Welcome and Grand Overview

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NIH NATIONAL CANCER INSTITUTE

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Thank You to the Organizing Committee

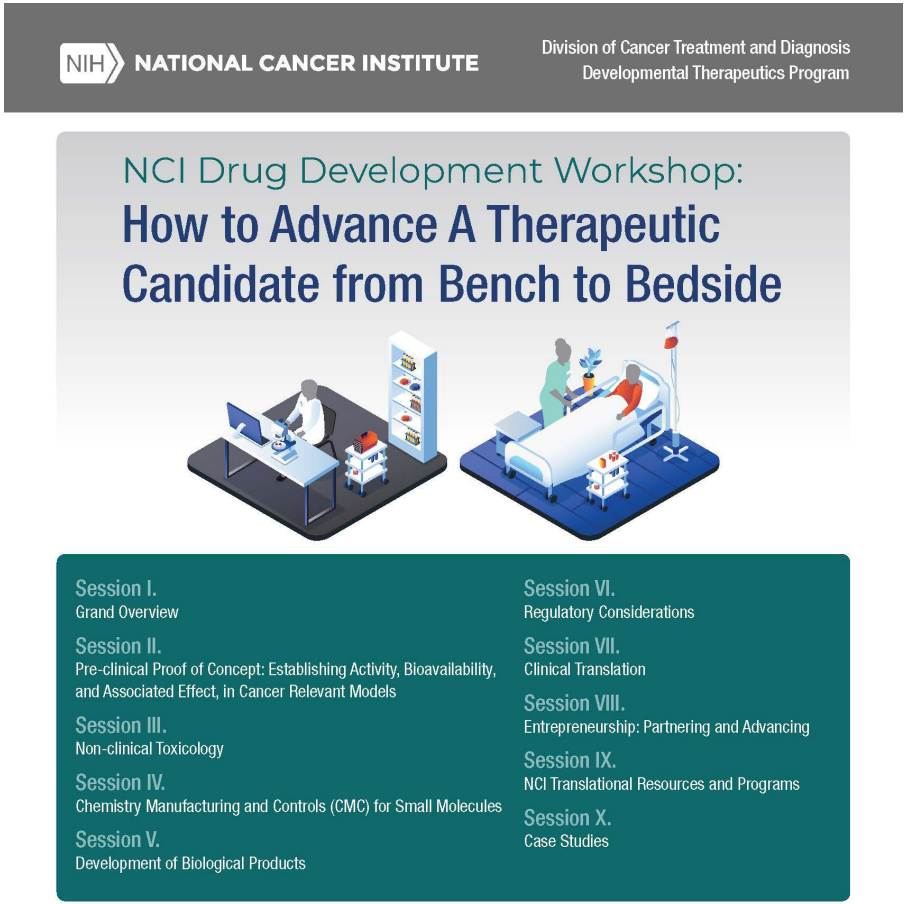
Weiwei Chen, Program Director, PTGB, DTP

Rachelle Salomon, Program Director, BRB, DTP

Sharad Verma, Program Director, PTGB, DTP

Jason Yovandich, Chief, BRB, DTP

Sundar Venkatachalam, Chief, PTGB, DTP



Introduction to the Developmental Therapeutics Program

In 1955, congress created the Cancer Chemotherapy National Service Center which evolved, both structurally and functionally, into today's Developmental Therapeutics Program (DTP). DTP's involvement in the discovery or development of many anticancer therapeutics on the market today demonstrates its indelible impact on efforts to improve the health and well-being of people with cancer.

Approved Cancer Therapies with DTP Assistance

2018 Moxetumomab pasudotox-tdfk
2015 Dinutuximab (Unituxin, NSC 764038)
Ecteinascidin 743 (NSC 648766)
2012 Omacetaxine (homoharringtonine, NSC 141633)
2010 Eribulin (NSC 707389)
Sipuleucel-T (NSC 720270)
2009 Romidepsin (NSC 630176)
Pralatrexate (NSC 713204)
2004 Azacitidine (NSC 102816)
Cetuximab (NSC 632307)
2003 Bortezomib (NSC 681239)
2000 Entinostat (706995)
1998 Denileukin diftitox (NSC 697979)
1996 Polifeprosan 20 w/carmustine implant (NSC 714372)
Topotecan (NSC 609699)
1995 All-trans retinoic acid (NSC 122758)
1992 2-Chlorodeoxyadenosine (NSC 105014)
Paclitaxel (NSC 125973)
Teniposide (NSC 122819)
1991 Fludarabine phosphate (NSC 312887)
Pentostatin (NSC 218321)
1990 Hexamethylmelamine (NSC 13875)
Levamisole (NSC 177023)
1989 Carboplatin (NSC 241240)
1988 Ifosfamide (NSC 109724)
1987 Mitoxantrone (NSC 301739)

1983 Etoposide (NSC 141540)
1982 Streptozotocin (NSC 85998)
1979 Daunorubicin (NSC 82151)
1978 Cisplatin (cis-platinum) (NSC 119875)
1977 Carmustine (BCNU) (NSC 409962)
1976 1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosurea (CCNU) (NSC 9037)
1975 Dacarbazine (NSC 45388)
1974 Doxorubicin (NSC 123127)
Mitomycin C (NSC 26980)
1973 Bleomycin (NSC 125066)
1970 Floxuridine (FUDR) (NSC 27640)
Mithramycin (NSC 24559)
Mitotane (o-p'-DDD) (NSC 38721)
1969 Cytarabine (ARA-C) (NSC 63878)
Procarbazine (NSC 77213)
1967 Hydroxyurea (NSC 32065)
1966 Pipobroman (NSC 25154)
Thioguanine (NSC 752)
1964 Melphalan (NSC 8806)
Actinomycin D (NSC 3053)
1963 Vincristine (NSC 67574)
1962 Fluorouracil (NSC 19893)
1961 Vinblastine (NSC 49842)
1959 Cyclophosphamide (NSC 26271)
Thiotepa (NSC 6396)
1957 Chlorambucil (NSC 3088)

Overview of DTP Activities

Mission: To support discovery and development of innovative new cancer therapies

Provide resources and services to the extramural research community

- Academic, non-profit, biotech, pharma
- Cost-free, IP involved in rare cases

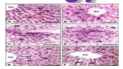
Maintain a robust infrastructure for drug discovery and development

- Facilities at Frederick National Laboratory for Cancer Research (Frederick, Maryland)
- Contracted resources with CROs, CMOs(nation wide)

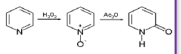
Manage a large portfolio of grants pertinent to drug discovery and preclinical development

DTP: Ten Branches Supporting Discovery and Development

Molecular Pharmacology:
NCI-60, 2D, 3D
Target validation & screening

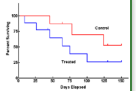



Drug Synthesis & Chemistry:
Chemical Repository
Synthetic Chemistry

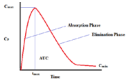


Natural Products:
Collection & Repository
Pre-fractionated library
Screening & identification


Biological Testing:
PDX Repository
Model development & testing
Tumor Repository


Toxicology & Pharmacology:
Nonclinical and GLP studies
Investigative Toxicology lab

Immuno-oncology:
Grant portfolio:
Immuno-oncology, immunotherapy
Canine Immunotherapy


Biological Resources:
GMP biologics, analytics
Biologics Repository
Grant portfolio:
Biotechnology innovation

Pharmaceutical Resources:
GMP manufacture API,
Analytical testing, Dose formulation


Information Technology:
COMPARE, ALMANAC,
Structure-based Medicinal Chemistry

Preclinical Therapeutics Grants:
Grant portfolio for Small Molecule Therapeutics discovery & development

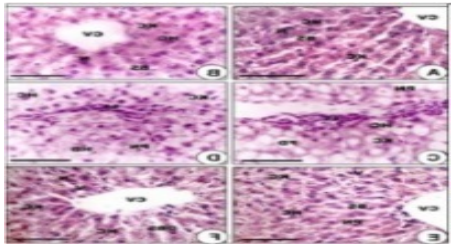
Molecular Pharmacology Branch

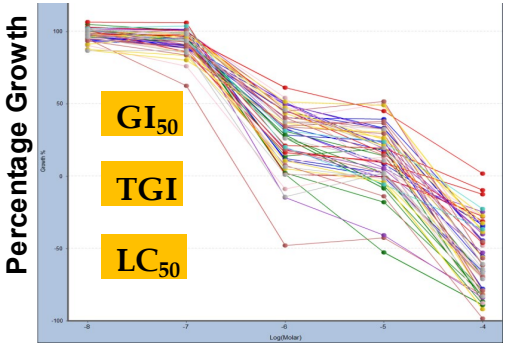
NCI60 Cell Screen:

- 60 human tumor cell lines representing leukemia, melanoma and cancers of the lung, colon, brain, ovary, breast, prostate, kidney; data can be assessed in pattern recognition algorithms

Functional Genomics, Target Validation and Screening

NEW: Organoid and spheroid screening, HTS in 384 well platform





Drug Synthesis and Chemistry Branch

NCI Chemical Repository: >200,000 compounds

- Acquire, Synthesize and Distribute Chemical Samples for Research
- Plated sets: Diversity, Mechanistic, Approved Oncology Drug Sets

Synthetic and Medicinal Chemistry Resource and Expertise

- Develop IT Chemistry Solutions

External Synthesis Contracts	• Supports NExT project Initiatives • Synthesis of benchmark clinical and preclinical candidates
NCI Chemical Repository	• Manages new compounds submitted by extramural researchers • Distribution of compounds for intramural and extramural research activities
Laboratory of Synthetic Chemistry	• Supports NExT discovery / development projects • Provides chemical synthetic enablement expertise and service, across DCTD, including natural products

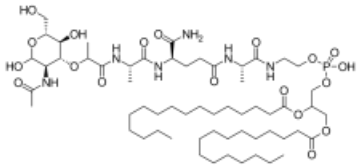
Natural Products Branch

Collection of Natural Products

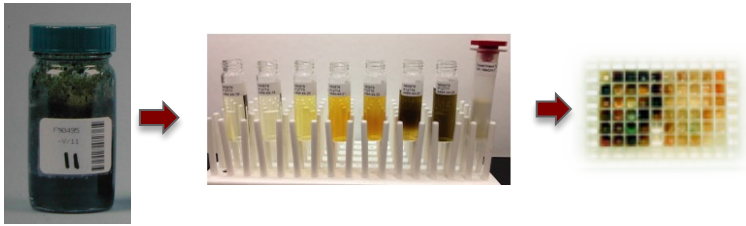
- Screening & identification of active compounds
  >170,000 crude extracts
  (plant, marine organisms, microbes)

Natural Products Repository:

- Aqueous & organic extracts
- Isolated natural products set (expanding)



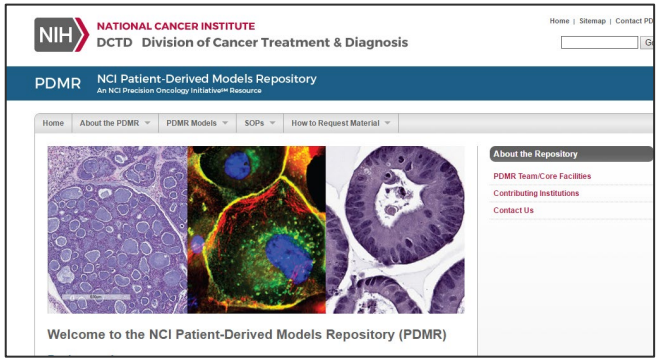
Pre-fractionated extract library: Automated fractionation and plating for distribution and use in drug discovery

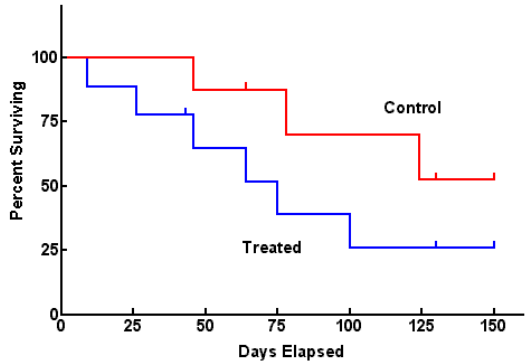


Biological Testing Branch

Efficacy Testing of Drugs in Cancer Models

- Pharmacokinetic Profiling, Dosage Testing, MTD
- Extensive Tumor Repository for Distribution
- **Patient Derived Models Repository**
- Collaborates with Molecular Characterization Laboratory **(MoCha)** and Pharmacodynamic Assay Development and Implementation Section **(PADIS)**

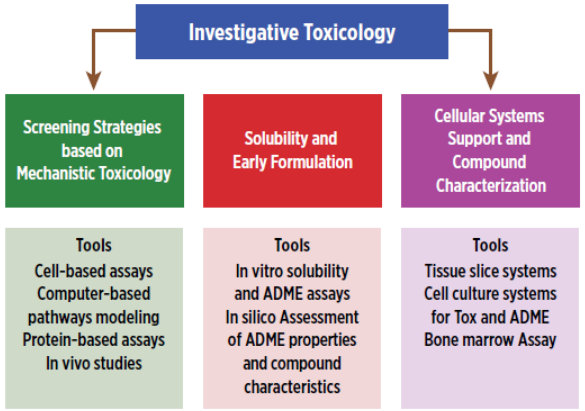


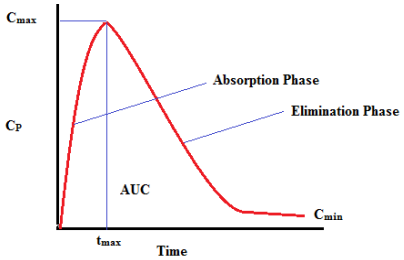


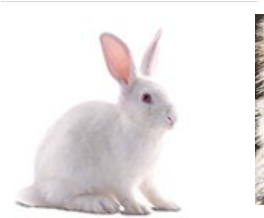
Toxicology and Pharmacology Branch

GLP and non-GLP studies:

- Pharmacokinetic and toxicological profile, ADME
- Development of special target organ toxicity assay
- Preclinical MTD, DLTs and clinical starting dose
- *in vitro* studies
- IND-directed safety studies including toxicokinetics
- Documentation for IND filing





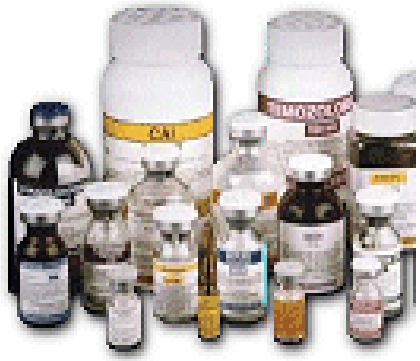


Pharmaceutical Resources Branch

GMP production of active pharmaceutical ingredient (API) and final drug product (FDP): scale-up, purification

Drug Formulation: clinical dosage form, storage conditions, shelf life, compatibility with delivery devices

Analytical chemistry: assay identity, purity, potency, drug stability release specifications



Biological Resources Branch

Biopharmaceutical Development:

- Expression optimization
- Purification process development, GMP manufacture Analytical assay development, testing and stability
- **NEW:** Adoptive cell therapy and virus vector manufacturing, CRISPR editing of cell therapies

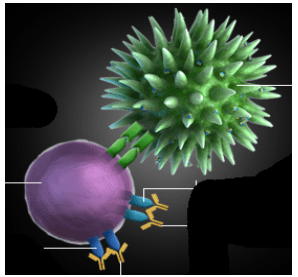
Grant Portfolio:

- Biopharmaceutical technology: antibodies, antigens, recombinant proteins, plasmids, oligonucleotides, peptides, vaccines, virus vectors

Biologics Repository:

- Murine and human cytokines, growth factors, immunomodulators
- Anti-murine and anti-human monoclonal Abs

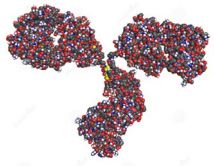
Immuno-oncology Branch



Support immuno-oncology investigators and augment pipeline for immunotherapy trials

Grant portfolio:

- Immuno-oncology
- Comparative Oncology (Canine Immunotherapy)
- Cell therapy
- Immunotherapy
- Therapeutic models
- Mechanisms of action




Open access Short report

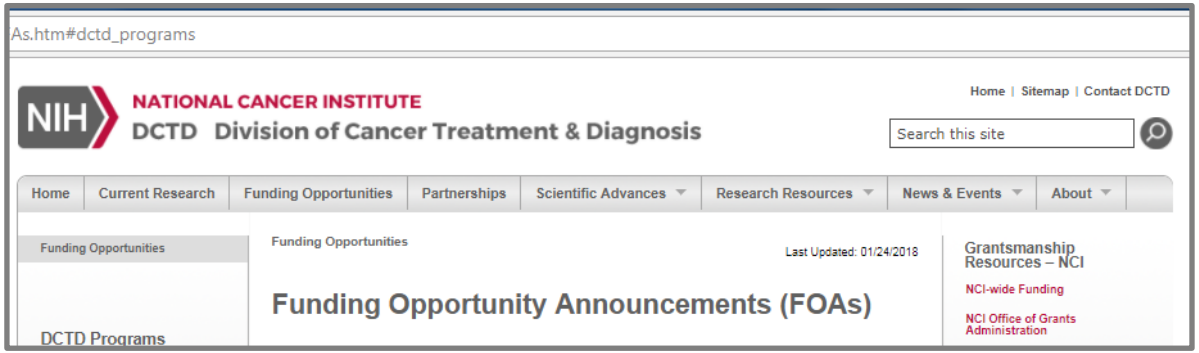
Journal for ImmunoTherapy of Cancer

Challenges and next steps in the advancement of immunotherapy: summary of the 2018 and 2020 National Cancer Institute workshops on cell-based immunotherapy for solid tumors

Preclinical Therapeutics Grants Branch

Grant portfolio for small molecule therapeutics discovery & development:

- Molecular targets
- Biochemistry
- Synthetic/Medicinal Chemistry
- Mechanism of action
- Therapeutic models
- Pharmacology/Toxicology
- Novel delivery & Nanomolecules



Information Technology Branch

Bulk data for download, browsing & searching:

- NCI-60 screening, *in vivo* anti-cancer, *in vitro* and *in vivo* gene expression data (microarray)
- Chemical structure data
- Molecular target characterization data
- Sarcoma project data

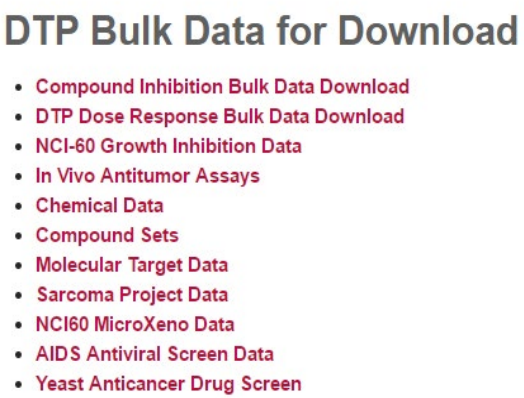
NCI-ALMANAC

- Data showing how well pairs of FDA-approved cancer drugs kill tumor cells from the NCI-60 Human Tumor Cell Lines

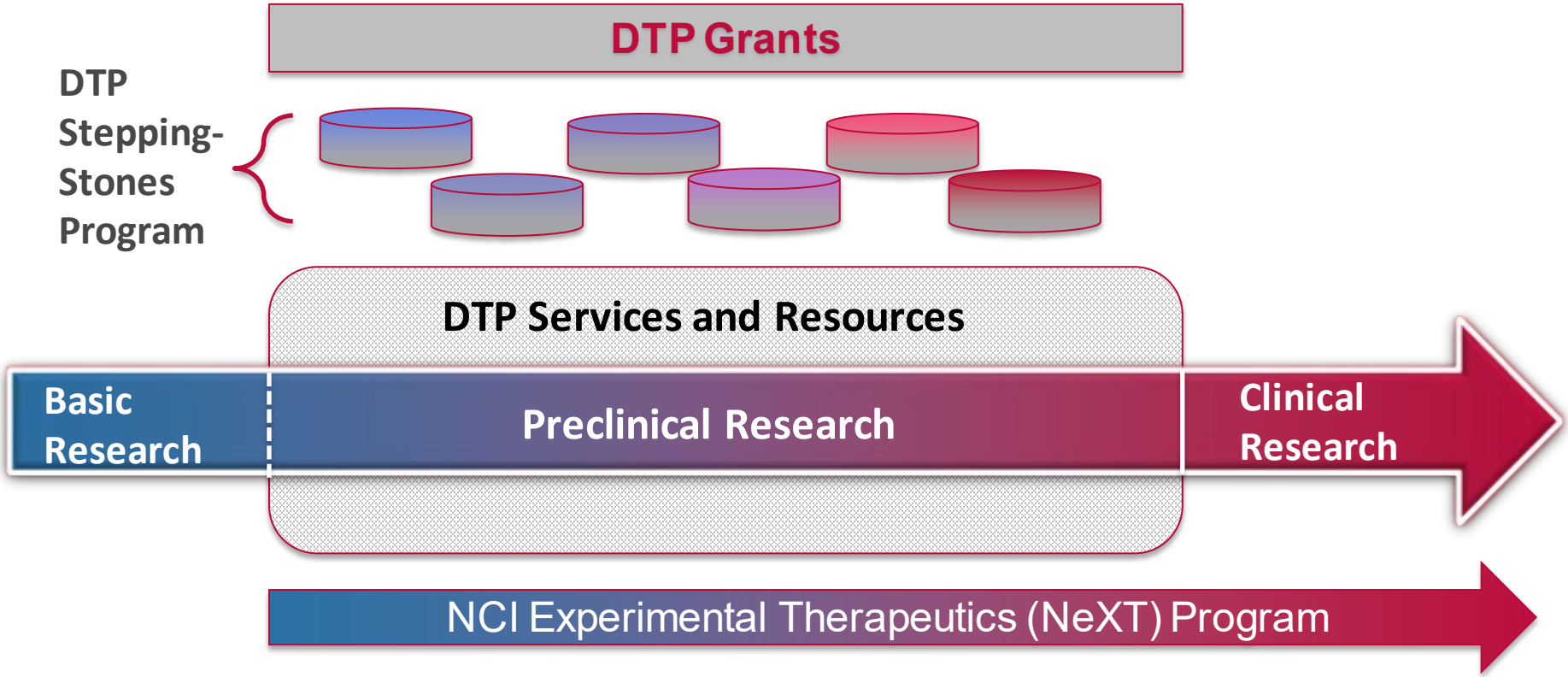
COMPARE - Pattern-recognition algorithm

- Compare degree of similarity in activity profiles of NCI-60 in vitro screen

NEW: Development dashboard to integrate databases and allow data analytics



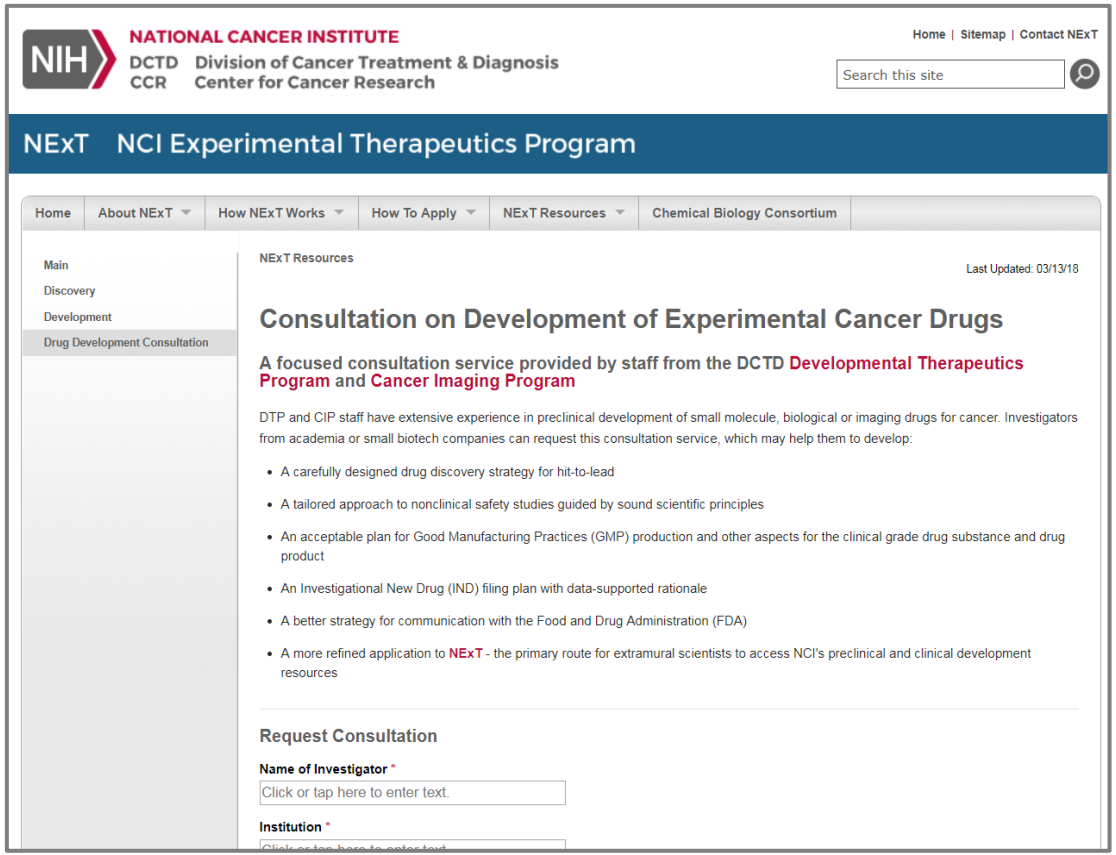
Overlapping Support for Discovery and Development



DTP/DCTD Preclinical Development Consultation Service

https://next.cancer.gov/experimentalTherapeutics/form.htm

- Confidential
- Provides broad product development
- Small molecules, biologics, cell therapies



The Critical Path to the Clinic: Plan Backward and Develop Forward

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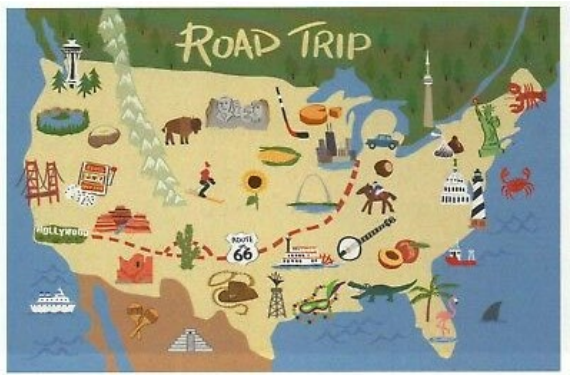
What are your summer vacation plans?

PLANNING AHEAD IS ESSENTIAL

- Where will you go?
- How will you get there?
- How much money can you spend?
- How long will you stay?
- Who should come with you?
- What activities will be included?
- What should you bring with you?



Developing a New Therapeutic Requires Planning Ahead!

Working Backwards on the Critical Path

1. Clinical Indication: What is the unmet clinical need?
2. Clinical Protocol: Patient population, dosing formulation, route, schedule, inclusion/exclusion
3. IND-ready Drug Product: Identity, Strength, Quality, Purity
4. Is the drug safety profile acceptable?
5. Is it a ‘drug-like’ candidate?
6. Do I have a robust screening assay?
7. Do I have a good target?

Working Backwards on the Critical Path

1. Clinical Indication: What is the unmet clinical need?
    a. Incidence of disease
    b. Standard of care/available treatments
    c. Competitive landscape
    d. Differentiated Product Profile (better safety, easier dosing, greater efficacy)

Working Backwards on the Critical Path

1. Clinical Indication: What is the unmet clinical need?
2. Clinical Protocol: Patient population, dosing formulation, route, schedule, inclusion/exclusion
    a. Is there a clinical site identified for enrollment?
    b. Is the dosing schema/formulation practical?
    c. Are there assays and biomarkers to support the trial?
    d. Are there specific regulatory considerations to address?
        a. Biologics vs small molecule drugs

Working Backwards on the Critical Path

1. Clinical Indication: What is the unmet clinical need?
2. Clinical Protocol: Patient population, dosing formulation, route, schedule, inclusion/exclusion
3. IND-ready Drug Product: Identity, Strength, Quality, Purity
    a. Target Product Profile; Certificate of Analysis
    b. Can it be manufactured at clinical scale?
    c. Proper analytical characterization assays, storage and stability
    d. Relevant *in vitro* data to demonstrate mechanism of action, target engagement, and proof-of-concept *in vivo* efficacy data
    e. Biologics/Immunotherapies: animal model considerations

Working Backwards on the Critical Path

1. Clinical Indication: What is the unmet clinical need?
2. Clinical Protocol: Patient population, dosing formulation, route, schedule, inclusion/exclusion
3. IND-ready Drug Product: Identity, Strength, Quality, Purity
4. Is the drug safety profile acceptable?
    a. Safety/toxicity: appropriate species, appropriate dosing, histopathology, correlative biomarkers, target organs for toxicity
    b. Pharmacokinetics: acceptable drug exposure, clearance rate, therapeutic window
    c. Biologics: Immune response (anti-drug antibody), PK considerations, animal model considerations

Working Backwards on the Critical Path

1. Clinical Indication: What is the unmet clinical need?
2. Clinical Protocol: Patient population, dosing formulation, route, schedule, inclusion/exclusion
3. IND-ready Drug Product: Identity, Strength, Quality, Purity
4. Is the drug safety profile acceptable?
5. Is it a 'drug-like' candidate?
    a. Activity, solubility, stability, large scale manufacture, biodistribution properties, acute toxicity (MTD, ADME)
    b. Biologics: sterile processing, storage/stability considerations

Working Backwards on the Critical Path

1. Clinical Indication: What is the unmet clinical need?
2. Clinical Protocol: Patient population, dosing formulation, route, schedule, inclusion/exclusion
3. IND-ready Drug Product: Identity, Strength, Quality, Purity
4. Is the drug safety profile acceptable?
5. Is it a 'drug-like' candidate?
6. Do I have a robust screening assay?
    a. Based on mechanism of action, specificity, reproducibility, cost effective/high throughput, rigorous end-points

Working Backwards on the Critical Path

1. Clinical Indication: What is the unmet clinical need?
2. Clinical Protocol: Patient population, dosing formulation, route, schedule, inclusion/exclusion
3. IND-ready Drug Product: Identity, Strength, Quality, Purity
4. Is the drug safety profile acceptable?
5. Is it a 'druggable' candidate?
6. Do I have a robust screening assay?
7. Do I have a good target?
    a. Novel, specific, characterized, assayable
    b. Sufficiently validated with association to disease

NCI Drug Development Workshop: *How to Advance a Therapeutic Candidate from Bench to Bedside*

Session II. Pre-clinical Proof of Concept: Establishing Activity, Bioavailability, and Associated Effect, in Cancer Relevant Models

Session III. Non-clinical Toxicology

Session IV. Chemistry Manufacturing and Controls for Small Molecules

Session V. Development of Biological Products

Session VI. Regulatory Considerations

Session VII. Clinical Translation

Session VIII. Entrepreneurship: Partnering and Advancing

Session IX. NCI Translational Resources and Programs

Session X. Case Studies

Session I: Grand Overview

- **Topic 2: Key milestones in drug development and components of an IND-package**

  Phil Jones, Ph.D., The University of Texas MD Anderson Cancer Center

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