HAZEL SIVE: All right, let's look at some of your questions. A bunch of them are-- you know what, I'm probably going to use that screen most of the time. Because this one's not fitting. But let's look on this screen.

Your questions really focused around IPS cells and the kind of magic of IPS cells. And there were a couple of major questions that came up. What's the problem with using IPS cells therapeutically?

Well, there are a number. One, they're so new that really we don't know what kinds of cell types these IPS cells can make, so it's not clear how to use them. Another problem actually, which my colleague, Professor Jaenisch works on is the question of how to actually grow these cells.

I have a voice issue this morning. So you know, the quieter you are, the more you'll be able to hear my words.

IPS cells, human cells, grow very slowly in the laboratory. And it's very difficult to grow them. So there are some basic questions in biology, as to how to grow these cells to enough numbers that would actually be useful.

But here's another one that's very important. The transcription factors that we use to convert adult cells into IPS cells included an oncogene called c-Myc. And Myc is the kind of gene you don't want floating around your body nice and active in your cells, because it will give you cancer.

So the challenge is how to actually use Myc and other potent transcription factors to turn adult cells into stem cells but not have the stem cells give the recipient cancer. And there's some very clever ways that people are trying to get around this.

It is really impossible to teach you, if there are groups of you talking. I just cannot do it. So those of you talking, please don't. Thank you.

All right, so what's the big deal about IPS cells? Well, the big deal is they can be your own. In theory-- and maybe in practice, a decade, five years maybe from now-- your own cells, your skin cells could be removed from you, could be dealt with in the laboratory, turned into your

own stem cells, and put back into your own body, and they'd be your own.

So of course, they wouldn't be rejected by you. And that is an enormous deal. They're called autologous cells. There's an ethical issue, in that you don't have to harvest any embryos to get stem cell lines. And that's a big deal.

And here's a conceptual deal. When we talked about development, we talked about this directional pathway, where uncommitted cells became committed became differentiated. It was really thought that that was a one-way pathway.

But what IPS cell technology has shown-- let's look at this-- all right, we can get the idea from one of these two screens. What IPS cell technology has shown is that you can reverse differentiation. You can take differentiated adult cells and with the right regulatory factors, you can turn them into stem cells. And so conceptually, that's a big deal. Very good, great questions.

My next office hours are on Monday, 12-1. Come along or email me. But now we're going to turn to a new module, and that is the nervous system. And this is where we are in the course.

You've done all the foundational material. We've talked about formation. And now we're going to talk about systems and the nervous system in particular.

Let's start with the question of what a system is. Building up, the complexity of what we're talking about in life. A system refers to many organs that work together with one common function. Many organs working together with one overall function.

And you will talk about two in the course. You'll talk about the nervous system and the immune system with Professor Jacks. The nervous system, which is the topic of the next three lectures, has to do with communication-- has to do with communication from the outside to the inside of an animal's body, has to do with communication within the body, and has to do with communication to get the organism-- the animal, because plants don't have nervous system-- the animal to do something. So the nervous system is about communication to or from or within the body of an animal.

We've had a number of electrical analogies in the course. You will remember the famous signaling analogy of turning on the light switch over there on the wall. But now we move on to another electrical analogy, which is actually a truer one.

And I'm going to use the analogy for the nervous system of talking about wires that transmit the signal, by which cells communicates. I'm going to talk about connectors between the wires. And then I'm going to talk about circuits.

And those are going to be the topics of the next three lectures. So wires, connectors, and circuits. And those will be nervous system 1 to 3, the lectures in this module.

Today, we're going to talk about the wires. And there will be three topics. The first is the cell type that's got something to do with the wiring for this communication. The second is something called the action potential, which is the signal by which cells communicate within themselves. And the third has to do with the ion channels and pumps.

But let's start by phrasing the problem in a kind of a cool way. If you look in the human-- let's look on this screen. If you look in the human, and you outline the nerves. And if you went to see the living, plasticized human exhibits, you would have seen the plasticized nerves.

They're really extraordinary. The network of nerves, which are the unit of communication throughout the body. Is enormous. And it embraces every single part of the body, almost.

The cell that's involved in communication-- we'll draw this out in a moment-- is the neuron. And one of the things about neurons is that they've got very long processes, called axons, that we will deal with in depth today.

But let's phrase things more intuitively. This is what our brains look like. They in fact do not have nerves innovating them. And so if you actually have brain surgery, you can really be awake during surgery. Because there are no nerves within the brain, or at least no pain receptors within the brain. Of course, the brain has nerves, but there are no pain receptors in the brain.

Human brain. Billions and billions and trillions of neurons. We'll talk about numbers in future lectures. But let's look a little more deeply in the brain, so you can see how packed it is with neurons and how the connections between the neurons are so unbelievably complex that thinking about how you use circuitry to construct the human nervous system-- or indeed that of most animals-- is an enormous problem.

Professor Sebastian Seung here-- whose name is off the screen, and I apologize to him, it's the screen snafu, it will be on your power points when you download these from the web-- is

working on the task of putting together all the connections in the human brain. And starting with a little cube of brain-- this is about 100 microns, it's not quite a cube, but it's approximately a 100-micron cube-- he's worked to try to figure out what all the cell connections are and what all the cells are, within this little tiny cube of brain, which is just a tiny, tiny fraction of your brain.

So look at this. This is an electron micrograph that he's put a bunch of electron micrographs together, to build this 3D structure. And now his students and those of Professor Lichtman at Harvard go and outline a particular cell in serial sections, through this cube. These are very tiny sections. These are about five nanometer sections.

And then they put these sections together. And you can get the three dimensional structure of the neuron, as it's going through the cube. And you can start to map how this neuron lies next to other neurons. OK, there it's going backwards.

And there are two cells lying next to one another that you can get in 3D rendering, with this very painstaking process of first, getting sections of the brain, putting them all together into a chunk, and then deconstructing the individual cells shapes within that chunk. If you do that for the whole chunk of tissue, this is what you get. There's that red and that green neuron. Here is a blue one, there's a yellow one, lime, purple, red, dark blue, yellow, orange. It's daunting.

There you go. In that tiny little chunk of brain, that is how packed the cells are. And the connections between them are enormous. And that is just less than a millionth of your brain.

So to figure out all the connections, all the circuitry in the nervous system, is an enormous task. And we don't know it. We'll talk about what we do know later on. But I wanted to frame the problem for you, so that you have a sense of where we're trying to go.

Let's go back to the neuron. And let's talk about cell type and how cell type is important for thinking about signaling in the nervous system. So like everything else in the body, communication uses cells as its currency. And the cell type is the special kind of cell type, which is the neuron. So neurons are the connecting/wiring cells.

There's a second type of cell in the nervous system that is really pivotal for nervous system function that are called glia. And these are cells which are referred to as support cells. But that's not really fair. They guide neurons, and as we'll mention later, they also insulate neurons, so that the wires don't short circuit. So they guide and insulate neurons.

The structure of the neuron is important to understand its function. Like all cells, it's got a

nucleus and cytoplasm. And here it is, the nucleus, the cytoplasm. And this region of the neuron is called the cell body.

But unlike other cells, coming out from this cell body there are processes. And they are very substantial processes. On one side of the cell body are usually fairly short processes. They can be branched, and there can be bunches of them. And these are called dendrites.

Dendrites are processes that receive a signal. So they are the place where there is a signaling-- let me get rid of that dendrite-- there is a signaling input. The signal that dendrites receive moves through the cell body and into another process, which is called the axon and is very long.

And the fact that it is very long is actually what this lecture is all about. So the axon is the wire. Axons can be up to a meter long. Here's the axon.

And there are axons that start in your spinal cord and move all the way down your leg, from a single cell. We'll talk about why that is in a moment. These axons branch at their ends. And they connect to another neuron or something else, but we'll draw another neuron.

Here's another neuron with its dendrites and another axon. The connection-- here is neuron 1 and neuron 2. And the connection between axons and dendrites-- or as you'll discover, axons in the cell body-- is called a synapse. Some people say synapse-- that's the connection-- either is OK.

And the thing is that this input that is way over on the left hand side of the board is transmitted, along the axon, into the next neuron, and then along the next neuron. This is the signal. And we have to think about why cells might want to have these very long processes to do this, and then how the signal is transmitted.

The reason that cells have got these long processes rather than-- well, let's actually step back a moment. Let's think about how cells might communicate with one another. You could imagine a whole bunch of little round cells, all lined up, so that there a meter of them that go from your spinal cord down to your leg. And that would give you a chain of communication from your spinal cord to your leg. And you could have one back to your brain and so on.

And that in theory would work OK. But it turns out that cell-cell communication is very slow, and that cells have figured out a way to transmit a signal along their own length that is very

rapid.

You know that there is a finite time between getting a stimulus and a response. You know, you touch something hot, you can tell it actually takes a moment before you figure out it's hot. That's the speed of transmission of the signal, up into your brain. And you say, wow, that's hot, move my finger.

If you had cells that were connecting rather than long processes of one cell, it would take you that much longer to actually make that-- maybe 10 times longer-- to make that connection. And you'd get a bad burned finger.

So the axon is the thing that allows rapid transmission of the signal. So the axon is long. It leads to an intracellular signal. And this is very rapid, relative to an intercellular signal.

But how do you transmit a signal along a cell? Well, axons do this by using movement of ions. So the signal along the axon is due to movement of ions. And this is called an action potential, as we will discuss.

And this process draws on a property of all cells that neurons have capitalized on. So almost all cells have got a potential difference across their membrane, because there is a charge difference across the plasma membrane. So almost all cells have what is called a membrane potential, which is a membrane potential difference.

And in general, cells are more positive outside than they are inside. So outside the cell-- and this is worth your remembering-- it is more positive. And it's more positive because there's a lot of sodium ion. You'll see the why this is important. There's low potassium ion, and there's some high chloride ion. But really, the thing that's important is that there's very high sodium concentration outside the cell.

Conversely, inside the cell is obviously more negative. Sodium is low. Potassium is higher but still not very high. And there's a bunch of ions that are kind of trapped in the cell.

Why is this important? Let me see what I have next here. OK, most cells show a potential difference. Here it is. Here is written the potential difference. Neurons are somewhere between minus 70 and minus 60 millivolts, where you are talking about the relative potential difference inside to outside, that's why it's negative. And you can see tumor cells actually have got a very low membrane potential, which may or may not be significant.

What is the nature of the signal that neurons use to transmit from the input, along the axon, to the next cell? Particularly, what is the signal that's transmitted along the axon? And the answer is something called an action potential. It's the signal transmitted along the axon, the wire that I referred to.

And an accident potential, which I'm going to abbreviate as AP, will define-- and you'll understand this in a moment-- as a local, transient depolarization. Local, transient-- just lasts a moment-- depolarization, change in membrane potential. And I'm going to do most of this on the board. You have a hand-out, but I'm going to do most of this on the board because it works better as a conversation than a demonstration.

Let's draw a a bit of an axon. Here is the axon. Two plasma membranes-- outside, inside, outside. So this is the axon. Plasma membrane, PM.

And what we are going to do-- and here is a cytoplasm-- what we are going to do is take a chunk of the axon and blow it up and focus on just one plasma membrane, on one side of the axon, and look and see in detail what is going on there. So let's take this chunk and blow it up, so that we now have the plasma membrane--and you remember it's a lipid bilayer. But I'm drawing it as a single line, because it's really a pain control to draw it as a lipid bilayer. But you know it's a lipid bilayer.

On one side-- and here is outside the cell and inside the cell. On one side, there are lots of positive charges. And on the other side, there are fewer and relatively more negative charges.

When the axon looks like this, with this balance of positive and negative charges, it's said to be at resting potential. And resting potential is about minus 60 millivolts.

OK, what's our goal? Our goal is to start here, at this asterisk, and to transmit a signal along the length of this piece of axon and to transmit the signal in a directional way. So our goal is to transmit a directional signal.

Let's draw three time points, each of which have a plasma membrane of this particular segment of axon. And let us-- I'm going to move over a bit, to this side of the board-- let's have them here, here, and here. And so we're going to have a time vector going diagonally across the board.

And we started off with something that looked like it did on the board above at resting potential. And now, we're going to-- over a very short segment of membrane, we're going to

reverse the membrane charge, or the cell's going to do it. So that on the outside now, there's a little part of the membrane that's negative outside and positive inside. And the rest is positive outside and negative inside.

Over time, this is called a depolarization, a reversal of the membrane potential. Over time, that depolarization, that initial depolarization is going to rectify. It's going to go back to how it was.

So you'll get positive charges outside again. But the segment of membrane next door is going to depolarize, so it now becomes negative outside and positive inside. And the rest is positive outside and negative inside.

That little piece of membrane, the second-- so that's depolarization 1, here's depolarization 2. Again, over time, you're going to get rectification of that second depolarization. And you've got the idea now, it's going to move further down the axon.

So here is depolarization 3. And you recall that this is outside and inside the axon. So if you look at my diagram-- I haven't given you any mechanism-- but you can see here we have got a signal that is moving in this direction, along the axon.

Each of these depolarizations that I've drawn is called an action potential. And I'll give you, in a moment, some more properties, so that you'll know an action potential when you see one. But there are a couple of questions that arise from this easy-to-draw diagram.

Firstly, how does this really happen? How do charges reverse across the membrane? Secondly, why is the signal unidirectional? Why doesn't it go backwards? And thirdly, how do you reset the depolarization once it's happened?

And all of these things you will see are connected, but let's raise these questions. So how does this happen? Why is it unidirectional? And what does it mean-- or what is the mechanism of resetting the membrane potential, after a depolarization has happened? As for example here, you have reset the membrane potential.

So the answer to all of this is complex. And we'll answer it in chunks, as we tend to do in this class. And the first thing we'll answer with respect to is changing membrane potential.

Let's start off again with our axon chunk, with outside and inside, and the charge distribution that is at resting potential. And along comes some kind of input. It might be touch, it might be another neuron touching a second neuron. It might be vision, light, that comes along, some

kind of input.

Here it is. And this input acts on a very local part of the membrane. And it changes the membrane potential just a tiny bit, such that the membrane potential might reach something called threshold potential.

So let's look, let's draw it out. Here it is. Just over a one little tiny bit of the membrane, there's some kind of charge reversal. The positive charges come from outside, and they move inside. And we'll call this potential difference threshold potential. And if you want a number, it's about minus 55 millivolts.

What happens after threshold? Well threshold, you understand what threshold is. It means something happens because you have reached a point of no return. And what happens is that there is now an action potential, and there is a massive movement of the positive sodium ions into the cell.

So from threshold potential there is a massive movement, again out and in. So now you've got instead of this little tiny region of depolarization, you've got a large region of depolarization. So this is a small, depol-- for depolarization-- leading to a very large depolarization of the kind that I drew on the board before.

This large depolarization is called the action potential. And it has several properties. The action potential reverses the membrane potential almost completely. So now in this region of the membrane, it's at about plus 60 millivolts. So it's a massive depolarization. You completely reverse the ion distribution over a small region of the membrane.

It's very local, however. An action potential occurs over-- or this massive depolarization occurs over about a micron of membrane. It takes one to two milliseconds to set up. It involves the movement of about 10 to the 5th ions, from the outside in. And I've told you the potential.

The other thing that is really critical that you have to understand is something called all or none. The depolarization you get with an action potential is either complete, or it doesn't happen. If you reach threshold, you reverse polarity, and you get this complete depolarization to plus 60 millivolts from minus 60. You do not get a partial depolarization to plus 10 or 20 or 30 sometimes, or 35.

For a given neuron, you get a specific action potential. And it either happens, or it doesn't

happen. So all on none, very important. No little or big action potentials.

And now we've got a depolarization, but we haven't answered two questions. We haven't answered the question of unidirection, and we haven't answered the question of resetting. So let's do that on the next board.

And let's start off, actually, with an action potential. And I'm actually going to draw an action potential, kind of in the middle of this axon. You'll see why.

When you get an action potential, what's happening is that sodium ions are moving from the outside inside. And those sodium ions-- because they're just ions-- will start to diffuse in the cytoplasm. And as they diffuse next door, they'll change the membrane potential, which will reach threshold, which will trigger an action potential in the membrane chunk next door. And then those ions will diffuse, to make the chunk of membrane next door reach threshold potential. And you'll get an action potential triggered, and so on.

But the ions, of course, because they're just ions, can move in either direction. So the ions can move back. If this is where your action potential took place, the ions could move in that direction and trigger an action potential going back, up the axon, towards the cell body.

Why doesn't that happen? It doesn't happen because once you've triggered an action potential, that membrane becomes refractory, unable to trigger another action potential for a while. And during that time where the membrane is unable to respond and make another action potential, the ions have diffused away and gone on down the axon. And so you get a unidirectional propagation.

Let's try to draw that out. So here's an action potential. And the ions that are moving in will diffuse. And they will take the membrane next door to threshold. And so they'll trigger an action potential next door.

Those ions fusing backwards can't do anything. Because once the membrane has had an action potential, it can't have another one for a while. So this membrane here, next door to the action potential, is refractory to depolarization-- that is a really horrendous spelling job there, depolarization-- for some period of time. Let's say for about a second or a little less than that, but somewhere around there.

And so that means that the action potential is unidirectional. The ions can diffuse in both directions, but the action potential can only go in one. So that gives you a direction of your

signal.

And also, I have cavalierly drawn on there that the membrane potential reverses and resets itself, where the action potential previously occurred. And we'll talk about that more in a moment. So here, the membrane potential has reset.

So this is a theoretical walk through action potentials. And I gave you a bunch of handouts. But I'm not going to go through them, because you can use them as a test or as an exercise after class, to see how much you understood.

One of the things about conductance along an axon is that it's very quick. It takes a very short time from touching that hot thing to realizing you've touched it. But one of the reasons it's so short is because you're not sending an action potential all the way along an axon like we're drawing.

You don't really get successive parts of the membrane depolarizing. Because that actually, although it's faster than intercellular connections, is still quite slow. So there's a way that a cell insulates itself, an axon insulates itself, to give you action potentials just to particular places. And that really speeds up the rate of transmission of an action potential.

And I've got that on the slide here, and we're right on the board. So that during depolarization and after and all the time, ions leak from the axon. And this decreases the frequency of action potential formation.

And so what cells do, it's kind of like a short-- no, it's not quite short circuiting, but it's a bad electrical wire. And so what the cell has done is to insulate itself with layers of fatty cells. And these cells are really kind of amazing.

Most of the cells that insulates the neurons in the nervous system wrap around the neurons, as in this diagram. You can see here is a cell. And these lines are because a single cell has wrapped itself around the neuron. You know that the plasma membrane is lipid. It doesn't conduct ions, and so you've got really a fatty layer of insulation.

And the thing that insulates the cells is something called a myelin sheath, which is lipid plus some protein. But it's a really hydrophobic layer that wraps around the neurons and insulates them.

Along the neurons that are insulated, there are specific places where there is no insulation.

And that's where action potentials take place. So action potentials take place at nods without myelin.

And this is one way that neurons really speed up their conductance rate. And so I put here action potential frequency, but actually that's not correct. I'm going to talk about rate of transmission.

So how does this all go together? Let's look at a movie, where here's the neuron, and here is the axon, transmitting an action potential along its length. And here's a different way of depicting the action potential, as a graph of voltage against time. And that's something that you'll practice in section.

But what I want you to see is that there's an action potential moving along the axon. And the axon can transmit many, many action potentials, one after the other, with a short recovery period in between.

We still have not answered quite the question of how action potentials work. And the answer to that is to consider ion channels and pumps, because all of this charge distribution doesn't just happen. It's set up by the cell, and it's set up by ion channels and pumps, which we can write Regulate Membrane Potential.

Let's review very briefly what ion channels and pumps are. We've talked about them a bunch. But you need to know some essences for this particular module.

Ion channels allow ions across the membrane by diffusion. So here is an ion channel. And I'm drawing a channel which is open. And the ions move by diffusion, across the channel.

But there are other classes of ion channels, which are not always open. They are called gated. And we talked about them, when we talked about protein secretion, protein localization.

So gated channels under a particular stimulus can be closed and then change to the open confirmation, after they've been given the appropriate stimulus. So here there is some kind of stimulus. And a channel that is gated will open.

A third kind of way of getting ions across the membrane is to use a pump, where a pump is localized in the plasma membrane as well. But instead of a diffusion-governed process to get ions across the membrane, the pump is actively moving ions across the membrane.

So ion pumps actively transport ions. And they generally require energy, ATP, in order to do so. And all of these things are essential to set the membrane potential and to change it during action potential formation.

If we consider the resting potential-- actually, let me see what I have on the slides here. This is a really cool thing. All right, let me get through our board work, and then we'll do what is really cool after or on Monday.

In order to set up the resting potential, there are several kinds of channels and pumps that you need to be aware of. One of them-- which is a biggie and for which a Nobel Prize was given some decades ago-- is called the sodium potassium pump. And this is really a big thing. It's also called the sodium potassium ATPase. And what it does is to pump three sodium ions out of the cell and put two potassium ions into the cell. And this is an enormously important pump for life. And you can see what it does is to increase the sodium concentration outside the cell and increase the potassium concentration inside.

There is also something called an open potassium channel that will allow all this potassium that's being pumped in by the sodium potassium pump to start diffusing out of the cell. But in actual fact, it doesn't all diffuse out. Because it hits the positive charges of the sodium ions on the outside, and there's an electrostatic repulsion.

And so that limits how much potassium-- by Monday, I will either be able to speak by Monday or I will have completely lost my voice. You'll have the option. So the open potassium channel allows potassium out by diffusion, until it is repelled or stopped by electrostatic forces coming from the sodium ions. And then a third ion that's open, an ion channel that's open is the chloride channel, which we won't discuss right now.

During the action potential, there is an enormously important ion channel that is the last thing I'll mention today. And that's called the voltage gated sodium channel. This is an ion channel that, like many ion channels, consists of a complex of proteins. We'll make a note of that, I'll make a note of that next time.

But the voltage gated sodium channel is sensitive to membrane potential. And when threshold potential is reached, there is a change in the confirmation of this channel, which is closed normally at resting content but becomes open at threshold potential, to lead to the action potential. And it becomes open through actually the sliding of one of the alpha helices that make up the proteins of the channel. And the sliding alpha helices slide because their charges

change, the charges of the amino acids change. And that opens up the channel.

So I'm going to show you one picture of the last of the sodium channel, the voltage gated sodium channel. Here it is. And then we'll finish.

Take a look at this quickly. Here is the voltage gated sodium channel closed. Amino acids blocking up the pore. And there it opens up, to let the ions in. And we'll finish this on Monday.