

CHAPTER IX: SUMMARY AND Q+A

So, with that, I will quickly summarize that this is an important field that, in many ways, has its origins, if you will, from important natural products, such as heparin, that have been studied for a number of years. But, fundamental tools arose in biological processes were difficult to understand because of lack of tools is that, not only are they linear, but they're branch, complex information, information dense. And, then we have new tools and technologies to be able to access SAR. I walked you through quite a few examples to give you a flavor of what these are. And, I think there are going to be many more interesting applications, including infectious disease that I briefly pointed out.

So, with that, I just want to very quickly tell you that, with regard to the area of carbohydrates has always been this, people think we have been digging holes. Once you have some kind of tools, you're looking for a treasure you find a few dirty rocks, roots, and some disgusting things. And, the idea being that, if you get the right techniques and tools, you'll be able to access treasure.

So, with that, I'd like to thank NIH, various foundations for support, collaborators. Thank you very much. And, I'm happy to take any questions.

DR. CHESNEY: Thank you very, very much for a very interesting, intriguing look at the future. I know some people probably have to leave because we're running a little bit late, but we do have time for a few questions if there are any. Please come up to the microphones.

Question: Hi, thanks for a really nice lecture. So, I think you explained really nicely about the tremendous diversity caused by this glycation of proteins and how you use the state of the art methods to characterize this diversity. But, I was wondering if you

could elaborate a little further on what is the evidence that tremendous diversity actually encodes functions? So, in other words, you said, for example, erythropoietin, there's 150 different kinds. So, are there really 150 specific biological functions for those different kinds of erythropoietin, or is it just, I mean, the examples that you gave are a lot of glycation, a little bit, intermediate, something like that.

DR. SASISEKHARAN: That's a very good question. I think the specific answer with regard to EPO, we don't know. But, we do know that there are different tropisms associated with these molecules. I think we're beginning to scratch the surface of that. But, what I can do is, using heparin as an example, we now know that there are close to 60 or 70 different family of molecules that they bind. And, the idea is that we're accessing specific structures to see what the functions are. But, I think it would be very interesting to see whether erythropoietins and molecules like those, what the unique modifications might correlate to with regard to, for instance, the locations of salic acid and clearing mechanisms or tissue tropism and so on and so forth. And, I think we're just beginning to access those kinds of issues.

QUESTION: BUT, COULD YOU SPECULATE A LITTLE BIT ON YOUR EXPECTATION? I MEAN, DO YOU REALLY EXPECT THAT THERE'S 150 DIFFERENT BIOLOGICAL FUNCTIONS FOR EACH ONE OF THOSE DIFFERENT GLYCO-STRUCTURES?

DR. SASISEKHARAN: I don't think so. I think the way to look at it is what are the set of structures or the ensemble of structures or classes of structures that do have functions, rather than distinct structures have distinct functions.

Question: I want to take off on that, and go back to your point about mixtures. So, is it important and it actually speaks to an important difference between biologicals and natural products and herbals and drugs, pharmaceuticals. That is, that many of these

are mixtures. So, is the fact that it's a mixture, do you think, important in the biological activity? I mean, you can isolate the individual biologic activities of the components of the mixture, but is it important in the overall activity, and how would you get at that?

DR. SASISEKHARAN: I think it's an excellent question, and I think it's probably going to be context specific. I mean, these molecules are made as an ensemble in mixtures, obviously, to regulate function in that fashion. So, would it be important? My guess is yes. But, to your point, could we take a strategy where we could take the components or compartments to see what the structure function basis is, yes. But, if you need to reconstitute it with regard to the application, it absolutely begs that question. And, I think the more we have high throughput approach of taking multiple pieces of information, looking at the correlations and how each attribute sort of influences the other, rather than viewing them as discrete pieces, the more we think that way, we'll be able to get to the heart of this challenge. But, I think that's an excellent question.

DR. SASISEKHARAN: So, the question is do we know what are all the various players and their location, if you will, that are important in the assembly of these molecules. I think, again, that's one of the probably the most central questions in the field. What regulates bio synthesis? And, how do the various enzymes that make these molecules come together and in what fashion.

I think the short answer is, we're, again, at the very early stages of trying to really identify the various enzymes. Do they act in sequence, do they act in concert? How do they really come together to make an ensemble of these kinds of structures? But, what we do know is that there are various isoforms, which are tissue specific, that enable, when you have these assembly of enzymes that are trying to, you know, display these

structures, there's a lot of slippage associated with how these enzymes work. In fact, there's no proof reading, again, begs the question of is there a feedback or there isn't or what regulates those things.

So, I think it's going to be a very important area of work in glycobiology to really unravel the biosynthesis of these molecules.

DR. SASISEKHARAN: That is a good question, and I think there are instances, depending on what species that you do see them in particular operands, and there are those that aren't, and I think we're just accessing them, more of these biosynthetic enzymes, particularly with the GAG area, are being, you know, looked into.

DR. CHESNEY: Thank you so much. I want to thank all of you for coming to NCCAM's Distinguished ecture, and invite you to our next one, which will be in the spring of 2007. It will delivered by Dr. Jerome Groopman of Harvard. And, again, applause for Dr. Sasisekharan.