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Hibernating Squirrels And Exercise In A Pill: The Next Wave of Cardiometabolic Therapies

by Andrew McConaghie

Early-stage companies pioneering new modalities discussed the future of cardiometabolic therapy and partnering with big pharma at the LSX conference in London.

Novo Nordisk's Wegovy and *Eli Lilly*'s Zepbound have turned weight loss treatments into a multi-billion-dollar field but the sector is already looking to new approaches to see where cardiometabolic therapies can go next.

Start-up companies are benefitting from an explosion of interest generated by the GLP-1 receptor agonist-based drugs and four biotech leaders discussed their scientific and partnering strategies at the LSX biopharma conference in London on 29 April.

Going Beyond Fat And Muscle Loss

The existing therapies have several drawbacks, including the loss of muscle mass as well as fat. Another is maintaining long-term weight loss with most Wegovy (semaglutide) and Zepbound (tirzepatide) users eventually stopping treatment and putting the pounds and kilograms back on.

Fauna Bio is one of the many early-stage companies researching a multitude of new mechanisms. It uses genomic-based research on mammals capable of

Key Takeaways

- Obesity and cardiometabolic disease has been one of the hottest deal making areas in recent times
- A new generation of companies are looking to find therapies to complement or even outperform the GLP-1 drugs in terms of safety, efficacy and durability of

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surviving extreme conditions to identify drug targets to treat human disease.

benefits

CEO and co-founder Ashley Zehnder said its work followed on from the story of the Gila monster, a type of lizard whose saliva contained hormones which inspired the development of the first GLP-1 receptor agonist, *AstraZeneca*'s Byetta (exenatide).

Fauna's work includes research on a species of gopher called the 13-lined ground squirrel. Before entering a six-month hibernation period, it doubles its own body fat, but does so without causing any cardiometabolic problems, as this would in humans.

"They're adorable. They go through this cyclical pattern of massive weight gain [and loss] but do not get liver disease or cardiovascular disease or have to go through cycles of malnutrition that we see in humans," she said.

The company uses an AI platform to leverage genomic analyses across 452 mammal species, including 65 hibernators, with the goal of discovering new compounds to help humans achieve healthy weight loss.

ASHLEY ZEHNDER

It began working with Novo Nordisk four years ago, and then in December signed a drug discovery deal with Lilly worth up to $494m in development payments and potential royalties. This partnership will explore novel alternatives to GLP-1 or complementary to GLP-1 in obesity only, giving Fauna room to work internally or with other partners on areas such as heart failure, liver disease and renal disease.

BioAge Labs is a clinical-stage biotech developing novel therapies for obesity and metabolic diseases by harnessing the biology of aging. Its lead compound is azelaprag, an oral apelin receptor agonist, which is being studied in combination with Zepbound and other incretin-based obesity treatments. These combination studies are expected to begin in mid-2024, in collaboration with Lilly's Chorus organization.

In a Phase Ib trial, azelaprag was shown to promote muscle metabolism, increased energy expenditure and prevented muscle atrophy in healthy older volunteers, who, for the purposes of

the study, remained in bed. In preclinical studies, azelaprag doubled the weight loss achieved on incretin drugs with improvements in body composition and muscle function.

The company's chief business officer Peng Leong said azelaprag was discovered using proteomics, metabolomics and genomics to tease out why some people age well without developing metabolic disease, while others do. Azelaprag mimics the activity of the exerkine apelin, a peptide that is released in response to exercise – which Leong and his company believe could eventually become like "exercise in a pill."

He added: "For those who don't want to go to the gym, they could take a pill. There are other mechanisms, such as mitochondrial uncouplers, which promote just burning energy from your food intake without it being stored in the body... we're all looking for complementary mechanisms to combine with GLP-1s."

Aphaia Pharma, a Swiss biotech, is developing an oral glucose formulation. This aims to restore endogenous signaling mechanisms and metabolic homeostasis in people with obesity, with the goal of mimicking the metabolic effects of bypass surgery without the adverse effects. Its lead drug candidate is currently in a Phase II proof-of-concept study in individuals with obesity, and another Phase II in people with pre-diabetes.

Safety And Durability

Chief scientific officer Steffen-Sebastian Bolz said new alternatives were needed and raised a note of caution about GLP-1 drugs. He said the drugs were in effect a kind of hormone replacement therapy and their potential to increase rates of cancer could not be ruled out. "We've thrown in a nuclear option, hormone-wise, on a system that is related to growth. And the elephant in the room is malignant growth of cells, right?"

He said there had been no "really dramatic" data to suggest this so far in humans but some evidence in animal studies. "We'll have to wait for larger datasets over longer periods and different doses but it's not out of the discussion."

Resalis Therapeutics is developing non-coding RNA therapies to modulate genes based on the discovery that a single microRNA, miRNA-22, is involved in a range of molecular pathways underlining metabolic disorders, including obesity and fatty liver disease.

The firm raised €10m ($11m) in a series A financing in January, which will help fund a first-in-human Phase I trial and reach Phase II readiness for Resalis's lead program, RES-010, in obesity. Resalis believes the therapy can help longer-lasting weight reduction and extend treatment durability in combination with approved therapies. He told *Scrip* the company was open to early pharma alliances, and had designed its trial program to make them as meaningful and attractive to partners as possible.

Addressing wider questions about how modern society promotes over-consumption and obesity, CEO Alessandro Toniolo said that long-term weight control required much greater patient education and added that there was already "over-reliance" on GLP-1s to address the problem. "Patients should be able to maintain diet and exercise, because that will help when they have to later stop the treatment, or else they will rebound. We need more education for patients in this area."