mTOR: Alzheimer's disease prevention for APOE4 carriers

$L /LQJ /LQ ' $OODQ %XWWHU¿HOG DQG $UODQ 5LFKDUGVRQ

Alzheimer's disease (AD) is the most common form of dementia and the 6th leading cause of death in the US. ,QKHULWDQFH RI WKH $SROLSRSURW... VWURQJHVW JHQHWLF ULVN IDFWRU IRU... FDUULHUV DFFXPXODWH EHWD DP\ORLG... tau tangles earlier and with more extensive pathology compared to non-carriers. However, decades before the DJJUHJDWLRQ RI $ DQG WDX FR... FDUULHUV KDYH GHYHORSHG QHXUR... UHGXFHG FHUHEUDO EORRG ÀRZ... EUDLQ EDUULHU %%% LQWHJULW\... WKDW EUDLQ SK\VLRORJ\ LV DOWHUHG... EHIRUH FOLQLFDO PDUNHUV VXFK... PHPRU\ GH¿FLWV DSSHDU VXJJHVWLQJ... SUHGLVSRVH $32(FDUULHUV WR G... HDUO\ LQWHUYHQWLRQV WKDW FDQ... to normal could be critical in potentially preventing the development of AD-related neuropathology and cognitive impairment. In a recent study, using magnetic resonance imaging (MRI), Lin et al. reported that young, DV\PSWRPDWLF $32(WDUJHWHG U... ZLWK UDSDP\FLQ KDG UHVWRUHG... WR WKH OHYHO RI ZLOG W\SH FR... vasculature was associated with amelioration of incipient OHDUQLQJ GH¿FLWV RI WKH $32(... VLJQL¿FDQFH RI WKLV GLVFRYHU\... pharmacologically reversible and AD potentially could be SUHYHQWHG LQ DV\PSWRPDWLF $32(...

5DSDP\FLQ LV D GUXJ DSSURYHG... $GPLQLVWUDWLRQ)'$,W KDV EHHQ... settings and was originally used as an immunosuppressive agent to prevent rejection of organs in transplant patients. %\ +HLWPDQ DQG FR ZRUNHUV... 7DUJHW RI 5DSDP\FLQ 725 > @ ,Q... LV VSHFL¿HG DV PDPPDOLDQ 725... the serine/threonine kinase that is the regulatory nexus in the response of eukaryote cells to nutrients, growth IDFWRUV DQG FHOOXODU HQHUJ\ VWDWXV 5DSDP\FLQ LV D P725 LQKLELWRU $ PDMRU EUHDNWKURXJK RFFXUUHG LQ ZKHQ LW ZDV VKRZQ WKDW UDSDP\FLQ ZKLFK UHGXFHG P725 signaling, increased the lifespan of mice (see review in > @ ,Q DGGLWLRQ UDSDP\FLQ KDV EHHQ VKRZQ WR UHGXFH a variety of cancers in mice as well as atherosclerosis in mouse models fed high fat diets as well as improve LPPXQLW\ LQ HOGHUO\ KXPDQV > @ $V UHJDUG WR WKH KXPDQ central nervous system, several studies have shown that LQKLELWLRQ RI P725 E\ UDSDP\FLQ WUHDWPHQW LPSURYHV cognition, slows brain aging, and impedes the progress of

neurodegenerative disorders through pathways associated with autophagy, glucose metabolism and mitochondrial ...

In Lin et al. ... WKDW P7... reduced ... WKDW RWKHUZLVH LPSDLU %%% LQ... WUDQVJHQLF PLFH > @ /RVV RI %%%... one of the initiating events that lead to AD-like ... %%% DQG LPSDLUV %%% ... > @ ... memory ... reported ... oxide synthase and causes the release of nitric oxide, a ... in mice. ... found ... WKDW UDSDP\FLQ UHVWRUHG WKHLU ... ZKLFK ZHUH DVVRFLDWHG ZLWK UHGX... and cerebral amyloid angiopathy, and improved memory > @ &ROOHFWLYHO\ WKHVH ¿QGLQJ... alters neurovascular functions through multiple potential ... LQKLELWLRQ PLJKW EH DQ HuHFWLYH... brain vascular functions and consequently slow or prevent the progress of AD development.

,Q FRQFOXVLRQ P725 LQKLELWLR... to increase lifespan and healthspan in various species. Rapamycin (or its derivatives, rapalogues) has been ... humans, and these compounds have been given to cancer patients for relatively long periods of time with little change in the quality of life. Lin et al. further demonstrated that rapamycin restores and preserves neurovascular ... results may provide the basis for future AD prevention WULDOV LQ KXPDQ $32(FDUULHUV.

Ai-Ling Lin: ... ZKHQ

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REFERENCES

%HOO 5' HW DO 1DWXUH
/LQ $/ HW DO - &HUHE %ORRG)ORZ 0HWDE 3XE0HG

+HLWPDQ - HW DO 6FLHQFH
5LFKDUGVR(QS$*HHUWRQ DQG0RO
%ODJRVNORQQ\ 09 2QFRWDUJHW GRL
RQFRWDUJHW
3HUOXLJL 0 HW DO 1HXURELRORJ\ RI 'LVHDVH
/LQ $/ HW&HDUHE %ORRG)ORZ 0HWDE