

Global Research Collaboration for Infectious Disease Preparedness

Ongoing and upcoming research on the Zika virus

28 April 2016

GloPID-R

GloPID-R¹ is a network of funders of emergency outbreak research. The network has 23 members from across the globe, with the WHO as an observer, and is chaired by the European Commission together with Brazil, Canada, France, South Africa and South Korea. GloPID-R has set the goal of initiating a coordinated international research response within 48 hours of a declared public health emergency anywhere in the world.

GloPID-R members coordinate research on Zika through working groups on aetiology, diagnostics, and vaccines. This report is based on teleconferences and written contributions from the participants of these groups. Its scope is to map the Zika funding activities of GloPID-R members, and thus enable the identification of funding gaps and opportunities for collaboration among the research teams funded by members.

Members of GloPID-R

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Bill & Melinda Gates Foundation, USA – Represented by Penny Heaton

Canadian Institutes of Health Research (CIHR), Canada – Represented by Marc Ouellette (vice-chair of GloPID-R)

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¹ <http://www.glopid-r.org/>

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International Development Research Centre (IDRC), Canada – Represented by Dominique Charron

Japan Agency for Medical Research and Development, Japan – Represented by Kensuke Nakajima

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Ministry of Science, Technology and Productive Innovation, Argentina – Represented by Monica Silenzi

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South African Medical Research Council, South Africa – Represented by Jeffrey Mphahlele

Thai National Institute of Health, Department of Medical Sciences, Thailand – Represented by Aree Thattiyaphong

U.S. Department of Health and Human Services, USA – Represented by Nicole Lurie

Wellcome Trust, United Kingdom – Represented by Jeremy Farrar

Observer organisation

World Health Organization (WHO) – Represented by Bernadette Murgue and Martin Friede

The findings of the following Zika research working groups are included in this report:

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Zika vaccine research by GloPID-R members

1) Short Overview of Zika vaccine research landscape

The fact that we already have significant experience and successful vaccines for other flaviviruses (Dengue, Japanese Encephalitis, Yellow Fever) is encouraging, as this experience can be leveraged to develop a vaccine candidate for Zika.

On the other hand, the difficulties encountered during the development of dengue vaccines signal that Zika vaccine development might not be straightforward.

At the moment, no vaccine candidate has entered clinical testing in humans. Several (> 20) research teams, from academic institutions as well as industry, have already started or are preparing to start working on the preclinical vaccine development. First phase I clinical trials in humans expected Q4 2016. The most advanced research teams/candidates to date are:

- **Inovio/Gene One**: Inovio announced² on 17 February that they have already tested in an animal model (mice) a DNA Zika vaccine candidate, that 'showed robust and durable immune response', but it seems they have not tested for efficacy yet. They plan to test next in a NHP model, and enter clinical phase I studies before the end of 2016.
- **Bharat Vaccines** announced³ on 3rd February that they develop two Zika vaccine candidates (an inactivated and a recombinant vaccine). These candidates are currently undergoing testing in an animal model and they plan to enter clinical phase I studies before the end of 2016.

- **NIAID**: is developing a range of vaccine candidates:

- Most advanced (though still in early discovery) is a plasmid DNA vaccine undergoing preclinical evaluation now, and planning to enter clinical phase I studies in Q4 2016.
- Based on a dengue vaccine candidate currently undergoing phase III clinical trial in Brazil (with Butantan Institute), they are developing a live-attenuated Zika + dengue vaccine candidate (5valent: Zika+4 dengue serotypes). A series of phase I studies is being planned for end Q4 2016-Q1 2017.
- A whole-virion inactivated vaccine candidate, being developed through an inter-agency collaboration with BARDA and DoD. DoD used a similar approach developing a dengue and JEV vaccine candidate.

² <http://ir.inovio.com/news/news-releases/news-releases-details/2016/Inovio-Pharmaceuticals-DNA-Vaccine-for-Zika-Virus-Induces-Robust-Immune-Responses-in-Preclinical-Study/default.aspx>

³ <http://www.bharatbiotech.com/media/press-release/?pryear=2016>

- A live-attenuated vaccine candidate based on rVSV. Timing for clinical studies is uncertain.
 - Other vaccine candidates in earlier stages of preclinical development.
- **Institut Pasteur:** is developing 3 advanced vaccine candidates:
- A lentiviral-vectored Zika vaccine candidate, to be tested (immune response and efficacy) in a mouse animal model in March, planning to enter clinical phase I studies before the end of 2016.
 - A measles-vectored Zika vaccine, plans to be tested in a mouse animal model in Q2 2016, planning to enter clinical phase I studies before the end of 2016.
 - A DNA Zika vaccine, development process already streamlined as two other DNA vaccine candidates (for cancer and immunotherapy) are already in phase I.
 - Other candidates (e.g. VLPs) in early stages of development.
- **Brazil:** Butantan and FIOCRUZ Institutes are working on several vaccine candidates, of which most important are:
- Priority is an inactivated Zika vaccine (as the fastest approach to a vaccine suitable for pregnant women). Butantan is working on the development of a chemically-inactivated vaccine. Conditions to grow the virus at pilot scale under GMP conditions had been established. The procedure to inactivate the virus by chemical treatment has also been advanced as well as the choice of the adjuvant to be tested. The experimental conditions to measure virus neutralization activity and virus replication enhancement of anti-ZIKV antibodies have been established in collaboration with University of São Paulo (USP). The two institutions are also working in the establishment of in vivo models (mouse) to measure the protective immunity induced by the inactivated vaccine. Butantan and USP are also working with Institute Pasteur on the use of in vivo (mouse) ZIKV challenge models.
 - FIOCRUZ is developing a series of experimental vaccine approaches at laboratory level only. The research priorities now focus on chimeric yellow fever (YF/17D) virus capable to express ZIKV prM/E proteins, based on the presently available platform at the institution, and subunit vaccines based on recombinant proteins, with emphasis to VLPs (different backbones) and DNA vaccines .
 - Butantan is collaborating with NIAID for the development of the 5-valent live attenuated Zika + Dengue vaccine.
- Several teams (NewLink, GeoVax, Sanofi-Pasteur, Valneva, Sementis, GSK, Takeda, Oxford University and others) have announced that they are working

in earlier stages of preclinical development, often based on experience with similar candidates for flaviviral and other diseases etc.

2) Important Research Gaps Identified

We are still missing information important for a Zika vaccine development. This includes not only vaccine-specific research, but also overall information about the Zika virus-host interaction, the immune response to Zika infection, and the epidemiology of Zika infection and its complications. Therefore, ongoing basic and public health research are expected to also contribute significantly in Zika vaccine development.

a) **Innate and adaptive immune response to ZIKV infection:** Correlates of risk? Correlates of protection? The protective immune response is Abs or cell-mediated? Does infection lead to lifelong protection? Is cross-immunity conferred by infection by other flaviviruses (implications for the clinical evaluation of vaccine candidates)? etc.

- France: Reported ongoing (by U1187 INSERM-CYROI in La Reunion) and under development (CIMI-Paris/UMR-S1135) research programmes on Innate and Adaptive immunity to Zika infection.

b) **Animal Models:**

- Small animal model: particularly an animal model suitable for efficacy testing. As animal model development is in early stages of exploration for Zika, it is unknown if animals should be immunodeficient (in mice flaviviruses tend to cause transient viraemia without disease):

- Institut Pasteur has INFAR (Interferon Type I receptor knock out) mice, and hCD46-INFAR mice (suitable for measles-vectored vaccines). Brazil is discussing with IP for using the INFAR mice for testing the Butantan/FIOCRUZ vaccine candidates.
- NIAID is supporting small animal model development, though potential application to vaccines is uncertain at this time.
- It is not reported what animal model was used for the reported animal testing of the Inovio and Bharat vaccine candidates.

- NHP animal model:

- France (CEA/IDMIT) is developing an NHP experimental model of Zika virus infection.
- NIH reported that their collaborators in Wisconsin are developing an NHP Zika model (pregnant and non-pregnant rhesus macaques).

- c) **Virus seed:** Discussions on the appropriate virus seed for vaccine development are ongoing under WHO coordination.
- EC is funding the global European Virus Archive⁴ (EVAg), a non-profit network of virology labs aiming to track/ collect/ amplify/ characterize/ standardise/ authenticate/ distribute viral material. Since December 2015, they have responded to more than 190 lab inquiries for Zika viral material, and distributed more than 250 viral products, to more than 30 EU and non-EU (US, Singapore, China etc) countries.
 - NIH is funding two repositories – the Biodefense and Emerging Infections Research Resources Repository and World Reference Center for Emerging Viruses and Arboviruses, both of which have samples of viral isolates and other clinical specimens. These are available for distribution to commercial developers and other researchers.
- d) **Target Product Profile:** The WHO is developing a Zika Vaccine Target Product Profile (TPP) with the primary aim of Protecting Women of Child-Bearing Age during the Public Health Emergency of International Concern (PHEIC). The WHO is supported by a working group of the PD-VAC advisory group. An advanced draft will be shared in a public consultation phase, including regulators, vaccine developers and all GloPID-R members by the end of April 2016. Based on that feedback, the TPP will be finalized. WHO plans for a consultation with regulators and vaccine developers to discuss regulatory pathways for the assessment and licensure of vaccines as proposed by the TPP.

3) Funding from GloPID-R members on Zika Vaccine Development:

a) **European Commission:**

- Currently open and recent calls relevant to Zika Vaccine Development:
- Topic SC1-PM-06-20165: 'Vaccine development for malaria and neglected infectious diseases'. It addresses preclinical and early clinical (up to phase I) vaccine development. Zika is eligible as a neglected emerging viral epidemic disease. Total budget € 40 million. Deadline for submission was 13th April 2016, proposals are under evaluation.

⁴ <http://global.european-virus-archive.com/>

⁵ <http://ec.europa.eu/research/participants/portal/desktop/en/opportunities/h2020/topics/3052-sc1-pm-06-2016.html>

- Topic SC1-PM-22-20166: 'Addressing the urgent research gaps against the Zika virus and other emerging threats in Latin America'. Total budget € 10 million. Call is currently open, deadline for submission is 28 April 2016. Among others, it addresses the formation of a network suitable for the clinical testing of candidate Zika vaccines and treatments.
 - IMI2 call 87: Addresses the pre-clinical and clinical development of vaccines, treatments and diagnostics against Ebola and other filoviruses. Proposals for the development of adaptable platforms, which may address other priority pathogens (including Zika), in addition to filoviruses, are also eligible. With a total budget € 70 million, this call is continuously open for a period of two years with rolling cut-off dates for proposal submission (previous deadline was 16 March 2016, next deadline is 15 September 2016).
- Currently open calls relevant to other vaccine-related research:
- The above mentioned topic SC1-PM-22-2016 'Addressing the urgent research gaps against the Zika virus and other emerging threats in Latin America' allows for research on the innate and adaptive immune response to Zika infection, on animal models, on the epidemiology of Zika infection and its complications etc.
- Other: EC is funding the global European Virus Archive (EVAg)⁸, a non-profit network of virology labs aiming to standardise and distribute viral material to research teams globally.

b) **Canadian Institutes of Health Research:**

Currently CIHR is not specifically funding Zika vaccine research, as at the moment they are focusing on a joint call with the International Development Research Centre related to aetiology/diagnostic/vector studies field.

c) **NIH/NIAID:**

NIH is supporting research on several vaccine candidates. It also supports research on NHP and mouse models. The U.S. Congress is considering the transfer of limited funds from the Ebola emergency supplemental to support Zika research.

⁶ <http://ec.europa.eu/research/participants/portal/desktop/en/opportunities/h2020/topics/16069-sc1-pm-22-2016.html>

⁷ <http://www.imi.europa.eu/content/imi-2-call-8>

⁸ <http://global.european-virus-archive.com/>

- Currently open calls relevant to Zika Vaccine Development: NOT-AI-16-026⁹ 'Notice of NIAID's Interest to Highlight High-Priority Zika virus (ZIKV) Research Areas': Among its targeted topics are:

- Development of effective ZIKV vaccines and vaccination strategies based on evolving knowledge of host/pathogen interactions and identification of relevant biomarkers.
 - Studies to develop animal models to study ZIKV pathogenesis (especially neurological manifestations and teratogenic potential) and evaluate candidate therapeutics and vaccines;
 - Evaluation of the immune response to ZIKV infection and/or vaccination including cell-mediated and innate immunity;
 - Evaluation of the immunological interactions between ZIKV and other flaviviruses (especially dengue and yellow fever virus)
 - Also Partnerships for Countermeasures Against Select Pathogens (R01)10 and 11. The latter allows for rapid review of smaller proposals (up to \$275,000 over two years).
- NIH has issued supplemental funding of ongoing relevant grants.
- Also has the flexibility to award contracts for specific research tasks.

d) **BARDA:**

BARDA is working closely with HHS interagency partners to support the development of medical countermeasures for Zika virus that will 1) detect who is or has been recently infected by Zika virus through development of diagnostics; 2) prevent infection of people from Zika virus through development of vaccines, and 3) ensure the safety of the blood supply by supporting rapid screen assays for donated blood and the development of pathogen reduction systems for donated blood products.

BARDA has been working closely with industry to monitor and assess the landscape of Zika vaccine candidates as they enter development. BARDA utilizes an established forum called Tech Watch to facilitate communication between industry and USG partners. BARDA has already hosted several developers who are working on Zika vaccine candidates and is pleased to see some of these candidates making progress and moving into nonclinical development.

⁹ <http://grants.nih.gov/grants/guide/notice-files/NOT-AI-16-026.html>

¹⁰ <http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-16-034.html>

¹¹ <http://grants.nih.gov/grants/guide/pa-files/PAR-16-106.html>

For Zika vaccines, BARDA is working closely with colleagues at the US National Institutes for Health (NIH) to evaluate, develop and manufacture new specific vaccines for Zika. In addition, with supplemental funding support, BARDA plans to provide support for Zika vaccine development in three main areas:

- 1) The development of vaccine platform technologies for multiple emerging infectious diseases, including Zika virus;
- 2) An inter-agency collaboration with NIH and US Department of Defense (DoD) to develop and evaluate an inactivated, whole-virion Zika vaccine candidate; and
- 3) Support the manufacturing infrastructure at Butantan (Sao Paulo, Brazil) to develop and produce Zika vaccine candidates.

In addition, BARDA has made available its National Medical Countermeasure Response Infrastructure, that includes resources to support non-clinical and clinical development, regulatory and quality affairs, manufacturing, facilities and engineering, and its Centers for Innovation in Advanced Development and Manufacturing (CIADM) and the Fill-Finish Manufacturing Network.

As companies and other organizations approach BARDA for collaboration and support, they are referred to the current opportunities by BARDA through Broad Agency Announcements:

- BAA-16-100-SOL-00001 will support point of care (POC), laboratory based and blood screening assays.
 - Technical Point of Contact: Rodney Wallace: rodney.wallace@hhs.gov
- BAA-16-100-SOL-00003 will support innovation through development of platform technologies that enhance capabilities for development and manufacturing of MCMs.
 - Technical Point of Contact: Mark Craven: mark.craven@hhs.gov

Additionally, they are referred to present their technologies to BARDA staff through our Technology Watch program.

Request a Tech Watch meeting through www.medicalcountermeasures.gov

- Contact Jonathan Seals, Director Strategic Science and Technology Division: jonathan.seals@hhs.gov

Furthermore, BARDA refers companies to the NIH Federal Funding Opportunities.

e) **France:**

The important work being done by Institut Pasteur on Zika vaccine development, as well as by other institutes (INSERM, CEA/IDMIT, CIMI-Paris etc) is internally supported by in kind contributions by the institutes. No additional funding has been allocated specifically for Zika vaccine development.

f) **Brazil:**

The Ministry of Health has announced that it will invest R\$ 20 million (roughly US\$ 5 million) in Zika research, of which about US\$ 2 million for vaccine research.

g) **Spain:**

Is considering of launching a bottom-up call for Zika research, but details on the scope/budget are not yet available.

h) **Gates Foundation:**

Mostly focusing on funding vector control research, no significant funding specifically allocated for Zika vaccine development. They have been funding entities (e.g. Novavax) for other vaccine development, entities that now have expressed an interest in developing Zika vaccine candidates.

i) **Wellcome Trust:**

Is funding research in broad areas related to zika virus including vector control, epidemiology, and development of microcephaly and Guillain-Barre syndrome as well as ethical considerations. Specific vaccine related activities include:

- a. The Medical Research Council (MRC), the Newton Fund and the Wellcome Trust are jointly funding £3.2M research¹² to help answer many of the unanswered questions, covering diagnostics, vaccine development, establishing links with microcephaly and Guillain-Barre syndrome, Vector control and modelling. The scope is for short term (12 – 18 month) proposals cover the nature of the risk posed by the Zika virus and/or potential avenues for its management or prevention,

¹² <https://www.mrc.ac.uk/news/browse/research-funders-join-forces-to-tackle-zika-virus-with-3-2m/>

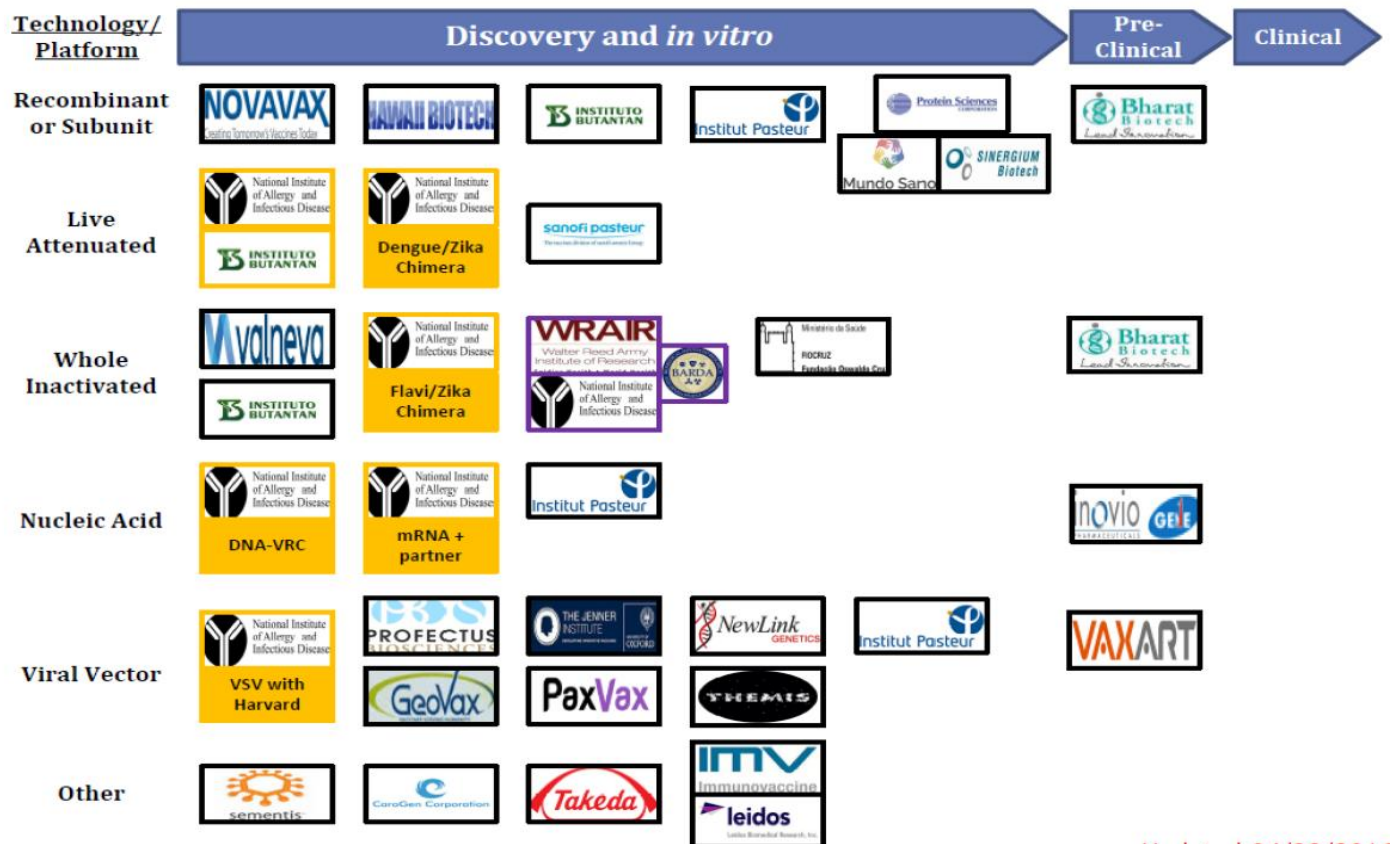
including Zika vaccine development. Projects¹³ specifically relating to vaccines include:

- 1) Yorgo Mordis (University of Cambridge) 'Defining the antigenic epitopes in the Zika virus envelope protein'.
 - 2) Tom Blanchard (University of Manchester) Zika: a safe recombinant vaccine with proof of efficacy in rodents.
 - 3) Danny Altmann (Imperial College London) Zika: a safe recombinant vaccine with proof of efficacy in rodents.
- b. Leading health bodies including academic journals, NGOs, research funders and institutes including the Wellcome Trust have committed to sharing data¹⁴ and results relevant to current Zika crisis and future public health emergencies as rapidly and as openly as possible.

¹³ <https://www.mrc.ac.uk/documents/pdf/zika-award-list-summaries/>

¹⁴ <http://www.wellcome.ac.uk/About-us/Policy/Spotlight-issues/Data-sharing/Public-health-emergencies/index.htm>

ZIKV Vaccine Landscape



'Provided by Rick Bright - HHS-BARDA'

Participants in the Zika Vaccine Working Group

- CIHR: Michelle Peel
- NIH/NIAID: Hilary Marston
- BARDA: Rick Bright (supported by Tanimia Sinha)
- Brasil: Luis Ferreira
- France: Brigitte Autran
- Spain: Juan Riese
- B&M Gates Foundation: Peter Dull
- Wellcome Trust: Charlie Weller
- European Commission: Maria Klimathianaki
- WHO: Joachim Hombach

In case of enquiries, please contact the chair of the working group: Maria Klimathianaki (Maria.Klimathianaki@ec.europa.eu).

Zika aetiology research by GloPID-R members

Ongoing Research

GloPID-R members are currently funding the following research projects with regards to establishing a causal link between Zika virus infection and neurological disorders:

1. Case control study on microcephaly and Zika virus infection – Pilot study

Funder: Wellcome Trust
Location: Recife, Brazil
Objective: To compare the clinical history and serology of mothers of cases of microcephaly with mothers of normocephalic neonates
Timing: Started in Nov 2015 - completed
Budget: £30,000

2. Cohort study of pregnant women with rash in Pernambuco State – Pilot study + continuation

Funder: 1. Wellcome Trust – Pilot study
2. Wellcome Trust/DFID/MRC/Newton Fund for continuation of study
Location: Recife, Brazil
Objective: To establish the magnitude of risk and type of malformation in neonates, according to the time of viraemia during pregnancy
Timing: Started in Dec 2015
Budget: £40,000 for pilot study
£112,361 for continuation of study

3. Cohort study of newborns with microcephaly – a 2-year follow up

Funder: Wellcome Trust
Location: Recife, Brazil
Objective: To investigate disabilities, growth and development, associated with microcephaly, in the first two years of life
Timing: Started in Feb 2016
Budget: £38,400

4. Cellular mechanisms of microcephaly due to Zika virus infection in mice

Funder: Wellcome Trust/DFID/MRC/Newton Fund
Location: University of Oxford
Objective: To model microcephaly using in utero injection of Zika virus in pregnant mice during the peak of foetal neurogenesis, and to determine the capacity for Zika virus infection to produce microcephaly.
Timing: Will start end of April 2016
Budget: £79,926

5. Investigating the link between Zika virus infection and neurological disease in ex vivo and in vivo models

Funder: Wellcome Trust/DFID/MRC/Newton Fund
Location: University of Liverpool
Objective: To establish whether there is a definitive link between neurological disease and Zika virus infection and to investigate the biology behind this.
Timing: Started in April 2016
Budget: £130,700

6. Development of an online data-sharing platform for images of foetal and newborn heads - An urgent need in the context of the Zika virus outbreak

Funder: Wellcome Trust/DFID/MRC/Newton Fund
Location: University of Oxford
Objective: To develop a platform to help screen for microcephaly by automating the measurement of head size and shape, and exploring facial characteristics as potential diagnostic markers.
Timing: Started in April 2016
Budget: £144,456

7. Establishment of enhanced birth defect surveillance in South America

Funder: Wellcome Trust/DFID/MRC/Newton Fund
Location: Ulster University
Objective: An epidemiological analysis of microcephaly preceding Zika virus introduction, and a comparison to the period of Zika virus outbreak for each country, together with enhanced surveillance of history of maternal viral infection.
Timing: Started in April 2016
Budget: £50,000

8. Association studies with Guillain-Barre syndrome (GBS) and neurotropism

Funder: Wellcome Trust/DFID/MRC/Newton Fund
Location: University of Glasgow
Objective: To investigate the underlying causation of neurological deficits, focusing on GBS; generally considered an autoantibody-mediated disorder.
Timing: Started in April 2016
Budget: £120,000

9. Zika virus - Guillain-Barre syndrome: A joint Brazil-Colombia-UK infrastructural project

Funder: Wellcome Trust/DFID
Location: University of Glasgow
Objective: To systematically gather and store samples and catalogue clinical features from clinically defined cohorts using well developed protocols from existing networks in Brazil and Colombia.
Timing: Started in April 2016
Budget: £141,000

10. A prospective case-control study to examine the role of Zika virus in Guillain-Barré syndrome in Brazil

Funder: Wellcome Trust/DFID/MRC/Newton Fund
Location: University of Liverpool/Rio de Janeiro
Objective: Recruitment of adults with GBS to define the role of Zika virus as a risk factor.
Timing: Started in April 2016
Budget: £108,071

11. Observational studies on consequences of Zika virus infection during pregnancy

Funder: French Ministry of Health / INSERM
Location: Martinique, Guadeloupe and French Guiana
Objective: Study 1: Cohort of pregnant women infected by Zika virus infection
Study 2: Cohort of infants born from women with suspected or confirmed Zika virus infection during pregnancy

Timing: Started in Mar/Apr 2016
Budget: Study 1: €1,520,000 (€1,456,000 including locally paid salaries)
Study 2: €2,500,000 EUR (€3,250,000 including locally paid salaries)

12. Cohort study of arbovirus infections, including Zika virus infection, based on hospital cohort of children and adults with suspected arbovirus infection

Funder: French Ministry of Health / INSERM
Location: Martinique, Guadeloupe, French Guiana and Continental France
Objective: Substudy 1: Natural history of arbovirus infection
Substudy 2: Guillain-Barré syndrome and arbovirus infection
The objectives are to identify demographic, clinical, biological, virological, immunological and genetic factors that are
1) associated with, or predictive of, severe complications of arbovirus infection in a cohort of children and adults with confirmed arbovirus infections;
2) predictive of altered quality of life after confirmed acute arbovirus infection.
Timing: Integration in ongoing cohort study
Budget: €913,000 (€1,186,000 including locally paid salaries)

13. Sexual transmission of Zika virus: longitudinal analysis of genital secretions in Zika infected patients

Funder: REACTING / INSERM
Location: Martinique, Guadeloupe
Objective: To assess importance of sexual transmission of Zika virus infection
Timing: Start in May 2016
Budget: €35,000 (€45,000 including locally paid salaries)

14. Pesticides concentration in Zika virus infected pregnant women with and without foetal abnormalities

Funder: REACTING / INSERM
Location: Martinique, Guadeloupe, French Guiana
Objective: To assess importance of pesticides in foetal abnormalities
Timing: Start in May 2016

Budget: €250,000 (€325,000 including locally paid salaries)

15. Experimental studies on Zika virus neurotropism

Funder: REACTING / INSERM

Location: Toulouse, Montpellier, Lyon, Paris

Timing: Started in Apr 2016

Budget: €100,000 (€130,000 including locally paid salaries)

16. Development of animal model to evaluate the immune response as well as the possible correlation with microcephaly

Funder: São Paulo Research Foundation - FAPESP

Location: São Paulo, Brazil

Objective: To assess the influence of previous flavivirus infections, specifically Dengue virus, on Zika virus infection and also the correlation between Zika infection and microcephaly in experimental models using different strains of mice.

Timing: Started in December 2015

Budget: US\$200,000

Ongoing Calls

1. European Commission

Topic: Addressing the urgent research gaps against the Zika virus and other emerging threats in Latin America

Deadline: 28 April 2016

Link:

<http://ec.europa.eu/research/participants/portal/desktop/en/opportunities/h2020/topics/16069-sc1-pm-22-2016.html>

Topic: Integrating activities for advanced communities: Research Infrastructures for the control of vector-borne diseases

Deadline: 30 March 2016

Link:

<http://ec.europa.eu/research/participants/portal/desktop/en/opportunities/h2020/topics/2124-infraia-01-2016-2017.html>

Topic: Vaccine development for malaria and/or neglected infectious diseases

Deadline: 13 April 2016

Link:

<http://ec.europa.eu/research/participants/portal/desktop/en/opportunities/h2020/topics/3052-sc1-pm-06-2016.html>

2. US National Institutes of Health

Topic: Rapid assessment of Zika virus (ZIKV) complications (R21)

Deadline: 30 April 2016

Link: <http://grants.nih.gov/grants/guide/pa-files/PA-16-106.html>

3. US National Institutes of Health and National Institute for Allergies and Infectious Diseases

Topic: Tropical medicine research centers (U19)

Deadline: 3 May – 3 June 2016

Link: <http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-16-002.html#>

Participants in the Zika Aetiology Working Group

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- CIHR: Serge Desnoyers
- European Commission: Barbara Kerstiëns and Evelyn Depoortere
- Hôpital Bichat Claude-Bernard, France: Yazdan Yazdanpanah
- ISCIII: Irene Sanchez Garcia
- National Institute for Infectious Diseases Lazzaro Spallanzani: Giuseppe Ippolito
- NIH: Cristina Casseti and Nahida Chakhtoura
- São Paulo Research Foundation: Jean Pierre Schatzman Peron
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In case of enquiries, please contact the chairs of the working group: Barbara Kerstiëns (Barbara.Kerstiens@ec.europa.eu) and Evelyn Depoortere (Evelyn.Depoortere@ec.europa.eu).

Zika diagnostics research by GloPID-R members

This document presents the summary findings of the GloPID-R Zika research working group on diagnostics; the findings are based on the written response received to the questions outlined below, and a teleconference meeting held on March 3rd, 2016, as well as an email consultation in April 2016.

What research is currently ongoing related to diagnosis of Zika?

The following describes the methods that have been used to identify ZIKV infections in human specimens¹⁵:

- Viral culture
- Antibody detection (IgM, IgG)
- Antigen detection – have not yet been developed
- RNA detection (rRT-PCR)

¹⁵ Waggoner JJ, Pinsky BA. Zika Virus: Diagnostics for an Emerging Pandemic Threat. *J Clin Microbiol.* 2016 Feb 17. pii: JCM.00279-16. [Epub ahead of print] PubMed PMID: 26888897.

GloPID-R Zika Research Working Group on Diagnostics - Summary findings

	Objective of the research	Type of study being implemented	Estimated timeline	Geographical scope
<i>NIAID funded research and pre-clinical services efforts that support the development of diagnostics for Zika virus (ZIKV)</i>				
NIAID	Funding for the development of antibody and antigen reagents and serological tests that are suitable for diagnostic evaluation of ZIKV exposure (ELISA, Lateral flow devices, rapid neutralization assays)	<ol style="list-style-type: none"> a. Development of highly specific IgG and IgM antibodies and use of these in prototype lateral flow devices for detection of ZIKV. Other efforts to discover and engineer ZIKV-specific antibodies are anticipated, including those with ScFv and camelid antibodies. b. Cell culture assays to measure neutralizing antibodies against ZIKV and adaptation of flow cytometry methods to improve throughput and precision of plaque neutralization assays. c. Phage display and related structure-based methods to identify immunologically-specific ZIKV protein epitopes; such data will inform the construction of recombinant antigens that can discriminate among endemic arboviruses. d. Development of point of care diagnostic devices to support triage and evaluation of patients. 	Current NIAID funding is done via administrative grant supplements. Additional awards in response to new solicitations are expected later this year.	United States and Latin America

	Objective of the research	Type of study being implemented	Estimated timeline	Geographical scope
NIAID	Funding for development of molecular assays to evaluate patients in endemic areas and to support the testing of blood supplies and related products	<ul style="list-style-type: none"> a. Development of RT-PCR methods for multiplexed assay of arboviruses (ZIKV, dengue, Chik, JEV, etc.) using clinically approved molecular assay platforms. b. New NGS methods to rapidly characterize complete coding regions of viruses with sensitivities that are comparable to RT-PCR. c. Studies to document ZIKV in current blood supplies and to experimentally establish, in animal models, ZIKV stability and infectivity in blood and tissues products (NHLBI). 	Current NIAID funding is done via administrative grant supplements. Additional awards in response to new solicitations are expected later this year.	United States and Latin America
NIAID	Funding for collection of ZIKV patient samples, from ongoing and planned clinical studies, that will support testing and validation of diagnostics.	<ul style="list-style-type: none"> a. Clinical protocols of natural history will be used to obtain specimens (blood, urine, saliva, PBMCs) to document the time course and tissue distribution of virus replication and the immunological response to ZIKV. b. Plasma and serum will be obtained and thoroughly characterized from properly consented patients for use as reference materials in diagnostics validation. 	Current NIAID funding is done via administrative grant supplements and contracts for clinical services. Additional awards in response to new solicitations are expected later this year.	United States and Latin America
NIAID	Funding for collection, propagation and distribution of viral isolates needed for diagnostic development.	<ul style="list-style-type: none"> a. Multiple isolates of ZIKV, as well as strains of endemic viruses and other pathogens, have been / will be characterized and deposited in the 	Current NIAID funding is done via administrative grant supplements and contracts for pre-	United States and Latin America

	Objective of the research	Type of study being implemented	Estimated timeline	Geographical scope
		<p>NIAID repository of pathogens (BEI resources, see below)</p> <p>b. Genomic sequencing of ZIKV and other arboviruses and subsequent bioinformatics analysis will be used to identify specific primers sets for molecular diagnostics applications</p>	<p>clinical services. Additional awards in response to new solicitations are expected later this year.</p>	
NIAID	<p><u>Repository for pathogens</u></p> <p>NIAID retains a repository for pathogens, which is available free of charge to investigators in the area of infectious disease, and we are currently making additions that are highly relevant to ZIKV efforts. The link for the BEI Resources repository, and the requirements for obtaining samples, can be found at https://www.beiresources.org/. There may be some recently deposited ZIKV isolates of value to current work in this area.</p>			
European Commission				
<p>The European Commission has pre-published a call for proposals.</p> <p>The call is expected to be officially published on 15 March 2016.</p>	<p>To establish a multinational and multidisciplinary consortium across Latin America and other affected or at risk regions, able to implement the urgently needed research during the ongoing ZIKV outbreak. The proposal should address inter alia the development of improved ZIKV diagnosis and differential diagnosis assays.</p>	<p>Not defined.</p>	<p>Publication date: 15 March 2016 - Deadline for submission of proposals: 28 April 2016 – Evaluation of proposals: May 2016 - Grant Agreement Preparation: 1 June 2016 - Signing of Grant(s): July/August 2016. The duration of the</p>	<p>Even though Latin America is mentioned in the topic title/background/impact as the region currently most severely affected, in the scope it is clearly stated that 'other affected or at risk regions' are eligible. These include the Caribbean, the French Polynesia and South Pacific region, overseas territories of EU Member States, and any other affected or at risk country regardless of its geographic location. Plus, the scope clearly</p>

	Objective of the research	Type of study being implemented	Estimated timeline	Geographical scope
			project will be in line with the work foreseen	mentions the possibility to extend the geographic scope, depending on the evolution of the epidemic.
European Commission's Horizon 2020 Work Programme 2014-15	Biomarkers. This topic is very broad but could potentially include Diagnostics for ZIKA (when developed by SMEs)	Clinical research for the validation of biomarkers and/or diagnostic medical devices	Several cut-off dates and is continued under topic SMEInst-05-2016-2017 : Supporting innovative SMEs in the healthcare biotechnology sector.	
Spain				
ALGENEX (SME) - Madrid	Development of diagnostic methods	Fast development (in record-time) of diagnostic kits based on antibody detection. Reduced production costs.	n.a.	Global
AROMICS (SME) - Barcelona	Development of diagnostic methods	Lab-on-a-chip-based diagnostic technology.	n.a.	Global
Centro Nacional de Biotecnología (CNB) - Madrid	Development of diagnostic methods	Identification of viral and cellular determinants of the viral replication cycle (HCV1). Development of cell-based screening assays.	n.a.	Global
CIBIR (Technological Center and associated	Microbiological, epidemiological and clinical studies of arthropod-borne diseases	Development of molecular assays for the Identification of emergent and new infectious diseases.	n.a.	Spain

	Objective of the research	Type of study being implemented	Estimated timeline	Geographical scope
public hospital) - Logroño (La Rioja)				
GENETIC ANALYSIS STRATEGIES (SME) - Elche (Alicante)	Genetic analysis, RDI on qPCR-based kits	New qPCR assay for ZIKV under development	n.a.	Global
La Paz- Carlos III' Hospital - Madrid	Development of MAbs in Ebola virus.	Development of diagnostic method for ZIKV based on the strong expertise with Ebola virus and other infections	n.a.	Spain
Ramón y Cajal' Hospital - Madrid	Development of molecular diagnosis assays for ZIKV by RT-PCR following the Lanciotti protocol.	Development of an algorithm for a step-by-step-diagnosis of arboviruses.	n.a.	Spain
General University Hospital -Valencia	Implementation of diagnostic procedures	Adaptation of existing methods to the diary clinical practice	n.a.	Regional
INGENASA (SME) - Madrid	Development of diagnostic methods	Expression and production of recombinant proteins, selection and production of MAbs for the development of diagnostic assays.	n.a.	Global
INIA (Public Technology Center) - Madrid	Viral zoonosis. High expertise in flaviviruses from different points of view	Development of diagnostic tests.	n.a.	Global
IRTA (Public Technology Center) - Barcelona	Development of diagnostic methods a.o.	Adaptation of existing assays.	Continuous research line without time limit	Spain

	Objective of the research	Type of study being implemented	Estimated timeline	Geographical scope
Health Institute 'Carlos III' (ISCIII) - Madrid	Specialized Dept. in arboviruses: diagnosis and surveillance. Development of sensitive and specific methods for diagnosis, monitoring and control of viruses by adapting existing assays. ISCIII is member of the ViroRed network that coordinates Latin American (México, Guatemala, Nicaragua, Costa Rica, Panamá, Venezuela, Colombia, Ecuador, Brazil, Perú, Bolivia, Paraguay, Argentina and Uruguay) and European (Spain and Portugal) Public Health laboratories, with the focus on emerging viruses (arboviruses and respiratory viruses). Their objectives include the exchange of scientific and technique knowledge amongst participant labs, educational aspects and sharing knowledge.	Distribution of protocols for diagnosis of Zika virus infections, including PCR, viral isolation, and serology (immunofluorescence and neutralisation), including new developed assays. Establishment of algorithms for differential diagnosis with other arboviral infections (Chikungunya virus, Dengue virus, West Nile virus).Distribution of Quality Controls to harmonize diagnostic approaches for Zika virus infections. Availability of clinical (including congenital infections) and mosquito samples from participant countries to obtain virological data and to validate diagnostic methodology	Continuous research line without time limit	Spain, Latin America and Caribbean countries
MASTERDIAGNOSTICA (SME) - Granada	Development, production and manufacturing of in vitro diagnostic products	Multiplex PCR-based molecular technologies for the development of a new tropical disease detection kit including ZIKV in collaboration of Fiocruz (Brazil) and ISCIII	n.a.	Global

	Objective of the research	Type of study being implemented	Estimated timeline	Geographical scope
Puerta el Mar' University Hospital - Cádiz	Molecular techniques	Design and evaluation of molecular techniques by RT-PCR	n.a.	Regional
University Hospital Donostia - San Sebastián	Development of ad-hoc in-house diagnostic methods	In-house ZIKV PCR method in use included to the panel of PCR methods	First results are being originated	Regional
University Hospital - Granada	Development of PCR methods for ZIKV, a.o.	Development of new diagnostic tools for ZIKV based on the use of nanobody technology	n.a.	Regional
VACUNEK (SME) - Derio (Bilbao)	Diagnostic tools and vaccines	Development of singleplex and multiplex diagnostic methods based mainly on RT-PCR and specific immunoassays	n.a.	Global
Vall d'Hebron University Hospital Health Research Institute – Barcelona	Development of diagnostic tools	Development of diagnostic methods for ZIKV	n.a.	Regional
Canadian Institute of Health research (CIHR)				
CIHR is preparing a call for proposals. This will be done in collaboration with the International Development Research Centre (IDRC)	The specific objectives of this funding opportunity are to gain critical information on the possible causal link between Zika virus infection and the severe reported complications, including microcephaly, as well as the development of diagnostic tests for Zika virus.	Strong epidemiology linkages, clinical work, and animal studies for solidifying the link between microcephaly and GBS and Zika. Natural history of infections. Point of care diagnostics and serology testing. Clinical research for testing or implementing new strategies for the prevention, management or treatment of Zika infections	Launch April-May 2016; Application deadline: June 2016; Duration of funding: August 2016-July 2019.	Research will be conducted in Canada and Latin America. Efforts through GloPID-R for coordinating and reinforcing this CIHR-IDRC call with the EU call

Welcome Trust				
Funding Source	Principal Applicants & RO	Duration (months)	Project title	Funded
MRC-WT/DFID-Newton	Professor Richard Seton Tedder, UCL, Public Health England	12	Zika: Development of a type specific Zika virus antibody assay for use in Brazil	£121,935
MRC-WT/DFID-Newton	Nicholas James Loman University of Birmingham	12	Zika: Open genomic surveillance of Zika virus in Brazil using a novel portable real-time sequencing device	£123,955
MRC-WT/DFID-Newton	Dr Janet Daly University of Nottingham	18	Zika: Harnessing plant power for rational design of immunogens for use in diagnostic assays	£93,638
MRC-WT/DFID-Newton	Luis E Cuevas Liverpool School of Tropical Medicine	18	Zika: Novel point-of-care molecular diagnostics for the simultaneous diagnosis of Zika, chikungunya and dengue infections in Latin America.	£150,000
MRC-WT/DFID-Newton	Michael John Griffiths University of Liverpool	12	Zika: Improved diagnostics for Zika virus infection in South America through an established laboratory partnership between Brazil, Colombia and the UK.	£93,600
WHO				
<p>In order to address the limitations and gaps of current diagnostic tests for Zika, WHO and several key stakeholders have developed target product profiles (TPPs) to test for the disease. TPPs define the desired characteristics of Zika diagnostic tests, and are aspirational in nature.</p> <p>WHO invites experts to comment and give input on these TPPS by 11 April 2016. The contact information is at the end of the TPPs.</p>				

The TPPs include a brief summary of additional important considerations that highlight technical challenges to test development and the limits to scientific understanding of the virus at this stage of the Zika response

<http://www.who.int/csr/research-and-development/consultations/en/>

Brazil

Since we are dealing with increasing number of cases of ZIKV in the South East of Brazil and are also interacting with other States in the Northeast of Brazil (that were already badly hit) and, based on the demands from the scientific community as a whole, we are observing a need to:

- 1) Prioritize the building & sharing of comprehensive serum/sample panels for validation of several alternative serological e molecular diagnostics platforms. This is crucial for pregnant women cohorts, where we are observing that false positives can have a devastating effect for patients and health care agents, alike.
- 2) Improve nucleic acids detection sensitivity in general, because of the usual low titers of ZIKV in human samples. In the same vein, we need improvement in NGS sequencing technology that needs to become efficient to obtain good coverage when sequencing samples having Real Time PCR Ct values from 30 to 37 (and above!). At the moment only a few groups have enrichment protocols that function at Cts near 30. Low ZIKV titers also constitute a potential problem for blood transfusion quality control that needs to avoid false negative blood.
- 3) Improvement on viral isolation & growth, possibly via testing of alternatives to the usual C6/36 and Vero cells. Ideally, these approaches could help boosting viral titers and improve item 2) above.
- 4) There is a need to develop rapid detection tests to be applied at the point of care (e.g., health care settings) or point of action (e.g., researchers doing field work need it for improving positive samples collection)

Diagnostic research gaps include:

- Specificity & Sensitivity
 - Diagnostic test specific for the current Zika infection outbreak.

- Specific and sensitive point of care test capable of reliably detecting a recent Zika infection in pregnant women considering whether to continue with pregnancies.
- Improved serologic diagnostics that are highly sensitive and specific.
- Improved antigens for serologic testing.
- Generation and screening of antigens /antibodies / detecting reagents to support serological identification of ZIKV without the problems of cross-reacting materials.
- Problems with ELISA + PRNT (too heavy and unclear results mostly). Starting to test alternatives NAPAA, Luminex with antigen panels, etc in the laboratory. Therefore fast, discriminating methods are at the essence.
- Immuno-chromatography test that could be taken to the point-of-action and provide reliable results from blood would ideal.

- Adaptability
 - Development of fast and cheap multiplex diagnostic methods should be fostered that could be used in geographically isolated regions. The alternative strategy (not exclusive), development of singleplex ZIKV tests that could be implemented in those regions that should be necessarily fast and cheap.

- Coordination of approaches
 - Fragmentation of human resources: Involved researchers are working in silos, some overlapping of efforts in diagnostic related research is being observed.
 - Fostering the creation of multidisciplinary and international consortia with the critical participation of countries with ZIKV cases and thus obtaining a critical research and innovation on RDI is needed towards avoiding fragmentation and duplication of efforts.

- Flexibility
 - Molecular and immunological assays that will permit more user-friendly, accurate and early diagnosis of the disease, as well as facilitate retrospective diagnosis of suspicious cases.
 - Diagnostic test to confirm past infection in setting of multiple flaviviruses.
 - Serological tests can be very useful, simple and fast.

- Validation

- An assay validation 'platform' – an agreed procedure and reagents for validating diagnostic assays. Many are developing diagnostic assays; the bottleneck is in validation and comparison.
- Assessment of diagnostic platforms having the greatest near-term value for serological analysis of patient samples.
- Access to standardized reference materials (to design/validate/calibrate the tests) □ WHO is coordinating the development of these reference materials in collaboration with partnering organizations.
- The variability of quality and performance of assays developed in similar circumstances for Ebola virus highlighted the importance of a mechanism for independent assessment of these assays and their manufacture. In response to this, WHO has invoked the Emergency Use Assessment and Listing (EUAL) Procedure for evaluation of Zika diagnostics. The purpose of the WHO EUAL Procedure is to provide guidance on diagnostic quality, safety and performance to interested United Nations procurement agencies and national regulatory authorities (NRAs) of relevant WHO Member States.

- Definition and Prioritization of the needs

- Better definition and prioritization of the needs (for patients presenting symptoms, surveillance, research, patient monitoring, when and where will the tests be used, multiplex tests...) □ WHO is developing TPPs (and conducting a pipeline analysis) in collaboration with multiple partners.

- Immune response

- We need more data on duration of IgM and IgG in blood, impact on IgM and IgG response from prior flavivirus infection.
- Clinical samples, collected from patients exposed to ZIKV and other endemic viruses, to inform diagnostics development and to enable testing and validation.

Participants in the Zika Diagnostic Working group

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