Organ Health – BMT

- Accurate quantitation of genomic DNA in a chimeric sample
- Application in bone marrow transplantation

The opportunity
The global transplant diagnostics market is valued at $530M for 2017, expected to grow at CAGR of 6.5% during 2014-2019 and reach a value of $650 Million in 2019. Bone marrow transplantation is steadily increasing in prevalence, and for each procedure ongoing chimerism monitoring needs to be performed to track the success of engraftment. To date, traditional chimerism methods such as STR typing, SNP genotyping and FISH have presented various problems associated with precision, sensitivity, workflow, reliance on gender mismatches, and ability to resolve complex cases. There are >50,000 BMT procedures each year at an estimated market opportunity of $112m for chimerism monitoring, with >20,000 of these procedures coming from the US alone, at an estimated market opportunity of $45m for chimerism monitoring.

A bone marrow transplant (BMT) is used to replace diseased, non-functioning or dysfunctional bone marrow with healthy functioning bone marrow.

BMTs are used as a therapeutic intervention for a range of diseases including, but not limited to, leukemias; severe aplastic anemia; lymphomas; multiple myeloma; immune deficiency disorders; and metabolic disorders.

After a BMT, effective graft surveillance is important to allow timely assessment of engraftment and disease relapse. For haematological disorders, the success of the transplant is determined by how effectively the donor bone marrow transplant engrafts. For haematological malignancy, both the level of engraftment and the level of recipient bone marrow, which represents the minimal residual disease, is clinically significant.

Current methods of detecting donor and recipient cells include:

- FISH, which is only suitable for sex – mismatched pair and does not have the sensitivity needed for early relapse detection;
- STR, SNP and indels markers, which all require numerous loci to be analysed and are not always informative, particularly in highly related donors and recipients.

Researchers at the Murdoch Children’s Research Institute have developed a cost effective, non-invasive, sensitive and quantitative test for detecting engraftment levels and minimal residual disease in patients that have received a BMT.

The technology
Organ Health BMT is a chimerism assay designed for use after bone marrow transplantation. It measures the proportion of peripheral blood or bone marrow cells that are recipient or donor in origin (chimeric fraction) through droplet digital PCR-based profiling of a specifically selected panel of up to 38 assays. The test utilises assays located within copy number variation (CNV) loci that have population copy number deletion (bi-allelic null genotype) frequencies of 0.4-0.6, which maximises the potential of the panel to distinguish multiple individuals, including related individuals. Cells can be unsorted or flow sorted cells depending on the clinical application. Extended applications could include monitoring fate of stem cell therapies and emerging therapeutic cytotoxic T cell infusion therapies.

The combination of this CNV approach with a digital PCR based quantification platform permits the following significant advantages over current standards such as STR-typing, SNP and FISH:

- Ability to resolve complex (multi-donor and/or closely related) cases, through the high informativity of the CNV panel. Double donor, sequential and related-pair transplants are increasingly common.
Superior sensitivity permits earlier clinical decision-making. Regular testing as a means to identifying early recurrence of primary disease, but also indicating and monitoring outcomes from interventions such as immunosuppression adjustment and donor lymphocyte infusions.

Precision measurable in each case, high reproducibility. We have identified poor clinician confidence in chimerism results as an issue with standard methods (e.g. STR typing, SNP genotyping), particularly at extremes of the dynamic range. The CNV approach, through use of multiple informative markers per individual, permits provision of a standard deviation for every test result, adding confidence.

No reliance on donor/patient gender mismatch or other reference markers.

Robust methodology with validation under standard conditions published/peer-reviewed. Experimental Haematology validation paper attached.

Daily turn-around, simpler automated workflow likely to drive more frequent testing.

Figure 1. outlines an example of the patient chimerism result that Organ Health-BMT could provide to a clinician. This non-invasive, sensitive and quantitative test will provide more accurate and timely information to make treatment decisions.

Supporting Data
Results from the Quality Assurance Program (QAP) of the Royal College of Pathology Australia (RCPA) demonstrated that Organ Health BMT measured target chimerism values more consistently and accurately that most other laboratories (Figure 1).

Figure 1: The Organ Health BMT test adopted by VCGS more consistently and accurately measures chimerism, including low levels of chimerism, compared against other laboratories.

Opportunity for partnership
Murdoch Children’s Research Institute is seeking a partnership with a suitable investor or industry partner for the further development and commercialisation of Organ Health BMT.

Intellectual Property
The Murdoch Childrens Research Institute has filed a patent application in relation to this technology. The patent application describes the method and its application in identification and quantitating genomic DNA from a chimeric sample and gives details of the CND markers identified. Intellectual property position at PCT stage (PCT/AU2016/050499).

Key publications


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