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Immunization Via Mosquito Bite With Radiation-attenuated Sporozoites (IMRAS)



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ClinicalTrials.gov Identifier: NCT01994525

[Recruitment Status](#) ⓘ : Completed

[First Posted](#) ⓘ : November 25, 2013

[Last Update Posted](#) ⓘ : September 17, 2019

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Sponsor:

U.S. Army Medical Research and Development Command

Collaborators:

Seattle Children's Research Institute (SCRI)

Bill and Melinda Gates Foundation

Information provided by (Responsible Party):

U.S. Army Medical Research and Development Command

[Study Details](#)

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[No Results Posted](#)

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Study Description

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Brief Summary:

This study is to assess the safety, tolerability, and biomarkers of protection in healthy malaria-naïve adults, who will receive bites from *Anopheles stephensi* mosquitoes either infected with *Plasmodium falciparum* Sporozoites (PFRAS) (true-immunization) or noninfected (mock-immunization).

| Condition or disease ⓘ | Intervention/treatment ⓘ | Phase ⓘ |
|--|--|-------------------------|
| Malaria | Biological: PFRAS Biological: Placebo Other: Challenge | Phase 1 |

Detailed Description:

This is a Phase 1 open-labeled study. In addition to safety and tolerability of *Plasmodium falciparum* Sporozoites (PFRAS), this study is a comprehensive, systems biology-based effort to identify and validate biomarkers of protection with PFRAS immunization, comparing sterility protected to nonprotected study subjects. The goal of the trial design is to achieve approximately 50% sterile protection in order to facilitate the identification of biomarkers and correlates of protection.

Following true-immunization or mock-immunization, study subjects and nonimmunized infectivity controls will receive a challenge via the bites of 5 *An stephensi* mosquitoes carrying infectious *P falciparum* sporozoites within a controlled clinical environment (controlled human malaria infection, CHMI) to determine the level of sterile protection.

Study Design

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[Study Type](#) ⓘ: Interventional (Clinical Trial)

[Actual Enrollment](#) ⓘ: 54 participants

[Allocation](#): Randomized

[Intervention Model](#): Parallel Assignment

[Masking](#): None (Open Label)

[Primary Purpose](#): Prevention

[Official Title](#): Phase 1 Trial With Challenge to Assess the Safety and Biomarkers of Protection in Malaria-naïve Adults of Immunization Via Mosquito Bite With Radiation-Attenuated *Plasmodium Falciparum* Sporozoites (IMRAS)

[Actual Study Start Date](#) ⓘ: January 24, 2014

[Actual Primary Completion Date](#) ⓘ: December 20, 2016



Actual Study Completion Date ⓘ: February 2017

Resource links provided by the National Library of Medicine[MedlinePlus](#) related topics: [Malaria](#) [Mosquito Bites](#) [Vaccines](#)[Genetic and Rare Diseases Information Center](#) resources: [Malaria](#)[U.S. FDA Resources](#)**Arms and Interventions**

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| Arm ⓘ | Intervention/treatment ⓘ |
|---|--|
| <p>Experimental: Cohort 1: PfRAS-infected</p> <p>5 doses (immunizations) of approximately 200 infectious bites (200-400 bites total) from PfRAS-infected mosquitoes (true-immunization). The target dose is 960 infectious bites.</p> <p>Challenge occurs 3 weeks after final immunization.</p> | <p>Biological: PfRAS</p> <p>Radiation-attenuated Plasmodium falciparum sporozoites (PfRAS) administered by the bite of infected Anopheles stephensi mosquitoes</p> <p>Other Names:</p> <ul style="list-style-type: none"> • True-immunization • PfRAS infected Anopheles stephensi mosquitoes <p>Other: Challenge</p> <p>5 infectious Anopheles stephensi mosquito bites carrying infectious Plasmodium falciparum sporozoites within a controlled clinical environment.</p> |
| <p>Placebo Comparator: Cohort 1: Noninfected</p> <p>Placebo immunization. 5 doses of approximately 200 noninfected bites (200-400 bites total) from irradiated uninfected mosquitoes (mock-immunization). The target dose is 960 noninfected bites.</p> <p>Challenge occurs 3 weeks after final immunization.</p> | <p>Biological: Placebo</p> <p>Administered by the bite of noninfected Anopheles stephensi mosquitoes</p> <p>Other Names:</p> <ul style="list-style-type: none"> • Mock-immunization • Noninfected Anopheles stephensi mosquitoes |

| Arm  | Intervention/treatment  |
|---|---|
| | <p>Other: Challenge</p> <p>5 infectious <i>Anopheles stephensi</i> mosquito bites carrying infectious <i>Plasmodium falciparum</i> sporozoites within a controlled clinical environment.</p> |
| <p>Cohort 1: Nonimmunized</p> <p>No protective intervention given.</p> <p>Challenge occurs directly after screening.</p> | <p>Other: Challenge</p> <p>5 infectious <i>Anopheles stephensi</i> mosquito bites carrying infectious <i>Plasmodium falciparum</i> sporozoites within a controlled clinical environment.</p> |
| <p>Experimental: Cohort 2: PfRAS-infected</p> <p>3 to 7 doses (immunizations) of approximately 200 infectious bites (200-400 bites total) from PfRAS-infected mosquitoes (true-immunization). The target dose is dependent on protection results in cohort 1.</p> <p>Challenge occurs 3 weeks after final immunization.</p> | <p>Biological: PfRAS</p> <p>Radiation-attenuated <i>Plasmodium falciparum</i> sporozoites (PfRAS) administered by the bite of infected <i>Anopheles stephensi</i> mosquitoes</p> <p>Other Names:</p> <ul style="list-style-type: none"> • True-immunization • PfRAS infected <i>Anopheles stephensi</i> mosquitoes <p>Other: Challenge</p> <p>5 infectious <i>Anopheles stephensi</i> mosquito bites carrying infectious <i>Plasmodium falciparum</i> sporozoites within a controlled clinical environment.</p> |

| Arm  | Intervention/treatment  |
|---|---|
| <p>Placebo Comparator: Cohort 2: Noninfected</p> <p>Placebo. 3 to 7 doses of approximately 200 noninfected bites (200-400 bites total) from irradiated, uninfected mosquitoes (true-immunization). The target dose is dependent on protection results in cohort 1.</p> <p>Challenge occurs 3 weeks after final immunization.</p> | <p>Biological: Placebo</p> <p>Administered by the bite of noninfected <i>Anopheles stephensi</i> mosquitoes</p> <p>Other Names:</p> <ul style="list-style-type: none"> • Mock-immunization • Noninfected <i>Anopheles stephensi</i> mosquitoes <p>Other: Challenge</p> <p>5 infectious <i>Anopheles stephensi</i> mosquito bites carrying infectious <i>Plasmodium falciparum</i> sporozoites within a controlled clinical environment.</p> |
| <p>Cohort 2: Nonimmunized</p> <p>No protective intervention given.</p> <p>Challenge occurs directly after screening.</p> | <p>Other: Challenge</p> <p>5 infectious <i>Anopheles stephensi</i> mosquito bites carrying infectious <i>Plasmodium falciparum</i> sporozoites within a controlled clinical environment.</p> |
| <p>Experimental: Hyperimmunity PfRAS-infected</p> <p>Cohort 1 sub-cohort</p> <p>3 doses (immunizations) of approximately 200 infectious bites (200-400 bites total) from PfRAS-infected mosquitoes. This arm will receive the first 3 immunizations of Cohort 2.</p> <p>Challenge occurs at the same time as Cohort 2 (3-20 weeks after the final immunization)</p> | <p>Biological: PfRAS</p> <p>Radiation-attenuated <i>Plasmodium falciparum</i> sporozoites (PfRAS) administered by the bite of infected <i>Anopheles stephensi</i> mosquitoes</p> <p>Other Names:</p> <ul style="list-style-type: none"> • True-immunization • PfRAS infected <i>Anopheles stephensi</i> mosquitoes <p>Other: Challenge</p> <p>5 infectious <i>Anopheles stephensi</i> mosquito bites carrying infectious <i>Plasmodium falciparum</i> sporozoites within a controlled clinical environment.</p> |

| Arm i | Intervention/treatment i |
|-----------------------|--|
| | |

Outcome Measures

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Primary Outcome Measures [i](#):

1. Solicited adverse events [Time Frame: 7 days]
Occurrence of solicited adverse events (AE) from administration of study immunization (PfRAS)
2. Unsolicited adverse events [Time Frame: 14 days]
Occurrence of unsolicited adverse events (AEs) from administration of immunization (PfRAS)
3. Laboratory adverse events [Time Frame: 7 days]
Occurrence of laboratory AEs from administration of study immunization (PfRAS)
4. Serious adverse events [Time Frame: 52 weeks]
Occurrence of serious adverse events (SAEs) from administration of immunization (PfRAS)
5. Signs and symptoms related to malaria infection [Time Frame: 7 days]
Occurrence of signs and symptoms related to malaria infection starting 7 days post-Controlled Human Malaria Infection (CHMI) (these will not be recorded as adverse events because they are expected as a result of malaria infection)
6. Parasitemia [Time Frame: 52 weeks]
Development of parasitemia and time to parasitemia after malaria challenge

Secondary Outcome Measures [i](#):


1. Identify and validate immunological PBMC biomarkers [Time Frame: 52 weeks]
Compare Peripheral Blood Mononuclear Cell(s) (PBMC) read-outs between protected and nonprotected subjects and between immunized and mock-immunized subjects.
2. Identify and validate immunological serum biomarkers [Time Frame: 52 weeks]

Compare serum read-outs between protected and nonprotected subjects and between immunized and mock-immunized subjects.

3. Identify and validate whole blood immunological biomarkers [Time Frame: 52 weeks]

Compare whole blood read-outs between protected and nonprotected subjects and between immunized and mock-immunized subjects.

Eligibility Criteria

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Information from the National Library of Medicine



Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the contacts provided below. For general information, [Learn About Clinical Studies](#).

Ages Eligible for Study: 18 Years to 50 Years (Adult)

Sexes Eligible for Study: All

Accepts Healthy Volunteers: Yes

Criteria

Inclusion Criteria:

- Healthy adults (male or non-pregnant, non-breastfeeding female) 18-50 years of age (inclusive).
- Available and willing to participate for duration of study.
- Able and willing to provide written informed consent.
- Able to complete an Assessment of Understanding with a score of at least 70% correct.
- In good general health with no clinically significant health problems as established by medical history, physical exam and laboratory screening.
- Females of childbearing potential must have a negative pregnancy test at screening and agree to not become pregnant or breastfeed for the duration of the study. She must be willing to use a reliable form of contraception during the study. Reliable forms of birth control include use of condoms, diaphragm or cervical cap, birth control pills, IUD or sperm killing products.
- Agree to refrain from blood donation (except as required in this study) for 3 years following *P falciparum*

challenge.

- Agree not to travel to a malaria-endemic region during the study.
- Good peripheral venous access.

Exclusion Criteria:

- Positive HIV, HBsAg, or HCV serology.
- Positive sickle cell screening test, including evidence of sickle trait.
- Reactivity by CSP or AMA1 ELISpot assay or ELISA as determined by IMRAS Study Specific Procedure #204.
- Anemia (below normal reference laboratory value of hemoglobin) on screening.
- Weight less than 110 pounds (this does not apply to infectivity controls as it is a weight cut-off for subjects undergoing leukapheresis procedure)
- Any history of malaria infection or travel to a malaria endemic region within 6 months prior to first immunization.
- History of long-term residence (> 5 years) in area known to have significant transmission of Pf [cumulative lifetime exposure].
- Use of systemic immunosuppressant pharmacotherapy for greater than 10 days within 60 days of scheduled first immunization (inhaled and topical steroids are allowed; short duration or tapered corticosteroid regimens of 10 days or less that have been discontinued prior to first immunization are allowed).
- Current significant medical condition (cardiovascular, hepatic, renal, pulmonary, or hematological) or evidence of any other serious underlying medical condition identified by medical history, physical examination, or laboratory examination (includes bleeding disorders).
- Plan for surgery between enrollment and day 28 post-challenge (minor procedures, elective corrective vision surgery, and dental procedures are allowed).
- Receipt of immunoglobulin and/or any blood products within 90 days of scheduled leukapheresis or immunization. Version 13.0 (08May2015) 70 US Government Proprietary Deleted: 8 Deleted: 08JULY2014
- Has evidence of increased cardiovascular disease risk (defined as > 5%-10%, 5-year risk) as determined by the method of Gaziano (2008). Risk factors include sex, age (years), systolic blood pressure (mm Hg), smoking status, body mass index (BMI, kg/m²), reported diabetes status, and blood pressure.
- An abnormal electrocardiogram (ECG), defined as one showing pathologic Q waves and significant ST-T wave changes; left ventricular hypertrophy; any non-sinus rhythm excluding isolated premature atrial contractions; right or left bundle branch block; or advanced (secondary or tertiary) A-V heart block.
- History of a splenectomy.
- History of any other illness or condition that, in the investigator's judgment, may substantially increase the risk associated with the subject's participation in the protocol or compromise the scientific

objectives. This may include psychiatric disorders (such as personality disorders, anxiety disorders, or schizophrenia) or behavioral tendencies (including active alcohol or drug abuse) discovered during the screening process that in the opinion of the investigator would make compliance with the protocol difficult.

- History of anaphylactic or severe response to mosquito bites, retinal or visual field changes, or known allergy to the antimalarial chloroquine phosphate, which will be used to treat subjects developing malaria after CHMI.
- Participation in any study involving any investigational vaccine or drug within 30 days prior to the screening visit, or plan to participate in another investigational vaccine/drug research during or within 1 month following participation in this study.
- Use or planned use of any drug with antimalarial activity that would coincide with immunization or challenge.
- History of psoriasis or porphyria, which may be exacerbated after treatment with chloroquine.
- Anticipated use of medications known to cause drug reactions with chloroquine or atovaquone-proguanil (Malarone) such as cimetidine, metoclopramide, antacids, and kaolin during the day 7 to 28 post-challenge period.
- Any other significant findings which, in the investigator's judgment, may substantially increase the risk associated with the subject's participation in the study or compromise the scientific objectives.

Contacts and Locations

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Information from the National Library of Medicine



To learn more about this study, you or your doctor may contact the study research staff using the contact information provided by the sponsor.

Please refer to this study by its ClinicalTrials.gov identifier (NCT number):

NCT01994525

Locations

United States, Maryland

Naval Medical Research Center Clinical Trials Center (CTC)
Bethesda, Maryland, United States, 20889

Sponsors and Collaborators

U.S. Army Medical Research and Development Command


Seattle Children's Research Institute (SCRI)

Bill and Melinda Gates Foundation

Investigators

Principal Investigator: Nimfa Teneza-Mora, MD Naval Medical Research Center

More Information

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Publications automatically indexed to this study by ClinicalTrials.gov Identifier (NCT Number):

[Du Y, Hertoghs N, Duffy FJ, Carnes J, McDermott SM, Neal ML, Schwedhelm KV, McElrath MJ, De Rosa SC, Aitchison JD, Stuart KD. Systems analysis of immune responses to attenuated *P. falciparum* malaria sporozoite vaccination reveals excessive inflammatory signatures correlating with impaired immunity. *PLoS Pathog.* 2022 Feb 2;18\(2\):e1010282. doi: 10.1371/journal.ppat.1010282. eCollection 2022 Feb.](#)

[Sedegah M, Hollingdale MR, Ganeshan H, Belmonte M, Huang J, Belmonte A, Inoue S, Velasco R, Hickey B, Teneza-Mora N, Lumsden J, Reyes S, Banania JG, Reyes A, Guzman I, Richie TL, Epstein JE, Villasante E. IMRAS-Immunization with radiation-attenuated *Plasmodium falciparum* sporozoites by mosquito bite: Cellular immunity to sporozoites, CSP, AMA1, TRAP and CelTOS. *PLoS One.* 2021 Aug 20;16\(8\):e0256396. doi: 10.1371/journal.pone.0256396. eCollection 2021.](#)

[Hickey B, Teneza-Mora N, Lumsden J, Reyes S, Sedegah M, Garver L, Hollingdale MR, Banania JG, Ganeshan H, Dowler M, Reyes A, Tamminga C, Singer A, Simmons A, Belmonte M, Belmonte A, Huang J, Inoue S, Velasco R, Abot S, Vasquez CS, Guzman I, Wong M, Twomey P, Wojnarski M, Moon J, Alcorta Y, Maiolatesi S, Spring M, Davidson S, Chaudhury S, Villasante E, Richie TL, Epstein JE. IMRAS-A clinical trial of mosquito-bite immunization with live, radiation-attenuated *P. falciparum* sporozoites: Impact of immunization parameters on protective efficacy and generation of a repository of immunologic reagents. *PLoS One.* 2020 Jun 17;15\(6\):e0233840. doi: 10.1371/journal.pone.0233840. eCollection 2020.](#)

Responsible Party: U.S. Army Medical Research and Development Command
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 Other Study ID Numbers: S-12-22
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 Last Update Posted: September 17, 2019
 Last Verified: March 2019

Additional relevant MeSH terms:

Malaria

Protozoan Infections

Parasitic Diseases

Infections

Vector Borne Diseases