SYSTEMATIC EXCELLENCE SM

Flow Cytometry Applications for Isolating and Analyzing Complex Heterogeneous Stem Cell Cultures

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Manager, Stem Cell Research and Development
BD Biosciences

23-15381-00

Overview

- Background
- Immunophenotyping Screens
- Improved Sorting of Pluripotent Stem Cells
- Enrichment for hiPSCs during Reprogramming
- Monitoring Lineage Specification Using Multiparameter Flow Cytometry
- MSC Characterization Using Flow Cytometry

Applications and Challenges in Stem Cell Research

Applications of stem cell research:

- Cell therapy
- In vitro disease models
- Basic research

Heterogeneity of cell cultures is a major challenge.

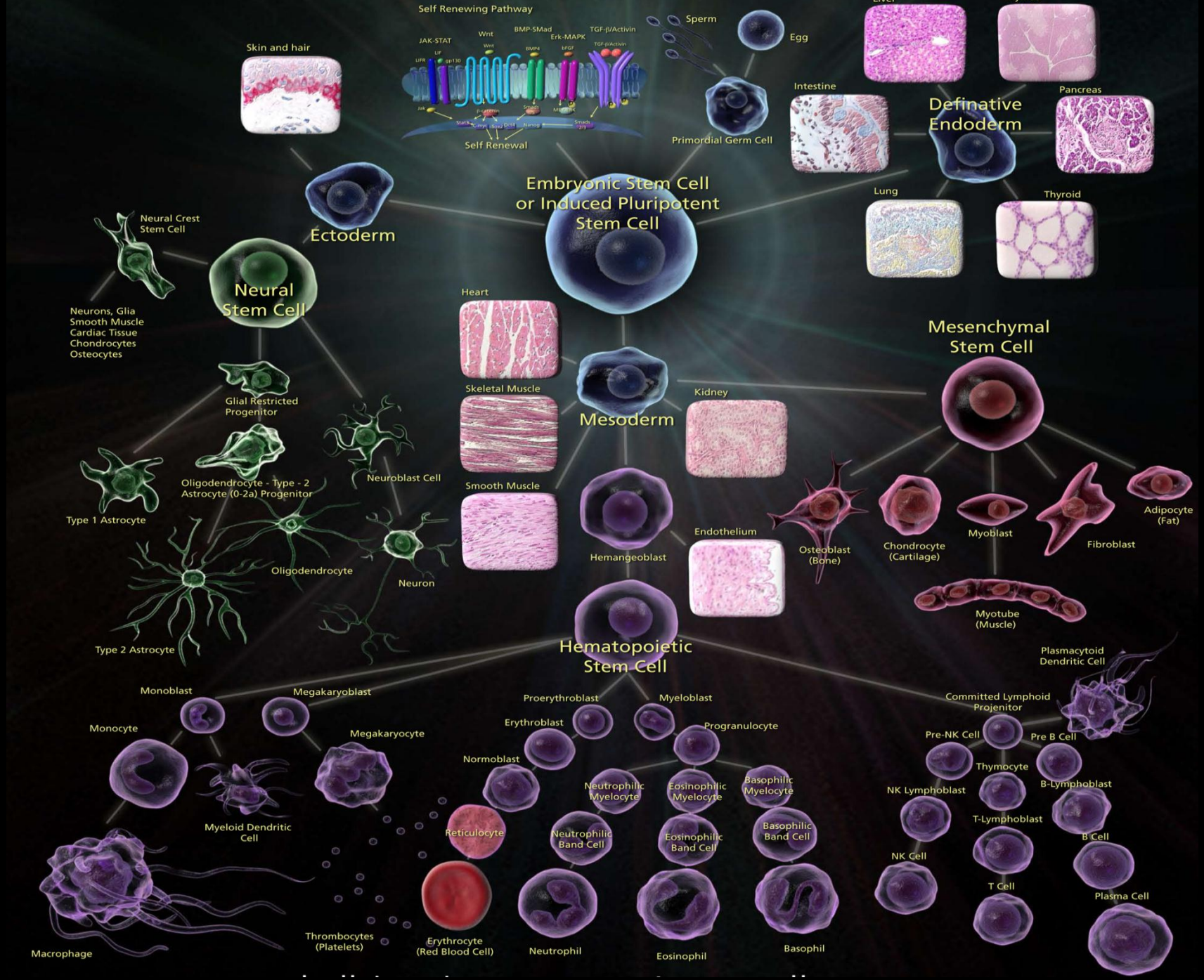
The field is in need of:

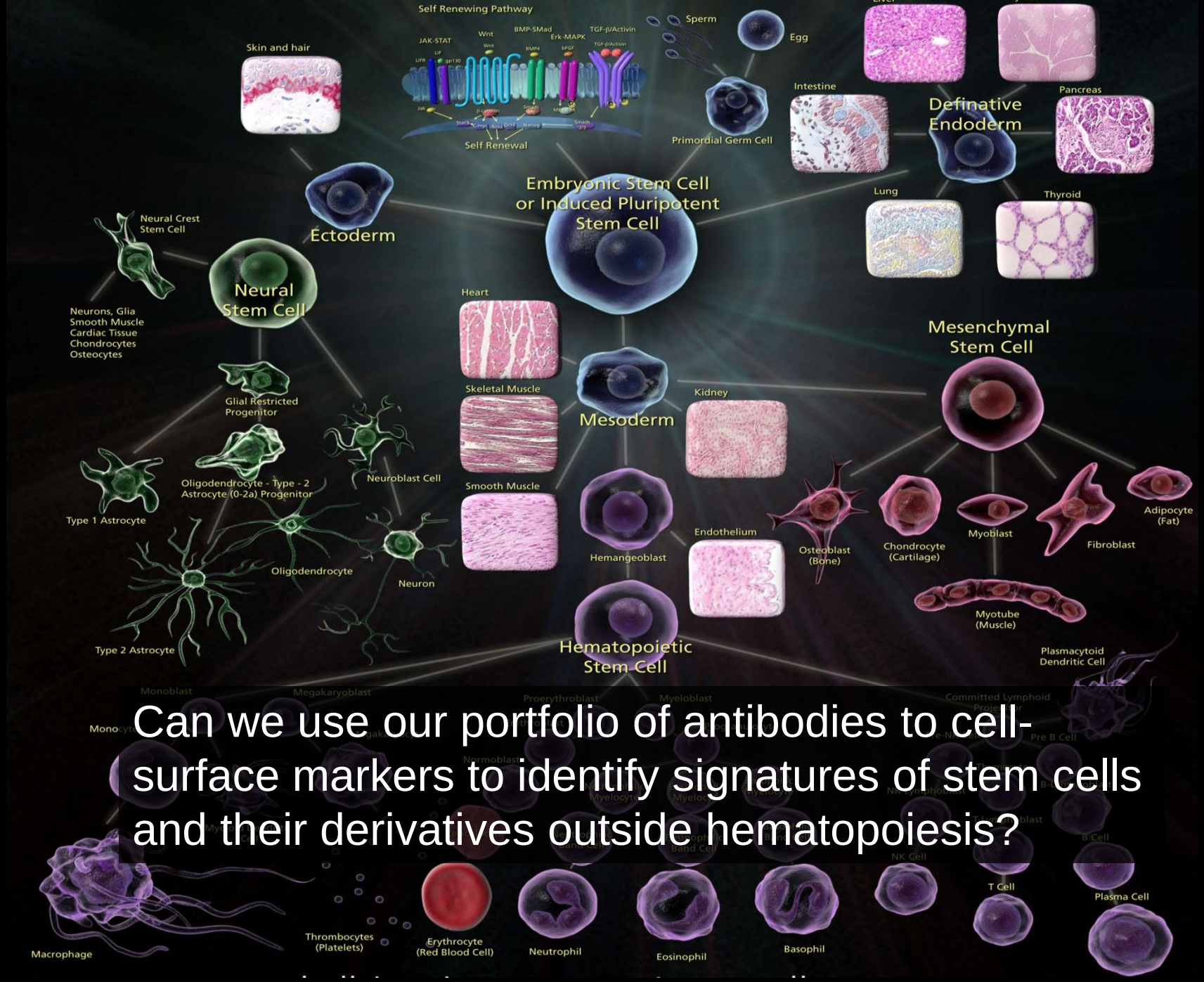
- Defined cell-surface signatures for pluripotent stem cells and their derivatives
- Robust methods for cell sorting
- Quantitative analysis tools for heterogeneous cell cultures

The BD Biosciences Stem Cell Research group in La Jolla, CA is addressing these hurdles:

- Developing antibody-based reagents and applications for flow cytometry and bioimaging technology platforms
- Working with key opinion leaders in technology development

Immunophenotyping Screens for Identifying Cell-Surface Signatures of Human Embryonic Stem Cell (hESC) and Human Induced Pluripotent Stem Cell (hiPSC) Derived NSCs, Neurons, and Glia by Flow Cytometry


Self Renewing Pathway
JAK-STAT
Wnt
BMP-SMad
Erk-MAPK
TGF-β/Activin
Self Renewal
Sperm
Egg
Primordial Germ Cell
Skin and hair
Intestine
Definative Endoderm
Pancreas
Lung
Thyroid
Embryonic Stem Cell or Induced Pluripotent Stem Cell
Ectoderm
Neural Crest Stem Cell
Neurons, Glia
Smooth Muscle
Cardiac Tissue
Chondrocytes
Osteocytes
Neural Stem Cell
Glial Restricted Progenitor
Type 1 Astrocyte
Oligodendrocyte - Type - 2 Astrocyte (0-2a) Progenitor
Neuroblast Cell
Oligodendrocyte
Neuron
Type 2 Astrocyte
Heart
Skeletal Muscle
Smooth Muscle
Mesoderm
Hemangeoblast
Kidney
Endothelium
Mesenchymal Stem Cell
Osteoblast (Bone)
Chondrocyte (Cartilage)
Myoblast
Fibroblast
Adipocyte (Fat)
Myotube (Muscle)
Hematopoietic Stem Cell
Monoblast
Megakaryoblast
Monocyte
Megakaryocyte
Myeloid Dendritic Cell
Macrophage
Proerythroblast
Myeloblast
Erythroblast
Progranulocyte
Normoblast
Neutrophilic Myelocyte
Eosinophilic Myelocyte
Basophilic Myelocyte
Reticulocyte
Neutrophilic Band Cell
Eosinophilic Band Cell
Basophilic Band Cell
Thrombocytes (Platelets)
Erythrocyte (Red Blood Cell)
Neutrophil
Eosinophil
Basophil
Plasmacytoid Dendritic Cell
Committed Lymphoid Projenitor
Pre-NK Cell
Pre B Cell
Thymocyte
NK Lymphoblast
B-Lymphoblast
T-Lymphoblast
B Cell
NK Cell
T Cell
Plasma Cell



Can we use our portfolio of antibodies to cell-surface markers to identify signatures of stem cells and their derivatives outside hematopoiesis?

BD Lyoplate™ Screening Panels

Enabling researchers to immunophenotype cell populations by flow cytometry or immunofluorescence microscopy using BD's portfolio of monoclonal antibodies

- Accelerate the discovery of unique cell-surface "signatures"
- A unique, cost-effective alternative to screening using hundreds of single-vial reagents

Product	Contents	Size
BD Lyoplate™ *Human* Cell Surface Marker Screening Panel Cat. No. 560747	• 242 CD markers* • Isotype controls • Alexa Fluor® 647 second step	5 tests
BD Lyoplate™ *Mouse* Cell Surface Marker Screening Panel Cat. No. 562208	• 176 CD markers • Isotype controls • Biotin second step • Alexa Fluor® 647 streptavidin third step	5 tests
*CD and other cell-surface molecules. One marker per well.		

Stem Cell Research Screening Applications

August 2011, Volume 6, Issue 8

PLoS one

Efficient and Scalable Purification of Cardiomyocytes from Human Embryonic and Induced Pluripotent Stem Cells by VCAM1 Surface Expression

Hideki Uosaki[1,2], Hiroyuki Fukushima[1,2], Ayako Takeuchi[3], Satoshi Matsuoka[4], Norio Nakatsuji[5], Shinya Yamanaka[6], Jun K. Yamashita[1,2]*

nature biotechnology

October 2011, Volume 29, Issue 11

SIRPA is a specific cell-surface marker for isolating cardiomyocytes derived from human pluripotent stem cells

Nicole C Dubois[1], April M Craft[1], Parveen Sharma[2], David A Elliott[3], Edouard G Stanley[3], Andrew G Elefanty[3], Anthony Gramolini[2] & Gordon Keller[1]

December 2012, Volume 7, Issue 12

PLOS | ONE

Differential Expression of Surface Markers in Mouse Bone Marrow Mesenchymal Stromal Cell Subpopulations with Distinct Lineage Commitment

Maria Rostovskaya, Konstantinos Anastassiadis*

March 2011, Volume 6, Issue 3

PLoS one

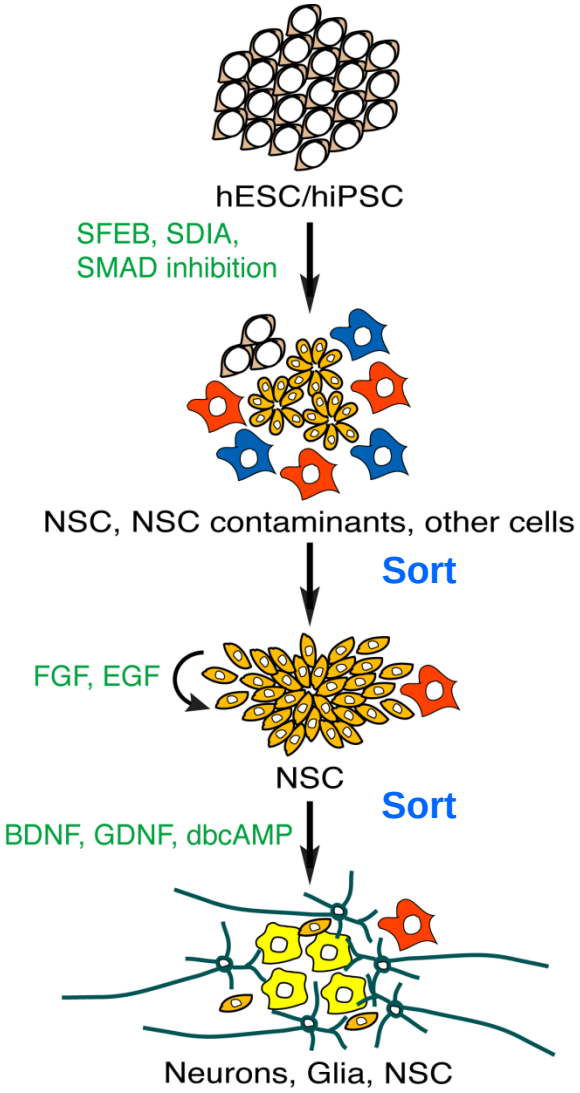
Cell-Surface Marker Signatures for the Isolation of Neural Stem Cells, Glia and Neurons Derived from Human Pluripotent Stem Cells

Shauna H. Yuan[1,2], Jody Martin[3], Jeanne Elia[3], Jessica Flippin[1], Rosanto I. Paramban[3], Mike P. Hefferan[4], Jason G. Vidal[3], Yangling Mu[5], Rhiannon L. Killian[1,6], Mason A. Israel[1,6], Nil Emre[3], Silvia Marsala[4], Martin Marsala[4,7], Fred H. Gage[5], Lawrence S. B. Goldstein[1], Christian T. Carson[3]*

1 Howard Hughes Medical Institute and Department of Cellular and Molecular Medicine, School of Medicine, University of California San Diego, La Jolla, California, United States of America, **2** Department of Neurosciences, School of Medicine, University of California San Diego, La Jolla, California, United States of America, **3** BD Biosciences, La Jolla, California, United States of America, **4** Anesthesiology Research Laboratory, Department of Anesthesiology, University of California San Diego, La Jolla, California, United States of America, **5** Laboratory of Genetics, The Salk Institute for Biological Studies, La Jolla, California, United States of America, **6** Biomedical Sciences Graduate Program, University of California San Diego, La Jolla, California, United States of America, **7** Institute of Neurobiology, Slovak Academy of Sciences, Košice, Slovakia

BD

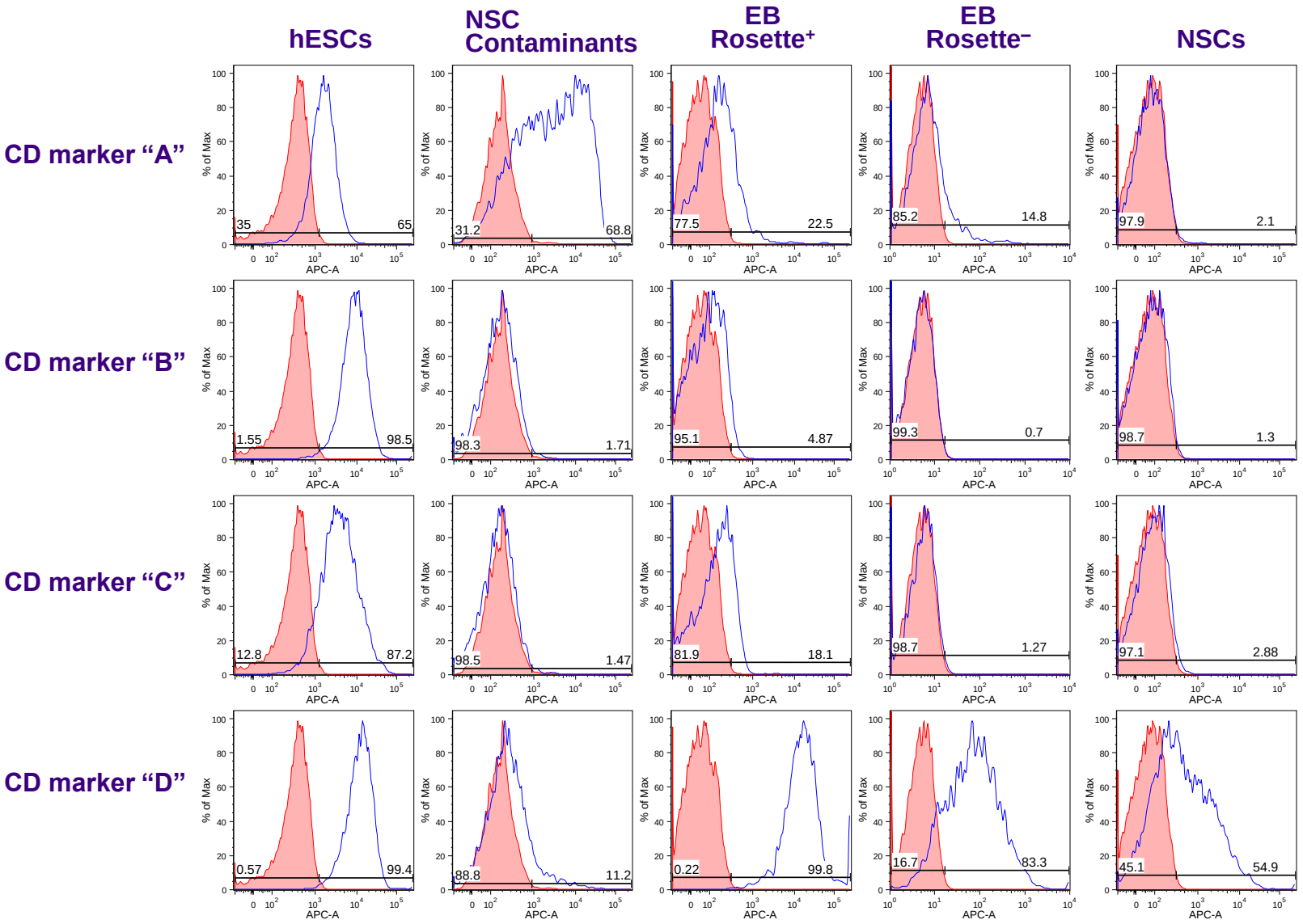
Neural Induction of Pluripotent Stem Cells



Characterization of cell-surface signatures enables:

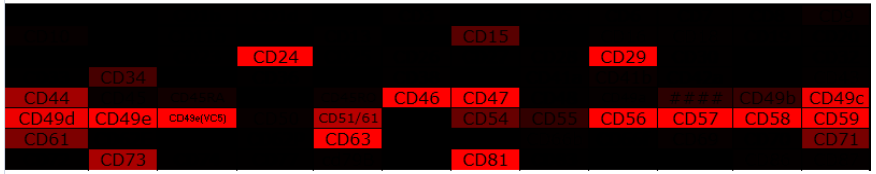
- Identification of subpopulations
  - Transplantation
- Isolation of pure populations
  - Arrays
  - Biochemistry
  - In vitro assays and models
- Development of quality control assays for cell preparations
  - Purity assessment
  - Contaminant identification

Cell Surface Marker Screen: Flow Cytometry

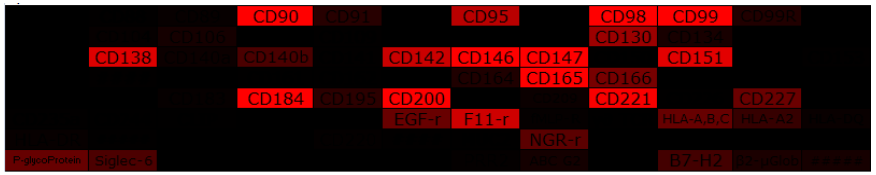


Analysis

% Positive Plate 1

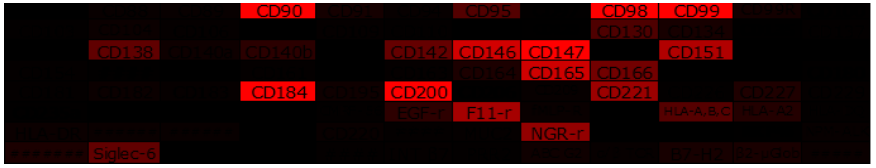


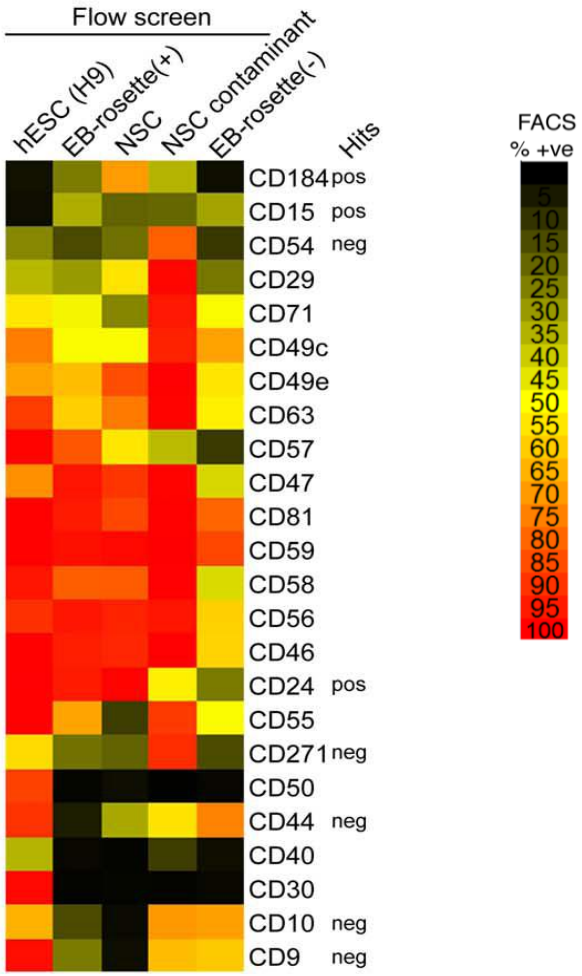
% Positive Plate 2



MFI Plate 1

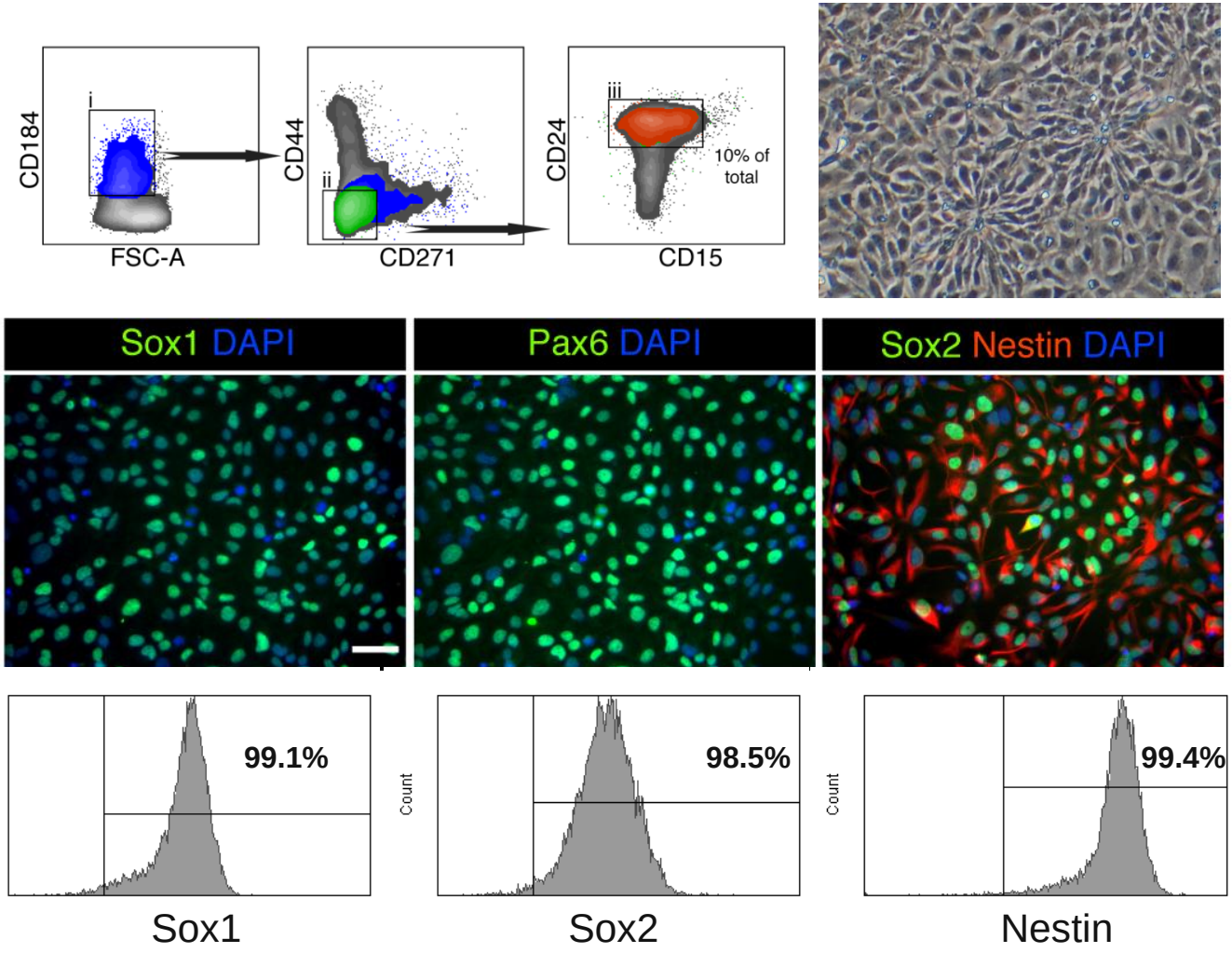
MFI Plate 2





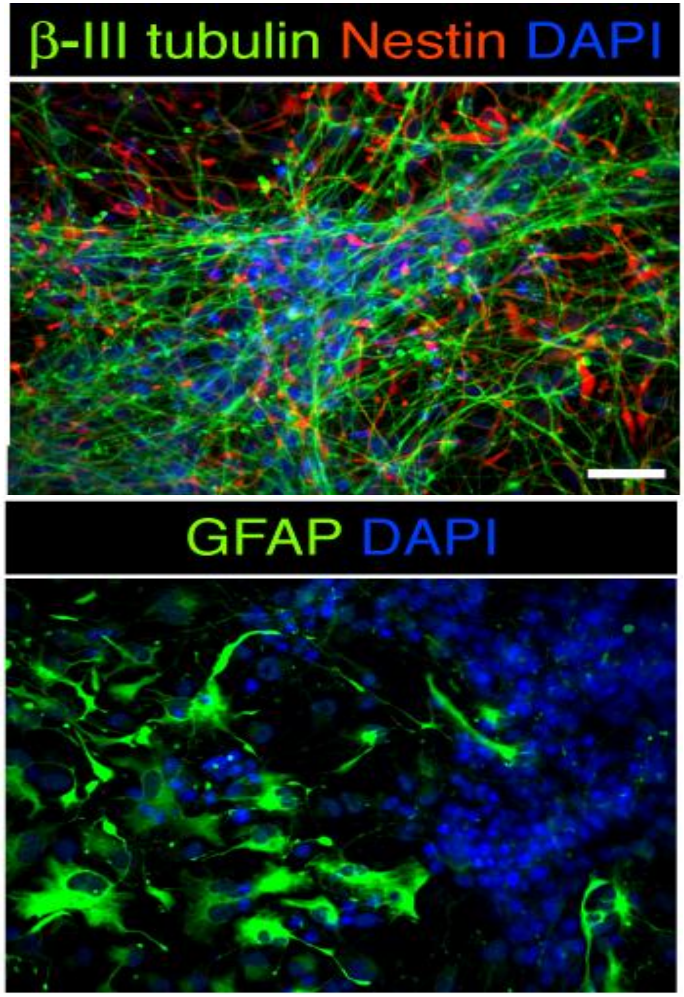
bdbiosciences.com/resources/stemcell/

CD184+/CD44−/CD271−/CD24+ Define a Cell-Surface Signature for the Isolation of NSCs

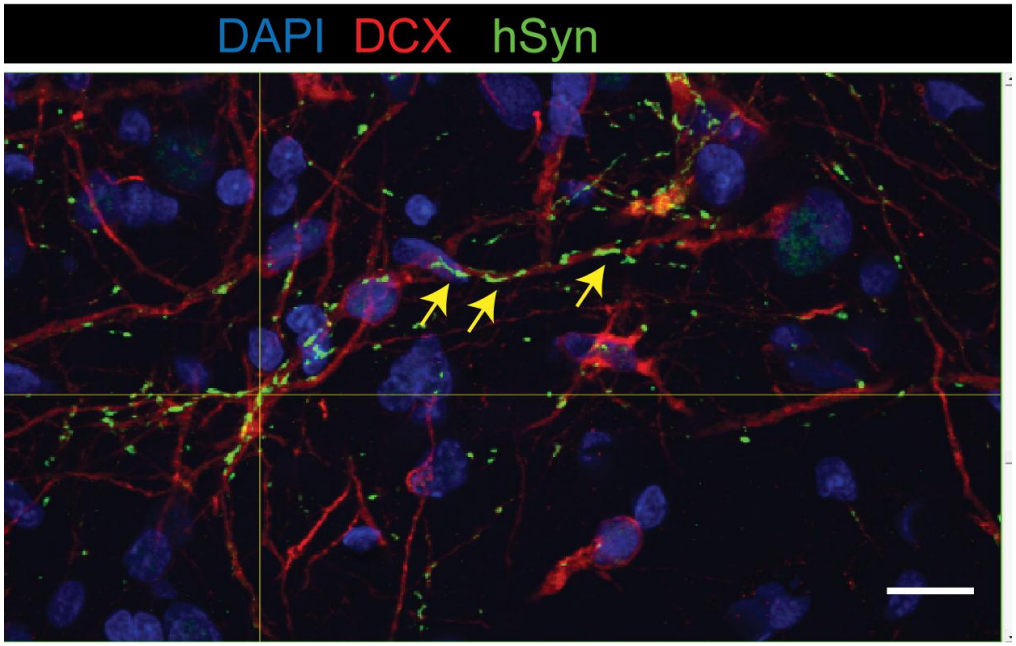


Sorted NSCs Differentiate to Mixed Cultures of Neurons and Glia

H9 NSCs differentiated for 3 weeks

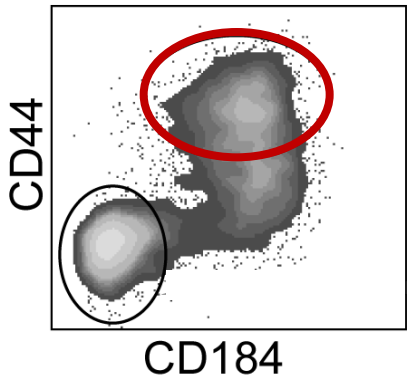


HUES-9 NSCs 8 weeks post-engraftment in rat spinal cord



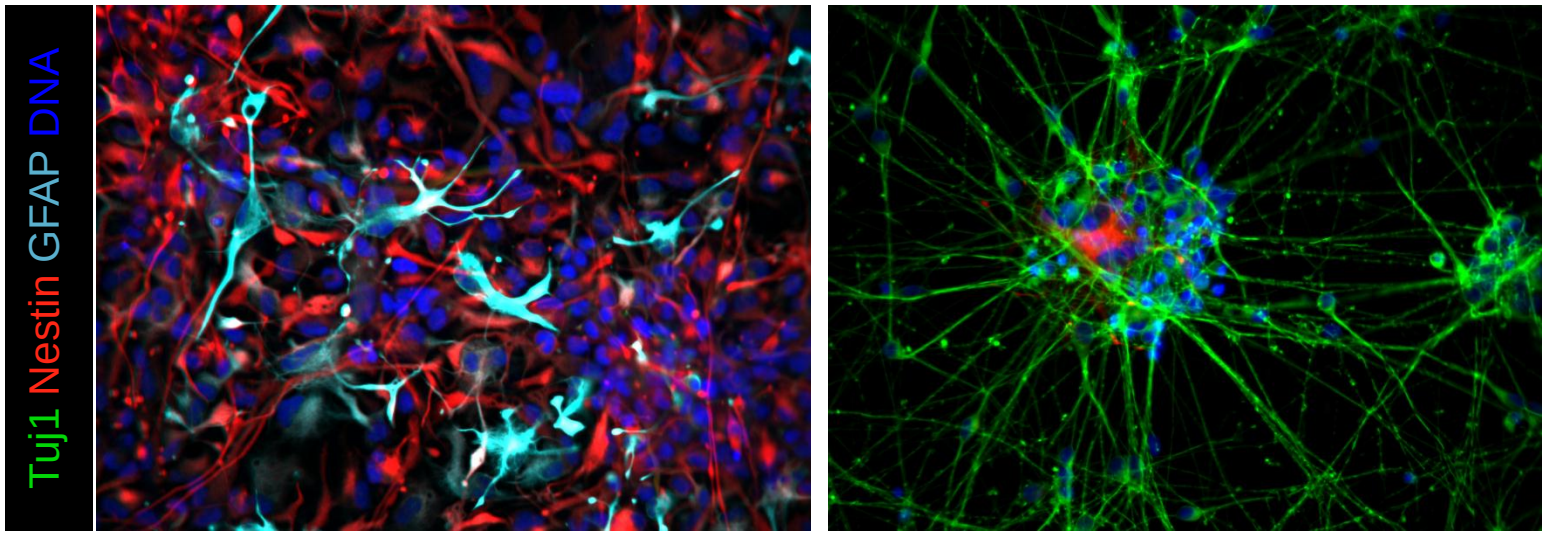
Data courtesy of Mike Hefferan and Martin Marsala, UCSD

Isolation of Neurons and Glia by Sorting

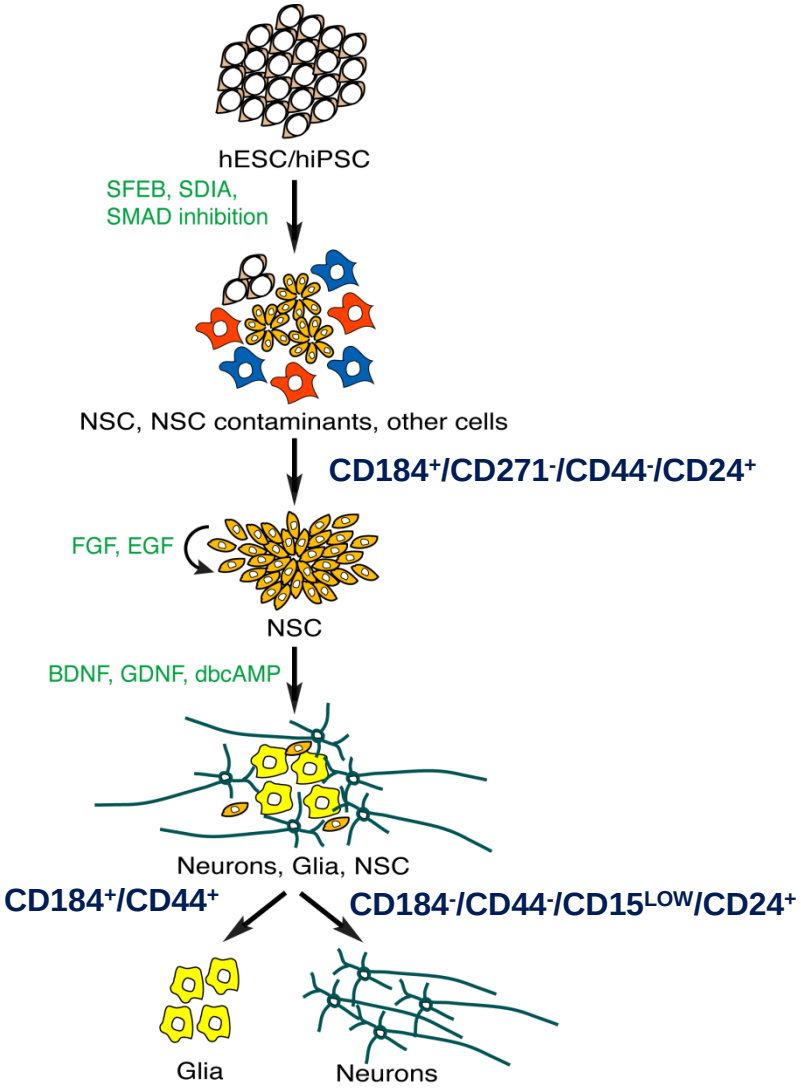


Glia:
$CD184^{+}/CD44^{+}$

Neurons:
$CD184^{-}/CD44^{-}/CD15^{lo}/CD24^{+}$



Summary

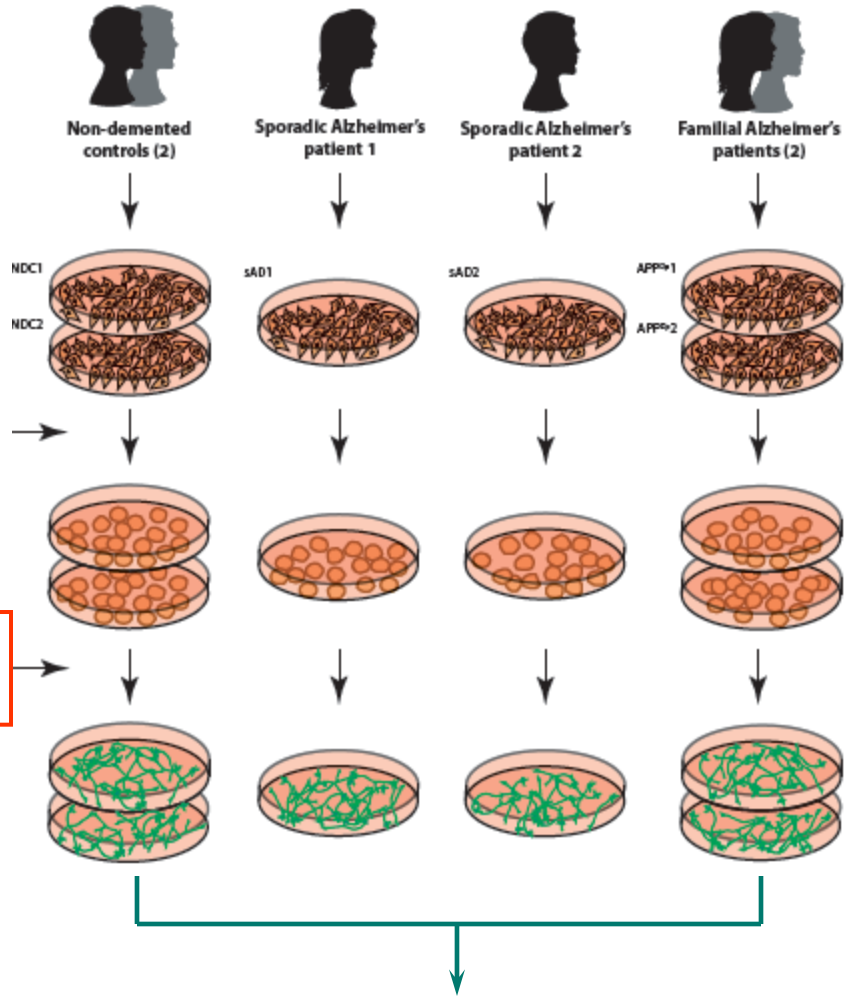


- Defined cell-surface signatures for NSCs, neurons, and glia
- Signatures enable:
  - ✓ Standardized and robust isolation of hESC-derived neural stem cells
  - ✓ Downstream applications requiring consistent or pure cell populations
- The immunophenotyping principle can be applied in other stem cell fields.

Probing sporadic and familial Alzheimer's disease using induced pluripotent stem cells

Nature January 2012, Volume 482, Issue 7384

Mason A. Israel[1,2], Shauna H. Yuan[1,3], Cedric Bardy[4], Sol M. Reyna[1,2], Yangling Mu[4], Cheryl Herrera[1], Michael P. Hefferan[5], Sebastiaan Van Gorp[6], Kristopher L. Nazor[7], Francesca S. Boscolo[8], Christian T. Carson[9], Louise C. Laurent[8], Martin Marsala[5,10], Fred H. Gage[4], Anne M. Remes[11], Edward H. Koo[3] & Lawrence S. B. Goldstein[1,3]



Fibroblasts

Reprogramming

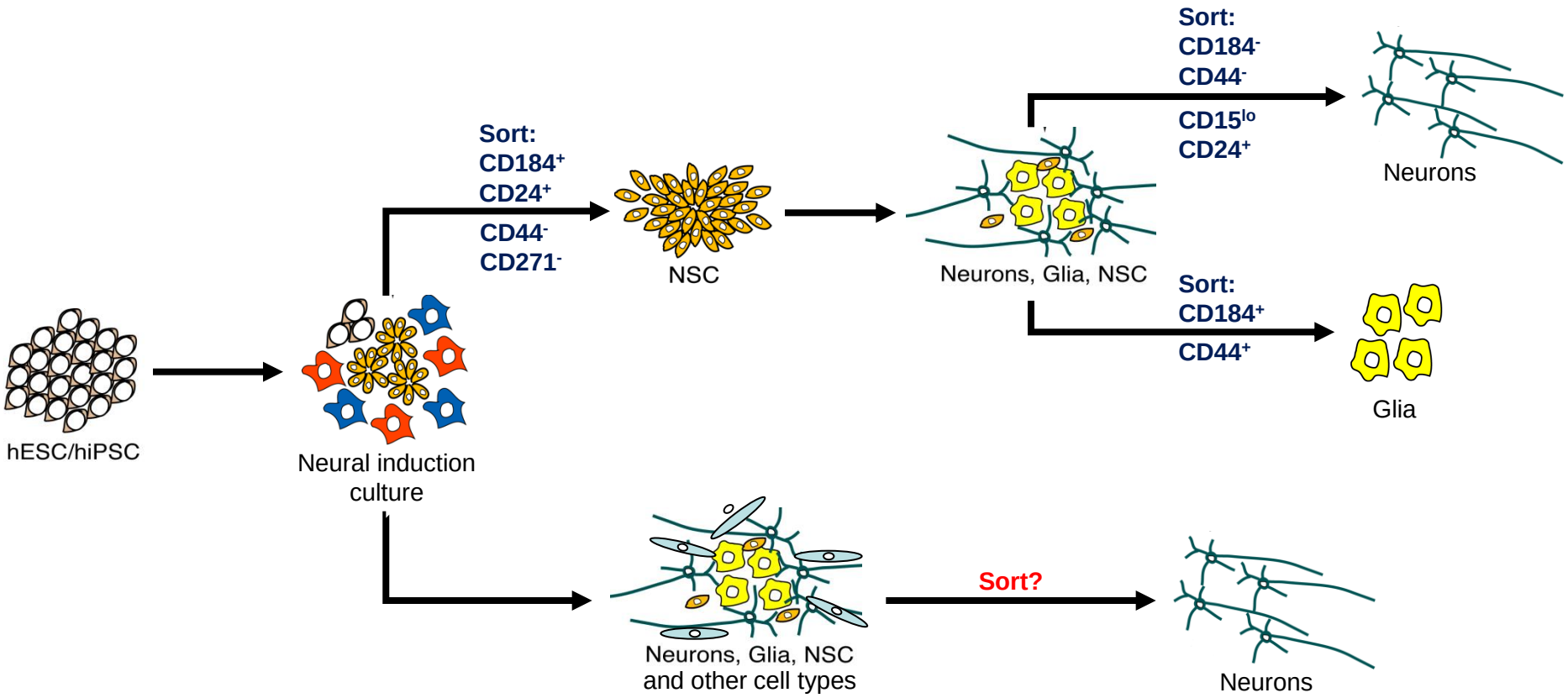
iPSCs

Directed neuronal differentiation and sorting purification

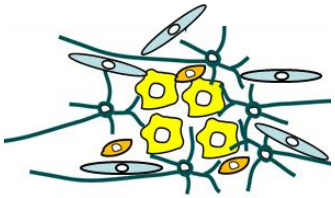
Purified Neurons

Alzheimer's disease biochemical marker comparative analysis

Cell-Surface Signatures for the Isolation of Neurons



Identification of Cell-Surface Marker Signatures of Neurons



6-Week Neural Induction Culture

Disassociate Cultures

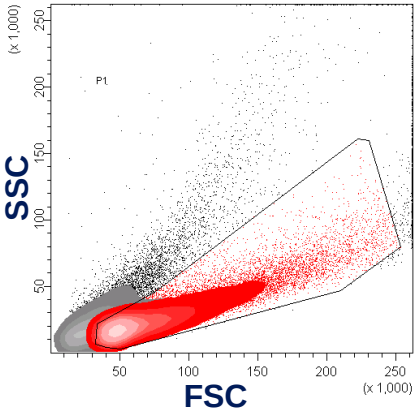
Stain with BD Lyoplate™ Human Cell Surface Marker Screening Panel

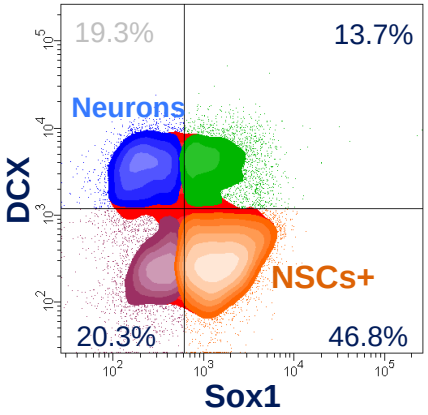
Fix Perm

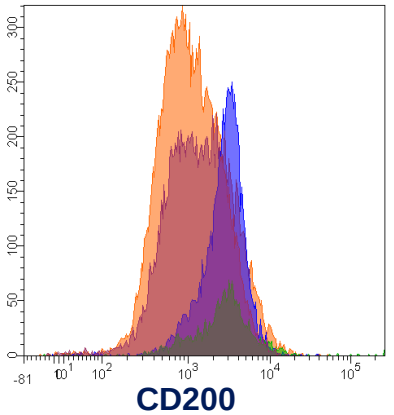
Stain with Sox1, Sox2, Pax6, and DCX

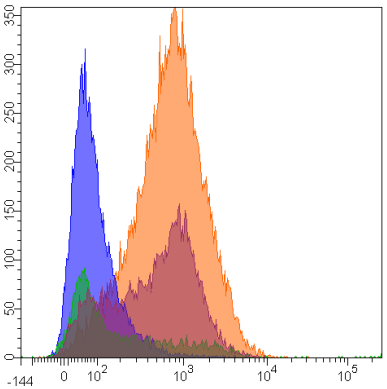
HTS Flow Cytometry

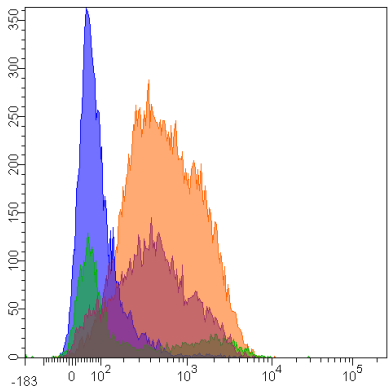
Analyze cell-surface marker expression of populations defined by intracellular markers

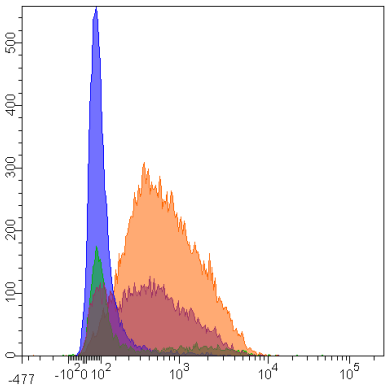




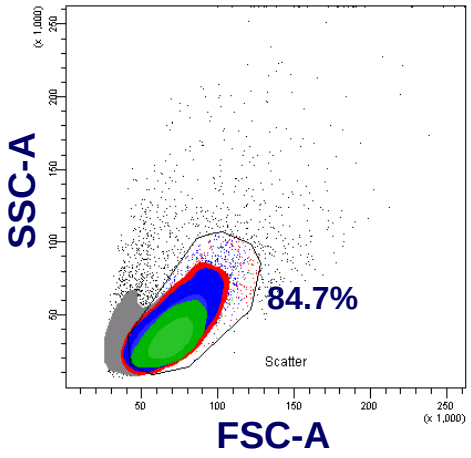


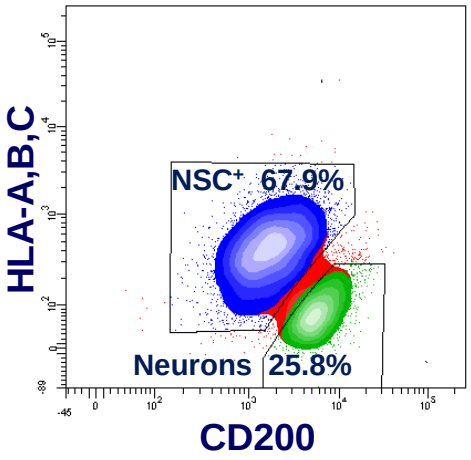


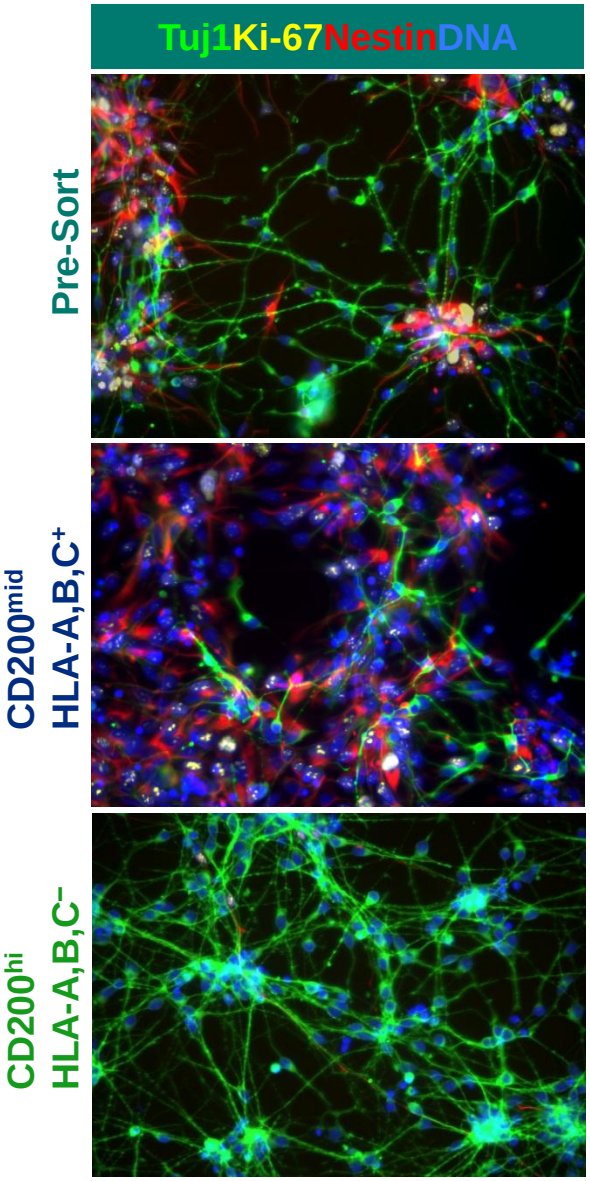


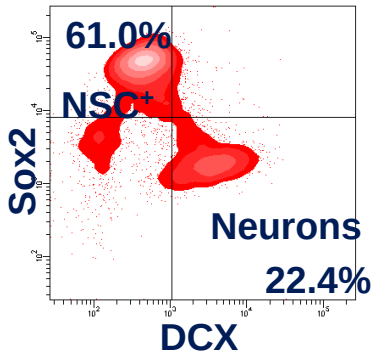


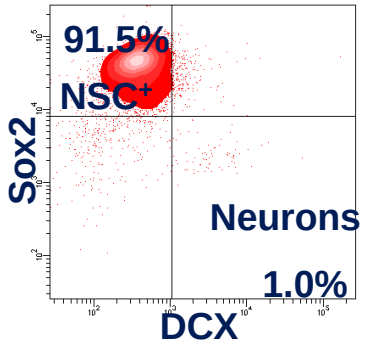
Isolation of Neurons Using CD200 and HLA-A,B,C

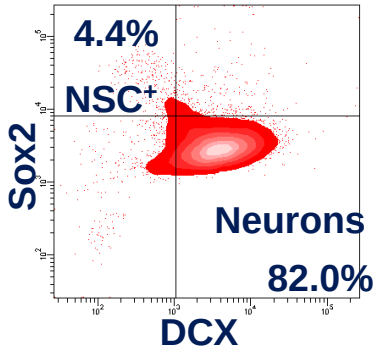




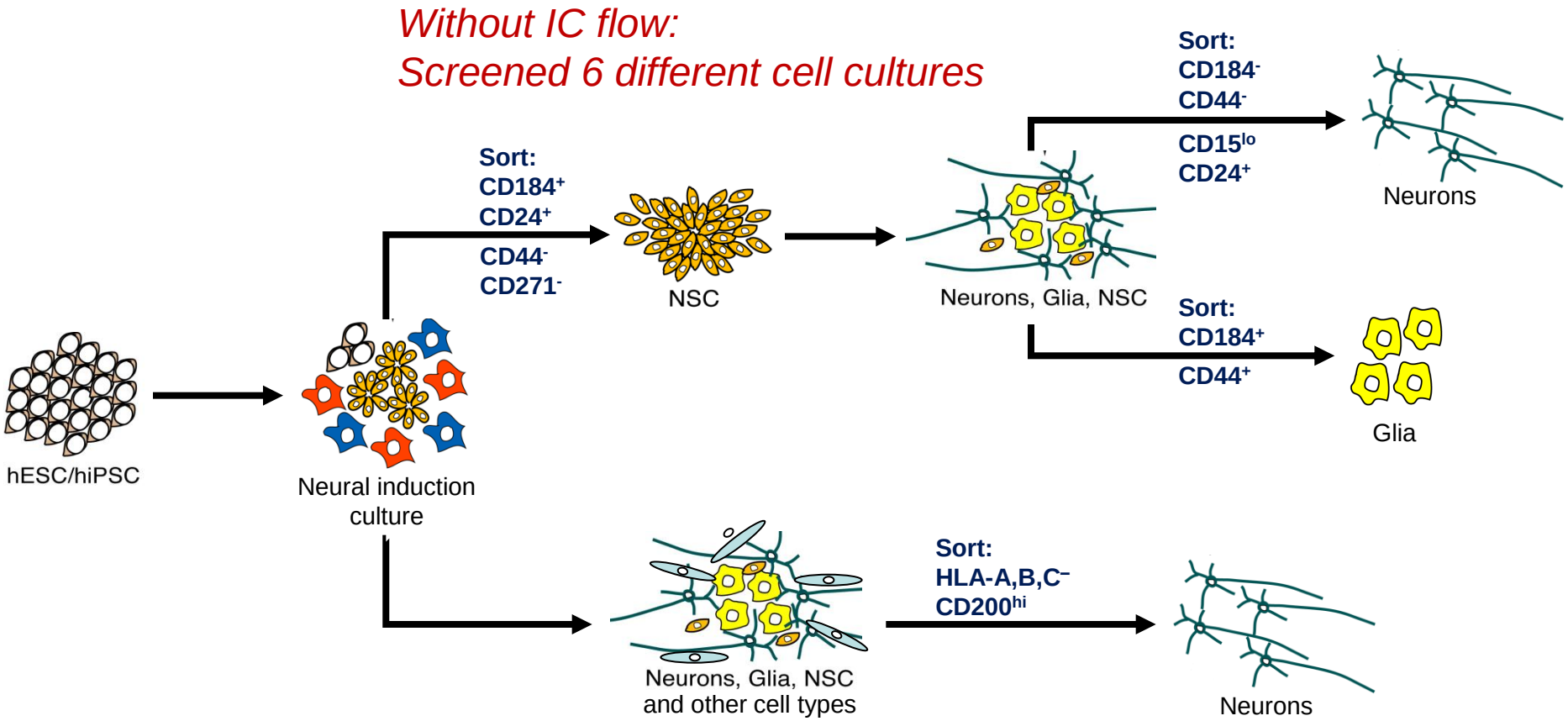








Cell-Surface Signatures for the Isolation of Neurons



Improved Sorting of Pluripotent Stem Cells

Sorting and Analysis of Pluripotent Stem Cells

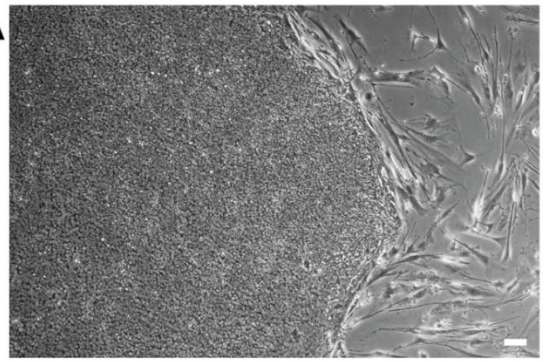
- Are sorted hESCs viable?
  - Fong CY, Peh GS, Gauthaman K, Bongso A. Separation of SSEA-4 and TRA-1-68 labelled undifferentiated human embryonic stem cells from a heterogeneous cell population using magnetic-activated cell sorting (MACS) and fluorescence-activated cell sorting (FACS). *Stem Cell Rev.* 2009;5:72-80.
  - Nicholas CR, Gaur M, Wang S, Pera RA, Leavitt AD. A method for single-cell sorting and expansion of genetically modified human embryonic stem cells. *Stem Cells Dev*. 2007;16:109-117.
  - Sidhu KS, Tuch BE. Derivation of three clones from human embryonic stem cell lines by FACS sorting and their characterization. *Stem Cells Dev.* 2006;15:61-69.
- Do sorted cells still express markers of pluripotency?
- Are sorted cells capable of further differentiation?
- No commercial, standardized methods for sorting hESCs by flow cytometry.

Sorting and Analysis of Pluripotent Stem Cells

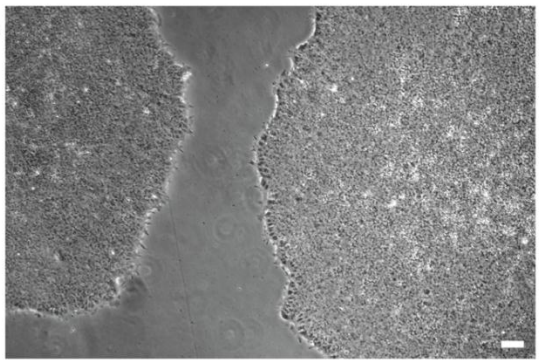
- The ROCK inhibitor, Y-27632, enhances survival of hESCs after single-cell dissociation.
  - Narumiya S, Ishizaki T, Uehata M. Use and properties of Rock-specific inhibitor Y-27632. *Methods Enzymol.* 2000;325:273-284.
  - Watanabe K, Ueno M, Kamiya D, et al. A Rock inhibitor permits survival of dissociated human embryonic stem cells. *Nat Biotechnol.* 2007;681-686.

Sorting Based on Markers for Pluripotency and Differentiation

A



B



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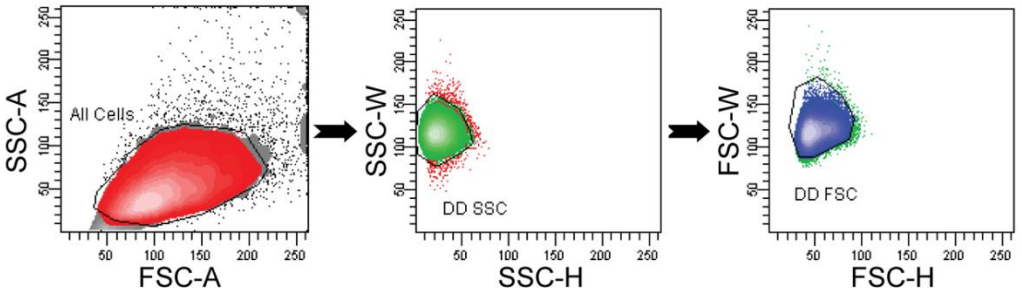

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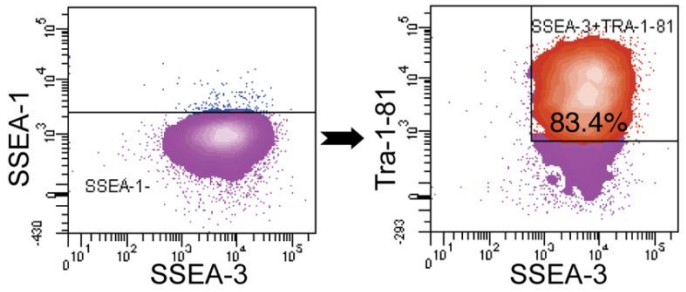
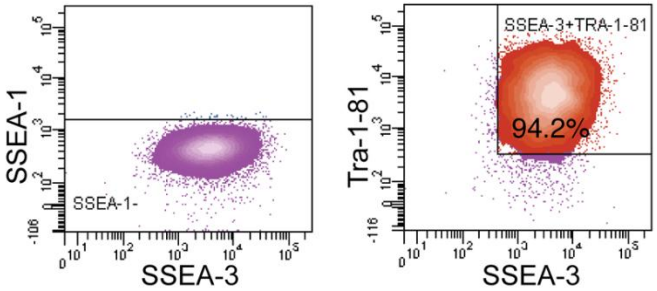


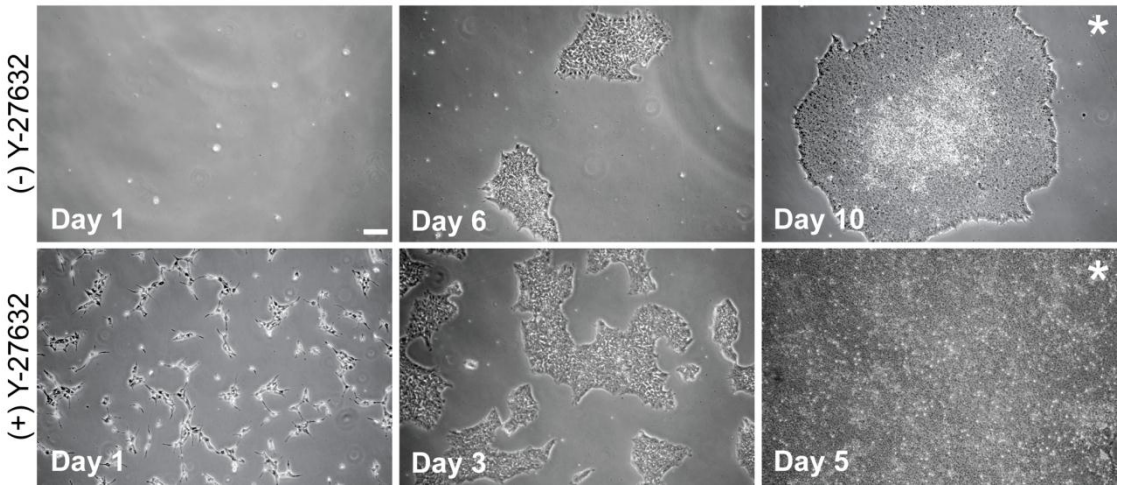
E

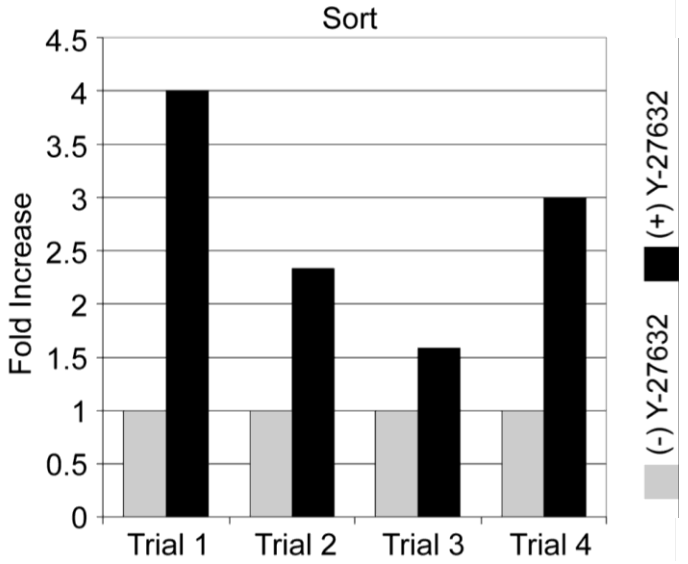
Population	%Parent	%Total
All Events	####	100.0
All Cells	83.7	83.7
DD SSC	89.3	74.8
DD FSC	91.9	68.7
SSEA-1-	97.6	67.0
SSEA-3+TRA-1-81+	83.4	55.9

F

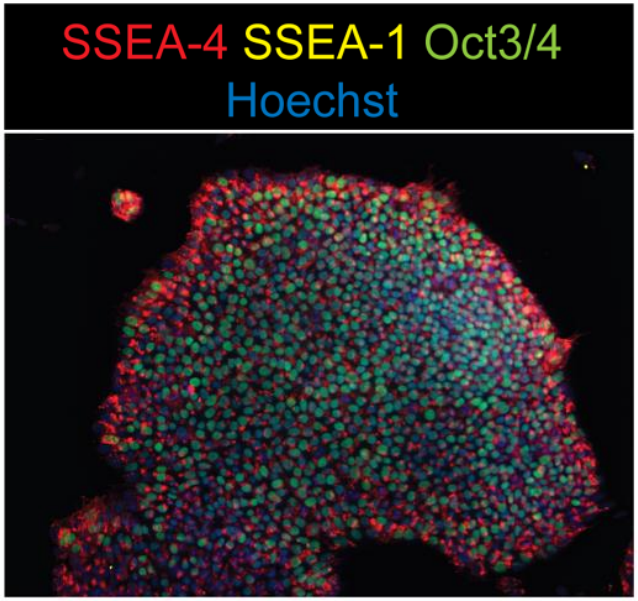


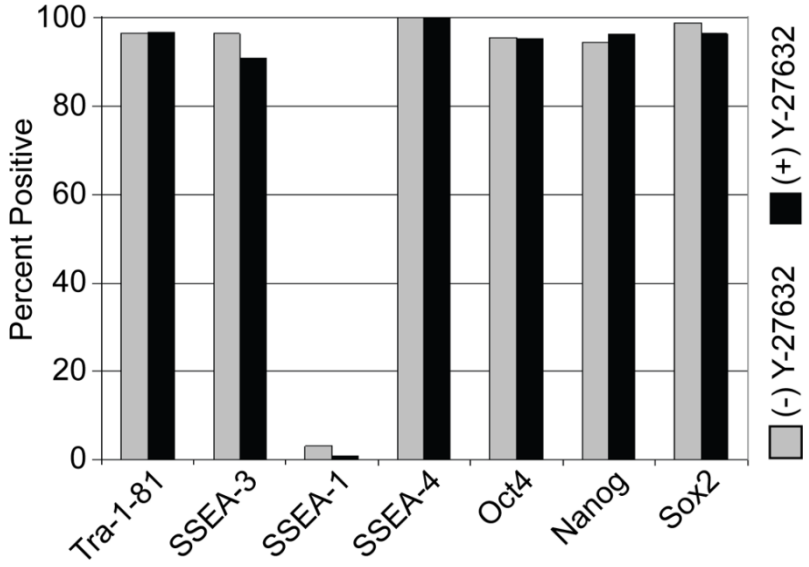
ROCK Inhibitor Y-27632 Increases Cell Recovery Post Sort

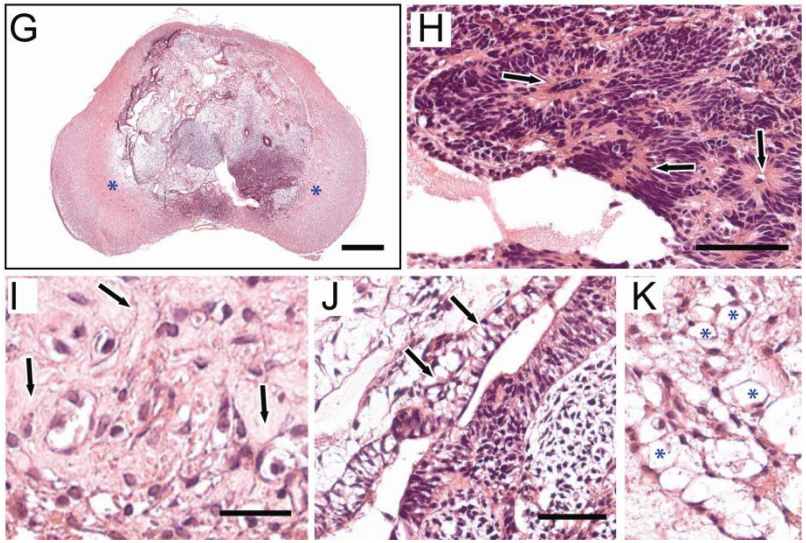


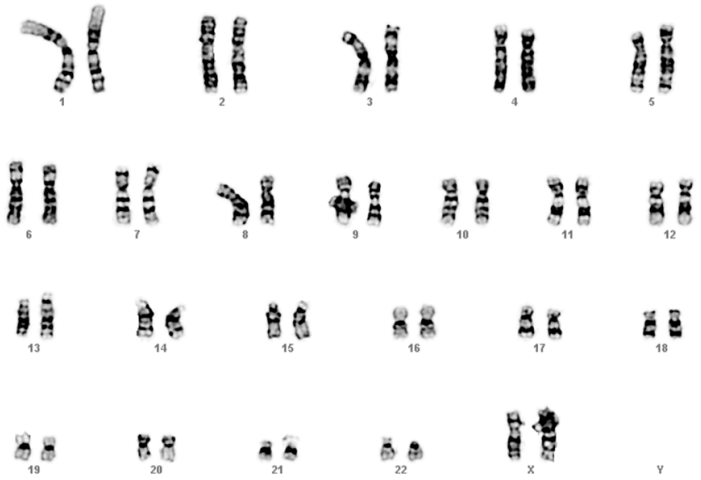


Sorted hESCs Retain Pluripotency









Sorting and Analysis of Pluripotent Stem Cells

The ROCK inhibitor Y-27632 improves recovery of human embryonic stem cells after fluorescence-activated cell sorting with multiple cell surface markers. Nil Emre, Jason G. Vidal, Jeanne Elia, Eric D. O'Connor, Rosanto I. Paramban, Michael P. Hefferan, Roman Navarro, Danielle S. Goldberg, Nissi M. Varki, Martin Marsala, and Christian T. Carson. *PLoS One,* 2010.

- Sorted hESCs are viable and recoverable.
- Recovery of cells is improved by the addition of Y-27632.
- Sorted cells express markers of pluripotency, are able to differentiate, and can maintain a normal karyotype.
- Standardized method for sorting hESCs by flow cytometry.

Enrichment for hiPSCs During Reprogramming

Flow Cytometry and hiPSCs

PLoS One. 2013;8(3):e59867. doi: 10.1371/journal.pone.0059867. Epub 2013 Mar 29.

Improved methods for reprogramming human dermal fibroblasts using fluorescence activated cell sorting.

Kahler DJ, Ahmad FS, Ritz A, Hua H, Moroziewicz DN, Sproul AA, Dusenberry CR, Shang L, Paull D, Zimmer M, Weiss KA, Egli D, Noggle SA.

The New York Stem Cell Foundation, New York, New York, United States of America.

Sci Rep. 2013;3:1179. doi: 10.1038/srep01179. Epub 2013 Jan 31.

Optimized surface markers for the prospective isolation of high-quality hiPSCs using flow cytometry selection.

Abujarour R, Valamehr B, Robinson M, Rezner B, Vranceanu F, Flynn P.

Fate Therapeutics Inc., 3535 General Atomics Court Suite 200, San Diego, CA 92121, USA.

Sci Rep. 2012;2:213. Epub 2012 Jan 6.

A novel platform to enable the high-throughput derivation and characterization of feeder-free human iPSCs.

Valamehr B, Abujarour R, Robinson M, Le T, Robbins D, Shoemaker D, Flynn P.

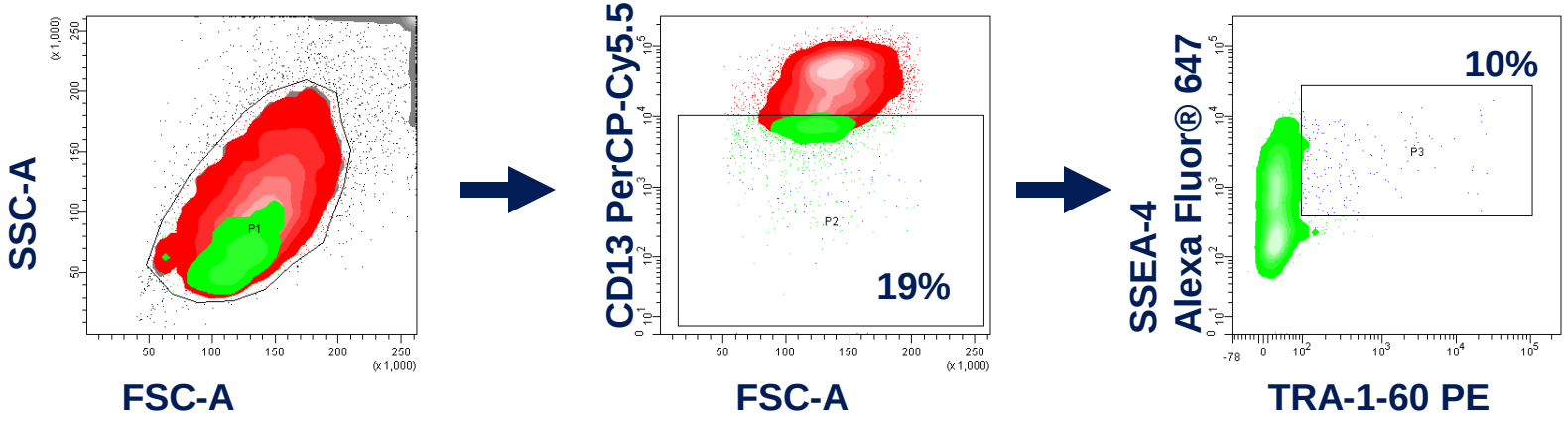
Fate Therapeutics Inc. , San Diego, CA, USA.

BD Stemflow™ Human Induced Pluripotent Stem Cell Analysis and Sorting Kit

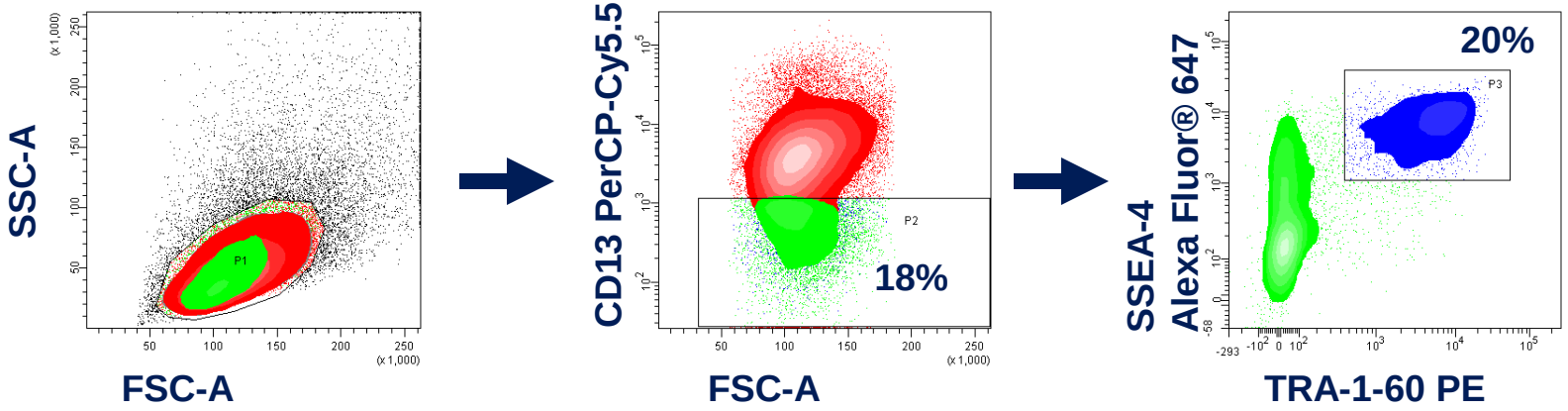
BD

Reprogramming Time Course

Cells at Day 21 Post-Transduction

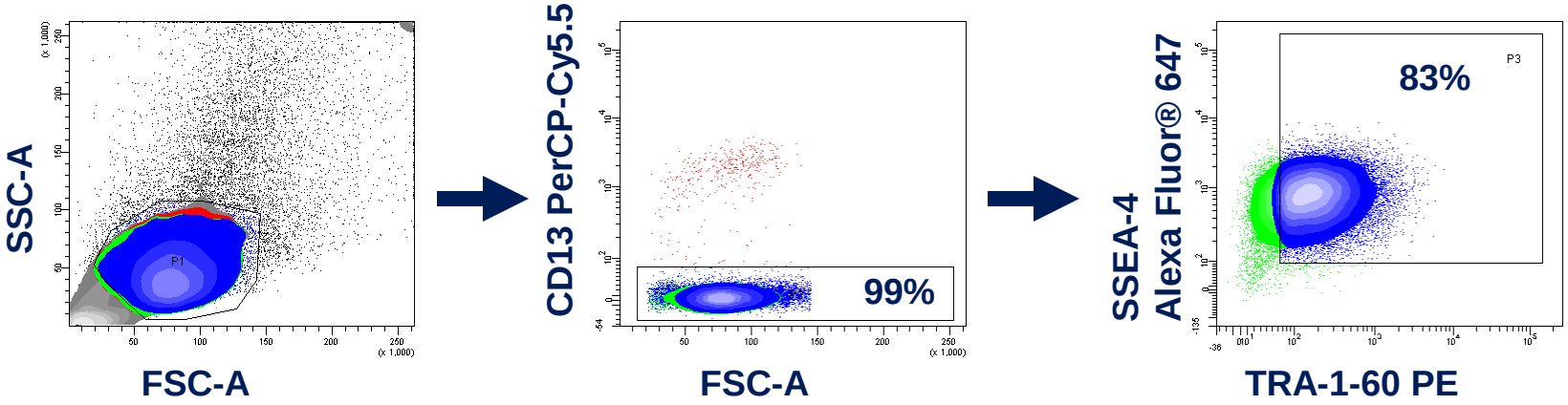


Cells at Day 35 Post-Transduction

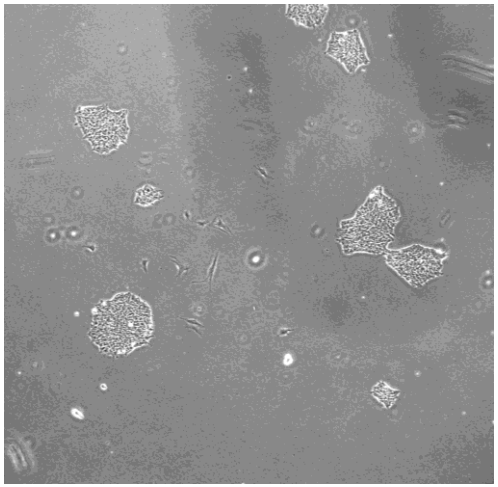


Data courtesy of Peter Flynn and Bob Valamehr, Fate Therapeutics

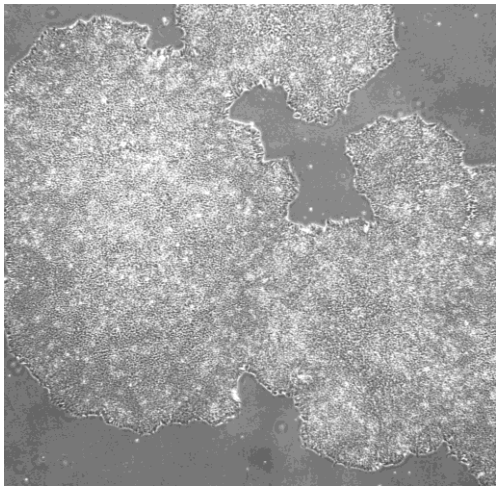
Sorting Established hiPSC Lines



Day 6 Post-Sort



Day 11 Post-Sort



Data courtesy of David Kahler, New York Stem Cell Foundation

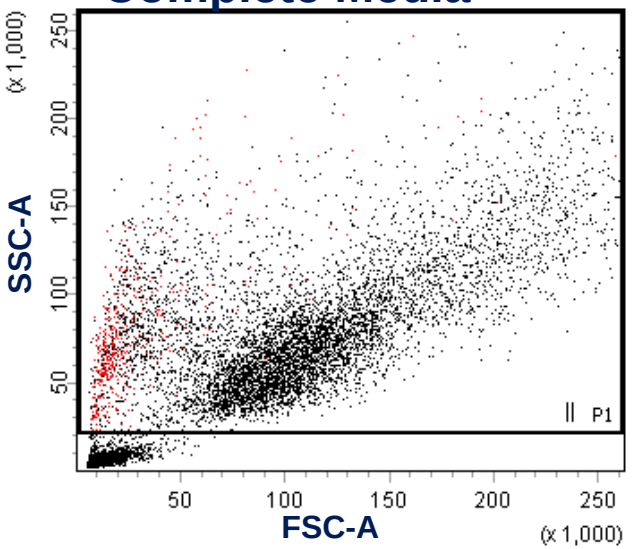
BD Pharmingen™ Cell Sorting Preparation Buffer Set

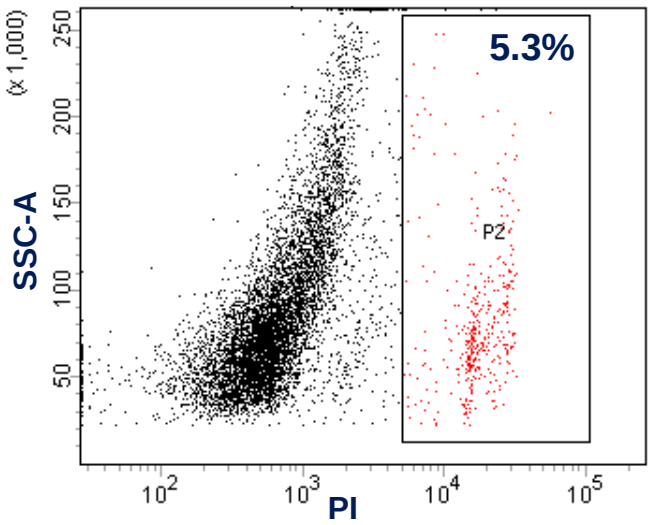
- Preparation and maintenance of single-cell suspensions for sorting and analysis

- Cell types tested for sorting applications:
  - Human bone marrow
  - T cells
  - Regulatory T cells (Tregs)
  - hESCS
  - NSCs
  - Neurons

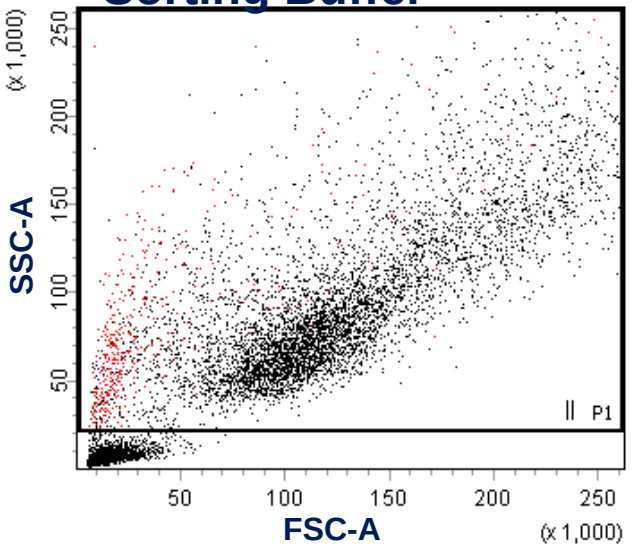
End of Sort Viability Comparison: hESCs

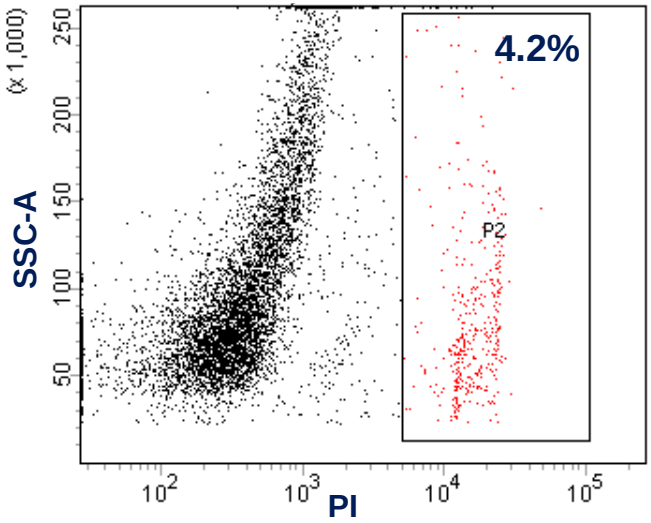
Complete Media





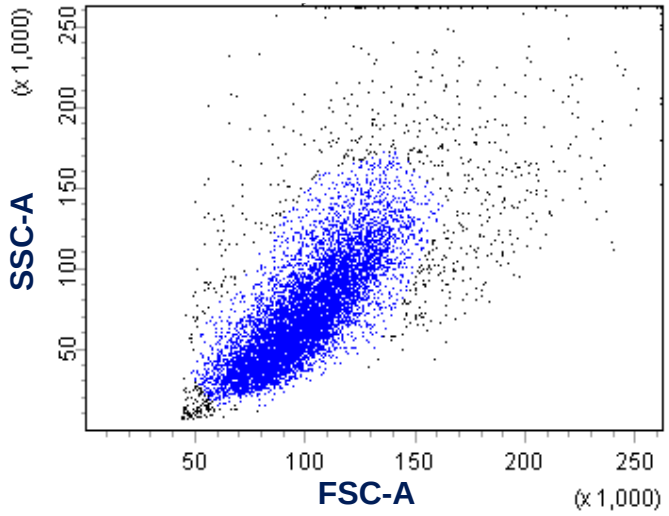
Sorting Buffer

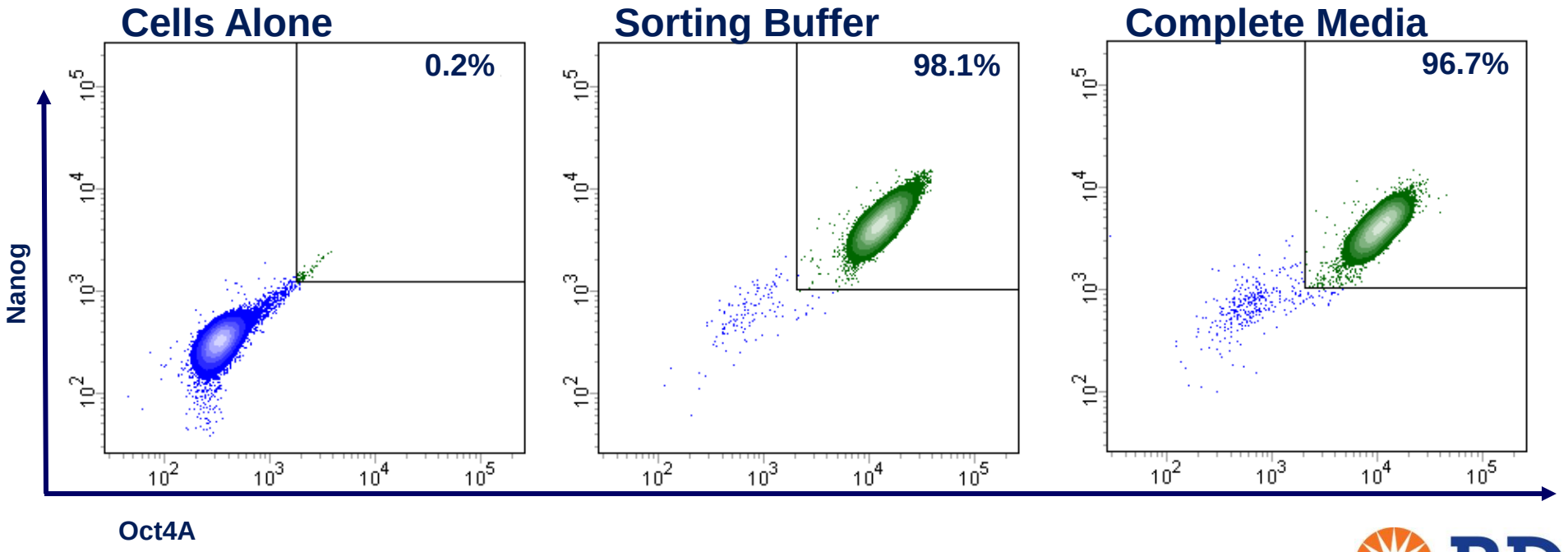




BD

Post-Sort Analysis: hESCs

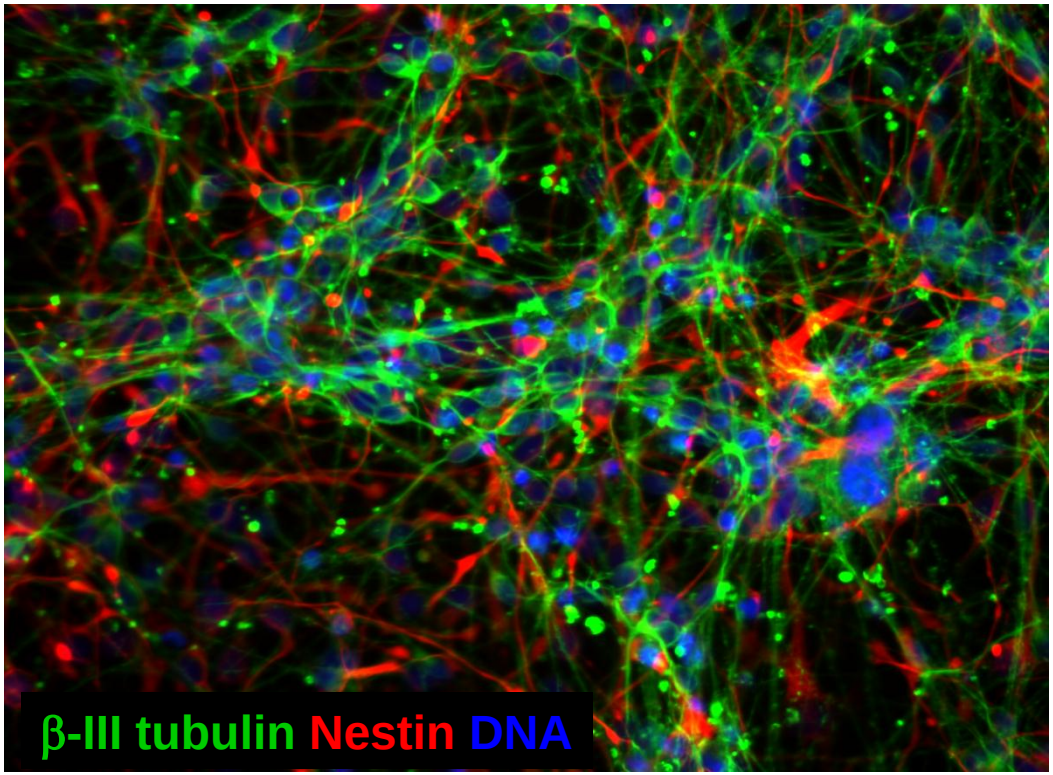




Monitoring Neural Ectoderm and Endoderm Differentiation from hESCs using Multiparameter Flow Cytometry

BD Stemflow™ Neural Lineage Analysis Kit

Differentiation of hESC-derived NSCs to neurons and glia

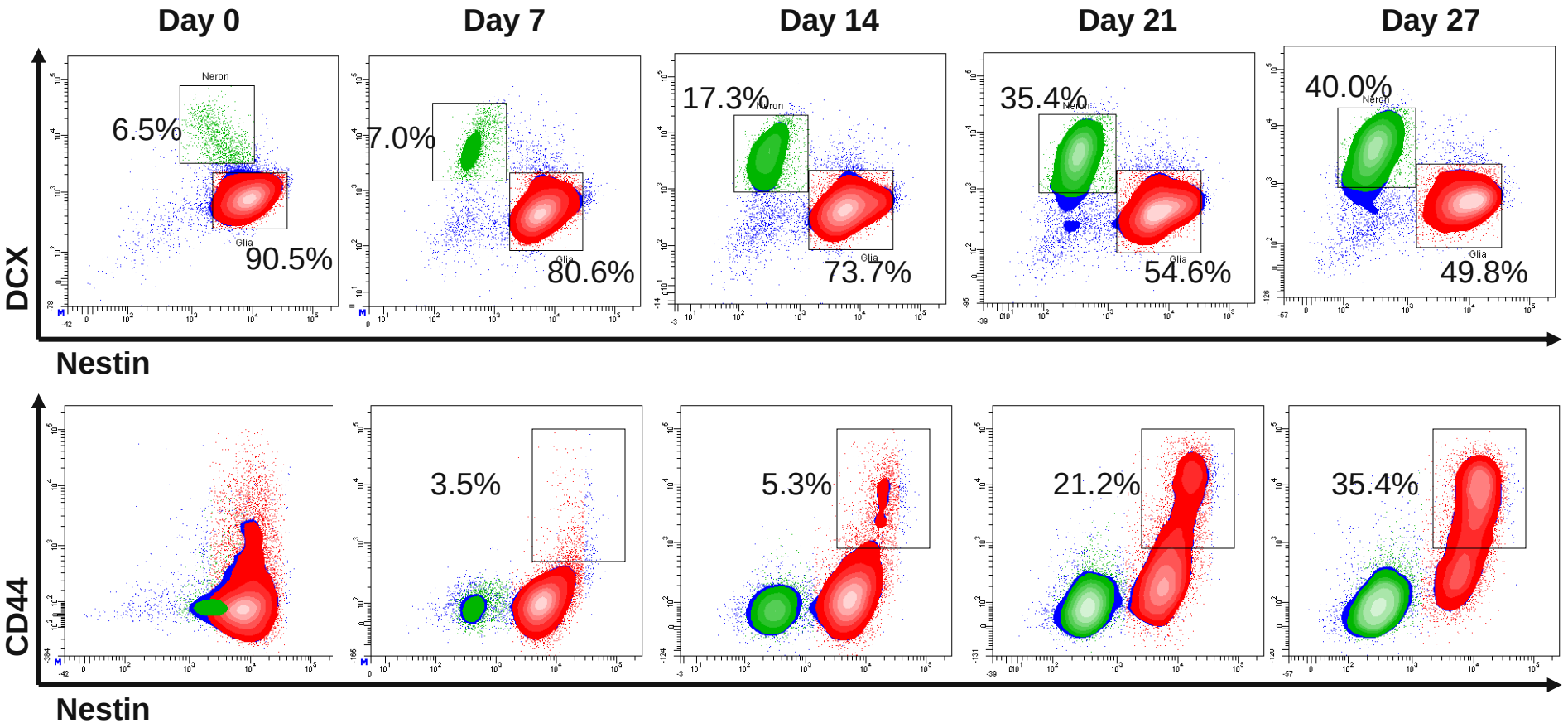


BD Stemflow Neural Lineage Analysis Kit

Specificity	***Format***	***Molecule***	***Neural Cell Population Identified***
CD44	FITC	H-CAM	Glial precursors, astrocytes
Ki-67	Alexa Fluor® 488	Proliferation marker	All proliferating cell types
Doublecortin	PE	Neurofilament	Immature neurons
Sox2	PerCP-Cy™5.5	Transcription Factor	NSCs, glial precursors
Sox1	PerCP-Cy5.5	Transcription Factor	NSCs, glial precursors
GFAP	Alexa Fluor® 647	Filament	Mature astrocytes
Nestin	Alexa Fluor® 647	Filament	NSCs, glial precursors
Buffers Included			
BD Cytofix™ fixation buffer			
BD Phosflow™ perm buffer III			

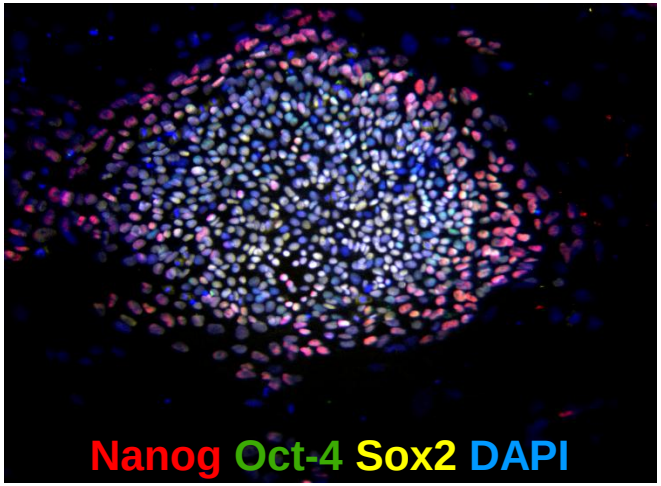
BD Stemflow Neural Lineage Analysis Kit

Differentiation of hESC-derived NSCs to neurons and glia



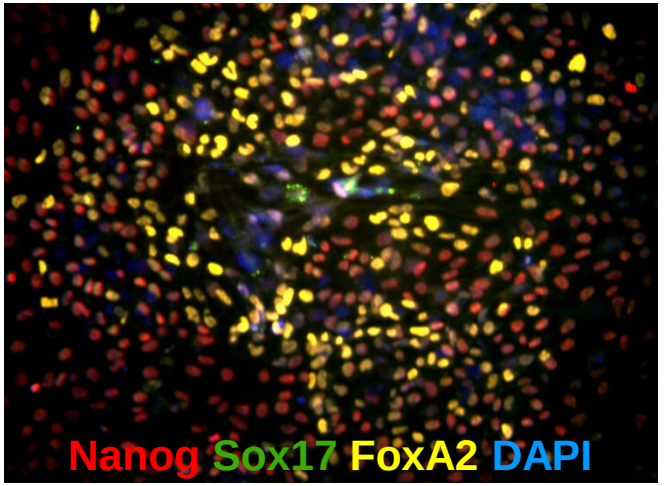
Endodermal Differentiation from hESCs

hESCs



3 Days
Low FBS, Activin
(D'Amour et al, 2005)

Definitive Endoderm

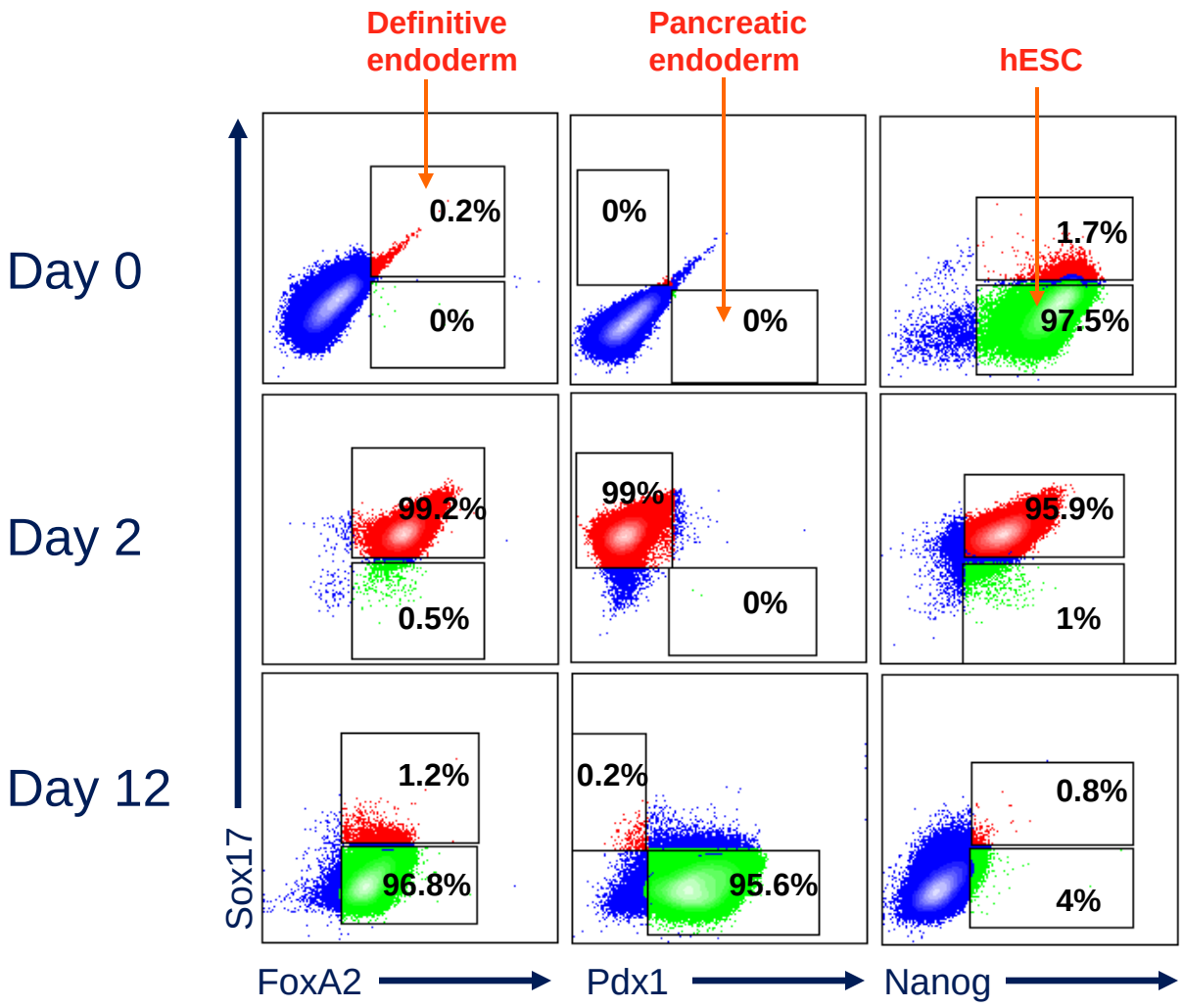


Goal: To develop quantitative flow cytometric assays to monitor endodermal differentiation

BD Stemflow™ Definitive and Pancreatic Endoderm Analysis Kit

Panel Components			
Specificity	Clone	Isotype	Format
Pax-6	O30-1330	mIgG$_1$, κ	Alexa Fluor® 488
PDX-1	658A5.1.37	mIgG$_1$, κ	PE
FoxA2	N17-280	mIgG$_1$, κ	PE
Sox2	O30-678	mIgG$_1$, κ	PerCP-Cy5.5
Sox17	P7-969	mIgG$_{2a}$, κ	PerCP-Cy5.5
Nanog	N31-355	mIgG$_1$, κ	Alexa Fluor® 647

Monitoring Endodermal Differentiation Using Flow Cytometry



CyT49 hESCs

Mark Moorman, ViaCyte, Inc.

MSC Characterization using Flow Cytometry

MSC Definition

International Society for Cellular Therapy ISCT

Cytotherapy (2006) Vol. 8, No. 4, 315–317

Taylor & Francis
Taylor & Francis Group

POSITION PAPER

Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement

M Dominici[1], K Le Blanc[2], I Mueller[3], I Slaper-Cortenbach[4], FC Marini[5], DS Krause[6], RJ Deans[7], A Keating[8], DJ Prockop[9] and EM Horwitz[10]

- *MSCs must be plastic adherent.*
- *MSCs must express CD73, CD105, and CD90 and lack expression of CD45, CD34, CD14, CD11b, CD79a, and CD19.*
- *MSCs must differentiate into osteoblasts, adipocytes, and chondrocytes in vitro.*

BD

MSC Variability

Source:

- Bone marrow
- Adipose tissue
- Umbilical cord

Intra-population heterogeneity:

- Early vs late passage in culture
- Normoxia vs hypoxia
- Serum vs serum free
- Subsets of MSCs with distinct functions and potential

MSC Heterogeneity

Neural Ganglioside GD2 Identifies a Subpopulation of Mesenchymal Stem Cells in Umbilical Cord

Jie Xu[1], WenBin Liao[1], DongSheng Gu[1], Lu Liang[1], Meng Liu[1], WeiTing Du[1], PengXia Liu[1], Lei Zhang[1], ShiHong Lu[1], ChunLan Dong[1], Bin Zhou[2] and Zhongchao Han[1]

The Globoseries Glycosphingolipid SSEA-4 Is a Marker of Bone Marrow-Derived Clonal Multipotent Stromal Cells In Vitro and In Vivo

Michael Rosu-Myles,[1] Jennifer McCully,[1] Joel Fair,[2] Jelica Mehic,[1] Pablo Menendez,[3] Rene Rodriguez,[4] and Carole Westwood[1]

Perivascular support of human hematopoietic stem/progenitor cells

Mirko Corselli, Chee Jia Chin, Chintan Parekh, Arineh Sahaghian, Wenyuan Wang, Shundi Ge, Denis Evseenko, Xiaoyan Wang, Elisa Montelatici, Lorenza Lazzari, Gay M. Crooks and Bruno Péault

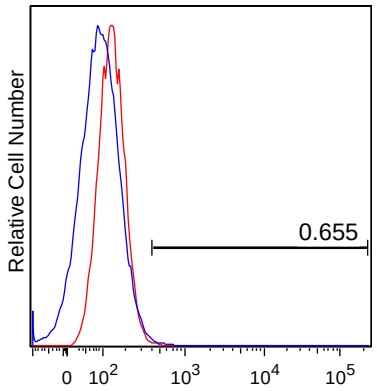
Engineering bone tissue substitutes from human induced pluripotent stem cells

Giuseppe Maria de Peppo[a], Iván Marcos-Campos[b], David John Kahler[a], Dana Alsalman[a], Linshan Shang[a], Gordana Vunjak-Novakovic[b], and Darja Marolt[a,1]

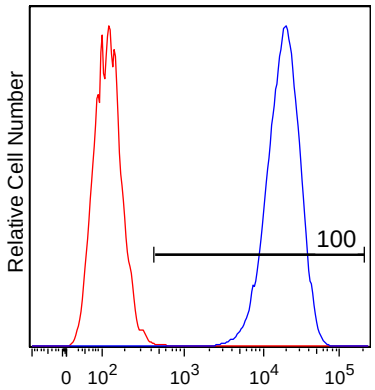
Tra1-60	0.6	0.3	1.1	1.6	1.1	0.7
SSEA4	18.9	39.4	7.3	55.7	67.7	4.8
SSEA1	0.7	0.3	1.0	1.4	1.0	1.0
CD14	0.7	0.2	1.0	1.3	1.1	0.8
CD31	0.7	0.2	1.2	1.3	1.0	3.3
CD34	0.6	0.3	0.9	1.3	1.1	0.9
CD45	0.7	0.2	0.9	1.5	1.1	0.9
HLA-A2	72.9	0.2	60.5	45.5	1.1	74.5
HLA-DM	0.9	0.2	0.9	1.0	1.3	0.6
HLA-DR	0.9	0.1	0.8	1.3	1.0	0.7
HLA-ABC	5.0	1.1	2.7	3.6	1.1	3.6

ALP	75.3	26.3	8.2	11.6	10.6	3.3
CD49a	21.8	12.4	9.5	1.8	1.4	10.4
CD49b	89.1	90.7	71.0	87.2	74.0	11.5
CD49c	53.1	59.4	90.7	88.3	67.6	47.1
CD49d	23.8	13.4	37.0	19.9	21.4	55.0
CD49f	35.7	37.1	54.0	75.2	64.8	34.5
CD51/61	17.7	7.7	43.7	3.4	7.8	4.9
CD54	47.4	31.8	66.9	66.7	22.5	16.7
CD140b	46.2	40.5	51.8	32.1	23.0	0.9
CD146	15.6	29.1	57.7	67.9	52.1	26.2

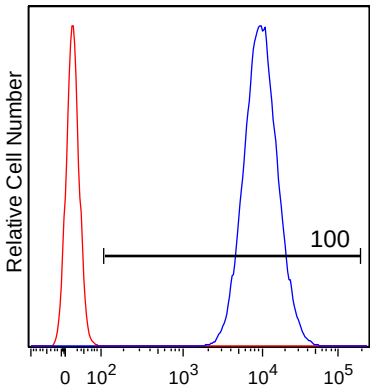
BD Stemflow™ Human MSC Analysis Kit



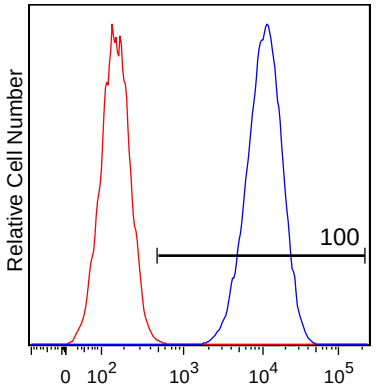
Lin PE



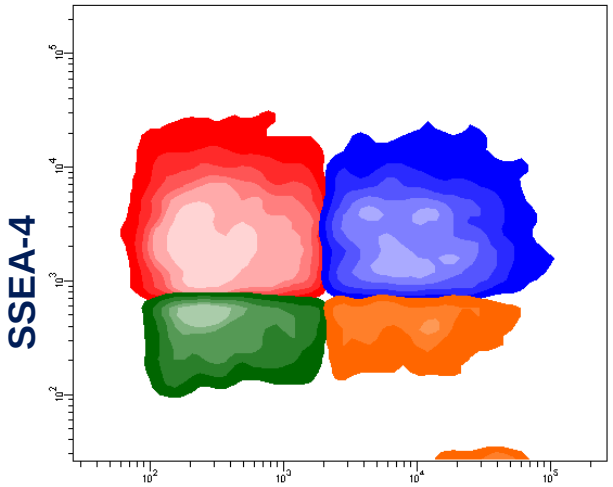
CD90 FITC

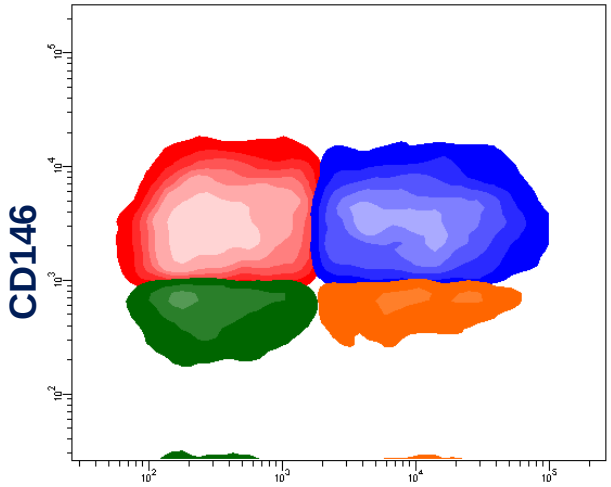


CD73 APC



CD105 PerCP-Cy5.5





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The Devil is in the Details: Heterogeneity

Heterogeneity of stem cell cultures is a major challenge

Potential solution:

- **Defined cell-surface signatures for stem cells and their derivatives**
  - BD Lyoplate™ Human Cell Surface Marker Screening Panel
  - BD Lyoplate™ Mouse Cell Surface Marker Screening Panel
- **Robust methods for cell sorting**
  - BD Stemflow™ Neural Sorting Kit
  - BD Stemflow™ Pluripotent Stem Cell Sorting and Analysis Kit
  - BD Stemflow™ Human Induced Pluripotent Stem Cell Analysis and Sorting Kit
  - BD Pharmingen™ Lineage Cocktail 4 (lin 4)
  - ROCK Inhibitor (Y-27632)
  - BD Pharmingen™ Cell Sorting Preparation Buffer Set
- **Quantitative analysis tools for heterogeneous cell cultures**
  - BD Stemflow™ Definitive and Pancreatic Endoderm Analysis Kit
  - BD Stemflow™ Neural Lineage Analysis Kit
  - BD Stemflow™ Human MSC Analysis Kit
  - BD Stemflow™ Human and Mouse Pluripotent Stem Cell Analysis Kit
  - BD Stemflow™ Human Pluripotent Stem Cell Transcription Factor Analysis Kit
  - BD Stemflow™ Mouse Pluripotent Stem Cell Transcription Factor Analysis Kit

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Matthew Zimmer

If you have further questions:

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or e-mail: ResearchApplications@bd.com