Asymmetric Self-Renewal By Distributed Stem Cells:

Misunderstood in the Past, Important for the Future

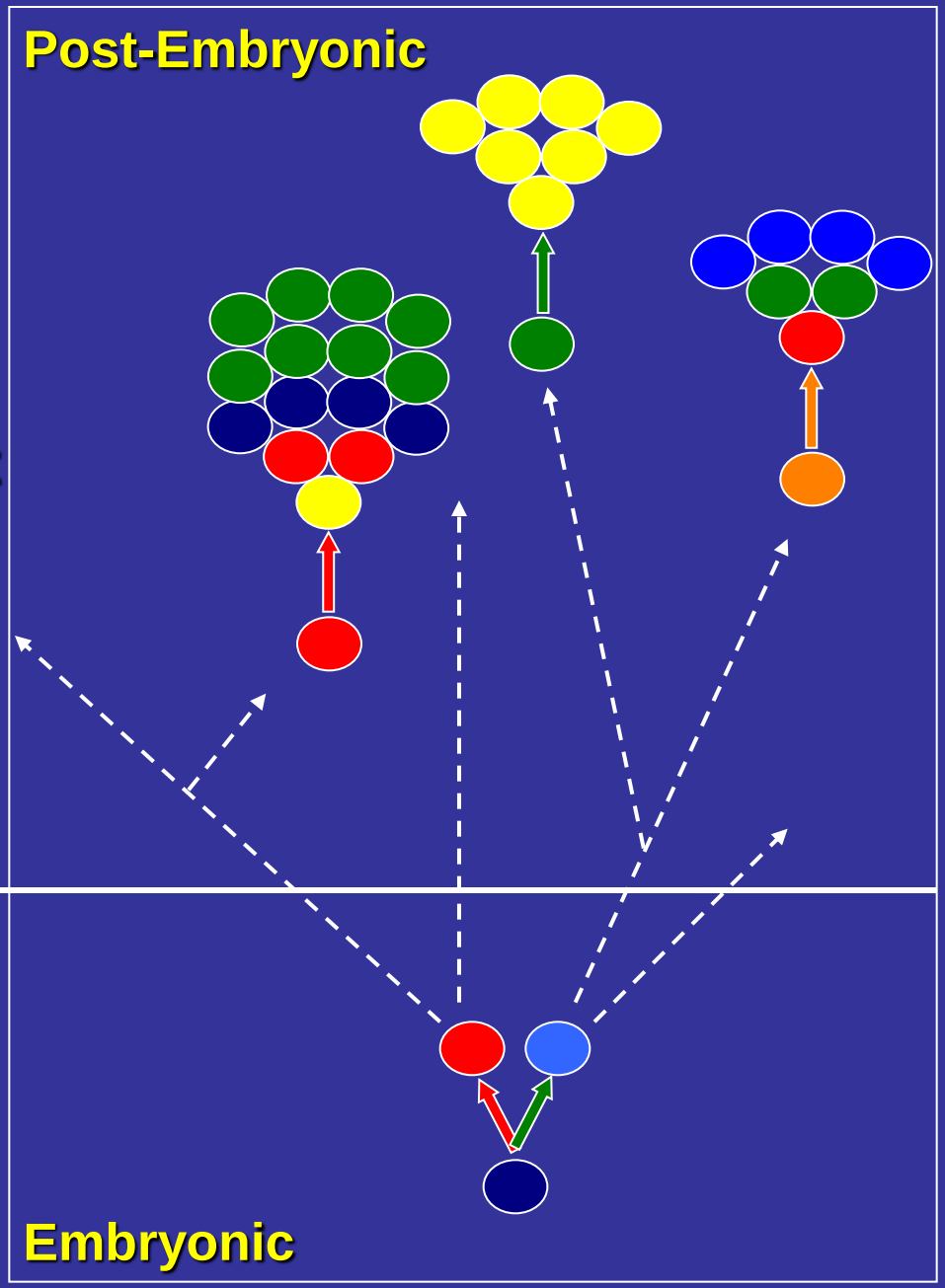
James L. Sherley, M.D., Ph.D.
Director

The Adult Stem Cell Technology Center, LLC
Boston, MA, USA

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Distributed Stem Cells? (DSCs)

Sources of Stem Cells (SCs) During Mammalian Development



Fetal SCs
Germline SCs
Post-natal SCs
Somatic SCs
Tissue SCs
Adult SCs

Fetal, Neonatal, Adult Development

Early Embryonic Development

Epiblasts [embryonic SCs]
Embryonic precursors

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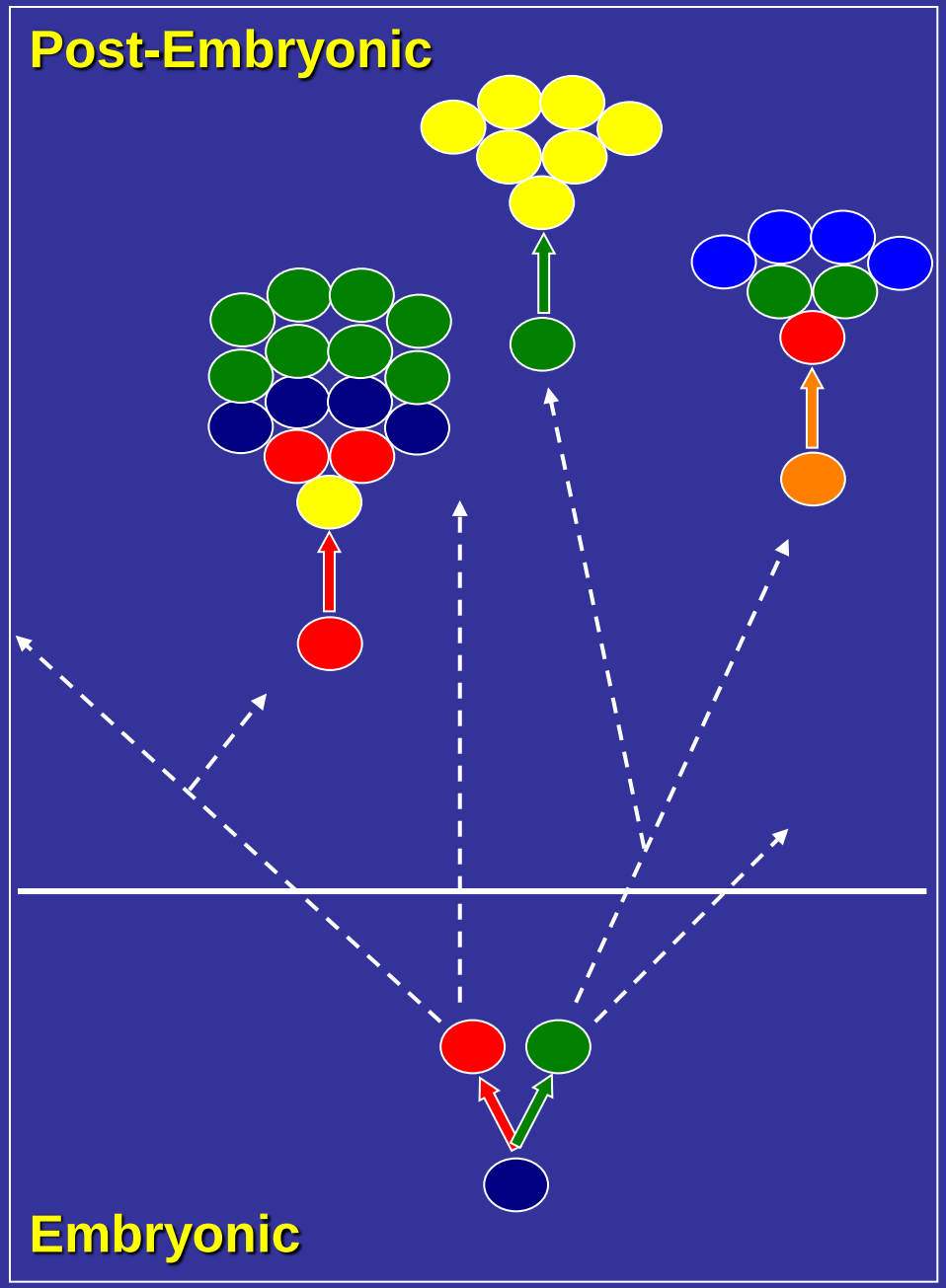
“DISTRIBUTED STEM CELLS”
DSCs

(Sherley, 2008,
Breast Disease **29**, 37-46)

For *Distributed* Potency

Asymmetric Self-Renewal
In vivo and in vitro

Embryonic stem cells
Primordial germ cells
Induced pluripotent SCs
Symmetric Self-Renewal
In vitro

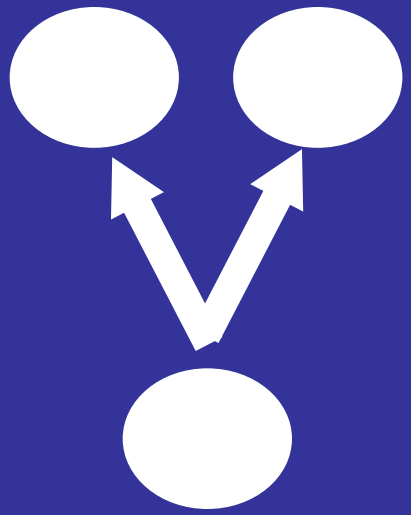


Fetal SCs
Germline SCs
Post-natal SCs
Somatic SCs
Tissue SCs
Adult SCs

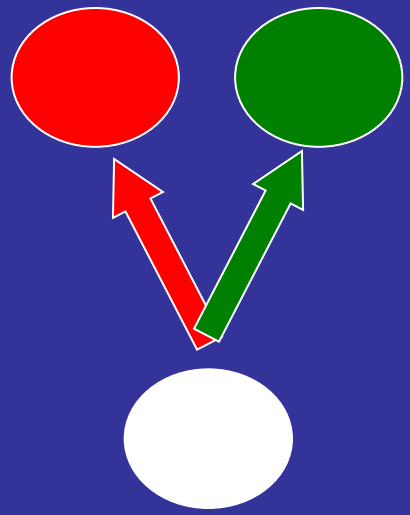
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The Pervasive Stem Cell Definition:

Self-renewal or *Differentiation*



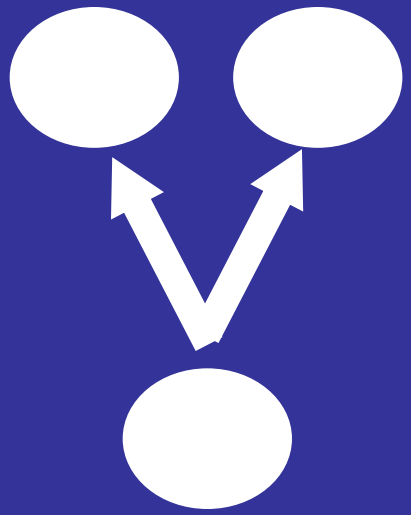
Symmetric
Self-renewal



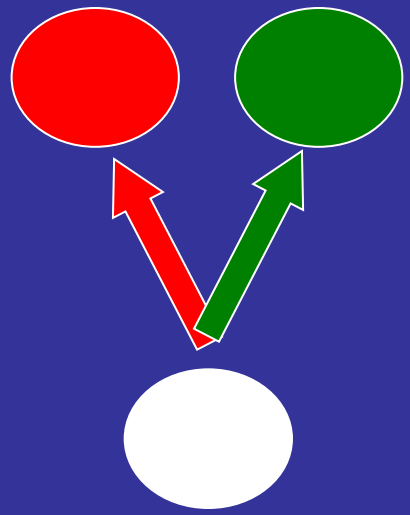
An Inadequate Definition For Distributed Stem Cells

The Pervasive Stem Cell Definition:

Self-renewal or *Differentiation*

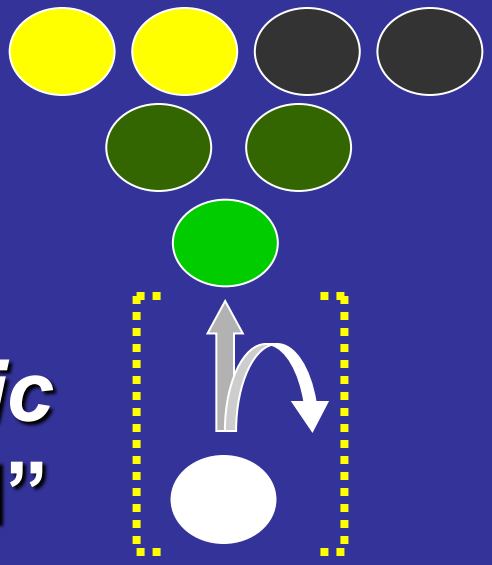


Symmetric
Self-renewal



A Gnomonic for Distributed Stem Cells:

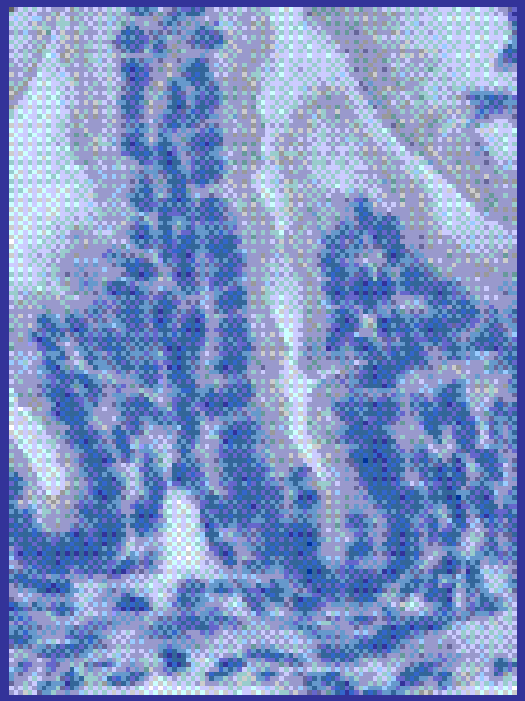
Self-renewal *AND* *Differentiation*,
continuously and simultaneously



"Asymmetric
Self-renewal"

Tissue Cell Turnover

The mark of distributed stem cells (DSCs): *Asymmetric Self-Renewal*



Potten *et al*., 2003

Death

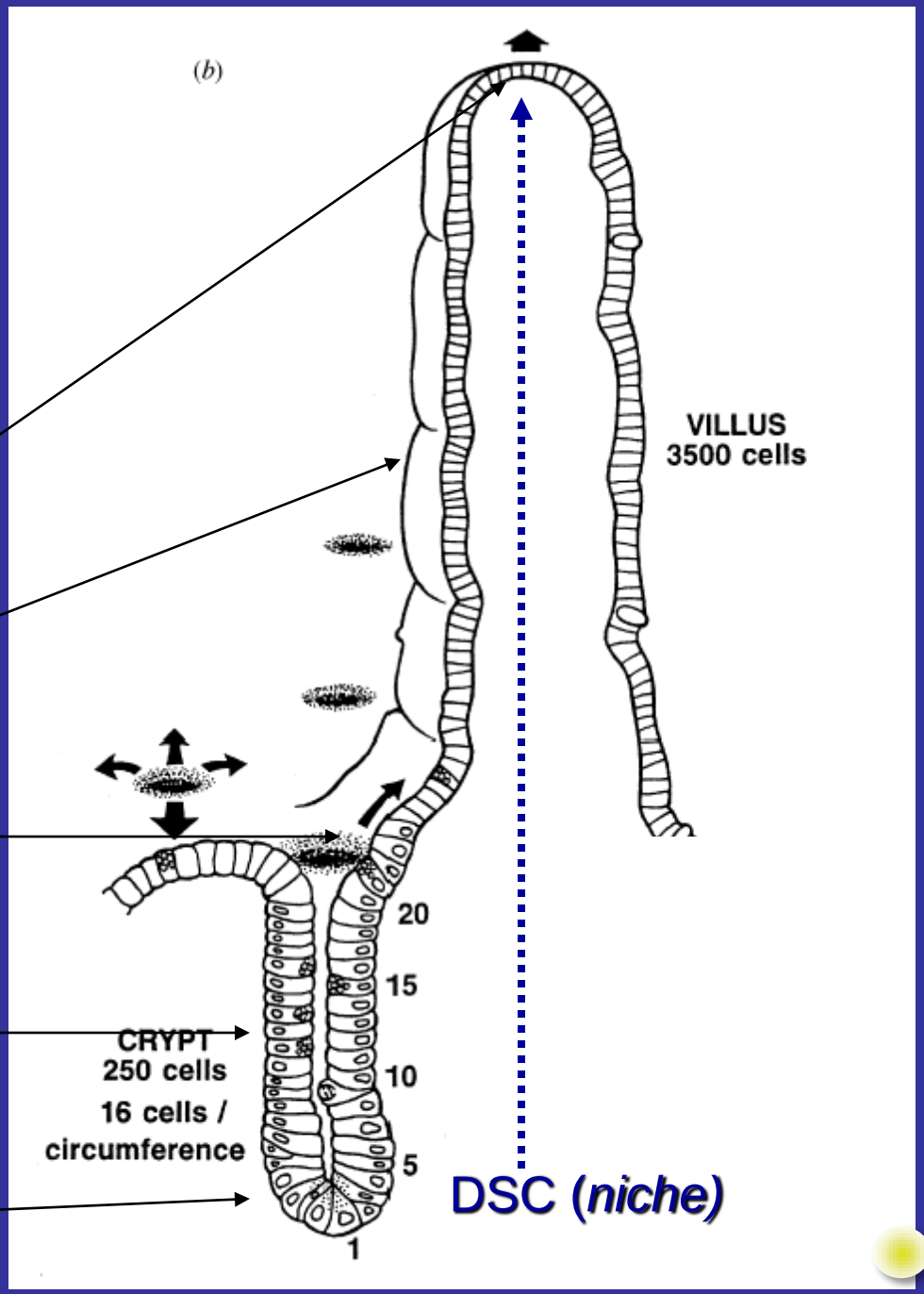
Terminal Arrest

Differentiation

Symmetric Kinetics

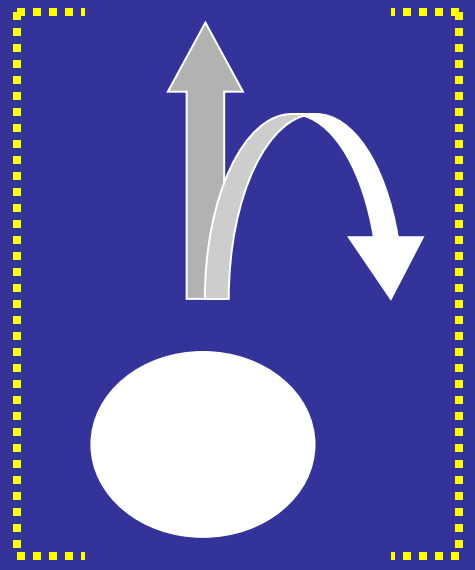
Asymmetric

- Self-renewal
- Cell Kinetics



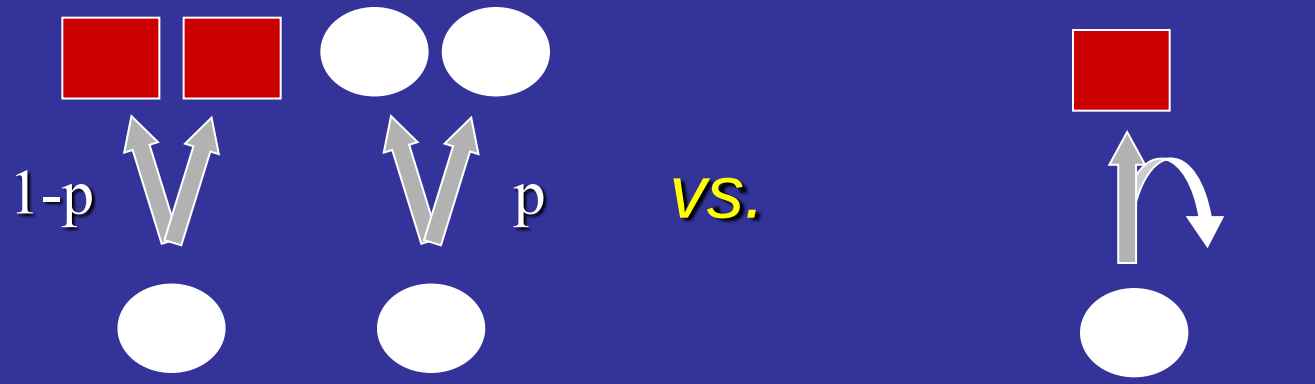
A CENTRAL QUESTION:

What is the cell kinetics form of asymmetric self-renewal?



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Mathematical Identity, but



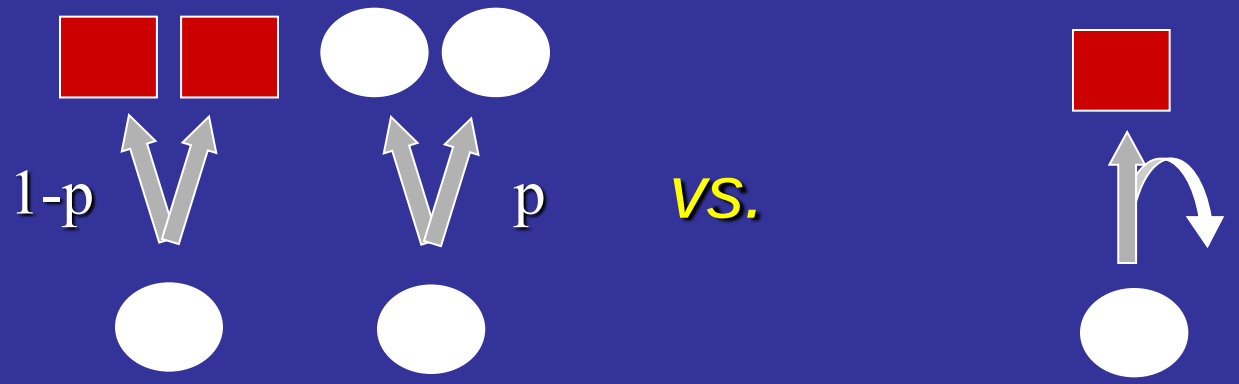
Stochastic

Determined

Biological Distinctions

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Biological Distinctions



Stochastic

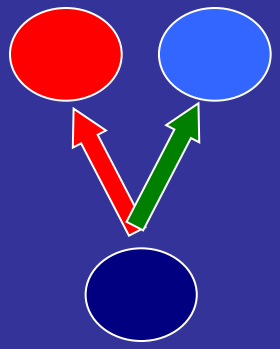
1. Extinction probability
2. Mutation accrual

Determined

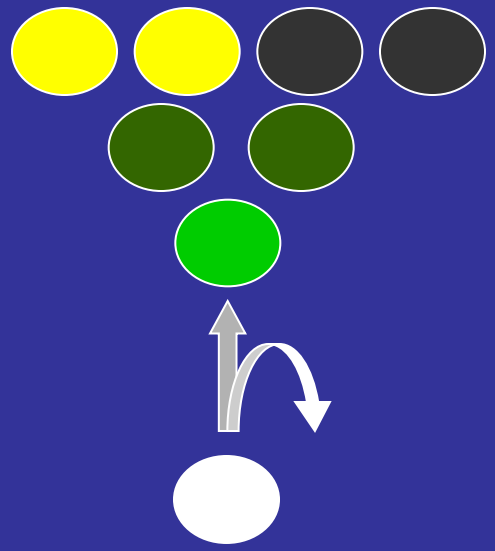
1. No DSC differentiation
2. Individual asymmetric division
3. Mutation avoidance?
4. ***Unique cellular programs!***

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Developmental Asymmetric Divisions Are Not Equivalent to Asymmetric Self-Renewal Divisions



≠

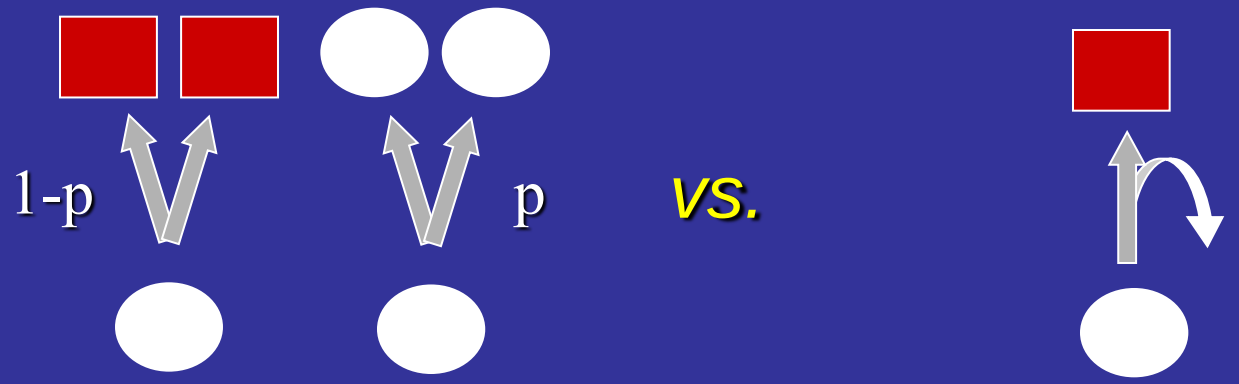


<u>Asymmetric Division</u>
- Sisters unequal
- Both sisters differ from parent
- Limited

<u>*Asymmetric Self-Renewal*</u>
- Sisters unequal
- One sister equal to parent
- Continuous over lifespan

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Biological Distinctions



Stochastic

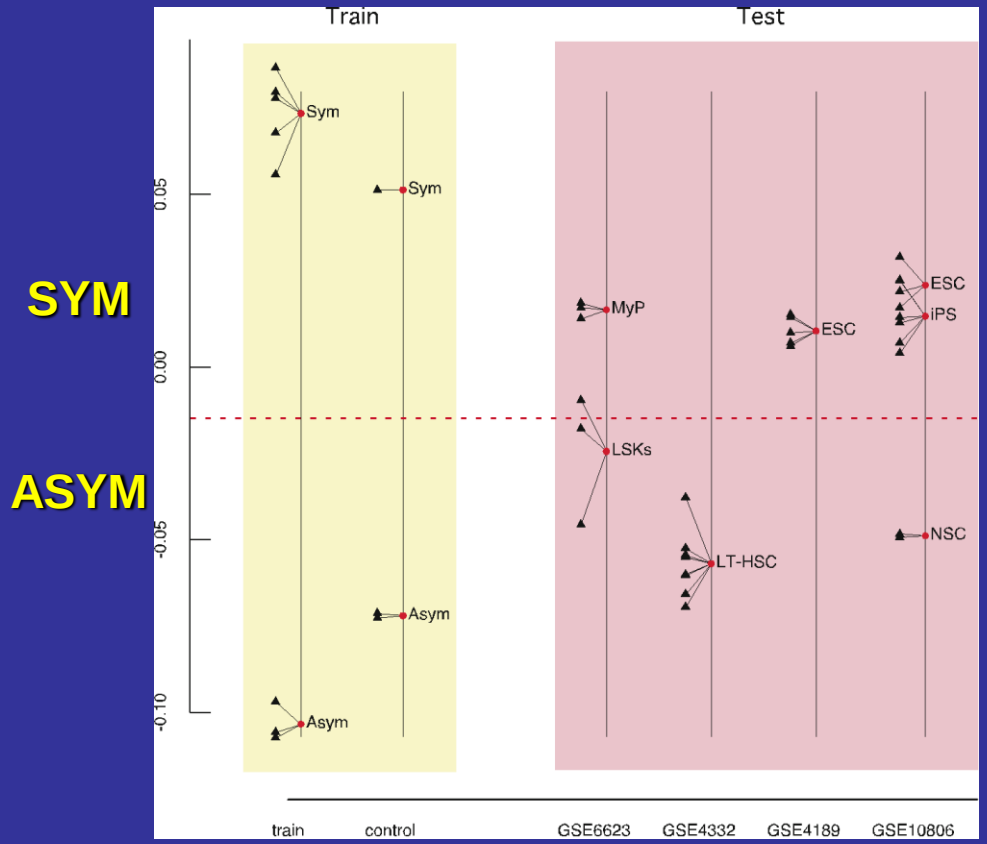
1. Extinction probability
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Determined

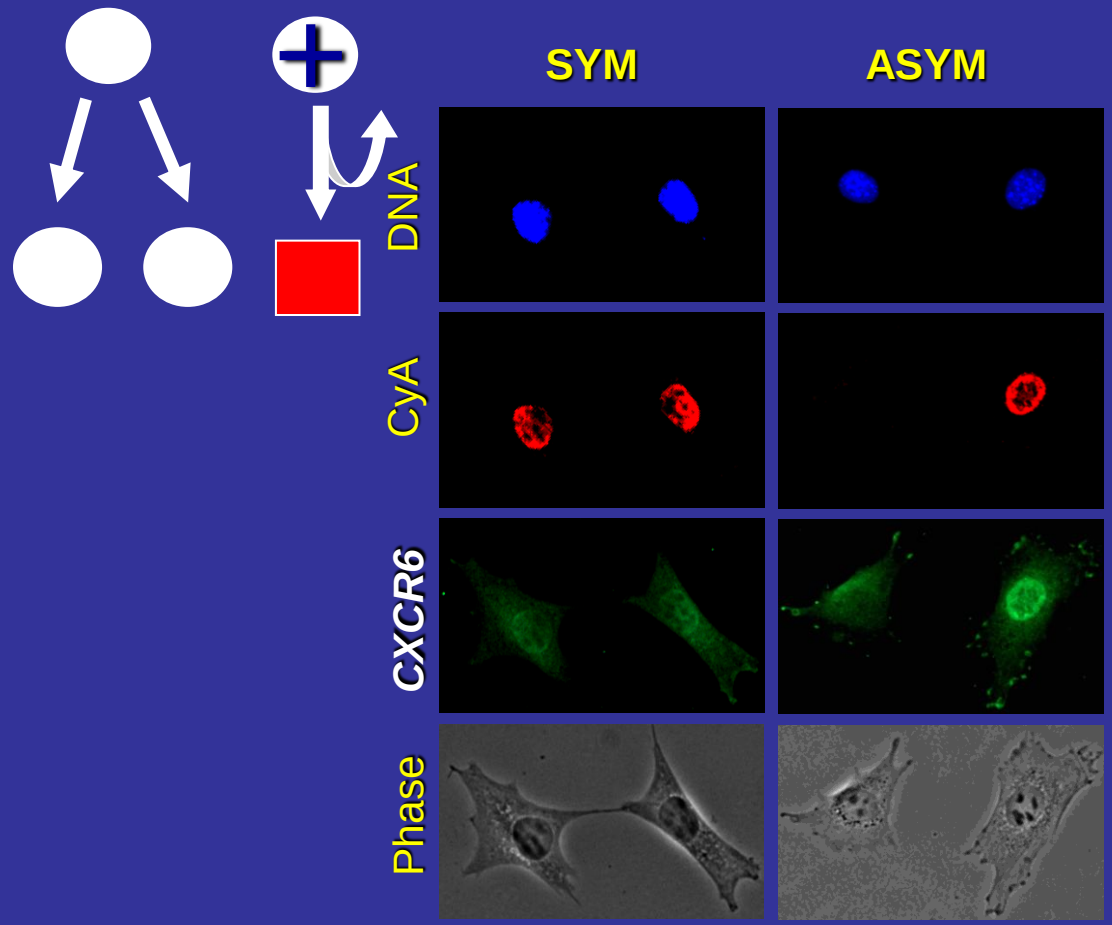
1. No DSC differentiation
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3. Mutation avoidance?
4. ***Unique cellular programs!***

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Asymmetric Self-Renewal Associated (ASRA) Genes: Highly Specific Biomarkers for DSCs



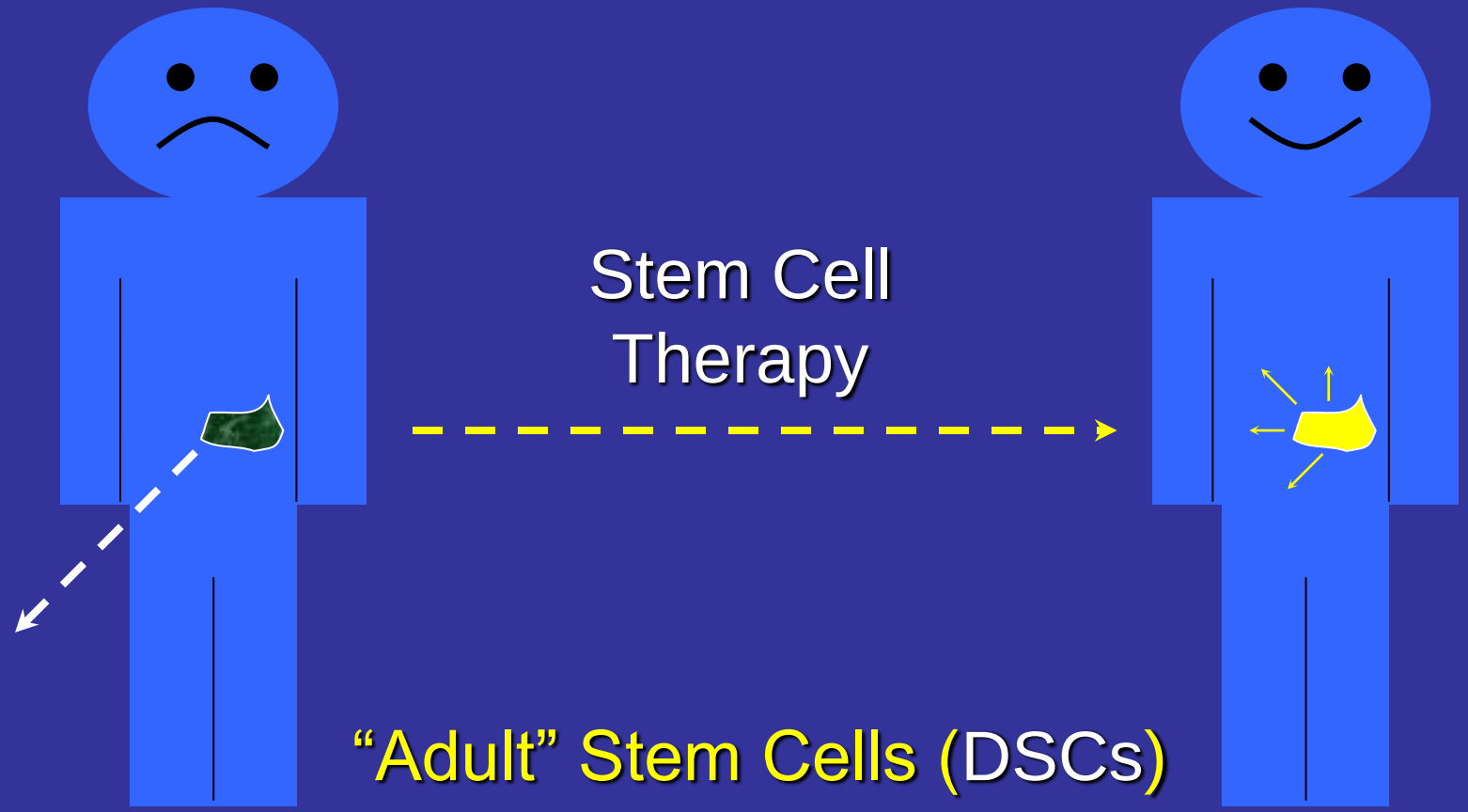
[Noh *et al.* 2011, *PLoS ONE*]



[Taghizadeh *et al.*, 2010, *PLoS ONE*]

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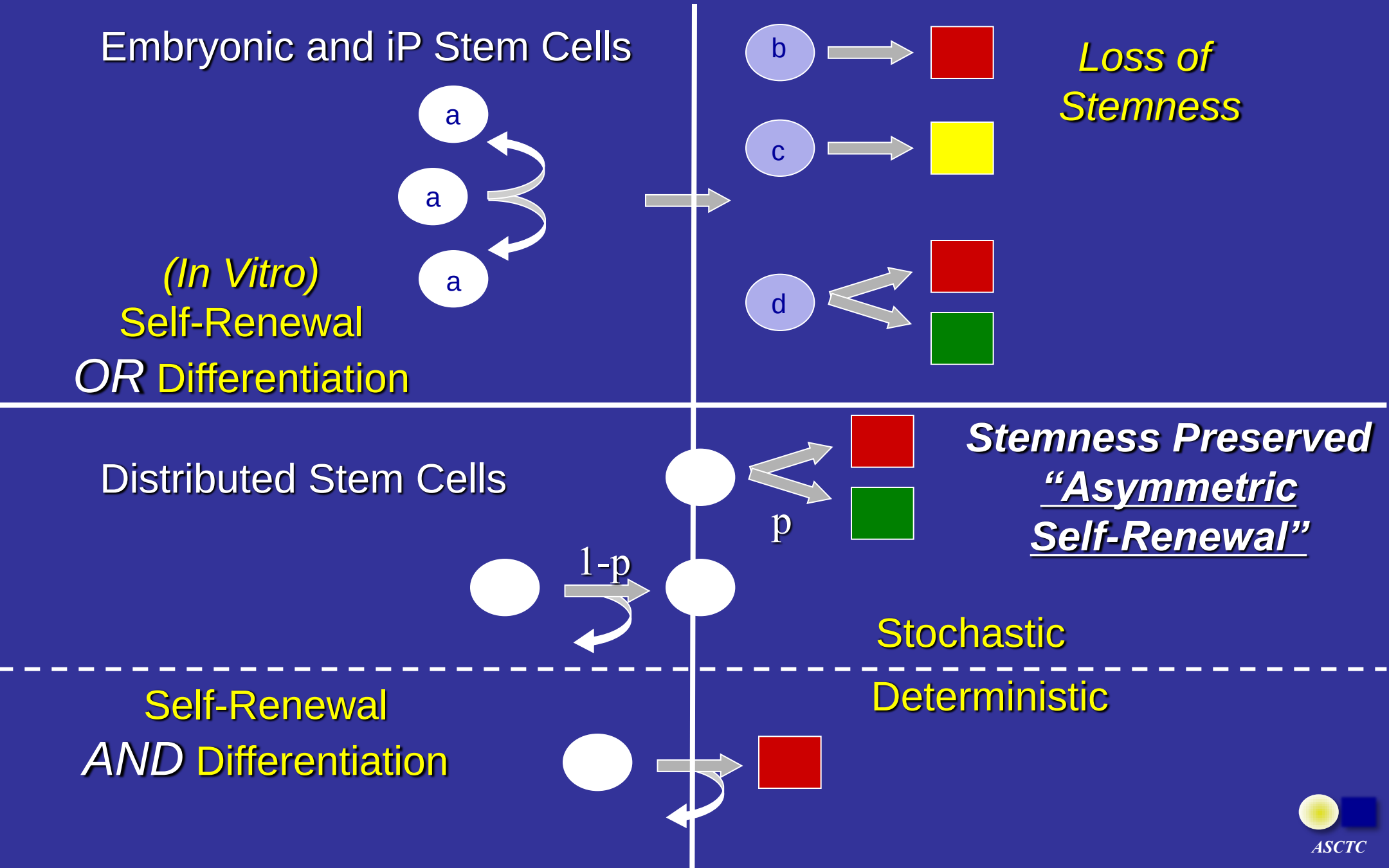
Proposed Stem Cells for Tissue Replacement



"Adult" Stem Cells (DSCs)
Embryonic Stem Cells (ESCs)
Induced Pluripotent Stem Cells (iPSCs)

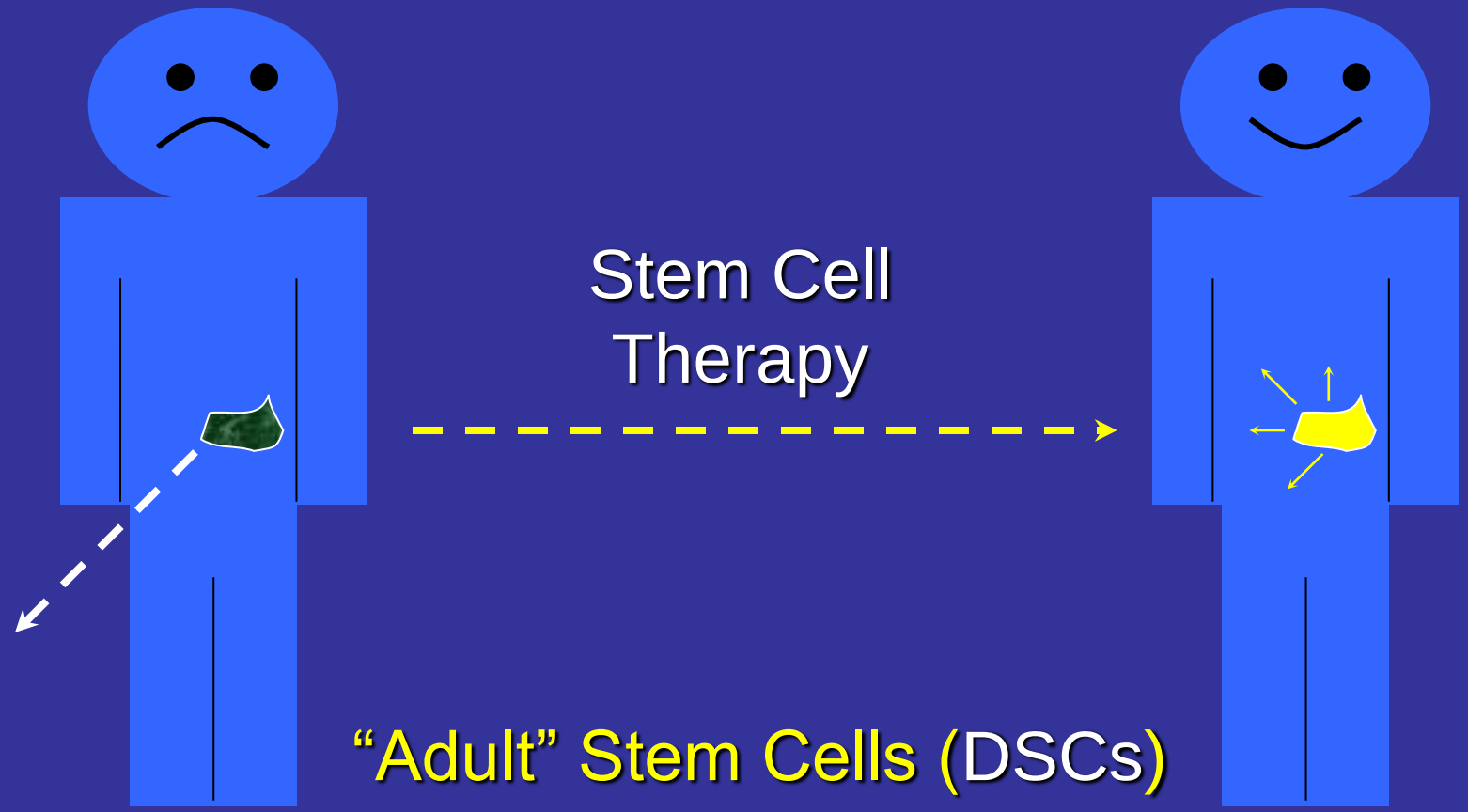
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Mathematical Features of Cell Production with Differentiation



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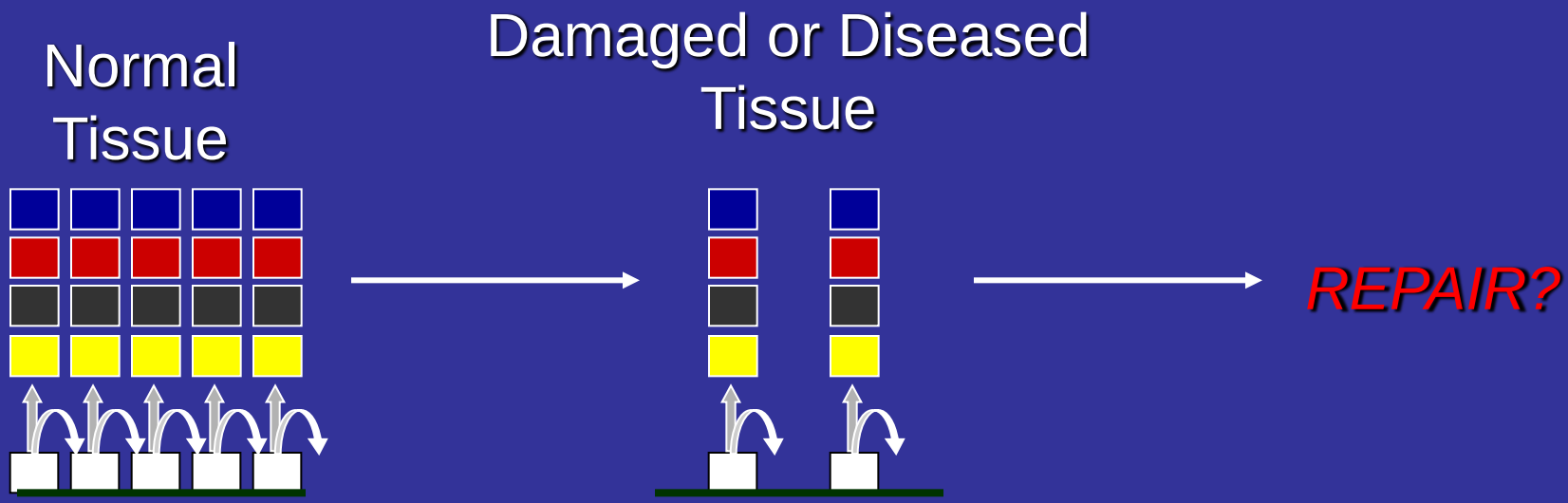
Proposed Stem Cells for Tissue Replacement



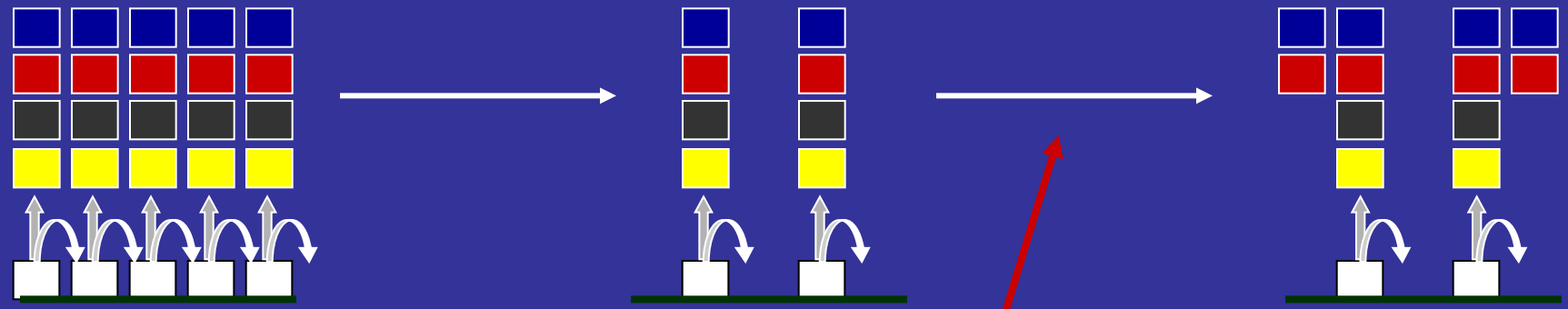
"Adult" Stem Cells (DSCs)
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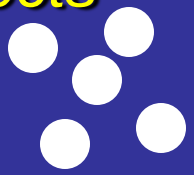
Tissue Therapy with ESCs and iPSCs?



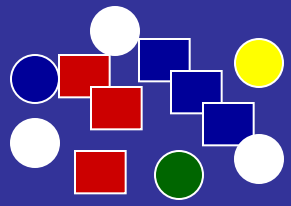
Tissue Therapy with ESCs and iPSCs



<u>hESCs and iPSCs</u>
- ethical issues (hESCs)
- *epigenetic defects*
- *genetic defects*



"Develop *In Vitro*"

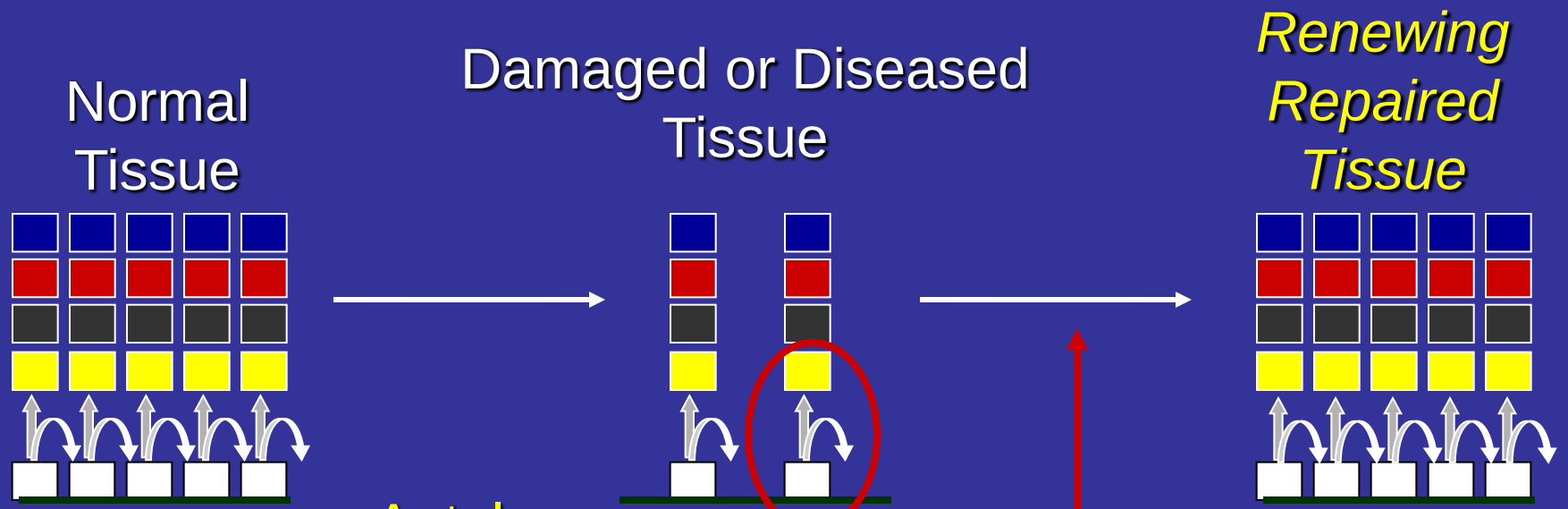


Differentiated Cells (Immature)

Purification
- ESCs!
- iPSCs!
- other differentiated cells

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Tissue Therapy with Distributed Stem Cells



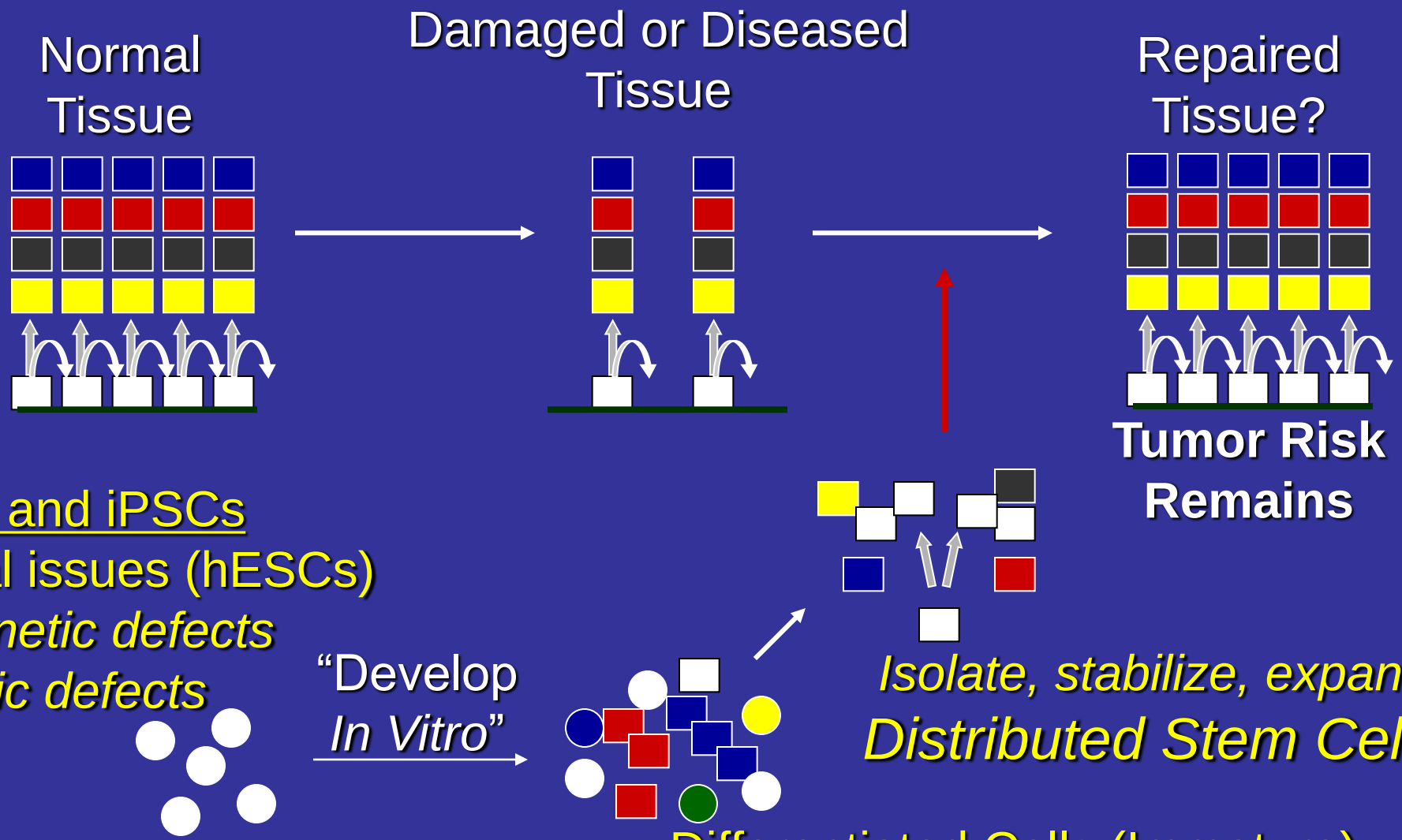
- Autologous
- Allogeneic
- *Informed Consent*

- purity not required
- expansion not always critical

DSC Expansion *is* possible!

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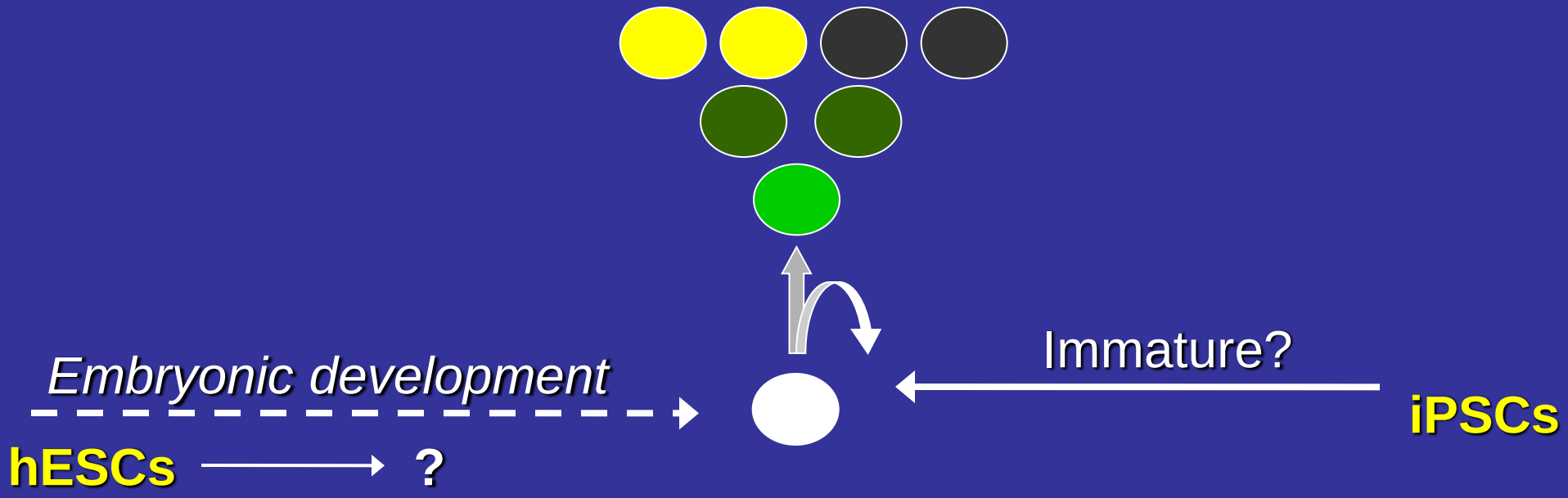
An DSC Bottleneck for Tissue Therapy



[Sherley, J. L. 2004, *J. Biomed. Biotech*. 2, 71-72.]

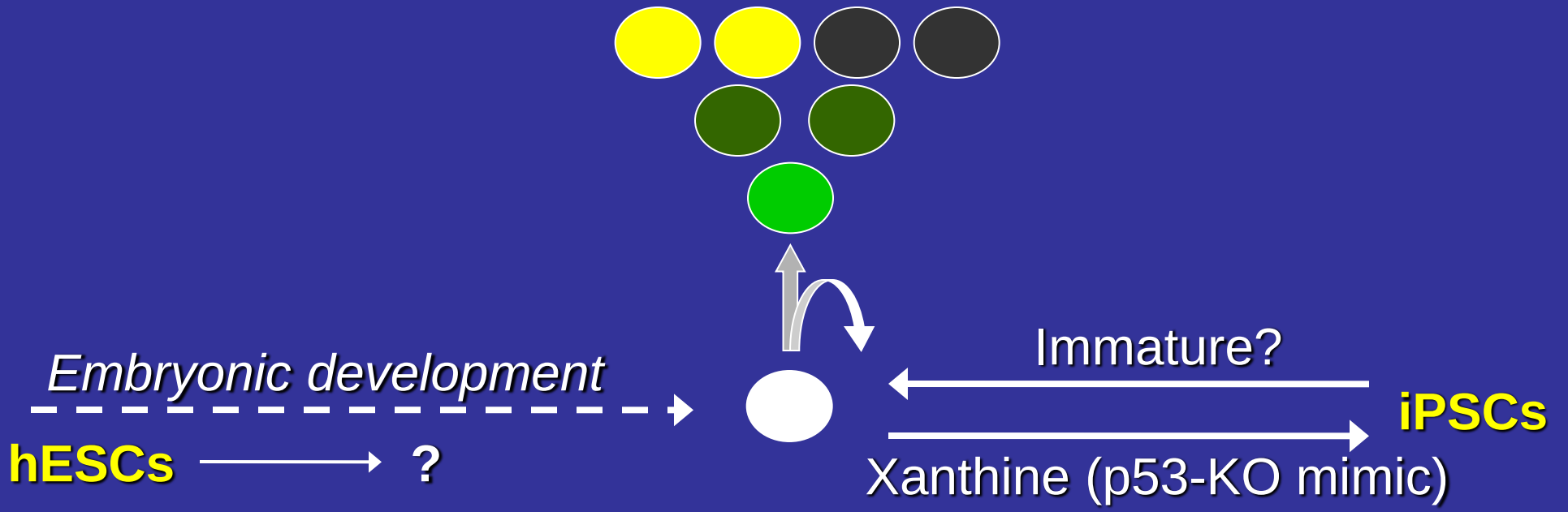
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Distributed Stem Cell Asymmetric Self-Renewal



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Distributed Stem Cell Asymmetric Self-Renewal



Pare & Sherley, 2011, *J. Biomed. Biotech.*

New Patent: USPTO No. 8,759,098, June 24, 2014

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