LETHAL WEAPON

TARGETING CANCER BY SYNTHETIC LETHALITY

According to Cancer Research UK, there are approximately 385,000 new cases of cancer every year in the UK. We therefore declare cancer public enemy number one.

The scientific community is facing a tough challenge – to avoid harmful side effects in patients, there is a need to develop treatments which specifically target cancer without affecting healthy cells...

Imagine two thieves are plotting a

BANK HEIST

Leading up to the heist, one of the thieves is arrested after an anonymous tip off. Consequently, the remaining thief replans the heist so that they can successfully pull it off solo. However, when the remaining thief's plan is discovered by a nosy neighbour, they promptly report the thief, leading to their arrest. This completely foils the plan, and the heist fails.

This is because the two thieves have a

SYNTHETIC LETHAL RELATIONSHIP

This phenomenon also applies to cancer cells...

Different genes play roles in the defining functions (or pathways) of a cancer cell – such as cell division, repair of broken DNA, and migration. In cancer, it is common for a gene to mutate, which handicaps the pathway in which this gene functions. Cancer cells then become dependent on another gene to compensate for this loss. Therefore, if we target the compensatory gene – such as with a drug designed to inhibit its function – then the cancer cell will DIE

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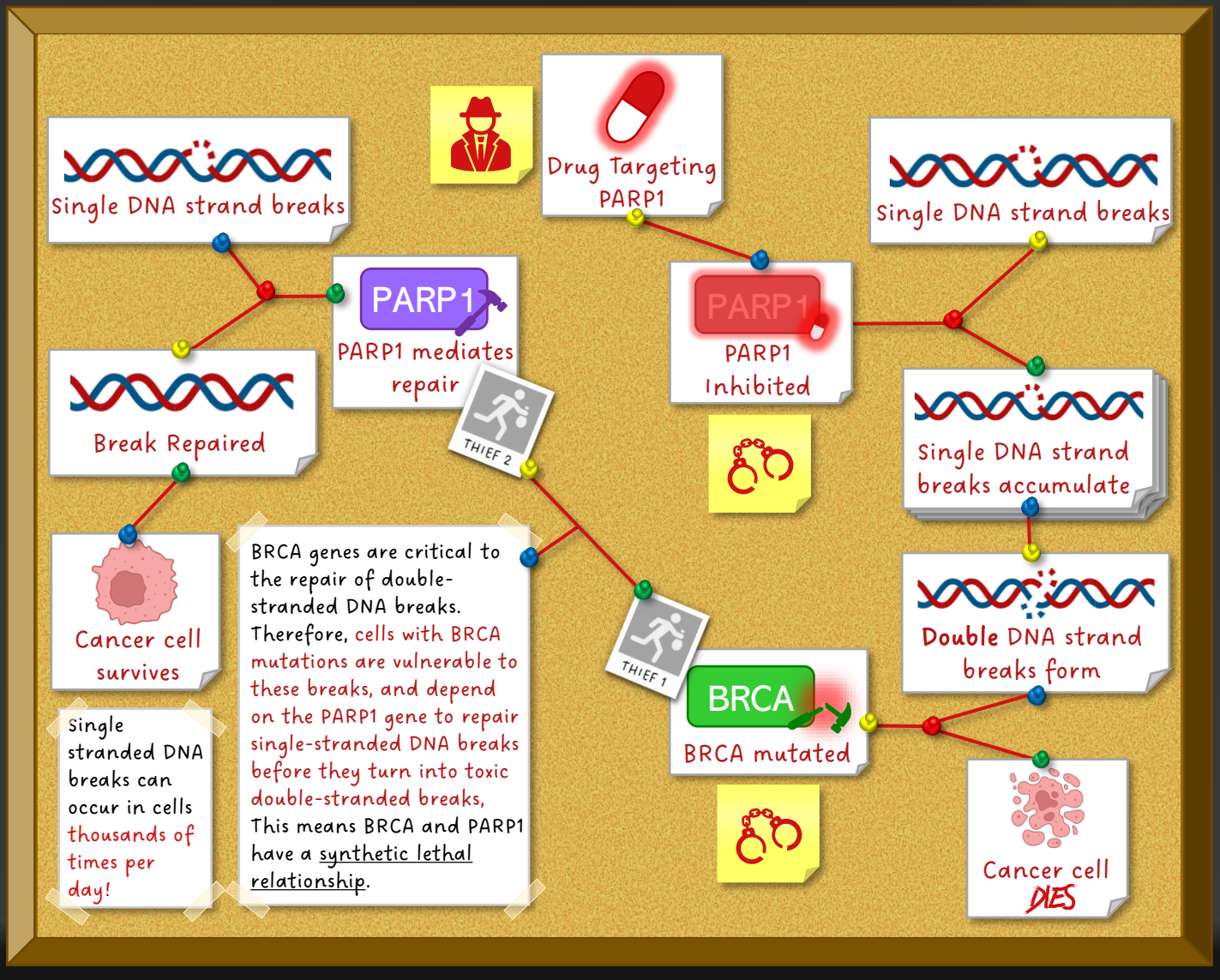
Genetic mutations are an inherent characteristic of cancer as a disease. Different mutations lead to different genetic dependencies, which normal healthy cells do not have. If we identify genes that have a synthetic lethal relationship with known mutated genes in cancer, they can be exploited for the targeted killing of cancer cells.

For example, mutations in the genes BRCA1 and BRCA2 are common in breast and ovarian cancer. Based on the concept of synthetic lethality, scientists developed drugs called PARP inhibitors to selectively kill breast and ovarian cancer.

Let's explore how this works...



Multiple PARP inhibitors have been approved by the Food and Drug Administration for the treatment of cancers with BRCA1 or BRCA2 mutations. However, other synthetic lethal strategies are also being explored in clinical trials…

As a common dependency in cancers, ~70% of synthetic lethal drugs being developed target genes involved in DNA damage repair

A cancer cell must temporarily stop dividing to allow time for DNA damage repair. This is controlled by cell cycle checkpoints

STOP!

These checkpoint genes are often mutated in cancer (e.g. the p53 gene) ...so we can target related genes to induce synthetic lethality

GO!

Target Examples:

- **ATR** – synthetic lethal with genes p53 and ATM
- **WEE1** – synthetic lethal with genes p53 and ATRX
- **DNA-PK** – synthetic lethal with genes BRCA1 and MYC
- **RAD52** – synthetic lethal with genes BRCA1 and BRCA2

FURTHER READING

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