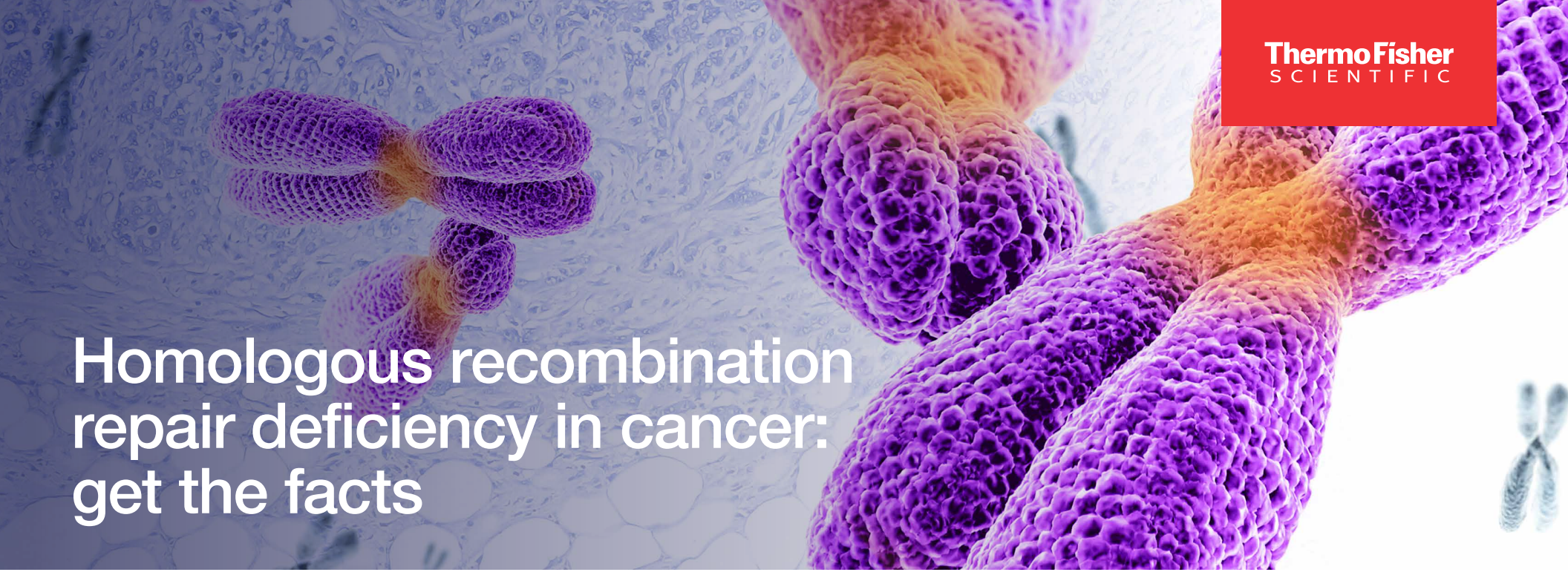

Homologous recombination repair deficiency in cancer: get the facts

What is homologous recombination repair?

Homologous recombination repair (HRR) is a DNA repair mechanism that enables template-dependent, high-fidelity repair of complex DNA damage, including DNA double-stranded breaks [1].

- HRR has an important role in maintaining stability of the genome and tumor suppression
- The inability of a cell to effectively employ the HRR mechanism on DNA damage is termed **homologous recombination repair deficiency (HRD)** [1]
- In contrast, tumors can also display **homologous recombination proficiency (HRP)** if they do not have HRD [1]
- HRD is often observed in cancer as resulting in genomic instability, and it can be the driver of tumorigenesis and one of the hallmarks of cancer [2]

HRD prevalence in ovarian cancer

Taking ovarian cancer as an example, it is estimated that about 50% of ovarian cancers are HRD-positive, while only 25% carry *BRCA1/2* mutations, highlighting the importance of HRD detection through genomic analysis in addition to the *BRCA1/2* mutational status [3].

What is the relevance of HRD for cancer treatment?

Determining if cancer cells have HRD can be utilized to target them through the concept of **synthetic lethality with drugs such as poly(ADP-ribose) polymerase (PARP) inhibitors** [3].

- Inhibition of PARP prevents the repair of single-stranded DNA breaks, which can lead to an accumulation of double-stranded DNA breaks through the collapse of replication forks [4]
- Cells displaying HRP can tolerate PARP inhibition since they have other functioning DNA repair mechanisms [3]
- However, in the presence of HRD, PARP inhibition is highly toxic to cells, as they are unable to repair the double-stranded DNA breaks and the accumulation of DNA damage ultimately results in cell death [3]
- Advances in cancer research have led to a greater understanding of HRD presence in different cancer types and utilization of HRD as a biomarker for predicting responses to targeted therapies [5]

How is HRD detected?

Detection of HRD in cancer cells relies on 3 main approaches [3]:

- **Detect mutations in genes involved in the HRR pathway** that can be considered causative of HRD, including *BRCA1* and *BRCA2*
- **Measure the genomic "scars" or genomic instability** in the cells arising as a consequence of HRD, regardless of the underlying cause
- **Perform functional assays** as a readout of HRD or HRP, such as detection of nuclear RAD51 foci

Improving patient outcomes

The benefits of HRD detection for improving treatment stratification and patient outcomes have been well documented in many clinical studies, and several approaches exist for determining HRP status [6,7].

What are the causes of HRD?

Several genes act as key players in HRR, including the **breast cancer genes *BRCA1* and *BRCA2***, and ***RAD51*, *RAD51C*, *RAD51D*, *PALB2*, and *ATM*** [1].

- Somatic or germline loss-of-function mutations (including chromosomal aberrations) in *BRCA1* and *BRCA2* genes are considered to be genetic factors contributing to HRD [5,8]
- However, in many cases the cause of HRD remains unknown [5]
- The number of genes involved in HRD is high, and the causative effect of mutations in HRR-related genes other than *BRCA1* and *BRCA2* is still being explored
- The impact of these mutations is diverse, and with complex interactions it is difficult to establish the level of contribution to HRD based on these and other mutations alone [1,5]

How is genomic instability measured in cancer cells?

The consequences of HRD can be measured by probing the genome for evidence of genomic scarring, which includes larger genomic alterations [1,8].

- **Loss of heterozygosity (LOH)** refers to chromosomal regions, usually >15 Mb, showing lack of heterozygous single-nucleotide polymorphisms [8]
- **Telomeric allelic imbalance (TAI)** refers to the number of regions with allelic imbalances in the sub-telomeric part of the chromosome [8]
- **Large-scale transitions (LST)** refer to chromosomal aberrations including deletions, duplications, or inversions [8]
- The assessment of HRD based on these parameters is independent of the cause of HRD and is based on a genome-wide genetic analysis, which can be performed using **microarray or next-generation sequencing technologies** [6,8,9]

Predictive power of genomic assays

Detection of *BRCA1/2* mutational status and measurement of genomic instability scores are currently considered to have among the highest clinical validity and clinical utility for predicting treatment responses to PARP inhibitors in ovarian cancer [3].

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