

American Chemical Society AMA Series: I'm Mark Blaskovich, from Open Antimicrobial Drug Discovery. We help chemists around the world discover new antibiotics, ask me anything about antimicrobial resist

AmerChemSocietyAMA<sup>1</sup> and r/Science AMAs<sup>1</sup>

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## ABSTRACT

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As a healthcare worker, I have a couple of very important questions that I'd like to see if you can answer.

In your professional opinion, based on the rapid growth of several different varieties of superbugs in recent years, and the low selection and availability of the stronger antibiotics used to treat those specific superbugs, how long is it going to be before we're at the end of the veritable rope? Basically, when we create, either by accident or on purpose, a bug that for all intents and purposes can't be killed?

Also, do you believe that due to the chemical and genetic changes an organism goes through when becoming resistant to antibiotics, for example *Staphylococcus Aureus* becoming MRSA, that those superbugs have essentially evolved into a separate and improved organism? Could you say we've seen evolution happen before our very eyes, albeit on a very small scale

Thank you for this AMA and thank you for your time.

EDIT: Formatting.

[LakontheGreat](#)

Another great question. In some cases, we're already at the end of the rope - XDR TB is resistant to almost everything. We have a collection of strains of highly resistant bacteria isolated from patients around the world, that show resistance against 40 or 50 different antibiotics, including 'last resort' antibiotics such as colistin. People with these infections die - it takes too long to find the one antibiotic or combination of antibiotics that still work. The bacteria indeed do evolve in front of our eyes - actually within you. There are studies showing the evolution of resistance within patients as they have been treated with several different antibiotics. Bacteria are also really good at sharing the resistance genes they have developed, which is one of the reasons resistance can spread so quickly. Mark B

Hi, to what extent is computer simulations being used in drug discovery, do you think there would ever be a time when most of the work is being done 'in silico'?

### [dinosaursarentdead](#)

There are some excellent answers to this question already, but I'll reply from an antibiotic discovery perspective. Computer simulations work when you have a known isolated target to start from - but most antibiotics have been discovered from what are called phenotypic screens, when you treat the whole organism (bacteria) and see if it lives or dies. The molecular targets of most antibiotics have since been identified, but there are still some antibiotics (such as the polymyxins) where their exact mode of action remains poorly defined, despite being in use for over 50 years. The target based approach has not been very successful for discovering new antibiotics - GSK wrote a paper on this in 2007 (Nature Rev Drug Disc 2007 p29) Mark B

Just to add to my answer - part of the CO-ADD initiative is to establish a database of compounds correlated with antimicrobial activity under standardised conditions. The hope is that this would allow researchers to examine what types of physicochemical properties help produce antimicrobial activity, potentially allowing for more selective screening/synthesis of compounds in a similar fashion to rules focused on producing orally available compounds. Mark B

**Hello Mark, fellow medicinal chemist here. With all the tools we have at our disposal (high-throughput screening, computational modeling/docking, combi Chem, etc.) why is it still so difficult to discover selective inhibitors that get brought to market? Also, if you could pick one target (specific protein/pathway) that you think could afford an efficacious antibiotic upon inhibition/regulation, what would it be?**

**Edit: Clarification**

### [bassx901](#)

One of the biggest problems is finding a target in bacteria that differs from one in humans cells, so you can selectively kill the bacteria without harming the human. Existing antibiotics target most of the obvious ones, such as the peptidoglycan layer surrounding bacteria. It has been very difficult to find new ones that actually work, and part of the problem is that bacteria are very efficient at getting rid of anything that tries to get inside them - they have efflux pumps that quickly expel drugs, and, especially for Gram-negative bacteria (like E. coli), have membranes that make it difficult for drugs to enter in the first place. Bacteria are also very efficient at mutating targets so that drugs quickly become ineffective - especially protein targets. That is one of the reasons that the recent discovery of teixobactin received so much attention - it targets a non-protein cell wall component, so was proposed to potentially be resistance-proof. Unfortunately, that is highly unlikely, as other antibiotics already target membrane components (i.e. colistin and polymyxin B target Lipid A), and these too have mutated to create resistance. Mark B

**Can you speak to agriculture and animal husbandry, as we currently operate in the 1st world, being drivers creating or worsening the superbug problem?**

### [CaptainCompost](#)

The excessive use of antibiotics in the livestock industry, particularly low concentrations in feedstock as growth promoters, is undoubtedly part of the problem. The same classes of antibiotics that we need to save lives are being used to increase food production. Mark B

**What do you think is the most under funded/reported disease that should be getting more attention?**

### [space-tech](#)

That's a tough one - but really, the general rise of drug resistant bacteria is a major unfunded issue. We have organisations dedicated to TB, malaria, and other neglected diseases, but there are no high

profile efforts targeting drug-resistant bacteria. Fortunately this is changing, with the Chief Medical Officer of Britain annual report in 2013 and Obama National Action Plan for Combating Antibiotic-Resistant Bacteria raising the profile. Mark B

**Instead of trying to identify new and stronger/better antibiotics, how about inhibiting the enzymes responsible for the resistance? I work with synthesis of new metallo- $\beta$ -lactamase inhibitors and these together with an antibiotic seem to work really well. It might not be a revolutionary new class of antibiotics, but it could extend the lifetime of current antibiotics many decades. What are your thoughts about this? Could the CO-ADD platform also be used to screen for inhibitory activity against key resistance enzymes?**

[shalalam](#)

There is certainly a lot of research into some aspects of this area - the pharmaceutical companies in particular are pursuing the lactamase inhibitor/lactam combination therapies. Small biotech companies like Helperby are trying to develop other 'resistance' breakers that extend the life of existing antibiotics. Your questions re whether CO-ADD could screen for these compounds is very perceptive. Our original proposal did include trying to test for synergy between some existing antibiotics and the new compounds we are testing, but the pilot funding we received was not sufficient to include this. There is definitely a role for searching for these non-antibiotic compounds, which could extend the lifetime of our existing antibiotics until we can find the 'dream' new antibiotic(s). Mark B

**Do you think [quorum sensing](#) disruption is a possible solution to "superbugs"?**

**Do you use [iChip for bacteria culturing](#) for your line of work?**

**Are [teixobactins](#) all they are cracked up to be?**

[donotclickjim](#)

1) Disruption of quorum sensing is another potential tool in the arsenal to fight infections - it's not just 'superbugs' as regular bacteria form biofilms that make them more difficult to kill, and potentially help foster the development of resistance. 2) We do not use the iChip or do other forms of natural product screening - we feel that there are plenty of other researchers taking this approach, including companies and academics that are trying to grow bacteria/fungi in unusual conditions to force the generation of new natural products, or looking at genomic sequences for possible non-expressed unusual natural products. Our approach is to mine the synthetic chemistry world for unusual chemical diversity, from chemists who make weird and wonderful molecules for a range of reasons (method development, natural product synthesis) but never consider testing them for antimicrobial activity. 3) Teixobactins received a lot of press (the article is at <http://www.nature.com/nature/journal/v517/n7535/full/nature14098.html>, but Wikipedia has a nice summary). The isolation is exciting, but they had to search through a lot of compounds before they found it. The main problem is, it's only active against Gram positive (there are more antibiotics still effective against this class of bacteria), bacteria will probably overcome the 'lack of resistance', and it is still years away from actually becoming an approved antibiotic, if ever - identification of an active compound is only the first step in a very long process towards approval, with in vivo pharmacokinetic characteristics and toxicity the main barriers. Mark B

**I have read a lot about health care applying silver, copper, titanium and even graphene coatings on to surfaces through out health care facilities to prevent the spread of disease. Does this stuff actually keep a surface "germ free" for as long as it is present?**

[Bkeeneme](#)

The metal treatments can work - I guess one of the issues is keeping the surface clean enough without

removing the coating e.g. a layer of dirt over the metal would then let the bacteria grow, but if you scrub too hard to remove the dirt, you might lose the coating. Mark B

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Thanks for that - better watch what I say! Mark B

**As we strive to create new antibiotics, are we in turn allowing for these "superbugs" to become even further resistant to new technologies and treatments and helping to create "megabugs"?**

[MedicSF](#)

Some excellent answers already below. One problem is most 'new' antibiotics are improved versions of existing antibiotics, so often the resistance mechanism remains in place. There have been some studies showing that, by judicious selection of the appropriate antibiotics, you can cycle treatments between two classes where the fitness cost of resistance against one antibiotic makes it susceptible to the second antibiotic, and vice versa. Mark B

**Hello! I'm a college student in the U.S. Currently studying Biomedical Engineering. I have always had a passion for research, and have been looking forward to this AMA. Could you tell me a bit about your every day? Going into a field of research from the outside sounds fantastic, but I've also heard from people currently in the field that it can be unenjoyable at times, or that they wished they had chosen a different career path. Your studies sound very similar to what I hope to do, so I would love your input on this! Also, are there any tips or hints you could give an aspiring researcher? Thank you so much for your time!**

[moohing](#)

The landscape has changed a lot since I started. If you have a passion for research, it can be very rewarding, but (particularly for drug discovery) you really need to be an eternal optimist, believing that, while my first 99 attempts have failed, this next one will surely work! I'm more into project management than actually in the lab these days, so sitting at a computer is not as much fun. The research component of the job is very enjoyable, but I spend an awful lot of time trying to raise funds through grant writing.

I really enjoyed my time working for smaller biotech companies - the start-up environment, where you have to do many different jobs but can really see the impact you make, can be very fulfilling. My main tip would be to find something you're passionate about and people you enjoy working with - the long hours and repeated failures are difficult without that. Mark B

**Ahh, this is so cool. I like discussing antibiotics (with whatever limited knowledge I have)!**

**What are some of the newest, coolest antibiotics being developed right now and what are they made from? :D**

**Why is there an empty antibiotic discovery pipeline?**

**What is the scariest thing to you about the future of antimicrobial resistance and superbugs?**

**What can we do, as a worldwide community, to reduce the problems of antimicrobial resistance and superbugs?**

**Also, are there any new superbugs on the verge of breaking loose?**

[lazylearner](#)

1) The pipeline is empty largely due to financial reasons. Pharmaceutical companies need to make money, and antibiotics are not valued highly by society in general. People will pay \$100,000 for an anticancer treatment that prolongs life for a few months, but an antibiotic treatment that saves lives costs only \$100s of dollars.

Part of the problem is that an antibiotic treatment lasts 1-2 weeks and the patient is cured, as opposed to cholesterol-lowering drugs that are taken for the rest of your life. There are some government initiatives that are attempting to address this problem by providing more incentives to develop antibiotics.

2) Scariest thing - if we can't find new solutions, we'll be back to a preantibiotic era. If some of the existing strains become widespread, we'll have a serious problem.

3) Public education will help a lot - don't use existing antibiotics unnecessarily. Don't ask for antibiotics from your doctor if you have a cold or flu.

4) There are highly resistant strains around - whether they 'break loose' depends on an outbreak of infections.

Mark B

**Microbiologist here. What are the microbes you are using for your screening assays? Do you think that the microbes you have chosen to screen against are a fairly good representation of the larger microbial community? Do you include any extensively drug resistant strains such as xdr-Mtb?**

**Thanks for doing an awesome AMA!**

[IronMaiden0329](#)

We screen against MRSA as a Gram-positive representative, then 4 Gram-negative pathogens of high concern - E. coli, Klebsiella pneumoniae, Acinetobacter baumannii, and Pseudomonas aeruginosa. We also test against two pathogenic fungi - Candida albicans and Cryptococcus neoformans. Other than MRSA, we are using susceptible strains to increase our chances to identify hits. We think they provide a good representation of some of the most serious pathogens that are not already being addressed (e.g. TB has the TB Alliance). Any hits from our single concentration primary screen are followed up with an MIC determination, and if active we then test against a much larger panel of bacteria/fungi that include a range of resistant strains. In the future, we hope to expand CO-ADD to test our growing 'compound bank' against other pathogens like TB, malaria and dengue. And thanks for an excellent question! Mark B

**Hello Mark!**

**It's no secret that traditional screens have not been very successful at discovering antimicrobial agents with novel mechanisms of action that are fit for pharmacological use. I don't think most scientists are reasonably expecting a new era in which we discover many completely novel broad-spectrum antibiotics.**

**Do you think that this means that most of the "low-hanging fruit" has already been discovered, or that we're approaching screens incorrectly (e.g., not sampling the right chemical space)?**

**If it's the former, how do we move the ball forward? Perhaps by searching for multiple compounds in conjunction (e.g., Augmentin), or for more tailored narrow-spectrum treatments (similar to the way the cancer field is evolving)?**

**If it's the latter, how do you think we should be approaching chemical screens? What are we doing wrong?**

[subito\\_lucres](#)

I think it is a combination - we have certainly discovered the low-hanging fruit, but we are making it more difficult for ourselves by searching in the wrong chemical space, and filtering compounds for 'drug-like' properties, which would rule out most current antibiotics. This is the hypothesis that CO-ADD is attempting to answer - if we try to sample greater chemical diversity without filtering out compounds, can we find more antibiotics? Searching for 'resistance breakers' that work to increase the activity of existing antibiotics is a good approach, but quickly becomes a logistical nightmare with the number of potential combinations. Narrow spectrum compounds are certainly another approach, but in general I think this will be difficult with small molecules - other than selectivity between Gram-positive and -negative bacteria, the number of compounds that we see with selective activity for only one strain is very limited. Biological approaches would have more promise for this. Mark B

**Is it possible to "rotate" antibiotics? I mean to say, if bacteria become resistant to a certain antibiotic, can we take it out of use for few decades with the expectation that the bacteria in the future will no longer be resistant to it?**

**I'm sorry if this question is redundant. I looked at all of the other questions before I posted it and I didn't see a similar one.**

[servohahn](#)

The short answer is, potentially yes.

There's a nice article in Science Translational Medicine: Use of Collateral Sensitivity Networks to Design Drug Cycling Protocols That Avoid Resistance Development Lejla Imamovic and Morten O. A. Sommer Sci Transl Med 5, 204ra132 (2013); DOI: 10.1126/scitranslmed.3006609  
<http://stm.sciencemag.org/content/5/204/204ra132.full.html>

Mark B

**What is your view on the lack of science papers studying the effectiveness of the antimicrobial activity of natural substances like Tea-Tree Oil. (among others) Is it because there is nothing to dig in that direction or is it a field of research that is worth to be investigated ?**

[ptitquillaume](#)

Most of these substances do get studied - a quick search finds, among other papers: Antimicrobial activity of the major components of the essential oil of Melaleuca alternifolia. J Appl Bacteriol. 1995 Mar;78(3):264-9. Abstract: Tea tree oil, or the essential oil of Melaleuca alternifolia, is becoming increasingly popular as a naturally occurring antimicrobial agent. The antimicrobial activity of eight components of tea tree oil was evaluated using disc diffusion and broth microdilution methods....

The main problem is most often the active ingredients work topically, but are unsuitable for systemic use (inside the body) because of toxicity issues. MarkB

**How optimistic are you with regards to discovering new antibiotics from soil bacteria?**

**Do you think there is a limit to how far conventional organic synthesis can go in the hunt for new and unusual antibiotics?**

**How much of a role do you see things like contact-active antimicrobial surfaces playing in the future?**

[Aquapig](#)

I think it will be difficult to discover new ones from soil, as first you have to eliminate all the ones that have already been discovered. Hopefully CO-ADD will show that organic synthesis has a lot of promise. The number of compounds that can be made by organic chemistry is essentially infinite. Contact-active surfaces will be important for things like implants and stents, and to reduce the spread of bacteria in, for example, hospital environments. Mark B

**Hi Mark! I'm a grad student working on mechanisms of aminoglycoside resistance.**

**Because of microbe evolution, antimicrobials are a fundamentally different kind of compound than most other therapeutics. Do you worry about sustainability of drug discovery for antimicrobials? Do we risk running out of new potential compounds at some point? The search for new compounds seems to depend on the premise that if we look hard enough, we'll definitely find something, but I don't know if we check that premise as often as we should.**

**Interested to hear your thoughts!**

[superhelical](#)

The sustainability is a real issue, particularly due to the departure of many researchers from the field. We're trying to do a survey of pharmaceutical companies, but we're estimating that there may be less than 1000 antibiotic researchers left in industry in the whole world. That's scary! CO-ADD is trying to test your last premise - chemists make > 5 million new compounds every year, so hopefully there's something useful in that. Mark B

**Hello! Thanks for doing this AMA. I'm currently a student for microbial research and bioinformatics. I've always had an interest for bacteria and virus. While everyone was busy trying to kill them off out of fear of getting sick I was trying to explain not all microbes are destructive or bad for humans and that we in fact have many different species of all kinds of microbes that live inside us and keep us alive and healthy!**

**My question to you is:**

**How did you start out on your career? I'm currently stuck in an hourly minimum wage sales job. But I've been trying to get started in a related field. Did you start with a low paying job while still working on your bachelors? Or did you manage to get an entry level job while in the process?**

**I ask also because I noticed that while I have most the requirements for an MLT certification I'm still having trouble getting basic lab jobs. While my 21 year old younger brother landed a lab job with no college. Although he's only doing agar preparation and petri sterilization its something I'd love to do!**

[ItsSilver](#)

Thanks for your questions. I managed to get my B.Sc while funded by scholarships and work during what was called a Chemistry Coop program, where you go to a semester of school, then get a paid industry placement. I took a year off after graduating, working for Atomic Energy of Canada developing radiopharmaceuticals (I had a Coop work placement with them a year earlier). I then had a Canadian government scholarship for my PhD, and a fellowship for postdoctoral studies. I got my first job in a biotech company as an industrial postdoc, based on a contact made at a conference. My extensive involvement in antibiotic research started 5 years ago, when I joined Matt Cooper's group to help develop a new glycopeptide antibiotic. Mark B

