We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Zika Virus, Microcephaly and its Possible Global Spread

Syed Lal Badshah, Yahia Nasser Mabkhot,
Nasir Ahmad, Shazia Syed and Abdul Naeem

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/intechopen.72507>

Abstract

Zika virus is an arbovirus that is spreading at an alarming state in the American continents and now in Asian countries. The *Aedes* mosquitoes are the vectors for the spread of this virus beside other ways of transmission. Currently, there are no vaccines or drugs available for its treatment. The Zika virus-related microcephaly cases are reported in fetuses of pregnant women who got this viral infection. However, the exact mechanism of Zika virus and microcephaly is still not established. Here we review Zika virus epidemiology, its unusual relationship with microcephaly in fetuses and current scientific research progress on it.

Keywords: Zika virus, microcephaly, *Aedes* mosquitos, epidemic, vaccines

1. Introduction and background

Zika virus (ZIKV) of the family Flaviviridae was on the list of neglected diseases, and like all neglected diseases, it is now an epidemic causing microcephaly in new-born and Guillain-Barré syndrome in adults [1]. The *Aedes aegypti* mosquitoes are the main vectors for it beside other reported species like *Aedes hensilli* [2]. Historically, it was identified back in 1947, and recently, Chang et al. have thoroughly discussed its full history [3] and several authors have reviewed the literature [4–9], but still there is a need for updated information. In the past 70 years, different strains of Zika virus have been isolated from time to time in different parts of Africa [10–15]. It is generally believed that the current progress in human travel technology and its frequent use by people and the spread of *Aedes* due to its invasive nature cause the global spread of Zika virus [6]. Zika virus infection was also reported in a few returning travelers in the Netherland and Switzerland, so its possible spread to the Europe is also difficult to avoid [16–18]. It was recently reported that another vector mosquito called *Aedes albopictus* has the capacity to spread Zika virus in North America and Europe [19].

The threat of Zika virus to the United States population was not given importance initially, but several reports from Puerto Rico, Texas, and other parts alarm bells in the scientific community and a wake-up call to National Institute of Health [20, 21]. Zika virus is now on the door step of Asia with cases reported from Manila (Philippines), and parts of Singapore, Thailand, India, etc., which have favorable environmental conditions for *Aedes* mosquitos, and in the past, minor outbreaks were also recorded [14, 22–24]. This is an alarming situation and there is no preparation on the emergency basis. In the past, several cases of Zika virus were reported in Asian countries like Cambodia [25] and Senegal in Africa [26, 27], but it was not that widespread. Before 2007, few cases were reported at different places in different times, but it is suggested that increase in mosquito breeding and environmental changes due to human activities may cause mutation in the RNA genome of Zika virus and it becomes more adaptable to the mosquitos [28, 29]. In 2014–2015, Zika virus infection spread in South and Central America and Caribbean regions and is now spreading to other parts of the world [20, 30]. The spread of Zika virus in northeastern parts of Brazil occurred in the beginning of 2015 when it was observed that some patients had mild fever, rash, conjunctivitis and arthralgia and their tests were negative for dengue virus [31]. Later on, the reverse transcription-polymerase chain reaction from the sera showed the presence of Zika virus and its classification showed that it belonged to the Asian group [31]. The human skin fibroblasts cells are permissive to Zika virus entry. The viral replication in infected cells causes activation of an antiviral innate immune response with the production of type I interferons [32].

2. Transmission

The common possible ways of spreading beside the mosquito bites and transplacental transmission are blood transfusion, transplantation of organs, sexual activities, breastfeeding [33], respiratory along with sweat and tear droplets and animal bite [28, 34]. In North America and European countries, the spread through sexual contacts are more as these regions are not favorable for *Aedes* mosquitos [35]. In such areas, blood and semen donations should be properly checked for the presence of Zika virus, and further, people coming from affected areas should take care when they donate blood and semen in unaffected areas [36].

3. Relation between Zika virus and microcephaly

Microcephaly is one of the associated medical effects of Zika virus infection in mothers with their new born babies [36–40]. In the past, cases of Zika virus with microcephaly were not that common, but in Brazil, it was observed that the rate of microcephaly is twenty times more, which is quite alarming and new cases are still emerging [41]. Zika virus has the capacity to cross the placental barrier and infect the fetus [42, 43]. The infected mothers of these babies have rashes in the first and second trimesters [44]. Beside microcephaly, brain calcifications, cataracts and intraocular calcifications of eyes in fetuses are also reported [45]. In other cases, agyria, hydrocephalus and associated cortical displacement and mild focal inflammation are also present [46–48]. Similarly in another case in addition to the above-mentioned symptoms,

ultrasound of the infected fetus showed damaged lesions of posterior fossa and ascites along with subcutaneous edema [49]. Recent studies also suggested that the brain tissue and cells are favorable places for Zika virus growth as it targets the brain tissues in the neonate very easily [50, 51]. Zika virus decreases the viability and growth of neurospheres and brain organoids, and in that way, it targets the brain to cause microcephaly [52, 53]. Bullerdiek et al. hypothesized that the virus proteins affect the mitotic spindle proteins and their apparatus and this could be the possible way through which Zika virus causes teratogenic effects like microcephaly [54].

There are also ambiguities about the role of Zika virus and microcephaly, as in the past microcephaly was not linked with Zika virus infection, and the cases of microcephaly were very low and it is possible that other factors may be involved in it [55, 56]. Evans et al. suggested that the insecticide pyriproxyfen that is used for the control of mosquito populations in drinking water is the possible agent for microcephaly in Brazil [57]. The insecticide pyriproxyfen has shown to act as juvenile hormone and has cross-reactivity with most of the fat soluble molecules like retinoic acid (a metabolite of vitamin A) and a ligand for RXR receptor [57]. The RXR receptor is a type of nuclear receptor and this cross-reactivity of two agents results into abnormal activity of RXR receptors with the ultimate abnormality of microcephaly [57]. However, experiments on zebra fish models showed that pyriproxyfen did not cause any deformities in the central nervous system [58]. To counter such ambiguities, different groups are studying the effect of Zika virus on mouse models, and in one of the recent reports, the researchers showed that when a mouse is infected with a Brazilian Zika virus strain, it causes intrauterine growth restriction and signs of microcephaly were also observed [59]. They also showed that Zika virus attacks the human cortical progenitor cells and destroys them, and further the viral infection also damages the human brain organoids with a decrease in proliferative zones and damages the cortical layers [59]. In different brain and neural cells infected with Zika virus, it has been observed that the viruses halt the process of mitoses and damage the centrosome and the structural organization of the dividing cell with ultimate result of cell death [60]. It has been observed that a single point mutation of serine to asparagine (S139 N) in the ZIKV polyprotein resulted in high virulence ability in human progenitor cells [61]. This mutation occurred before the 2013 French Polynesia and was maintained during the later spread of ZIKV in the Brazil and its neighbors [61]. ZIKV has the capacity to infect the placental barrier cells and thus damage the fetus [62]. ZIKV has the sole capacity to interact with anaxelekto, meaning uncontrolled (AXL) receptor, which is a tyrosine kinase receptor on the placental barrier cells while other Flaviviridae viruses cannot link with these receptors [62]. The other important arboviruses that damage the nervous system include the Japanese encephalitis virus (JEV) from the family Flaviviridae [63]. The vector for JEV is *Culex* mosquito species that feeds mostly on birds and livestock blood while humans are the accidental host of the virus [63, 64]. JEV causes birth defects and certain neurological complications [63]. A number of vaccines are available, but it is still endemic in South East Asian countries [63, 65]. Beside its effects on nervous system, Zika virus also damages the kidneys, eyes and genital organs [66–69].

4. Current scientific progress

For understanding the pathobiology and development of vaccines and drugs, it is important to sequence the genome and crystallize the important proteins of Zika virus. Recently, a Zika

virus strain named ZikaSPH2015 genome has been fully sequenced that contained all the structural and nonstructural proteins. This strain was isolated from a patient in São Paulo, Brazil [70]. In the past, a Zika virus strain from French Polynesia was also sequenced and the results showed its Asian background [71]. It is important to compare the genome of different strains and observe the differences in them for the possible mutations. Previous phylogenetic studies showed that there are basically two strains, one Asian and the other African, with some modifications due to glycosylation of amino acid sequence [72]. Recently, Kostyuchenko et al. have resolved a 3.7 Å resolution structure of Zika virus through cryoelectron microscopy [1], while Sirohi et al. have resolved a 3.8 Å resolution structure of mature particles [73]. As compared to other flaviviruses, Zika virus is stable even at 40°C. They also showed that its envelope (E) protein is similar in structure and function to that of West Nile and Japanese encephalitis viruses and dengue virus [1].

The isolation, purification and crystallization of different Zika virus proteins are also in progress and they will be helpful in designing vaccines and chemotherapeutic agents (**Figure 1**) [74]. The nonstructural protein (NS1) crystal structure showed unique electrostatic properties at the host interaction site and it is possible in different modes of action as compared to other NS1 proteins of flaviviruses [75]. It was also observed that the NS1 codons are helping more in adaptation to humans, as in the past Zika virus was more restricted to the zoonotic cycle [76]. Tian et al. resolved the crystal structure of helicase of Zika virus and they observed that

Figure 1. Sketch of the 11 kb genome of ZIKV and its important proteins. (A) The polyprotein and its cleavage products. (B) Topology of the polyprotein inside the membrane [85].

structurally it is similar to that of dengue virus but there are some differences in the motor domain [77]. That is why, Zika helicase binds to RNA differently and certain conformational changes can be seen in the motor domain [77]. Jain et al. resolved a 1.6 Å resolution structure of nonstructural (NS3) protein that acts as an RNA helicase of Zika virus, which was a French Polynesia strain [78]. This NS3 has similarity with that of dengue NS3 but there are some variations in its binding loops of ATP and RNA. This NS3 structure might be helpful in making necessary drugs to control Zika virus [78]. Rossi et al. studied Zika virus in murine models and this study could be helpful in the development of vaccines and drugs [79]. Shan et al. made an infectious cDNA clone of Zika virus using the clinical isolated strain of Zika virus of Asian origin [80]. This cDNA clone can infect the brain cells in mice and it can also infect the *Aedes* mosquito; thus, it is a useful tool to study the virus transmission, related diseases and research suitable therapeutics [80]. Like dengue virus, model studies suggested that there are chances that it will spread throughout the world [81, 82] and it may be possible to spread along with other flaviviruses like dengue, West Nile virus, chikungunya and Stratford virus due to the common vector *Aedes* [83, 84].

5. Vaccine and drugs

Some scientific groups have suggested releasing the *Wolbachia*-harboring mosquitoes in the environment as competitors for *Aedes* mosquitoes because they are resistant and they do not carry Zika virus; in this way, we can control the spread of Zika virus [86]. There is no vaccine or medicine available for the treatment of Zika virus, so it is important to be safe from mosquito bite and sexual contacts in Zika virus-affected places, which is the only solution [34, 87]. The health departments of USA are giving guidelines from time to time for prevention and control of Zika virus [88, 89]. Currently, different research institutes are working in developing a vaccine against this virus, but it will certainly take time in preparing it [90–93]. It has been observed that the polyphenol epigallocatechin 3-gallate (EGCG) inhibits the entry of Zika virus into the cell [94]. This polyphenol is present in green tea and is also part of many dietary supplements. Such observations were also recorded previously for other viruses, especially hepatitis C and herpes simplex, but how efficient this compound exactly is and its mechanism of action are still not clear [95–99]. Larocca et al. made DNA vaccines that express the premembrane and envelope protein of Zika and offer protection against the Brazilian virus challenge in murine models [100]. This initial vaccine development is a positive sign of a more effective vaccine development and its marketing in the near future for the control of Zika virus. It is also reported that those parts of Brazil where yellow fever vaccination was done have lower level of microcephaly cases due to Zika virus [101]. Thus, there is a possibility that the yellow fever vaccine may be helpful for the treatment of Zika virus infection. An opposite case to this was reported where a male American traveler had yellow fever vaccination record but still he developed symptoms of Zika virus infection like rash, fever, extreme fatigue, back pain and conjunctivitis [102]. There are also suggestions to develop better mouse and other ani-

mal models that can be used to study the pathogenesis and vaccine development of Zika virus; further, the already present neuroteratogenic problem-causing virus models can also be utilized for Zika virus infection [103–106]. Computational studies predicted that the antibodies are produced in humans during Zika virus and the infection causes an autoimmune response that results in rash, microcephaly and other symptoms [107]. Therefore, remedy for such autoimmune proteins should also be considered for treatment during development of vaccines and drugs. On the drug and development side, it was noted that the 7-deaza-2'-C-methyladenosine (7DMA) has the potency to inhibit the replication of Zika virus in mice, and further trials should be performed to check its efficiency against different strains of Zika virus [108]. Eyer et al. tested a series of substituted nucleoside bases to inhibit the replication of Zika virus and they observed that the 2'-C-methylated nucleosides are promising drug candidates [109]. For research purposes, it has been suggested that the famous adenosine analog NITD008 that has been used in the past against other viruses [110–112] also has the antiviral activity both *in vitro* and *in vivo* against Zika virus [113]. Now, the sequences and in some cases the crystal structure of different important Zika virus proteins are available and they can be targeted through computational drug designing techniques [114–117]. Similarly, the already available data on the closely related viruses like dengue virus enzymes can be exploited for novel drug design [118]. In mouse model, it was noted that 25-hydroxycholesterol prevents the entry of virus particles inside the cell and is the first line of defense molecule [119]. One of the positive aspects of ZIKV is that it can be utilized for brain cancer treatment. It was observed that the ZIKV possesses oncolytic properties and it can destroy brain cancer cells called glioblastoma with high specificity [120].

6. Conclusions

The way Zika virus is spreading silently first in South America and now in Asian countries is quite alarming. If the spread continues and microcephaly cases increase, then a whole generation born might be a patient of microcephaly. Zika virus has already affected the tourism economy of different countries, and if this spread persists in Asia, then the loss will be too large. There is a need to figure out how exactly Zika virus causes microcephaly. The current research progress in terms of vaccine and drug development is at a snail pace and collaborative efforts are required to control this viral disease. Further, the spread of Aedes mosquitoes is also alarming as they are the source of other viruses too, and controlling the vector means control on ZIKV, dengue and chikungunya.

Acknowledgements

We appreciate the Deanship of Scientific Research at King Saud University for its funding to this Prolific Research group (PRG-1437-29). The authors declare no competing interests.

Author details

Syed Lal Badshah^{1*†}, Yahia Nasser Mabkhot^{2*†}, Nasir Ahmad¹, Shazia Syed³ and Abdul Naeem⁴

*Address all correspondence to: shahbiochemist@gmail.com and yahia@ksu.edu.sa

1 Department of Chemistry, Islamia College University, Peshawar, Pakistan

2 Department of Chemistry, College of Sciences, King Saud University, Saudi Arabia

3 Department of Zoology, University of Peshawar, Peshawar, Pakistan

4 National Center of Excellence in Physical Chemistry, University of Peshawar, Peshawar, Pakistan

† Both authors contributed equally in design and discussion of this review manuscript

References

- [1] Kostyuchenko VA, Lim EXY, Zhang S, Fibriansah G, Ng T-S, Ooi JSG, Shi J, Lok S-M. Structure of the thermally stable Zika virus. *Nature*. 2016;**533**:425-428. DOI: 10.1038/nature17994
- [2] Ledermann JP, Guillaumot L, Yug L, Saweyog SC, Tided M, Machieng P, Pretrick M, Marfel M, Griggs A, Bel M, Duffy MR, Hancock WT, Ho-Chen T, Powers AM. *Aedes hensilli* as a potential vector of Chikungunya and Zika viruses. *PLoS Neglected Tropical Diseases*. 2014;**8**. DOI: 10.1371/journal.pntd.0003188
- [3] Chang C, Ortiz K, Ansari A, Gershwin ME. The Zika outbreak of the 21st century. *Journal of Autoimmunity*. 2016;**68**:1-13. DOI: 10.1016/j.jaut.2016.02.006
- [4] Petersen LR, Jamieson DJ, Powers AM, Honein MA. Zika Virus. *The New England Journal of Medicine*. 2016;**374**:1552-1563. DOI: 10.1056/NEJMra1602113
- [5] Sampathkumar P, Sanchez JL. Zika virus in the Americas: A review for clinicians. *Mayo Clinic Proceedings*. 2016;**91**:514-521. DOI: 10.1016/j.mayocp.2016.02.017
- [6] Imperato PJ. The convergence of a virus, mosquitoes, and human travel in globalizing the Zika epidemic. *Journal of Community Health*. 2016;**41**:674-679. DOI: 10.1007/s10900-016-0177-7
- [7] Martínez de Salazar P, Suy A, Sánchez-Montalvá A, Rodó C, Salvador F, Molina I. Zika fever. *Enfermedades Infecciosas y Microbiología Clínica*. 2016;**34**:247-252. DOI: 10.1016/j.eimc.2016.02.016
- [8] Zanoluca C, Duarte dos Santos CN. Zika virus—An overview. *Microbes and Infection*. 2016;**18**:295-301. DOI: 10.1016/j.micinf.2016.03.003
- [9] Jamil Z, Waheed Y, Durrani TZ. Zika virus, a pathway to new challenges. *Asian Pacific Journal of Tropical Medicine*. 2016;**9**:626-629. DOI: 10.1016/j.apjtm.2016.05.020

- [10] Weinbren M, Williams M. Zika virus: Further isolations in the zika area, and some studies on the strains isolated. *Transactions of the Royal Society of Tropical Medicine and Hygiene*. 1958;**52**:263-268. DOI: 10.1016/0035-9203(58)90085-3
- [11] Haddow AJ, Williams MC, Woodall JP, Simpson DI, Goma LK. Twelve isolations of zika virus from *Aedes (Stegomyia) Africanus* (Theobald) taken in and above a Uganda forest. *Bulletin of the World Health Organization*. 1964;**31**:57-69
- [12] Kirya BG, Mukwaya LG, Sempala SDK. A yellow fever epizootic in zika forest, uganda, during 1972: Part 1: Virus isolation and sentinel monkeys. *Transactions of the Royal Society of Tropical Medicine and Hygiene*. 1977;**71**:254-260. DOI: 10.1016/0035-9203(77)90020-7
- [13] Dick GWA. Zika virus (II). Pathogenicity and physical properties. *Transactions of the Royal Society of Tropical Medicine and Hygiene*. 1952;**46**:521-534. DOI: 10.1016/0035-9203(52)90043-6
- [14] Wong PSJ, Li MZI, Chong CS, Ng LC, Tan CH. *Aedes (Stegomyia) albopictus* (Skuse): A potential vector of Zika virus in Singapore. *PLoS Neglected Tropical Diseases*. 2013;**7**. DOI: 10.1371/journal.pntd.0002348
- [15] Simpson DIH. Zika virus infection in man. *Transactions of the Royal Society of Tropical Medicine and Hygiene*. 1964;**58**:339-348. DOI: 10.1016/0035-9203(64)90201-9
- [16] Goorhuis A, Von Eije KJ, Douma RA, Rijnberg N, Van Vugt M, Stijns C, Grobusch MP. Zika virus and the risk of imported infection in returned travelers: Implications for clinical care. *Travel Medicine and Infectious Disease*. 2016;**14**:13-15. DOI: 10.1016/j.tmaid.2016.01.008
- [17] Ioos S, Mallet HP, Leparc Goffart I, Gauthier V, Cardoso T, Herida M. Current Zika virus epidemiology and recent epidemics. *Médecine et Maladies Infectieuses*. 2014;**44**:302-307. DOI: 10.1016/j.medmal.2014.04.008
- [18] Gyurech D, Schilling J, Schmidt-Chanasit J, Cassinotti P, Kaeppli F, Dobec M. False positive dengue NS1 antigen test in a traveller with an acute Zika virus infection imported into Switzerland. *Swiss Medical Weekly*. 2016;**146**:w14296. DOI: 10.4414/smww.2016.14296
- [19] Basarab M, Bowman C, Aarons EJ, Cropley I. Zika virus. *BMJ*. 2016;**1049**:i1049. DOI: 10.1136/bmj.i1049
- [20] Gatherer D, Kohl A. Zika virus: A previously slow pandemic spreads rapidly through the Americas. *The Journal of General Virology*. 2016;**97**:269-273. DOI: 10.1099/jgv.0.000381
- [21] Lucey DR, Gostin LO. The emerging Zika pandemic: Enhancing preparedness. *Journal of the American Medical Association*. 2016;**315**:865-866. DOI: 10.1001/jama.2016.0904
- [22] Darwish MA, Hoogstraal H, Roberts TJ, Ahmed IP, Omar F. A sero-epidemiological survey for certain arboviruses (Togaviridae) in Pakistan. *Transactions of the Royal Society of Tropical Medicine and Hygiene*. 1983;**77**:442-445. DOI: 10.1016/0035-9203(83)90106-2
- [23] Bhide P, Kar A. Birth prevalence of microcephaly in India. *Bulletin of the World Health Organization*. 2016:1-11. DOI: 10.2471/BLT.16.172080

- [24] Shinohara K, Kutsuna S, Takasaki T, Moi ML, Ikeda M, Kotaki A, Yamamoto K, Fujiya Y, Mawatari M, Takeshita N, Hayakawa K, Kanagawa S, Kato Y, Ohmagari N. Zika fever imported from Thailand to Japan, and diagnosed by PCR in the urines. *Journal of Travel Medicine*. 2016;**23**:tav011. DOI: 10.1093/jtm/tav011
- [25] Heang V, Yasuda CY, Sovann L, Haddow AD, da Rosa APT, Tesh RB, Kasper MR. Zika virus infection, Cambodia, 2010. *Emerging Infectious Diseases*. 2012;**18**:349-351. DOI: 10.3201/eid1802.111224
- [26] Diallo D, Sall AA, Diagne CT, Faye O, Faye O, Ba Y, Hanley KA, Buenemann M, Weaver SC, Diallo M. Zika virus emergence in mosquitoes in Southeastern Senegal, 2011. *PLoS One*. 2014;**9**. DOI: 10.1371/journal.pone.0109442
- [27] Diagne CT, Diallo D, Faye O, Ba Y, Faye O, Gaye A, Dia I, Weaver SC, Sall AA, Diallo M. Potential of selected Senegalese *Aedes* spp. mosquitoes (Diptera: Culicidae) to transmit Zika virus. *BMC Infectious Diseases*. 2015;**15**:492. DOI: 10.1186/s12879-015-1231-2
- [28] Chan JFW, Choi GKY, Yip CCY, Cheng VCC, Yuen KY. Zika fever and congenital Zika syndrome: An unexpected emerging arboviral disease. *The Journal of Infection*. 2016;**72**:507-524. DOI: 10.1016/j.jinf.2016.02.011
- [29] Marcondes CB, Ximenes, De FF, De M. Zika virus in Brazil and the danger of infestation by *Aedes* (*Stegomyia*) mosquitoes. *Revista da Sociedade Brasileira de Medicina Tropical*. 2015;**49**:4-10. DOI: 10.1590/0037-8682-0220-2015
- [30] Lancet T. Zika virus: A new global threat for 2016. *Lancet*. 2016;**387**:96. DOI: 10.1016/S0140-6736(16)00014-3
- [31] Zanluca C, de Melo VCA, Mosimann ALP, dos Santos GIV, dos Santos CND, Luz K. First report of autochthonous transmission of Zika virus in Brazil. *Memórias do Instituto Oswaldo Cruz*. 2015;**110**:569-572. DOI: 10.1590/0074-02760150192
- [32] Hamel R, Dejarnac O, Wichit S, Ekchariyawat P, Neyret A, Luplertlop N, Perera-Lecoin M, Surasombatpattana P, Talignani L, Thomas F, Cao-Lormeau V-M, Choumet V, Briant L, Desprès P, Amara A, Yssel H, Missé D. Biology of Zika virus infection in human skin cells. *Journal of Virology*. 2015;**89**:8880-8896. DOI: 10.1128/JVI.00354-15
- [33] Colt S, Garcia-Casal MN, Peña-Rosas JP, Finkelstein JL, Rayco-Solon P, Weise Prinzo ZC, Mehta S. Transmission of Zika virus through breast milk and other breastfeeding-related bodily-fluids: A systematic review. *PLoS Neglected Tropical Diseases*. 2017;**11**. DOI: 10.1371/journal.pntd.0005528
- [34] Oster AM, Brooks JT, Stryker JE, Kachur RE, Mead P, Pesik NT, Petersen LR. Interim guidelines for prevention of sexual transmission of Zika virus—United States, 2016. *MMWR. Morbidity and Mortality Weekly Report*. 2016;**65**:120-121. DOI: 10.15585/mmwr.mm6505e1
- [35] Musso D, Roche C, Robin E, Nhan T, Teissier A, Cao-Lormeau VM. Potential sexual transmission of Zika virus. *Emerging Infectious Diseases*. 2015;**21**:359-361. DOI: 10.3201/eid2102.141363

- [36] European Centre for Disease Prevention and Control. Zika virus disease epidemic: Potential association with microcephaly and Guillain–Barré syndrome. Rapid Risk Assessment. 2016. <http://ecdc.europa.eu/en/publications/Publications/zika-virus-rapid-risk-assessment-8-february-2016.pdf>
- [37] Barton MA, Salvadori MI. Zika virus and microcephaly. *CMAJ*. 2016;**188**:e118-e119. DOI: 10.1503/cmaj.160179
- [38] Rasmussen SA, Jamieson DJ, Honein MA, Petersen LR. Zika virus and birth defects—Reviewing the evidence for causality. *The New England Journal of Medicine*. 2016;**374**:1981-1987. DOI: 10.1056/NEJMs1604338
- [39] Mlakar J, Korva M, Tul N, Popović M, Poljšak-Prijatelj M, Mraz J, Kolenc M, Rus K, Vipotnik T, Vodusek V, Vizjak A, Pižem J, Petrovec M, Županc T. Zika virus associated with microcephaly. *The New England Journal of Medicine*. 2016;**374**:951-958. DOI: 10.1056/NEJMoa1600651
- [40] Michael PD, Johansson A, Mier-y-Teran-Romero L, Reefhuis J, Gilboa SM, Hills SL, Mlakar J, Korva M, Tul N, Popović M, Poljšak-Prijatelj M, Mraz J, Kolenc M, Resman Rus K, Vesnaver Vipotnik T, Fabjan Vodusek V, Vizjak A, Pižem J, Petrovec M, Avšič Županc T, Rasmussen SA, Jamieson DJ, Honein MA, Petersen LR. Zika virus associated with microcephaly. *New England Journal of Medicine*. 2016;**374**:1-3. DOI: 10.1056/NEJMs1604338
- [41] Cunha AJ, Magalhães-Barbosa MC, Lima-Setta F, Prata-Barbosa A. Evolution of cases of microcephaly and neurological abnormalities suggestive of congenital infection in Brazil: 2015-2016. *Bulletin of the World Health Organization*. 2016:1-15. DOI: 10.2471/BLT.16.173583
- [42] Tang BL. Zika virus as a causative agent for primary microencephaly: The evidence so far. *Archives of Microbiology*. 2016;**198**:595-601. DOI: 10.1007/s00203-016-1268-7
- [43] Garcez PP, Nascimento JM, de Vasconcelos JM, Madeiro da Costa R, Delvecchio R, Trindade P, Loiola EC, Higa LM, Cassoli JS, Vitória G, Sequeira PC, Sochacki J, Aguiar RS, Fuzii HT, de Filippis AMB, da Silva Gonçalves Vianez Júnior JL, Tanuri A, Martins-de-Souza D, Rehen SK. Zika virus disrupts molecular fingerprinting of human neurospheres. *Scientific Reports*. 2017;**7**:40780. DOI: 10.1038/srep40780
- [44] Paixão ES, Barreto F, Da Glória Teixeira M, Da Conceição M, Costa N, Rodrigues LC. History, epidemiology, and clinical manifestations of Zika: A systematic review. *American Journal of Public Health*. 2016;**106**:606-612. DOI: 10.2105/AJPH.2016.303112
- [45] Oliveira Melo AS, Malinger G, Ximenes R, Szejnfeld PO, Alves Sampaio S, Bispo De Filippis AM. Zika virus intrauterine infection causes fetal brain abnormality and microcephaly: Tip of the iceberg? *Ultrasound in Obstetrics & Gynecology*. 2016;**47**:6-7. DOI: 10.1002/uog.15831
- [46] Mlakar J, Korva M, Tul N, Popović M, Poljšak-Prijatelj M, Mraz J, Kolenc M, Resman Rus K, Vesnaver Vipotnik T, Fabjan Vodusek V, Vizjak A, Pižem J, Petrovec M, Avšič Županc T. Zika virus associated with microcephaly. *The New England Journal of Medicine*. 2016;**10**:951-958. DOI: 10.1056/NEJMoa1600651

- [47] Duffy MR, Chen T-H, Hancock WT, Powers AM, Kool JL, Lanciotti RS, Pretrick M, Marfel M, Holzbauer S, Dubray C, Guillaumot L, Griggs A, Bel M, Lambert AJ, Laven J, Kosoy O, Panella A, Biggerstaff BJ, Fischer M, Hayes EB. Zika virus outbreak on Yap Island, Federated States of Micronesia. *The New England Journal of Medicine*. 2009;**360**:2536-2543. DOI: 10.1056/NEJMoa0805715
- [48] Schuler-Faccini L, Sanseverino MTV, Vianna FSL, da Silva AA, Larrandaburu M, Pereira CM, Abeche AM. Zika virus: A new human teratogen? Implications for women reproductive age. *Clinical Pharmacology and Therapeutics*. 2016;**100**:28-30. DOI: 10.1002/cpt.386
- [49] Sarno M, Sacramento GA, Khouri R, do Rosário MS, Costa F, Archanjo G, Santos LA, Nery N, Vasilakis N, Ko AI, de Almeida ARP. Zika virus infection and stillbirths: A case of hydrops fetalis, hydranencephaly and fetal demise. *PLoS Neglected Tropical Diseases*. 2016;**10**. DOI: 10.1371/journal.pntd.0004517
- [50] Calvet G, Aguiar RS, Melo ASO, Sampaio SA, de Filippis I, Fabri A, Araujo ESM, de Sequeira PC, de Mendonça MCL, de Oliveira L, Tschoeke DA, Schrago CG, Thompson FL, Brasil P, dos Santos FB, Nogueira RMR, Tanuri A, de Filippis AMB. Detection and sequencing of Zika virus from amniotic fluid of fetuses with microcephaly in Brazil: A case study. *The Lancet Infectious Diseases*. 2016;**16**:653-660. DOI: 10.1016/S1473-3099(16)00095-5
- [51] Krauer F, Riesen M, Reveiz L, Oladapo OT, Martínez-Vega R, Porgo TV, Haeffliger A, Broutet NJ, Low N. Zika virus infection as a cause of congenital brain abnormalities and Guillain–Barré syndrome: Systematic review. *PLoS Medicine*. 2017;**14**. DOI: 10.1371/journal.pmed.1002203
- [52] Garcez PP, Loiola EC, Madeiro da Costa R, Higa LM, Trindade P, Delvecchio R, Nascimento JM, Brindeiro R, Tanuri A, Rehen SK. Zika virus impairs growth in human neurospheres and brain organoids. *Science*. 2016:aaf6116. DOI: 10.1126/science.aaf6116
- [53] Vermillion MS, Lei J, Shabi Y, Baxter VK, Crilly NP, McLane M, Griffin DE, Pekosz A, Klein SL, Burd I. Intrauterine Zika virus infection of pregnant immunocompetent mice models transplacental transmission and adverse perinatal outcomes. *Nature Communications*. 2017;**8**:14575. DOI: 10.1038/ncomms14575
- [54] Bullerdiek J, Dotzauer A, Bauer I. The mitotic spindle: Linking teratogenic effects of Zika virus with human genetics? *Molecular Cytogenetics*. 2016;**9**:32. DOI: 10.1186/s13039-016-0240-1
- [55] Cauchemez S, Besnard M, Bompard P, Dub T, Guillemette-Artur P, Eyrolle-Guignot D, Salje H, Van Kerkhove MD, Abadie V, Garel C, Fontanet A, Mallet HP. Association between Zika virus and microcephaly in French Polynesia, 2013-15: A retrospective study. *Lancet*. 2016;**387**:2125-2132. DOI: 10.1016/S0140-6736(16)00651-6
- [56] Panchaud A, Stojanov M, Ammerdorffer A, Vouga M, Baud D. Emerging role of Zika virus in adverse fetal and neonatal outcomes. *Clinical Microbiology Reviews*. 2016;**29**: 659-694. DOI: 10.1128/CMR.00014-16
- [57] Evans D, Nijhout F, Parens R, Morales AJ, Bar-Yam Y. A possible link between pyriproxyfen and microcephaly. *bioRxiv*. 2016:48538. DOI: 10.1101/048538

- [58] Dzieciolowska S, Larroque A-L, Kranjec E-A, Drapeau P, Samarut E. The larvicide pyriproxyfen blamed during the Zika virus outbreak does not cause microcephaly in zebrafish embryos. *Scientific Reports*. 2017;**7**:40067. DOI: 10.1038/srep40067
- [59] Cugola FR, Fernandes IR, Russo FB, Freitas BC, Dias JLM, Guimarães KP, Benazzato C, Almeida N, Pignatari GC, Romero S, Polonio CM, Cunha I, Freitas CL, Brandão WN, Rossato C, Andrade DG, Faria DDP, Garcez AT, Buchpigel CA, Braconi CT, Mendes E, Sall AA, Zanotto PM d A, Peron JPS, Muotri AR, Beltrão-Braga PCB. The Brazilian Zika virus strain causes birth defects in experimental models. *Nature*. 2016;**534**:267-271. DOI: 10.1038/nature18296
- [60] Onorati M, Li Z, Liu F, Horvath TL, Lindenbach BD, Sousa AMM, Nakagawa N, Li M, Dell'anno MT, Gulden FO, Pochareddy S, Tebbenkamp ATN, Han W, Pletikos M, Gao T, Zhu Y, Bichsel C, Varela L, Szigeti-Buck K, Lisgo S, Zhang Y, Testen A, Gao X-B, Mlakar J, Popovic M, Flamand M, Strittmatter SM, Kaczmarek LK, Anton ES, Sestan N. Zika virus disrupts Phospho-TBK1 localization and mitosis in human neuroepithelial stem cells and radial glia. *Cell Reports*. 2016;**16**:2576-2592. DOI: 10.1016/j.celrep.2016.08.038
- [61] Yuan L. A single mutation in the prM protein of Zika virus contributes to fetal microcephaly. *Science* (80-). 2017;**7120**:eaam7120. DOI: 10.1126/7120
- [62] Richard AS, Shim B-S, Kwon Y-C, Zhang R, Otsuka Y, Schmitt K, Berri F, Diamond MS, Choe H. AXL-dependent infection of human fetal endothelial cells distinguishes Zika virus from other pathogenic flaviviruses. *Proceedings of the National Academy of Sciences*. 2017;**114**:2024-2029. DOI: 10.1073/pnas.1620558114
- [63] Mansfield KL, Hernández-Triana LM, Banyard AC, Fooks AR, Johnson N. Japanese encephalitis virus infection, diagnosis and control in domestic animals. *Veterinary Microbiology*. 2017;**201**:85-92. DOI: 10.1016/j.vetmic.2017.01.014
- [64] Duong V, Choeung R, Gorman C, Laurent D, Crabol Y, Mey C, Peng B, Di Francesco J, Hul V, Sothy H, Santy K, Richner B, Pommier J-D, Sorn S, Chevalier V, Buchy P, de Lamballerie X, Cappelle J, Horwood PF, Dussart P. Isolation and full-genome sequences of Japanese encephalitis virus genotype I strains from Cambodian human patients, mosquitoes and pigs. *The Journal of General Virology*. 2017;**98**:2287-2296. DOI: 10.1099/jgv.0.000892
- [65] García-Nicolás O, Ricklin ME, Liniger M, Vielle NJ, Python S, Souque P, Charneau P, Summerfield A. A Japanese encephalitis virus vaccine inducing antibodies strongly enhancing in vitro infection is protective in pigs. *Virus*. 2017;**9**:124. DOI: 10.3390/v9050124
- [66] Roach T, Alcendor DJ. Zika virus infection of cellular components of the blood-retinal barriers: Implications for viral associated congenital ocular disease. *Journal of Neuroinflammation*. 2017;**14**:43. DOI: 10.1186/s12974-017-0824-7
- [67] Singh PK, Guest J-M, Kanwar M, Boss J, Gao N, Juzych MS, Abrams GW, Yu F-S, Kumar A. Zika virus infects cells lining the blood-retinal barrier and causes chorioretinal atrophy in mouse eyes. *JCI Insight*. 2017;**2**:e92340. DOI: 10.1172/jci.insight.92340

- [68] de Paula Freitas B, de Oliveira Dias JRJ, Prazeres J, Sacramento GAG, Ko AI, Maia MM, Belfort RJ. Ocular findings in infants with microcephaly associated with presumed Zika virus congenital. *JAMA Ophthalmology*. 2016;**134**:529-535. DOI: 10.1001/jamaophthalmol.2016.0267
- [69] Uraki R, Hwang J, Jurado KA, Householder S, Yockey LJ, Hastings AK, Homer RJ, Iwasaki A, Fikrig E. Zika virus causes testicular atrophy. *Science Advances*. 2017;**3**: e1602899. DOI: 10.1126/sciadv.1602899
- [70] Cunha MS, Esposito DLA, Rocco IM, Maeda AY, Vasami FGS, Nogueira JS, de Souza RP, Suzuki A, Addas-Carvalho M, Barjas-Castro MdL, Resende MR, Stucchi RSB, Boin Id FSF, Katz G, Angerami RN, da Fonseca BAL. First complete genome sequence of Zika virus (Flaviviridae, Flavivirus) from an autochthonous transmission in Brazil. *Genome Announcements*. 2016;**4**:2015-2016. DOI: 10.1128/genomeA.00032-16
- [71] Baronti C, Piorkowski G, Charrel RN, Boubis L, Leparç-Goffart I, de Lamballerie X. Complete coding sequence of zika virus from a French polynesia outbreak in 2013. *Genome Announcements*. 2014 pii: e00500-14;**2**. DOI: 10.1128/genomeA.00500-14
- [72] Haddow AD, Schuh AJ, Yasuda CY, Kasper MR, Heang V, Huy R, Guzman H, Tesh RB, Weaver SC. Genetic characterization of zika virus strains: Geographic expansion of the asian lineage. *PLoS Neglected Tropical Diseases*. 2012;**6**. DOI: 10.1371/journal.pntd.0001477
- [73] Sirohi D, Chen Z, Sun L, Klose T, Pierson TC, Rossmann MG, Kuhn RJ. The 3.8 Å resolution cryo-EM structure of Zika virus. *Science* (80-). 2016;**5316**:1-7. DOI: 10.1126/science.aaf5316
- [74] Badshah S, Naeem A, Mabkhot Y. The new high resolution crystal structure of NS2B-NS3 protease of Zika virus. *Virus*. 2017;**9**:7. DOI: 10.3390/v9010007
- [75] Song H, Qi J, Haywood J, Shi Y, Gao GF. Zika virus NS1 structure reveals diversity of electrostatic surfaces among flaviviruses. *Nature Structural & Molecular Biology*. 2016;**23**(5):456-458. DOI: 10.1038/nsmb.3213
- [76] Freire CCM, Iamarino A, Neto DFL, Sall AA, Marinho P, Zanotto A. Spread of the pandemic Zika virus lineage is associated with NS1 codon usage adaptation in humans. *bioRxiv*. 2015:1-8. DOI: 10.1101/032839
- [77] Tian H, Ji X, Yang X, Zhang Z, Lu Z, Yang K, Chen C, Zhao Q, Chi H, Mu Z, Xie W, Wang Z, Lou H, Yang H, Rao Z. Structural basis of Zika virus helicase in recognizing its substrates. *Protein & Cell*. 2016;**7**:562-570. DOI: 10.1007/s13238-016-0293-2
- [78] Jain R, Coloma J, Garcia-Sastre A, Aggarwal AK. Structure of the NS3 helicase from Zika virus. *Nature Structural & Molecular Biology*. 2016;**23**:752-754. DOI: 10.1038/nsmb.3258
- [79] Rossi SL, Tesh RB, Azar SR, Muruato AE, Hanley KA, Auguste AJ, Langsjoen RM, Paessler S, Vasilakis N, Weaver SC. Characterization of a novel murine model to study Zika virus. *American Journal of Tropical Medicine and Hygiene*. 2016;**94**:1362-1369. DOI: 10.4269/ajtmh.16-0111

- [80] Shan C, Xie X, Muruato AE, Rossi SL, Roundy CM, Azar SR, Yang Y, Tesh RB, Bourne N, Barrett AD, Vasilakis N, Weaver SC, Shi PY. An infectious cDNA clone of Zika virus to study viral virulence, mosquito transmission, and antiviral inhibitors. *Cell Host & Microbe*. 2016;**19**:891-900. DOI: 10.1016/j.chom.2016.05.004
- [81] Bogoch II, Brady OJ, Kraemer MUG, German M, Creatore MI, Kulkarni MA, Brownstein JS, Mearns SR, Hay SI, Groot E, Watts A, Khan K. Anticipating the international spread of Zika virus from Brazil. *Lancet*. 2016;**387**:335-336. DOI: 10.1016/S0140-6736(16)00080-5
- [82] Hayes EB. Zika virus outside Africa. *Emerging Infectious Diseases*. 2009;**15**:1347-1350. DOI: 10.3201/eid1509.090442
- [83] Attar N. ZIKA virus circulates in new regions. *Nature Reviews. Microbiology*. 2016;**14**:62. DOI: 10.1038/nrmicro.2015.28
- [84] Toi CS, Webb CE, Haniotis J, Clancy J, Doggett SL. Seasonal activity, vector relationships and genetic analysis of mosquito-borne Stratford virus. *PLoS One*. 2017;**12**. DOI: 10.1371/journal.pone.0173105
- [85] Shi Y, Gao GF. Structural biology of the Zika virus. *Trends in Biochemical Sciences*. 2017;**42**:443-456. DOI: 10.1016/j.tibs.2017.02.009
- [86] Leandro H, Dutra C, Rocha MN, Braga F, Dias S, Mansur SB, Caragata EP, Moreira LA. Wolbachia blocks currently circulating Zika virus isolates in Brazilian *Aedes aegypti* mosquitoes. *Cell Host & Microbe*. 2016;**19**:1-4. DOI: 10.1016/j.chom.2016.04.021
- [87] Ther JCB, Zhao Y. Challenges in searching for Zika therapeutics. *Journal of Chemical Biology & Therapeutics*. 2016;**2**:1-2. DOI: 10.4172/jcbt.1000e102
- [88] Staples JE, Dziuban EJ, Fischer M, Cragan JD, Rasmussen SA, Cannon MJ, Frey MT, Renquist CM, Lanciotti RS, Muñoz JL, Powers AM, Honein MA, Moore CA, Munoz JL, Powers AM, Honein MA, Moore CA. Interim guidelines for the evaluation and testing of infants with possible congenital Zika virus infection—United States, 2016. *MMWR. Morbidity and Mortality Weekly Report*. 2016;**65**:63-67. DOI: 10.15585/mmwr.mm6503e3
- [89] Petersen EE, Staples JE, Meaney-delman D, Fischer M, Ellington SR, Callaghan WM, Jamieson DJ. Interim guidelines for pregnant women during a Zika virus outbreak—United States, 2016. *MMWR. Morbidity and Mortality Weekly Report*. 2016;**65**:30-33. DOI: 10.15585/mmwr.mm6502e1
- [90] Cohen J. Infectious disease. The race for a Zika vaccine is on. *Science* (80-). 2016;**351**:543-544. DOI: 10.1126/science.351.6273.543
- [91] Check Hayden E. The race is on to develop Zika vaccine. *Nature*. 2016. DOI: 10.1038/nature.2016.19634
- [92] Shan C, Xie X, Barrett ADT, Garcia-Blanco MA, Tesh RB, Vasconcelos PFDC, Vasilakis N, Weaver SC, Shi PY. Zika virus: Diagnosis, therapeutics, and vaccine. *ACS Infectious Diseases*. 2016;**2**:170-172. DOI: 10.1021/acsinfecdis.6b00030

- [93] Dawes BE, Smalley CA, Tiner BL, Beasley DW, Milligan GN, Reece LM, Hombach J, Barrett AD. Research and development of Zika virus vaccines. *Npj Vaccines*. 2016;**1**:16007. DOI: 10.1038/npjvaccines.2016.7
- [94] Carneiro BM, Batista MN, Braga ACS, Nogueira ML, Rahal P. The green tea molecule EGCG inhibits Zika virus entry. *Virology*. 2016;**496**:215-218. DOI: 10.1016/j.virol.2016.06.012
- [95] Isaacs CE, Wen GY, Xu W, Jia JH, Rohan L, Corbo C, Di Maggio V, Jenkins EC, Hillier S. Epigallocatechin gallate inactivates clinical isolates of herpes simplex virus. *Antimicrobial Agents and Chemotherapy*. 2008;**52**:962-970. DOI: 10.1128/AAC.00825-07
- [96] Ciesek S, von Hahn T, Colpitts CC, Schang LM, Friesland M, Steinmann J, Manns MP, Ott M, Wedemeyer H, Meuleman P, Pietschmann T, Steinmann E. The green tea polyphenol, epigallocatechin-3-gallate, inhibits hepatitis C virus entry. *Hepatology*. 2011;**54**:1947-1955. DOI: 10.1002/hep.24610
- [97] De Oliveira A, Adams SD, Lee LH, Murray SR, Hsu SD, Hammond JR, Dickinson D, Chen P, Chu TC. Inhibition of herpes simplex virus type 1 with the modified green tea polyphenol palmitoyl-epigallocatechin gallate. *Food and Chemical Toxicology*. 2013;**52**:207-215. DOI: 10.1016/j.fct.2012.11.006
- [98] Dhiman RK. The green tea polyphenol, epigallocatechin-3-gallate (EGCG)-one step forward in antiviral therapy against hepatitis C virus. *Journal of Clinical and Experimental Hepatology*. 2011;**1**:159-160. DOI: 10.1016/S0973-6883(11)60232-6
- [99] Chen C, Qiu H, Gong J, Liu Q, Xiao H, Chen XW, Sun BL, Yang RG. (-)-Epigallocatechin-3-gallate inhibits the replication cycle of hepatitis C virus. *Archives of Virology*. 2012;**157**:1301-1312. DOI: 10.1007/s00705-012-1304-0
- [100] Larocca RA, Abbink P, Peron JPS, Zanutto PM, de A, Iampietro MJ, Badamchi-Zadeh A, Boyd M, Ng'ang'a D, Kirilova M, Nityanandam R, Mercado NB, Li Z, Moseley ET, Bricault CA, Borducchi EN, Giglio PB, Jetton D, Neubauer G, Nkolola JP, Maxfield LF, La Barrera RAD, Jarman RG, Eckels KH, Michael NL, Thomas SJ, Barouch DH. Vaccine protection against Zika virus from Brazil. *Nature*. 2016;**536**:474-478. DOI: 10.1038/nature18952
- [101] De Góes Cavalcanti LP, Tauil PL, Alencar CH, Oliveira W, Teixeira MM, Heukelbach J. Zika virus infection, associated microcephaly, and low yellow fever vaccination coverage in Brazil: Is there any causal link. *Journal of Infection in Developing Countries*. 2016;**10**:563-566. DOI: 10.3855/jidc.8575
- [102] Summers DJ, Acosta RW, Acosta AM. Zika virus in an American recreational Traveler. *Journal of Travel Medicine*. 2015;**22**:338-340. DOI: 10.1111/jtm.12208
- [103] Lazear HM, Govero J, Smith AM, Platt DJ, Fernandez E, Miner JJ, Correspondence MSD, Diamond MS. A mouse model of Zika virus pathogenesis. *Cell Host & Microbe*. 2016;**19**:1-11. DOI: 10.1016/j.chom.2016.03.010

- [104] Shah A, Kumar A. Zika virus infection and development of a murine model. *Neurotoxicity Research*. 2016;**30**:131-134. DOI: 10.1007/s12640-016-9635-3
- [105] Kim K, Shrestha S. Neuroteratogenic viruses and lessons for Zika virus models. *Trends in Microbiology*. 2016;**24**(8):622-636. DOI: 10.1016/j.tim.2016.06.002
- [106] Bardina SV, Bunduc P, Tripathi S, Duehr J, Frere JJ, Brown JA, Nachbagauer R, Foster GA, Krysztof D, Tortorella D, Stramer SL, García-Sastre A, Krammer F, Lim JK. Enhancement of Zika virus pathogenesis by preexisting ant flavivirus immunity. *Science* (80-). 2017;**356**:175-180. DOI: 10.1126/science.aal4365
- [107] Homan J, Malone RW, Darnell SJ, Bremel RD. Antibody mediated epitope mimicry in the pathogenesis of Zika virus related disease. *bioRxiv*. 2016:44834. DOI: 10.1101/044834
- [108] Zmurko J, Marques RE, Schols D, Verbeken E, Kaptein SJF, Neyts J. The viral polymerase inhibitor 7-Deaza-2'-C-methyladenosine is a potent inhibitor of in vitro Zika virus replication and delays disease progression in a robust mouse infection model. *PLoS Neglected Tropical Diseases*. 2016;**10**. DOI: 10.1371/journal.pntd.0004695
- [109] Eyer L, Nencka R, Huvarová I, Palus M, Joao Alves M, Gould EA, De Clercq E, Růžek D. Nucleoside inhibitors of Zika virus. *The Journal of Infectious Diseases*. 2016;**214**(5):707-711. DOI: 10.1093/infdis/jiw226
- [110] Qing J, Luo R, Wang Y, Nong J, Wu M, Shao Y, Tang R, Yu X, Yin Z, Sun Y. Resistance analysis and characterization of NITD008 as an adenosine analog inhibitor against hepatitis C virus. *Antiviral Research*. 2016;**126**:43-54. DOI: 10.1016/j.antiviral.2015.12.010
- [111] Yin Z, Chen Y-L, Schul W, Wang Q-Y, Gu F, Duraiswamy J, Kondreddi RR, Niyomrattanakit P, Lakshminarayana SB, Goh A, Xu HY, Liu W, Liu B, Lim JYH, Ng CY, Qing M, Lim CC, Yip A, Wang G, Chan WL, Tan HP, Lin K, Zhang B, Zou G, Bernard KA, Garrett C, Beltz K, Dong M, Weaver M, He H, Pichota A, Dartois V, Keller TH, Shi P-Y. An adenosine nucleoside inhibitor of dengue virus. *Proceedings of the National Academy of Sciences of the United States of America*. 2009;**106**:20435-20439. DOI: 10.1073/pnas.0907010106
- [112] Deng C-L, Yeo H, Ye H-Q, Liu S-Q, Shang B-D, Gong P, Alonso S, Shi P-Y, Zhang B. Inhibition of enterovirus 71 by adenosine analog NITD008. *Journal of Virology*. 2014;**88**:11915-11923. DOI: 10.1128/JVI.01207-14
- [113] Deng Y-Q, Zhang N-N, Li C-F, Tian M, Hao J-N, Xie X-P, Shi P-Y, Qin C-F. Adenosine analog NITD008 is a potent inhibitor of Zika virus. *Open Forum Infectious Diseases*. 2016;**3**. DOI: 10.1093/ofid/ofw175
- [114] Carrasco JPC, Coronado Parra T. Application of computational drug discovery techniques for designing new drugs against Zika virus, drug des. *Open Access*. 2016;**5**. DOI: 10.4172/2169-0138.1000e131
- [115] Ekins S, Mietchen D, Coffee M, Stratton TP, Freundlich JS, Freitas-Junior L, Muratov E, Siqueira-Neto J, Williams AJ, Andrade C. Open drug discovery for the Zika virus. *F1000Research*. 2016;**5**:150. DOI: 10.12688/f1000research.8013.1

- [116] Ekins S, Liebler J, Neves BJ, Lewis WG, Coffee M, Bienstock R, Southan C, Andrade CH. Illustrating and homology modeling the proteins of the Zika virus. *F1000Research*. 2016;5:275. DOI: 10.12688/f1000research.8213.1
- [117] Ramharack P, Soliman MES, Faye O, Freire CCM, Iamarino A, Faye O, de Oliveira JVC, Diallo M, Bhakat S, Karubiu W, Jayaprakash V, Soliman MES, Chen LH, Hamer DH, Campos GS, Bandeira AC, Sardi SI, Mahfuz M, Khan A, Al MH, Hasan M, Parvin A, Rahman N, Roa M, WHO, Musso D, Roche C, Robin E, Nhan T, Teissier A, Cao-Lormeau VM, Ekins S, Mietchen D, Coffee M, Stratton T, Freundlich J, Freitas-Junior L, Singh RK, Dhama K, Malik YS, Ramakrishnan MA, Karthik K, Tiwari R, Lissauer D, Smit E, Kilby MD, Pettersen EF, Goddard TD, Huang CC, Couch GS, Greenblatt DM, Meng EC, Panchaud A, Stojanov M, Ammerdorffer A, Vouga M, Chibueze EC, Tirado V, Olukunmi O, Mlakar J, Korva M, Tul N, Popović M, Poljšak-Prijatelj M, Mraz J, Turmel JM, Amgueguen P, Hubert B, Vandamme YM, Maquart M, Guillou-Guillemette HL, Art IL-G, Melo ASO, Malinger G, Ximenes R, Szejnfeld PO, Sampaio SA, De Filippis AMB, Plourde AR, Bloch EM, Calvet G, Aguiarv RS, Melo AS, Sampaio SA, de Filippis I, Fabri A, Petersen LR, Jamieson DJ, Powers AM, Honein MA, Waggoner JJ, Pinsky BA, Gourinat AC, Connor O, Calvez E, Goarant C, Dupont-Rouzeyrol M, Charrel RN, Leparc-Goffart I, Pas S, de Lamballerie X, Koopmans M, Reuskens C, Haddow AD, Schuh AJ, Yasuda CY, Kasper MR, Heang V, Huy R, Hayes EB, Dick GWA, Kitchen SF, Haddow AJ, Duffy MR, Chen T-H, Hancock WT, Powers AM, Kool JL, Lanciotti RS, Malone RW, Homan J, Callahan MV, Glasspool-Malone J, Damodaran L, Schneider ADB, Basarab M, Bowman C, Aarons EJ, Cropley I, Saiz J-C, Vázquez-Calvo Á, Blázquez AB, Merino-Ramos T, Escibano-Romero E, Martín-Acebes MA, Ekins S, Liebler J, Neves BJ, Lewis WG, Coffee M, Bienstock R, Hughes JP, Rees SS, Kalindjian SB, Philpott KL, Noble CG, Chen YL, Dong H, Gu F, Lim SP, Schul W, Perera R, Khaliq M, Kuhn RJ, Chappell KJ, Stoermer MJ, Fairlie DP, Young PR, Agnihotri S, Narula R, Joshi K, Rana S, Singh M, Tian H, Ji X, Yang X, Xie W, Yang K, Chen C, Song H, Qi J, Haywood J, Shi Y, Gao GF, Youn S, Ambrose RL, Mackenzie JM, Diamond MS, Beatty PR, Puerta-Guardo H, Killingbeck SS, Glasner DR, Hopkins K, Harris E, Stahla-Beek HJ, April DG, Saeedi BJ, Hannah AM, Keenan SM, Geiss BJ, Sirohi D, Chen Z, Sun L, Klose T, Pierson TC, Rossmann MG, Courageot M, Frenkiel M, Dos SD, Deubel V, Desprès P, Duarte C, Hamel R, Dejarnac O, Wichit S, Ekchariyawat P, Neyret A, Luplertlop N, Noppakunmongkolchai W, Poyomtip T, Jittawuttipoka T, Luplertlop N, Sakuntabhai A, Chimnaronk S, Hirsch AJ, Zhang R, Miner JJ, Gorman MJ, Rausch K, Ramage H, White JP, Mahfuz M, Ali K, Mahmud HA, Mahmudul H, Parvin A, Nazibur R, Badier SM, Kostyuchenko VA, Lim EXY, Zhang S, Fibriansah G, Ng T-S, Ooi JSG, Dai L, Song J, Lu X, Deng Y-Q, Musyoki AM, Cheng H, Barba-Spaeth G, Dejnirattisai W, Rouvinski A, Vaney M-C, Medits I, Sharma A, Weltman JK, Mandal S, Moudgil M, Mandal SK, Song CM, Lim SJ, Tong JC, Bamborough P, Cohen FE, Anderson AC, Huang HJ, Yu HW, Chen CY, Hsu CH, Chen HY, Lee KJ, Honarparvar B, Govender T, Maguire GEM, Soliman MES, Kruger HG, Hooft RW, Sander C, Vriend G, Chetty S, Soliman MES, Fathi SMS, Tuszyński JA, Lionta E, Spyrou G, Vassilatis DK, Cournia Z, Ramesh M, Vepuri SB, Oosthuizen F, Soliman ME, Reddy SS, Pati PP, Kumar PP,

- Pradeep H, Sastry NN, Sliwoski G, Kothiwale S, Meiler J, Lowe EW, Kumalo HM, Soliman ME, Delvecchio R, Higa LM, Pezzuto P, Valadao AL, Garcez PP, Monteiro FL, Dowall SD, Graham VA, Rayner E, Atkinson B, Hall G, Watson RJ, Larocca RA, Abbink P, Peron JPS, De PMAZ, Iampietro MJ, Badamchi-Zadeh A, Maharaj Y, Soliman MES, Hernandez M, Gherzi D, Sanchez R, Tambunan USF, Zahroh H, Utomo BB, Parikesit AA, Niyomrattanakit P, Chen YL, Dong H, Yin Z, Qing M, Glickman JF, Eyer L, Nencka R, Huvarova I, Palus M, Alves M, Gould EA, Moonsamy S, Bhakat S, Soliman MES, Liao C, Sitzmann M, Pugliese A, Nicklaus MC, Thompson JD, Gibson TJ, Higgins DG, Eswar N, Webb B, Marti-Renom MA, Madhusudhan MS, Eramian D, Shen MY, Somarowthu S, Yang H, Hildebrand DGC, Ondrechen MJ, Huang B, Irwin JJ, Shoichet BK, Koes DR, Camacho CJ, Trott O, Olson AJ, Case DA, Cheatham TE, Darden T, Gohlke H, Luo R, Merz KM. Zika virus drug targets: a missing link in drug design and discovery—A route map to fill the gap. *RSC Advances*. 2016;**6**:68719-68731. DOI: 10.1039/C6RA12142J
- [118] Chakraborty S. MEPPitope: Spatial, electrostatic and secondary structure perturbations in the post-fusion Dengue virus envelope protein highlights known epitopes and conserved residues in the Zika virus. *F1000Research*. 2016;**5**:1150. DOI: 10.12688/f1000research.8853.1
- [119] Li C, Deng YQ, Wang S, Ma F, Aliyari R, Huang XY, Zhang NN, Watanabe M, Dong HL, Liu P, Li XF, Ye Q, Tian M, Hong S, Fan J, Zhao H, Li L, Vishlaghi N, Buth JE, Au C, Liu Y, Lu N, Du P, Qin FFX, Zhang B, Gong D, Dai X, Sun R, Novitch BG, Xu Z, Qin CF, Cheng G. 25-hydroxycholesterol protects host against Zika virus infection and its associated microcephaly in a mouse model. *Immunity*. 2017;**46**:446-456. DOI: 10.1016/j.immuni.2017.02.012
- [120] Zhu Z, Gorman MJ, McKenzie LD, Chai JN, Hubert CG, Prager BC, Fernandez E, Richner JM, Zhang R, Shan C, Wang X, Shi P-Y, Diamond MS, Rich JN, Chheda MG. Zika virus has oncolytic activity against glioblastoma stem cells. *Journal of Experimental Medicine*. 2017. DOI: 10.1084/jem.20171093

IntechOpen