

## **Request for Applications (RFA)**

### **India-U.S. Collaborative Research Grants on Vaccine Adjuvant Development**

#### **DBT& NBM-BIRAC JOINT CALL**

Vaccine research and development is a priority area in the Department of Biotechnology (DBT) supported through an important mission called the National Biopharma Mission (NBM). NBM is an Industry-Academia Collaborative Mission of Department of Biotechnology for Accelerating Early Development for Biopharmaceuticals; being implemented by Biotechnology Industry Research Assistance Council (BIRAC), a Public Sector Undertaking of DBT aiming to create an ecosystem for innovative indigenous product development by researchers, startups and SMEs (Small and Medium Enterprises) to make Indian biotech industry globally competitive. Considering vaccine adjuvant research as an important area for vaccine development **Department of Biotechnology** in collaboration with **National Institute of Allergy and Infectious Diseases (NIAID)- National Institutes of Health (NIH)** invites proposals for the discovery, development, and/or preclinical testing of vaccine adjuvants under the aegis of **Indo US Vaccine Action Programme (VAP)**. VAP is one of the oldest bilateral programmes that supports a wide range of collaborative activities related to immunology, infectious disease biology and vaccine research.

The NIAID at the United States NIH support discovery and development of vaccine adjuvants, as described in the recently issued [NIAID Strategic Plan for Research on Vaccine Adjuvants](#). Programme accomplishments include the screening of more than 2 million compounds and the development of more than 100 different adjuvants/formulations, encompassing eight different adjuvant types or classes. NIAID also supports: the development of novel high- throughput screening approaches to evaluate adjuvant candidates; comprehensive formulations expertise to maximise adjuvanticity while minimising reactogenicity; and technology development for *in vitro* assessment of adjuvants to aid the evaluation and down-selection for human studies, including at-risk populations. Collaborations between Indian and U.S. investigators would further accelerate adjuvant and vaccine research in both countries.

Department of Biotechnology invites proposals for the discovery, development, and/or preclinical testing of vaccine adjuvant research to be supported under the National Biopharma Mission being implemented by BIRAC. The aim of this call is to strengthen vaccine adjuvant research in India. This joint DBT & NBM-BIRAC call will leverage the funding expertise of both the organizations.

This programme will support collaborations, both between academic institutions as well as between academia and industry partners. The aim is to build capacity for discovering and developing new adjuvants that can improve vaccine efficacy and also enhance career development.

## Research Objectives

The intent of this programme is to foster collaborations between Indian and U.S. investigators to accelerate vaccine adjuvant research. Activities associated with adjuvant discovery include: the screening of compound libraries, *in vitro* or *in silico*, to identify molecules capable of stimulating (human) cellular receptors or pathways that result in enhanced innate/adaptive immune responses; identification of molecular or cellular mechanisms-of-action of novel adjuvants; optimisation of novel adjuvants through structure-activity-relationship (SAR) studies, involving medicinal chemistry approaches; and preclinical testing of novel adjuvants in animal models with pathogen-derived antigens or licensed vaccines to determine the safety, immunogenicity and efficacy of the novel combination. The goal of adjuvant development is to advance novel vaccine-adjuvant combinations towards licensure for clinical use. Adjuvant development activities include: characterisation of immune profiles and potential immunotoxicity induced by vaccines formulated with novel adjuvants; improvement of an adjuvant's *in vivo* efficacy and reduction of reactogenicity through formulation or modification of delivery routes; toxicology, stability testing, pharmacokinetics or adsorption, distribution, metabolism and excretion studies to generate data required for initiating clinical testing of novel adjuvanted-vaccines. Adjuvant research also encompasses the development and evaluation of combination adjuvants, such as: the systematic pairing of novel or previously described adjuvants to identify highly synergistic combinations; identification of molecular or cellular mechanisms underlying synergistic adjuvant action in such combinations; or development of approaches to optimise the co-delivery of multiple adjuvants, either through carriers or other formulations, or chemical linkers. This new programme supports a wide variety of adjuvant research activities conducted collaboratively by Indian and U.S. investigators.

### Areas of collaborative research may include, but are not limited to:

- Discovery of novel compounds with adjuvant activity;
- Systematic optimisation of lead adjuvant compound(s);
- *In vitro* or *in vivo* (animals) evaluation of novel adjuvants (single compounds or combinations) combined with antigens associated with pathogenic infections, candidate vaccines, or licensed vaccines;
- Mechanism-of-action studies of adjuvants, including identification of molecular targets, signaling pathways, or immune effector functions (*e.g.*, soluble mediators, cellular targets);
- Formulation/optimisation of novel adjuvanted vaccines, including those for at-risk populations; and
- Systematic side-by-side *in vitro* and/or *in vivo* (animal) comparison of adjuvants to down-select for subsequent product development.

This programme will NOT support:

- Cancer-related adjuvant discovery/development; and
- Clinical trials.

## Clinical Trial Definition

For the purpose of this programme, the NIH definition of a clinical trial will be applied:

A clinical trial is a research study in which one or more human subjects are prospectively assigned<sup>1</sup> to one or more interventions<sup>2</sup> (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioural outcomes.<sup>3</sup>

<sup>1</sup>The term “*prospectively assigned*” refers to a pre-defined process (e.g., randomisation) specified in an approved protocol that stipulates the assignment of research subjects (individually or in clusters) to one or more arms (e.g., intervention, placebo, or other control) of a clinical trial.

<sup>2</sup>An *intervention* is defined as a manipulation of the subject or subject’s environment for the purpose of modifying one or more health-related biomedical or behavioural processes and/or endpoints. Examples include: drugs/small molecules/compounds; biologics; devices; procedures (e.g., surgical techniques); delivery systems (e.g., telemedicine, face-to-face interviews); strategies to change health-related behaviour (e.g., diet, cognitive therapy, exercise, development of new habits); treatment strategies; prevention strategies; and, diagnostic strategies.

<sup>3</sup>*Health-related biomedical or behavioural outcome* is defined as the pre-specified goal(s) or condition(s) that reflect the effect of one or more interventions on human subjects’ biomedical or behavioural status or quality of life. Examples include: positive or negative changes to physiological or biological parameters (e.g., improvement of lung capacity, gene expression); positive or negative changes to psychological or neurodevelopmental parameters (e.g., mood management intervention for smokers; reading comprehension and /or information retention); positive or negative changes to disease processes; positive or negative changes to health-related behaviours; and, positive or negative changes to quality of life.

## Scope of this Call

From this Joint Call, the Department seeks new innovative approaches that have the potential to transform the vaccine sector on a national or global scale by identifying and filling gaps in knowledge on the discovery/development of novel adjuvants that enhance vaccine performance without interfering in its activity. This Joint Call is aimed to support **collaborative proposals that combine complementary and synergistic research strengths in any of the aforementioned areas**. This call invites consortia-based concept proposals from academia (with/without industry) with already established/identified leads and explicitly outlined deliverables for further validation.

## Eligibility

**Primary Applicant:** The primary applicant (Principal Investigator- PI) for this call should be mandatorily from Indian Academia. Applications can be proposed jointly between:

1. Academia with academia
2. Academia with industry

All applications of the collaborative projects MUST include at least one investigator from India (as PI) AND one investigator from the U.S. (as Co-PI) with eligible NIAID support (e.g. able to receive administrative supplements).

A list of interested, eligible U.S. investigators is provided at the end of this announcement. Indian investigators who are interested in collaborating with U.S. investigators not listed below must have the U.S. investigator contact either of the following NIAID program staff to discuss eligibility:

- Wolfgang Leitner, Ph.D; [wleitner@niaid.nih.gov](mailto:wleitner@niaid.nih.gov) ; 240-627-3575
- Kentner Singleton, Ph.D; [singletonkl@niaid.nih.gov](mailto:singletonkl@niaid.nih.gov) ; 240-669-5499

Please note that the basic eligibility criteria for Indian academia and industry is as below:

### 1. Eligible Indian Organizations

- a) Central/State Govt. Institutions of Higher Education
- b) Private Institutions of Higher Education
- c) Research institutes, universities, medical schools, IIT's and other engineering institutions, other recognized research laboratories in the public sector and not-for-profit institutions.
- d) The institution must be recognized by Department of Scientific & Industrial Research (DSIR) as a Scientific and Industrial Research Organization (SIRO), if outside public sector.

### 2. Required Registrations

Private institutions/Hospitals/NGOs should be registered in Darpan Portal, Niti Aayog website. (<https://ngodarpan.gov.in/>)

### 3. Eligible Indian Investigator(s)

Scientists working in Universities/Academic Institutions/National Laboratories/Industries (DSIR)-Recognized R&D Centre & Non-Profit Organizations with necessary facilities and strong scientific background in the proposed area as the Principal Investigator(s) are invited to develop an application for support jointly with academia or Industry.

#### **4. Eligible Industry (Companies)**

An Indian company is defined as one which is registered under the Indian Companies Act, 2013, and minimum 51% of shares of the Company should be held by Indian citizens holding Indian passport (Indian Citizens do not include Persons of Indian Origin (PIO) or Overseas Citizen of India (OCI) holders).

#### **Terms of Award**

Human Subjects: Before award, all U.S. studies with human subjects must conform to NIH policies on the protection of human subjects (<https://grants.nih.gov/grants/policy/hs/index.htm>).

Before any funds can be expended for in-country research activities in a foreign country, the grantee institution must show evidence of compliance with both the U.S. and Indian regulations for the conduct of research involving human subjects. Additional information on the U.S. requirements can be found at the HHS Office for Human Research Protections at <https://www.hhs.gov/ohrp/>. Additional information on Indian requirements can be found in the Revised ICMR National Ethical Guidelines for biomedical and health research involving human participants ([https://www.icmr.nic.in/sites/default/files/guidelines/ICMR\\_Ethical\\_Guidelines\\_2017.pdf](https://www.icmr.nic.in/sites/default/files/guidelines/ICMR_Ethical_Guidelines_2017.pdf)).

Intellectual Property: The provisions of the Agreement on Science and Technology Cooperation between the Government of the United States of America and the Government of the Republic of India (<https://www.energy.gov/sites/prod/files/US-India%20ST%20Agreement.pdf>) will govern the allocation of intellectual property, copyright, and patent rights relevant to awards from this programme.

Data Sharing Policy: In keeping with the NIH Data Sharing Policy ([https://grants.nih.gov/grants/policy/data\\_sharing/](https://grants.nih.gov/grants/policy/data_sharing/)), applicants will be required to provide a data sharing plan within one month after the award. Each data set will be determined in consultation with NIAID staff. The National policy of India relating to data sharing will be applicable.

#### **Peer Review of Applications**

Review will follow the two-step procedure, with a primary critique focused on scientific merit and conducted by an ad-hoc panel of extramural experts from the scientific community, including prominent Indian scientists. The final review will be conducted by DBT and NIAID taking note of the comments made by the scientific experts.

The following review criteria will be used, and each application will receive an overall score based on a 1 (best) – 9 (worst) numerical scoring system:

- Overall Impact: likelihood for the project to exert a sustained and powerful influence on the research field.
- Significance: importance of the project in terms of advancing concepts or technologies that drive the field.
- Investigators: appropriateness of the proposed investigators for the project, with well-integrated and complementary expertise, and evidence of ongoing records of accomplishment.
- Innovation: potential to change paradigms in the field.
- Approach: clear presentation of well-reasoned and appropriate strategies, methods, and analyses; and potential problems and alternative approaches.
- Environment: appropriate institutional support, equipment, and other physical resources.

## **Budget Issues**

Appropriate budget based on the objectives proposed in the application will be funded by DBT/BIRAC for the Indian component. In case of Joint applications specific budgetary requirement for Academia & Industry component should be indicated for funding support. The maximum duration of the project will be three years. NIAID funding for the U.S. component should be commensurate with the level of involvement of the NIAID-supported investigator(s).

Applicants must provide detailed budgetary requirements separately with justification for the Indian and U.S. components. Each of these justifications also should include separate detailed budgets/justifications for any U.S. or Indian institution serving as a subcontractor or collaborator to the parent U.S. and Indian components, respectively.

The Indian budget component should follow DBT guidance, using the format available at the eProMIS portal of DBT: <http://dbtepromis.nic.in/>. Please refer to the Section on Budget Particulars of Proposal Submission form for R&D Projects.

The proposed U.S. and Indian budgets shall include Non-Recurring (for equipment) and Recurring budgets (for Overhead, Manpower, Consumables and Contingency) for a period of three years.

## **Mode of Submission**

Proposals may be submitted in the prescribed format, clearly stating “Request for Application: ‘India-U.S. Collaborative Research Grants on Vaccine Adjuvant Development’ through online DBT eProMIS portal: <https://www.dbtepromis.nic.in/> under the area Vaccine Research and Diagnostics, as per DBT format. Subsequently, two hard copies should also be sent to: Dr. Jyoti M Logani, Scientist ‘E’, Department of Biotechnology, Room No.516, 5th floor, CGO Complex, Lodhi Road, New Delhi – 110003. Also, PDF document should be mailed to [jyoti.logani@nic.in](mailto:jyoti.logani@nic.in). **(Submission of applications through eProMIS is mandatory & Call on eProMIS closes on 7<sup>th</sup> October, 2019)**

The application must contain the following information:

1-Biographical Information for proposed Project Leader and any other key personnel; including:

- Name, degree, and current position title;
- Education/training and field(s) of study;
- Relevant research experience; and
- Current research support including the % effort already committed for currently funded projects.

2-Description of proposed work to include:

- Rationale: how the project will advance vaccine adjuvant development; include discussion of complementary expertise and/or resources brought by each Project Leader and other collaborators, as well as feasibility of completing the work within the timeline;
- Each Project Leader's prior work in the field of adjuvant R&D, etc.;
- Background information;
- Preliminary data;
- Justification for collaborative work with US side and clear work plan and role of the Indian and US team respectively.
- Resources available to complete the work, including sources of human samples, and any samples to be obtained from an independent clinical study (if obtaining samples or other resources from an independent source, include a letter from the director of the independent study confirming the availability of the samples or resources);
- Research strategy: a detailed description of the proposed work that includes the central hypothesis(es) or research question(s), specific aims, experimental approaches and sample size calculations offering adequate statistical power; Inclusion of work plan indicating work to be done in India and U.S. respectively to address the objectives proposed. The applications must clearly indicate justification of the need of collaboration with the US investigator;
- Description of the statistical, bioinformatics, and/or systems biology methods to be employed for analysis of results; and
- Description and justification on the exchange of samples within the scope of the project must be clearly indicated.

3-Bibliography: limited to essential references.

4-Protection of Human Subjects: Provide a detailed description of the procedures to be used with human subjects, the measures that will be employed to protect human subjects, and the total numbers of each definable population included in the study (3 pages maximum).

5-Letter(s) of Agreement: from independent sources of human samples or other resources, if applicable.

6-Biohazard descriptions: if applicable.

7-Data Sharing Statement

8-Appendix: only 2 documents are allowed (e.g., in-press manuscript).

**Timeline:**

Call for Proposals opens: 7<sup>th</sup> August, 2019

Call for Proposals closes: 7<sup>th</sup> October, 2019

Announcement: 7<sup>th</sup> December, 2019 (tentative)

**Inquiries**

Direct inquiries regarding scientific, review, or budgetary matters to:

**For India-based investigators:**

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**For U.S-based investigators:**

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## ELIGIBLE U.S. INVESTIGATOR COLLABORATORS

Listed below are eligible NIAID-supported Principal Investigators who have expressed an interest in collaborating with Indian investigators on adjuvant research.

PRINCIPAL INVESTIGATOR/ Institution/ EMAIL	RESEARCH FOCUS	ADJUVANTS, EXPERTISE, RELATED RESOURCES  (most adjuvants are at pre-clinical stage/animal testing of development, unless otherwise noted)
Carson, Dennis/ U. of California, San Diego/ <a href="mailto:dcarson@ucsd.edu">dcarson@ucsd.edu</a>	Discovery/development of novel, small-molecule adjuvants and immunomodulators	<ul style="list-style-type: none"> <li>• Small-molecule TLR4 and TLR7 agonists</li> <li>• TLR4-7 combination adjuvant</li> <li>• Small-molecule immunomodulators to blunt acute, but extend adjuvant-induced activation of APCs by TLR agonists</li> </ul>
David, Sunil/ Virovax/ <a href="mailto:sdavid@virovaxllc.com">sdavid@virovaxllc.com</a>	Discovery/development of novel TLR agonists and non-conventional adjuvants; development of flavivirus vaccines	<ul style="list-style-type: none"> <li>• Small-molecule TLR7, 8, 7/8 agonists</li> <li>• Synthetic TLR2 agonists</li> <li>• TLR combination adjuvants</li> <li>• Delivery platforms for directing TLR agonists to draining lymph nodes (<i>e.g.</i>, Alhydroxiquim™)</li> <li>• Novel re-engineered subunit dengue and Zika virus vaccines</li> </ul>
Esser-Kahn, Aaron Palmer/ U. of Chicago/ <a href="mailto:Aesserkahn@uchicago.edu">Aesserkahn@uchicago.edu</a>	Development of novel combination adjuvants and immunomodulators	<ul style="list-style-type: none"> <li>• Chimeric TLR agonists (TLR4, 6, 7, 9)</li> <li>• Combination adjuvants of TLR agonist and inflammasome stimulator</li> <li>• Combination adjuvant of TLR agonist and immunomodulators</li> </ul>
Evans, Jay/ U. of Montana and InImmune/ <a href="mailto:jay.evans@umontana.edu">jay.evans@umontana.edu</a>	Discovery/development of novel TLR and CLR (C-type lectin receptor) agonists, exploration of delivery	<ul style="list-style-type: none"> <li>• Synthetic TLR4 agonists (Phase I-Phase III clinical trials),</li> <li>• Small-molecule TLR7, 8, 7/8 agonists</li> <li>• Small-molecule and carbohydrate-based Mincle agonists</li> </ul>

	routes/formulation requirements	<ul style="list-style-type: none"> <li>• TLR combination adjuvants</li> <li>• Adjuvant formulation processes</li> </ul>
DeFilippis, Victor/ Oregon Health & Science U./ <a href="mailto:defilipp@ohsu.edu">defilipp@ohsu.edu</a>	Novel vaccines and adjuvants for flaviviruses	<ul style="list-style-type: none"> <li>• cGAS/STING agonist</li> <li>• Chikungunya and Zika VLP vaccines</li> </ul>
Fattom, Ali/ NanoBio and Blue Willow / <a href="mailto:Ali.Fattom@nanobio.com">Ali.Fattom@nanobio.com</a>	Development of nanoemulsion-based adjuvants for intranasal and intramuscular delivery	<ul style="list-style-type: none"> <li>• Nanoemulsion (NE) adjuvants for intranasal (Th17 induction) and intramuscular (Th1/Th2 induction). Nanoemulsions self-attenuate pathogens used as vaccines.</li> </ul> (Phase I clinical trials)
Levy, Ofer/ Boston Children's Hospital and Harvard U./ <a href="mailto:Ofer.Levy@childrens.harvard.edu">Ofer.Levy@childrens.harvard.edu</a>	Discovery/development of adjuvants for vaccines used for vulnerable populations	<ul style="list-style-type: none"> <li>• Small-molecule TLR7/8 agonists formulated with alum</li> <li>• Small-molecule STING agonist formulated with alum</li> <li>• “<i>In vitro</i> immunization” system to predict adjuvanticity in different populations</li> </ul>
Norton, Elizabeth/ Tulane University/ <a href="mailto:enorton@tulane.edu">enorton@tulane.edu</a>	Development of adjuvants based on <i>E. coli</i> enterotoxin	<ul style="list-style-type: none"> <li>• dmLT: parenterally delivered adjuvant that induces Th17 responses and mucosal immunity (multiple clinical trials)</li> <li>• LTA1: for mucosal (IN) vaccine delivery (Th1/Th17)</li> </ul>
Petrovsky, Nikolai/ Vaxine PTY LTD/ <a href="mailto:Nikolai.petrovsky@flinders.edu.au">Nikolai.petrovsky@flinders.edu.au</a>	Discovery and development of novel adjuvants and adjuvant combinations	<ul style="list-style-type: none"> <li>• Advax: Inulin-based, anti-inflammatory adjuvant (multiple clinical trials)</li> <li>• Advax-CpG: novel combination adjuvant (Phase I)</li> <li>• Next-gen delta inulin: antigen-binding, carbohydrate-based adjuvant</li> <li>• CpG-ODN: library of novel, non-natural CpG sequences with activity in different species, incl. inhibitory ODN for various routes</li> <li>• Combination adjuvants: Advax with</li> </ul>

		<p>TLR agonists</p> <ul style="list-style-type: none"> <li>• Saponins: novel marine saponins with low reactogenicity</li> </ul>
<p>Putnam, David/ Cornell University/ <a href="mailto:Dap43@cornell.edu">Dap43@cornell.edu</a></p>	<p>Development of <i>E. coli</i> outer membrane vesicles as adjuvants</p>	<ul style="list-style-type: none"> <li>• OMV adjuvant for multi-TLR/NLR stimulation</li> </ul>
<p>Martin, Tyler/ Adjuvance Technologies/<a href="mailto:tyler@adjuvancetech.com">tyler@adjuvancetech.com</a></p>	<p>Development of synthetic QS21 and QS21 derivatives</p>	<ul style="list-style-type: none"> <li>• Saponex™: synthetic QS21 (Phase I)</li> <li>• Titerquil-1055™: synthetic QS21 derivative with high adjuvanticity but no reactogenicity (stable and non-hemolytic saponin adjuvant)</li> </ul>
<p>Roy, Krishnendu/ Georgia Tech/ <a href="mailto:krish.roy@gatech.edu">krish.roy@gatech.edu</a></p>	<p>Adjuvant immune-engineering</p>	<ul style="list-style-type: none"> <li>• Combination adjuvants (TLR4, 7/8, 9; STING) formulated with nano/microparticulates at adjustable adjuvant densities, for delivery by different routes</li> </ul>