Zika virus (ZIKV) is a member of the genus Flavivirus from the Flaviviridae family, first isolated following blood analyses of a rhesus monkey in 1947, in a forest in Uganda, called Zika (Dick, 1952). ZIKV is classified as an arbovirus, because it is transmitted by the female Aedes aegypti mosquito bite. However, more recently, vertical (maternal to fetal) and sexual transmission have been described (Besnard, Lastère, Teissier, Cao-Lormeau, & Musso, 2014; D’Ortenzio et al., 2016; Musso & Gubler, 2016; Figure 1).

ZIKV has been associated with a mild, self-limiting illness characterized by fever, rash, joint pain, and conjunctivitis. However, there are some reports associating ZIKV infection with meningoencephalitis and other immune system-mediated manifestations, such as acute myelitis and Guillain-Barré syndrome (GBS; Cao-Lormeau et al., 2016; Musso & Gubler, 2016; Figure 1).

ZIKV has been associated with microcephaly in newborns. Intrauterine ZIKV infections have been associated with a spectrum of clinical findings, including skeletal disorders such as arthrogryposis and hip dislocation, craniofacial disproportion, ocular (retinal) derangements, hearing loss, and other neurological alterations such as convulsions and hypotonia, which characterize a new medical entity called the congenital Zika syndrome (CZS; Alvarado & Schwartz, 2017). Supporting these clinical findings, strong evidence correlating ZIKV infection with damage in the central nervous system (CNS), such as microcephaly, has been reported in mouse fetuses after viral vertical transmission (Cugola et al., 2016). Here, we review the effects of ZIKV infection and exposure in the CNS and its consequences, both in adults and in newborns.

1 | INTRODUCTION

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Summary
Starting with the outbreak in Brazil, Zika virus (ZIKV) infection has been correlated with severe syndromes such as congenital Zika syndrome and Guillain-Barré syndrome. Here, we review the status of Zika virus pathogenesis in the central nervous system (CNS). One of the main concerns about ZIKV exposure during pregnancy is abnormal brain development, which results in microcephaly in newborns. Recent advances in in vitro research show that ZIKV can infect and obliterate cells from the CNS, such as progenitors, neurons, and glial cells. Neural progenitor cells seem to be the main target of the virus, with infection leading to less cell migration, neurogenesis impairment, cell death and, consequently, microcephaly in newborns. The downsizing of the brain can be directly associated with defective development of the cortical layer. In addition, in vivo investigations in mice reveal that ZIKV can cross the placenta and migrate to fetuses, but with a significant neurotropism, which results in brain damage for the pups. Another finding shows that hydrocephaly is an additional consequence of ZIKV infection, being detected during embryonic and fetal development in mouse, as well as after birth in humans. In spite of the advances in ZIKV research in the last year, the mechanisms underlying ZIKV infection in the CNS require further investigation particularly as there are currently no treatments or vaccines against ZIKV infection.

KEYWORDS
brain damage, congenital Zika syndrome, flaviviruses, microcephaly, Zika, ZIKV

2 | MICROCEPHALY AND THE CZS

At the beginning of the ZIKV outbreak in Brazil, an increase in the number of newborns with microcephaly was observed. Actually, from mid-July 2015 to December 2016, about 2,000 cases of ZIKV infection and microcephaly in newborns in Brazil were confirmed. This increase in cases has raised serious concerns correlated to an increase in the number of newborns with microcephaly in Brazil.
Brazilian Ministry of Health. At the beginning of the outbreak, the correlation of microcephaly and ZIKV infection was done based on serology and epidemiological data. A causal relationship was later proved by means of carefully designed experimental models described below (Cugola et al., 2016).

The condition of microcephaly due to congenital ZIKV infection is a complex assembly of cephalic defects readily detected by clinical and image examinations. These include microcrany with prominence of occipital protuberance, redundant scalp, a small brain with nonsymmetric lobes bearing dilations of ventricular cavities, variable amount of calcifications, irregular in shape and location, simplification of brain gyrus pattern, malformation of corpus callosum, and enlargement of extra axial spaces (Hazin et al., 2016; Soares de Oliveira-Szejnfeld et al., 2016). The definition of microcephaly is key for the correct clinical identification of the condition; otherwise, misinterpretation can occur. The World Health Organization describes microcephaly as a reduction in the circumference of the head (cephalic perimeter) with the occipitofrontal measurement of a newborn with 37 weeks of gestation as equal or less than 31.9 cm for boys and 31.5 cm for girls.

Microcephaly results in serious neurological faults, such as cerebral palsy, seizures, and mental retardation (Ashwal et al., 2009). Although microcephaly due to ZIKV infection is better characterized after birth, it is possible to identify brain malformations by gestational ultrasound examination observing a small skull, small brain, ventricular malformation, cerebral atrophy with calcifications, and, in some cases, abnormal blood flow (Brasil et al., 2016; de Fatima et al., 2016; Rasmussen et al., 2016).

Although microcephaly is the most shocking consequence of ZIKV exposure during pregnancy, a spectrum of fetal malformations, associated with intrauterine infection, have been described, giving rise to the designation of CZS (Alvarado & Schwartz, 2017). CZS includes a series of neurological manifestations, like microcephaly, lissencephaly, hydrocephalus, polymicrogyria, agyria, ventriculomegaly, holoprosencephaly, and brain calcifications (Alvarado & Schwartz, 2017). Apart from the above neurological findings, CZS includes abnormalities in the development of musculoskeletal system (arthrogryposis, scoliosis, and hip dislocation), ocular (retinal disorders), craniofacial disproportion, genitourinary and pulmonary systems, and intrauterine growth
3 | EXPERIMENTAL FINDINGS THAT CLARIFIED ZIKV PATHOLOGY IN THE CNS

The use of in vitro and in vivo models has greatly advanced knowledge of the mechanisms and consequences of ZIKV pathology in the CNS. In vitro and in vivo systems have been used to address the link between ZIKV and microcephaly, as well as other neurological impairments.

Until 2015, ZIKV was not related to neurological symptoms or brain damage in humans.

However, in vitro systems have been successfully established to investigate this link using advances from the stem cell field such as induced pluripotent stem cells (PSC) and embryonic stem cell lineages (ESC; Yamanaka et al., 2007). PSC have been successfully differentiated into neuroprogenitors, neurons, glial cells, and into brain organoid structures. This platform has been very important for understanding ZIKV behavior in general and its effects, particularly in the brain. ZIKV was not associated with neurological symptoms or brain damage in humans until 2015 when a new circulating strain, called ZIKV BR, was identified. This strain was first investigated in vitro revealing itself as highly neurotropic, causing cellular death, especially in neuroprogenitor cells (NPC) and immature cortical neurons (Cugola et al., 2016). Both cell types allowed viral replication, which induced apoptosis and which was compatible with the missing brain tissue observed in the malformation of the cortex and in the microcephaly as a whole (Tang, Hammack, Ogden, & Jin, 2016). The Brazilian ZIKV strain looked more aggressive and seemed to affect neurogenesis much more than other strains reported previously (Brasil et al., 2016; Liang et al., 2016), particularly when compared with the original ZIKV strain, the MR766 (Cugola et al., 2016). Other strains, IbH30656, H/PF/2013, and FB-GWUH-2016, were also reported to cause infection and impair growth of human fetal neural stem cells (NSCs) in vitro, thereby affecting the neurogenesis. Furthermore, these strains were related to the depletion of progenitors in the cortical layer of brain organoids (Gabriel et al., 2017; Liang et al., 2016; Tsai, Chang, Lee, & Kao, 2009). The strain isolated from Porto Rico (ZIKV-PRVABC59) was able to infect primary human fetal NPC, showing replication up to 28 days, but with a limited cytopathic effect (Hanners et al., 2016).

As ZIKV can infect several cell types, it is essential to identify cellular receptors used for viral attachment. Because the virus is transmitted by a mosquito bite, epithelial cells are probably the first targets for viral infection and were used to investigate ZIKV target receptors (Hamel et al., 2015). The TAM receptors (Tyro3, AXL, and Mer), T cell immunoglobulin and mucin domain receptors, phosphatidylinositol, C-type lectin receptors, and DC-SIGN receptors have already been reported to serve as flavivirus entry pathways (Hamel et al., 2015; Perera-Lecoin, Meertens, Carnec, & Amara, 2013). The TAM receptors are a family of tyrosine kinase receptors whose roles are essential for homeostatic regulation of immune responses (Lemke, 2013). TAM receptors also act to maintain neurogenesis in the adult brain (Johnson & Ji, 2015) and support NSC survival, proliferation, and differentiation (Ji et al., 2014). Despite the fact that TAM receptors are not essential for embryonic brain development, they are present in cortical neuronal progenitor cells during embryogenesis (Wang et al., 2011), as well as in NPCs derived from PSC (Cugola et al., 2016). AXL is considered a candidate for ZIKV entry, also being the TAM receptor most expressed in NPCs (Cugola et al., 2016; Hamel et al., 2015; Nowakowski et al., 2016). However, because ZIKV was able to infect cells in epithidymis and testis in Axl^+/− transgenic mice, AXL is clearly not the only receptor used for ZIKV infection, suggesting that other molecules could also be involved in this process (Govero et al., 2016).

After infection, some cells will undergo apoptosis. p53 is a key protein in the apoptotic pathway, and in ZIKV-infected NPCs, p53 protein levels were increased as well as the amount of phosphorylated p53, which is compatible with genotoxic stress and apoptosis induction (Ghouzzi et al., 2017). In ZIKV-infected neuroepithelial cells and neural cortical stem cells, phosphorylated TANK-binding kinase-1 (pT8K1), a protein that participates in cell cycle and in the antiviral innate immune response, was reallocated from centrosomes to the mitochondria, thereby altering the cell cycle and consequently inducing cell death (Onorati et al., 2016). Interestingly, cranial neuro crest cells also present a degree of apoptosis after ZIKV infection. These cells release cytokines as a response to viral damage, promoting cell death and aberrant neurogenesis by NPCs (Bayless, Greenberg, Swigut, Wysocka, & Blash, 2016), the process responsible for populating the brain with neurons (Götz & Huttner, 2005). One of the key pathways in neurogenesis is the PI3K-Akt-mTOR axis that induces cellular differentiation, migration, and maturation (Lee, 2015; Wahane et al., 2014). After exposure to the two nonstructural ZIKV proteins, NS4A and NS4B, the PI3K-Akt-mTOR pathway was strongly suppressed, leading to upregulation of the autophagy and impairment of neurogenesis in fetal NSC (Liang et al., 2016).

Three-dimensional in vitro CNS models (brain organoids) have also proved advantageous to study the mechanisms involved in ZIKV pathogenesis (Cugola et al., 2016; Lancaster & Knoblich, 2014; Marton & Pasca, 2016). Such studies have revealed that the MR766 ZIKV strain caused a decrease in overall size of the organoid (Dang et al., 2016) whereas another study using the Brazilian ZIKV strain led to more pronounced reduction of the cortical layer compared to MR766. This reduction correlated with cell death of the immature cortical neurons (Cugola et al., 2016), which was also observed using the ZIKV Asian strain (Qian et al., 2016).

When the outbreak began, the correlation between ZIKV infection and newborns with microcephaly was based on epidemiological and serological findings, focusing on mothers infected with ZIKV during pregnancy and their newborns presenting microcephaly (Brasil et al., 2016). Later, the demonstration of viral particles found inside the brain of a fetus infected vertically made the case stronger (Mlakar et al., 2016). Later, the demonstration of viral particles found inside the brain of a fetus infected vertically made the case stronger (Mlakar et al., 2016). However, the firm evidence came when the offspring of SJL mice, which were infected by the Brazilian ZIKV strain during pregnancy, showed symptoms of CZS. This was key proof that the virus was able to pass through placental tissue and reach the fetus. The brains of the pups presented viral RNA; a reduction of the cortical layer, had fewer brain cells, and exhibited viral cytopathic effects
During the ZIKV outbreak in French Polynesia, 42 patients with ZIKV disease were found to have the GBS, which represented a marked increase given that only five cases annually were detected during the previous 4 years (dos Santos et al., 2016). GBS is a post infectious, immune-mediated disorder characterized by transient bilateral flaccid limb weakness and dysautonomic manifestations attributable to peripheral nerve damage (Hughes & Cornblath, 2005). This condition was recently associated with ZIKV infection also in the Americas, especially, the acute inflammatory demyelinating polyneuropathy form of this syndrome (Parra et al., 2016). In Colombia and Puerto Rico, around 60% of symptomatic GBS patients were serologically positive for ZIKV (Dirlikov et al., 2016).

### 4 | Therapeutic Strategies and Prevention Against ZIKV Infection

There are currently no prescribed drugs to prevent or treat the neurological damage caused by ZIKV exposure. Scientists around the world have been focusing on FDA-approved drugs in order to find an effective treatment as fast as possible (Bullard-Feibelman et al., 2017; Onorati et al., 2016; Retallack et al., 2016; Xu et al., 2016). Recently, 774 approved drugs were tested, and some drugs such as daptomycin, sertraline-HCl, ivermectin, bortezomib, cyclosporin A, mycophenolic acid, and pyrimethamine showed pharmacological potential for reducing flavivirus infection (Barrows et al., 2016). Currently, in terms of preventing ZIKV infection, there is no available vaccine. However, the Brazilian government and National Institutes of Health have plans to produce an effective vaccine in the next few years (Chang, Ortiz, Ansari, & Gershwin, 2016).

### 5 | Final Remarks

The number of newborns with microcephaly has emerged as a public health problem, mainly in Brazil, due to the high number of cases. Despite ZIKV infection causing a congenital syndrome, microcephaly was the symptom that received most attention. Given the still early clinical follow-up of children infected with the virus and ones born with CZS, we still do not know what will happen as far as these children develop further. Some are now manifesting progressive signs of neurological damage, such as gradual blindness, hydrocephaly, muscular weakness, and acquired microcephaly (for ones born with normal head circumference). Considering the consequences of ZIKV exposure to the CNS, we hypothesize that these children will grow presenting varying degrees of cognitive and mental impairment. Given the substantial impact of ZIKV infection, there is an urgent need to develop therapies to treat infection and prevent CNS damage as well as design strategies to prevent transmission. As Brazil is a tropical country that is propitious for mosquito proliferation, an urgent strategy should be the development of a vaccine to prevent ZIKV infection. Nevertheless, despite tremendous advances in ZIKV research over the last year, the underlying mechanisms of ZIKV infection still need to be further investigated to provide the basis for the development of such preventative and therapeutic strategies.
CONFLICT OF INTEREST

Authors have no conflict of interest to declare.

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