University of Louisville: Craft Seminar
November 8, 2018

A Journey: From Bench Scientist to NIH Program Officer

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NIH/NIAID/DAIDS/PSP

DHHS/NIH Required Disclaimer

The views expressed are those of the presenter and do not necessarily reflect the official policies of the Department of Health and Human Services (HHS), nor does mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government

Conflicts of Interest

None to report

I Am Going to Take You On a Journey

"The only real voyage of discovery consists in not seeking new landscapes but in having new ideas"

Marcel Proust

HIV Non-vaccine Biomedical Prevention (nBP)

DEFINITION

- ✓ A safe, effective and acceptable agent delivered as a single, combination or multi-component strategy
  - Topically –applied to a mucosal surface:
    gel, tablet (insert), film, enema/douche, suppository and/or device (i.e. ring, diaphragm, IUD)
  - Systemically:
    oral, injection, transdermal or implant.

- ✓ Prevents transmission and acquisition of HIV and possibly other sexually transmitted infections at the female and male genital and gastrointestinal mucosa

- ✓ For all individuals at risk for HIV infection:
  - HIV negative
  - In a serodiscordant relationship

Some Basic Facts About HIV/AIDS

Risk for HIV Infection

- **Vaginal HIV Transmission**
  Est. Risk per act: 1:100 to 1:1000

- **Rectal HIV Transmission**
  Est. Risk per act: 1:10 to 1:100

  Anal intercourse is not just a "gay man" issue:
  Depending upon age, race, geographic location, education, poverty status, and gender power relationships estimates are that from 5% to 60% of heterosexual couples may practice receptive anal intercourse (RAI).

  - Other Forms of Transmission
    - Intravenous Drug Use (IDU) –1:1 to 1:10 –depends upon viral load
    - Mother to Child Transmission – With antivirals approaches 0 (without antivirals 1:2 to 1:7)

Global HIV Statistics

Although great progress has been made toward controlling the AIDS Pandemic

2016, HIV infection is the:
Leading cause of death of reproductive age women (15-49 years of age)
Second leading cause of death in women (15-24 years of age) in Africa

Increases in AIDS-related mortality have occurred over the past decade in the Middle East and North Africa (48% increase) and eastern Europe and central Asia (38% increase).

Global summary of the AIDS epidemic | 2016

Number of people living with HIV	Total	**36.7 million** [30.8 million–42.9 million]
	Adults	**34.5 million** [28.8 million–40.2 million]
	Women (15+ years)	**17.8 million** [15.4 million–20.3 million]
	Children (<15 years)	**2.1 million** [1.7 million–2.6 million]
People newly infected with HIV in 2016	Total	**1.8 million** [1.6 million–2.1 million]
	Adults	**1.7 million** [1.4 million–1.9 million]
	Children (<15 years)	**160 000** [100 000–220 000]
AIDS-related deaths in 2016	Total	**1.0 million** [830 000–1.2 million]
	Adults	**890 000** [740 000–1.1 million]
	Children (<15 years)	**120 000** [79 000–160 000]

Translates to →

Globally
~5000 new infections a day
~4500 in individuals 15 years or older
43% women
37% ages 14-25

HIV in the U. S.

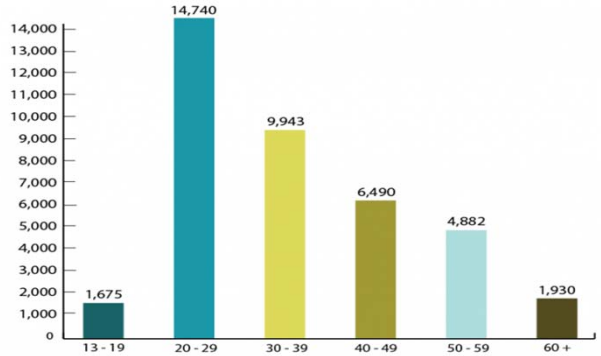
CDC Factsheet

There were an estimated 37,600 new HIV infections in 2016.

Today 1 in 7 (14%) HIV infected individuals do not know they are infected.

An estimated 44% (~2300) of adolescents and young adults age 13 to 29 did not know they were infected with HIV.

Diagnosis of HIV by age (2016)



African Americans and Hispanics/Latinos are disproportionately affected by HIV. In 2016:

- **African Americans** represented 12% of the population, but accounted for 44% (17,528) of new HIV diagnoses.
- **Hispanics/Latinos** represented 18% of the population, but accounted for 25% (9,766) of new HIV diagnoses.

US Geographically. The population rates (per 100,000 people) of people who received an HIV diagnosis were highest in the South (16.8), followed by the Northeast (11.2), the West (10.2), and the Midwest (7.5).

What we know (or think we know) about HIV infection in the female and male genital and gastrointestinal tracts.

What Are the HIV Target Tissues?

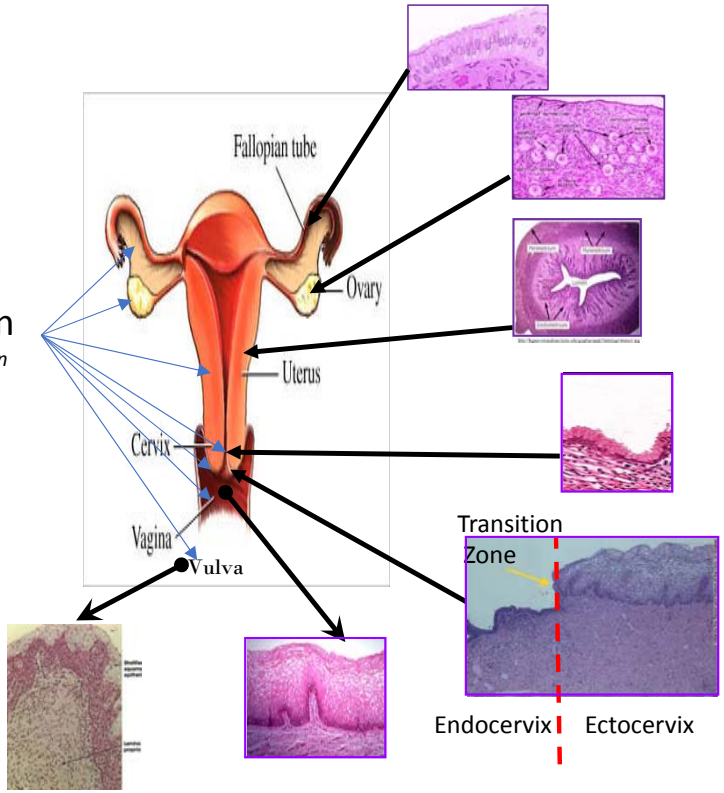
TH17 T cells and other cells in the genital and GI tracts are HIV targets

Dendritic Cells, Langerhans Cells and monocyte/macrophages

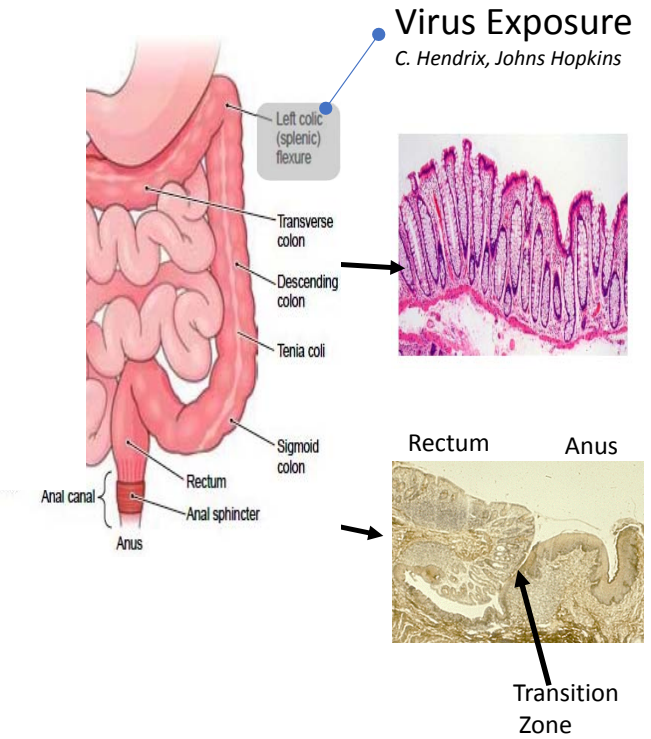
Sun Tzu
The Art of War
"Know your enemy and know yourself"

Female Genital Tract

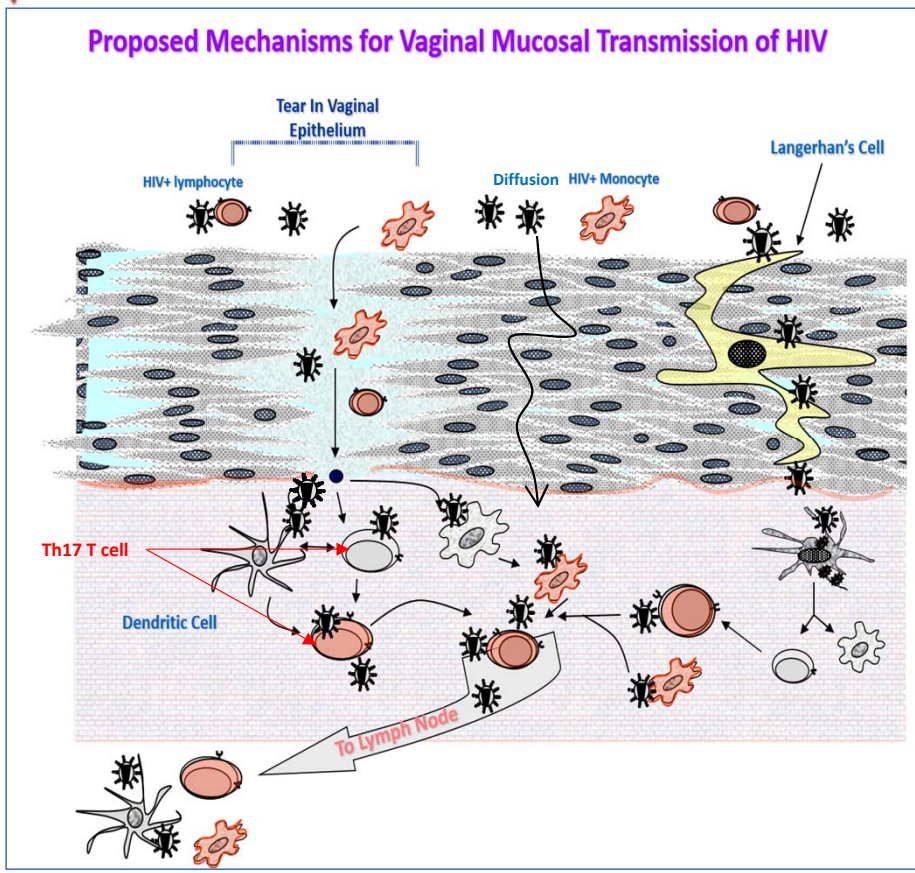
HIV Infection
T. Hope, Northwestern

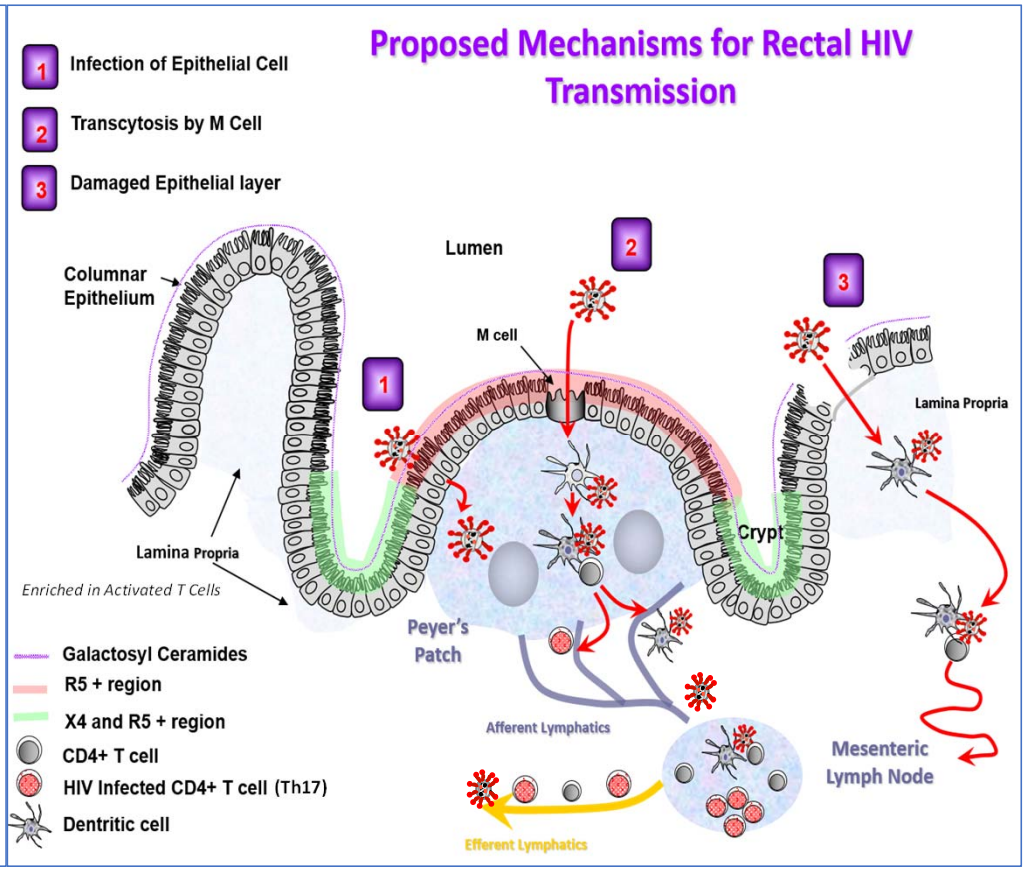


GI tract

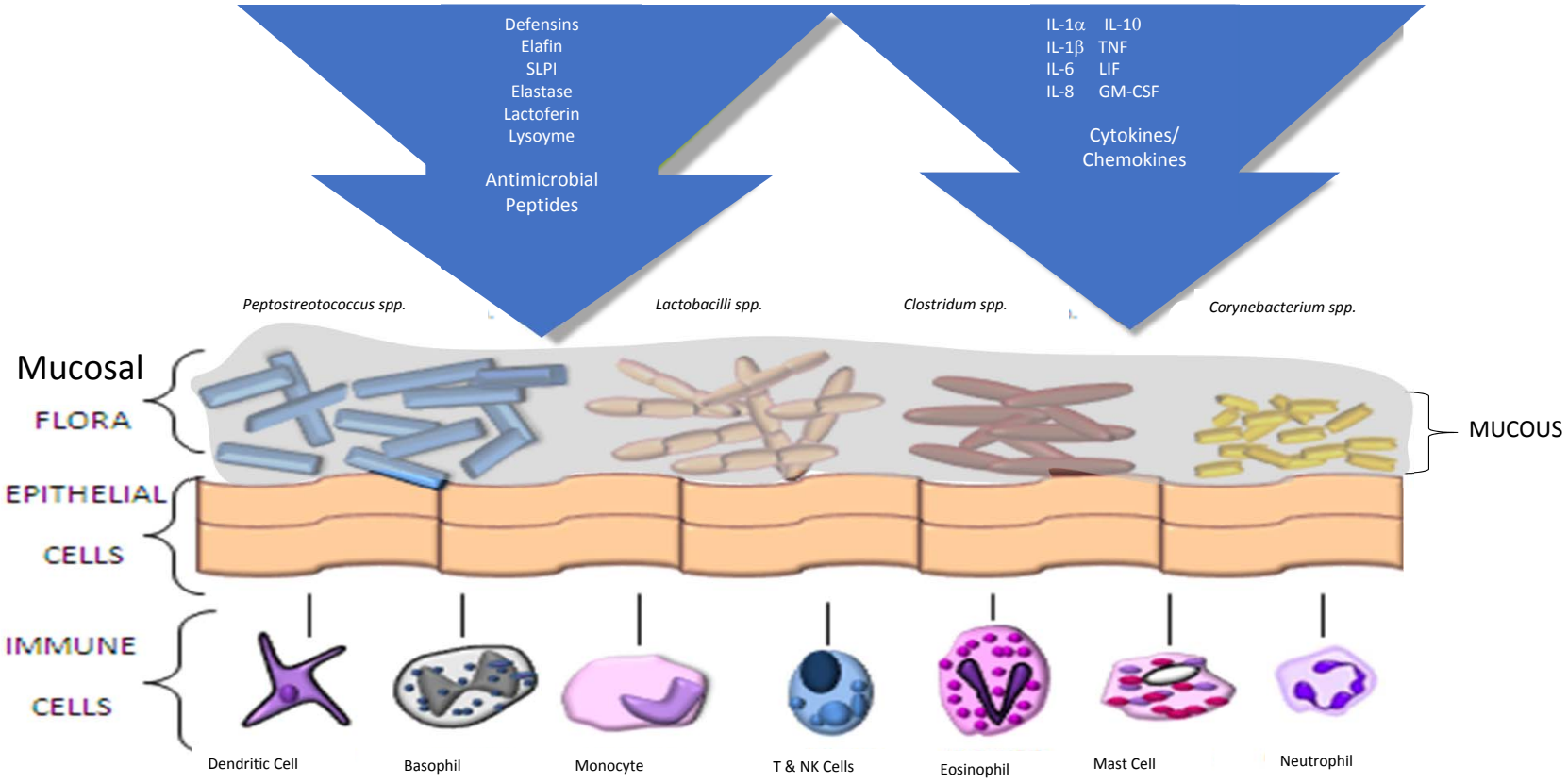


Vaginal and Rectal HIV Transmission





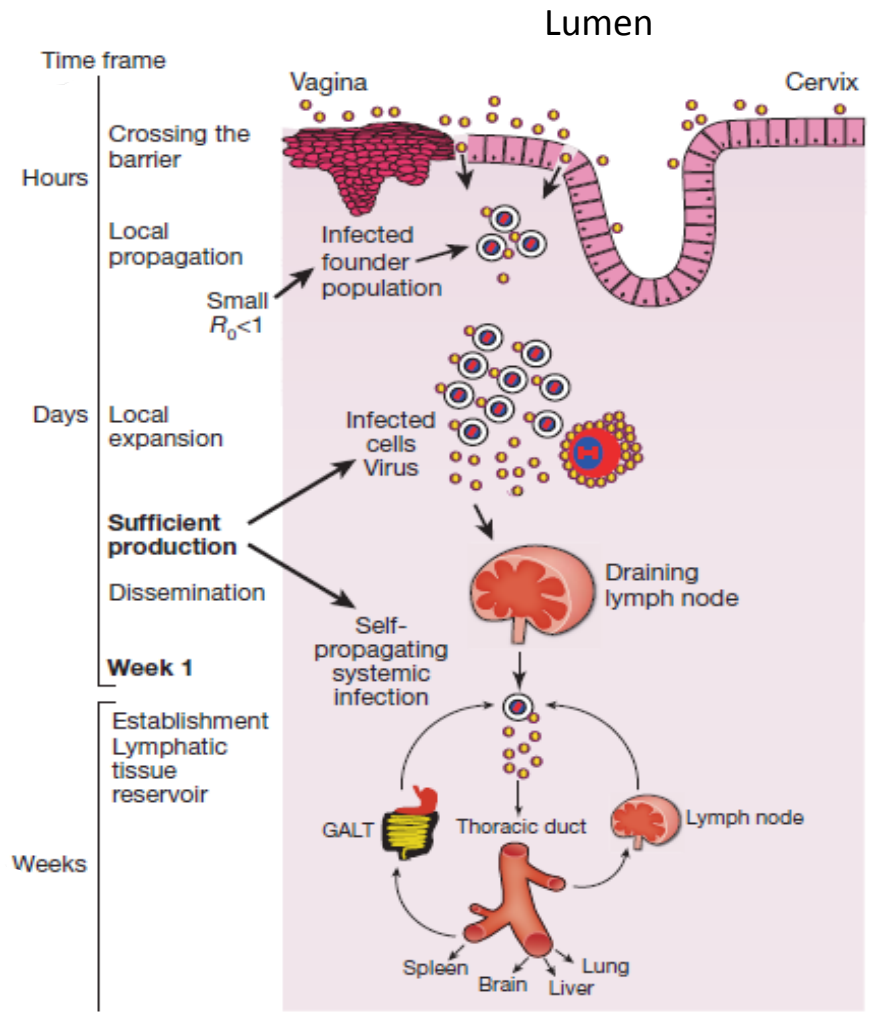
Natural Mucosal Barriers to HIV Infection



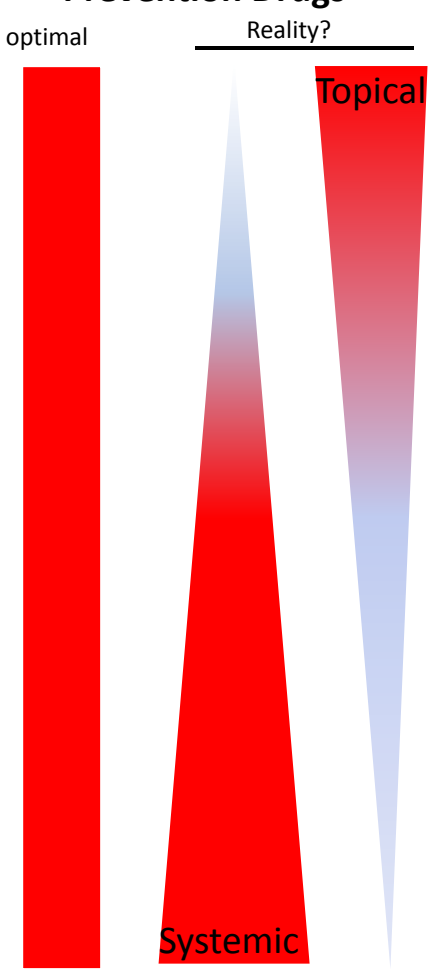
Adapted from: Cu-Uvin, CROI 2012 and Hector Mendez-Figueroa; Brenna Anderson
Expert Rev of Obstet Gynecol. 2011;:629-641

How Long Does It Take HIV To Establish Infection?

However, Monkey studies suggest dissemination to tissues may occur in a matter of **minutes to hours**!



Haase Nature Review2010 464:217



A short history of the development of HIV non-vaccine biomedical prevention strategies

An Abbreviated Clinical History of HIV Non-vaccine Biomedical Prevention

Phase IIB and III Entry Inhibitor Microbicide Trials

1. Phase III SAVY (C31G) Stopped for **Low Incidence**
1. Phase II Dextran Sulfate Stopped for **Possible Harm**
2. Phase III Carraguard 27% adherence, **No Efficacy**
3. Phase IIB/III HPTN035 PRO2000 and BufferGel –**No Efficacy**
4. Phase III MDP 301 PRO2000 2% futility, 0.5% **No Efficacy**

Phase IIB and III Pre Exposure Prophylaxis (PrEP) Trials

Phase III iPrEX:Oral Daily, TDF/FTC **44% Efficacy**
Phase IIB/III VOICE: Oral Daily, TDF or TDF/FTC **No Efficacy**
Phase III Fem PrEP: Oral Daily, TDF/FTC **No Efficacy**
Phase III Partners in PrEP: Oral Daily:
~~TDF 62% Efficacy~~
TDF/FTC **73% Efficacy**
Phase III TDF2: Oral Daily, TDF/FTV **62% efficacy**
Open Label PROUD: Daily/Deferred, TDF/FTC **86% Efficacy**
Phase III IPREGAY: Daily TDF/FTV **86% Efficacy**

Pre-Exposure Prophylaxis (PrEP)

U=U

Zeda Stein coins the term Topical Microbicide

HPTN 052
Treatment to Prevent Infection (TaSP)
96% efficacy

1990 2002 2010 2016 2018 Licensure

Phase IIB and III Topical Microbicide Antiviral (ARV) Trials

Phase II CAPRISA 004 1% Tenofovir gel **37% Efficacy, HSV 51%**
Phase IIB/III VOICE 1% Tenofovir gel Stopped for **Futility**
Phase III FACTS 001 1% Tenofovir gel **No Efficacy**

30 day Dapivirine Intravaginal Ring (IVR)

Contraceptive Detergent (N-9)
Phase II/III Col-1492
Multiple daily use **increased HIV transmission** by 50%

30 day Dapivirine Intravaginal Ring (IVR)
Phase III ASPIRE **27% Efficacy**
Age <21 0% efficacy, >21 65% efficacy
Phase III The Ring Trial **31% Efficacy**
Age <21 15% efficacy, >21 37%efficacy

Women MSM Discordant Couples

Clinical Success and Failure –its all about adherence

Efficacy: Per Protocol vs. Analytical (Drug in Blood)

Study	Per Protocol Efficacy	Drug in Blood Efficacy
Gay Men and Men who have Sex with Men (MSM)		
iPrEx	44%	73%
iPrEx OLE	49%	71%
PROUD	86%	86%
IPERGAY	82%	86%
Women		
CAPRISA 004	37%	50-60%
FACTS 001	0%	43%
VOICE	0%	28%
FemPrEP	0%	6%
Discordant Couples		
Partners in PrEP	67%	82%
TDF2	62%	84%

Note –a Sub analysis without statistical power to show a "real" effect; whereas' Per Protocol is powered to identify a statistically significant effect

TDF/FTC licensed in U. S. for HIV Prevention as PrEP

All Studies Self-Reported Adherence >90%

1% Tenofovir gel

Before PrEP licensed

Prior to TDF/FTC PrEP licensure

Lessons Learned from Clinical trials

- If the prevention strategy is used it will probably work.

- Men and Women must desire to use the prevention strategy.
  - Many people do not recognize their risk, this is especially true for adolescents and young adults
  - Recognition of risk does not always translate to prevention strategy use

    Make it and they will come is a fallacy

- Self-report of adherence over estimates pharmacological adherence.

  must be able to directly measure use, delivery system, placebo and drug in clinical trials

- There are big differences between men and women: TDF/FTC PrEP PK favors less adherence in men vs. women

  When using PrEP to prevent HIV infection:

  - *Men: 28% adherence (2-3 doses per week) to prevent HIV infection*
  - *Women: 85% adherence (6 to 7 pills a week) to prevent HIV infection*

Cottell J. et al. Infect. Dis 2016 214:55. A Translational Pharmacology Approach to Predicting Outcomes of Preexposure Prophylaxis Against HIV in Men and Women Using Tenofovir Disoproxil Fumarate With or Without Emtricitabine

Bench Scientist to Program Officer

Education

Small Liberal Arts College
University of Evansville 1976 to 1980
Biology Major, B.S.

Exposed to Immunology, Macrophages and Cancer Immunotherapy

1980 Grad School:
Graduate School of Biomedical Sciences, University of Texas, Houston, TX (UT-GSBS)
Now
MD Anderson Cancer Center UT Health Graduate School of Biomedical Sciences

Graduate School -UT-GSBS

Selected Events

1980

Tutorials in Immunogenetics, Cancer Immunotherapy and Retrovirology (pre-HIV)

MD Anderson Hospital
Joined Department of Clinical Immunology led by Dr. Evan M. Hersh, MD
"Godfather of Cancer Immunotherapy"

1984

Research Tech.
Dr. Josh Fidler, Ph.D.
Monocyte activation and tumoricidal activity

Assigned to new faculty:
Dr. Gabriel Lopez Berestein, MD
Human Monocytes and Cancer control

1986

Research Topic:
Human monocyte/macrophage maturation and heterogeneity

1988 Ph. D. in Biological Sciences with Specialization in Immunology

Relevant Outcomes

M. S. Dissertation: Oxidative burst heterogeneity during in vitro maturation of human monocytes

Ph.D. Dissertation: Effect of maturation on the function and tumoricidal activity of human monocytes

Science Does Not Happen in Vacuum

World Events

1981
- June 5th, CDC Publishes Morbidity and Mortality Weekly Report (MMWR) 5 young Gay Men rare lung infection *P. carinii*
- July 3rd 41 cases of Kaposi's sarcoma
- End of year 207 Cases in gay men 121 deaths

1982
September 24th CDC uses term AIDS
10,000 +estimated to be infected

1983
First cases in women (Partners of Men infected with AIDS)

1984, June
AIDS caused by Virus

1987
President Ronald Reagan makes first speech about AIDS and establishes commission

December 1, 1988 First World AIDS day

1980

1984
Masters

1986

1988 Ph. D. in Biological Sciences with Specialization in Immunology

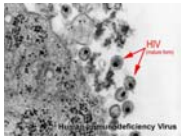
Local Happenings

MD Anderson Cancer Clinics:
Increase in presentation of Kaposi Sarcoma

1982-1983 Multiple CDC briefs at MD Anderson on this new emerging immunodeficiency syndrome

- Gay men/ men who have sex with men (MSM)
- Hemophiliacs
- Women

1987 Seminar: Dr. Monte Meltzer, WRAIR
HIV infects Human Monocytes



NOTE: October 26, 1990 AZT licensed by FDA as first treatment for HIV/AIDS

Academia, Contract Research and Government Service

Had a Ph. D. wanted to understand how infections impacted monocyte maturation /differentiation

Real World

Research Chemist, Walter Reed Army Institute of Research
Monte Meltzer's Department

- Monocyte/macrophages –Differentiation and disease
  HIV Dengue Leishmania Francisella Tularensis (rabbit fever)
- **Cellular and molecular factors controlling HIV replication in monocytes**

Research Scientist, NCI –Frederick, MD
Ft. Detrick, MD

- **HIV drug** and assay **development**
- Introduced to **HIV Prevention** and **Topical Microbicides**
- **Concluded: Anti-HIV drugs could control disease, but not eliminate--- Vaccines were not going to be easy—HIV Prevention was doable**

Contract Research Organizations (CRO)
Southern Research Institute, Frederick
Therimmune Research, Inc

- PI for NIAID/DAIDS HIV Topical Microbicide Screening Contract
- First NIH grant: U19 IPCP development of Cyanovirin-N as a Tropical Microbicide
- **Regulatory Science ---Meeting the Federal requirement's to get drugs to clinical testing**

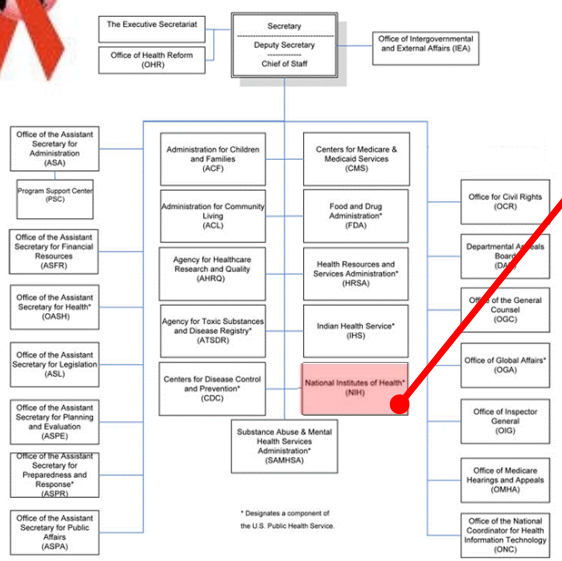
Today

National Institute of Allergy and Infectious Diseases, Division of AIDS

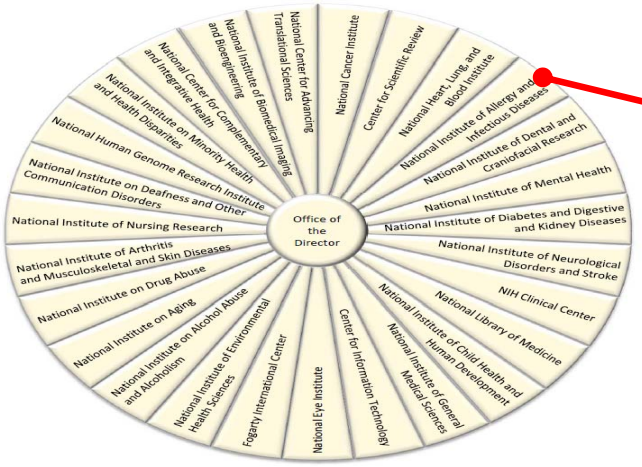
- *Program Officer: May 3, 2003 Started as a Program Officer DAIDS HIV Topical Microbicide Group*
- **2010 Chief** of the newly formed **Preclinical Microbicides and Prevention Research Branch**

Part of A Big Government Organization

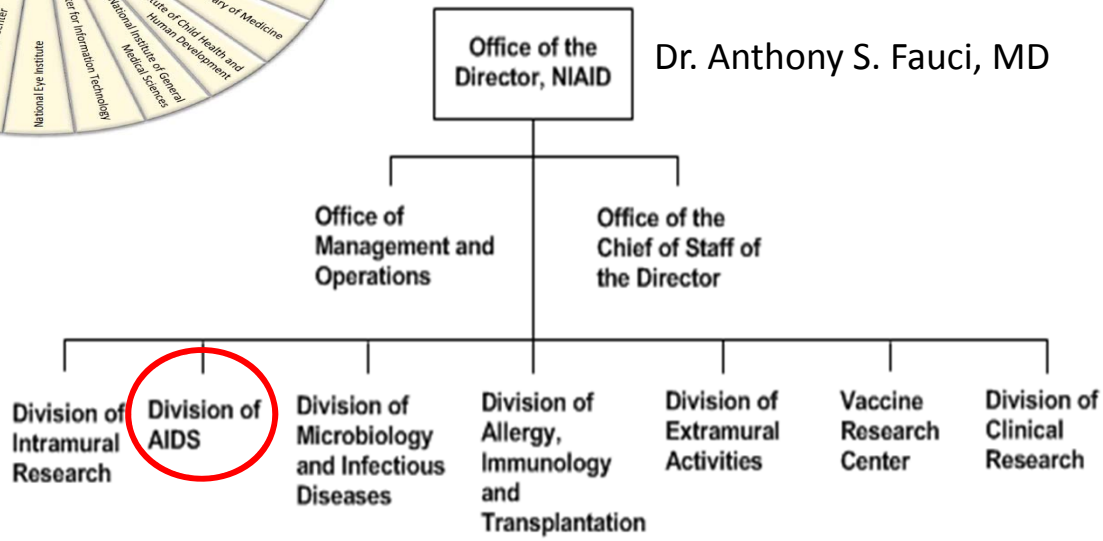
DHHS



National Institutes Health (NIH)



National Institute of Allergy and Infectious Diseases (NIAID)



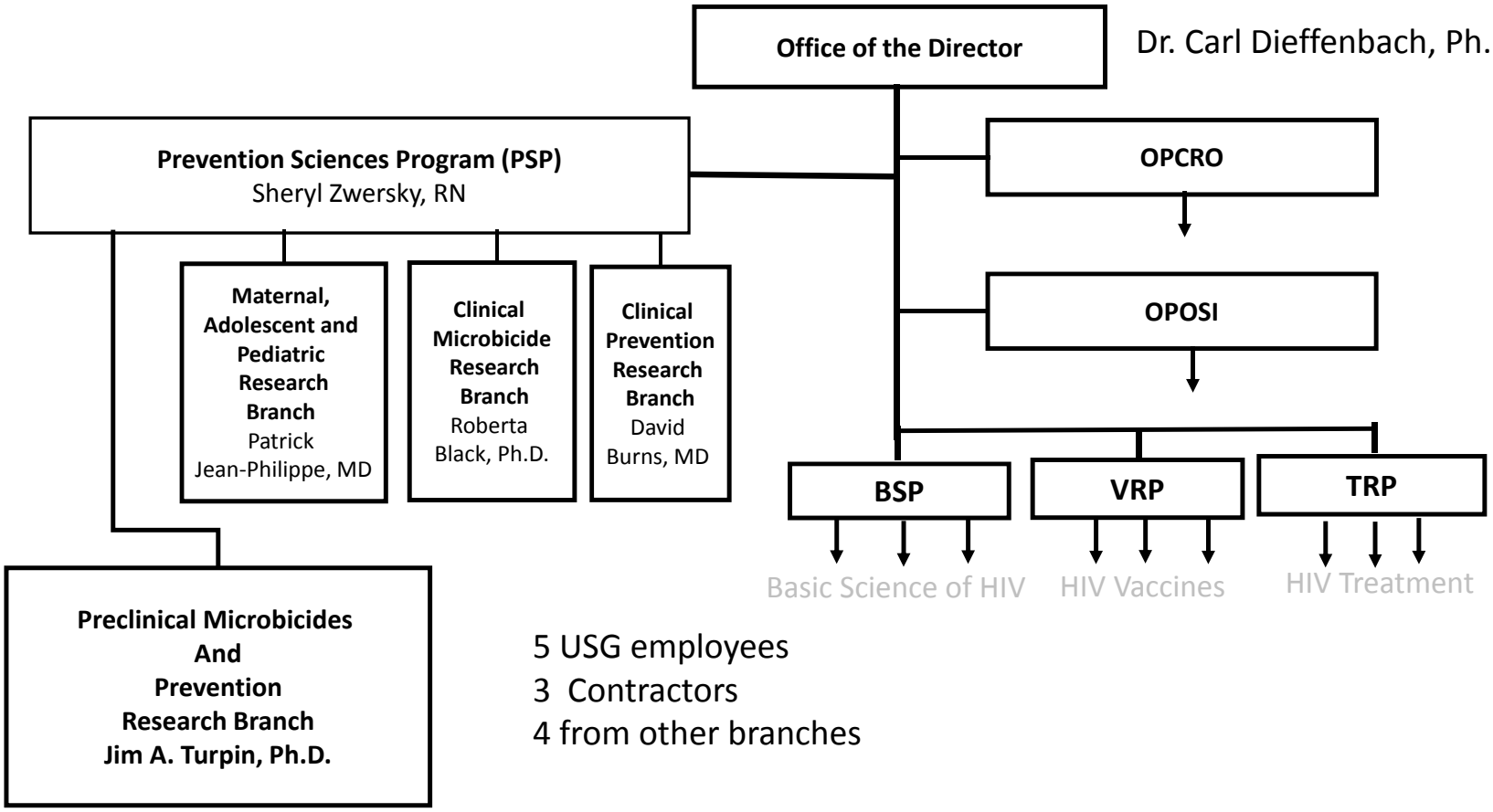
National Institutes of Health (NIH)

27 Institutes and Centers dedicated to developing new health innovations to increase the health and well-being of Americans and citizens of the World

NIAID Mission Conduct and support basic and applied research to better understand, treat, and ultimately prevent infectious, immunologic, and allergic diseases.

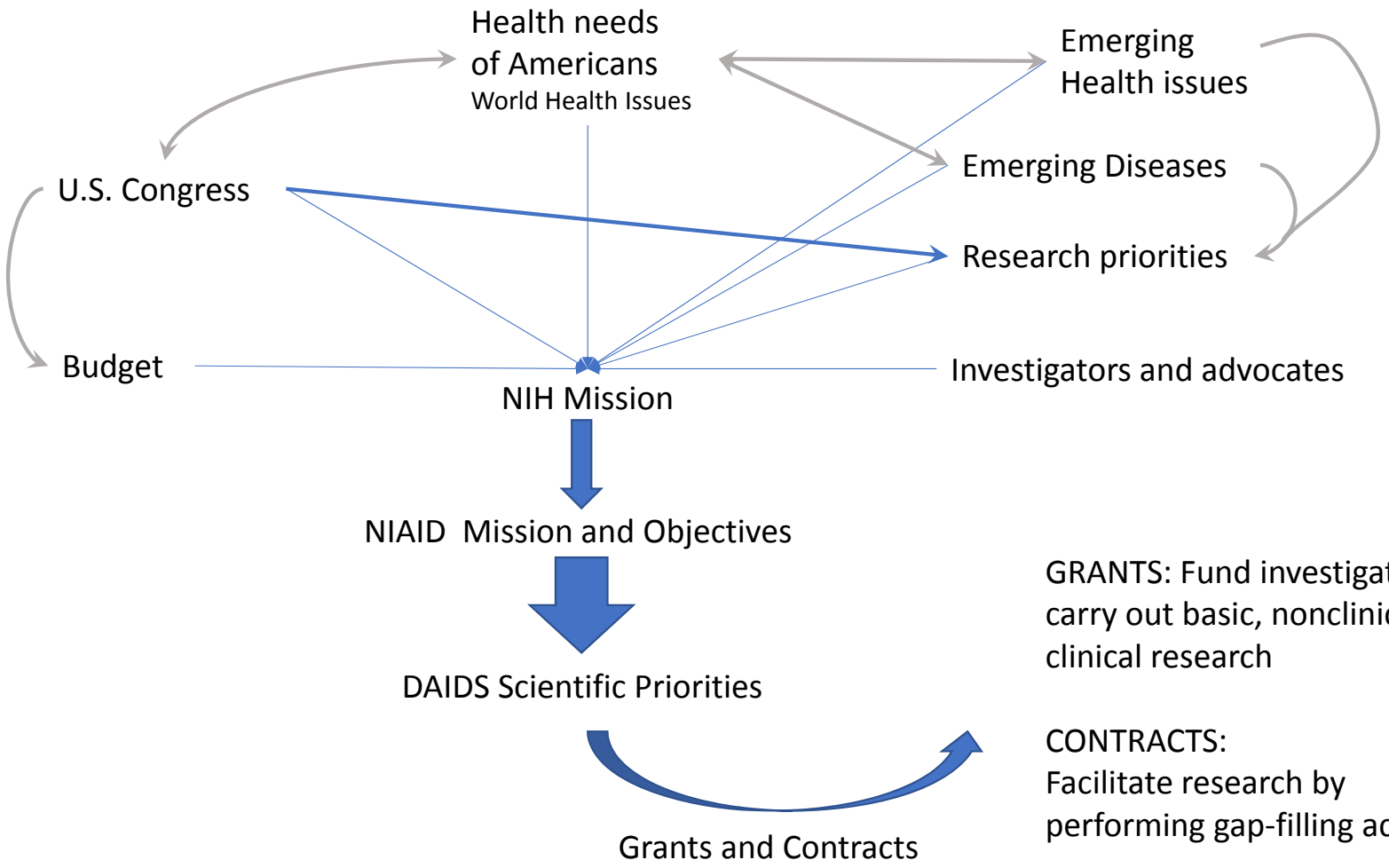
Division of AIDS (DAIDS)

DAIDS Mission: End the AIDS Pandemic by understanding the biology of virus infection and by supporting development of new treatment and prevention drugs and strategies for those infected by the HIV virus or at-risk for HIV infection.



5 USG employees
3 Contractors
4 from other branches

Who Defines Missions and Scientific Priorities?



GRANTS: Fund investigators to carry out basic, nonclinical and clinical research

CONTRACTS:
Facilitate research by performing gap-filling activities

The Role of the Program Officer

A view from the NIH bridge: perspectives of a program officer

Marion Zatz

Mol Biol Cell. 2011 Aug 1; .doi: 10.1091/mbc.E11-04-0346 PMCID: PMC3145542

Program Officer (PO)

Administrative Duties

1. Provides policy advice/guidance to grant applicants: grantsmanship, etc.
2. Make funding recommendations to Leadership (POs do not fund, we recommend)
3. Oversee and document the scientific progress of funded research, and research areas
4. Enforces research policies/regulations/laws, e.g. Public Access, Human Subjects, Vertebrate Animal Use, etc.

Scientific Duties

5. Acts as an advocate for research:
   - The investigator/ grant applicant
   - The research priority, e.g. HIV non-vaccine Biomedical Prevention
6. Develop workshops and consultations to develop Program scientific priorities and communicate them to the scientific community
7. Support priority research by developing funding mechanisms (initiatives and contracts)

What I do at NIH/NIAID/DAIDS/PSP

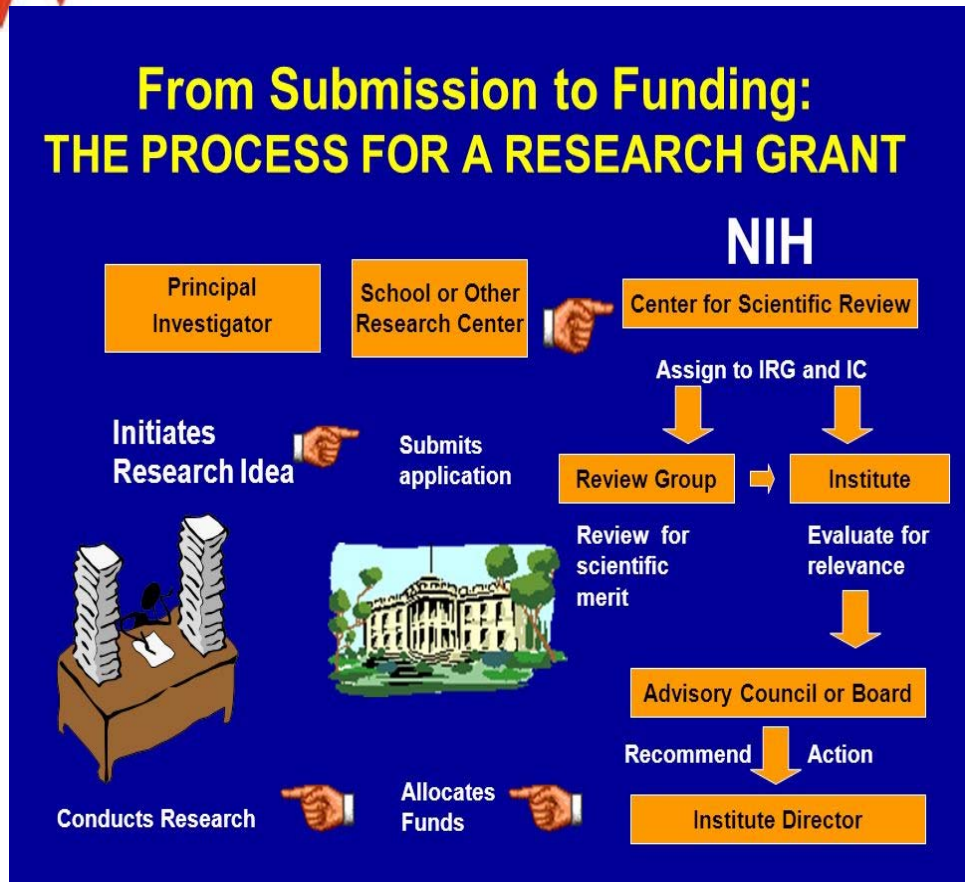
I am a Program Officer at NIH/NIAID
and
Lead a Branch in the Division of AIDS (DAIDS), Prevention Sciences Program

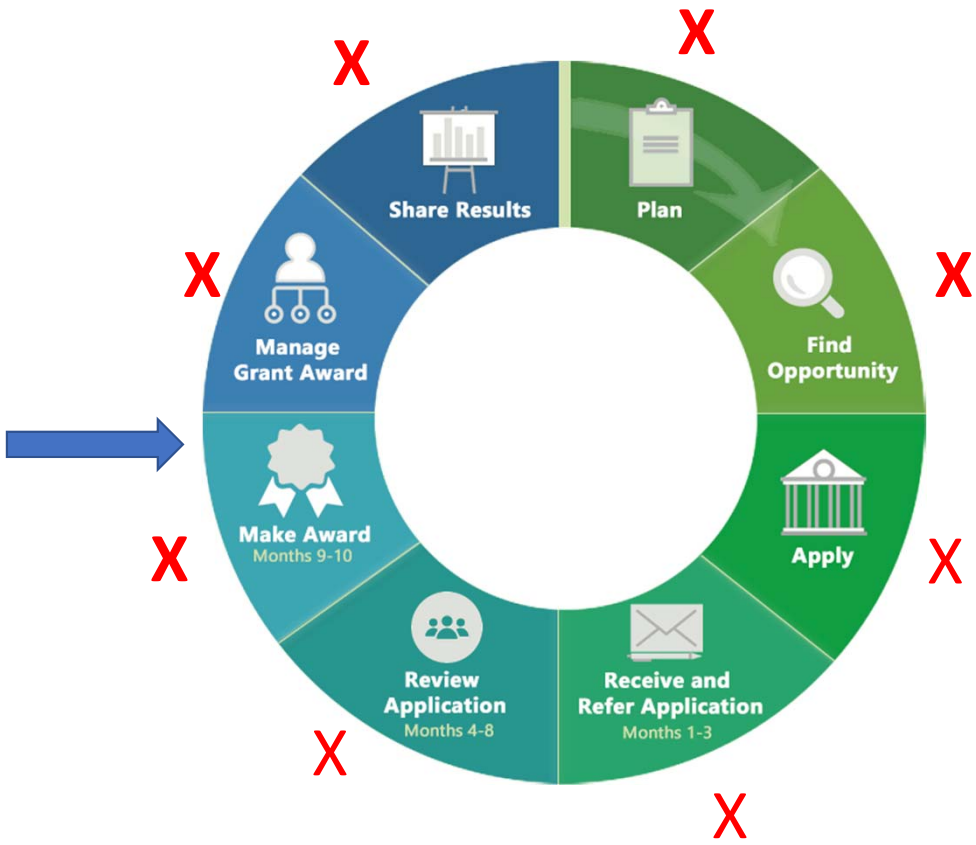
Job Description:

Support investigator-initiated grants and develop grant and contract programs to support the discovery and development of new HIV Non-vaccine Biomedical Prevention drugs and their delivery systems, and the technologies required to facilitate prevention research.

Succinctly: I support the development of new safe and effective HIV prevention strategies and drugs by overseeing a portfolio of research grants

The Grants (Contracts) Process and the Program Officer





Managing Grants and Contracts: It Takes A Village!

Senior Review Official **(SRO)**: Federal Official responsible for contract or grant review and assuring compliance with required by Federal laws and policies on Committees.

Grants Management Official (**GMO**): Federal Official responsible for assuring all grant awards meet Federal laws and policies governing them.

Grants Management Specialist (**GMS**): Federal Official responsible for assuring all requirements are documented and Awards the grant after GMO approval

Contracting Officer (**CO**): Federal Official responsible for assuring all contract awards meet Federal laws and policies governing contracts.

Contract Specialist (**CS**): Federal Official responsible for assuring all requirements are documented and awards the contract after CO approval

Program Officer (**PO**): Federal Official responsible for assuring Federal and research laws and policies are implemented before and after grant award and tracking the Scientific progress during the award

Contract Officer Representative (**COR**): Federal Official responsible for assuring USG Federal contracting laws and policies are implemented before and after contacts award and documenting contract deliverables

SRO ≠ GMO/GMS ≠ **PO**
CO/CS ≠ **COR** → A PO can also be a COR

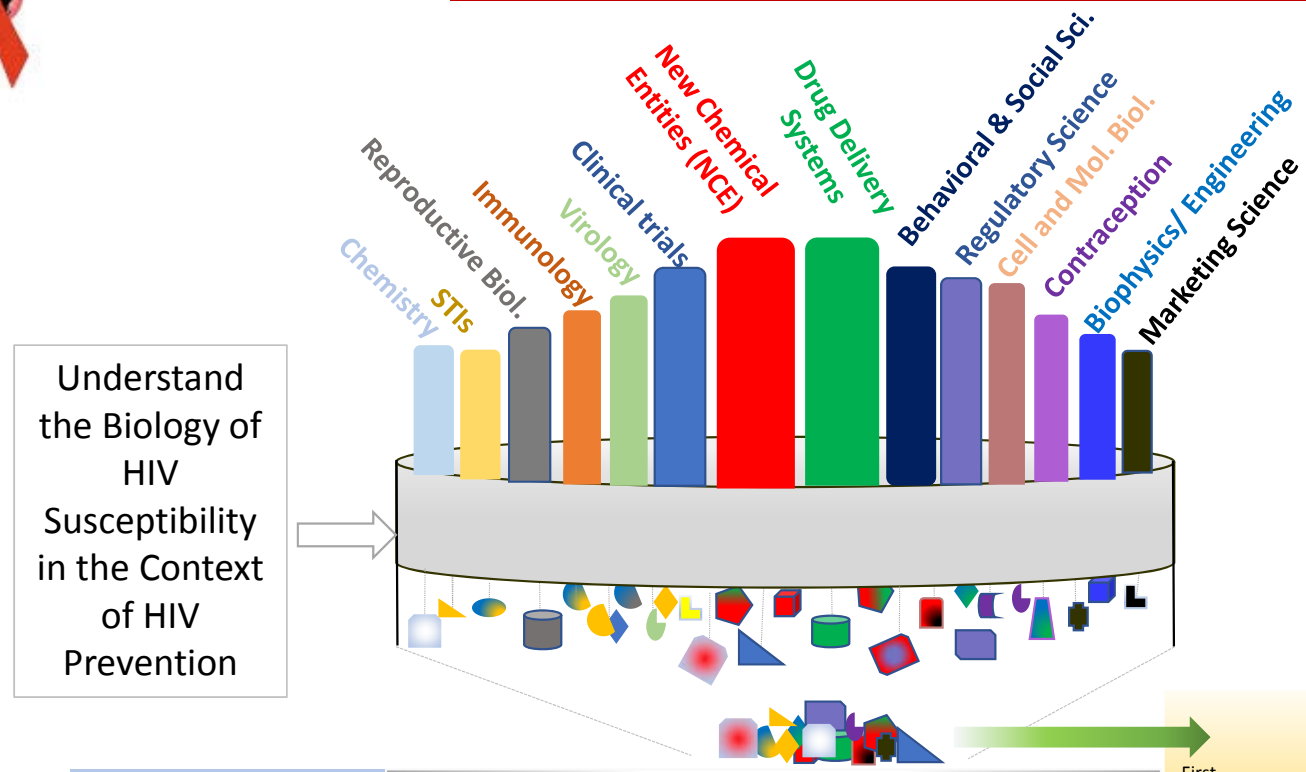
Program Officer enables scientific priorities through support of grants and contracts

But, how do you translate what we know about HIV and HIV prevention into mechanisms (Grants and Contracts) to fund investigators to create new better HIV prevention strategies?

Or

Predicting the future---how do you identify the science that needs to be funded to advance HIV prevention?

Prevention Drug Development: Specialization Without Specialization



Understand the Biology of HIV Susceptibility in the Context of HIV Prevention

Need some expertise in 3 areas:

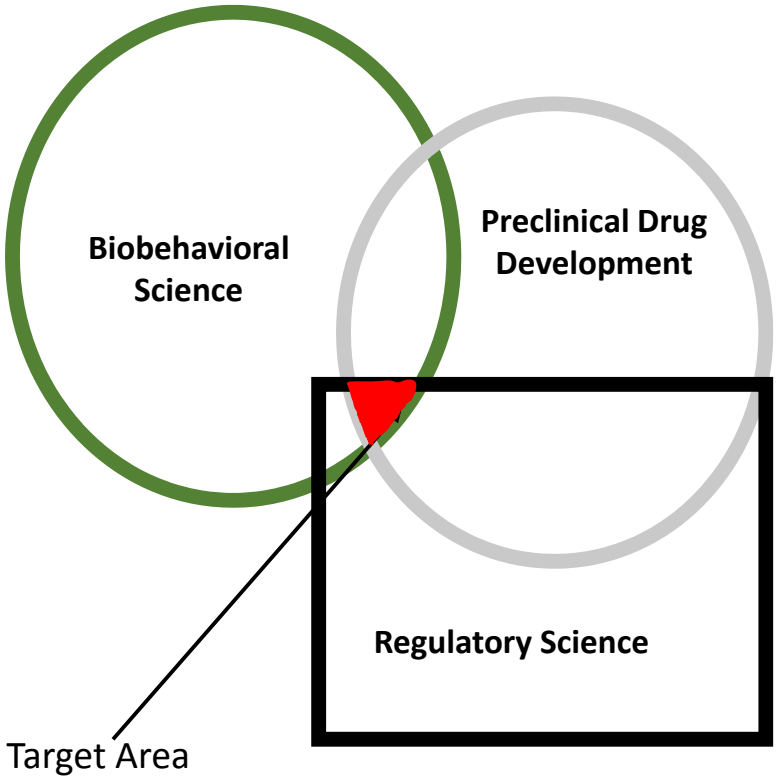
- Drug development
- Biobehavioral science
- Regulatory science
  - Preclinical
  - Clinical

QUESTION: How do you achieve the integration of preclinical drug development, biobehavioral sciences and regulatory sciences to create new non-vaccine biomedical prevention strategies?

ANSWER: Support investigator-initiated research, communicate scientific priorities and by designing initiatives (grants (RFA)) and contracts (RFP) designed to support research to discover, develop and clinically test new non-vaccine biomedical prevention drugs and strategies

CRITICAL: The scientific scope and objectives of supported science is driven not only by what we know about HIV virology and prevention, but also by what scientific gaps we suspect remain!

The Scientific Scope of Non-Vaccine Biomedical Prevention



Preclinical Drug Development:

- Identify a candidate
- Formulate it—stable, easy to use
- Test it in animals for safety and efficacy
  (Carcinogenesis, Reproductive, Respiratory, CNS, etc.)
- Understand its in vivo properties
  (PK, Bioavailability, excretion, metabolism, etc.)

Biobehavioral Science:

- Understand the individual's needs
- How it will be used
- How it fits into the life of users
- Create a need and desire to use

Regulatory Science (Code of Federal Regulations, CFR):

- Study its safety and in characteristics --Good Laboratory Practices (GLP)
- Manufacture it-- Good Manufacturing Practices (GMP)
- Do clinical studies– Good Clinical Practices (GCP)

Filling in the Target Area: Three Critical Factors

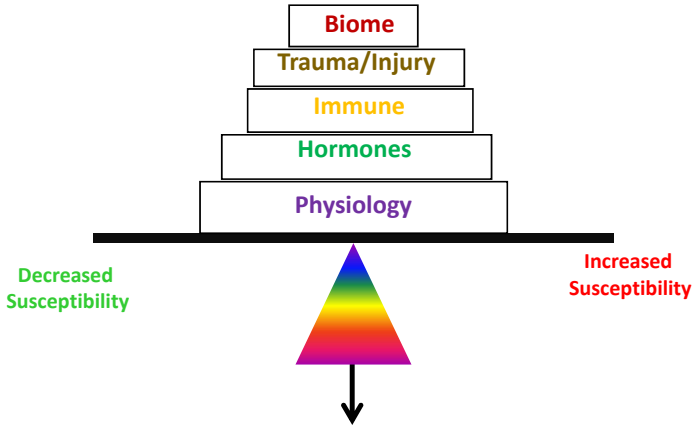
New drugs and strategies that :

- Do no harm *(preclinical drug development)*
- Products that are more likely to be used *(biobehavioral science)*
- Can be licensed for use *(regulatory science)*

New drugs and strategies that :

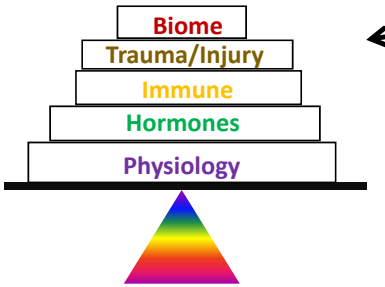
- Do no harm *(preclinical drug development)*
- Products that are more likely to be used *(biobehavioral science)*
- Can be licensed for use *(regulatory science)*

Many Factors Can Influence Susceptibility to HIV Infection (Harm)

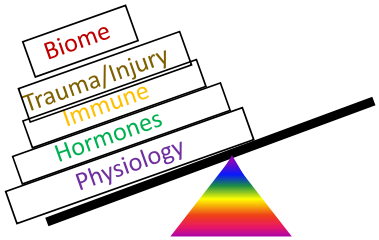


Mucosal susceptibility to HIV Infection is controlled by multiple factors which in aggregate determine the overall degree of susceptibility to infection

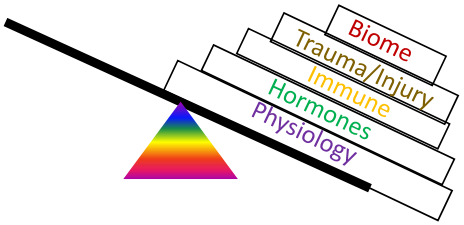
Exogenous Factors, e.g. IPV Trauma/Injury, STIs, Hormonal Contraception, etc.
Prevention Factors, e.g. products, drug delivery systems



OR



Decreased Susceptibility



Increased Susceptibility

New drugs and strategies that :

- Do no harm *(preclinical drug development)*
- Products that are more likely to be used *(biobehavioral science)*
- Can be licensed for use *(regulatory science)*

Relationship Between Drug Use (Adherence) and Prevention of HIV Infection (Efficacy)

How do you convince healthy people to protect themselves from a risk that seems remote, when engaging in HIV prevention may result in undesirable drug side-effects and/or harm/social stigma?

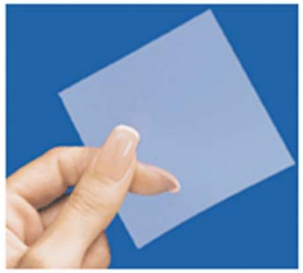
Furthermore, the prevention strategy may need to be used from sexual debut to end-of-life, so user wants/needs may change

Increase adherence and use through

1. Increasing user choices.
2. Increase convenience---Behaviorally congruency (fits into life and sexual practices).
3. Increase compliance---Design usage into the strategy, e.g. long lasting injectable.

Increase User Choices ---Same Drugs, Different Ways to Delivery

Gels



Films
- Fast dissolving
- Slow dissolving

Devices +/- Gels

Reengineered IUD

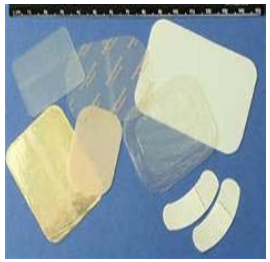
Implants
- Biodegradable
- Non-biodegradable

Foam

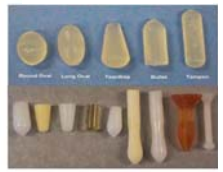
Intravaginal Rings (IVR)
- Matrix
- Reservoir
- Segmented
- Pod

Injection

Quick Dissolve Inserts



Transdermal patches
- Diffusion
- Nano-syringe



Suppositories Vaginal and Rectal

Enema/ Douche

Convenience and Compliance

Timing

- Before Sex (pre-coital)
- After Sex (post-coital)
- Before and After Sex (BAT24)
- Episodically: single dose protects for a period of time, e.g. 1 week
- Sustained/extended release: months to years protection

Behavioral Congruency

- Creating desire—Marketing Science
- Create a product that fits into sexual behavior(s)
- Couple HIV prevention with a prevention behavior that is highly desirable to the user, and maybe actively sought

Multipurpose Prevention Technologies (MPT) HIV drug +

- STI prevention, e.g. Herpes
- Pregnancy prevention

New drugs and strategies that :

- Do no harm *(preclinical drug development)*
- Products that are more likely to be used *(biobehavioral science)*
- Can be licensed for use *(regulatory science)*

Advancing to Clinical Testing and Licensure

Driven by Laws, Regulations and Guidance's

LAWS: Code of Federal Regulations (CFR)

- ❖ Good Laboratory Practices (GLP: 21 CFR Part 58)
- ❖ Good Manufacturing Practices (GMP: 21 CFR part 110-225)
- ❖ Good Clinical Practices (GCP: 21 CFR 50,54,56,812,814)
- ❖ Data and Computer standards (21 CFR Part 11)
- ❖ Good Farming Practices (GFP)—drug made in plants

✓ U.S. Food and Drug Administration (FDA) Guidance's

–Issue approx. 100 revised/new guidance's per year!

- ❖ Devices
- ❖ Microbicides
- ❖ Antivirals
- ❖ Combination Drugs
- ❖ Etc.

✓ International Conference on Harmonization (ICH) Guidance's

✓ United States Pharmacopeia (USP)

✓ International Organization for Standardization (ISO)

✓ U. S. and Foreign commerce and drug regulations and laws

Translate Code of Federal Regulations (CFRs) and FDA Guidance's to Required Preclinical Studies

Will it inhibit HIV

Reduce the Chance of Harm to Humans

Identity: Its what we say it is

General Preclinical Virology

- Antiviral activity
- Toxicity Cell lines/Primary cells
- Range of Action—Virus Subtypes
- Mechanism of Action
- Mechanism of resistance
- Activity in combination other drugs
- Active in relevant matrices

Preformulation

↓

Formulation

- Stability
- Sterility
- Homogeneity
- Purity

Prevention Specific

Lab

- Condom Compatibility
- Effect on Lactobacilli
- Effect of Matrices
  - –Seminal Plasma
  - –Cervical fluid
  - –Mucin
- Impact on other STIs
- Cervical Explants
- Murine, NHP safety and efficacy

Specific Mucosal Irritation Testing

- Vaginal Irritation
- Rectal Irritation
- Penile Irritation

2 Animal Model Safety, Pharmacokinetics (PK) and Toxicology

- Maximum tolerated dose (MTD)
- Acute Toxicity
- Chronic Toxicity, 90+ days
- Specific system toxicity, e.g. neuro-, immuo-, cardio-, pulmonary-toxicity etc.
- PK and Metabolites (Absorption, Distribution, Metabolism and Excretion, ADME)
- Genotoxicity
- Carcinogenesis
- Reproductive toxicology
  - –Seg. I Reproductive performance
  - –Seg. II Teratology
  - –Seg. III Perinatal/Post natal
- Dermal/systemic Hypersensitivity
- Dermal/ systemic Photosensitivity
- Extractable and Leachables:
  - — Devices
  - — Packaging
  - — Applicator

Chemistry Manufacturing and Control (CMC)

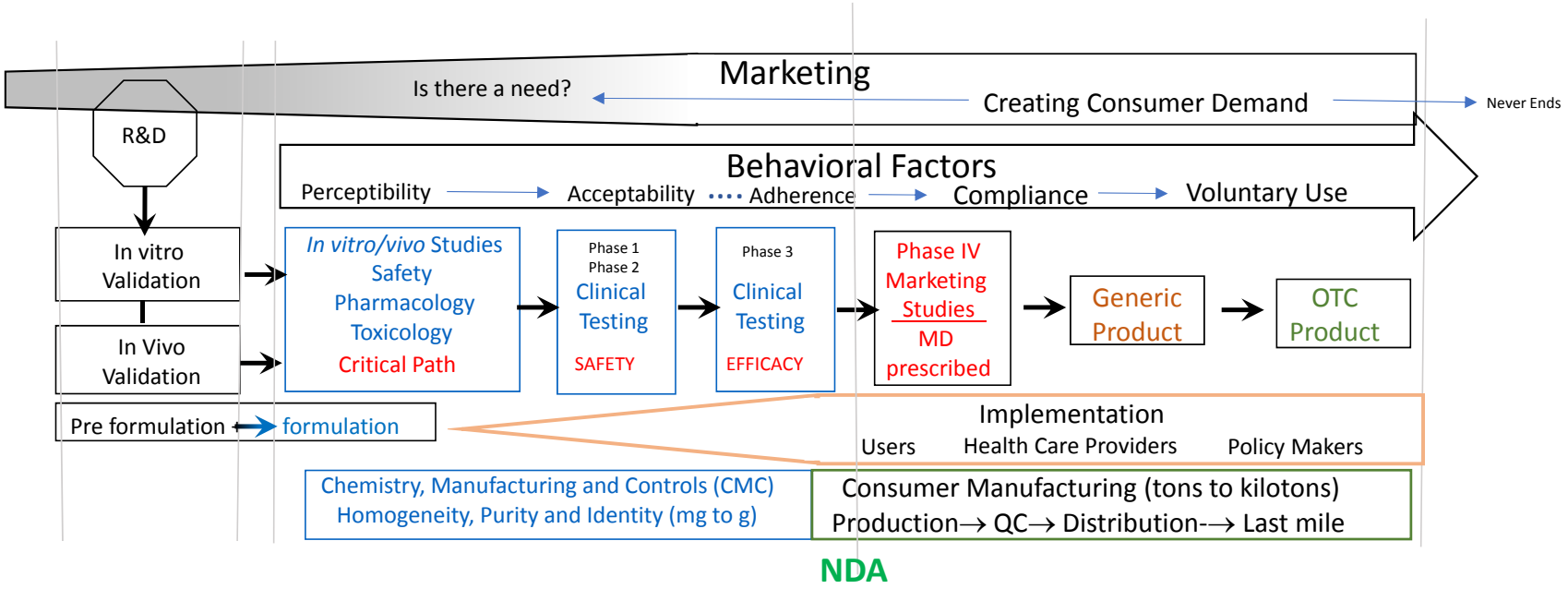
Drug (Drug Substance) — Formulated Drug (Drug Product)

Stability, Sterility, Packaging, Storage

Applicator

Selection Stability Compatability Labeling Acceptability Use (Human Factors) Filling

Putting It All Together?



Federal, State and Local Laws, Regulations and Guidance's

100's to 1000's Candidates

1 licensed Drug

Pennies to $1000's

Millions of Dollars

Pennies/Dollars

FACTOIDS

Time and cost (discovery to approval): **10 to 17 years and $2.6 Billion**

Probabilities of Success

Discovery to Clinical Testing: ~1%

Drugs: Phase 1 to approval: 9-12 %

Clinical testing:

- 60% drop out in Phase I
- 30% percent drop out in Phase II
- 45% fail in Phase III

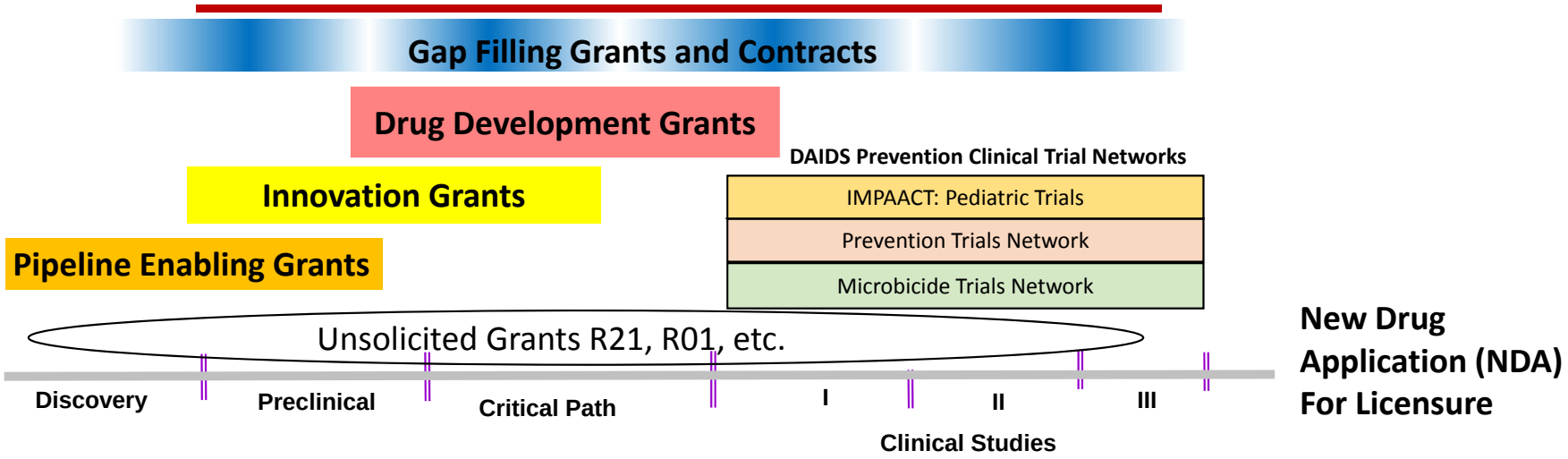
NDA-- Successful Phase III candidates only 20-25% are approved (Licensed) as drugs by the FDA

Does not take into account failure of doctors to prescribe or consumers to use

After licensure only 1 of 5 drugs recoup their development cost

PIPELINE : Creating an Infrastructure to Meet Scientific Objectives

Initiatives (Grants and Contracts) to Create New nBP



Pipeline Enabling: Grants designed to address basic research gaps that enable development of prevention drugs and strategies.

Innovation: Grants designed to support the high-risk innovative research required to create new prevention strategies.

Drug Development: Grants designed to advance prevention products through nonclinical safety studies and into First-in-Human clinical testing.

Gap-Filling: Contracts or Grants designed to overcome barriers to advancement of prevention products or address a specific research topic, e.g. adolescents in all phases of the development pipeline.

Summary: Program Officers Do

Administrative Duties	Acts as the touch-point and resource for investigators to help them meet grant policies and be successful in their research and enforces research laws, regulations and policies.
Scientific Duties	Support and sometimes create programs that address scientific objective(s) of their Institute/Division /Program/Branch.

Wrapping Up

Evolution as a metaphor for what I have become as a Scientist and Program Officer

Charles Darwin

"It is not the strongest of the species that survives, nor the most intelligent that survives. It is the one that is the most adaptable to change."

Charles Sanders Peirce (Father of Pragmatism)

"All the evolution we know of proceeds from the vague to the definite."