

Accelerating Cancer Diagnosis and Drug Development

TURNING MOLECULES INTO

medicines

The Use of Acquisition Resources to Achieve the Goals of DCTD

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DEVELOPMENTAL THERAPEUTICS PROGRAM
DIVISION OF CANCER TREATMENT & DIAGNOSIS

<http://dctd.cancer.gov/>



Mission Statement / Functional Statement of DCTD

- ❖ To improve the lives of the American public by discovering and conducting better ways to diagnose, assess, treat and cure cancer through stimulating, coordinating and funding a national program of cancer research.

Type of Acquisition Mechanisms Used to Support DCTD's Goals

- ❖ Grants
 - ★ R01, P01, P20, P50, etc.
- ❖ Contracts
 - ★ N01, N02
 - ★ WA-Managed, Completion, LOE
 - ★ 44 in DTP for drug development
- ❖ Cooperative Agreements
 - ★ U10 (Coop Grps), U19 (NCDDGs),
- ❖ SBIRs/STTRs (R41/R42, R43/R44)
- ❖ FFRDC (SAIC-F) Contract & Subcontracts

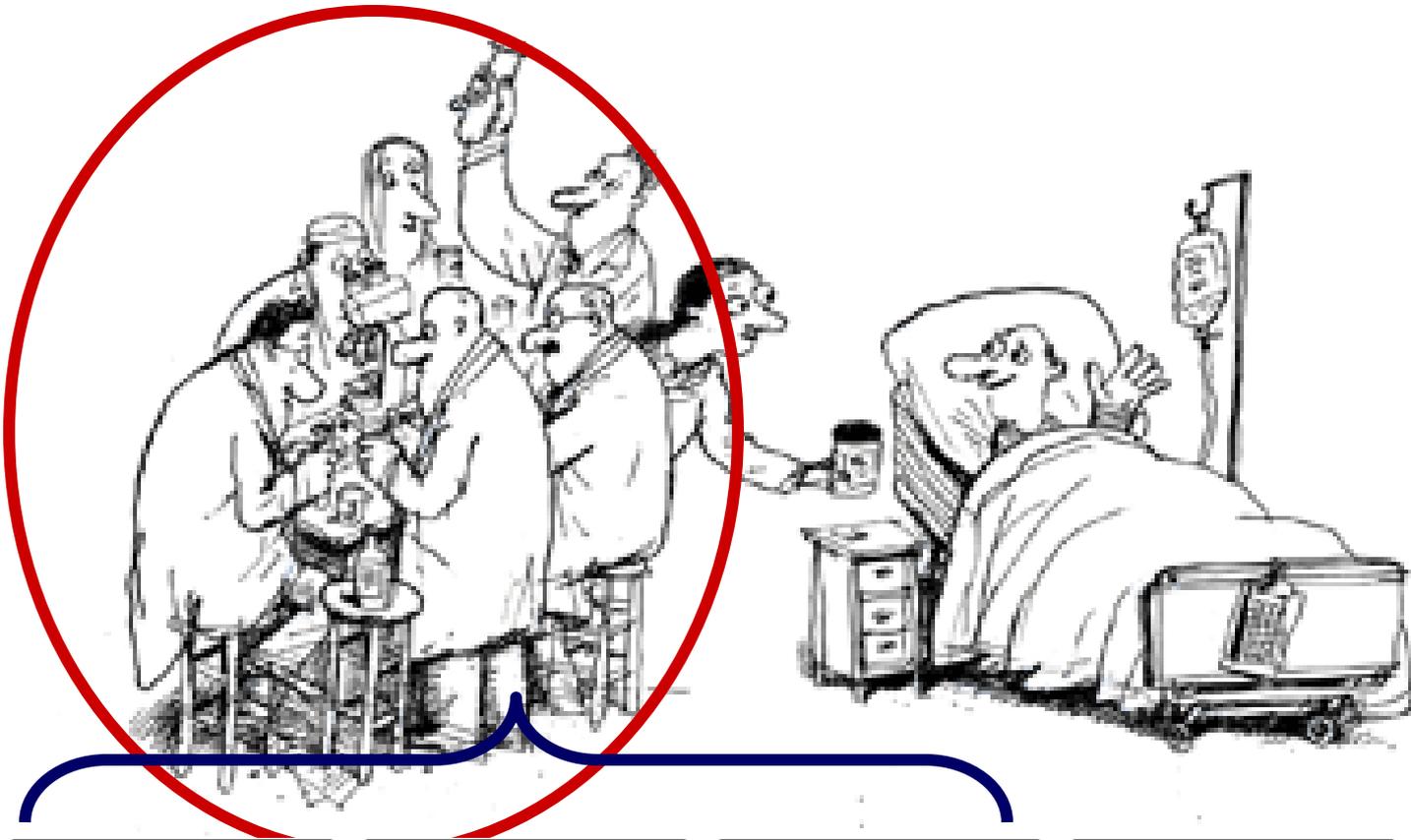
DCTD Budget Figures

❖ Total Budget	~\$1.2B
❖ Operating Budget	\$445M
❖ SPORs (62-P50, 3-P20)	\$123M
❖ Coop Groups (11-U10)	\$145M
❖ Contracts Budget (Includes SAIC-F)	\$114M
❖ Grant Portfolio (>2300)	~\$750M

Where Does DCTD Fit into the NIH Budget Picture?

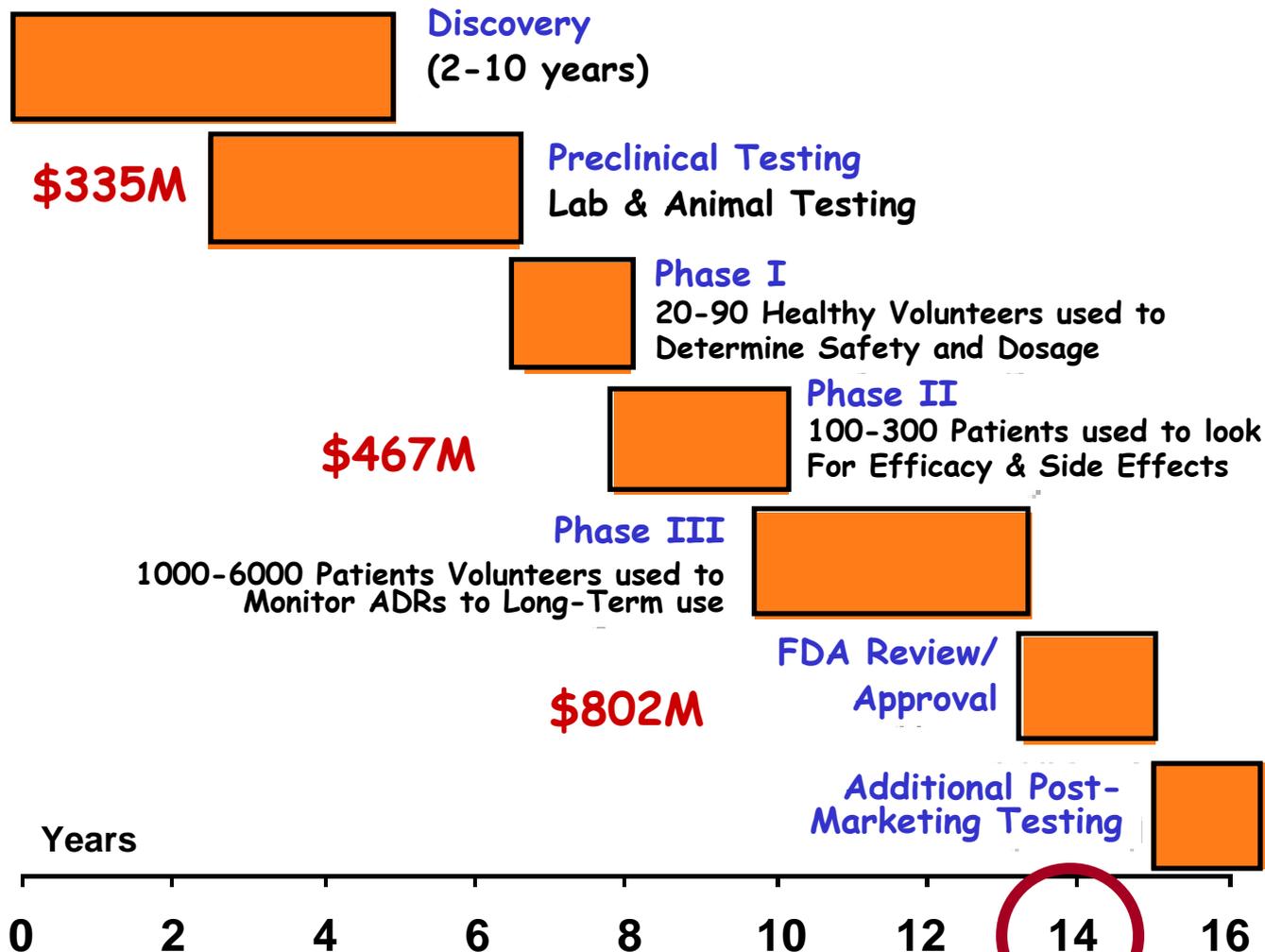
NIH I/Cs	FY2008 Budget
NIH	\$ 29.46B
1. NCI	\$ 4.80B
2. NIAID	\$ 4.56B
3. NHLBI	\$ 2.92B
4. NIGMS	\$ 1.94B
5. NIDDK	\$ 1.70B
6. NINDS	\$ 1.54B
7. NIMH	\$ 1.40B
8. NICHD	\$ 1.25B
9. DCTD, NCI	\$ 1.22B
10. NCRR	\$ 1.15B
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26. FIC	\$ 66.5M

From Bench to Bedside: The Concept

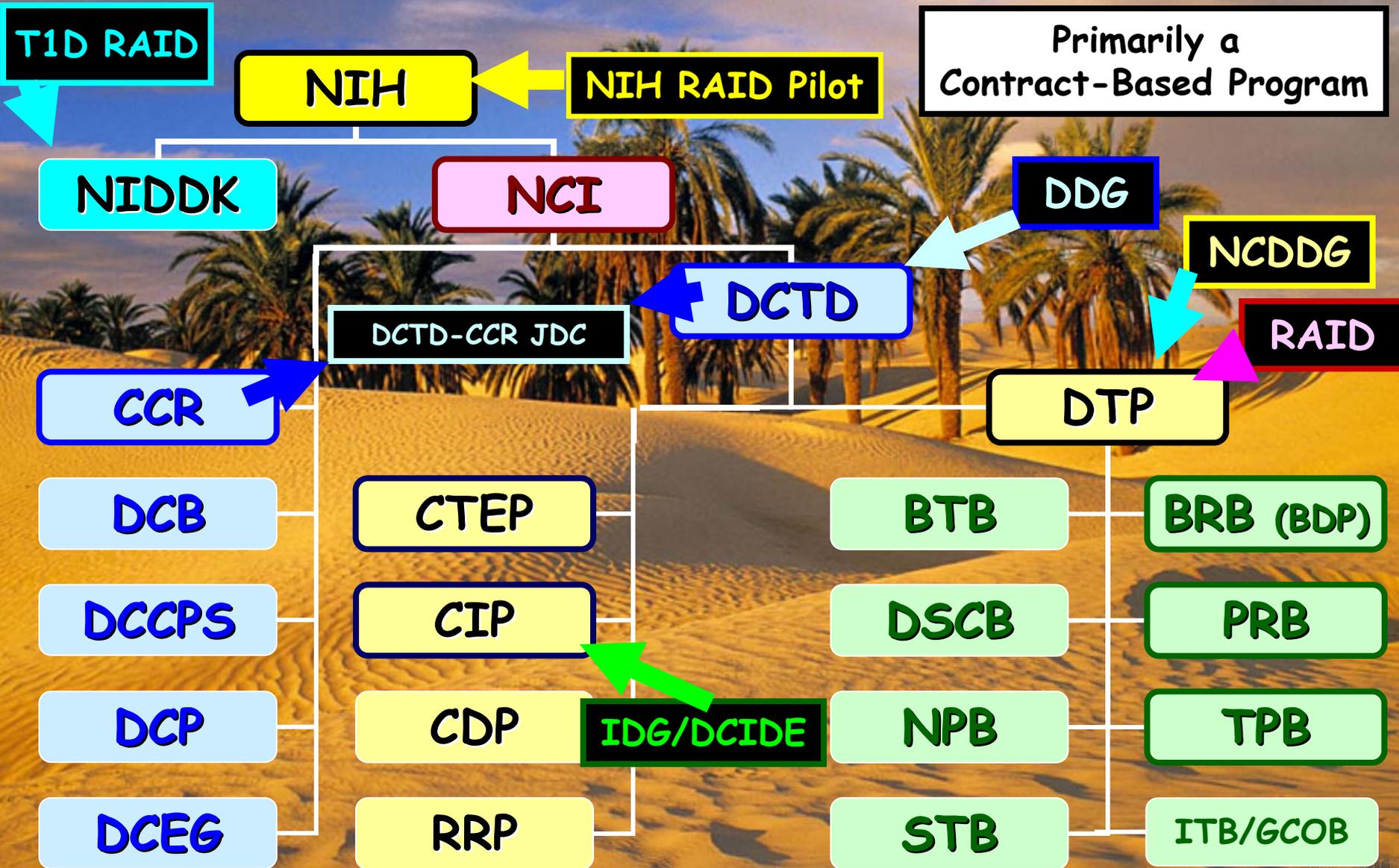


Compound Success Rate By Stages

(Source: PhRMA, based on data from the *Center for the Study of Drug Development*, Tufts University, 1995)



Drug Development Programs at the NCI & NIH



DTP - Chronological Change In Responsibilities

- ❖ Cancer (1° Sm Molec) Drugs 1955 - Present
- ❖ AIDS Drugs 1986 - 1997
- ❖ Cancer Biologicals 1992 - Present
- ❖ Cancer Vaccines 1993 - Present
- ❖ Cancer Gene Therapy 1995 - Present
- ❖ Imaging Agents 1996 - Present
- ❖ AIDS-Related Agents (OIs) 2000 - 2004
- ❖ Other Therapeutics 2002 - Present



DTP Organizational Structure

Discovery

Acquisition and *In vitro* testing of New compounds; Natural Products, Grants; Web Site, Data Management And Storage

To

Development

Biologics; *In vivo* models; Formulation, Bulk Synthesis, Stability Testing, Pharmacology and Range-Finding Tox, IND-Directed Toxicology

NME



IND

Drug Synthesis & Chemistry
(Open)

Natural Products

Dave Newman

Screening Technologies

Bob Shoemaker

Information Technology

Dan Zaharevitz

Biological Testing

Melinda Hollingshead

Grants & Contracts Operations

Mary Wolpert

Biological Resources

Steve Creekmore

Pharmaceutical Resources

Rao Vishnuvajjala

Toxicology & Pharmacology¹⁰

Myrtle Davis

Grant/Contract Support for Discovery

Supported by:

- ❖ **Grants and Contracts Operations Branch, DTP**
 - *"Assistance of the Developmental Therapeutics Program - N02"*
 - Marita Murphy - CS Dr. Wolpert - PO
 - NOVA Research Company
 - *"Grant Portfolio (~400)"* GCOB Program Directors
- ❖ **Information Technology Branch, DTP**
 - *"Operation and Maintenance of the Biological Processing System - N02"*
 - Tim Crilley - CS Marie Hose - PO
 - Addis Inc

Contract Support for Discovery

Supported by:

- ❖ **Drug Synthesis and Chemistry Branch, DTP**
 - *"Preparation of Radiolabeled Materials - N02"*
 - T.Shroff & M.Murphy - CS Dr. Risbood - PO
 - Research Triangle Institute (N02-CM-52208)
 - *"Synthesis of Non-GMP Molecules" (4-N02)*
 - Theresa F... Dr. Risbood - PO
 - Alchem Laboratories, Ash Stevens Inc, Research Triangle Institute, SRI International
 - *"Non-GMP Synthesis of Compounds for Drug Development - N02"*
 - James Carder - CS Dr. Risbood - PO
 - Starks (N02-CM-52209)

Can we make it?

Efficacy Studies in DTP

- ❖ Biological Testing Branch, DTP
 - ★ Supported by Laboratory Animal Science Program and Applied & Developmental Directorate, SAIC-Frederick, Inc., Operations and Technical Support Contractor for the NCI at Frederick (FFRDC)

In Vivo Efficacy Models

- ❖ Hollow Fiber



- ❖ Human xenografts/tumor cell lines

- ★ Immunodeficient mice (nude, SCID, NOD.SCID)

- ❖ Syngeneic rodent tumor cell lines

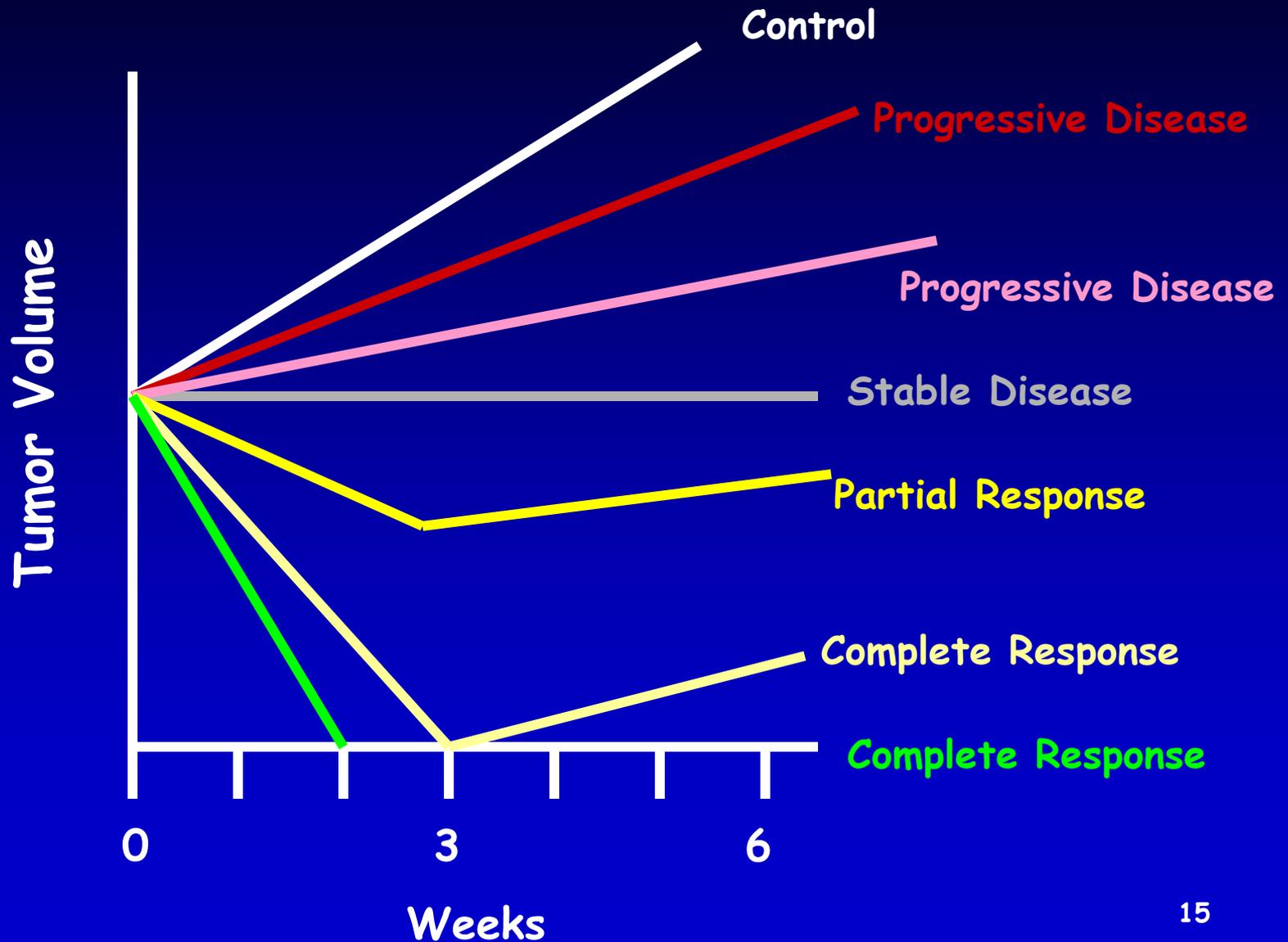
- ❖ Genetically Engineered Mice

- ★ Transgenic
 - ◆ Tissue-specific expression
 - ◆ Inducible models
- ★ Knock out/Knock in



Modeling Cancer Therapy:
Is it effective?

Scoring Tumor Responses



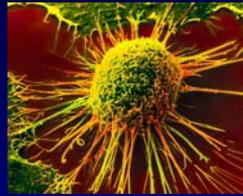
DTP Repositories

For NCI and the Cancer Community

Supported by the Charles River
Contract, SAIC-F and TSB, NCI

DTP Tumor & Animal Repositories

Human and Murine
Cell Lines



Tumors from:

Humans
Guinea pigs
Hamsters
Rabbits
Mice
Rats



Mice

Inbred
Outbred
Hybrid
Congenetic
Nude



Rats

Inbred
Outbred
Nude

Guinea Pigs



DTP Synthetic Repository



❖ Plated Sets

- Open compound set (140,000 samples)
- Diversity sets (880 - 1,990 samples)
- Challenge set (57 samples)

❖ Individual Vials

❖ Radiolabeled Compounds

Do we have the compound?

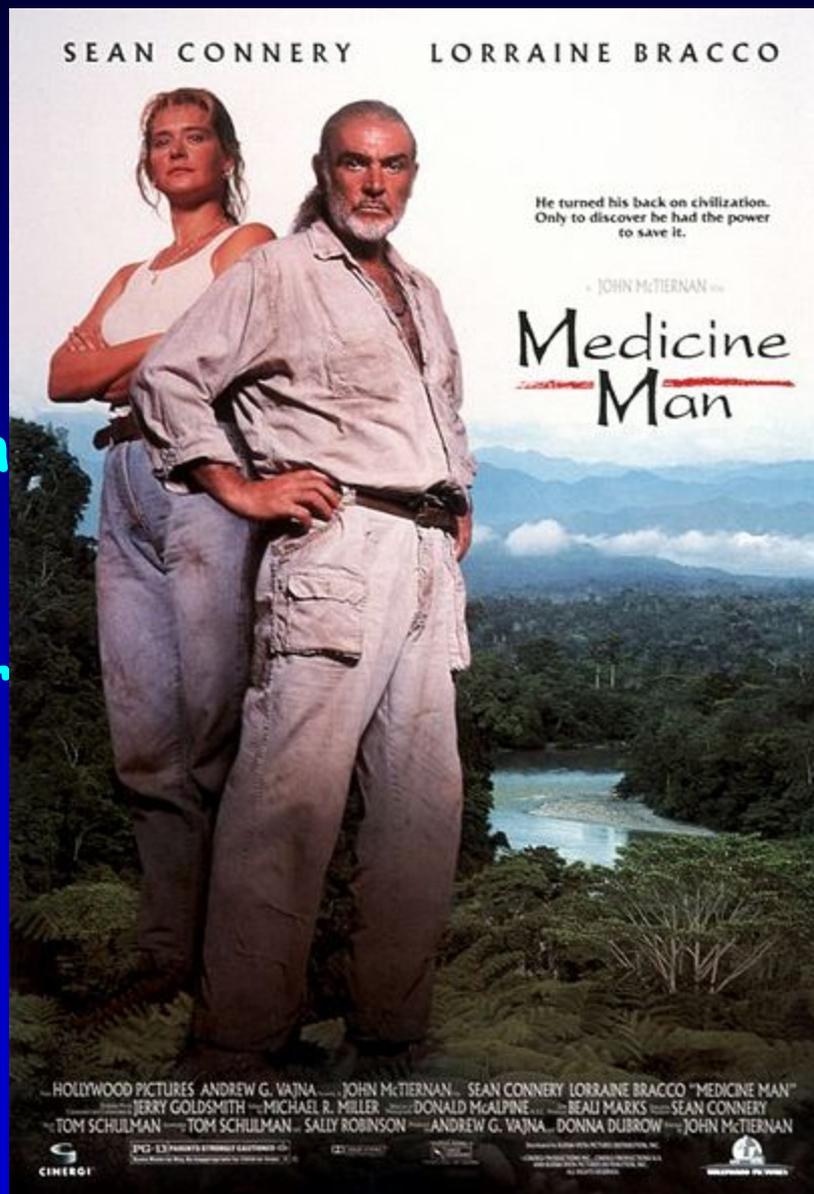


DTP Natural Products Repository

Aqueous &
Organic
Extracts

>50,000 Plant
Samples

>10,000 Marine
Samples

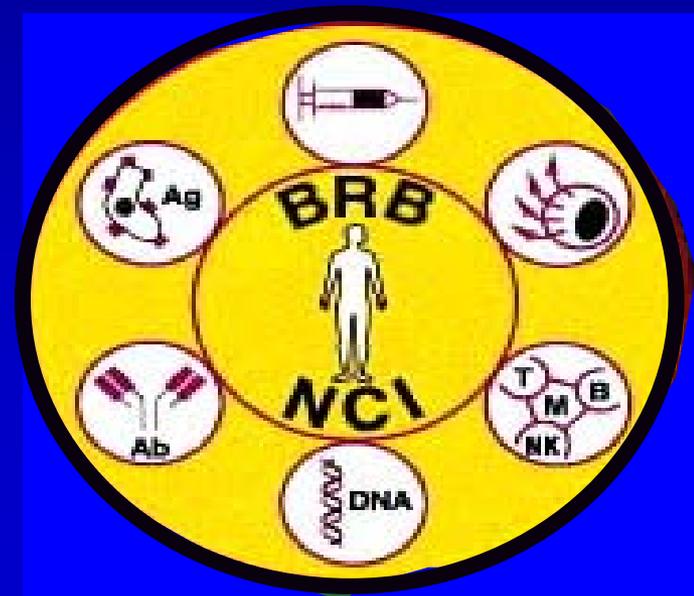


ern for:
biological diversity
collaboration with



DTP Preclinical Biologicals Repository

- ❖ Murine and Human Cytokine Standards
- ❖ Bulk Cytokines
- ❖ Anti-Murine and Anti-Human MoAbs
- ❖ Growth Factors
- ❖ Interferons
- ❖ Interleukins



Comprehensive Preclinical Services

Supported by:

❖ BRB, DSCB, PRB, DTP

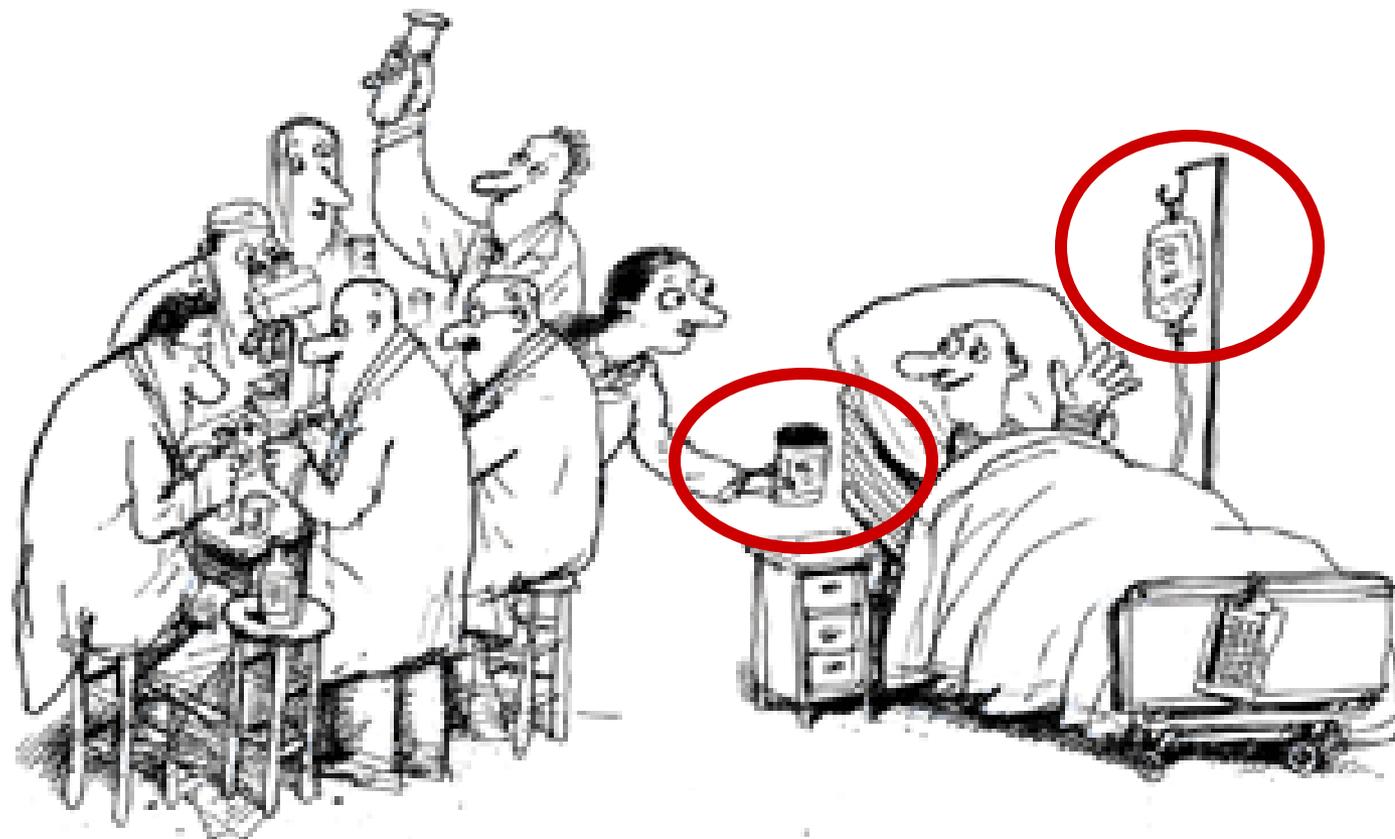
➤ *"Storage and Distribution of Chemicals and Drugs"*

- Tim Crilley - CS
- Dr. Rose Aurigemma - PO
- Dr. Raj Misra - PO
 - Fisher BioServices (N02-CM-2008-00005 & 62211)

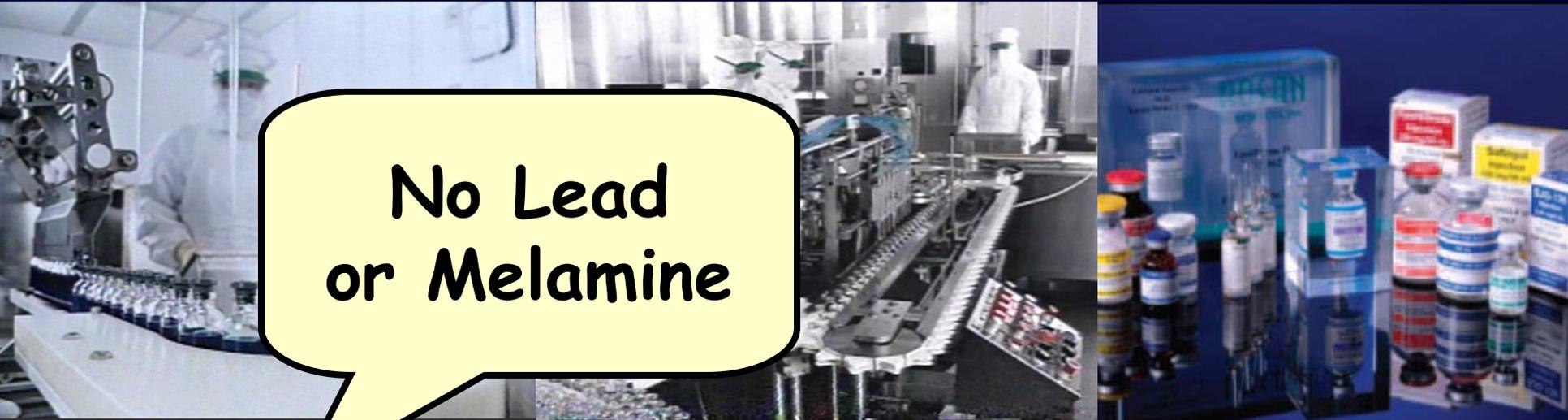
❖ Natural Products Branch, DTP

➤ *"Collection and Taxonomy of Shallow Water Marine Organisms"*

- Andrea Spinelli/Robin Irving - CS/CO
- David Newman - PO
 - Coral Reef Foundation



DTP Comprehensive Pharmaceutical Services



No Lead
or Melamine

- **GMP Synthesis Production** - scale-up, purification.
- **Formulation Research** - dosage form manufacture, storage conditions, shelf life, compatibility with delivery devices.
- **Analytical** - assay identity, purity (>98%), potency, establish release specifications, drug stability.

Comprehensive Pharmaceutical Services

❖ Pharmaceutical Resources Branch, DTP

Supported by:

➤ *"Development and Manufacture of Oral and Topical Dosage Forms"*

- Marita Murphy - CS Dr. Tabib - PO
- University of Iowa (102-CM-

➤ *"Analysis of Anticancer Chemotherapy Agents for Pharmaceutical Development"* (3)

- ... Paul Liu - PO

... Triangle Institute, Midwest Research, SRI International

➤ *"Development and Production of Parenteral Dosage Forms for Clinical Studies"*

- Theresa Shroff - CO/CS Dr. Shankar Gupta - PO
- Ben Venue Inc.

Can we make a drug?

Comprehensive Pharmaceutical Services

❖ Pharmaceutical Resources Branch, DTP

Supported by:

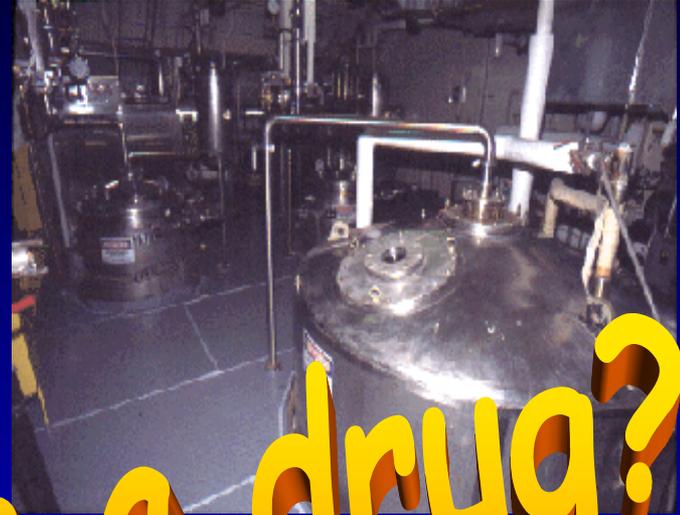
- *"Development of Dosage Forms and Delivery Systems for Anti-Tumor Agents" (3)*
 - Drake Russell - CS Dr. Tabibi - PO
 - Univ of Arizona, Univ of Kansas, Univ of Kentucky
- *"Shelf Life Evaluation of Investigational Dosage Forms"*
 - Marrita Murphy - CS Dr. Shankar Gupta - PO
 - Midwest Research Institute
- *"Manufacture of Bulk Chemical and Bulk Pharmaceutical Ingredients for Preclinical and Clinical Studies" (3)*
 - Marrita Murphy - CS Dr. Sung Kim - PO
 - Alchem, Ash Stevens Inc, Starks

DTP GMP Manufacture of Bio-Pharmaceuticals

❖ Biological Resources Branch, DTP

Supported by: Biopharmaceutical
Development Program, SAIC-F (FFRDC)
and under subcontract elsewhere when
necessary.

DTP GMP Manufacture of Bio-Pharmaceuticals



Can we make a drug?

- ❖ Optimization of expression of recombinant proteins
- ❖ Bulk production of monoclonal antibodies
- ❖ Fermentation for production of recombinant proteins
- ❖ Development and execution of purification protocols

Preclinical Pharmacology and Toxicology

❖ Small Molecules

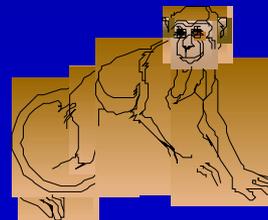
- Two Species - Rodent & Non-rodent
- Clinical Route & Schedule
 - Follow NCI Guidelines
- Pharmacokinetics - Optional
- Identity, stability, purity



❖ Biologicals

- ❖ Most Relevant Species
- ❖ Clinical Route & Schedule
- ❖ Biodistribution

Is it safe?



Study Designs are Agent-Directed, Not Simply Designed to Check a Regulatory Box.

Preclinical Pharmacology and Toxicology

❖ Toxicology and Pharmacology Branch, DTP Supported by:

➤ *"Preclinical Pharmacological Studies of Antitumor and Other Therapeutic Agents"* *(7 NO1 Contracts)*

- Kathy Giuliano - CS
- Dr. Covey - PO
- Dr. Jia - PO
- Dr. M. ...

What the Body does to the Drug!

- Univ. of Texas/MD Anderson
- Univ. of Ohio
- Mayo Foundation
- Univ. of Alabama

Preclinical Pharmacology and Toxicology

❖ Toxicology and Pharmacology Branch, DTP Supported by:

- *"Preclinical Toxicology and Pharmacology of Drugs Developed for Cancer, AIDS, and AIDS-Related Illnesses"*
(5 NO1 Contracts)

- Dean Guidi - CS

- Dr. [Name] - PO

- [Name] - PO

- Dr. Jim Peggins - PO

- Dr. Myrtle Davis

- Battelle Memorial Institute

- Bridge Global Pharmaceutical Services Inc.

- IIT Research Institute

- Southern Research Institute

- SRI International

What the Drug does to the Body!

Preclinical Pharmacology and Toxicology

❖ Toxicology and Pharmacology Branch, DTP

Supported by:

➤ *"Pathology & Veterinary Support"*

- Dean Guidi - CS Dr. Susan Donohue - PO
- PAI/A Division of Charles River Laboratories

Drug Development Programs Supported by DTP

Do we get our money's worth?

Drug Development Programs Supported By DTP

- ❖ DCTD DDG (Former DNC) - NCI IND
- ❖ DTP NCDDGs
- ❖ NCI CCR (DCS / DBS)
- ❖ NIH Clinical Center PET Dept DCTD
- ❖ NCI RAID - Investigator IND
- ❖ NCI / NIAID AIDS IIP (Until 2004)
- ❖ DCTD DCIDE/IDG
- ❖ DCTD R*A*N*D
- ❖ Other NIH I/Cs (*e.g.*, NIMH)
- ❖ 2004 - NIDDK T1D (Type 1 Diabetes)
- ❖ 2005 - NIH RAID (All Therapeutics)
- ❖ 2005 - DCTD-CCR JDC Phase 0
- ❖ 2008 - NCI Chemical Biology Consortium

NCI RAID Program Status (Nov 2008)

- ❖ First Round - August 1998
- ❖ 19 Rounds through February 2008

- ❖ 397 Applications / 129 Approved
- ❖ 103 Projects Complete / 26 On-going
- ❖ 46 INDs Filed
- ❖ 38 Agents Licensed

- ❖ 4 Exceptions Approved / 4 Complete
- ❖ 3 INDs, 2 Licensed

NCI RAID Program Success

❖ Has spawned the following clones:

- NCI / NIAID AIDS IIP (Until 2004)
- DCP RAPID
- DCTD R*A*N*D*
- DCTD DCIDE
- NIDDK T1D RAID (Start 2004)
- NIH RAID Pilot (NIH Roadmap) (Start 2005)

Cancer Imaging Program: DCIDE

- ❖ This competitive program is designed to expedite and facilitate the development of promising investigational imaging enhancers (contrast agents) or molecular probes from the laboratory to IND status.
- ❖ CIP Funding and Review
- ❖ NCI DTP Drug Development Resources and Management (1° PRB, TPB)
- ❖ <http://imaging.cancer.gov/programsandresources/specializedinitiatives/dcide>

NIDDK T1D RAID Program

(Initiated 2004)

- ❖ This program is designed to assist translation to the clinic of novel therapeutic interventions for Type 1 Diabetes and its complications.
- ❖ NIDDK Funding and Review
- ❖ NCI DTP Drug Development Resources and Management (1° BRB, PRB, TPB)
- ❖ <http://www.niddk.nih.gov/fund/diabetesspecialfunds/T1D-RAID/>

NIH RAID Pilot Program (Initiated 2005)

- ❖ Makes available, on a competitive basis, certain critical resources needed for the development of new small molecule therapeutic agents.
- ❖ Sponsored by: NHLBI, NIA, NIAAA, NIAID, NIAMS, NICHD, NIDCD, NIDCR, NIDDK, NIEHS, NIMH, NINDS
- ❖ NIH Roadmap + I/C Funding and Review
- ❖ NCI DTP Drug Development Resources and Management (1^o - PRB and TPB)
- ❖ <http://nihroadmap.nih.gov/raid/>

NIH RAID Pilot Program

- ❖ The 12 PRB and 13 TPB Contracts listed on slides 24-25 and 29-31 support this effort along with the NCI RAID Program, the NIDDK T1D RAID Program and the DCIDE Program

NIH RAID Program Results to Date

- ❖ 55 total applications submitted since 2005
 - ★ 12 approved, 14 await funding decisions, 29 declined
- ❖ Status of approved projects
 - ★ 5 completed, 7 active
 - ★ 3 of the projects have lead to INDs in 2008
 - ★ 1 product licensed
- ❖ IC involvement
 - ★ 10 ICs have contributed funding to NIH-RAID projects

Diseases Addressed by NIH-RAID Applications

- ❖ Acute Lung Injury
- ❖ Alzheimer's
- ❖ Amyloidosis
- ❖ Anthrax exposure
- ❖ Axonopathy
- ❖ Bipolar disorder
- ❖ Brain Cancer
- ❖ Cancer
- ❖ Cerebral Edema
- ❖ Cognitive Impairment
- ❖ Crohn's
- ❖ Cutaneous pathologies
- ❖ Cytomegalovirus
- ❖ Depression
- ❖ Drug Abuse
- ❖ Endocarditis
- ❖ Friedreich's Ataxia
- ❖ Heart Disease
- ❖ Hepatic Fibrosis
- ❖ HIV
- ❖ Hypertension
- ❖ Hypogonadism
- ❖ Infectious Disease
- ❖ Lactation Insufficiency
- ❖ Liver Disease
- ❖ Multiple Sclerosis
- ❖ Pneumonia
- ❖ Schizophrenia
- ❖ Sickle Cell
- ❖ Thalassemia
- ❖ West Nile Virus

On the Horizon - New Program under Development/Implementation



Proposed NCI Chemical Biology Consortium (CBC)

The NExT Step in Drug Discovery and Development

NExT = NCI Experimental Therapeutics



NCI Chemical Biology Consortium (CBC)

- ❖ Mission: Dramatically increase flow of early stage drug candidates into NCI therapeutics pipeline
- ❖ Vision:
 - ❖ **Develop integrated network** of chemists, biologists, and molecular oncologists, with synthetic chemistry support
 - ★ Active management by NCI and external advisory boards
 - ★ Unify discovery with NCI pre-clinical and clinical development
 - ★ Linked to other NCI initiatives; CCR chemistry integral partner
 - ★ Active mining of grant pool
 - ❖ **Focus on unmet needs** in therapeutics: “undruggable” targets, under-represented malignancies
 - ❖ **Enable a clear, robust pipeline** all the way from target discovery through clinical trials for academic, small biotech, and pharma investigators
- ❖ *Re-establish the NCI as a world leader in the area of innovative cancer therapeutics discovery*

Chemical Biology Consortium

❖ The following DTP contracts will support this effort:

★ 6 DSCB Contracts listed on Slide 12

★ 1 NPB Contract listed on Slide 21

★ Repository Contract listed on Slide 21

★ 12 PRR Contracts listed on slides 24-31

★ 10 Other Contracts listed on slides 32-41

★ FFRDC and DCTD Support:

- ◆ Project Management Office
- ◆ Center for Synthetic Chemistry
- ◆ Laboratory Animal Science Program
- ◆ Laboratory of Human Toxicology and Pharmacology
- ◆ Numerous subcontracts to be awarded

Leverage NIH Roadmap
Investment in MLSCN!

Is it Worth it?

Recent DTP Therapeutic Developments

❖ 11 Approved Drugs with DTP involvement

Paclitaxel

Videx^{AIDS}

Hivid^{AIDS}

Epivir^{AIDS}

*Hycamtin

*Gliadel

*Ontak

Temodar

Velcade

Vidaza

*Erbitux

❖ Close, but...

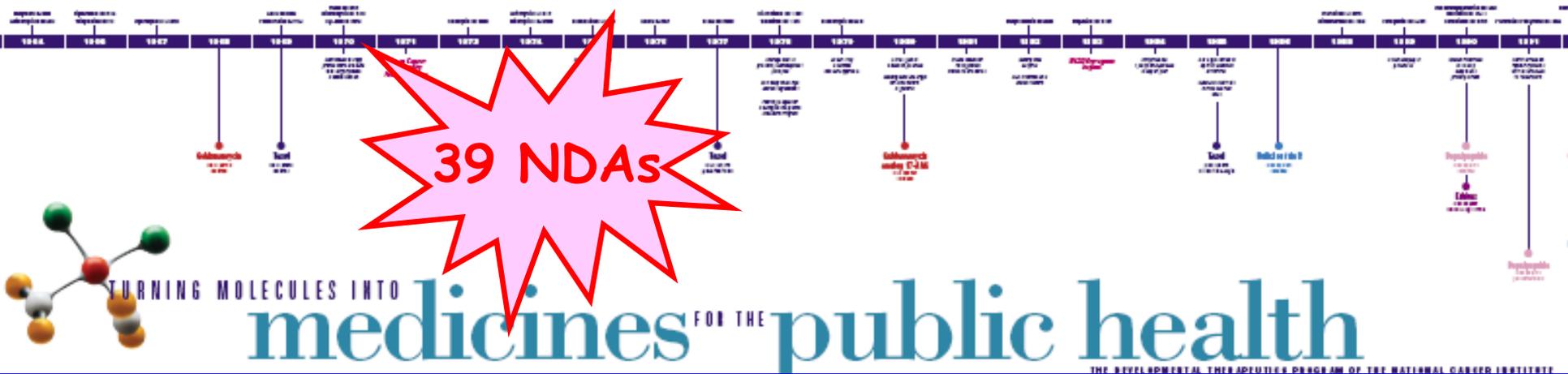
Genasense

BL22 / HA22

*Provence

*NCDDG, Others are
DNC/DDG

1955 to 2005: 50TH Anniversary of the creation of the Cancer Chemotherapy National Service Center (CCNSC)... The predecessor of DTP



**From Bench to
Bedside:
The Reality**



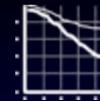
Acknowledgements 1988-2008

Earlier Days:

- ❖ Beverly Lott Wyatt
- ❖ Clyde Williams
- ❖ Elsa Carlton
- ❖ Jacqueline Ballard
- ❖ Carolyn Swift
- ❖ Therese Dick
- ❖ Jeannette Johnson
- ❖ Odessa Henderson
- ❖ Joyce Crooke
- ❖ Mary O'Leary
- ❖ Mike Veesart
- ❖ Nancy Carrick
- ❖ Diane Stalder
- ❖ Maybe: Others I can't remember?

More Recently:

- ❖ Vic Buyny
- ❖ MaryAnne Golling
- ❖ Robin Irving
- ❖ Tim Crilley
- ❖ Kathy Giuliano
- ❖ Dean Guidi
- ❖ Marrita Murphy
- ❖ Drake Russell
- ❖ Theresa Shroff
- ❖ Andrea Spinelli
- ❖ Todd Cole
- ❖ Jack Campbell
- ❖ All DCTD Staff
- ❖ All Contractors/Grantees⁵⁰

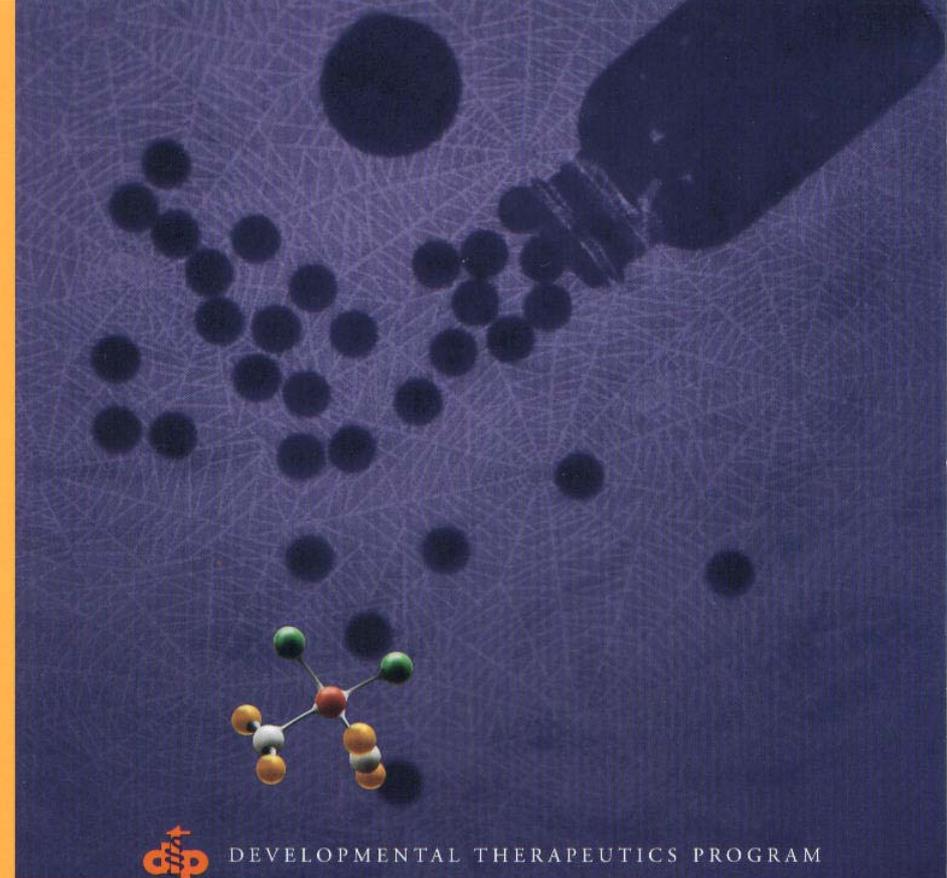


Accelerating Cancer Diagnosis and Drug Development

Questions and Discussion

Thank you!

<http://dctd.cancer.gov/>



DEVELOPMENTAL THERAPEUTICS PROGRAM

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