it is NOT junk

a blog about genomes, DNA, evolution, open science, baseball and other important things

The Villain of CRISPR

By MICHAEL EISEN | *Published:* JANUARY 25, 2016

There is something mesmerizing about an evil genius at the height of their craft, and Eric Lander is an evil genius at the height of his craft.

Lander's recent essay in *Cell* entitled "The Heroes of CRISPR" is his masterwork, at once so evil and yet so brilliant that I find it hard not to stand in awe even as I picture him cackling loudly in his Kendall Square lair, giant laser weapon behind him poised to destroy Berkeley if we don't hand over our patents.

This paper is the latest entry in Lander's decades long assault on the truth. During his rise from math prodigy to economist to the *de facto* head of the public human genome project to member of Obama's council of science advisors to director of the powerful Broad Institute, he has shown an unfortunate tendency to treat the truth as an obstacle that must be overcome on his way to global scientific domination. And when one of the world's most influential scientists treats science's most elemental and valuable commodity with such disdain the damage is incalculable.

CRISPR, for those of you who do not know, is an anti-viral immune system found in archaea and bacteria, that until a few years ago, was all but unknown outside the small group of scientists, mostly microbiologists, who had been studying it since its discovery a quarter century ago. Interest in CRISPR spiked in 2012 when a paper from colleagues of mine at Berkeley and their collaborators in Europe described a simple way to repurpose components of the CRISPR system of the bacterium *Streptococcus pyogenes* to cut DNA in a easily programmable manner.

Such capability had been long sought by biologists, as targeted DNA cleavage is the first step in gene editing – the ability to replace one piece of DNA in an organism's genome with DNA engineered in the lab. This 2012 paper from Martin Jinek and colleagues was

Michael Eisen

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quickly joined by a raft of others applying the method *in vivo*, modifying and improving it in myriad ways, and utilizing its components for other purposes. Among the earliest was a paper from Le Cong and Fej Ann Ran working at Lander's Broad Institute which described CRISPR-based gene editing in human and mouse cells.

Now, less than four years after breaking onto the gene-editing scene, virtually all molecular biology labs are either using, or planning to use, CRISPR in their research. And amidst this explosion of interest, fights have erupted over who deserves the accolades that usually follow such scientific advances, and who owns the patents on the use of CRISPR in gene editing.

The most high-profile of these battles pit Berkeley against the Broad Institute, although researchers from many other institutions made important contributions. Jinek's work was carried out in the lab of Berkeley's Jennifer Doudna, and in close collaboration with Emmanuelle Charpentier, now at the Max Planck Institute for Infection Biology in Berlin; while Cong and Ran were working under the auspices of the Broad's Feng Zhang. Interestingly, the prizes for CRISPR have largely gone to Doudna and Charpentier, while, for now at least, the important patents are held by Zhang and the Broad. But this could all soon change.

There has been extensive speculation that CRISPR gene editing will earn Doudna and Charpentier a Nobel Prize, but there has been considerable lobbying for Zhang to join them (Nobel Prizes are, unfortunately, doled out to a maximum of three people). On the flip side, the Broad's claim to the patent is under dispute, and is the subject a legal battle that could turn into one of the biggest and most important in biotechnology history.

I am, of course, not a disinterested party. I know Jennifer well and an thrilled that her work is getting such positive attention. I also stand to benefit professionally if the patents are awarded to Berkeley, as my department will get a portion of what are likely to be significant proceeds (I have no personal stake in any CRISPR-related patents or companies).

But I if I had my way, there would be no winner in either of these fights. The way prizes like the Nobel give disproportionate credit to a handful of individuals is an injustice to the way science really works. When accolades are given exclusively to only a few of the people who participated in an important discovery, it by necessity denies credit to countless other people who also deserve it. We should celebrate the long series of discoveries and inventions that brought CRISPR to the forefront of science, and all the people who participated in them, rather than trying to decide which three were the most important.

And, as I have long argued, I believe that neither Berkeley nor MIT should have patents on CRISPR, since it is a disservice to science and the public for academic scientists to ever claim intellectual property in their work.

Nonetheless, these fights are underway. Which beings us back to Dr. Lander. Although he had nothing to do with Zhang's CRISPR work, as Director of the Broad Institute, he has taken a prominent role in promoting Zhang's case for both prizes and patent. But rather than simply go head-to-head with Doudna and Charpentier, Lander has crafted an ingenious strategy that is as clever as it is dishonest (see Nathaniel Comfort's fantastic "A Whig History of CRISPR" for more on this). Let's look at the way Lander's argument is crafted.

To start, Lander cleaves history into two parts – Before Zhang and After Zhang – defining the crucial event in the history of CRISPR to be the demonstration that CRISPR could be used for gene editing in human cells. This dividing line is made explicit in Figure 2 of his "Heroes" piece, which maps the history of CRISPR with circles representing key discoveries. The map is centered on a single blue dot in Cambridge, marking Zhang as the sole member of the group that carried out the "final step of biological engineering to enable genome editing", while everyone who preceded him gets labeled as a green natural historian or red biochemist.

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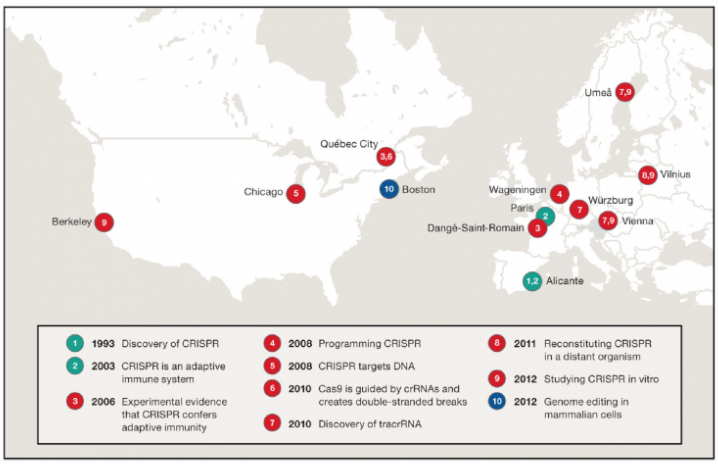

Figure 2. The Twenty-Year Story of CRISPR Unfolded across Twelve Cities in Nine Countries
For each "chapter" in the CRISPR "story," the map shows the sites where the primary work occurred and the first submission dates of the papers. Green circles refer to the early discovery of the CRISPR system and its function; red to the genetic, molecular biological, and biochemical characterization; and blue to the final step of biological engineering to enable genome editing.

(Note also how he distorted the map of the world so that the Broad lies almost perfectly in the center. What happened to Iceland and Greenland? How did Europe get so far south and so close to North America? And what happened to the rest of the world? Where's Asia, for example? Shouldn't there be a big blue circle in Seoul?)

While some lawyer might find this argument appealing, it is a scientifically absurd point of view. For the past decade, researchers, including Zhang, have been using proteins – zinc finger nucleases and TALENs – engineered to cut DNA in specific places to carry out genome editing in a variety of different systems. If there was a key step in bringing CRISPR to the gene editing party, it was the demonstration that its components could be used as a programmable nuclease, something that arose from a decade's worth of investigation into how CRISPR systems work at the molecular level. Once you have that, the application to human cells, while not trivial, is obvious and straightforward.

The best analogy for me is the polymerase chain reaction (PCR) another vital technique in molecular biology that emerged from the convergence of several disparate lines of work over decades, and which gained prominence with the work of Kary Mullis, who demonstrated an efficient method for amplifying DNA sequences *in vitro*. Arguing that Zhang deserves singular credit for CRISPR gene editing is akin to arguing that whomever was the first to amplify human DNA using PCR should get full credit for its invention. (And I'll note that the claim that Zhang was unambiguously the first to do this is questionable – see this and this for example).

I want to be clear that in arguing against giving exclusive credit to Zhang, I am not arguing for singular credit to go to any other single group, as I think this does not do justice to the way science works. But if you are going to engage in this kind of silliness, one should at least endeavor to do it honestly. The only reason one would ever argue that CRISPR credit should be awarded to the person who first deployed it in human cells is if you decided in advance that full credit should go to Zhang and you searched *post facto* for a reason to make this claim.

Even Lander seems to have sensed that he had to do more than just make a tenuous case for Zhang – he had to also tear down the case for Doudna and Charpentier. And this wasn't going to be easy, since their paper preceded Zhang's, and they were already receiving widespread credit in the biomedical community for being its inventors. Here is where his evil genius kicks in. Instead of taking Doudna and Charpentier on directly, he did something much more clever: he wrote a piece celebrating the people whose work had preceded and paralleled theirs.

This was an evil genius move for several reasons:

First, the people whose work Lander writes about really are deserving of credit for pioneered the study of CRISPR, and they really have been unfairly written out of the history in most stories in the popular and even scientific press. This established Lander as the good guy, standing up to defend the forgotten scientists, toiling in off-the-beaten-path places. And even though, in my experience, Doudna and Charpentier go out of their way to highlight this early work in their talks, Lander's gambit makes them look complicit in the exclusion.

Second, by going into depth about the contributions of early CRISPR pioneers, Lander is able to almost literally write Doudna and Charpentier (and, for that matter, the groups of genome-editing pioneer George Church and Korean scientist Jin-Soo Kim, whose CRISPR work has also been largely ignored) out of this history. They are mentioned, of course, but everything about the way they are mentioned seems designed to minimize their contributions. They are given abbreviated biographies compared to the other scientists he discusses. And instead of highlighting the important advances in the Jinek paper, which were instrumental to Zhang's work, Lander focuses instead on the work of Giedrius Gasiunas working in the lab of Virginijus Siksnys in Lithuania. Lander relates in detail how they had similar findings to Jinek and submitted their paper first, but struggled to get it published, suggesting later in the essay that it was Doudna and Charpentier's savvy about the journal system, and not their science, that earned them credit for CRISPR.

The example of Gasuinas and Siksnys is a good one for showing how unfair the system we have for doling out credit, accolades and intellectual property in science can be. While Gasuinas did not combine the two RNA components of the CRISPR-Cas9 system into a single "guide RNA" as was done by Jinek – a trick used in most CRISPR applications – they demonstrated the ability to reprogram CRISPR-Cas9, and were clearly on the path to gene editing. And neither Jinek or Gasuinas's work would have been possible without the whole body of CRISPR work that preceded them.

But the point of Lander's essay is not to elevate Siksnys, it is, as is made clear by the single blue circle on the map, to enshrine Zhang. His history of CRISPR, while entertaining and informative, is a cynical ploy, meant to establish Lander's bonafides as a defender of the little person, so that his duplicity in throwing Siksyns under the bus when he didn't need him anymore wouldn't be so transparent.

What is particularly galling about this whole thing, is that Lander has a long history of attempting to rewrite scientific history so that credit goes not to the forgotten little people, but to him and those in his inner circle. The most prominent example of this is the pitched battle for credit for sequencing the human genome, in which Lander time and time again tried to rewrite history to paint the public genome project, and his role in it, in the most favorable light.

Indeed, far from being regarded as a defending of lesser known scientists, Lander is widely regarded as someone who plays loose with scientific history in the name of promoting himself and those around him. And "Heroes of CRISPR" is the apotheosis of this endeavor. The piece is an elaborate lie that organizes and twists history with no other purpose than to achieve Lander's goals – to win Zhang a Nobel Prize and the Broad an insanely lucrative patent. It is, in its crucial moments, so disconnected from reality that it is hard to fathom how someone so brilliant could have written it.

It's all too easy to brush this kind of thing aside. After all Lander is hardly the first scientist to twist the truth in the name of glory and riches. But what makes this such a tragedy for me is that, in so many ways, Lander represents the best of science. He is a mathematician turned biologist who has turned his attention to some of the most pressing problems in modern biomedicine. He has published smart and important things. As a mathematician turned biologist myself, it's hard for me not to be more than a little proud that a math whiz has become the most powerful figure in modern biology. And while I don't like his scientific style of throwing millions of dollars at every problem, he has built an impressive empire and empowered the careers of many smart and talented people whose work I greatly value and respect.

But science has a simple prime directive: to tell the truth. Nobody, no matter how powerful and brilliant they are is above it. And when the most powerful scientist on Earth treats the truth with such disdain, they become the greatest scientific villain of them all.

This entry was posted in *Berkeley*, *CRISPR*, *science*, *University of California*. Bookmark the *permalink*. Both comments and trackbacks are currently closed.

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43 Comments

interested reader
Posted January 25, 2016 at 8:58 am | *Permalink*

what happened to Chylinski in all of this?

Cory
Posted January 25, 2016 at 10:25 am | *Permalink*

Thanks for the alternative perspective. I am a scientist in a different field, but I had read Lander's Cell article and did not question his retelling of the history at all. You'd think there would be some declaration of a conflict of interest given his association with the Broad Institute.

I'm also disillusioned that academics use public funds to patent their research. It's ridiculous and morally questionable.

Justin
Posted January 25, 2016 at 10:55 am | *Permalink*

My friend Eva couldn't help but see another parallel in this story. While it is clear that a lot of this is about the Broad trying to justify their patent rights (I think they will lose them) it also reflects some of the plight of women in science. It is not just Lander's piece that glorify Feng Zhang and even write about his childhood genius, but the media in general often glorifies male scientists and not female scientist. Here is a case where the leading scientists developing the science were female, as is the CEO (Rachel Haurwitz) of the company they founded, Caribou Bioscience, but almost all the hype I read in the mainstream media concerning CRISPR centers around Editas and Feng Zhang. Here article is here if you are interest, I believe it is an interesting point of view.

http://www.thehappytalent.com/blog/-two-female-scientists-discovered-a-revolutionary-gene-technology-predictably-men-are-trying-to-steal-their-patents

Michael Eisen
Posted January 25, 2016 at 11:06 am | *Permalink*

Yes. I pointed this out on Twitter. Lander is taking advantage of gender politics here, especially the fact that in many ways Doudna and Charpentier aren't "allowed" to fight back in that they would be judged far more harshly for doing so then men would be.

Pete
Posted January 26, 2016 at 12:12 pm | *Permalink*

Doudna is introduced by Lander as "a world-renowned structural biologist and RNA expert at the University of California, Berkeley." Charpentier is described as one of those "near the very start of their scientific careers." Doudna was born in 64, Charpentier in 68, so it's a little hard to see what he was getting at beyond belittling one of Zhang's rivals and perhaps implying that the other poached from junior

colleagues. It's definitely weird. And of course both of them hit back briefly and publicly, coming very close to accusing Lander of lying.

George McNamara
Posted February 6, 2016 at 2:54 pm | *Permalink*

To the commenter bashing Editas — The executive team of Editas Medicine – including the CEO, are women:
Katrine Bosley, Chief Executive Officer
Alexandra Glucksmann, Ph.D., Chief Operating Officer
Deborah Palestrant, Ph.D., Senior Director, Business Development and Strategy
Charlene Stern, Ph.D., J.D., Senior Director, Intellectual Property and Legal Affair
http://www.editasmedicine.com/about-team.php
p.s. and just had a successful IPO.

A. P.
Posted January 25, 2016 at 10:56 am | *Permalink*

Completely agree with you.

However, can we overlook the role of Cell in this? They should have never allowed a history of CRISPR to be written by someone who, first of all, has absolutely nothing to do scientifically with the CRISPR field, and second, has such a conflict of interest that it would be absurd to expect him to write an unbiased history. This is scientific publishing at its worst, and the evils here cannot be solely attributed to Lander.

Justin
Posted January 25, 2016 at 11:39 am | *Permalink*

Totally agree. I would expected this article as an op-ed in an MIT/Broad run news site, but not in Cell. Shame on you Cell.

Popcorn debate
Posted January 25, 2016 at 12:54 pm | *Permalink*

Dr. M Eisen spends way too much text trying to make a case for the Doudna/Charpentier duo's chances of winning a Nobel prize. The article is simply a Californian version of what Lander tried to do.

Yet for anyone else that does not live in the US, what is funny from all this debate is how from Landers' historical map of CRISPR that recapitulates the critical discoveries behind CRISPR, only the 2 last spots of this map (of course; California vs Boston, what else…) are the ones being debated for the glory of the Nobel prize.

Doudna did some nice work. So has done Zhang. But a number of ppl had already figured out EVERYTHING. Including that the system could be transplanted between bugs. Credit and honor should go to them.

This is a recurrent patern. Rajewsky and bostonians also jumped on reprogramming cells to pluripotency, made some great science out of it (and a horde of "top" papers) and improved the system. Hail to them. But the Nobel Prize went to Yamanaka.

Michael Eisen
Posted January 25, 2016 at 12:58 pm | *Permalink*

I don't think you actually read what I wrote. I think the whole way Nobel Prizes work is toxic, and I have no interest in making the case for anyone to win it.

Popcorn debate

Posted January 25, 2016 at 1:29 pm | *Permalink*

Sure…

1- “Interest in CRISPR, which had been largely confined to the microbiology world, spiked in 2012 when a paper from colleagues of mine at BERKELEY and their collaborators in Europe described a simple way to repurpose components of the CRISPR system of the bacterium Streptococcus pyogenes to cut DNA in a easily programmable manner.”

2- “Such capability had been long sought by biologists… …The 2012 paper from BERKELEY’S Martin Jinek and colleagues was quickly followed by a raft of others…”

3- “It is widely expected that CRISPR will earn Doudna and Charpentier a Nobel Prize, but there has been considerable lobbying for Zhang to join them.”

etc…

You have done exactly what you criticize from Lander. Use your post to praise your colleagues and their contribution, and to criticize Zhang “ala” Lander (by, for instance, just dropping a small sentence which questions whether he was first to use the system in human cells).

The spanish guy deserves more credit. Figuring out what these odd sequences could be, and having the smell to imagine that this was a bacterial immune system… That is the ice-breaker. And then of course, technologists with $$$ come and make it happen.

But of course, there is no patent-war nor lobbying for a guy in the mediterranean coast.

Michael Eisen

Posted January 26, 2016 at 2:02 pm | *Permalink*

I was saying Berkeley there to acknowledge my conflict of interest with those papers, not to try to argue for credit to Berkeley. I tried to make it clear that I am not arguing for Berkeley to win these fights, but I edited those passages.

As for the broader point about credit, I think there’s always an interesting discussion about who deserves credit for moving a field forward. In many ways this is a fool’s errand, but it’s one we all engage in. I agree with you that the people who stared at these repeats and realize, or at least suspected, that something interesting was going on there deserve a huge amount of credit. Because without them, who knows how long it would have taken for someone to stumble upon CRISPR in a different way (from genetics or something). I generally assume that virtually all scientific advances would be arrived at eventually. So the real question is who made these things happen faster. And in this case the sequence gazers made a big difference.

One of the things I really hate in science is our tendency to reward people for doing something obvious faster than everyone else who’s been trying to do it. I can’t tell you how many times I’ve shaken my head at people getting credit for knocking out the mouse ortholog of some newly identified human disease gene faster than the 10 other groups that were trying to do the same thing. What a waste of time and effort.

Claudiu Bandea
Posted January 27, 2016 at 4:48 pm | *Permalink*

The points you are making here are highly relevant and hope you'll continue to bring them forward. The extreme competition in science promoted by the current funding and promotional system gives many scientists little choice but hype or even distort their research and accomplishments, polluting science with unreproducible data and misleading concepts. This situation is particularly distressing when it happens in bio-medical fields affecting the live and well-being of many people, sometimes millions of people as I think is the case with the field of neurodegenerative diseases (see my comment below).

Michael Eisen
Posted January 25, 2016 at 1:04 pm | *Permalink*

"But if I had my way, there would be no winner in either of these fights. The way prizes like the Nobel give disproportionate credit to a handful of individuals is an injustice to the way science really works. The accolades for Doudna and Charpentier deny credit to countless other people who also deserve it. We should celebrate the long series of discoveries and inventions that brought CRISPR to the forefront of science, and all the people who participated in them, rather than trying to decide which three were the most important."

Claudiu Bandea
Posted January 27, 2016 at 4:49 pm | *Permalink*

The points you are making here are highly relevant and hope you'll continue to bring them forward. The extreme competition in science promoted by the current funding and promotional system gives many scientists little choice but hype or even distort their research and accomplishments, polluting science with unreproducible data and misleading concepts. This situation is particularly distressing when it happens in bio-medical fields affecting the live and well-being of many people, sometimes millions of people as I think is the case with the field of neurodegenerative diseases (see my comment below).

Claudiu Bandea
Posted January 29, 2016 at 10:51 am | *Permalink*

This comment is an accidental duplication of the one above. Michael, please remove it, if you can. Thanks.

Postdoc
Posted January 25, 2016 at 1:56 pm | *Permalink*

"What is particularly galling about this whole thing, is that Lander has a long history of attempting to rewrite scientific history so that credit goes not to the forgotten little people, but to him and those in his inner circle. "

Do you have any other examples you'd like to share besides this and the HGP?

Michael Eisen
Posted January 25, 2016 at 10:56 pm | *Permalink*

For starters, look at the mouse genome paper, which glosses over the contributions of Jim Weber and Gene Myers to shotgun sequencing and acts like it was always obvious that it was the right strategy to pursue, when neither the human or mouse sequencing projects were built to pursue this strategy. And then the Kellis and Lander paper on whole genome duplication in yeast which 'proves' something that had already been convincingly established by Ken Wolfe and Denis Shields.

Scerv Isiah
Posted January 25, 2016 at 3:16 pm | *Permalink*

Michael, when you write "This paper is the latest entry in Lander's decades long assault on the truth." I am sure you are not doing it lightly and have many more offenses in mind other than the CRISPR paper, and they are not limited to attribution and credit but also strict issues of science, in this case biology. I think it is urgent for you to rebalance your criticism covering issues of science unrelated to CRISPR or retract such a sweeping statement, which risks being reduced to an MIT-Berkeley feud. If you have in the past you should provide some references. Thanks.

Michael Eisen
Posted January 25, 2016 at 10:56 pm | *Permalink*

For starters, look at the mouse genome paper, which glosses over the contributions of Jim Weber and Gene Myers to shotgun sequencing and acts like it was always obvious that it was the right strategy to pursue, when neither the human or mouse sequencing projects were built to pursue this strategy. And then the Kellis and Lander paper on whole genome duplication in yeast which 'proves' something that had already been convincingly established by Ken Wolfe and Denis Shields.

Scerv Isiah
Posted January 26, 2016 at 11:18 am | *Permalink*

Thanks. These are important examples but also issues of proper credit. So I gather that your position is that Lander's assault on truth is limited to self-aggrandizing and credit redistribution. That in itself is reproachable, but I was more interested in errors of biology, e.g. the Kellis and Lander paper also contains "proof" of subfunctionalization in yeast, a largely debunked but never officially corrected assertion.

noob
Posted January 26, 2016 at 1:28 pm | *Permalink*

Another example: "lncRNAs" – previously discovered by others including Chris Ponting et al – Lander announced at BoG 2008(?) that his group had discovered and named them

Ken Weiss
Posted January 26, 2016 at 8:56 am | *Permalink*

People always have had their egos, spats and struggles for resources and credit. Our system, especially the rewards, publicity, funding and so on aspects, have created a snake pit. It hasn't been hard to see it develop over the past 30 years. In a broad sense, it owes its existence to the expansion of universities, their dependence on grant funds, and the precedents set by Manhattan and related WWII-era mega projects–the way to go if you want a secure job is to set up something too big to kill. The details of today's issues are consequences and reflections of this, each in its own way.

And, of course, if we allow snake pits to develop, we have to expect to find snakes inhabiting them. They're just going where the meat is.....

Claudiu Bandea
Posted January 26, 2016 at 4:20 pm | *Permalink*

One might think of Michael's essay as a glorification of Lander in disguise, as both authors combine their 'evil geniuses' to place the CRISPR story at the Broad/Berkely intersection, right where they happen to live. Or, they might be united behind a grand goal – that of elevating science from the brink of ridicule to a productive and fair enterprise devoid of heroes, money, and prizes? One sensible way of initiating a movement towards that goal is by showing, using 'antagonistic' approaches, how ridiculous and scandalous the current science is. But, what do I know about the politics of science? Instead, I'll focus here on some plain science lessons inspired by CRISPR.

As it is well known by now, CRISPR is an adaptive immune system found in archaea and bacteria that uses previously acquired viral sequences in a defense mechanism against related viral elements. Another microbial antiviral immune system, the restriction modification system, was discovered a few decades back, and it led to the celebrated recombinant DNA technology. More recently, the discovery of microRNA phenomenon, which has evolved as an antiviral defense system eventually co-opted as a gene-expression regulatory mechanism, was as exciting, promising, and prized as CRISPR. I must also note one of the most surprising discovery in biology, the 'introns' and 'spliceosomes', which have apparently evolved as a genomic immune system against insertional mutagenesis by viral elements. Not to mention to mention the co-option of viral sequences into during the evolution of many components of the classical immune system, including antibodies, T-cells receptors and MHC.

Are there any sensible lessons that we can to learn from CRISPR and all these extraordinary phenomena? What other enigmatic phenomena born from the co-evolution of viruses and their hosts are there in the waiting to be recognized as defense immune systems? Well, if the CRISPR publishing fiasco reported by Lander is correct, then we should search among the stories that are having a hard time penetrating the formidable protective wall surrounding conventional science.

Here I present two such phenomena, which are of extraordinary scientific and public health significance. I must first disclose, though, a 'conflict of interest': I have been working mostly undercover on these phenomena for a couple for decades, so they could be regarded as a shameless case of self-promotion. Please let know if you think so; I will highly appreciate it, seriously.

One of these phenomena is the C-value paradox or enigma, which has been investigated for more than half-of-a-century, but has remained one of the greatest unanswered questions in biology. We know that most of our genome is composed of viral sequences and their evolutionary derivatives, which currently are referred to as "junk DNA" (this subject should be well in the territory of Michael's blog entitled "it is NOT junk"). What if most of our genome is not "junk DNA" as traditionally perceived, but serves, just like CRISPR and spliceosomal introns, as a defensive immune system against insertional damage by endogenous and exogenous viral elements, such as retroviruses? http://biorxiv.org/content/biorxiv/early/2013/11/18/000588.full.pdf

The other phenomenon I bring forward is even more significant, because it concerns the etiology of a mysterious group of neurodegenerative diseases, including Alzheimer's, Parkinson's, Huntington's, ALS, and Creutzfeldt-Jakob disease, which affect the life of tens of millions of people worldwide, and cost us hundreds of billions of dollars every year. Despite decades of research and thousands of studies, the etiology of these diseases is not known, and there are no successful preventive or therapeutic approaches. Moreover, the physiological function of the proteins implicated in these diseases, APP/amyloid-beta, tau, alpha-synuclein, huntingtin, TAR DNA-binding protein 43 and prion protein, which are among the most studied

proteins in the world, is not known. What if these proteins are members of the innate immune system? The evidence for this theory (http://biorxiv.org/content/biorxiv/early/2013/11/18/000604.full.pdf) is increasing (see http://www.ncbi.nlm.nih.gov/pubmed/26719256/ for the latest evidence), but it clashes with the primary working hypotheses in the field the field, the highly acclaimed and prized 'protein misfolding' and 'prion' paradigms, which have directed the research and the scientific careers of an entire generation of scientists.

George H.
Posted January 28, 2016 at 3:52 am | *Permalink*

Hey, Mr Bandea, very interesting comment in the size of mini article. Granted, I am not one of those who spent 'couple of decades' in the trenches of bioscience research, it's very hard for me to digest your sophisticated analysis. I still can grasp the core of your hypothesis and sense depth of your passion and knowledge on the subject matter. So- why don't you consider starting your own blog to promote valuable ideas that so far have not penetrated the walls of conventional science. Please also remember that the for 1% of super-experts/scientists, who can decipher your deeply technical points, there is 99% of otherwise well educated and passionate readers like me- you might consider creating less complicated version of your presentations for wider audience. Thank you for your post.

Claudiu Bandea
Posted January 29, 2016 at 10:45 am | *Permalink*

Hi George,

Thanks of your comment and BTW you can call me by my first name :). I'm glad you grasped the core of my hypotheses, which are based on reinterpretation and integration of the vast amounts of data and observations in the respective fields into conceptual frameworks that, I believe, make biological and evolutionary sense. I don't think they are highly sophisticated, as there are based primarily on common sense, attention to details, and some imagination feed by relentlessly asking "Why?" and "How?".

Regarding your point about presenting my ideas to a wider audience, I think scientists should *not* present their studies or ideas to a larger, non-expert audience, until they are fully evaluated and validated by the majority of their peers. I know, that's not a very popular approach, but there is not much I can do about that.

What I'm trying do, though, is to bring these ideas to the attention of people who have the expertise to evaluate them, but are not necessarily vested in the current working hypotheses. You see, my ideas challenge the primary working hypotheses in the respective fields and, unfortunately, within the current funding and promotional system the proponents of these working hypotheses have little choice but to maintain the status quo. There is no question that even under the broken system, science will ultimately prevail, but for many patients and their families, that might be too late.

Let me finish by saying that Michael has built an extraordinary blog with wide audience, including, I hope, some "free" thinkers and experts, who might evaluate these new paradigms. One day, we might have a funding and promotional system that encourages or even mandates an open and comprehensive evaluation of all ideas and studies in a field, but until then I thank Michael for this opportunity.

Ela
Posted February 8, 2016 at 6:45 pm | *Permalink*

There has been the recent finding in relation to schizophrenia – a gene of the immune system being involved. It blew me away but it has been my thought that scientific advancement with respect to solutions to certain pressing questions is not because we don' t have the answers. It's just because people have become so secluded in their o called fields of specialization.

Ela
Posted February 9, 2016 at 8:47 am | *Permalink*

To Claudiu's comment: There has been the recent finding in relation to schizophrenia – a gene of the immune system being involved. It blew me away but it has been my thought that scientific advancement with respect to solutions to certain pressing questions is not because we don' t have the answers. It's just because people have become so secluded in their o called fields of specialization.

Claudiu Bandea
Posted February 14, 2016 at 1:38 pm | *Permalink*

Ela,

Thanks for bringing forward the recent finding pointing to the complement system (C4) as a key factor in schizophrenia.

I agree that specialization, albeit essential for producing data and observations, is often contra productive. For example, regarding the model on the etiology of Alzheimer's, Parkinson's, Huntington's, ALS, and CJD as described above, if we ask researchers in the field of neurodegenerative diseases to evaluate it, the answer is they don't have the expertise in virus/host co-evolution or immunology. Immunologists, apparently don't have the expertise in neurodegenerative diseases, viruses, or evolution, and virologists and evolutionists don't have expertise in neurodegenerative diseases and immunology, etc.

Peter Allen
Posted January 26, 2016 at 6:09 pm | *Permalink*

We already knew about all of this in 'The Double Helix.'
Also in 'A short history of everything' in which Bill Bryson gives numerous examples in history, especially paleontology, where fear and loathing were common.

And in Michael Crichton's 'Next' where he warns about patenting genetics.

Klas Udekwu
Posted January 26, 2016 at 11:37 pm | *Permalink*

Nice retort of sorts! Even more sad within the context of the Nobel prize is the fact that active canpaigning goes on for what ought to be a merit-based prize. When heads of juggernaut labs from Asia and the Americas come visiting the Karolinska Inst. Sweden incessantly with 1000 publications, billions seemingly in research funds and an army of ASS Profs in the bag, a dark cloud subsumes science. Thankfully it is only Medicine that the KI 'awards'. I agree with your stance on the 'silent' majority being lost in the drive to reward a few with what is truly a collaborative effort. Hopefully the establishment that is US gets real about what we are truly here for; 'Da people' as a dear mentor of mine likes to stress.

Virginia Savova
Posted January 27, 2016 at 8:46 pm | *Permalink*

This is what happens when science turns into business, when institutes are run as corporations, with "deliverables", productivity, and patents as the measure of success. The American government is the customer, and the scientists are made to constantly "sell" their product to it by writing grants. They also must entertain politicians on occasion. Why is it surprising then, the kind of characters such science breeds? The question is, how do we change the culture, the incentives, so that we can promote sharing and openness in the name of our common goal of understanding the world and curing disease, rather than this corrupting concept of competition? (I dare sign this with my real name)

Querolus
Posted January 31, 2016 at 12:09 am | *Permalink*

That is the best short comment ever written to describe science… It is exactly the core problem in science (and in any other discipline pursuing the 'truth' such as journalism)

Zachary Pitluk
Posted January 29, 2016 at 2:11 pm | *Permalink*

Look, you assign triviality to the development of prokaryotic systems in eukaryotes. What have you been smoking? Millions of experiments have failed to cross this divide. Then you invoke Zn fingers, a eukaryotic motif, without mentioning this. You'd need to get smarter to classify as a lost. Get lost.

Michael Eisen
Posted January 29, 2016 at 6:46 pm | *Permalink*

Yes, it is often difficult to transfer systems between taxa, especially bacteria and archaea to eukaryotes. But we're not dealing in abstractions or generalizations here. We are talking about the specific case of the application of CRISPR-based gene editing to humans. And in this case, while I wouldn't say the transfer was trivial, it was fairly straightforward, as evinced by the fact that at least five groups did it more or less simultaneously after working on it for a fairly short period of time.

Anonymous Stem Cell
Posted January 29, 2016 at 7:45 pm | *Permalink*

I guess we've been looking at different sets of "millions of experiments"then. Even leaving aside the specific case, once the restriction enzymes were cloned out, it was pretty trivial/straightforward to adapt them to euakaryotic systems, like I-SceI . Even the phage integrases required not that much effort. The TALEs did it through evolution. Mike is totally right in this case. By the time we got to 2012, all

the really hard work had already been done.

I have no idea what parallel universe or subfield you live in Zachary, but it sounds like somewhere I would never want to visit.

Steve Elledge
Posted January 31, 2016 at 10:55 am | *Permalink*

Zachary, Thanks for pointing out the difficulties in transferring functions from bacteria to eukaryotes and mammals in general. I was not aware that so many failures were out there. I was having trouble thinking of one. I was wondering if you could list 5 or 10 examples of bacterial enzymes that fail to function in mammals. Every time I think of an enzyme it always seems to have worked, beta galactosidase, beta lactamase, neomycin phosphotransferase, chloramphenical acetyl transferase, all restriction enzymes, Dam methylase, T7 RNA polymerase, DNA ligases, DNA binding proteins like lacI, tetR, bacterial and phage integrases. All the amino acid biosynthetic enzymes from bacteria seem to work wherever they are expressed. It would be great if you could list some counter examples so I could get a better grasp of the things that have been tried.

macketons
Posted February 4, 2016 at 4:49 am | *Permalink*

Lander may well have shot himself in the foot with this article. Let me elaborate:

Although the intention of Lander in writing this article is clear, it has shed light into a much more important issue that nobody was paying attention to: all the knowledge of CRISPR was already on the table when Doudna-Zhang jumped in to just make the final step and convert it into a gene editing tool. It's sad but here in Spain nobody knew who Francisco Mojica was until this article came out in Cell. Now, everyone here is talking about our next Nobel Prize. I thought it was just chauvinism until I started reading about the discovery story (mainly Lander's article…). I have used the CRISPR tools for gene editing myself, extensively, and I did not know anything about these guys (Mojica, Horvath, Siksnys, van der Oost…). Instead, I thought that Doudna-Zhang developed CRISPR almost from scratch, with the help of only some small previous insights from the field of microbiology. But it was indeed the work of the microbiologists who struggled with the lack of funding, the rejection of the groundbreaking idea, the publication bias, the ones who believed all the time the idea of an adaptive immune system in bacteria, along with the subsequent work of those who deciphered every step of the mechanism. Those who made it possible are the ones who deserve the prizes, the glory, the credit… And we know that now because of Lander's "The Heroes of CRISPR" article (who knew it before this article besides maybe those in the field of microbiology?), even if it's clearly biased. At least this is my conclusion after reading the paper: as useful as Doudna-Zhang lab work has been, I don't see it a real part of the intellectual contribution that has changed (and will continue changing) the way we do science. Don't get me wrong, this last step has been extremely useful, but it is more the kind of work that Life Sciences could do developing a new kit to help us carry out our lab protocols in our everyday bench work: clone the pieces in plasmids, overexpress in cells, and voilà.

One last thing, there is a sentence in Lander's article that explains why Lander himself, Doudna, Zhang, etc. and the rest of "big labs" were not there at any moment during the CRISPR discovery process. Quoting from Lander's article: "Like Mojica, Philippe Horvath could hardly have chosen a thesis topic that was more local or less sexy…". Lander is unconsciously giving us the key of why CRISPR came out of small labs all around the world and not from the big "science leaders": these big labs don't understand that the greatest of the discoveries can be hidden inside an apparently "ugly" hypothesis. I know very well what I'm saying: I worked at one of this "big labs" for several years and I was in many meetings in which my supervisors rejected my ideas promptly by saying "that's not sexy" or even "that's not a Nature" (or even by just saying "bullshit", believe it or not). These labs work like this: they choose to explore very attractive ideas, with almost no grounds but the kind of ideas you can easily picture in Nature's cover (we could call them "risky", I prefer to call them crazy ideas). And then they work them out all the way until they get to Nature or Cell, no matter what the results of the experiments showed (please take a look to Pubpeer to see what I

am talking about…). Alternatively, they can take something that's almost ready, and put a huge amount of money and researchers/time to finish it before anyone else in the world can, taking advantage of their excellent connections with top journals and their huge funding. The latter was the case of Doudna-Zhang role in CRISPR, in my opinion.

But even if nowadays that's sadly what succeeds in terms of publication-funding-positions, that's not science. Science is what's waiting for you in a hidden corner on your way to hypothesis rejection (9 out of 10 hypotheses should, statistically, be rejected). Like crispr was waiting for Mojica in a hidden corner of his initially unappealing and probably unproductive "ugly" hypothesis about the genome of archeas growing in high salt environments. A hypothesis that Lander, Doudna, Zhang, et al would probably have never explored. So, even if Lander was trying to make the case for Zhang's Nobel Prize, in my opinion he has helped doing the opposite: he has shown us how a legion of researchers in small labs believed and worked hard in an initially unappealing idea that turned out to be one of the biggest discoveries of science history, doing a great job of collaborative science of outstanding quality. And how the guys that are always there ready to jump in and take the credit did it too late this time… I really hope that the Nobel Prize committee will also see this.

> **Anonymous Stem Cell**
> Posted February 5, 2016 at 11:40 pm | *Permalink*
>
> That assumes CRISPR/Cas9 editing will ever win an award. Leaving aside that we live in a world where FACS never won a Nobel Prize, making a knockout/transgenic organism already has won and so has DNA repair.
>
> So how would the award for CRISPR be structured that it doesn't overlap with those previous awards?
>
> (If anything, I think that zinc finger nucleases will win before Cas9.)
>
> Also, as Mike has pointed out before, Doudna was working on the CRISPR/Cas before it was cool, so to lump her lab in with Feng's is a bit unpalatable.

Stuart Linn
Posted February 5, 2016 at 11:25 am | *Permalink*

While I agree with some of Eisen's points, I strongly believe that this way-too-long Trump-style diatribe is not appropriate for Cell. Let's stick to real science and short comments, Cell.

bob
Posted February 6, 2016 at 10:02 am | *Permalink*

The philosopher/historian of biology David Hull liked to say that the creation of the Nobel Prize was the worst thing that had ever happened to science. I always thought that this was an exaggeration; perhaps it was not.

p_r
Posted February 7, 2016 at 1:56 am | *Permalink*

Feeling poetic about this topic today:

"BOROMIR
It is a strange fate that we should
suffer so much fear and doubt over so
small a thing…such a little thing."

name
Posted February 9, 2016 at 6:15 am | *Permalink*

Aren't we all standing on the shoulders of the giants? So how come we only give prizes to some 3 people like we're not giving credit at all to the giant itself given how massive the prestige and prize is? It's like gene transcription and only the CPSF gets all the credit to protein heaven because they're the last ones transcribing the RNA. Deep down I kind of wish these kind of prizes are actually given to people that worked hard

on this with bare funding some 15+ years ago, and all people that worked afterwards get to vote for 5-10 nobel prizes not from their group. This way everyone gets credit: the most recent ones get the “nobel prize voter” for prestige and we can finally see the biggest credit ($$ and prestige) go to the giants.

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