Exhibit U

Science 101

The Science of Sirtuins, “Guardians of the Genome”

Sirtuins help regulate your cellular health and play a role in aging. Here’s what you need to know about how they work, what they can do for your body, and why they rely on NAD+ to function.

Sirtuins are a family of proteins that play a role in aging by regulating cellular health. They're responsible for critical biological functions like DNA expression and aspects of aging. However, sirtuins can only function in the presence of NAD+, nicotinamide adenine dinucleotide, a coenzyme found in all living cells.

How Sirtuins Regulate Cellular Health with NAD+

Think of your body's cells like an office. In the office, there are many people working on various tasks with an ultimate goal: stay profitable and fulfill the mission of the company in an efficient manner for as long as possible. In the cells, there are many pieces working on various tasks with an ultimate goal, too: stay healthy and function efficiently for as long as possible. Just as priorities in the company change, due to various internal and external factors, so do priorities in the cells. Someone has to run

the office, regulating what gets done when, who's going to do it and when to switch course. In the office, that would be your CEO. In the body, at the cellular level, it's your sirtuins.

Sirtuins — nicknamed "the longevity genes" — are a family of seven proteins that play a role in aging by controlling cellular health. Sirtuins can only function in the presence of NAD+, nicotinamide adenine dinucleotide, a coenzyme found in all living cells. NAD+ is vital to metabol ism and hundreds of other biological processes. If sirtuins are a company's CEO, then NAD+ is the money that pays the salary of the CEO and employees, all while keeping the lights on and the office space rent paid. A company, and the body, can't function without it. But levels of NAD+ decline with age, limiting the function of sirtuins with age as well. Like all things in the human body, it's not that simple. Sirtuins manage everything that happens in your cells in order to keep the body as productive as possible.

Sirtuins Are Proteins. What Does That Mean?

Sirtuins are a family of proteins. Protein might sound like dietary protein — what's found in beans and meats and well, protein shakes — but in this case we're talking about molecules called proteins, which work throughout the body's cells in a number of different functions. Think of proteins as the departments at a company, each one focusing on its own specific function while coordinating with other departments.

A well-known protein in the body is hemoglobin, which is part of the globin family of proteins and is responsible for transporting oxygen throughout your blood. The myoglobin is the hemoglobin's counterpart, and together they make up the globin family.

Your body has nearly 60,000 families of proteins — a lot of departments! — and sirtuins are one of those families. While hemoglobin is one in a family of two proteins, sirtuins are a family of seven.

Of the seven sirtuins in the cell, three of them work in the mitochondria, three of them work in the nucleus and one of them works in the cytoplasm, each playing a variety of roles. The basic role of sirtuins, however, is that they remove acetyl groups from other proteins.

Acetyl groups control specific reactions. They're physical tags on proteins that other proteins recognize will react with them. If proteins are the departments of the cell and

DNA is the CEO, the acetyl groups are the availability status of each department head. For example, if a protein is available then the sirtuin can work with it to make something happen, just as the CEO can work with an available department head to make something happen.

Sirtuins work with acetyl groups by doing what's called deacetylation. This means they recognize there's an acetyl group on a molecule then remove the acetyl group, which tees up the molecule for its job. One way that sirtuins work is by removing acetyl groups (deacetylating) biological proteins such as histones. For example, sirtuins help protect DNA in that they deacetylate histones, proteins that are part of a condensed form of DNA called chromatin. The histone is a large bulky protein that the DNA wraps itself around. Think of it as a Christmas tree, and the DNA strand is the strand of lights. When the histones have an acetyl group, the chromatin is open, or unwound.

This unwound chromatin means the DNA is being transcribed, an essential process. But it doesn't need to remain unwound, as it's vulnerable to damage in this position, almost like the Christmas lights could get tangled or the bulbs can get damaged when they're unwieldy or up for too long. When the histones are deacetylated by sirtuins, the chromatin is closed, or tightly and neatly wound, meaning gene expression is stopped, or silenced, protecting the DNA from damage, the same way an organized strand of Christmas lights would be less susceptible to damage.

We've only known about sirtuins for about 20 years, and their primary function — which earned them the nickname "the longevity genes" — was discovered in the 1990s. Since then, researchers have flocked to study them, identifying their importance for health and aging while also raising questions about what else we can learn about them.

The Discovery and History of Sirtuins

Geneticist Dr. Amar Klar discovered the first sirtuin, called SIR2, in the 1970s, identifying it as a gene that controlled the ability of yeast cells to mate. Years later, in the 1990s, researchers found other genes that were homologous — similar in structure — to SIR2 in other organisms like worms, fruit flies, and these SIR2 homologues were then named sirtuins. There were different numbers of sirtuins in each organism. For example, yeast has five sirtuins, bacteria has one, mice have seven, and humans have seven.

> **The fact that sirtuins were found across species means they were "conserved" with evolution. Genes that are "conserved" have universal functions in many or all species. What was yet to be known, though, was how important sirtuins would turn out to be.**

In 1991, Elysium co-founder and MIT biologist Leonard Guarente, alongside graduate students Nick Austriaco and Brian Kennedy, conducted experiments to better understand how yeast aged. By chance, Austriaco tried to grow cultures of various yeast strains from samples he had stored in his fridge for months, which created a stressful environment for the strains. Only some of these strains could grow from here, but Guarente and his team identified a pattern: The strains of yeast that survived the best in the fridge were also the longest lived. This provided guidance for Guarente so he could focus solely on these long-living strains to more efficiently identify which genes were involved in aging.

This led to the identification of SIR2 as a gene that promoted longevity in yeast. The Guarente lab thus found that removing SIR2 shortened life span dramatically, while most importantly, increasing the number of copies of the SIR2 gene from one to two increased the life span. So activating SIR2 prolonged life. But what activated SIR2 naturally had yet to be discovered.

This is where acetyl groups come into play. It was initially thought that SIR2 might be a deacetylating enzyme — meaning it removed those acetyl groups — from other molecules, but no one knew if this were true since all attempts to demonstrate this activity in a test tube proved negative. Guarente and his team were able to discover that SIR2 could only deacetylate other proteins in the presence of the coenzyme NAD+, nicotinamide adenine dinucleotide. Remember NAD+? It's the coenzyme that keeps the body running.

In Guarente's own words: "Without NAD+, SIR2 does nothing. That was the critical finding on the arc of sirtuin biology."

How Sirtuins Relate to Calorie Restriction

NAD+ plays a key role in metabolism by turning nutrients into energy. So Guarente's finding that sirtuins required NAD+ to function told scientists that there's a link between sirtuins and metabolism. This ignited a theory around sirtuins' relationship to calorie restriction, which has been shown to increase longevity and delay the onset of age-related diseases in mice, worms, and monkeys. Calorie restriction basically forces cells to make energy more efficiently because they're running on less fuel. Sirtuins play an important part in orchestrating the benefits associated with calorie restriction.

As background, scientists have long been pursuing research on how calorie restriction can benefit health, with evidence showing potential benefits of various kinds of fasting. For example, early research in animals has demonstrated the benefits of periodic fasting. A 2015 study from Valter Longo found that mice who periodically fasted had vast improvements in areas like cognitive function immunity as well as decreased risk factors for aging, diabetes, and cardiovascular disease. And a 2017 human study from Longo found that humans on a fasting-mimicking diet — meaning they restricted calories for five consecutive days per month for three months — had reduced blood pressure and a reduction in an insulin-like growth factor that could play a role in aging. Other calorie-restricted diets have gained interest. For example, the 5:2 diet, which has been scarcely studied in humans and consists of a low-calorie, low-carb diet for two days each week, is being touted as a way to improve disease markers and has shown it's an effective option for weight loss.

But calorie restriction is an excessively severe lifestyle choice and could require cutting calories by up to 50 percent. Further, we do not know for sure that these diets will work in humans. So the possibility that sirtuins might be activated by small molecules created a distinct opportunity. Indeed, the NAD+ precursor nicotinamide riboside, or NR, raises NAD+ levels in animals, activates sirtuins, and confers many health benefits, including increased longevity. In addition, it has been shown that one of the seven human sirtuins, SIRT1, can be activated by the natural compounds called polyphenols, of which the most promising may be pterostilbene or PT found in blueberries. Combining NR and PT may pack the strongest punch to activate sirtuins in humans, and this combination forms the underlying principle of Basis.

The Future of Sirtuins

Sirtuins research has largely been tied to aging and metabolic activity. Recent research in mice has even identified sirtuins as being relevant to obesity, Alzheimer's,

kidney disease, liver disease, inflammatory diseases, osteoporosis, and cancer. For instance, activating SIRT1 in mice can reduce neurological protein build up that's attributed to Alzheimer's. While this research has not been translated to humans, it shows great promise.

"There are maybe 12,000 papers on sirtuins now," Guarente's said. "At the time we discovered the NAD+ dependent deacetylase activity the number of papers was in the 100s."

As the sirtuins field continues to expand, this leaves room for incredible research opportunities into how activating sirtuins with NAD+ precursors can lead to not only longer but also healthier lives.

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What is NAD+ and Why Is it Important for Aging and Health?

You can't live without the coenzyme NAD+, nicotinamide adenine dinucleotide. Here's why it's so important, how it was discovered, and how you can get more of it.

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