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Biological testing of novel telomerase inhibitors

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As of 2011, cancer was the leading cause of death in the United States, second only to heart disease. As cancer continues to become an ever-increasing threat to human health, the race is on to find an effective telomerase inhibitor. This inhibitor has to be functional enough to render the cancer cell unable to divide, while leaving the surrounding healthy cells relatively untouched. Research has established that the molecular structure of a compound known as BIBR 1532 has proven to be an effective telomerase inhibitor. Cancer is often referred to as being “immortal” because of its ability to divide an infinite amount of times. Normal cells are limited in the number of times they can divide by the caps on the ends of their chromosomes, called telomeres. These caps become degraded over time, signaling the cell to die when they become too short. An enzyme known as telomerase lengthens the ends of telomeres in cancer cells, granting them immortality. Current research has shown that BIBR 1532 inhibits telomerase by preventing it from extending the copied strand any further than the length of the original strand of DNA. If telomerase is inhibited, the telomeres of cancer cells can no longer be elongated. Stripped of their immortality, the telomeres of cancer cells will become degraded and die. Research has not yet discovered what portion of BIBR 1532 causes it to be such a good telomerase inhibitor. Research has shown that there are three substructures that must be present in order for it to act as a telomerase inhibitor: an aromatic ring containing a carboxylic acid and a conjugated amine group.

During the summer of 2013, three novel compounds were made via synthesis of cinnamoyl chloride derivatives. These three compounds all contain active sites that are identical to those identified on BIBR 1532, with one key difference in the element attached to the aromatic ring. The compounds were purified and then tested against PC3 prostate cancer cell lines. Prostate, breast, and pancreatic cancers all have relatively high levels of telomerase activity, which is a primary reason why prostate cancer was chosen as a target cell line. The compounds were tested at three different concentrations: 50uM, 75uM, 100uM. Drug assay were performed in order to determine at which concentration the compounds showed significant anti-cancer activity, while leaving behind enough cancer cells to harvest telomerase and test for telomerase inhibition. After performing the assays, it was determined that the ideal concentration of the compounds was 75uM. All three compounds were shown to be more effective than BIBR 1532 at this concentration. The next step will be to test for telomerase inhibition using the TRAPEze assay. If these compounds prove to be telomerase inhibitors, it would be a breakthrough as to how BIBR 1532 functions and could potentially lead to a more effective cancer treatment. While the compounds were tested using metastatic prostate cancer cells, these potential treatments have applications in both breast and pancreatic cancers as well.

*This scholar and faculty mentor have requested that only an abstract be published.