Podcast Interview: Jef Boeke

PNAS: Welcome to Science Sessions. I’m Paul Gabrielsen. Researchers working with engineered or potentially harmful microorganisms need a safeguard in place to prevent growth of the organism outside the laboratory environment in case of theft or accidental release. Biocontainment technology may provide such a safeguard, by engineering safety switches into living organisms to make their growth dependent on controlled conditions. Recently, three independent research groups took on the challenge of designing biocontainment systems. The work of one of those teams, led by Jef Boeke of the New York University Langone Medical Center, was published in PNAS. Boeke and his colleagues describe methods to control the growth of brewer’s yeast. I spoke with him over the phone.

Boeke: So, the basic idea of our approach, and we were not the only ones thinking along these lines, was to use small molecules as a type of special sauce, if you will, that would keep the microorganisms alive, so the microorganisms would be wired up to be dependent on not just one small molecule, but at least two different ones in the eventual application of this technology. And then that way you can provide this special sauce with the small quantities of these molecules. So, in the presence of this special sauce, the microorganism would grow, and it would grow normally, like a normal microorganism of that type, but in the absence of the special sauce, it would fail to grow. What we showed is that when you operate with just one of these systems in place, you get so-called escape mutants. The system can evolve a way around it. If you plate out enough yeast, you will get a survivor, or bacteria. So, typically, with just one system in place, you would get somewhere between one in a hundred million and one in a million survivors. But by combining two such systems into one, you should theoretically get the product of those two numbers, so one in a million times one in a million would be one in $10^{12}$ . . . And that is a very large number of cells, so large that it’s actually difficult to do the experiment to definitively measure whether or not there are any survivors. And both groups were able to develop systems that had such unmeasurable escape frequencies by combining just two such systems.

PNAS: What are the challenges that lie ahead in developing biocontainment technologies?

Boeke: Well I think even though we’ve made a lot of progress with the first publications, one of the biggest challenges is that the number of small molecules that we have available to control expression of genes and so on is relatively small, and we have begun to look for additional small molecules and gene systems that respond to them, but it’s kind of a long, slow process, and what we really need is a breakthrough that would enable us to discover hundreds of these switches controlled by small molecules. The second challenge associated with that is that the small molecules that we use should be active at a very very low concentration so that they’re difficult to detect. And a third challenge is that they should be of very low cost because otherwise they wouldn’t be practical, particularly for industrial use where there’s a large scale-up involved.

One other interesting aspect of our proposal for how to safeguard recombinant microorganisms is that we intend to make the special sauce difficult to decode. In theory, it would be possible to determine the nature of the small molecules that make up the special sauce, then that would enable some nefarious actor to be able to continue to culture the microorganism of choice. So one other concept that we put out there is the concept of decoy compounds, where we would
actually intentionally contaminate the special sauce with a number of low-cost small molecules that actually do nothing, but are there to make it difficult to determine which small molecules are really important, and also as the number of those molecules increases, the nature of the critical combination of small molecules becomes harder and harder to decipher, and then similarly one could imagine building in decoy genes, or decoy gene circuits, so that even if someone were able to sequence the DNA of the microorganism, the combination of the unknown number of small molecules and the unknown number of genes would make it even more difficult to crack the code, so to speak.

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