NIMH Global and Domestic NeuroAIDS Programs

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Division of AIDS Research, National Institute of Mental Health

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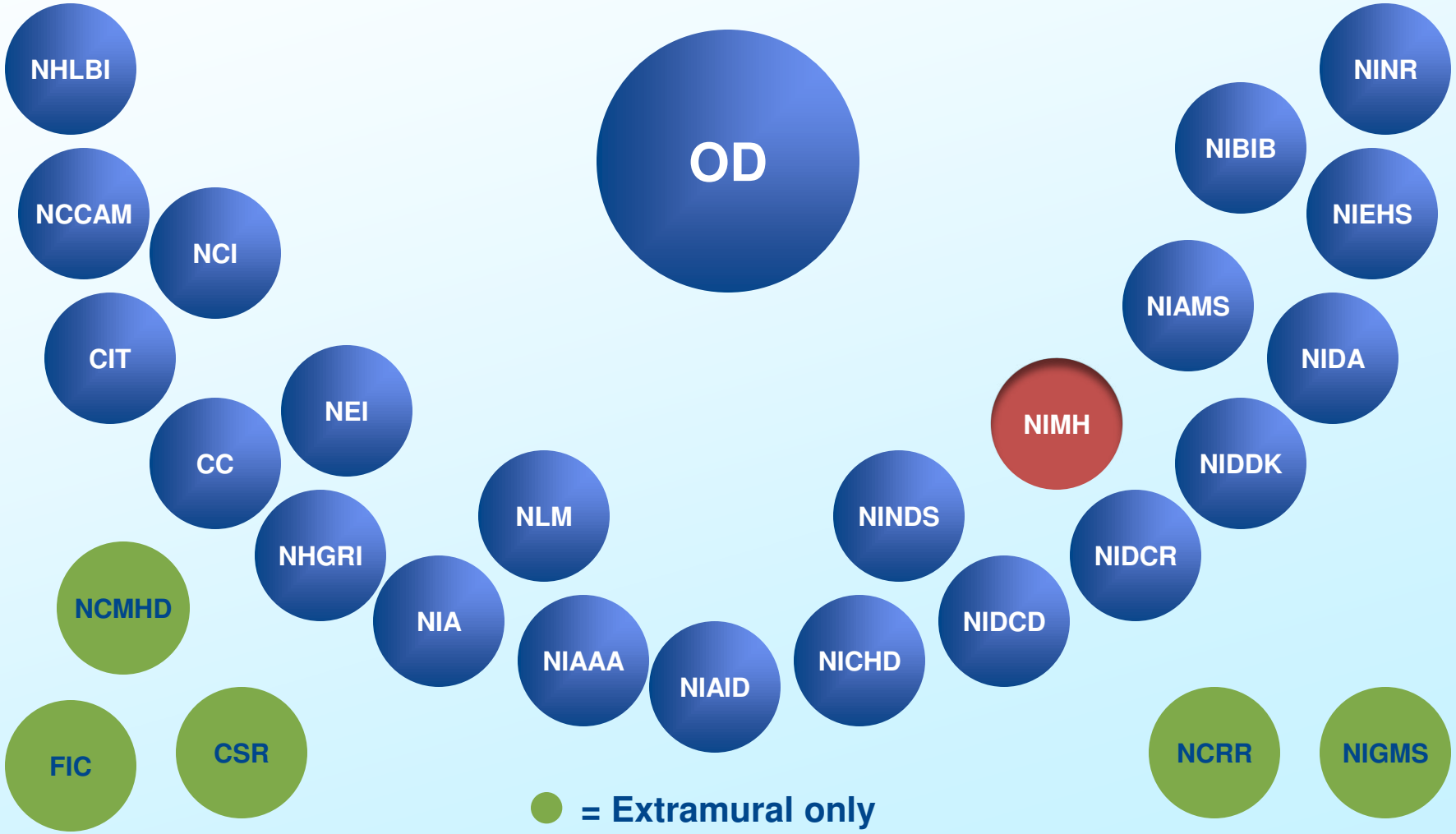
ARROW 2015

National Institute of Mental Health

NIH consists of 27 Institutes and Centers



Integrated Research Programs on the Mental Health of AIDS

Basic & Clinical NeuroAIDS

Neuropathogenesis
Viral/Host Genetics
Neuropsychiatry
Therapeutics

HIV Primary Prevention

Social Epidemiology
Primary Prevention

Division of AIDS Research

HIV Secondary Prevention & Translation

Secondary Prevention
Adherence
Community Implementation
Translational

Cross-Cutting HIV Programs

AIDS Centers
Infants, Children, Adolescents
International
Training
Health Disparities
Technology Transfer

- Epidemiology
- Genetics
- Infectious Diseases
- Neuroimmunology
- Neurology
- Neuropathology
- Neuroscience
- Nursing
- Psychiatry
- Psychology
- Public Health
- Radiology
- Social Work
- Sociology

http://www.nimh.nih.gov/dahbr/9a-as.cfm

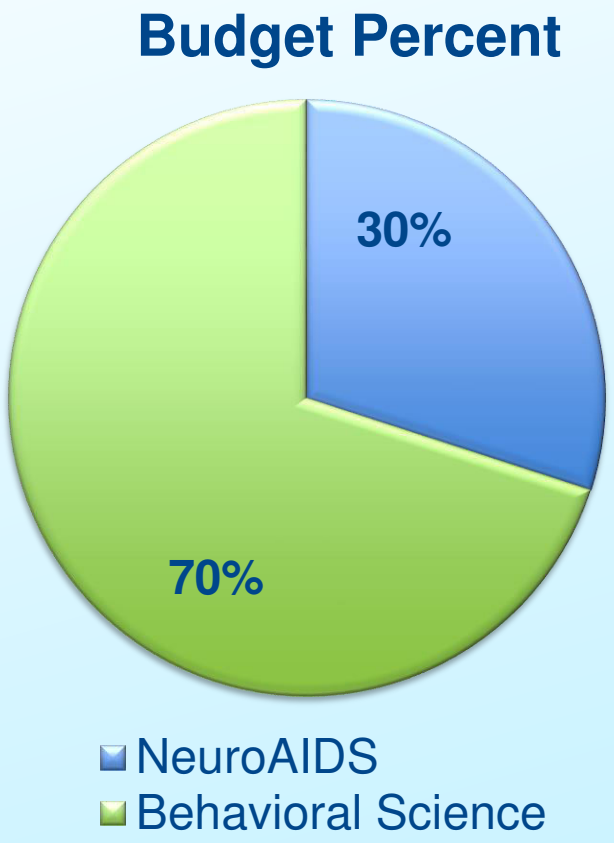
Research Foci for NIMH/DAR

Behavioral Science

Develop, test, and implement interventions to prevent the spread of HIV infection through behavior change and improve health outcomes

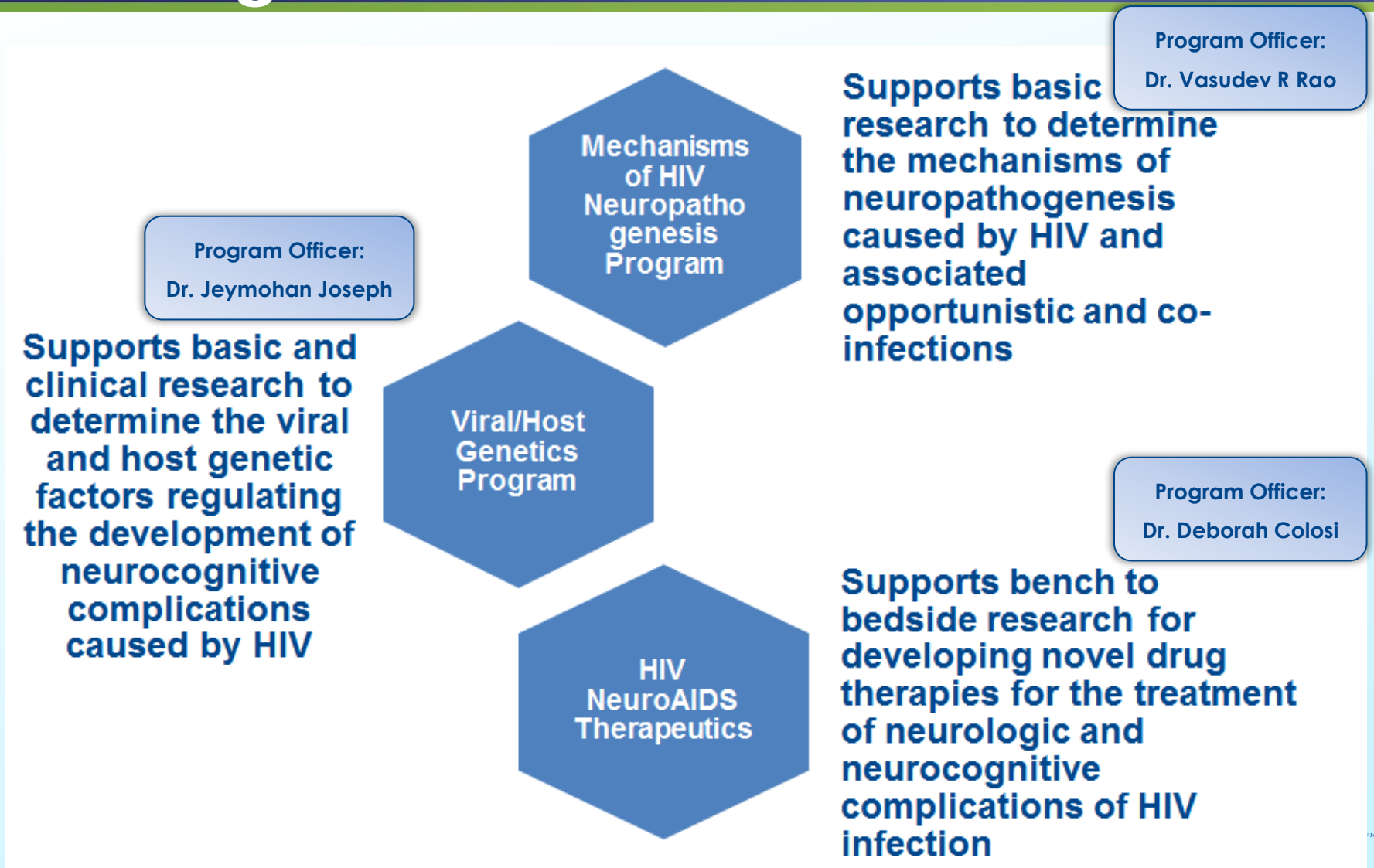
Basic Neuroscience

Identify mechanisms underlying HIV-induced CNS dysfunction, and develop therapeutic strategies to prevent and treat them



National Institute of Mental Health

HIV Neuropathogenesis, Genetics, and Therapeutics Branch Programs



Office of AIDS Research: High priority areas of research

http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-137.html

High Priority topics of research for support using AIDS-designated funds

- Reducing Incidence of HIV/AIDS including: developing and testing promising vaccines, developing and testing microbicide and pre-exposure prophylaxis candidates and methods of delivery, especially those that mitigate adherence issues; and developing, testing, and implementing strategies to improve HIV testing and entry into prevention services.
- Next generation of HIV therapies with better safety and ease of use including: developing and testing HIV treatments that are less toxic, longer acting, have fewer side effects and complications, and easier to take and adhere to than current regimens. Additionally, implementation research to ensure initiation of treatment as soon as diagnosis has been made, retention and engagement in these services, and achievement and maintenance of optimal prevention and treatment responses.
- Research toward a cure including: developing novel approaches and strategies to identify and eliminate viral reservoirs that could lead toward a cure or lifelong remission of HIV infection, including studies of viral persistence, latency, reactivation, and eradication.
- HIV-associated comorbidities, coinfections, and complications including: addressing the impact of HIV-associated comorbidities, including tuberculosis, malignancies; cardiovascular, neurological, and metabolic complications; and premature aging associated with long-term HIV disease and antiretroviral therapy.
- Cross cutting areas: Basic research, health disparities, and training including:
- Basic Research: understanding the basic biology of HIV transmission and pathogenesis; immune dysfunction and chronic inflammation; host microbiome and genetic determinants; and other fundamental issues that underpin the development of high priority HIV prevention, cure, co-morbidities, and treatment strategies.
- Research to Reduce Health Disparities in the incidence of new HIV infections or in treatment outcomes of those living with HIV/AIDS.
- Research Training of the workforce required to conduct High Priority HIV/AIDS or HIV/AIDS-related research.

Office of AIDS Research: Medium and Low priority areas of research

Medium Priority topics of research for support using AIDS-designated funds include projects that demonstrate HIV/AIDS is a meaningful component of the project and/or knowledge about HIV will be enhanced by the project, as evidenced in the specific aims.

Several examples of research that could be considered as Medium Priority include:

- The project examines a fundamental scientific question (or questions) that has a clear or potential link to HIV/AIDS;
- The project includes people (or biological specimens from people) who are living with HIV, are HIV exposed, and/or are at elevated risk for HIV infection as part of a broader sample or as a comparative cohort;
- The project addresses health and social issues that are clearly linked with HIV (transmission/acquisition, pathogenesis, morbidity and mortality, stigma) and examines them in the context of HIV (i.e., in populations or settings with high HIV prevalence or incidence), such as other infectious pathogens and diseases, non-infectious pathogens and diseases, substance use/addiction, and mental health disorders;
- The project meaningfully includes HIV/AIDS (or SIV) outcomes/endpoints; or
- The results of the project will advance HIV treatment or prevention and/or provide tools/techniques and/or capacity beneficial to HIV research (including training and infrastructure development).

Low Priority topics of research will not be supported with AIDS-designated funds; however, highly meritorious projects could be eligible for support with non-AIDS funds by an NIH Institute or Center. Several examples of research that will be considered Low Priority include:

- Research on natural history and epidemiology that is entirely focused on a co-morbidity and does not have any focus on or inclusion of HIV (e.g., malaria, TB, and drug abuse);
- Basic virology research on pathogens that are co-infecting, but not in the context of HIV infection; and basic immunology studies of general relevance, but not specific to HIV including - basic virology and neurobiology research of co-infecting pathogens not in the context of HIV infection (e.g., Herpesviruses, HPV, TB, Malaria, hepatitis C and B, syphilis, Cryptococcus, flaviviruses, JC virus, etc.); basic cancer-related immunology studies not in the context of HIV infection; or studies on co-morbidities of general relevance, but not in the context of HIV (e.g., diabetes, lipid defects, endocrinology);
- Data analysis and systems tools that are not HIV-related, e.g., genomics studies of little or no relevance to HIV; or
- Studies of behaviors (e.g., sexual activities, drug use activities) or social conditions that have multiple negative outcomes where HIV/AIDS is only one of many outcomes being studied without a focus on how HIV/AIDS is unique in that context.

http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-137.html

DAR, NIMH- Pathogenesis/Genetics Priority Areas

- Identify pathophysiological mechanisms driving HAND in the context of effective ART and minimal viral replication
- Study alterations in neuronal excitability, synaptic plasticity, neuromodulation and neural circuit activity caused by HIV
- Develop physiologically relevant in-vivo, ex-vivo and in-vitro models that mimic the clinical presentation of HAND in the ART era
- Identify roles played by factors like exosomes, neuronal receptors, neuronal transmitters and neuroprotective agents
- Assess CNS toxicity and any adverse impact of ART regimens

DAR, NIMH- Pathogenesis/Genetics Priority Areas

- Identify biomarkers linked with HIV neuropathogenesis and clinical outcomes in HAND
- Novel neuroimaging techniques that can identify pathophysiological mechanisms of HAND in the absence of structural deficits
- Study of impact of aging and associated co-morbidities on pathophysiology of HIV-associated CNS disease
- Better understand the role of global genetic diversity of HIV-1 and host genetic factors in HIV neuropathogenesis
- Examine the role of neurovascular unit and the blood brain barrier in the pathogenesis of HAND

DAR, NIMH- Therapeutics Priority Areas

- Improved CNS bioavailability of ART

- Novel neuroprotective agents:
  - Adjunctive therapies using targeted discoveries from basic research of HIV neuropathogenesis
  - Repurposed FDA-approved anti-neuro-inflammatory agents
  - Small molecule synthetic mimetics
  - Drug candidates to modulate inflammation at the Blood brain barrier
  - Stem cell therapeutics

- Clinical trials for HAND therapeutics

DAR, NIMH- Therapeutics Priority Areas

- Improve CNS bioavailability of ART
- Novel neuroprotective agents:
  - Repurposed FDA-approved anti-neuro-inflammatory agents
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  - Small molecule synthetic mimetics
  - Research drug candidates to modulate inflammation at the Blood brain barrier
  - Stem cell therapeutics
- Clinical trials for HAND therapeutics
- Small molecule drug delivery agents for enhanced delivery of therapeutics across the blood brain barrier

HIV-1 Eradication

HIV-1 Eradication Research is a High Priority for the field and NIH

- Current eradication focus is on central and transitional memory T cells in the periphery
- Eradication must eliminate HIV from ***all*** reservoirs; including the brain

Eradication: The Brain Sanctuary

The brain is a distinct anatomical compartment in which HIV-1 may replicate and evolve independently. Penetration of ART across the blood-brain barrier into the brain tissue may be compromised.

Potential Cellular Reservoirs of HIV-1 in the Brain
T cells
Monocytes
Perivascular Macrophages
Microglia
Astrocytes

DAR, NIMH- Eradication Priority Areas

- Understanding the mechanisms of HIV-persistence in the CNS
- Characterizing functional changes in persistently infected cells in the CNS that could impact the total HIV reservoir or viral rebound
- Developing animal models and physiologically relevant primary cell models to study CNS reservoirs in the context of viral suppression with HAART
- Developing strategies for targeting persisting HIV in the CNS with optimal drug penetration profiles
- Develop unique class of HIV drugs that can inhibit and silence viral production from stable reservoirs and reduce residual viremia

NIMH and NINDS: National NeuroAIDS Tissue Consortium (NNTC)

As of February 25, 2014	4 Clinical Sites	2,813 enrolled participants	1,905 individuals have donated CNS specimens and data	NNTC Cohort: • 549 HIV+ • 37 HIV- individuals

Cooperative Agreement Awards (U24)
NIMH: Dianne Rausch, Debbie Colosi, Jeymohan Joseph (Project Scientist)
NINDS: May Wong

5 Grants

$3.85 million

The NNTC functions to:

- Collect, store, and distribute samples of brain tissue and peripheral nervous system tissue, cerebrospinal fluid (CSF), blood and other organs
- Conduct extensive ante mortem neurological characterization
- Collect biofluids taken during life (CSF, Plasma, etc) and tissues collected at death (brain, other)
- **Make these research resources available to scientific investigators.**

Current Branch Initiatives

Branch FOAs:

- **PA-14-095: Eradication of HIV-1 from Central Nervous System Reservoirs (R01)**
- **PA-14-094: HIV Infection of the Central Nervous System (R01)**
- **PAR-MH-13-267: Novel NeuroAIDS Therapeutics: Integrated Preclinical/Clinical Program (P01)**

Eradication of HIV-1 from CNS Reservoirs NIMH PA-14-095

Key Highlights		
Program Officer: Jeymohan Joseph		
Mechanism(s): **R01**		
Objectives and Scope	The objective of this announcement is to foster investigations solely focused on CNS HIV-1 latency and tailored eradication strategies	
	Examples of pertinent research include, but are not limited to:	• Identify all potential cellular reservoirs • Develop neuroimaging approaches • Determine new cellular markers of HIV infection
The goals of this initiative are to define and characterize the sources of HIV persistence in the CNS for people on suppressive HAART and foster translational research to enable eradication of HIV-1 from the brain.		

PA-14-094: HIV Infection of the CNS NIMH

Key Highlights		
Program Officer: Jeymohan Joseph		
Mechanism(s): **R01**		
Objectives and Scope	The objective of this announcement is to define the pathogenic mechanisms involved in HIV-Associated Neurocognitive Disorders (HAND) and, identify therapeutic strategies to treat and prevent the neurobehavioral and neurological effects of HIV-1 on the central nervous system (CNS).	
	Examples of pertinent research include, but are not limited to:	• HIV Neuropathogenesis in the HAART era • Viral and Host Genetics • Aging, Co-morbidities, Co-infections and HAND • Therapeutics

Integrated Preclinical/Clinical Programs
NIMH PAR-13-267

Key Highlights
Program Officer: Deborah Colosi
Mechanism(s): **P01**
The goals of this FOA are to foster: ✓ Translation of research discoveries to advance a strategy and/or drug to treat HAND ✓ Research focused solely on CNS HIV-1 latency to provide a foundation for HIV-1 eradication
Applications focused on a plan to advance the program from discovery to clinical research are encouraged.

Current Branch Initiative Co-Sponsorships with DAIDS

Branch Co-Sponsorship of FOAs with DAIDS:

- PAR-AI-15-041: Targeting Persistent HIV Reservoirs (TaPHIR) (R21/R33)
- PAR-14-248: Basic Research on HIV Persistence (R01/R21)
- RFA-AI-14-004: Beyond HAART: Innovative Approaches to Cure HIV-1 (U19)
- RFA-AI-15-029: Martin Delaney Collaboratory: Towards an HIV-1 Cure (U19)
- PAR-15-280: Multidisciplinary Studies of HIV/AIDS and Aging (R01)

FY 17 Branch Initiative: : Novel Strategies for Targeting HIV-CNS Reservoirs without Reactivation

Purpose

- The goal of this initiative is to stimulate research on identifying latently infected cells in the CNS compartment and developing strategies for viral silencing without proviral reactivation and inhibition of the virus production from CNS reservoirs

NIMH International NeuroAIDS Studies

National Institute of Mental Health

DAR, NIMH- Global Priority Areas

- Epidemiology and natural history of Neurologic and Neuropsychiatric Complications resulting from HIV and Associated Opportunistic/Co-Infections from a Global Perspective
- Viral and Host Genetic factors regulating HIV-1 associated CNS disease
- Mechanisms of HIV-1 latency in the CNS and eradication of CNS reservoirs
- Long-Term CNS Consequences of Treatment During Acute HIV-1 Infection

Active International NeuroAIDS Studies

- Dr. Christian Achim (Romania)
  - HAND in a Cohort of Long-Term Surviving Romanian Young Adults on HAART
- Dr. Ned Sacktor (Uganda)
  - Neurologic Sequelae of HIV Subtype A and D Infection and ART Rakai Uganda
- Dr. Alex Sigal (Durban-South Africa)
  - Ongoing HIV replication as a CNS persistence mechanism in the face of cART
- Dr. Mark Cotton (Cape Town – South Africa)
  - Latent reservoir characterization and correlations with neurocognitive functioning
- Dr. Georgette Kanmogne (Cameroon)
  - HIV Genetic Diversity and Viral Neuropathogenesis

Active International NeuroAIDS Studies

- Dr. Madhavan Nair (Hyderabad- India)
  - Mechanisms of Neuro-AIDS by HIV 1B and C Clades
- Dr. Victor Valcour/Dr. Serena Spudich (Thailand)
  - Long-Term CNS Consequences of Treatment During Acute Infection
- Dr. Mellisa Churchill (Melbourne- Australia)
  - Transcriptional HIV-1 latency in astrocyte and macrophage reservoirs of the central nervous system
- Dr. Bharat Biswal/ Dr. Ernesta Meintjes (Cape Town- South Africa)
  - Longitudinal, multimodal analysis of HIV and ART effects on brain metabolism

NIMH Global NeuroAIDS Conferences/ Meetings (2005 – 2015)

- NeuroAIDS in Brazil, Rio de Janeiro, Brazil, July 2005
- Assessment of Resources and Opportunities for NeuroAIDS Research in Nigeria/West Africa, Abuja, Nigeria, June 2006
- Assessment of NeuroAIDS in Africa II, Arusha, Tanzania, July 2006
- West Africa NeuroAIDS Consortium Meeting, Venice, Italy, 2007
- NeuroAIDS in Asia and the Pacific Rim, Sydney, Australia, July 2007

NIMH Global NeuroAIDS Conferences/ Meetings (2005 – 2015)

- NeuroAIDS in Africa, Cape Town, South Africa, July 2009
- NeuroAIDS in Eastern Europe and Central Asia, Stresa, Italy, October 2009
- Global NeuroAIDS Roundtable, 11th International Symposium on Neurovirology, New York, May 2012
- NeuroAIDS in Africa, SONA, Rabat, Morocco, June 2013
- NeuroAIDS in Africa: Neurological and neuropsychiatric complications of HIV, Durban, South Africa, March 2015

Prevalence of NeuroAIDS in international settings – Reports from Global Roundtable 2012

Yes for HIV-1

- Cameroon (Kanmonge)
- Uganda (Sacktor; Boivin)
- Nigeria (Royal)
- South Africa (Paul)
- Zambia (Wood)
- India (Marcotte)
- Brazil (Ellis/Smith)
- Thailand (Sithinamsuwan)
- Romania (Achim)
- China (Letendre/Heaton)
- Asia Pacific (Brew)

No for HIV-2 (Clifford)

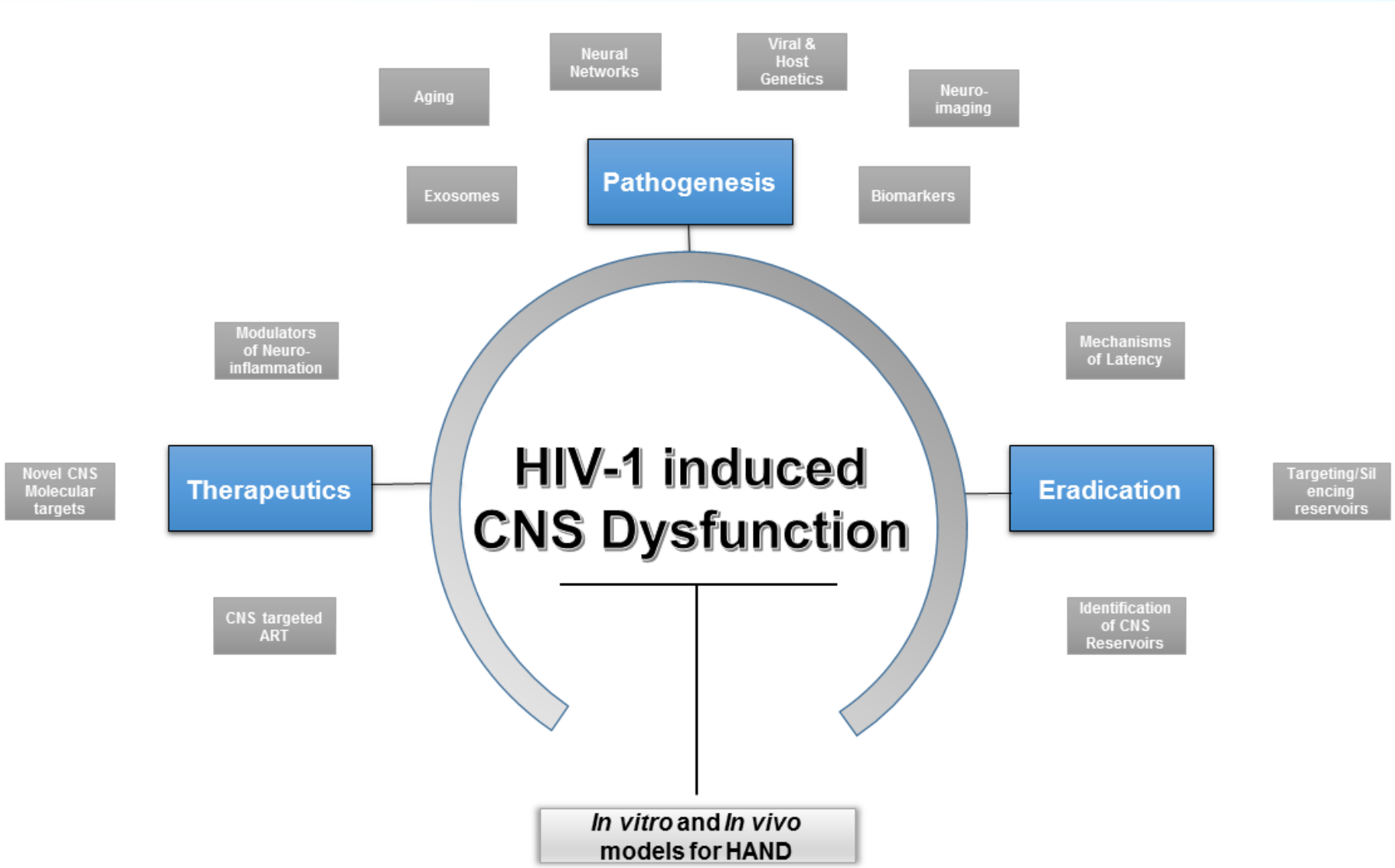
Do Clades influence NeuroAIDS - Reports from Global Roundtable 2012

- Rates similar in Pune, India (Clade C) to USA (Clade B in CHARTER) using comparable NP methods (Marcotte)
- Rates similar in Thailand, (A/E) to USA (clade B in CHARTER) (Sithinamsuwan)
- Rates similar in Romania (clade F) (Achim)
- C & B relatively similar in South Africa (Paul)
- C & B similar in Brazil (Smith)
- D > A neuro in Uganda in more immunosuppressed (Sacktor)
- A > D neuro in children (Boivin)
- Geographical genetic differences in Clade C might influence severity of NeuroAIDS (Prasad)

FOAs

- Global Brain and Nervous System Disorders Research across the Lifespan (R21) (PAR-14-331)
- Global Brain and Nervous System Disorders Research across the Lifespan (R01) (PAR-14-332)
- Global Infectious Disease Research Training Program (D43) (PAR-14-193)
- Limited Competition: Fogarty HIV Research Training Program for Low- and Middle-Income Country Institutions (D43)

Thank you for your attention.



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