Tanya Domi: Hi, this is Tanya Domi. Welcome to The Thought Project, recorded at the graduate center of the city University of New York. Fostering groundbreaking research and scholarship in the arts, social sciences and sciences. In this space we talk with faculty and doctoral students about the big thinking and big ideas generating cutting edge research, informing New Yorkers and the world.

The study of neuroscience encompasses broad terrain covering everything from the root of mental disorders such as depression, to the cause of neurodegenerative diseases such as multiple sclerosis. Dr. Patricia Casaccio joins us today to discuss her research in this important field that is seeking a cure for nearly 1 million people living with this disease in the United States today. Dr Casaccio is the Einstein professor of biology at the graduate center, founding director of the neuroscience initiative at the advanced science research center, and the CO director of the Joint CUNY Mount Sinai Glial Center. She received her medical degree with honors from the University of Rome and a PHD degree in neurobiology from the State University of New York Health and science center, Brooklyn.

Cassacio's lab is working to uncover how factors like stress, the bacteria inside our guts, environment, and other influencers can trigger or contribute to the progression of neurological diseases. Her team, for example, has identified links between obesity and the progression of multiple sclerosis, natural disaster in infant mental health, and exposure to stress and reduced proliferation of the cells that create the protective sheath around our nerves. Dr. Casaccio is here to talk with us about this growing area of discovery and how it offers a promising possibility for developing new therapies and interventions. Welcome to The Thought Project, Patricia Casaccio.

Patricia C.: It's a pleasure to be here. Thank you for the invitation.

Tanya Domi: So, Dr. Casaccio, I'd like to start out by giving our audience a baseline understanding of your particular area of interest known as epigenetics. Can you explain to us what epigenetics are and how they have a different determining factor on our genes rather than on our DNA?

Patricia C.: So I think that is an important distinction between genetics, which defines the study of the information that's present on our genes and in our genome, in our and DNA, and epigenetics where the prefix epi comes from Greek, right? It means on top of or in addition of, and so the entire concept is that the fact that our genes can be modified by our lifestyle environment exposure. So to give you an analogy, I thought perhaps this is pretty interesting. You can envision the genome as the words in a book. You can imagine, you might have the DNA with many words, this represents the book. Well, the epigenome would be your highlighter or your tags that you can place to highlight certain words-

Tanya Domi: Aspects.

Patricia C.: ... or to read certain pages while others can be ignored. So why is this important?

Tanya Domi: I see. So how did you become interested in this area of research? What led you to it?

Patricia C.: So, first of all, I just think that there is something quite interesting that is happening nowadays, which is you may have heard there is the the 123andMe, right? Many people are trying now to understand their genome and to understand what genes do I have. And sometime people are also scared. If you have a genetic predisposition, for instance, to neurodegenerative disorders, oftentimes they seen that as a something inevitable. But there is nothing like that, right? You still have the ability to affect which genes are expressed.

So just to give you an example, we all have a single DNA molecule throughout our bodies, right? Every single cell, right? So if you are part of skin, hair, if you are a bone, muscle, or a brain cell, you will have the same DNA. And yet, you have an exquisite level of cellular diversity, very high specialization. So the genes do not change. What changes are these epigenetic tags is the fact that brain cells read certain tags, muscle cells readed other tags.

Tanya Domi: I see.

Patricia C.: And that's the entire concept of epigenetics. Similarly for the diseases, it's quite similar.

Tanya Domi: So this led you to, I understand, to really explore the whole disease process of MS. Your lab recently made a pretty significant discovery showing that MS patients who are overweight and obese have more severe disease progression. Can you talk to us about the mechanisms that contribute to a high burden of disease and overweight patients? which is a huge-

Patricia C.: Well-

Tanya Domi: Excuse me, which is a significant issue in America today.

Patricia C.: Well, the entire concept of overweight, obesity and the relationship to neurodegenerative diseases is much broader than just multiple sclerosis. I mean, there are clear studies that reveal the impact that being overweight might have on the Alzheimer, Huntington, or Parkinson disease as well. So our interest was from a perspective of are there changes to the epigenome that can be related to this? And if so, what are they?

Tanya Domi: Can you talk to us about how that contributes, these mechanisms, how they contribute to the higher burden on overweight patients?

Patricia C.: So I think we need to step back a little bit.

Tanya Domi: Okay, please.

Patricia C.: Okay. And just to start us, so let's go back and try to understand a little bit more of what is epigenetics. So I started out with this analogy, right? And the analogy was the book versus the textbook.

Tanya Domi: Right.

Patricia C.: But if now we try to look at a molecular level, what does it mean? So what does it mean exactly, right? The genes are formed by letters, right? That are encoded in our double helix, which is the DNA.

Tanya Domi: Right.

Patricia C.: But this double helix is very long. If you think, it's almost two meters and it has to fit within each single tiny cells, which is just a few microns large.

Tanya Domi: Right.

Patricia C.: How is this achieved? Well, the way it's achieved is because each cell wraps this genomic DNA around little proteins. We can envision them almost like little balls right around which this DNA is wrapped. And if it's tightly wrapped, sometimes cannot be expressed. So the genes is silenced. If it is in a situation where it can loop out, the gene can be expressed. So epigenetics is the study of molecular changes occurring that are allowing these wrapping to be very tight and genes not to be expressed, or molecules to be placed on the DNA, certain letters. For instance, the C can be methylated and methyl cap that it is placed would silence certain genes.

So you can see the importance of this is broad, right? It's broad, and it may depending on the type of cell that it affect, it could have a tremendous impact. So in our case, for instance, you can almost see that for humans, epigenetic has been shown as an adaptation to the environment. So to give you an example, if you think of the Second World War in the Netherlands, there was the Dutch Famine. And the Dutch Famine in some of the farm provinces was induced by the fact that some of the trains were stopped by the Germans do that food and fuel could not reach people in these areas.

Tanya Domi: Those areas, right.

Patricia C.: So at around 1945 there were 20000 people who died in these specific regions and some were more pregnant, right? So now you have children. And those children ended up having tremendous metabolic problem. They ended up with the obesity, diabetes. Why? Is Because being in utero while the mother-

Tanya Domi: Was under that stress.

Patricia C.: Not just the stress.

Tanya Domi: Right.

Patricia C.: But under severe food deprivation.

Tanya Domi: Right.

Patricia C.: Taught the epigenome that they had to modify the DNA in such a way that they should be able to extract from food as much nutrient as possible, as many nutrients as possible.

Tanya Domi: Interesting.

Patricia C.: And when those children grew up and now they are, you know, my age and they have their own children those people tend to be more obese or to have a greater percentage of diabetes. This is because they learned from their mother, the genome learned from their mother to introduce. So you can see now this, this is just to give a sample of metabolism.

Tanya Domi: Sure.

Patricia C.: If now we move this to the diseases itself and to look at our study, just to tell you what was the study, we follow at the multiple sclerosis clinic at Mount Sinai, we follow two groups of patients. And what we noticed is that the epigenome in some of the blood cells of the patients who were overweight was changed compared to the epigenome of patients who were not overweight, who had the normal body mass index.

Tanya Domi: That's interesting.

Patricia C.: And what was determining this were specific fats that are present in the blood and they're called ceramides. So these are lipids. Many times we hear about cholesterol, triglycerides, right? You may have heard it.

Tanya Domi: Of course, of course.

Patricia C.: But now there are these new fats that are becoming of high interest and they're called ceramides.

Tanya Domi: Ceramides.

Patricia C.: And what's interesting is that if you have a process already occurring in your brain, some of the membrane can ... Some of the cells may die. Some of these

fats that from the membrane may be released, and together with the intake of fats from your diet they synergize, and they can create more changes that might affect the epigenome of immune cells that eventually will travel to the brain and attack more your neurons. So the link is exactly from the diet to the type of fats that you have in the blood. We could actually label these fats and show that they can directly enter inside the nucleus of the cells and attached to the DNA where then they can modify this gene expression.

Tanya Domi: So you have this partnership with Mount Sinai Glial Center and you've been looking at, just what you explained to me, about the mechanisms with respect to MS. What are you doing right now with Mount Sinai? What kind of work specifically are you researching?

Patricia C.: So we are very interested that in understanding this specific question of why some patients have a stable course of the disease, some of the multiple sclerosis patient have a stable course of the disease while others tend to progress relatively fast. So they tend to need the help of a cane and then the wheelchair. What is the difference between those patients? So, one of the study that we were discussing about, but in other study is trying to understand if there are specific changes that we can detect in the cerebral spinal fluid. And the cerebral spinal fluid is this fluid that surrounds the brain and the spinal cord.

Tanya Domi: Right, right.

Patricia C.: So we have been looking at molecules that can be differentially present. And once again, the ceramides popped up as one of these molecules that are present there.

Tanya Domi: Interesting.

Patricia C.: And what we think is happening is that the satellites also have the ability to enter inside the neurons. And in the neurons we have these little canals that are called mitochondria. The mitochondria are the energy producing cells. So if you have a lot of energy, you feel good, right?

Tanya Domi: Right.

Patricia C.: If you don't have energy, you feel fatigued. It's very similar for our brain, right? If neurons have a lot of energy, they are capable of proper function. If they are not, they become severely affected and damaged. So we are trying to understand what is this mechanism? How does it work and what can we do to try to fix it? So this is the work that we have with the multiple sclerosis clinic there, more specifically with the Dr. Elena Katz, who has been our partner for many of those studies.

Tanya Domi: Yeah, there's nearly one million people in the United States living with this disease and I have some personal friends that have this disease. And as you've

described, some people are highly mobile and active and you would never know that they had MS, whereas others rapidly diminish.

Patricia C.: Correct.

Tanya Domi: Yeah. That's very, very striking how different it can be in how it presents itself.

Patricia C.: Yes. And this is why I've been interested also in epigenetics because also in my case there is familiarity for multiple sclerosis. Right? I have MS in my own family and so I had been really interested in understanding as perhaps many listeners, right? When you know that you have a genetic predisposition of this, or someone in your family has it, is that anything that you can do to improve it? And this has been a lot of our work.

Tanya Domi: So that's been an informative factor in your research?

Patricia C.: Absolutely.

Tanya Domi: So your work is described as being really very cutting edge, and you recently received this very prestigious award from the National Institute of Neurological Disorders and Stroke. It's the outstanding investigator award. This is going to be accompanied by money as well for your research. Tell me what this means to you.

Patricia C.: I think that a life of a scientist, it has two components, right? Has a component of excitement, which is linked to to research. But there is also a component that it is a struggle, and they struggle because doing research is not cheap, right? It cost a lot of money for experiments. The type of machines that we need to use, the type of reagents that we need to use. So the way we can perform research is by applying for what are called these competitive awards from the federal government, which are highly competitive grants that are peer reviewed by several other scientists. So for me to receive this award has been both a tremendous sign of relief, because I'm able-

Tanya Domi: You'll be able to research.

Patricia C.: Exactly.

Tanya Domi: Yes.

Patricia C.: And also it's really humbling because it means that my peers have acknowledged the quality of the work of my team. Right? And this is a team work., so I couldn't have done this without my team at ASRC.

Tanya Domi: So your work though, it really seems to focus on neurological disease and it also has become more and more apparent when you like read in popular media,

brain, mind, brain, mind, brain. You see these articles all the time now about the brain and how little we know. And so your research and your work is an aspect of the mind/brain behavior. In general, people are trying to figure out, well, what we don't know about the brain seems to be significant.

Patricia C.: Well, you have to think complexity of this organ, right? If you think of a liver has few cell types, or even in muscle it's very simple as an organ. The brain has billions of cells. And those cells are interconnected in many ways. Not only you have neurons and neural network, you have all those glial cells that serve a number of functions. For the longest period of time, we have focused on one of those cell types, neurons. And what we have been interested in, what we are advocating, is to really understand better glial cells. So they are in contact with blood vessels. You have to think of how they're sensing constantly the elasticity of the blood vessels, the type of metabolites that are present in the blood. There is this communication, right? The blood services center of communication from the periphery to the brain, right?

Tanya Domi: Right.

Patricia C.: And if you think that are relationship between the gut microbiota, right, and the type of brain, so what we are trying to understand is understand more how those glial cells function from a molecular perspective in response not only to neural activity, but also to metabolic signals that are coming from the periphery, and also physical signals. I feel that in biology we have forgotten oftentimes simple rules, right? The fact that we perceive temperature, right? Temperature differences. Animals adjust to temperature differences and climate changes. Do human also adjust? And if so, do they use epigenetics for doing that?

Within the molecular level, if you think an atherosclerotic blood vessel is very hard and stiff versus the the blood vessels can be elastic in someone who is healthy. What happens to the cells that contact with blood vessels? Do they perceive stiffness, do they feel this stiffness in terms of perception, physical forces? And if so, is this the reason why we have not been able to treat certain disorders up to now, because we have focused solely on one aspect and we have forgotten that there are many other parameters to take into consideration. So this is what this grant is about, is about biosensors. And biosensors in the sense that cells are indeed these biological little sensors of micro environment both in terms of chemical and physical signals.

Tanya Domi: Well, this is a significant area of research. What you're doing at the ASRC is groundbreaking work. I want to take the opportunity to thank you so much for coming in today and sharing your research with us and we want to congratulate you on this significant award.

Patricia C.: Okay. Thank you so much.

Tanya Domi: Thanks for tuning into The Thought Project, and thanks to today's guest, Dr. Patricia Casaccio of the advanced science research center at the Graduate Center, CUNY.

The Thought Project is brought to you with production, engineering and technical assistance by Sarah Fishmen. I'm Tanya Domi. Tune in next week.