

## TISSUE SPECIFICITY

Devise approaches to prevent or treat cancer based on mechanisms that determine tissue specificity of some cancer genes



### CONTEXT

In recent years molecular profiling has transformed our understanding of the genes that are dysregulated or mutated in specific tumour types. However, there remains a simple but confounding question of why, despite being expressed in a wide variety of tissues, some cancer genes contribute to tumorigenesis only in certain tissues but not in others. This is observed in hereditary cancer predisposition syndromes whereby, for example, germline mutations in BRCA1 and BRCA2 primarily cause breast and ovarian cancers. It also extends to somatic mutations where aberrations in cancer genes are frequently observed in some cancers but not others, for example APC in colorectal cancer and KRAS in pancreatic cancer.

The mechanisms that determine the tissue specificity of cancer genes remain poorly understood but are likely to be multifactorial including intrinsic, extrinsic and environmental factors. Further biological insights into these pathways could enable the development of novel preventative and/or therapeutic interventions for specific cancer types.

### OPPORTUNITIES AND BARRIERS

This Grand Challenge calls for innovative approaches to elucidate the underlying biology responsible for the observed tissue specificity of cancer genes, with the intention to use this knowledge to develop novel preventative or treatment strategies.

Given the current lack of insight on the topic, there is an opportunity for teams to present ambitious and powerful mechanistic approaches to address this challenge in unexpected ways. Examples of the types of questions that could be addressed in this challenge include (but are not limited to):

- Why do proto-oncogenes that are expressed in many tissues become cancer causing only in some?
- Do the mechanisms that allow tissue specificity of cancer genes highlight unique features that can be exploited therapeutically for approaches that are specific for a cancer gene only in a particular cellular environment?
- Do protected or "safe" tissues that resist tumorigenesis of otherwise cancer-causing mutations contain features that can block tumour development?

### VISION AND IMPACT

The aim of this Grand Challenge is to uncover novel biological insights into the tissue specificity of cancer of cancer genes. Although it may not be feasible to develop and validate novel interventions within the timescale of a Grand Challenge, it is anticipated that proposals addressing this challenge

will focus on the mechanisms with the potential to inform future approaches to prevent or treat cancer.