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Editorial Open Access

Application of Computational Drug Discovery Techniques for Designing New Drugs against Zika Virus

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Editorial

The Zika virus (ZIKV) has been an uncommon zoonotic virus since it was discovered in Uganda in 1947. It has been associated to a large impact into the equatorial region of Africa by infecting primates while causing sporadic mild infections in humans [1]. Nonetheless, over the last few years, a combination of factors such as increased populations of Aedes mosquito vectors, changes in codon usage and immune enhancement associated to previous flavovirus epidemics, e.g., Dengue [2], has led to an explosive propagation of ZIKV to Southeast Asia (2013-14) and South-Central America (2015).

Even though ZIKV generally causes a mild or asymptomatic disease, pandemic infections in these areas yield to a 20-fold increase in the number of cases of microcephaly in newborns as well as to concomitant epidemics of Guillian-Barré Syndrome and other neurologic conditions. As a consequence, a public health emergency of international concern was declared by the World Health Organization (WHO) in February 2016.

However, a direct causal relationship remains to be experimentally established. Recent reports of mother-fetus and sexual transmission together with the possibility that ZIKV adapts to be transmitted by more widely-spread and efficient vectors, are further causes for concern.

The current rate of spread ZIKV has drawn increasing attention from worldwide scientific community for developing candidate vaccines by investigating murine models and viral pathogenesis [3-5]. In spite of such efforts, there is neither a vaccine nor a specific antiviral therapy for the prevention or treatment of infections by ZIKV, though recent studies have demonstrated antiviral activity when 2′-C-methylated nucleosides were tested [6]. The viral polymerase inhibitor 7-deaza-2′-C-methyladenosine (7DMA) has been identified as a potent ZIKV inhibitor in a ZIKV infection model in mice [5].

These in vitro cellular assays could allow to screen for and validate novel inhibitors of ZIKV replication. The final solution will clearly require a joint work in an interdisciplinary environment. In that framework, we are positive that computational chemistry field would be able to significantly contribute into both identifying molecular targets and designing drugs with improved properties. This Editorial briefly touches the main techniques that might be applied to help to resolve this healthcare crisis.

Advanced computational drug screening (the so called Virtual Screening techniques, or VS) such as docking techniques will play an important role in the discovery of novel bioactive compounds in the context of ZIKV. The available crystal structures from parts of the virus and new homology models might be already used as an early state of a computational protocol. More advanced docking techniques, including Blind Docking simulations could be subsequently applied to process large databases of compound libraries [7-11]. Ligand-based virtual screening (LBVS) methods might be also helpful in the search of new drugs against ZIKV since their performance does not depend directly on the availability of crystallographic structures of the protein targets. Indeed, recent studies have also applied LBVS to find potential inhibitors against viruses [12].

The above-mentioned techniques have been shown to provide first valuable description of a wide panel of problems of biological interest, with a largely favourable quality/computational cost rate. However, as any simulation protocol, such approaches have an inherent limitation: their resolution is not accurate enough to delineate the main drug-target chemical contacts during the binding process. More refined techniques that account for the electronic description of the biological processes, e.g., molecular dynamics (MD) and quantum mechanical (QM) calculations, could be used to further refine the structures while simultaneously leading to more precise interaction energies.

However, we would like to point out the possibility of using alternative approaches others than molecular modeling based methods. For instance, advanced machine learning methods (i.e. deep learning) are suitable techniques to capture complex statistical patterns between thousands of descriptors extracted from drug compounds. As recently demonstrated by Ma and co-workers [13], deep neural networks (DNN) can routinely make better prospective predictions than other standard machine learning methods on Kaggle competition data sets. In addition, Hughes et al. [14] built a deep machine learning network in order to identify the site of epoxidation and to separate epoxidized and non-epoxidized molecules, just to name two relevant examples.

In view of the different and interesting approaches that are ready for discovering novel compounds in the context of the Zika virus, we foresee that nanomolar inhibitors could be discovered in coming few years. This knowledge will open up the expansion towards enhanced therapeutic approaches in the eradication of the ZIKV. It is worth ending this Editorial by highlighting a very recent contribution by Ekins and co-workers [15].

As stated by these authors, no crystal structures of ZIKV targets have been deposited in public databases such as PDB, ChEMBL and PubChem, which is certainly a major handicap to the application of computational techniques.

However, homology models for 15 proteins involved in ZIKV disease are freely accessible since March 2016, including NS5, FtsJ, NS4B, NS4A, HELICc, DEXDc, peptidase S7, NS2B, NS2A, NS1, E stem, glycoprotein M, propeptide, capsid and glycoprotein E [16]. Ekins and co-workers propose to use such models as starting point for a open drug discovery effort.

We fully agree with this collaborative strategy, which will require the use of High Performance Computing architectures such as Supercomputers and GPUs [17-19] aiming at combining some, or even all of the discussed techniques herein (LBVS, Docking, MD, QM) with the final goal of beating ZIKV together.

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