NATHAN LEBRASSEUR: So we've had a very strong interest in age and disease related muscle loss. So as many people know, population aging is something that we're facing, with 11,000 people turning the age of 65 everyday. And what a lot of people under appreciate is that with aging, most of us will lose 30% of our muscle mass between our 40s and our 80s. And that has severe implications for our ability to maintain function and independence, to prevent falls, and to conduct activities of daily living without issue. So there are really several reasons for improving muscle health in the context of aging and disease.

And first and foremost, particularly in the field of rehabilitation medicine, we're focused on improving muscle health as a means to enhance or improve or maintain physical function. And those can be very simple tasks such as getting in and out of bed, rising from a chair, climbing stairs, walking, really critical features in maintaining independence. An area that's often overlooked in terms of muscle health is its role and whole body metabolism.

So we see a very high incidence of type 2 diabetes with aging, and particular with the obesity epidemic. And muscle is a critically important organ in maintaining whole body metabolism. So with the loss of muscle with advancing age, it's not that we're losing weight, but that that weight loss and lean mass is actually mashed with an increase in fat mass. So by improving muscle health, we think we can have a really profound effect on the whole body metabolism.

Muscle is the primary site in which sugar is stored. If you eat a meal, 80% of the sugar in that meal is going to be positive within muscle. And many of us know that muscle is a primary determinant of our basal metabolic rate. So just how much fuel our body burns at rest is really dictated by how much muscle we have.

Clinically, the area that's getting the most traction with respect to muscle is the concept of frailty. And frailty refers to our lack of resiliency to stress. And you think about all the stressors that we apply to individuals. At a medical institution it could be very invasive surgeries, it could be relatively benign surgeries, it could be vaccines, a number of things. We know that older persons have less resiliency to those stresses. And what happens, is when they're exposed that stress, they kind of breakdown and never kind of recover to the point where they were before.

And we have colleagues in oncology, colleagues in pulmonary, colleagues in cardiovascular, orthopedics try to understand who these individuals are that have low resiliency distress. And we've identified now that many of these individuals really have poor muscle health. And that can be measured either by their muscle mass, using different imaging techniques, or it could be assessed by looking at their muscle strength, by simple things such as how strong they can squeeze or grip. And it can also be assessed by looking at their mobility, so things like gait speed.

And finally, I would also emphasize one of the most interesting areas about muscle that's emerging now today is that muscle is clearly an endocrine organ, meaning that it secretes factors that influence the health of other tissues. And this is very new, and just an area that starting to gain interest. But during things such as exercise where muscle is very active, it's releasing proteins into the circulation that probably affect the health of other organs such as the brain, the liver, the pancreas, and adipose tissue. So this is going to be an exciting area moving forward.

The lab is very active right now studying a protein called myostatin. And myostatin is unique to skeletal muscle. It's predominantly produced in muscle, but it's also secreted by muscle into the circulation. So myostatin is a negative regulator of muscle mass. It's something that regulates how large our muscles get.

And it sounds a bit odd, but our body produces proteins that regulate organ size. And for muscle, that protein is myostatin. What happens, however, is that when myostatin's activity is not regulated, it can actually cause deterioration in wasting of skeletal muscle. So we've been looking at ways such as antibody based approaches, or soluble decoy receptors that are ways to almost put a sponge into the circulation to sop up myostatin, and prevent it from having its negative effects on skeletal muscle.

So we've shown in mouse models of aging in obesity that we can markedly increase muscle mass by providing these types of interventions. Those improvements in muscle mass translate into improvements and strength, improvements in physical function, improvements in whole body metabolism. So it's really quite encouraging.

We've been very active lately at designing ways to measure myostatin in humans. So one thing that we don't understand about this protein is how it's involved in age related processes or disease related processes. So we've been interesting in developing ways to measure myostatin to determine whether or not it's a biomarker for muscle health in different populations. So we've been working with our pancreatic cancer spore. We have a study going on in frail individuals.

We have studies with our colleagues in urology, where we're taking blood samples and assessing what are the circulating myostatin concentrations in these patient populations. So we've been very keen to identify new ways to measure myostatin in humans. And this is really important because myostatin was just discovered in 1997. And we're already at the point now where clinical trials are starting. But we don't understand the biology or its natural history in aging or disease that while yet. So we're really making incredible gains in that space.

And finally, I'd mention that we're also actively involved in the clinical trial space. So we've recently had a clinical trial approved. This is in partnership with Novartis where we will be giving individuals over the age of 70 who have low muscle mass and slow gait speed what's called an antagonist to the myostatin receptor. So by doing this, we expect to have pretty marked increases in muscle mass and these individuals. And our goal is to see how it improves physical function as measured by the six minute walk distance.

This is very exciting for me as a scientist and an individual focused on skeletal muscle because oftentimes, in the field of muscle research, we're trying to harness pathways that cause cells to grow. And if you think about it, that's just the opposite of what the cancer field is doing. So it's a little bit risky and dangerous. So having a protein that's unique to muscle, that really regulates its size and its growth, is an incredible opportunity, and we're very excited about this next generation of interventions.

We've been most interested in myostatin because we think it has adequate horsepower to drive sufficient gains in muscle mass to translate to improvements in function. And one area where we've fallen short in the past is with different interventions with testosterone or exercise based interventions. Sometimes they don't cause enough of an increase in lean mass to translate into improvements in function. And this is something that's probably important to discuss a little further in that the regulatory agencies have made it very clear that interventions that simply increase mass but not function aren't going to get approved.

And that's a big challenge, because physical function is really regulated by multiple organ systems. And here, we're just trying to improve muscle health. And we need to show that that translates into improvements in physical function. So that's a challenge. We think these are probably robust and potent enough. But if you think about it, again, if many of us lose 20 or 30 kilograms of muscle over the course of our lifetime, is something that increases muscle mass just by a couple of kilograms going to be enough at the end of the day to translate into improvements in function?

There are a couple of other strategies that are worth mentioning. One is referred to as selective androgen receptor modulators. Those agents modify testosterone in a way where it removes the risk of causing growth in the prostate, or eliciting concerns about prostate cancer. And those are very interesting. Those are a little bit earlier on in their development, but clinical trials will be underway soon to test how well those work.

Another interesting strategy is something that makes muscle more sensitive to the nerve activating it. When you think about muscle, the way that muscle makes a contraction is that contract how proteins and muscle overlap and contract, they shorten. And it's called the cross bridge. And these drugs make the muscle more sensitive to the electrical signal that tells it to become active and contract.

This is a very outside of the box approach that I think is incredibly interesting. It may be more relevant to conditions such as ALS or neuromuscular conditions where there is more difficulty in recruiting some of the muscle fibers in tissues. But it could be relevant to aging and disease as well.

The space I'd be most interested in, in terms of spinal cord injury would be number one, improving the health of the muscles that remain functional. And the second element is that the incidence of type 2 diabetes in individuals with spinal cord injury is incredibly high, largely due to inactivity and disuse of again, the body's largest metabolically active tissue. One important element of this is that the field of physical medicine and rehabilitation interacts with every department and division at the institution. And we're working closely with our colleagues in these different divisions and departments to really discuss what are the challenges that patients with COPD are facing? What are the challenges that patients with cancer are facing?

What are the challenges that patients that are frail and scheduled for surgery facing? And how can the types of interventions that we're talking about be leveraged to improve outcomes in those different cohorts? And I think this is very exciting. And part of it reflects the fact that we're doing a better job of taking care of these patients for a longer period of time. And their health and well-being and their quality of life is largely affected by the quality and health of their skeletal muscle.

So exercise based interventions are and will remain, and the best thing we can do for these patients. But if we can augment those exercise based interventions with novel and emerging therapies that also impact muscle health, I think that's a really powerful combination.