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THE CURRENT APPROACHES TO ZIKA VIRUS VACCINATION

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The aim of the review was to emphasize the importance of producing new generation high standardized synthetic peptide Zika vaccines which induce both humoral and cellular immunity and eliminate side effects of traditional vaccines. The information was done about Zika virus that is an artropod-born virus, member of the genus *Flavivirus* in the family *Flaviviridae*. Zika virus has caused outbreaks in many countries the conditions in adults such as Guillain–Barre syndrome by the dramatically increasing number of cases. According to announcement by World Health Organization, 4 million people could be infected with Zika virus in Americas.

The importance of the development of peptide vaccines against the virus Zika of the new generation, which are the most promising direction of the prevention and treatment of viral infection has emphasized.

Key words: Zika virus, peptide vaccines.

Zika virus (ZIKV) is an arthropod-born virus, member of the genus *Flavivirus* in the family *Flaviviridae* [1]. ZIKV was first isolated in 1947 from serum of a Rhesus monkey from Zika Forest, Uganda [1]. ZIKV in human was first confirmed in 1952 in Nigeria. Until 2007, 14 human ZIKV cases were reported [2]. Unreported cases are possible due to high cross-reactivity between other *flaviviruses* [3]. First ZIKV outbreak was seen in 2007, more than 70% of Yap Island (Micronesia, Pasific Islands) residents were affected [4]. After virus spread to other Pasific Islands, another outbreak was reported in Brazil in 2015. As of June 2016, continuing mosquito-borne transmission was reported in 60 countries and territories [5]. ZIKV infected people can show symptoms including mild fever, conjunctivitis, skin rash, muscle and joint pain and headache up to 7 days [2]. ZIKV has been associated with microcephaly [6] and neurologic conditions in adults such as Guillain–Barre syndrome by the dramatically increasing number of cases [7].

Zika virus

ZIKV is an artropod-born virus, member of the genus *Flavivirus* in the family *Flaviviridae* [1]. It is a positive sense single-stranded RNA molecule, approximately 10 thousand bases long [8]. The order of proteins encoded in the ORF (*Parapoxvirus* is a genus of viruses, in the family Poxviridae, in the subfamily Chordopoxvirinae; Orf is an exanthemous disease caused by a parapox virus and occurring primarily in sheep and goats. It is also known as contagious pustular dermatitis, infectious labial dermatitis, ecthyma contagiosum, thistle disease and scabby mouth. *Orf virus* is zoonotic — it can also infect humans) is 5′-C-prM-E-NS1-NS2A-NS2B-NS3-NS4A-NS4B-NS5-3′ and translated into a polyprotein that is cleaved into capsid (C), precursor membrane (prM), envelope (E) and 7 non-structural proteins (NS) [9].

Zika virus Transmission

ZIKV is a mosquito-transmitted infection related to other *Flavivirus* species such as dengue, yellow fever and West Nile virus. It is

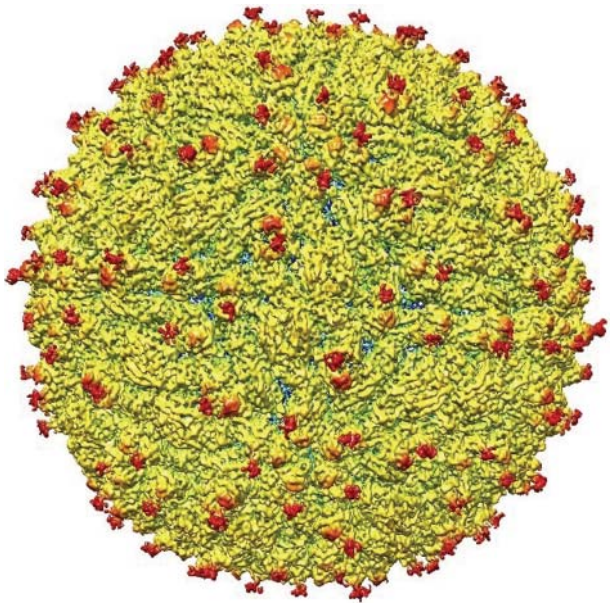

Fig. 1. **The cryo-EM structure of ZIKV at 3.8**

spread to people primarily through the bite of infected *Aedes* mosquitoes [10–12].

A pregnant woman can pass Zika virus to her fetus during pregnancy [13]. A pregnant woman already infected with Zika virus can pass the virus to her fetus during the pregnancy or around the time of birth [14].

Altough incubation period of Zika virus is unknown, when similarity with other *Flaviviruses* is considered, it is expected to be less than 1 week [15, 16].

Zika virus Symptoms

ZIKV symptoms may be easily confused with other *flavivirus* infections such as DENV and CHIKV. Symtoms of ZIKV are mild fever, rash, conjunctivitis, and arthralgia, lasting for several days to a week. These unspecific symptoms are seen only in 20–25% of infected individuals [4, 17].

According to the study of the Centers for Disease Control and Prevention (CDC) scientists have concluded ZIKV is a cause of microcephaly and other severe fetal brain defects [18]. Excessive increase of microcephaly after ZIKV outbreak is seen in Fig. 2. Also unusual increase in Guillain-Barr syndrome after ZIKV outbreak is being investigated for possible association [19].

Microcephaly is a birth defect defined as baby's head is significantly smaller than other babies's heads of the same sex and age. Smaller head indicates baby's brain has not developed properly [21]. Affected children may have seizures, intellectual disabilities, hearing and vision problems depend on severity of microcephaly [22]. According to CDC (Centers for Disease Control and Prevention) report, when outbreak in Brazil analyzed, the risk of microcephaly by ZIKV disease is increasing during the first trimester of pregnancy.

Diagnosis of Zika virus

Thus, sympthoms of ZIKV disease are non-specific and similar to the other arbovirus infections, diagnosis relies on laboratory testing [23, 24]. Therefore, different methods for diagnosis of ZIKV are investigated for quick, functional and precise results. RT-PCR, immunologic assays and virus isolation methods are used for the diagnosis of ZIKV RNA or to detect viral proteins or virus [16, 25, 26]. RT-PCR method is frequently used since it provides sensitivity [26, 27]. Serologic assays are limited since ZIKV antibodies are highly cross-reactive with other *flaviviruses* [25].

In the diagnosis of virus, the factor which constitutes a major problem is low load of ZIKV in blood and urine. For this reason, virus could not be detected in many patients [28].

It is a rapid test for Ebola virus. By adapting paper-based sensors to ZIKV, virus was detected at low concentrations on blood. Programmed RNA sensors bind to viral RNA and trigger a reaction that causes changes on the colour of paper. With this test, sensitive results are obtained in 3 hours [29].

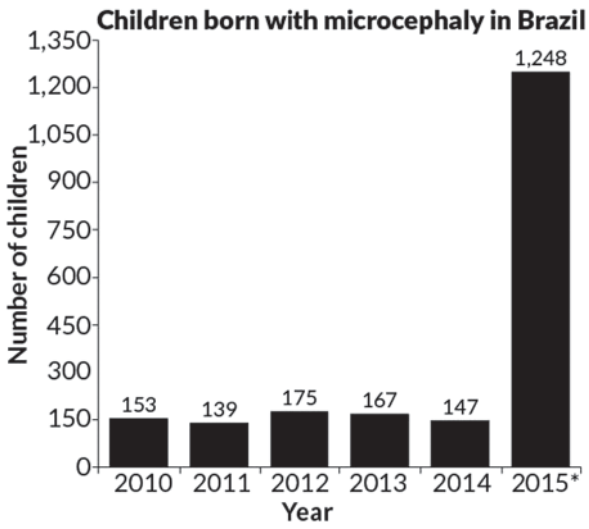

Fig. 2. **Children born with microcephaly in Brazil: suspected cases as of November, 28 [20]**

Vaccination against Zika virus

Currently, there is no licensed vaccine or medication against ZIKV. One serious obstacle for clinical development of ZIKV antiviral is risky group who are infected by virus are pregnant women [30].

In the areas where people infected by virus, they have been exposed to Dengue virus outbreak, which is another kind of *Flavivirus* structurally similar to ZIKV. Studies have been done to understand if there is a serological cross reactivity between Dengue and Zika viruses [31–33].

In a study of Barba-Spaeth et al. [31] antibodies which were taken from have had Dengue, neutralize Zika virus by targeting a conformational epitop area. Since these viruses are targets of the same antibody, a common vaccine can be developed for both viruses.

In a related paper, researchers found that antibodies generated by who has had Dengue virus cause to improve the replication and development of ZIKV. It means enhancement of virus infection [33].

The risk of cross reactivity for whom previously has had Dengue and who has ZIKV alone must be considered together in order to develop a vaccine for either Dengue or ZIKV and minimize the side effects.

ZIKV has causally associated with microcephaly in both humans [6] and mice [34]. As a result of studies with mice 100% immune protection towards Zika Brazilian strain is provided by a purified inactivated Zika virus vaccine and plasmid DNA vaccine. By DNA vaccine, full-sized pre-membrane and membrane proteins injected. Complete immunization has achieved 3 days after vaccination with single dose. These findings give hope for an effective and safe vaccination for humans [35].

Although classical vaccines such as modified live vaccines or attenuated virus or recently became popular vaccines such as recombinant vaccine are considered as they have many advantages, they also have significant limitations. These can be counted as high costs in development, effectiveness of the immune response and toxicity [36–39]. Peptide based subunit vaccines are also has gained importance since they don't include live or attenuated microorganisms the risk of autoimmunity, allergic reactions reduce [40]. By our project group synthetic peptide vaccines are recommended since they may provide more specific immune response and they can prevent the unwanted side effects.

In a study for the development of synthetic peptide vaccine against Zika, ZIKV envelope glycoprotein sequence was obtained from a protein database and examined with *in silico* approaches in order to determine the most immunogenic epitopes of B and T cells. By the help of bioinformatics, the most immunogenic ZIKV envelope glycoprotein B and T cell epitopes which induce both humoral and cell mediated immune response has determined. Considering IFN-gamma immune response and hydrophobicity is also important factors to develop a peptide vaccine. To keep hydrophobicity low and limit peptide sequence between 8–22 amino acids are suggested to develop peptide vaccine [41].

The peptide sequence between 123–141 amino acids DAHAKRQTVVVLGSQEGAV were predicted as the most immunogenic epitope for B cells. This sequence is 19 residues long and hydrophilic with molecular weight of 1965.17g/mol. Suggested epitope for CD8+ T cell peptide sequence is from position 250 MMLELDPPF is hydrophilic with molecular weight of 1092.33 g/mol. This epitope also has the highest epitope conservancy [41]. Lack of RNA polymerase proofreading activity raise the significance of epitope conservancy towards ZIKV mutation tendency [42]. ZIKV envelope glycoprotein can also induce IFN gamma production. The sequence from 124 AHAKRQTVVVLGSQEGAVHT 143 with the molecular weight of 2088.33 g/mol demonstrate the highest score of induce antiviral defense [42]. Molecular weight calculations were done from INNOVAGEN' peptide calculator (http://pepcalc.com/).

So, this review informs about ZIKV, its globally prevalence and importance of vaccine development. In our previous studies binding synthetic peptides to adjuvant featured carrier polymers such as polyacrylic acid (PAA) [43,44], Poly (N-vinyl-2-pyrrolidone-co-acrylic acid) [P(VP-co-AA)] [45,46], Poly(N-isopropylacrylamide-co-acrylic acid) P(NIPAA/AA) [45–47], etc. and proteins such as Bovine Serum Albumin (BSA) [48], etc. to form peptide-polymer conjugates and use as vaccine prototypes, high antibody titres obtained. Based on our previous studies, in this review we suggest that by binding of the specified antigenic peptide epitopes to various carriers, effective immune response will be achieved by new generation synthetic peptide vaccines.

The results obtained suggest being perspective for peptide vaccine development. For further studies, our aim is to test *in silico* approaches by producing *in vitro*, in accordance with the previous studies of our group, to increase the antigenic properties by binding to a polymeric carrier that shows the adjuvant feature. Outcomes of this review will lead researchers who develop ZIKV vaccine.

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СУЧАСНІ ПІДХОДИ ДО ВАКЦИНАЦІЇ ПРОТИ ВІРУСУ ЗІКА

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Метою огляду було наголосити на важливості створення високостандартизованих вакцин нового покоління проти вірусу Зіка на основі синтетичного пептиду, які індукують як гуморальний, так і клітинний імунітет, та усунути побічні ефекти традиційних вакцин. Вірус Зіка за своїм походженням є артропоїдним, членом роду *Flavivirus* родини *Flaviviridae*. Цей вірус спричинив епідемії в багатьох країнах світу у дорослих з такими виявами, як синдром Гієна–Барре. Згідно з повідомленням Всесвітньої організації охорони здоров'я, 4 млн. осіб можуть бути інфіковані вірусом Зіка в Північній і Південній Америці. Зроблено висновок про актуальність розроблення пептидних вакцин проти вірусу Зіка нового покоління, що є найбільш перспективним напрямом профілактики і лікування цієї вірусної інфекції.

Ключові слова: вірус Зіка, пептидні вакцини.

СОВРЕМЕННЫЕ ПОДХОДЫ К ВАКЦИНАЦИИ ПРОТИВ ВИРУСА ЗИКА

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Целью обзора было подчеркнуть важность создания высокостандартизированных вакцин нового поколения против вируса Зика на основе синтетического пептида, которые индуцируют как гуморальный, так и клеточный иммунитет, и устранить побочные эффекты традиционных вакцин. Вирус Зика по своему происхождению является артропоидным, членом рода *Flavivirus* семейства *Flaviviridae*. Вирус Зика вызвал эпидемии во многих странах мира у взрослых с такими проявлениями, как синдром Гийена–Барре. Согласно сообщению Всемирной организации здравоохранения, 4 млн. человек могут быть инфицированы вирусом Зика в Северной и Южной Америке. Сделан вывод об актуальности разработки пептидных вакцин против вируса Зика нового поколения, что является наиболее перспективным направлением профилактики и лечения этой вирусной инфекции.

Ключевые слова: вирус Зика, пептидные вакцины.