National Cooperative Drug Discovery Group (NCDDG) Program

SUCCESS STORY

NCDDGs—The First NIH Public-Private Partnerships

Created in 1982 by the NCI Board of Scientific Counselors, Division of Cancer Treatment & Diagnosis, the NCDDG Program has been adopted by four other NIH institutes. The NCDDG Program aims to:

- Support multidisciplinary team research to discover new targeted anticancer therapies.
- Address the need for new therapies with greater selectivity.
- Use new technologies to speed discovery (i.e., molecular targets, compound libraries, high-throughput screening, imaging).
- Protect intellectual property.
- Foster high-risk, translational research with potential high payoff.

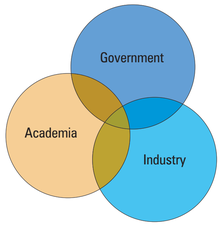
NCDDG Public-Private Partnerships Work

Win, Win, Win Relationship

Government (Provides Funds and Assistance)
- Win: New treatments.

Industry (Provides Technology and Development)
- Win: Risk sharing and access to new ideas and talent for increased competitiveness.

Academia (Provides Concepts and Expertise)
- Win: Test of hypotheses.



Benefits and Costs: 1984 (First Awards) to 2004

Benefits
- Discovery: 42 funded NCDDGs (diverse approaches to drug discovery).
- Development: 12 developed to clinical trial (includes 1 fast-track).
- Delivery: 4 marketed agents (3 first-in-class).

Costs
- Overall grant support (highly leveraged): About $203 million ($50 million per marketed agent).
- FY 2004 cost: $12 million (about 6% of DTP's grant portfolio).

Results: Four Marketed Agents

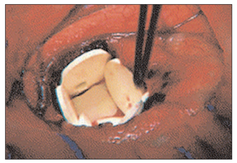
Topotecan: Example of Roles of Academic-NCI-Industry Partnership

Principal Investigator
- Leroy Liu, Johns Hopkins University.

Overview
- Dr. Liu discovered that DNA Topoisomerase I is a molecular target in the 1980s.
- NCI supported Monroe Wall and Mansukh Wani, Research Triangle Institute, to isolate camptothecin on contract. Sodium camptothecin failed in NCI trials in the 1970s. NCI provided camptothecin to an NCDDG at the University of Florida in the 1980s and supported phase II clinical trials of topotecan in the 1990s.
- SmithKline Beecham produced a semi-synthetic, water soluble derivative and supported formulation, toxicology, production, and phase I clinical trials.
- Topotecan was manufactured by SmithKline Beecham as Hycamtin®. Sales were $203.5 million in 2003.

BCNU for Brain Tumors

Principal Investigators
- Henry Brem, Johns Hopkins University; Robert Langer, Massachusetts Institute of Technology.

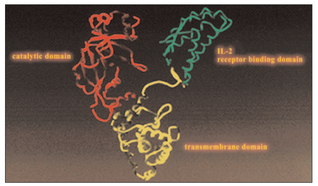


Overview
- Dime-sized wafers release BCNU over 2–3 weeks. It is the only FDA-approved implant of its kind.
- BCNU increased median survival in recurrent glioblastoma from 11.6 to 13.9 months.
- Licensed to Guilford Pharmaceuticals and marketed as Gliadel®.
- In 2003, Gliadel® was marketed for malignant glioma (glioblastoma multiforme and anaplastic astrocytoma).

Diphtheria Toxin-IL2 Fusion Protein DAB_{389}-IL2 (Denileukin Diftitox)

Principal Investigator
- John R. Murphy, Boston University Hospital.

Model Three-Dimensional Structure of Diphtheria Toxin: IL2 Fusion Protein DAB_{389}: IL2

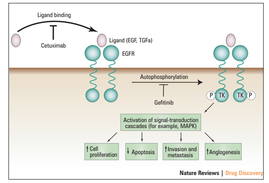


Replacement of the native receptor binding domain of DT with IL2 drives targeting.

Overview
- Objective: Kill the leukemic cell.
- Challenge: Replace native diphtheria toxin (DT) receptor binding domain with IL2—the ligand for the IL2 receptor (Il2R).
- Concept: IL2 receptor is overexpressed in leukemic cells.
- Agent: Diphtheria toxin—a potent inhibitor of protein synthesis.
- Approved for cutaneous T-cell lymphoma.
- Under development for chronic lymphocytic leukemia.
- Licensed to and marketed by Ligand Pharmaceuticals, Inc. as Ontak®.

Cetuximab

Principal Investigator
- John Mendelsohn, University of Texas, M.D. Anderson Cancer Center.



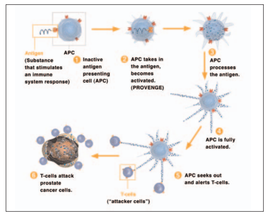
Graham, J. et al, Nat. Rev. Drug Discov. *2004; 3:549-550*

Overview
- Cetuximab is the only FDA-approved recombinant, chimeric monoclonal antibody against the extracellular domain of the human epidermal growth factor receptor (EGFR, HER1, c-ErbB-1).
- A DTP contractor chimerized monoclonal antibody with the permission of the originator.
- Combined with irinotecan, cetuximab yields a 23% response rate with a median response duration of 5.7 months.
- DTP and Imclone Systems signed an MTA for development of Erbitux®.
- Imclone Systems and Bristol-Myers Squibb marketed Erbitux® in 2004 for treatment of metastatic colorectal cancer.

New Agents in Clinical Trials

Provenge® (NSC 720270): A Prostate Cancer Vaccine

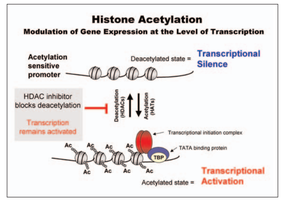
Principal Investigator
- Dr. Ronald Levy, Stanford University.



Overview
- Provenge® is a cancer vaccine based on prostatic acid phosphatase.
- It is licensed to NCDDG corporate partner Dendreon Corporation.
- It is now seeing significant responses in a phase II clinical trial for advanced prostate cancer (FDA fast-track status).

NVP-LAQ 824 (HDAC Inhibitor)

Principal Investigators
- Phillip Crews, University of California, Santa Cruz; Novartis Biomedical Research Institute.



Overview
- Psammaplin A: Lead discovered from marine sponge *Druinella purpurea* through partnership.
- Drug development was conducted at Novartis through structure biology-guided SAR incorporating psammaplin, trichostatin A, and tripoxin B pharmacophores.
- A phase I trial started in August 2002.

Examples of New NCDDG-Discovered Agents in Development

- PNP Gene Therapy Technology:
  - An enzyme from the gene converts prodrug to drug.
  - It is licensed to Mayne Pharmaceutical, Australia, for planned prostate cancer trials in 2005.
- PI-3 kinase inhibitor from Garth Powis, Arizona Cancer Center.
  - Related to Wortmannin which had *in vivo* activity, but toxicity prevented development to clinic.
- Telomerase Inhibitor from Geron Corporation.
- Sig/E7HSP70 vaccine for HPV-16+ cervical cancer (RAID production).
- LM-E7 vaccine in regulatory review for cervical cancer (RAID production).

Lessons Learned

- Good science is not sufficient.
- Industry is an asset—it increases speed of development but can be market-driven and risk-averse.
- Production of clinical-grade products can be rate-limiting.
- Projects are long-term investments. Payoff often comes after grant is over.
- Activities are time-intensive for NCI staff.