

# Phase 0 Trials

Breakout Discussion

October 4, 2007

# Cancer Drug Discovery and Development

*Current*

Cancer Categories defined by tissue types, lines of indications and occasional markers

Target selection driven by association of specific target alterations with known pathways

Targeted therapies are largely focused on protein kinase inhibitors and MAb's

Preclinical validation limited to assessing anti-proliferative effects in xenografts and scans for off-target-tox at MTD

Trials primarily driven by signals in phase I mono-therapy trials in advanced stage patients using RECIST criteria

*Future*

Cancer categories capable of driving Rx choices

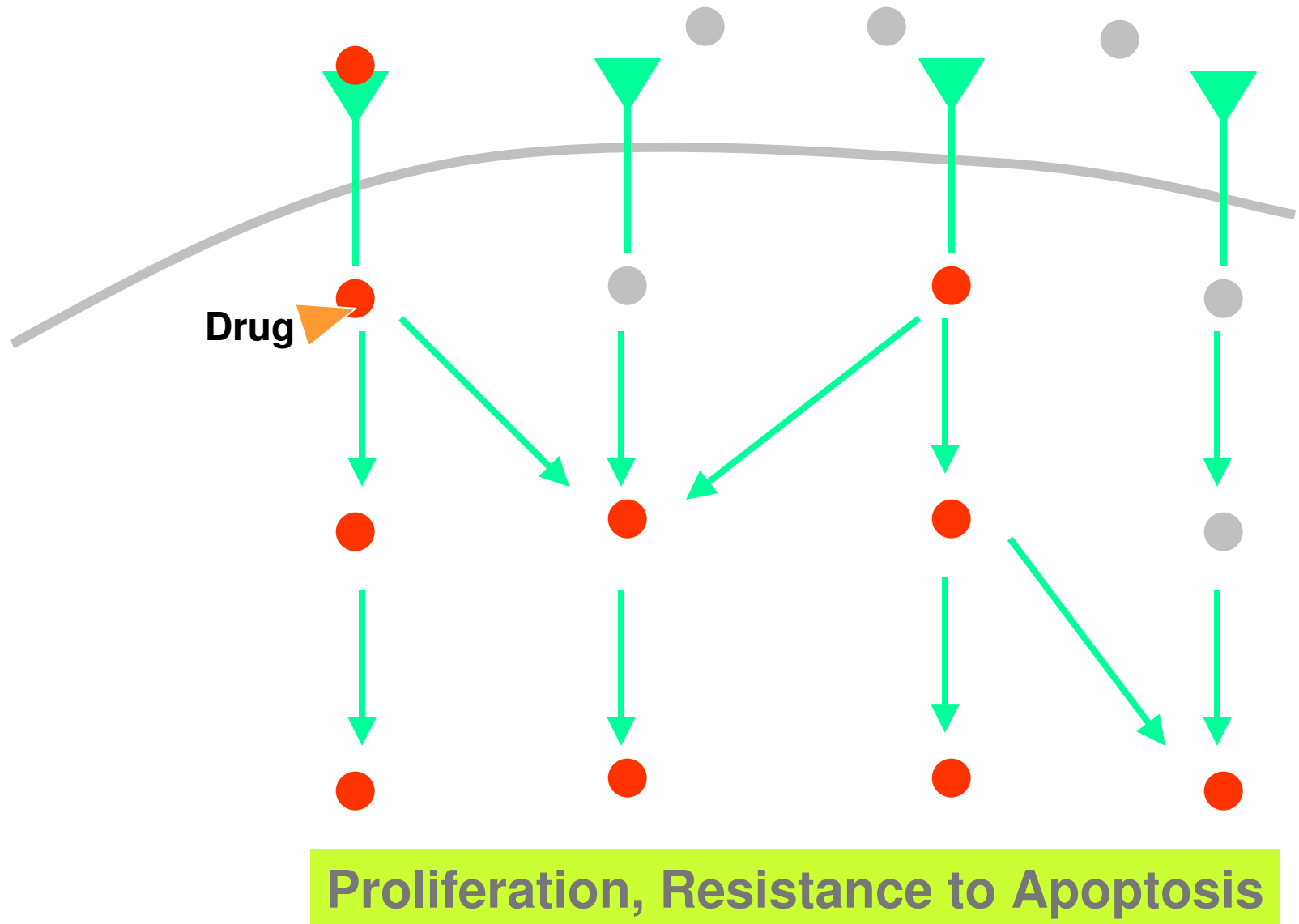
Pathway Mapping that defines modules driving treatment opportunities and target ID

Full complement of Rx modalities  
  
(RNAi Nanoparticles)

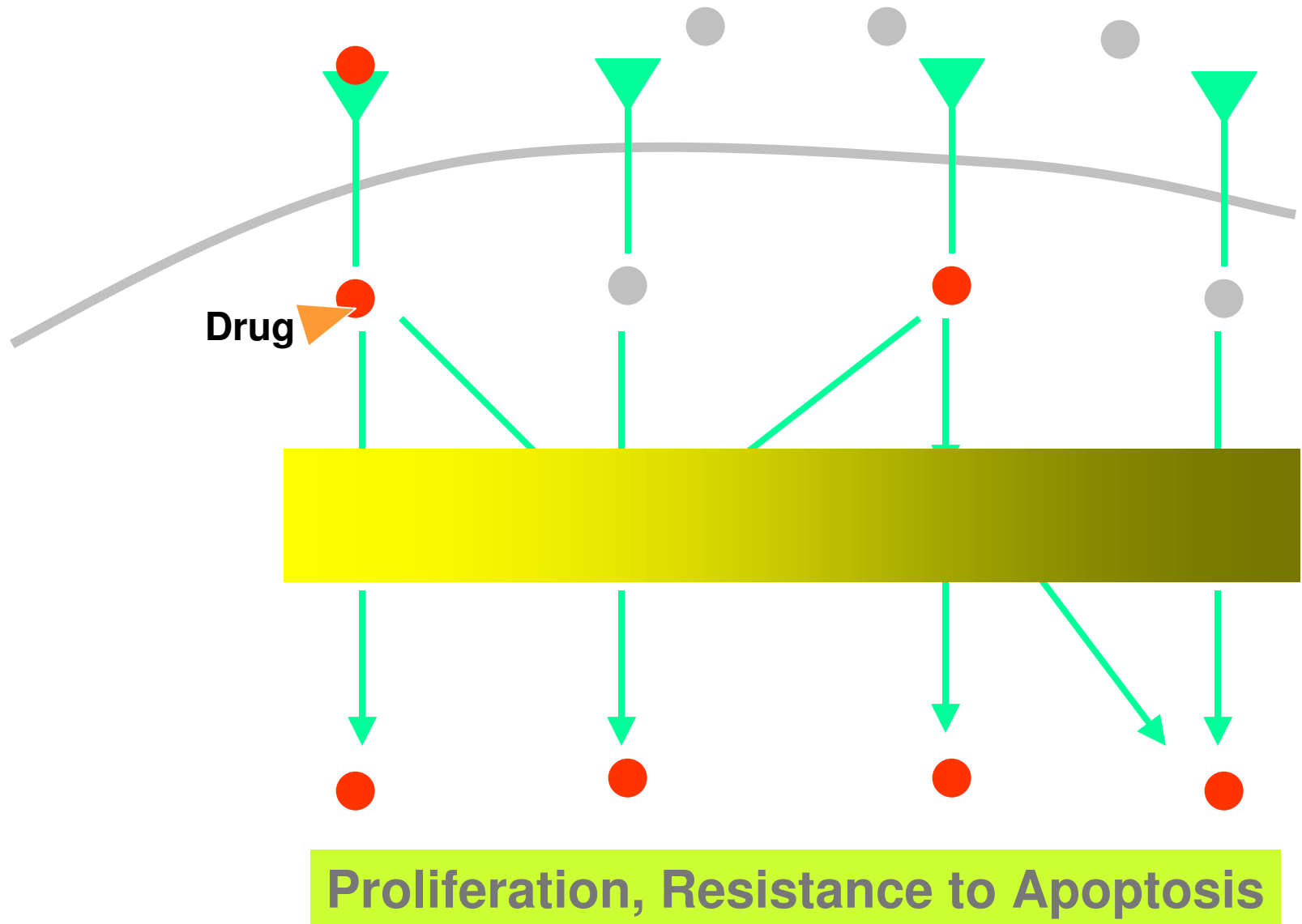
Preclinical Animal Models that recapitulate biology of tumors accurately to weed out false positives

Trials Accompanied by enabling biomarkers for Segmentation Prediction Response

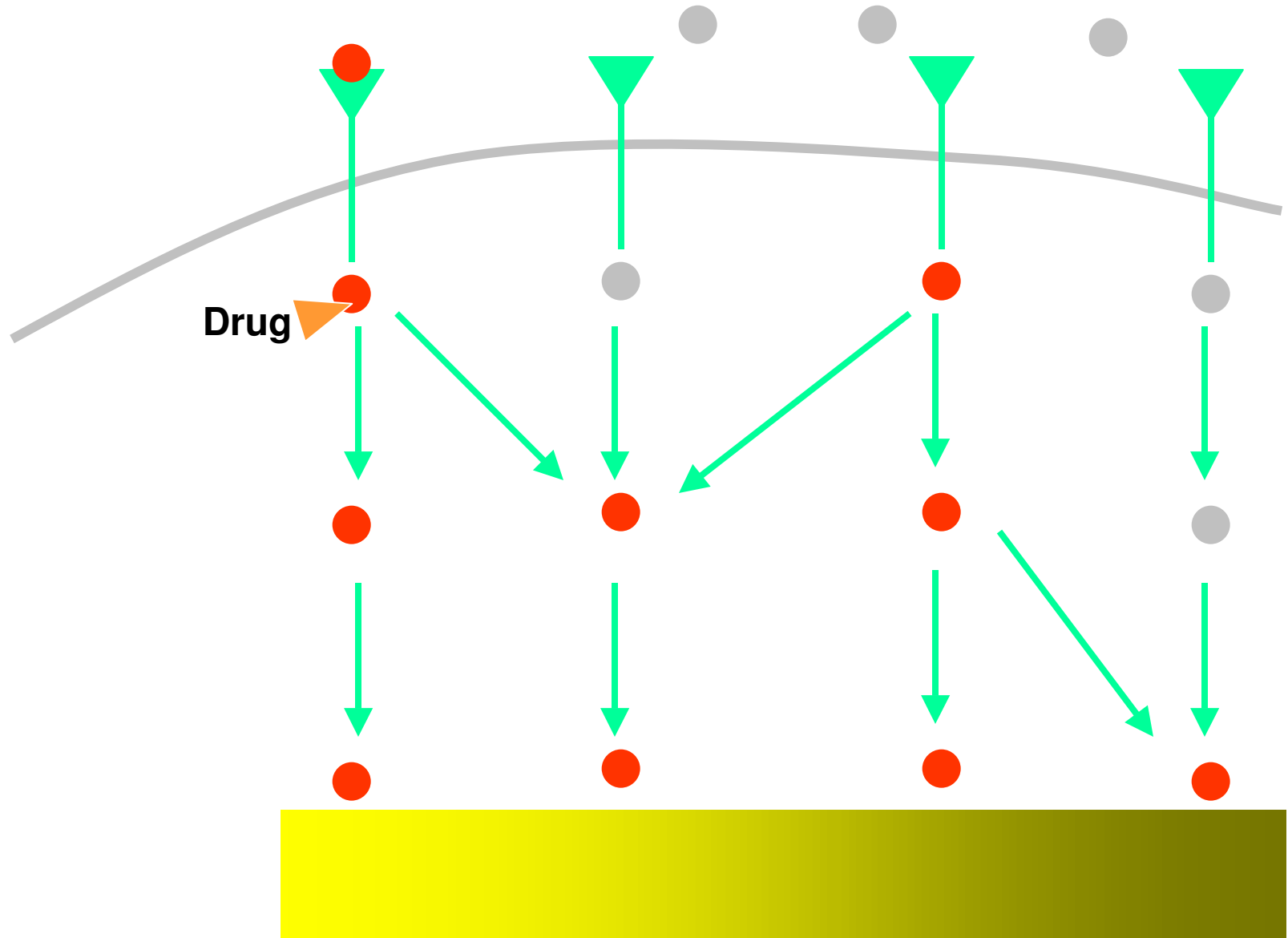
# Parallel Pathway Alterations - *and Newly Created Genetic Interactions* - can Affect Response to Inhibitors



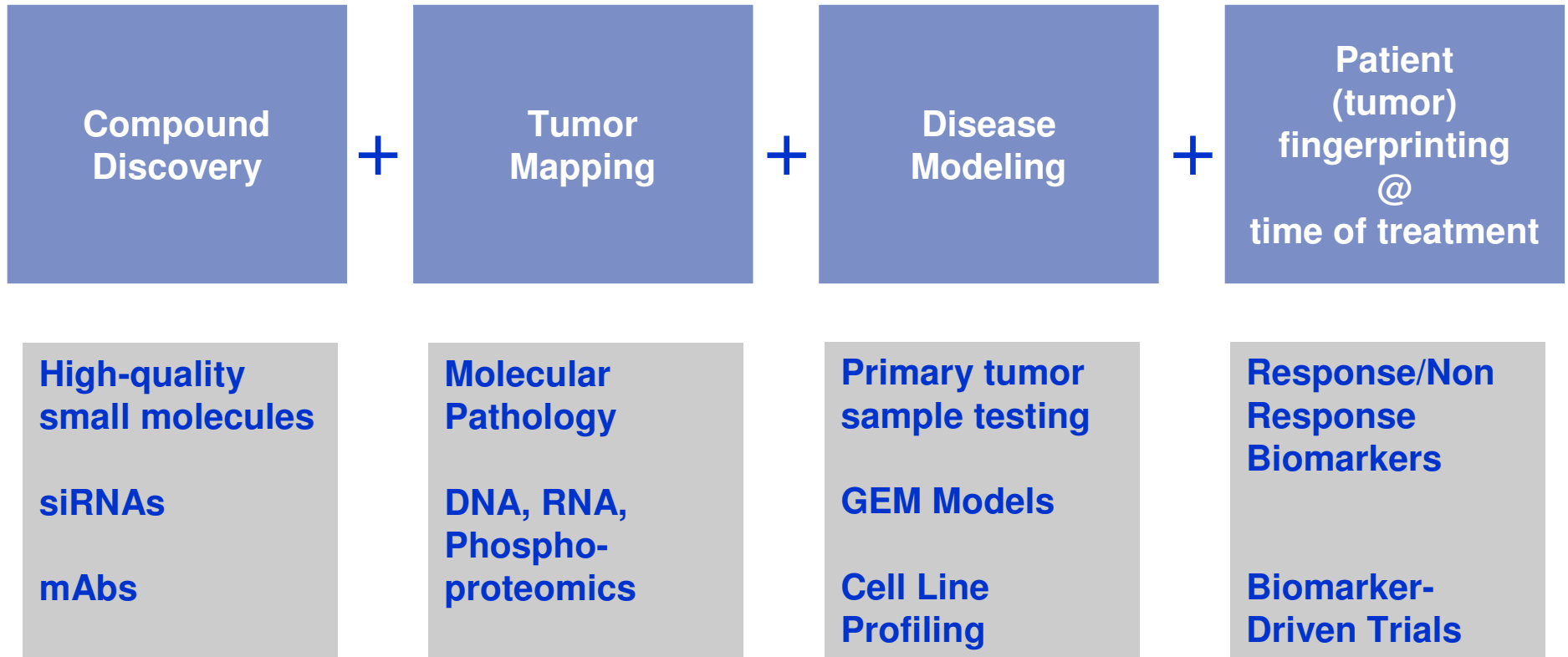
# What are the biological consequences of blocking certain pathways?



# How to best identify patient subpopulations that might benefit from a given treatment?

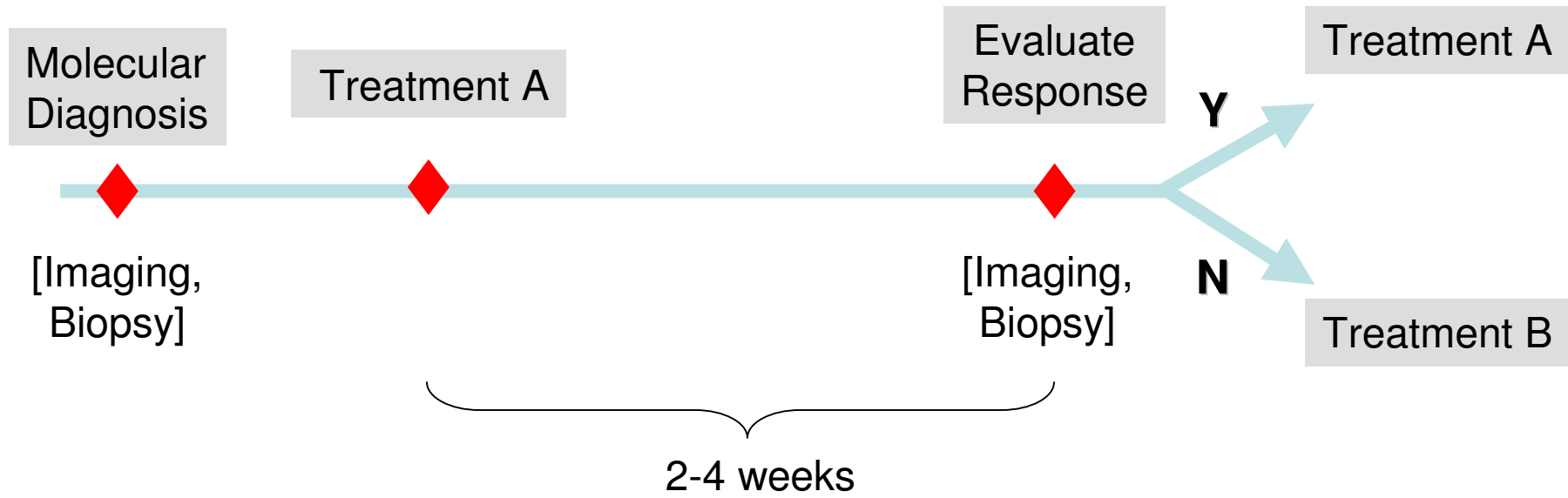


# Changing the Approach



***These elements are all ESSENTIAL!***

# The ideal state...



# Exploratory INDs – Phase 0 Trails

## *Mechanisms available for investigators to use now!*

- § Limited prework, limited resources, potential big advantage
- § Only useful to small segments for limited # of agents and studies ?

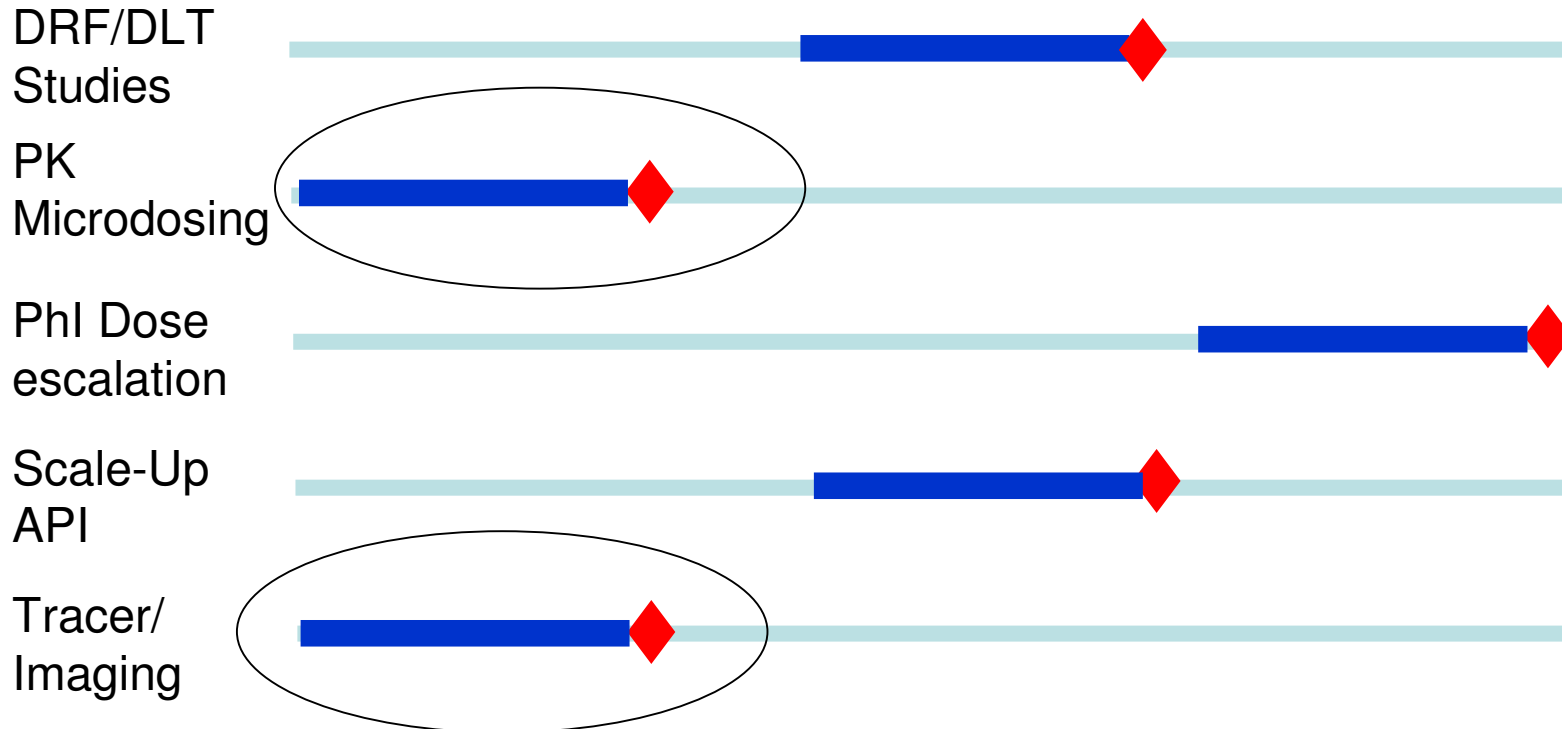
## *Tracer/microdosing/biodistribution/lead candidate selection*

- § Agreement on ease to use
- § Valuable information for compound triage

## *Pharmacological endpoints*

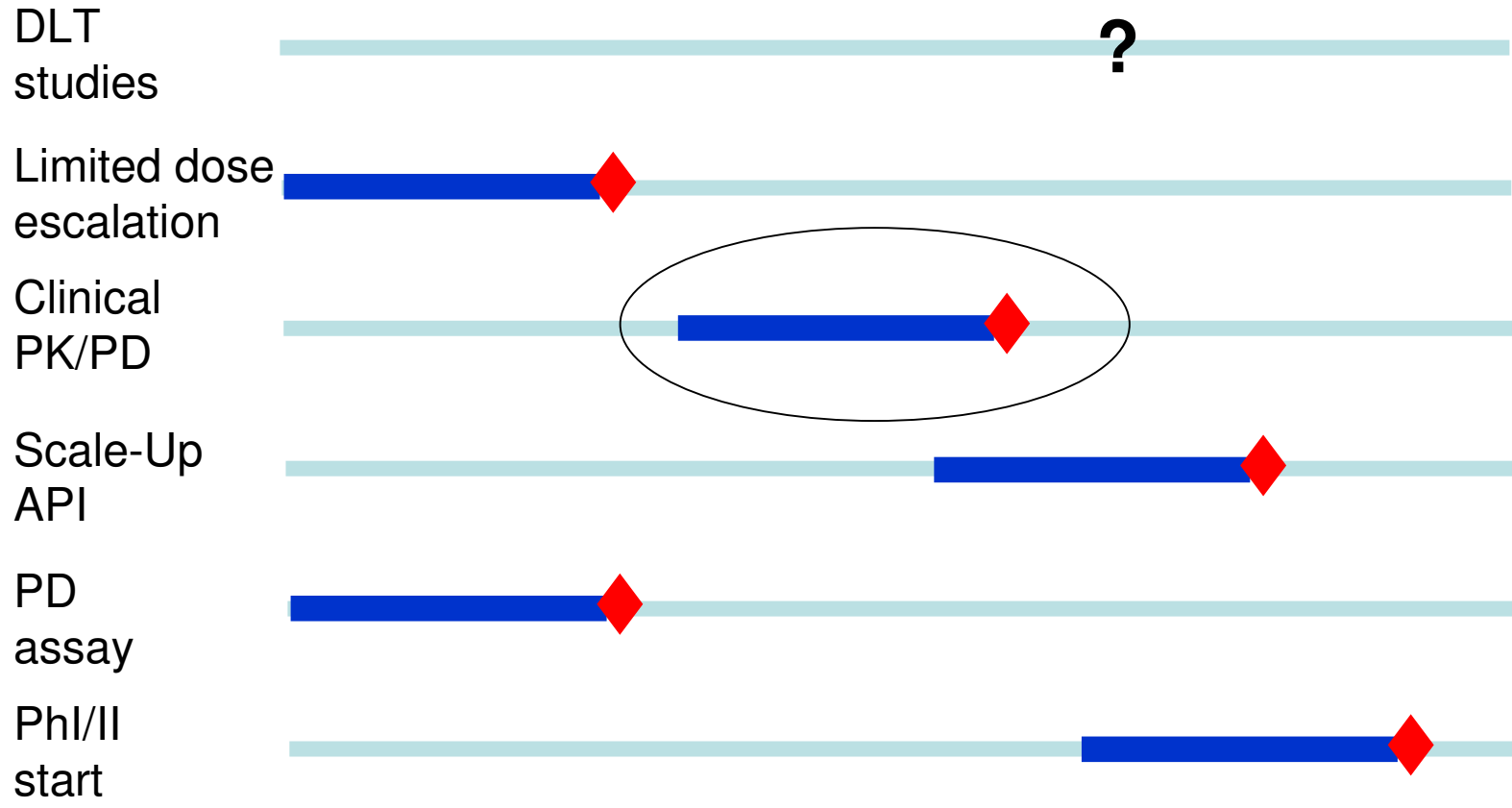
- § Unquestioned benefits of addressing early biological endpoints in patients: impact on target and potentially down-stream biology
- § Requires heavy prework: PD assay development in animal and then human tissues
- § How broadly applicable?

# Exploratory IND : Biodistribution - Microdosing - Tracers – Biologics – Lead Candidate Selection



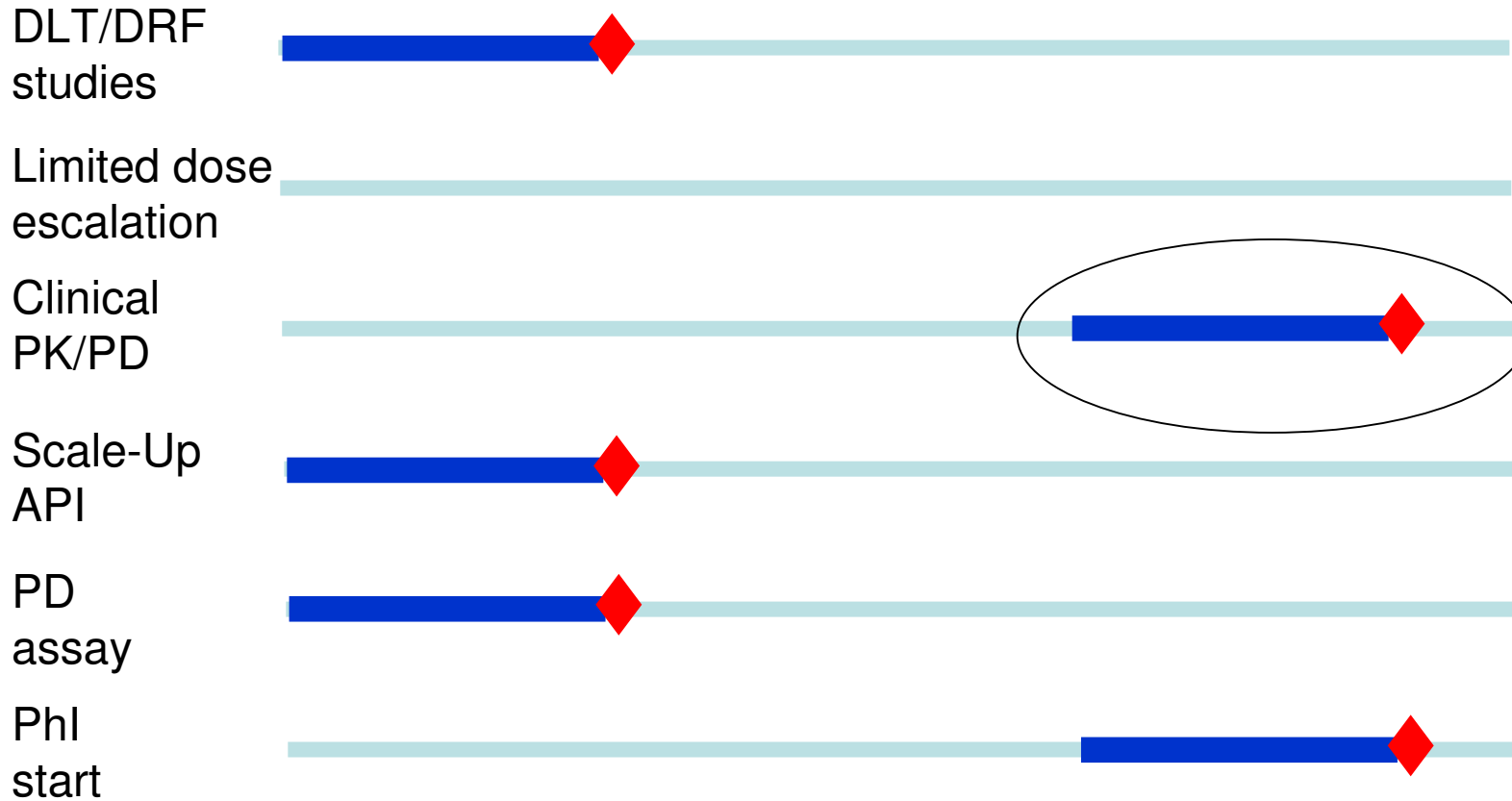
**Unquestioned Advantage in Aiding Lead Candidate Selection**

# Exploratory IND: Pharmacological Endpoint (PD)



**Spend the time to know what you are doing: for molecular targeted therapies, cannot wait until Phase II to know whether you are hitting the tumor target**

# Conventional IND: Dose Escalation to MTD or Biologically Active Dose



**Unquestioned Value of Providing PD assay at PhI Start**

# Ethical Issues and Potential Mitigation

*No curative intent*

*What's in it for the patient?*

*Incentives?*

*IRB/Ethics Committees provide appropriate guidance*

*Patients choice highlighted*

*Equivalent to normal volunteer study*

*Longtime experience in imaging studies in patients indicates broad acceptance of concept*

§ Develop imaging techniques that might be useful for the community at large not the patient being treated

*Involve patient advocates early in the process to gain feedback on benefits and communication*

# Technical/Scientific Issues and Potential Mitigation

## ***Pharmacological EP studies***

- § Potentially advantageous for academic investigators to pursue limited studies with the eIND mechanism
- § Example presented difficult to apply outside of optimal setting – hard to transfer to an academic clinical center
- § Validating assays in surrogate tissues vs. tumor themselves
- § Interspecies difference; translation of PK.PD relationships from animal to human
- § Do not always know the target of the drug!

*Could NIH Clinical Center provide assays development and transfer to interested parties?*

# Costs and Potential Mitigation

## *How to cover costs*

- § biomarker development
- § tissue handling

## *Phase 0 Trails outside of normal health care system*

- § Unclear who would pay for them

*Could NIH Clinical Center provide assays development and transfer to interested parties?*

*Should clinically validated PD markers become a requirement for initiation of clinical trials sponsored by pharmaceutical companies?*