药学院傅磊课题组在顶级学术期刊PNAS杂志发表最新文章

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傅磊课题组阶段性地完成了“通过化学手段干预线粒体活性”的研究，在PNAS杂志上刊出文章 “Moderation of mitochondrial respiration mitigates metabolic syndrome of aging” 。 (https://doi.org/10.1073/pnas.1917948117)

Mito-Fu 或能延长人类健康寿命的药物

Mito-Fu, Probable Drugs for Human Health Span

人类健康寿命（Health Span）是指他健康的时间长度，而不仅仅是活着的时间。根据美国国家科学院院刊（PNAS）2020年4月17日的一篇文章[1]，上海交通大学和斯坦福大学的科学家们设计了一类新化合物，2-(2-(4-甲基噻唑-5-基)乙氧基)-2-氧乙基三唑的三苯基膦衍生物（简称TPP-噻唑，是Mito-Fu家族的成员）。在小鼠体内，这类化合物能精准地靶向线粒体，缓解衰老相关的疾病，阻止年龄相关性肥胖和血糖并发症的发生，并延长小鼠健康寿命。

A person’s health span is the length of time that the person is healthy – not just alive. According to a paper in the April 2020 issue of Proceedings of the National Academy of Sciences of the United States of America (PNAS)[1], scientists from Shanghai Jiao Tong University (SJTU) and Stanford University

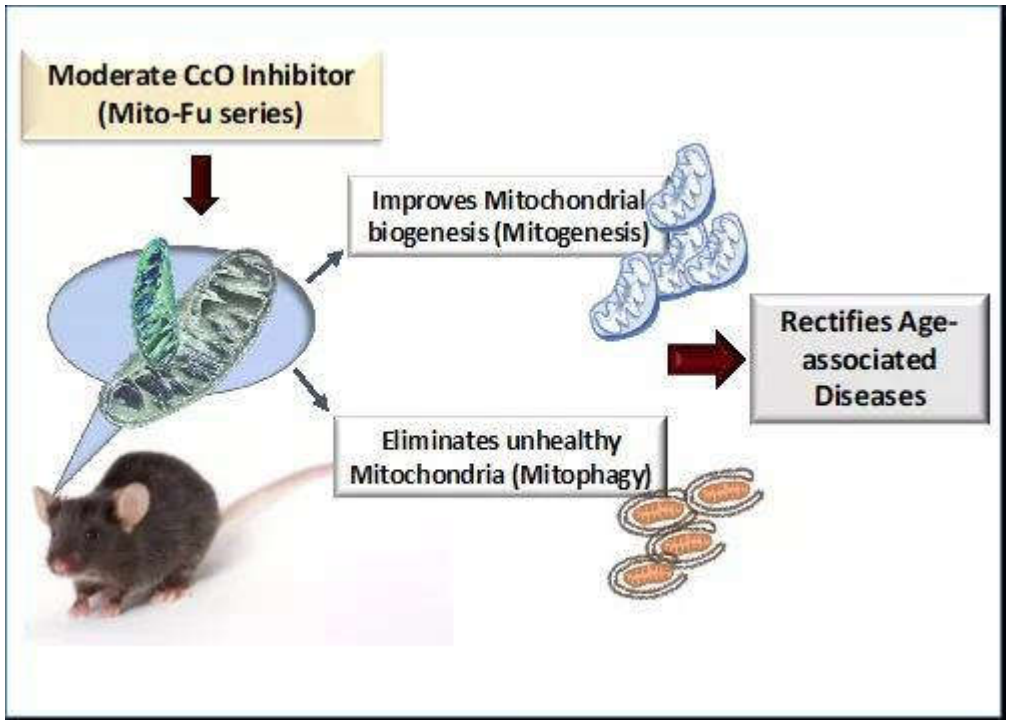
designed a novel drug, a triphenyl-phosphonium derivative of the 2-(2-(4-methylthizol-5-yl) ethoxy)-2-oxoethyl triazole (TPP-thiazole), a member of Mito-Fu family. This compound specifically targets mitochondria and consequentially alleviates aging diseases, impedes the onset of age-associated obesity, blood glucose complications, and improves health span in mice.

该论文的通讯作者、上海交通大学药学院傅磊教授说，“我们发现了一种独特的作用机制，它可以提高模型动物的线粒体数量和质量。从小鼠身上观察到的这些令人信服的结果表明，基于这种独特的机制，这类化合物值得进一步研究，并会有许多潜在的临床应用。”

“We have discovered a proprietary mechanism to improve mitochondrial quality and quantity in the animal model.” says Professor Fu at SJTU School of Pharmacy, a corresponding author of this PNAS paper, “these compelling results in mice show that the impact of this compound deserves a closer look as there are many potential clinical applications based on this proprietary mechanism.”

斯坦福大学的Collman教授强调：“这项研究报道了一种新型、无害的药物，它能抑制小鼠的呼吸，大大降低衰老的不利影响，并促进新的线粒体产生。线粒体是所有依赖空气生存动物的能量工厂。Mito-Fu是一类水溶性化合物，还可以用来治疗II型糖尿病和炎症相关的疾病。”

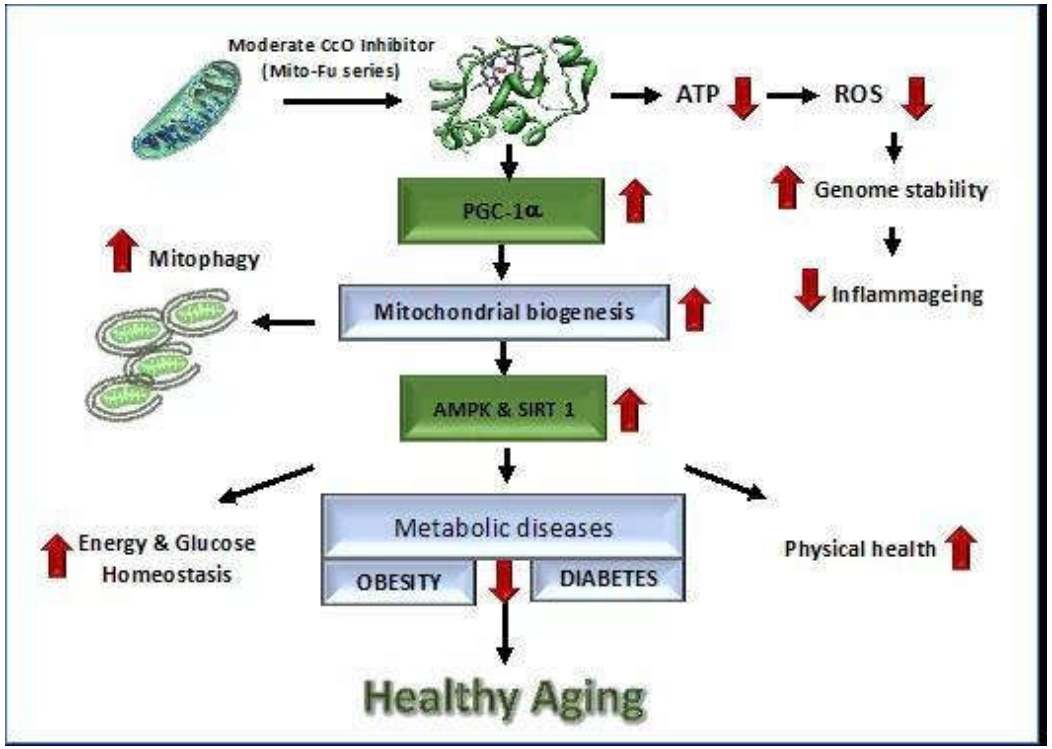
“This study reports a new, seemingly innocuous drug that inhibits respiration in mice, strongly diminishing the adverse effects of aging and creating new mitochondria, the power cells of all air-breathing animals. This water-soluble compound treats type II diabetes and reduces inflammation.” Professor Collman at Stanford emphasizes.



线粒体存在于真核细胞，它将营养物质转化为能量，但线粒体的功能会随年龄增加而衰退。该研究论文的第一作者，傅磊课题组的博士研究生M. Tavallaie解释道：“线粒体就像体内的发电机，提供细胞运行所需的能

量，但同时也会产生有害的‘副产物’。这些副产物会加速衰老，引起年龄相关性疾病。因此，我们通过干预细胞器，诱导有规律的停顿，使它们恢复活力。”

Mitochondria are the part of eukaryotic cells that convert nutrients to create energy. Mitochondria decay with age. “Mitochondria are like a furnace in the body; they produce energy but at the same time make harmful byproducts which accelerate aging and expedite the age-linked diseases. Therefore, we believe that this intervention by inducing a regulated pause to these organelles allows them to rejuvenate,” according to the study's lead author, M. Tavallaie, a Ph.D. candidate in Dr. Fu’s lab at SJTU School of Pharmacy.



这项研究源自于一类仿生化合物的合成，该化合物模拟线粒体中的细胞色素c氧化酶（CcO）。基于这种模拟酶，斯坦福大学Collman教授的研究团队发现了一系列新的化合物[2-6]。

This research stemmed from the synthesis of a biomimetic compound that imitates the respiratory enzyme, cytochrome c oxidase (CcO) in the mitochondria. Based on this enzymatic mimic a series of novel compounds were discovered by the Collman group at Stanford [2-6].

在这篇PNAS文章中，傅磊教授的研究小组将60只雄性小鼠随机分为给药组和对照组，在18个月的给药过程中，研究人员检测了线粒体的多项功能，如呼吸能力、线粒体生物能量和生物合成，以及一些与衰老相关的指标，包括小鼠的活性氧化物（ROS）生成、葡萄糖异常和肥胖。研究结果表明，慢性中度抑制CcO可减少ATP合成，促进线粒体生成和线粒体自噬，从而减少ROS生成和线粒体衰退，调控重要的细胞能量代谢调节因子；因此，该化合物可以有效地调节能量平衡，抑制肥胖和与衰老相关的葡萄糖异常。

In this PNAS paper, the SJTU research team randomly divided 60 male mice into compound-treated and control groups and characterized a variety of mitochondrial functions, such as respiratory activity, mitochondrial bioenergetics, and biogenesis, and few age-associated comorbidities including reactive oxygen species (ROS) production, glucose abnormalities and obesity in mice over a period of 18-month treatment. The team was able to demonstrate that chronic moderate inhibition of CcO reduces ATP synthesis, promotes mitochondrial biogenesis and mitophagy, subsequently decreasing ROS production and mitochondrial decay, and rectifying vital cellular energy metabolism regulators; thus, effectively refining energy homeostasis and curbing obesity and glucose irregularities linked to aging.

“我们已经证明，Mito-Fu系列的一个成员可以促进新陈代谢，缓解衰老并发症。新的衍生化合物正在进一步的研究中。未来的研究会在更大的动物身上测试这些药物，并最终用到人身上。”傅磊教授说到，“目前我们已经合成了大量具有活性的低毒性小分子化合物，还发现了提高这类新药活性的简单策略。深入了解其作用机制使我们能够开发出活性更好的化合物，针对特定疾病予以临床干预。”

“We have demonstrated that a member of Mito-Fu family boosts metabolism and mitigates aging complications. New derivatives are being examined for efficacy. Future research will test these drugs on larger animals with an ultimate application in humans.” Dr. Fu added, “at this point, we have uncovered a myriad of active compounds. These are small molecules with low levels of toxicity. We have also discovered a simple strategy to increase the activity of this new class of drugs. Understanding the underlying mechanism may allow us to develop even more active chemicals directed specifically in particular disease states and to translate the intervention in humans.”

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