Isaac:

(Narration) Hello! My name is Isaac and welcome to another episode of our Young Scientist Spotlight series where we meet young scientists across the world and have fun conversations about their life stories and their research. DNA is known as the building block of life. Today, we meet with Dr. Arun Richard Chandrasekaran, a scientist at the University at Albany, who takes this saying literally and engineer complex machines out of DNA molecules. DNA is not something we can physically touch - you can't use a tweezer to hold onto DNA. So… Arun uses a super special secret technique to fold long strands of DNA into complex structures that can sense changes in temperature or even deliver medicine to your body. Well… I am not going to spoil what it is! Stay tuned to find out how Arun is able to construct these amazing DNA contraptions.

[CTOR tag]

Isaac:

Welcome Arun! We are super excited to have you. Can you give a brief self-introduction for our audience?

Arun:

I'm Arun. My background has always been working with DNA in some fashion. Right now I am a research scientist in Ken Hal(Kenneth Anders Halvorsen)'s lab at the State University of New York at Albany. So we have an Institute called the RNA Institute here, which is where our lab is housed. For my background, I did my PhD at New York University with Ram Seeram (Seeram Ramakrishna). For my postdoc, I moved to Suny Albany. I briefly worked in a biotech startup, and I'm here right now. Overall, my trajectory has taken many detours. so I did an undergrad in zoology, studying animals and their classification in, and then a master's in nanoscience. and then my PhD is in chemistry. So I've taken different routes throughout my scientific career. Even though it looks like I didn't know what I wanted to do. I would like to think that, these detours happened because I wanted to explore revenues that interested me at the time. and in hindsight, I think it's, it has been an advantage for me, since I believe scientific research right now is so interdisciplinary. So it gives me an advantage of being in different fields and combining different perspectives in my research.

Isaac:

One point I find interesting is you're working in the RNA Institute in Albany, but your main true passion is in DNA. So what's the connection behind that?

Arun:

Uh, I guess, the lab I work in just happens to be in the RNA Institute, the reason or the connection, between the DNA focus and being in the RNA Institute is that, our biosensing, work

is from the sensing or detecting RNA molecules. and these are, some mostly biologically relevant and in some cases, disease, relevance.

Isaac:

So when I think about DNA, I think a lot of biologists and, people tend to think of it as, um, like the major purpose of DNA is just to make proteins. Um, so what kind of properties does DNA have that make it a suitable material for building these structures? And can you use other materials to build these structures as well, or are these unique to DNA itself?

Arun:

DNA certainly has some unique properties. and as you mentioned, in my research presentation, one of the key aspects I try to stress in the beginning is to tell the audience, forget all about the biology they connect DNA with. So here we are just using it as a chemical molecule, to use it to construct different shapes and structures. The advantage of using DNA is that it's, it's very programmable. So, you know, DNA sequence has these four nucleotides adenine, guanine, thymine and cytosine. And we can control that order based on the DNA sequence. so we can program these sequences to be in any format, and we can also make them in relatively easy and cheap fashion. Now, DNA strands are available commercially. if you wanna buy a 30 nucleotide fragment for less than $5, so it's very cheap, so it's all synthetic.

So it gives us enough material to work with. And it's also very flexible in terms of programming it, some of the advantages, for example, include DNA is a natural material. So when you want to use it for biological applications, it's biocompatible and biodegradable, meaning it's not as toxic as some of the other metallic nanoparticles or other things. And then it can also be dynamic. For example, you can tune, certain sequences to bind to each other or come apart based on other stimuli, this could be light. This could be other molecules such as proteins or DNA, or other environmental stimuli, for example, temperature or pH. So this allows you to have some sort of reversibility in these structures as well. So these are some of the advantages of using DNA as material. There are of course other biomolecules, which can be used useful in a similar way. I know people have started using, proteins and peptides to build or self assemble these material. DNA is just more convenient to work with.

Isaac:

Where do you put these DNA nanostructures and how are they used in different settings?

Arun:

So, for example, the biosensing work, we do, it's all ex vivo, meaning outside the body. so the way, it'll be useful is to use it in terms of, a diagnostic purpose, using biofluilds such as blood, or serum or urine. this is one aspect of it. There are also biosensors based on DNA that are useful in vivo. For example, you can find out how ion fluctuations happen within cells and certain pH sensing molecules within cells. and one other biological application, we can think of for DNA based nanostructures is in drug delivery. So in that you can use these DNA structures as carriers

for different types of drugs, and then you can also functionalize them so that they can deliver drugs to a certain type of cells. For example, you can add specific ligand that can recognize, for example, a cancer-specific subtype in the body, and they can deliver it to specific cells. so drug delivery is one other biological, application for these DNA-based structures.

Isaac:

Wow that's amazing! So DNA molecules themselves do not have these pH sensing or drug-delivering capability. How is it that you are able to add all these extra functionalities to DNA?

Arun:

So, generally, if you want, if there's a biosensor for any nucleic acid, if you wanna detect a DNA or RNA, I think almost ex exclusively all these biosensors use DNA in some way, because it all depends on having a DNA probe that is complimentary to the target nucleic acid that you want to detect. so that's universal in terms of using DNA nanostructure specifically. There is some programmability that, makes, it more useful. For example, you can easily build a structure which directly changes shape on binding a target by a molecule. And in this case, it may be easier to design and implement, in a solution without requiring any surface or expensive equipment specifically in the work we do here at Albany. we create what we call a DNA nanoswitch. So you can imagine it as a linear molecule with two probes that are complimentary to, a target molecule. You wanna detect, for example, microRNAs or viral RNAs, which, everyone knows now, for example, SARS-CoV2. So when the detector segments bind into this target, the switch turns from the off position to the on state, which is a different structure, and that's how we read it out. But this conformational flexibility also allows key design parameters for DNA biosensing.

Isaac:

Was there a point in your life where you found your passion for DNA?

Arun:

Yeah, so during my masters, in our last semester, we were required to do a research project. so I worked with, a professor who was a DNA crystallographer by training.

Isaac:

(Narration) Ok! so what is a DNA crystallographer? Well DNA crystallography is a technique that allows scientists to determine the three-dimensional structure of DNA molecules. Normally, DNA is invisible to the naked eye. To visualize DNA structure, scientists bombard DNA molecules with a powerful X-ray beam. The beam is scattered upon colliding with atoms in the DNA. Based on the scattering pattern of the beam, scientists can draw inferences and deduce the structure of DNA. This is what Rosalind Franklin did to discover the double helix structure of DNA. Now back to Arun.

Arun:

So there, my specific project involved crystalizing a particular DNA sequence. There were two curious things about this project. One was this particular sequence formed a lefthanded double helix, which is called z-DNA, this is in contrast to the widely known, right-handed helix. we are all familiar with. And the crystals we grew, they were also hollow and not a solid block. And they were these hexagonal ring-shaped structures, which was, very unique. And this is when I started being more involved with DNA-related work, and, in one of the classes, at the time I started reading about how people have used DNA to build different nano-scale structures. And I thought it was really cool. so that's when I realized, you know, I really loved this and, I wanted to do my PhD in this field. so I applied to NYU where, Ram Seeram, worked, he's considered the founder of the field of DNA nanotechnology. Um, and then I got into NYU and I started work, and I think the rest is just history.

Isaac:

So how easy is DNA to work with? What kind of machinery or methodologies do you use to make these structures out of DNA?

Arun:

So I guess the first thing we do is try to model the structure we wanna build. so this could be physical model. In my former lab, we used to have these sticks and wires where we build physical models to see whether the structure can actually be folded and we also build computer models to see how the DNA strands might weave together to form the structure. For example, you imagine a DNA cube and you can, you can sort of model it first and then you'll know how many DNA strands it might require.

And it is this design that is most important, right? We make sure that these segments are complimentary so that they can be paired with another segment in the strand and nowhere else. And then that's how we design it. Then we buy the sequences, and typically, you know, once we put all the DNA molecules together, there's a heating step involved,you heat it up, you cool it down, we call it annealing. And then, DNA hybridization happens. And these molecules come together. There is some titration in this going back and forth, from design to experimental analysis. And then sometimes if the structures don't form, we might have to tweak the design and go back and forth.

Isaac:

I see. So, once you have designed the correct sequences, they would just form these structures once you apply the heating step.

Arun:

Yes. So we heat it up so that each of the DNA strands involved, do not fold on themselves. So the heating step, makes sure that we start with linear chains of DNA. And then when we cool it down, the DNA molecules pair with each other, based on the hybridizing regions and insert in certain fashions. So as for the structure, the pace at which we heat and cool it down, also

matters, and complex structures, require the cooling step to be much slower. and in some cases, complex DNA or structures might need, the solution to be cooled down over multiple days for the structures to form well.

[Music break]

Isaac:

Do you have a favorite DNA structure, one that you have engineered yourself?

Arun:

Uh, I do. So in my PhD and in one of my recent works, I work with paranemic crossover DNA. We call it PX DNA in short. So that's one of my favorite molecules because it hasn't been worked on a lot. so I, I think it, it still has some mystical characteristics to it. And it's a very cool structure. It's a four-stranded DNA structure. you can imagine it as two, double-helical domains, which are connected to each other and placed equidistant to each other. Um, and the four strands are designed in a way that, it's a duplex of duplex. So that's, that's a crude analogy of thinking about the molecule. So I think that molecule is really cool and, a lot more to learn about it. It hasn't been crystallized yet, so that, you know, we have some idea of what the structure is, but we don't know exactly how it looks. so there's still some aspects of it that, we would hope to, learn more about.

Isaac:

Um, yeah, that's very cool. You have mentioned the term, DNA origami and I'm just wondering how similar DNA is to like a piece of paper. So theoretically, can you like fold DNA into any shape or are there some sort of limitations to the structure of DNA itself? Are there structures that you just cannot make?

Arun:

Theoretically? I think there are no limitations. so the field itself is relatively new. I would say like 20 to 30 years is, is like the age of the, the DNA nanotechnology field. and in terms of folding DNA, like people who are familiar with the term, they know origami is about folding paper, into different shapes. when it comes to DNA, origami works in a way where we take this a long piece of single standard DNA, and we can now fold that into any shape we want. This could be 2D or planar structures or something in three dimensions as well. And, and once we know how we want to fold this long piece of DNA, we hold it in place by adding short pieces of DNA that are complementary to different regions of this long piece. So we call these staple strands because they sort of staple scaffold and position.

And so that's how we design and build this. There used to be limitations, in terms of, synthesizing such large-scale molecules and in terms of designing how these folds and come together. but I believe many of those limitations are now, behind us. So previously, all the three-dimension structures used to be bundles. For example, they are closed-back structures, but of late, there are also many, works from other labs who have shown that you can build,

hollow structures, for example, DNA vases and DNA spheres. One limitation there I could think of is, expanding the size. So right now, you can, you can imagine these structures to be anywhere between 10 nanometers to about, 2 or 300 nanometers in dimensions. but that is also being addressed. so in building just one large piece of nanostructure, you can now build multiple smaller structures and put them all together to build an even larger structure. So that's the way people have scaled this up to build larger structures.

Isaac:

And so, if you're able to build larger structures you would also be able to get more complexity and build more complex structures with more sophisticated functions.

Arun:

Yeah. So larger structures allow you to sort of, bridge the gap between the nano and the micro realms. Cause in some cases, these structures are small and that might limit the functionality. So when you have a larger structure, you might have more spatial resolution to address more functionality for these structures and also of the complexity.

Isaac:

Yeah. Awesome. So where do you see the field going in like the next, like five to 10 years?

Arun:

Uh, I think in general, the field is moving more towards applications. so, you know, including my own research, I started off, being, in the more structural aspects of the field in trying to design motiffs that can self assemble. And now I think the field, in general, is moving more towards applications on realizing, how these molecules can actually be useful. so I see, more promise in drug delivery. there, there were a couple of recent works that showed effective drug delivery using DNA nanostructures in mouse models. Um, and I thought this was a big step moving forward, from all the cell studies that came before this work, and many other labs are also, addressing fundamental issues, in addressing certain drawbacks in using DNA material.

Arun:

For example, DNA is biocompatible, but at the same time, it can also be very biodegradable, which is not good in some cases. Yeah. so my work and others have shown, different or worked on different strategies to enhance the biostability of these structures so that they can be used in vivo in a much better fashion. so overall, I, I think, the field is moving more towards application, especially in biosensing and drug delivery and, outside biology. There's also, more focus on applications in material science, for example, in data storage where the sequence of DNA could be used to encode information. typically it requires you to use multiple DNA strands create libraries where each sequence will code for a specific, line of text or an image. And then when you sequence these strands, you can read it out as a JPG or TIFF. and I know Microsoft invents invested a lot of money recently, in DNA based data storage. So I think is, is a cool application that's being looked at.

Isaac:

Yeah, it's so cool that you can actually store data in DNA and like put it in a random cell and you can have the cell replicate. And the data basically lives forever.

Isaac:

Where do you get the DNA from? Are you extracting them from humans or mice?

Arun:

So all the DNA we use is synthetic. So, once we design the DNA sequences, what we do is we order it from a company. there are many companies that sell DNA now, and especially with, an increase in the number of DNA, nanotechnology labs, as well as, you know, you can imagine other biotech labs also using DNA primers. And so, so there are companies that synthesize DNA commercially. So once we design the DNA strengths, we order it from a company. So it, it, we usually get it in one or two days. So it's very fast and it's very cheap.

Isaac:

So, you don't do any animal work at all in your PhD lab?

Arun:

No, we don't.

Arun:

For, for building, yeah. For, for using the DNA and for building nanostructures, it's all chemistry, in terms of applications, I haven't done animal work myself, but we do work with other biologists, for example, when we want to see how effectively these DNA nanostructures are taken up within the cells, and in some cases our biologists provide samples that we use to detect specific microRNAs and viralRNAs.

[Music break]

Isaac:

I want to talk a bit more about, your PhD training. So, you were originally from India, right? And you moved to New York for your PhD. So how was that transition for you?

Arun:

Uh, one thing, I'm not trying to generalize, but from my personal experience, I found that, science here in the US has been more hands On even at the undergraduate level, which, I wish I had in India. so, you know, for example, undergrad get a lot of research opportunities here, which I think is great, regardless of whether they go into grad school or med school or some other career later, it's a great experience. So that was, something I found very different coming here. and

even as a grad student, I mentored other undergrads and, it was, it was a great time doing hands-on research. otherwise I really enjoyed having peers, you know, for example, let's say I, I started as a first-year grad student, um, a fifth year grad student wouldn't be any, different or like have a halo around them. So it was very nice to be collegial, among peers, especially in research, and work.

Isaac:

You mentioned there's a lack of undergraduate research opportunities in India. Um, so how would you go about encouraging professors or PIs to take in undergraduate students cuz they're kind of a burden, like they don't know anything and they tend to screw things up. So what are some of the incentives that we can give to professors to take in students?

Arun:

The way I think about undergraduate research or providing more options, opportunities to undergrads is, I think of it as a time investment, with rewards. So, the way I might push or convince a PI to take an undergrad is that, you know, if you train an undergrad for the first few weeks and make them independent, I know some undergrads who have worked as well as a grad student with full efficiency. so if we can get an undergrad to start in a research lab just to explore, see how they feel about scientific research in their freshman year or sophomore, then they'll have two to three years within which they can contribute a lot to the lab in terms of, research progress. So I think that's valuable for any research lab and for any PI.

Isaac:

I just started my PHD and when I look at my peers, people in my cohort, they have so much, research experience in their undergrads already. It's really valuable for us to have those early exposures.

Arun:

There are also programs that some schools have. Albany has started one recently where, they're trying to create a sort of a paid program, which allows a few freshman students to work in a lab for six months and then they can decide if they like it, they can continue. So this also takes the stress out of PIs to, you know, pay undergrads before they even know how well they work. so this works for both parties, for the PIs to know how well the student is without having to commit. And for the undergrads, it's good to explore the research opportunities without having to worry about working part-time elsewhere because I know, some undergrads also cannot take time off their work to contribute enough time to the research lab. So having, you know, some sort of financial program to allow them to work in the research lab would aid in helping many more students come to the research lab.

Isaac:

Some people just can't afford to do unpaid work and having just some financial assistance would definitely help them a lot and get more people access to these opportunities.

[Music break]

Isaac:

I know you also have some industry experience. could you talk about that a bit as well?

Arun:

So when I was a post doc, the biosensing work I mentioned, using the DNA nano, was to create the diagnostic assay that will allow detecting multiple different types of biomarkers. So our lab and another lab at Harvard med were both working on this and one of the grad students in the other lab just decided he wants to start a company. so he, started a company with a couple of other people, to use this DNA nanoswitch, to develop, a suite of assays. and since I also worked in the same area, I interviewed for the job and I was the fourth employee in that biotech startup. It was a, a really cool two years of work there. so we worked a lot on developing a diagnostic assay for fertility and ovulation.

Uh, so this is, focused on, there are already pregnancy tests available out there. So the focus here was, more, an early detection method that will allow people to plan pregnancies, especially those who are struggling with it. so the company did not survive, which brought me back to academia at the time. so I think it has given me a unique perspective of being on both sides of the spectrum.

Isaac:

Are there things you would say that academia can learn from industry?

Arun:

I can't say there's much academia can learn from industry. however, I don't think there is a gap, between the academic and the industry setting, you know, as researchers, we, we have the freedom to do whatever we like to work on. So I think that's, a key luxury that industry does not have compared to academia.

Uh, but the gap lies in how, how academic research connects with industry. so for example, we recently had a chat with one of our big biotech companies that were interested in, a method we developed in our lab. So during that discussion, I realized that the way we academics think of research problem is different from the way people who work in a company think about, so there, the research questions and answers they think of is more generalized, like for example, how this can be scaled up, how it can connect with multiple people and multiple purposes but here for example, I might work with just a collaborator in mind and not, you know, multiple countries that might need such an assay. so I think having, having such interactions or having more interactions between academic universities and industries will help, direct research progress better and to translate academic research, more into research. And I think it'll also help streamline, the workforce of skilled PhDs into more industry positions because I believe, you know, that's where most of the PhDs go to work for and not in universities.

Isaac:

Do you have a preference for one over the other? On Twitter especially, there seems to be this sentiment of people leaving academia because of just how competitive the environment is and how poorly people are compensated for their work. The workplace can be very toxic for some people as well.

Arun:

I really like academia. the fact that it is competitive, that the pay scale is not as high as industry, and the stress might all be true. but those are all also addressable in my opinion. Maybe not right away and maybe not by me, but they are addressable. I really love academia and I'm inclined to stay. However, I feel, academic job prospects are right now confined only to tenure track positions. So if I wanna stay in academia, my own route seems to be, you know, applying for a tenure track job and then become an assistant professor and move up the ladder. I wish there were more, independent research positions like PI positions, which do not require a teaching component. So you could still work, in academia. You could still have your lab, but you don't have teach if you don't really want to.

Isaac:

Yeah, I definitely would appreciate more job fairs so that I can know, like I can do stuff, outside of a post doc. That's not the only track people go to.

Arun:

So one of the things, going back to, you know, the state of academic affairs and like PhD skills, one thing I go back to thinking, is how, you know, there's a lot of skilled labor people with PhDs and so many smart people. And, we used to have these alternate careers seminars for students, which focus on, you know, non-academic jobs. there might be others who think like me, but I believe that academic jobs are in fact, the alternate career, because a very minor fraction of PhDs actually end up in academic jobs. so I think it's, there could be a paradigm shift in the mindset in thinking that, you know, there's more to research and it doesn't have to be done only in universities. and you know, people who quit a tenure track job, it doesn't mean they're quitting research. They can still do research elsewhere. so I, that's something I keep thinking about. and then we have many PhDs who, you know, work elsewhere. So I think the general mindset of, research could be changed for the positive.

Isaac:

Outside of science, what are some of the things you like to, work on and do?

Arun:

I watch a lot of movies, and I think I pride myself, in watching even the crappy movies. so that's, I spend a lot of time watching movies and it also helped me sometimes to connect with people. for example, even in my science talks, I like using pop culture references, which are mostly

movies. so it helps me connect with, especially the general audience when I can discuss science and related to a movie or an episode of a TV show. Beyond that, I like writing poetry. I was excited last year when one of my poems was published. yeah. So, and then I sing sometimes in choirs, and then more recently, lately I tried my hand at, designing graphic artwork for magazine covers.

Isaac:

That's super cool! Thank you so much for coming today and sharing your work with us!

Arun:

I really appreciate the chance to showcase my work with Carry The One. When I saw it on Twitter, I thought it was, uh, I didn't realize it has been going on for over ten years now. 'So it's really cool, it's a really cool initiative that you guys are doing. Yeah! Thanks for having me.

[Music break]

Isaac:

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