**PRESS RELEASE**

# IITMandi team findsthetarget protein for action of antimalarial drug against Zika Virus

## Hydroxychloroquine found to inhibitthe activity of an important enzyme of Zika virus

**MANDI,28thJanuary 2019**: Indian Institute of TechnologyMandi Researchers are making rapid strides in finding a drug to treat the Zika virus (ZIKV) that has affected more than a million people across the world. A led by Dr. Rajanish Giri, Assistant Professor of Biotechnology, IIT Mandi, is working on this subject.

Following an earlier finding by Prof. Indira Mysorekar from Washington University at St. Louis, USA, that hydroxychloroquine (HCQ), a drug commonly prescribed for treatingmalaria, reduces ZIKV transmission from mother to foetus, Prof. Giri's lab has identified the target viral protein on which HCQ acts. Prof. Giri has collaborated with Prof. Mysorekar and Prof. Sanjeev Kumar Singh from Alagappa University, Tamil Nadu, on this work and their findings have recently been published in ACS Omega, an Open Access journal of the American Chemical Society.

The Zika virus is a mosquito-borne emerging global pathogen belonging to the *flavivirus* genus. Other members of this genus includedengue virus, yellow fever virus, and Japanese Encephalitis virus.ZIKV infection leads to fever, headaches, lethargy, conjunctivitis-like symptoms and may even be associated with neurological diseases such as Guillain-Barré syndrome. More seriously, ZIKV infection is associated with devastating foetal diseases such as microcephaly. Earlier in July 2017, Prof. Mysorekar's group showed that HCQ inhibitsviral-induced autophagy and thereby reduces viral transmission to the foetus.

"While Prof. Mysorekar's grouporiginally selected HCQ for its ability to inhibit autophagy, its mechanism of action against ZIKV target proteinwas not known", explains Prof. Giri, adding, "Our work has identified a viral protein on which HCQ acts".This finding is important as development of drugs againstZIKV hinges on understanding the interactions between the potential drug and the targetcomponents of the virus.

Viral proteases are enzyme inviruses and are good targets for drug action. "To block Zika virus activity we targeted an important enzyme called protease. This enzyme governs the polyprotein maturation, leading to survival and pathogenesis of the virus" says Prof. Giri. In the case of the Zika virus, the*NS2B-NS3 protease*is important forviral multiplication in the host.

In order to find molecules that can inhibit the action ofNS2B-NS3 protease, Prof. Giri's teamfirst performed high throughput virtual screening of an FDA-approved drug

library and identified five compoundsthat showed promising affinity towards Zika virus protease. One of the five compounds was HCQ.

"Repurposing approved drugs can be an efficient method to identify drug compounds, which may be capable of activating or inhibiting new targets", the researchers mention in their ACS Omega research article. They add that such an approach can reduce development time and cost and improve safety. The top five compounds identified through screening were subjected to molecular dynamics simulation. "Various amino acid residues are involved in stabilizing drug molecules at the active site of the NS2B-NS3 protease of Zika virus", the researchers write.

Prof. Giri then choseHCQ from the five drug molecules for further analysis, based on the computational drug discovery work and validation by molecular dynamics simulations.

The research team designed and cloned the protease gene construct of the Zika virus and expressed and purifiedits NS2B-NS3 protease enzyme. HCQ inhibited the enzyme activity, showing that HCQ is a promising drug for ZIKV infection.

In the next step, the research team treated trophoblast cells infected with ZIKV with HCQ and noticed that there was significant reduction of viral burden.*In vitro*enzyme inhibition and computational simulation studiesshowed thatthe HCQ bonded with the NS2B-NS3 protease complex, thus competitively inhibiting its ability to contribute toviral multiplication.

Understanding the interactions between molecules such as HCQ and important viral enzymes such as proteases is an important step in the development of drugs that can attack the virus and prevent it from multiplying in the host cells. Drawing inspiration from earlier studies in this area, Prof. Giri and his team have identified potential candidates within existing banks of drugs thatstop the growth/spread of the Zika virus within the host. In future, this discovery may hasten implementationof effective therapies against ZIKV infections.

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**About IIT Mandi (http://www.iitmandi.ac.in/)**
Nestled in Sivalik Range of the Himalayas, IIT Mandi is fast emerging as a leader in science and technology education, knowledge creation and innovation, in an India marching towards a just, inclusive and sustainable society. Since the first batch of students took place in July 2009, IIT Mandi has grown to host 1,276 students including 274 PhD, 46 MS and 17 I-Ph.D. research scholars, 104 Faculty, 150 staff, and attracted funding to the tune of over Rs.70 crore for Research Projects. A growing body of alumni, nearly 850 in number, will become the champions of this institute as they assume leadership positions in industry, academia and administration.

From 1,280 students in 2018, the Institute aims to grow to 5,000 B.Tech, M.Tech/M.Sc. and M.S./Ph.D. by 2029. Currently, the campus has completed about 80,000 sq.m. of construction.

Another 1,50,000 sq.m. is currently under construction. IIT Mandi has a fully residential campus with all students and 95 percent of the faculty residing within it.

Since 2010, IIT Mandi's faculty has bagged nearly 180 projects worth more than Rs. 85 Crore. IIT Mandi, in just 9 years of its existence, has been able to develop several labs and facilities on its campus here at Kamand, creating an extraordinary research ambiance. The Advanced Materials Research Centre (AMRC), created with an investment of about Rs. 50 crore, houses advanced instruments for the characterization of materials with scope for drug delivery, electrical, electronics and biological applications. Since its inception in 2013, the AMRC has contributed to more than 200 research publications.

The institute has an Interdisciplinary Academic Culture which is Design-oriented. The B.Tech. curriculum focuses on Real-World team projects from the Year One to Four A strong humanities component as well makes the IIT Mandi curriculum even more relevant to the society at large. There are many active MoUs with TU9 in Germany since May 2011.

Launched in 2016, IIT Mandi's very own technology-business incubator Catalyst is the first Technology Business Incubator (TBI) in Himachal Pradesh. It aims to incubate technology-based startups focused on economic and/or social impacts. EWOK (Enabling Women of Kamand Valley) is another very innovative program being run by IIT Mandi which focuses on Skills training village-scale businesses by village women using Internet and pervasive mobile network and Serving local and global customers.

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