ENGELBERG CENTER for Health Care Reform at BROOKINGS

FRIENDS of CANCER RESEARCH

Conference on Clinical Cancer Research

Panel One:

Alternative Trial Designs Based on Tumor Genetics/Pathway Characteristics

November 10, 2011 • Washington, DC

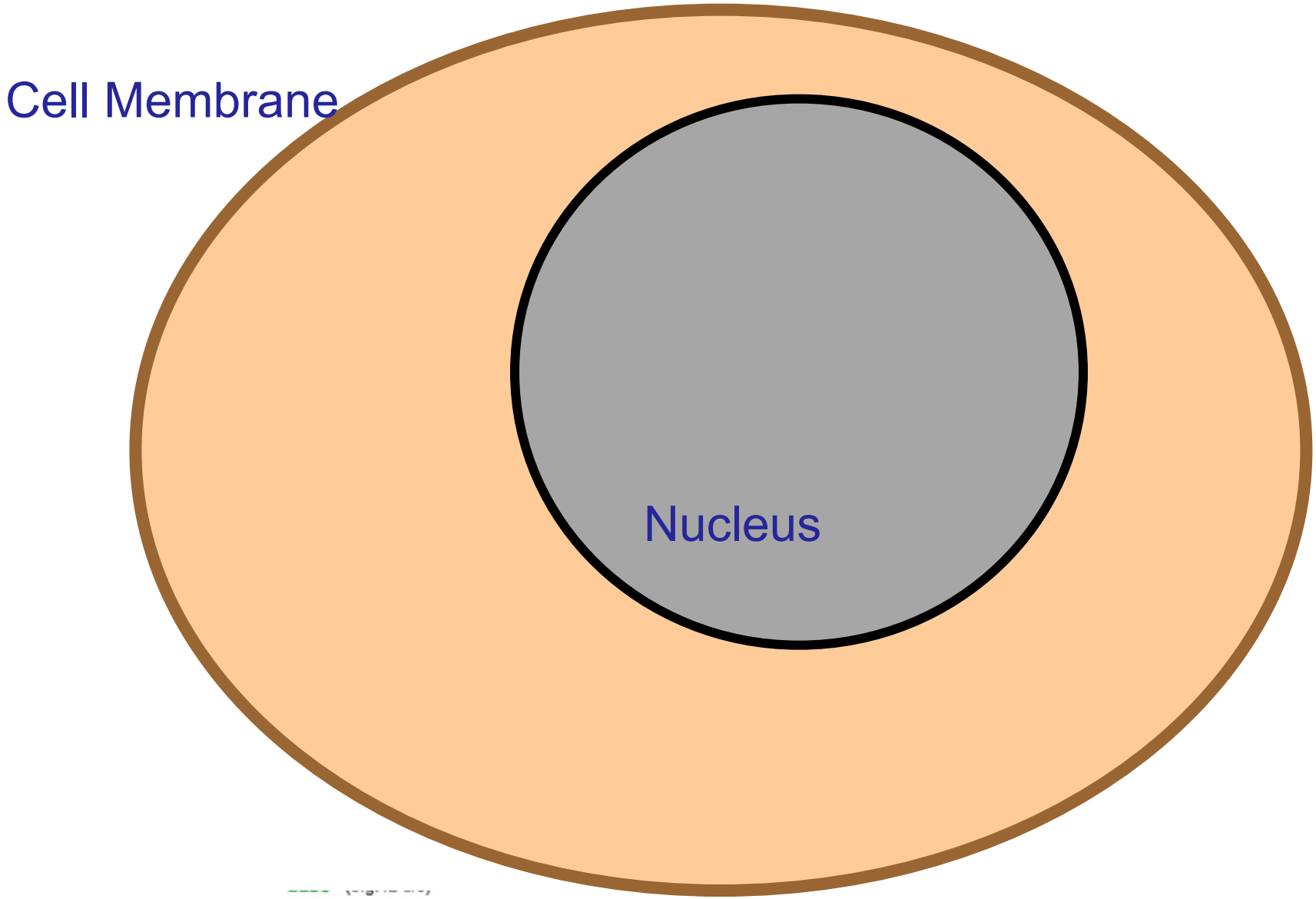
Alternative Trial Designs Based on Tumor Genetics and/or Pathway Characteristics Instead of Histology

George D. Demetri, MD

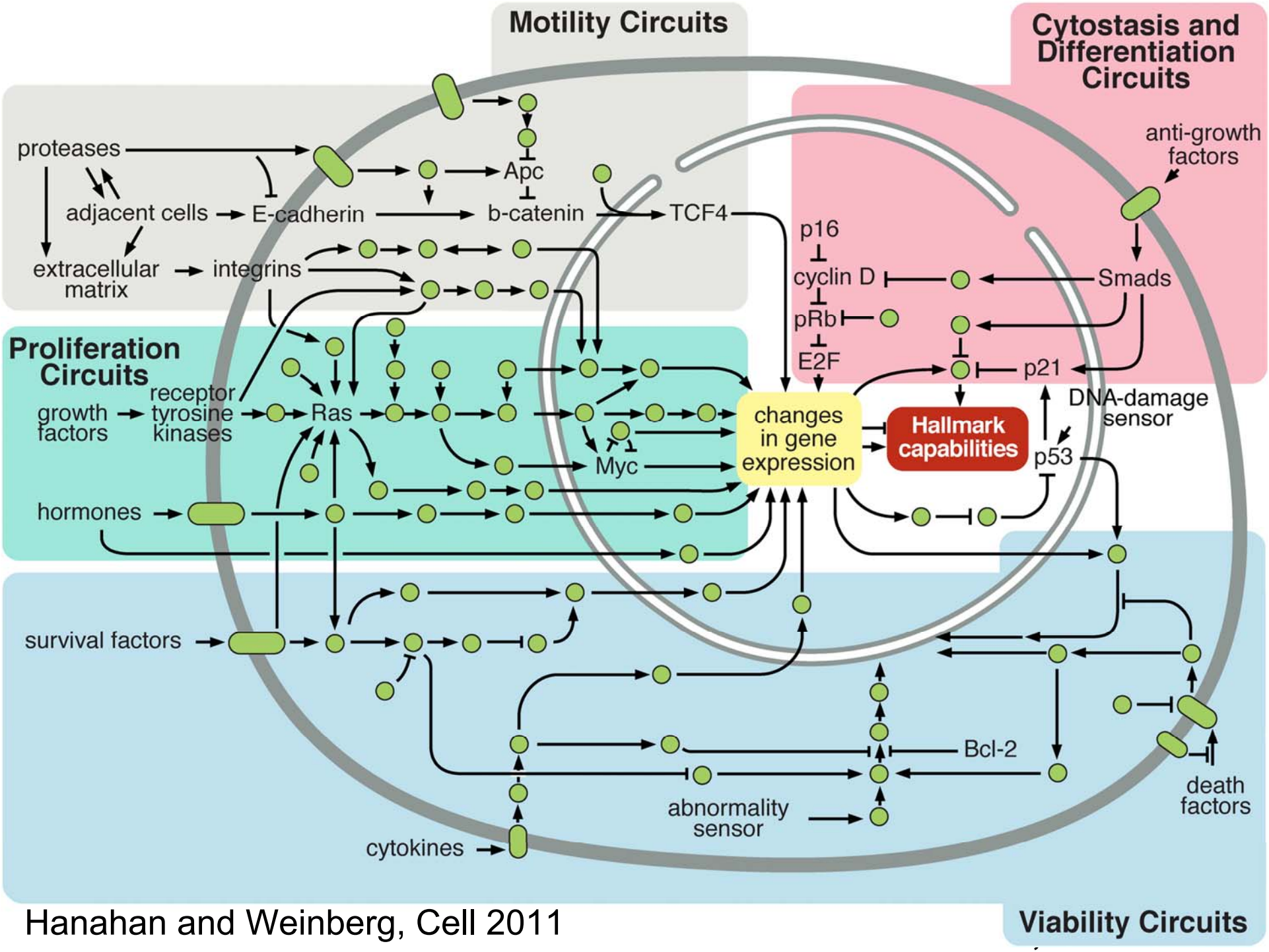
Senior Vice President for Experimental Therapeutics
Dana-Farber Cancer Institute

Ludwig Center at Dana-Farber/Harvard Cancer Center
Harvard Medical School
Boston, Massachusetts
gdemetri@partners.org

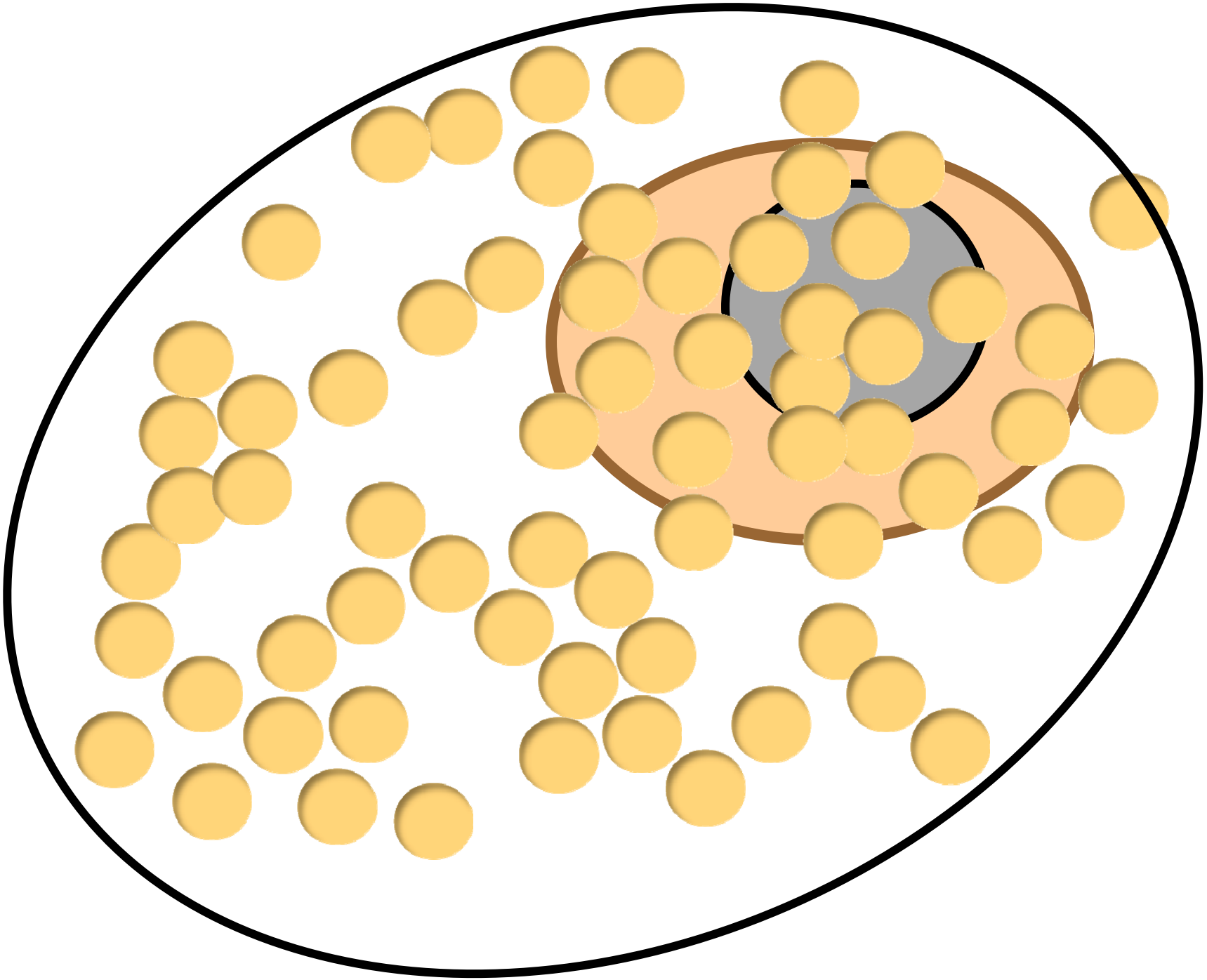
We now have better understanding of pathways in cancer



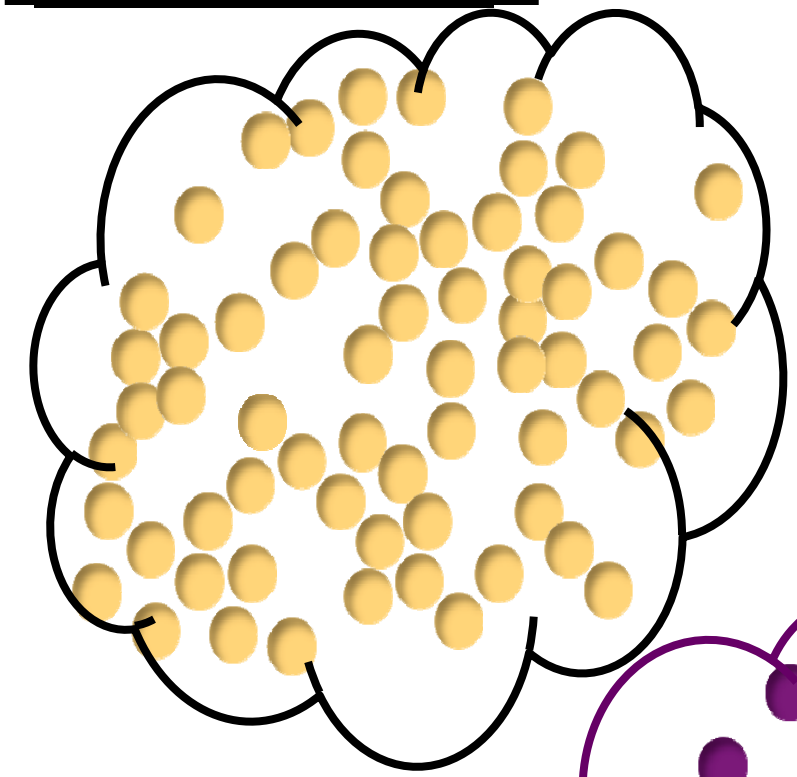
Adapted from **Dawelbait G et al. Bioinformatics 2007;23:i115-i124**

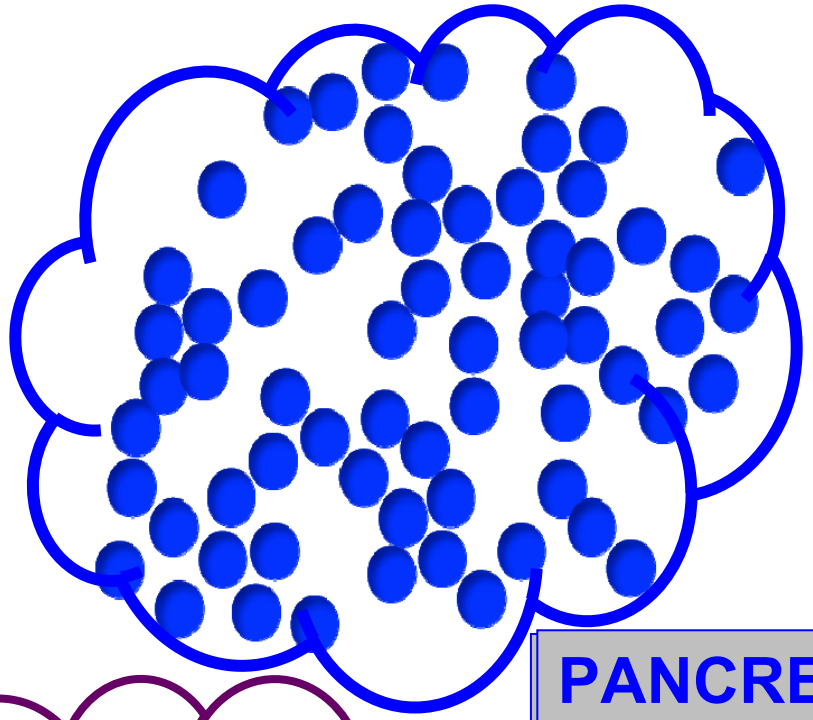


Hanahan and Weinberg, Cell 2011

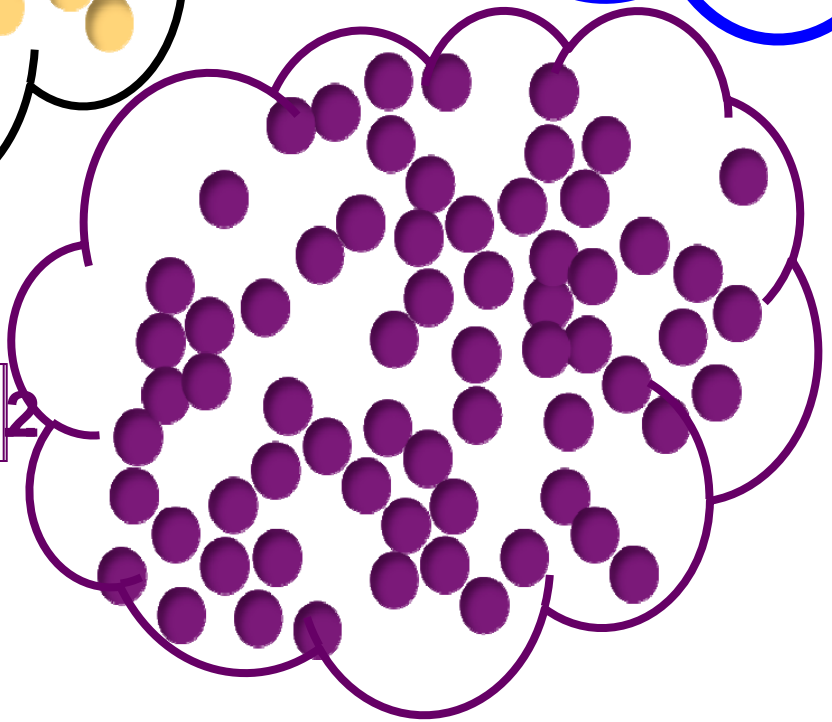


BREAST CANCER



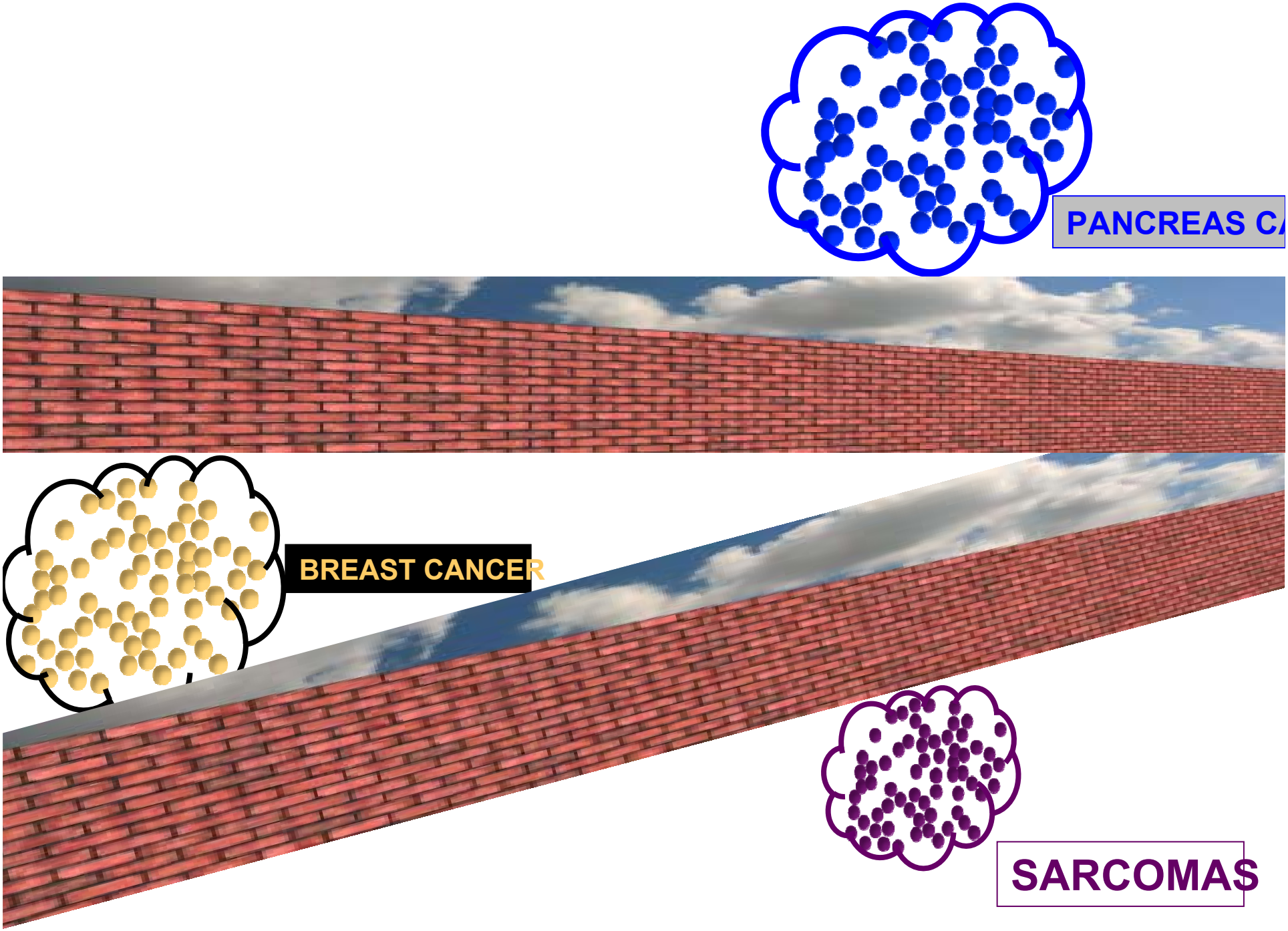


PANCREAS CA

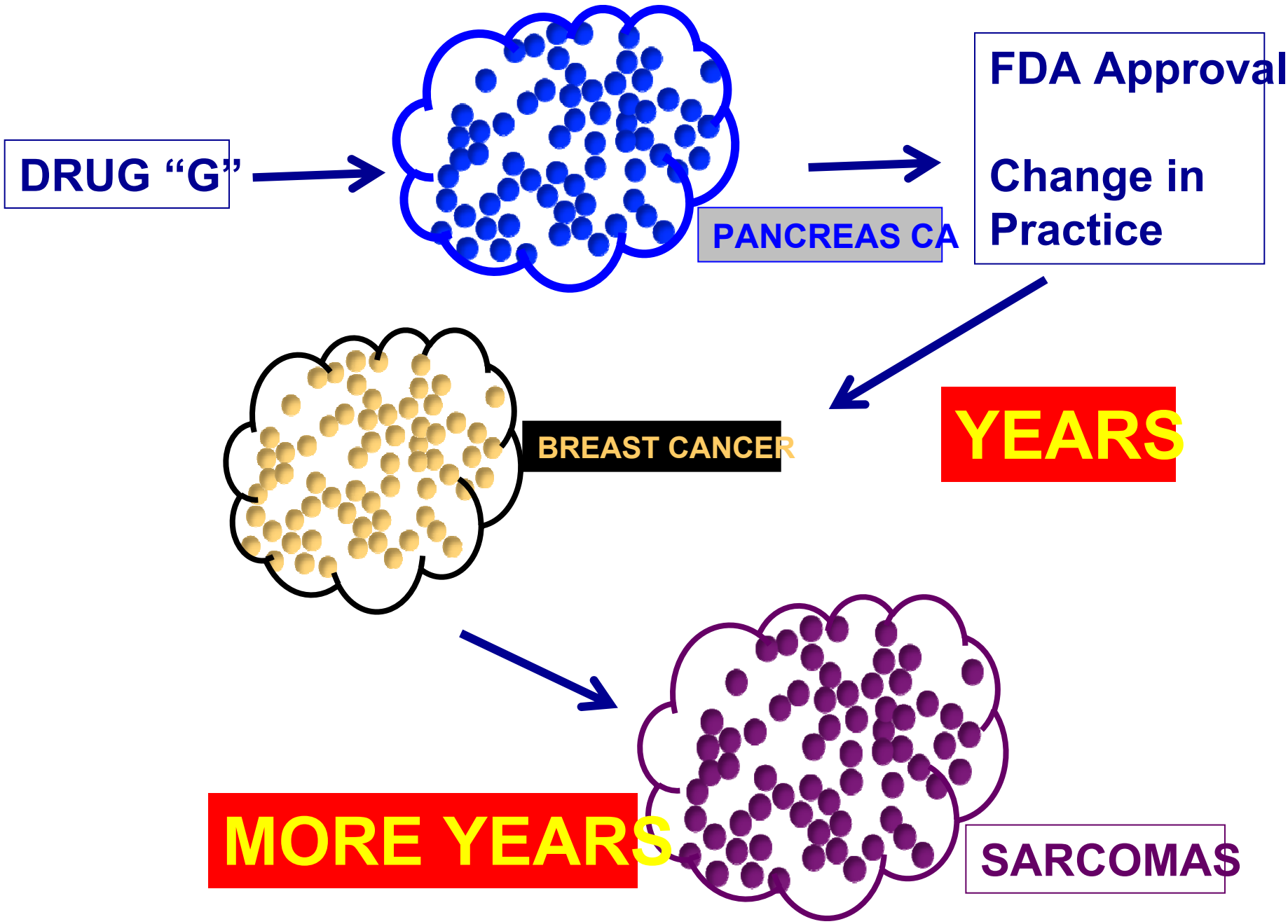


…SARCOMAS.2

Cancers are often managed based on where the first tumor starts


PANCREAS CA
BREAST CANCER
SARCOMAS

What is the "standard process" for anticancer drug development?


DRUG "G"
PANCREAS CA
FDA Approval
Change in Practice
YEARS
BREAST CANCER
MORE YEARS
SARCOMAS

How can we accelerate this process to bring the right new drugs to the right patients as efficiently as possible?

A MOLECULAR TARGET THAT DRIVES CANCER

FDA Approval 2001

LEUKEMIA

2002

GIST / SARCOMA

2009

Blood Cancer #2 (ALL)

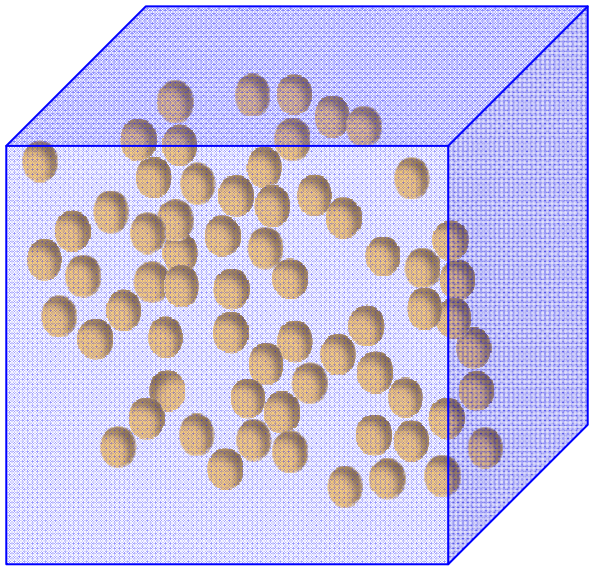
SARCOMA #2 (DFSP)

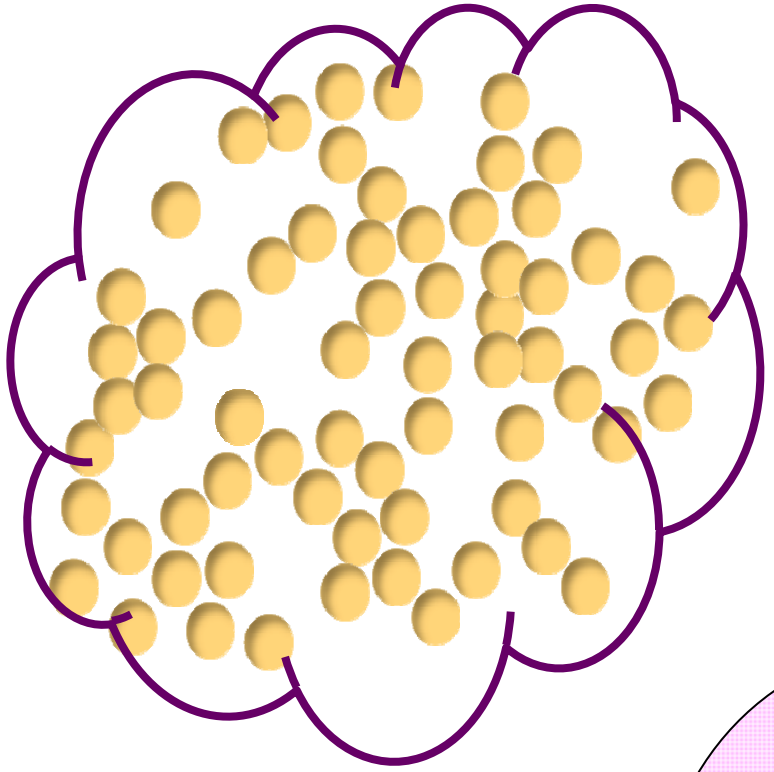
Mast Cell Cancer

Hypereosinophil Cancer

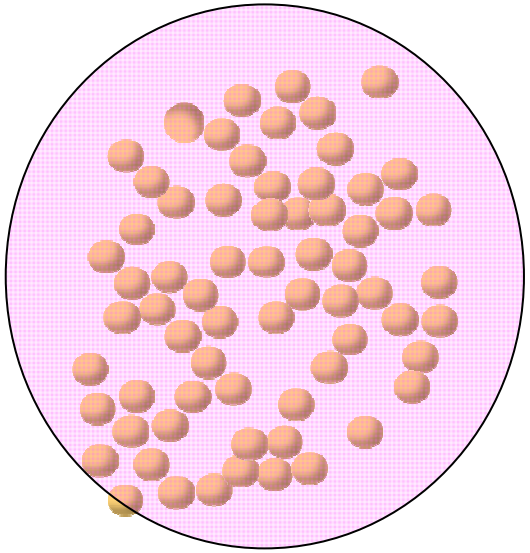
Pre-leukemia (MDS / MPD)

GIST / SARCOMA





MELANOMA



LEUKEMIA

Identifying challenges to the success of this process

Challenge # 1:

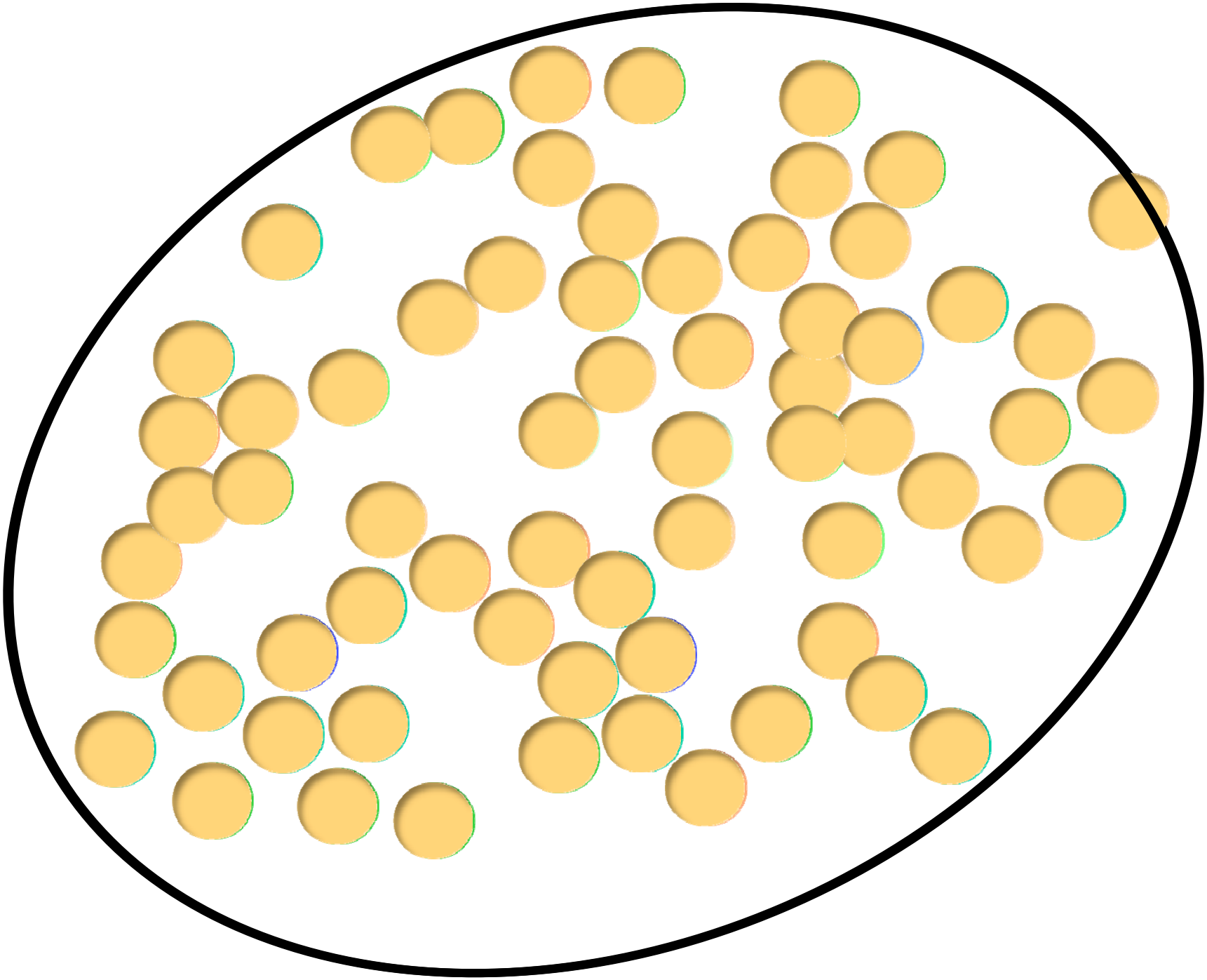
Measuring the value of tumor cell origin (histology) while aggregating cancers by molecular target

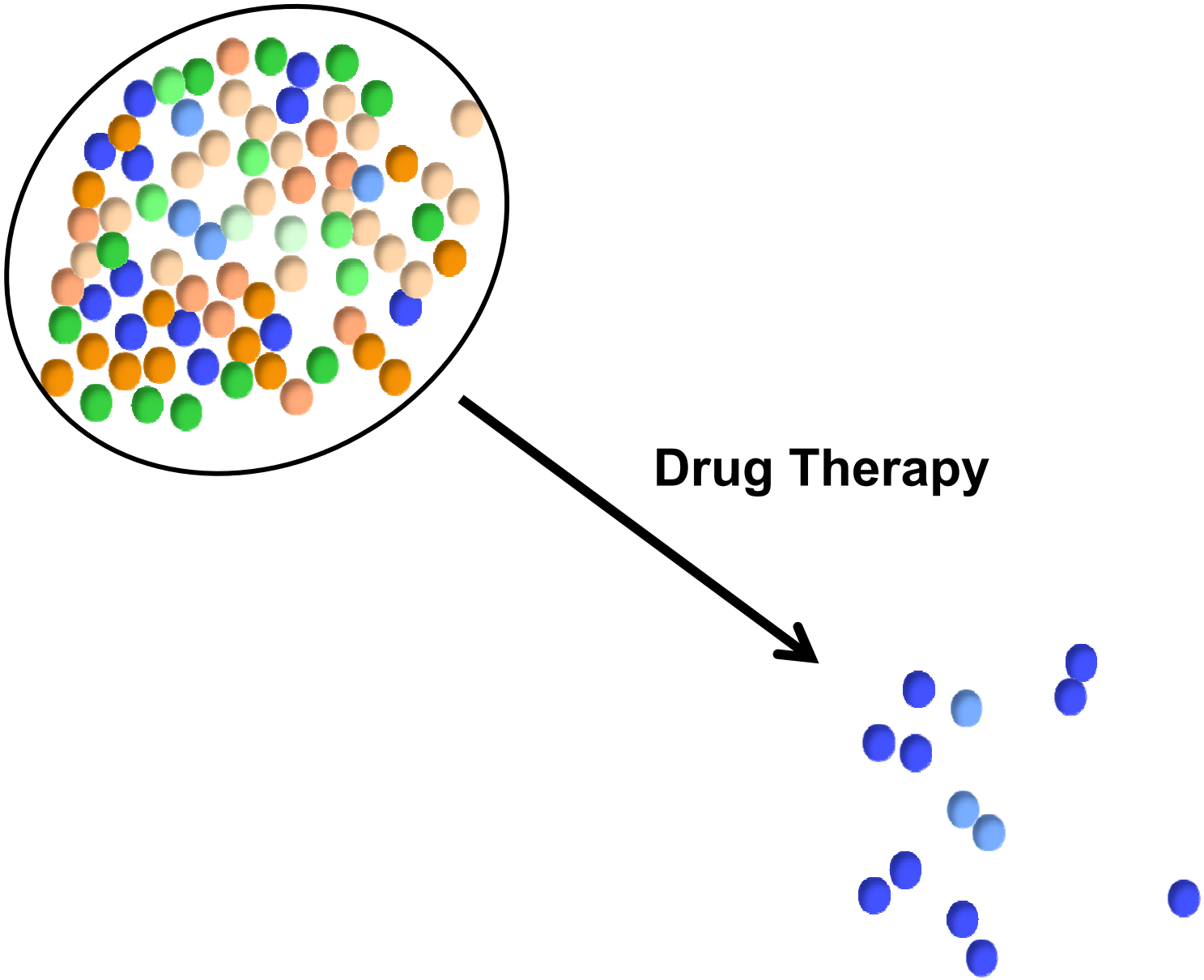
Challenge # 2:

Working with regulatory authorities
to agree on transparent metrics for success of new trial designs across cancer types

Challenge # 3:

Biology and complexity of cancer




Drug Therapy


USERNAME / SmilesforMiles01
"Mowing the lawn is very therapeutic."
Member Sign In
match.com
There's a whole new world inside. Discover it now
I'm a
looking for
Treatment
Between ages 25 and 35
Near ZIP/Postal code
CONTINUE »
GET THE 6 MONTH GUARANTEE. GO »

Different perspectives in addressing this today:

Patient and Advocate Perspective:
Josh Sommer (Chordoma Foundation)

NCI perspective: Dr. James Doroshow

A Modest Proposal with Industry Support:
Dr. Perry Nisen (GlaxoSmith Kline)

FDA perspective: Dr. Robert Becker

Regulatory Overview: Dr. Janet Woodcock (FDA)

ENGELBERG CENTER for Health Care Reform at BROOKINGS

FRIENDS of CANCER RESEARCH

Conference on Clinical Cancer Research

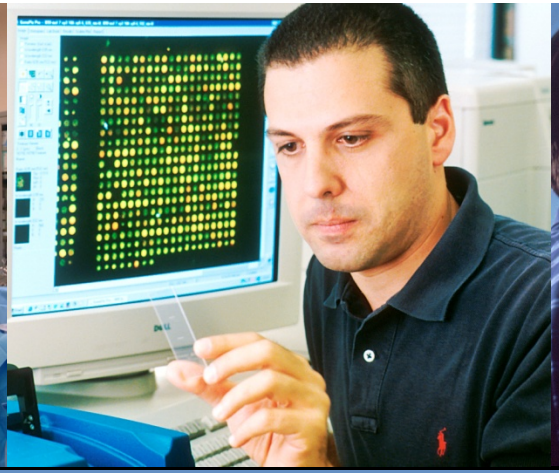
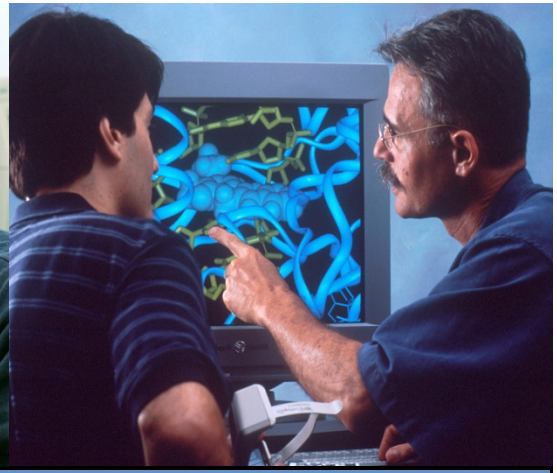
Alternative Trial Designs Based on Tumor Genetics/Pathway Characteristics

Josh Sommer, Patient Advocate

The Chordoma Foundation

November 10, 2011 • Washington, DC

National Cancer Institute

Alternative Trial Designs Based on Tumor Genetics/Pathway Characteristics Instead of Histology

James H. Doroshow, M.D.
Deputy Director for Clinical and Translational Research
National Cancer Institute

Friends of Cancer Research & Brookings Institution
Conference on Clinical Cancer Research

November 10, 2011

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

National Cancer Institute

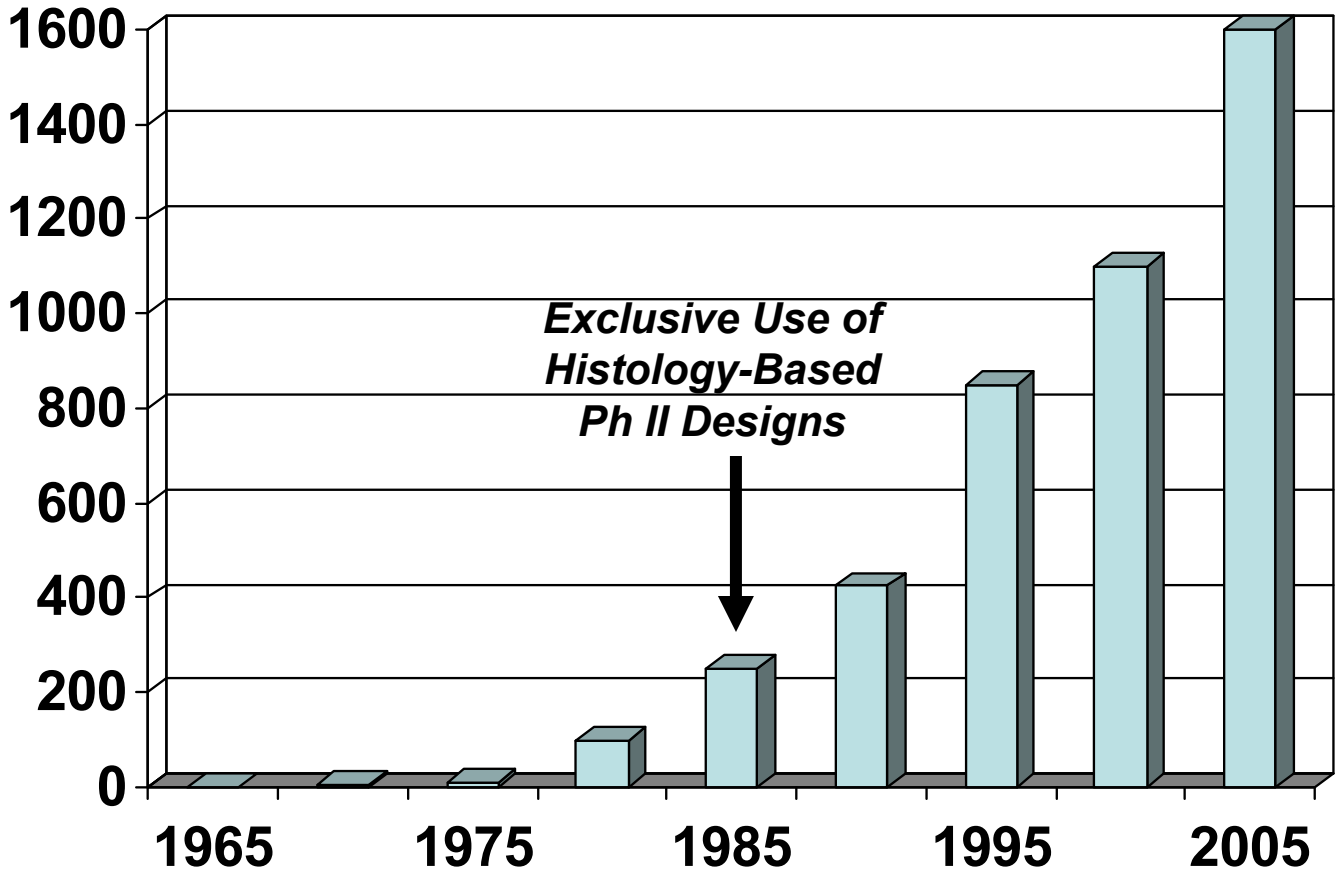
Phase II Cancer Trials: Historical Context

- **1985-2005: *Dogma*: Two-stage Fleming or Simon Designs; occasional randomized phase II's**
  - ✓ **Purpose: Estimate an objective response rate of patients with a specified tumor type to a particular drug**
  - ✓ **At least two trials with 'adequate' numbers of patients in each major tumor type (N=14-25)**
  - ✓ **All patents entered must have measurable disease**
  - ✓ **All patients must have maximum performance status and minimum prior therapy**
  - ✓ **If no objective responses seen in 25 patients, drop Rx**
  - ✓ **Large phase II studies to define levels of activity are generally not indicated**

R. Wittes et al., Cancer Treat. Rep. 70: 1105, '86

National Cancer Institute

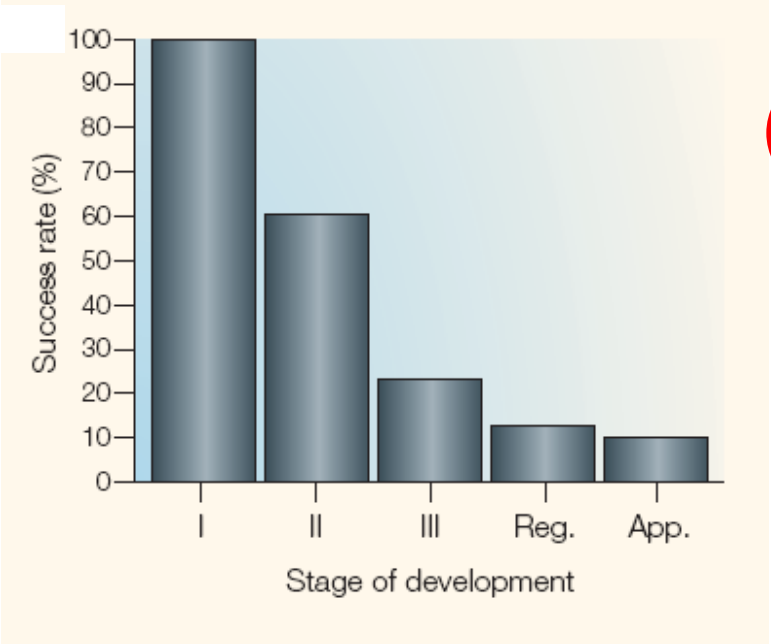
Published Phase II Cancer Treatment Trials: 1965-2005



National Cancer Institute

Most Drugs Fail in Late Stages of Development- Particularly in Oncology

Rates of success for compounds entering first in man that progress to subsequent phase



- **70% of oncology drugs that enter Phase 2 fail to enter Phase 3**
- **59% of oncology drugs that enter Phase 3 fail**
- **Late stage failure leads to enormous risk**

Kola & Landis; Nature Reviews Drug Discovery 2004

National Cancer Institute

Why Continue to Focus On A "Given Tumor Type"?

"Primary objective of phase II trials is to screen for preliminary evidence of efficacy in a given tumor type."[Defined histologically;

J. Clin. Oncol. 26: 1346, 2008]

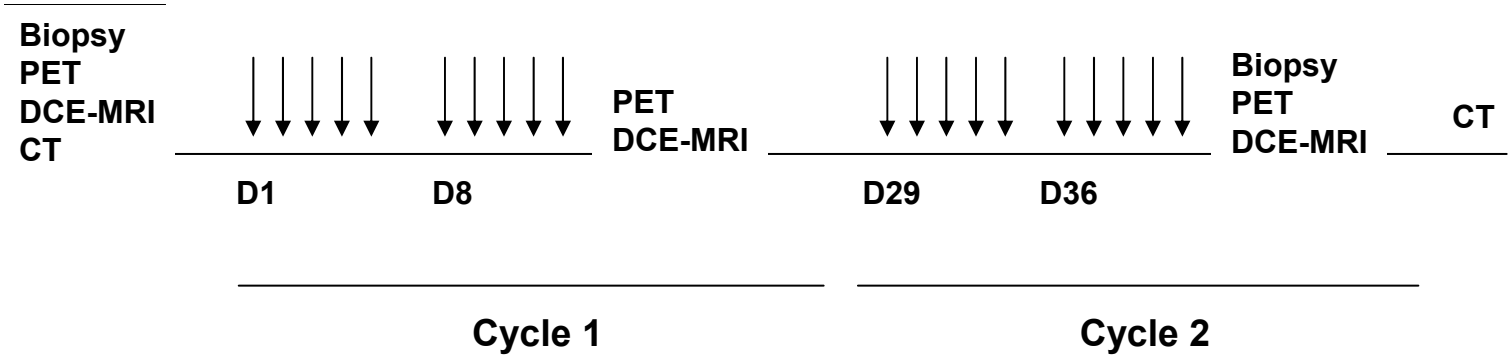
- Limited by modest availability of qualified molecular classifiers in therapeutics
- Limited by the complexity of performing evaluations of appropriate molecular markers in Phase II
- Limited by the lack of funding for these critical studies

National Cancer Institute

Target Inhibition as the Endpoint of a Phase II Trial: Proof of Concept Study of Oral Topotecan in Advanced Solid Neoplasms Expressing HIF-1α

NCI-05-C-0186: Giovanni Melillo, MD PI

- **Eligibility: HIF-1α +ve solid tumors of *any histology* (>10% of tumor cells by IHC)**
- **Treatment: Oral chronic topotecan (1.2 mg/m2 PO daily x 5 days x 2 wks q28 days)**
- **Primary endpoint: Inhibition of HIF-1α expression in tumor**
- **Schema:**



PD endpoints:

- IHC (MVD, Glut-1)
- mRNA expression (HIF-1 target genes, VEGF, PGK-1, CAIX)
- serum/plasma markers (VEGF, osteopontin)
- CEP (circulating endothelial precursor cells)

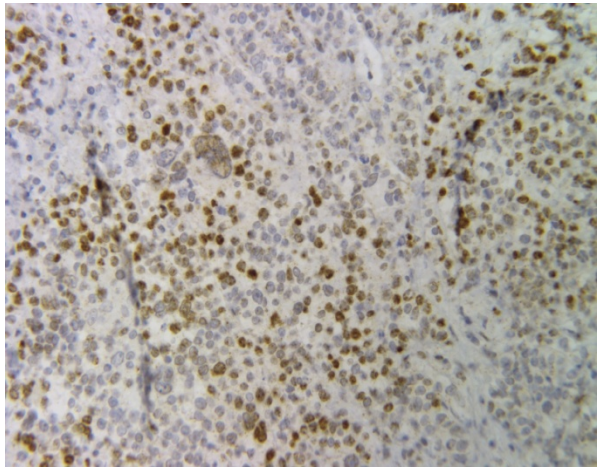
National Cancer Institute

Pilot Study of Oral Topotecan in Advanced Solid Neoplasms Expressing HIF-1α

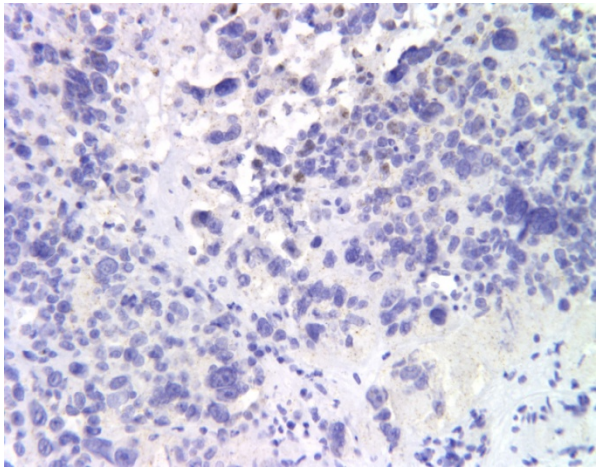
✓Accrual: 16 patients
- 12 evaluable: 1 melanoma, 1 bladder, 1 breast, 2 ovarian ca., 1 SCLC, 1 bladder, 1 H/N, 4 CRC [PRs in SCLC, Ovarian cancer]
- 4 not evaluable: 1 ASPS, 1 adrenal, 1 colon, 1 pancreas

✓Toxicities: myelosuppression, diarrhea (first 2 pts., at 1.6 mg/m^2), well tolerated at 1.2 mg/m^2

HIF-1α staining in patient #4 (breast cancer)



Baseline Biopsy

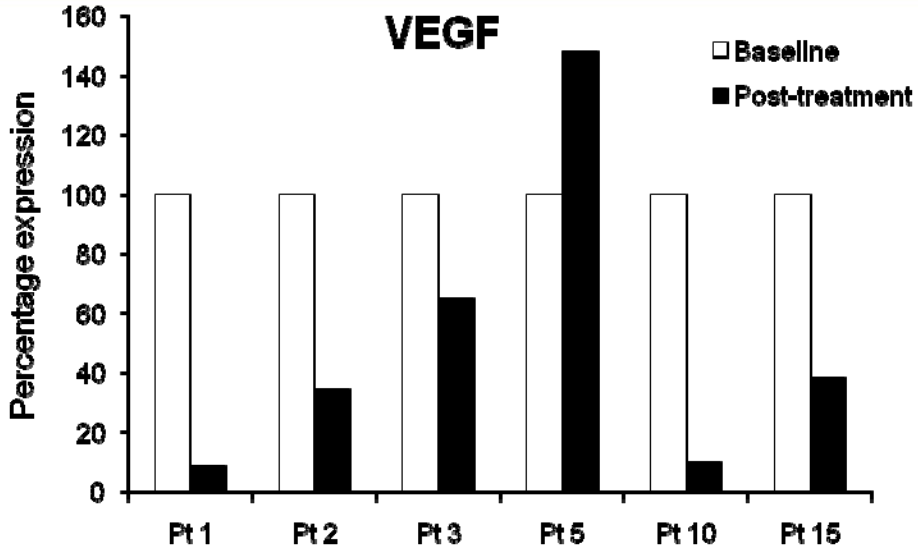


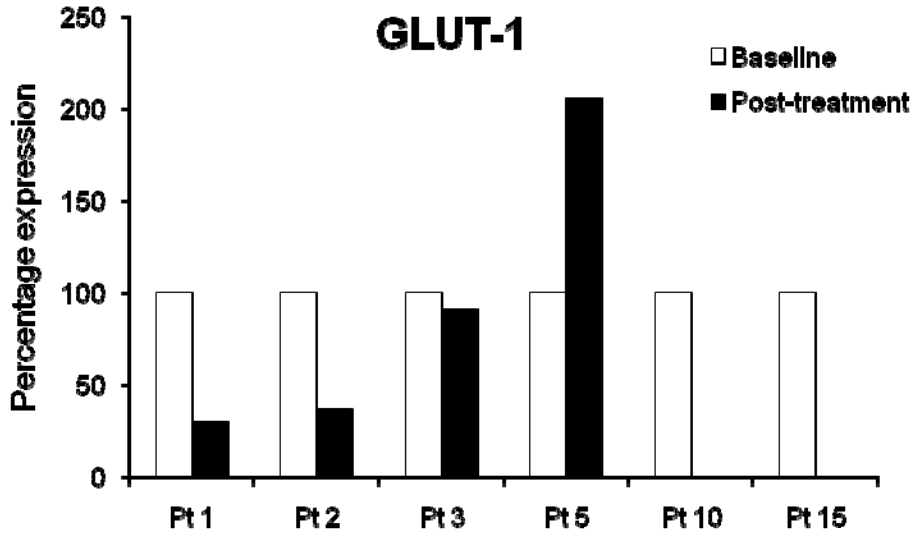
After 2 Cycles of Topotecan

Clin. Cancer Res. 17: 5123-5131, 2011

National Cancer Institute

mRNA Expression of HIF-1α Downstream Targets After Topotecan





Clin. Cancer Res. 17: 5123-5131, 2011

National Cancer Institute

Design Studies Based on Molecular Characteristics

Because:

- Current trial designs are not based on predictive, disease-specific preclinical models or (often) on predictive tumor biology
- Potentially more efficient: decrease regulatory and administrative burden—1 protocol; still requires appropriate sample sizes for each investigational group studied
- May speed up the evaluation of target effects of agent(s) across tumor types with potential to improve biomarker development/qualification
- May provide opportunity “borrow” efficacy and toxicity experience across all patients enrolled in the study

ENGELBERG CENTER for Health Care Reform at BROOKINGS

FRIENDS of CANCER RESEARCH

Conference on Clinical Cancer Research

Alternative Trial Designs Based on Tumor Genetics/Pathway Characteristics

Perry Nisen
Oncology R & D, GlaxoSmithKline

November 10, 2011 • Washington, DC

ENGELBERG CENTER for Health Care Reform at BROOKINGS

FRIENDS of CANCER RESEARCH

Conference on Clinical Cancer Research

Alternative Trial Designs Based on Tumor Genetics/Pathway Characteristics

Bob Becker
CDRH, U.S. FDA

November 10, 2011 • Washington, DC

ENGELBERG CENTER for Health Care Reform at BROOKINGS

FRIENDS of CANCER RESEARCH

Conference on Clinical Cancer Research

Alternative Trial Designs Based on Tumor Genetics/Pathway Characteristics

Janet Woodcock
CDER, U.S. FDA

November 10, 2011 • Washington, DC