

## Challenges in Searching for Zika Therapeutics

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Zika virus was discovered nearly 70 years ago, but received little attention prior to 2015, as the virus infection causes no or only a mild, self-limiting illness without need for treatment. However, large scale outbreaks in South and Central America and the Caribbean in 2015 strongly suggested Zika epidemic may have associations with the increased cases of birth defect called microcephaly. Microcephaly is a condition in which a person's head is significantly smaller than normal for their age and sex, and occurs most often when a baby's brain has not developed properly during pregnancy. The microcephalus babies may have life-long intellectual or physical disabilities. Now, a compilation of evidences solidified the link between the Zika virus infection in pregnant mothers and microcephaly of their babies. As the Zika virus has 'explosive' pandemic potential in Africa, Southeast Asia, the Pacific Islands and the Americas, the World Health Organization (WHO) declared Zika virus a Public Health Emergency of International Concern in early 2016.

Zika virus is a positive single stranded RNA virus with a genome size of about 11 kb nucleotides long. This single transcript gives a polypeptide which processed into 3 structural proteins (capsid [C], premembrane/membrane [prM] and envelope [E]) and 7 non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, NS5), as shown schematically on Figure 1A. The structural proteins form the viral particles. The non-structural proteins may contribute to viral replication, virion assembly and modulation of the host immune system. For example, the viral RNA polymerase NS5 is not only used for the viral RNA replication, but it also can promote the proteasomal degradation of host signal transducer and activator of transcription 2 (STAT2) to inhibit type I interferon (IFN) signalling and thus antagonize the host antiviral response [1]. Zika is mainly transmitted by the mosquito species *Aedes aegypti* or *Aedes albopictus*. It may also be transmitted by blood transfusion or unprotected sex. Once the Zika virus get into the bloodstream of a pregnant woman, the virus may cross the placenta and infect the foetus's neural progenitor cells (NPC), which form the brain's outer layer. Damaged NPC creates fewer neurons, leading to decreased brain volume [2,3]. It is suggested that even if a pregnant women is exposed to a low dose of the virus for a short period of time, it may still damage the baby's brain development, especially in the first trimester of pregnancy. In experimental model of cultured human embryonic stem cell-derived cerebral organoids, Zika can shrink the size of the organoids significantly [4]. It was demonstrated that Zika viral RNA can activate the Toll-like receptor 3 (TLR3), and lead to down stream pathways modulating neurogenesis and apoptosis [2]. The central nervous system (CNS) developmental axon guidance molecules, netrin-1 (NTN1) and receptor tyrosine kinase ephrin type-B receptor 2 (EphB2) may particularly be relevant to Zika pathogenesis [2].

Structural biology, aimed at the study of molecular mechanisms at near atomic level, may help in understanding the Zika virus' pathogenesis and provide molecular basis for drug design or improving the effectiveness of available drugs. The Zika virus cryo-EM structures have been determined [5,6], as illustrated in Figure 1B and 1C. The protein prM and E are visible in the virus particle structure. 3 copies of prM/E form an asymmetric unit (Figure 1B) and 60 copies of such units assemble the whole virus particle (Figure 1C). The envelope E

glycoprotein is the major protein responsible for receptor binding and fusion of host cells, and thus may be serve as a good target for the development of therapeutics. The crystal structure of E and its complex of a neutralizing antibody has been determined by X-ray crystallography [7]. The receptors for the E glycoprotein have not been clearly defined. A receptor tyrosine kinase AXL (AXL named from the Greek word 'Anexelekto', meaning uncontrolled) has been proposed to be one of the candidate for the Zika's entry receptor [8], and it is highly expressed in neural stem cells. The single span transmembrane AXL has a large extracellular part containing two Ig-like and two fibronectin domains with the cellular part containing a protein kinase domain. The AXL plays an important role in inhibition of TLR signalling. Interestingly, the Zika virus induces NPC damage by promoting the TLR3 signalling, suggesting a good link between AXL receptor and Zika's pathogenesis. The structure of the two Ig-like domain of AXL is available [9], as shown in Figure 1F. It is interesting to note that the AXL two Ig-like domain exhibits a good surface charge complementary to that of viral E protein (Figure 1E). The biochemical data showing the direct interaction of AXL and Zika E protein remains to be demonstrated. If they interact directly, the complex structure would provide valuable information for drug designing. For the Zika's non-structural protein structures, the c-terminal fragment of NS1 has been obtained [10], as shown in Figure 1D. The structure for NS5, a RNA polymerase has not yet been determined, however, it can be modelled with the Japanese encephalitis virus NS5 structure (PDB code: 4K6M) [11]. The modelled structure shows large cavities as shown in Figure 1G. These cavities may be used for docking of potential inhibitors, especially nucleotide analogues. One nucleotide analogue, 7-Deaza-2'-C-Methyladenosine (7DMA, chemical structure shown in Figure 1H), originally used for inhibition of the close related Hepatitis C virus (HCV) RNA polymerase, has been shown effectively inhibit the Zika virus replication in mouse model [12]. In order to design powerful specific inhibitors, the actual structure in complex with inhibitors will be required.

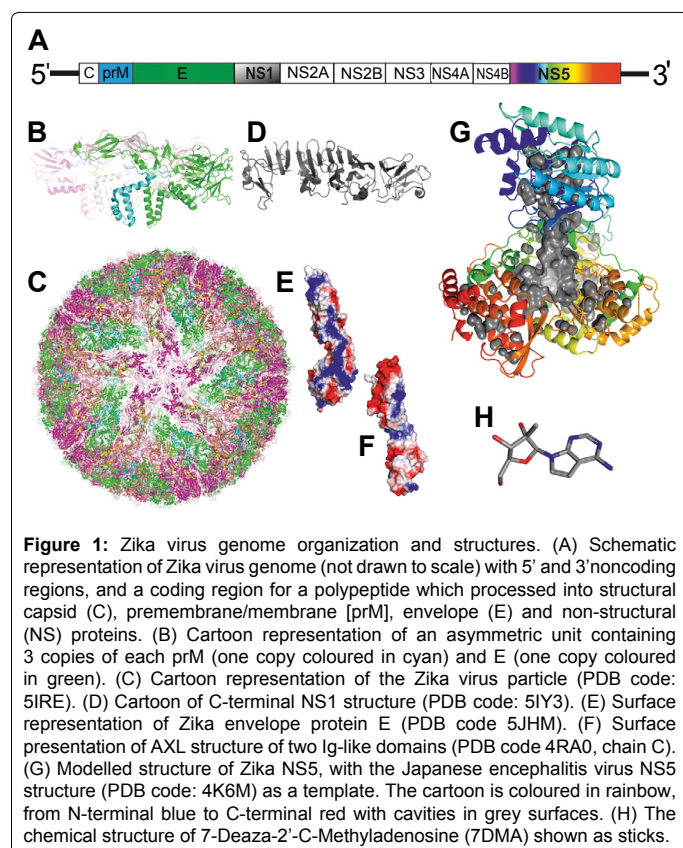
Developing brand-new drug takes an enormous amount of time, money and effort. The potential strategies to reduce the time frame, decrease costs and improve success rates may be drug repurposing. Many Food and Drug Administration (FDA) approved drugs have been developed or are being developed for treatment of diseases not initially purposed. These drugs have good safety records, and could be readily used for clinical trials. Much like in the case for Ebola, some anticancer drugs from selective estrogen receptor modulators (SERM) were discovered to be able to inhibit Ebola infection in animal models

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[13]. More recently, the complex structure of a SERM compound with Ebola glycoprotein was achieved in our laboratory. It provides valuable information for further development of powerful anti-ebola drugs (Zhao Y, Ren J et al., to be published in Nature). Searching for repurposed drugs for Zika has just started. The American National Centre for Advancing Translational Sciences (NCATS) is taking the leading role in this field. It is claimed that one compound has been identified which is capable of blocking the Zika induced caspase 3 activity, and thus stops the viral induced apoptosis in the infected cells. Additionally, advances in reverse genetics of Zika virus may also facilitate the large scale drug screening. For example, an infectious Zika virus cDNA clone was engineered with an insertion of a *Renilla luciferase* reporter gene. This recombinant virus allows rapid luciferase assay be used for large scale drug screening. The compound, NITD008, has been identified by this assay [14]. NITD008 is very similar to 7DMA, both are nucleotide analogues targeting the viral RNA polymerase NS5. There is a long way to go before we could know if these potential compounds could actually be used for the treatment of Zika infection in pregnant women.

Vaccination is a common way of fighting viral diseases. Vaccines for other members of same *flavivirus* family is available, for example, yellow fever and Japanese encephalitis vaccines. To develop a Zika vaccine, the recombinant virus-like particles (VLP) may be a good choice. This can be achieved by recombinant expression of prM/E genes with a part of C sequence. The resulting VLP contains no virus non-structural genes, and thus, is a safe form of vaccine which retains full antigenicity.

Currently, there is no FDA approved vaccine or drugs for the Zika virus infection. Searching for Zika therapeutics for pregnant woman

is especially challenging, as foetuses are particularly vulnerable to substances that may influence their development. For the time being, the personal protection from mosquito bite is the most effective way of preventing Zika infection. Some mosquito repellent, such as N, N-diethyl-meta-toluamide (DEET) can be safely used for pregnant women [15]. With the rapid progress in understanding molecular mechanisms of Zika pathogenesis, and joined efforts from both academic research and commercial development, the therapeutics for Zika will be available in the near future.

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