

The following is the correspondance from May 2006 between James Randerson and Drew Endy regarding the possibility of demonstrating that it is possible to mail-order synthesize the DNA encoding human pathogens.

Dr. Randerson published the following articles:

Lax laws, virus DNA and potential for terror
<http://www.guardian.co.uk/terrorism/story/0,,1796805,00.html>

Tighter laws needed on sale of DNA samples, says research chief
<http://www.guardian.co.uk/science/story/0,,1797837,00.html>

From: James.Randerson@guardian.co.uk
Date: May 9, 2006 10:25:27 AM EDT
To: endy@mit.edu
Subject: Journalist enquiry

Hi Dr Endy,

I am a science journalist with the Guardian newspaper in London. We are a national daily paper. I am hoping to put together an investigative piece on how easy (or not) it would be for a would-be terrorist to put together the genome of a nasty organism like anthrax from scratch. For the purposes of the piece I am planning to approach a DNA synthesis company and ask them to make a fragment of a nasty toxin gene. Some companies have safeguards in place to prevent this kind of thing but others do not.

I was speaking to Robert Jones of Craic Computing and he suggested that I get in touch with you. My background is in genetics, but I need someone to help walk me through the molecular biology. I know that oligo synthesis companies can handle sequences up to around 150 bp. Would this be large enough to be a meaningful fragment of a toxin gene? Could you suggest a test fragment to try out? Obviously, I want to be very sure that I'm not asking anyone to produce something that would make a functional protein. I wanted to make initial contact by email, but perhaps we could have a brief conversation by phone later today.

Many thanks
James

Dr James Randerson
Science Correspondent

+44 (0)20 7239 9604 (Direct line)
+44 (0)20 7239 9787 (Fax)
+44 (0)7970 569495 (Cell)

The Guardian
119 Farringdon Road,
London EC1R 2ER
www.guardian.co.uk

[DE Note. Following up on his email, James Randerson called my office and we spoke by phone. During our conversation I stated that I agreed that there was a concern, that there was significant action underway to address the concern, and that a high-profile public demonstration of the current state of affairs would increase the risk that the technology be intentionally misapplied without contributing to a useful solution.]

From: James.Randerson@guardian.co.uk

Date: May 11, 2006 12:01:42 PM EDT

To: endy@mit.edu

Subject: test sequence

Dear Prof Endy,

Sorry to bother you again. I have got a potential sequence to use suggested by Robert Jones at Craic Computing, but I want to run it by a couple of people to be very sure that this would not be dangerous to receive in the post. As you will see, the sequence is part of a gene for a viral coat protein (not a toxin gene) and he has introduced some stop codons into the sequence to be doubly sure that it will not manufacture anything functional. Even with the changes it would apparently still be picked up by the Blackwatch software.

I appreciate your position that you think this enterprise is proving something that the academic community is well aware of, but I am sure that the man on the street has no inkling that this is possible. That is why I believe that journalistically this is an important and valid exercise.

Do you think you would have time to look at the sequence and give me your professional opinion on whether you think it will achieve the aims of the exercise and whether it is safe to order? I know you said that you thought this project would not be the best use of your time, but I wondered since part of the work is already done whether you might change your mind. Alternatively, could you suggest anyone else who might be willing to help out.

Yours Sincerely
James

[DE note. I believe that what follows comes from Rob Jones of Craic Computing]

What I've come up with for your test is a 120 nucleotide segment taken from the smallpox genome. Specifically, in its INITIAL form, it represents positions 33138 to 33019 inclusive of genbank entry VARCG (complete genome smallpox virus). This in turn encodes part of the major envelope protein of the virus, specifically amino acid 100 through 139 inclusive.

The major envelope protein is not a toxin, does not replicate the viral genome, does not integrate DNA with other genomes - it does serve as an antigen for smallpox vaccine as it sits on the outside of the virus. So there should be nothing dangerous about the envelope gene per se, and likewise, nothing dangerous about this particular segment.

But then I've made a total of 7 changes to the sequence in order to prevent this sequence being translated into a protein if it were, somehow to be placed into a cell in a form that could be translated. These changes add stop codons to the forward, in phase, reading frame for the gene segment as well as other reading frames.

Here is the original sequence, shown as two lines of 60nt each:

You'll need to view it in a fixed width font like Courier for it to line up properly. The lines f1-f3 show the stop codons that block translation of the forward strand, r1-r3 show the reverse strand. You can see that there are no stops on the fwd frame 1 (as expected) or the 'r3' frame

Original:

```

|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
ataaatttataaccgtaataattgataaaaaaataacgtaggactactactggatgt
f1> none
f2> TAA   TAA           TAG
f3>      TAA TGATAA   TAA
r1<   AAT   AAT           GATGAT
r2< none
r3< none

```

```

|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
tttgggtatcagatgatgaaagatggtatgtaggaaacgcgctattactggaggatct
f1> none
f2>                TAG
f3>      TGATGA
r1<                AAT
r2<   AGT           AGT
r3< none

```

So I made 7 changes to create additional stop codons that serve to block any translation of the sequence in any reading frame. Those changes are shown in upper case in the sequence

Modified:

```

|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
ataaatTTataaccgtaataattgataaTTaaaataacgtaggactactactATgatgt
f1>          TAA          TGA
f2> TAA  TAA          TAG
f3>          TAA TGATAA  TAA
r1<   AAT  AAT          GATGAT
r2<          GAT
r3<          AAT

```

```

|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
ttttAggtatcagatgatgaaagatgtCatgtaggaaacgcgctattactggaTgatct
f1>  TAG          TGA
f2>          TAG
f3>    TGATGA
r1<          AAT
r2<   AGT          AGT
r3<          AGT

```

Visit Guardian Unlimited - the UK's most popular newspaper website
<http://guardian.co.uk> <http://observer.co.uk>

The Newspaper Marketing Agency
 Opening Up Newspapers
<http://www.nmauk.co.uk>

This e-mail and all attachments are confidential and may also be privileged. If you are not the named recipient, please notify the sender and delete the e-mail and all attachments immediately.

Do not disclose the contents to another person. You may not use the information for any purpose, or store, or copy, it in any way. Guardian Newspapers Limited is not liable for any computer viruses or other material transmitted with or as part of this e-mail. You should employ virus checking software.

Guardian Newspapers Limited
 A member of Guardian Media Group PLC
 Registered Office
 164 Deansgate, Manchester M3 3GG
 Registered in England Number 908396

From: endy@mit.edu
To: James.Randerson@guardian.co.uk

James Randerson
Science Correspondent
The Guardian

Dear James,

With apologies for my delayed response; as you know, we're just completing classes for the semester and I am working 100% to finish plans for the Synthetic Biology 2.0 conference that is being held at Berkeley 20-22 May 2006. As I mentioned when we spoke by phone last week, the academic and industrial communities will be spending Day 3 of the meeting (May 22) to finalize the community-wide implementation of a scheme that would screen DNA sequence information upstream of commercial DNA synthesizers. It should be worth reporting the results of these deliberations (webcasts from the conference are expected to be freely available online).

To restate what I said earlier, I am not now able to evaluate whether or not what you are proposing is safe or dangerous. But, let me point out that even with the changes to the smallpox DNA given below, you might still be able to produce a peptide that could provide a false signal in an assay for detecting infectious smallpox particles present in the environment.

Because you appear to be continuing with a demonstration that is not needed for your story and that has, at best, no positive outcomes, I am copying my email to your Readers' Editor. I have also BCC'd this email to contacts at various gene synthesis companies and others so that they do not unknowingly aid your project.

Sincerely,
Drew

—

Drew Endy
Cabot Assistant Professor
MIT Biological Engineering
<http://mit.edu/andy/>

From: James.Randerson@guardian.co.uk
Date: May 15, 2006 6:05:12 AM EDT
To: Drew Endy <endy@MIT.EDU>
Cc: Robert Jones <jones@craic.com>
Subject: Re: test sequence (smallpox DNA fragment)

Dear Prof Endy,

Thanks for your response. When we spoke on the phone you said you support the idea that this issues deserves a public airing. I agree that there is a strong public interest in this issue being aired and the existing "loopholes" being closed. I know that this is an issue that those in the field of synthetic biology are taking very seriously and are discussing steps to make it harder for would-be terrorists to get hold of dangerous sequences. There is clearly no simple answer to this, so I recognise that putting measures in place will take considerable work to find a practical and effective solution.

To be clear about what I propose, my intention is to find out whether it is possible to get hold of a sequence of DNA from an organism that could potentially be used as a bioweapon. I do not intend to express this as protein and as soon as I get hold of the sample I will destroy it. In case the DNA is somehow taken up by a bacterium in the environment, I do not intend to use DNA from a whole gene and I do not intend to use a toxin gene. I also plan to take steps to alter the sequence to make sure the fragment is not expressed in full. I do not intend to break the law.

You say in your email that the demonstration I propose is not needed for the story. I'm afraid that I have to disagree with you. A story saying that it is probably possible to do this or that "experts say" it is possible to do this would carry far less weight than a demonstration that it is actually possible to do. Such a story would be more likely to run in the paper and be given high prominence. That would give the debate a higher profile.

Having said that, it is obviously paramount to do this responsibly and not to put anyone at risk in the process. This is why I am consulting extensively with experts in the field. I am disappointed that you have opted not to engage with that.

Yours Sincerely
James

Dr James Randerson
Science Correspondent

+44 (0)20 7239 9604 (Direct line)
+44 (0)20 7239 9787 (Fax)
+44 (0)7970 569495 (Cell)

The Guardian
119 Farringdon Road,
London EC1R 2ER
www.guardian.co.uk

From: endy@MIT.EDU
Subject: Re: test sequence (smallpox DNA fragment)
Date: May 15, 2006 8:50:40 AM EDT
To: James.Randerson@guardian.co.uk
Cc: jones@craic.com, reader@guardian.co.uk

Dear James,

I have engaged with you and provided you with, at the limits of my knowledge and resources, an expert opinion that what you are doing is at best irresponsible. You are asking me to help you do something that I consciously object to. Your last email does not acknowledge the possibility that what you proposed to synthesize, a fragment from a smallpox coat protein, could disrupt an assay to detect this important human pathogen in the environment. Presumably, you will be happy to explain to your colleagues at the Guardian why a fragment of smallpox DNA is now in the home office?

Meanwhile, here is a reference to a paper from four years ago that demonstrates that it is possible to synthesize de novo a full, intact, infectious copy of poliovirus from scratch using oligonucleotides ordered by mail. You could choose to alert your readers to this more powerful demonstration and the steps people are taking to remedy the situation in place of pursuing a stunt.

Cello J, Paul AV, Wimmer E.

Chemical synthesis of poliovirus cDNA: generation of infectious virus in the absence of natural template.

Science. 2002 Aug 9;297(5583):1016-8. Epub 2002 Jul 11.

Please consider reporting the news instead of creating it.

Sincerely,
Drew

—

Drew Endy
Cabot Assistant Professor
MIT Biological Engineering
<http://mit.edu/andy/>