In the past decade, virologists have revealed a novel arm of intracellular, cell-autonomous immunity that mammalian cells mount against a variety of viral infections. In collaboration with colleagues Michael Emerman and Adam Geballe, we have used an evolutionary approach that identifies potential antiviral genes based on evolutionary signatures: higher than expected rates of amino acid changes that are fixed by selection (positive selection). We have used the signature of positive selection to identify the amino acid residues in antiviral proteins that are responsible for specific recognition of viral components. For example, we recently showed that such an evolution-guided approach could also reveal the interaction interface of the broadly acting MxA antiviral protein, which had eluded investigations that used more traditional virology and biochemical approaches. We can also employ this signature to elicit better versions of antiviral proteins via combinatorial mutagenesis of positively selected residues.

We postulate that viruses much older than those in the present day have driven selection for our current antiviral specificities. This has led us to propose an alternate approach of "indirect paleovirology," i.e., inferring the presence and action of ancient viruses by virtue of the evolutionary episodes of selection they drive in host antiviral genes. Together with the identification of fossilized imprints of ancient viruses in animal genomes, these reveal an ancient tapestry of viral infections throughout animal evolution. Occasionally, some genes of these ancient viruses are usurped by genomes for host function. We are interested in identifying such cases and understanding the host biology they participate in. Thus, evolution can provide a means to identify potential antiviral genes, to reveal functional sites of host-virus antagonism and ancient viruses themselves, and to understanding differences in susceptibility to infectious diseases. Host-virus arms-races exemplify genetic conflicts that can occur in many arenas of biology.