Project Title: Structure function analyses of p53 cancer mutants with corrector drug leads
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Cancer can only develop when growth promoting pathways in normal cells become overactive (e.g. oncogene expression), and when the cells own protection against uncontrolled cell proliferation becomes inactivated. The latter is mediated by tumor suppressor proteins, which prevent normal cells from becoming tumor cells. Most notably is the tumor suppressor protein p53, which is thought to be inactivated or bypassed in all tumors. Tumors depend on keeping p53 inactive, because reintroduction of active p53 in animal models by genetic tricks leads to tumor cell death and rapid tumor regression. Restoring p53 activity in human cancer could lead to the development of radically different personalized cancer therapeutics with potentially dramatic effects on cancer survival rates. Indeed, such therapeutics that restore the body's own defense against cancer, namely the tumor suppressor p53, may be feasible goals for many recurring cancers. We discovered several small, drug-like molecules that help the mutated p53 protein to regain its active 3-dimensional conformation. When added to cancer cells, these small molecules restore p53 activity and induce cancer cell death. Similarly, tumor development is completely halted by administration of our compounds to animal cancer models. Thus, these molecules can serve as drug leads for a novel class of "p53 reactivation" therapeutics. In order to progress these compounds to patients, these lead molecules need to be improved. To this end we are proposing to determine how these compounds bind to mutant p53 at the atomic level using X-ray crystallography. These studies will be essential for drug development, because they will reveal what parts of the compound can be chemically modified to further improve activity and optimize pharmacological behavior such as stability in plasma and distribution to tumor cells.
Success of this proposal will form the basis for the development of cancer drugs that restore the body's own protective mechanism against cancer, namely the tumor suppressor p53.