JOHN ESSIGMANN: I work in the field of genetic change. In a perfect world, you would say, guanine would always pair with cytosine and adenine would always pair with thymine. It turns out, however, that sometimes chemicals from the environment can react with our normal nucleotides and change their coding characteristics so that mistakes are made when polymerases try to read them.

These are mutations, and mutations cause genetic diseases. My role in the field of toxicology is as a person, who is both a biologist and a chemist, who studies how chemical damage to our informational molecules is converted into changes in coding that results in genetic change.

I'll emphasize, of course, this is the basis for all genetic disease, but it's also the basis for evolution. In other words, mutations happen naturally. That means that we're not all-- we don't all look alike. And that means there's diversity in a population, and that's because of mutations.

And evolution is a really good thing, because if we were all alike when the environment changed, then the chance of extinction might be very high. If there's diversity in a population, that's actually a hedge that life uses in order to be able to make sure something's going to survive, because some members in the population, while they may be considered quote unquote "weaker" in the initial environment, when the environment changes-- they're the ones, for example, with hair on them, and survive the global winter that happens after the meteor strikes.

So, we are interested in chemical modification of DNA and RNA as it relates to the causation of disease, but we're also interested in the rates at which genetic change happens in a population, and how that's a good thing, and that it provides for the continuance of life.

One example of our work in evolution comes from recent work that we've been doing on HIV. When a virus infects one of our cells, our cells respond by trying to limit the growth of the virus. They try to kill it.

And one of the strategies that used by what's called our innate immune system is to induce a number of enzymes that start to rip apart the DNA bases. They really take the amino groups off of cytosines and adenines in order to try to convert them into non-coding nucleotides or miscoding nucleotides.

What happens is, if you take a cytosine and you take away it's amino group, it makes it into a uracil, and then, rather than pair with a guanine, it'll pair with an adenine. Because these are enzymes that kind of move along the viral genome, they create a huge number of mutations.

The process is called lethal mutagenesis, because what happens is, eventually the number of mutations is so large that you can no longer produce a functional protein or nucleic acid. That's a natural strategy that we use.

And thinking about this, some years ago, given my lab's expertise in knowing about the structural modification of normal bases that makes them mutagenic, we wondered if we could contaminate the nucleotide pool of a cell with mutagenic nucleotides that would force a virus to mutate even quicker.

HIV, it turns out, almost goes extinct, but not quite. In other words, our innate immune system, in one day, creates every single point mutation in the virus, but it also creates every single drug-resistant variant. And it just doesn't push hard enough to be able to push the virus to extinction.

So, we wondered whether-- if we could push a little harder by using creatively designed molecules-- derivatives of cytosine, that would pretend sometimes they're a cytosine and sometimes they pretended that they were a thymine-- that we could push the virus over the top.

And we found that it did work, OK. In other words, we were able to push the virus to a technical state of extinction using our understanding of the chemistry of the molecules that the cell has the capability to use in replication.

It may seem unwise to intentionally put mutagenic chemicals into people, and, obviously, we worked out a strategy to prevent mutations in people in the drug design process. Specifically, it turns out there are pathways called DNA repair pathways that repair damage in our nuclear genomes, and they happen in the nucleus. That's where the enzymes are located.

It turns out that the early stage in HIV replication involved replication in the cytoplasm. There are no repair enzymes in the cytoplasm. So, the virus has no defense against the mutagenic affects of these compounds.

We picked compounds that, if they were to get into our nuclei-- it turns out that our polymerases don't like them very much, anyway, but if they did get in, they're very rapidly

repaired. So, it creates what we call a therapeutic index which is very favorable in favor of killing the virus but not putting mutagenic chemicals into us.