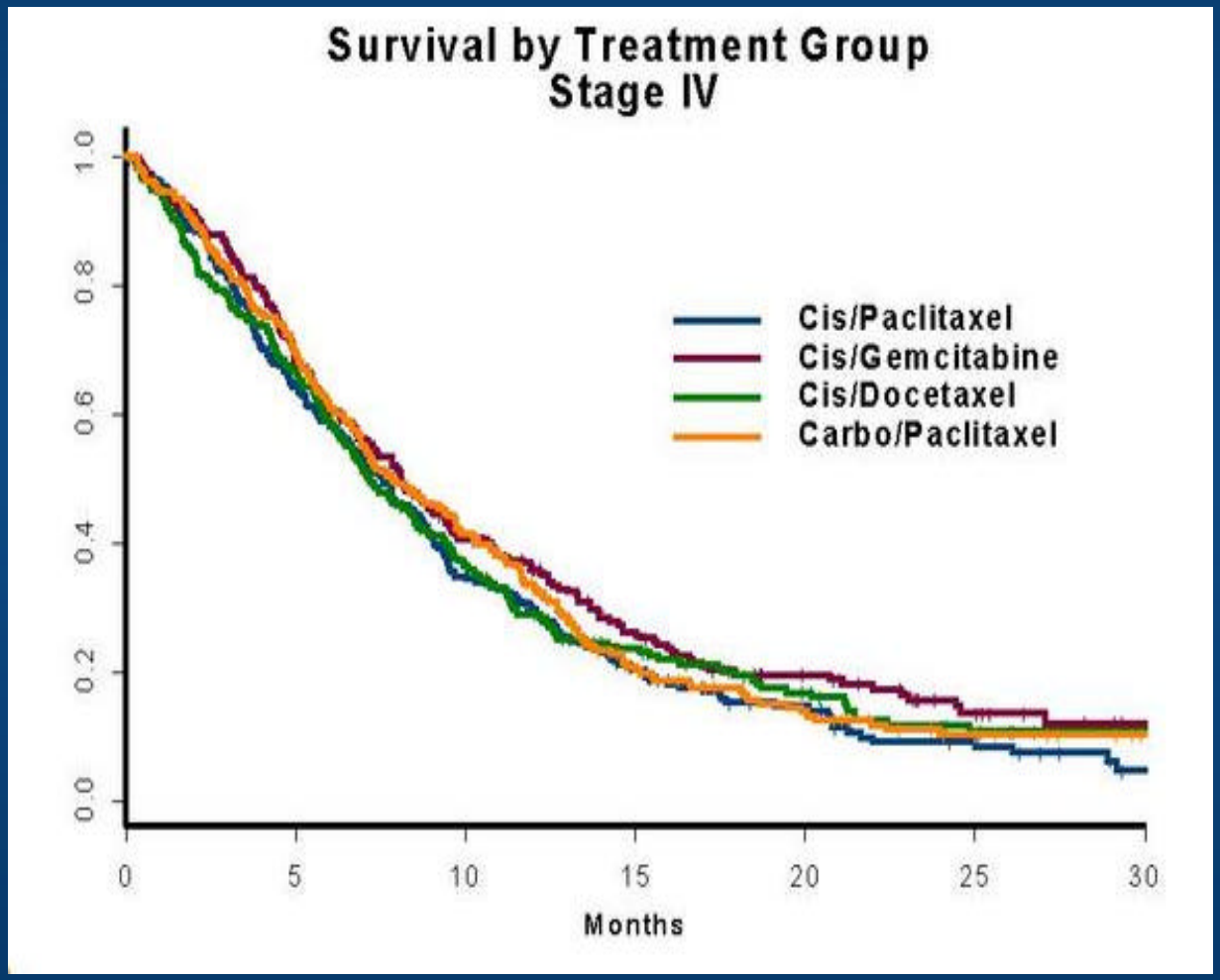
Cancer

Oncology represents the largest therapeutic area being commercialized in biotech:

	Oncology	CV	ID	CNS
Number of companies	181	78	>100	>100
Number of products In development	395	123	256	250

Burrill & Co., January, 2004

A Paradigm Shift Was Needed



All recent randomized studies have similar results.

No clear efficacy benefit for non-platin combinations or triplet combinations.

A paradigm shift is needed!!

Schiller JH et al. *NEJM* 2002

Paradigm Shift

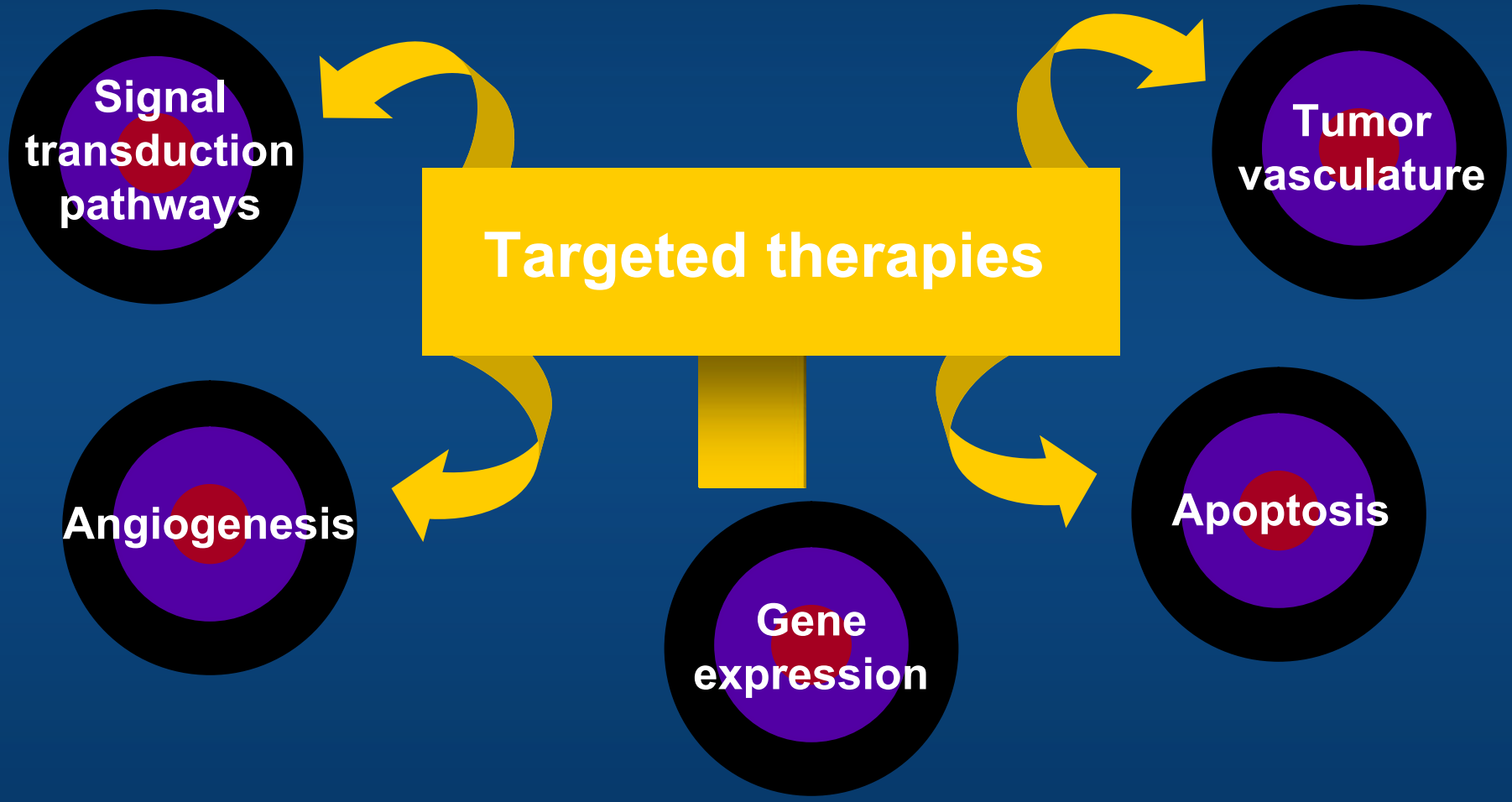
FORWARD VENTURES

- Old paradigm:
  - Kill tumor cells by intefering with rapidly dividing cells
  - Side effects: nausea, diarrhea, hair loss, weakened immune system
- New paradigm:
  - Control tumor cells by fixing the specific molecular problem and preventing their recurrence and spread
  - Side effects: hopefully, hardly any

New Paradigm: Targeted Therapy

- Medication that blocks the growth of cancer by interfering with specific targeted molecules that the cancer cells depend on for growth and/or metastasis.
- Absolute dependency – highly selective
  - dependency on just one or few genes –"Achilles' Heel"
    - "Oncogene addiction" - e.g. Imatinib (bcr/abl), herceptin (Her-2)
    - BRAFi for V600Emutation, Tarceva for EGFR mutation, Crizotinib for ALK
    - Strong selective pressure for drug resistance mutations
    - Escape from oncogene addiction through mutations of other genes
      - e.g. K-Ras mutation in EGFR over expression
- Partial dependency - partial selectivity
  - dependency on multiple genes
    - Bevacizumab (Avastin), PARPi, SERMS, HDACi, Bortezomib (Velcade)

Targeted Therapeutics



more effective and less toxic

New Targets – Session 2

Moderator:

- **Ivor Royston, MD, *Forward Ventures***

Panel:

- **Robert Forrester, COO, Verastem**
- **Scott Biller, PhD, CSO, *Agios Pharmaceuticals***
- **Daniel Silver, MD, PhD, Asst Prof Medicine, *Dana Farber***
- **Keith Flaherty, MD, Dir Develop Ther, *Mass General***
- **Ellie Guardino, MD,PhD, Med Direc, T-DM1, *Genentech***
- **Michael Myers, MD, VP Heme/Onc Compd Develop, *J&J***

Novel Targets with Recent Advances

- **Session 1**

  PI3K(delta), MEK, mTOR

- **Session 2**
  - **Cancer Stem Cells - (Verastem) - Mr. Forrester**
  - **IDH1/2 - Brain Ca, AML (Agios) - Dr. Biller**
  - **PARP-1 - Breast ca (Sanofi, AstraZeneca, Abbott) – Dr. Silver**
  - **BRAF – Melanoma (Plexxikon/Roche, GSK) – Dr. Flaherty**
  - **T-DM1 – Breast ca (Immunogen/Genentech) –Dr. Guardino**
  - **CYP17 – Prostate ca (Cougar/J&J) – Dr. Meyers**

Additional Novel Targets

- **Cellular Targets**

  FLT3 – AML (Ambit)

  ALK – NSCLCof lung (Pfizer)

  MET - NSCLC (Pfizer, ArQule, Genentech)

  Cox-2 – NSCLC (Tragara)

  Hedgehog ligands – Pancreatic Ca, basal cell ca (Genentech)

  CD30 – Hodgkin's Disease (Seattle Genetics)

- **Stromal Targets**

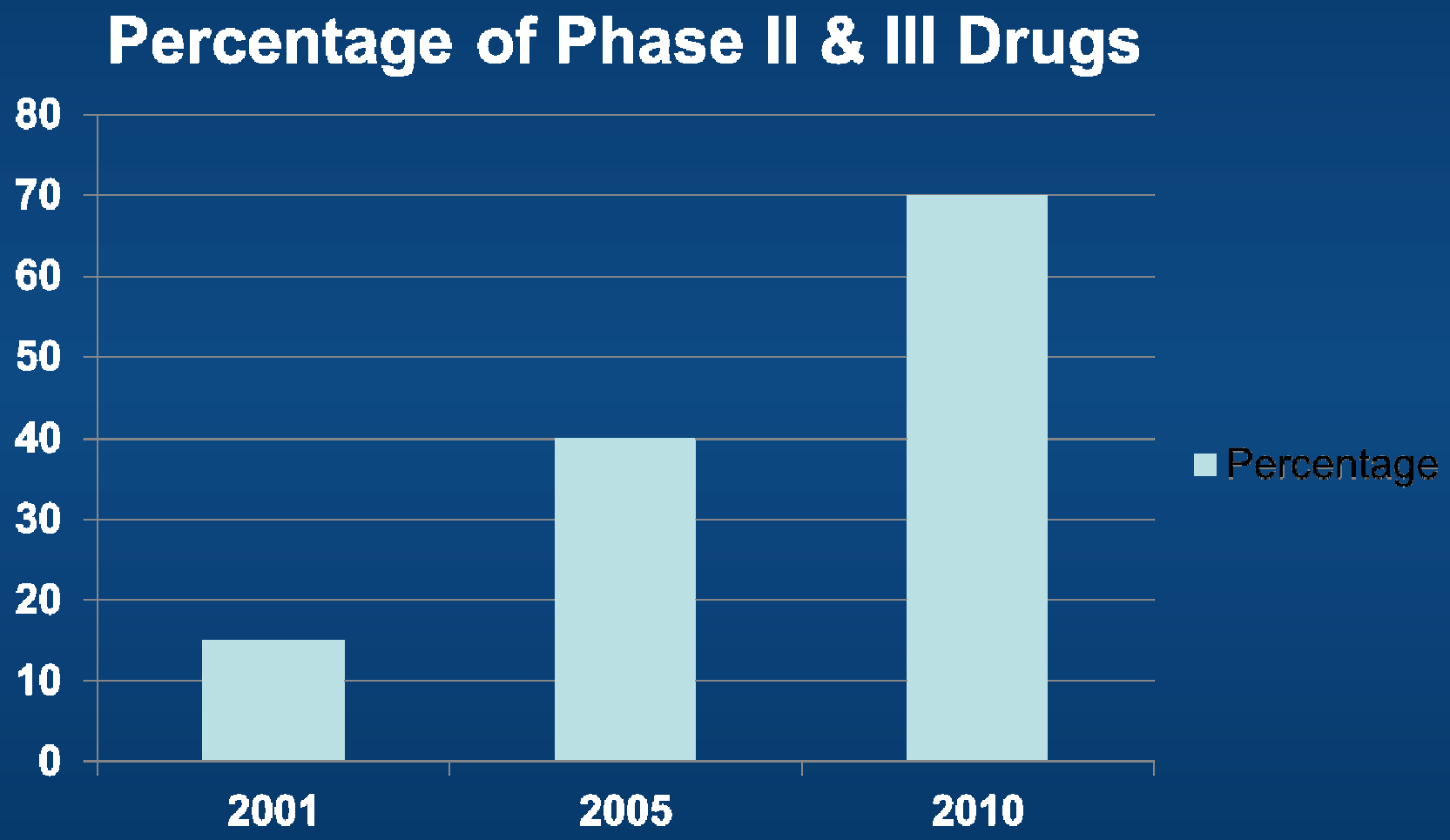
  Hyaluronic Acid – Pancreatic Ca (Halozyme)

  Hedgehog ligands – Pancreatic Ca (Genentech)

- **Vascular Targets**

  Cytoskeleton - NSCLC (Nereus)

Biomarker-driven Clinical Trials



Challenges

- Identification of relevant target cancer subpopulations
- Short duration of response - Overcoming resistance
- Validated companion diagnostics with less invasive techniques, e.g. CTC's
- Optimal combination use
- Side effects (common & unsusal)
- Clinical trial endpoints
- Reimbursement for high value Diagnostics