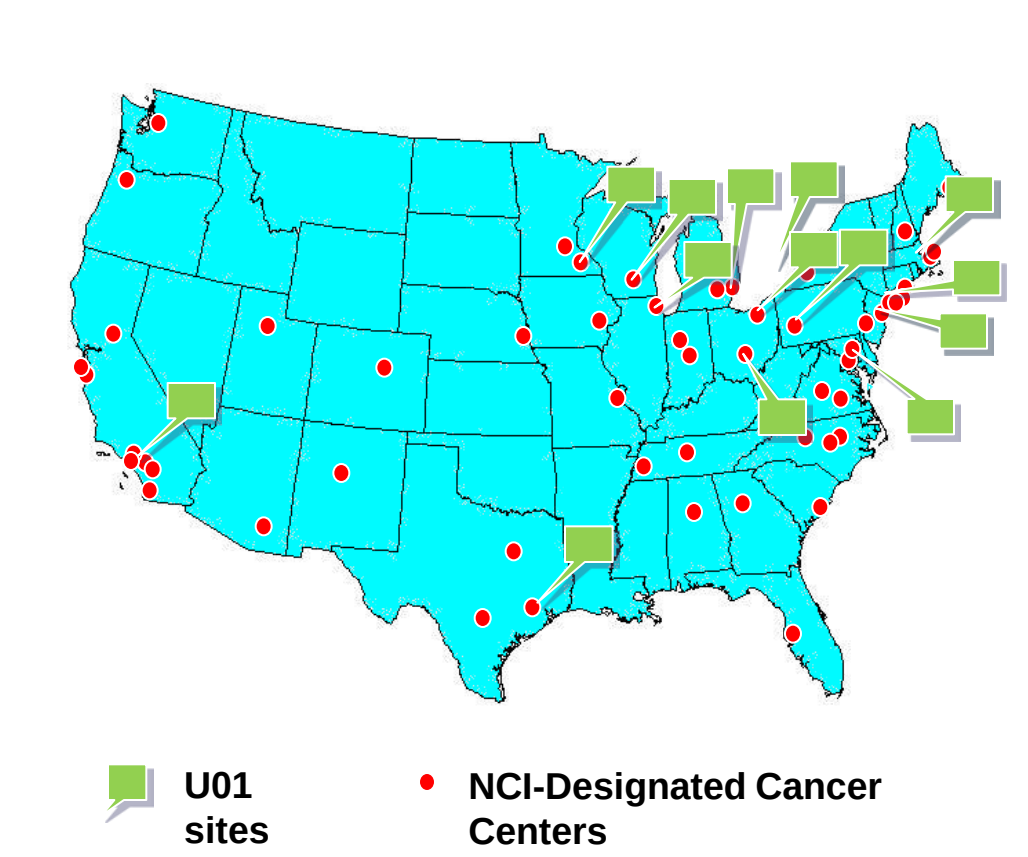
Overall Phase II Success Rate 18% (2008-2009)

Nature Rev. Drug Discov. 10: 1, 2011

NCI Experimental Therapeutics Program with Phase 1 Emphasis (U01)

Current U01 Experimental Therapeutics Program:

- Current budget: ~**$8.87 M / yr**
- Annual accrual across 14 sites: **898 – 1290 / yr**
- Average number of open trials: **120**
- Active INDs: 80
- Anticipated INDs in 2012: **15**



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Challenges for NCI-Supported Early Phase Clinical Trials

- Accrual
  - ✓ New agents may be very active in tumors with specific mutations or other defined genotypes
  - ✓ However, smaller patient populations with the specific molecular characteristics must be identified
  - ✓ Studies will require multi-site participation if biomarker-driven
  - ✓ A program of sufficient breadth and flexibility capable of rapidly adapting to variable accrual needs is required versus current focus on single site trials
  - ✓ Develop resources that can support scientific requirements and IRB review in early phase trials across sites
- Biomarkers
  - ✓ Validated assays in qualified labs; cannot continue without them
- Translation
  - ✓ Understanding MOA and mechanism of resistance in humans

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DCTD: Transitioning to the Future

- Choose agents for NCI's early trials only if time frame allows for the development of an appropriately qualified molecular marker
- Develop agents that can be brought to the clinic under conditions that could demonstrate POM in Phase 0/1 or POC in Phase II/III

  [No tissue, No marker, No study]
- Facilitate the transfer of the full range of tumor biology expertise that exists uniquely in NCI's major translational programs into the NExT pipeline through the development of a new Early Phase Network
- Provide the essential core laboratory resources to ensure that for every clinical trial supported by DCTD we will understand at its conclusion why it succeeded or why it did not

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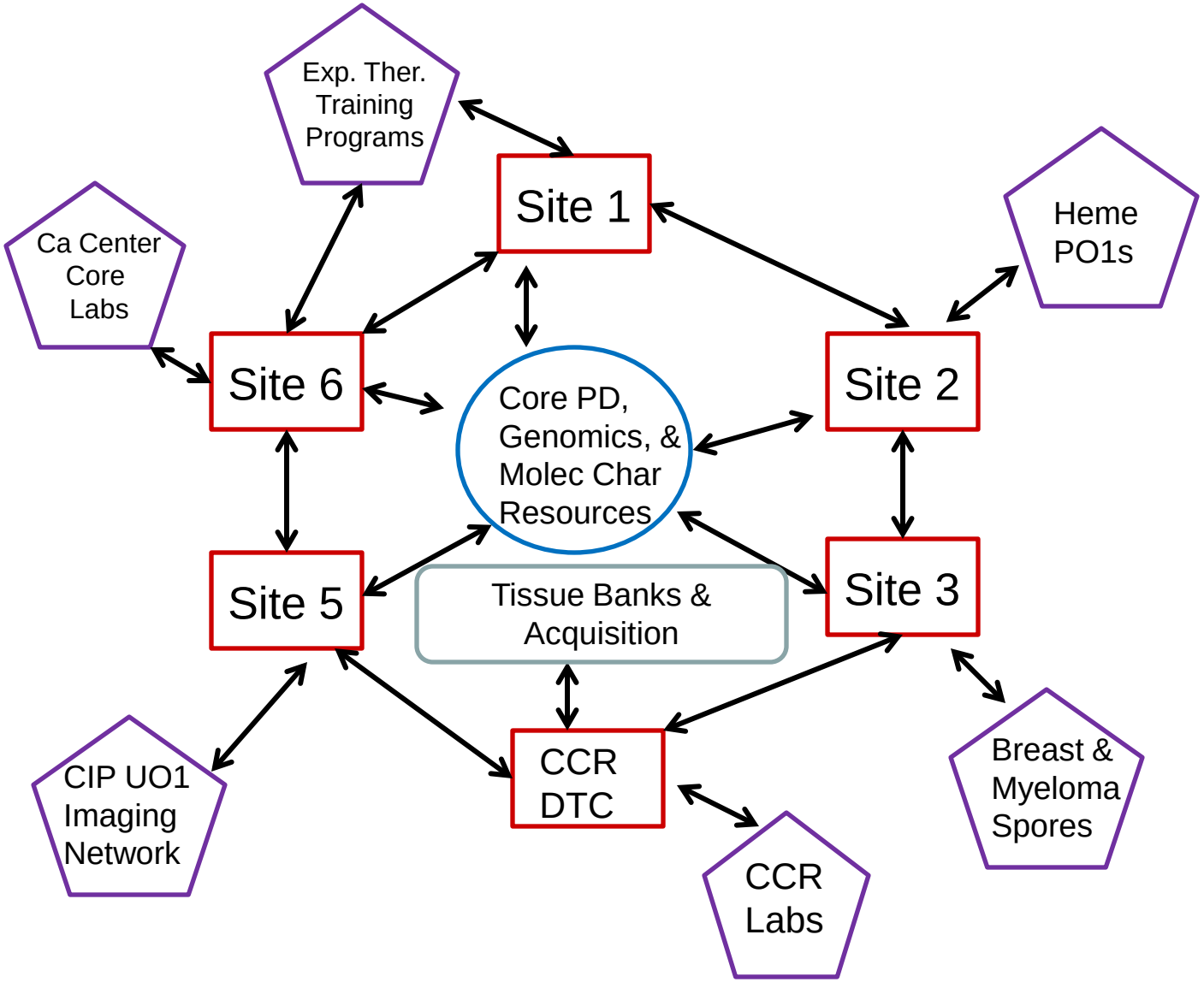
Possible NCI Early Phase Therapeutics Network



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How Should the NCI's Early Phase Network Change?

- Serve as nexus for enhanced collaboration across NCI-sponsored programs: Centers, SPORES, PO1s, Mouse Models
  - ✓ Provide broader access to critical pharmacodynamic and clinical genomic core resources for early phase clinical trials utilizing facilities in Frederick and/or extramural core laboratories
  - ✓ Ensure standardization of clinical genomic and molecular marker testing, as well as data handling, storage, and analysis in concert with the NCI's overall clinical genomics program

- Reprogramming of current resources to a smaller number of early phase clinical sites performing fewer trials should support:
  - ✓ Critical imaging studies
  - ✓ Repetitive biopsies for molecular characterization
  - ✓ Core tissue handling and storage resources specifically for early phase trials (not currently available)
  - ✓ Utilization of translational cores now funded by NCI Center, PO1, and SPORE grants by early phase trialists

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What Do We Need To Do?

- Develop a national consensus around a re-defined early phase clinical trials model
- Enhance the capacity of the new NCI-Frederick-based molecular characterization laboratory and/or the clinical assay development network initiated with ARRA funds (a collaboration comprised of both academic and molecular diagnostics concerns) in the area of specific multi-analyte assays (i.e. next generation sequencing panels of targeted mutations or exome-capture sequencing)
- Develop the additional data acquisition, storage, and analysis capabilities in concert with the extramural community to support a modern early phase network that will conduct trials at multiple sites based on the availability of an expanding range of molecular information (that must ultimately be placed in a confidential, but widely accessible database)
- Work with Industry partners to establish how molecular characterization data will be developed, utilized, and shared over multiple, sequential clinical trials involving a variety of agents (from different companies) that a single patient may enter

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Concerns

- Fewer, but better resourced, sites will be required to perform substantially more sophisticated clinical investigations; however, the network sites will all have to interact with a much larger group of academic/industry collaborators than currently
- Many more, and more complicated, components to the new network
- A database sufficient to hold new clinical genomic information will need to be established; quantitatively and qualitatively different than current capabilities
- A molecular analysis and reporting pipeline will need to be developed and validated
- New core of (probably extramural) bio-informaticians will need to be recruited to participate in this effort
- Pharma collaborators will have to agree to sharing patient response data and permitting NCI and affiliates to use this for future research (clinical) studies

Initiating a pilot program at the Clinical Center to test new approaches to many of these concerns