Ruth Adewuya, M...: Hello, you are listening to Stanford Medcast, Stanford CMSs podcast where we bring you insights from the world's leading physicians and scientists. This podcast is available on Apple Podcast, Amazon Music, Spotify, Google Podcast, and Stitcher. If you're new here, consider subscribing to listen to more free episodes coming your way. I am your host, Dr. Ruth Adewuya.

This episode is part of our Hot Topic's miniseries, and today it is my pleasure to chat with, Dr. Carolyn Bertozzi. Dr. Carolyn Bertozzi, completed her undergraduate degree in chemistry at Harvard University and her PhD at UC, Berkeley, where she focused on the chemical synthesis of Oligosaccharide analogs. A Howard Hughes Medical Institute investigator since 2000, she came to Stanford University in June 2015, among the first faculty to join the Interdisciplinary Institute called ChEM-H, Chemistry, Engineering and Medicine for Human Health.

She's now the Baker Family Director of Stanford, ChEM-H. Professor Carolyn Bertozzi's research develops chemical tools to study underlying diseases such as cancer, inflammation, tuberculosis, and Covid-19. She's inventor of bioorthogonal chemistry, a class of chemical reactions compatible with living systems that enable molecular imaging and drug targeting. Dr. Bertozzi, has received many awards and honors and most recently the Noble Award in Chemistry in 2002. Thank you so much for chatting with me today.

Carolyn Bertozz...: My pleasure. Thank you for having me.

Ruth Adewuya, M...: I'm really honored to be having this conversation. If you could tell us a little bit about your journey to chemical research and how did you know that this was going to be your path?

Carolyn Bertozz...: Well, for me, I discovered chemistry when I was in college, and I didn't really give it any thought before then. It was just a class a person had to take when they were in high school. And then when I got to college, I started out thinking I would be pre-med, and so I declared myself a biology major at first because that was the best overlap between the requirements for the pre-med track and also for a major.

And you have to take some chemistry classes as a bio major and as a pre-med. So I, once again, took chemistry in college, not because I wanted to, but because I had to. And then I was taken by pleasant surprise when I had an affinity for organic chemistry, which would've been the last chemistry class I ever had to take. And so when I went into it, I thought, "Wow, finally the last chemistry class and this is it. I'll never have to do another one. Yay." And then I just absolutely fell in love with the subject and switched my major to chemistry and decided I was meant to be an organic chemist. And then I did take a lot more chemistry classes.

Ruth Adewuya, M...: I'm very surprised that organic chemistry was what inspired you to continue chemistry. I know that organic chemistry was what made me decide that I can't go into chemistry, and you had the opposite effect, which is just impressive. What about the concepts of an organic chemistry sparked your interest in it?

Carolyn Bertozz...: First of all, it's a very visual subject, and so it's all about seeing molecules in three dimensions and understanding their structures and how that relates to their reactivity. And it just made a lot of sense to me. And I'm a visually minded person and I like to draw pictures and little shapes set off a lot of neurons in my brain, where I felt like it just was very beautiful and elegant and it had a lot of intrinsic logic to it.

And I also really loved how it explained so much of the biology that I had been learning, especially this was in the 1980s, so the molecular biology revolution was underway, and so people were all excited about the ability to make recombinant DNA and take DNA and cut it out of this organism and paste it into that organism. And so organic chemistry explained why DNA is a double helix and how restriction enzymes work, and there was just so much cool chemistry, that for me was really exciting.

Ruth Adewuya, M...: That's amazing to hear. So you completed your undergrad, you did your chemistry, and then you ended up doing a PhD at UC, Berkeley. What led you to come to Stanford and join ChEM-H?

Carolyn Bertozz...: Well, I had been at Berkeley as a faculty member since 1996, and my lab at Berkeley was a hybrid between an organic chemistry lab and a cell biology lab. So I had this kind of duality in my training, and the central theme around it was a field called glyco science, which is basically the science of complex carbohydrates. And I had gotten interested in that during my PhD and in my postdoc I worked in an immunology lab on cell surface glycosylation and the role of that in the immune system.

So at Berkeley, I was very happy to be in a situation where I could have people from the chemistry department, people from the biology department, I had a joint appointment in both departments and we were able to do some really exciting things in my lab. But as the years went on, our work was leaning more and more towards translational work, and we had made some discoveries in biology and developed some platform technologies from chemistry and we wanted to bring it together and make new kinds of therapeutic molecules. But it was hard to do that at Berkeley because it's not a place with a medical center.

So there's no hospitals, no physician scientists, no MD PhD students. It's a very science and engineering kind of institution. And I just felt like it would be really hard for me to figure out how to take my work to the next level where it really is about translating discoveries to make new medicines. And so then it was just my good fortune that around mid 2013, I got a phone call from Chaitan Khosla, at Stanford, and he had basically come up with this idea of a new institute that

brought together chemistry, biology, engineering and medicine, and we hadn't branded it ChEM-H. That came later.

But at the time, there was this idea and a groundswell of interest at Stanford to build an institute around this theme, and he had gotten the green light to hire some senior faculty to kickstart the institute. So he reached out to me and he said, "We want to do this institute. We want to hire 20 faculty at some point, but first and foremost, a couple of senior people with a vision and I think you'd be a good fit." he said.

And it didn't take me long to realize that moving my lab from Berkeley to Stanford would situate me much closer to the clinical sciences, and it was just the right time for me to think about that. So that was my thought process. And then I ended up moving in 2015 and I brought my whole lab down from Berkeley and set up shop at Stanford. In the meantime, we branded the concept of the institute as ChEM-H, and when I landed at Stanford, Chaitan, was the Inaugural Director of ChEM-H. Then a few years later, I joined him as a Co-Director, and then a few years after that I became the Director.

So now I'm the Director, and we also now have renamed the institute Sarahfan ChEM-H in recognition of our very generous philanthropist who supports the institute.

Ruth Adewuya, M...: That's an incredible story, and it's impressive that you made the decision after being at Berkeley for so long. That can be a challenge.

Carolyn Bertozz...: When you've been in a place that long. And remember, I also did my PhD at Berkeley. I really was in Berkeley from 1988 to 1996 with a three-year gap in between as a postdoc. And I had turned down offers to move elsewhere from institutions because it just didn't seem quite like the right move at the time. And so I think when you make a decision to leave a place you love, and I loved Berkeley, I was very happy there. That decision usually has to be motivated by some draw to something new that's just really compelling. I do think, yeah, after you've been working in a place for 20 years, it's good to try something new.

Ruth Adewuya, M...: This is true, but I think that's a testament to the scientist mindset to explore and seek new ways and forge new ground. I want to switch gears to talking about your work, bioorthogonal chemistry. I don't even know if I'm saying that the correct way, but it's an integral and revolutionary part of your work and your deemed to be the creator of this field. Could you explain this concept to us and how does it differ from traditional chemistry?

Carolyn Bertozz...: Well, you actually pronounced it quite well. And the funny thing is at the time that we coined the term, which is way back in the late nineties, early two thousands didn't occur to me at all back then that people might someday need to pronounce this word. So we didn't really think about it, but it really has a very

literal meaning to chemists anyways, which is that we use the word orthogonal to describe two things that have no interaction with each other.

And so bioorthogonal means basically chemistry that has no interaction with biology.

Ruth Adewuya, M...: Got it.

Carolyn Bertozz...: That's literally what that means. And in practice, what it means is we invent chemical reactions between two components. So two different reactants, you can call them A and B, and they react with each other with very high mutual selectivity and they have no interaction with anything in a biological setting.

And there's lots of chemicals in biology and there's a lot of chemistry that your body is doing. And so bioorthogonal chemistry is a kind of chemistry that ignores all of that, but still allows you to do a reaction where two things combined to make a third new thing. And reactions of that type can actually be performed in biological systems because they won't interact with the system. It's just inert to them.

And so what that means is these chemistries allow you to build molecules, literally, inside living cells or in living animals, and now it's actually being done in human cancer patients. And there's lots of interesting applications for these chemistries having to do with basic biological research. So in the early days, our motivation to invent these reactions was because we wanted to do some molecular imaging experiments of cell surface sugars in living systems to study their biology, and there was no way to image the sugars.

And so we came up with this idea for how to do it, but it required doing a chemical reaction in the living animal. And so that's why we said, "Well, there's no chemistry that allows you to do that. We have to invent some chemistry." So the bioorthogonal chemistry really was originated from an unmet need in molecular imaging that we were pursuing. But then once we had these reactions developed, we realized that there's actually so many things you can do with chemistries that don't interfere with or interact with biology.

And the field took off after we published our first few papers and we started using the chemistry for lots of other interesting applications, and so did the rest of the world.

Ruth Adewuya, M...: First of all, I'm just going to say that I think if you were my chemistry teacher, I might have been more interested in chemistry because I understood all of that.

Carolyn Bertozz...: It makes a big difference. And I had a really good organic chem professor. If I had a different O Chem Professor, then the subject might have died on the vine.

Ruth Adewuya, M...: What a shame for all of us. I think it's incredible to hear how this came up because of this unmet need and this gap in chemistry. With the discovery of this, how has this changed our understanding of cellular processes and the role of biomolecules in disease?

Carolyn Bertozz...: There's just been so many interesting studies over the last 20 years now in which people have used bioorthogonal chemistry as a tool. And I couldn't even recount all the discoveries that have been made with it. But in my own lab, I can tell you since our focus has been on glyco science, we've used bioorthogonal chemistry to look at changes in cell surface glycosylation that accompany, for example, embryonic development and tumor development and cancer.

And that has led to the identification of some interesting targets for new types of therapeutics for cancer, and we work on that too. So we make therapeutic model compounds, we test them in the lab and have then spun out a bunch of companies to try to progress those tool molecules into actual human therapeutics. Mostly in the space of cancer immunology actually.

One of the discoveries we made many years ago now, in using bioorthogonal chemistry as a tool in the research lab has now led to the development of a immune therapy, which is in a phase two clinical trial at the moment.

Ruth Adewuya, M...: We'll talk more about some of those areas in medicine where there's a lot of impact. And I want to take a step back and just talk about your journey again. In the past, you've talked a lot about the importance of mentorship and the value that it holds to you. Could you talk more about the impact of mentorship on your journey and how does this shape your approach through the students that you now mentor?

Carolyn Bertozz...: I had some really important and very impactful mentors in my early training years, for sure. The funny thing is when I was a student, we didn't talk much about mentoring or mentorship, and I don't even remember ever using that word until I was a professor much later. But the concept of course has been important since the dawn of time, and especially in the sciences where our training experience, in a way, has the feeling of an apprenticeship.

You join a lab as an undergraduate, and then later as a PhD student, and you have a PI, right? You have a professor who's your supervisor, but who you're really learning from, almost like in an apprenticeship. They teach you techniques in the laboratory, but then you also watch how they do their job, how they think about new problems, how they put project ideas together. You help them write grant proposals to get funding for the project.

You watch them present the research which you did in the lab, and they're presenting it and you see how they present it. And I learned by observation from some people early on, I had a really cool undergraduate advisor who I learned certain things from. And then I worked for a summer at Bell Labs in New

Jersey. That was another experience. But then I would say probably the two most important influences on me were my PhD graduate advisor and then my postdoctoral mentor.

And these two guys couldn't have been more different, personality wise and in the style in which they ran their labs. And I learned things from those two people that were quite different. And you know how it is whenever you're in a job in an environment, there's good things that you like about it and then there's bad things that you don't like about it. And so I learned from those two experiences to try to take the good things from each of those different people and make the most of those good things when I set up my own lab. And the way I interact with my students, again, it's like a hybrid of my experiences with those two guys.

Ruth Adewuya, M...: What are some of those key values that you emphasize or that you promote now in your lab?

Carolyn Bertozz...: There's some things that are very important to me, of course. First and foremost, everyone in the lab has to understand we are a team and science is a team sport, and you don't get very far by focusing entirely on yourself as an individual. You have to think of the role that you play in the bigger picture, and everyone does better as a consequence. So I try to make it clear to people in my lab that I expect them to be collegial, collaborative, transparent and generous. That those are qualities that I think make for good science.

Also, my lab puts a high premium on diversity, equity, inclusion and respect. And I do my best to recruit people into my lab that represent all different kinds of vectors of diversity. And I think that allows us to think more creatively and to pursue problems that really mainstream thinker might think is too risky, too outside of the box. But when you have a diverse group of people that are not bounded by group think, you get to do some really cool creative stuff. And so that is also important to me. It makes the job more fun, and I think the science that we do is therefore more impactful.

Ruth Adewuya, M...: You have different work environments and you have the good and the bad and sometimes we take the bad with us to our next environment. And so it's great that you're aware of being intentional about bringing the good of the experiences and also really highlighting diverse voices and diverse perspectives in your lab and the impact that it can have in science and how we do research.

It's a great segue to my next question, that as being a woman in science, being part of the LGBBTQ+ community, unfortunately we know that there are sometimes associated challenges that arise because of implicit bias. Could you talk more about your story? What are some of the obstacles that you might have encountered and how have you navigated those obstacles to get to where you are right now?

Carolyn Bertozz...: Oh, it's a great question. With my age and my background and my training experiences, I've had a lot of privilege. So yes, I'm a queer woman, grew up in Massachusetts, a liberal environment, went to college at Harvard even in the 1980s that was a fairly liberal environment. And then I made a point of getting myself to the San Francisco Bay Area for grad school and have stayed in the Bay Area ever since.

And of course that was because I felt a queer person had a better shot at a peaceful life and the opportunity to pursue a career without all the encumbrances of very homophobic environments. I wanted to be in the Bay Area because it was an epicenter of queer activism in the eighties and nineties. And so as a person who's put myself in the best possible situation to succeed as a queer person, I probably had a lot fewer negative experiences based on that compared to anyone else who didn't live in the Bay Area and didn't have the privilege of being able to situate themself geographically wherever they want to be, which I had that privilege.

Having said that, I would say probably the biggest difficulties that I've encountered were not so much because of being queer, at least not to my knowledge, but more to being female in chemistry, which back then was very gender imbalanced. A typical PhD program in my day would be 10% female, 90% male. That was pretty typical. And nowadays, you don't see those lopsided numbers in chemistry. But I was pretty minoritized at the time that I pursued my PhD, and it was not an easy time to be a woman in science. So most of the difficulty, most of the heartbreak and the frustration was more due to sexist attitudes and exclusion of women and not so much about homophobia.

Ruth Adewuya, M...: I appreciate the thoughtfulness of your response in framing your experience and recognizing things that you made the ability that you had to position yourself in a place that will get you the most success. And also just the awareness that it's not possible for everyone. But despite all of that, there's all these vectors, I think as you mentioned, where implicit biases and issues still come up. It's not because you're queer, it's because you're a woman or one thing or the other.

And so I'm going back to my last question and the intentionality now that you put into setting up spaces that don't have that, that allow for that diversity, it's just so powerful. And clearly we need more people who are intentional in the space.

Carolyn Bertozz...: Academia is frustrating this way because just the nature, the whole structure of the enterprise is one in which when you make a change today, you don't sometimes feel the effects of that change for decades. And there's reasons for this that are complicated, but they have to do with the fact that, for example, professors start jobs in academia and they often stay there for 50 years. They don't retire. They don't move on until they're very old, much of the time. So that's number one.

So that means if a department undergoes like a faculty turnover and you hire a bunch of people, if you don't do your diligence and make sure that the hires you make during that turnover period reflect the diversity of the workforce that you would like to have in the future, you have to wait another half century before you get another shot at that. So that's problem number one.

Problem number two is academia in general is very much an insider's game. It's a kind of an enterprise where if you don't know the unspoken rules and systems and pathways and strategies, it's really hard to break in. And the data is obvious in this regard because you can see that, line up the faculty from your top 50 universities of interest and ask where did they come from? And you'll see that they all were trained in a very small number of feeder institutions.

And in the sciences it's even worse because not only do they come from a limited number of feeder institutions, they even come from a limited number of labs where they were trained. So there's a lot of nepotism and legacy benefits and stuff like that in academia. And this isn't written anywhere, but it's obvious when you analyze the data.

And so I think the question is if you want to change the face of academia and change it so that it's higher functioning, and more productive, and more impactful, and reflects the world we live in, you really have to be very intentional about it because the system itself will never change on its own. There's too much insider behavior.

And so for me in my career have been an insider most of the time. I was born in an academic family. My dad is a professor or he's retired now, but he was a professor at MIT. So that's the ultimate insider is growing up where your dad's a professor in the sciences. And even though I was an outsider because of my minoritized identities, and I did get a degree from Harvard, and then I went to Berkeley and UC, Berkeley as an insider type of university.

And I've been on the faculties at top universities and now I have a Nobel Prize, you just don't get any more insider than that. And so the question is, with all of the power of that insider privilege, what can you do to actually break down the barrier between insider and outsider and ultimately erase the whole concept of the insider to begin with? And I think that is now incumbent on me and really any professor at Stanford who by definition is an insider, that's what we all have to do now.

Ruth Adewuya, M...: That is such an incredible call to action for clinicians who are in academic institutions and have the ability to be part of those conversations and those decisions because you're so spot on. There's this unspoken rule. There's unspoken processes and policies that the engine just continues to run. If you don't pay attention, it's just going to continue to turn out the same type of people and the same groups.

I'm just amazed that you are considering that something that is your responsibility to change, which I hope that others think of it that way as well. And when you think about all of the students that come from under-resourced areas who have interest in chemistry, how do you break into this when you're not born into an academic family? It just seems like the barriers are just so high. And what can we do as an organization to fix that?

Carolyn Bertozz...: That's a great question, and obviously we are struggling because you can look at the numbers and the needle hasn't moved as much as you would think it should. And I think there's two things. On the one hand, I think we could do more to reach out and look outward and figure out how can we open doors and remove barriers for people that didn't come from that cookie cutter clone, insider background.

And by reaching out, that means we also have to provide people with the information and the training that they need to be alongside the insiders and not feel like an outsider. But at the same time, you can't just put the whole onus on, "How do we get people who are not prepared to join the inside club and make them insiders?" I think the institution has to change so that we are not an exclusive club anymore. And so how do we do that?

I can tell you one thing that we're trying at ChEM-H, we started a post-baccalaureate program, a post-bacc, we call it program. And we have raised money for this. And the theme of the program is to bring in people who just finished their undergrad but maybe don't have the package needed to compete for PhD positions at good programs because maybe their undergraduate institution didn't have a lot of research capability, and so they didn't really get much exposure to research.

And also they maybe come from a background where there weren't enough insiders telling them the secret rules of the game. So they just don't know. And we want them to be able to do a PhD if they want to. And so the idea of the post-bacc program is we take students from backgrounds where they would be considered underprivileged or under-resourced, and we bring them to Stanford and pay them for two years. They do research in a Stanford lab with a mentor, and we screen these mentors very carefully to make sure that they really are dedicated to the time and the energy it takes to really mentor someone and train them how to do research.

And then we also have activities for these post-bacc students where we teach them how to write an NSF grant proposal so that they can apply for a fellowship. We teach them like what is the GRE and how does it work and how do you prepare for it? And when you're doing research, how do you make a slide deck to describe your research in a group meeting? They're really basic skills that you get starting as an undergrad in many institutions, but not all colleges have that.

And then the idea is after two years in our post-bacc program, we help them apply to grad schools and hopefully they get into amazing PhD programs and hopefully Stanford is a place that they consider. And so therefore there's a self-serving element here where we might actually be creating a pipeline of more diverse applicants to our own PhD program. That's one thing that we're trying, but I'm sure there's many other things we could be doing.

Ruth Adewuya, M...: That's an incredible program and definitely a step in the direct direction, and I hope people get inspired to continue to do that. And once they're in, as you mentioned, create a place of belonging for all of them, which is also very important.

We took this sidestep journey into that. Going back to bioorthogonal chemistry, I'm curious, what areas of medicine does bioorthogonal chemistry hold the most potential to impact?

Carolyn Bertozz...: Well, I think it's such a powerful tool and people use it all across the spectrum of drug development actually. And right now, in fact, there are a handful of human medicine candidates that are in clinical testing that were made using bioorthogonal chemistry. Some of them are what we call site-specific antibody drug conjugates. So these are next generation cancer medicines, and there's a bunch of those that are in the clinic that were built using the chemistries that we invented in my lab back at Berkeley.

There's a company that's actually doing bioorthogonal chemistry in the human body, and they use it as a way to target chemotherapeutic drugs very selectively to tumor environments and keep those drugs away from the rest of the body so that the side effects are less. And that's happening right now. That company just finished its first phase one clinical trial. So right now you can see products of bioorthogonal chemistry in medicines that are in human testing.

But at the same time, it's a really nice tool to have just for the researcher. And there's just lots of experiments that have been enabled with bioorthogonal chemistry, including molecular imaging platforms. People use it to identify the targets of drug candidates in animal models. People use it to do what we call chemo proteomics for drug development and drug discovery.

Ruth Adewuya, M...: It seems like there are real life applications in terms of in medicine and also just advancing the field itself, so that's fantastic. As you look into the future, if I may ask you to look into the proverbial crystal ball, what are some of the most exciting and potentially transformative directions and it's applications to medicine that you can see?

Carolyn Bertozz...: If any of these drugs get approved, which I think will happen in the next few years, you can say then that these are medicines that could not have been made without bioorthogonal chemistry. So you couldn't even build the molecules

without this kind of chemistry. So I think that's in the near term, that'll be a quite obvious important outcome.

In the longer term. I really think, again, it's as versatile as other technologies that are now taken for granted. For example, monoclonal antibodies. We use monoclonal antibodies as tools in our laboratory every day to answer questions about biology, lots of questions. We also use monoclonal antibodies as therapeutics. They're probably the largest category of drugs that are approved by the FDA right now.

So I think bioorthogonal chemistry will have some parallels to monoclonal antibodies in that it's just a tool that's baked into the fabric of every research lab and also medicines are being made with it, and monoclonal antibodies were also recognized with a Nobel Prize, by the way.

Ruth Adewuya, M...: I'm really excited to see what the future hold to some of the drugs that come out of it, and it's just kind of part and parcel of how we do things, and so that's incredible to see that's where this field is going. As we wrap up our conversation, the last question that I would ask generally, what are some key takeaways that you have for clinicians or researchers who are interested in this field or navigating what their next steps are?

Carolyn Bertozz...: One thing I've noticed is that there's actually been a huge uptick in the diversity of therapeutic modalities that physicians can treat their patients with. Just as a case in point, I'm thinking back 10 years ago, drugs that physicians used to treat their patients were either small molecules like Lipitor, statins and things like that, or monoclonal antibodies were still new to the scene, but making an impact.

Drugs like Herceptin or Rituxan, and those were two categories of medicines, there were small molecules and biologics, which were mostly antibodies and a couple of different hormones. Fast-forward now today, just in the last 10 years, we've seen the development of antibody drug conjugates, which are part biologic, part chemical. We've seen approvals for gene therapies based on adenoviral vectors, viruses as therapeutics. We've seen RNA medicines, SIRNA medicines, antisense oligonucleotide medicines, and we've seen mRNA vaccines. And now there are cell therapies and all of these cool therapeutic modalities.

They were considered science fiction just a decade ago, and now they've become the standard of care for many different disease categories. And so maybe the lesson for the physician is, "You really want to make sure you stay abreast of what medicines look like and how they act and how they function because the innovations are happening so quickly now, you could easily fall behind." You want to understand enough chemistry to appreciate what an antibody drug conjugate is. You want to understand enough molecular biology

to understand how mRNA vaccines are engineered and designed and delivered, and the delivery involves some material science, some engineering.

So I think a physician, for example, someone at Stanford who's in an academic center and happens to be at a campus that's world-class basic science, chemistry, and engineering should really avail themselves of what's happening across campus drive because it very much could impact their clinical practice much more quickly than you might think.

Ruth Adewuya, M...: That's incredible. Thank you so much for underscoring the importance of keeping up to date with advances in medicine because ultimately we would provide better patient care for our patients that we encounter. Thank you so much for chatting with me today. I appreciate you sharing your story and giving us some insight into the incredible work that you do.

Carolyn Bertozz...: Thank you so much for having me on. I appreciate it.

Ruth Adewuya, M...: Thanks for tuning in. This episode was brought to you by Stanford, CME. To claim CME for listening to this episode click on the Claim CME link below or visit medcast.stanford.edu. Check back for new episodes by subscribing to Stanford Medcast wherever you listen to podcasts.