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Science AMA: I'm Dr.Todd Rider and I invented DRACOs with the hopes of treating a broad spectrum of viruses. AMA!

Dr-Todd-Rider [1] and r/Science AMAs[1]

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April 17, 2023

Abstract

I studied both biomedicine and engineering at MIT, including coursework at Harvard Medical School, and spent my career inventing novel biotechnology projects by combining molecular and cellular biology tools with a systems engineering approach. In 1997 I joined MIT Lincoln Laboratory and the MIT Center for Cancer Research and invented the CANARY biosensor, which uses genetically engineered lymphocytes to identify pathogens within seconds with very high accuracy and sensitivity. I engineered and demonstrated the first CANARY cell lines, as reported in my widely publicized 2003 Science paper. I invented the DRACO antiviral approach, designed the therapeutics and experiments, personally conducted many of the in vitro and in vivo experiments, and recruited and supervised a team in carrying out the rest. My DRACO research has been called "visionary" by the White House (National Bioeconomy Blueprint, April 2012, p. 9), named one of the best inventions of the year by Time magazine (November 28, 2011, pp. 58, 78), and featured on the BBC Horizons TV program (2013). DRACOs work to target the dsRNA that virtually all viruses make and initiate apoptosis (cell suicide). For more information on the science and the results of previous DRACO experiments, see the article published in PLOS ONE: http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0022572 I will be back at 1 pm EST (10 am PT, 6 pm UTC) to answer your questions, ask me anything! UPDATE: This AMA is now closed. Thank you for your questions. I will continue to check this page intermittently and respond to any questions.

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DR-TODD-RIDER R/SCIENCE

ABSTRACT

I studied both biomedicine and engineering at MIT, including coursework at Harvard Medical School, and spent my career inventing novel biotechnology projects by combining molecular and cellular biology tools with a systems engineering approach. In 1997 I joined MIT Lincoln Laboratory and the MIT Center for Cancer Research and invented the CANARY biosensor, which uses genetically engineered lymphocytes to identify pathogens within seconds with very high accuracy and sensitivity. I engineered and demonstrated the first CANARY cell lines, as reported in my widely publicized 2003 Science paper. I invented the DRACO antiviral approach, designed the therapeutics and experiments, personally conducted many of the in vitro and in vivo experiments, and recruited and supervised a team in carrying out the rest. My DRACO research has been called “visionary” by the White House (National Bioeconomy Blueprint, April 2012, p. 9), named one of the best inventions of the year by Time magazine (November 28, 2011, pp. 58, 78), and featured on the BBC Horizons TV program (2013).
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Hi and thanks for doing this AMA. This sounds likes cool project, but I have some concerns about the strategy that DRACO employs. Hopefully you can help me navigate those concerns:

1. As I understand it, DRACO is intended to induce all virus-infected cells to commit suicide. But at any given time, humans are host to a number of viruses, most of them not terribly pathogenic. I assume DRACO would kill cells infected by these viruses as well as cells infected by the pathogenic virus. That could potentially add up to a lot of cells being killed by DRACO. How much does that concern you as you seek to transition DRACO to the clinic?

2. What about ERVs and other endogenous elements? These are integrated in our genome, and transcriptionally active. How does DRACO avoid these elements?

3. What about viral resistance? Targeting the dsRNS is an evolutionarily conserved tactic for fighting viruses. Unsurprisingly, many viruses have evolved ways to circumvent these defenses. Ebola, for instance, defends against the host double stranded RNA response via the viral protein VP35 which binds dsRNA and inhibits PKR activation. I imagine such resistance mechanisms would be rapidly selected for I the face of DRACO.

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4. What in vivo models has this been tested in? The paper you linked only mentions cell culture experiments.

SirT6

1. 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. 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. 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.

2. Most ERVs 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 theory 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.

3. You are quite correct that Ebola and some other viruses try to hide their dsRNA to avoid activating cellular defense proteins such as PKR. Several of the viruses against which we have already tested DRACO had similar dsRNA countermeasures, yet DRACO was effective against all of them. Currently my best explanation is that the viral countermeasures may be sufficient to inhibit the more modest interferon and inflammatory responses that natural cellular proteins try to initiate, but may not be sufficiently effective to inhibit the rapid apoptosis initiated by DRACO. If we do encounter viruses that are more resistant, we have a variety of different DRACO designs that could be used to overcome that resistance. In general, newly evolved resistance is much more likely with highly specific therapeutics, where the virus can slightly mutate the structure targeted by that therapeutic, and should be less of a problem for very broad-spectrum therapeutics such as DRACO.

4. As shown in our PLoS ONE paper, we have done a number of successful trials in BALB/c mice. As discussed in the online SENS presentation and presentations we have given at American Society for Microbiology and other conferences, we have also successfully tested DRACO in AG129 mice. If we can test and optimize DRACOs against herpesviruses in cells, we would love to move on to test in rodent models of herpesviruses too.

The DRACO strategy relies on getting large proteins into cells in a human being. This is an incredibly difficult endeavor, and the strategy applied in your PLoS One paper (transduction tags) has never succeeded in a clinical setting. How do you plan to achieve intracellular protein delivery in vivo, and why do you think everyone else has been unable to do this?

Wackademic

Delivering protein therapeutics inside cells is fairly new, so it is not surprising that therapeutics using that approach are not already being used clinically in humans. However, in addition to DRACO, there

are many other therapeutics in the research pipelines (for cancer, etc.) that rely on delivering protein therapeutics inside cells. Because of that motivation, other researchers have developed a wide range of proven delivery tags, such as those we have already successfully used with DRACOs in human cells and in mice, and others that we hope to try in our continuing DRACO experiments.

You occasionally mention that it would be difficult for viruses to evolve resistance to DRACOs. Given that many viruses have mechanisms to sequester dsRNA away from the cell's dsRNA sensing pathways (for example, the poxvirus E3L dsRNA binding protein used in some of the DRACO constructs), it seems likely to me that such viruses would find it fairly easy to increase resistance to DRACOs, perhaps by increasing expression or affinity of their dsRNA binding proteins. Do you think this couldn't happen, and if so, why?

zmil

You are quite right that some other viruses try to hide their dsRNA to avoid activating cellular defense proteins such as PKR. Several of the viruses against which we have already tested DRACO had similar dsRNA countermeasures, yet DRACO was effective against all of them. Currently my best explanation is that the viral countermeasures may be sufficient to inhibit the more modest interferon and inflammatory responses that natural cellular proteins try to initiate, but may not be sufficiently effective to inhibit the rapid apoptosis initiated by DRACO. If we do encounter viruses that are more resistant, we have a variety of different DRACO designs that could be used to overcome that resistance. In general, newly evolved resistance is much more likely with highly specific therapeutics, where the virus can slightly mutate the structure targeted by that therapeutic, and should be less of a problem for very broad-spectrum therapeutics such as DRACO.

Hello there, i really do think it's high time more innovative and translational approaches are used to address medical issues. I've had my heart set on this ever since i entered med school and now that I'm finished I'm looking into doing a PhD in molecular biology or immunology or other domains with problem-solving potential. How hard would it be for an MD. to break into this field(I'm referring to the engineering part which i like but have no training in)?

Lecsicon

There are many people working in this general field with just an M.D., just a Ph.D., or both. Congratulations on finishing medical school and for wanting to really make a difference, and good luck with your career!

Will we soon to be able to cure virus induced diseases as "easily" as bacteria induced diseases (due to the related antibiotics)? Will we be able to cure a normal cold or influence in a day or two?

Jadeyard

I believe DRACO has the potential to revolutionize the treatment and prevention of viral infections, just as antibiotics previously revolutionized the treatment and prevention of bacterial infections. We have already shown that DRACO is effective against rhinoviruses (common cold viruses) in cells, and effective against influenza (flu) viruses both in cells and in mice. If we can raise enough support on IndieGoGo, we plan to continue to develop and demonstrate DRACO therapeutics. I really hope to see them advance toward human trials ultimately.

Do humans have any analogues to the double-stranded RNA (dsRNA) activated caspase that DRACO targets? Any known side effects from this interaction?

discofreak

That is a great question! 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. 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 appears to be nontoxic both in cells and in mice.

As a medical student I would like to say that your work is nothing short of amazing. Keep it up!!

BaghdadBeauties

Thank you very much for your support, and good luck with your studies!

I was wondering if there is resistance to fund something which cures as opposed to something which people will have to take for the rest of their lives. When I first heard about DRACO I naturally assumed I would never hear about it again because curing disease doesn't seem as profitable as chronic disease management.

Rumpel_Tumskin

A number of people have wondered about that, but I have not seen any evidence thus far that that is actually a problem. The resistance to DRACO and other new approaches that I have seen seems to arise because those approaches are so novel, not because they might be so effective. In my opinion, industrial and government sponsors have become much more averse to more novel, riskier, and/or longer-term scientific development, opting instead for relatively minor variations on existing approaches such as vaccines, nucleoside/nucleotide analogues, etc. And those existing approaches generally do have real limitations.

Hi,

How much money would it cost to produce Dracos at a large industrial scale ? How much will they cost when they re going to enter the market ?

Linux1337Hexxor

The ultimate cost per dose for DRACO treatment, if it is eventually approved for human use, will be determined many years down the road and by many factors, including the cost to scale up and consistently produce very high-quality DRACO batches, the amount of DRACO required for efficacy, the costs of large-scale animal and human trials, the number of users over which those costs can be spread, and many other factors. I certainly want DRACO to benefit as many people as possible and hope to do whatever I can to keep the final cost as low as possible.

Hi Dr. Rider, my boss here in Germany has been trying to get in touch with you since the summer RE: possibly using DRACO technology for treatment. What is the best way to get in touch with you privately? (In case you were wondering, your old MIT and Draper lab email accounts that show up on

Google searches no longer work, and no one at the Lincoln lab knew how to get in touch with you.)

screenplaytoglitter

Please send your or your boss's email address to info@killingsickness.com and I will contact you directly. Thank you very much!

Dr. Rider, if you manage to get the $100K from your IndyGoGo campaign what DRACO combos will you test against HSV and why do you expect them to work given HSV LAT's pan-caspase inhibitory effect?

Wouldn't any virus using this method to prevent premature cell death inherently inactivate DRACO's mechanism of action?

HoneycombQ

A number of viruses (including HSV) block the natural cellular apoptosis (cell suicide) pathways to prevent infected cells from dying before the viruses can finish replicating in those cells. However, virtually all of those viruses (including HSV) block apoptosis upstream of caspases, in signaling pathways that activate caspases but are not caspases themselves. Thus the viruses should not be able to inhibit DRACO-based apoptosis, and that is indeed what we have found in our previous experiments with a number of viruses that routinely block apoptosis. If we do encounter viruses that are able to block DRACOs, we have a variety of different DRACO designs and approaches that we can use to hopefully overcome any viral countermeasures.

I understand it's only been tested on lab animals yet. Could the current version work for humans too, or are there still unsolved challenges?

Could it be a cure for HIV?

When is the earliest it may be available for humans, assuming all goes well?

Minthos

We have a number of DRACO designs and approaches but do not currently know which if any would be effective against major clinically relevant viruses such as herpesviruses and retroviruses. The fastest, cheapest, and safest path forward is to test and optimize DRACOs against clinically relevant virus families in cells. If we can successfully obtain such data in cells, we believe those results should persuade pharmaceutical companies to carry DRACOs through large-scale animal trials and hopefully into human trials. The timeline depends on funding levels (including how much funding pharmaceutical companies are willing to commit later) and whether any unforeseen scientific difficulties arise in the experiments. However, if everything goes well, we hope that DRACO could enter human trials within a decade or even less.

Hi, I've read that your PhD was actually in electrical engineering and computer science, and your doctoral thesis addressed the question of energy consumption and radiation emissions from hot fusion reactors. My question is, how have you been able to transition from engineering, and physics into biology? Did you take grad courses in biology, or did you achieve this through self study? The idea that one can get a PhD in a certain field, and subsequently do research in a completely unrelated field is inspiring given the highly specialized and constricting nature of modern scientific disciplines.

ksbrooksjr

Thank you for inquiring about my misspent youth! :-) I spent 9 years at MIT including undergraduate and grad school, and I really wanted to combine engineering and biology, doing a detailed engineering systems analysis of biological systems and then finding ways to reengineer the components of those biological systems to work better or to do something else useful. At that time, I had to study biology and engineering in completely separate departments, and each side of the fence thought I was crazy for wanting to do that. (Nowadays there are whole departments and fields for what I was doing at the time, which is now commonly called biological engineering or synthetic biology.) Fortunately I was able to cross-register from MIT into Harvard Medical School, and at the time MIT's EE Ph.D. program allowed people to declare a minor with their Ph.D. if they had enough coursework in another area. I took as many biomedical classes as I could at MIT and Harvard and declared a minor in biomedicine for my Ph.D. During grad school, I honed my research approach by applying systems analysis to a variety of engineering and biological systems to find novel approaches. Since getting my Ph.D., I have spent the last 20 years developing revolutionary new ways to analyze and engineer biological systems, including my CANARY rapid pathogen identifier and my DRACO antiviral therapeutics.