Question 1

Biological robustness is the ability of a biological system to retain its functions regardless of intrinsic and extrinsic disruptions like mutations. Robustness enables biological systems to adapt by allowing flexibility in changes of the system's structure and components in response to perturbations while still preserving specific functions. Unexpected mutations render biological networks fragile, making them susceptible to disruption.

An example of biological robustness would be the highly regulated cell division cycle in eukaryotic cells. There are two stages in eukaryotic cell division, interphase and mitosis (M) phase. Interphase comprises of synthesis (S) phase where DNA is replicated, and gap (G) phases, G1 and G2 which comes before S phase and after S phase, prior to M phase respectively. G1 and G2 are critical stages in regulation of the cell cycle as they serve as checkpoints which are vital in maintaining the integrity of the process. These checkpoints determine the progression or termination of the cycle. At G1, cells are either set to commit to cell cycle and proceed to S phase, remain in G1 or exit the cell cycle and become non-proliferating cells. Similarly at G2, cells are set to either proceed on to M phase, where mitosis and cytokinesis takes place, or halted.

Cyclin-dependent kinase (CDK) activity plays a predominant role in cell cycle regulation. CDK are activated by distinct cyclins that are accumulated throughout the various stages of the cell cycle. Activated CDKs phosphorylates transcription factors that promotes cell cycle-regulated transcription, driving the progression of the cell cycle.

In this essay, I will focus on the entry into S phase from G1. CDK activity during G1 phase is crucial for initiating DNA replication and committing to the cell cycle. The E2F-dependent transcriptional network comprises several genes responsible for controlling cell cycle, DNA replication, genome protection, and growth. It is stimulated by mitogens and growth signals that increases CDK activity. During the G1 phase, RB inhibits E2F-dependent transcription. CDK-dependent phosphorylation inactivates RB, resulting in E2F-dependent transcription and S phase cyclins expression. This. further boosts CDK activity, leading to more RB phosphorylation and complete inactivation of RB. As a result, E2F-dependent genes are expressed, creating a positive feedback loop that facilitates entry into S phase. The robustness of the regulation of the cell division cycle is crucial for proper cellular functions in our body, whereby uncontrolled proliferation of mutated cells within the body leads to cancer.

Biological fragility refers to the susceptibility of biological systems to unforeseen disruptions. One example of biological fragility would be cancer. Typically if any damage in DNA is detected throughout the cell cycle, the cell either undergoes DNA repair, remain dormant or exit the cell cycle through apoptosis or senescence if DNA damage is beyond repair. This is regulated by the p53-dependent pathway throughout interphase. However, a mutation associated with any of the cell cycle checkpoints can affect the cycle's integrity. p53 mutation hinders cell cycle exit and enabling its progression despite the accumulation of errors in DNA, resulting in uncontrolled proliferation of genetically mutated cells, or cancer. On top of that, E2F-dependent transcription is activated by mutations in tumour suppressors facilitating the progression into S phase and impeding cell cycle exit at G1.

We can tackle cancer through exploiting the mechanisms that are critical in enabling its progression. By targeting cell cycle regulation pathways that are vital in cancer cells but unnecessary in healthy cells is a promising approach, given the increased dependence of cancer cells on cell cycle control. Most healthy cells in our body are non-proliferating cells, as opposed to cancer cells which are highly proliferative. Since cell cycle progression is predominantly governed by CDK activity, introducing CDK inhibiting drugs will likely cause cancer cells to exit the cell cycle permanently, stop proliferating and become senescent. Subsequently, these senescent cells can then be eradicated by senolytics.

References:

Kitano, H. (2004). Biological robustness. *Nature Reviews Genetics*, *5*(11), 826–837. https://doi.org/10.1038/nrg1471

Matthews, H. K., Bertoli, C., & de Bruin, R. A. (2021). Cell cycle control in cancer. *Nature Reviews Molecular Cell Biology*, *23*(1), 74–88. https://doi.org/10.1038/s41580-021-00404-3