NEW DRUGS FOR PANCREATIC CANCER

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Pancreatic ductal adenocarcinomas (PDAC), is a highly aggressive and lethal cancer, which has only a 5-year chance of survival. This type of cancer tends to be resistant to normal therapies, and thus makes a crucial area for drug design. PDAC grows and spreads around the body with incredible speed, giving patients with little hope of survival. Research indicates that these cancers create and pump out large amounts of a small protein called S100P, and this has been linked to the aggressive progression of disease.

Our team of computational and synthetic chemists developed a bank of 93 new compounds based on the known asthma drug Cromolyn. These computer generated synthetic compounds would in theory have the ability to block S100P from binding to its target on the cell surface, a receptor known as RAGE. The aim of the project was to find out which of the 93 compounds have the optimal structure to prevent S100P from binding RAGE, and therefore stop the progression of the cancer.

Using molecular biology techniques, involving making the human S100P protein in bacteria, purifying this protein and then measuring whether the new compounds prevents S100P binding to RAGE. In order to make sure that the results were reliable, each drug was tested a total of 9 times at 4 different concentrations (10μM-10nM), and from this assay 18 compounds were identified that could be further investigated. These candidate drugs were then screened to check and see how toxic these drugs are. These assays indicated that the compounds weren't killing the pancreatic cells even over long periods of time (up to a week). However, further experiments were conducted to measure how the 18 lead compounds could change the way in which pancreatic cells migrate. For this, human pancreatic cancer cells (BxPC-3) and human pancreatic cancerous cells (non- S100P expressing) Panc-1 cells were grown in 3-D matrix which allows them to grow through and migrate to the other side. This represents the way in which cells would migrate and proliferate in a human organs. After 48 hours of exposure to each of the 18 drugs, 13 of the compounds prevented the cancerous BxPC-3 cells from migrating, but not the human Panc-1cells.

These 13 drugs will next be tested to see if they can prevent the formation of new blood vessels in chicken egg membranes. As cancers grow they require a greater blood supply, and so any drug that prevents this development will help to slow the growth and lethality of the disease.

The newly synthesised drugs provide us with a greater insight into how we can tackle this pernicious and devastating disease. From these structure of these compounds, we will better understand how to prevent the rapid migration of the pancreatic cancer, and direct the chemists to further develop the drugs so that they will be safely given to man within the next few years. Evidence from other laboratories indicate that when you prevent the S100P from increasing proliferation and migration of cells, we can also make the cancers more prone to normal therapies such as chemotherapy. There are several other types of cancer that are also driven by S100P, and any resulting drug would therefore have the potential to stop the progression of some types of lung and breast cancers. The results so far indicate that we have the potential to have created a new therapy for pancreatic cancer that will be non-toxic to cells, prevent migration and thus make pancreatic cancer a treatable disease.