



# How GSK is using synthetic lethality to develop cancer therapies

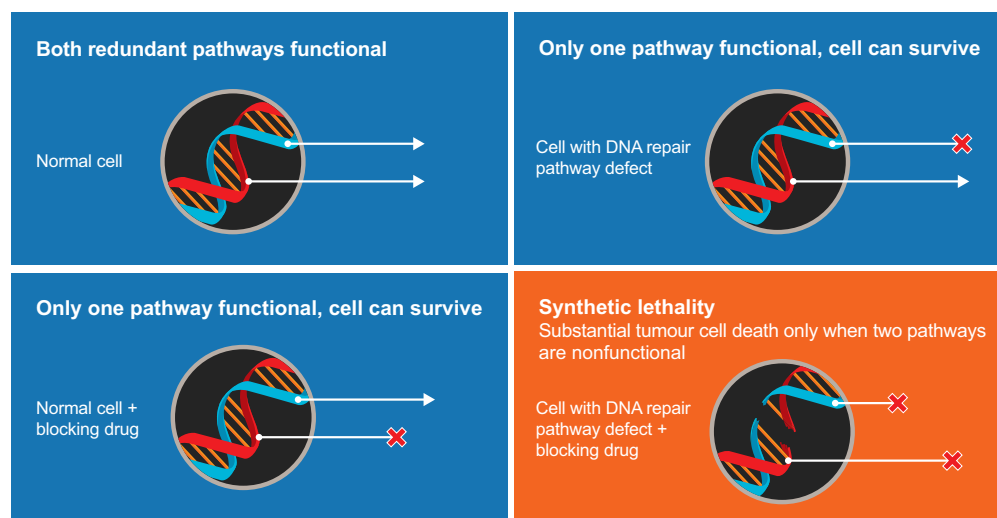
**At** GlaxoSmithKline (GSK) we are focused on developing novel medicines and advancing the understanding of what's possible for treatment options to fight cancer.

## CANCER THERAPY HISTORY

Oncology is a rapidly evolving field within medicine. We are in an age of precision medicine, with targeted therapies and novel science and technology driving the progress being made in oncology and its impact on patient care at an expeditious rate<sup>1</sup>. Targeted therapies and immunotherapies currently make up the majority of the mechanisms for newly approved medicines. These treatments represent how we currently think about the disease and cancer therapies, however, methods have evolved over the millennia.

For the first few thousand years of recorded history, cancers were removed surgically, with rather low success rates<sup>2</sup>. The first significant advancements were in the nineteenth century, when the association of certain tumour types with hormones was first recognised.

The first successful nonsurgical interventions began with the introduction of radiation and radium at the turn of the twentieth century<sup>3</sup>. The next major advancement in cancer treatment came more than four decades later with the introduction of chemotherapies in the 1940s. Chemotherapies represented a major paradigm shift. While these highly effective treatments work broadly by killing rapidly dividing cells, they



**Figure 1. The concept of synthetic lethality.** Blue panels indicate conditions that allow cell survival; the orange panel indicates conditions in which synthetic lethality has been induced.

do cause collateral damage to a patient's healthy cells.

Despite tremendous research efforts, another 40 years passed before the next wave of innovation emerged, focusing on specific targets that could be treated with pharmaceuticals to improve systemic cancer treatment and reduce the harsh side effects of chemotherapy. Targeted therapies, which were first introduced in the 1980s, are drugs that precisely identify and attack molecular entities such as cell-surface proteins on cancer cells. These innovations have led to the development of therapies that categorically improved outcomes for patients with many cancer types.

After the introduction of targeted therapies, immunotherapies were developed, starting in the late 1990s. Immunotherapies leverage the body's own immune system in defence against cancer cells.

In parallel with the development of targeted therapies and immunotherapies, another innovative treatment approach called synthetic lethality has recently emerged. Synthetic lethality is a strategy for developing cancer therapies and doesn't fit neatly into any of these previous definitions of cancer treatment.

## WHAT IS SYNTHETIC LETHALITY?

Synthetic lethality is a term that was originally established in genetics research. The term was first used in 1946, although the concept was first described in 1922. Synthetic lethality describes a type of lethal cell interaction in which the co-occurrence of two events results in cellular death. Essentially, because of functional redundancy, cells can tolerate the loss of a single gene in isolation, but not the combined loss of the redundant genes or pathways.

Redundant pathways allow the cell or organism to continue functioning and reproducing despite the failure of an important pathway<sup>4</sup>.

Synthetic lethality occurs when the primary and the redundant gene or pathway are inactivated: even though blocking only one of these pathways would not be lethal, the cell cannot survive the loss of both. Synthetic lethality can be induced through genetic mutation, drug intervention or a combination of factors.

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### WHY USE SYNTHETIC LETHALITY AS AN APPROACH IN ONCOLOGY?

Targeted therapies have been developed that inhibit cancer-associated over-activity of specific genes or proteins. When the target is a druggable change, such as the use of tyrosine kinase inhibitors in epidermal growth factor receptor-mutated non-small cell lung cancer, a synthetic lethality approach is not necessary. When direct targeting works, it works well. However, the proportion of tumours with druggable targets, to date, represents the minority. Synthetic lethality is more likely to be considered in cases of loss of function in tumour suppressor genes where conventional approaches using inhibitors are not useful<sup>5</sup>.

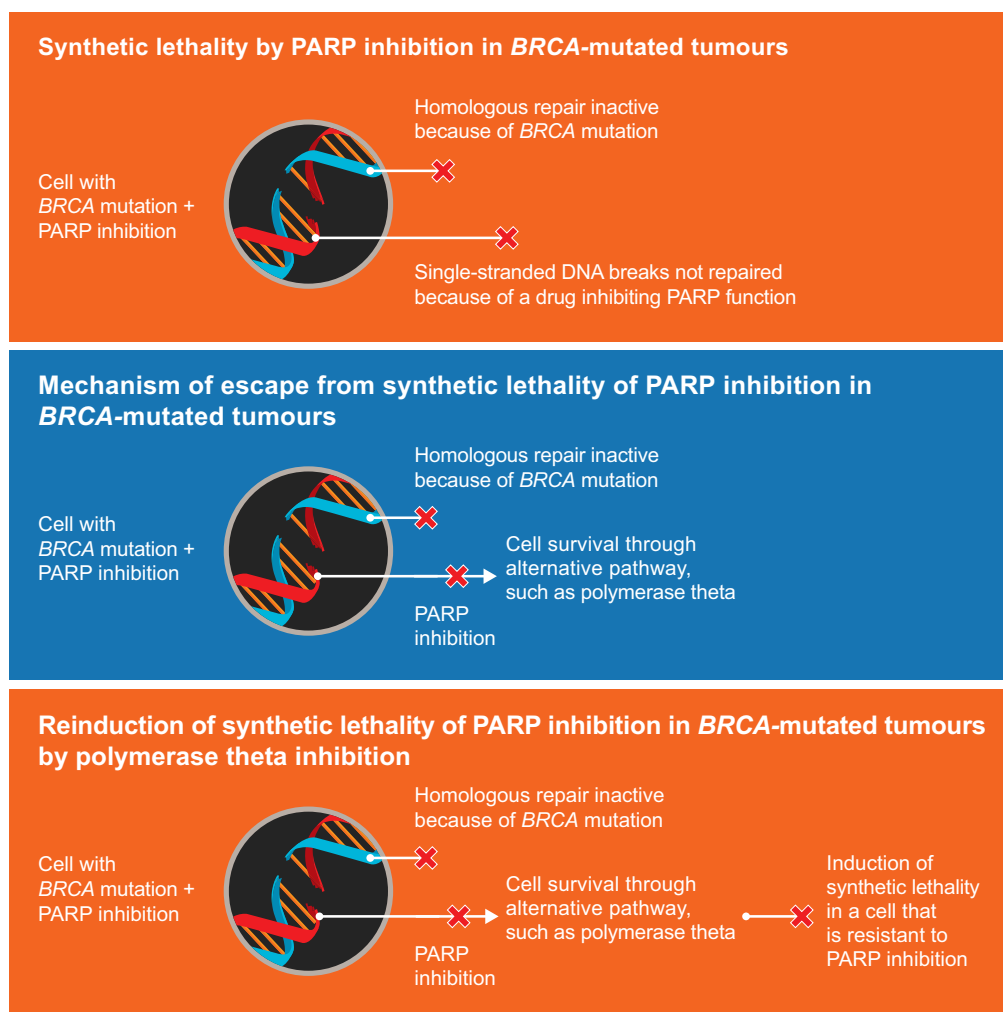
Cancerous cells frequently have accumulated mutations, very commonly in pathways involved in DNA repair<sup>6</sup>. While it's not always clear if these defects are the cause or the result of tumorigenesis, these mutations are often present when a patient is initially diagnosed. Cancer-associated mutations in DNA repair proteins force the cells to rely on an alternative pathway for repair. Thus, these tumour-associated mutations provide the first pathway block, and synthetic lethality can be accomplished by targeted blocking of one alternative pathway (Fig. 1).

Synthetic lethality as a strategy does not dictate a particular drug type. Thus, chemotherapies, targeted therapies or immunotherapies may be used to induce synthetic lethality in cancer cells. In oncology, synthetic lethality is an innovation in thinking about how to approach cancer therapies.

### SYNTHETIC LETHALITY IN ONCOLOGY

#### PARP inhibitors: a bench-to-bedside success story

Beginning in 2014, poly(ADP-ribose) polymerase (PARP)



**Figure 2. Synthetic lethality and poly(ADP-ribose) polymerase (PARP) inhibitors.** Synthetic lethality using a poly(ADP-ribose) polymerase (PARP) inhibitor in cells with a breast cancer-associated (*BRCA*) gene mutation (top panel). Escape from PARP inhibitor-induced synthetic lethality (middle panel), and reinduction of synthetic lethality by polymerase theta inhibition in cells with a breast cancer-associated (*BRCA*) gene mutation (bottom panel).

inhibitors became the first oncology drugs that rely on synthetic lethality to be approved for clinical use as a treatment for ovarian cancer. Synthetic lethality in PARP inhibitors is a straightforward mechanism: the PARP protein is involved in the repair of both single-stranded and double-stranded DNA breaks (Fig. 2). PARP inhibitors block PARP from repairing single-stranded breaks, exacerbating DNA damage and leading to double-stranded breaks. With PARP inhibition, cells must rely on other pathways to repair the accumulating double-strand breaks. In cells with a breast

cancer gene (*BRCA*) mutation, homologous recombination – a main pathway for detecting and repairing double-stranded breaks – is not functional. The DNA cannot be fully repaired, and the accumulation of DNA damage leads to increased genomic instability and eventually cell death.

PARP inhibitor activity is thought to work through several mechanisms. Although synthetic lethality through PARP inhibition, in combination with defects of the homologous recombination pathway, is considered to be the major mechanism, PARP inhibitors have demonstrated efficacy in tumours that lack

*BRCA* or other homologous recombination mutations<sup>7</sup>. Investigations into mechanisms outside of synthetic lethality are the subject of ongoing research.

### ONGOING RESEARCH IN SYNTHETIC LETHALITY AT GSK

We are in a new generation of personalized medicines based on synthetic lethality. And while a tremendous amount of work has been done to get us to this point, there is still a lot of research left to do. Building on the principles of PARP inhibition, GSK is developing novel therapies that use synthetic lethality approaches. The GSK synthetic lethality research

## Synthetic lethality by Werner helicase inhibition in dMMR cells

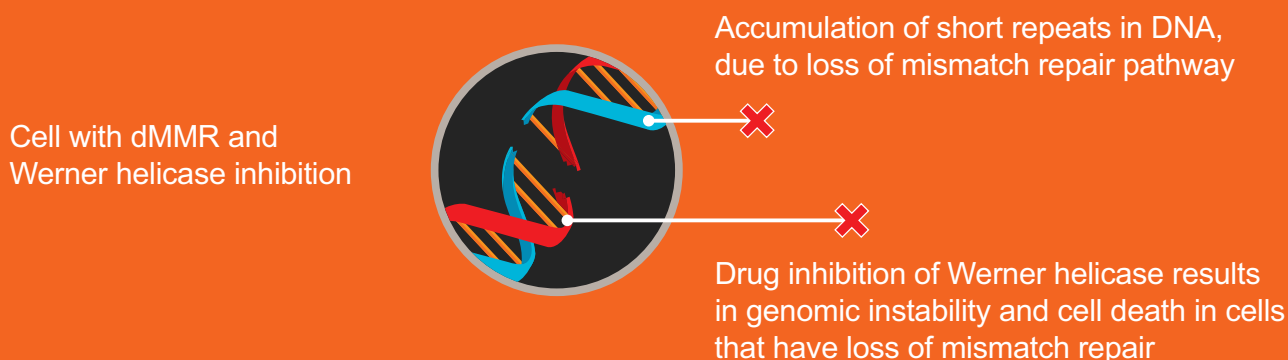


Figure 3. Synthetic lethality of mismatch repair deficient (dMMR) cells with Werner helicase inhibition.

unit is focused on targeted therapies that exploit endogenous weaknesses in cancer cells.

Cellular processes are complex, and when designing drugs that induce synthetic lethality, there may be more than one way to successfully achieve synthetic lethality in any given pathway. These possibilities give researchers options to test different approaches, and if the medicines demonstrate efficacy when evaluated in clinical trials, it may offer opportunities for oncologists to customise treatments for patients in the future. Here we give an overview of some of the early-phase synthetic lethality research ongoing at GSK. These concepts are currently under investigation and active development because they may show potential as future therapies.

### POLYMERASE THETA

Although PARP inhibitors are an effective treatment for specific cancers, such as ovarian, breast, and prostate cancers, they are not effective in every patient. The identification of new molecules that use the synthetic lethality approach and target overlapping pathways could lead to the development of additional medicines or alternative treatment options for patients beyond those currently available.

Polymerase theta (also called POLQ) inhibitors are a class of compounds currently under development that utilise a new way of inducing synthetic lethality in certain tumour types and may work synergistically with PARP inhibitors and other anticancer therapies<sup>8</sup>.

Similar to PARP, the polymerase theta protein is involved in repair of DNA defects. Research shows that polymerase theta-mediated DNA repair may be a mechanism that allows cells to avoid the synthetically lethal mechanism of PARP inhibition. Therefore, polymerase theta inhibition may be useful to resensitise cancer cells that have natural or acquired resistance to PARP inhibitors (**Fig. 2**).

Polymerase theta has potential uses as a single agent (monotherapy) or as a combination therapy with PARP inhibitors or other medicines. This is an area of active research that could one day provide new therapeutic options in difficult-to-treat cancers like ovarian cancer.

### WERNER HELICASE

Similar to polymerase theta, which is being researched, in part, to work in cases of cancers that are resistant to PARP inhibitors, Werner helicase is being studied in cancers that have a different type of

DNA repair defect, called mismatch repair deficiency (dMMR), and are resistant to the medicines currently used for those cancers. dMMR is common in endometrial and colorectal cancers, but less common in ovarian cancer<sup>9</sup>. Similar to ovarian cancer, patients may initially respond to surgery and chemotherapy, but then the cancer may return, causing the patient to relapse. Immunotherapies are commonly used for patients with dMMR cancers and have shown promising results. Despite advancements in treatment options, some patients don't respond to conventional treatments or a patient may respond but then become resistant to those same treatments.

Unlike *BRCA* and homologous recombination defects that lead to DNA instability, dMMR cells show an accumulation of short sequences in the genome that get repeated excessively. These excessive repeats can make DNA replication difficult, and cancer cells become dependent on Werner helicase activity (WRN) activity to bypass these lesions. Blocking WRN activity induces synthetic lethality specifically in these dMMR cancer cells (**Fig. 3**)<sup>10</sup>.

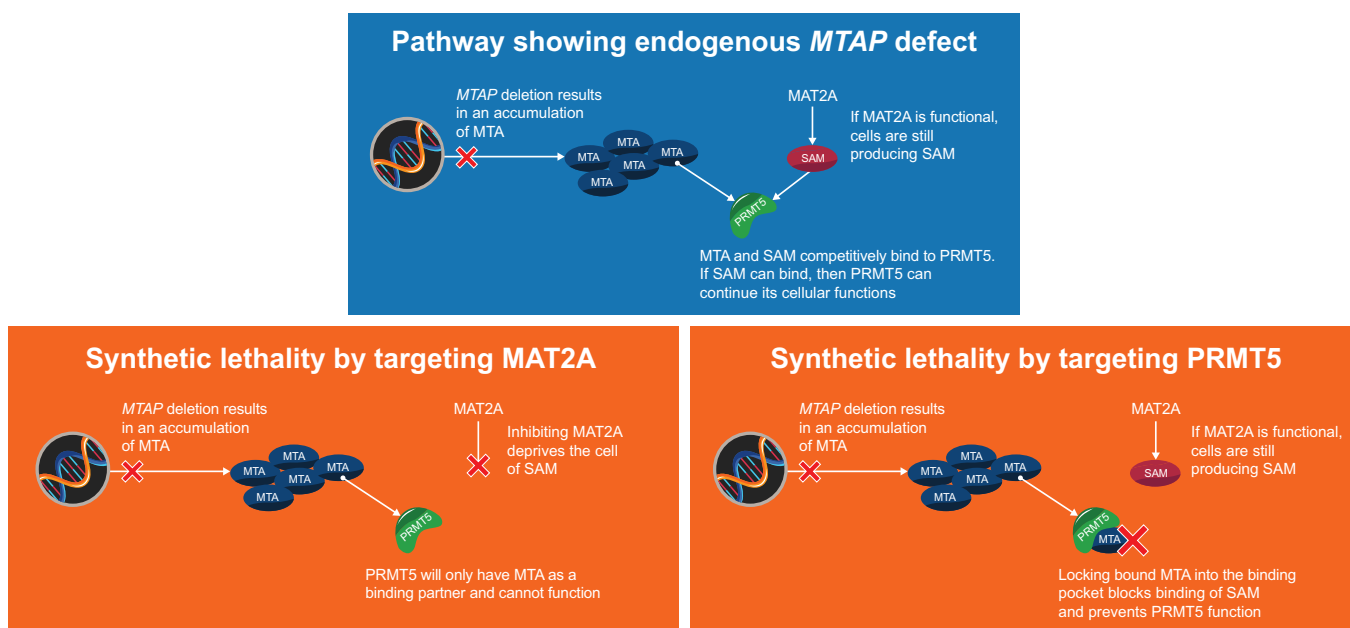
Werner helicase inhibitors have the potential to become a transformational medicine to treat patients whose dMMR-associated cancer did not respond to current treatments or have become resistant to treatments despite initially responding.

### MAT2A

A more complex example of synthetic lethality that is being developed is inhibition of MAT2A (methionine adenosyltransferase 2A) in *MTAP*-deleted (S-methyl-5'-thioadenosine phosphorylase) cancers (**Fig. 4**).

In approximately 15% of all cancers, the *MTAP* gene, which is located adjacent to the *CDK2A* tumour suppressor gene, is collaterally co-deleted<sup>11</sup>. In normal cells, *MTAP* is involved in converting MTA (methylthioadenosine)

GSK is excited to be at the forefront of developing and delivering novel medicines, including synthetic lethality agents, for patients with cancer.



**Figure 4. Synthetic lethality in *MTAP*-deleted cells.** The panels show two different targeting strategies to achieve synthetic lethality, either by targeting MAT2A (methionine adenosyltransferase 2A) to inhibit the production of SAM (S-adenosyl-L-methionine), or by holding MTA (methylthioadenosine) into the binding pocket on PRMT5 (protein arginine methyltransferase 5).

to produce adenine. In the absence of a functioning *MTAP* enzyme, MTA will accumulate. The higher concentrations of MTA in the cell will partially inhibit PRMT5 (protein arginine methyltransferase 5), but this decrease is not sufficient to induce cell death.

PRMT5 methylates many cellular targets, including several proteins involved in the splicing of pre-mRNA. Disruption of PRMT5 activity has been shown to lead to reductions in several DNA repair proteins due to this splicing defect<sup>12</sup>. *MTAP*-deleted cells can continue to function despite the accumulation of MTA because PRMT5 is not completely inhibited. PRMT5 requires SAM (S-adenosyl-L-methionine) for its actions. MAT2A is the primary enzyme that catalyses the creation of SAM. Thus, inhibition of MAT2A leads to depletion of SAM, and further inhibition of PRMT5 results in synthetic lethality specifically in *MTAP*-deleted cells.

Within the pathway shown in **Fig. 4**, there are two options for a potential second (or synthetically lethal) target, either inhibition of MAT2A upstream

of SAM or an MTA co-operative PRMT5 inhibitor. Studies have demonstrated that *MTAP*-deleted tumour models are sensitive to PRMT5 inhibition; the same synthetically lethal action can also be achieved by combining MTA accumulation with MAT2A inhibition (which leads to a depletion of SAM levels)<sup>13</sup>.

Loss of PRMT5's methylation function leads to defects in RNA splicing, gene expression and genome integrity, eventually leading to cancer cell death. PRMT5-based synthetic lethality has the potential to be useful in a variety of tumour types including breast, lung and gastric cancers and B cell lymphoma. Similar to the example above of PARP inhibition and polymerase theta as an option when cancers escape that synthetic lethality, having multiple ways of targeting the PRMT5 pathway will allow additional treatment options and better individualised care.

#### GSK'S FOCUS ON SYNTHETIC LETHALITY

In 2019, GSK began adding oncology as an area of focus with the acquisition of over 20 compounds at various stages

of development. This was an opportunity for the organisation to position itself on the cutting edge of innovation and to advance the field of oncology by developing novel, practice-changing medicines for patients.

GSK's oncology divisions are divided into four mechanistic platforms: immuno-oncology; oncology cell therapy; tumour cell targeting; and synthetic lethality (**Fig. 5**). These four pillars are areas of current innovation that have substantial promise for future therapies.

By building the in-house capabilities for research and development in these four focus areas, GSK brings the resources and expertise to develop medicines from preclinical to clinical application.

#### FUTURE PERSPECTIVE FOR SYNTHETIC LETHALITY

Although the current synthetic lethality medicines tend to be small molecules, this focus may reflect the type of first generation of CRISPR screens used to discover these targets.

As new types of CRISPR screens are run (for example with tumour and immune cells

mixed together), synthetic lethality will remain a relevant concept for exploiting inherent weaknesses and attacking undruggable targets with more diverse types of medicines.

As new therapy types come forward for patients with difficult-to-treat cancers, synthetic lethality will remain a relevant concept for exploiting inherent weaknesses and attacking undruggable targets. Synthetic lethality will play an important part in alternative mechanisms for treating difficult-to-treat cancers, providing a different avenue for thinking about how immunotherapies, cell therapies and targeted therapies can be used to treat cancers.

#### PARTNERSHIPS AND OPPORTUNITIES FOR SYNTHETIC LETHALITY IN CANCER THERAPIES

GSK is developing compounds in the synthetic lethality portfolio that have the potential to improve patients' lives through practice-changing medicine. Synthetic lethality offers a variety of innovative ways for GSK to use its scientific expertise to create and

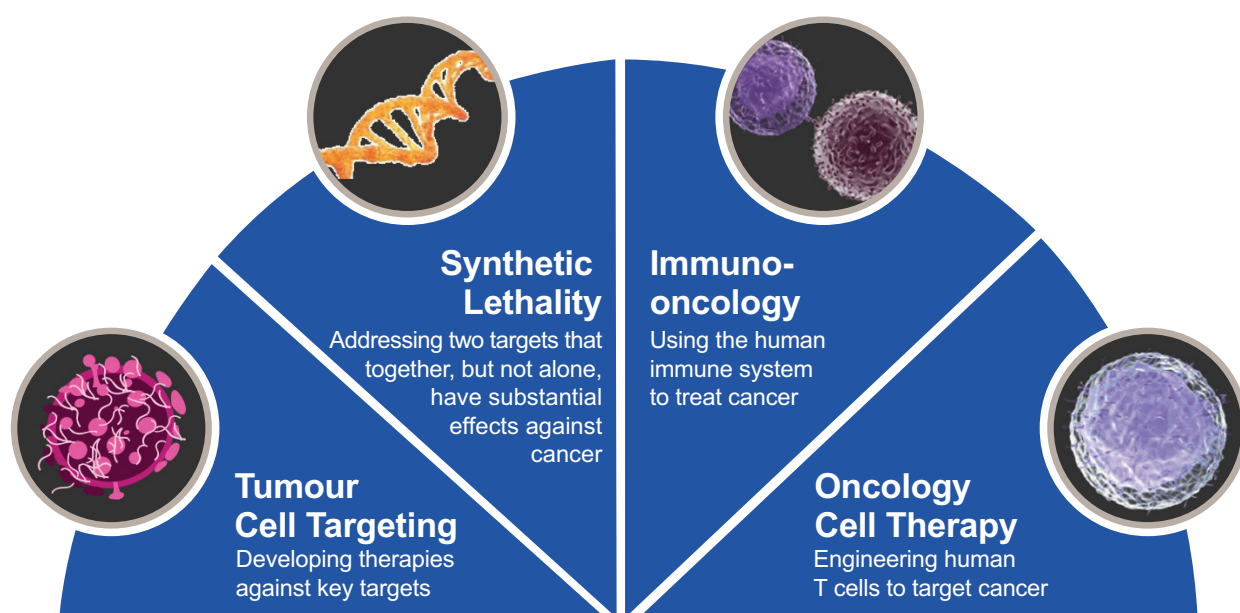


Figure 5. The four research units in GSK Oncology.

develop transformative medicines that expand treatment options for patients with cancer.

In addition to its own pipeline, GSK has collaborative partnerships to expand the development of synthetic lethality targets across a broader range of cancer types. GSK has an exciting partnership with IDEAYA Biosciences, an oncology company headquartered in South San Francisco, California, United States, that includes developing therapies focused on polymerase theta, Werner helicase, and MAT2A in synthetic lethality approaches.

Despite the promise of novel mechanisms and therapies, any drug candidate may fail in clinical trials. GSK is committed to ensuring that any potential therapy is developed in

accordance with industry best practices, through registered, prospective clinical trials.

Given the broad nature of their mechanisms, drugs that kill cancer cells across multiple tumour types through synthetic lethality represent an advancement in oncology treatments and will continue to be exploited by scientists as a critical future pillar of cancer treatment. GSK is excited to be at the forefront of developing and delivering novel medicines, including synthetic lethality agents, for patients with cancer.

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