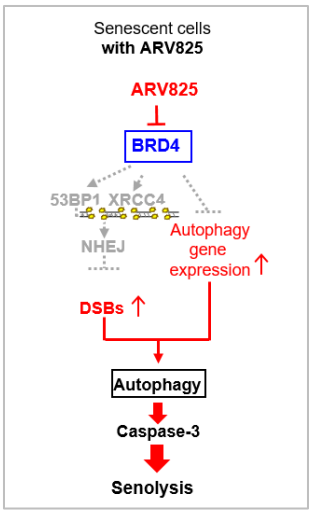
A BET family protein degrader provokes senolysis by targeting NHEJ and autophagy in senescent cells

Although cellular senescence acts primarily as a tumour suppression mechanism, the accumulation of senescent cells in vivo eventually exerts deleterious side effects through inflammatory/tumour-promoting factor secretion. Thus, the development of new drugs that cause the specific elimination of senescent cells, termed senolysis, is anticipated. Here, by an unbiased high-throughput screening of chemical compounds and a bio-functional analysis, Eiji Hara (Aging Biology, IFReC/RIMD, Osaka University) identify BET family protein degrader (BETd) as a promising senolytic drug. BETd provokes senolysis through two independent but integrated pathways: (i) attenuation of non-homologous end joining (NHEJ), and (ii) up-regulation of autophagic gene expression. Notably, BETd treatment eliminates senescent hepatic stellate cells in obese mouse livers, accompanied by the reduction of liver cancer development. Furthermore, the elimination of chemotherapy-induced senescent cells by BETd substantially increases the efficacy of chemotherapy against xenograft tumors in immunocompromised mice. These results reveal the vulnerability of senescent cells and open up the possibilities for its control.



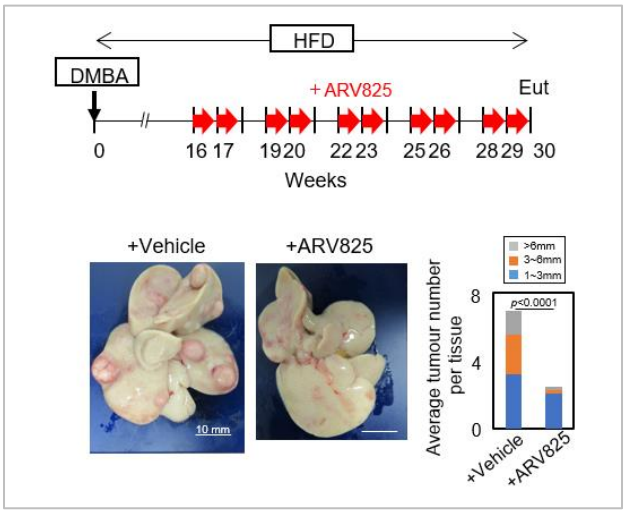


Fig.1 ARV825 induces apoptosis in senescent cells. **Fig.2 ARV825 prevents obesity-induced liver cancer**

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Authors: Masahiro Wakita, Akiko Takahashi, Osamu Sano, Tze Mun Loo, Yoshinori Imai, Megumi Narukawa, Hidehisa Iwata, Tatsuyuki Matsudaira, Shimpei Kawamoto, Naoko Ohtani, Tamotsu Yoshimori, & Eiji Hara