The systems biology of host pathogen interactions.

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Editorial

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INTRODUCTION

Infectious diseases constitute a major public health burden, particularly in developing countries. Amongst the pathogens afflicting humans, malaria, HIV, shigellosis and tuberculosis (TB) cause a large number of deaths. Whilst antivirals, antibiotics and anti-parasitic drugs have all helped to reduce the burden of disease, problems of drug resistance are increasingly common, presenting the need to come up with alternative approaches to disease prevention. Ideally, effective prophylactic vaccines would be developed against each of these infections, but unfortunately with the exception of TB, no vaccine is currently available against the other three infections.

Baring a breakthrough, coming for example from the application of newer more potent adjuvants to vaccine candidates, new paradigms are needed to help tackle these infectious diseases. In this edition of the journal, Dr. Apte presents his ideas for a new approach to screening of plant extracts for anti-parasitic drugs applying an 'evolutionary drug design' paradigm. Using the example of malaria, a disease that has co-evolved with humans over many thousands of years, he proposes that, rather than traditional approaches based on drugs that are parasiticidal, we should instead try to work with the parasite, rather than against it, developing drugs that will modify its behavior, rather than kill it.

In fact, revolutionary as it might sound, this idea is not entirely new as Apte acknowledges. For example it is the basis of all live attenuated vaccines such as the Bacillus-Calmette-Guerin (BCG) vaccine against TB or the live oral polio vaccine. Live attenuated vaccines are contracts wherein, in return for humans committing to culture these bacteria or viruses, the pathogen returns the favor by becoming less pathogenic thereby helping to protect humans against more virulent relatives. The fascinating aspect of this relationship between humans and the attenuated pathogens is that both benefit from the compact. This shows the power to use evolution to come up with mutually beneficial arrangements. Likewise human gut commensals have a similar compact whereby their human host feeds and protects them while they help to produce important nutrient compounds and protect against colonization by pathogens.

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Can, as Dr. Apte suggests, similar concepts be applied to the identification of plant-based drugs whereby such drugs modulate pathogen behavior and reduce their virulence rather than attempt to kill the pathogen outright? In a similar vein can the host response be modulated with such drugs to enable infected humans to cope with a larger parasite load? In particular, can the burden of disease in malaria be reduced by selective pressure directed against only the asexual form of *Plasmodium*, rather than seeking eradication of the malaria parasite? This is an intriguing idea worthy of further exploration.

One problem with such an approach could be the risk of reversion to wild-type, whereby the attenuated pathogen reacquires its virulence. The classic example of this is the current live oral polio vaccine (OPV). Poliomyelitis is caused by a polio enterovirus which has 3 serotypes, type 1, 2 & 3. Current vaccines against poliomyelitis take two forms, i.e., the Sabin OPV and the Salk inactivated polio vaccine (IPV). The advantages of the OPV includes low cost, ease of administration and ability to induce robust long-term immunization protection. The major dis-advantage of the OPV, however, is its propensity to revert to wild-type and thereby cause rare cases of polio-induced paralysis. As inactivated vaccines cannot cause disease, the global polio eradication program will need to switch from the OPV to IPV in order to match the achievement of the smallpox vaccine, where the virus was finally eradicated from nature by an effective vaccine strategy that gave the virus no evolutionary quarter. Hopefully the human polio virus will similarly be driven to extinction by similar strategies. Unlike extinctions of other higher animals, we should not feel guilty about such extinctions of viruses, since there is no evidence that the world is a poorer place for their absence.

So while strategies of evolutionary manipulation of pathogens such as those proposed in the associated paper in this edition of the journal may play a valuable role in reducing the burden of disease, they at the same time accept the price of having to live life long with the infecting organism, albeit with the infection trained to be relatively asymptomatic. This will reduce the burden of disease and save lives in the developing world, but may lead to periodic reversion of the parasite to wild-type and sporadic clinical disease. Hence, it may not do away with the need to find ways to completely eradicate human *Plasmodium* strains, and this should remain the preferred long-term solution if it can be achieved. But innovative solutions like those proposed by Dr. Apte may be a beneficial interim solution and are certainly worthy of further exploration.