Science AMA Series: I'm George Church, professor at Harvard and MIT, founder of PersonalGenomes.org. My lab develops technologies for sequencing genomes, editing DNA in living cells, and harnessing DNA as a molecular tool. AMA!

George-Church [1] and r/Science AMAs[1]

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GEORGE-CHURCH R/SCIENCE

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Your lab's success is quite a few standard deviations above the mean. What factors (funding, exposure, personnel, relationships, leadership, vision, institutional support etc) are most critical to your continued success?

Second question. Do you have any big ideas you'd like to take but the technology just isn't quite there yet? In this case would you say you follow technological advances or you pioneer them (as in the case of CRISPR)?

MacBelieve

Q1: Wonderful students and postdocs, selected to be nice, interdisciplinary, and out-of-the-box thinkers. An environment in which we can fail fast, analyze and try again. Teams of 3 people. Two projects per person, one full of passion and risk, a second which is safer -- not due to mediocrity but due to maturity of the project. Aim for radically open sharing (like personalgenomes.org, addgene.org) and radical cost reduction (like NGS).

Q2: We prefer tech-development over tech-adoption. Mixtures of various cutting edges. Ideally, the most disruptive, transformative and broadly applicable (even beyond bio). CRISPR is not our first or last genome engineering technology (for example, MAGE and integrases work better for our 4 Mbp scale projects). Technology that wasn't there in 1999 but now is there: nanopores and in situ sequencing.

Hello Dr. Church,

I work at a neurology clinic and I have encountered a lot of concern from patients with regards to the sharing of genetic information, so much so that they do not want to be tested. In the United States, we have laws protecting people against genetic discrimination by insurance companies, but despite these assurances patients are still wary.

Sequencing everyone, healthy or not, seems to be the best way to understand genetic penetrance and expression in humans. Much of the time we are working from partial information in trying to interpret

and assess genetic mutations. The more data, the better we are able to diagnose and treat disease.

How can we encourage the sharing of genomic information while ensuring the privacy and autonomy of every day people?

OrangeAstronaut

The Genetic Information Non-discrimination Act (GINA) of 2008 covers health and employment, not life insurance or long-term care. Genomic info can help or hurt our insurability. For example, my genome says that I have a low risk of senile dementia. If I exploited this info, it might be unfair to other insured citizens. Perhaps we need to get insured before we get sequenced, but this is increasingly happening prenatally. Knowing your genome is probably a net positive especially for family planning to avoid very serious heritable diseases like Tay Sachs. In terms of sharing, note that hackers are now targeting conventional medical records as 20-fold more valuable than credit cards, so we are all "sharing" involuntarily. The benefits to society of careful, voluntary sharing (as in personalgenomes.org) could be huge, but require careful reflection with your immediate family.

Hey professor Church, huge fan of your work. A couple of quick questions. Firstly, with your idea of using pigs as organ donors, have you received any blow back from ethics committees? How far away are we from having a functional organ that can be implanted in a human? What technology do you think will have the biggest impact on the way we perform biotech research in the next couple of years?

Prot00ls

All new medical technologies have safety and other ethical concerns until clinical trials are complete. My group has a keen interest in innovative bio-safety strategies. In this case we addressed the 15+ year old challenge of pig viruses which infect human cells (particularly concerning in immunocompromised organ recipients). We used genome editing to eliminate 62 viral genes at once. We have similar efforts on immune tolerance and universal donor strategies extending recent successes in T cell therapies.

Hi Dr. Church, big fan!

1. What are your thoughts on the CRISPR patent controversy? How should we decide who gets credit?
2. Besides CRISPR, what are you most excited about in the coming years? What would be your ultimate blue-sky scientific dream?

bbctol

Q1: Most technologies require multiple patents and this is no exception. Many patents have already been issued on CRISPR without dispute. Only one topic (Cas9 use in eukaryotes) is controversial -- a odd leftover from the old patent law. The tremendous creativity in this field is reflected by 75 labs freely sharing their tech through addgene.org and seeing credit and rewards via this global community. Q2: Our blue sky within the BRAIN initiative (Innovative Neurotechnologies) is "molecular ticker-tape" to turn cellular activity time-series into compact DNA records. Also aging-reversal gene therapy and gene-drives for malaria.

A few years ago you were talking about creating lifeforms with reversed chirality (mirror images of all the molecules, e.g. left-handed DNA instead of right-handed). You were even talking about using them to fight global warming - by sequestering carbon dioxide in metabolically inaccessible bizarro glucose, I

think? How's that coming along?

Epistaxis

We have progress on mirror peptide synthesis that should be ready for publication in a few months as well as collaborations on mirror polymerase and ligase moving along swiftly too. Still quite far from a free-living mirror cell.

Hello Dr. Church.

I'm curious on your take if translational bioinformatics is going to be able to keep up with the pace of discovery in translating it to clinical practice. While the exponential growth in knowledge and understanding coming out of bioinformatics is very exciting, I worry that the lack of medical professionals with the proper training to deploy it will become a bottle neck.

DiscursiveMind

An analogy: We had exponential growth in PCs and Web, with too few expert professionals to counsel each new user, but the market responded with a variety of creative solutions. Genetics is poised to be even faster and bigger. The best medical professionals are teaming up with the best programmers to make effective user interfaces for moving targets such as *actionable* genetic test results. The goal isn't necessarily the longest reports, anymore than it would be for cell phone GPS apps.

Don't know if this is a stupid question, but Can you / will you ever be able use genetic engineering to make people feel less pain ?

Crapatusernames

Some people have natural genetic variants that make them insensitive to pain (for example, the SCN9A gene). This could become a target for conventional pharma, or a novel gene editing therapy with tissue location and/or timing controls. Unlike opioids or anesthetics this could eliminate pain with no dulling of cognition.

What is your stance on law enforcement using personal genomes produced by private companies to look for "criminals?"

Turbid_toaster

I encourage caution about many new technologies. I'm even more concerned about non-police uses -- increased levels of computer hacking of medical data and private investigators analyzing "abandoned" DNA that we leave everywhere.

Hi Dr.George

Lets go back many years ago. Do you think it was a mistake for the FDA to shut down hundreds of gene therapy trials and intensely regulate the field of gene therapeutics after the incident with Jesse Gelsinger?

Also: pigs as donors. Would you just have to remove surface antigens or receptors that the immune system detect as foreign? In the near future, would it be possible to tailor the pig's DNA (or cell surface at the very least) to be similar to a specific person? (Think designer pigs)

And lastly... Any tips for an aspiring molecular biologist/immunologist? :)

Thanks for your amazing work! I really can't put into words how much I look up to scientists such as yourself!

NovemberTerra

Q1: It wasn't just Jesse (Adeno hyperimmune reaction). Other problems involved the therapeutic retroviral-vector randomly integrating near the LMO2 oncogene (PMID: 14564000). The FDA caution reduces even more serious problems (for example, the unfortunate thalidomide approval in Europe not US). Q2: It would be possible to have custom donor types, but strategies for universal donor immune tolerance are emerging when gene editing of the donor cells is feasible, as in UCART therapies already and xenotransplantation hopefully soon. Universal donor methods require far less complicated inventory and distribution systems. Q3: It is a great time to study molecular immunology. In addition to transplantation and immunotherapy for cancer (both of which tend to be reactive medicine), synthetic biology can play a huge role in preventative medicine if we pay attention to interactions with microbiome and other environmental factors.

I submitted my DNA to 23andMe 5 or so years ago. My wife, who is a bit of a privacy nut, for lack of a better word (she won't give out her phone # or email to any group, for instance), thinks it was foolish of me to do that because of unforeseeable future risks.

What do you think are the risks possibly associated with giving your DNA over to a private organization?

randomunsourcedfacts

Ideally, the wide range of privacy preferences would be respected, however, we should be aware that we leave our DNA everywhere and the cost of DNA analysis is low and plummeting lower every day. Also, the motivation for hacking medical records has risen dramatically. http://www.reuters.com/article/us-cybersecurity-hospitals-idUSKCN0HJ21I20140924 An alternative to treating the privacy symptoms, is decreasing the underlying core problem which are stigmas associated with hiding. Examples (still work in progress) include more frank discussion than before of gay rights, depression, brain trauma, cancer, etc.

First of all, thanks for doing the AMA! I'm still unsure how I feel about genetic engineering. Its great that you're able to develop treatments for diseases, but im worried that this could be abused. What's your take on this and the moralities behind modifying the human genome? (Sorry if any of these questions are ignorant)

whyreason

Good question. See: http://www.wsj.com/articles/should-heritable-gene-editing-be-used-on-humans-1460340173

Hello Dr. Church,

CRISPR/Cas9 seems to have opened many new doors for treating aging in humans. Moving forward, what do you think is the most promising method for delivering anti-aging treatment to adult cells? Does an ex-vivo approach seem feasible, or would a DNA vector in a living human be required?

superscience3000

We are testing 45 gene therapies for aging-reversal, only 2 involve CRISPR. These use systemic (whole body, in vivo) gene delivery or targeted to specific tissues depending on the gene. Many of these genes have been validated in simple organisms extending longevity 2 to 10-fold, but utility in adult animals needs to be determined now.

Hello Dr. Church,

CRISPR/Cas9 seems to have opened many new doors for treating aging in humans. Moving forward, what do you think is the most promising method for delivering anti-aging treatment to adult cells? Does an ex-vivo approach seem feasible, or would a DNA vector in a living human be required?

superscience3000

We are testing 45 aging-reversal gene therapies in my lab, but only 2 of these involve crispr. We are using systemic (whole body, in vivo) delivery as well as targeting specific tissues depending on the detailed physiology of each.

How much does something like epigenetics complicate the work you do?

buboniccronic

I hesitate to call it a complication, more like an great opportunity, since we greatly benefit from epigenetics as a tool for reprogramming skin cells into stem cells and then into nearly any tissue of the body. We also use epigenetics to make sensor circuits for essentially any molecule and couple these to many other bio-mechanisms.

How much does something like epigenetics complicate the work you do?

buboniccronic

I hesitate to call it a 'complication', since we love using it as a tool -- 1) to reprogram skin cells into stem cells to almost any other tissue or organ, 2) to build novel sensor circuits for almost any molecule, 3) to monitor aging reversal.

Hello Dr. Church! I think you were one of the first to warn the scientific community at large about the potential for runaway gene drives. You and your lab have already been working on developing safety measures and best practices to decrease those risks. Can you talk a little bit about what kind of regulation you think is necessary for responsible CRISPR use in this context? Do we need a regulatory body to approve CRISPR construct design? Or just better education for scientists about dual use potential?

And how do we protect ourselves from bioterrorism that uses gene drives lacking these safeguards? Is it even feasible to start regulating CRISPR use given how quickly the technology has spread into practically every bio lab?

On the more positive side, what could the government or institutions do to support responsible CRISPR-based research into larger-scale (but controlled) ecosystem research?

biocuriousgeorgie

Fortunately, gene drives spread slowly via breeding (unlike rapid spread via infection). Our original

warning included methods for reversal (since then tested successfully), which are needed along with surveillance of approved and unapproved releases. This does not seem a likely source of bioterror (relative to say in appropriate dispersal of natural pathogens), but now is a great opportunity (as you note) to raise awareness and support for a variety of ecosystem research projects.

Hi Dr Church -- thanks very much for participating with us

my brother and i probably have genetic damage; our dad worked in the power industry in the 1950s when PCB oil was considered harmless. at that time big transformers were built in vats of PCB, and dad was up to his elbows in it every day working on the transformers. the guys there used to wipe it off their hands with a rag, and then eat sandwiches. my dad must have ingested a considerable amount, and also unknowingly spread it all over his belongings and household environment.

i am all too aware of PCB's reputation as a mutagen, even in tiny amounts

should my brother and i get sequenced? if so, do you recommend a particular provider?

is CRISPR able to repair genetic damage in adults at this time?

thanks for offering your thoughts, and please know you are tremendously admired for your achievements.

sighbourbon

Q1: Polychlorinated biphenyl toxicity seems to be mainly due to hormonal effects rather than mutagenic. Nevertheless, there are potential advantages of genetic counseling for all of us. Q2: http://arep.med.harvard.edu/gmc/genome_services.html
Q3: There are 2200 gene therapies in clinical trials at present, but it may be years before these are approved, lower cost and in widespread use.

Hi Mr Church!

I wrote a paper on your work for an assignment on new developments in Biology, and found it extremely interesting in researching it.

My question is, how soon do you see the first nanorobot injections being brought to the wider public, through doctors or directly?

Thanks!

bitchtitfucker

These will go through the normal (phase 1,2,3) FDA approval process, after the current animal testing phase. Probably will take several years.

I'm taking a molecular bio class this semester, and just today we were talking about CRISPR/Cas9. My professor mentioned that this type of technology is sort of a "kitchen tool." What she meant is that you don't need extremely specialized technology to use CRISPR, and it is slightly more accessible than other technologies. In her view the relative simplicity of CRISPR makes it a "genie's out of the bottle" opportunity.

How true is this statement? Do you think this type of gene editing technology is accessible to labs that don't have a large research budget? Do you think that this is something an average person with some

extra cash could use? And if so, what would this mean for both the ethics of gene editing and the popularization of science ? Thanks!

kakoivrach

CRISPR is not unique in this regard. Many DIYBIO labs (and IGEM) have been practicing molecular biology on a shoestring budgets worldwide. We have encouraged bioethics (human practices) as a core component of these grassroots operations and hope that part is even more 'accessible' than the technology. It is crucial to engage a very broad public in such discussions (including AMA!)

Hi Dr. Church!

My question is about using DNA as an archival medium. What is the long-term fidelity of storage like? Will information be lost due to mutation or just chemical degradation over time?

superhelical

The record for DNA persistence is 700,000 years (stored under less than ideal circumstances in a yukon horse). Stored in a dry, anoxic state this could be longer. As with other archival systems, redundancy is key. No energy is required during storage, the physical format doesn't change, and the size/density is a million times better than other current methods. Although the cost of copying is low (70 billion copies of a book was nothing), the cost of the original copy still needs to come down.

How does your lab approach encoding data into stable DNA sequences without the benefit of natural selection to select against unstable sequences?

Abigail15

We can use laboratory-based evolution to optimize stability. If long term stability of DNA is needed (for example for archival information storage) this can be accomplished in non-living systems. Both could possibly last for a million years.

Hi George, thanks for doing this AMA! Has any intrinsic function for the DNA molecule itself(aside from encoding information) ever been found? Have we ever been able to make it do anything physically interesting in that regard?

razor5cl

DNA is also used in cells in a (non-gene-encoding) roles such as centromere and telomeres. DNA is also used as a 'material' to make nanorobots, drug delivery, measure forces, etc.

Why are you a professor at more than one university? How do you split your time between them?

SingularityIsNigh

Harvard and MIT have many bridges, including Health Sciences and Technlogy (HST) founded in 1970, the Broad and Wyss Institutes and the MIT Media Lab. They also share with the whole world via open courseware and MOOCs. I have participated in all of these.