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CCM Biosciences Scientists Report Discovery of First-in-Class Longevity Therapeutics

Novel therapeutics rejuvenate a previously undruggable mitochondrial regulator of aging through a groundbreaking mode of enzyme activation

Compounds that enhance enzyme activity show promise for cellular rejuvenation and treating age-related diseases. However, their development has proven challenging due to reliance on allosteric modulation, a mechanism feasible in less than 10% of proteins. In a landmark study, scientists at the longevity therapeutics division of biopharmaceutical company CCM Biosciences, Inc. have overcome this hurdle by discovering first-in-class enzyme activators that restore a previously undruggable mitochondrial regulator of aging to youthful activity levels.

Leveraging a newly identified biophysical mechanism of enzyme activation, researchers at the diversified biopharma company CCM Biosciences, Inc., have discovered and characterized first-in-class enzyme activators for a previously undruggable master regulator of cellular energy production. These first-in-class compounds fully restore the enzyme's activity to youthful levels and hold significant potential for clinical development to address a range of age-related disorders, including Alzheimer's, Parkinson's, cardiovascular conditions, and metabolic diseases.

The ability to add just one year of healthy life to the global population has been estimated to be worth over $10 trillion, and the largest XPRIZE in history was recently announced with a seven-year plan to rejuvenate cells. Many chronic, age-related disorders could be mitigated by enhancing the activity of enzymes that regulate biochemical signaling pathways. However, despite this intense global interest, finding enzyme-activating compounds has been a challenge because they typically rely on a mechanism called allosteric modulation, a process that is known to be feasible in less than 10% of proteins.

Recently, a team of scientists at CCM Biosciences and its affiliated R&D center Chakrabarti Advanced Technology expanded the scope of enzyme activation beyond allosteric modulation by introducing new physical principles for enzyme activation and successfully applied computational and experimental design methods based on these principles to identify new compounds that dramatically enhance the activity of previously undruggable enzyme Sirtuin-3 (SIRT3), which is centrally involved in regulating human aging. This study was published in *Physical Review X*, the flagship journal of the American Physical Society (APS), on October 22, 2024.

Billions of dollars have been invested over the past two decades in efforts to upregulate sirtuin enzymes due to their role in regulating healthspan and lifespan. The biotechnology company Sirtris Pharma, founded based on the work of longevity researchers from Harvard

and MIT, was bought by GlaxoSmithKline for $720 million, but the development of its drug candidates, which were allosteric activators, was subsequently terminated due to the observation that they only functioned with a limited number of substrates for one of the seven sirtuin enzymes. Due to the difficulty of identifying activators that upregulate more sirtuin enzymes under more physiologically relevant conditions, companies such as Elysium Health (MIT) had largely abandoned the efforts to develop targeted sirtuin activators and instead turned to marketing nutraceuticals to increase sirtuin activity.

Notably, SIRT3, the major mitochondrial sirtuin enzyme, plays a critical role in determining human health span and lifespan through the regulation of mitochondria—the energy production powerhouses of cells that decline with age—but was considered undruggable due to lack of a known allosteric site. The lead compounds recently discovered by CCM scientists greatly increase the sensitivity of SIRT3 to the essential metabolic cofactor NAD^+ (nicotinamide adenine dinucleotide), whose levels decrease with age and play a major role in the onset of many age-related diseases. While researchers had identified protein mutations in sirtuins that could increase the sensitivity of a related enzyme SIRT1 to NAD^+, they were not successful in designing druglike compounds that could achieve this effect.

CCM compounds fully recovered the activity of SIRT3 in the face of NAD^+ levels decreasing by a factor of two, as observed in old age. The scientists have also shown that their compounds increase SIRT3 activity in the face of declining NAD^+ for multiple cell lines employed in aging studies. The proposed compounds are also undergoing animal testing in mice for age-related disorders, including infertility, where they have outperformed both NAD^+ supplements and other sirtuin activators.

In recent years, investment in therapeutic interventions for age-related disorders has surged, with invested capital in 2024 exceeding $5 billion. Notable examples include Calico (an Alphabet company) and Altos Labs, each of which has received over $3 billion in funding. However, very few proprietary first-in-class drug candidates have been advanced to clinical trials for efficacy in against age-related disorders. By contrast, the drug programs of CCM Biosciences for age-related disorders are entering clinical trials for efficacy in 2025.

Dr. Michael Pollak, Professor of Medicine, Oncology, and Pharmacology at McGill University and an expert on clinical trials for age-related disorders and the biochemistry of sirtuin-regulated signaling pathways, says that *“Efforts have been underway for decades to activate signaling pathways regulated by sirtuins to combat age-related disorders, but prior efforts have encountered significant hurdles. The discoveries by CCM Biosciences pertaining to the design of drug candidates that can activate the major mitochondrial pathways regulated by sirtuins, along with the clinical development plan for evaluation of efficacy as well as safety of these drug candidates, revitalize this area of drug development.”*

Reference

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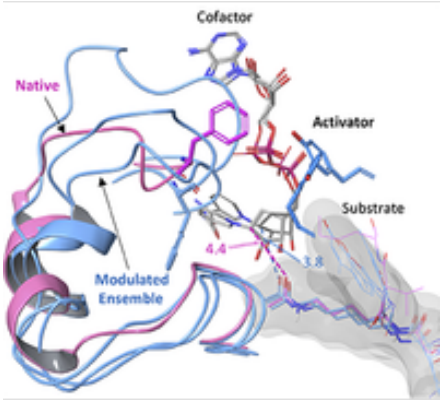

Image Title: Enzyme activation through targeted changes in protein structure
Image Caption: Researchers present novel therapeutics that rejuvenate a previously undruggable mitochondrial regulator of aging through a new mode of enzyme activation.
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