Identifying Small Molecule Inhibitors of Programmed Cell Death 1 for Cancer Immunotherapy Using Pharmacophore-Based Virtual Screening

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Immunotherapy activates the body's immune response against cancers by inhibiting interactions between cancer cells and T-cells (cells that fight against foreign substances or in this case, cancer). On the surface of T-cells lie immune checkpoint proteins, such as programmed cell death 1 (PD-1), that bind with proteins found on other cells, whose interaction signals to the T-cells whether or not to attack. Cancer bypasses this system by presenting proteins, like programmed cell death ligand 2 (PD-L2), that do not elicit an immune response and may even harm the T-cells. Small molecule drugs can be used to inhibit such PD-1/PD-L2 interactions and increase immune response against cancer. Small molecule treatments are advantageous in that they have better oral bioavailability, lower costs, better tissue penetration, and a shorter half-life than other treatment options. This project identifies such small molecules that bind to programmed cell death 1 (PD-1) to inhibit PD-1/PD-L2 interactions specifically. First, computational methods were used to determine the existence of PD-1 binding pockets based on geometric and energy-based requirements, then to identify compatible small molecules with pharmacophore screening using the ZINC database (containing over 21 million small molecules). The successful small molecules were screened with simulated docking based on docking energy and finally screened once more to determine each compound's druglikeness based on Lipinski's rules. 16 eligible compounds were identified, including one in particular with an especially promising result. With further physical screening, these molecules may be eligible for future use in patients. This new treatment option will diversify optimal patient experience and could lead to lower cancer mortality.