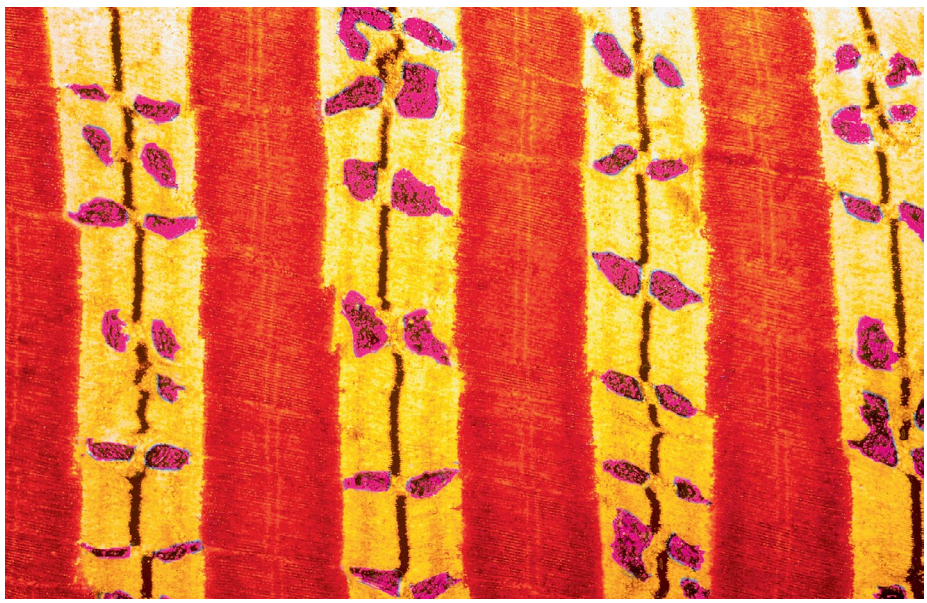
# After obesity drugs' success, companies rush to preserve skeletal muscle

**A growing number of companies are testing muscle-building agents to counter the side effects of dramatic weight loss and potentially to preserve lean muscle into old age.**



Skeletal muscle takes a hit during weight loss. To reduce the impact on muscle mass, biotechs are pairing obesity drugs with exercise mimetics.

By Carrie Arnold

Even as obesity treatments Ozempic and Mounjaro continue their surge in popularity, drug hunters are asking whether it is possible for people to lose weight on these glucagon-like peptide-1 (GLP-1) agonists without losing muscle. Drug candidates originally designed to build, preserve or regenerate skeletal muscle for treating muscle atrophy in degenerative conditions or ageing are now being tested in combination with GLP-1 agonists used for obesity to spare lean muscle.

One such biotech is BioAge Labs. In February, the company announced a $170-million series D financing, which will allow it to combine its apelin receptor agonist azelaprag (BGE-105) with Eli Lilly's GLP-1 agonist Mounjaro (tirzepatide) in phase 2 studies. The combination preserved lean body tissue in phase 1 studies and animal models and boosted weight loss by 10–15% compared with Mounjaro alone, effectively "supercharging" weight loss, says BioAge co-founder and CEO Kristen Fortney. "You get a profound, profound synergy," Fortney says. "We see not only an amplification of weight loss but also an improvement of body composition and function, which is really exciting."

The news came on the heels of Regeneron's intention to launch a phase 2 trial pairing the company's muscle-preservation monoclonal antibodies (the anti-myostatin trevogrumab and the anti-activin A garetosmab) alongside Novo Nordisk's Ozempic (semaglutide). "If you can lose more fat by preserving your muscle, then that's the best of all worlds," says David Glass, vice president of research for aging and age-related disorders at Regeneron. "That's really what we're trying to achieve."

What used to be a pharmaceutical dead zone is now coming alive, with at least ten compounds in development to improve muscle mass, boost strength or prevent muscle loss, a condition known as sarcopenia (Table 1). "For the longest time, people have talked about skeletal muscle function as being undruggable, but in the last ten years or so, that has changed," says Daniel Rooks, executive director, musculoskeletal translational medicine at Novartis Biomedical Research. Industry insiders will be closely watching those clinical trials launching in 2024, says Rooks.

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Beginning at age 30, humans lose on average 3–8% of their muscle mass per decade, and this accelerates after age 60. In old age, muscle loss or sarcopenia leads to reduced mobility and is linked to falls, frailty and cardiovascular disease. Nathan LeBrasseur, director of the Robert and Arlene Kogod Center on Aging at the Mayo Clinic, says that the problem with targeting sarcopenia is that it is generally seen as a symptom of aging and prolonged immobility rather than a stand-alone condition. Standard interventions for sarcopenia include strength training and nutritional counseling to ensure adequate protein consumption. In theory, this approach is extremely effective, LeBrasseur says. But the presence of other chronic conditions, inflammation, injuries and mobility challenges can make it hard for people to recover.

A prime need is a treatment to help adults hospitalized for hip fractures, says Fortney. The prolonged immobilization needed for bone healing makes it almost impossible for many patients to regain their former strength and physical endurance.

Pharma's early muscle-directed efforts were mostly focused on ramping up testosterone and blocking myostatin, a negative regulator of myogenesis. Mice and dogs that lack myostatin have double the muscle mass of their wild-type counterparts. To pharma, myostatin seemed like the perfect target, says Rooks. But early myostatin inhibitors trialed in adults did not create super-buff humans or

News in brief

# In vivo CRISPR agent cuts HAE attacks 95%

A CRISPR–Cas9-based gene editing therapy from Intellia Therapeutics reduced monthly swelling attacks by 95% in people with hereditary angioedema (HAE). The results from a small phase 1 trial were published in the *New England Journal of Medicine* in February. HAE is a rare genetic disorder characterized by recurrent bouts of subcutaneous and submucosal swelling that can be life threatening. Kallikrein, an enzyme that is elevated in the disease, interacts with the complement system, leading to its overactivation. Intellia's CRISPR-based gene editing therapy NTLA-2002 targets and inactivates the *KLKB1* gene, which encodes the precursor to the kallikrein enzyme. Using lipid nanoparticles, the company's non-viral platform delivers a guide RNA specific for the *KLKB1* gene and mRNA encoding the Cas9 enzyme to the liver, where they carry out the precision editing.

The trial involved ten people with HAE who received a single shot of NTLA-2002 in three different doses. The patients were followed for 16 weeks and, although the responses were not dose dependent, NTLA-2002 reduced kallikrein protein in patients' plasma by 67–84% and monthly attacks diminished by 95% on average. Adverse events included infusion-related reactions and fatigue. The phase 2 placebo-controlled portion of the trial is ongoing.

The goal of NTLA-2002 treatment is to provide lifelong control of angioedema attacks after a single dose. Nevertheless, several treatments exist, including those that target kallikrein. Takeda's Kalbitor (ecallantide) is a recombinant protein injected on demand; Takhzyro (lanadelumab), developed by Shire and then bought by Takeda, is a preventative monoclonal antibody injected once every two weeks; while BioCryst's Orladeyo (berotralstat) is a preventative, oral, once-daily small-molecule inhibitor.

**Table 1 | Selected agents in clinical trials for the prevention of muscle loss**

| Sponsor | Drug | Target | Details |
|---|---|---|---|
| University of Texas Health Science Center at San Antonio | Metformin | AMPK activator | Phase 2; NCT02570672 |
| Biophytis | Ruvembri (BIO101) | MAS receptor agonist | Phase 2b |
| BioAge | Azelaprag (BGE-105) + Mounjaro | Apelin receptor agonist + GLP-1/GIP receptor agonist | Phase 2 |
| Biohaven | Taldefgrobep alfa | Myostatin inhibitor | Phase 3 for spinal muscular atrophy |
| Immunis | IMMUNA | Non-cell-based secretome product | Phase 1/2a; NCT05211986 |
| Juvena | JUV-161 | Non-cell-based secretome product | IND-enabling |
| MyMD | MYMD-1 | TNF inhibitor | Phase 2 |

GLP-1, glucagon-like peptide-1; GIP, glucose-dependent insulinotropic polypeptide; IND, Investigational New Drug; TNF, tumor necrosis factor. Source: company websites, Clinicaltrials.gov.

even a meaningful increase in muscle strength, and pharma seemed to lose interest.

Biotech companies have now cast a wider net, identifying and zooming in on different mechanisms that control muscle mass. One potential approach is to block activin, a protein through which myostatin sends its muscle atrophy signals. It's the strategy used by Versanis Bio, a biotech acquired by Lilly in July 2023 for $1.925 billion. Academic scientists have shown that the myostatin–activin pathway also has a profound influence on fat accumulation, emphasizing the deep biological links between muscle and adipose tissue, both in humans and in animal models. A team at University of Toulouse in France treated mouse models of chronic kidney disease with a synthetic version of apelin. They found that apelin treatment partially ameliorated the usual muscle loss that accompanies kidney disease.

Another potential target is the mammalian target of rapamycin complex-1 (mTORC1), a pathway involved in controlling muscle size. mTORC1 activation promotes muscle building, but if constantly stimulated it can also induce muscle breakdown by activating proteasome degradation. Others are looking to promote muscle regeneration by stimulating muscle stem cells, tweaking variables such as the stiffness of the extracellular matrix or engineering extracellular vesicles to deliver therapeutics.

Immunis and Juvena Therapeutics are zooming in on the muscle stem cell secretome – the collection of proteins, including growth factors, cytokines, chemokines and extracellular matrix components, secreted by muscle cells. The secretome kicks in to boost proliferation in response to exercise or to enhance cellular interactions to accelerate wound healing, for example, and it declines markedly with age.

For Paris-based Biophytis, the focus is on the shared pathways between age-related sarcopenia and neuromuscular disease such as Duchenne muscular dystrophy. Its lead candidate is ruvembri (BIO101), a small molecule that targets the MAS receptor, which is present in cardiorespiratory and skeletal muscles. MAS activates the AKT and AMPK kinase pathways downstream, stimulating protein synthesis and energy production, respectively.

"There is a clear impact not only on skeletal muscle but also cardiorespiratory muscles, both of which are very important for mobility," says Stanislas Veillet, founder and CEO of Biophytis.

Such similarities between skeletal and cardiac muscle will open other crossover uses. "We started our work focused on cardiac muscle, but we very rapidly recognized that what we were doing was applicable to all muscle types," says Robert Blum, president and CEO of Cytokinetics, a company developing drugs to treat heart failure.

BioAge, another Bay Area biotech, has applied its AI-powered platform to identify an oral apelin receptor agonist called azelaprag. Apelin has been dubbed an "exerkine," as it is a peptide hormone involved in glucose and lipid metabolism that is released in response to physical activity. The company is trialing an apelin mimic to replicate these effects in older adults. Results from a phase 1b trial showed that azelaprag significantly reduced muscle atrophy in healthy adults aged 65 and up compared with placebo.

Companies with muscle-building drugs are now blazing a trail in obesity studies to counter the skeletal muscle atrophy that accompanies fat-loss treatments. The often dramatic weight loss experienced by people who have undergone bariatric surgery or are taking GLP-1 agonists such as Mounjaro and Ozempic leads to the loss of muscle as well as fat. As a consequence, biopharma companies are on the lookout for drugs to use alongside GLP-1 agonists to preserve lean muscle mass. BioAge has teamed up with Lilly to begin testing its apelin agonist, azelaprag, in people taking Lilly's weight loss drug. In obese mice, the combination increased weight loss and preserved lean body tissue compared with Mounjaro alone. Apelin increases metabolism and improves glucose uptake by cells, thus improving insulin sensitivity.

Biohaven is conducting a phase 3 trial of taldefgrobep alfa, a myostatin inhibitor, to improve muscle mass in spinal muscular atrophy. The recombinant protein works by lowering myostatin directly as well as blocking activin signaling pathways. The drug proved successful in preserving muscle mass during weight loss in an obesity mouse model, prompting Biohaven to test it in combination with Ozempic in phase 2 trials.

Muscle-building agents — with a view to combinations — are driving hefty acquisitions. Lilly's acquisition of Versanis and its drug bimagrumab is an example. The monoclonal antibody was initially developed by Novartis for use in a muscle disorder known as sporadic inclusion body myositis. Trials showed that the drug did not lead to significant differences in muscle function, although it did help adults with a body mass index over 25 reduce body fat, perhaps by increasing metabolic rate. Versanis later licensed the drug and is now taking it through phase 2b trials in combination with Ozempic. For many in the field, the potential applications for sarcopenia therapeutics in the treatment of obesity represents a huge promise — and a huge payoff.

"Muscle is critically important for movement and function, but it's also our largest metabolic organ," says LeBrasseur.

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**News in brief**

# US bill targets Chinese biotechs

The United States is seeking to prevent four Chinese biotech companies from doing business in the country, citing them as "companies of concern" that threaten national security. The Biosecure Act, introduced in both the Senate (S.3558) in December and House of Representatives (H.R.7085) in January, would prohibit the federal government from contracting with certain biotech providers connected to foreign adversaries. The ban could extend to institutions that receive funding from the National Institutes of Health or other US government agencies, which would include almost all universities, research centers, hospitals and life science companies. The companies named in the bill are BGI Group, MGI Tech, Complete Genomics and WuXi AppTec — all Chinese-owned companies that provide instruments or services associated with the collection, sequencing or analysis of genetic information. The Senate bill's sponsor and chairman of the Senate Committee on Homeland Security & Governmental Affairs, Gary Peters (D-Mich.), said S.3558 was "critical legislation to strengthen our national security and combat risks posed by biotech companies from adversarial nations like China" and that "it is incredibly important that we advance this legislation quickly." In a press release on H.R.7085, sponsor Mike Gallagher (R-Wis.), chair of the House Select Committee on Strategic Competition between the United States and the Chinese Communist Party, said "The CCP will undoubtedly use the genetic data collected by BGI to further its malign aggression, potentially even to develop a bioweapon used to target the American people." Rachel King, CEO of industry trade group the Biotechnology Innovation Organization, responded in a letter to the Senate committee that the legislation would hamper US innovation, saying it would "do untold damage to the drug development supply chain both for treatments currently approved and on market as well as for development pipelines decades in the making."