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NEWS AND COMMENTARY

Minority report: targeting emerging viruses before their emergence

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In his 1956 story 'The Minority Report,'[1] *science fiction author Philip K Dick described a crimeless society where psychics can predict future crimes, allowing the police to apprehend offenders before their crimes actually occur.*

Because RNA viruses typically replicate with short generation times, high mutation rates and produce extensive quantities of offspring, they have the unique ability to evolve very rapidly. Consequently, therapeutic strategies, such as siRNA, that aim at targeting viral sequences need to take into account their exceptional mutagenic potential. Throughout continuous replication, RNA viral genomes follow evolutionary trajectories inside a sequence space, a maximally large, high-dimensional space representing the landscape of every possible genome sequence for a given virus. However, evolutionary trajectories are restricted to a much lower dimensional viability space, which includes all the mutations that allow the virus to continue replication in a given environment, thereby accounting for the fitness costs of mutations.[2]

Upon cross-species transmission, viral sequences follow directional evolutionary trajectories to adapt to a new viability space, which is function of their host (Figure 1, top). The evolutionary forces that constrain viral sequences to a given viability space include, but are not limited to: the need to encode functional protein sequences, constraints on codon usage, physical constraints to maintain nucleic acids secondary structures and host immune pressures. Such constraints naturally imply a theoretical framework for evolutionary analysis of how each constraint reduces the dimensionality of viability space. This can be addressed using tools from statistical physics and information theory, as each constraint reduces the entropy of sequences which may be realized.[3] Importantly, the effect of host immune pressures on viral sequences during cross-species transmission has been directly observed, both by evolutionary and experimental studies.[4] In the pages xxx of this issue, Wada *et al.* tackles the significant problem of viral sequence evolution and how to predict the nature of future emerging viral mutants in order to target them prospectively with therapeutic oligonucleotides.

ANALYZING ANCESTRAL EVOLUTIONARY TRAJECTORIES TO PREDICT FUTURE MUTANTS

In their study, Wada *et al.* followed the occurrence of specific siRNA targets in thousands of sequences of influenza virus genomes collected from 1930 until today, reflecting the natural evolution of the virus throughout its adaptation to human host. By doing so, they were able to identify and to date-specific mutations, which rapidly fixate in influenza genome and destroy validated siRNA target sequences. As some of these new mutated nucleotides showed high levels of genetic stability, the authors proposed alternative siRNA sequences that would target these *de novo* mutations. The fact that similar evolutionary trajectories were observed in distant influenza subtypes suggest that reconstructing ancestral evolutionary trajectories may be sufficient to predict what the authors called the 'awaiting-type' mutations of future zoonotic influenza strains, upon their adaptation to human (Figure 1, middle). Accordingly, this would allow the design of siRNA-targeting viral mutants before their natural emergence. In principle, a sufficiently large collection of such siRNAs could be assembled prior to an emerging pandemic.

TOWARD COMPLETE HOST-SPECIFIC VIABILITY SPACE CHARACTERIZATION

Interestingly, emerging viral diseases may also concern viruses that lack documented history of former human infection, as exemplified by the recent Zika virus epidemic.[5] In this case, one can wonder if it is possible to predict future viral evolution trajectories upon adaptation to their new hosts (Figure 1, bottom). One possible approach to this question consists in quantifying what defines a viability sequence space in human hosts. This considerable challenge may start with a comprehensive listing of which sequences are sensed by the innate system and targeted by antiviral defense effector molecules. As the sensitivity to specific sequences may vary among species, it is reasonable to expect viruses to evolve so as to avoid new immunostimulatory sequences upon transmission to new hosts. Interestingly, the existence of counter-strategies developed by viruses to avoid detection by innate immune sensors might allow them to maintain immunostimulatory sequences, in the absence of any cost to their replication fitness.[6]

Finally, immune system pressures are not the only forces that constraint viruses to specific evolutionary trajectories, though they may have particular importance for the virulence of emerging pathogens. Any such constraint can, in principle, be characterized *in vitro* while holding other constraints fixed and perturbing the constraint of interest to see how much diversity may be generated. The constraints that are the least robust to such perturbations would exert the greatest pressure on sequence entropy. Consequently, the characterization of what form a viable viral sequence space in human will require a complete understanding of all the forces involved in the shaping of viral sequences in order to prioritize the creation a of viable therapeutic targets.

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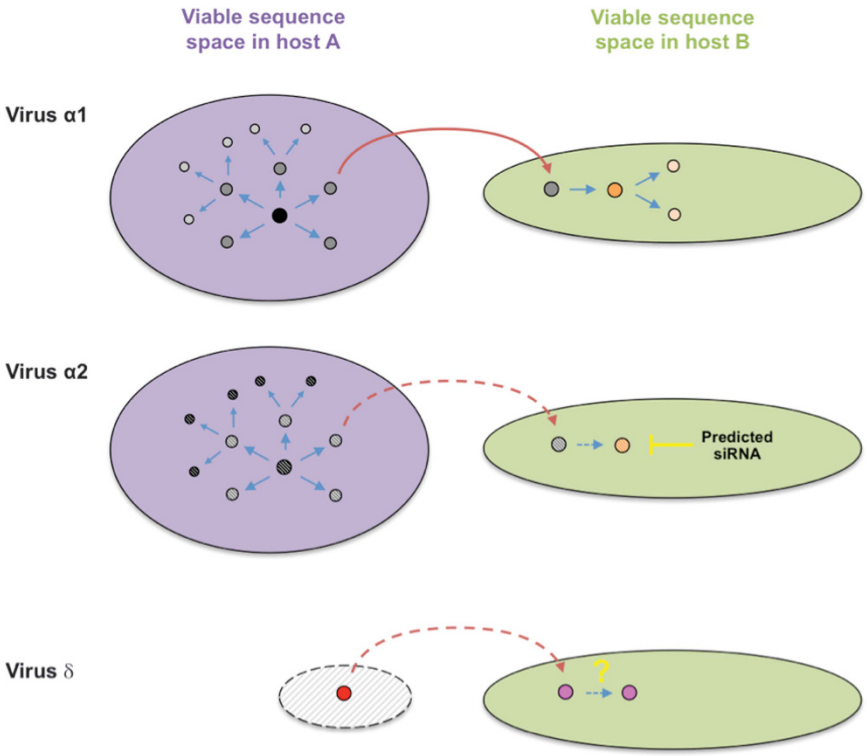

Figure 1. Strategies to design siRNAs that target predicted viral mutants. In the top scenario, a virus α1 is well adapted to host A and its sequence evolves primarily due to random drift. However, upon host switch, analysis of its evolutionary trajectories shows that the viral sequence evolves with a certain level of directional change and adapts under selection to a new viable sequence space in host B. In a second scenario, a new virus α2, related to α1, is expected to switch from host A to host B. Based on observations from α1 evolution, it is possible to predict what would be an expected viral trajectory of α2 in host B. This prediction can be used to design oligonucleotide targeting, a potential future mutant. In a final scenario, a new virus δ emerges for which no pre-existing evolutionary information exist. In this case, it is challenging to predict its evolution upon transmission to a new host, unless all the parameters that define its viable sequence space in this new host are fully described.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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