JOHN ESSIGMANN: At the end of the course, when there's so many pathways out there that things start to get really, really complicated, we try to increase the number of physiological scenarios, again, to try to get the students sufficiently interested in a pathway and thinking about how the whole pathway works, not just each individual step-- to get the student to like the example so that he or she will go right in there and study it.

And one of the areas that I think really important these days in basic metabolic biochemistry is in oncology-- cancer biology. JoAnne mentioned that not that many years ago, academic programs wondered whether teaching metabolic pathways was really the best use of time, because so many other things were happening in the molecular biology revolution.

And certainly in 5.07 we decided to maintain emphasis in this, because we-- just because these are the first pathways that were studied doesn't mean they aren't important. They're medically very important. They were originally studied because of medical or economic reasons that-- fermentation, for example-- that these pathways were right in front and center. They're always very topical.

But what happened in I'd say the last 10 years is that there's been a reawakening of the understanding of how metabolic pathways redirect themselves in order to accomplish disease goals-- for example, with a tumor. And one of the things we teach is that a tumor is a lot like a running muscle. And Matthew Vander Heiden, who is here in our biology department and teaches the comparable course is a real expert, a pioneer in this area.

But what we've learned is that cancer cells tend to be addicted to glucose. They would much prefer glucose over any other fuel. In fact, they-- when you think about what a cancer cell really is, it's a cell that's not terribly different from all our other cells. It's acquired some small number-- we'll call driver mutations, maybe seven or so driver mutations. There are many more passenger mutations, but maybe seven or so genetic differences that separate it from a normal cell.

But among the things that has happened to it is reprogramming of its metabolic needs. And it has acquired the commitment to unremitting cell division. If you think about what's needed for a cell to divide, probably the principal structural resource-- which, again, this would come from JoAnne's part of the course-- is membranes. You've got to recreate the outside of the cell and

all those organelles.

And what that means is fatty acid biosynthesis is absolutely going to be paramount. One way that we now know that tumors work, if you understand all the pathways, is a tumor will consume glucose, it will convert that glucose to acetyl-CoA. The acetyl-CoA takes a ride on the molecule citrate until it gets put out into the cytoplasm, and then in the cytoplasm it becomes a factory for producing-- out of acetyl-CoA, it produces the lipids that are necessary for membranogenesis. That's absolutely critical for cancer cell development.

Now, the reason that's important is that understanding it, it tells us that, well, there are certain enzymes in the pathway. One of them is called ATP citrate lyase. Another one is called malic enzyme. So, when you look at the charts, you'll see these things. These are enzymes that are necessary for cell division, because they're necessary for fatty acid biosynthesis, and they represent good targets-- next-generation targets-- for cancer chemotherapy.

A normal cell, you can tell it not to divide, and it won't divide. But if you can tell a cell that's committed to divide and you tell it not to divide, oftentimes that cell will kill itself. So by blocking these critical points-- test points, we'll call them, in this metabolic chart-- you're able to selectively kill cancer cells-- we hope, anyway. But this study of metabolic biochemistry has identified these new targets.

Another thing that's, I think, an important anecdote about cancer cells is that they need other cells in order to survive. If you think about the problems that a tumor faces-- remember, it started from a normal cell that acquired new mutations, converted into a cancer cell, and then started to grow out into a tumor. As it grows, it becomes more remotely placed relative to the blood supply.

OK, now, certainly there will be a response, and the blood supply will try to grow toward the tumor cells. But the core of a tumor is hypoxic. It doesn't have enough oxygen to do real respiration. So, what happens is, the cancer cell tries to hard-wire the glycolysis pathway to be on. And rough estimates are that through this-- initially, a hypoxia-inducing factor, which is a transcription factor-- you get an upregulation by 10 to 20-fold of almost all of the enzymes of the glycolytic pathway.

So, what happens is, the cancer cell becomes a specialist at glycolysis. It does high-throughput glycolysis-- glucose to pyruvate. But, again, we don't have the metabolic equipment to do a lot of-- we don't have the metabolic equipment to be able to do respiration if

you're removed from oxygen.

So, the pyruvate gets converted into lactate. Lactate gets pumped out into the blood, and, as I mentioned before, it acidifies the blood. That's what happens with a working muscle. But the tumor sends the lactate into the blood. It's picked up by the liver. The liver is a specialist in gluconeogenesis. The liver then rebuilds the lactate into glucose, sends this back out into the blood.

So, the tumor is then able to re-eat the lactate that it sent out. So a partnership emerges between the liver-- the gluconeogenic organ-- and the tumor. So, the tumor finds that it's fed by-- unwittingly-- by the liver. And the liver is contributing to providing the nutrition that's eventually going to kill the organism if something doesn't go in to stop it.

But, again, understanding the pathways can give you ideas with regard to how to intervene. So, metabolic biochemistry is pretty critical to understanding this generation's cancer scientific agenda.