Interview Prof. Joshua Lederberg, Rockefeller University
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Q: I am writing an article about the development of new antibiotics and what do you think how urgent is the situation with antibiotics?
A: Well, you know the answer to that question. We're running out of possibilities for a number of reasons and if we get back to vancomycin-resistant Staphylococcus it will be quite desperate.
Q: As I understand, we have already the first vancomycin-resistant Enterococci.
A: Enterococcus is not a serious – is not a quantitatively important problem. If it gets to Staph, that really gets complicate – every surgery will be a risk. You've heard this from many others, I'm sure.
Q: Not so much. I know that vancomycin-resistant Staph is one of the main targets for the new antibacterial agents. And what I think the most promising and the most advanced in development are the cationic peptides by XOMA Corporation, Elsbach in New York, Tom Ganz in California?
A: I actually don't have information about that. But you had a question whether these are more or less likely to evoke resistance?
Q: Yes, mainly.
A: I don't think it doesn't take us anywhere to predict that. The bugs are very clever and we may think we got rid of them and they find new mechanisms to resist we haven't thought about. But that's a purely empirical matter.
Q: So there's no answer possible right now until we have those agents in the clinic?
A: An antibiotic is a substance, which is toxic to some species and harmless to others, okay? So therefore, it is genetically possible to have organisms resistant to the antibiotic. It wouldn't be an antibiotic if that were not the case. Therefore, how can you know in advance whether you can get further evolution of your target organism to be like the organisms that are inherently resistant?
Q: A lot of these companies – or some of the researchers think that those cationic peptides will be the end of antibacterial resistance...
A: It's nice to have some optimism and as far as people work hard on it I don't want to dampen this. But we will know when we find out.
Q: I also talked to Richard Carlton from Exponential Biotherapeutics. To use bacteriophages seems to be a pretty interesting approach. Do you think this could become also a widespread application?
A: Well, I think there will be uses for phage but I don't think it's a panacea – phages have been around for – how long now, since 60, 80 years now?
Q: 1915, I think.
A: So, 85 years. There have been many many people trying to find good therapeutic application and well, Carlton and Merril did a nice job. It's very interesting. I don't think it's gonna be the final answer. I wrote a little editorial about that in PNAS.
Q: I've read this.
A: So I still have those same views. And we very badly need alternatives. But, you know for one thing, phage is bound to evoke antibodies to the phage. So you won't be able to use it again after the first usage. And it's a very large particle and it's not diffused so readily into tissue spaces and so on.

Q: So it's more like a one-time use in life-threatening situations?
A: Well, that's right. I think there will be applications for it. What we need are more things like penicillin that will be with a pretty broad spectrum. I know people would prefer to have narrow-spectrum antibiotics but then you have to have very precise diagnosis of what your target is. And when you can't get a very broad spectrum then you want some intermediate range. Now, I think an answer to resistance that needs to be investigated more is combination therapy. For good theoretical reasons, why some combinations of antibiotics could on the one hand be synergistic with each other, and on the other hand tend to defeat resistance. But the FDA has all kinds of rules that make it very very difficult to use combination. You have to do complete thorough tests on each of the individual components and then go on from there. So, it is an almost active discouragement of that approach.
Q: Back to the FDA. You said we're running out of options concerning antibiotics. Some of the reasons why we have this problem is abuse and misuse.
A: Oh, absolutely. That's the primary concern. Also ignorance. The abuse is when people give antibiotics and there is no justification for it. The ignorance is people give antibiotics and people giving them aren't aware of problems that they induce. They have wrong information to sell unnecessary antibiotics in any given situation. But I'm sure you talked to the association for prudent use of antibiotics.
Q: No, not yet. I'm trying to talk to George Poste from SmithKline Beecham.
A: Okay, but you should talk to Stuart Levy.
Q: Stuart Levy at Tufts University?
A: I'll give you his phone number – 617 636 6764.
[...]
Q: If we get new antibacterial agents, do you think the FDA should completely change their policy to prevent abuse and misuse? And ignorance.
A: I think you have to be very careful that you don't destroy the motivation for development in the first place. If it's too restricted nobody will invest and try to make them. So, parallel of taking that radical approach, is very heavy government subvention for their development. Now, I would think we should do best in both ways that is to say have the government offer subsidies to those companies who want to operate under a restrictive regime. So that's the trade. A bit like election reform. If you're willing to limit how much you take in from other sources than you can get some help from the campaign fund. So I think we need to have both approaches. But I think it is impractical to simply regulate the distribution unless there is an agreed upon contract between the government and the developer.
Q: Another question: what do you think of those attempts to prevent adhesion?
A: These are great. I think therefore what you want to do is to minimize the effects of virulence of the organism. And we would be very well of if there were non-toxic variants of all the major pathogens still floating around in our environment but not capable of inducing severe disease. Then we have a chance to develop immunity as well.
Q: So have you heard of Neose Technologies' attempt?
A: Well, they are using glyco - polysaccharides or pseudoanalogues, right?.
Q: Those pentasaccharides.
A: Well, they are part of the story. I think they are – again, I don't think there is any kind of panaceas in this world, but I think... They are a new angle, a new approach, very

ingenious but how effective they will be and whether they will evoke resistance and so on... We don't have such a robust theory that we can be quite certain about it.
Q: And a last question: a lot of those agents will take years until they come to the market.
A: Yes, I'm afraid so.
Q: How long do you think it will take for Staphylococcus aureus – vancomycin-resistant Staph - to be spread widely?
A: The strains so far are only partially resistant. We don't really understand why it hasn't spread much more quickly. The must be some physiological barriers that vancomycin-resistance is to some degree incompatible with spread and pathogenicity, otherwise we would have seen much more. Since we don't know that and don't understand it, it's very hard to make predictions that are not based on... What I've just said is a slap in your face that you know: hahaha you're so smart how would you not know about that? So I think we have to be very careful about sweeping predictions in this field. Very complicated natural history and physiology all mixed together.
Q: Ok, thank you for your time Dr. Lederberg...

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