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Editorial: Viruses, Genetic Exchange, and the Tree of Life, Volume II

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10 Editorial on the Research Topic

11 Viruses, Genetic Exchange, and the Tree of Life, Volume II

12 The Volume II of “Viruses, Genetic Exchange, and the Tree of Life” was inspired by the
13 extraordinary success of Volume I of the same topic we published in 2019-20 (Nasir et al., 2019). As
14 of 28 July 2023, articles published in Vol. I have been viewed >185K times with ~21K downloads
15 indicating a continued interest in the research topic. Specifically, Volume I addressed some of the
16 most difficult questions in biology related to viral origins, evolution, and epidemic spread along with
17 how to position microbial/viral taxa onto the broader “Tree of Life”, a metaphor to describe our roots
18 and relatedness. These questions are not purely academic in nature. Only by understanding the past
19 and present of viruses, we can strive to contribute to the development of effective prevention, control,
20 and response strategies, and make tangible contributions to scientific knowledge and public health.
21 Unfortunately, these fundamental questions have remained contentious among scientists for decades,
22 contributing to ongoing debates and differing viewpoints. In Volume II, we continued to receive
23 contributions addressing these outstanding questions. Below we introduce the latest viewpoints
24 dealing with virus outbreaks, taxonomy, origins, and evolution.

25 Abidi et al. reconstructed the evolutionary history of one of the worse pediatric HIV-1 outbreaks
26 known to mankind. In 2019, hundreds of children tested positive for HIV-1 in the Ratodero area of
27 Larkana district in Pakistan. The unprecedented scale of the HIV-1 outbreak and its spillover to
28 children caused uproar and outrage in the country. The outbreak was initially linked to a private
29 clinic (i.e., a single-source outbreak). Abidi et al. generated *pol* gene sequences from a subset of
30 infected children and analyzed the genetic diversity, transmission clusters, subtype distribution, and
31 drug resistance mutations to trace the origin of the outbreak. The authors identified two common
32 HIV-1 subtypes and four transmission clusters in the outbreak samples providing strong evidence for
33 a multi-source rather than a single-source outbreak. The multiple introductions of the “Larkana
34 strain” was therefore likely a result of poor infection control and prevention strategies that were
35 rampant in the region of Larkana. The article emphasizes the urgent need to implement better
36 hygienic practices across the country, especially in the healthcare clinics, to avoid future outbreaks
37 and to ensure effective control of deadly pathogens.

38 Caetano-Anollés et al. prompt an urgent reevaluation of the changes recently adopted by the
39 International Committee on Taxonomy of Viruses (ICTV) to (re)-classify viruses. For example, the

40 ICTV abandoned the widely used and intuitive Baltimore system for classification of viruses,
41 introduced the concept of ‘realms’ that are assumed to be monophyletic groups equivalent to
42 ‘kingdom’ level classification in cellular organisms, endorsed virus discovery and naming from
43 metagenomic sequence data alone without the need to validate their existence via culturing, and
44 introduced new names that obscure the scientific history of pathogens, sometimes grouping double-
45 stranded DNA viruses under the higher rank of *Monodnaviria* (hence ssDNA). The authors highlight
46 major problems with these updates such as ignoring the complex evolutionary histories of viruses
47 that are almost impossible to be recovered via traditional sequence or alignment-dependent
48 phylogenetic analyses, the integration of viruses into ‘holobionts’ that invalidate the concept of
49 taxonomic units, assuming monophyly in the absence of a valid test, and confusion about the very
50 definition and nature of viruses, among other challenges. This review is a must read because accurate
51 taxonomic assignment is critical to our understanding and communication about key pathogens and
52 diseases. The burden is now on the ICTV to address the raised criticism.

53
54 The research article of Deng et al. explores the use of genomic synteny and codon usage preference
55 as tools for determining genera demarcation within the *Iridoviridae* family of viruses. The
56 researchers analyzed the genomic sequences of various viruses within the family and investigated
57 patterns of conservation of gene order (synteny) and codon usage. Their findings suggest that these
58 genomic features can provide valuable insights into the classification and differentiation of genera.
59 This study holds significant importance for both virology and viral taxonomy. It highlights the
60 potential of genomic analysis techniques in understanding the evolutionary relationships among
61 *Iridoviridae* viruses. Moreover, by utilizing the genomic features of synteny and codon usage
62 preference as novel tools, the study offers a more robust and reliable approach of virus classification
63 and taxonomic delineation. This type of research contributes to a deeper understanding of virus
64 diversity and evolution, thereby enhancing our knowledge of viral biology and paving the way for
65 more effective strategies in virological studies, diagnostics, and antiviral development.

66
67 The review article by Harris and Hill opens discussion on important topics that align with the overall
68 theme of the research topic. The authors revisit the definition of life and the place of viruses in the
69 overall ‘Tree of Life’, along with reviewing the popular hypotheses describing the origins of viruses
70 and previous work on investigating the origins of viruses in the light of popular viewpoints. While
71 the article dismisses one of the most promising data-driven investigations of virus origins and
72 evolution by Nasir and Caetano-Anollés (2015) and ignores important follow-up work by the same
73 and other authors revisiting the very definition and nature of viruses (Nasir et al., 2020), it provides a
74 comprehensive examination and synthesis of the evidence supporting the integration of viruses into
75 the tree of life. In particular, the review sheds new light on the role of viruses in shaping biological
76 diversity and evolution, leading to a more holistic understanding of the interconnectedness of all
77 living organisms on Earth.

78
79 In his article, Philip JL Bell revisits the eukaryogenesis hypothesis, initially proposed as early as
80 2001 (Bell, 2001; Takemura, 2001) then revitalized following the discovery of the first giant viruses
81 (Claverie and Abergel, 2010). The conceptual starting point of this hypothesis is that the strict
82 functional segregation between DNA replication/transcription in the nucleus and protein translation
83 in the cytoplasm perfectly mimics the distribution of roles between the viral factory and the
84 cytoplasm in a cell infected with a large DNA virus. Alternatively, the nucleus can indeed be seen as
85 an intracellular parasite replicating its genome by taking advantage of the metabolic and translational
86 resources confined to the cytoplasm. In the updated and detailed scenario, eukaryotes are now
87 interpreted as superorganisms, where the nucleus descend from a viral factory, the mitochondria from
88 an alpha-proteobacterium, and the cytoplasm and plasma membrane were inherited from an archaeal

89 host whose genome has been lost. This new vision, which restores the central role of viruses in the
90 evolution of life on earth, is sure to provoke further debate.

91
92 The Volume II of Viruses, Genetic Exchange, and the Tree of Life thus presents new and exciting
93 developments in the conceptually and technically challenging field of evolutionary virology. We
94 hope that this collection will become a useful reference for future studies in this challenging field and
95 will have applications in both basic and applied virology research.

96 **Conflict of Interest**

97 AN is a shareholder and employee at Moderna, Inc. The remaining authors declare that the research
98 was conducted in the absence of any commercial or financial relationships that could be construed as
99 a potential conflict of interest.

100 **Author Contributions**

101 All authors listed have made a substantial, direct and intellectual contribution to the work, and
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