Faculty of Biology · Paper of the Month

June 2014

Awarded to Graduate Student Daria Krutauz

For first authorship of "Extended ubiquitin species are protein-based DUB inhibitors" by **Daria Krutauz**, Noa Reis, Mark A Nakasone, Peter Siman, Daoning Zhang, Donald S Kirkpatrick, Steven P Gygi, Ashraf Brik, David Fushman & Michael H Glickman accepted in June 2014 for publication in July issue of NCHEMBIO 2014

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Extended ubiquitin species are protein-based DUB inhibitors

Daria Krutauz[1], Noa Reis[1], Mark A Nakasone[1,2], Peter Siman[3], Daoning Zhang[2], Donald S Kirkpatrick[4], Steven P Gygi[4], Ashraf Brik[3], David Fushman[2] & Michael H Glickman[1]*

A frameshift mutation in the transcript of the ubiquitin-B gene leads to a C-terminally extended ubiquitin (Ub), UBB+1. UBB+1 has been considered to inhibit proteasomes and as such to be the underlying cause for toxic protein buildup correlated with certain neuropathological conditions. We demonstrate that expression of extended Ub variants leads to accumulation of heterogeneously linked polyubiquitin conjugates, indicating a pervasive effect on Ub-dependent turnover. 20S proteasomes selectively proteolyzed Ub extensions, yet no evidence for inhibition of 26S holoenzymes was found. However, among susceptible targets for inhibition was Ubp6, the primary enzyme responsible for disassembly of Lys48 linkages at 26S proteasomes. Processing of Lys48 and Lys63 linkages by other deubiquitinating enzymes (DUBs) was also inhibited. Disruption of Ub-dependent degradation by extended Ub variants may therefore be attributed to their inhibitory effect on select DUBs, thus shifting research efforts related to protein accumulation in neurodegenerative processes from proteasomes to DUBs.

TUESDAY, JULY 15, 2014 • THE JERUSALEM POST

Technion 'breakthrough' opens avenues for Alzheimer's cure

• By JUDY SIEGEL

A vital mechanism that causes the accumulation of protein plaques in the brain has been discovered by scientists at Haifa's Technion-Israel Institute of Technology and may eventually lead to a cure for the fatal dementia.

The team, who called the work a "breakthrough," published the findings on Monday in the online edition of *Nature Chemical Biology*.

Dementias affect an esti-

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