Timothy Max commented on Eliezer Yudkowsky's link. Re DRACOs

Timothy Max

November 17 at 9:56am

"I forwarded many of these questions to Dr.Rider via the campaign. Here are the responses. 1. Delivery of potential therapeutic proteins into cells in vitro and in vivo is a very large and well-funded field, since it would facilitate not only DRACO but also many therapeutics for cancer and other diseases. Other researchers have developed a large number of suitable delivery tags and successfully demonstrated that those tags can efficiently carry cargo proteins (even cargo proteins much larger than DRACO) into a wide variety of cell types in vitro and into tissues in vivo in numerous animal models. Since these protein delivery tags are still relatively new, it is not surprising that they are not yet in clinical use in humans, but many therapeutic proteins with those delivery tags are in the pharmaceutical pipelines and will likely be in clinical use soon."

Chris: agreed. My comments have been revised to acknowledge that uptake into cells is being tested in various applications.

In terms of our own experiments, we have successfully demonstrated DRACO uptake in 13 different human and animal cell types so far, including cells from a variety of organs.

Chris: very believable

We have also successfully demonstrated DRACO uptake in a wide range of tissues when administered to live mice in our experiments.

Chris: This is what we need to see in the literature. However, I don't think that 45 day trials would put min mind at ease that there are no long-term effects. I think that for something like this they would need to include lifetime studies (i.e., about 2 years for mice) to see if there is any early mortality or other effects.

We will continue to test and to optimize uptake in our new DRACO experiments for which we are trying to raise funding. 2.1. A wide variety of viruses make long double-stranded RNA (dsRNA) while they replicate inside infected cells. Healthy human and animal cells contain short dsRNA (for example, siRNA and regions of tRNA and rRNA) but **should not** contain long dsRNA.

Chris: cannot depend on theory here. There are lots of unknowns in biology.

DRACO borrows from natural cellular defense proteins such as protein kinase R (PKR) that have been optimized by nature to detect viral dsRNA but not normal cellular RNAs**. In theory** DRACO should not be toxic in uninfected cells, and in our experiments thus far DRACO indeed appears to be nontoxic both in a wide range of human and animal cells and also in numerous mouse trials.

Chris: cannot depend on theory here. There are lots of unknowns in biology.

2.2. From both the scientific literature and our previous experiments, virtually all viruses (even DNA viruses) make long double-stranded RNA (dsRNA) in infected cells, whereas healthy human cells do not. Even latent viruses still have some viral gene expression to maintain their latent state. DRACOs are designed to sense dsRNA from this broad range of viruses. Thus far we have successfully demonstrated DRACO against 18 different viruses in cells, and 4 of those viruses in mice. 2.3.

Chris: agreed. The concept is interesting and the in vitro results go in the right direction.

The actual number of infected cells generally appears to be quite small, so we hope that DRACO can be used without any harmful effects, or at least no more damage than the viruses would have caused.

Chris: I think it may depend on which virus and when you intervene. Some virus infections can impact a lot of cells. And some of the impacted cells (eg nerves) do not regenerate so killing them off is very undesirable. Think polio.

We have done a number of experiments in mice and seen good efficacy against the viruses with which we had infected the mice, but no apparent toxicity otherwise. The mice appeared healthy and active while alive, even with daily doses of DRACO, and appeared to remain normal even after several weeks. We performed necropsies on a number of mice at various time points after they had received large DRACO doses and saw no apparent tissue damage in any organs. Although we tried to prevent the mice from coming into contact with viruses other than those we were testing, these were large colonies of your average lab mice and likely had other viruses, yet DRACO did not appear to cause any problems.

Chris: This is what we need to see in the literature. However, I don't think that 45 day trials would put min mind at ease that there are no long-term effects. I think that for something like this they would need to include lifetime studies (i.e., about 2 years for mice) to see if there is any early mortality or other effects.

We hope that will continue to hold true in future animal trials, and hopefully in human trials ultimately, though of course we will not know for certain until we do the experiments. In our mouse trials we also found that DRACO could be preferentially targeted to certain tissues with the right delivery tags and administration methods, so if necessary, DRACO could be targeted toward the intended infected tissues and not toward other tissues if that proves desirable.

Chris: Good concept but needs a lot of work.

2.4. Most endogenous retroviruses have been inactivated or nearly inactivated by accumulated mutations, and they generally do not appear to be producing long double-stranded RNA (dsRNA), which is why cellular defense proteins have been optimized to look for that to distinguish invading viruses from normal cellular processes. DRACO is based on those natural cellular defense proteins, so in principle it should not harm otherwise uninfected cells. In our experiments thus far, DRACO appears to be nontoxic in a wide variety of human and animal cell types, and also in live mice. 2.5. A wide variety of other protein-based therapeutics are already on the market or approaching clinical use, and those do not appear to have problems with immune responses. We have not observed any immune inhibition of DRACO efficacy in mice in our previous trials, although we will continue to examine such questions in our new DRACO experiments for which we are trying to raise funding.