3D Genomics and targeted cancer therapies

Anthony Schmitt, PhD., Senior Vice President, Science at Arima Genomics, discusses the applications of 3D genomics in cancer research.

Efforts to fulfil the promise of precision medicine, including the use of targeted cancer therapies, necessitate that patients be treated based on the specific genetic alterations that drive their individual cancers. It is now more common for cancer patients to be offered genomic testing to identify genetic mutations, and for oncologists to subsequently prescribe targeted therapies that are matched to the patient's cancer mutation profile.

But what about the patients whose genomic tests do not identify a cancer driver matched to an existing targeted therapy?

Current methods to detect genetic mutations that guide therapeutic decision-making fail to identify a driver matched to a therapy in approximately 50% of advanced cancers. However, just because current genetic tests do not identify a druggable target doesn't necessarily mean a druggable target isn't present in that tumour sample – rather, it means we need improved tools to find those druggable targets. 3D genomics is one such tool demonstrating utility in identifying actionable cancer drivers missed by other technologies.

New possibilities

Before the advent of next-generation sequencing (NGS) technologies, which power most assays used to match cancer patients to targeted therapies today, other technologies were (and still are) used to detect cancer driver mutations. For example, fluorescence in situ hybridisation (FISH) assays are a commonly used cytogenetic approach for identifying a specific type of cancer driver – a gene or chromosomal rearrangement. However, FISH assays test for only a single gene rearrangement per test, making it a low-throughput and impractical approach for comprehensive detection of the variety of known cancer driving gene rearrangements. In addition, karyotyping and chromosomal microarrays help detect chromosomal abnormalities but carry their own set of technical limitations (eg, genomic resolution, the need for live cells, detecting balanced rearrangements, etc.) with regards to detecting cancer driver mutations.

NGS-based assays were adopted because they overcame these limitations, allowing concurrent analyses of numerous genes in the tumour genome to ultimately identify driver mutations in clinical samples, at scale. But these traditional NGS assays, which predominantly use 'short-read' sequencing technologies to generate linear sequences of bases, do not elucidate all potential cancer drivers. Therefore, while traditional NGS-based approaches have greatly improved the detection of cancer drivers, many tumours are still deemed 'driver negative'. Alternatively, a 3D genomics approach allows scientists to capture both the linear sequence and the three-dimensional (3D) organisation of the genome, enabling the detection of additional cancer drivers that would otherwise be missed with traditional NGS.

Revealing oncogenic gene and proximity fusions

Today, labs are leveraging 3D genomics to overcome the limitations of traditional NGS to identify cancer drivers in previously characterised driver-negative tumour samples. 3D genomics is particularly useful for detecting gene rearrangements, also known as fusions events, including gene fusions and proximity fusions, both of which are challenging to detect using traditional NGS assays. Moreover, this information can be actionable for cancer patients, including those with tumours previously identified as driver-negative and those newly diagnosed with cancer.

More specifically, a gene fusion occurs when two genes are joined together via chromosomal rearrangement. Since the genes are fused, the chimeric RNA transcripts encode different proteins, altering their function. On the other hand, a proximity fusion also occurs via chromosomal rearrangement – however in this case, the oncogene is not fused to another gene and therefore remains fully intact. Proximity fusions can lead to altered oncogene expression, such as the activation of an oncogene, thus driving cancer. While proximity fusions are widely accepted in haematological cancers, they are relatively underappreciated as a cancer driver in solid tumours.

Figure 1: *Comparison of traditional next-generation sequencing (NGS) and 3D genomics approaches.*

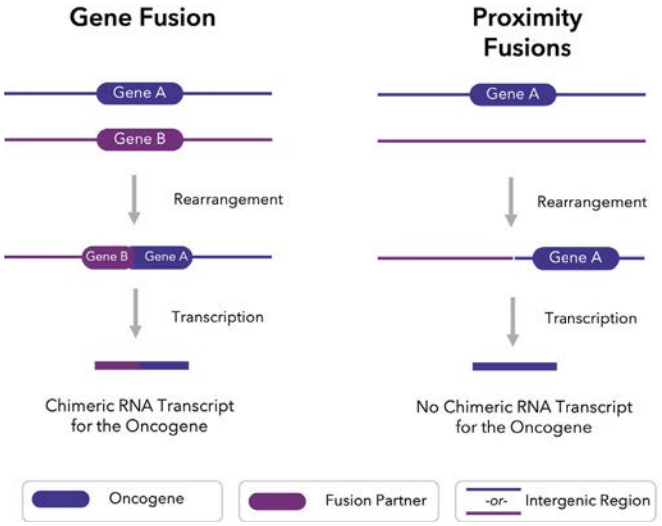


Figure 2: *Gene fusions result from rearrangements and generate chimeric RNA transcripts. In contrast, a proximity fusion leaves the oncogene intact, so no chimeric RNA transcript is produced.*

The value of 3D genomics

During a presentation at the 2022 American Association for Cancer Research (AACR) annual meeting, Matija Snuderl, MD, Director of Molecular Pathology and Diagnostics at New York University Langone Health, presented data from his clinical lab showing the utility of 3D genomics in clinical practice.

He shared the story of an adolescent patient with a glioneuronal tumour. The initial tumour was resected but recurred six months later as glioblastoma. A 3D genomic analysis of the tumour identified a novel PD-L1 proximity fusion, which was later confirmed with immunohistochemistry. The patient was then able to be treated with anti-PD-L1 immunotherapy. The patient was reported to have stable disease at the time of the presentation.

New targets, new potential

Leveraging 3D genomics to understand cancer drivers not detected with current standard-of-care testing protocols can also offer companies an opportunity to identify new targets for cancer therapy development and new possibilities for broader utilisation of existing targeted therapies. However, identifying these opportunities may be challenging without the broader adoption of 3D genomics.

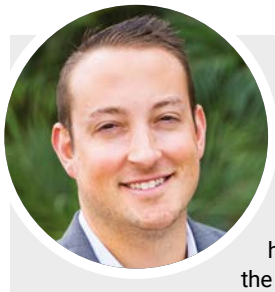
For example, paediatric brain cancer researcher Lukas Chavez, Ph.D. at the University of California San Diego, initially used traditional NGS to study dozens of ependymomas, a class of rare and aggressive childhood brain cancers, but no underlying genetic cause of the disease was identified. Using 3D genomics, he and his team identified several previously unknown gene and proximity fusions and demonstrated the potential for therapies to effectively target these alterations in preclinical models.

One proximity fusion involved the REST Corepressor 2 (RCOR2) gene, which was also overexpressed in the ependymoma tumour subtype RELA. The team tested the effect of suppressing RCOR2 expression in patient-derived tumour cells and observed that this gene suppression caused cancer cell death. This work underscores the potential for developing new treatments for RELA ependymoma, either with new molecules or by utilising existing therapies.

The case for exploring proximity fusions in solid tumours

While the haematological cancer community has long recognised the clinical significance of proximity fusions in haematologic cancers, these characteristics are primarily used to adjust treatment regimens rather than target different pathways. In addition, the overall importance of proximity fusions has not been well-characterised in many solid tumour cancers. Still, the advent of 3D genomics is helping researchers understand that these fusion events are far more common in solid tumour cancers than previously appreciated.

Internal research at Arima Genomics analysed many types of driver-negative cancer tissue samples and identified a clinically actionable cancer driver in roughly 52% of samples, of which the cancer driver was a proximity fusion in approximately 75% . These findings, confirmed with immunohistochemistry, illustrate that for many cancer patients, proximity fusions activate oncogenes matched to targeted therapies, which may offer patients previously unknown benefits and enable pharmaceutical companies to pursue broader utilisation of their targeted therapies if clinical trials show clinical benefits.



About the author:

Anthony Schmitt, PhD, is the Senior Vice President of Science at Arima Genomics – a San Diego-based biotech focused on leveraging 3D genomics to improve human health. Anthony received his PhD from the University of California, San Diego, where he developed novel methodologies to understand mechanisms of gene regulation.