Dr Samuel Sternberg - CRISPR

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Margaret Flinter: Welcome to Conversations on Health Care with Mark Masselli and Margaret Flinter, a weekly show where we speak to the top thought leaders in health innovation, health policy, care delivery, and the great minds who are shaping the health care of the future. This week, Mark and Margaret speak with Dr. Samuel Sternberg, renowned expert on the leading edge of CRISPR gene editing technology and co-author of A Crack in Creation: Gene Editing and the Unthinkable Power to Control Evolution, which examines the limitless potential of this emerging approach to editing DNA.

Lori Robertson also checks in, the managing editor of FactCheck.org, looks at misstatements spoken about health policy in the public domain, separating the fake from the facts. We end with a bright idea that's improving health and well-being in everyday lives. If you have comments, please email us at chcradio@chc1.com or find us on Facebook or Twitter. We love hearing from you. You can find us on iTunes, or Stitcher, or wherever you listen to podcasts. Please feel free to leave us a review. Now, stay tuned for our interview with CRISPR expert, Dr. Samuel Sternberg, on Conversations on Health Care.

Mark Masselli: We're speaking today with Samuel Sternberg, Ph.D., biochemist, an internationally renowned expert on CRISPR gene editing technology. Dr. Sternberg is an assistant professor in the department of biochemistry and molecular biophysics at Columbia University, who also runs a research lab, developing new tools for advancing genome engineering technology. He earned his Ph.D. in chemistry from the University of California, Berkeley, under the mentorship of Dr. Jennifer Doudna, co-creator of the CRISPR technology for genome editing. He's also written extensively as an expert on the subject, including co-writing with Dr. Doudna, A Crack in Creation: Gene Editing and the Unthinkable Power to Control Evolution. Dr. Sternberg, welcome to Conversations on Health Care.

Dr. Samuel Sternberg: Good to be with you.

Mark Masselli: Sam, CRISPR technology has brought us to the brink of unprecedented potential for scientific breakthroughs. You're one of a small cadre of scientists who are on the leading edge of this technology. I wonder if you could share with our listeners just how vast the potential is and conversely the possible Pandora's box of harm that could be unleashed with CRISPR-Cas9.

Dr. Samuel Sternberg: I think that the potential to do good in the world is unprecedented because for so long we've been limited by relying on natural random mutations as a way of being the work stuff of evolution. Now with tools like CRISPR, scientists have the capability to go into the genome,

which is made up of DNA, and make pinpointed precision changes to that genetic material. That can really change the way that scientists think about treating disease in human patients and editing the DNA of plants and animals that we rely on for food and other kinds of industrial biotechnology. Already we've seen a complete transformation of the way that biomedical research is being done because of the ability to now go into the genome and make changes as a way of designing better experiments to understand things like the way that cancerous cells proliferate, how we can design better drugs to target those cells, and really virtually any sector of biological research can be now studied better with tools like CRISPR.

Margaret Flinter: Sam, in your book and in your many speeches around the world on CRISPR technology, you start by asking the question, what if it were as easy to edit faulty genes in our DNA as it is to fix a typo in Microsoft Word? You say that's exactly what CRISPR-Cas9 technology has the potential to do, that's fast by most research standards, and it's efficient. The million dollar question for our listeners I think is can you help them understand exactly how CRISPR works to achieve these dramatic results?

Dr. Samuel Sternberg: Yeah. CRISPR is often described as a pair of molecular scissors that run based on a pair of GPS coordinates, provided by a molecule, called RNA, or ribonucleic acid. The general premise is we have a way of cutting DNA in defined locations, and then repairing that broken DNA using the repair mechanisms that cells are very good at doing. Program the CRISPR molecules in a way that we can edit the gene that we might be interested in studying or in repairing. CRISPR was certainly invented as a technology. It comes from a very natural immune system that we discovered in bacteria. It kind of came out of this decades long struggle to understand what these funky CRISPR molecules are even doing in nature. Once we and others had solved that problem, it became very clear how we could harness those same biomolecules for this kind of molecular scissors cut and paste functionality. Pretty much any cell type or organism you can think of studying in the laboratory has now been edited with CRISPR technology.

Mark Masselli: You can do it on one cell. I think the question is, how do you spread it to the billions of cells that might be in the body to effectuate change? Maybe walk through -- don't get too sciency on us, for the lay listener, but how does it scale up in the body? What techniques are out there to spread it to a billion cells?

Dr. Samuel Sternberg: Yes. That's going to be the big question and the big hurdle in realizing the potential for harnessing CRISPR as a therapeutic tool for treating disease because you have to actually deliver CRISPR into every cell you'd like to edit. It's not going to spread on its own unless you can

edit stem cells inside the body. Actually we can start with disorders of the bloodstream, which are some of the first that are being tackled because it's possible to edit cells that are blood stem cells, meaning if you edit just a small number of blood stem cells, those will end up proliferating and turning into cells like red blood cells where disorders such as beta thalassemia or sickle cell disease have their greatest effect.

One type of therapy, if you were targeting these blood diseases, would be editing blood stem cells. In the laboratory, you can actually remove those cells from patients, repair the causative mutation in the lab, and then return those edited stem cells back into the patient's bone marrow. This would now give that patient a new reservoir of stem cells, from which healthy blood cells could be produced for the remainder of that patient's lifetime. When you talk about now the neurological diseases, diseases that affect organs like the heart or the lungs, now we have a much greater challenge because those therapies [inaudible 00:06:41] delivered directly into the patient's body in a way that can target many, many different cells of a given tissue type or organ.

Researchers are looking at using different kinds of viral vectors to try to spread those CRISPR molecules into many cells as possible in the patient. As you can imagine, this is going to be very, very difficult. I think there's a big gap between how easy it’s become to do this cut and paste in the laboratory versus transforming this into a therapy that's going to work in living patients.

Margaret Flinter: I have something similar to the feeling that I had when I learned that we had completed the full mapping of the Human Genome Project, which was something like the way I felt when we saw the first step on the moon, just huge world changing events. All these achievements come about through collaboration, and in this case, really a pretty global collaboration among thousands of scientists working together.

There’s always an element of competition in discovery. I understand there's been some competition between the labs, including Dr. Doudna’s lab at Berkeley and another group at MIT. As scientists around the world work to apply CRISPR technology to new protocols, how do you find the right balance between collaboration and competition in this really very new and emerging body of science?

Dr. Samuel Sternberg: Well, I think there are very few people I can think of that are holding on to knowledge. Even with this ongoing patent dispute, any researcher in the world that wants to be using CRISPR can actually go to a not-for-profit company, called Addgene, and obtain the resources they need for just $60 to start developing CRISPR tools in their own laboratory. I actually think the collaboration is something we can celebrate here. Even the work that came in out of Jennifer's lab, that

was actually a very productive collaboration between Jennifer and Emmanuelle Charpentier, who's now leading a Max Planck Institute in Germany. Feng Zhang, Private MIT, has done incredible work.

I think what's really exciting for someone like myself, who's been a researcher starting as a Ph.D. student, now starting my own lab, is seeing new discoveries coming out every day in scientific journals, meeting people at conferences, and brainstorming together. I think it's exciting that many people are working in this space. I think at the end of the day, it's just exciting to have so many different brilliant minds, focusing on this problem, and thinking creatively about how to develop the technology quicker, better, faster, and how to start realizing some of these lofty goals that I think are going to be made possible with CRISPR.

Mark Masselli: We're speaking today with Samuel Sternberg, biochemist, an assistant professor in the department of biochemistry and molecular biophysics at Columbia University, where he also runs a research lab aimed at developing new tools for advancing genome engineering. He is the co-author along with CRISPR co-creator, Jennifer Doudna, A Crack in Creation.

Sam, this technology does not come without some controversy. It's also being engaged in across the globe. I know there are Chinese scientists. There is some fear about doing experiments on embryos, leading to fears of baby engineering. Recently it was reported that some CRISPR experiments unleashed an uncontrolled chain reaction. How founded are some of these fears? How do we mitigate the threat?

Dr. Samuel Sternberg: Maybe the last thing you mentioned is these unintended effects of CRISPR, genomic events that CRISPR can cause that are often not what scientists are attempting to do. There's a major body of research right now aimed at making sure CRISPR can be developed as safely as possible, and that if you are using CRISPR to let's say repair genetic mutation, that we really understand exactly what's happening at the cellular and at the DNA level when CRISPR goes in and makes that edit.

There's been a couple of high profile papers in the last few months that there are some risks associated with making edits to the genome, which can involve either making additional mutations elsewhere in the genome at unintended sites, or even the edits being something that can't be easily controlled, where you accidentally deleted a whole big chunk of the gene that you're trying to repair. I think in terms of safely deploying CRISPR, whether it's human therapeutics, or an agricultural, or a research tool, we're still learning how to best use this tool and use it in a way that's safe and predictable.

Then we can talk certainly about the other very controversial aspect of CRISPR, which is, as you mentioned, researchers have also shown that it can be delivered into human embryos as a way of installing genetic changes at the earliest point in sexual reproduction and development. That brings about this kind of futuristic scenario where my parents use a tool of CRISPR in the context of an in vitro fertilization clinic to make designer changes to their future children. That's something that is no longer purely the stuff of science fiction because tools like CRISPR now make that feasible. There's a growing body of researchers, of ethicists, of regulators, of religious leaders who are grappling with this question of what kinds of applications should we really be pursuing with this technology.

Margaret Flinter: We in health care have the option to be so saddened by the really devastating diseases and conditions that families experience in the realm of inherited diseases, cystic fibrosis, and sickle cell, and certainly Alzheimer's and Huntington's. We now think of that in some way. You've really laid out the potential for appending the whole approach to disease cures and possibly even prevention with CRISPR technology. How soon you see this having an impact on actually treating and preventing some of the most dreaded diseases?

Dr. Samuel Sternberg: Well, I think for just about all of the diseases you just mentioned, there have been multiple publications already showing that CRISPR can repair the mutations associated with those diseases. In terms of the core technological platform to make these changes, CRISPR has been proven to be effective at doing that. In terms of these yielding real therapies that work in patients, that comes back to these challenges about delivery, about how to introduce CRISPR into the body. I think it's still going to be many years until we see therapies making their way through clinical trials.

I will say that there's been one area of therapeutics where CRISPR is already being tested. That's in the treatment of cancer where CRISPR is used to engineer immune cells in the area of cancer therapy, called cancer immunotherapy, whereby patient's own immune cells can be engineered to become better at hunting down cancer cells in the body.

I think that might be one of the areas where we see the first commercialized drugs that use CRISPR as a way of engineering the genome in cells being used as the main mode of this therapy. There's a number of different trials that are already ongoing. I believe they're slated to begin later this year for skin cancer, if I'm not mistaken. I think cancer immunotherapy is where we might see therapies come the quickest. Many of those other diseases, it's going to be a matter of taking these experimental successes and transitioning them into clinical trials that are tested on patients.

Mark Masselli: Well, with such excitement around the new technologies that CRISPR potentially offers, then one starts to think about what the cost will be. While you say that developing the CRISPR interventions is actually quite affordable by scientific research standards, cost often escalates. How do you envision the cost of these highly personalized approaches? As we move forward with CRISPR-aided interventions, how do you see this intersection of that venture capital we talked about with the ultimate cost of any therapies that get developed?

Dr. Samuel Sternberg: Yeah, that's something I struggle with. That's something I don't know a lot about beyond the fact that it's extremely expensive. Certainly when you move towards personalized therapies, the price is going to go even higher than drugs that are going to be broadly effective. While the initial therapies are going to be very expensive, that's hopefully just one time point on a path towards the core technology becoming better, such that over time the costs will go down. I can't really speak to how that's going to be possible. I think we got to start somewhere. Hopefully we'll get there.

Margaret Flinter: Well, one thing that seems really clear to me is that all this is going to have quite a profound effect on how we educate and train the next generation of health care professionals and the research scientists. I'm curious, is there much talk yet about how this really is going to change the education of both the clinical people, physicians, and nurses, and genetic counselors. Even those of us in primary care then have to be sort of educated to a whole new special area of talking with patients about what we assume at some point will be a different level of screening and mapping. What changes to education are going to be needed?

Dr. Samuel Sternberg: Well, I'll tell you one thing that's been pretty amazing for me to experience is going and giving some talks and having high school students come up to me afterwards, and not just say they know what CRISPR is, but they've actually done CRISPR experiments in high school in their biology laboratories. I think that gives you a sense for how quickly this technology has spread beyond the confines of Ph.D. and post-doctoral level research into back down to high school, certainly to the undergraduate level, and I think increasingly into the health care arena. I think the impact for patients, that will take much longer to come about. Tools like CRISPR and other [inaudible 00:16:41] approaches, I think they've already transformed the way that we think about how we can study the genome.

You cannot really be a biologist today and be maximally successful if you don't have an understanding of how these technologies work because it's really changing the way that we can think about designing experiments. Maybe in the 10, 20 years, it’s going to change the way that we need to think about how to treat disease. I think maybe the

dream is that we'll be able to say goodbye to the days when a genetic disease had to always be treated by daily or weekly injections of some enzyme. Hopefully we can welcome a new era where you might have a one shot therapeutic that permanently repairs the causative mutation and permanently reverses the symptoms in patients working with that disease. I think that's the kind of the Holy Grail of a dream that we could be working towards in the health care arena.

Mark Masselli: We've been speaking with Dr. Samuel Sternberg, assistant professor in the department of biochemistry and molecular biophysics at Columbia University, and co-author of A Crack in Creation with Dr. Jennifer Doudna. You can learn more about his work by going to shsternberg.com, or you can follow him on Twitter @shsternberg. Also, you can see him present his latest findings at this year's Jacques's Health Forum, Dr. Ed Lu's Shop here in Farmington Connecticut on October 24th and 25th.

Sam, thank you for sharing your exciting and pioneering work in this growing field and for joining us on Conversations on Health Care today.

Dr. Samuel Sternberg: Thanks, Mark and Margaret. It's been a pleasure.

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Mark Masselli: At Conversations on Health Care, we want our audience to be truly in the know when it comes to the facts about health care reform and policy. Lori Robertson is an award-winning journalist and managing editor of FactCheck.org, a nonpartisan, nonprofit consumer advocate for voters that aim to reduce the level of deception in U.S. politics. Lori, what have you got for us this week?

Lori Robertson: President Donald Trump touted "record business for new health insurance plans under a federal rule that hasn't yet gone into effect." In fact, since at least December 2017, he has periodically and prematurely boasted that millions of people are already signing up for these association health plans. The federal rule pertaining to those plans takes effect August 20th. It doesn't start applying to association plans until September 1st. At a July 26 roundtable discussion in Iowa, the president singled out Labor Secretary, Alex Acosta, whose department is responsible for the new rule on association health plans. He said he heard there had been a record business and incredible numbers for plans that he said "just opened about two months ago." Association health plans are created by a group of employers such as those in a similar industry. The Labor Department has been working on a new federal rule to expand and change the regulation of these plans and issued its final rule on June 19.

The final rule though says it won't begin applying to association plans

until September 1st. Yet the president has been talking about millions of people signing up for these plans for months. For example, at a rally in North Dakota in June, Trump said that “millions and millions of people are signing up.” Now, it's quite possible that millions of people will eventually sign up for these plans under the new regulations. The nonpartisan Congressional Budget Office estimated in May that the then proposed rule would result in about 4 million people joining association plans starting in 2023. Avalere Health estimated that the proposed rule would cause 2.4 million to 4.3 million people over five years to move to association plans.

Under the new rule, associations could form for those in the same trade, or industry, or for businesses in the same state or metropolitan area. They would need to have at least one business purpose unrelated to providing insurance, provided couldn't deny coverage or charge more based on health status. The plans could be cheaper than other options on the individual market. They could offer more limited benefits. That's my fact check for this week. I'm Lori Robertson, managing editor of FactCheck.org.

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Margaret Flinter: FactCheck.org is committed to factual accuracy from the country's major political players and is a project of the Annenberg Public Policy Center at the University of Pennsylvania. If you have a fact that you'd like checked, email us at chcradio.com. We'll have FactCheck.org’s Lori Robertson check it out for you here on Conversations on Health Care.

Each week, Conversations highlights a bright idea about how to make wildness a part of our communities and everyday lives. It's estimated that a majority of a person's lifelong health expenditures are often spent in the final months of life. Death is one of those topics that generates the least amount of conversation in the clinical setting and American health care. For folks who end up critically ill or facing a terminal diagnosis like late stage cancer, this can often lead to poorly communicated end of life wishes being discussed with the clinician who then often resorts to extreme interventions.

Female: In oncology, notoriously, we are under prepared to have these conversations with patients. Actually most studies have shown that when you provide honest prognostic information to patients and allow patients to be part of the decision-making about their goals of care, they are more appreciative of it.

Margaret Flinter: Dr. Manali Patel is a clinical researcher at Stanford University School of Medicine. Her earlier research had yielded an interesting finding. Patients felt more comfortable talking about end of life issues with a layperson as opposed to a clinician. She and her fellow researchers

followed patients at the Veterans Administration Palo Alto Health Care System for 15 months after they were diagnosed with stage 3, or 4, or recurrent cancer. Half the people were randomly assigned to speak with a lay worker about the goals of care over a six-month period. The control group was given no such intervention. The lay workers were given a rigorous 80-hour course and clinical observations before being assigned to the study.

Female: We found that she learned as she went. At the end, she was completely proficient. She came to that realization that these conversations really are not scary and shouldn't be medicalized, and maybe she didn't need all that training. We had hired her because she had a very supportive [inaudible 00:23:25].

Margaret Flinter: 92% of the participants who received the layperson intervention compared to only 18% of the control group were likely to have end of life directives in their electronic health record and more likely to have communicated their wishes to their clinicians as well, often choosing hospice over emergency room interventions as their conditions deteriorated. The average cost of care for the intervention group in the last month of life was about $1,000 versus $23,000 for the control group. Dr. Patel said one of the more interesting findings was much higher patient satisfaction among those who'd received the intervention.

Female: We found overwhelmingly that the patients in the intervention arm were very satisfied with the decisions that they had made regarding their medical treatments and regarding their life.

Margaret Flinter: The results are published in this month's JAMA Oncology. A low resource, patient-centered intervention that assists terminally ill patients, their families, and their clinicians to have a frank discussion about end of life wishes, improving patient satisfaction at such a sensitive and challenging time, that's a bright idea.

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Mark Masselli: You've been listening to Conversations on Health Care. I'm Mark Masselli.

Margaret Flinter: I'm Margaret Flinter.

Mark Masselli: Peace and health.

Margaret Flinter: Conversations on Health Care is recorded at WESU at Wesleyan University, streaming live at chcradio.com, iTunes, or wherever you listen to podcasts. If you have comments, please email us at chcradio@chc1.com, or find us on Facebook or Twitter. We love hearing from you. This show is brought to you by the Community Health Center.

Dr Samuel Sternberg - CRISPR

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