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Julia just mentioned that a few of you had commented, when we were talking about the genetic code, that some of you thought the fact that it was degenerate, it had some redundancy in it, like multiple codons or threonine, that that was kind of cool, and some of you thought it was sort of a waste and would have maybe designed the thing differently. That's, you know, part of when you study biology you don't get to design it from first principles.

You found out what happened during evolution and what got selected for. And once it gets selected for then that gets sort of fixed in nature. If there were four nucleotides then you could have one, two and three-letter words. And it's going to be a three-letter word to have at least 20 then you've got some degeneracy or redundancy, but that's not necessarily a bad thing. And, in fact, if you go into the evolution of the code more deeply, people are beginning to suspect it evolved from a simpler one.

And there actually are some relationships between some of the codons that go back to the similarities, the chemical similarities between the amino acids. And it also allows some things for some cells, for example, if they want proteins to be present at very low levels they will use a codon that has just a very low level of the corresponding tRNA. And if they want to make a lot of the protein they'll use a tRNA that it makes in abundance.

And so it's sort of another way of controlling levels of proteins. There are a lot of different subtleties in here. And also in biology redundancy is not necessarily a bad thing. It's just like on a space flight, if something goes wrong and if there's some kind of redundant function then you've got some backups, too. OK. Well, in any case, today is a pretty interesting first part of the lecture. I've heard a few people express the view that why can't I just teach what's in the textbook and get on with it?

And I think this part, for those of you who are following, really trying to understand what I'm trying to do with this course, I hope this will help you to see this. Because what I've talked about, this thing that Crick called the "central dogma" which was the direction of information flow in biology which was from DNA to RNA to proteins.

And I'll just remind you, although proteins do many things they are, for example, enzymes that are biological catalysts. And it was pretty well-established, even by the time I was an undergrad that this was the way information flow went in

biology and this was how it worked. And there were various statements in the literature that what was true for E. coli was true for an elephant.

And it is still true today in a broad sense that, as I've tried to emphasize throughout the course, when you get down to a cellular molecule level there's an awful lot in common and things look much more alike than different compared to what we see at a more macroscopic scale. However, that doesn't mean that all the details are the same. And maybe you could begin to get a glimmering of that when I told you that although the genetic code is virtually universal.

That almost every organism, with only a couple very tiny exceptions, uses exactly the same genetic code to have nucleotides correspond to three-letter words in the nucleic acid alphabet correspond to particular amino acids in a protein. But the other languages that are written in there such as the sequence to start transcribing a gene, making an RNA copy are stopped. Those are different between different organisms. Yeah?

Glycolysis enzymes are amazingly similar. They are very clearly, they arose once, and they have stayed right through evolution. You could, in principle, sometimes in evolution you get something that creates a function and something that starts out, and then like what they call convergent evolution you end up with two things that came from a different evolutionary origin but have learned to do, let's say, catalyze the same biochemical reaction or something.

Glycolysis came once. But if you were to look inside E. coli or yeast, let's say E. coli and look at how those enzymes are regulated, the thing that says this is the start of a gene, start making the RNA, it would look totally different than if you looked in a mouse because the language, the promoter does not have the same sequence in an E. coli and in a human or in a mouse. And I'll tell you more about that today. But there were --

I want to just now tell you sort of three things that were sort of exceptions to this general way of thinking. Every one of them generated a Nobel Prize. And this is a fun lecture for me to give because the individuals involved in all of these things had a very, very close association with MIT. And when I told you when Crick called this a central dogma he meant a hypothesis, or at least an idea for which there was not reasonable evidence.

And he learned later it was something a true believer cannot doubt. And once this gets established it does get in the textbook and it does get in your thinking. And so information goes down this way. But there were a few oddities. I mean there were some viruses that had RNA inside them. They didn't have DNA. So how were these handled?

Well, there turned out to be two classes of RNA virus. One that was studied quite heavily called, it's a plant virus called the tobacco mosaic virus. And it had

a coat. And then it had in it a piece of RNA. Now, you can see if that virus were to inject RNA in the cell it could encode proteins.

But that genetic material has to be copied. And the RNA was copied --

-- by an RNA dependent RNA polymerase.

And so it's sort of just like the RNA polymerase before, except instead of using DNA as its template it can use RNA. So that sort of somehow would be a little loop in here about RNA being able to copy itself that hadn't been anticipated. And although this is an important virus in the plant industry, for plants and agriculture, it's not so important for humans.

But there's another class of RNA viruses that are very important. And these are called retroviruses. And the reason these are so important is that the HIV-1 virus that's associated with AIDS is such a retrovirus. It's a virus that has a coat and it has an RNA that's its genetic material.

And the person who worked out how this goes was a person at MIT, Dave Baltimore. He was a colleague of mine here for many years. He was the person who founded the White Head Institute and got that up and going. And he then finally, to move up one more administrative challenge, went to Caltech to be president.

And that's where he is today. And David was working on this problem trying to figure out how these retroviruses work. And they're important. Not only the HIV-1 virus, but there are certain viruses that are associated with cancer. In general, what they do is they've picked up what's called an oncogene which is sort of often a mutated version of one of your normal genes.

And if that virus gets inside one of your cells and brings in this mutated gene it's sort of kind of the same consequence as mutating one of your own genes along that progression of cancer. So it can kind of, say, bring in a cell that screws up the control on when cells are supposed to replicate and stop dividing and so on. So David started to work on these, and what he discovered was that these viruses encoded, they had information encoding proteins.

And one of the proteins encoded in their RNA is an enzyme de-characterized which is given the name "reverse transcriptase". And what this can do is take an RNA template and make the corresponding complimentary DNA strand in this way. So that if we took the --

We'll just take this RNA out of the virus. What this virus encodes then is an enzyme that's able to take this RNA and make the corresponding DNA copy. So there's the original RNA that was in the virus. There is the RNA that it started

out. And so what is happening, if you will in that case, is the information is flowing in the other direction.

That was a marvelous discovery. And it was discovered by someone who wasn't willing just to take what was in the textbooks but was trying to figure out what could possibly be going on here. Now, the way these viruses work then, once they've done this it's not so bad because they've got their information now in the form of DNA.

So this strand of DNA can be made into a double-stranded DNA by just using the kinds of enzymes that we've already talked about. A DNA dependent DNA polymerase will be able to copy the other thing. And now you've got a DNA copy of the information that used to be in the virus. But what happens to that is that you have a piece of the host DNA.

And this viral DNA then inserts into it, so you end up with this situation where you have DNA from the host, and this is the virus DNA.

So this is the DNA that encodes the information needed for the virus. And if this was our DNA then it would be inserted that way. And there are just a handful of health messages I've tried to drive home in this thing. I mentioned smoking the other day. If you smoke --

If you stop smoking you basically, well, let me try another way. The risk of smoking is about equal to the sum of everything else you can possibly do in your life that will affect your chances of getting cancer, leaving aside what you inherited from mom and dad. The one single thing to not do if you want to avoid cancer, or to help loved ones who smoke avoid cancer, is just don't smoke, or if you do smoke, stop.

You freeze the risk of whatever increased risk you've got, and then just live with that, but it doesn't keep getting worse with time. The other one is practice safe sex, and this is why. HIV-1 is a retrovirus. If you get infected with it, it makes a DNA copy of the RNA, it makes the other strand of the DNA, and it sticks itself in. So what you've got is your DNA here, your DNA there.

And HIV-1 is a permanent traveling companion for the rest of your life. There's no way of getting that out of there right now. All the systems for dealing with AIDS are just managing the infection. So when someone is HIV-1 positive, they've got those viral genes now permanently integrated into their DNA.

So it's extremely important that you be aware of that, or if you know people who don't appreciate this because they haven't got so much of a biology background that you help them understand that. OK. So I just wanted to show you, I found one other picture last night. And this is you see all these old scientists, right? Of course, David didn't look like this when he was doing his work. In fact, I think

he's fairly cleaned up here. I found this one in the Cold Spring Harbor archives last night.

I've seen pictures of him looking considerably more shaggy and perhaps disreputable and stuff. But anyway, when David was making all these discoveries he was still quite a young man. I believe he got his Nobel Prize when he was still in his thirties. And so many of these discoveries are made by people that are not all that much older than you. But, again, it's trying to understand why we know what we know and then trying to fit other things into it.

Now, the next thing I want to tell you about that has some of this same character, I've sort of told you that you have a piece of DNA. Let's say there's a gene here and this is the coding region, and then we make a mRNA copy, and then we use the genetic code and we make the protein.

And so if we sequence the DNA and find the beginning of this protein we can read along using that genetic code and away it should go. And that was beautifully worked out, understood, just like I sort of finished up telling you the other day. So Phil Sharp who got a Nobel Prize for this work and his colleague in the Biology Department.

He's in the Cancer Center just across the street from the building I'm in. That was the cancer center that Salvador Luria, who Jim Watson trained with, had founded. And Phil was studying this process. It was before we could sequence DNA. It was in the mid '70s. And he was working with the tools we had then trying to map the relationship of an RNA to a gene that was on a virus.

It was a DNA virus, not an RNA virus, so don't get yourself mixed up with that. But what he had was basically a fragment of DNA that he knew encoded the gene. So he knew somewhere on this piece of DNA there was a gene somewhere in here, and he had isolated the mRNA. And one way you could map, physically see the relationship of an RNA and a DNA would be to take, let's just take away one of these strands.

So we have the complimentary strand of the DNA to the RNA. And if we mix them together and let them slowly cool down they will form hydrogen bonds. They'll form a DNA-RNA hybrid just the same way two strands of DNA come on. And so if the gene was a little shorter than the piece of DNA then you might have expected to see something that looked like this.

And the way you'd see this, if you looked in an electron microscope --

-- perhaps it would look sort of like this. You cannot actually see the two strands, but you'd see a thick part. That would be the RNA duplex. So this would be just DNA.

And the thick part is RNA base paired with a single strand of DNA. You got it? That's what textbooks said you should have seen. And so this is more. This is data from Phil's paper describing this. And let me focus on this one in particular. That's what he actually saw.

You guys got any idea what's going on? Why don't you take a minute, find somebody who's near you and see if you can come up with any ideas. Here's the hybrid. Forget about this little bit at the 3 prime end. That's not a worry. Here is the thing. And this, I think, is a piece of single stranded DNA sticking out the end.

But it looks a bit more complicated. Any ideas? Most people put this data in their drawers. Phil didn't. Phil and his colleagues didn't. What they realized was, I'm going to try and redraw this just very slightly to help you see what's going on.

What they were seeing was something that looked rather like what they were expecting. They were seeing a region of hybrid DNA and they were seeing a region of single-stranded DNA like this, but what it looked like was there were little loops of single-stranded DNA sticking out. And what Phil had discovered was a phenomenon we now know as RNA splicing.

And here's what goes on. In bacteria, with very few exceptions, you can look at the DNA, you can find the open reading frame and you can just read off the sequence of the protein. You find the ATG, AUG, methionine codon, and then it keeps going no stops, and finally you come to a stop codon and you see there is the protein. So the coding information is essentially continuous in almost all bacterial genes.

And there's a few, some genes like that in eukaryotes, but many eukaryotic genes are constructed, it's almost as if you took the gene you'd find in a bacterium and then you'd cut it in a bunch of places and stuck extra DNA in between all of the pieces. So you'd get something like this where there's, in the DNA there'd be coding information.

And then non-coding information and another block of coding information. And then a block of non-coding and say another one of coding information. So this is a double-stranded DNA. And what happens then when the cell makes RNA is the whole thing gets copied into what's known now as a pre-messenger RNA.

And so there's a bit of coding stuff here, there's a bit of coding stuff here, and there's some more coding stuff there. But what the cell has is sort of like your unedited footage from your family summer vacation when you were running the video camera.

And maybe you don't want to show everybody ever second of video that you took during the thing. So what you do, you get in there and you edit it. In the old days you used to have to take the film and splice it. And now you can all do it with iMovie or something like that. But what you do is take the pieces of information you want, and this is what the cell is doing. It takes this part of the RNA.

And this part of the RNA, and joins it together, and then this part. And when it's done it has the mRNA that now looks like the kind of mRNA that you would find in a bacterium where you can find the start codon.

And then you could read in three-letter words all the way through to the end of the protein. So, in essence, what Phil found was that in many organisms at least there's another step in here where we get RNA splicing. And only after that you get down to proteins.

What was quite remarkable about this result and why I'm kind of hammering on it a little bit is this is the data that's out of Phil's paper. You can look it up on the Internet. Type in Phil Sharp 1977 and you'll find this original paper with that figure in it. The moment Phil realized what he was and talked about it at a meeting, a whole lot of people suddenly sort of almost simultaneously discovered RNA splicing because they opened their drawers and there were all these uninterpretable electron micrographs they had.

And they were in very short order able to save it in the system. The same thing was going on, but it was just confusing, it didn't fit, and to some extent most people's minds were set by this paradigm, this central dogma as something that a true believer cannot doubt. And you had to have a flexible enough mind to be able to see that.

And so this is an important piece of biology that hadn't been anticipated. And it can be quite remarkable. I'm just going to give you a couple of extreme examples. Well, not even extreme examples. But just show you how much non-coding information there can be. Factor 8 is a protein that plays a part in blood clotting. And the gene is 200 kilobase pairs.

And the pre-mRNA is just a direct copy, so it's 200 kilobases. It's just a single strand so it's not a base pair. And the actually spliced mRNA when it's done is 10 kilobases. So that means that only 5% of the gene is coding information and 95% of that information gets thrown away when the RNA gets spliced.

And even a more extreme example is a protein called dystrophin. This is what's affected in a human genetic disease known as Duchenne muscular dystrophy.

In this case, the gene is two mega base pairs. So of course then the pre-mRNA is also two mega bases but the pre-RNA is 16 kilobases. So in this case less than 1% of the gene has coding information for making a protein.

There are a lot of interesting reasons as to why it would be like this. One this, things can evolve more rapidly sometimes because you have parts of proteins that are sort of like modules and evolution can probably connect them.

In fact, it also provides ways of regulating because we now know there are alternative ways of splicing RNA. So you can take one RNA and then splice it in different ways in different cells and end up generating different proteins that were all encoded by one particular gene. And so it gives cells different kinds of regulatory strategies they can use.

Now, the third sort of thing that came out that falls in this same kind of thing of people having their minds open and not fixed by the current understanding or bounded by the current understanding is the discovery that RNA can act as an enzyme. And I've already talked to you about that and I've told it was ribozyme, but it was discovered by Tom Cech. Tom is currently president of the Howard Hughes Medical Institute, but he did his post-doctoral work at MIT with Mary Lou Pardue.

I've been a post-doc at Berkeley when he was just finishing his graduate work, and I met him out there. And then he came to MIT to do his post-doc. And a year later I got a job so I'd become friends there and became friends when we started here. So I had a pretty close link to this particular story. Here's a picture of Tom together with Phil. That's actually my wife right there who was in this picture. But Tom actually looks much more like that.

He's very colorful, very fun, a very interesting person. But anyway, when Tom left MIT to take a faculty position at Boulder he was interested in trying to understand the biochemistry of RNA splicing. And so he went --

He did what a good scientist will do. They'll try and find an experimental system where the question they want to address is simple enough you can actually get an answer. There's a kind of way of doing science where you pick a system that's too complicated and you never actually get an answer. It sounds very important because you're working on something that's important but you cannot, you don't have the tools you need to get to the answer. So Tom wanted to work on the biochemistry of RNA splicing because that had just been discovered.

And so he went to a small little tiny organism called tetrahymena. And the reason he looked at that was because it had a ribosomal RNA, so it was an RNA that was made in great abundance within the organism. And it only had one of these non-coding regions. I'll tell you the words for these coding and non-coding. To me they're non-intuitive, but I guess you should know them.

The coding region is called, the part that codes is called an exon and the non-coding part is called an intron. So, anyway, Tom worked on this organism because the pre-mRNA was basically this.

Or the pre-RNA before the splicing looked like this. This was going to give this like that. He could get large quantities of this RNA, so he was all set to make extracts of the cells of this organism and then start cooking up this RNA substrate with all sorts of cell extracts.

And then his plan was to purify the enzymes that did the RNA splicing. And so I first heard about this, Tom was working on this when he was here. And he went off to, I guess it was Denmark to learn how to grow this organism. Then they were back and he was off at Bolder. And we used to play squash all the time.

And whenever I got out to Bolder we'd try and get in a squash game. So I was out there at a meeting and we were sitting around in the locker room. And I said so how's the splicing biochemistry projecting going? Tom says, well, it's going OK, I guess. There's only one little problem, he says. The controls are splicing. Now, what he meant was if you were trying to add cell extract and get this thing to go what you would start out with is the RNA in a tube basically.

And that would be your control. And then you'd start adding stuff to it and start looking for splicing. And what Tom was finding was that if you just took this RNA and let it sit in a test tube that the splicing happened without him putting anything in. And here he was already to find all the enzymes, the proteins that did it. And Tom did an absolutely gorgeous piece of science to prove that what was happening was the RNA was catalyzing its own splicing.

And he had to work very, very hard to prove that it wasn't a contaminating protein. Remember we had this sort of discussion? We were talking about is DNA the genetic material and how would we know that it wasn't just a little tiny bit of something else in our DNA perhaps that was doing it. Tom had to go through pretty much a similar exercise, but this was one of these key insights that lead to the proof that RNA could function as a catalyst, what we now know as a ribozyme.

And I've shown you now we now sort of accept that the actual ribosome itself is a ribozyme and that the formation of the peptide bond, the thing that's the heart of all proteins is made by a ribozyme, not catalyzed by ribosomes and not by a protein. OK. So the next topic that I want to try on which sort of we've already set up from this is that if the information is all in DNA to begin with then if you make an RNA copy you're only taking a segment of that information at a time.

And that gives the cells a lot of possibilities for regulating how they respond to the environment or just controlling what genes are expressed. And there are

basically two kinds of strategies that are involved in these regulatory decisions. They can either be --

Can either be reversible changes.

For example, a bacterium and a food source. If you're a bacterium and you've got enzymes that let you eat a hundred different kinds of food and you're in an environment where there's only one of them there, you're really wasting energy if you make the proteins to make the other 99. So you might guess that somehow evolution has selected four systems that have learned how to turn on and off the things they need to eat certain food sources depending on whether the food source is available.

We only carry umbrellas when it rains. If you had to carry an umbrella and a snowsuit and a surfboard, everything all the time, it would slow you down in evolution. So the other type, which we've talked about as well when we talked about starting as a single cell and going up to the 14 cells that make us up, then many of those changes, as those cells go along and progressively more specialized need to be irreversible.

And this is particularly important in development. We don't want a cell in our retina suddenly deciding it should be part of a heart and start to make a heart in the middle of your eye or something like that. So things in development tend to be once you're off you're off or once you're on you're on or something. And just to give you another little look at that picture I've shown you before of the nematode.

And at the time, the first time I showed you this, I was just trying to emphasize that we could take the gene encoding green fluorescent protein and put it in anything and it would go green. In this case, Barbara Meyer who is at Berkeley now but used to be my office-mate at MIT for many years, what she's done is she's taken that green fluorescent protein, the gene for that, and she's put it under the control of a regulatory system, a gene that is made to be expressed in the esophagus of the worm.

And so even though that gene is present in all the cells of that organism, it's under the control of a system that usually permits the genes to be made that are needed for making esophagus but not in other parts of the body. So you probably didn't pick that part up now but sort of take another look at that same thing and see something different. So how do we learn about gene regulation?

The key work, like so many of these things, started kind of inauspiciously, if you will. There were two French scientists, Jacques Monod, who is a biochemist, Francois Jacob who was a geneticist. And they were working on the metabolism of lactose by *E. coli*.

Lactose is galactose, beta 1,4 glucose. And you don't have to know exactly the structure. You can just remember there were a lot of different hydroxyls, and that was one particular linkage. And there's an enzyme that cleaves this into galactose and glucose. And this can go right into glycolysis and make energy for the organism.

And the galactose undergoes a couple of different transformations, and it can get in there as well. But in order to get at the energy that's in those carbohydrates, this linkage has to be broken. And it was broken by an enzyme called beta-galactosidase. That's a protein that's able to catalyze the cleavage of those two sugars.

That's what Jacques Monod and Francois Jacob were studying. They were helped out in this exercise. I guess part of the reason they got going on this was people had noticed for many years that if you grew E. coli in glucose there was no beta-gal.

I'm going to abbreviate this as beta-gal just so I won't have to keep writing the same thing. But if they grew E. coli in lactose beta-gal was present. And they had to be able to assay for this enzyme. And they used --

There were standard types of biochemical assays you could use. But some chemists that helped design a very clever kind of substrate that helped them, that could be used in these kinds of studies, and I'll show you one of them. What this enzyme really looks at is it looks at, let's see, galactose.

What it sees is sort of the galactose side of this linkage, and then it reaches in and catalyzes the cleavage of what's joined to it. And it turns out not to be specific for whether glucose is on the other side. It can accept substrates that have other things as well. So some chemists made some variants like this. This is a compound that's commonly known as X-gal. If you talk to it in the lab it's got a longer chemical name.

But what happens if beta-galactosidase is there, it's able to cleave this substrate so you get galactose, which is colorless. But if you get just X, this is colored, but up here this original material is also colorless. So this is very convenient because if you use a substrate such as this you could put the cells on a plate with this indicator.

And if they are colored, and the color is blue, you'd know they were making beta-galactosidase. And if you don't see a color, you know they're not. There are a variety of ways of assaying for this enzyme. With that I'm just trying to give you a little bit of flavor of one of the different ways that they could assay for it. Now, one of the issues was it looked as though E. coli didn't have any beta-galactosidase activity if lactose was absent when growing a glucose.

And they made it if lactose was present. Well, that would be kind of what you would expect evolution would have figured out how to do, only make the enzyme for metabolizing lactose if the lactose is present, but they had to figure out what the molecular basis of this was. And one of the possibilities was that the protein was made that it was all sort of unfolded, and when the substrate came in then it folded all around it and then it could cleave it.

Or another possibility, which would be the kind we're talking about now, is the protein is not made until the lactose is present, and then it makes it new. So they had to figure out, between these two, which of these two was true. When you see the lactose present, is it just beta-galactosidase is already made but it's inactive, or is it being made de novo when you add the lactose?

So what they did was they grew cells in glucose plus radioactive C14-leucine for a long time. So all the proteins --

-- were radioactive. And once they got, that's going for a long time. So every protein being made is radioactive.

Then they add excess unlabeled leucine. So this means that from now on any new proteins that are made will not be radioactive because you're just going to swamp out any radioactive stuff with this. And they added glucose, excuse me, now they added lactose through the cells.

And then they isolated the beta-gal enzyme. It was actually pretty easy to do. It's a huge enzyme and it's a tetramer. So very large. Even in those days it was fairly easy to isolate this enzyme. And then they looked to see is it radioactive? If it's radioactive it was there all along and it's refolded to become the active enzyme.

Or if it had been only after lactose then it would be made de novo in response to it. And what they found was that it was non-radioactive.

Which implied that it was made after you added the lactose.

So they knew then that they were studying a system in which a protein was only made after the cells had experienced a particular growth substrate. And so a lot of work went into figuring out how this system worked. Let's see. We're a little short on time.

So I'll tell you what I'll do. I'll tell you, I'll just put out quickly the mechanics of what they saw, and we'll start in on the regulation on how this works. And some of you may be able to figure it out. What we now know is that the gene that encodes beta-galactosidase is in a stretch of DNA that's pretty interesting. It's got three genes. It's the gene lacZ. This is the gene for beta-galactosidase.

And another gene called lacY and lacZ. There's a promoter. That's a start signal for transcription. Remember that? So there's a sequence here that says start transcription. Down here is a terminator.

Another word written in the nucleic acid alphabet that means stop making mRNA. And there is one long mRNA, as you can see, that has the peculiarity of encoding three different genes. So if you have more than one gene in a single message then that's called an operon.

You've got one mRNA. But, in any case, so whenever beta-galactosidase was being made then RNA has to start being made here, goes to there. And we won't worry about the functions of these other two genes.

But, as you might guess from the way evolution has selected for it, they have related activities to what beta-galactosidase does. And for bacteria it's a very efficient way to control the expression of a bunch of genes at once. Then there was another gene up here known as lacI that had a promoter and a terminator, and it made an mRNA as well.

And that mRNA encoded a protein that's known as the lac repressor. And what that lac repressor does, it's a protein that has the ability to recognize a very, very specific DNA sequence and bind there. And I'm just going to kind of blow up this part of the thing.

So what we have here is the, this is the promoter here. And it happens that the binding sequence --

-- for lac repressor overlaps with the promoter. Weird, right? Maybe not.

So I'll tell you, well, you can think about this over the weekend, if you haven't run into this system before. So this gene gets made all the time. So this protein gets made all the time. What does that protein do if it's just like this? Its job in life is to look for this sequence and bind to it. If it binds to it, it covers up the promoter.

And the beta-galactosidase gene is not expressed because the cell cannot make mRNA. So this may seem a little obscure, but there's something very important here. Now the conditionality on whether this gene is expressed or not is controlled by a protein, right? It's controlled by this lac repressor. If it's on there the gene will be made. And if it's off the gene now you can make it.

There's a promoter and the RNA polymerase will see it. And so you've learned something about proteins. They can bind various things. And so what lac repressor has, it's got a little binding site that lactose is able to bind to and change the conformation of the lac repressor. So why don't you take those pieces of information and see if you can figure out how the circuitry goes.

Yeah? Did I do something wrong? Sorry. Oh, sorry. Excuse me. Yes, Z-Y-A. Excuse me. OK? We'll walk through that on Monday, but focus on the fact that if the repressor is there and lactose isn't, it binds to this sequence.

The repressor is made all the time, but this repressor is something that can tell you whether lactose is there or not. So you can put the circuit together, OK?