Overview of Biologic Types and Various Applications in Cancer

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NIH NATIONAL CANCER INSTITUTE

DTP Drug Development Workshop
Session V – Development of Biological Products
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Presentation Outline

~ What is a Biologic?

~ Brief History of Biologics Cancer Treatment and Diagnosis

~ Regulation of Biologics

~ Overview of Translational Pathways

~ NCI and Other Resources

Biologic – Definition

A treatment that uses substances made from living organisms to treat disease. These substances may occur naturally in the organism or may be engineered and produced in the laboratory.

In cancer, some biological therapies stimulate or suppress the immune system to help the body fight cancer (e.g., *immunotherapies*). Other biological therapies attack specific cancer cells (e.g., *targeted therapies like ADC*). They may also lessen certain side effects caused by some cancer treatments or can be used to image tumors for diagnosis or disease monitoring.

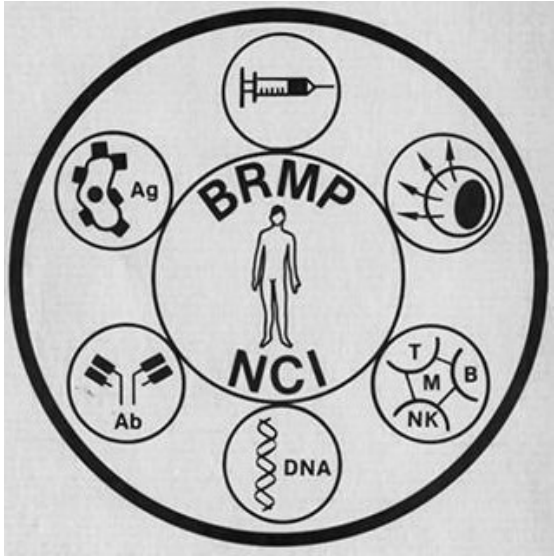
Types of biological therapy include immunotherapy (such as cytokines, cancer treatment vaccines, and some antibodies) and some targeted therapies. Also called biological response modifier therapy, biotherapy, and BRM therapy.

A Brief History of Biologic Therapies and Diagnostics for Cancer

Evolution of Biologics

- Biologic isolates and extracts
- Recombinant proteins
- Antibodies
- ADCs and imaging agents
- Viruses/VLPs and bacteria
- Autologous CAR T cells
- *Engineered Cells and Synthetic Biology*

Biological Response Modifiers Program, NCI



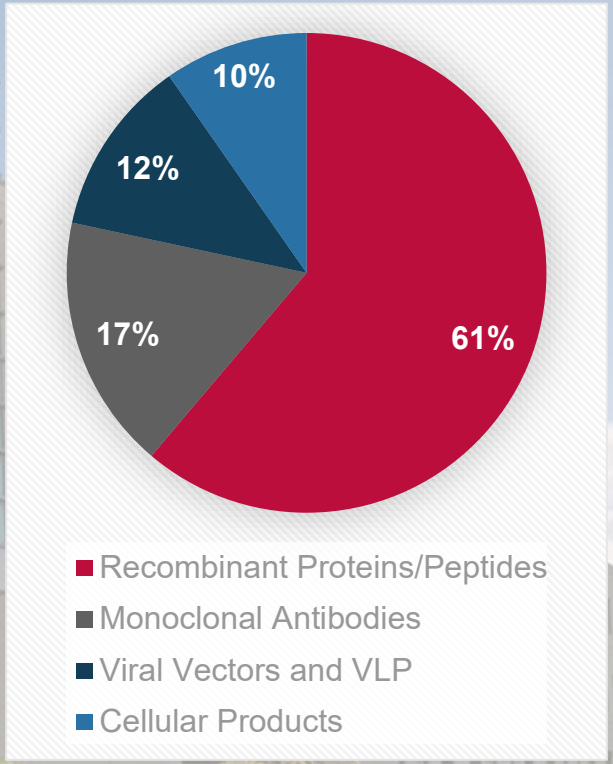
- Interferon studies in the 1970s
- NCI grants, contracts, and clinical trial support
- Monoclonal antibody production and acquisition
- Tumor vaccines
- Cell and gene therapies
- Oncolytic viruses and bacteria

Biopharmaceutical Development Program at the Frederick National Laboratory for Cancer Research

NCI established the BDP in 1993 to:

- Provide specialized and unique technical expertise and services not available in the commercial market
- Feasibility studies of project candidates
- Development of manufacturing process and assays
- Perform GMP manufacturing, filling, testing, and release
- FDA and international regulatory filings
- Technology transfer to commercial entities

>150 investigational agents since 1998



Regulation of Biologics

FDA CBER, CDER

ICH Guidelines

Tragedies Prompt Regulations

1800s Patent Medicines – Many injured or killed

1901 Diphtheria antitoxin contaminated with tetanus

1902 **Biologics Control Act**

1906 Bureau of Chemistry (Dr. Harvey Wiley)

1930 Food and Drug Administration

1937 Elixir of Sulfanilamide - diethylene glycol contamination, 105 killed

1938 **Federal Food, Drug, and Cosmetic Act**

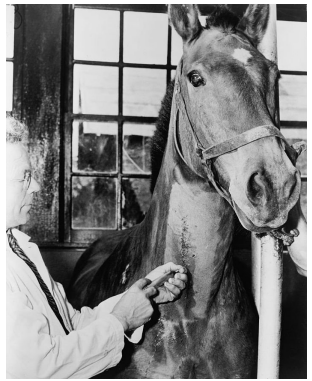
1954-56 Polio vaccine contaminated with SV-40 virus

1960 Thalidomide ~12,000 affected

1962 **Kefauver-Harris Drug Amendments** (cGMPs, safety testing)

1972 Control of biologics passed from PHS to FDA (CBER established)

http://www.fda.gov/AboutFDA/WhatWeDo/History/Overviews/ucm056044.htm



Good Manufacturing Practices (GMP) Regulations

- 21 CFR 110 GMPs for human food
- 21 CFR 111 GMPs for dietary supplements
- **21 CFR 210 GMPs for drugs: general**
- **21 CFR 211 GMPs for finished pharmaceuticals**
- 21 CFR 225 GMPs for medicated feeds
- 21 CFR 226 GMPs for Type A medicated articles
- **21 CFR 606 GMPs for blood & blood components**
- 21 CFR 820 GMPs for medical devices
- **21 CFR 1271 Human Cells, Tissues, and Related Products**

Purpose of GMPs

- Identify critical areas and procedures for control to ensure the quality of the product
- Identify minimum requirements for control in these areas
- Require written procedures to describe HOW this control will be assured
- Require that written procedures be FOLLOWED and DOCUMENTED.

It's All About Control

What is a Quality Biologic/Drug?

Safety	Does no harm
Identity	Is what it's supposed to be
Strength	Sufficiently potent
Quality	Meets specified requirements
Purity	Free of contamination

SISQP

FDA - CBER

Center for Biologics
Evaluation and Research

Industry.Biologics@fda.hhs.gov
800-835-4709
240-402-8010

What they regulate

- Cell & Gene Therapies
- Vaccines & Allergenics
- Tissue- & Blood-based Products
- Certain Devices

Offices and contacts

- Office of Vaccines Research and Review (OVRR)
- Office of Tissues and Advanced Therapies (OTAT)
- Office of Blood Research and Review (OBRR)

FDA - CDER

Center for Drug
Evaluation and Research

ONDCommunications@fda.hhs.gov
301-796-0700

What they regulate

- OTC, Prescription, & Investigational Drugs
- Generic Drugs & Well-characterized Biologics

Office of New Drugs - investigational biologics

- Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)
- Immunology and Inflammation (OII)
- Rare Diseases, Pediatrics, Urologic/Reproductive Medicine (ORPRUM)
- Infectious Diseases (OID)
- Neuroscience
- Nonprescription Drugs (ONPD)
- **Oncologic Diseases (OOD)**
- Specialty Medicine (OSM)

FDA Consultation

Type B, Pre-IND Meeting

- Clinical, Pre-clinical/Tox, CMC
- Propose an approach with scientific justification

INTERACT Meeting:

Initial **T**argeted **E**ngagement for **R**egulatory **A**dvice on **C**BER Produc**T**s

- Informal, non-binding
- Intended for innovative biologics with unique challenges that could impact safety

Overview of Translational Steps for Biologics

Basic Research vs Drug Development

Basic research is driven by hypothesis-driven research that results in new knowledge and thus grows new branches on the tree of knowledge.

Drug development is product development and thus is driven more by the engineering paradigm of '***keep the end in mind***'.

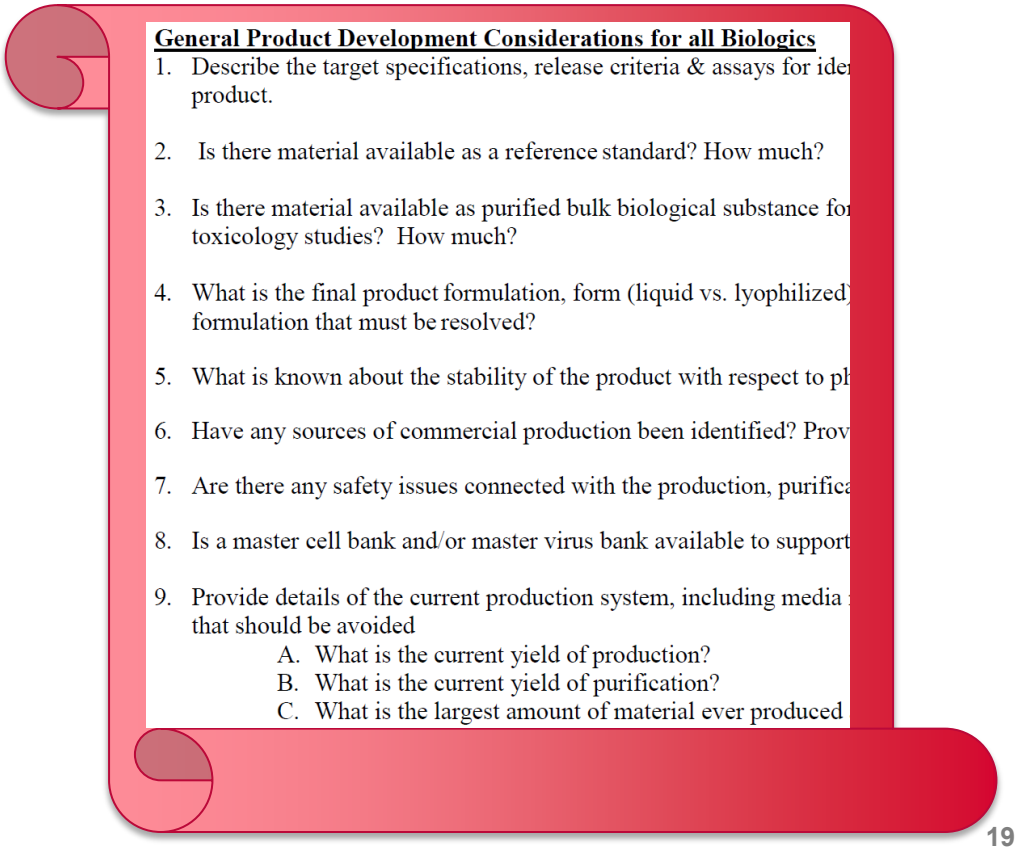
Typical Milestones for Translation of a Biologic

- Is it what you think it is? Due diligence of R&D/preclinical material and analysis of starting materials for GMP suitability (SISQP, cell line history, etc.)
- Can you make enough? Process development for scale-up feasibility, purification, assay development and SOPs, formulation stability, etc.
- Generate reference material: reference lot, cell banks, virus banks
- Set testing specifications: Analytical qualification for QC product release; forced degradation studies to inform the stability program
- Can you make the clinical lot? Pilot manufacturing, "GMP dress rehearsal": often use product for IND-directed toxicology studies and infusion stability studies
- IND-directed safety studies: Range finding, toxicology, biodistribution
- cGMP manufacturing: QC/QA release - CoA, CMC, IND submission
- Real-time stability: Subset of release assays that will detect degradation and contamination

Generic Questionnaire for Biologics

https://next.cancer.gov/content/docs/Biologics_Product_Development_Questionnaire.pdf

- Gauge the developmental readiness of a biologic
- Address SISQP
- Specific questions for recombinant proteins, viral vectors, oligonucleotides, peptides, and cell products



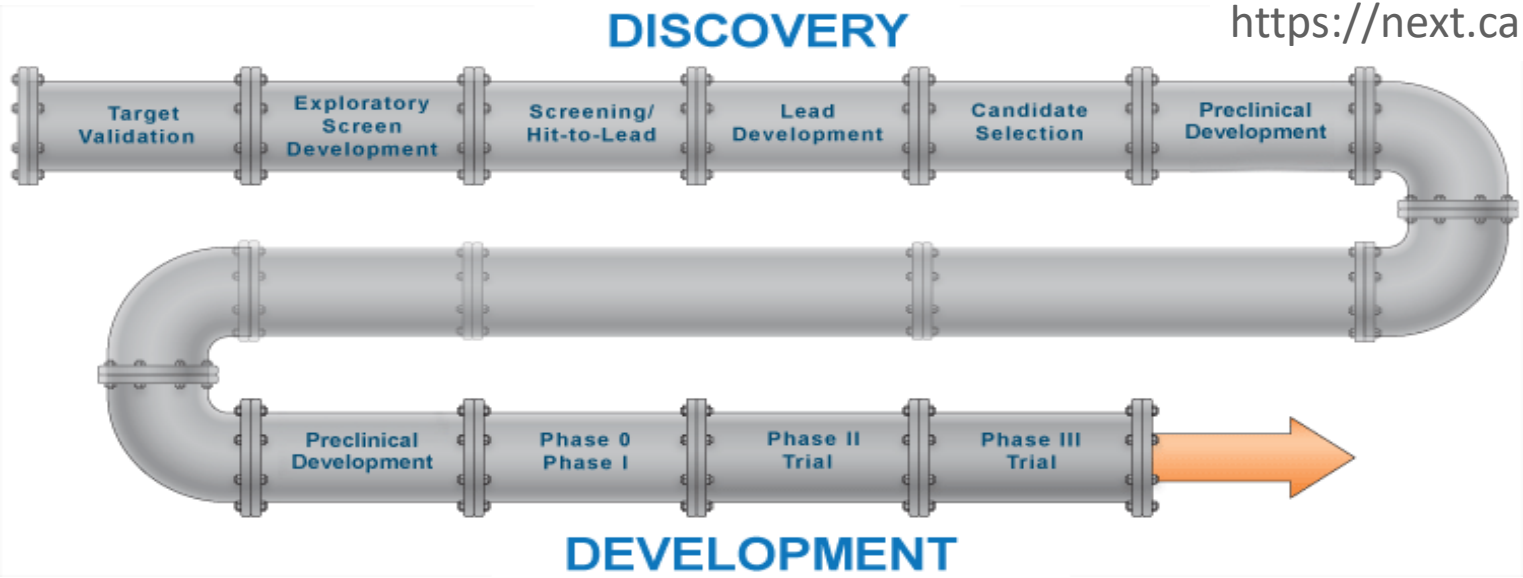
General Product Development Considerations for all Biologics

1. Describe the target specifications, release criteria & assays for ide product.
2. Is there material available as a reference standard? How much?
3. Is there material available as purified bulk biological substance fo toxicology studies? How much?
4. What is the final product formulation, form (liquid vs. lyophilized) formulation that must be resolved?
5. What is known about the stability of the product with respect to pl
6. Have any sources of commercial production been identified? Prov
7. Are there any safety issues connected with the production, purifica
8. Is a master cell bank and/or master virus bank available to support
9. Provide details of the current production system, including media that should be avoided
   A. What is the current yield of production?
   B. What is the current yield of purification?
   C. What is the largest amount of material ever produced

NCI and Other Resources

NCI Experimental Therapeutics Program - NExT

https://next.cancer.gov



- Not a grant; no funding is provided to applicant
- Requires clear path to clinic/patient benefit
- Provides access to NCI drug development resources
- Applicant is a key member of the Project Team: involved in project planning, implementation, and has full access to data
- Free consultation service

PREVENT Cancer Preclinical Drug Development Program

- Not a funding mechanism but a contract resource provided by NCI
- Focus is on cancer prevention
- Flexible entry points for agents and biomarkers into the development pipeline

- https://prevention.cancer.gov/major-programs/prevent-cancer-preclinical-drug-development-program

NCATS Translational Research Resources

Bridging Interventional Development Gaps (BrIDGs)
(ncats.nih.gov/bridgs)

- Process development, scale-up, formulation, cGMP production
- IND-directed pharmacology and toxicology studies

Therapeutics for Rare and Neglected Diseases (TRND)
(ncats.nih.gov/trnd)

- IND-enabling studies including all the above in BriDGs

NHLBI Translational Research Resources

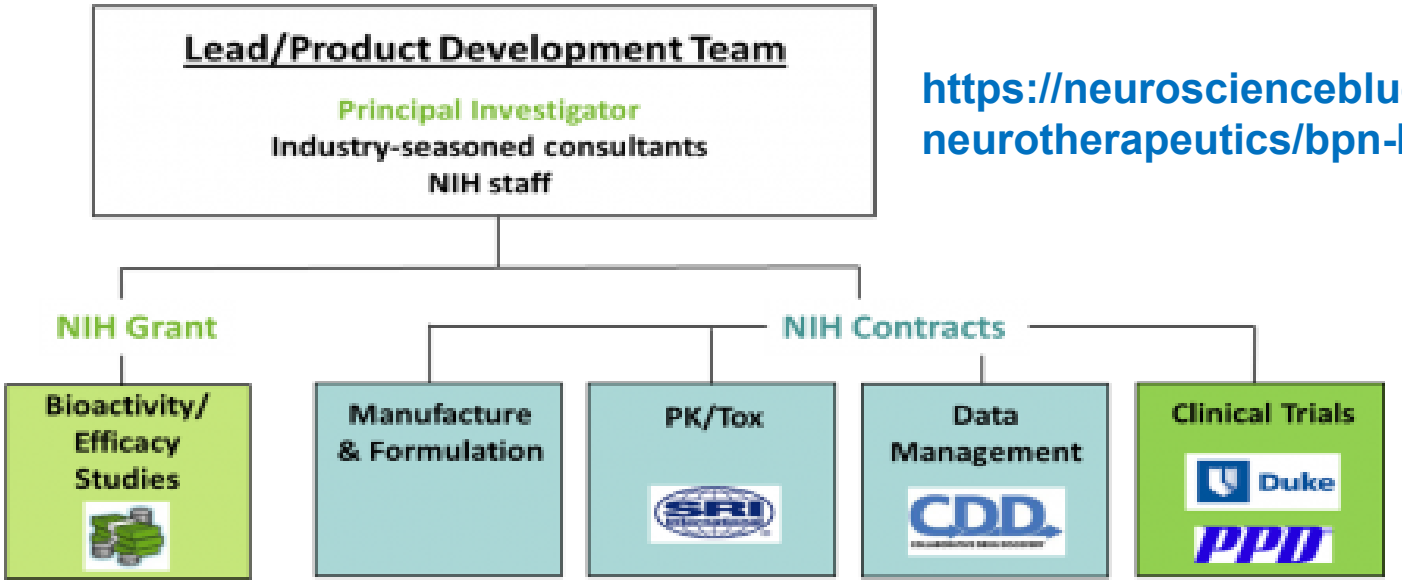
- Gene Therapy Resource Program (www.gtrp.org)
  - Clinical grade AAV and Lentivirus
  - IND-directed pharmacology and toxicology studies
  - Regulatory support

Gene Therapy Resource Program

Funded by the National Heart, Lung, and Blood Institute

NINDS: Blueprint Neurotherapeutics Network for Biologics, BPN-Biologics

Leveraging a combination of cooperative agreement grants and resource contracts



https://neurosciencebluprint.nih.gov/neurotherapeutics/bpn-biologics

UG3/UH3 (**PAR-21-163)** for Discovery/Lead Optimization, Product Development, IND-enabling Studies, and Phase I Clinical Trial (or U44 **PAR-21-233**)

THANK YOU!

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