Discovery of DNMDP

Figure 1. Viability assay results against mutant and wild-type p53 cancer cell lines identifies DNMDP as a selective hit

Figure 2. a) DNMDP is potent and selective hit, killing 26 out of 766 cancer cell lines with nM potency
b) Enantiospecific cell killing

Figure 3. DNMDP is a selective hit without kinase activity

DNMDP is a PDE3 inhibitor, but most PDE3 inhibitors do not kill cancer cells

Figure 4. No correlation between PDE3 inhibition and HeLa cell viability

Figure 5. HeLa cells rescued from DNMDP analog-induced death by non-toxic PDE3 inhibitor

PDE3A Binds to SLFN12 with DNMDP

Figure 6. Proteomic analysis of PDE3A antibody pulldown identifies SLFN12 binding to PDE3A in presence of DNMDP but not non-toxic trequinsin

Figure 7. High PDE3A and SLFN12 expression predicts DNMDP sensitivity, with 50% prediction accuracy

SAR

Figure 8. SAR about DNMDP analogs

Figure 9. Representative EC50 of DNMDP analogs (HeLa) NA = not active

Figure 10. Western blotting demonstrates PDE3A/SLFN12 binding increases with more active compounds

DNMDP Analogs are active in vivo

Figure 11. High dose treatment in HeLa xenograft shows drastic tumor shrinkage

Figure 12. Low dose treatment in HeLa xenograft shows dose dependent anti-tumor effect

Conclusion

Differential viability assays discovered a small molecule, DNMDP, which potently killed mutant p53 cancer cells but not wild type p53 cancer cells. DNMDP is a selective PDE3 inhibitor and genetic profiling of sensitive and non-sensitive cells (data not shown) indicated PDE3A as the sole molecular target. However, most known PDE3 inhibitors were not effective and actually rescued cells from DNMDP-induced death.

Proteomic experiments showed that a protein of unknown function, SLFN12, binds to PDE3A in the presence of DNMDP inducing cell death. Chemical optimization produced low molecular weight, highly soluble and very potent compounds which were active in xenograft models at low doses.