1135-92-2257 **Aleesa Monaco*** (aleemonaco@gmail.com), **John D. Nagy** (jdnagy@asu.edu) and **Kalle Parvinen** (kalparvi@utu.fi). *Coevolving cancer hallmarks: The angiogenic switch is modulated by clonal selection on proliferation.*

Angiogenesis and dysregulated tissue homeostasis are thought to arise by clonal selection. However, natural selection's role in generating the angiogenic switch is not well understood. Here we show that the angiogenic switch is likely to evolve by early positive selection on angiogenic ability which eventually becomes reversed to negative selection in older tumors. Importantly, this reversal is driven by directional selection on proliferation ability. In our model, competing clones vary their ATP allocation to proliferation, angiogenic signaling, and cell maintenance in a realistic way. Adaptive dynamics analysis of this coevolutionary dynamic predicts that as selection drives proliferation towards its ESS, the once-favored angiogenic clones become susceptible to "free-rider" mutants, which reallocate metabolic energy from angiogenesis production to proliferation. These free-rider clones have an evolutionary advantage over their angiogenic counterparts. The ultimate result is predicted to be necrosis by vascular hypoplasia. However, an analogous stochastic model shows that these deterministic endpoints are rarely realized. Tumors often reach lethal size before selection on angiogenesis has much impact. (Received September 25, 2017)