APPROXIMATE WAIT TIME < 1 MINUTE

Project Information

5R01AI110173-03

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Project Number:	5R01AI110173-03	**Contact PI / Project Leader:**	BADLEY, ANDREW D
Title:	PRIME SHOCK AND KILL FOR HIV ERRADICATION	**Awardee Organization:**	MAYO CLINIC ROCHESTER

Abstract Text:

DESCRIPTION: The primary reservoir of HIV consists of latently infected resting memory CD4 T cells. Emerging information indicates that these cells are intrinsically resistant to apoptosis fr two distinct reasons: (i) chronic HIV infection of T cells induces an apoptosis resistant phenotype by virtue of HIV proteins causing altered expression of a wide variety of apoptosis regulatory proteins, and (ii) resting memory T cells, by virtue of being an historical archive of prior immune responses developing a quiescent and apoptosis resistant state in order to preserve the memory responses. Current approaches to "cure" HIV broadly involve gene therapy, immune based therapy, and viral reactivation. The latter strategy involves reactivating HIV pharmacologically, with the expectation that CD4 T cells which reactivate virus will die from the cytotoxic effects of viral protein expression. Work to date has established that viral reactivation is possible (e.g., with suberoylanilide hydroxamic acid, SAHA) and safe, but given the intrinsic resistance of these cells to apoptosis, it is not surprising that the cells that reacivate virus neither die after reactivation, nor are they efficiently killed by cytotoxic T lymphocytes. e have characterized the expression of select apoptosis regulatory proteins in resting memory CD4 T cells which contain latent HIV, and found the cells to have low levels of the proapoptotic protein procaspase 8 and high levels of the antiapoptotic protein Bcl2. We propose that this imbalance is the reason why latently HIV infected CD4 T cells

do not die after HIV reactivation, despite the fact that they express potent apoptosis-inducing proteins intracellularly - HIV Tat, nef, Vpr and protease after viral reactivation. Therefore, the cells that were latently infected do not die even after they are induced to express proapoptotic HIV proteins such as HIV protease. The overarching goal of the proposed study is to identify ways to alter latently infected HIV T cells such that they die in response to viral reactivation. In this application, we present three independent lines of evidence that this approach is justified and these cells can be altered in such a way that when HIV is reactivated, the cells will die. First using the Lewin model of HIV latency in primary CD4 T cells, we show that pharmacologically up-regulating the host protein procaspase 8, in resting memory CD4 T cells, allows these cells to be killed after viral reactivation, resulting in lower HIV replication (because infected cells are killed) and less integrated HIV copies. Next we summarize our previously published work that treatment of resting memory CD4 T cells from HIV infected patients with TRAIL agonists reduces that amount of replication competent HIV and the amount of HIV provirus, without deleterious effects on uninfected bystander cells. Finally, we present preliminary evidence that the first in class Bcl2 inhibitor, ABT-737, primes latently infected cells to undergo death upon HIV reactivation. These approaches specifically target HIV infected cells to die because, using this tactic, all cell will be primed to become apoptosis susceptible, however, only those cells which contain intracellular HIV proteins (the HIV infected cells) contain the apoptosis inducing stimulus. Having shown proof of concept for our "Prime Shock and Kill" model of HIV eradication, we now propose to adopt a high throughput screening approach to identify optimum pharmacologic methods of i) inducing apoptosis sensitivity, and then, ii) test these treatments in combination with stimuli that induce viral reactivation. This approach will then be tested for their ability to cause latently HIV infected T cell death using in vitro models of HIV latency and ex vivo testing of primary resting CD4 T cells from HIV-infected patients. Ultimately successful approaches will be fully vetted using the BLT mouse model of HIV infection.

Public Health Relevance Statement:

PUBLIC HEALTH RELEVANCE: When a person encounters an infectious agent or a vaccine for the first time, they develop an immune response to that agent or vaccine. Some of the cells which respond to that agent or vaccine then persist for years to decades, and become memory T cells, so that if the infectious agent is again encountered, the immune response to it can be rapid. As these cells need to persist for long periods, these cells have developed mechanisms to resist the normal process of cell turnover - i.e. these cells resist death signals. HIV infectin is now a chronic, manageable disease, but as yet cannot be cured, due to the persistence of HIV in memory CD4 T cells that are resistant to cell turnover and death. In T cells that are not memory CD4 T cells, when HIV replicates, HIV proteins are toxic and kill the T cell. Conversely when HIV is reactivated in memory CD4 T cells, these same HIV proteins do not kill the cell, for unknown reasons. We believe that the reason that these memory CD4 T cells do not die after HIV is reactivated is because they are intrinsically resistant to cell death. In the field of cancr treatment, treating cancer cells with traditional chemotherapy does not always kill the cancer cell. One strategy to overcome this resistance of cancer cells to chemotherapy has been to prime cells to become susceptible to chemotherapy, and then treat with chemotherapy. We propose to use a similar priming strategy for resting memory CD4 T cells which contain HIV. This strategy involves identifying agents which prime HIV infected cells, so that when HIV is reactivated, these cells die due to the toxic effects of HIV proteins. This novel approach has never before been tested with HIV and has the attractive advantage that it would target only HIV infected cells, leaving the rest of the body untouched, and can be used on a large scale. Our lab has been studying how HIV causes the death of the cells that it infects, and why HIV does not kill cells that are latently infected that are induced to reactivate HIV. We have identified tht when cells contain HIV but do not die, these cells have a deficiency in some proteins which are required for death and too much of other proteins which protect the cell from dying. These observations suggest that altering the balance of these death regulatory proteins might allow for cells which reactivate HIV to die when HIV is induced to replicate. Already we have identified several compounds which modify death regulatory proteins, so that when HIV is induced to replicate, the HIV infected cells, but not the uninfected cells, die. In the experiments planned over the life of the current proposal, we will optimize means of altering death regulating protein expression, optimize strategies for reactivating virus, and determine whether combinations of the two will cause the death of all cells containing HIV. If successful, these studies will lay the foundation for developing treatments designed to cure patients from HIV infection.

Project Terms:

Acute; Adopted; Agonist; Anti-Retroviral Agents; Apoptosis; Archives; base; cancer cell; Cause of Death; CD4 Positive T Lymphocytes; Cell Death; cell killing; Cell model; Cell physiology; Cells; Cessation of life; Chemosensitization; chemotherapy; Chronic; clinical application; Communicable Diseases; Communities; cytotoxic; Cytotoxic T-Lymphocytes; Disease; Equilibrium; Exhibits; expectation; Foundations; gene therapy; genetic regulatory protein; Goals; Health; high throughput screening; HIV; HIV Infections; HIV Protease; HIV tat Protein; HIV therapy; Immune; immune activation; Immune response; in vitro Model; Infection; Infectious Agent; inhibitor/antagonist; Killings; Lead; Left; Life; macrophage; Malignant Neoplasms; Memory; memory CD4 T lymphocyte; Methods; Modeling; Modification; mouse model; Myeloablative Chemotherapy; neoplastic cell; novel; novel strategies; Patients; Peptide Hydrolases; Persons; Pharmacologic Substance; Phenotype; Predisposition; prevent; Production; protein expression; Proteins; Proviruses; Publishing; research study; Resistance; response; Rest; Sampling; Shock; Signal Transduction; Stem cell transplant; Stimulus; T memory cell; T-Lymphocyte; Testing; therapy design; Time; TNFSF10 gene; Toxic effect; Vaccines; Viral; Viral Proteins; Virus; Vorinostat; Work

Contact PI Information:	**Program Official Information:**	**Other PI Information:**
Name: BADLEY, ANDREW D **Email**: Click to view contact PI email address **Title**: PROFESSOR	**Name**: MILLER, ROGER H. **Email**: Click to view PO email address	Not Applicable

Organization:	**Department / Educational Institution Type:**	**Congressional District:**
Name: MAYO CLINIC ROCHESTER **City**: ROCHESTER Country: UNITED STATES (US)	Unavailable Unavailable	State Code: MN District: 01

Other Information:

FOA: PA-11-260 **Study Section**: AIDS Immunology and Pathogenesis Study Section (AIP) **Fiscal Year**: 2016 **Award Notice Date**: 7-JAN-2016	**DUNS Number**: 006471700 **Project Start Date**: 15-FEB-2014 **Budget Start Date**: 1-FEB-2016	**CFDA Code**: 855 **Project End Date**: 31-JAN-2019 **Budget End Date**: 31-JAN-2017

Administering Institutes or Centers:

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

Project Funding Information for 2016:

Total Funding: $690,241	**Direct Costs:** $434,114	**Indirect Costs:** $256,127

Year	Funding IC	FY Total Cost by IC
2016	NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$690,241

History:

Project Number	Sub #	Project Title	Contact Principal	Organization	FY	Admin IC	Funding IC	FY Total Cost

		Investigator				by IC
5R01AI110173-03	PRIME SHOCK AND KILL FOR HIV ERRADICATION	BADLEY, ANDREW D	MAYO CLINIC ROCHESTER	2016 NIAID	NIAID	$690,241
5R01AI110173-02	PRIME SHOCK AND KILL FOR HIV ERRADICATION	BADLEY, ANDREW D	MAYO CLINIC ROCHESTER	2015 NIAID	NIAID	$555,091
1R01AI110173-01	PRIME SHOCK AND KILL FOR HIV ERRADICATION	BADLEY, ANDREW D	MAYO CLINIC ROCHESTER	2014 NIAID	NIAID	$555,091

Subprojects:

Project Number	Sub #	Project Title	Contact Principal Investigator	Organization	FY	Admin IC	FY Total Cost by IC
No Subprojects information available for 5R01AI110173-03							

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Project Information

5KL2TR000136-10

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Project Number:	5KL2TR000136-10	**Contact PI / Project Leader:**	KHOSLA, SUNDEEP
Title:	MAYO CLINIC CENTER FOR CLINICAL AND TRANSLATIONAL SCIENCE (CCATS)	**Awardee Organization:**	MAYO CLINIC ROCHESTER

Abstract Text:

The overall goal of the Mayo Clinic CTSA is to continue to build a broad-based and integrated home for clinical and translational science (CTS) at Mayo Clinic that will ultimately improve human health. In this context, we seek to make the Mayo CTSA and the resources it leverages both an engine of efficiency for clinical and translational research and at the same time a driver of innovation. We also seek to integrate our local activities with consortium wide efforts directed at coordination and alignment. To achieve our goal we have six overarching specific aims for this renewal: Aim 1 - Train and maintain an outstanding multidisciplinary clinical and translational sciences workforce. This workforce includes teams of both investigators and support staff. Aim 2 - Eliminate barriers to the work of translation. This will be accomplished through a) continued efforts at regulatory and compliance streamlining, b) provision of outstanding design, biostatistics, and ethics support for investigators, and c) further integration of support services. Aim 3 - Collaborate with providers and communities to improve health care delivery and community health. This includes substantial commitments to practice-based research, communityengaged research and translating comparative effectiveness research into clinical practice. Aim 4 - Deploy advanced facilities and other core resources to increase the value of clinical research. With value defined in this context as the quotient of quality and cost, the goal is to increase quality, decrease costs, and provide resources to the full spectrum of clinical and translational investigation. Aim 5 - Stimulate novel research directions and methodologies by targeted support of innovative pilot and feasibility studies and fostering the development of novel methodologies. Aim 6 - Employ informatics to integrate and facilitate clinical and translational investigation. This encompasses a broad view of informatics including: a) developing a standardized electronic data capture and analysis tools for CTS, b) robust consultation and tools for medical informatics that leverage Mayo's commitments to electronic clinical systems, and c) bioinformatics services and capabilities that will help facilitate the application of the "new biology" to clinical and translational investigation. This vision is entirely consistent with the stated mission of Mayo Clinic: "To provide the best care to every patient every day through integrated clinical practice, education, and research."

Public Health Relevance Statement:

RELEVANCE (See instructions): Mayo Clinic Center for Translational Science Activities will bring together all the resources of the five schools within the Mayo Clinic College of Medicine and more than 100 years of scientific and medical research expertise, to discover innovative new methods that will speed the translation of research results into therapies, tools, and patient care practices that impact both our local and national communities by improving their health.

NIH Spending Category:

Bioengineering; Clinical Research; Comparative Effectiveness Research; HIV/AIDS; Health Services

Project Terms:

Address; Advisory Committees; base; Basic Science; Behavioral; behavioral/social science; Benchmarking; Bioinformatics; Biology; biomedical informatics; Biometry; career development; Caring; Center for Translational Science Activities; Clinic; Clinical; clinical epidemiology; clinical practice; Clinical Research; Clinical Sciences; Collaborations; college; Communities; Community Health; comparative effectiveness; Consultations; cost; design; Development; Education; Educational Curriculum; effectiveness research; electronic data; Electronics; Ensure; Ethics; Evaluation; experience; Feasibility Studies; Fostering; Goals; Health; health care delivery; health disparity; Health Services Research; Home environment; Human; improved; Informatics; innovation; Instruction; Interdisciplinary Study; Investigation; Knowledge; Learning; Measures; Medical Informatics; Medical Research; Medicine; Mentors; Methodology; Methods; Mission; multidisciplinary; next generation; novel; Outcome; Patient Care; Patients; Phase; Pilot Projects; Practice based research; Process; Program Evaluation; programs; Provider; Research; Research Design; Research Ethics; Research Personnel; Resources; Schools; Services; skills; social; social science research; Speed (motion); Staging; Structure; Students; System; Time; tool; Training; Training and Education; Translating; Translational Research; Translations; Vision; Work