**p53: The Guardian of the Genome Morphs into the Guardian of the Cancer Cell**

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Among the myriad of molecular alterations associated with cancer, loss of the normal tumor suppressive functions of p53, the “guardian of the genome,” is the most consistent. Indeed, *TP53* mutations result in the expression of mutant p53 proteins that become highly oncogenic: *the guardian of the genome morphs into the guardian of the cancer cell*. Gain of function p53 proteins not only lose the wild type p53 pro-apoptotic and DNA repair functions, but gain novel oncogenic functions. We have shown that these gain of function mutant p53 oncoproteins significantly enhance angiogenesis, inhibit T-cell tumor recognition and permit the over-expression of oncogenes such as Myc. Based upon preclinical data and with in-depth analyses of clinical studies including GOG 86P, NRG GY018 and RUBY, mutant p53 has been confirmed as a marker for sensitivity to bevacizumab (anti-VEGFA), pembrolizumab (anti-PD-L1) and dostarlimab (anti-PD-1) with significant improvements in both PFS and OS when added to chemotherapy compared to chemotherapy alone in advanced endometrial cancers. These data are the basis for the newly approved study, NRG GY035, which will commence in the coming months, designed as a three-arm trial comparing chemotherapy + bevacizumab versus chemotherapy + pembrolizumab versus chemotherapy +bevacizumab + pembrolizumab. Yet we hypothesize that directly targeting missense mutant p53 instead of downstream pathways has substantial advantages, and targeting oncogenic, mutant p53 proteins has long been a therapeutic goal. In new studies, we are developing a suite of p53 reactivator analogues of curcumin and have shown that these agents bind to mutant p53 (among other targets such as STAT3) and reinstate the wild type p53 transcriptome. Reactivators including APR-246, HO-3867 and AKT-100 are highly effective in preclinical models and are synergistic with chemotherapy and with PARP inhibitors. The novel curcumin analogue, AKT-100, is particularly effective and is a focus of our current work. Thus, along with new clinical trials combining approved agents with chemotherapy for p53 mutant gynecologic cancers, p53 reactivators under development hold promise as novel therapeutic agents to directly target missense mutant, gain of oncogenic function p53, that has morphed into the guardian of the cancer cell.