JOANNE STUBBE: My lab works on the only cool enzyme in the world-- ribonucleotide reductase. It's the only way in all organisms that you make the building blocks de novo that are required for DNA biosynthesis and repair. So if you inhibit this enzyme, you have no building blocks. You can't survive. So from a practical point of view, it's the target of drugs they use therapeutically in the treatment of cancer. And I think in probably not so distant future in the antibacterials because I think there are sufficient differences between humans and bacteria reductases that you could make specific inhibitors.

Why am I interested in it? Because the chemistry is sort of unbelievable. So I mean it was the first example where you learn, or you hear about-- you heard from John-- radicals. They're reactive oxygen species and nitrogen species that you can't control. They want to pick up an extra electron and form a stable octet. And if you leave them to their own demise, they react with anything and destroy it. Well nature has figured out how to harness the reactivity of radicals to do really tough chemistry with exquisite specificity. And ribonucleotide reductases have been the paradigm for thinking about that. And from bioinformatics now there are 50,000 reactions in metabolic systems that are going to be radical mediated transformations, yet we never talk about radicals in introductory courses. So I think that's all going to change.

So why is it unusual? Well, for the human ribonucleotide reductase, the key to making this work catalytically is the amino acid side chain tyrosine needs to be oxidized to a tyrosyl radical. So automatically nobody believes that. A tyrosyl radical in solution has a half-life of a microsecond. In the active site of these enzymes, the half-life of the enzyme can be on the order four days. And this radical, which is again one electron oxidized amino acid-- if you reduce it with an electron and a proton, the enzyme is completely dead.

So this was the first example of-- it would be another example of a post-translational modification that we talked about earlier-- modifying your amino acids. And so nature has figured out a way. How do you do this oxidation? She has a little metal cluster right adjacent to where this tyrosine is. And the function of this little metal cluster is to put this into the oxidized state, which is essential for the way the enzyme works.

So the other thing that's amazing about the enzyme is the chemistry. There are two subunits. The chemistry all happens in this subunit, but the tyrosyl radical is there. And this oxidation-- normally when you do an oxidation the two atoms are sitting within a few angstroms of each

other-- the oxidation happens over 35 angstroms. So that's unprecedented. It involves hopping radicals which no one has ever seen before. And so that was another thing that was completely fascinating from a chemical perspective about how the system works.

The other reason that people in biology are interested in this, besides the fact that makes a building block for DNA, is that if you believe in an RNA world where we have a ribosome where a catalysis of peptide bond formation is all with the RNA, not with the protein. How do you get from an RNA world to a DNA world? The only enzyme that does that transformation making these building blocks are ribonucleotide reductases. And there are many classes of ribonucleotide reductases-- one uses this tyrosyl radical-- but they all have the same active site and do the same chemistry, but they have different metal cofactors depending on where they evolved. And the function of the metal cofactors in all cases, even though one's cobalt, one's iron sulfur cluster, one's manganese, one's iron-- the function in all cases is to generate a radical in the active site and then the chemistry is the same in all these things.