ANNUAL RESEARCH REPORT
MARROCCO FAMILY AND BELMADAR
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GARVAN INSTITUTE OF MEDICAL RESEARCH

BACKGROUND - ACUTE MYELOID LEUKAEMIA

Acute Myeloid Leukemia (AML) is caused when genetic mutations resulting in the accumulation of immature white blood cells within the bone marrow, preventing the production of red blood cells. AML is the most common acute leukemia affecting adults and causes approximately 1% of cancer deaths worldwide. AML progresses rapidly and is typically fatal within months if left untreated. Fortunately, AML is a potentially curable disease if detected early and treated appropriately.

AML RESEARCH AT THE GARVAN INSTITUTE OF MEDICAL RESEARCH

Associate Professor Tim Mercer, Dr Jim Blackburn and the Transcriptomic Research Laboratory at the Garvan Institute of Medical Research, in conjunction with collaborators at St Vincent's Hospital, are developing a test able to detect genetic mutations responsible for AML (and other types of leukemia). Such a test will enable early and accurate diagnosis of AML, leading to rapid treatment.

The test works by detecting fusion genes, which are created when two different genes fuse together into a single faulty gene that causes cancer. Fusion genes play a role in the development of many solid and blood cancers, including AML. In fact over 200 fusion genes have been found in AML, and identifying which is responsible for cancer is critical to diagnosing AML, and informing potential treatment options.

Current tests, (based on fluorescent in situ hybridization) available to Australian patients are only able to detect 11 fusion genes and then only at substantial cost. By contrast, the new test can identify all known fusion genes, including those that have not been identified before, increasing the accuracy of diagnosis and suggesting new treatment opportunities.

RESEARCH OUTCOMES

Over the past three years, the research team has demonstrated both the sensitivity and precision of this test using bio banked cancer samples. This proof-of-principle study has demonstrated the use and advantages of the test, notably including the detection of many different fusion gene types.

Over the past twelve months the team have worked with collaborators to validate the test in a clinical setting to diagnose the presence of fusion genes in in 72 cancer patients –including 40 with solid tumour types (lung, prostate and sarcoma) and 32 with blood cancers (including AML). To date they have:

- Correctly detected fusion-genes in 26 out of the 29 (90%) samples with previous molecular diagnoses. This included identifying both fusion-gene partners in five samples where only one gene was previously identified.

- Identified 27 unique fusion-genes were identified across our clinical cohort**,** including a previously unknown *AFF1-MYC* fusion in an AML patient.
- Diagnosed fusion genes in 9 out of 15 (60%) AML patients, including *CBFB-MYH11, NSD1-NUP98, RUNX1-RUNX1T1, KMT2A-MLLT3, NUP214-DEK, MN1-ETV6, DDX3X-MLLT10, SEPT9-KMT2A, and PML-RARA* fusion genes.
- Identified fusion genes that helped inform treatment for 24 out of 52 (46%) patients. Fifteen of these actionable fusion-genes were not previously identified using alternative methods.
- Identified the immune response (T-cell receptoprs and immunoglobulin), produced by B-cells and T-cells to help with the recognition and response to cancer cells in each blood sample.

A description of the test validation, and the results described above have been prepared as a medical study manuscript entitled "*Diagnosis of fusion-genes using targeted RNA sequencing*" which will be submitted to a prominent journal in the coming weeks.

SUMMARY

The Laboratory has demonstrated the use, sensitivity and performance of the fusion-gene test using clinical patient samples. The test substantially outperformed current diagnostic methods and will provide faster, cheaper, earlier and more accurate diagnosis of blood cancers, such as AML.

Improved diagnosis will provide greater insight into the cause of cancers, leading to better-informed treatment and care for patients with AML as well as many other cancer types. More broadly, an improved understanding of fusion gene biology will also continue to advance research into better treatment options.

Throughout 2018 the team, with its collaborators, will expand the experimental validation in clinical cohorts (such as from the Molecular Screening and Therapeutics Trial).

In 2019 the fusion test will be available for clinical use (via the Kinghorn Center for Clinical Genomics) for patients at St. Vincent's Hospital whom are not diagnosed using current standard methods. In the coming years we anticipate the test will be available as an accredited test through a diagnostic partner, for any referring physician.

THANK YOU

Thank you so much for supporting AML research at the Garvan Institute. We would love to welcome you into Garvan for a Private Research Update with Dr Jim Blackburn and the opportunity for a tour of his laboratory. If this is of interest, please let us know when would be convenient.

Once again, on behalf of everyone at Garvan, thank you for recognising the value of medical research. Together we are making, and will continue to make, significant discoveries that will change the directions of science and medicine and have major impacts on human health.