Could new antibodies be key to treating Chikungunya?

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**KEYWORDS:** Chikungunya • monoclonal antibody • neutralization

Chikungunya virus (CHIKV) is an alphavirus transmitted to humans by mosquitoes. Initially isolated in Tanzania in 1952 [1], CHIKV has caused numerous recurrent outbreaks in Africa and Asia during the past 60 years. In 2005–2006, due to its sudden adaptation to replicate in a new mosquito vector, an unprecedented large CHIKV epidemic spread from the Indian Ocean islands to India and Southeast Asia [2]. In addition, outbreaks with local transmission have been recorded in Italy in 2007 [3] and in Southern France in 2010. Since the habitat of the CHIKV mosquito vector is widening to nontropical areas, the virus and its disease may continue to expand to previously unaffected temperate regions in the future [4].

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Most human infections by CHIKV are associated with clinical symptoms, such as high fever, headaches, rash, myalgia and arthralgia [5]. Even though the disease is often self-limiting, joint pain can persist for several weeks or months with up to 64% of patients reporting arthralgia 1 year post-infection [2,6]. Moreover, numerous cases of active and destructive CHIKV-associated rheumatoid arthritis have been reported [7-9]. Advanced age, prior joint pain and underlying osteoarthritis comorbidity were identified as risk factors for long-term rheumatic manifestations [10]. Vertical transmission has also been reported: when mothers are infected shortly before delivery, neonates are at high risk of developing CHIKV-associated encephalopathic complications, leading to disabilities or death [11].

As of 2011, there are no available vaccines or specific therapies against Chikungunya. Symptomatic treatments, such as paracetamol, are currently the only way to relieve patients suffering from CHIKV-associated symptoms.

In this context and with the purpose of developing a CHIKV-specific treatment, we recently isolated and characterized two unmodified human monoclonal antibodies (mAbs) from immortalized B cells derived from an individual previously infected with CHIKV who had fully recovered from the infection [12]. These two mAbs are capable, in vitro, of efficiently and specifically neutralizing the three identified CHIKV groups: West African, Central/East African and Asian. The potency of these antibodies still remains to be investigated in vivo before committing to further development. Notably, the antibodies should be tested in CHIKV-susceptible animal models, such as immunocompromised mice [13] or nonhuman primates [14].

Assuming they are effective in vivo, could these human mAbs be used as prophylactic tools? Although the typical means to prevent infection is by active vaccination, it is still unclear whether the current efforts for vaccine development against CHIKV will be successful. In addition, vaccine coverage is rarely universal and never instantaneously protective, and unvaccinated population niches may require immediate protection under the form of passive immunization. There is a precedent for the use of antibodies for prophylaxis of infectious diseases in palivizumab, a humanized antibody indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in pediatric patients [15]. Palivizumab-based prophylactic treatment of neonates reduces the number of hospital admissions for RSV-associated clinical complications by up to 55% [16]. Of note, the two
anti-CHIKV mAbs that we recently described have an IC_{50} of less than 100 ng/ml (i.e. a potency higher than that of palivizumab, which has an IC_{50} of 2 µg/ml when analyzed in similar assays) [15]. This comparison suggests that protective concentrations of CHIKV-neutralizing mAbs should be reachable in humans by administering standard antibody doses, namely 2–15 mg/kg.

However, even if these antibodies were shown to have favorable pharmacodynamics in vivo, their use may be hindered by socioeconomical and epidemiological constraints. The main issue for the implementation of the anti-CHIKV antibodies as preventive tools is the cost of antibody therapy, which is still extremely elevated. For instance, palivizumab is administered monthly during RSV peak season and a dose costs approximately US$1000; questions have been raised about the cost:benefit ratio of this treatment, which is in actual fact restricted to developed countries [16]. In the case of Chikungunya, the vast majority of infections still occur in tropical areas where such costs are often not affordable. Two situations may increase the demand of anti-CHIKV antibodies for disease prevention: the development of more efficient manufacturing processes leading to a drastic drop in antibody production costs; and the spread of CHIKV into temperate areas, which will widen the pool of potentially affected individuals who can afford this treatment.

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Currently, the elevated cost of antibody manufacturing restricts the treatment to a limited subpopulation at risk of severe disease. Elderly people, pregnant women, neonates and people with a history of joint problems, having already been identified as being at high risk of developing CHIKV-related severe clinical complications, might benefit from this preventive intervention. Between 2005 and 2009, at least 1.8 million Chikungunya cases have been reported [17]. During such large epidemics, even a small proportion of atypical and severe cases (estimated at 0.3% during the epidemic in La Reunion, France) will constitute a sizable population of high-risk individuals. In addition, the identification of new biomarkers enabling the prediction of severe CHIKV-related clinical complications may help in selecting individuals who should receive CHIKV-specific prophylaxis [18].

An alternative scenario to the use of antibodies for Chikungunya prophylaxis is their administration after a positive diagnosis of CHIKV infection (i.e., in a treatment setting). The viremia associated with acute CHIKV infection is high (up to 10^8 viral particles per ml of blood) but lasts only a few days [5]; circulating virus is likely to be undetectable at the time of antibody administration (i.e., after symptoms appear and diagnosis is made). General application of a costly antibody therapy in patients who for the most part will already be recovering from acute infection seems unlikely to bring any considerable benefit. However, this does not rule out all treatment applications for these antibodies. Indeed, despite the short post-infection viremia, long-lasting CHIKV-specific IgM have been detected [19,20]. This long-term immune response, also demonstrated for other alphaviruses, seems to correlate with chronic arthralgia/arthritis and might be due to persisting viral antigens [21]. The long-term CHIKV persistence, which has been recently described in a nonhuman primate animal model [14], suggests that chronic CHIKV-related symptoms may indeed correlate with viral persistence. Interestingly, the anti-CHIKV antibodies we discovered are also able to inhibit extracellular viral spreading from infected to uninfected cells [12]. If this phenomenon of viral persistence is confirmed in patients suffering from long-term CHIKV-related symptoms, and provided that the persistent virus is accessible to antibodies, antibody treatment of these patients may prove helpful.

In conclusion, we are still far from having a ready solution to the disabilities, social and economic problems caused by the spread of CHIKV. However, the discovery of these antibodies is perhaps part of the initial steps in the attempt to tackle some of these issues. Effective solutions to address CHIKV epidemics will need to be supported by further clinical understanding, technological improvements, and basic investigations on the pathogenesis of disease.

Financial & competing interests disclosure
I Warter and A Nardin are inventors in a pending patent on anti-Chikungunya antibodies. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.
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Bibliography


18 Ng LF, Chow A, Sun YJ et al.: IL-1β, IL-6, and RANTES as biomarkers of Chikungunya severity. PLoS One 4, E4261 (2009).

