National Cancer Institute

Perspectives on Combination Therapies from the NCI

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Center for Cancer Research

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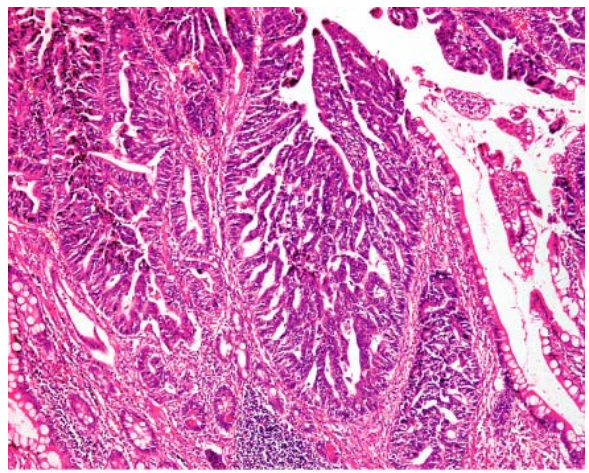
Outline

- Key Considerations for Moving Combinations Forward
- Challenges and Opportunities
- Role NCI is playing
  - Clinical Programs
  - Translational Approaches
  - Basic Science
  - Advanced Biomedical Technologies

Cancer Isn't a Single Disease

Men 720,280		Women 679,510	
Prostate	33%	Breast	31%
Lung & bronchus	13%	Lung & bronchus	12%
Colon & rectum	10%	Colon & rectum	11%
Urinary bladder	6%	Uterine corpus	6%
Melanoma of skin	5%	Non-Hodgkin's lymphoma	4%
Non-Hodgkin's lymphoma	4%	Melanoma of skin	4%
Kidney	3%	Thyroid	3%
Oral cavity	3%	Ovary	3%
Leukemia	3%	Urinary bladder	2%
Pancreas	2%	Pancreas	2%
All Other Sites	18%	All Other Sites	22%

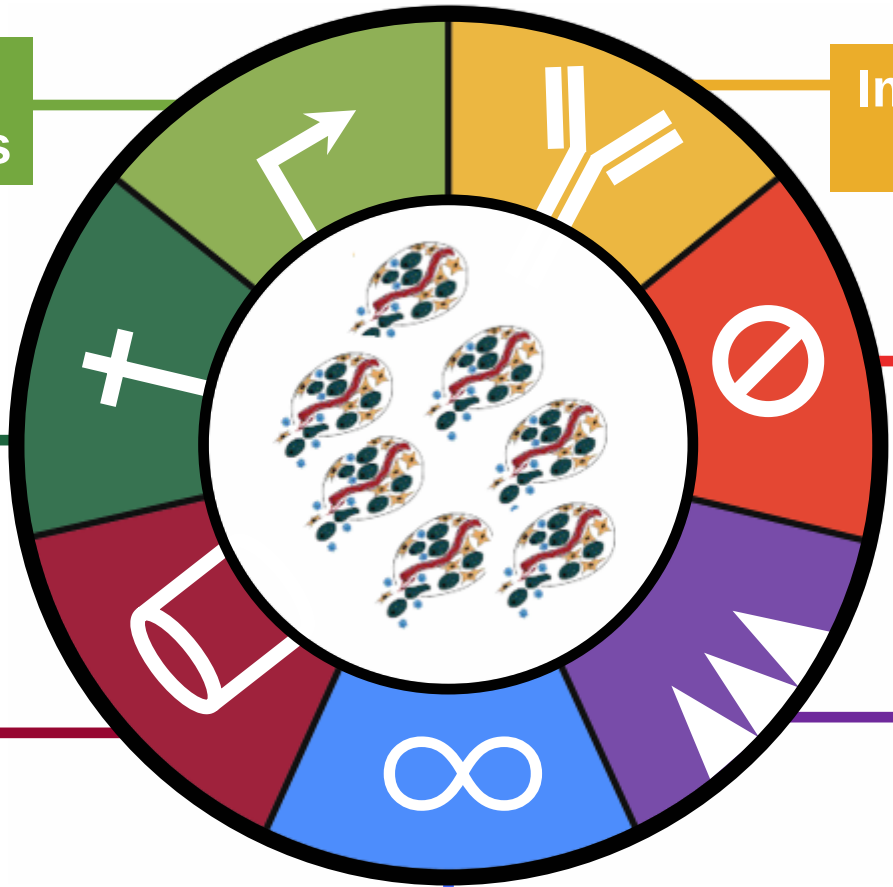
- **Heterogeneous collection**
- **Distinct cancers arise from unique tissues**



ACS Estimated 2006 Cancer Cases from SEER

Cancer is a Complex Foe

Essential aberrations of cancer



Self-sufficiency in growth signals

Immunologic tolerance

Insensitivity to growth signals

Evading apoptosis

Sustained angiogenesis

Tissue invasion and metastasis

Limitless replicative potential

Adapted from: Hanahan & Weinberg, Cell 100:57 (2000)

Oncology Practice is Changing

Diagnosis:		
Organ Site	⇉	Molecular Etiology
Late		Early
Classification:		
Histology	⇒	Molecular Defects
Focus:		
Therapy	⇒	Prevention/Early Intervention
Therapy:		
Non-Specific	⇒	Specific
Prognosis:		
Clinical	⇒	Biological

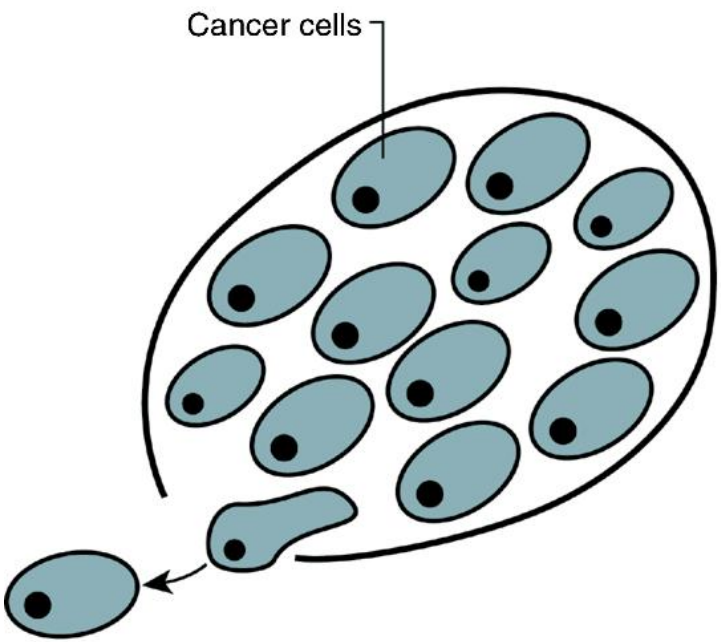
Adapted from L. Norton, ASCO 2002

Paradigm Shift

Traditional Practices	New Practices
Descriptive medicine	Understanding of disease mechanisms
Empirical diagnosis	Mechanism-based diagnosis/treatment
Grouped by Organ Site	Sub-grouped by molecular/biological classification
Uniform treatment	Individualized treatment
Retrospectively diagnose disease	Prospectively evaluate relative disease risk

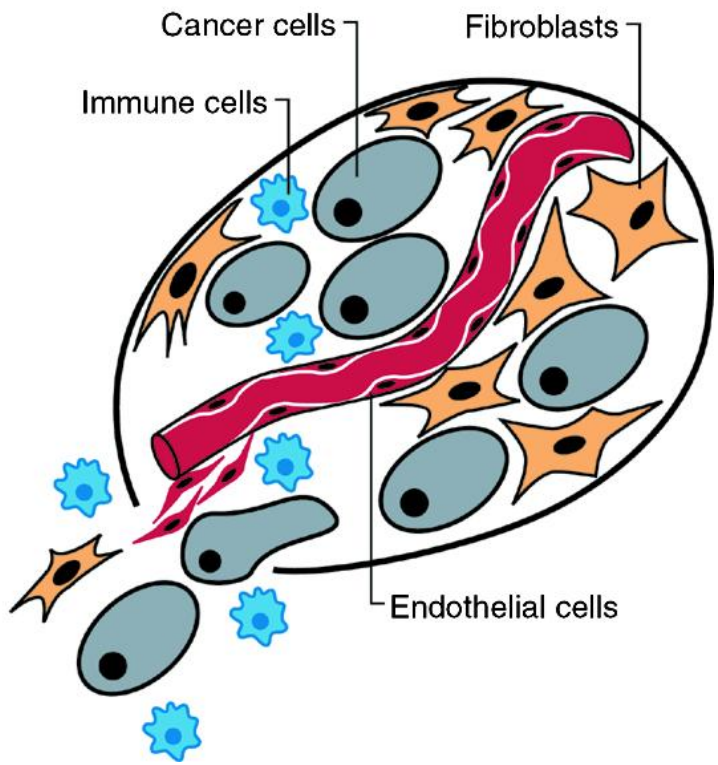
The microenvironment influences cancer growth

The Reductionist View



Cancer cells in isolation

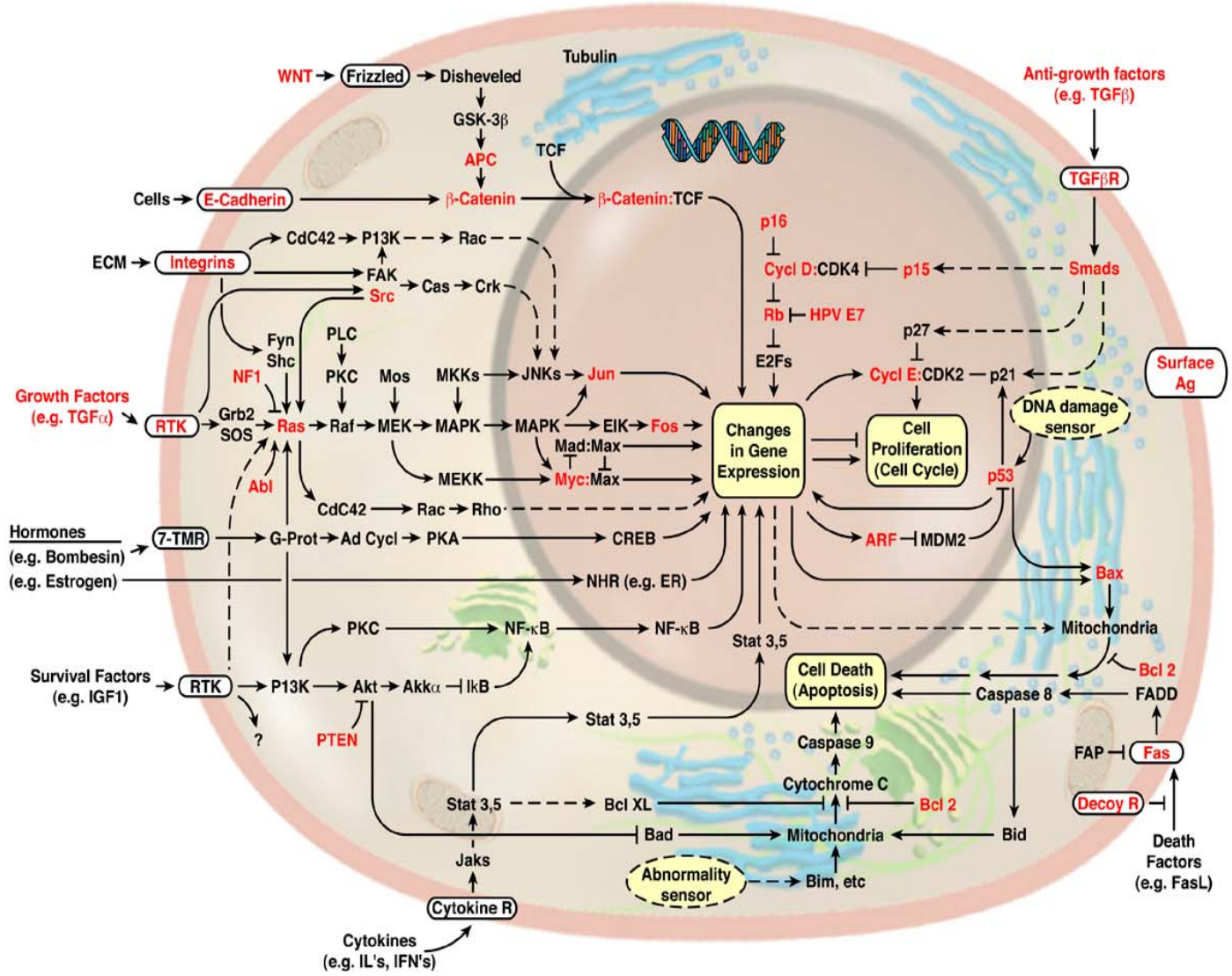
Systems Biology View



Cancer cells as part of the biosystem

Adapted from: Hanahan & Weinberg, Cell 100:57 (2000)

Thousands of Interconnected Pathways



Moving toward smarter combinations

The 20th Century Paradigm
"Search and Destroy"

- **Immune Serum**
- **Tumor Cell Vaccines**
- **Immune Cells**
- **Cytokines**

The Next Frontier:
Combinatorial Therapies

The New Paradigm
"Target and Control"

-Vaccines in Combination with:
- **Conventional Therapies**
- **Molecularly Targeted Therapies**
- **Other Biologics**

-Combinations of Biologics with Small molecules, Chemotherapy or Radiation

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Strategies for Combination Therapy

- Same target
- Same pathway (decreased toxicity)
- Different pathways (increased efficacy)
- Compensatory pathways/ new route pathways
- Drug resistance pathways

Challenges

- Appropriate molecular context in tumor
- No adverse pharmacological interaction(s)
- Non-overlapping mechanisms of resistance
- Non-overlapping toxicities
- Able to use at effective and/or modulating doses

Challenges

- Preclinical Data to inform:
  - Dose
  - Scheduling
  - Sequence
  - Prioritizing combinations
  - Drug/agent interactions
- Development of resistance
- Role of the microenvironment
- Pharmacodynamics
- Variability in biospecimen collection and processing

Challenges

- Pace and price of drug development
- Moving combinations into clinical trials
  - National networks needed to increase access
  - The science must be accessible to all patients
- Interactions with Industry
  - Risk, Intellectual Property Issues, Regulatory Issues, Time delay

Opportunities

- Accelerate pace of drug discovery and development
- Advance conduct of rationally based combination clinical trials
- Integrate and leverage use of advanced biomedical technologies
- Information Technology
  - Accessible to the community to interrogate science based options for treatment given tumor characteristics
- Standardization of biospecimen collection approaches
- Work with Industry to facilitate IP issues

Opportunities

- Leverage basic science discoveries to develop combination therapies:
  - Angiogenesis
    - Anti-VEGF
  - Signal transduction cascades
    - Kinase inhibitors
  - Stromal Cells/Microenvironment
    - MMP
  - Chromatin remodeling
    - HDAC, methylation inhibitors
  - Radiation
    - timing, dose

Targeting Multiple Cell Types in Tumors

- Treatment of bone metastasis in multiple myeloma patients by targeting both the cancer cells and the host cells to get a better therapeutic response. Rationale: Host cells are required for cancer cells to survive and grow.
  - Ken Anderson from the Dan Farber Cancer Institute

- Exploring macrophages as a be potential novel target. Research is focused on tumor associated macrophages and their contribution to angiogenesis and tumor growth.
  - Doug Hanahan and Lisa Coussens from UC San Francisco

- “Normalization of tumor vessels” First target tumor angiogenic vessel with vascular growth factor receptor antibodies and then follow it with chemotherapy. Rationale: Tumor blood vessels are functionally incompetent and thus interfere with drug delivery. Transient treatment of these vessels by inhibitors essentially "prunes" these vessels in such a way that now chemotherapy drugs can flow thru these "normalized" vessels and kills the tumor.
  - Rakesh Jain from Harvard

DCB funded research

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NCI Programs Available for Support of Combination Therapy Approaches

- CTEP - Moving Rational Combinations into Clinical Trials Nationally-Cancer Centers
- CCR/DCTD Early Therapeutics Development Program-Intramural/Extramural Partnership
- TRWG and CTWG Processes to Maximize Resources and Communication
- Basic Science Exploration and Discovery through Multiple Mechanisms
  - Intramural
  - Extramural

Clinical Programs

- CTEP Activities/Cancer Centers
- DCTD/CCR Early Therapeutics Development

CTEP's Critical Molecular Pathways Project

- Series of important proof of principle clinical trials combining novel targeted agents to modulate
  - Critical targets
  - Parallel pathways
  - Parallel/complementary processes
- Incorporate relevant correlative studies
  - Tissue banking
    - Because of the uncertainties about what to measure and how best to measure it
- Overcome barriers to industry collaboration
  - risk aversion
  - Intellectual property issues
  - Regulatory
- Identify appropriate molecular contexts to increase efficacy

M. Christian CTEP, NCI

Clinical trials of novel/ targeted combinations agents

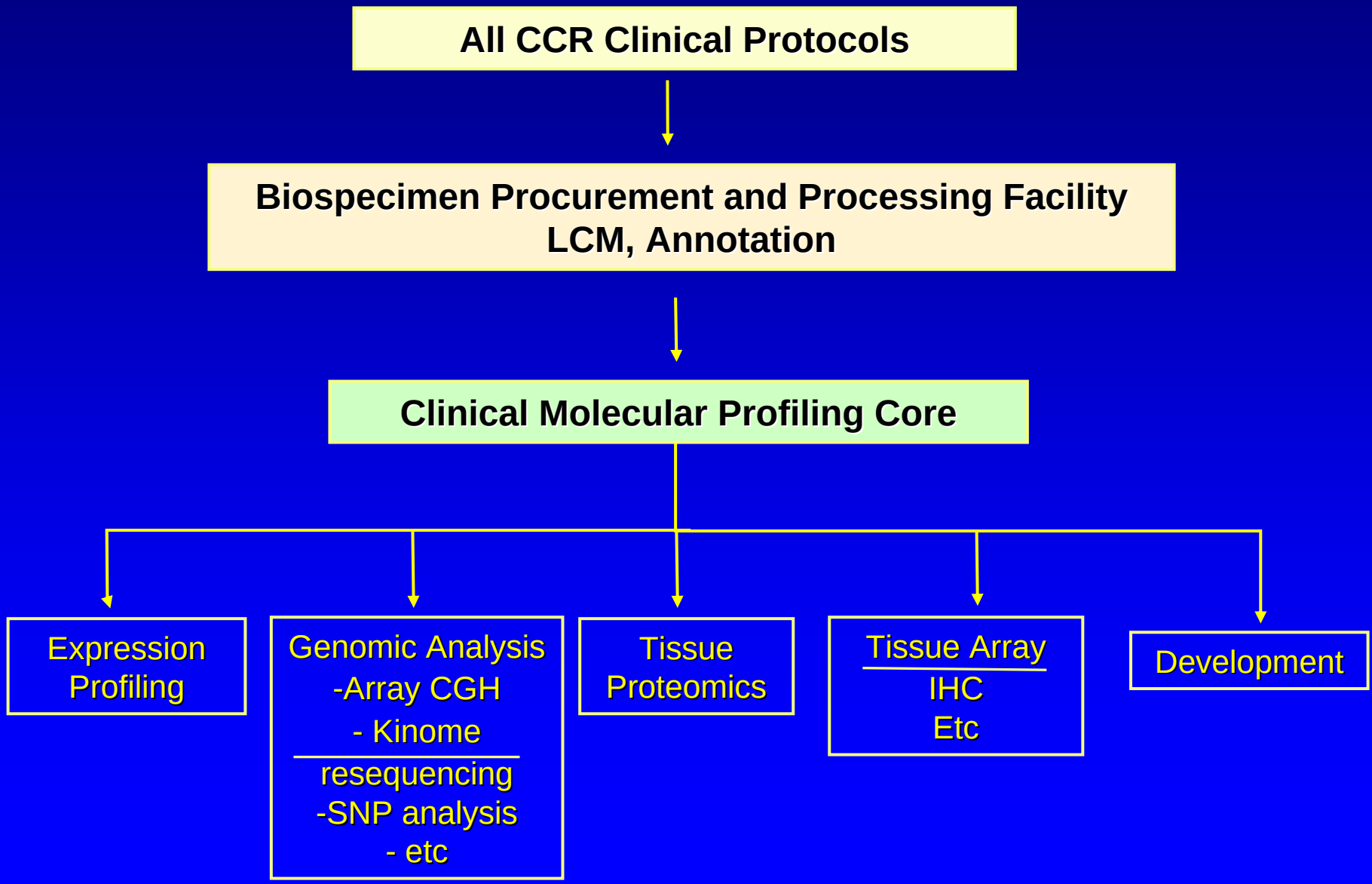
Targets	Clinical trials	Tumor types
VEGR + EGFR*	Bevacizumab + Cetuximab	Colon, Pancreatic
	Bevacizumab + Erlotinib	Breast, SCCHN, RCC, NSCLC, Pancreatic, Ovarian
VEGF + VEGFR/raf	Bevacizumab + Bay 43-9006	RCC
EGFR + EGFR TKI*	Cetuximab + Erlotinib	Colon,
VEGF + mTOR	Bevacizumab + CCI-779	RCC,
Her-2 + mTOR*	Trastuzumab + CCI-779	Breast
EGFR + mTOR	EGFR TKI + CCI-779	NSCLC, Glioma
Her-2 + CDK*	Trastuzumab + flavopiridol	Breast
HDAC + VEGF*	SAHA + Bevacizumab	RCC
Vaccine + immune modulator	Vaccine + anti-CTLA4 Ab	Melanoma, Prostate

There are > 20 ongoing trials

Joint DCTD-CCR Early Therapeutics Development Program

- CCR and DCTD combined strengths to create a program to perform limited-scale, first-in-human Phase 0 trials
- These studies will provide preliminary human data and the initial rationale for later-stage clinical development
- This initiative will capitalize on Exploratory IND Guidance
- Promising candidate therapeutic and imaging agents will be rapidly subjected to the preliminary evaluation of their pharmacokinetics, pharmacodynamics, and mechanism of action in people
- These early trials will be ideal for advanced technology applications aimed at developing clinically relevant assays
- Available for testing agents from both intramural and extramural investigators

Clinical Molecular Profiling Core



Examples of Possible Basic and Translational Approaches

- IL-15 in Combination with Vaccines, Adoptive Cell Transfer and Other Biological Agents
- Targeting Diverse Elements of the Microenvironment
- Biologics and Radiation
- Molecular Profiling to Inform Rational Combinations
- Computational and Systems Biology Advances

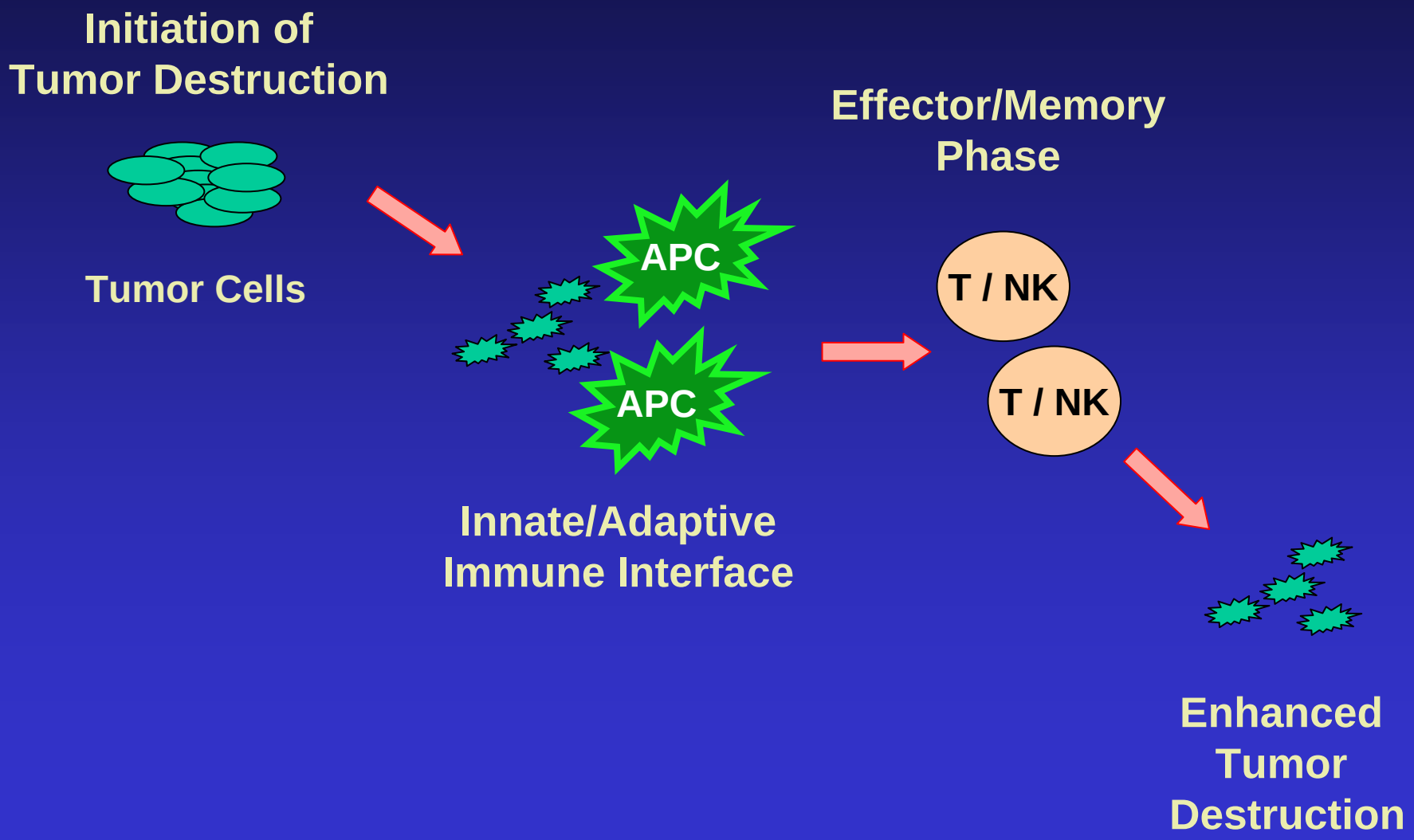
Incorporation of IL15 into Molecular Vaccines

IL-15 is a broad stimulant for both innate and adaptive immune lymphocytes

IL-15 enhances effectiveness of therapeutic cancer vaccines. Co-administration of an HIV vaccine with a vaccinia virus expressing IL-15 induced long-lasting CD8 mediated CTL immunity.

Partnership with NIAID to develop GMP IL-15 for Clinical Trials

IL-15 May be Active in Several Phases of Immune Response Generation Against Cancer

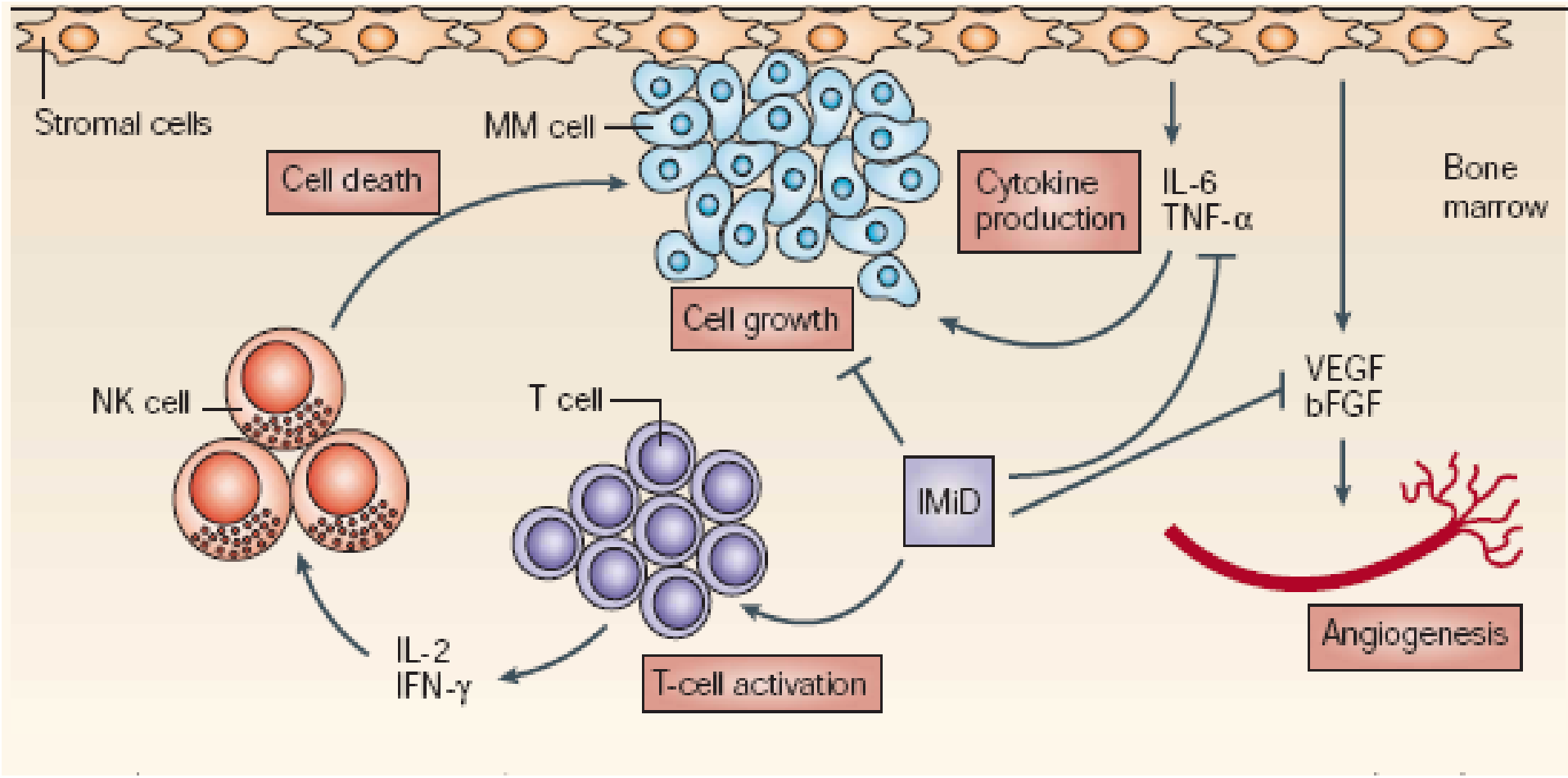


Leverage Basic Science of IL15

Beyond cancer:

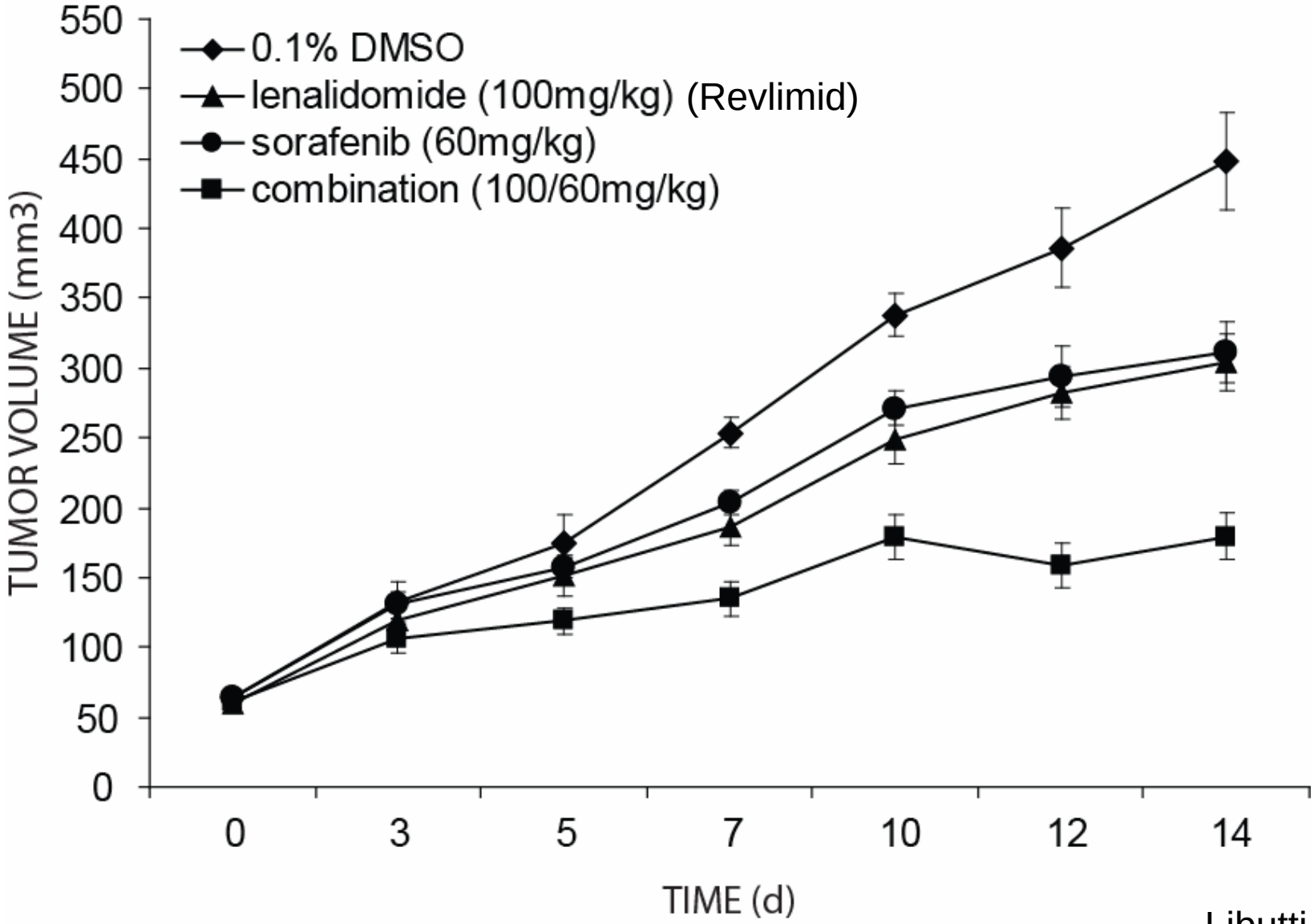
Abnormalities of IL-15 have been described in patients with rheumatoid arthritis, multiple sclerosis and inflammatory bowel disease and in diseases associated with the retrovirus HTLV-I. Monoclonal antibody humanized MiK-Beta-1 inhibits IL-15 actions. Observations of this blockade in animals is being translated to clinical trials in patients with rheumatoid arthritis, multiple sclerosis, LGL leukemia as well as those with disorders caused by the retrovirus HTLV-I.

Revlimid Targets Multiple Sites in the Microenvironment



The evolution of thalidomide and its IMiD derivatives as anticancer agents. Nat Rev Cancer. 2004 Apr;4(4):314-22. Review

Human Ocular Melanoma Grown Subcutaneously in Nude Mice



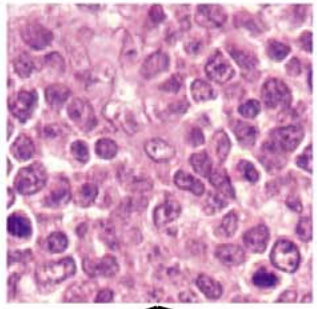
Libutti, CCR

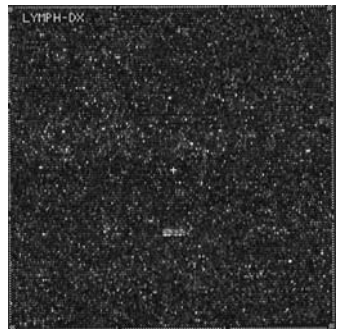
Combining Biologics with Radiation

- Clinical trial combining vaccine and radiation therapy is actively enrolling patients with CEA-positive tumors and liver metastasis
- Paradigm-shifting trial since radiation of tumor is not a standard of care for liver metastases
- Is being employed in this trial to modulate the phenotype of tumor cells as to render them more susceptible to T-cell-mediated killing
- Analysis of tumor biopsies on this study will seek to further expand in vitro data.

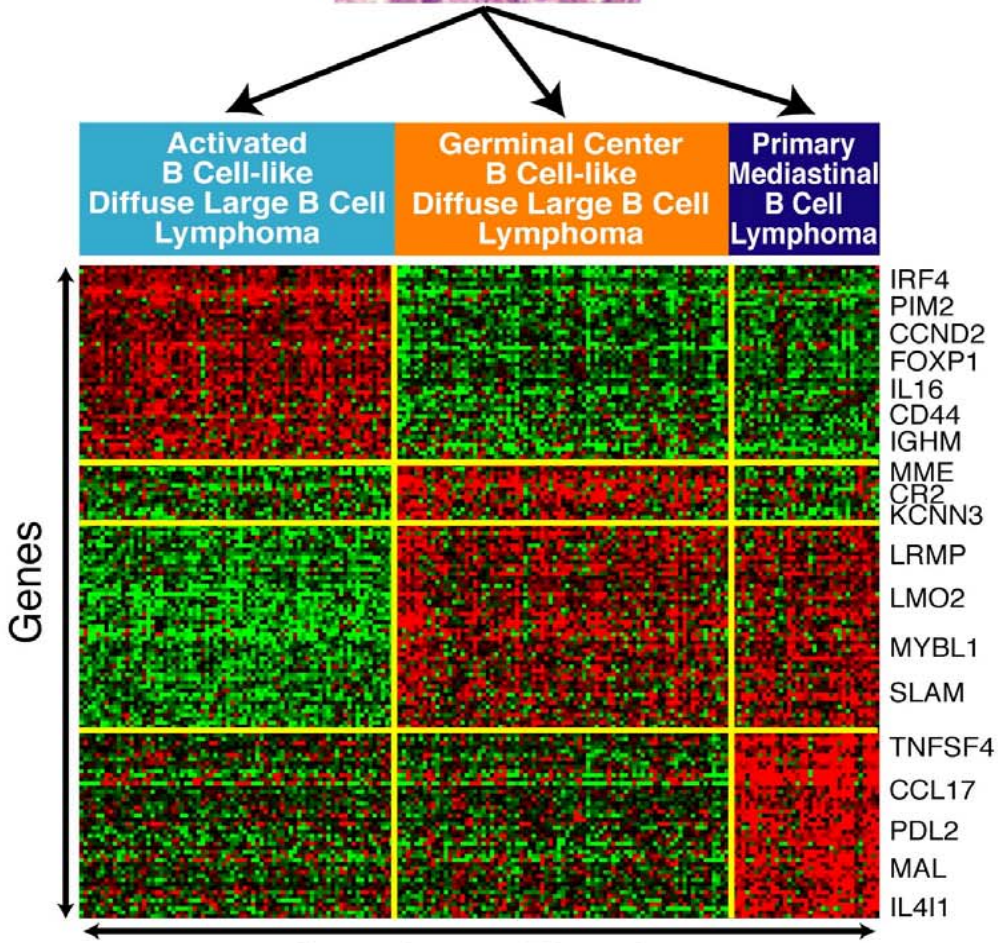
Dissecting a Cancer into Molecularly and Clinically Distinct Subgroups by Gene Expression Profiling

Diffuse Large B Cell Lymphoma





LymphDx microarray



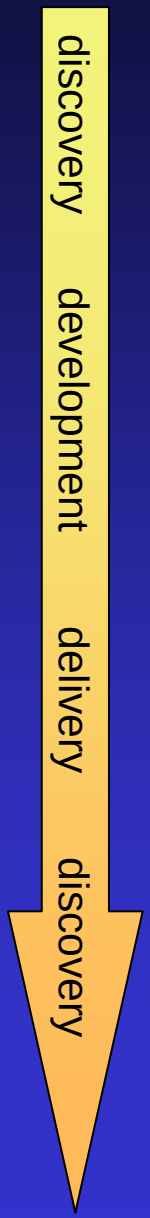
The Glioma Molecular Diagnostic Initiative "GMDI"

- **A national study through 2 NCI-funded brain tumor consortia**
- **More than 1000 patients with gliomas to be accrued**
- **Extensive prospective clinical data to be correlated with molecular data**

Objectives:

- Produce a biologically significant pathological classification of gliomas, with strong correlation to outcome of disease
- Find new molecular targets for therapy
- Produce a ***publicly accessible*** database

Cutting-Edge Childhood Rhabdomyosarcoma Research



Discovery

- Cutting-edge tissue-lysate array technology can accurately map signal pathways in human rhabdomyosarcoma samples
- Treatment responders vs. non-responders can be separated with 100% accuracy by 3 TOR pathway proteins
- This separation cannot be made histologically
- The TOR pathway is sensitive to rapamycin

Development

- Immunohistochemistry measures validated marker
- Approach is being extended to large series of cases and controls from randomized trial
- Design trial to test if rapamycin pretreatment of rhabdomyosarcoma patients can sensitize tumor to standard therapy

Helman and Liotta

Optimization of Targeted Therapy Aimed at Tumor Signaling Pathways Using Computational Modeling and Quantitative Biochemistry

- Development of the model based on available literature data
- Quantitative simulations of cellular response to growth factors and therapeutic interventions
- Verification of the model in the laboratory and introduction of necessary modifications of the model
- *In silico* optimization of therapeutic interventions aiming at selective blocking of signaling pathways
- Laboratory testing of efficacy of optimized molecular targeting alone or in combinations with chemo- and radiation therapy

Major NCI Technology Initiatives and Infrastructure in Support of Rational Combination Therapy Design and Development

- Nanotechnology
- Imaging
- Cancer Genome Project
- Cancer Centers and SPOREs
- caBIG - Information Technology
  - Accessible to the community to interrogate science based options for treatment given tumor characteristics
- Biospecimen and Biorepository Initiative
- Different strategies for addressing IP issues

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There are no bad anticancer agents, only bad clinical trial designs

Dan Von Hoff, M.D.

Richard and Hinda Rosenthal Fdn Award Lecture

American Association for Cancer Research

1998

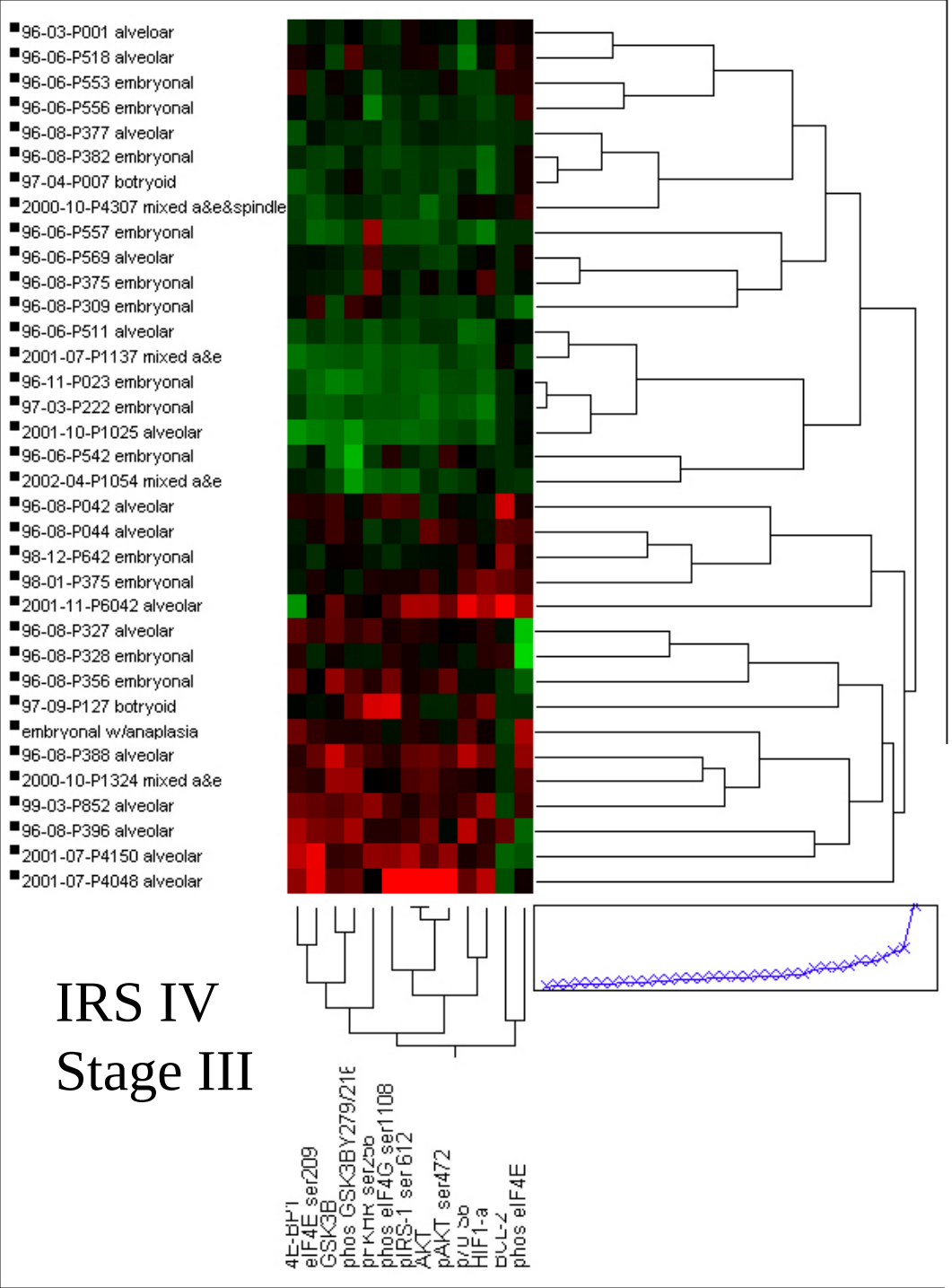
Clinical Trials

Clinical trials have often been based on empiricism.

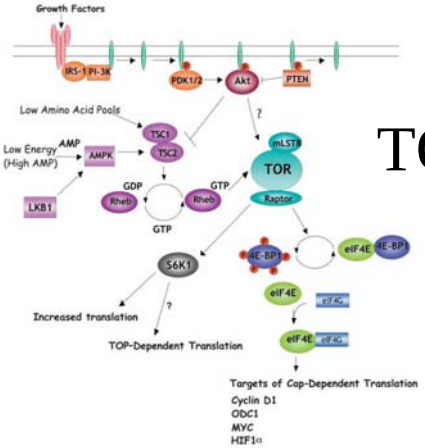
Science now allows a shift to a model more dependent on mechanism.

Innovation is needed to devise proper patterns of combinations tailored to mechanistic understanding of the pathogenesis of disease in individual patients.

Michael B. Sporn, JNCI 2002



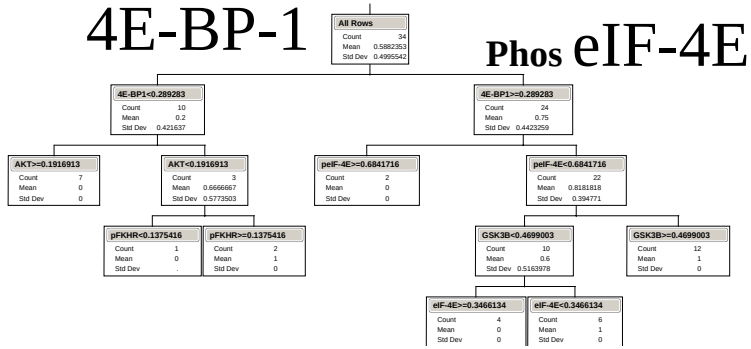
IRS IV
Stage III



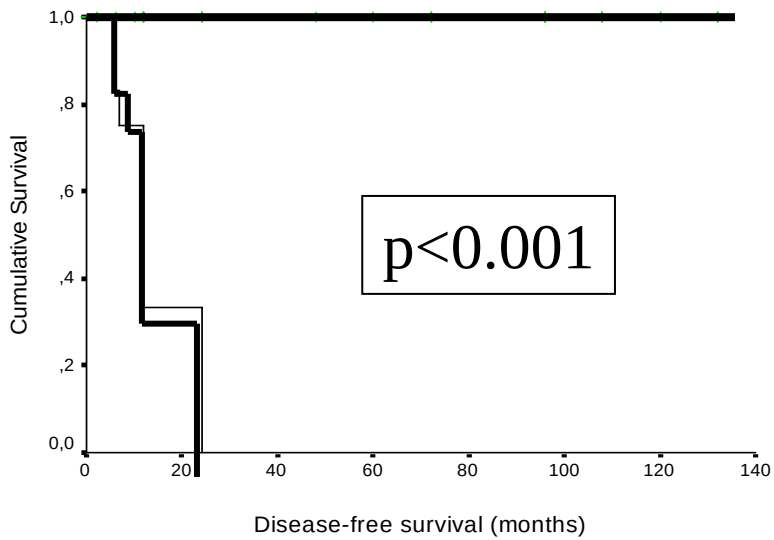
TOR

4E-BP-1

Phos eIF-4E



Rhabdomyosarcoma Survival



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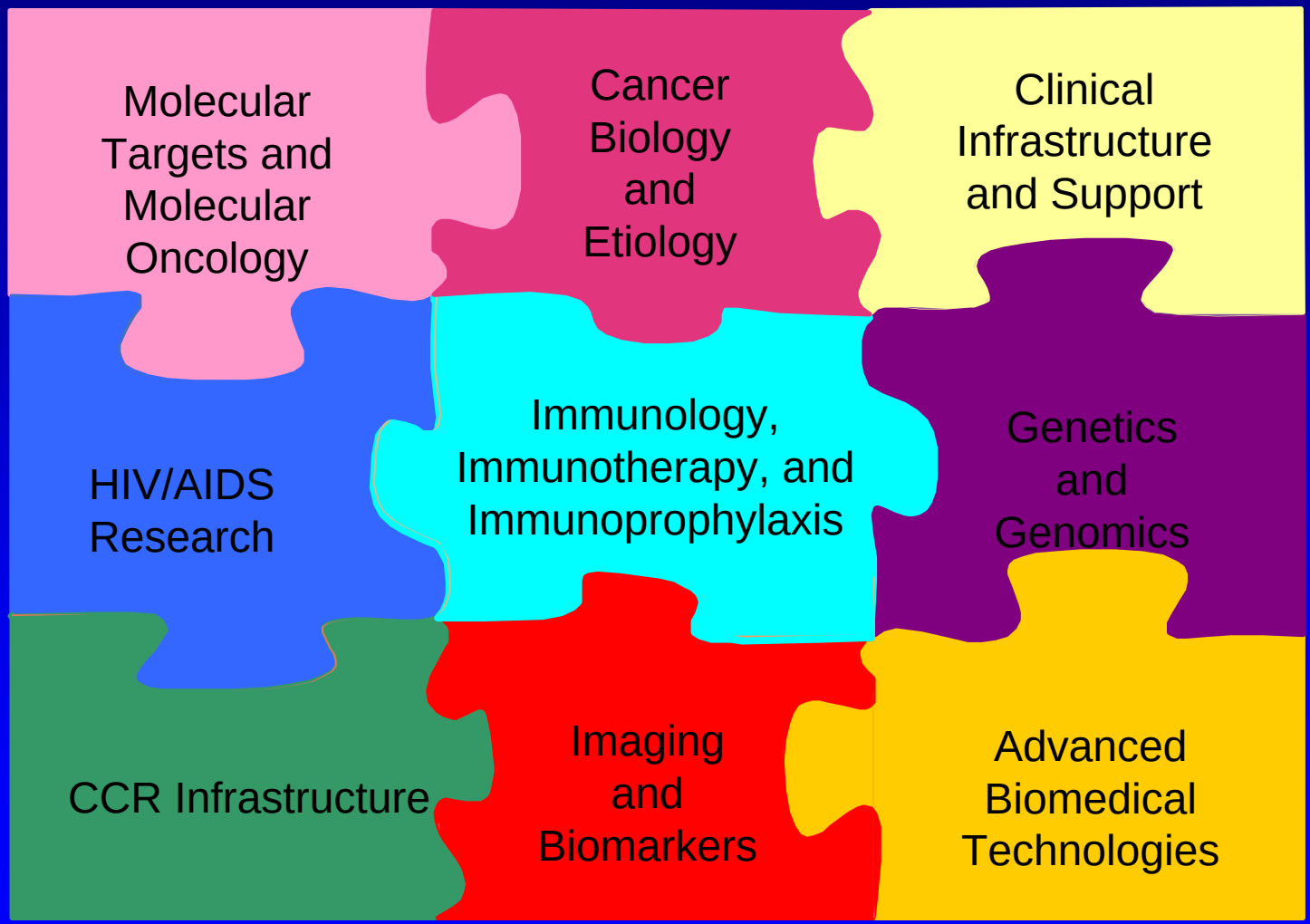
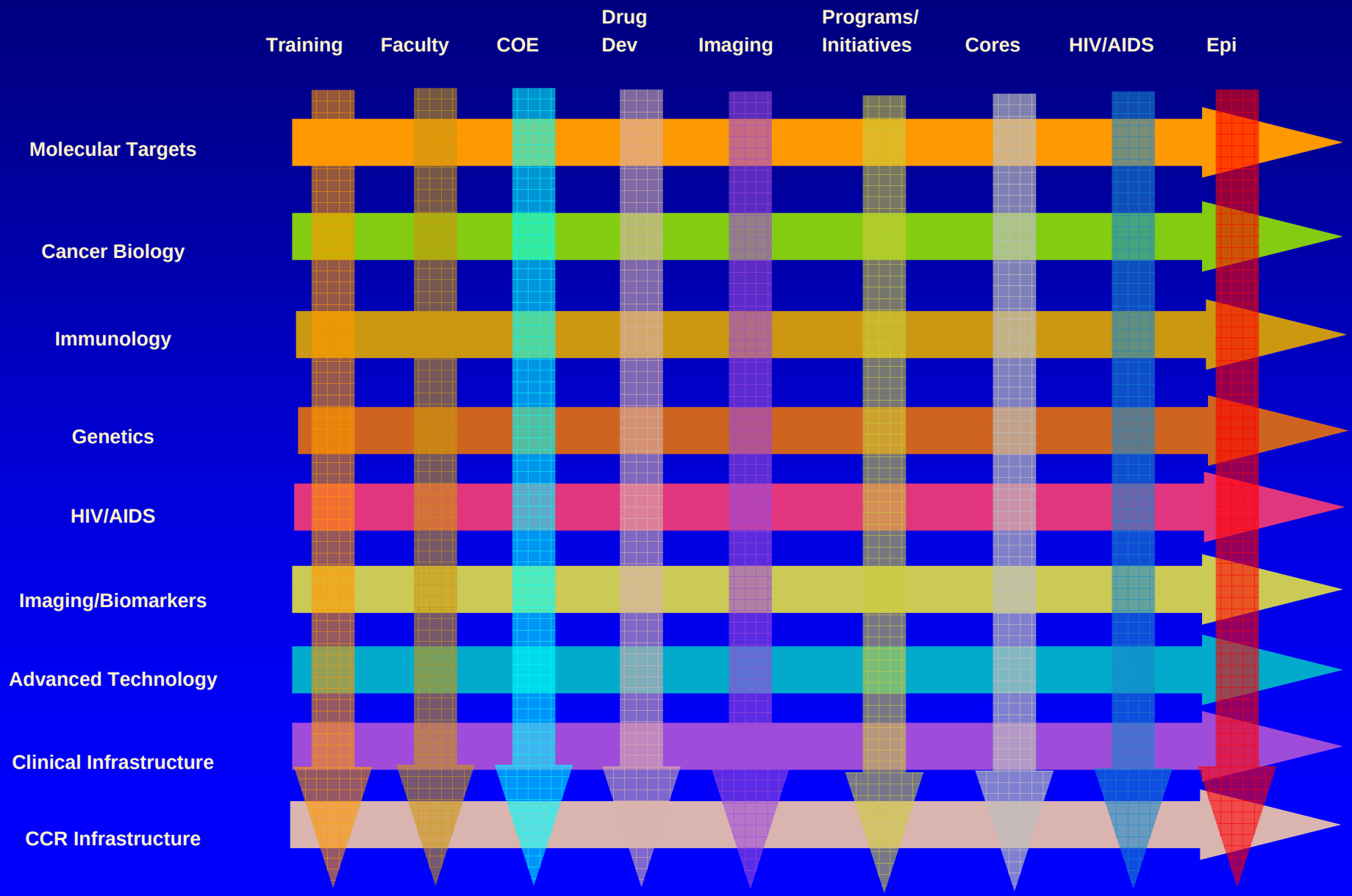
The Center for Cancer Research:
A Comprehensive Translational Research Program



Infrastructure to Support Translational Multidisciplinary Research



Combination Therapies

- Cancer is multistep, multigene process
- Fundamental cancer phenotypes
  - growth, death, immortalization, angiogenesis, metastasis
- Cancer Pathways
- How to test?
- Tumor resistance
- Tumor refractoriness
- Minimize toxicity

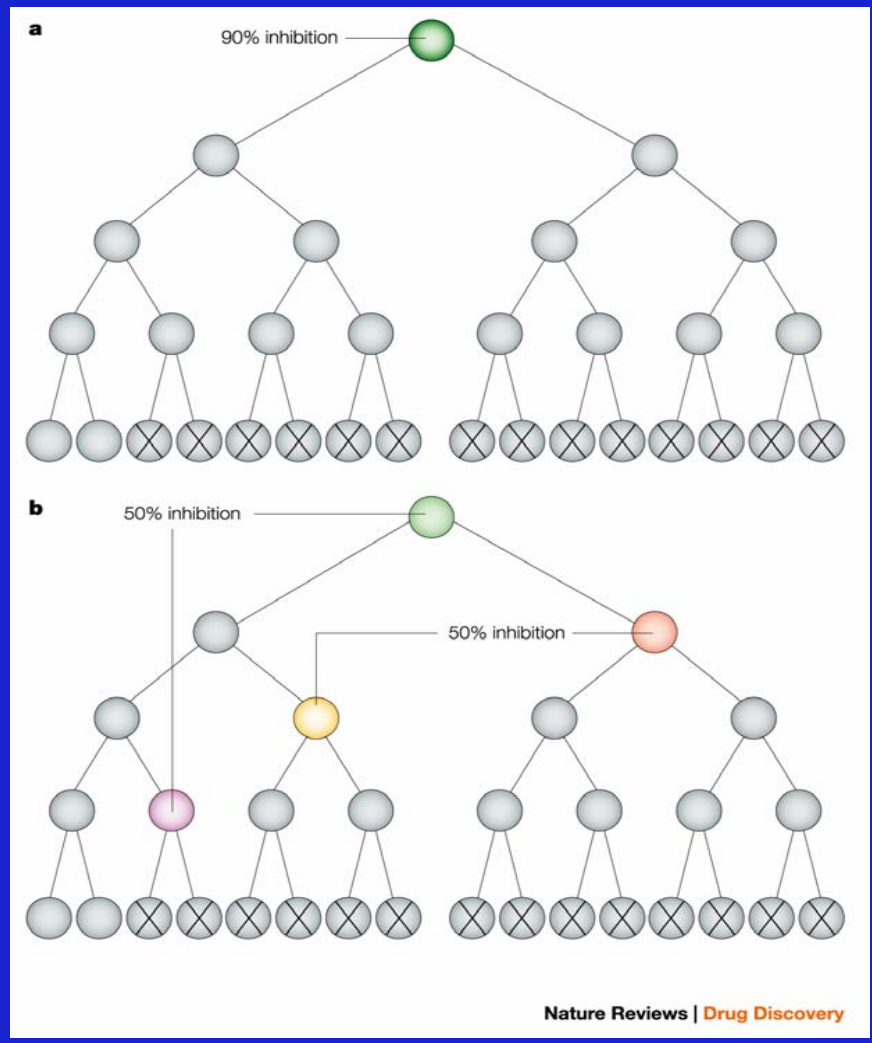
Oncology Drug Toxicity

- If cancer is turned into a chronic disease, treatments/preventions will be long term
- Need methods to detect toxicity in real time/acutely and over time

COMBINATORIAL THERAPY: CAN LESS OF EACH TRANSLATE TO MORE IS BETTER?

Hypothesis:

Partial inhibition at points in serial or parallel pathways may translate into greater therapeutic benefit of new molecularly targeted agents in solid tumors.



Opportunities

- Leverage basic science discoveries to develop combination therapies:
  - Angiogenesis
  - Signal transduction cascades
  - Stromal Cells/Microenvironment
  - Chromatin remodeling
  - Inflammation
  - Radiation

The NCI Intramural Clinical Research Program

- **The NCI intramural clinical program *is not* a large volume, full-service cancer center**

- **The NCI intramural clinical program *is* the largest cancer-focused clinical research center (CRC) in the world, capable of performing patient-intensive clinical research focused on developing new approaches for prevention, diagnosis, and treatment of cancer.**

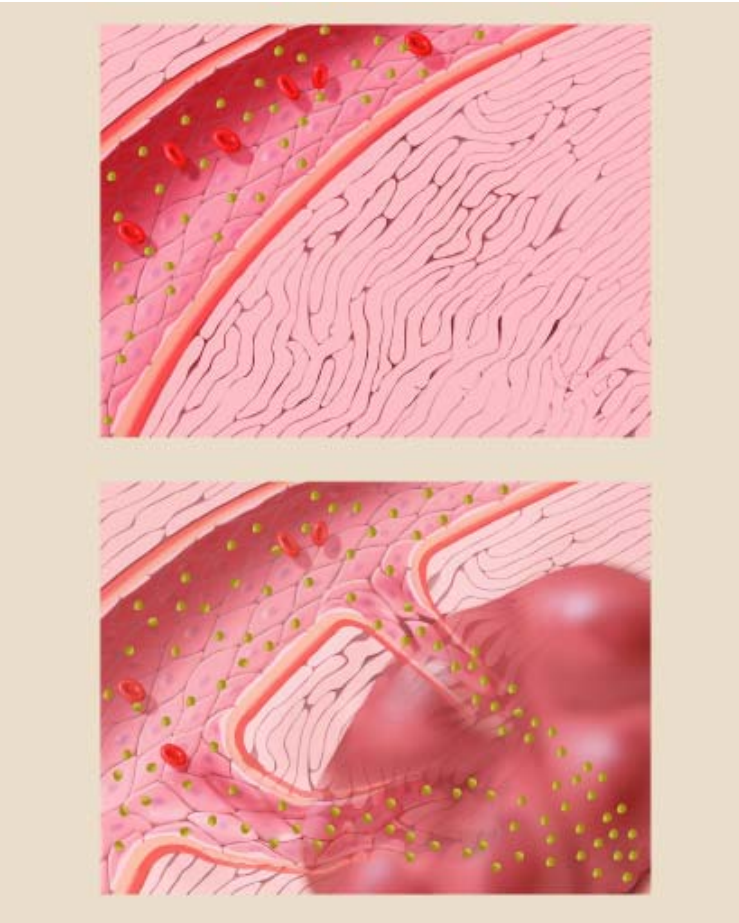
- **The NCI intramural clinical program is an important component of the nation's overall cancer program**

Integrated Imaging Across the NCI

From Molecules to Mice to Man

- Imaging at the sub-cellular and nano-scale in partnership with Industry
- Trans-NCI Initiative to integrate a strong small animal imaging on the Frederick Campus
- Novel non-invasive imaging agents for delivery into the clinical setting to monitor tumor progression

Nanoparticles to deliver therapy:



- Healthy blood vessels

- Leaky blood vessels ***in*** *and* ***around*** tumor

Novel Nanoparticle for Tumor Directed Cancer Therapy: Collodial Gold-TNF

Tumor Necrosis Factor (TNF)

- Cytokine with potent anti-tumor effect
- Cannot be administered systemically
- Used clinically in regional perfusion setting
- Good candidate for targeted delivery to the tumor
- TNF induces vascular permeability & hypercoagulability

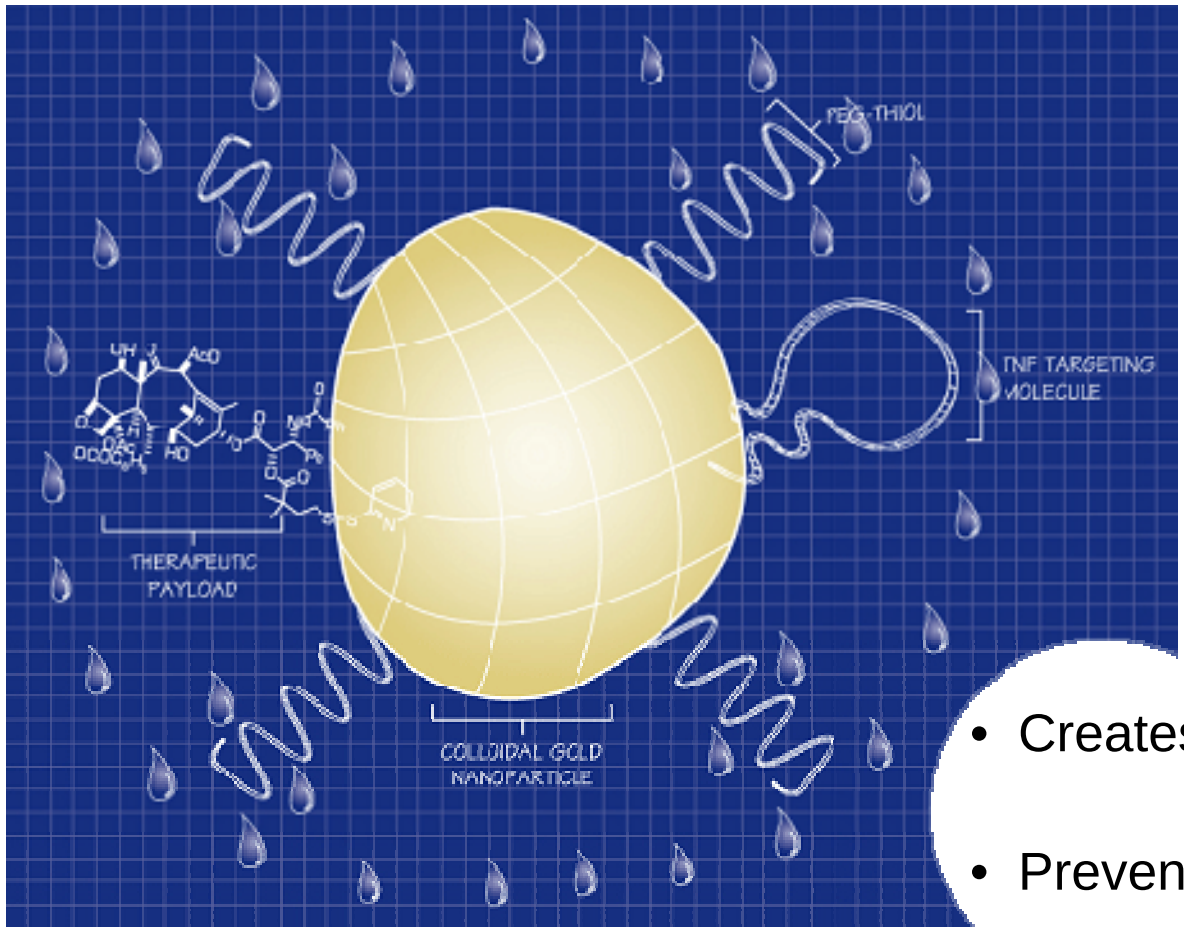
Colloidal Gold

- History of safety (colloidal gold used for 70+ years)
- Tumor targeted
- Improved biodelivery
- Increased efficacy with lower toxicities
- Highly versatile
- Ease of manufacturing

Libutti, CCR

Cytimmune Core Technology:

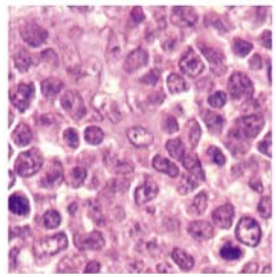
PEG-THIOL Particle Hydration after Intravenous Injection



- Creates a Water Shield
- Prevents Immune Detection

Gene Expression Subgroups of Diffuse Large B Cell Lymphoma Utilize Different Oncogenic Mechanisms

Diffuse Large B Cell Lymphoma

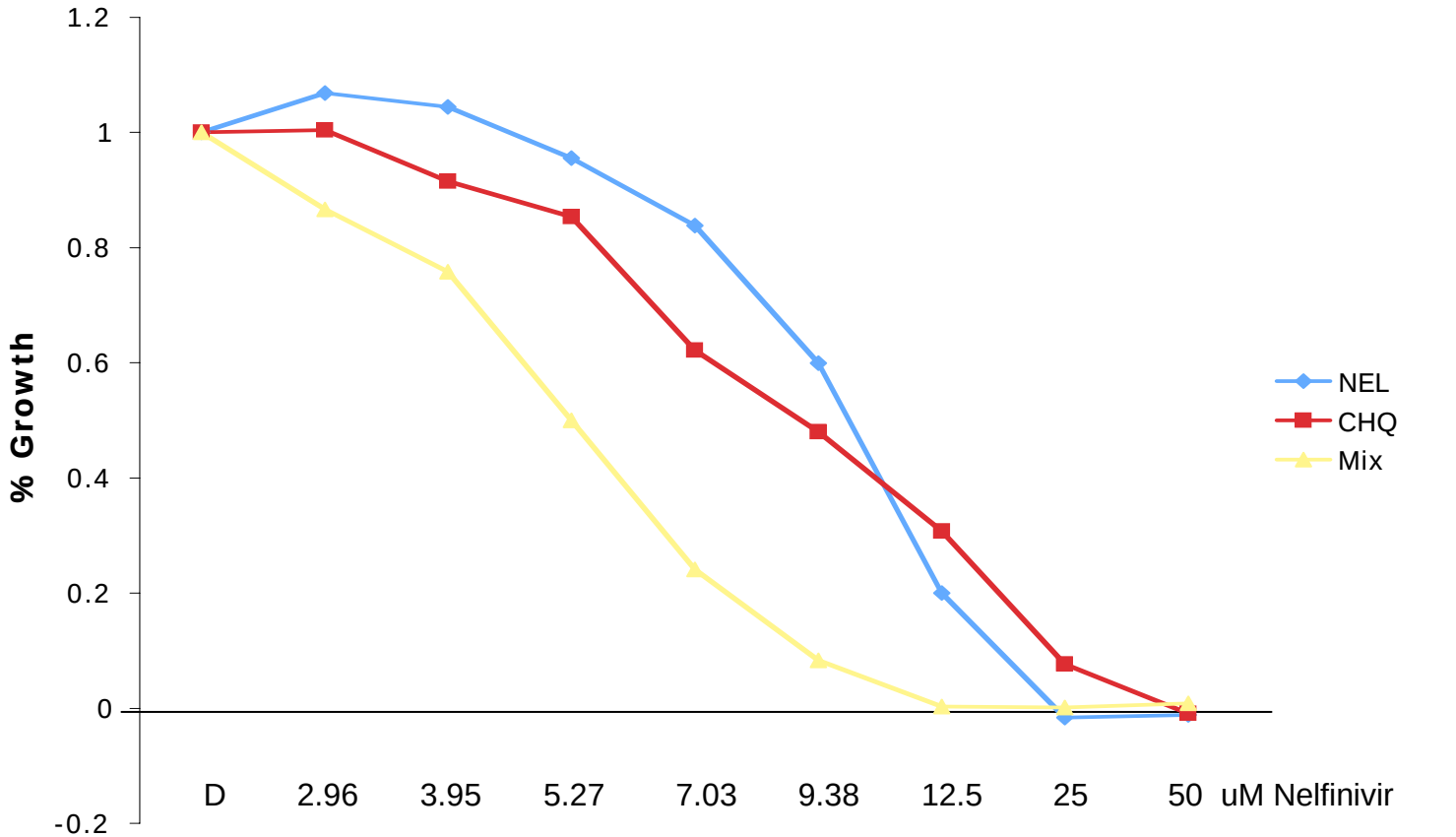


	GCB DLBCL	ABC DLBCL	PMBL
c-rel amplification	16%	0	25%
BCL-2 translocation	45%	0	18%
Gain Chromosome 3q	0	24%	5%
Gain/amp Chromosome 9p24	0	6%	43%
Constitutive NF-κB Activation	–	+	+

Combining a pleotropic agent that induces autophagy (nelfinavir) with an inhibitor of autophagy (chloroquine)

- HIV PI protease inhibitors were screened as anti-cancer agents because their toxicities mimic those observed in mice when Akt is inhibited.
- Nelfinavir was identified as a lead FDA-approved HIV protease inhibitor that inhibits activation of Akt, has broad activity in NCI 60 cell line screen, and induces apoptosis and autophagy *in vitro* and *in vivo*.
- Autophagy is used by tumor cells to escape death, and an inhibitor of autophagy that is unsuitable for human use increases nelfinavir-induced death *in vitro*.
- Chloroquine is a well-known anti-malarial drug that inhibits autophagy.
- Will chloroquine increase nelfinavir-induced death?

Nelfinavir + chloroquine synergistically inhibits proliferation of H157 cells (CI<1.0)



D	2.96	3.95	5.27	7.03	9.38	12.5	25	50 uM Nelfinivir
D	11.95	15.82	21.09	28.13	32.65	50	100	200 uM Chloroquine
CI Value	2.539	1.345	**0.485**	**0.180**	**0.072**	**0.005**	**0.012**	**0.049**

Dennis group, Medical Oncology Branch, CCR

Conclusions

- Because the MTD of nelfinavir as a single agent has never been reached, a Phase I trial at NCI will open soon.
- Based on the MTD in this Phase I trial, a Phase I/II trial combining nelfinavir and chloroquine will be performed.
- Such a trial could help establish the importance of autophagy in cancer therapy.
- Using drugs that are already FDA-approved could decrease the cost and time involved to develop new cancer therapeutics.