Weill Cornell Medicine

StraDiVari-RT for Improved Transcriptome Analysis in Fixed Samples

Lead Inventors:

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Background & Unmet Need

- Recent advancements in spatial and single-cell transcriptomics enable transcriptome profiling in degraded RNA samples using paired oligonucleotide probes that hybridize to targeted transcripts
- Current probe-based methods lose original RNA sequence information including mutations during ligation and sequencing, limiting genetic variant detection in fixed samples
- Existing approaches using non-contiguous probes with gaps are limited by reverse transcriptases (RT) that possess high strand displacement activity
- Standard RT enzymes continue synthesizing past the second probe during gap-filling, displacing downstream probes and preventing proper capture of original RNA sequences
- **Unmet Need**: A method that enables accurate capture of original RNA sequences and mutations in spatial and single-cell transcriptomic analysis of formalin-fixed samples

Technology Overview

- **The Technology:** StraDiVari-RT (Strand Displacement Variant Reverse Transcriptase) is an engineered enzyme that enables incorporation of original RNA sequences into locus-specific probe sets
- The enzyme contains engineered mutations that abolish strand displacement activity and eliminate RNase H activity to preserve target integrity
- **PoC Data:** StraDiVari-RT successfully resolves admixtures of wild-type and mutant cells at single-cell resolution in both fixed cell lines and primary samples from AML patients
- Compatibility with existing single-cell RNA-seq workflows was demonstrated through a cell line mixing experiment
- Probes targeting GAPDH and CTCF, with a 9-nucleotide space between probes, efficiently filled and ligated, enabling precise genotyping of these sequences in single cells

Inventors:
Dan Landau
Ivan Raimondi
Husain Danish

Patents:
PCT Application Filed

Publications:
N/A

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Technology Applications

- Research tool to detect mutations in tumor samples and understand their effects on cellular behavior
- Develop more precise diagnostic methods that account for genetic variations at the single-cell level
- Identifying cellular responses to drug treatments at a granular level, facilitating targeted therapy development

Technology Advantages

- Seamless integration with commercially available probe-based single-cell and spatial transcriptomics products
- Precise identification of mutations within RNA sequences, including small deletions or duplications
- Compatible with fixed samples

Supporting Data / Figures

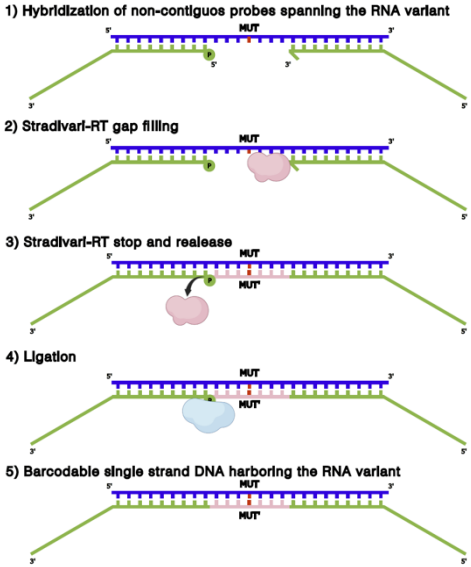

Figure 1: schematic diagrams showing profiling a target RNA sequence, including identifying mutations present with StraDiVari-RT

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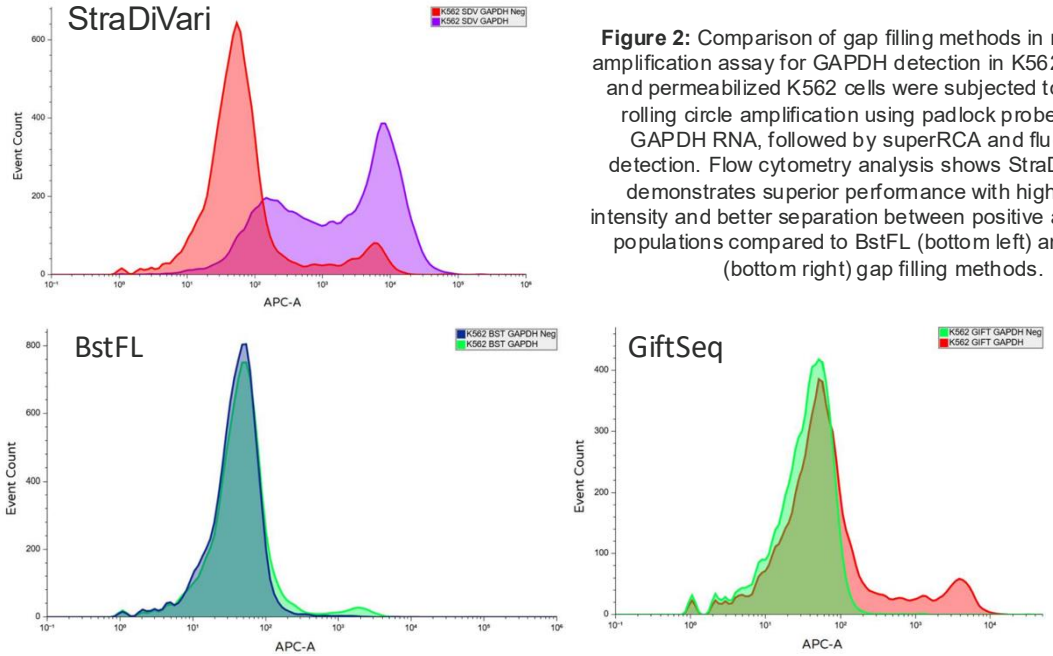

Figure 2: Comparison of gap filling methods in rolling circle amplification assay for GAPDH detection in K562 cells. Fixed and permeabilized K562 cells were subjected to gap filling rolling circle amplification using padlock probes against GAPDH RNA, followed by superRCA and fluorescent detection. Flow cytometry analysis shows StraDiVari (top) demonstrates superior performance with higher signal intensity and better separation between positive and negative populations compared to BstFL (bottom left) and GfitSeq (bottom right) gap filling methods.

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