

## **Nature Publication Reports Key Links Between Mechanisms of Aging and Metabolic Disorders; Obesity and Diabetes Seen as Accelerated Aging**

**CAMBRIDGE, Mass. July 5** -- CAMBRIDGE, Mass., July 5 /PRNewswire/ -- During the last decade researchers have made a number of important discoveries about the molecular mechanisms regulating aging. This research has suggested the exciting prospect that the rate of aging can be manipulated and slowed, leading to longer human lifespan. A major peer-reviewed article in the current issue of Nature Reviews Drug Discovery describes the intimate links between these pathways of aging and those of metabolic disease, such as type 2 diabetes and obesity. The authors describe how these insights open the door to novel classes of drugs, which can be developed to not only treat diabetes and obesity, but also effectively slow the aging process and extend lifespan. These and other findings are reviewed in the article, "Aging and Metabolism: Drug Discovery Opportunities," authored by Elixir Pharmaceuticals' researchers Drs. Rory Curtis, Bard J. Geesaman and Peter S. DiStefano and appearing in Nature Reviews Drug Discovery (July 2005, Vol. 4, No. 7).

John Kopchick, Ph.D., Goll-Ohio Eminent Scholar and Professor of Molecular Biology, Department of Biomedical Sciences, Konneker Research Center, Ohio University, commented, "This article provides an elegant and comprehensive survey of the essential connections between metabolic disease pathways and aging. The potential of this research is profound: Modulating these pathways may not only uncover yet unknown therapeutic targets and/or drugs to treat metabolic disease, but also has the potential to impact the progression of aging itself."

### Summary of the article

- Aging is a major risk factor for several major diseases including cancers, cardiovascular, metabolic and neurodegenerative diseases.
- Many of the genes discovered over the last decade that are known to affect lifespan belong to evolutionarily conserved biochemical pathways that are also intricately involved in the control of energy metabolism.
- Diabetes can be considered as an accelerated form of aging. Insulin resistance and visceral fat accumulation are culprits in the pathogenesis of metabolic disease and these factors predispose organisms to premature aging.
- Several of these gene products, i.e., the encoded proteins, represent good molecular targets for drug discovery for the major metabolic diseases (obesity, type 2 diabetes).
- The article provides a roadmap to identify drugs to treat and prevent metabolic diseases; biomarkers identified during the course of clinical trials with these drugs may lay the foundation for drugs that increase lifespan.

- Targeting the mechanisms of aging provides a novel means for discovering drugs to treat metabolic diseases as well as other important age-related diseases.

## Pathways of Aging

Much research has focused on the role of insulin resistance in aging. According to the authors, "in situations where plentiful high-calorie food is combined with a sedentary existence, the pancreas increases insulin secretion above normal levels in order to dispose of sustained excess blood glucose which, over time, leads to the deposition of visceral fat." Two major effects result: Increased visceral fat initiates a metabolic cascade that impairs insulin signaling in the body, and greater levels of insulin cause visceral fat to secrete substances that reduce insulin sensitivity in tissues.

As the authors note, "Eventually, this feed-forward cycle leads to an altered metabolic state involving very high levels of insulin (hyperinsulinemia) induced by resistance to insulin, even under fasting conditions. This state triggers a constellation of related complications, collectively referred to as metabolic syndrome."

According to the Nature authors, many of the genes implicated in the modulation of lifespan are well-conserved from lower organisms right up through humans. In addition, these genes code for receptors, enzymes and transporters, and are therefore suitable targets for drug development. These include: 1) the SIR2/SIRT class of deacetylases, known to increase lifespan when over-expressed in yeast and flies, 2) insulin/insulin-like growth factor receptor, which increases lifespan in worms and mice when deleted in certain tissues, 3) AMP kinase, an enzyme that acts as a fuel sensor and is a target of the anti-diabetic drug metformin, and 4) INDY ('I'm not dead yet'), a cell surface transporter known to increase lifespan in flies when mutated.

Dr. Kopchick stated, "The article by DiStefano et al. will stimulate a paradigm shift in our thinking about aging and age-related disorders. As pointed out by the authors, we are beginning to recognize that metabolic syndrome, in addition to being a precursor of serious diseases such as type 2 diabetes and cardiovascular disease, may be a sign of premature aging. For patients, this translates into the potential of a variety of novel drugs emerging from the science of aging, which then will be tested clinically in the treatment of metabolic diseases. What an exciting possibility!"

In the United States, nearly twelve million people have type 2 diabetes and another 60+ million are obese. The numbers are growing dramatically and are expected to double over the next 25 years. In addition to the direct burdens (e.g. patient quality of life, economic) of these metabolic diseases, diabetes and obesity are also risk factors contributing to higher and earlier rates of a variety of life-threatening conditions such as cancer, cardiovascular disease and Alzheimer's disease - all commonly referred to as diseases of aging.

## About Elixir Pharmaceuticals

Elixir is a biopharmaceutical company focused on exploiting its Optimal Aging scientific platform to discover, develop, and market new drugs for the treatment and prevention of metabolic disorders, as well as the prevention of age-related diseases. The Company's research and discovery programs are based on a unique

understanding of the genetics and biochemical pathways of aging. More information about Elixir is available at <http://www.elixirpharm.com/>

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