Reduced activity of the insulin/insulin-like growth factor signaling (IIS) pathway extends life-span in the worm, fly, and mouse and can also lower fecundity (1–3). How the evolutionarily conserved effects of IIS on these traits are mediated is not understood. IIS affects not only life-span and fecundity of the adult fruit fly Drosophila melanogaster, but also growth in the pre-adult period. We examined whether the adult phenotypes of altered IIS in Drosophila are a consequence of effects of lowered IIS in the adult or the pre-adult period, whether a downstream component of this pathway modulates life-span and fecundity, and whether altered signaling in a particular adult tissue can mediate these effects of altered IIS.

In the worm Caenorhabditis elegans, reducing function of the IIS receptor DAF-2 by RNA interference during development affects only adult fecundity, whereas reducing function during adulthood affects only life-span (2), suggesting that effects of IIS on fecundity and life-span are independent. A key target of IIS is a forkhead transcription factor, FOXO, that is inactivated by IIS in the worm, fly, and mouse (4). The worm ortholog, DAF-16, is necessary for life-span increase in response to mutations in IIS (5), and its overexpression extends life-span (6).

To investigate whether overexpression of the fly ortholog of DAF-16, dFOXO, during adulthood is sufficient to increase life-span and reduce fecundity, dFOXO was expressed in the adult fat body of long-lived Drosophila with overexpressed dFOXO in Adult Fat Body

Maria E. Giannakou,1 Martin Goss,1 Martin A. Jünger,2 Ernst Hafen,2 Sally J. Leeners,3 Linda Partridge1*

Fig. 1. Life-span and fecundity experiments. (A to C) Survival experiments on flies given either + RU486 (+dFOXO, solid circles) or –RU486 (–dFOXO, open circles) food. ([A] and [B]) Results of overexpression of an insert of dFOXO on chromosome 3 (replicates), showing survival of w51,106+/+;dFOXO/+ females. (A) Median life-span (m) and percent change between treatments: –RU486, m = 36; +RU486, m = 51; +41.6% change (P < 0.0001). (B) Median life-span and percent change between treatments: –RU486, m = 32; +RU486, m = 39; –21.8% change (P < 0.0001). (C) Results of overexpression of an independent insert of dFOXO on chromosome 2, showing survival of w51,106/dFOXO;+/+ females. Median life-span and percent change between treatments: –RU486, m = 25; +RU486, m = 36; +52% change (P < 0.0001). (D) Fecundity of w51,106+/+;dFOXO/+ females given + RU486 (hatched) and –RU486 (open) food. Mean and standard error bars are shown. *, P < 0.05; **, P < 0.0001.

References and Notes
8. The presence of RU486 has no effect on life-span (fig. S1), and the presence of the activated Geneswitch driver has no significant effect on life-span (10).
9. The presence of RU486 has no effect on fecundity (7, 10).
10. M. Giannakou et al., unpublished data.
12. Supported by a Wellcome Trust Functional Genomic Analysis of Aging Grant and by the Biotechnology and Biological Science Research Council.

Supporting Online Material
www.sciencemag.org/cgi/content/full/1098219/DC1
Materials and Methods
Fig S1
References and Notes
23 March 2004; accepted 12 May 2004
Published online 10 June 2004
10.1126/science.1098219
Include this information when citing this paper.

1Department of Biology, University College London, Darwin Building, Gower Street, London WC1E 6BT, UK.2Zoologisches Institut, Universität Zürich, Winterthurerstrasse 190, CH-8057, Zürich, Switzerland.3Growth Regulation Laboratory, Cancer Research UK, London Research Institute, Post Office Box 123, 44 Lincoln’s Inn Fields, London WC2A 3PX, UK.

*To whom correspondence should be addressed. E-mail: LPartridge@ucl.ac.uk