Presented at the American Association for Cancer Research's Pancreatic Cancer: Progress and Challenges conference, Lake Tahoe, NV, June 18-21. A diet high in fats and calories leads to obesity and metabolic disturbances and accelerates pancreatic cancer development in the conditional KrasG12D mouse model. Aune Moro, Aurelia Lugea, David Dawson, Steven Pandol, Anna Gukovskaya, Enrique Rozengurt, Vay-Liang Go, Guido Eibl. David Geffen School of Medicine at UCLA, Los Angeles, CA.

*Introduction:* There is strong epidemiologic evidence that obesity increases the risk of several human cancers, including pancreatic cancer. Several mechanisms, including inflammation and insulin resistance with hyperinsulinemia, are proposed, by which obesity may promote tumor development. However, the driving mechanisms in pancreatic cancer are still poorly understood.

*Aim:* Our aim was to investigate whether a diet high in fats and calories leads to obesity with metabolic disturbances similar to humans and promotes pancreatic cancer development in the conditional Kras<sup>G12D</sup> mouse model of pancreatic cancer.

*Methods and Results:* Offspring of Pdx-1-Cre and LSL-Kras<sup>G12D</sup> mice were randomly allocated to either a diet high in fats and calories (HFCD; ~4,535 kcal/kg; 40% of calories from fats) or control diet (CD; ~3,725 kcal/kg; 12% of calories from fats) for 3 months. Compared to control animals, mice fed the HFCD significantly gained more weight (16.9±2.1g vs. 7.1±3.1g; p<0.05) and developed hyperinsulinemia (501±311pM vs. 223±123pM; p=0.047), hyperglycemia (305±58mg/dl vs. 235±71mg/dl; p=0.034), hyperleptinemia (1375±276pM vs. 515±243pM; p<0.001), and elevated levels of IGF-1 (8.4±6.5ng/ml vs. 3.1±1.2ng/ml; p=0.048). The pancreas of HFCD-fed animals showed robust signs of inflammation with increased numbers of F4/80 positive macrophages, strong COX-2 expression, and increased desmoplastic reaction. Importantly, compared to CD-fed animals, the number of advanced murine PanIN lesions was significantly increased in HFCD-fed mice (p<0.05). The distribution of pancreatic ducts in HFCD-fed mice was: 5% normal, 20% PanIN-1, 50% PanIN-2, and 25% PanIN-3 (compared to 31%, 57%, 11%, and 1% in CD-fed mice, respectively). We did not observe any differences between female in male mice in regard to weight gain, metabolic disturbances, and PanIN lesions.

*Conclusion:* Our results demonstrate that a diet high in fats and calories leads to obesity and metabolic disturbances similar to the human condition, greatly enhances pancreatic inflammation, and strongly accelerates pancreatic cancer development in the conditional Kras<sup>G12D</sup> mouse model. This model and findings will provide the basis for more robust studies attempting to unravel the mechanisms underlying the cancer-promoting properties of obesity.