Design Brief

Telotargeter: A biosensor-based approach for detecting telomerase overproduction in cancer cells using an oligonucleotide sequence*

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Pancreatic cancer is one of the deadliest cancers, primarily due to the lack of effective tools for early detection. A major sign of pancreatic cancer is an excessive amount of telomerase, an enzyme that lengthens a cell's telomeres, enabling the cancer to replicate uncontrollably. To create an easy and accessible detection method, we are designing a synthetic biology system, here called 'Telotargeter',that can sense telomerase activity. This experiment will demonstrate that synthetic telomeres grow longer when telomerase is present, and the amount of growth is proportional to the concentration of telomerase present. We believe this system can show how telomerase activity is linked to pancreatic cancer and may help develop effective ways to detect it early. Since we can't use mammalian cells or their lysed contents in our lab, we will test the Telotargeter system using purified telomerase enzymes instead. We will use synthetic DNA strands with exposed 3' ends that are similar to real telomeres. These DNA strands will be mixed with different amounts of telomerase and free nucleotides to see how the system works. We will check if the DNA strands are getting longer using gel electrophoresis. By using synthetic biology and simple lab tools, our project hopes to create a low-cost and easy way to detect high telomerase activity, which could help catch pancreatic cancer earlier.

Keywords: Synthetic biology, biosensor, telomerase, pancreatic cancer, GFP, *Escherichia. coli*, *Caenorhabditis elegans*, *TERT*

Pancreatic cancer remains one of the deadliest forms of cancer worldwide, with a reported five-year survival rate of approximately 13% (American Cancer Society, 2024). This is mainly because pancreatic cancer is hard to detect early. By the time symptoms appear, it is often too late for effective treatment (Kleeff et al., 2016). In areas with limited medical resources, the five-year survival rate for pancreatic cancer is even lower. The need for affordable early detection tools for pancreatic cancer is urgent. Current methods like imaging scans (CT, MRI) and biomarker tests (such as CA 19-9) are often too expensive or invasive. Creating new, low-cost ways to detect pancreatic cancer, especially ones that can be used in places with fewer resources, is very important for saving lives. Telomerase, an enzyme that maintains the ends of

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chromosomes called telomeres, is a promising target for early cancer detection. In normal body cells, telomerase activity is greatly reduced to prevent uncontrolled growth. Each time a cell divides, its telomeres get shorter, and when they become too short, reaching what's called the Hayflick limit, the cell stops dividing or dies (Blackburn et al., 2015). Cancer cells avoid this by turning telomerase back on through the *TERT* gene, allowing them to keep their telomeres long and divide without limits.

Studies have shown that detecting telomerase activity is a very accurate way to catch cancer early. In pancreatic cancer, where other tests often fail, checking for telomerase looks especially promising. However, current tests for measuring telomerase, like the TRAP assay, are complicated, take a lot of time, and need special lab equipment (Kim et al., 2021).

To solve these challenges, our team created a biosensor using synthetic biology that can quickly and cheaply detect high levels of telomerase with little need for special equipment. In addition, executing this method may give us new information about the statistical relationship (correlation) between telomerase activity and telomere length, as highlighted in our experiment.

Our biosensor works by detecting the high activity of the *TERT* gene, which is common in cancer cells. We designed a system that reacts to increased telomerase levels and produces a visible signal, like a glow or color change, to show when cancer may be present. This innovation helps make cancer detection easier and more accessible, improving the chances of early treatment and survival. By targeting the key biological change behind pancreatic cancer—telomerase reactivation—our biosensor could make early detection easier, improve access to testing, and help save lives.

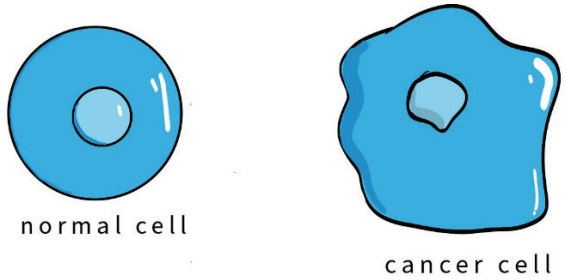

Figure 1. Shows the difference between a normal cell and a cancer cell.

Systems level

The objective of this experiment is to prove that A) our synthetic telomeres will lengthen in the presence of telomerase and B) the length of the synthetic telomeres after exposure is proportional to the concentration of telomerase it was exposed to. If this is true, our system woudl be able to accurately detect elevated telomerase in pancreatic cancer cells.

Due to our inability to use the cells we need (due to our lack of technology and lab restrictions), we will test the Telotargeter using pure telomerase. We plan to expose our synthetic DNA strands to varying concentrations of pure telomerase to see how much the DNA strands lengthen. Because we do not know the extent to which telomerase affects growth, the concentrations will vary greatly.

Device level

Telomere code (For Procedure A)

[5'-TTAGGG-TTAGGG-TTAGGG-3']
[3'-AATCCC-AATCCC-AATCCC-5']

Procedure A

1.1 Prepare 10 tubes with varying amounts of telomerase (0, 0.1, 0.5, 1, 2, 5, 10, 15, 30, 50)
1.2 Add synthetic telomeres (exposed 3' end) into each tube as well as free nucleotides
1.3 Incubate at 37°C for 60 min (or measure at 10 min, 30 min, and 60 min)
1.4 Heat at 95°C for 5 min to denature proteins and stop the reaction
2.1 Pre-run 8% agarose gel in X buffer at Y volts for 30 min2.2 Load each sample alongside a DNA ladder
2.3 Run until the dye is near the bottom
2.3 Visualize the result using what method? What do you expect to see?

Parts level

Our materials include: free nucleotides (dNTPs), a Tris-HCL buffer, purified telomerase enzyme, oligonucleotide sequence, electrophoresis components such as an 8% agarose gel, 1x TBE Buffer, DNA Ladder, loading dye, and DNA strain.

Safety

Our proposed system will be conducted in a high school BSL-1 lab under the supervision of our mentor. We will…

- Wear proper lab gear/PPE (tie back hair, close-toed shoes, no open skin, etc.)
- Ensure experiments are conducted properly with no disturbances or improper lab behavior
- Double-check that we're using proper quantities and measurements for the experiment
- Keep samples isolated and in proper conditions so we don't risk contamination or environmental release in the lab.

Discussion

While the experiment has not yet been conducted, previous studies indicate that telomerase activity is linked to approximately 95% of all cases of pancreatic cancer (Zisuh et al. 2012). The purpose of this study was to see if there was a frugal method of diagnosing pancreatic cancer earlier using telomerase targeting for it to be employed in underprivileged areas. To do this, our team designed an experiment that will take different sequences of isolated DNA with different lengths of telomerase, nucleotides, and polymerase protein to design a PCR and gel electrophoresis setup that could indicate how much polymerase activity there was depending on the amounts of telomeres on the isolated DNA sequences. This could be used to create a comparative analysis on how much telomerase would have to be active to deem a sequence as pancreatic cancer. We hypothesized that the more telomeres there would be, the more active telomerase would be, indicating that after a certain point, comparable to Hayflick's limit, the individual would have pancreatic cancer.

While this experiment does leave out other major human processes in *in vivo* settings that also tie into a full pancreatic cancer diagnosis, isolating telomerase activity specifically gives better insight into its pathways and to what extent it affects an overall pancreatic cancer diagnosis. It also provides the scientific community with insights into how much they should be focusing on solely telomerase-based targeting over other combinations of factors. Also, while this study specifically focuses on the gene *TERT*, which indicates the activation of the telomerase synthesis pathway and doesn't provide complete comprehension as to what other significant genes affect telomerase's involvement in pancreatic cancer, it is a good start for further research to expand on this study's future integrations into genomic studies related to telomerase's impacts in pancreatic cancer.

Next steps

At its current state, our project's experiment utilizes pure telomerase enzymes, which are useful for proving our biosensor works as predicted. In the future, testing the sensor with lysed cell contents to simulate a cell environment more closely would be ideal. The experiments would show how Telotargeter interacts and responds to miscellaneous cell contents, and how the results would look in a non-lab environment.

Author contributions

O.A. contributed to the Abstract and the References. S.S. contributed to the Keywords and Next Steps, and, along with O.A., contributed to the Background. C.J. and E.K. contributed to the Device Level section. M.M. and S.A. contributed to the Parts Level section. P.G., M.M. and S.V. contributed to the Safety section. S.V., S.A and P.G. contributed to the Discussion section. E.H. created the graphics and J.M. and M.M. worked on the Experiment. J.M. presented in the video. S.S. and E.K. contributed to the Next Steps section. All authors contributed to

the development of the Telotargeter system through their research on the *TERT* gene, telomerase enzymes, synthetic telomere DNA sequences, and DNA detection methods such as gel electrophoresis, all of which made this design possible.

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