

PRESS RELEASE

BIOMOL Researchers Identify the First Molecules that Extend Lifespan

Plymouth Meeting, PA , August 26, 2003 - BIOMOL Research Laboratories, Inc., in collaboration with Dr. David Sinclair, associate professor of pathology at Harvard Medical School, has identified the first molecules that extend lifespan. This work identified a class of molecules, present in red wine, peanuts and other foods, that extend lifespan in yeast. Experiments are providing similar results in other experimental systems including worms, flies, and human cells.

The findings are reported in the August 24 *Nature advanced online edition* (Howitz, K.T. et al. *Nature AOP*, published online 24 August 2003; doi:10.1038/nature01960). The research suggests a promising route to find and develop drugs to lengthen healthy life and prevent or treat aging-related diseases.

Published research from Dr. Sinclair and others have shown that sirtuin enzymes, a family of deacetylases conserved between yeast and human beings, are important for controlling the rate at which organisms age. Recognizing the importance of sirtuins in regulating longevity, Dr. Konrad Howitz, Director of Molecular Biology, and his staff screened for modulators of sirtuin activity using compounds from BIOMOL's collection of small molecules. Dr. Howitz and his team identified resveratrol and 17 additional compounds, all belonging to a class of molecules called polyphenols, as strong stimulators of sirtuin enzymes. In collaboration with Dr. Sinclair and his research team, these molecules were shown to extend lifespan in yeast up to 80% and promote survival of human cells following DNA damage.

The effect of polyphenols identified in the research mimics the effect of calorie restriction, which also increases longevity through a sirtuin pathway in yeast. Calorie restriction is a known stimulus of longevity in organisms ranging from yeast to mammals, and provides multiple beneficial effects in rodents including, cardioprotection, neurodegeneration, and cancer suppression.

Resveratrol, the most potent molecule identified in the study, has previously been thought to provide positive health benefits due to its antioxidant effects. However, this most recent work points to the sirtuin enzymes as being the important targets for the beneficial effects of resveratrol.

"The sirtuin stimulation provided by certain, but not all, polyphenols may be a far more important biological effect than their antioxidant action," said co-author Konrad Howitz.

The finding that certain small molecules promote longevity and survival through stimulation of sirtuins marks a milestone in aging research, and raises the possibility that drug discovery efforts could lead to therapeutics for a range of age-related diseases. Toward that end, BIOMOL is currently exploring synthetic variations on the molecules, which are called sirtuin activating compounds or "STACs," to improve the sirtuin stimulating activity. BIOMOL is also searching for endogenous activators that may naturally exist in human cells.

"This groundbreaking work opens new possibilities for drug discovery in the fields of cancer, heart, and neurodegenerative diseases," stated Dr. Robert Zipkin, President and co-founder of BIOMOL Research Laboratories.

BIOMOL is a biochemical reagents company located in Plymouth Meeting, PA, and is a leader in the supply of cutting-edge drug discovery tools including histone deacetylase (HDAC) and sirtuin research tools. Its products are available through Biomol GmbH, Hamburg. (Phone: 0800-2466651, www.biomol.de, info@biomol.de).

Details: next page.

FR104	Resveratrol	100 mg	76 €	500 mg	256 €
AK500	HDAC Fluorescent Activity Assay Kit for Drug Discovery	1 kit	400 €		
KI177	Fluor de Lys - SIRT1, Deacetylase Substrate	1 µmol	195 €		
SE239	SIRT1 (Sirtuin 1) (Human, recombinant)	100 U	400 €		
<i>More relevant products:</i>				<i>see page 3</i>	

Sirtuin Assay Reagents and Polyphenols

Many BIOMOL products were critical for our discovery of small molecule sirtuin activators that extend lifespan in yeast. Our initial screen was conducted using the Fluor de Lys Substrate/Developer System for measuring deacetylase activity. This fluorogenic assay system was developed at BIOMOL and has been embraced as a reliable and convenient assay for measuring deacetylase activity. Our HDAC assays and reagents have become best sellers, and we are very active in developing new reagents in this area. The advantages of the assay system are that it is performed without the need for radioactivity or extractions and works well with diverse sources of HDAC activity. It also works well as a cellular assay, and a new cellular kit should be available soon. In addition to the Fluor de Lys Kit (cat. # AK500), we offer a number of sources of HDAC activity including recombinant HDAC8 (cat. # SE145), SIRT1 (cat. # SE239) and SIRT2 (cat. # SE251). We also offer a number of different substrates including the Fluor de Lys Substrate (cat. # K1178) and several substrates based on sites of acetylation in p53 and histones (see below). In our screen, recombinant SIRT1 (cat. # SE239) was used with the Fluor de Lys-SIRT1 (cat. # K1177) deacetylase substrate.

Seventeen molecules were identified that could activate sirtuins, all of which are polyphenols, which include a large and diverse group of natural products found in many plants. Resveratrol (cat. # FR104) was the most potent molecule and increased lifespan in yeast to the greatest extent. While many of the molecules we identified are not catalog products, they are available individually or can be incorporated into custom libraries upon request. Our catalog of small molecule inhibitors and ligands is one of the strengths of BIOMOL. We have over 1000 carefully selected small molecules in our catalog. They are well characterized and serve as useful research tools, but at the same time many novel activities and applications have yet to be discovered. BIOMOL is an excellent source of small molecules for use as specific research tools or for screening.

A list of relevant products follows on the next page.

FR104	Resveratrol	100 mg	76 €	500 mg	256 €
AK500	HDAC Fluorescent Activity Assay Kit for Drug Discovery	1 kit	400 €		
K1177	Fluor de Lys - SIRT1, Deacetylase Substrate	1 µmol	195 €		
SE239	SIRT1 (Sirtuin 1) (Human, recombinant)	100 U	400 €		
	More relevant products:				see page 3

BIOMOL Products For Sirtuin and Aging Research

The following is a list of products associated with our recent finding that polyphenolic compounds stimulate sirtuin enzymes and extend lifespan in yeast. Visit www.nature.com/nature/ and click Advanced Online Publication (AOP) to view our recent article (Howitz et al., Nature Advanced Online Publication, Published online: 24 August 2003).

Polyphenol Compounds Cat.

Resveratrol	(FR104)
Ambroxol	(FR112)
Apigenin	(Inquire)
Butein	(Inquire)
Caffeic Acid Phenyl Ester	(FR102)
(+)-Catechin	(Inquire)
(-)-Catechin	(Inquire)
Chalcone	(Inquire)
Cyanidin chloride	(Inquire)
Daidzein	(ST110)
Deoxyrhapontin	(Inquire)
Delphinidin chloride	(Inquire)
5,4'-Dihydroxyflavone	(Inquire)
5,7-Dihydroxyflavone	(Inquire)
7,4'-Dihydroxyflavone	(Inquire)
(+)-Epicatechin	(Inquire)
(-)-Epicatechin	(Inquire)
(-) Epigallocatechin	(Inquire)
(-)-Epigallocatechin Gallate	(FR109)
L-(+)-Ergothioneine	(FR111)
Fisetin	(Inquire)
Flavanone	(Inquire)
Flavone	(Inquire)
(-)-Galocatechin	(Inquire)
Genistein	(E1147)
Gossypetin	(Inquire)
HBED	(FR113)
Hinokitiol	(FR110)
6-Hydroxyapigenin (Scutellarein)	(Inquire)
4'-Hydroxyflavone	(Inquire)
5-Hydroxyflavone	(Inquire)
Isoliquiritigenin	(Inquire)
Kaempferol	(Inquire)
Luteolin	(Inquire)
MCI-186	(FR103)
Morin	(Inquire)
Myricetin (Cannabiscetin)	(Inquire)
Naringenin	(Inquire)
Pelargonidin chloride	(Inquire)
3,4,2',4',6'-Pentahydroxychalcone	(Inquire)
3,5,7,3',4'-Pentahydroxyflavone	(Inquire)
3,7,3',4',5'-Pentahydroxyflavone	(Inquire)
5,7,3',4',5'-Pentahydroxyflavone	(Inquire)
Piceatannol	(E1271)
Quercetin	(Inquire)
Resveratrol	(FR104)
Rhapontin	(Inquire)
cis-Stilbene	(Inquire)
trans-Stilbene	(Inquire)
3,6,2',3'-Tetrahydroxyflavone	(Inquire)
3,6,2',4'-Tetrahydroxyflavone	(Inquire)
3,6,3',4'-Tetrahydroxyflavone	(Inquire)
7,3',4',5'-Tetrahydroxyflavone	(Inquire)
7,8,3',4'-Tetrahydroxyflavone	(Inquire)
Trolox	(FR105)
U-83836E	(FR101)

Fluor-de-Lys Deacetylase Assay Kits & Components

Kits	Cat. #
Fluor-de-Lys Assay Kit	(AK500)
Fluor-de-Lys Cellular Assay Kit	(AK503)*
*Coming Soon	

Targeted Fluor-de-Lys Substrates	Cat. #
Fluor-de-Lys- SIRT1	(KI177)
Fluor-de-Lys-SIRT2	(KI179)
Fluor-de-Lys-H4-AcK16	(KI174)
Fluor-de-Lys-HDAC8	(KI178)
H3-4-9	(Inquire)
H3-9-14	(Inquire)
H3-9-14/pS	(Inquire)
H3-14-18	(Inquire)
H4-1-5	(Inquire)
H4-12-16/diAc	(Inquire)

HDAC / Sirtuin Enzymes Cat.

SIRT1 (human, recombinant)	(SE239)
SIRT2 (human, recombinant)	(SE251)
HDAC8 (human, recombinant)	(SE145)

Libraries

Libraries of polyphenolic compounds can be prepared for customers on a custom basis. Contact us for more information: 0800-2466651 or ts@biomol.de.

Other HDAC/Sirtuin Products Cat.

Fluor-de-Lys Substrate (ε-acetyl lysine)	(KI104)
Fluor-de-Lys Developer	(KI105)
Fluor-de-Lys Developer II	(KI176)
HeLa Cell Nuclear Extract	(KI140)
Fluor-de-Lys Deacetylated Standard	(KI142)
Trichostatin A	(GR309)
Anti-HDAC1	(SA401)
Anti-HDAC2	(SA402)
Anti-HDAC3	(SA403)
Anti-HDAC4	(SA404)
Color-de-Lys, Colorimetric Assay	(AK501)

Descriptions, sizes and prices are all available on our website:

<http://www.biomol.de/>. Inquiries can be made at 0800-2466651, +49-40-8532600, or <mailto:ts@biomol.de>.

FR104	Resveratrol	100 mg	76 €	500 mg	256 €
AK500	HDAC Fluorescent Activity Assay Kit for Drug Discovery	1 kit	400 €		
KI177	Fluor de Lys - SIRT1, Deacetylase Substrate	1 μmol	195 €		
SE239	SIRT1 (Sirtuin 1) (Human, recombinant)	100 U	400 €		
More relevant products: see page 3					