

Zika Vaccine Working Group Overview

November 2016

A) PIPELINE OF VACCINE CANDIDATES:

Advanced Candidates already in clinical development:

- **Inovio DNA** vaccine (delivered through electroporation) candidate, phase I completed (June 2015, US & Canada), ongoing phase 2 in Puerto Rico (September 2016, placebo-controlled, double-blind trial involving 160 healthy adult volunteers to evaluate the safety, tolerability and immunogenicity. The study will recruit a subset of adults seropositive for the dengue virus. Inovio will also assess differences in Zika infection rates in participants given either placebo or vaccine as part of an exploratory endpoint.)
- **(NIAID(VRC)) DNA-based** vaccine candidate, ongoing phase I, scheduled phase II in early 2017.
A placebo-controlled phase 2b study of 2400 people will be initiated early next year at 30 sites in the Caribbean, Central and South America, and, if warranted, the southern United States.
- **(NIAID/BARDA/WRAIR/Sanofi Pasteur/+Fiocruz for clinical testing in Brazil) Whole-particle purified inactivated (ZPIV)** vaccine candidate, 3 phase I scheduled late 2016/early 2017, 1 phase 1 trial already ongoing. Phase II planned for early 2018.
(**BARDA** mentioned that it has awarded \$43 million to Sanofi, for 'Process development, manufacture and two Phase I/II clinical trials', option for further support if successful)
One study will evaluate an accelerated vaccination schedule (NHP experiments done with prime and booster dose after 4wks), and the other three phase 1 trials will evaluate efficacy in flavivirus-naïve patients, in dengue-experienced patients, and in people vaccinated against yellow fever virus and Japanese encephalitis virus.
(Of note: Purified immunoglobulin from ZPIV vaccinated monkeys also conferred passive protection in adoptive transfer studies!).

Candidates ready to enter clinical development in early 2017:

- **(NIAID/Butantan)** a pentavalent **live-attenuated** vaccine candidate (Zika + dengue) (based on the dengue vaccine currently in phase III in Brazil), phase I planned in early 2017.
- **(BARDA/Moderna)** mRNA vaccine candidate (\$ 8,2 million for 'Vaccine formulation, toxicology, two Phase I clinical trials'. If successful, option for up to \$125 million).

- **(Bharat) inactivated** vaccine candidate, completed preclinical development, in October asked permission from India regulators for phase I trial.

Candidates in late preclinical development, expected to enter phase I later in mid/late 2017:

- **(BARDA/Takeda)** an **inactivated, adjuvanted, whole** Zika virus vaccine candidate
BARDA will fund with \$19.8 million, for 'Process development, manufacture and two Phase I clinical trials', phase I scheduled in 2017. If successful, option for up to \$312 million.
- **(NIAID/GSK)** self-amplifying **mRNA** vaccine candidate, expected to enter phase I in mid/late 2017.
- **(BARDA/Emergent)** **inactivated, whole virus** vaccine candidate (\$ 18 million for 'Process development and manufacture of material for Phase I clinical trial + \$ 1.7 million supplement?')
- **(ProteinSciences/UMN Pharma Japan)** **recombinant E protein** of Zika virus, based on its similar vaccine candidates against West Nile Virus and Japanese Encephalitis Virus (also in preclinical development). Has announced it expects to start phase I in early 2017 (?!).
- **(NIAID) VSV-vectored** vaccine candidate, expected to enter phase I in late 2017.
- **(WRAIR/Harvard): plasmid DNA vaccine candidate** (has completed preclinical development)
- **(WRAIR/Harvard) recombinant rhesus adenovirus** serotype 52 vector vaccine, SINGLE-SHOT (has completed preclinical development)
- **(FioCruz) inactivated** vaccine candidate (entering NHP testing at end 2016)

Candidates in preclinical development

- **(Sanofi) live attenuated recombinant vaccine**, based on its licensed Dengvaxia dengue and JE vaccines.
- **(EVI/Inst. Pasteur) recombinant measles vector** candidate (funded by EU with € 5 million)
- **(GEOVAX) Modified Vaccinia Virus Ankara - Virus-Like Particle (MVA-VLP)** platform
- **(Valvena) purified inactivated** vaccine candidate, based on the same manufacturing platform as their licensed Japanese encephalitis vaccine. (Funded with € 25 million by the EIB, for their Lyme and Zika vaccine programme...).
- **(Butantan) inactivated vaccine** candidate.
- **(FioCruz) VLPs**

- **(FioCruz/Evandro Chagas Institut/University of Texas) live attenuated** vaccine candidate.
- **(FioCruz) Chimeric ZIKV/YF vaccine**, will be postponed as second generation effort.

B) Contributions from GloPID-R members:

1. NIH/NIAID

NIAID is investigating multiple Zika virus vaccine candidates, including vaccines based on technologies that have shown promise against other flaviviruses:

- o In August 2016, NIAID launched a Phase I clinical trial of a promising investigational **DNA-based Zika vaccine** developed by NIAID Vaccine Research Center scientists. Results from this Phase I trial are expected by the end of 2016. If the vaccine is shown to be safe and immunogenic, NIAID will launch a Phase II clinical trial in early 2017 to examine its safety and efficacy in countries where Zika is prevalent.
- o NIAID is collaborating with the Biomedical Advanced Research and Development Authority, the Walter Reed Army Institute of Research (WRAIR), and Sanofi Pasteur to develop a **whole-particle inactivated vaccine** (ZPIV) using an approach similar to that used by WRAIR to develop vaccines against the related Japanese encephalitis and dengue viruses. The ZPIV candidate is planned to be evaluated in 3 Phase 1 clinical trials beginning in late 2016/early 2017.
- o NIAID researchers, in collaboration with Butantan Institute in Brazil, are developing a **live-attenuated Zika virus vaccine candidate**, using a strategy similar to that used to develop a dengue vaccine that was shown to be safe and immunogenic in early-phase trials. The dengue vaccine candidate is currently being evaluated in a large Phase III clinical trial in Brazil. The Phase 1 clinical trial of the Zika vaccine candidate is planned to begin in early 2017.
- o NIAID researchers, in collaboration with GSK, are developing an **mRNA Zika vaccine candidate**. This candidate is currently in preclinical evaluation and a phase 1 clinical trial is planned for mid-to-late 2017.
- o NIAID-sponsored researchers are developing a **Vesicular Stomatitis Virus vectored vaccine candidate** that may enter a Phase 1 clinical trial in late 2017.

2. 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 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.

For Zika vaccines, BARDA is working with colleagues at the US National Institutes for Health (NIH) to evaluate, develop and manufacture new specific vaccines for Zika.

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

BARDA has made several awards to support Zika virus vaccine development:

- **Sanofi**
 - \$43 million contract under BAA-16-100-SOL-00003
 - Process development, manufacture and two Phase I/II clinical trials
- **Takeda**
 - \$19.8 million contract under BAA-16-100-SOL-00003
 - Process development, manufacture and two Phase I clinical trials
- **Moderna**
 - \$8.2 million contract under BAA-16-100-SOL-00003

- Vaccine formulation, toxicology, two Phase I clinical trials
- **Emergent**
 - \$18 million CIADM Task Order + \$1.7 million supplement
 - Process development and manufacture of whole virus inactivated Phase I clinical trial material
- **Butantan**
 - \$3 million supplemental to WHO Cooperative Agreement
 - Supporting development of inactivated vaccine and infrastructure

Additionally, companies are referred to present their technologies to BARDA staff through the Technology Watch program (Tech 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.

3. EU

Direct funding for Zika vaccine research:

- **(EVI/Inst. Pasteur)** recombinant measles vector candidate (funded by EU with € 5 million). The grant includes the development of an NHP model.
- **(Valvena)** purified inactivated vaccine candidate, based on the same manufacturing platform as their licensed Japanese encephalitis vaccine. (Funded with € 25 million by the European Investment Bank, for both their Lyme and Zika vaccine programme...).

Other EU-funded Zika vaccine-related research:

- A preparedness clinical research network with several sites in Latin America/Caribbean region (and the possibility to add new sites as the epidemic evolves) is being established with EU-funding. This network is put in place to facilitate clinical testing of medical countermeasures under development, including vaccines. EU is funding the capacity building (infrastructure, training, IT and communication set-up) and the networking (harmonisation of protocols and data sharing) activities of these sites.

This network of clinical research sites complements the respective EU preparedness clinical research network, as well as the one under preparation in Sub-Saharan Africa, which would be available for vaccine testing in case the epidemic moves on to these regions.

4. Brazil

- **Butantan:**

Priority is an inactivated Zika vaccine (as the fastest approach to a vaccine suitable for pregnant women). The Butantan Institute has established a vaccine formulation that is presently under experimental testing under in vivo conditions (mouse strains) to evaluate both the protective immunity and in vitro conditions, to evaluate virus neutralization activity and virus replication enhancement mediated by anti-zikv antibodies. Scaling up of the vaccine production is expected to begin by the first trimester of 2017.

Butantan is also collaborating with NIAID for the development of the 5-valent live attenuated Zika+Dengue vaccine.

- **Fiocruz:**

- is developing a series of vaccine approaches and has also decided to focus on an inactivated vaccine formulation that will start to be tested in rhesus monkey by the end of this year. Other vaccines under experimental evaluation are based on VLPs. The chimeric ZIKV/YF vaccine will be postponed for a second generation effort. Fiocruz is also participating in the development of an attenuated zika virus vaccine in partnership with Evandro Chagas Institute and the University of Texas.

5. Canada

Canada kindly provided an overview of their support for Zika research, but it does not include Zika vaccines in its primary objectives (it focuses on diagnostics, ZIKV virology and pathophysiology, and ZIKV transmission dynamics).

6. WHO

WHO has:

- published the TPP for Zika vaccines. The updated TPP has just completed public consultation.
- held a regulatory consultation related to Zika vaccine development.

7. France

French academic / Biotech and industry programs for Zika vaccines, September 2016

ZIKV vaccines						
Group	Contact	Vaccine type	Development stage		Funding	Partners
			March 2016	September 2016		
Pasteur Institut	Frédéric TANGY	Live replicating recombinant measles	Proof of concept in human for Chikungunya	GMP/tox done	EU H2020 Zikavax and Themis Bioscience	Themis Bioscience

Academic		Pierre CHARNEAU	Lentiviral non integrative vector	Similar strategy used for other Flaviviruses	Preclinical Immunization and efficacy studies done on mice model	Theravectys	Theravectys
		Simon WAIN-HOBSON	DNA vaccine with optimized delivery	Tested in two phase I clinical trial for cancer immunotherapy	Abandoned		
	U1187 INSERM (CYROI, La Réunion)	Robert MAMOUN	Prime-boost strategy : live attenuated	First POCs with other viruses = early and neutralizing	in vitro and in vivo validation ongoing	Inserm-Transfert	CILOA Co.
	Tours University	Philippe ROINGEARD	Subunit vaccine : VLP HBV-Zika	Pre-clinical development in mice and rabbits ongoing	In progress	French Technology Transfer Company	
Industry	Sanofi-Pasteur	Jean LANG	Inactivated purified Zika vaccine (ZPIV)	Development steps	\$43.2M from BARDA for phase I/II with an option for phase III	WRAIR and Bio-Manguinhos	
				July 2016: CRADA with Walter Reed Army Institute of Research (WRAIR) September 2016: BARDA announcement for funding of phase I/II October 2016: Principle of collaboration agreement between SP, WRAIR and Bio-Manguinhos (FIOCRUZ) for future development in Brazil Calendar: Phase I in progress Phase II planned for early 2018			
ZIKV animal models							
Group		Contact	Model	Development stage		Funding	
Academic	CEA / IDMIT	Roger LEGRAND	Non-human primates	Models of infection, challenge and antibody response already achieved.		CEA	

Programs related to Zika vaccine development				
Group		Contact	Description	Funding
Academic	CIMI-Paris UMR- S 1135	Hans Yssel	Research program on innate and adaptative immunity to Zika virus In progress	EU H2020 Zikalliance programme
	Sanofi- Pasteur	Jean LANG	Case definition study planned in Latin America in 2018 allowing a better definition of the seroprevalence of Zika in this region and well define the ability to detect and diagnose Zika infections using the clinical and diagnostic tools proposed to be used for the upcoming efficacy studies	SP