JOANNE STUBBE: We spend a lot of time looking at-- all proteins are made from amino acid building blocks. And so one question I get, and students hate this, is, why do I need to know? I make them memorize the side chains of the amino acids. Why do I do that? Because the side chains of the amino acids are the key to the way all the catalysts in your body function.

A catalyst simply enhances the rate of conversion of some small molecule into some other small molecule, and it can enhance the rate of the interconversion by 10 to the 15th fold. So if you didn't have that catalyst, you couldn't do anything. So amino acid side chains play a key role in catalysis. So thinking about the chemical properties of the amino acid side chains is key to understanding all the transformations in your body. So, what is the pKa of imidazole? You remember that? Huh?

GUEST SPEAKER: I don't. I don't.

JOANNE STUBBE: How can you not remember that?

[LAUGHTER]

Anyhow, the pKa of imidazole is close to seven, OK. So those physiological-- everything in the body is controlled. The pH has to be controlled. And so that means that you can protonate or deprotonate it. So knowing that is key to thinking about how the chemical reaction is going to work. The amino acid side chains now-- everybody thought there were 22 amino acids. But now we know almost all these amino acids can be modified once they get into the protein, so that's called post-transational modification.

So now we have, probably, another 250 modifications. And one of the modifications that is essential, not for the catalysis part of proteins, but for the structural part of proteins, is hydroxylation of the amino acid proline. So if you don't hydroxylate proline, then you can't make this molecule called collagen. And collagen is a structural protein. It's 25% of all humans' protein, OK. And it's found extracellularly. Gram per gram it has the strength of steel.

It has very complicated biosynthetic pathway. It has amazing tensile strength. It's found in cartilage and teeth and bone. And a key component of collagen is this hydroxylated proline. Because without it, you can't form the actual collagen structure. So collagen is this long-- most proteins, if you look at the structures, they look like little balls. They're globular. But collagen is a fibrillar protein, so it's very long. it's probably the longest protein, too. It's 3,000 angstroms long.

And it has three chains initially, and they they're left-handed sort of helixes but not real helixes, and they have to wind around each other to form a right-handed helix. This all happens inside the cell, then somehow has to get to the outside of the cell. People are studying that now. And then it forms additional fibrils, and they become insoluble. And that provides the strength-- the extracellular structures provide the strength that maintain the cell's shape and viability of the cell. And a key component of all that is hydroxylation of proline. And how did they find that? This goes back to, again, misregulation.

So, in the 1600s, or whenever they used to sail the ocean blue with no food, they didn't have enough vitamin C. So they didn't have any citrus fruit. So vitamin C has the vitamin ascorbate, and ascorbate plays a key role in the chemistry of allowing the proline to become hydroxylated. So it turns out, to get the proline to be hydroyxlated, you use, again, metal catalyzed reactions. So here's iron-2. And if that iron-2 reacts with oxygen, if it gets oxidized with iron-3, it can't react.

So the function of this vitamin is to keep the iron-2 in the reduced state. So there's an example. People study that. Took them many, many, many years, like 200 years later, when they really understand the details of how this post-translational modification actually occurs. And we understand a lot about that chemistry now. And this was the first one of these modifications discovered, and now they're finding this modification everywhere. So lots of amino acids turn out to be hydroxylated, not just proline.

So these modified amino acids now, because the technology we have is so mind boggling, we can find a needle in a haystack. Whereas in the beginning we were just trying to figure out what the amino acids were, now we have very, very sensitive analytical methods which allow us to see all of these modifications. Then the key question is, what is the function of the modification? And that's not so easy in terms of thinking about regulation, anyhow. And that's the focus of a lot of people's efforts right now.