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Ebola Outbreak Highlights the Need for Wet and Dry Laboratory Collaboration

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The recent Ebola outbreak in Western Africa taught us that Ebolaviruses can cause much larger outbreaks and represent a much greater health threat than many of us believed (or wanted to believe). As of 30th March, the outbreak had resulted in 28,646 confirmed cases and 11,323 deaths. Although the WHO stated that the Ebola epidemic in West Africa no longer represents a Public Health Emergency of International Concern, since Guinea, Liberia, and Sierra are now capable of controlling and maintaining further small outbreaks, flare-ups still occur, most recently, on 4th April when two new cases were reported in Liberia (www.who.int).

Our understanding of the Ebolavirus biology remains limited. A major reason for this is that Ebolaviruses are safety level 4 pathogens and that there is only a very limited number of appropriate containment level laboratories. Computational studies were suggested as a strategy to increase research on Ebolaviruses and to complement wet laboratory, clinical, and epidemiological studies. The International Society of Computational Biology (ISCB) acknowledged this and launched an award for computational biology studies on Ebola [1].

The performance of meaningful computational research depends on the availability of sufficient data for analysis. Indeed, the analysis of isolates from the current Ebola outbreak in West Africa resulted in a steep increase in sequencing data [2-8] that enable computational investigation.

A number of computational studies have already made use of these data in order to gain novel insights into the Ebolavirus biology. Two studies used similar bioinformatics approaches to identify potential microRNAs [9,10]. Further, two studies determined specific signatures as potential vaccine, diagnostic, or therapeutic targets [11,12]. Wet laboratory experiments will now be needed to validate these computational predictions.

The need for a close interaction between computational and wet laboratories is particularly emphasised by two recent studies that investigated the differencesin human pathogenicity between the *Ebolavirus* species. The two studies used similar approaches but came to different results [13,14]. Both studies compared the genomes of the four human pathogenic *Ebolavirus* species *Zaire ebolavirus* (type virus: Ebola virus), *Sudan ebolavirus* (type virus: Sudan virus), *Bundibugyo ebolavirus* (type virus: Bundibugyo virus), and *Tai Forest ebolavirus* (type virus: Tai Forest virus) to the available genomes of the Reston virus (species *Reston ebolavirus*) [13,14] that causes disease in primates but not in humans [15].

In order to identify variations that may cause the differences in human pathogenicity, Cong et al. [13] identified positions in Ebolavirus proteins that are differently conserved between human-pathogenic Ebolaviruses and Reston viruses. They could map 43 out of 215 differentially conserved positions onto structures or models of Ebolavirus proteins. This information was combined with ananalysis of the variations between human and primate host cell proteins that are known to interact with Ebolavirus proteins. The authors found differences in the Ebolavirus VP24 protein that may affect the interaction of VP24 and KPNA5 and in turn the VP24-mediated inhibition of STAT1 activation and interferon signalling. However, they concluded that differences in VP24, VP30, and VP40 are unlikely to be responsible for the differences in human pathogenicity because the host proteins that interact with these virus proteins are very similar. The host interaction partners of GP and VP35 displayed greater variability, and Cong et al. [13] thus, suggested that a cluster of differentially conserved residues in the C terminal region of GP and a cluster of changes in VP35 may cause the differences in human pathogenicity between the *Ebolavirus* species.

In the second study, we identified specificity determining positions (SDPs) [16] to identify positions that are differentially conserved between the sequences of human pathogenic Ebolaviruses and Reston viruses [14]. 47 out of 189 SDPs could be modelled onto protein structuresor models (generated using Phyre2 [17,18]) resulting in eight SDPs that potentially modify protein stability (2) or protein-protein interactions (6) [14]. Four of these SDPs occurred in VP24 with three of them being locatedin the VP24-KPNA5 binding site. A comparison of the three SDPs in the VP24-KPNA5 binding site with Ebola virus VP24 residues that when mutated are known to decrease VP24 binding to KPNA5 and in turn to impair the capacity of Ebola virus VP24 to inhibit interferon signalling, suggestedthat Reston virus VP24 is less effective in antagonising the interferon response in human cells than Ebola virus VP24. If this interpretation is correct, few mutations in VP24 may result in a human pathogenic Reston virus. Hence, our predictions differ substantially from those of Cong et al. [13,14].

In conclusion, computational studies can provide novel insights into the biology of safety level 4 pathogens like Ebolaviruses for which wet lab research is limited to a small number of high containment laboratories. However, to achieve their full potential computational approaches require exchange with wet laboratory researchers. Only if wet laboratory scientists take computational predictions into accountwhen planning their experiments and report their findings, computational researchers will be able to improve the predictive power and accuracy of their methods in an iterative approach. Whether this will happen will depend on the open-mindedness, tolerance, patience, curiosity, and preparedness to leave the comfort zone on both sides. Nevertheless, we are convinced that this is worth the effort because it will enable us as research community to make optimal use of all available resources.

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