Course Name: I Think Biology

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W3L14_Central Dogma

Hello and welcome to this lecture on the central dogma as part of the I Think Biology NPTEL course. My name is Kaustubh Rau. In the last lecture, we studied biomolecules where I stressed the structure and functional relationships of these molecules. In this lecture, we will try and figure out how we go from DNA to RNA to protein within the cell. And just to emphasize once again, my sources are the gene regulation primer from the I Think biology textbook, and also many of the images that I will use are from the Molecular Biology of the Cell which is a standard textbook used in the classroom and this is the 2002 version which is freely available online on the PubMed website.

So the central dogma was defined by Francis Crick in a lecture that he gave in 1957. And now this photo that you see of him is not from that talk but from a talk that he gave much later. But if you look at the blackboard behind him, you see that he has written down parts of what we know now to be the central dogma. So this lecture and the subsequent article that he wrote turned out to be important because it cleared up a lot of the confusion that was raining in biology at that time and laid the ground for a firm understanding of how we go from DNA to protein in a cell.

So let us try and ask what was known in 1957 when Professor Crick gave his lecture. We know that DNA is the molecule of heredity. There are the famous experiments of Avery and the Hershey Chase experiment. The DNA structure had been solved by Watson and Crick. We knew the self-replication model followed by DNA based on the very elegant experiment done by Meselson and Stahl. Biologists knew that there was a structure in the cell which was called a microzone but they did not know its function and they knew that RNA and proteins were associated with it.

But nobody knew what it did. We now know today that those are ribosomes. mRNA was not known. Its discovery came later in 1961. tRNA was also not known and Crick actually in his lecture predicted the existence of a tRNA-like molecule which he called the adaptor hypothesis.

So really what people thought at that time was very succinctly written down by James Watson in his book The Double Helix as DNA makes RNA and RNA makes protein. But nobody knew

how or where it happened. Nobody knew what was the unit of information. So how do genes work? And Crick actually in his talk gave a theory for how he thought all of this happened. And he gave it the name the central dogma.

So here is a record of Crick's actual paper and this is the first part of the prediction he made. So here it says that to go from DNA to RNA to protein, he called it a transfer of information. And what is the information that is being transferred is just a sequence of nucleotides that is being used as a template to make a piece of RNA and then that RNA is being used to make a protein. And for that to happen you needed an adaptor molecule that had some characteristics of a nucleotide and some characteristics of a protein and that's Crick's adapter hypothesis. So this doesn't mean, like I was saying in the earlier slide that DNA makes RNA makes protein. The way Crick meant it was that information was transferred from DNA to RNA and that information then RNA transferred on to making a protein. And there were certain allowed ways in which this information could be transferred and Crick has shown them over here.

So then as per Crick's scheme, we know that the kinds of information transfer that was allowed in DNA could serve as the template for making another molecule of DNA which we know as self-replication. DNA could serve as a template for making RNA which we now call transcription and then an RNA molecule could serve as the template for making a molecule of protein which we now call translation. Crick also predicted that RNA could be used as the template to make DNA and RNA could be used to make another molecule of RNA.

We now know of the existence of molecules that do these functions in the case of RNA serving as the template to make a piece of DNA. Retroviruses do this all the time using an enzyme called reverse transcriptase. In the tobacco mosaic virus or the coronavirus, an RNA strand serves as the template for making another RNA molecule. Crick said that it may also be possible to go directly from DNA to protein in the sense that the information contained in a DNA molecule could be used to make a protein molecule. But so far we have no evidence of that.

What Crick said is not allowed is that a protein molecule cannot serve as a template for making either DNA or RNA and a protein molecule can't serve as a template for making another protein molecule. So that was not allowed in his scheme. Now at the time that Crick gave the talk and then subsequently wrote the article, he said that this is all very speculative. And so he gave it the name the central dogma. He had misunderstood the meaning of the word dogma because the word dogma means something that is given by the church and it is a kind of edict that is to be followed without breaking any rules. Whereas Crick meant it more speculatively. But if you look at his predictions, you see that it has taken on the form of a dogma because he has been proved entirely correct in what he predicted.

So going on to the simple form of the central dogma, let's look at the two main processes in which DNA serves as the template for making a piece of RNA the process is called transcription

because in both DNA and RNA, the information is of the same form. It's a sequence of nucleotides and then RNA serves as the template to make protein. And this is called translation because the type of information which is contained in both is different. So there's a translation of the information contained in RNA to make a protein. And so now I'll look at the first step, which is transcription growing from DNA to RNA. And we know that in this case, one strand from the double helix serves as the template for making the subsequent RNA molecule. This is called the template strand. And here in this cartoon, you can see that it's the bottom strand that goes from the three prime directions to the five prime directions.

A question to ask would be, why don't cells use DNA directly as the template to make a molecule of protein? Why is RNA necessary within the cell? And here is one answer to that. There are many reasons why RNA is necessary for the cell. So one could be that RNA serves as a form of control. In the case of gene A, it's shown that during the transcription, you're producing many copies of the RNA. And so all these copies will then be transported out of the nucleus into the cytoplasm where ribosomes will be used to make proteins out of them.

So you can generate a large number of proteins from them. Whereas in the case of gene B, you're only transcribing a single copy of RNA. So you're making a small amount of protein. So this is one way of kind of tuning the efficiency of genes to get either a large amount of product or only as much product as you need. So this serves as a form of control.

Another reason could be that the cell receives a lot of insights from the environment, from chemicals to UV. So the DNA in some sense is kind of the master copy of instructions for making another cell. And you want to keep that copy safe and secure. So it's kept inside the nucleus. And you only transcribe small regions of that master copy into RNA. And then you use the RNA to make the products that you want. And then you can make this RNA on demand as is shown here so that you keep that master copy of DNA safe from harm.

There are also other reasons why RNA is produced because the RNA molecules themselves can serve as a form of control upon the gene that is on the DNA strand. But we'll come to that later.

So the molecule that accomplishes this generation of an RNA strand from a DNA template is called RNA polymerase. Shown here is a schematic of the RNA polymerase. So a strand of DNA is pulled into the RNA polymerase. Parts of it are unwound. From another channel, nucleotides are fed into the RNA polymerase. They use the DNA template to put in the complementary base to make the RNA strand. Then the RNA, the newly synthesized RNA strand, exits from a particular pore within the RNA polymerase. The RNA polymerase traverses the length of that DNA strand. So the arrow points to the direction of transcription. It points to the direction in which the RNA polymerase is moving.

Shown on the right is an electron micrograph where you see two strands or two DNA molecules which are those central dark lines. And then hanging off of that, you see a lot of RNA molecules

that have been transcribed. You can tell the direction in which the RNA polymerase is moving because the RNA transcripts which are on the right side of that central DNA strand are longer as compared to the left.

Looking at this sequence in more detail for a prokaryotic RNA polymerase. So bacterial RNA polymerases require another protein called a sigma factor. This binds to the promoter region and is responsible for pulling apart the two DNA strands. And once this is done, then the RNA synthesis can start to happen. And once, which is shown after step number three. And then once that is done, the sigma factor falls off as the RNA strand starts to be made. As the RNA polymerase moves along the DNA strand, new areas are opened up while the previous stretch of DNA which was pulled apart again comes back together as a double helix. As the RNA starts to exit the polymerase, it can also start to assume some structure as is shown here in step number six. You can start to see the formation of a hairpin bend which that RNA molecule is taking. And finally, you see the fully synthesized product which is a piece of RNA. So one thing to note is that the RNA polymerase has directionality. It only moves in a particular direction.

So in Figure A, the RNA polymerase is moving along the bottom strand from three prime directions to the five prime directions. The synthesized RNA strand is being made from the five prime to the three prime directions. And then vice versa in Figure B, the RNA polymerase is moving on the top strand, again from the three prime directions towards the five prime directions. And so it's making an RNA strand again from the five prime to the three prime. So this directionality is quite important and must be noted.

So if you look at the bacterial genome, bacteria typically have genes that are kind of placed one after the other and they can be on either strand. So for instance, here gene B, gene C, gene F, and gene G are on the bottom strand. So the RNA polymerase will have to move from left to right. And then genes E, D, and A are on the top strand. So that RNA polymerase, once it binds to the double helix, will have to move from right to left. You can also try and gauge the length of the gene because the scale bar shows you what is the length for 5,000 nucleotide pairs.

So bacterial cells have one RNA polymerase, whereas eukaryotes have three. And they have different functions. They transcribe different kinds of RNA molecules. For instance, RNA polymerase 1 transcribes rRNA, which is RNA associated with making the ribosome. RNA polymerase 2 transcribes RNA for making proteins, plus some forms of non-coding RNA, the SnO RNA and Sn RNA. And then RNA polymerase 3 makes tRNA and some ribosomal RNA and again some other kinds of non-coding RNAs. So the bacterial RNA polymerase and eukaryotic RNA polymerase 2, which makes RNA that codes for the protein, do have a structural similarity, which is shown here. So similar regions are shown in green. Many of the green helices and beta sheets can be seen here. And then the gray is additional regions from the eukaryotic RNA polymerase 2, which is larger than the bacterial RNA polymerase.

So if you look very carefully, you will see these kinds of blue spheres in there and they

represent zinc atoms, which are part of the structure. And then there's a sphere at the center, which is the magnesium site, which is the active site, where the polymerization takes place. If you remember one of the first slides I had in the lecture on biomolecules, where I showed the periodic table and said organisms use many metals in there as part of the biomolecules. So here's one example of that. So RNA polymerases from all three divisions of life, which are bacteria, archaea, and eukaryotes, are very closely related, which means that this molecule evolved before this great divergence happened, which again means that this process is quite old and also points to the unity of life.

So in DNA, the transcription process is quite simple. You make a piece of mRNA and then that is immediately translated into protein in the same cell because there's no compartmentalization within the cell and the RNA molecule is used as is. That's not the case for eukaryotes because the process is more complicated. First of all, the DNA of eukaryotes contains introns and exons. Exons are regions of the genome that code for proteins.

Introns do not code for protein. So when the RNA is transcribed, it contains both the intron part and the exon part. And the introns will have to be snipped out and the exons will have to be stitched together to make the final mRNA. Along with that, you need certain at both ends of the RNA, need certain structures that will protect the ends of the RNA. So there is a five-prime cap, which is added at the five prime and the three prime and you add a sequence or a string of adenine nucleotides. And only when all this is done, do we say that the RNA is ready for exporting out of the nucleus into the ribosome and can be used for translation. So there are many steps from making the primary RNA transcript to the final mRNA product.

But these are all ways to provide control. Shown here again in a little bit of detail on two genes, the human beta-globin gene is shown here. This is a small gene and it contains three exons, which can't be seen in the figure. But if you look at the full gene for the human factor eight, so this makes a protein called factor eight, which is used for clotting or it's part of the clotting cascade. So it has 26 exons, but they are widely separated and the full gene is almost two lakh nucleotide pairs long. So all these long genes will have to be fully transcribed and then these 26 exons will need to be stitched together to get the final product, which can be used to synthesize a protein. So why the eukaryotic genome has so many introns is a question that you can ask yourself. One reason being shown here is that you can combine exons in different arrangements to get variations on the same protein. So shown here is the alpha tropomyosin gene it makes the myosin protein and we have different forms of this protein in different muscle cells within our body, which are shown here.

So for instance, if you look at the striated muscle mRNA, it only contains a certain number of exons, whereas smooth muscle RNA contains a higher number of exons. So using the same genes due to the presence of introns, you can get variants on the same protein by combining different exons. So you're increasing the number of proteins that can be made from a single

gene. So that's a brief introduction to transcription. And so what are some implications and insights of that? One is that people realized that RNA could also serve as an enzyme to make more copies of itself.

I'm not going to go into any more detail on that. You can look up RNA enzymes to find out what that is about. The other is that it led to the hypothesis that maybe RNA was the first molecule and then this RNA had the catalytic property of making further copies of itself and also serving as a template to make short peptides. The third is the presence of introns and exons means that you can have splice variants, one gene, and many proteins. The fourth is that only a small percentage of the genome codes for protein, between 1.5 to 2% in the case of humans. And then almost two-thirds of the genome is transcribed for RNA. So what are all these different RNA molecules being used for? This is a question to ask.

So here is kind of a catalog of all different kinds of RNA molecules. We of course know mRNA, which is messenger RNA. That's the one that codes for protein. You have rRNA, which makes up the ribosomal structure, the actual structure that has the catalytic site for protein synthesis. You have tRNAs. So this is the molecule that was hypothesized by Trig to exist and he did this in discussion with Sydney Brenner. They thought it could almost be like an electrical plug where one side of the molecule will mimic a nucleotide so that it can sit on the mRNA. At that point, they didn't know the existence of mRNA, but on some nucleotides. And then the other side would have an amino acid, which could be part of the growing peptide chain.

Then you have a large number of non-coding RNAs. So you have snRNAs, snoRNAs, and then you have other non-coding RNAs like miRNA. And they have many different functions. So snRNAs are used in splicing pre-mRNA. So when you want to splice out these introns and then join the exons together, we make use of snRNA. The other non-coding RNAs are used as a kind of gene regulation. They can bind to certain stretches of DNA and stop the gene from being transcribed. They can be used for transport. Other applications are also given here.

So moving on from transcription to translation or from RNA to protein. And shown here in this cartoon are the two main molecules which are part of this process. The blue blob is our ribosomes and the tape is the mRNA molecule that is being translated. So ribosomes will sit on the mRNA transcript and then read it and synthesize proteins accordingly. And so the ribosomes here are making a joke saying how many of these histones are we supposed to make. Histones are proteins that are used in the winding and packaging of DNA to form the nucleosome and then later on the chromatin of that. And so they're kind of saying that look at how hard we're working in this cartoon.

But before we look at translation, let's try and understand the genetic code. So we know that there are these 20 amino acids and three nucleotides code for one amino acid. This was also

worked out by Crick in a series of experiments that he did. Because again at that point people didn't know if it was a triplet code, if there were four nucleotides, if it was two nucleotides, if it was overlapping or non-overlapping. None of that was known but actually, Crick worked it out through his experiment. So these triplets are called codons and shown here are all these codons that code for different amino acids. So you will see that one amino acid can have several different codons that code for it.

So if you look at, for instance, gly or glycine. So GGA, GGC, GGG and GGU all code for glycine. Certain amino acids only have one codon, others have up to six and there are two other features of the genetic code. AUG which codes for methionine is known as the start codon. So any RNA transcript will start with AUG because that tells the ribosome that this is the start of the transcript. And there are three stop codons so when those are read the ribosome knows that it has reached the end of the transcript and can fall off.

So what I referred to earlier is the codons are non-overlapping and so the ribosome needs to know that it's in the right frame. And so that's one of the functions of the start codon is to make sure that the ribosome is in the right frame. And shown here are possibilities of what could happen if you're not in the right frame. So suppose you're going from 5 prime to 3 prime and the mRNA is being read as CUC, AGC, GUU, and so forth.

So then that will code for leucine, serine, and valine. If in the second possibility what's shown is that if you miss out on the first C now the frame has shifted. So you have UCA, GCG, UUA, and those codes for serine, alanine, and leucine, totally different amino acids. And then in the third again the frame has shifted. So you could by having this frame shift you could make different kinds of proteins or you could also have a nonsense message that won't code for a protein. So the ribosome needs to know that it's in the correct frame.

And certain other features of the code are good to know a lot of words here. So first of all the code is universal. The same code is shared by bacteria, archaea, and eukaryotes. So again it points to our common ancestry. There are no commas in the code. So it's not like you have CUC and then you have a space and then you have AGC. So it's CUC, leucine followed by AGC which codes for serine. It's non-overlapping so you have a triplet and then you move and then you have the second triplet. It's not like the part of the first triplet is part of the second. It's non-ambiguous. So if I say CAC it will always code for histidine. It won't code for any other amino acid. So it's non-ambiguous.

Then the other thing is that is degenerate or redundant which I already said several amino acids are coded for by up to five or six codons. So there is some redundancy in there. And they also have a directionality. So it can only be read in one way. So AUG and GUA mean two different things. So it's good to remember all these features of the genetic code.

Let's look at some of the actors involved in translation. So here's one very important one which is the tRNA molecule. Shown at the bottom is the linear sequence of nucleotides which form a tRNA molecule. So going from 5' to 3'. And then within that, you will see that there are different colored stretches kind of pinkish and light blue and the yellow stretch. And then if you look at the figure above that in A you see how this tRNA molecule folds and base pairs at certain stretches to form what's called a clover leaf.

I mean it looks a little bit like a clover leaf. So if you start from the 5' end and go downwards you first have the one hairpin which is called the T-loop. And then moving on you come to a very important part of the tRNA molecule which is the anticodon. So this is the part that will seek out the mRNA to which it can bind by complementary base pairing. And then moving up you have another hairpin which forms the T-loop. And then at the very end at the 3' end is where an amino acid is attached. In this case, phe is shown or phenylalanine. And then in figures B and C show the 3D forms of the molecule. So if you look and see it's kind of an L-shaped molecule. Both the loops the D-loop and the T-loop are used to provide stability when it is part of the ribosome.

So another aspect of the tRNA molecule is that in the anticodon the first two nucleotides going from 3' to 5' the first two nucleotides are very important. And they need to have complete fidelity with the codon on the mRNA. But the third codon which is called in the wobble position there can be some ambiguity in what it could be. So for instance if you look at the table if in the codon the base is U then the possible anticodon could be A, G, or I which is another variant. It's a non-standard nucleotide. So what this means is that the third position of that anticodon is not as important as the first two for the binding of the tRNA to that section of the codon on the mRNA.

This is the other molecule that is important during translation. And it's called tRNA synthetase. And as the caption says there are two adapters which are needed. The first adapter we've already spoken about is tRNA and this is the second adapter. So the tRNA synthetase makes sure that the correct amino acid is linked with the correct tRNA.So every tRNA is specific to the amino acid that it carries. So this is the tRNA synthetase is an enzyme that has pockets for the correct amino acid and the correct tRNA. And then through a hydrolysis reaction, it uses the hydrolysis of ATP and the energy released due to that to bind the amino acid to the tRNA molecule. So that now the tRNA is ready to be inserted into the ribosome.

And this is how the tRNA links up amino acids to make a protein. Shown here is a tripeptide so you have amino acids one, two, and three. And for the third amino acid, the tRNA molecule is still attached to it. So the tRNA molecule which is labeled four comes along bringing the fourth amino acid. Then through the formation of a peptide bond and the donation of a proton to the tRNA, it gets a hydroxyl group which frees it from its linkage to its amino acid. The fourth amino acid is linked to that tripeptide. And then this reaction continues.

Coming to the main actor in this process of translation is the ribosome. So shown on the right is a cartoon of the structure of a bacterial ribosome. The ribosome is made up of two subunits, the small subunit and the large subunit. And these are seen face-on in this three-dimensional rendition. So the small subunit is shown in green and light green and the large subunit is shown in blue. And then on the left, we see that for a bacterial ribosome, the large subunit is called 50S and the small subunit is called 30S. The S refers to Svedberg units which is a unit where during centrifugation the molecules wherever they settle it's kind of a scale that is used. And that refers to actually their molecular mass. You can see that the large subunit in the case of the bacterial ribosome contains 34 proteins and the small subunit contains 21 proteins.

The number of nucleotides is also given there. So this is a very large and complex molecule made up of RNA and protein. And it's good to remember that the RNA is on the inside and the protein molecules are on the outside and it is thought that they provide stability to the whole structure. And the RNA does all the catalytic reactions which are necessary for the synthesis of proteins. At the bottom is shown an electron micrograph where you see the ER and a lot of ribosomes sitting which are marked by those magenta arrows which are sitting on the ER.So we know that as the rough ER. And there are also some freely floating ribosomes in the cell.

Here is a picture of a bacterial ribosome again showing only the RNA units of the ribosome. And if you look at B you'll see that all the RNAs have a specific structure which they form due to base pairing. They form all these hairpin bends and bulges.

So again the bacterial ribosome is shown here in some detail. If you look at A it's looking at its face on so the small subunit can be seen. And the large subunit is behind that. And in B they have been opened up like a book so that you can see both the large subunit and the small subunit. And within that, those three molecules shown in red, kind of brown, and yellow are tRNA molecules. So there are three sites within the ribosome for the tRNA molecule. And the tRNA molecule enters at the A site which is marked in yellow. It moves to the P site which is in the middle. Then it goes to the E site which is called the exit site and exits the ribosome from there.

So shown here is a cartoon of the whole process. So starting from the top at step one then going to step three. And then again you repeat steps one and two. So looking at step one you have a tripeptide that has been formed and which is still attached to the tRNA which is at the P site which is in the middle, the middle site in the ribosome. And you have an incoming tRNA which is marked as number four. And then what happens is that if the large subunit moves in its position tRNA which was at the P site is now moved to the E site which is the exit site. And the A site tRNA is now moved to the P site. And the growing peptide chain is transferred to this tRNA. After this step, the small subunit also moves along the mRNA. And now the A site is again free for a new tRNA molecule. The tRNA which was in the exit site can exit the ribosome and leave the E site also free. So now you have a new tRNA molecule which is marked as five come in. And then again the large subunit moves and so forth. So you can see that this process has a very mechanical aspect to it. So the large subunit moves so that it transfers the tRNA along

the respective sites and also transfers the growing peptide chain to the tRNA which is in the P site, allowing the tRNA in the E site to exit.

And then the small subunit moves so that the whole unit has moved almost like a machine. It is a machine that reads a tape and then uses that to produce a product. You can maybe think of different ways of, I mean there might be interesting ways of animating this whole process so that it's easier for visualization. We can think of making a GIF out of this. Or more interestingly we could think of making a flip book where this process can be drawn and it might make it easier to understand. For you.

You can also have polyribosomes. So you have one mRNA transcript and you have many ribosomes attached to it and they keep on making products. So if you look at this mRNA at the right you'll see AUG which is a start codon and then on the left you'll see UAG which is a stop codon. And then again you have the poly-A tail at the 3' end and the 5' cap. So the ribosome which is at the AUG codon has finished making its product and it will fall off whereas the ribosome which is at AUG which is at the start codon has just begun its journey in making that protein. So you can have these very large polyribosome structures and this is again another way of increasing the efficiency of the process. So you're making many copies of the same protein by attaching all these ribosomes onto it. And the sizes are also shown there. So if you think of 100 nanometers it's quite large on the scale of the cell.

So because this process is central to the life of a cell because you know if you think about it if you stop if the ribosome doesn't work then protein synthesis is going to stop and nothing in the cell is going to work. So many drugs work by inhibiting either RNA synthesis or protein synthesis and these are drugs that are familiar to us namely antibiotics. So for instance tetracycline you must have heard about it blocks the binding of a tRNA to the A site where the tRNA enters the ribosome. So if that is blocked then protein synthesis cannot happen or rifamycin prevents RNA synthesis right by binding to RNA polymerase. So because this process is so central any chemical or drug which can bind to any of these enzymes and stop their working will completely inhibit these process processes.

This is actinomycin which can work on both bacterial and eukaryotic RNA polymerases. So here it binds physically to DNA and blocks the movement of the RNA polymerase. Certain drugs work only on eukaryotes but not on bacteria so cycloheximide and this other one. So again these chemicals have been very very important in the study of the workings of these molecules. They have been used to understand the structure of these molecules when these structures were solved by x-ray diffraction. Finally, as the peptide polypeptide chain is being made it is still not a protein right because it hasn't attained its complete structure and that can start to happen as the peptide chain exits the large subunit of the ribosome.

And shown here is that very process where the ribosome is translating along the mRNA and the peptide chain is growing parts of it will start to attain the structure which is kind of encoded in

the amino acid chain. And so you can see the formation of a beta-sheet and an alpha helix here which is the domain in red and then you can see the formation of another domain where you have two alpha helices and a beta-sheet. And so finally after the last amino acid is synthesized and the polypeptide chain exits the ribosome it can be released and by that time it may have already actually folded to attain its full 3D conformation. So with that, that is kind of a description and some aspects of transcription and translation.

So what I thought I would do is try and see where we are again with the central dogma that we have and if can we add on all the things that we talked about onto it. So the arrows in gray are the standard kind of central dogma sequence DNA serving as a template to make RNA serving as a template to make protein. But now the arrows in red show some variations in the process. For instance, we now know that a single DNA gene can be transcribed to make several different kinds of RNA which can make different kinds of proteins like proteins X, Y, and Z. In terms of gene regulation a protein can go and bind to DNA and either turn on or turn off a gene so that's shown by the arrow going from protein Z to DNA.

An RNA can make non-coding RNA and these are used widely for a variety of purposes. Again they're used as a form of gene control and so there should be an arrow going from the non-coding RNAs to DNA. So the idea here is that you can take a basic picture of the central dogma and then you can add your arrows so that you enhance your understanding of all the things that are kind of embedded in that description of the process of transcription and translation. That brings me to the end of this lecture and thank you for joining.