Hi there. In this handout, we were really building on what we've talked about in the previous one, where we discussed amino acids and how they're joined together and ultimately how we have these peptide chains, and those peptide bonds and so on. So we learned lot about those building blocks and how proteins, what they're composed of. But now we need to kind of fold and twist and bend them into the right shape, so we call that protein structure and there's four levels that we mentioned towards the end of the last handout, primary, secondary, tertiary and quaternary. We've already kind of covered the primary structure, so primary is the identity and the order of the amino acids and now we need to look at how they're going to bend and twist into the final shapes and we know that the structure is governing function and that they're related and complementing each other. So first we I suppose, we reflected a little bit on some definitions we had to know such as folded conformations of proteins are called native proteins and then the word stability, if something was a stable protein it's related to the tendency it has to stay in its folded native form. We began to really define those kind of primary, secondary, tertiary and quaternary levels and we did a few examples in class around how secondary is really about local, and how would you say, changes or patterns that we see in part of the protein while tertiary is more 3D, where we're seeing the full structure of the whole protein, how it folds. Quaternary is where we join different subunits together, so we had a few diagrams where we talked through that but we decided we would progress and go into secondary structure first. Here, we looked at three predominant models of secondary structure. We looked at alpha Helix, beta sheet, and we looked at the beta turn and these are the three most prominent forms that we see in proteins. So we zoomed in on each of them, and we looked at some key features of each one. We reflected on how they're built, what kind of characteristics they have and also what they might bring to proteins. So particular things bring particular functions, so we were reflecting on that and what it might bring. You should have a study list, as we said in class, of your notes on alpha helices and beta sheets and on beta turns, and to be able to understand and see how they're folded. Having gone through those, so I mean there were obviously very big differences, we saw that in the diagrams but there were also similarities in some ways that we looked at, where functional groups were protruding, we looked at hydrogen bonding, there were there were things that we were discussing, even around directionality, and we talked even how these things stop so if a part of a region in an alpha Helix, well why doesn't it just keep continuing? Why sometimes does it stop and something else happens. So we talked a little bit about understanding about, back to the amino acids, that certain amino acids in certain places are dictating what happens. Hence, once we had gone through those, we were almost at the stage of kind of saying well let's look at examples of some proteins that might have particular secondary structures, or you know what they're going to look like. So the examples that we kind of focused in on were around keratin and collagen. These were proteins that a lot of you in the class had heard of before, or some of you had heard of one more maybe more than the other one. But we looked at keratin which we see in our skin, nails and our hair, and we looked at the difference between hard and soft keratins and how it's kind of different in the different tissues in our body, and then collagen, we know it's the comes from the Greek word for ‘glue’ because it's one of the most abundant and strongest proteins that we have in in our bodies in our connective tissues, primarily we see it in say ligaments, tendons, cartilage, and so on and it's a very strong entity so we were really looking here and seeing well there's these helical chains present in collagen and there's alpha helices present in keratin, but they started wrapping themselves around each other. And that way, we got kind of you know super helixes almost, which gave even more strength. Hence, we were talking a lot about that concept that these proteins are built in a particular way, to give strength, and it was just nice to kind of build on all the things we talked about before. We were relating some of those kind of fibrous proteins to even like a rope that we'd see at a dock land where the rope has strings wrapped around each other - it's the same idea. Then, we started then to zoom in on our tertiary structure, and that was the idea of the 3D concept, and we were relating it to 3D so you kind of get an idea of how it falls as a as a full unit, what it looks like in its final native folded form. We had to first think about the idea that certain amino acids that are far apart from each other in the primary structure are actually/can be close together based on how the chain folds and twists, and that's quite interesting because we'll meet that later on in other handouts where we see the idea that there are certain amino acids in an active site for an enzyme, but they're far apart when we consider the order of the amino acids, like the first amino acid and the last one could actually be quite close together in an active site based on how the protein is going to fold. Here we began to think about what governs, what controls, the way a protein folds into a final shape, and we went right back to the idea of hydrophobic and hydrophilic concepts and we saw that a lot of hydrophobic amino acids actually get buried in the inside, in the core of a protein, while the hydrophilic residues will remain on the outside. Those kind of forces, and even again I suppose we're back to the identity and the order of the amino acids, are dictating the final shape. Once we have a nice final shape of a protein and it is functional, we wanted to realise how does that get maintained, how does it not sort of denature and unfold somewhere along the lines, so we were looking a lot at the different types of bonds that can exist. We saw the idea of disulfide bonds was a main thing we looked at, between cysteine residues, we saw that with insulin, a good example where we met disulfide bonds a few times, we talked a little bit about ionic bonds, hydrogen bonds, hydrophobic interactions or even van der waals forces, all these connections help maintain the structure. And with the disulfide bonds, we will be meeting them again in the lab in a few weeks’ time, the idea of denaturing those disulfide bonds with a chemical called beta mercaptoethanol so we were looking at how that chemical actually works in helping to denature a protein. At this stage, we really jumped into our idea of tertiary proteins and in order to really grasp tertiary proteins, we had two examples of, I suppose, how they're how they're categorized. One was called fibrous, and one was called globular, so it's important to know the difference between each one and you'll see fibrous proteins are very much chains arranged in long strands or sheets, they're very related to structural components and structural function and they mainly have the same type of secondary structure. Whereas in globular, they're much more spherical and, like, an enzyme or a globular shape and they often have many different types of secondary structure. Even when we looked like a keratin, we saw the alpha Helix was kind of repeated and repeated and repeated, and it was primarily alpha helical where globular could have mixes and matches of some beta confirmations and some alpha. We saw that collagen would be a fibrous protein, and while it doesn't have alpha helices, it has alpha chains but still it has a very fibrous look to it. When we started reviewing the idea of these proteins I guess it's always good to have an example. The example that we really looked into here for tertiary structure was myoglobin, and we've already talked a little bit even now here about collagen and about keratin and fibrous proteins and what they look like, but for a globular protein we really focused in a myoglobin. I think the reason I wanted to kind of push that protein, was that you got the idea of how things have to fold, and we looked at the idea that a lot of it is alpha helical, but in different regions, and we saw how it's a very compact shape. We watched a few videos about how compact it is but how there's a tiny little gap left for something called a prosthetic group, and that prosthetic group was a protoporphyrin ring structure. it's a non-amino acid entity that has an iron ion in the middle to bind oxygen. We were really looking at the idea of these proteins leaving tiny little gaps for these prosthetic heme groups to fit into pockets, and because iron is in there we didn't want water to get in. So there's such a tight space to reduce the amount of water that can possibly fit into that groove, and again that comes right back to the idea of how proteins fold, and how proteins and actually fold into such a tight compact shape. It's a really good example to reflect on, and that's where we were talking about if water did get in well the Ferrous Fe2+ plus ion will convert to Fe3+ plus and will lose its power to bind oxygen, and that of course is the function of myoglobin - it is the oxygen carrier or storage in in muscle. And finally then we kind of zoomed out a little bit with quaternary structure. This idea that we have subunits sticking together to make a kind of a superpower protein and our example there was hemoglobin because that has four different subunits that all connect together to make a larger protein, and one that can carry four molecules of oxygen. So we were looking a little bit at how that oxygen binding is impacted, as in how it carries four oxygens when ‘full’. The last thing we kind of felt as a discussion point was around post translational modifications. So if you ask me for something that really, in an area of science, that really grabs my attention more and more, it's post translational modifications. it's an incredible kind of language almost inside the cell to try and learn and study. I suppose up to now we've talked about folding proteins into the right shape, so I know we've guided you in that concept of they've folded into a right shape, so they have a structure for a function. But now they get decorated, that's probably a general word, or tagged, by methyl groups or acetyl groups or phosphate groups being stuck on in particular places and what's amazing is those tags don't always stay there. They may be there one time and then they might not be there later on. And that's fascinating, because it's almost like as a signal as to something that's happening in the cell. So when we damage DNA in a cell, we know that there's a protein called a histone that has a serine that gets phosphorylated after damage, but when the damage is repaired by the cell, we know that that serine is no longer phosphorylated on the histone tail. So it’s fascinating to learn about these modifications. We talked a little bit about erythropoietin, a protein that has sugars on the outside, called glycoproteins, and these sugars can impact the length in which it stays in the body and functions. If you were building a therapeutic, having special sugars on the outside can mean that the drug stays in the patient's body a bit longer and doesn't get degraded. We talked a little bit about, as I said, the histone concepts and the histone protein. We discussed the idea of signaling even between molecules in the cell, talking to each other, instead of like passing a note to someone in the classroom beside you, this way we can tag the protein beside it and once it's tagged, it has a phosphate group attached (by a kinase), and now it can tag something else and tag something else, and we can signal and communicate within a cell. So post translational modifications or another word for that kind of area at the moment that people are trying to research is epigenetics, it's a an area that's been around for about 20 years but something so exciting, and has so much potential. I think it's something that textbooks will be rewritten in time over the developments that we discover in this in this space. So post translational modifications - very important to realise that proteins get folded but they also need to be decorated or tagged for functionality, or how long they live in the cell or different roles and that's vital for how things work. I think another example I gave you was an antibody, and how antibodies help us with our immune system, but if they don't have a little sugar added in a particular place, they're not as effective. Our immune system doesn't work as well with them (the non-glycosylated antibodies). So we really have to consider after a protein is built, how it's actually tagged or modified a little bit. That brought us to the end of our protein structure section, and we saw how proteins were built in the next handout, we're going to move to see a family of proteins in action and that's enzymes so we'll summarise that in the next clip.