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Life Cycle of an Investigational Biologic & Biologics Production at NCI-Frederick

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NCI-Frederick Advisory Committee
Frederick, MD
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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

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Therapeutic/Diagnostic Discovery & Development Support Provided by NExT

- Medicinal chemistry, HTS, lead optimization (F)
- Enhanced chemical synthesis of small molecules and peptides (F)
- Scale-up production of small molecules (N), biologicals (F), imaging agents (N)
- Isolation and purification of naturally occurring substances (F)
- Development of early stage, clinical pharmacodynamic assays (F)
- Exploratory toxicology studies and pharmacokinetic evaluation (N)
- PK/efficacy/ADME studies (bioanalytical method development) (N)
- Development of suitable formulations (N)
- Range-finding initial toxicology and IND-directed toxicology (N)
- Product development planning and advice in IND preparation (N)
- Later-stage preclinical development of monoclonal antibodies, recombinant proteins, therapeutic vaccines, and gene therapy agents (F)
- Manufacture of drug supplies (N)
- Analytical methods development for bulk material; formulation (N)
- CLIA-grade clinical assay development for later stage trials (F)
- Production of clinical dosage forms (N)
- Stability testing of clinical dosage forms (N)
- Regulatory support (N)

(N)=NCI; (F)=Frederick

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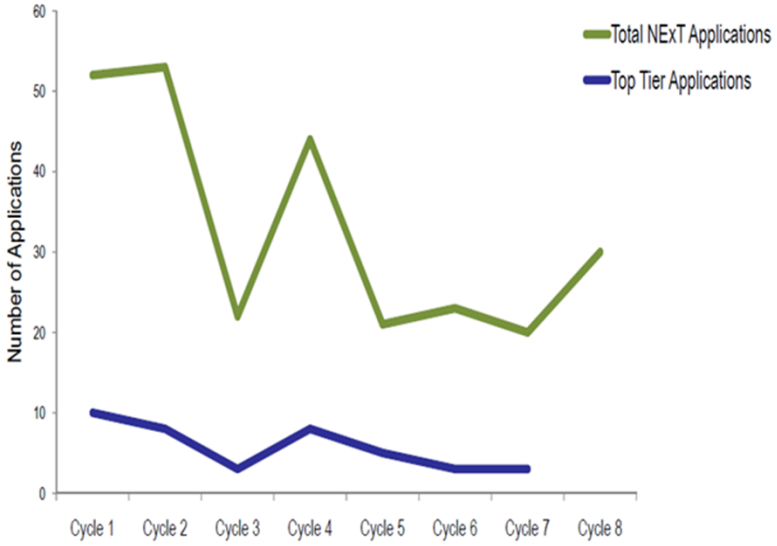
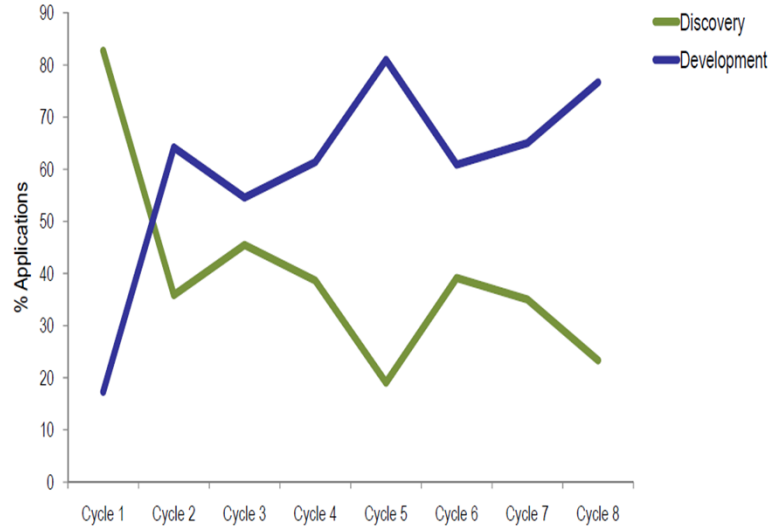
265 NExT Applications Received in Cycles 1-8

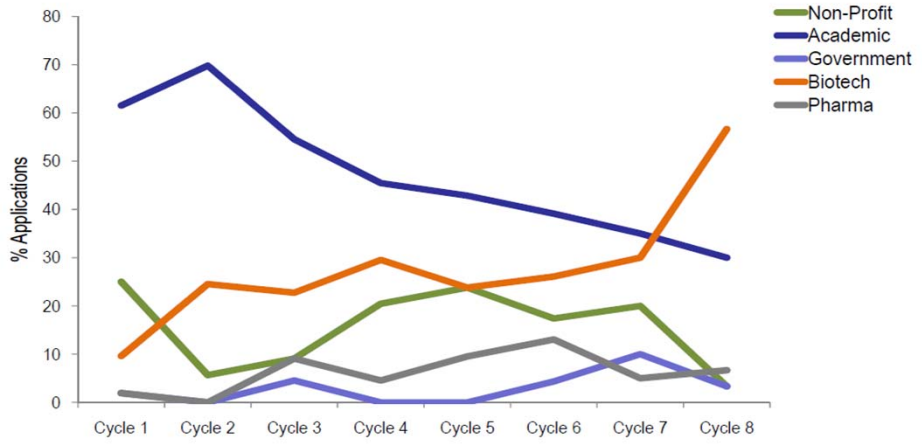


Overall, **17%** of applications have been ranked in the top tier.

*Cycle 8 top tier TBD



Overall, **44%** of applications requested early-stage discovery resources, while **54%** requested preclinical and clinical resources.



Source of NExT Applications

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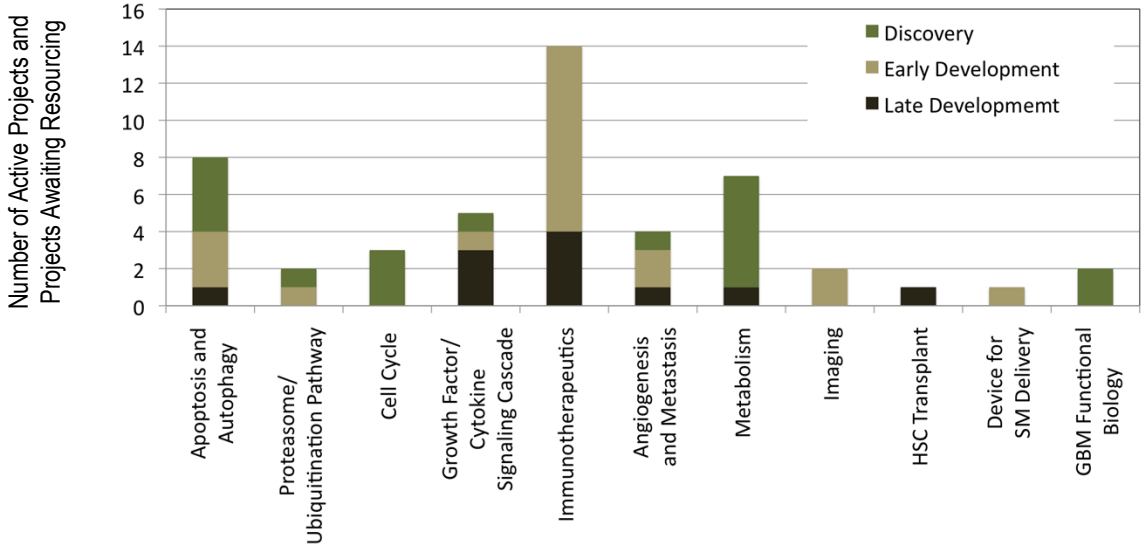
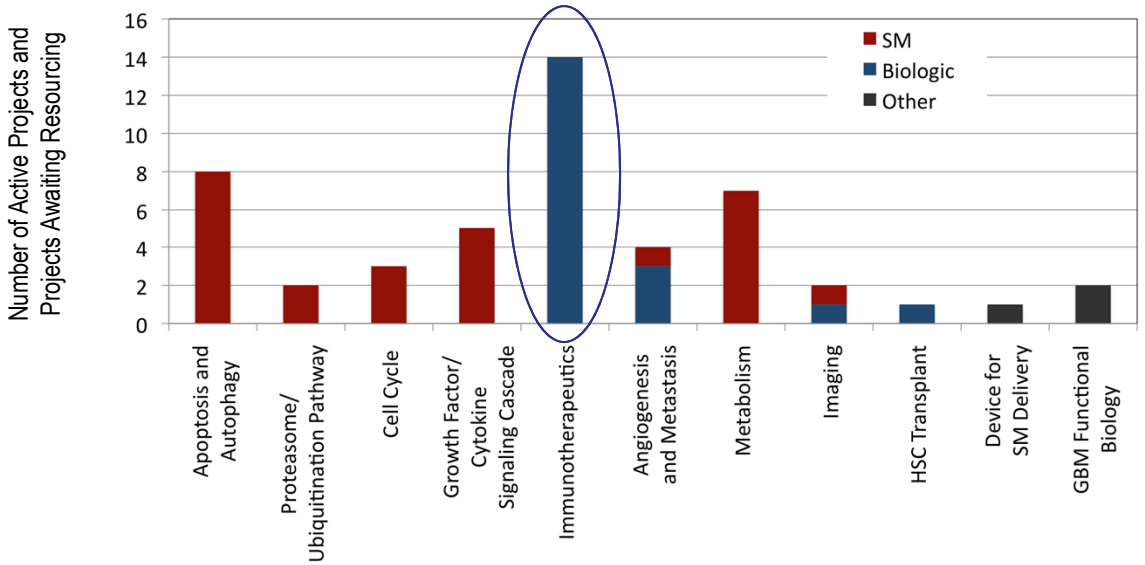
NExT Portfolio by Mechanism

Project Development Stage



Agent Type



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Immunotherapeutic Projects: 14 as of 1/2011

Late Development

1.	Phase 3: **CD22 mAb** (CAT-8015) conjugated to Pseudomonas exotoxin A	PI: Marapaka
2.	Phase 2: **Vaccine** (CDX-1308) to elicit **HER2/neu**-specific immunity	PI: Davis
3.	Phase 2: A bispecific **CD19/CD3 mAb** (blinatumomab) that triggers a CTL reaction	PI: Frankel
4.	Phase 2: **IL-2/IL-15Rβ mAb** (Hu-Mik-β-1) for treatment of Celiac disease	PI: Waldmann
5.	Phase 1: **rhIL-15** that stimulates expansion of functionally educated NK cells	PI: Miller

Early Development

6.	CC: **CD22 mAb** (NSC 725179)	PI: Tuscano
7.	CC: **Viral oncolytic agent** based on affinity to **CD155** (PVS-RIPO)	PI: Gromeier
8.	CC: **Viral oncolytic agent** using herpes virus vector (**C134**)	PI: Cassady
9.	CC: **Viral oncolytic agent** using conditional adenovirus (Ad5-Δ24RGD)	PI: Alvarez
10.	CC: **CMV-MVA vaccine**	PI: Diamond
11.	CC: **Hsp110-gp100** complex **vaccine**	PI: Kane
12.	CC: Plasmid **vaccine** against **HPV** (pNGVL4a-CRT/E7)	PI: Pai
13.	CC: **Vaccine** against **HPV16** (HPV L2E6E7)	PI: Roden
14.	CC: **Ig-4-1BB ligand** that stimulates T activation via **CD137**	PI: Woo

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Ongoing Prioritization of Biologics Portfolio

Special Emphasis Panel
Biologics Portfolio Priority Subcommittee

Mac Cheever, MD Chair
Univ. of Washington

Louis Weiner, MD
Georgetown

Mario Sznol, MD
Yale

David Parkinson, MD
Nodality

Gwen Fyfe, MD
Formerly Genentech

Mike Morin, PhD
Formerly Pfizer

Stephen Russell, MD
Mayo Clinic

November 28, 2011

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Prioritization Process Used To Ascertain Which Biologics To Move Forward?

- This selection is based on the following criteria.
  - Scientific Merit
  - Feasibility
  - NCI Mission
  - Novelty
  - Clinical Need
- For Biologics: Focus on production of molecules required by the immunotherapy community; supply agents to the Cancer Immunotherapy Trials Network
- This evaluation process to provide guidance about the priority utilization of the capacity – based resources provided by NCI—in particular, the Biologics Development Program

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Changing Priorities of Biologics Portfolio

Initial NCI-BRB prioritization:

High Priority
- Ch 14.18 anti-GD2 monoclonal antibody
- IL-15 cytokine (Growth factor for activated T cell & NK cells)
- ChII-1F4 anti-amyloidosis mAb
- GMP endotoxin*

Moderate Priority
- IL-7 cytokine (Homeostatic T cell growth factor)
- hATN-658 uPAR mAb
- HSV C134 oncolytic Herpes virus (Glioma)
- H1299 cellular vaccine (Lung cancer)

Low Priority
- HPV16 TA-CIN + GPI-0100 vaccine for HPV (HPV16 L2/E6/E7 fusion protein)
- hIg-h4-1BBL protein (T cell activator)

Close: 1. CD22mAb; 2. Ad5RGD viral oncolytic; 3. CMV vaccine; 4. CD 155 polio viral oncolytic completed

Biologics Subcmte. revised prioritization:

High Priority
- Ch 14.18 anti-GD2 monoclonal antibody
- IL-15 cytokine
- ChII-1F4 anti-amyloidosis mAb

Moderate Priority
- HSV C134 oncolytic Herpes virus (Glioma)
- hIg-h4-1BBL protein

Low Priority
- HPV16 TA-CIN + GPI-0100 vaccine for HPV
- hATN-658 uPAR monoclonal antibody
- H1299 cellular vaccine
- GMP endotoxin*

Hold
- IL-7 cytokine

***Moved to lowest priority at 12/7/2011 NExT SEP meeting.**

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Monitoring the NCI-Frederick Biologics Facility

Ongoing interactions

- Daily interactions between NCI and SAIC-F
- Monthly report of projects and budget
- Annual budget assessment and adjustment

Need for change identified in FY 2011

- Budgetary issues (cost overruns; NCI constraints)
- Change in work focus/scope
- Operational issues

Change process

- On site extramural review with extensive documentation-2 days (4/11)
- Three independent evaluations obtained
- SAIC/NCI discussion, response, and initiation of changes

Training	Affiliation	Expertise
PhD	Director, Center for Biomedicine & Genetics Research Institute	Immunotherapy, founding Director of the Center for Applied Technology Development
MD, PhD	Director, Center for Cell and Gene Therapy Medical School	Gene Therapy, Immunotherapy
PhD	Director QA, GMP Facility Research Institute	Director QA, responsible for putting together the GMP program

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BDP External Review: Summary & Outcomes

Issue	Outcome
Staffing: excessive for # projects	**Decrease** from 98 to 44 fte's with focus on redundant QC staff & enhanced cross-training; outsourcing
Cost Accounting: difficult to understand	**Interface** SAIC and NCI systems; initiate project-based cost tracking
Project Costs: overly costly	**Increase** outsourcing and subcontracting; require availability of initial starting material for QC; project development by PI not BDP
Facilities: underutilization of some areas	**Space re-evaluation:** 38% decrease in ATRF space requirements (22,291 vs. 35,721 sq.ft.)
Outsourcing: need to discern what projects require NCI manufacturing	**Budget:** Decreased from $16 M (including $5M ARRA) to $9M total