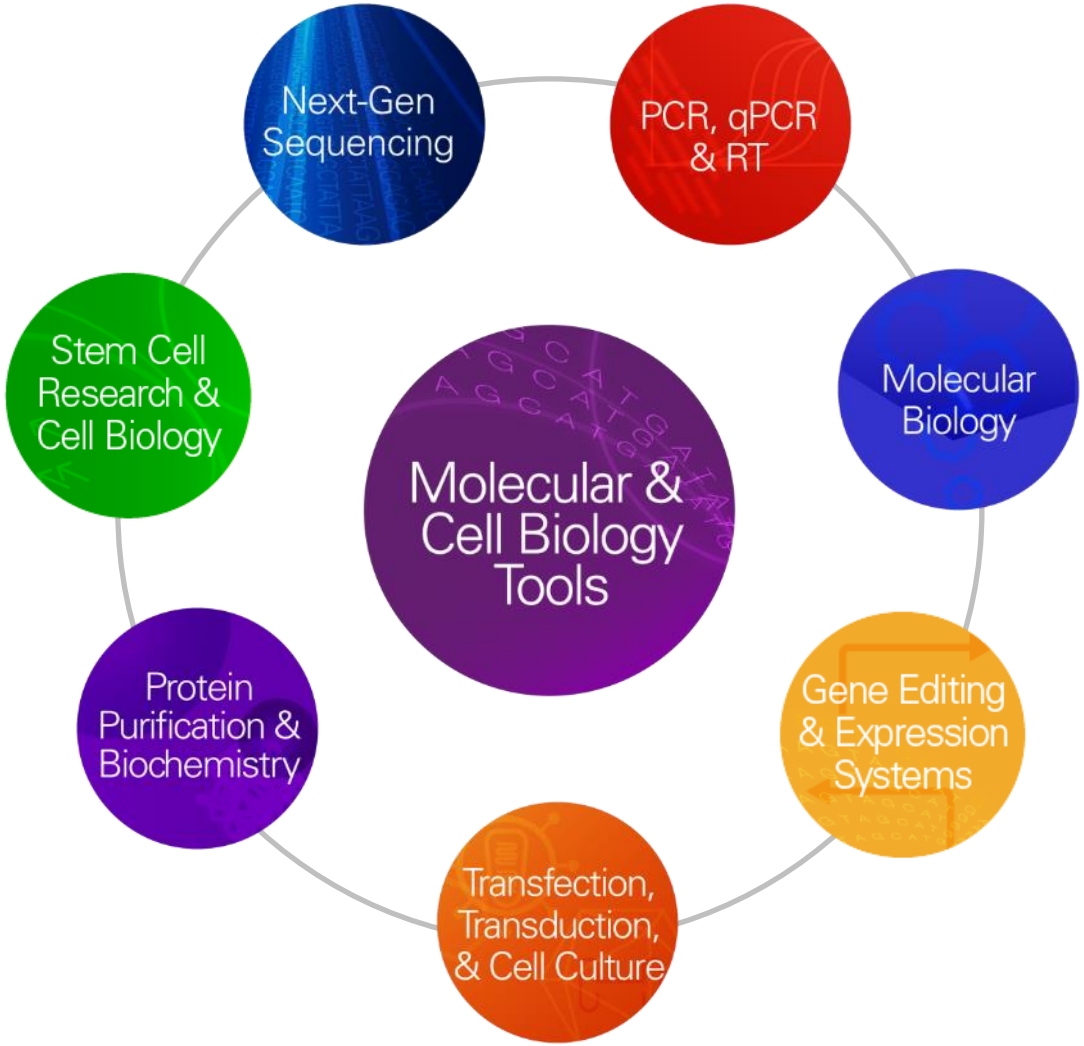
ICELL8 Single-Cell System

Philippe Joanin, PhD
Business Development Manager – Takara Bio Europe

WaferGen – part of Takara Bio Group

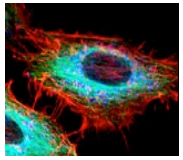
Clontech TaKaRa cellartis

Takara Bio



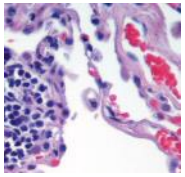
Next-Gen Sequencing

Low-Input Eukaryotic Samples



Single Cells

TCR Profiling



FFPE or Degraded Samples

Prokaryotic Samples

Automation Solutions

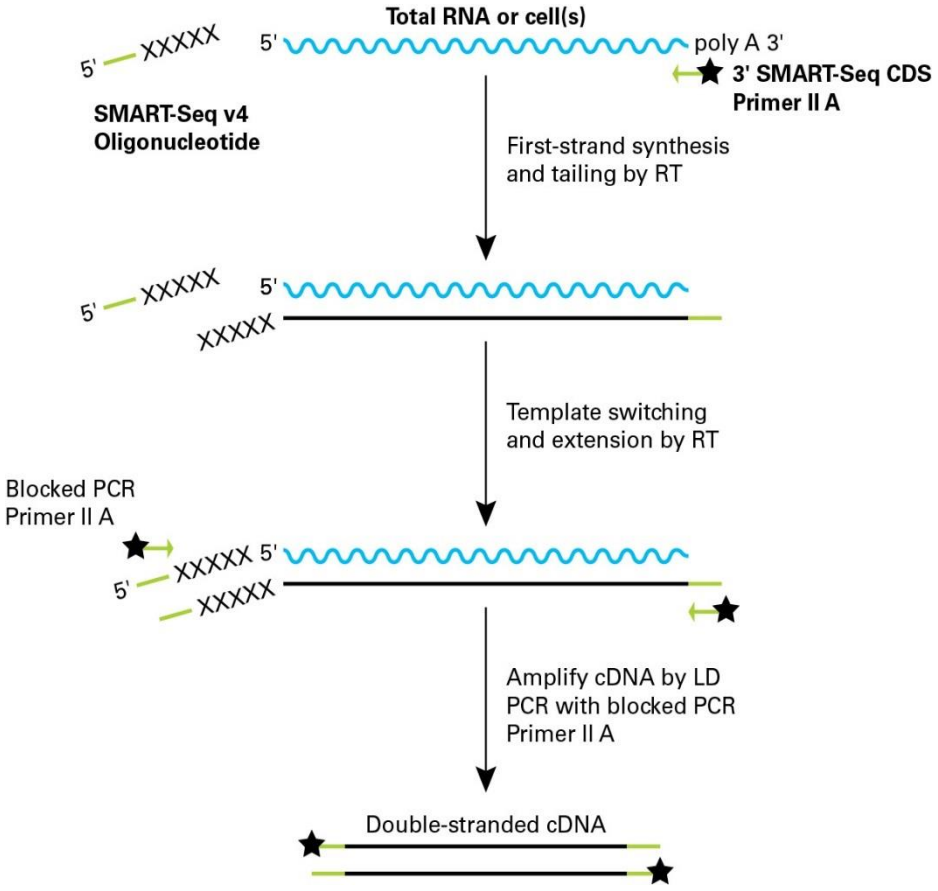
Technology for Low-Input RNA-Seq

Next-Gen Sequencing

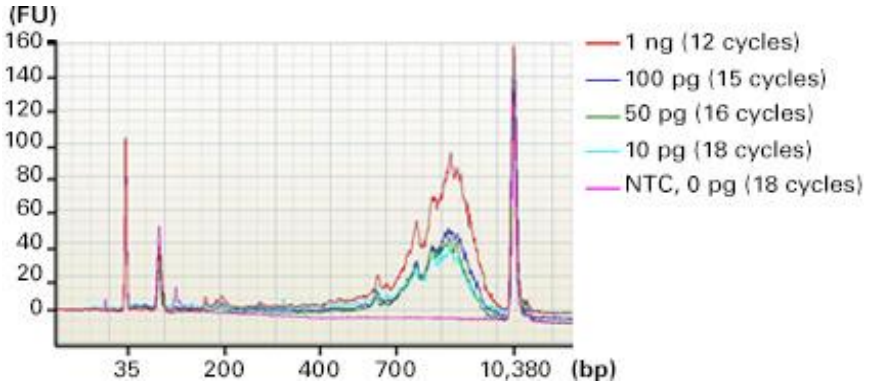
- Industry gold standard for low-input and single-cell RNA-seq
- Confidence in full-length sequence information
- Highest sensitivity in terms of transcripts identified
- Uniform gene-body coverage

Clontech TaKaRa cellartis

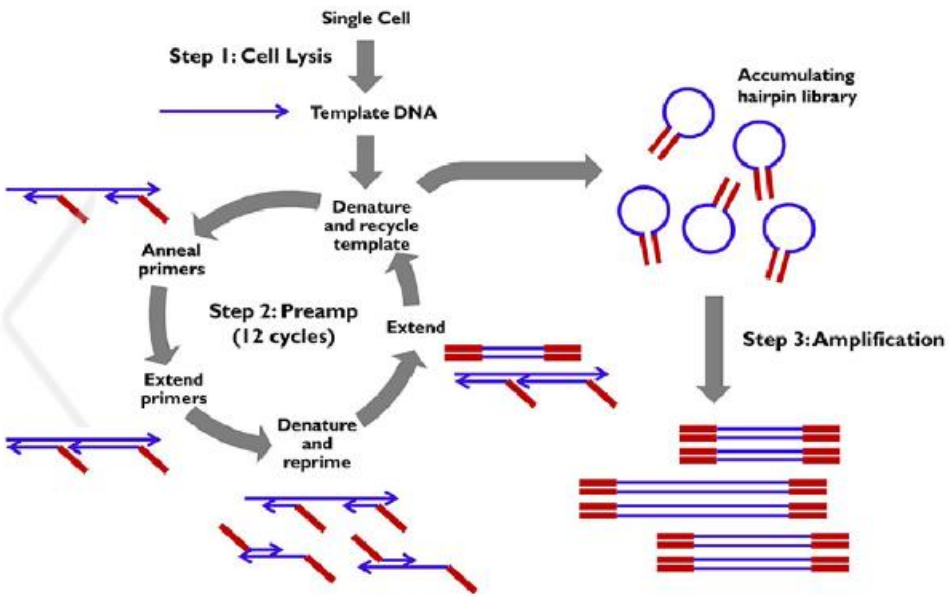
SMART-Seq v4 Ultra Low Input RNA Kit



- Can work directly with cells (1-1000) or total RNA (10pg-10ng)
- Oligo dT-primed. No rRNA removal, no DNAse treatment required
- Single tube workflow.
- Generates full-length cDNA compatible with Ion Torrent or Illumina® library preparation



PicoPLEX DNA-seq Kit



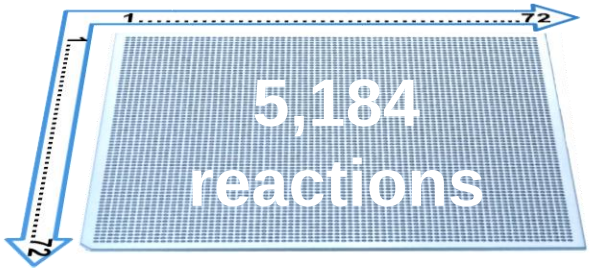
PicoPLEX WGA Kit Technology

Cells are lysed, quasi-random primers pre-amplify the DNA selectively, and a final PCR amplification adds the Illumina barcodes.

- Reproducible results from single cells (or <15 pg DNA)
- Superior reproducibility of allele representation
- Easy to use and automate
- Unambiguous results at all resolutions, microarray, and PCR

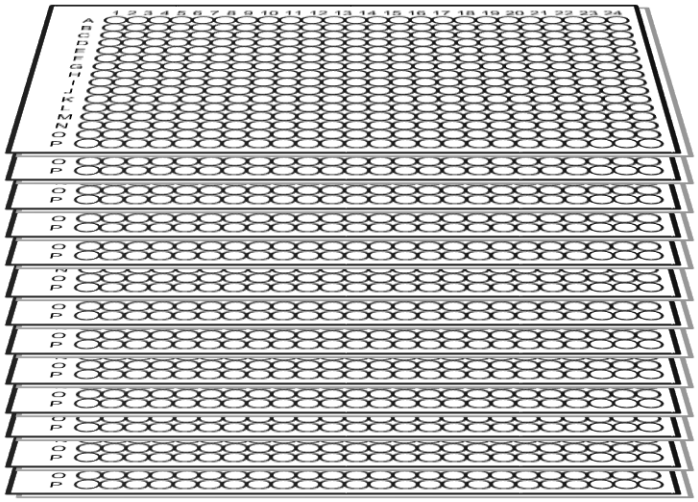
SmartChip

Massively-Parallel Singleplex PCR Technology



SmartChip™

vs.



1x 384-well plate

- 100nl reactions – less reagents, no pre-amplification
- Accurate, fast & flexible nanoliter-dispensing systems
- Target enrichment, gene expression and genotyping
- Single-cell isolation and processing

Comprehensive Portfolio for NGS Analyses

Target Enrichment	Library Prep	PCR Clean-Up	QC	Seq	Variant Verification

SmartChip TE™ & Seq-Ready™ TE

Apollo 324™

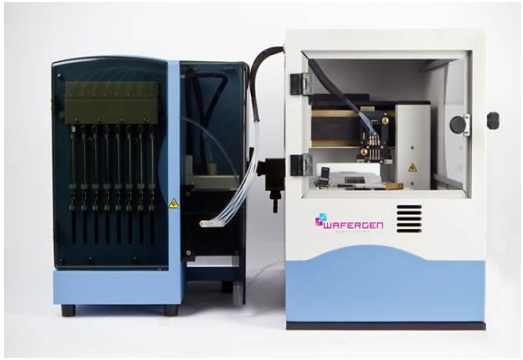
SmartChip MyDesign™

SmartChip MyDesign™

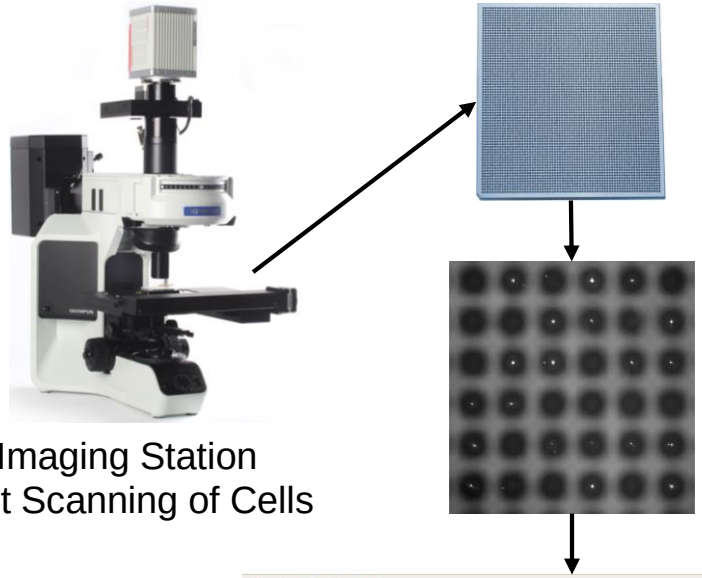
- Whole Genome
- Whole Exome
- RNA-Seq
- Targeted Panels

ICELL8 Single-Cell System

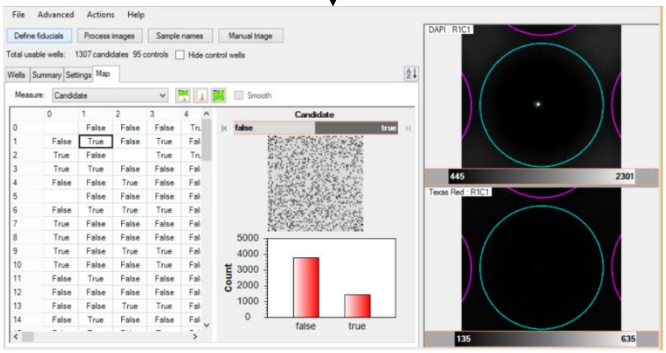
ICELL8 Chips and Reagents
Pre-dispensed with 5,184 barcodes



MultiSample NanoDispenser (MSND)
Rapid Dispensing of Cells and Reagents

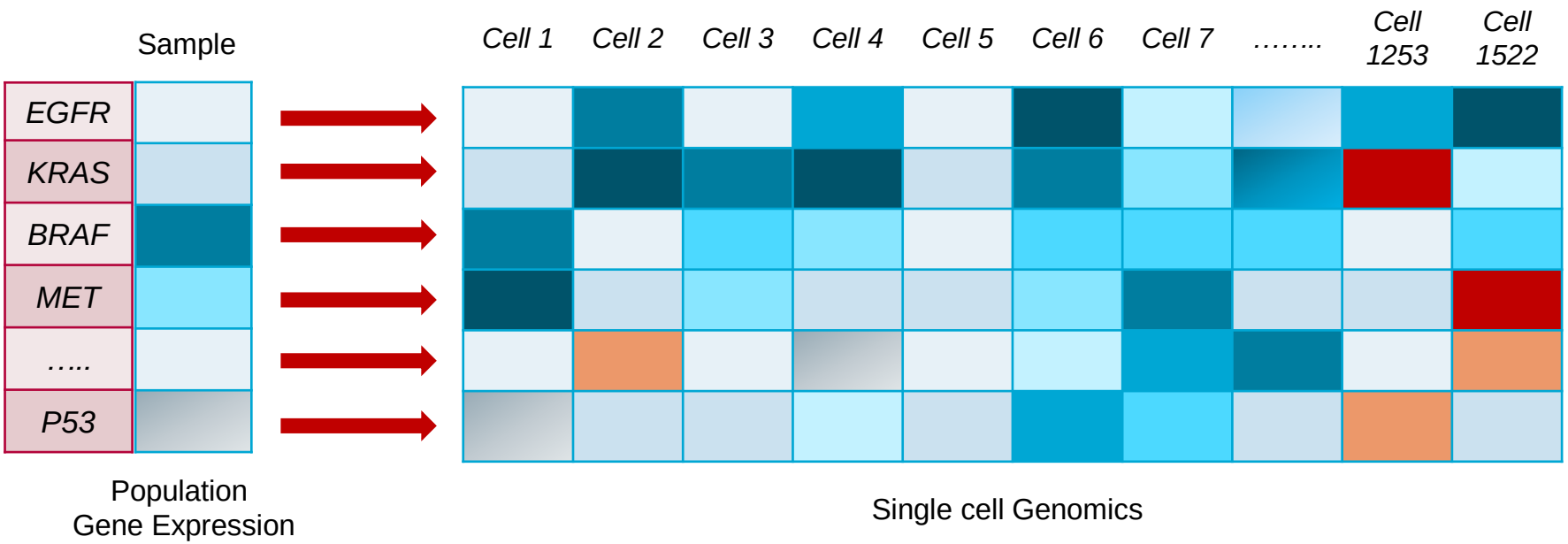


Imaging Station
Fast Scanning of Cells



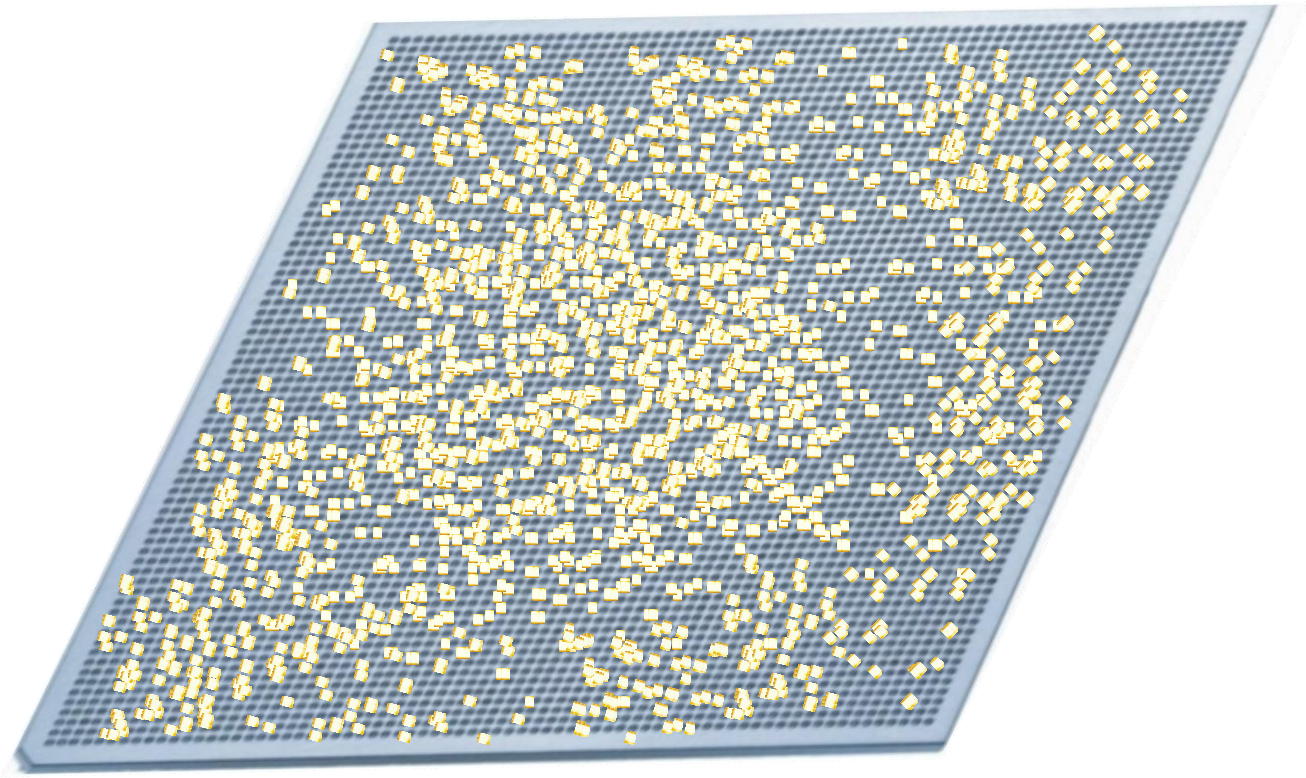
CellSelect Software
Choose Specific Cells of Interest

Issue #1: Power



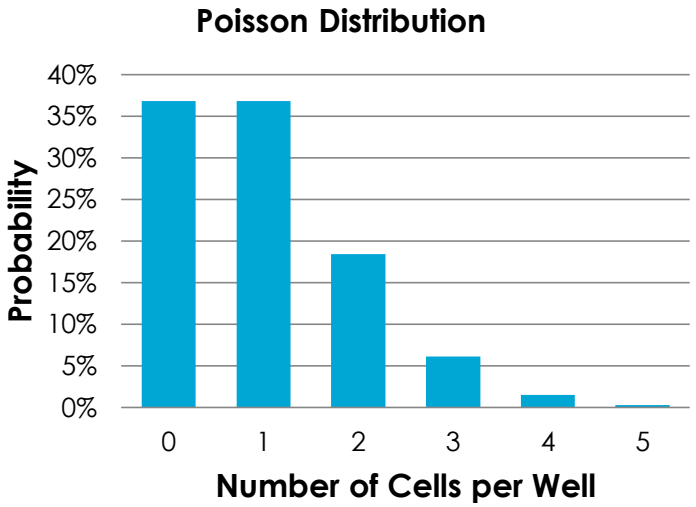
- Single Cell Genomics results in increased sensitivity to detect low frequency changes that are lost in averaged measurements
- Oncology, developmental biology, stem cell research, immunology, neurology etc.

ICELL8: 1800 Cells of Any Type

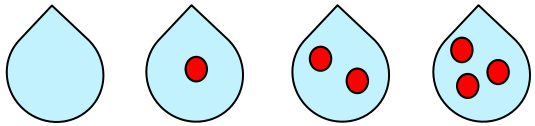


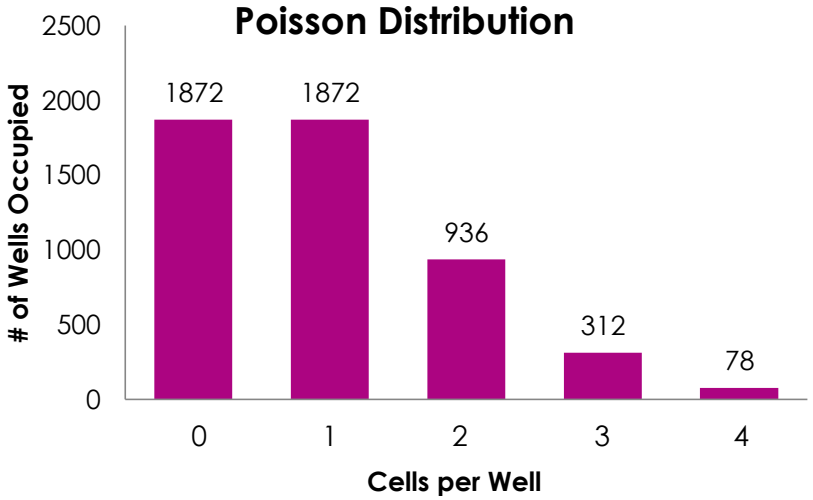
- Isolate more single cells per run
- Analyze cells of any size with unbiased cell isolation

Single-Cell Isolation – Poisson Distribution



Poisson Distribution - The probability of a number of events occurring in a fixed period of time if these events occur with a known average rate and are independent of the time since the last event.





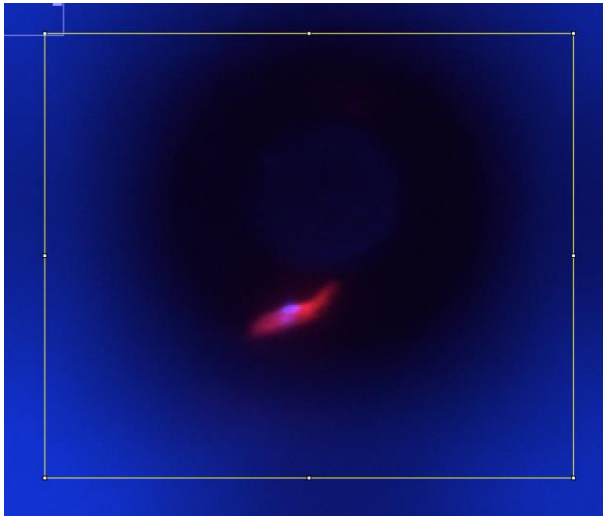
Cell Distribution - The probability of a well containing a single cell is dependent on the starting concentration of cells and the reagent dispense rate and volume to the chip.

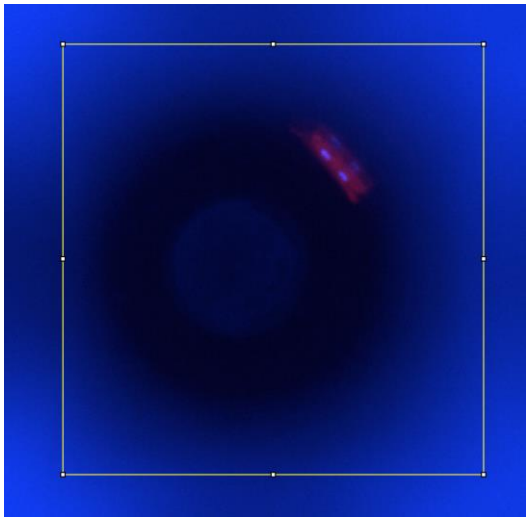
ICELL8 Flexibility

Cell line/type	Specie	Notes
307	Mouse	pancreas
3T3	Mouse	fibroblast
A-20	Mouse	b-lymphocyte
A-375	Human	melanoma
BaF/3	Mouse	pre-B cells
Beta-TC-6	Mouse	pancreas
Bone marrow	Mouse	primary cells
Cardiomyocyte - adult	Mouse	primary cells
Chicken	Chicken	unknown
CHO	Hamster	ovary
Differentiated ESC	Mouse	differentiated cells from ESC
Ear	Mouse	inner ear organs
Embryos	Mouse	primary cells
ESC	Mouse	embryonic stem cells
FACS-sorted lymphocyte	Human	bone marrow
Fetal cortex	Human	primary cells
Fetal neurons	Human	fetal brain
Gut cells	Mosquito	gut
H2452	Human	lung
HCT 116	Human	colon
HEK-293	Human	kidney embryo
HSPC	Mouse	hematopoietic stem cells

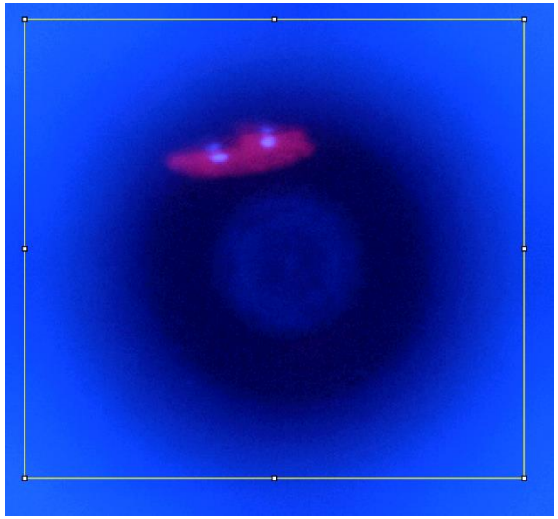
Cell line/type	Specie	Notes
K562	Human	bone marrow lymphoblast, CML
KU812	Human	blood, CML myeloblast
Lung epithelia	Mouse	primary FACS-sorted cells
MCF7	Human	breast
MDA-MB-231	Human	mammary gland
MIA PaCa-2	Human	pancreas
Nasal epithelia	Human	primary nasal scraping
NCH421K	Human	glioma/glioblastoma
NCH644	Human	glioma/glioblastoma
Neurons	Mouse	fresh dissection
Nuclei	Human	frozen lung tumour
Nuclei	Human	frozen breast cancer
PBMCs	Human	blood
Planaria SC	Planarium	stem cells
Retina	Mouse	primary cells
Scheider S2	Drosophila	embryo
SK-BR3	Human	breast
Skin	Zebrafish	skin
Spheroids	Human	MCF10CA-derived
U-87-MG	Human	glioblastoma; astrocytoma
UTHSC	Human	bone marrow EW-8 Ewing Sarcoma
Z-138	Human	B-cell lymphoma

Isolate Cells of Any Size



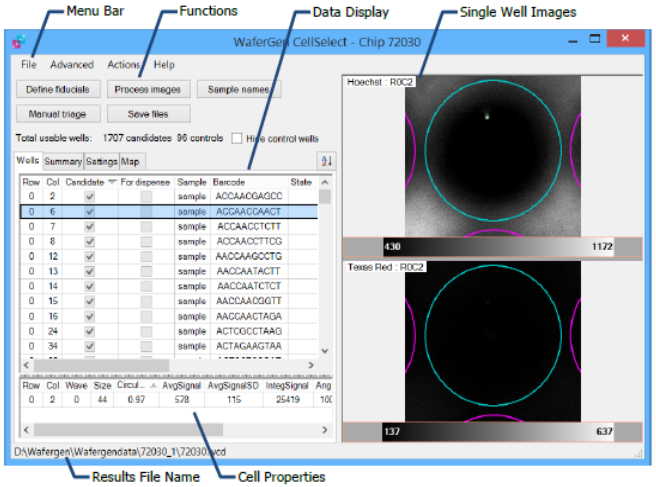


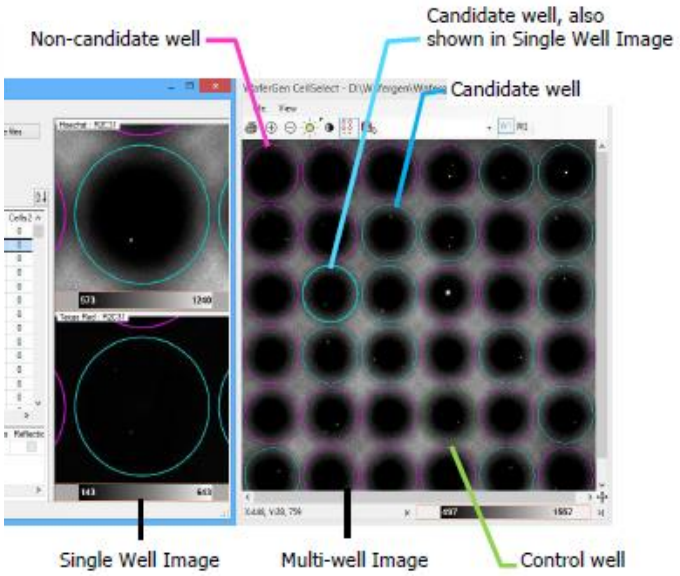
Freshly-isolated mouse cardiomyocyte



Courtesy of MPI for Heart and Lung Research

Power is Nothing Without Control





- Automated chip scanning (12 minutes total time)
- Automated identification of single-cell containing wells
- Tuneable selection to meet cell-specific parameters
- Phenotypic selection of cells of interest
- Optional down-selection to reduce sequencing costs

CellSelect™ Automatically Identifies Viable Cells

Human Fetal Neurons Isolated by FACS– Well Selected For RT Mastermix Dispense

File Advanced Actions Help

Define fiducials | Process images | Sample names | Manual triage | Save files

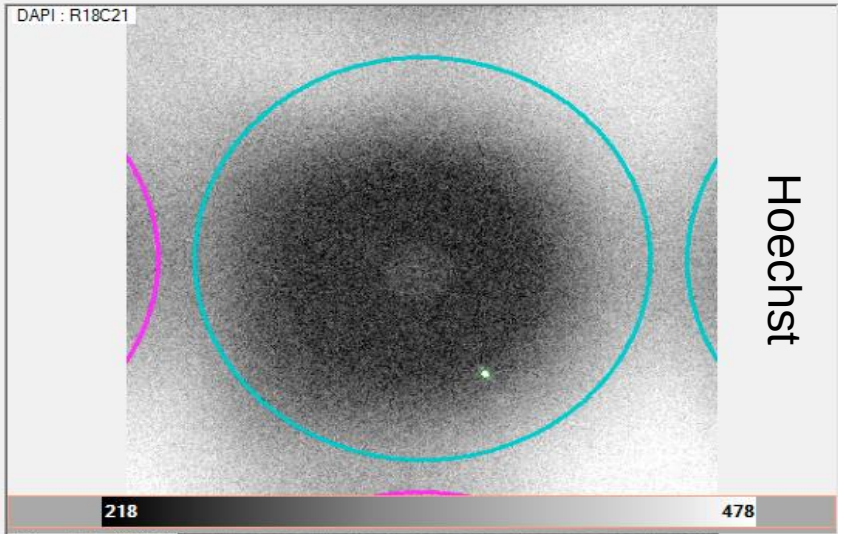
Total usable wells: 813 candidates 8 controls ☐ Hide control wells

Wells | Summary | Settings | Map

Row	Col	Candidate	For dispense	Sample	Barcode	State	Cells1
18	17	☐	☐	Sample	AGTTGGCAAGC	HasDeadCells	3
18	18	☐	☐	Sample	ATAACCAAGTT	HasDeadCells	4
18	19	☐	☐	Sample	ATAGTTCTCGT	MultipleCells	2
18	20	☐	☐	Sample	ATATAGTACCT	HasDeadCells	5
18	21	☑	☑	Sample	AGTTCTGATGA	Good	1
18	22	☑	☑	Sample	AGTTGCGAGGT	Good	1
18	23	☐	☐	Sample	AGTTGGTCTCG	NoCells	0
18	24	☑	☑	Sample	CCAAGAGACGG	Good	1
18	25	☐	☐	Sample	CCAAGCATTCG	MultipleCells	2
18	26	☑	☑	Sample	CCAAGCCGAGC	Good	1
18	27	☐	☐	Sample	CCAACTTATAA	MultipleCells	2
18	28	☐	☐	Sample	CCAACTTCGCA	HasDeadCells	6
18	29	☐	☐	Sample	CCAAGACTTCT	HasDeadCells	8
18	30	☐	☐	Sample	CCAAGATGCCG	HasDeadCells	3
18	31	☐	☐	Sample	CCAAGCCAGCT	MultipleCells	2
18	32	☐	☐	Sample	CCAAGCCATGG	Cluster	2
18	33	☑	☑	Sample	CCAACTGGCGA	Good	1
18	34	☐	☐	Sample	CCAAGAACTAA	HasDeadCells	2
18	35	☐	☐	Sample	CCAAGAGAACT	Inconclusive	1
18	36	☐	☐	Sample	ATTGACGCGCC	NoCells	0
18	37	☐	☐	Sample	ATTGATGATTC	HasDeadCells	2
18	38	☐	☐	Sample	ATTGCGACCTA	MultipleCells	2
18	39	☐	☐	Sample	ATTCGCGCGAA	HasDeadCells	6
18	40	☐	☐	Sample	ATTCGGCCTCA	MultipleCells	3

Row	Col	Wave	Size	Circularity	AvgSignal	AvgSignalSD	IntegSignal	Angle	Radius	Reflection
18	21	1	43	1.00	165	84	7109	296	99	☐

Fully automated chip scanning (6 min per 2 channels)



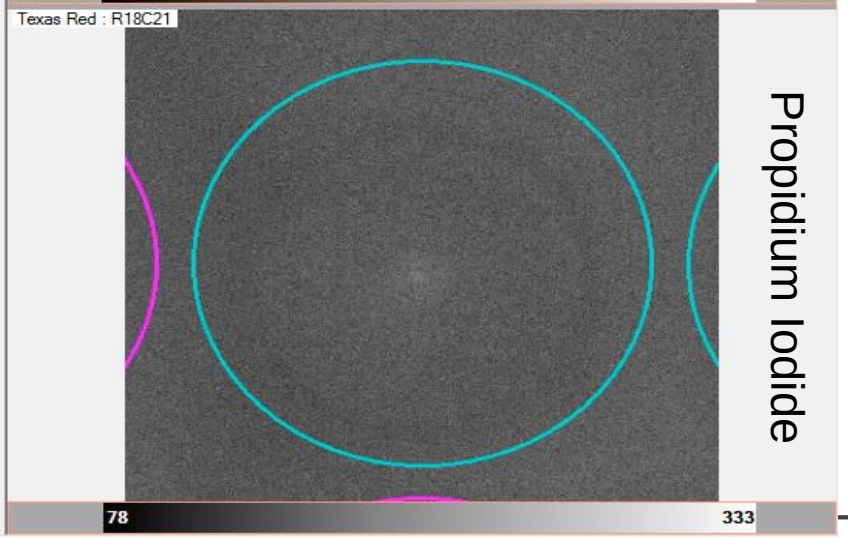
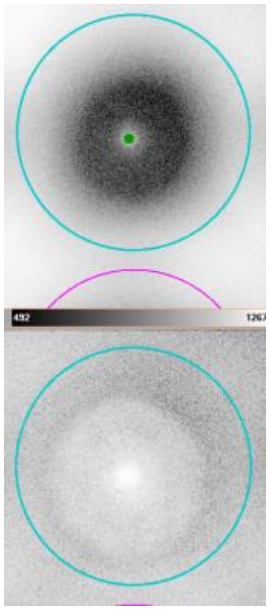


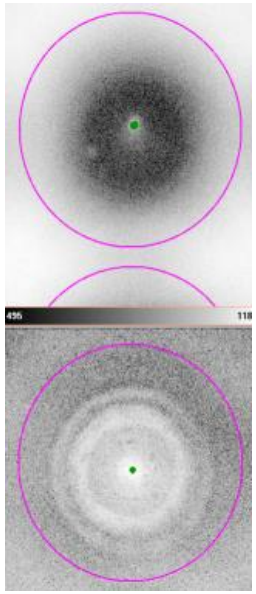
Image Analysis Software

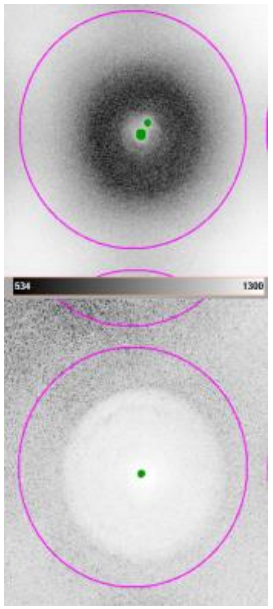
Automatically Identifies Viable Cells

Hoechst 33342
(DAPI) Total Cells

Propidium Iodide
"Dead"



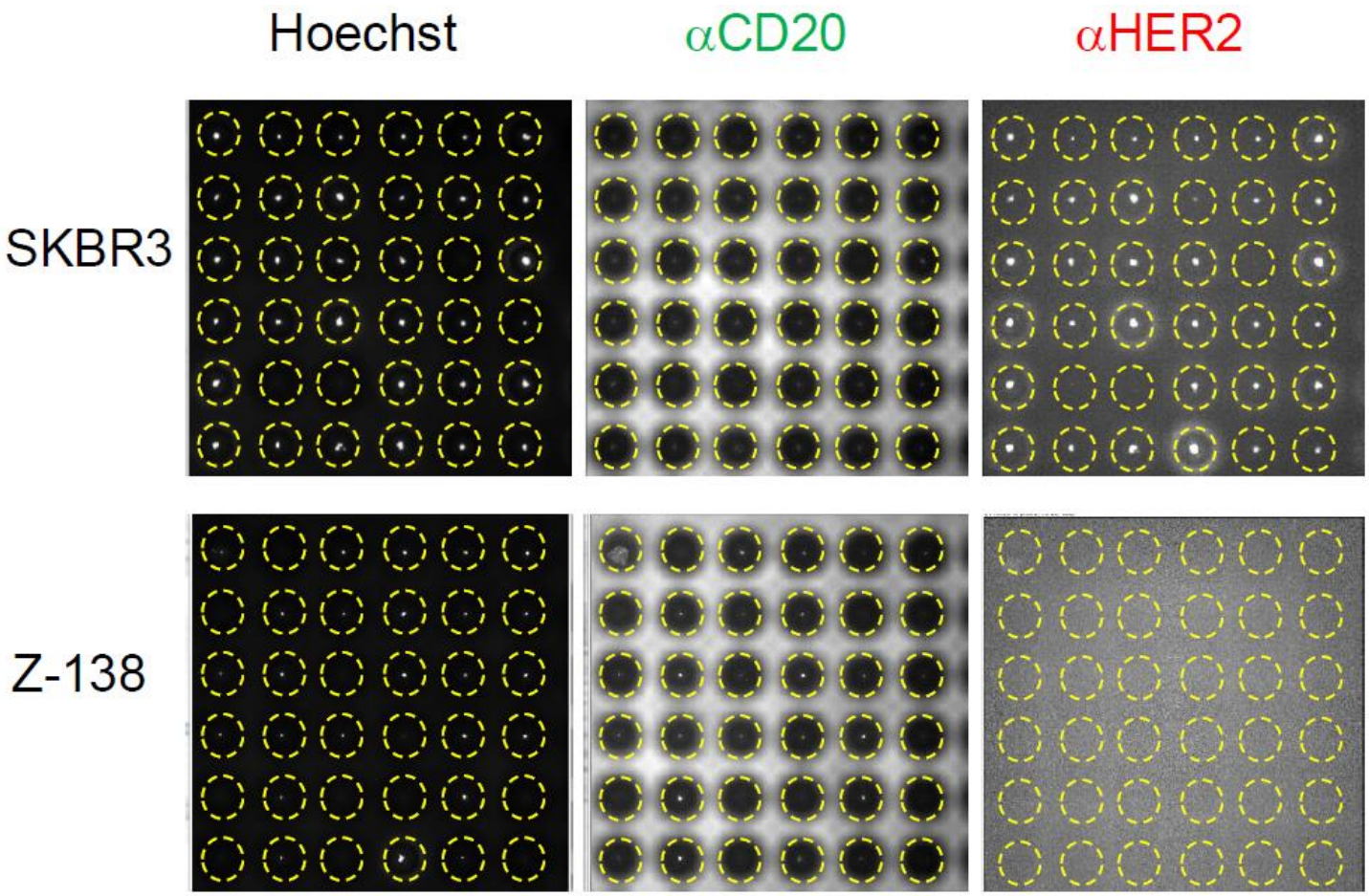




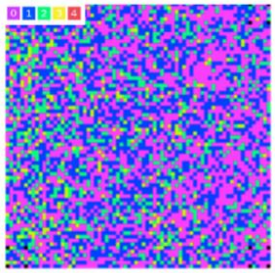
Has 1 cell No dead cells Accept	Has 1 cell Cell is dead Reject	Has 2 cells 1 cell is dead 1 cell is alive Reject

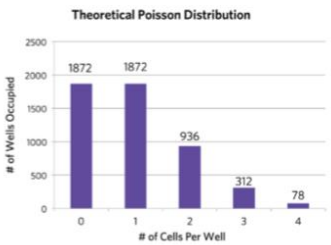
CellSelect Software allows stained cells from up to 8 different samples to be individually counted and selected for subsequent reagent dispense

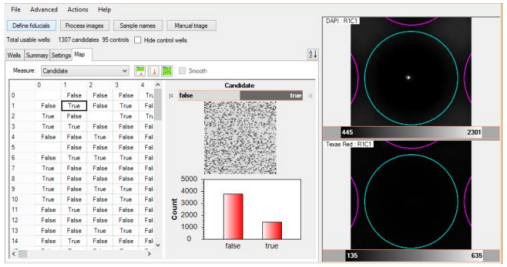
Antibody-based Selection

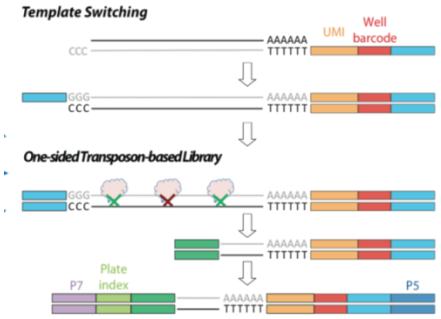


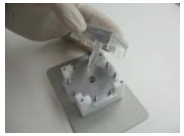
ICELL8 RNA-seq Workflow







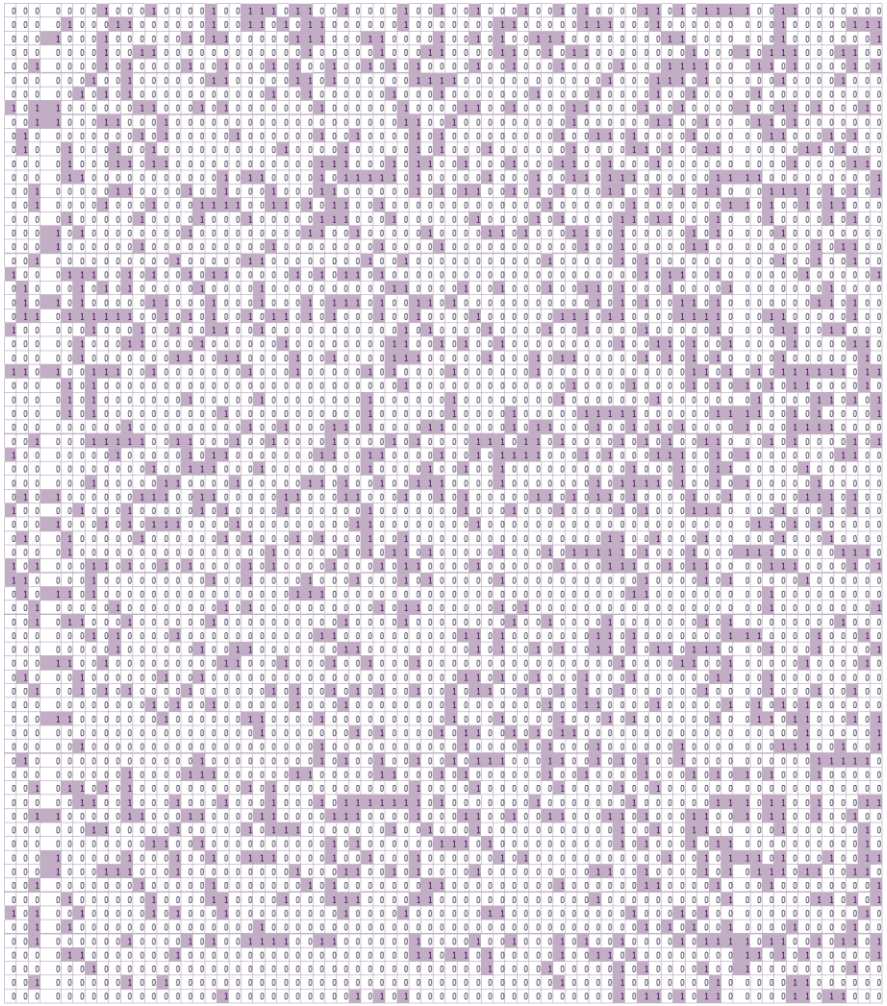




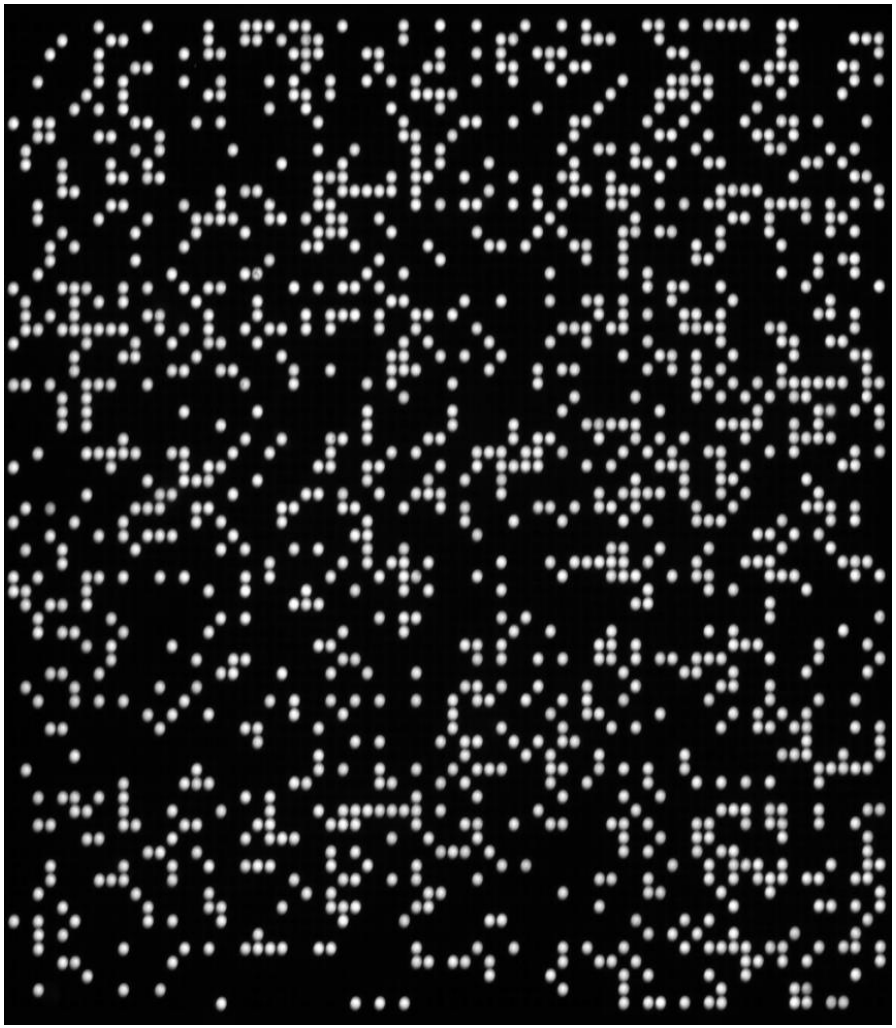
Cell preparation (dissociate, stain, and count)	Dispense cells, controls, and the fiducial	Image wells. Freeze the chip. Select nano-wells for processing	Dispense RT-PCR reagents and perform cDNA amplification	Amplicon extraction and concentration	Nextera® XT sequencing library preparation

ICELL8 Single-Cell System

High-Fidelity Reagent Dispensing to Selected Wells

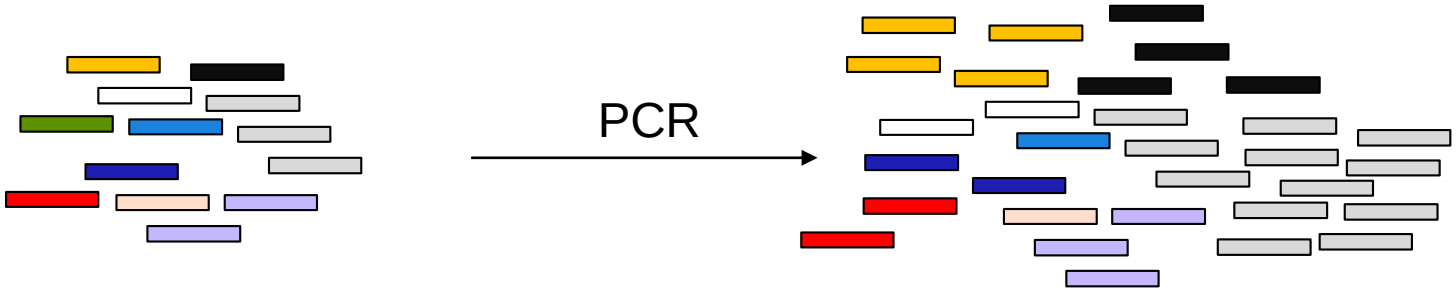


Filter File

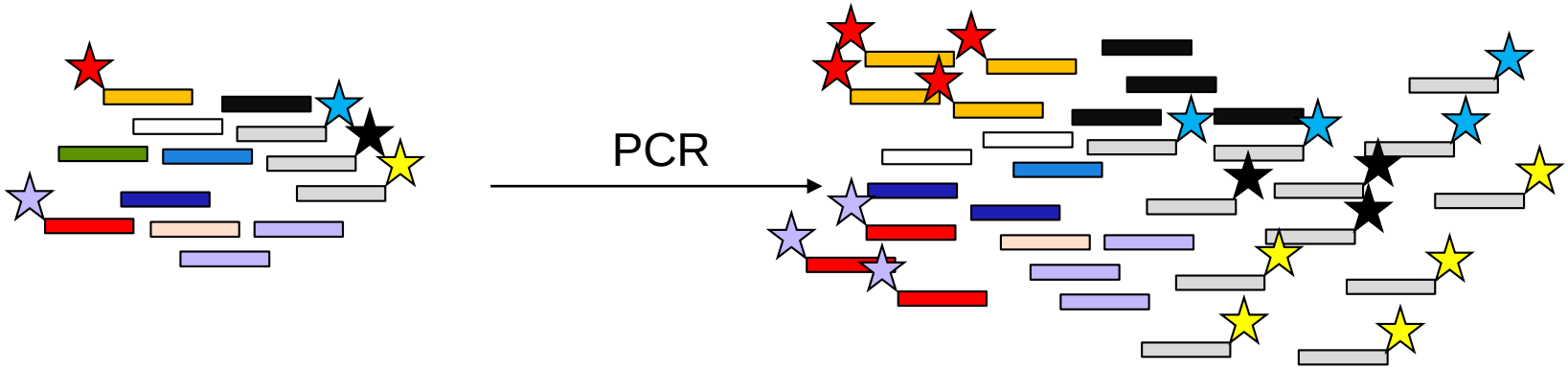


Dispense Map

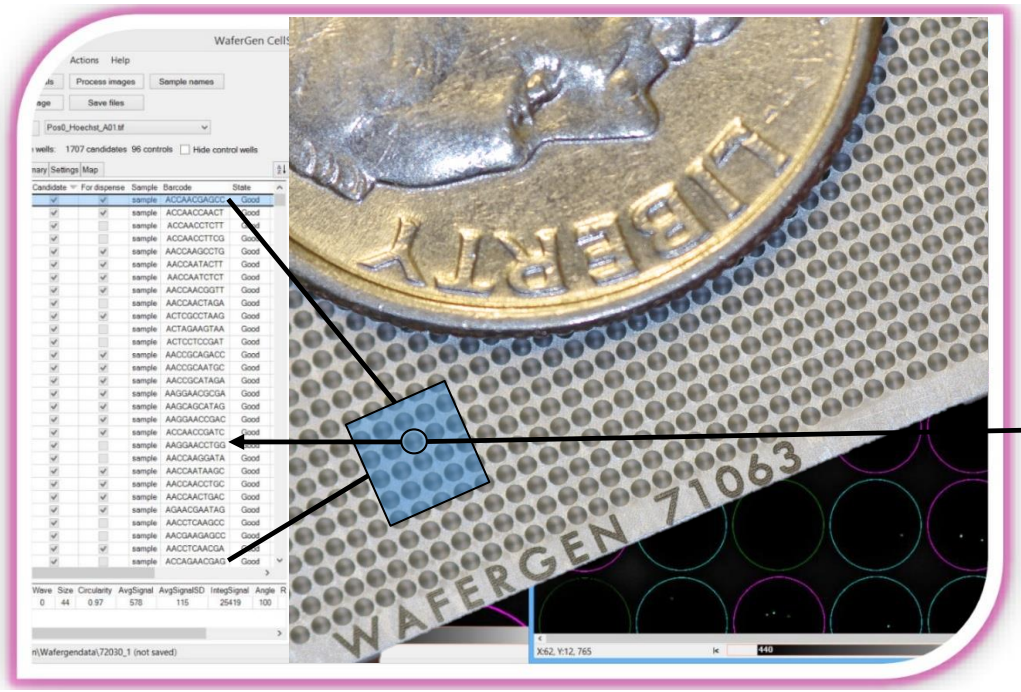
UMI for real counting



Transcript tagging with Unique Molecular Identifiers (UMI)



ICELL8 Chip NanoWell Technology



Well Barcode +

AAGGAACCTGG…

UMI N(11)

…AAGGAACCTGGG

…AAGGAACCTGGG

1

UMI combinations Per Well Barcode

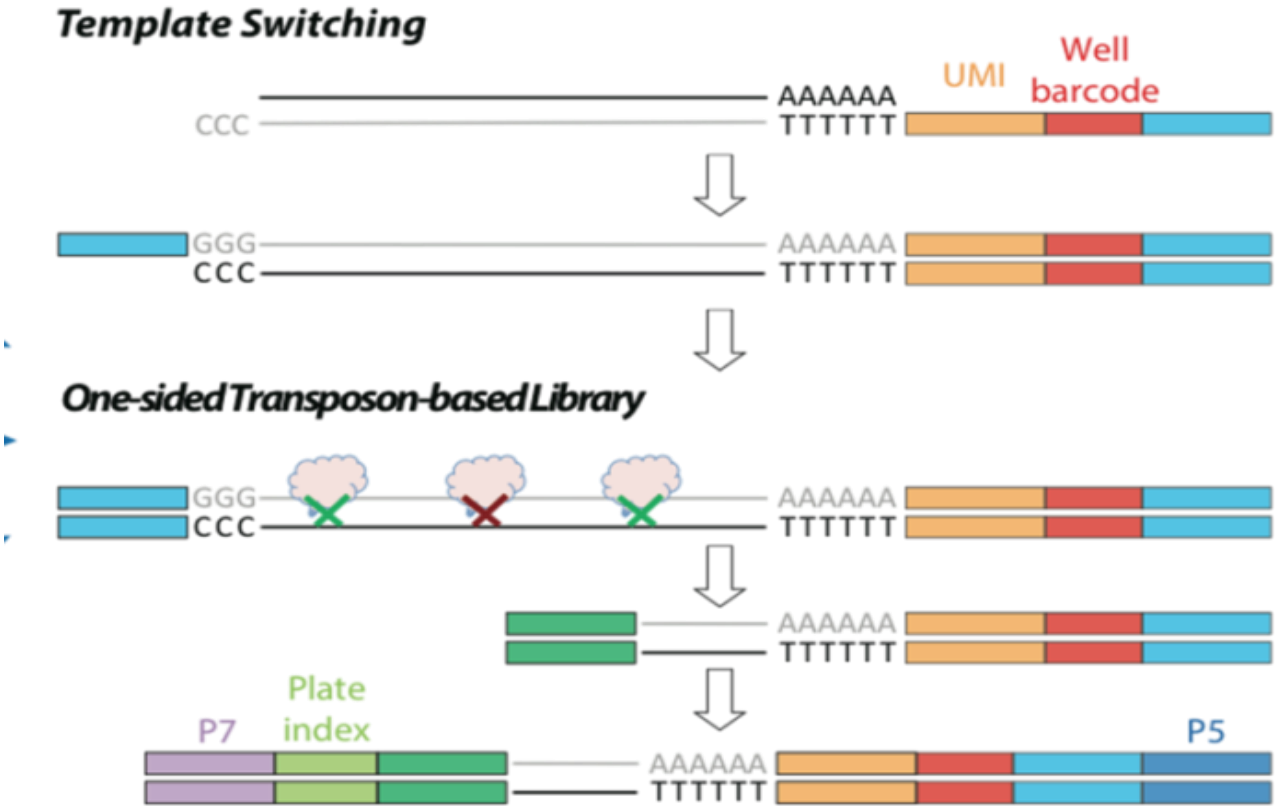
1,000,000

…AAGGAACCTGGG

- 5184 uniquely barcoded wells
- CellSelect software links well bar codes to image
- Over 1 Million Unique Molecule Identifiers per well barcode

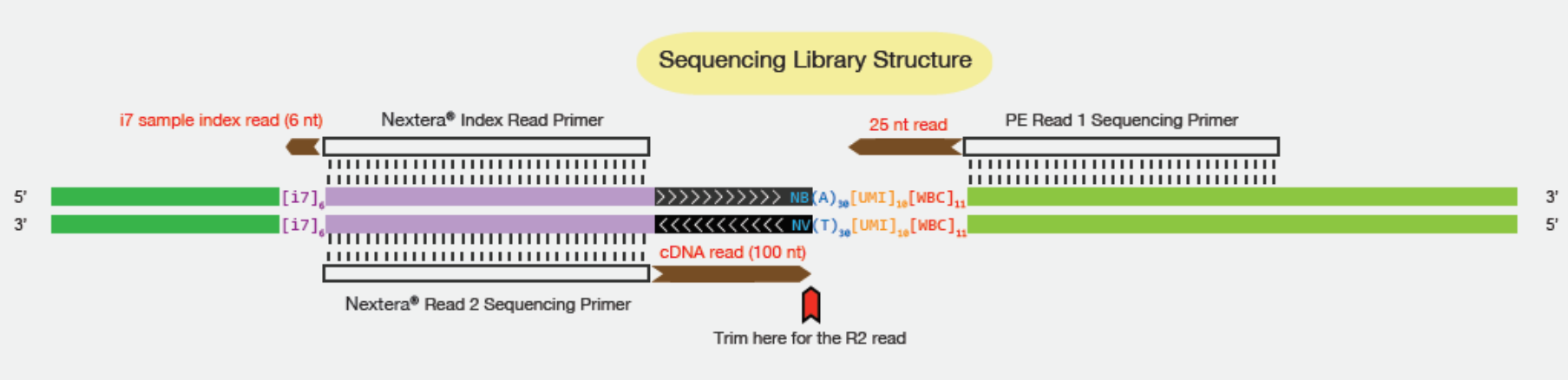
SmartChip Single Cell Workflow

Collaboration with the Broad Institute

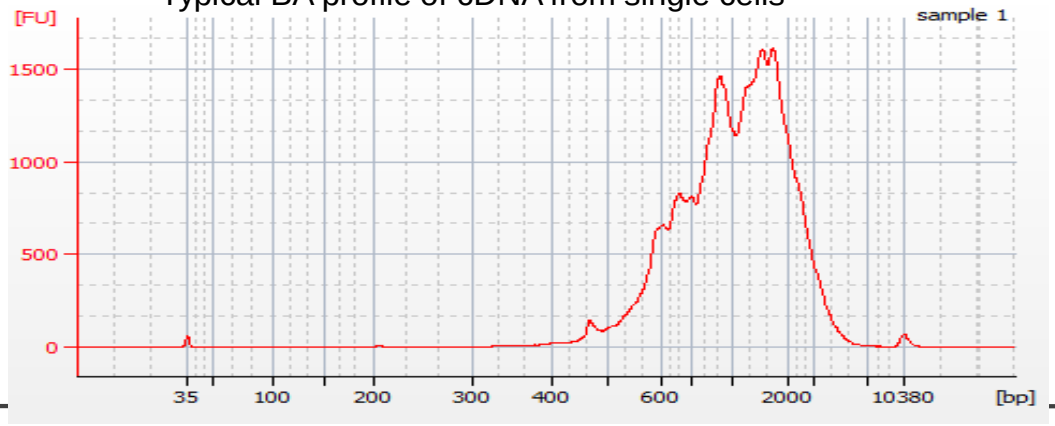


Library Structure – 3'Tag Counting

UMI = Unique Molecular Identifier (*de novo* transcript counting)
WBC = Nano-well barcode or cell specific barcode
Sample ID = Chip index



Typical BA profile of cDNA from single cells



Issue #2: Batch Effects

On the widespread and critical impact of systematic bias and batch effects in single-cell RNA-Seq data

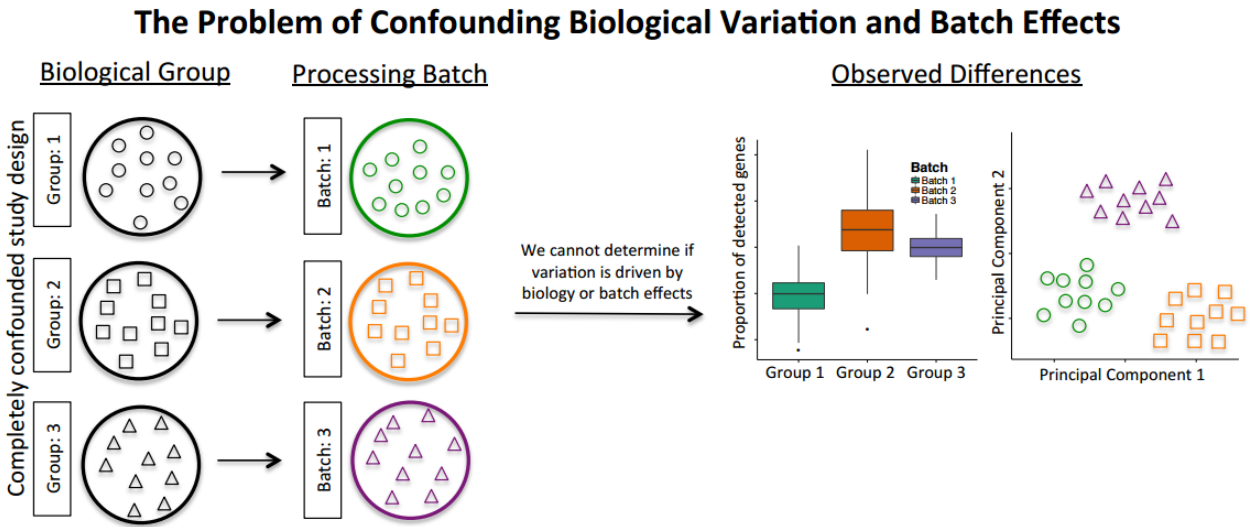
Stephanie C. Hicks[1,2] , Mingxiang Teng[1,2], Rafael A. Irizarry[1,2,*]

[1]Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute,

[2]Department of Biostatistics, Harvard School of Public Health

[*]Corresponding Author

Study Design



Issue #2: Batch Effects

Batch effects and the effective design of single-cell gene expression studies

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Issue #2: Batch Effects

Abstract

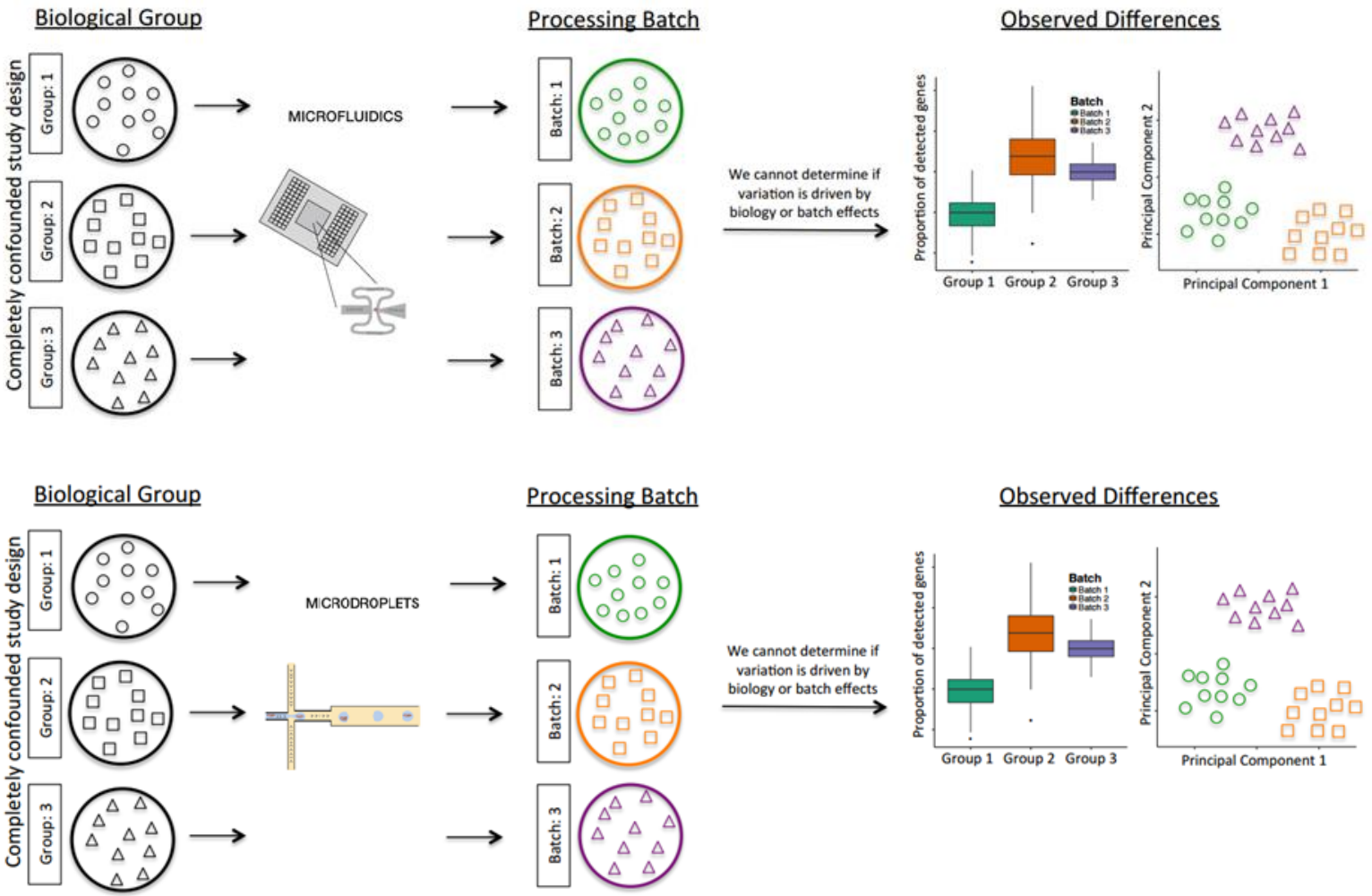
Single cell RNA sequencing (scRNA-seq) can be used to characterize variation in gene expression levels at high resolution. However, the sources of experimental noise in scRNA-seq are not yet well understood. We investigated the technical variation associated with sample processing using the single cell Fluidigm C1 platform. To do so, we processed three C1 replicates from three human induced pluripotent stem cell (iPSC) lines. We added unique molecular identifiers (UMIs) to all samples, to account for amplification bias. We found that the major source of variation in the gene expression data was driven by genotype, but we also observed substantial variation between the technical replicates. We observed that the conversion of reads to molecules using the UMIs was impacted by both biological and technical variation, indicating that UMI counts are not an unbiased estimator of gene expression levels. Based on our results, we suggest a framework for effective scRNA-seq studies.

Issue #2: Batch Effects

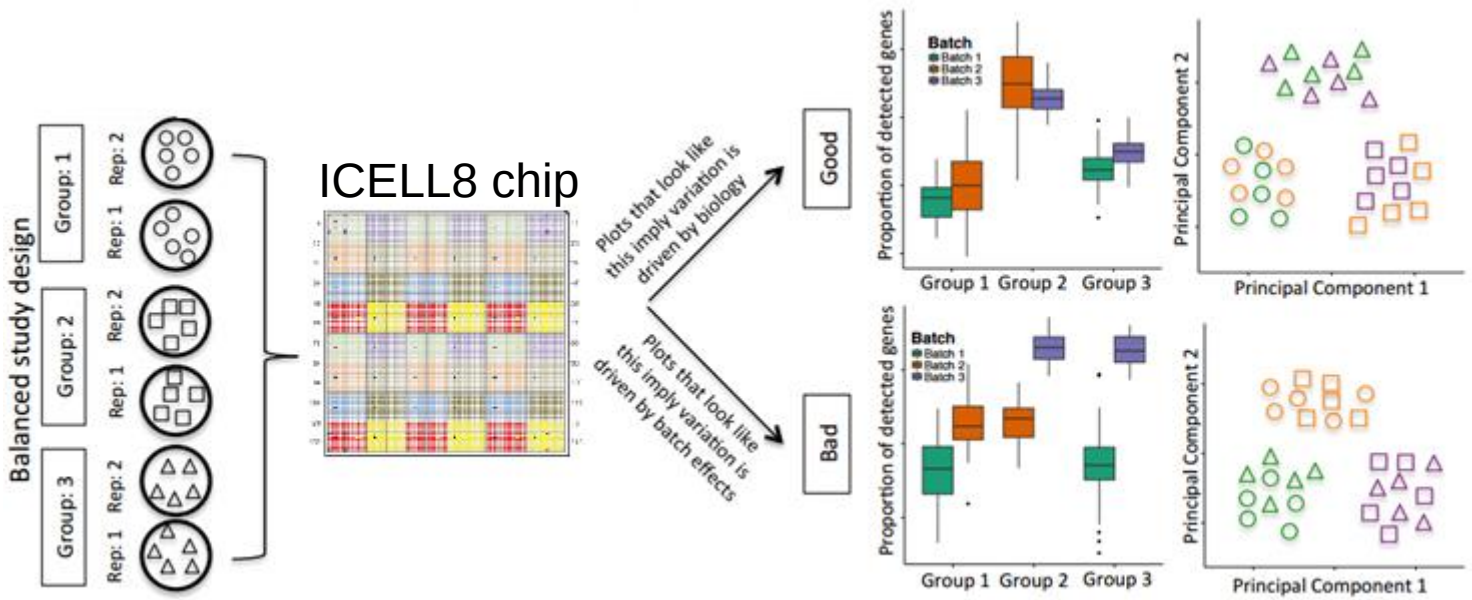
Outlook

Single cell experiments are ideally suited to study gene regulatory noise and robustness [32,33]. Yet, in order to study the biological noise in gene expression levels, it is imperative that one should be able to effectively estimate and account for the technical noise in single cell gene expression data. Our results indicate that previous single cells gene expression studies may not have been able to distinguish between the technical and the biological components of variation, because single cell samples from each biological condition were processed on a single C1 batch. When technical noise is properly accounted for, even in this small pilot study, our findings indicate pervasive inter-individual differences in gene regulatory noise, independently of the overall gene expression level.

Study Design



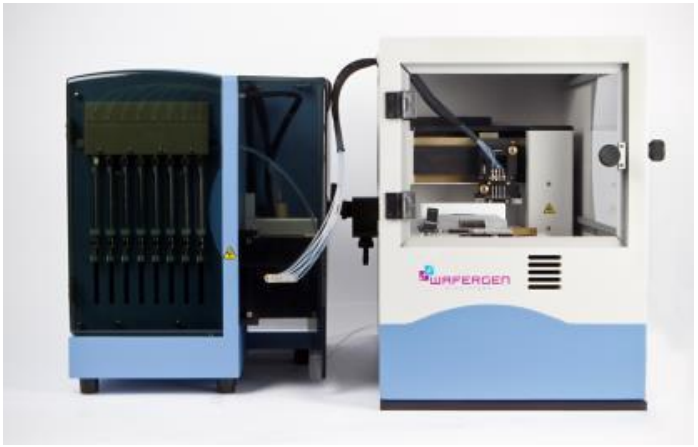
Study Design

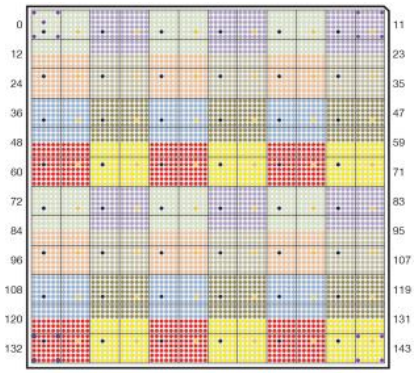


- Up to 8 samples per experiment
- Stopping points allow parallel processing
- No cell-size bias
- Hundreds of cells per sample

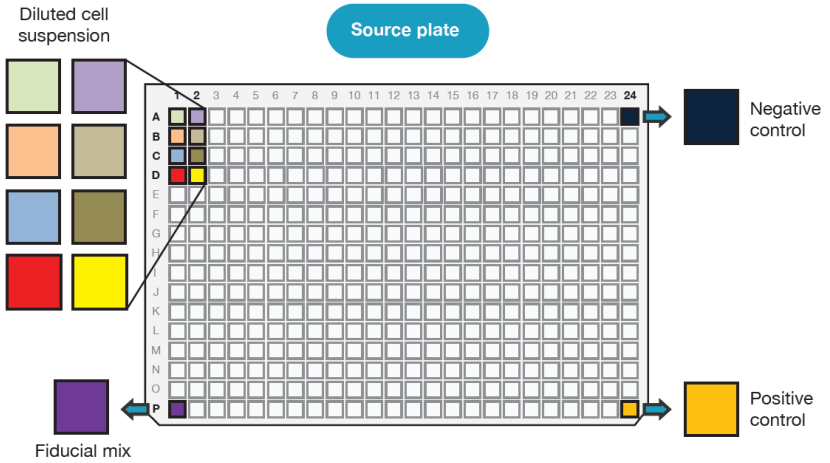
MultiSample NanoDispenser (MSND)

- 8 channel microsolenoid controlled dispenser
- 50nl dispensing volume in pre-programmed patterns
- Humidity and temperature control to minimize evaporation during dispensing and maintain cell viability
- Full chip dispensed in 13 minutes

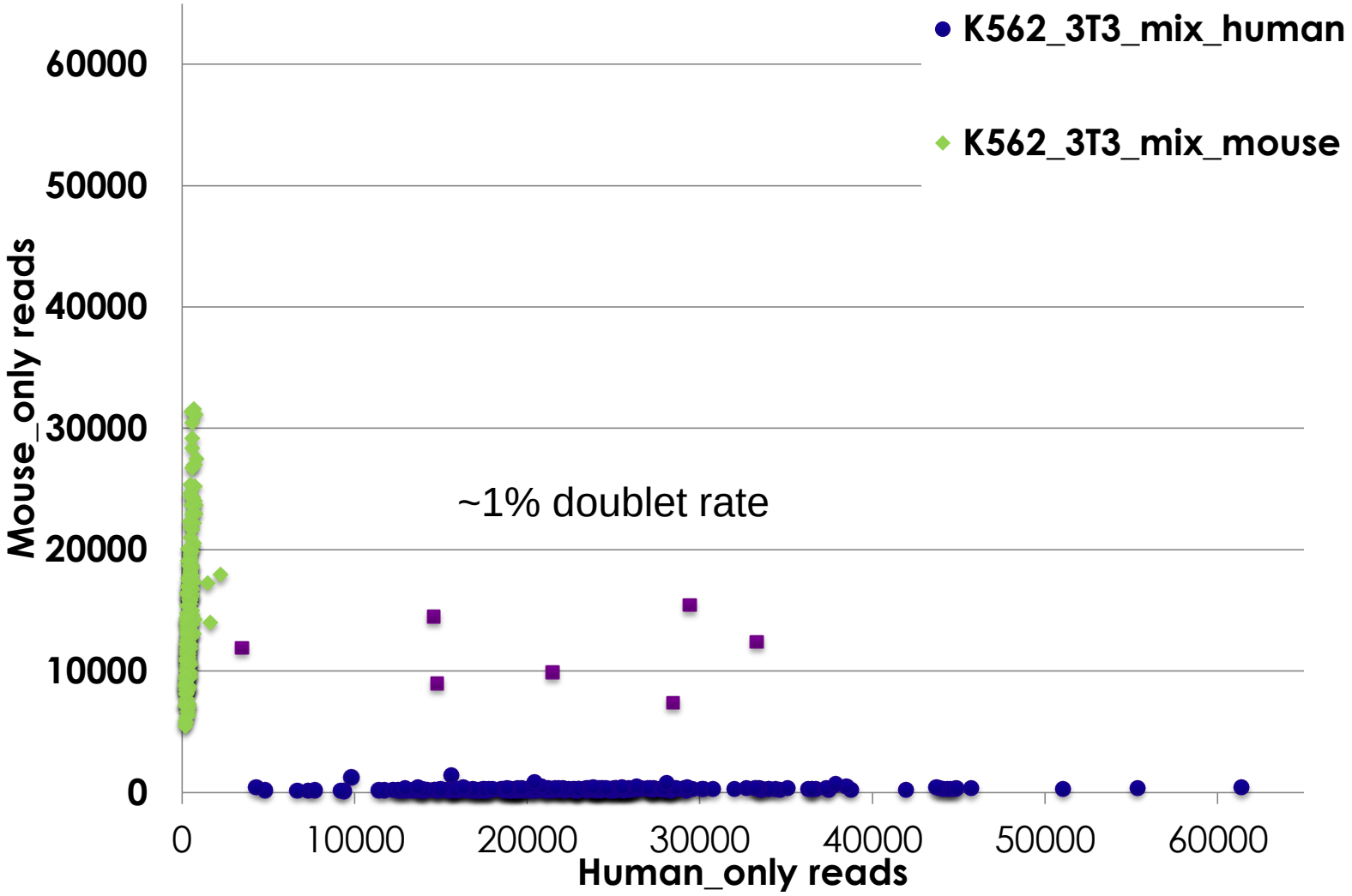




Simple/Flexible Plate Layout for up to 8 samples



Issue #3: Are They Really Single Cells?



Human Fetal Neurons Isolated by FACS

Wells Not Selected For RT Mastermix Dispense

File Advanced Actions Help

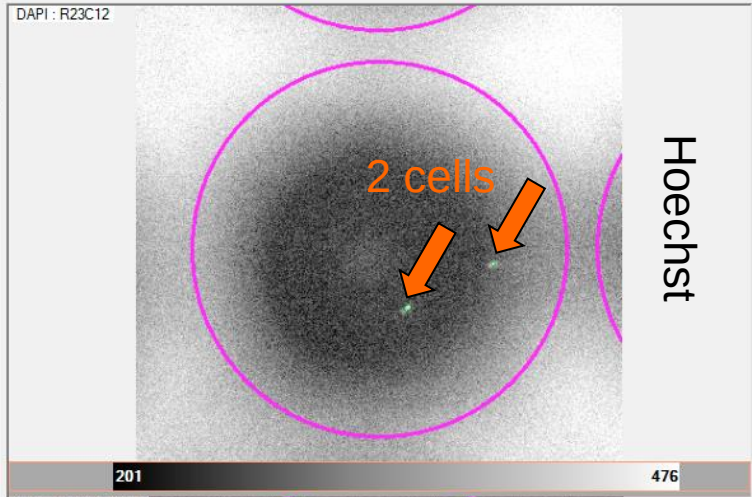
Define fiducials | Process images | Sample names | Manual triage | Save files

Total usable wells: 813 candidates 8 controls ☐ Hide control wells

Wells | Summary | Settings | Map

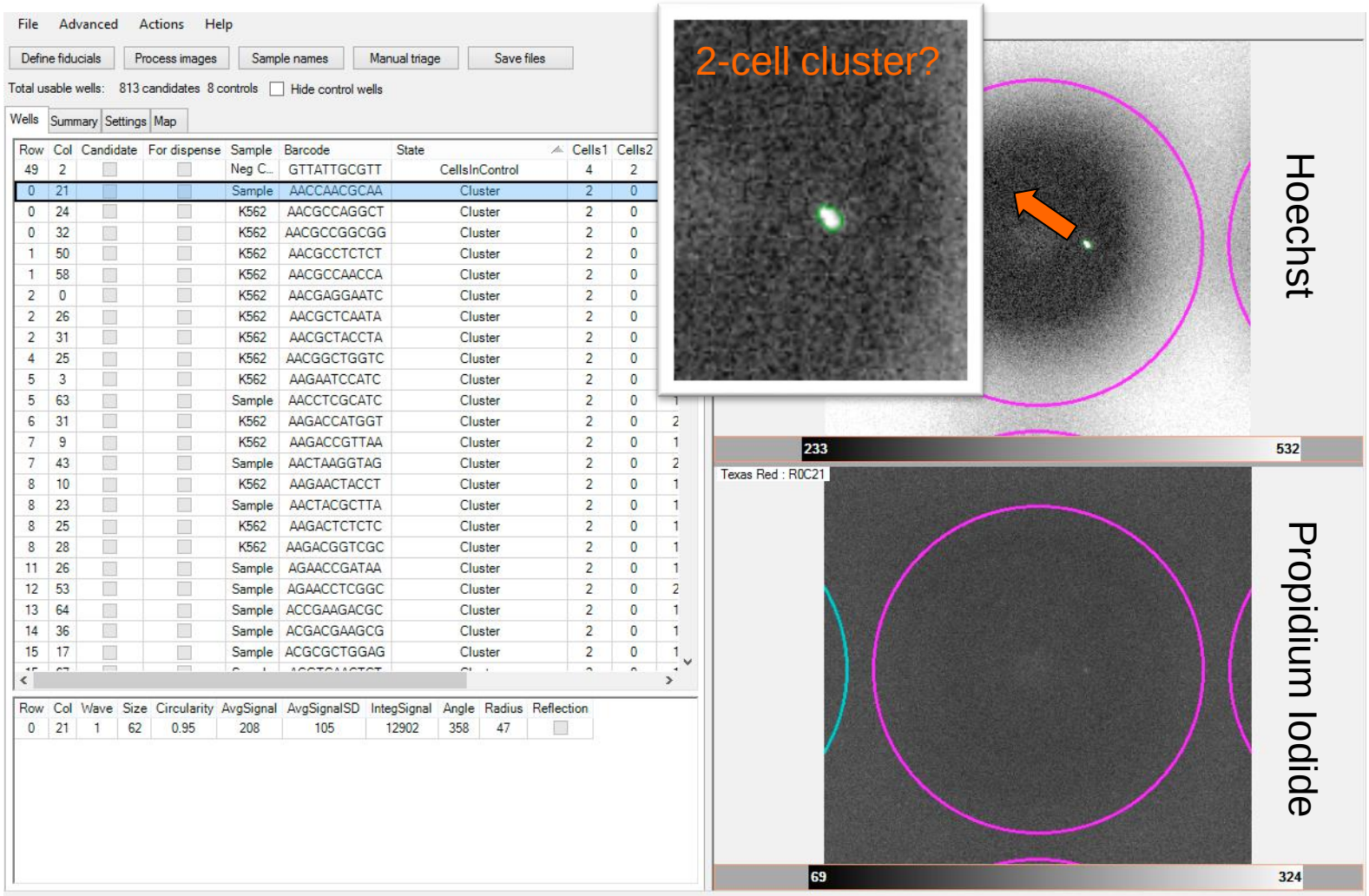
Row	Col	Candidate	For dispense	Sample	Barcode	State	Cells1	Cells2	Sig
23	4	☐	☐	Sample	CCTACGTCATG	MultipleCells	2	0	
23	5	☐	☐	Sample	CCTAGATAATA	NoCells	0	0	
23	6	☐	☐	Sample	CCTAGGACCAA	HasDeadCells	2	1	
23	7	☐	☐	Sample	CCTATTCATAT	HasDeadCells	3	2	
23	8	☐	☐	Sample	CCTATTGAATT	HasDeadCells	4	2	
23	9	☐	☐	Sample	CCTACGCTTGA	HasDeadCells	2	1	
23	10	☐	☐	Sample	CCTACTATGAC	NoCells	0	0	
23	11	☐	☐	Sample	CCTAGATTAAT	HasDeadCells	2	1	
23	12	☐	☐	Sample	CCATCGGAGTC	HasDeadCells	2	1	
23	13	☐	☐	Sample	CCATCTCGCTT	HasDeadCells	5	3	
23	14	☐	☐	Sample	CCATCTGCAGC	HasDeadCells	3	1	
23	15	☐	☐	Sample	CCATCCGCATA	HasDeadCells, Cluster	2	2	1
23	16	☐	☐	Sample	CCATCCGGCGT	HasDeadCells	5	1	
23	17	☐	☐	Sample	CCATCGCATAC	HasDeadCells	7	3	
23	18	☐	☐	Sample	CCATCGTTAAC	HasDeadCells	2	1	
23	19	☑	☑	Sample	CCATCTGAGAT	Good	1	0	1
23	20	☐	☐	Sample	CCATCTGATGG	HasDeadCells	3	1	
23	21	☐	☐	Sample	CCATCCATGAC	HasDeadCells	2	2	
23	22	☐	☐	Sample	CCATCCGTTAA	HasDeadCells	3	3	
23	23	☑	☑	Sample	CCATCGCTATG	Good	1	0	2
23	24	☑	☑	Sample	CCGCATGATAA	Good	1	0	3
23	25	☐	☐	Sample	CCGCCAAGGCG	NoCells	0	0	
23	26	☐	☐	Sample	CCGCCATAGGC	NoCells	0	0	
23	27	☐	☐	Sample	CCGCAGATCGT	HasDeadCells	3	2	

Row	Col	Wave	Size	Circularity	AvgSignal	AvgSignalSD	IntegSignal	Angle	Radius	Reflection
23	12	1	13	1.00	192	71	2491	352	95	☐
23	12	1	36	0.98	129	42	4637	296	54	☐
23	12	2	38	1.00	85	28	3234	296	54	☐



Human Fetal Neurons Isolated by FACS

Wells Not Selected For RT Mastermix Dispense



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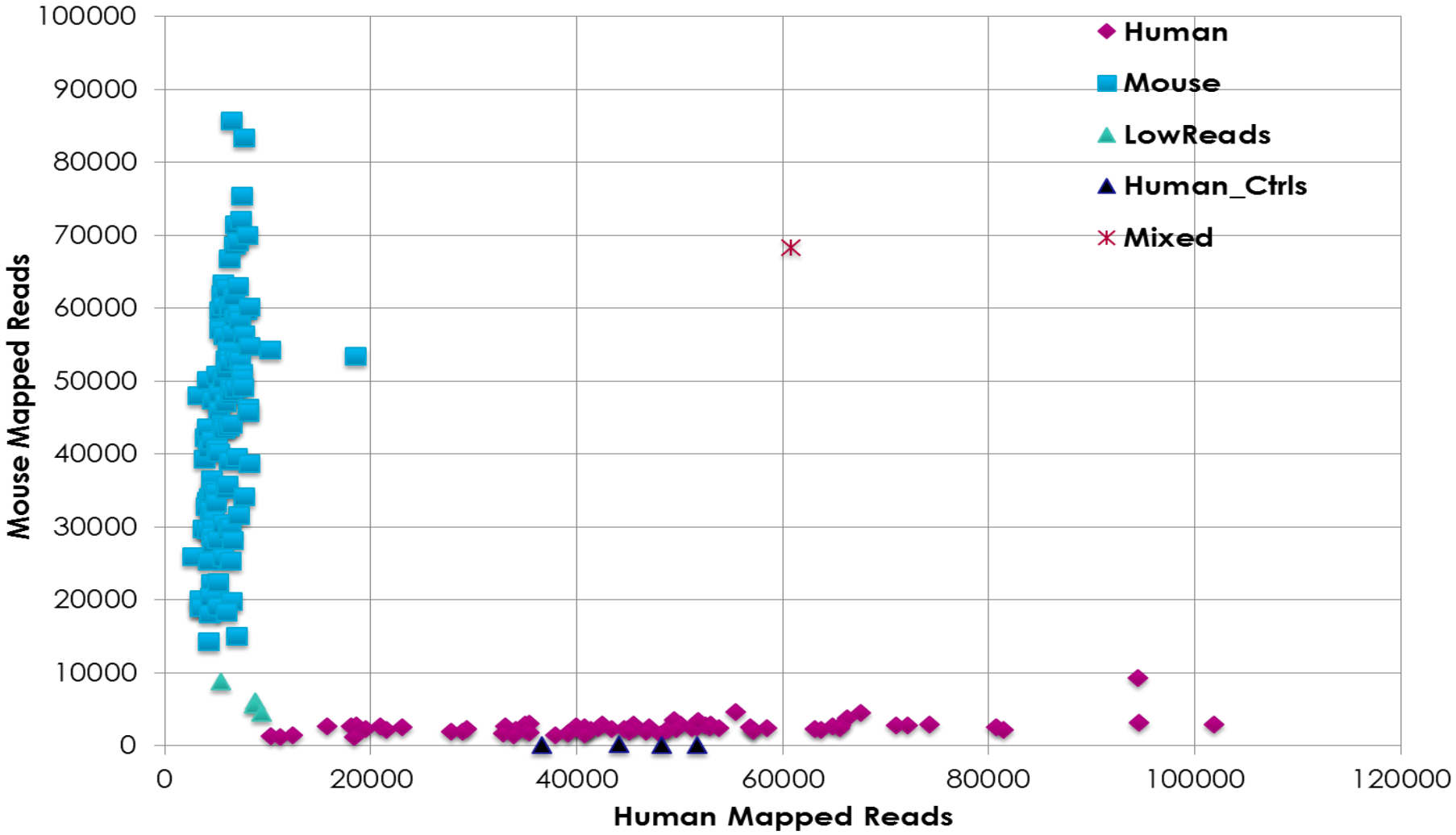


Issue #4: Cost

- FACS or microfluidics: **~20€/cell**
  - Total cost per sample: **1.920€** (up to 96 cells)
  - Cost per treated vs. control experiment (in triplicate – six runs): **11.520€**
- ICELL8: **~2€/cell**
  - Total cost per sample: **340€** (up to 225 cells)
  - Cost per treated vs. control experiment (in quadruplicate – one run): **2.720€**

Cost from sample to sequencing ready library

Issue #4: Cost

- ICELL8: **~2€/cell**
  - Total cost per sample: **340€** (up to 225 cells)
  - Cost per treated vs. control experiment (in quadruplicate – one run): **2.720€**
- 10X Genomics: **~1.4€/cell**
  - Total cost per sample: **1.400€** (up to 1000 cells)
  - Cost per treated vs. control experiment (in quadruplicate – one run): **11.200€**

Cost from sample to sequencing ready library

Product Configuration for ICELL8 Single-Cell System

System € 249,000

- MSND+
- Imaging Station
- Thermal Cycler
- CellSelecIt Software
- Additional Items include:
  - Chip holders for centrifuge
  - Chip chiller
  - Chip holders for the freezer (set of 5)
  - 1 Yr warranty
  - Installation
  - On-site training
  - 2 Reagent/chip Kits for their own use (not for installation or training)

Reagent/Chip kit €2,900

- 1 Chip – pre-printed with 5184 barcodes
- 1 Reagent kit
  - Fiducial Mix
  - Second Diluent
  - Amplification Primer
  - RT E5OLIGO
  - Nextera Primer P5
- Imaging Film
- PCR Film
- Collection Fixture
- RT buffer & kit

Issue #5: Applications

- Released:
  - RNA-seq (3’ counting)
- Under development:
  - T-cell Receptor sequencing
  - Other Takara/Rubicon solutions (WTS, DNA-seq etc.)
- Users developed protocols:
  - DNA-seq (under development)
  - ATAC-seq (under development) (A Method for Assaying Chromatin Accessibility Genome-Wide)

Issue #6: Reads depth

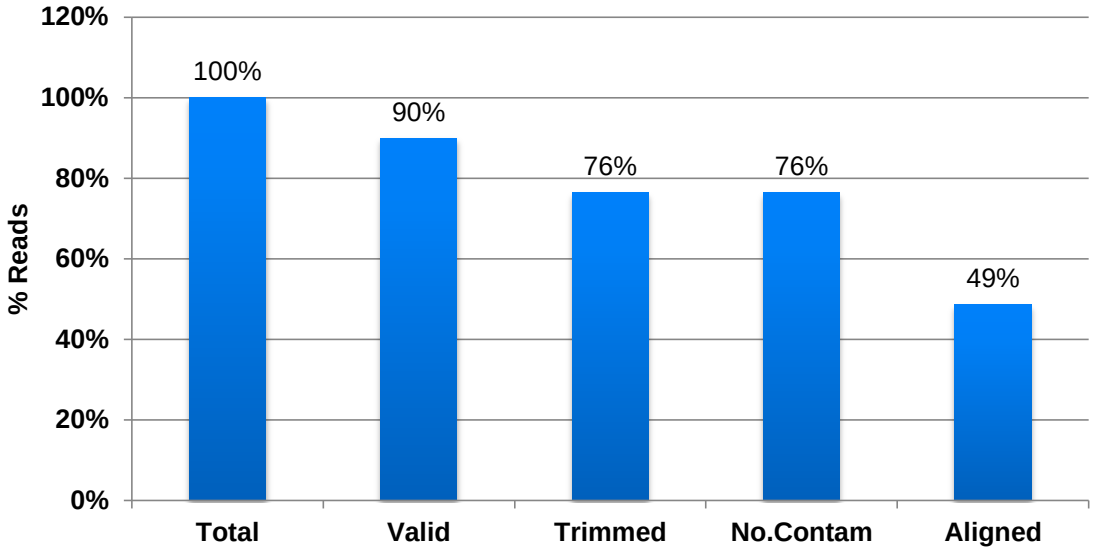
- NextSeq 500/550 system
  - Maximum Reads Per Run : 400 million reads (High-Output Flow Cell)
  - Reads per cell possible:
    - For 50.000 cells : 8.000 reads / cell
    - For 8.000 cells : 50.000 reads / cell
    - For 1.000 cells : 400.000 reads / cell
    - For 200 cells : 2.000.000 reads / cell

Real World Data: ESC Differentiation

- 3 frozen samples shipped to WaferGen Europe
- 3T3 in culture at WaferGen

Cell Type	Isolated single cells	PI negative single cells	Selected wells
ESC2 cells	346	279	125
d2.2 cells	420	340	125
d2.3 cells	309	248	125
3T3 cells	417	388	10
Pos_Ctrl – 3T3 RNA			10
Neg_Ctrl			10
TOTAL	1492	1255	405

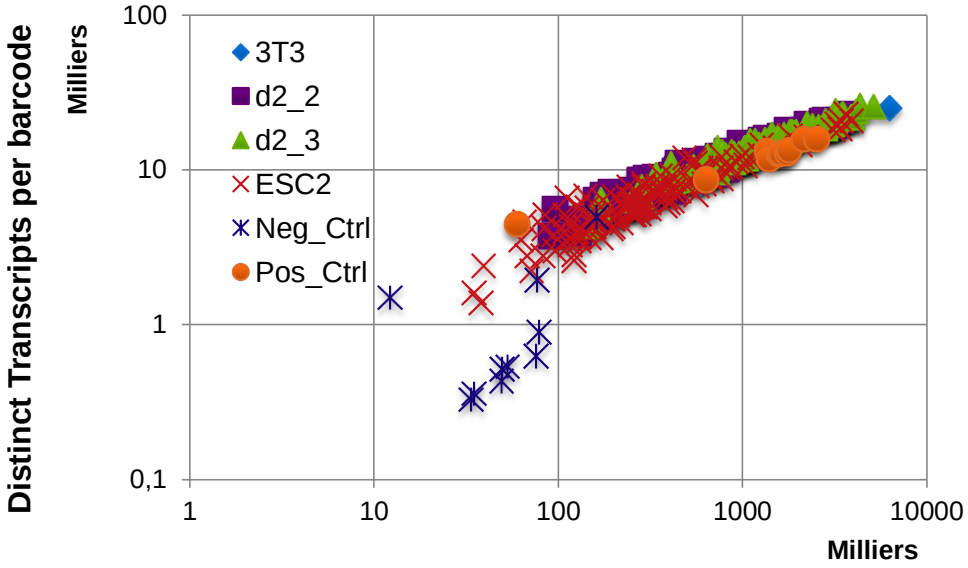
Reads Filtering



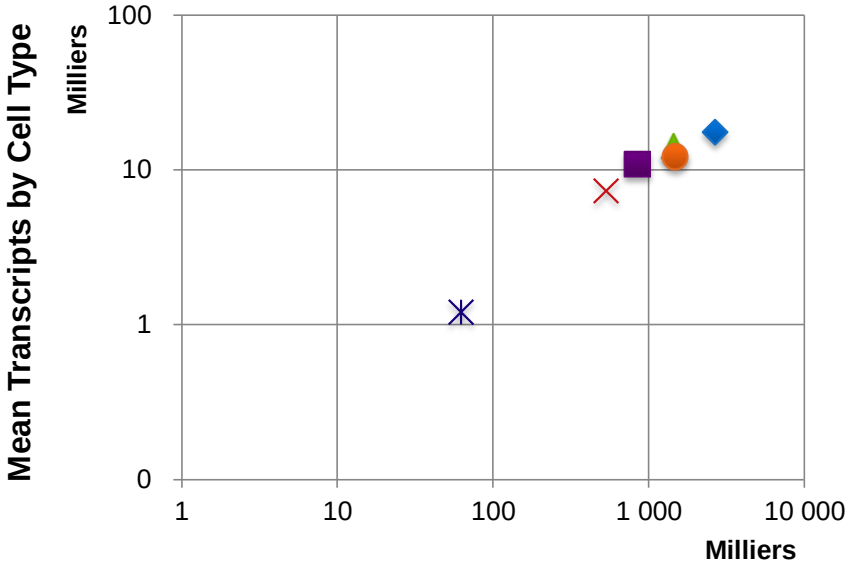
	Reads (M)
Total	439M
Valid	395M
Aligned	270M

- Data was generated on a NextSeq 500
- Filtering results were as expected
- Alignment of reads was against the Refseq mouse transcriptome

Gene Assignment



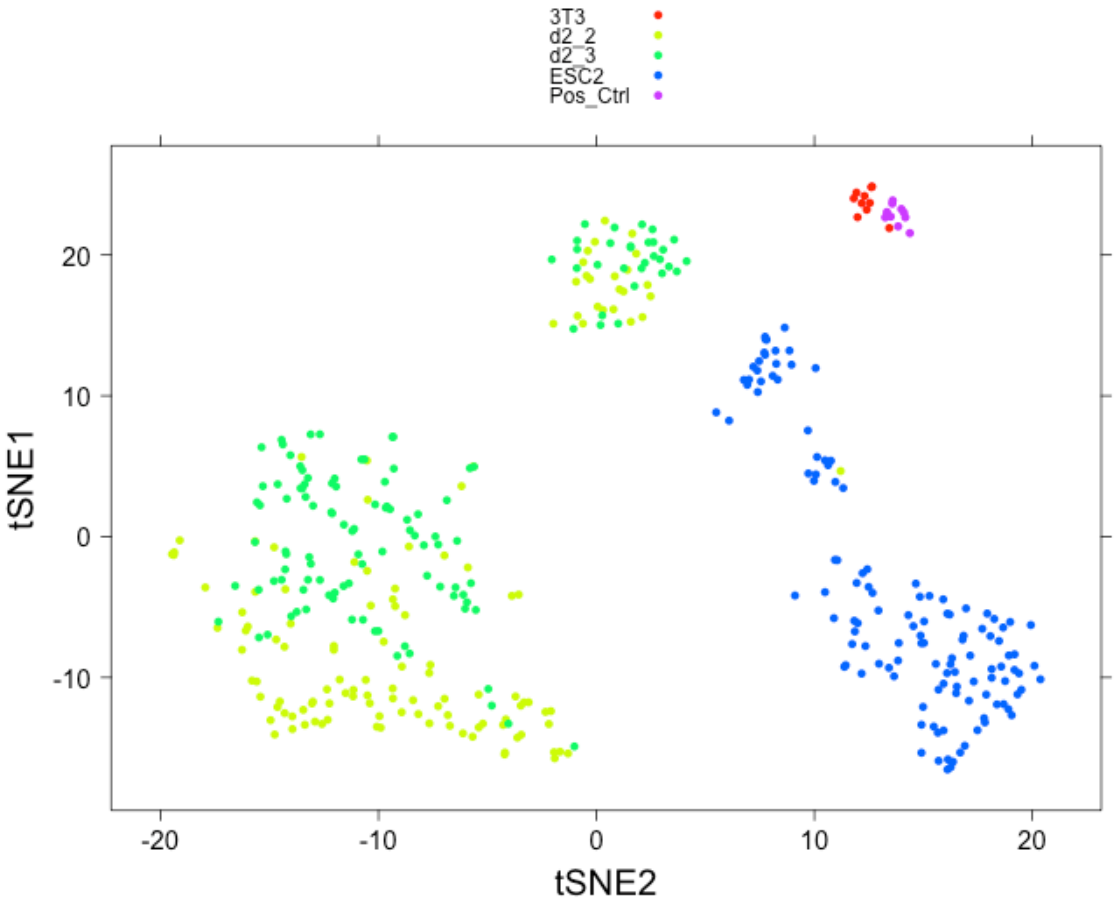
Valid Reads per barcode



Mean Reads by Cell Type

Cell Type	Mean Reads	Mean Transcripts	Mean Genes
ESC2	533,852	7,386	5,922
d2_2	845,299	10,873	8,448
d2_3	1,440,650	14,267	10,653
3T3	2,664,803	17,647	12,589
Pos_Ctrl	1,488,083	12,145	9,098
Neg_Ctrl	62,472	1,213	1,114

t-SNE Clustering

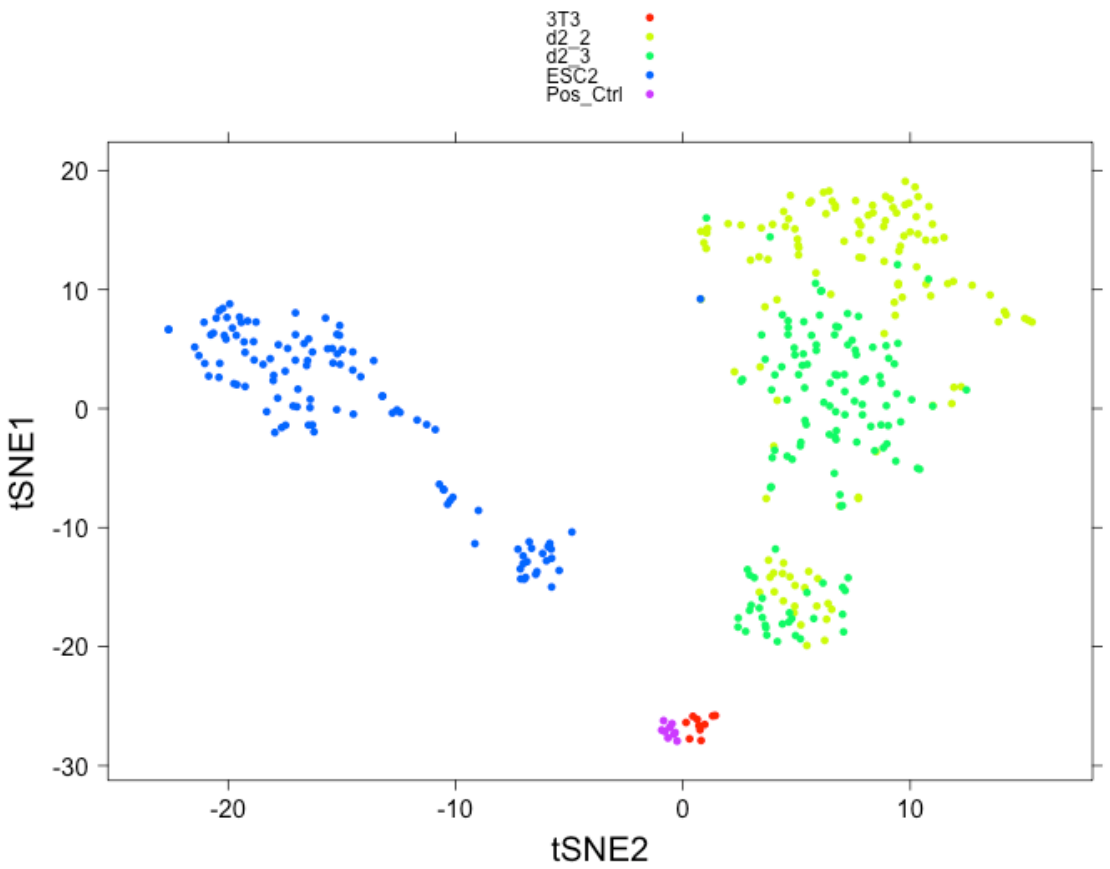


- PCA was first performed
- First 6 PCs were taken as input for t-SNE
- d2.2 & d2.3 cluster together
- And separate from ESC2
- 3T3 cells and 3T3 RNA cluster together and are distinct from all other samples

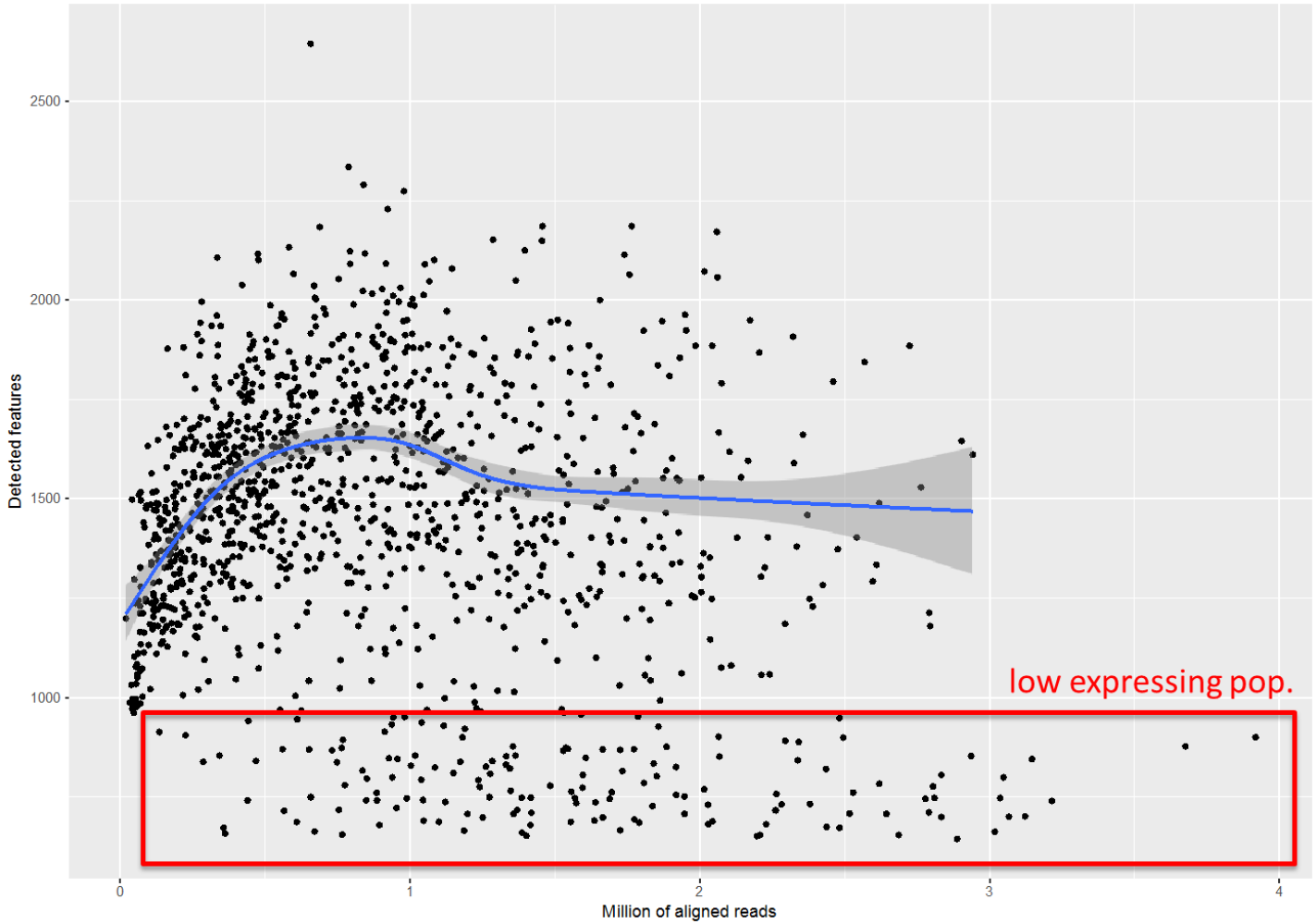
Down-sampling to 100k Reads/Barcode

At100k reads per barcode, d2 cells separate from ES cells and 3T3.

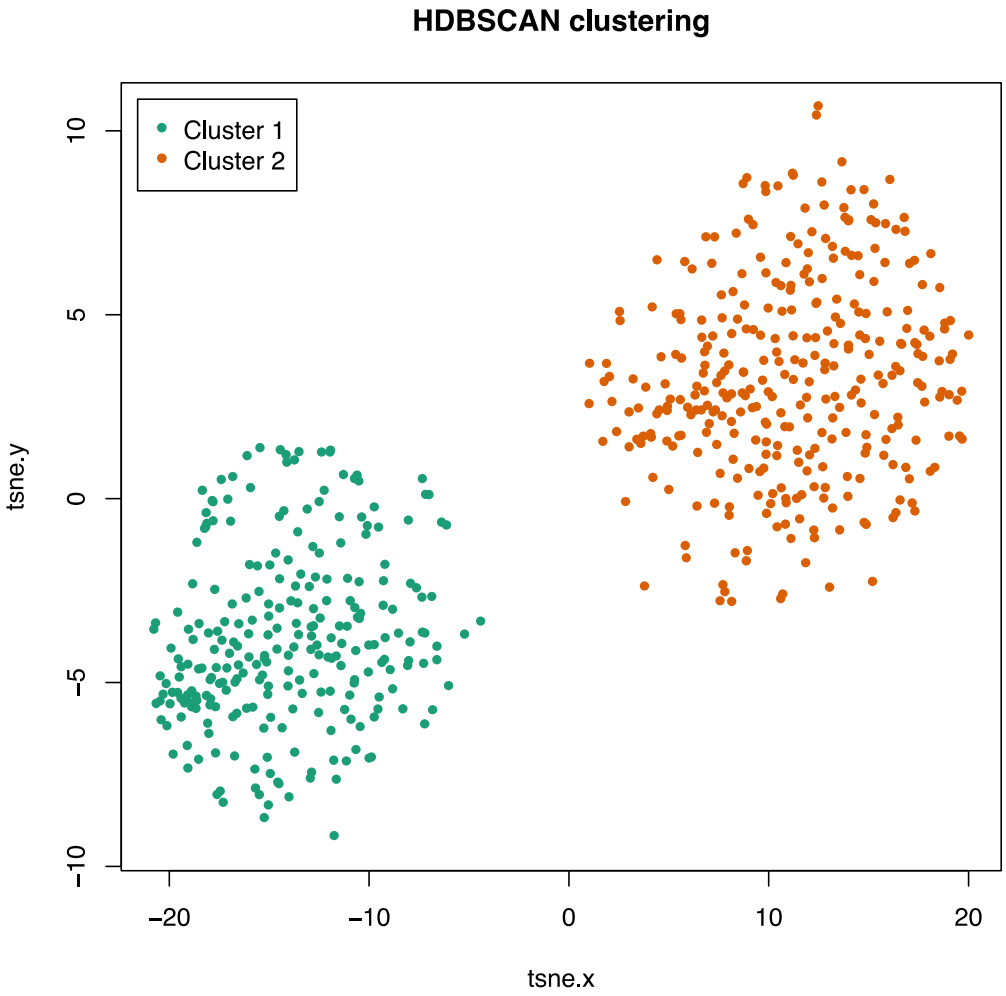
d2.2 and d2.3 still cluster together



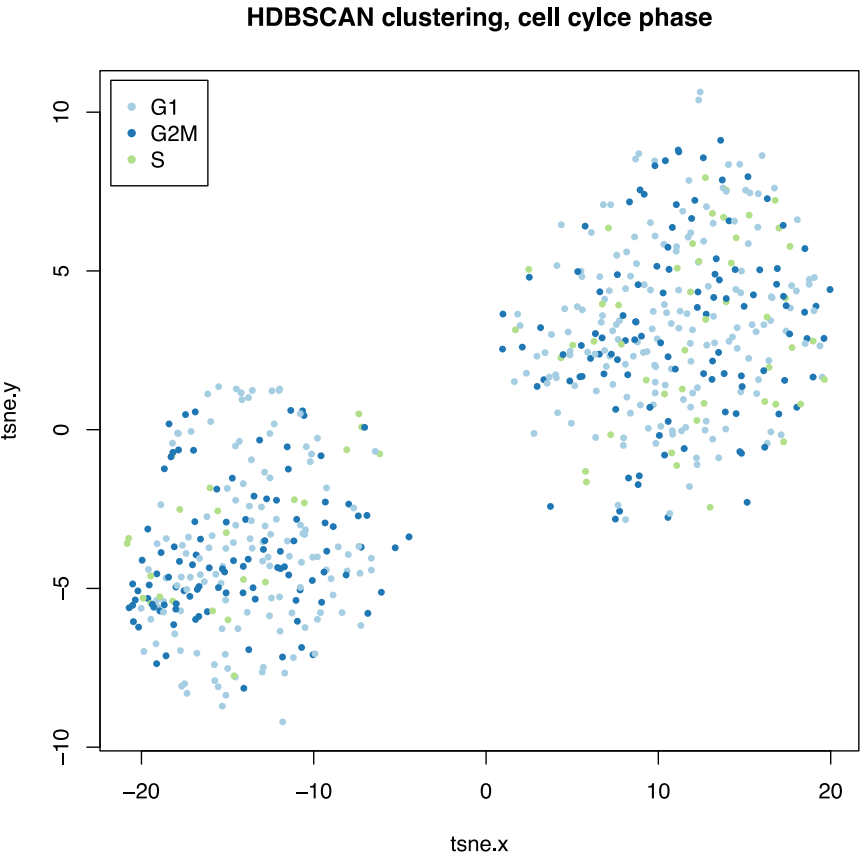
Real World Data: Primary Cardiomyocytes



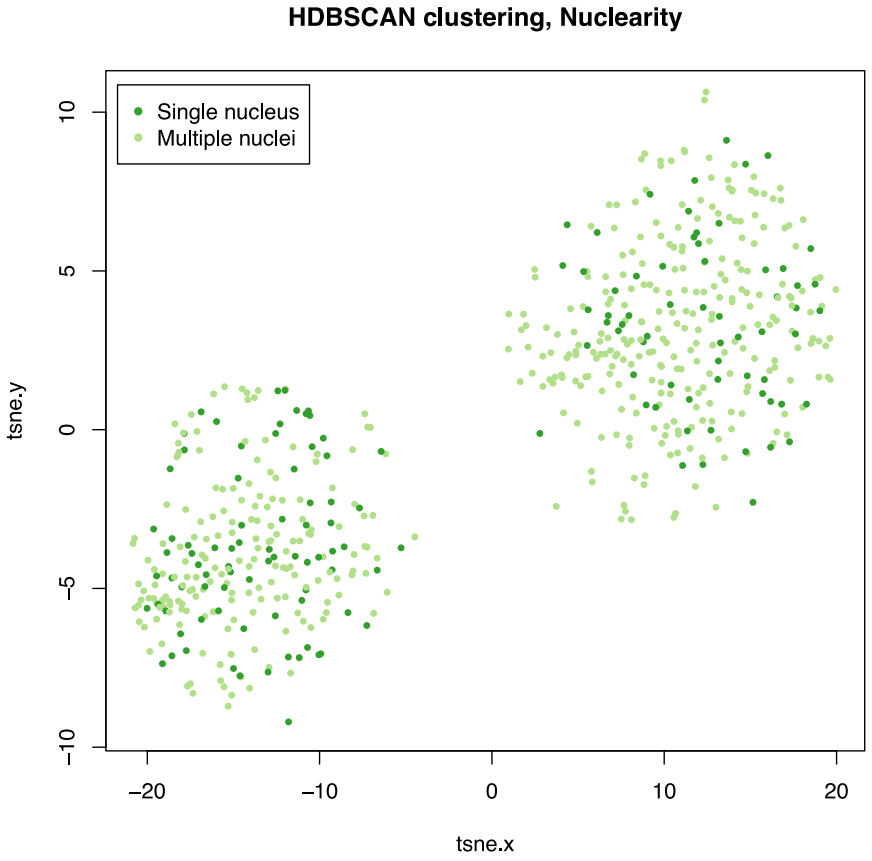
Primary Cardiomyocytes Clustering



Primary Cardiomyocytes Clustering

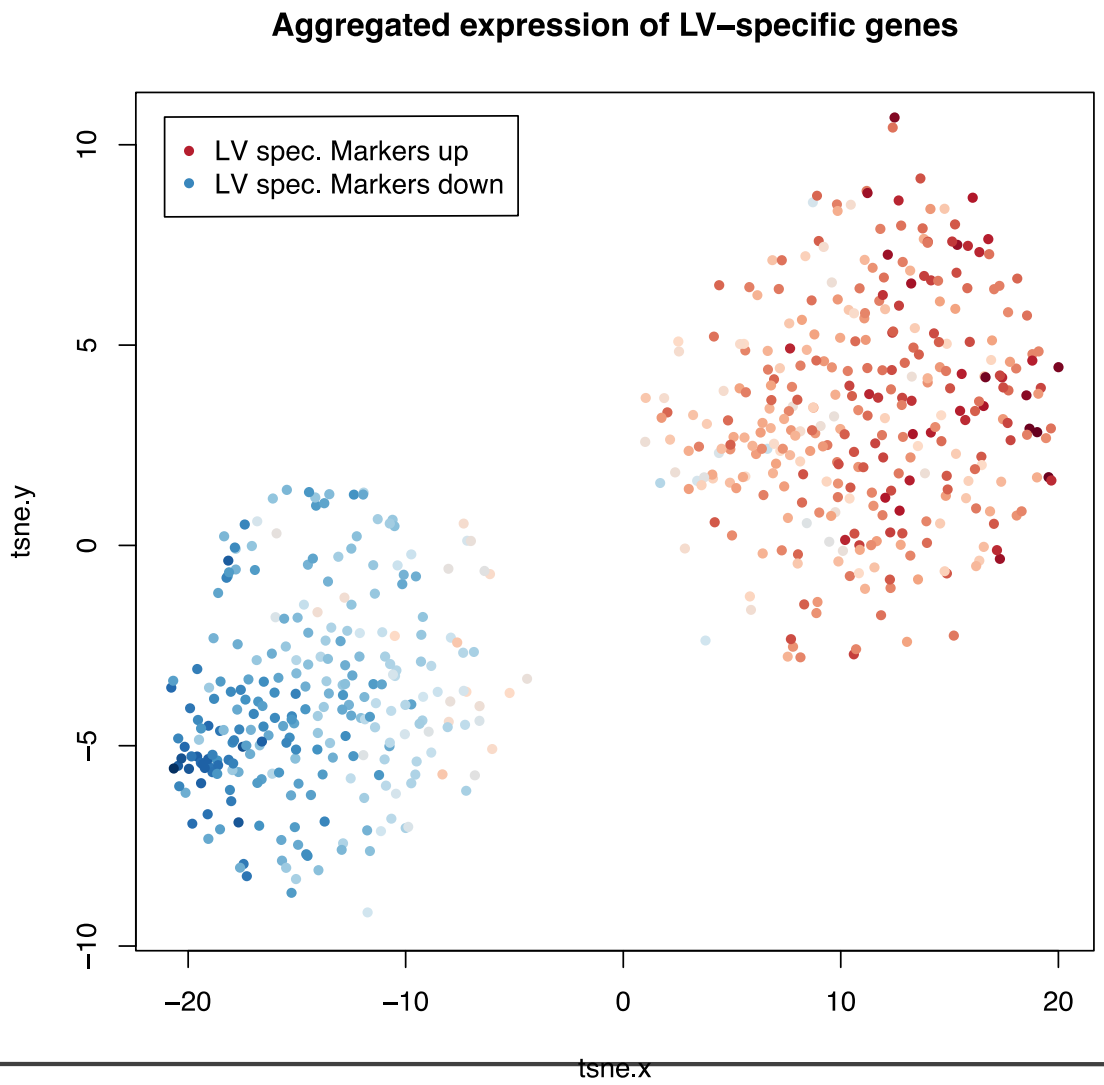


not cell cycle



not number of nuclei

Primary Cardiomyocytes Clustering



number of features is also connected to left/right ventricular identity of CM (right ventricle expressed number of genes is considerably lower than left ventricle)

- 19 LV specific genes based on Torrado et al.
- 9 were found within the data set
- average expression above/below threshold > decision for LV / RV

ICELL8 Users

Clontech TaKaRa cellartis

ICELL8 Poster or Oral Presentations

1. “Single-Cell RNA-seq Analysis of Mouse Cortex Using the ICELL8 System” Linnarsson S., Karolinska Institutet . Presented at AGBT 2016.
2. “ICELL8- A versatile Single-Cell processing System Using Nanowell Technology, Navin. N. MD Anderson. Presented at AGBT 2016
3. “Large-Scale Single-Cell Transcriptome Sequencing of the human airway Epithelium. Seibold. M National Jewish Hospital, Presented at AGBT 2016
4. “Comprehensive Analysis of Tumors at Whole Tissue to Single-Cell Level” Seshagiri. S Genentech, Presented at AGBT 2016
5. “ Use of single cell transcriptomics to study blood stem cell formation” Lancrin C. EMBL. Presented at 4th Annual Single Cell Analysis Congress, London Nov 10-11th 2016
6. “A SMARTer approach to profiling the human T-cell receptor repertoire” Gandlur et al. Takara Bio. Single Cell Genomics 2016.
7. “High resolution single cell analysis in complex adult tissues“. Günther S. et al. Max-Planck-Institute for Heart & Lung Research. Presented at qPCR, DPCR NGS 2017, Freising, Germany 3-7th April 2017

ICELL8 Publications

1. “Full-Length Single-Cell RNA-seq applied to a viral human cancer: applications to HPV expression and splicing analysis I HeLa S3 cells. Wu et al. Ciga Science 2015 4: 51
2. Ruli Gao, Charissa Kim, Emi Sei, Leong-Keat Chan, Maithreyan Srinivasan, Hong Zhang, Funda Meric-Bernstam, and Nicholas Navin. Nanogrid Single-Nucleus RNA Sequencing Reveals Phenotypic Diversity in Breast Cancer. *Under Revisions*
3. "Single cell transcriptomics reveals new insights on the dynamical factors during blood stem and progenitor cell formation”. Isabelle Bergiers, Tallulah Andrews, Özge Vargel Bölükbaşı, Andreas Buness, Ewa Janosz, Natalia Lopez-Anguita, Kerstin Ganter, Kinga Kosim, Cemre Celen, Gülce Itır Perçin, Paul Collier, Bianka Baying, Vladimir Benes, Martin Hemberg & Christophe Lancrin *Submitted for publication*
4. “Coupling shRNA screens with single-cell RNA-seq identifies mechanisms regulating senescence during reprogramming” J. Gill et al. Medical Research Council London *submitted, pending publication*
5. STRT-seq-2i: dual-index 5' single-cell RNA-seq on an addressable microwell array. Linnarsson et al. *pending publication*

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