Translational Research Working Group

Preparing for or a Revolution: NCI's Efforts in Translational Research

Anna D. Barker, Ph.D.
Deputy Director
National Cancer Institute

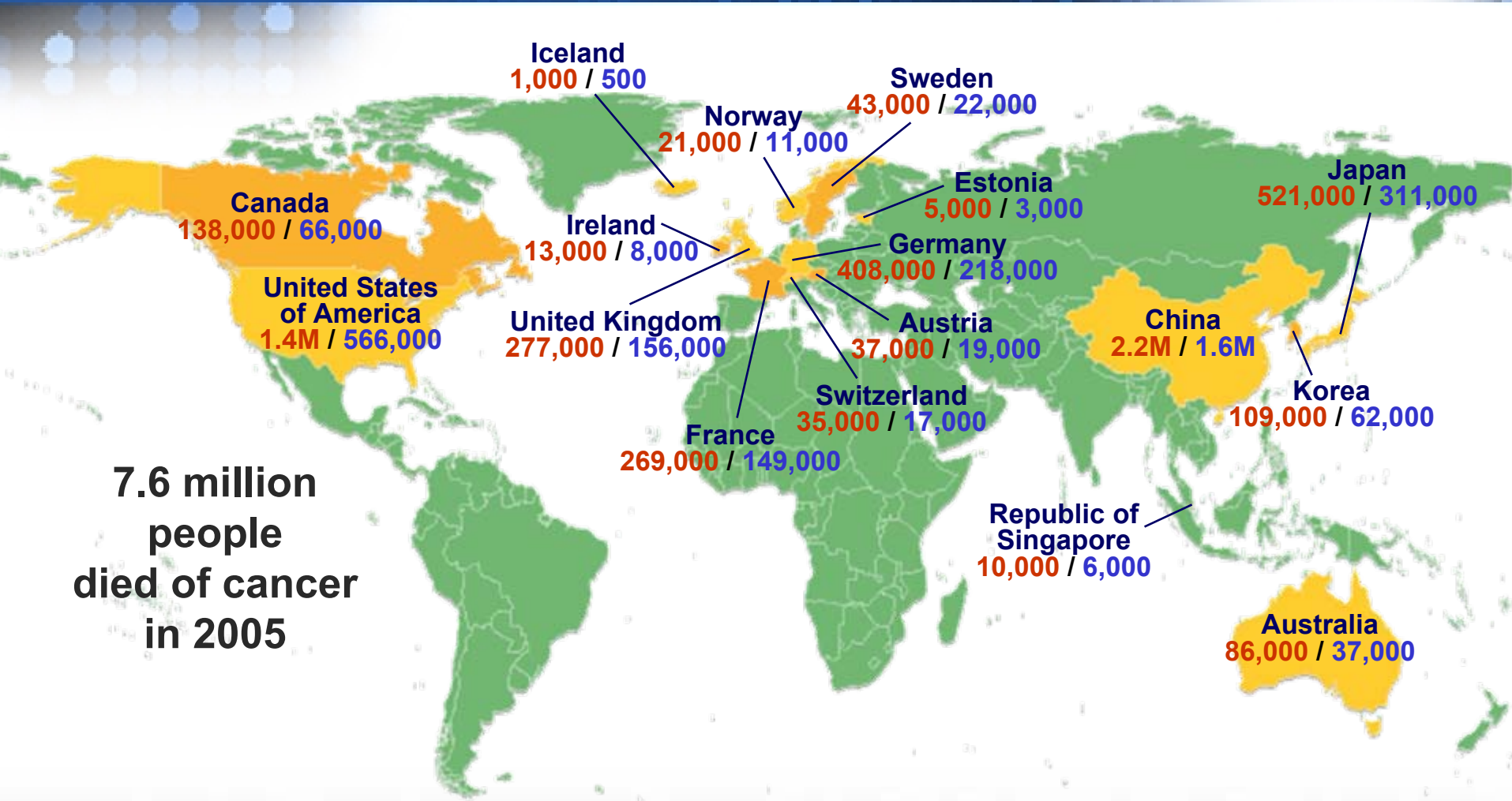
National Cancer Act of 1971

The Beginning!

President Richard Nixon signs
National Cancer Act on December 23, 1971

“Make the Conquest of Cancer a National Crusade”

A National and International Imperative to Eliminate the Cancer Burden



Cancer Incidence / Mortality per year

Source: Derived from International Agency for Research on Cancer, GLOBOCAN 2002 database

The Convergence of Molecular Biology/Genetics, Advanced Technologies, Bioinformatics, and Broadband

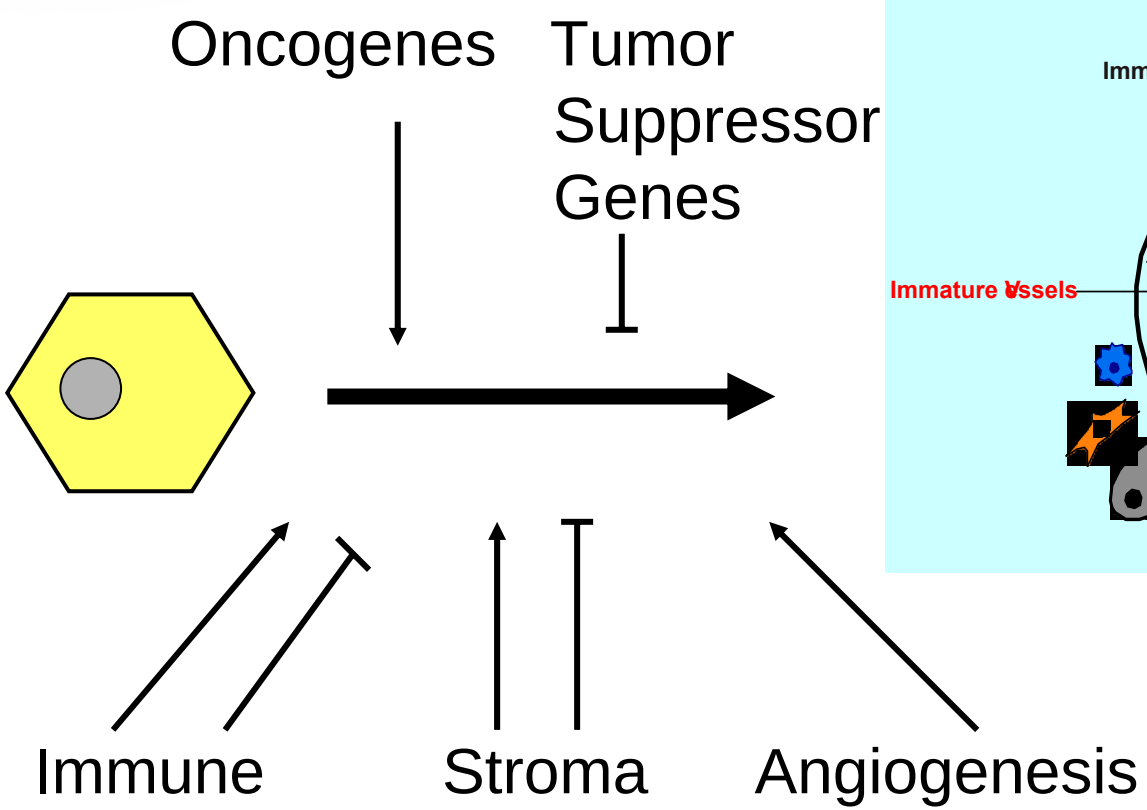
Image courtesy of *Nature*, Feb. 15, 2001

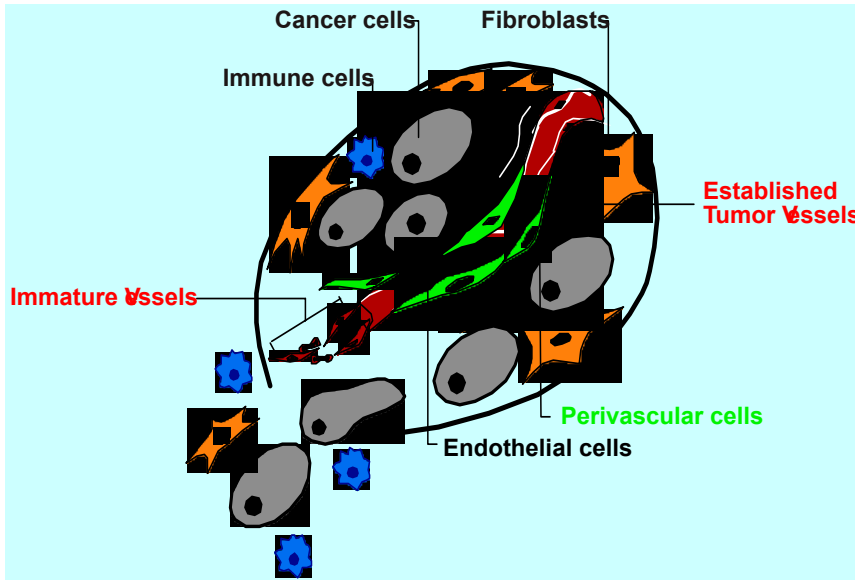
The Possible: Why Translational Research Focus – Why Now?

Advances in Molecular Research and Technologies

The Past Century	21st Century
Established system to treat established disease – a treatment/therapeutic focus (in cancer often too late)	Shift to targeted Interventions for prevention and treatment – shift in focus to early detection and prevention
Morphologic and pathologic diagnosis – drove treatment	Driven by the molecular characterization of disease – mechanistic understanding of pathways and processes
Expensive in all respects – not sustainable in 21st century	Evidence based – preserves human and financial capital – sustainable – Health becomes major national asset
Healthy population not a focus as a major national advantage/asset	

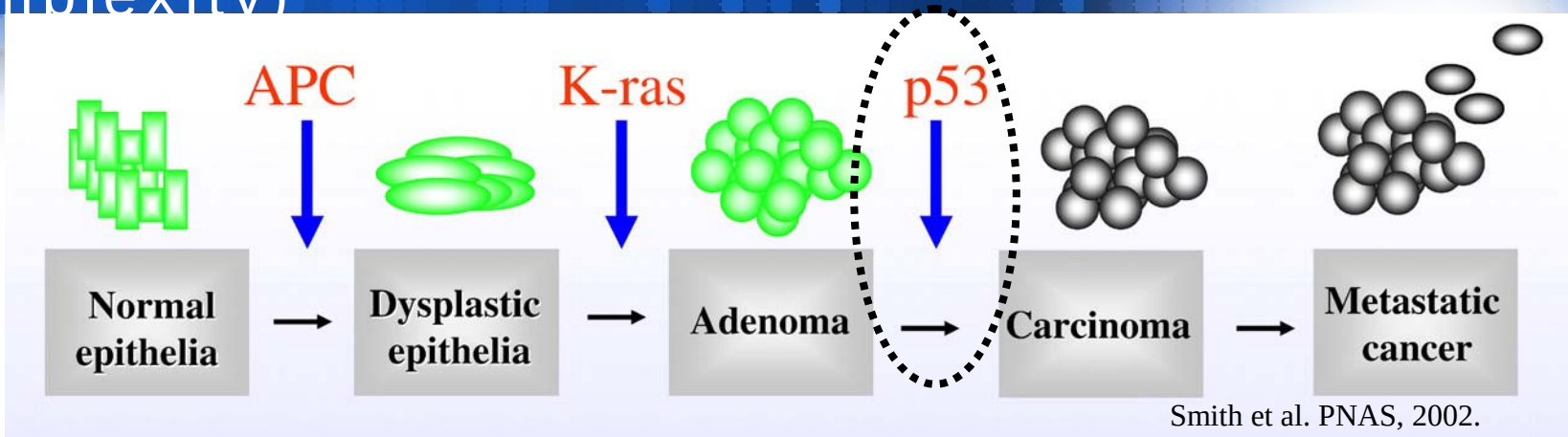
Major Challenge: Cancer's Complexity (Structural Complexity)





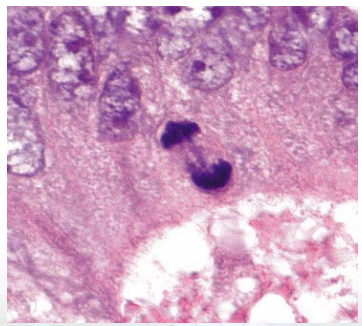
Courtesy Ron DePinho

Major Challenge: Complexity of Carcinogenesis (Multi-Plexed Temporal Complexity)



Smith et al. PNAS, 2002.

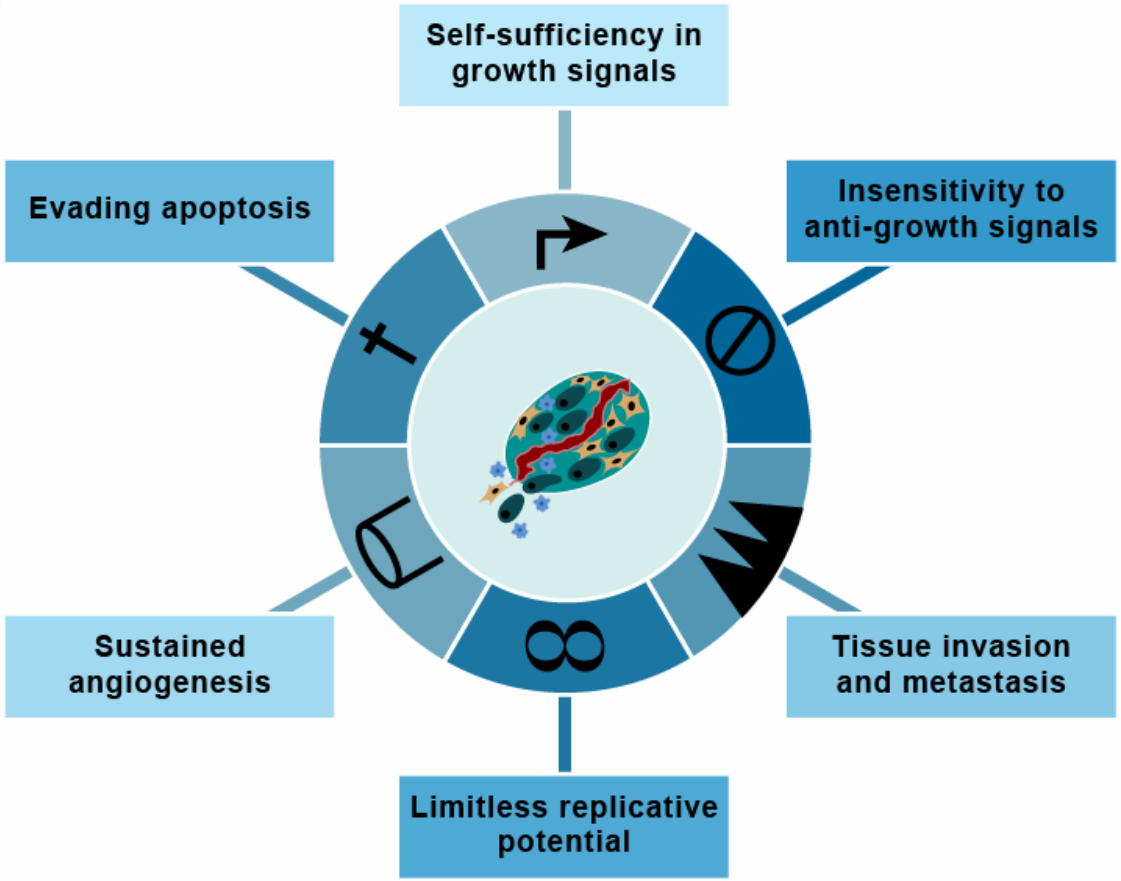
Chr. Structural Aberrations +/- +++ +++



*Colon Cancer

Lenhard Rudolph
Marcus Bosenberg
Slide – Ron Depinho

Major Challenge – Interacting Redundant Processes (Systems Complexity)



Source: Hanahan & Weinberg, Cell 100:57 (2000).

Current Status: High Cost of Complexity

The Enterprise

Large Numbers of Investigators and Research Approaches in Discovery

Significant Overlap and Duplication

Limited Integration of Data to Understand Systems

Slow to Engage Outside Established Disciplines – Form Truly Multi-Disciplinary Teams

Very Limited Infrastructure and Capabilities for Translational Research

Some Consequences

Cancer is a Difficult and High Risk Market - Drugs Fail Often

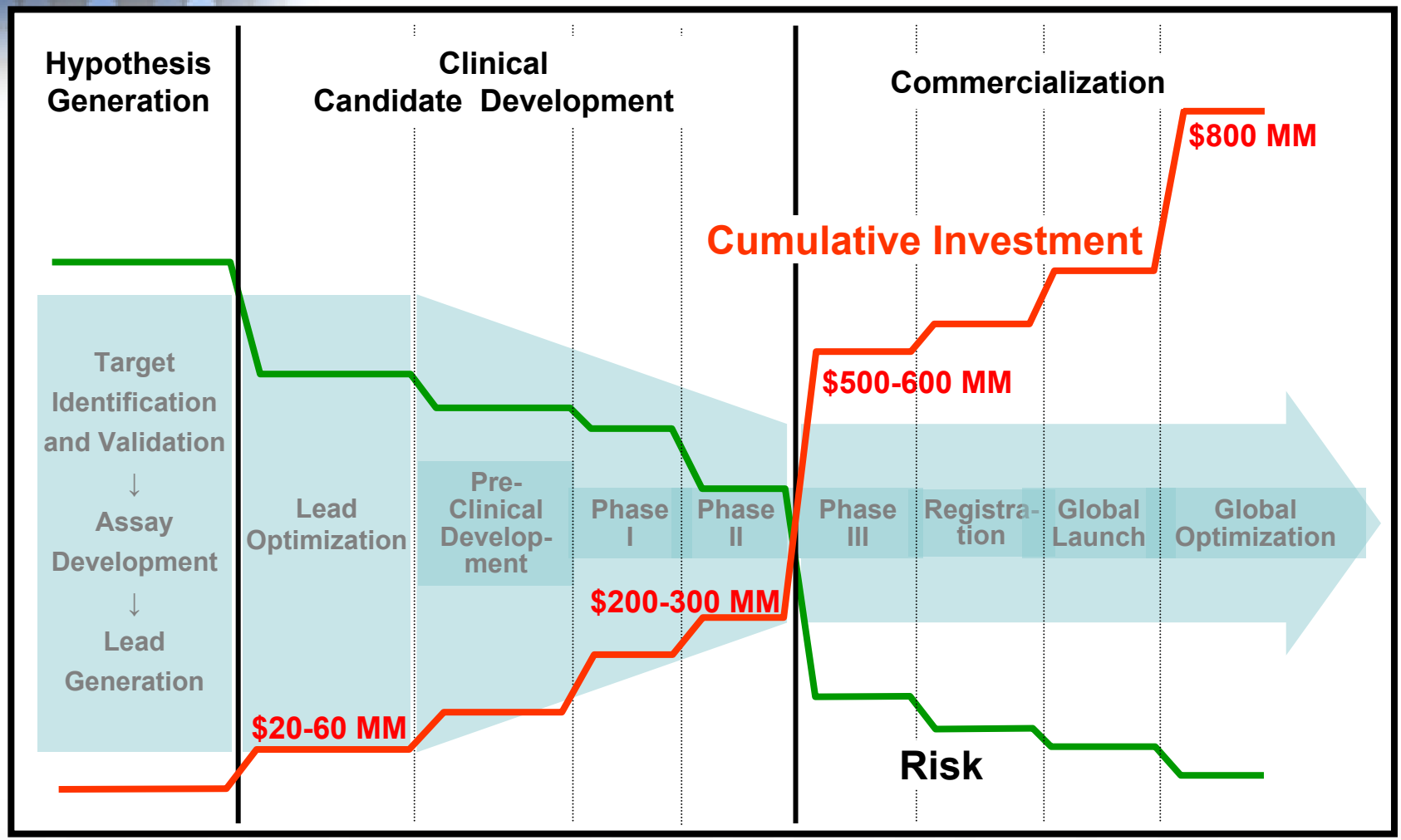
Small Number of Molecularly Targeted Agents

Cancer Diagnosed too Late too Often

Chemoprevention is Stagnant

All of that said – we stand at an inflection point in the conquest of cancer – unprecedented level of understanding – unimagined possibilities for progress (Paraphrased from Andy von Eschenbach - the 2015 challenge)

The Risk/Cost/ Time Development Paradigm



Why the 2015 Challenge – Why Focus on Translation Now?

Prior Progress Coupled with The Doubling of the NIH - and Not Quite Doubling - of the NCI's Budget Produced Enormous Change in Our Understanding of Cancer – Positioned the Field for Translation and Produced –

Absolute Need for Networks – Virtual Connectivity – Common Platforms

Need for Large Scale Science in Selected Areas

Need for Teams

Unprecedented Need for Systems and New Definition of Infrastructure

Opportunities to Leverage Advanced Technologies and Other Fields

Need for End to End Planning and Implementation

Needs for New Multi-Sector Partnerships

Post Doubling: NCI's Resource Base

- Unprecedented number of basic, translational investigators in cancer research
- 61 cancer centers
- 58 SPORES – translational infrastructure
- EDRN
- Major clinical trials infrastructure
- ~200,000 patients in NCI sponsored clinical trials
- Strategic cancer enterprise initiatives

Complimentary Infrastructure, Capabilities, Investment

- National Laboratories
- Regional/state efforts in innovation and biotechnology centers
- Philanthropic investment in cancer and biomedical technologies
- Investment by private sector and venture capital

Enabling Translation: Some Scientific Challenges

- A Compendium of genetic changes in all cancers — germline and somatic (HAPMAP, CGEMs, TCGA in progress)
- Integrated databases of somatic and germline changes to assess risk and stratify populations (Evolving)
- A Clear definition of the array of changes required for transition from very early genetic changes to pre-cancer to cancer
- Definition of the molecular taxonomy of every cancer (biomarkers – NCI SPORES - Clinical Protemics Initiative)- Multiple Philanthropic Efforts)
- Systems biologic understanding of the temporal relationships in the carcinogenesis process (Integrated Cancer Biology Initiative)

Enabling Translation: Some Technical Challenges

- **Specifically detecting very early genomic/proteomic changes in cancer – very early detection**
- **Capability to measure and interpret large number of parameters simultaneously**
- **Bioinformatics platforms – algorithms to interrogate data – pattern recognition – in silico drug discovery, development**
- **Ability to monitor genomic/proteomic changes and molecular and other signaling in real time**
- **Targeted delivery of agents for treatment and/or prevention**
- **Surrogate endpoints of effectiveness of interventions**
- **Multi-plexing of diagnosis, targeting, delivery, monitoring**

Molecular Oncology: NCI's Strategy and Strategic Initiatives

- Sustain and Enable Basic Research, Discovery and Innovation
- Deal with the Data Deluge – Connect the Enterprise - Bioinformatics
- Provide Common Research Infrastructure – Biospecimens, Genomics, Proteomics
- Apply, Provide, Leverage Advanced Technologies – Advanced Imaging, Nanotechnology, Systems Biology
- Optimize Clinical Trials for the New Science
- Ensure Delivery, Outcomes Research, Economic Models
- Build Science-/Based Partnerships with Regulatory Bodies, Foundations and Industry

Cancer Research Enterprise Initiatives to Enable Individual and Large Scale Post Genomics Translational Research

- **Basic Infrastructure**
  - Bioinformatics – caBIG
  - Biospecimens – biobanks
  - Clinical Research - CTWG
- **Common Technology Platforms**
  - Biomarkers - Proteomics*
  - Human Cancer Genome Pilot Project
- **Advanced Technologies**
  - Advanced Imaging
  - Nanotechnology*
- Integrated, Multi-disciplinary Teams, Networks and Partnerships

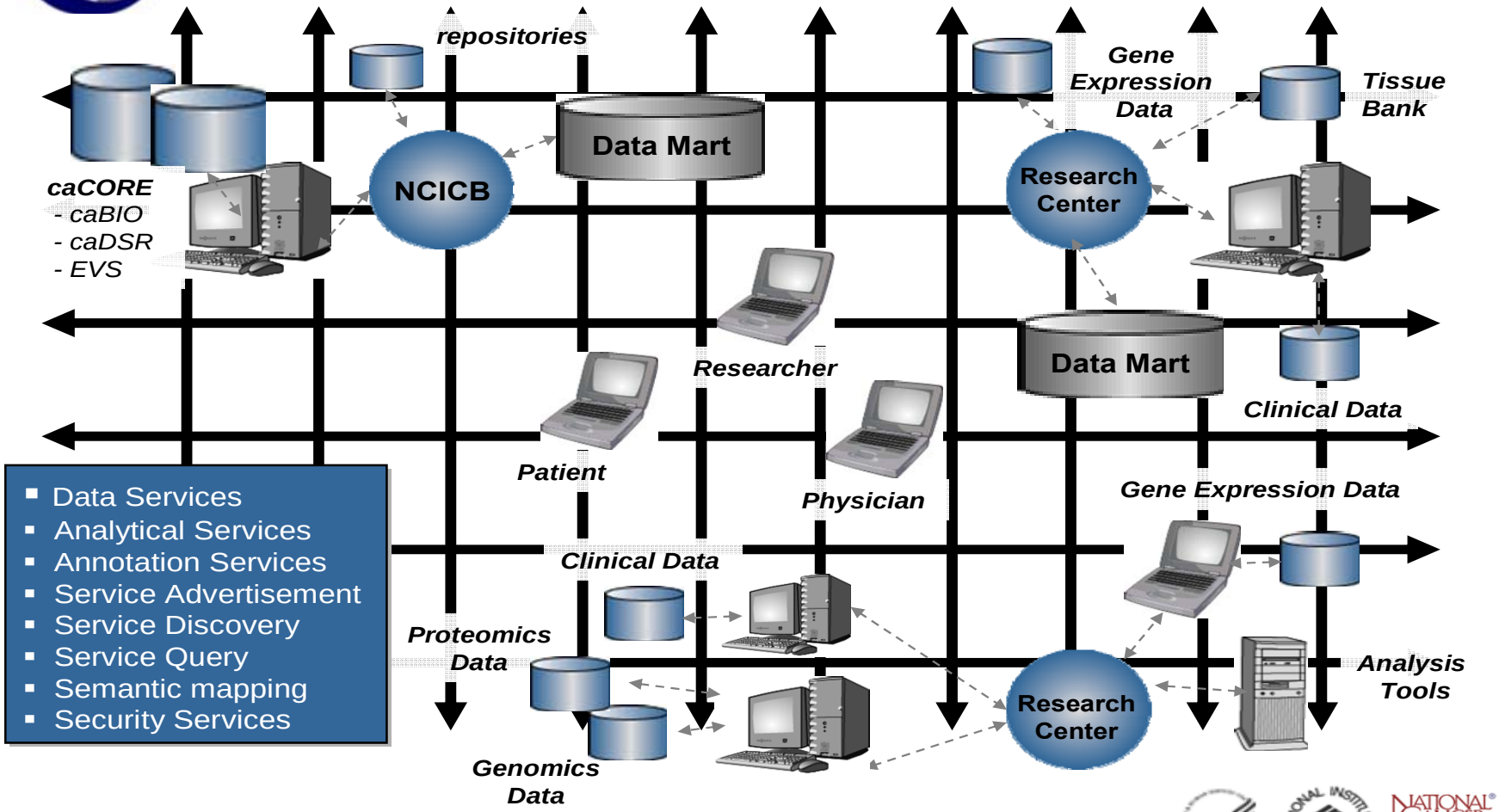
The Cancer Bioinformatics Grid (CaBIG)

- A unifying bioinformatics system
- Empowering systems biology, clinical trials, electronic medical records, etc.
- Open source – “plug and play”
- Rapidly developing connectivity – common language, common software and systems
- Pilots underway in cancer centers
- Standards based– (e.g, clinical trials; biospecimens; genomic and clinical data)
- Public private partnerships

caBIG cancer Biomedical Informatics Grid

Center for Bioinformatics

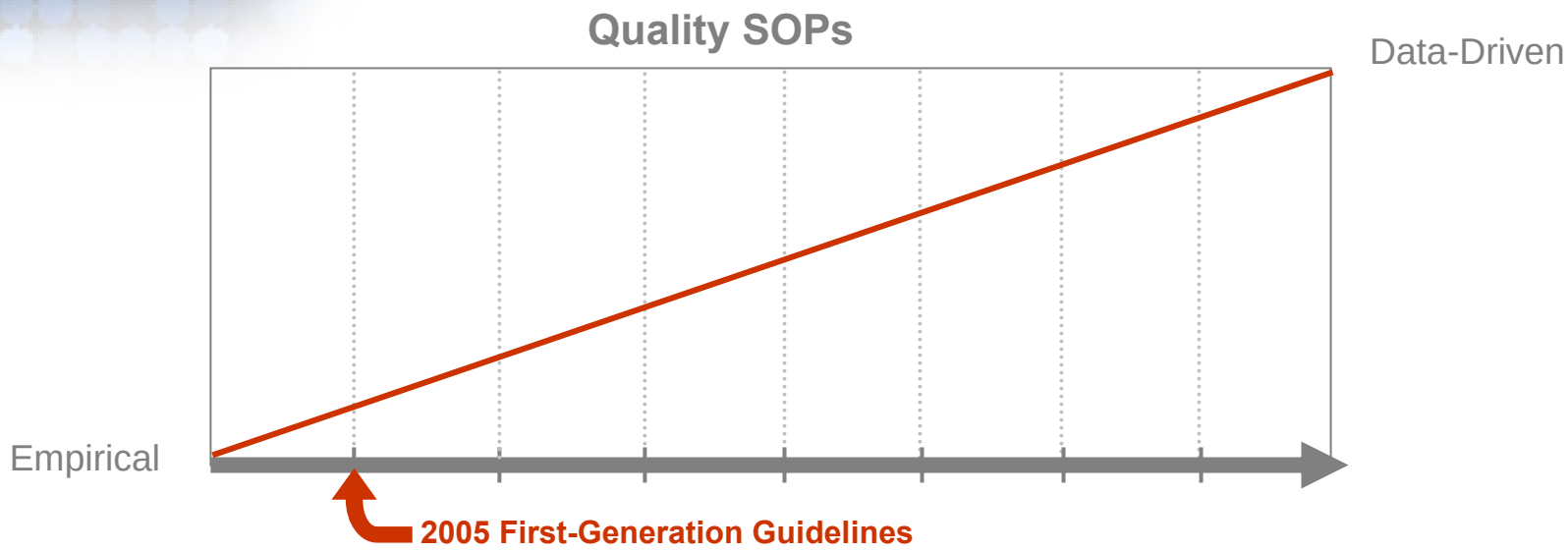
caGrid

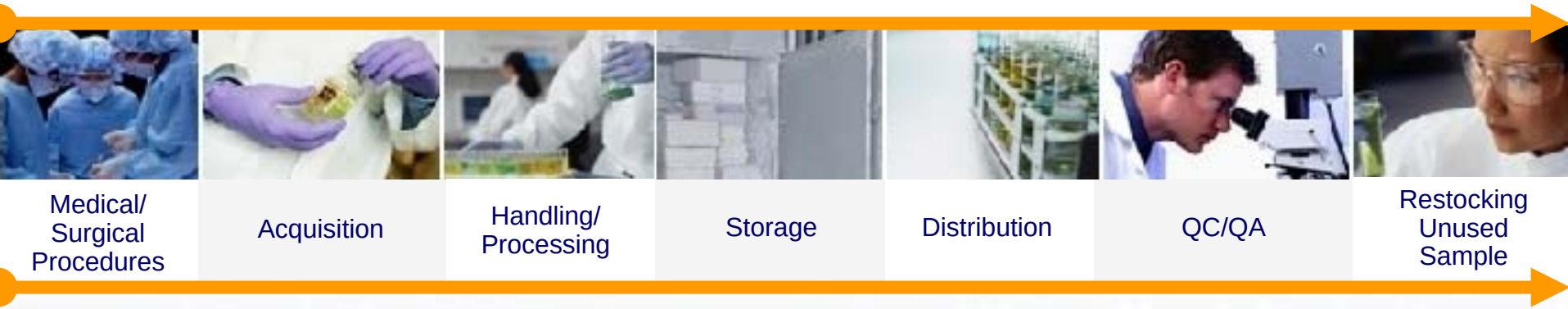


Ensuring Highest Quality Biospecimens for Cancer research

- No unified system with broad access
- Much of tissue collection and/or storage practices not compatible with genomic/proteomic analysis
- Data comparison reproducibility difficult
- HIPAA and legal concerns as data is shared
- “Ownership” barriers - impede tissue sharing among researchers
- Data from tissues sold to companies is not in the public domain
- **NCI is Developing Cancer Enterprise Best Practices/Standards for Biospecimens – 1st Generation Guidelines – 1st Quarter 06**

NCI's Path from First-Generation Guidelines to Evidence-Based Biospecimens/Biobanks





NCI's Strategy for Biospecimens: Build a National Network – Harmonize Internationally

- **NCI Goals for 2006 and Beyond:**
  - **Large numbers of high-quality, clinically annotated samples**
  - **Diversity of cancer types and populations**
  - **Pathology and clinical (including longitudinal) annotation of specimens**
  - **Access through a centralized peer-review process**
  - **Management of ethical and legal issues for a chain of trust**
  - **Resources provided without intellectual property restrictions**
  - **Best practices-based SOPs for reproducible results**
  - **Bioinformatics infrastructure for building *in silico* capability**

The Cancer Genome Atlas Pilot Project (TCGA)

Goal: A three-year pilot to address key questions to determine the feasibility of a full-scale project that will ultimately facilitate the development of a complete "catalogue" of all genetic alterations in cancer

Enabling Factors:

- Significant knowledge base resulting from the NCI's investments in understanding molecular biology and genetics of many cancers
- Reference sequence from the Human Genome Project
- Rate of progress of genomics analysis technologies - $1,000 genome sequencing looking possible
- NHGRI's complimentary high throughput projects and investments

Key Emerging Issue for TCGA

- Biospecimens and data release are key issues:

- The ideal for biospecimens:
  - source - clinical trial (simple vs. complex)
  - fresh frozen
  - matched normal and blood
  - sufficient quantity
  - single histopathologic type
  - single grade and single stage
  - low contamination

- The ideal for data release – open, immediate, pre-competitive – public policy-enabled

The Promise of Biomarkers for Molecular Oncology

- New **target discovery** (understand underlying biology)
- Drug **development** – markers of toxicity, metabolism, etc.
- **Early detection** (broad or specific detection / corroboration of specific disease stage)
- Identify **molecular basis of disease phenotypes**
- Assessment of disease **aggressiveness**
- **Rational** choice of **treatments**
- **Assessment** of treatment **effectiveness**
- **Prevention markers**

Proteomics – Major Barriers to Sensitivity, Reproducibility and Discovery *

(No technology currently interrogates more than 1% of the proteome)

A. Gel Based

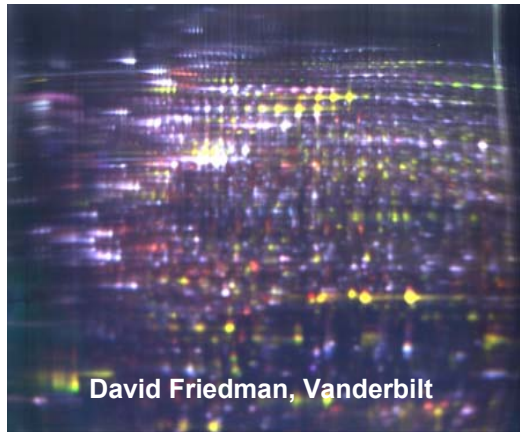
- 2-D Gel electrophoresis
- LC / LC / Gel electrophoresis

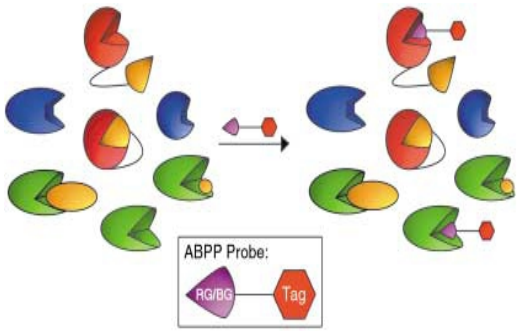
B. Mass Spectrometry Based

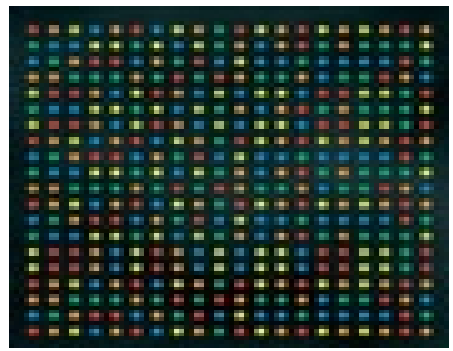
- LC proteins - MS / MS protease derived peptides
- LC / MS / MS - complex peptide mixtures
- MALDI MS – direct tissue analysis, activated surfaces

C. Chip / Array Based

- Antibody probes
- Activity based probes
- Chemically activated surfaces







No Lack of Standards –Everyone Has One

* Slide from Richard Caprioli

NCI Clinical Proteomics Initiative

- Broad consortia to **standardize samples, proteomics technologies and develop protocols using common and specific models**
- Multidisciplinary teams
- Coordinated and virtually integrated
- Real time data exchange – broad access - reproducibility
- Large numbers of standardized antibodies
- Standards development
- High throughput capabilities
- Funds to drive proteomics technology development
- Common data capture, analysis, and interrogation platforms

Creating the Future – New Thinking – New Science

Nanotechnology

Advanced Imaging

RX/DX

Networks

Regulatory Science

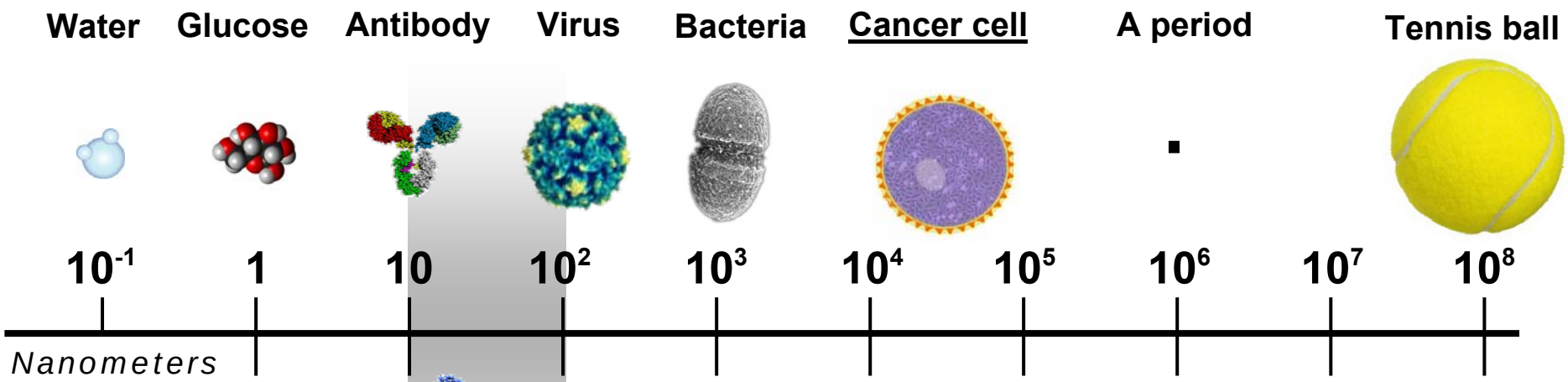
Why It's the Right Time for Advanced Technologies – e.g., Nanotechnology, Molecular Imaging

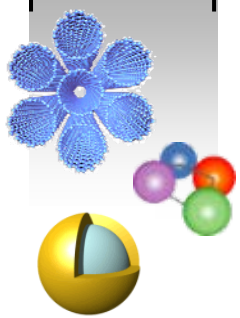
- **Understanding of cancer at the molecular level is progressing exponentially**

- **Nano-based devices and drugs for cancer and all diseases are increasing – a direct result of private investment***
  - 68% increase in the clinical pipeline from 2005
  - 130 nanotech-based drugs and delivery systems
  - 125 devices or diagnostic tests

* Source: 2006 Nanomedicine, Device & Diagnostic Report, National Health Information, LLC.

Nanotechnology in Perspective





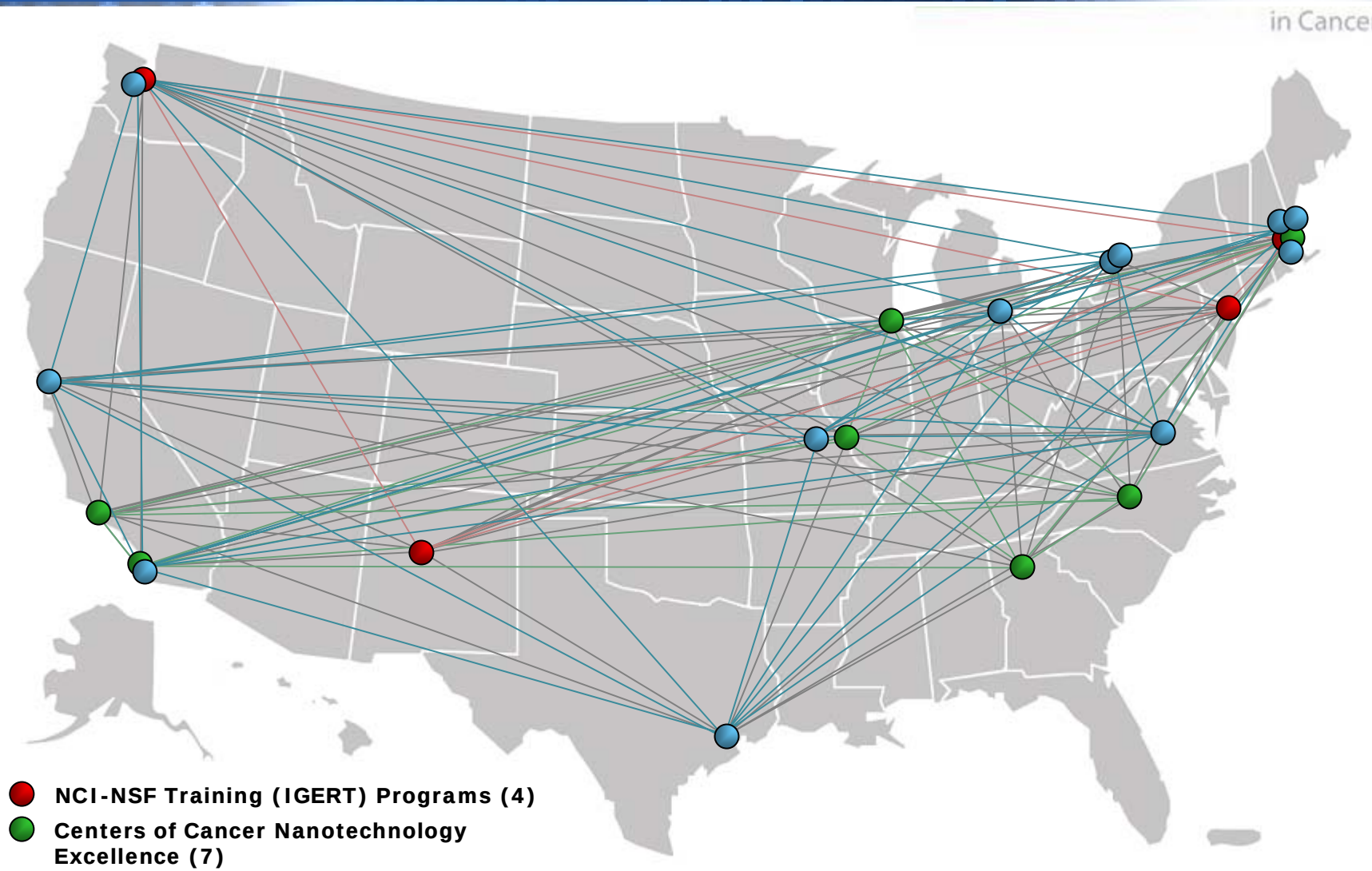
Nanodevices:

Nanopores
Dendrimers
Nanotubes
Quantum dots
Nanoshells

NCI Launched the Alliance for Nanotechnology in Cancer in 2004

- Designed to “ignite” team building, nano-product development and commercialization
- Encompasses public and private sectors
- **Six key areas of focus:**
  - **Molecular Imaging and Early Detection**
  - ***In Vivo* Imaging**
  - **Reporters of Efficacy**
  - **Multifunctional Therapeutics**
  - **Prevention and Control**
  - **Research Enablers**

NCI' Nanotechnology Alliance



- NCI-NSF Training (IGERT) Programs (4)
- Centers of Cancer Nanotechnology Excellence (7)
- Cancer Nanotechnology Platform Partnerships (12)

Sample of Current Alliance Projects

- Novel semiconducting nanocrystals for cancer detection *(MIT-Harvard CCNE)*
- Ultrasensitive chemical probing at the single molecule level using surface enhanced Raman scattering in local optical fields of gold nanoparticles *(MIT-Harvard CCNE)*
- Molecular beacons and activatable probes for cancer detection and analysis *(Emory-GT CCNE)*
- Multiplexed Raman nanotags for cancer molecular profiling *(Emory-GT CCNE)*
- Ex vivo sensors and “phenotypers” for cancer cells *(UCSD CCNE)*
- Nanofluidics devices for rapid single cell analysis *(UNC CCNE)*
- Development of bio-barcode assays for early cancer detection *(Northwestern CCNE)*

Nanoproducts Under Development

Product	Type of nanomaterial	Indication	Phase	Company
AmBisome	liposome	fungal infections	approved	Gilead Sciences
Doxil	pegylated liposome	metastatic ovarian cancer	approved	OrthoBiotech
VivaGel	dendrimer	topical microbicide for HIV	Phase I	StarPharma
MRX-952	branching block copolymer self-assembled nanoparticulate formulation of irinotecan metabolite	oncology	preclinical	ImaRx Therapeutics
Definity	lipid-encapsulated octofluoropropane nanospheres	echocardiogram contrast agent	approved	ImaRx/BMS
MRX-815	nanobubbles	vascular thrombosis	Phase I	ImaRx
Abraxane	nanoparticulate albumin	non-small cell lung cancer, breast cancer, others	NDA filed	American Pharmaceutical Partners
Cyclosert-camptothecin	cyclodextrin nanoparticle	metastatic solid tumors	IND filed	Insert Therapeutics
TNT-Anti-Ep-CAM	polymer-coated iron oxide	solid tumors	preclinical	Triton BioSystems
Rapamune	nanocrystalline drug	immunosuppressant for kidney transplantation	approved	Elan/Wyeth
Emend	nanocrystalline drug	nausea	approved	Elan/Merck
Leunesse	solid lipid nanoparticles	cosmetics	on market	Nanotherapeutics
Verigene platform	DNA-functionalized gold nanoparticles	diagnostics	on market	Nanosphere
INGN-401	liposome	metastatic lung cancer	Phase I	Introgen
Combidex	iron oxide nanoparticle	tumor imaging	NDA filed	Advanced Magnetics

Source: M. Ferrari, G. Downing, Biodrugs 19, 203 (2005)

Early Detection of Cancer

Nanotechnology-based sensors

- **Potential for use in genetic and protein-based monitoring of cancer processes**
  - High sensitivity and specificity
  - Label-free detection
  - DNA and protein detection on the same platform
  - *In vivo* localized sensing

Development of BarCode Assays for the Detection of Ovarian Cancer

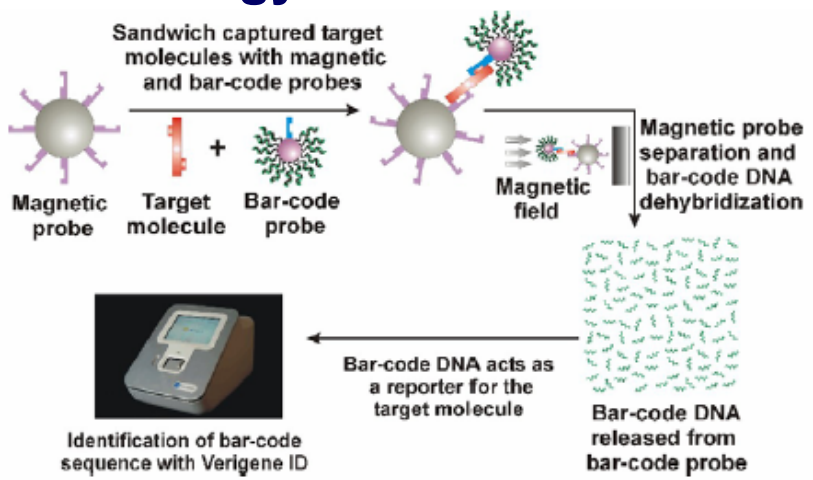
Problem

- Ovarian cancer is the leading cause of gynecologic cancer death
- With early diagnosis, the cure rate is high. However, ~70% of patients present in later stages of the disease
- Better biomarkers with higher sensitivity are needed

Approach

- Nanoparticle-based bio barcode assay allows for the identification and study of protein markers at concentrations many orders of magnitude lower than conventional assays

Technology

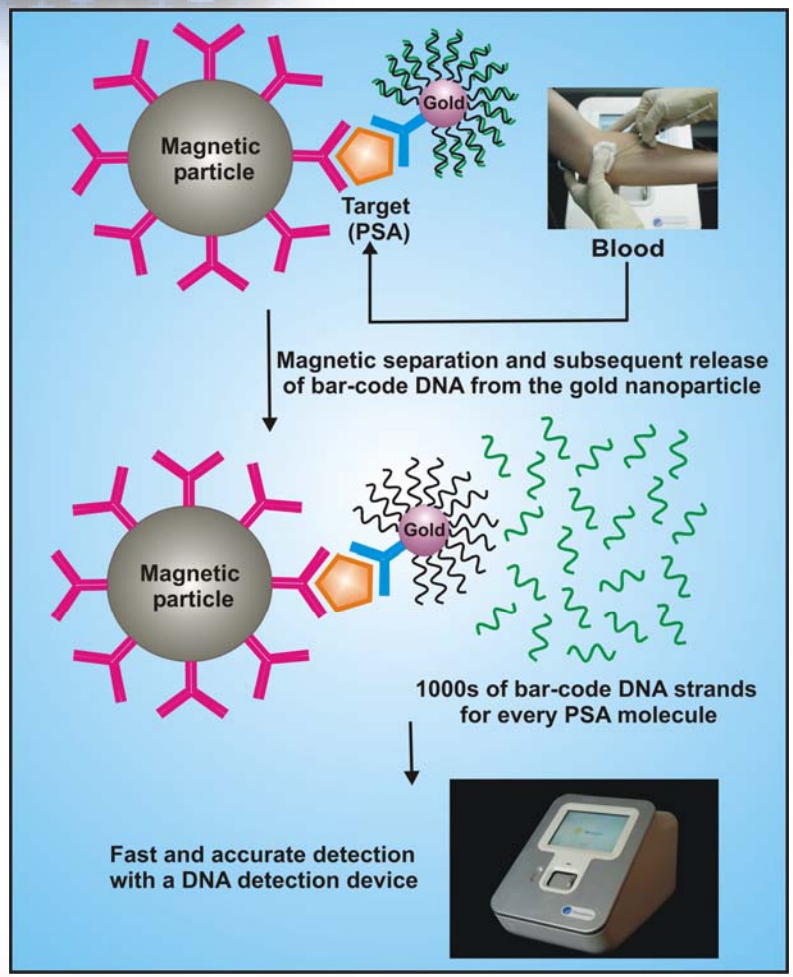


Goal

- Use bio barcode assay to develop a gynecologic oncology screening tool capable of identifying patients in early stages of ovarian cancer or cancer recurrence (simple, sensitive, highly multiplexed)

Northwestern University CCNE
Contribution: Chad A. Mirkin, Ph.D.

Multiplexed, High Sensitivity Detection of Protein Cancer Markers with Bar Code Assay



- 10^4 - 10^6 more sensitive than ELISA
- Changing what proteins we look for and where we can look for them in terms of disease detection.
- One platform that can detect protein and nucleic acid markers with the sensitivity of PCR

Northwestern University CCNE
Contribution: Chad A. Mirkin, Ph.D.

The Future: Integrating Diagnosis and Treatment – Enabling Personalization (Rx/Dx)

- **Diagnostic and therapeutic procedures are disconnected – Different businesses**
- **Patient's genotypic and other data unavailable and/or unconnected to clinical data**
- **Diagnosis can take a long time**
- **No pre-knowledge of optimum drug/patient - long periods of unnecessary side effects**
- **Must identify right patients for right drugs (i.e., Gleevec® , Herceptin®)**
- **"Lab-on-a-Chip" -** potentially deployable at point of care
- **Multifunctional nanoparticles** - enable "real time" monitoring and personalization

Building Networks for Translational Research

...Discoveries in basic cancer research over the past 30 years have produced breakthroughs such as the human genome, transcriptome and the emerging proteome

….Advanced technologies and bioinformatics have set the stage for unprecedented progress against cancer

….We face different barriers to optimize and accelerate these advanced cancer technologies into effective interventions for patients

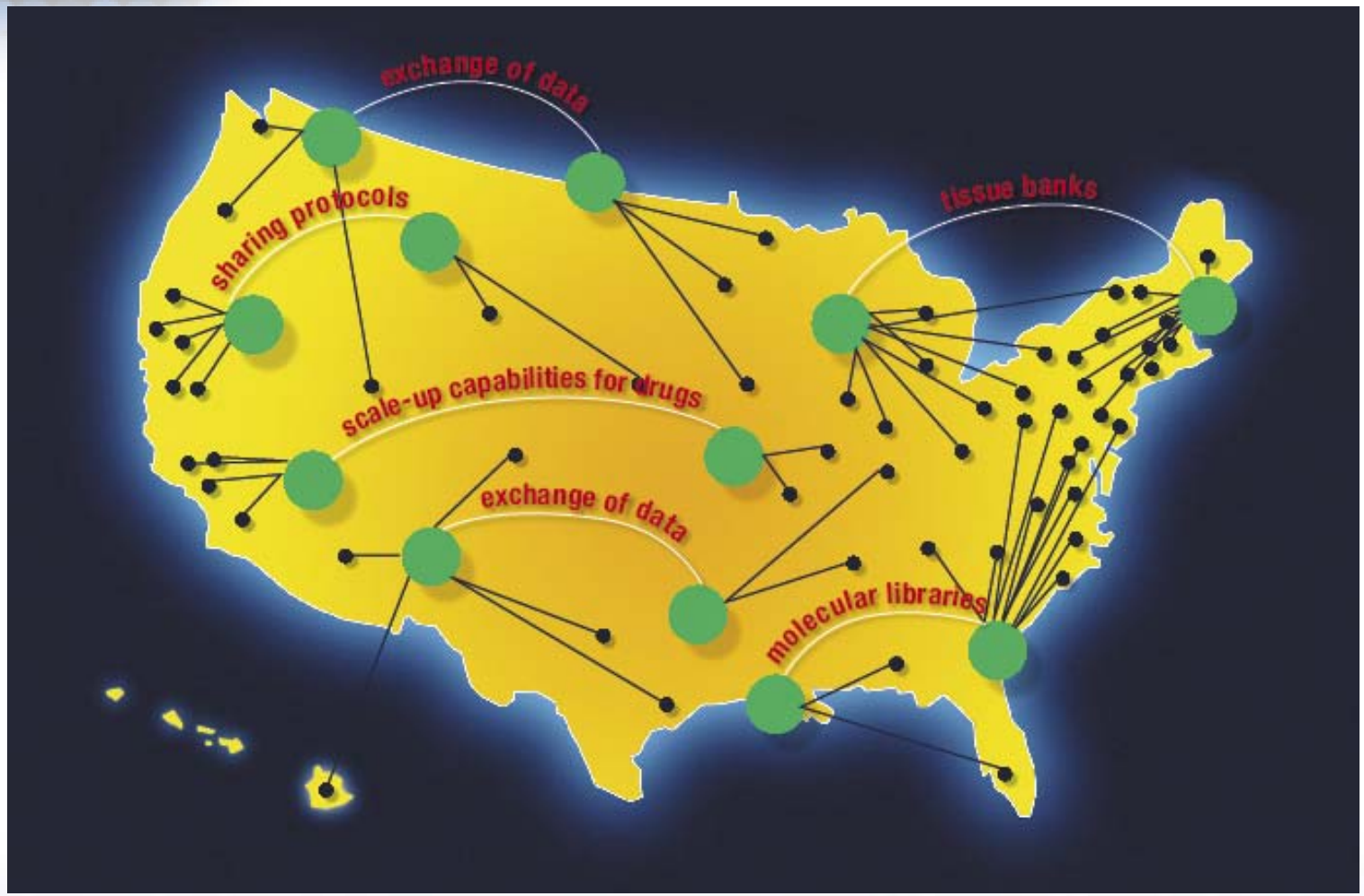
… There is no system to optimize and leverage this vast portfolio of resources

…Real time interactive networks will be the working translational and development model for the future

…A "network of networks" is needed to capitalize on prior investments and current scientific and technology opportunities

…Virtual networks will enable development and multi-sector partnerships - drive progress and regional economic growth

NCI's Concept for a National Advanced Technology Initiative for Cancer - A Nationwide Virtual "Network of Networks"



NCI – FDA Interagency Oncology Task Force (IOTF)

Science to Optimize Cancer Drug Development and Throughput*

- Interagency Agreement – FDA/NCI Partnership – May, 2003*
- Process Enhancement – Exploratory INDs for Small Molecules; New GMP Regulations for Experimental Agents.
- Biomarkers Qualification –Imaging Endpoints; Biomarker-Driven Diagnostics; Biochemical Endpoints
- New Common Bioinformatics Platforms – Standards for Clinical Trails Submissions; e-INDs; CRIX Project
- Advanced Technologies - Critical Path Initiatives (Nanotechnology and Molecular Diagnostics)
- Training and Joint Appointments – 3 Training Programs for Ph.Ds and MDs

*** Using FDA's Critical Path**

National Cancer Act of 1971

The End of the Beginning; The Middle; The Beginning of the End?

President Richard Nixon signs
National Cancer Act on December 23, 1971

“Make the Conquest of Cancer a National Crusade”