Frederick National Laboratory
for Cancer Research

sponsored by the National Cancer Institute

Biopharmaceutical Development Program at the Advanced Technology Research Facility

Transitioning Products from "Bench to Bedside"

DEPARTMENT OF HEALTH AND HUMAN SERVICES • National Institutes of Health • National Cancer Institute

Frederick National Laboratory is a Federally Funded Research and Development Center operated by Leidos Biomedical Research, Inc., for the National Cancer Institute

Our Mission

Frederick National Laboratory for Cancer Research

"Our goal is the rapid translation of innovative scientific discoveries into therapeutic products that hold the real hope for preventing and curing cancer and other diseases."

- **NCI established the BDP in 1993 to:**
  - Provide specialized and unique technical expertise and services not available in the commercial market
  - Perform feasibility studies of project candidates
  - Develop manufacturing process and assays
  - Conduct GMP manufacturing, filling, testing, and release
  - Generate and submit FDA and international regulatory filings
  - Conduct technology transfer to commercial entities

BDP GMP Operations

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- **Typical projects involve small markets, novel technologies, or regulatory hurdles (first-in-class).**
- **Intellectual Property (IP)**
  - Federal regulations allow the project originators to retain the rights to their IP provided in the project.
- **Sources of BDP Projects & funding**
  - Extramural NCI projects (selected competitively); funded by NCI/DCTD
  - Intramural NCI projects, funded by IDIQ Task Order
  - Other NIH Institutes such as NIAID or other agencies such as DOD can access (with NCI approval) underused BDP resources with full cost recovery under Economy in Government Act; funded by IDIQ Task Order
  - Collaborative Research and Development Agreements (CRADAs) between companies and the government; funded by collaborator and/or government

BDP Product Types

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- **Monoclonal Antibodies**
- **Recombinant Proteins**
- **Oncolytic Viruses**
- **Gene Therapy Vectors**
- **Whole Cell Products**
- **DNA/RNA Based Products**

- **Vaccines**
  - Peptide
  - Viral
  - Recombinant protein
  - Plasmid
  - Adsorbed
  - Cellular

A Tour of the BDP

Primary GMP Manufacturing Areas

Layout of Primary GMP Manufacturing Area and Virus Production Suite

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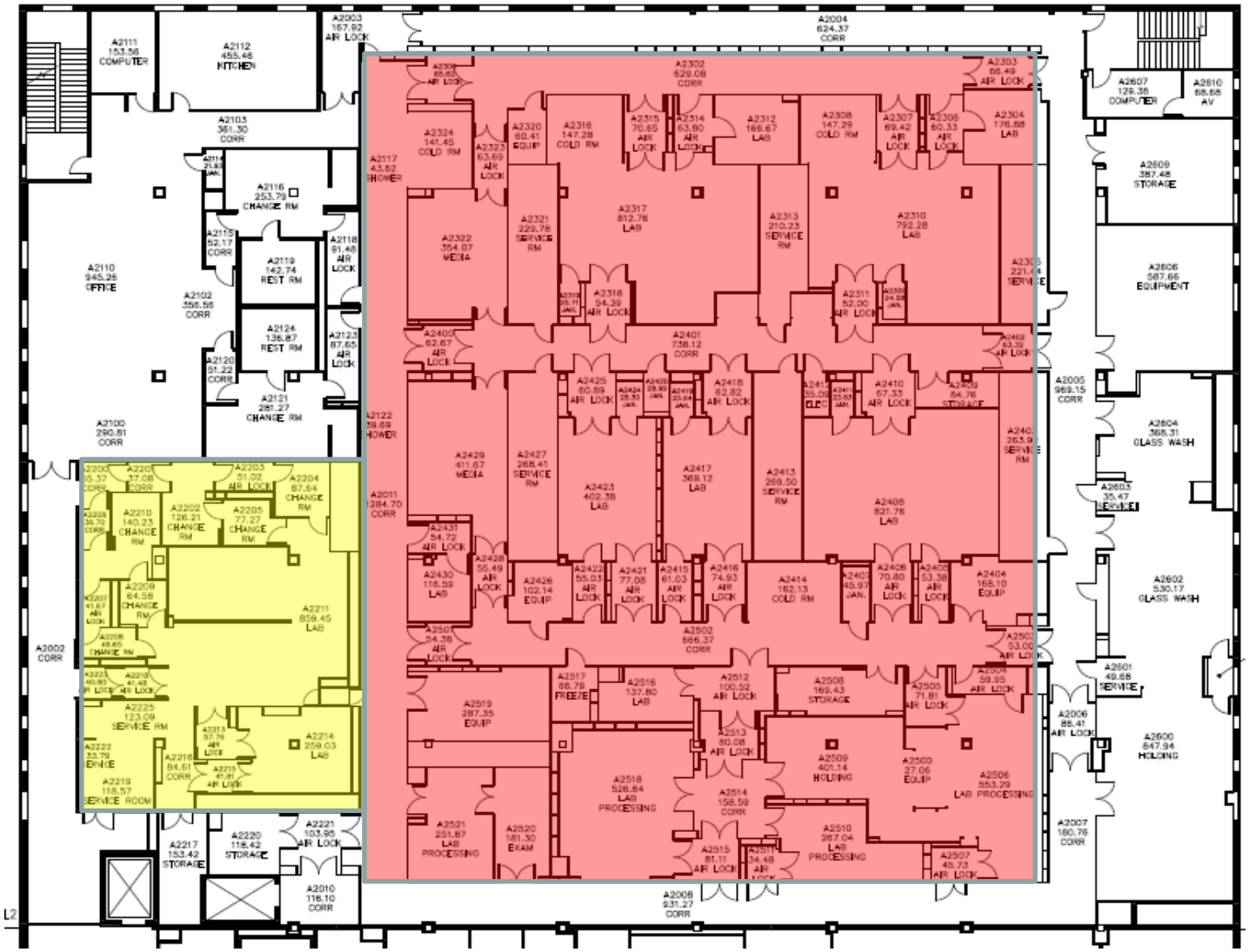

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A Tour of the BDP

Virus Production Suite

Virus Production Suite

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Biological Safety Cabinet Configuration for Large Scale Production

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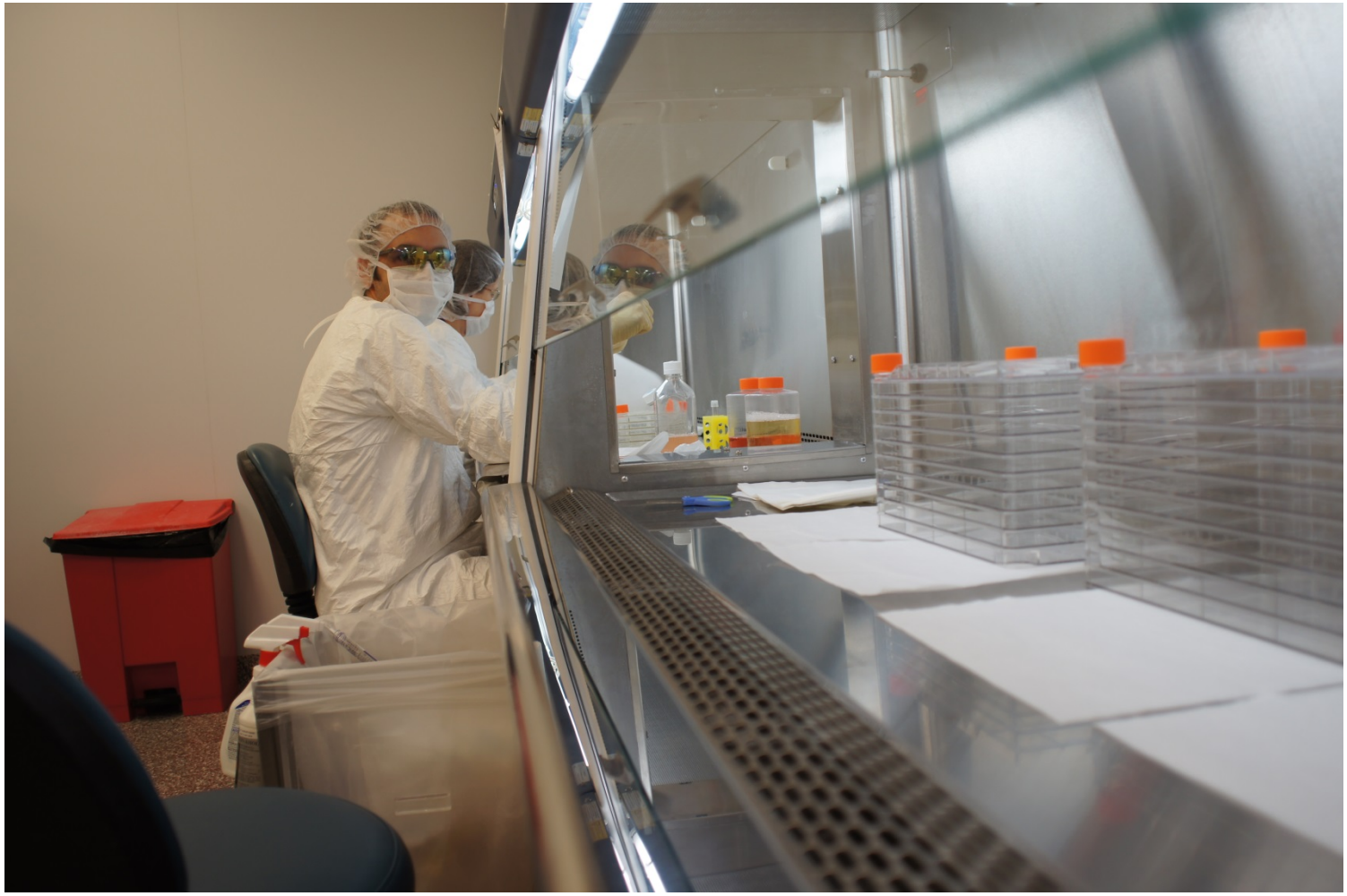

CellSTACKS in Stericult Incubators

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A Tour of the BDP

Eukaryotic and Prokaryotic Production Systems

Upstream: Fermentors and Bioreactors

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These 150-L and 500-L fermentors are used to grow prokaryotic cells to high densities (O.D. of 280). Once induced to begin production of the desired protein, they can produce up to 500 grams of raw product.

This 1000-L bioreactor is used to grow eukaryotic cells in suspension. Yields of up to 300 grams of raw product can be obtained.

Downstream: Protein Purification

Column chromatography is usually our method of choice to purify protein products. Three different types of columns are usually required to purify each product.

Vial Filling

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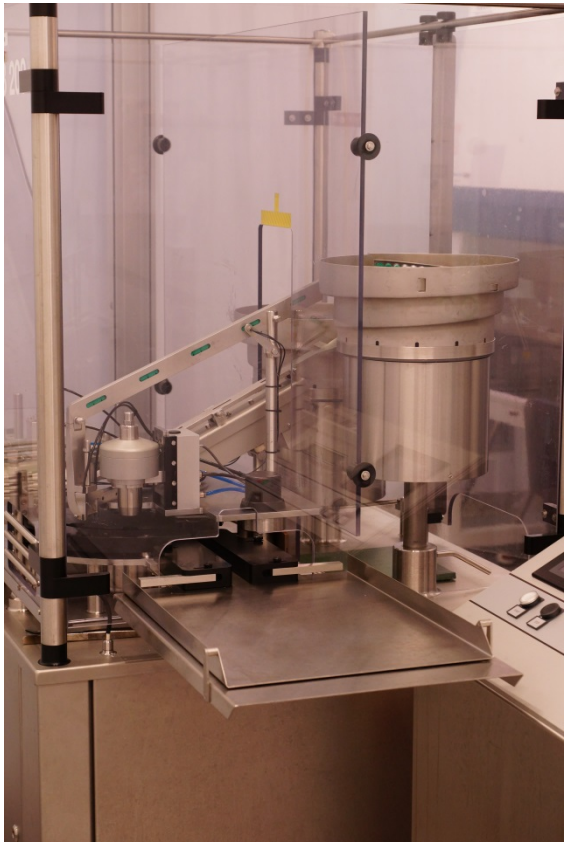

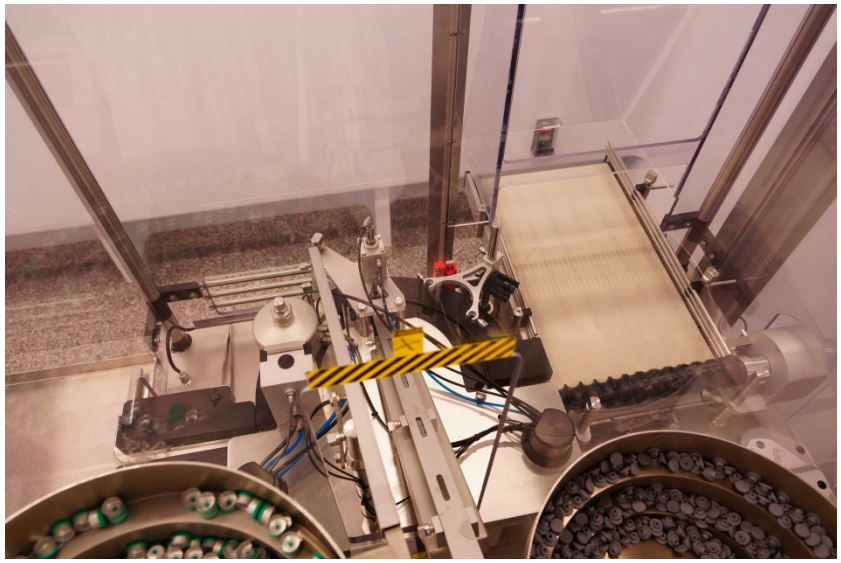

This semi-automatic vial filling machine is completely enclosed to protect the product from contamination.

Product Testing and Characterization

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The Process Analytics Department utilizes a variety of technologies to test our raw materials and products. These methodologies include HPLC; UPLC; IEF; FACS; DLS; DSC; CD; TOC; BIAcore; electrophoretic gels; fluorometry; cell-based assays; and others.

Agilent 1290 HPLC

Waters Electrospray MS-MS Mass Spectrometer

BDP Products Since 1998

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- More than 250 lots of product have been released for clinical use.
- More than 130 distinct products have been manufactured.
- More than 60 products have been or are in human clinical trials.
- Two products have been licensed and are commercially available.
- More than 14 products are being readied for licensure.
- At the present time, 21 products are on active stability at the BDP.

A Sampling of BDP Products

BL22 / HA22

- **BL22 and HA22 are immunotoxins that target cancer cells with CD22 receptors on their surface.**

- **In an early clinical trial in hairy cell leukemia, the administration of BL22 resulted in 11 out of 16 patients achieving complete remission of their cancer.**

  Kreitman RJ, Wilson WH, Bergeron K, Raggio M, Stetler-Stevenson M, FitzGerald DJ, Pastan I. Efficacy of the anti-CD22 recombinant immunotoxin BL22 in chemotherapy-resistant hairy-cell leukemia. N Engl J Med. Jul 26;345 (4):241-7, 2001.

- **HA22, the next generation of BL22, has been licensed for commercial use:**

ch14.18

- **Neuroblastoma is the most common solid cancer that affects young children.**
- **ch14.18 is a monoclonal antibody that targets the GD2 receptor on the surface of neuroblastoma cells.**
- **The NCI Children's Oncology Group (COG) performed a clinical trial led by Dr. Alice Yu at UCSD in children with high-risk neuroblastoma. The trial showed improved progression-free survival (58%->73%) when ch14.18 together with cytokines IL-2 and GM-CSF were added to the standard treatment regimen.**

  Yu, A.L., A.L. Gilman, M.F. Ozkaynak, et al. (2010). Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. N Engl J Med. 363:1324-1334.

- **The BDP developed the manufacturing process for ch14.18 and manufactured the national supply for clinical trials in the USA, Canada, Australia, and New Zealand.**
- **The product, Unituxin (dinutuximab), is now available commercially.**

IL-15

- **IL-15 is an interleukin that stimulates specific immune cells.**
- **The IL-15 clone was developed in the intramural laboratory of Dr. Tom Waldmann.**
- **The BDP has manufactured IL-15 for use in multiple clinical trials.**

  Biotech. Progress 28(2), Mar/Apr 2012.

  - The clinical trials are helping determine if IL-15 can be used as a direct treatment for many types of solid tumors such as melanoma, lung, and renal cell cancers.
  - Other clinical trials use IL-15 to stimulate a person's immune cells that have been engineered and grown in culture. These cells are then re-introduced into the body to attack melanoma and acute lymphoblastic leukemia.
- **IL-15 is also being studied as an immune adjuvant to boost the effectiveness of new vaccines (e.g., HIV) and cancer immunotherapies (e.g., checkpoint inhibitor combinations).**

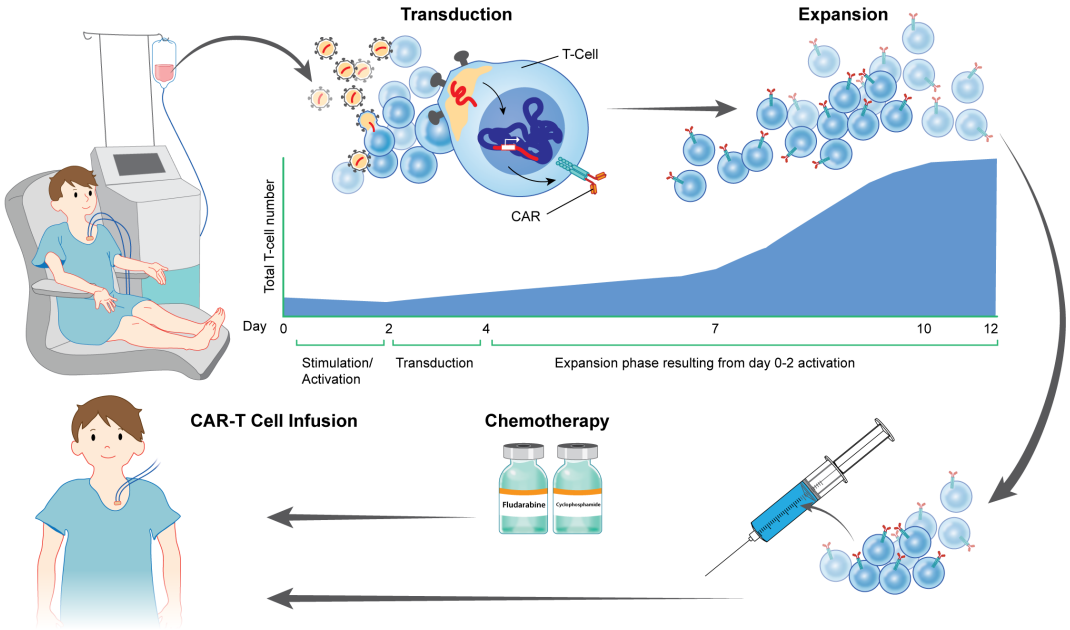
Viral Vectors
PVS-RIPO (Oncolytic Polio Virus)

- PVS-RIPO is a vaccine strain of Polio virus that was genetically modified by Dr. Matthias Gromeier, Duke Medical Center to treat Glioblastoma.
- Glioblastoma is the most common type of brain tumor and the most lethal.
- It took many years of testing before the FDA could give approval to use this product in humans.
- The first patient treated with PVS-RIPO was a 20 year old nursing student with Glioblastoma who had failed all standard treatments. Her tumor is gone and has not returned for more than 6 years.

- Additional studies in pancreatic cancer and other malignancies are under consideration.

Autologous Cell Therapy Manufacturing

- Autologous products require raw material (apheresis) and product chain logistics: cryopreservation, scheduling manufacturing, chain of custody.
- Rapid product release: QC/QA systems to review and ship cryopreserved product 6 days post-harvest. Interim COA shipped with product prior to 14-day sterility completion (minimum 3-day sterility data with all other safety tests). FDA accepted this approach in the first IND BDP has supported.



Process Qualification:

- Evaluate production using identical donor apheresis
- Demonstrate Prodigy manufactured cells work in a preclinical model.
- Shipping qualification study to insure product stability during shipping

Recent / Ongoing Projects, Non-NCI Funded

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- RLIP76: Radical ion transporter protein for Acute Radiation Syndrome (***NCATS/NIAID***)
  - BDP improved production and purification process (~40% → >95% purity)
- GP-350- and gH/gL/gp42-Ferritin nanoparticles: Vaccine for Epstein Barr Virus (***NIAID/NCI***)
  - BDP developed production and purification process for multi-component vaccine
- AGIL-AADC: AAV-based gene therapy for the treatment of Rare Disease Aromatic L-amino acid Decarboxylase (AADC) deficiency (***NCATS***)
- TTHX1114: Engineered FGF-1 protein for the treatment of Rare Disease Fuchs Endothelial Corneal Dystrophy ***(NCATS)***

BDP – A History of Assistance to Others

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- **International Collaboration** – Setting up programs similar to the BDP
- **45 Internships, Volunteers, and Visitors**
- **Training Programs**
  - Joint workshops with FDA / FDA trains investigators at BDP / GMP training
- **Working with Principal Investigators and optimizing interactions among government, academia, and industry**
- **BDP Website – http://ncifrederick.cancer.gov/Programs/Science/BDP**
  - >300 SOPs, manufacturing and testing, quality system, and training documents

Accessing the BDP

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- **BDP Website**
  - http://ncifrederick.cancer.gov/Programs/Science/BDP
- **The BDP Is Not a CMO**
  - Projects are brought into the BDP via application to the NCI.
- **Intramural and Extramural**
  - The NCI Experimental Therapeutics Program (NExT)
    - http://next.cancer.gov

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Thank you for your interest in the BDP

SAIC Frederick