AccuraCode®: A High-Throughput RNA-seq Method For Efficient Drug Screening

Singleron Biotechnologies, Cologne, Germany

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From Single Cell Multi-omics to Precision Medicine

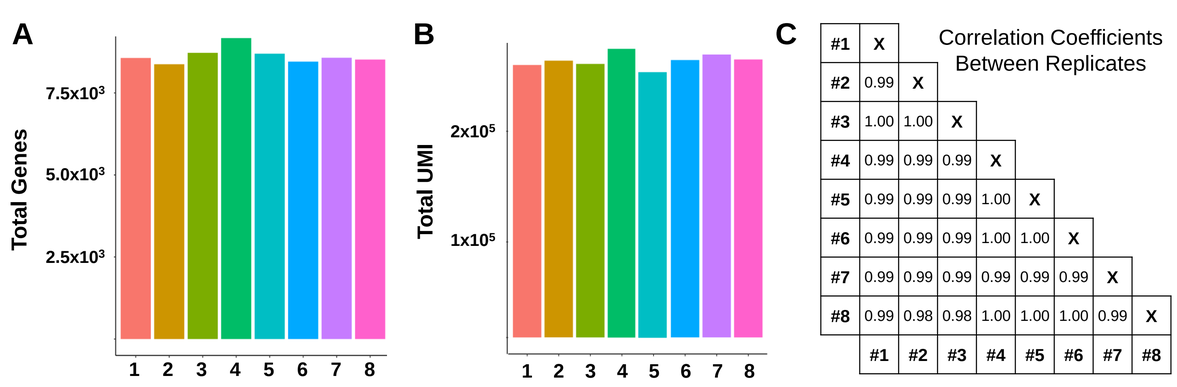
Introduction

High-throughput screens are an essential component of drug discovery and development. RNA-seq can be used to generate comprehensive information on how drugs effect the transcriptome, which then can be used to determine both the efficacy and mechanism of action for a compound. However, RNA-seq library preparation is a costly and tedious procedure, making it difficult to scale up RNA-seq experiments in high-throughput drug screens.

To overcome these challenges we have developed AccuraCode®, a high-throughput RNA-seq library construction method that drastically reduces time and costs compared to traditional RNA-seq. Cell cultures from 384-well plates are barcoded in-plate, followed by a one-step whole transcriptome amplification to yield the cDNA with unique sample barcodes. Since 384 samples can be processed simultaneously in 1 library preparation reaction, the hands-on time and expenses are reduced by more than 90%. Thus, AccuraCode® provides a fast, cost-effective high throughput method which could greatly facilitate the drug discovery process.

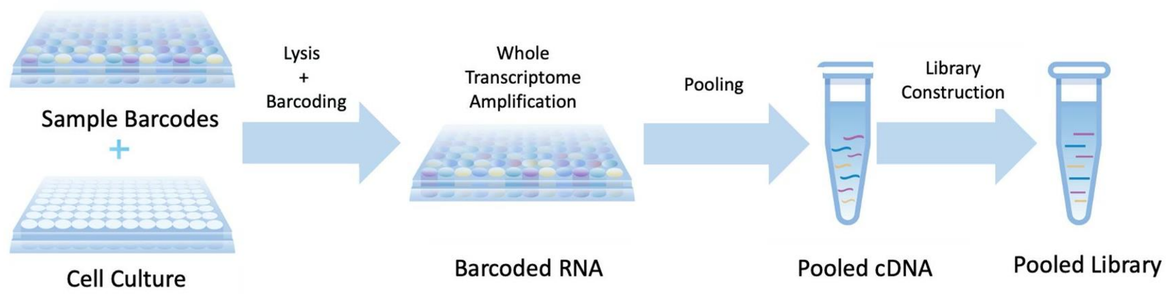
High Reproducibility

Eight samples were processed in parallel and sequenced at 1M reads per sample to examine reproducibility of data output. Total genes (A) and UMI (B) were consistent among the eight replicates. Correlation of the overall gene expression patterns (C) between those eight replicates revealed high reproducibility.

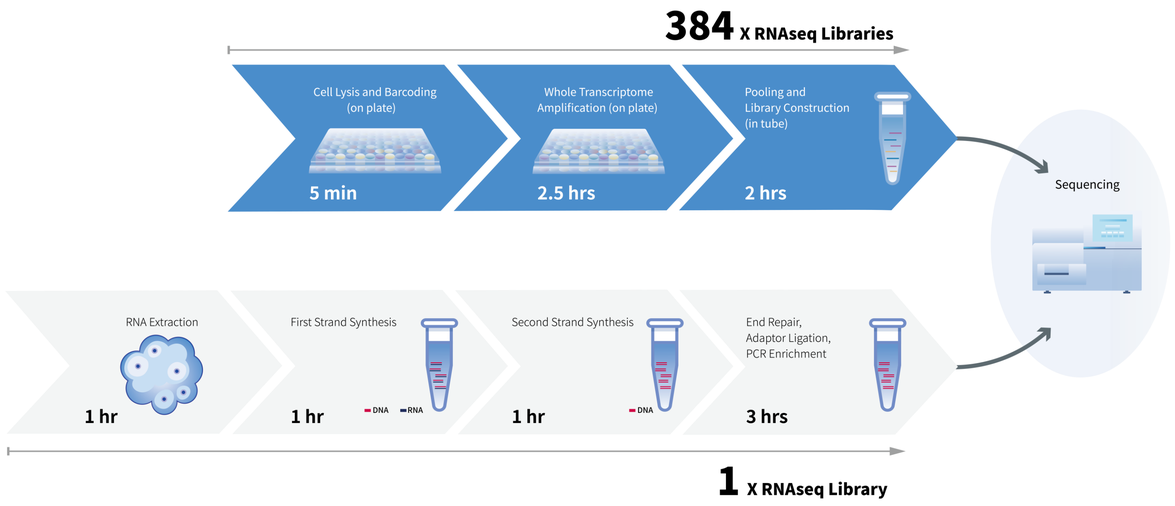


Example Workflow

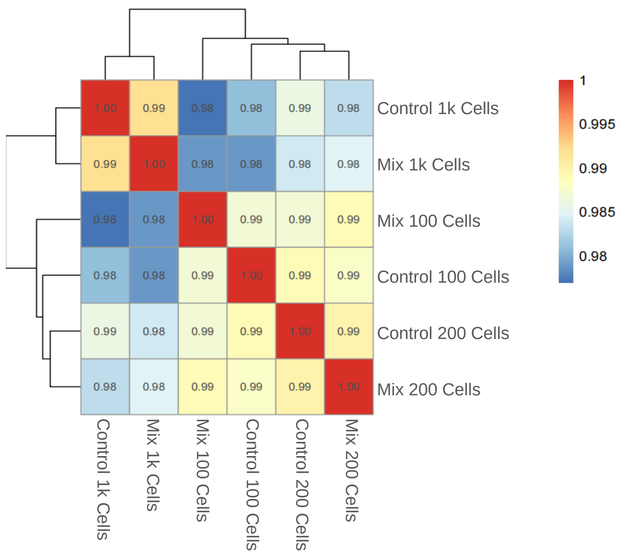
This bulk RNA-sequencing, ultra-high-throughput library construction technology enables drug discovery and screening of drug responses at large scale. Cell lysis, barcoding, and one-step whole transcriptome amplification, are all performed on-plate in 96-well or 384-well plates, then cDNA from plates are pooled and one library construction is conducted. This method massively reduces labor, time and cost by more than 90%.



Time, Labor, And Cost Savings



High Sensitivity

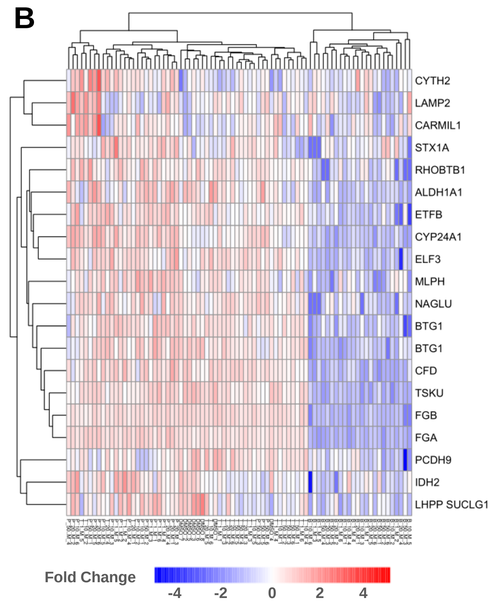


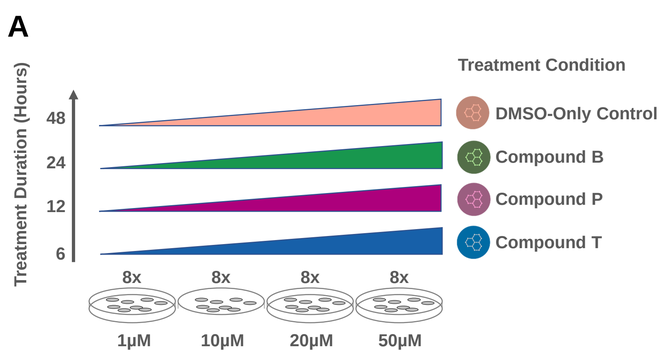
To test whether low cell input has an impact on data reproducibility, we performed library preparation and sequencing of 100, 200, and 1000 cells originating in technical duplicates.

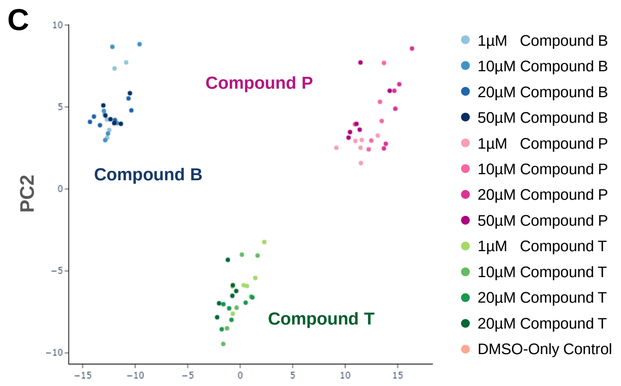
Correlation analysis revealed excellent reproducibility independent of the number of cells processed within one well. Thus, AccuraCode® provides an ultra-high-throughput solution with high sensitivity.

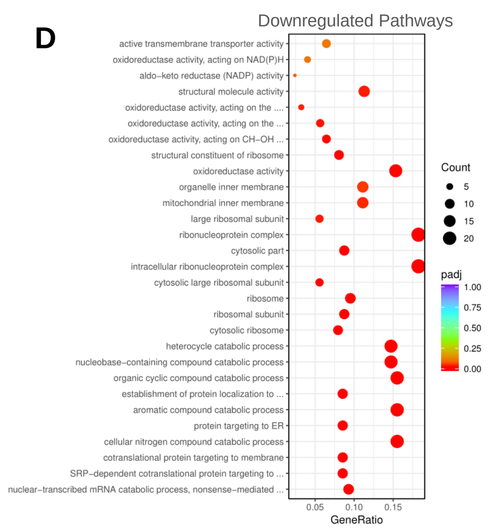
Drug Screening And Drug Response Study

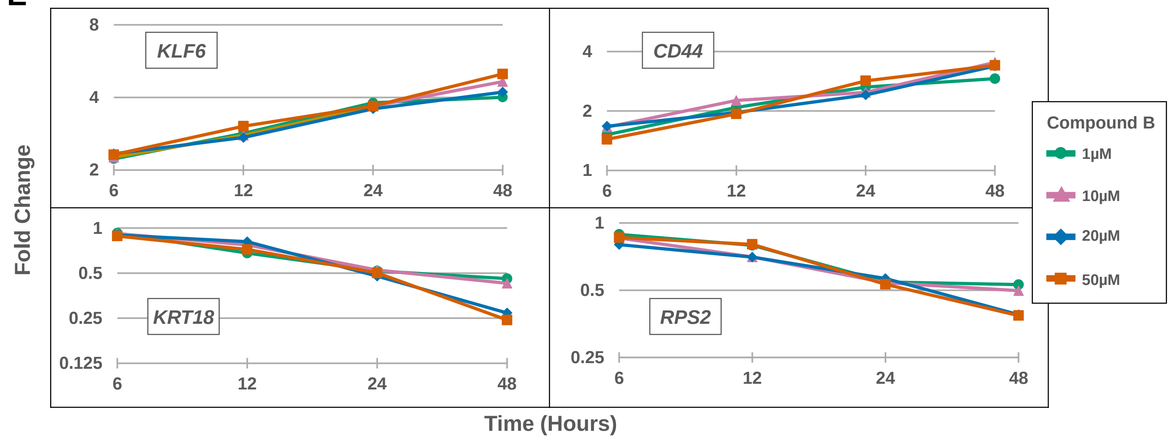
To examine AccuraCode® performance, A549 human lung cancer cells were treated with Compounds B, P, and T for 6-48 hours. (A) Experimental overview. (B) Drug treatment resulted in sample specific changes of various transcripts allowing to decipher the exact molecular mechanisms induced upon drug treatment. (C) Principal component analysis revealed clustering of samples treated with the same drug. (D) Further pinpointing transcriptional changes GO-Term enrichment analysis revealed significant decreases in multiple cellular pathways. (E) Differentially expressed genes could also be tracked in a time-resolved manner.











Conclusion

AccuraCode® is an easy high-throughput RNA-seq method to prepare 384 sample libraries simultaneously within 5 hours and shows high sensitivity, reproducibility, and accurate transcriptome profiles with as few as 100 cells.

AccuraCode® enables efficient transcriptome profiling for drug discovery and screening, and can optimize drug choice, dosing, and timing for treatment.

Contact

info@singleronbio.com
www.singleron.bio
Singleron Biotechnologies GmbH
Gottfried-Hagen-Strasse 60, 51105 Cologne, Germany
Phone: + 49 221 168 24 777