Targeted Inhibition of BRD-NUT Oncoproteins

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We propose to develop a new drug to improve treatment of an incurable cancer, NUT midline carcinoma (NMC). NMC affects people of all ages with nearly zero survival. NMC is defined by mutation of the NUT gene, which is abnormally fused to a gene called BRD4 in most cases, forming a chimeric BRD4-NUT fusion gene that is the cause of this lethal entity. Despite its rarity, NMC has sparked great interest because it was in this cancer that a new class of anti-cancer therapy was discovered that target the BRD4 aspect of the BRD4-NUT gene. While this new class of drug effectively inhibits NMC tumor growth, it also inhibits normal BRD4 function, which is required for the health and maintenance of normal cells; thus, the BRD4 inhibitors are toxic at therapeutic doses. Moreover, resistance to BRD4 inhibitors has already been seen in both NMC and other cancers. Thus, new drugs to inhibit only the BRD4-NUT cancer protein are needed to more effectively treat this disease while minimizing toxicity. Here, we propose to inhibit the NUT protein, which is only expressed in NMC and in human testes, thus minimizing toxicity. We have found that inhibition of the binding of the NUT protein to another protein completely inhibits the function of the BRD4-NUT protein and the growth of NMC cells. Here, we propose to use the AlphaScreen to identify small molecules that inhibit the interaction of NUT with this other protein, which will then be developed into drugs to treat NMC patients.