



**MORGRIDGE**

INSTITUTE FOR RESEARCH

AT THE UNIVERSITY OF WISCONSIN-MADISON

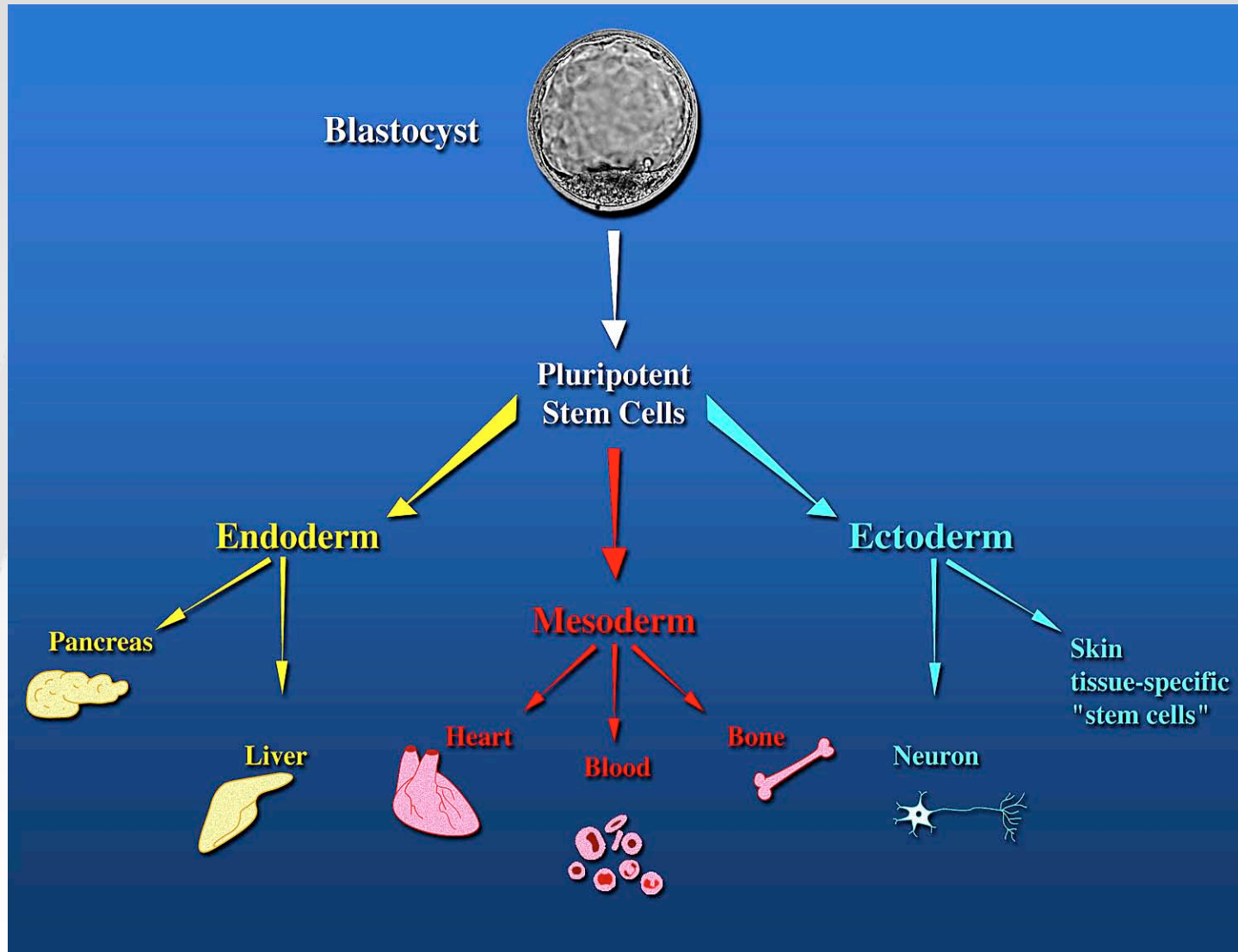
**Cyberinfrastructure for Regenerative Personalized Medicine:  
The Vision and Challenges**

Sangtae Kim

Morgridge Institute for Research

Presentation at HUBbub2011 (Indianapolis), Apr. 6, 2011

# Differentiation Potential of Stem Cells



Slide courtesy of R. Shevde

# STEM CELL SCIENCE

## A Landscape Created by Many Currents



THE UNIVERSITY  
of  
**WISCONSIN**  
MADISON

University of Wisconsin–Madison  
Department of Medical History and Bioethics  
Linda Hogle, Ph.D., Benjamin Nisler and Sarah Wynn

### EVENTS KEY

-  SCIENTIFIC DISCOVERY
-  ORGANIZATIONAL ACTION
-  GOVERNANCE ACTION
-  SOCIAL/CULTURAL TRENDS
-  UW–MADISON



**1952** Briggs & King are first to clone an animal (frog) using nuclear transfer. In 1962, Gurdon expands technique to somatic cells, demonstrating nuclei of adult cells retain ability to make all cell types (totipotent).

**1953** Stevens cultures pluripotent stem cells through mouse teratomas.

**1973** Roe v. Wade

**1973** Recombinant DNA (rDNA) enables gene modification, sets stage for cloning, gene therapy, transgenic plants & animals. Introduces questions about ethical and social implications.

**1977** Congress creates Ethics Advisory Board (EAB) to recommend guidelines for federally-funded embryo research.



**1978** Edwards & Steptoe develop in vitro fertilization (IVF) techniques that lead to first "test tube" baby birth.

**1981** Evans, as well as Kaufman and Martin derive mouse embryonic stem cells.

**1993** President Clinton authorizes National Institutes of Health (NIH) to fund human embryo research. President nullifies requirement for EAB approval for federally-funded embryo research projects, ending moratorium begun in 1980.

**1925** Wisconsin Alumni Research Foundation (WARF) established to develop UW–Madison discoveries.

**1907** Carrel adds embryonic material to cell cultures. Improves wound healing in living animals and lays foundation for understanding tissue development and transplantation.

**1907** Harrison cultures cells outside of the body.

**1910** Loeb induces sea urchin egg to develop without fertilization (parthenogenesis). Opens research to IVF techniques and cloning.

**1935** Carrel partners with aviator Charles Lindbergh to engineer a tissue bioreactor.

**1956** Thomas performs first successful bone marrow transplant.

**Early 1970's** Transplant medicine takes off with cyclosporine discovery that suppresses immune reactions.

**1975** At Asilomar Conference, scientists self impose a moratorium on recombinant DNA work pending guidelines.

**1979** EAB issues report requiring approval of any protocol involving human embryos. Research allowed up to 14 days of development. Four months later, EAB charter expires, creating moratorium on federally-supported embryo research, but approval requirement remains.

**1980** Bayh-Dole Act created to stimulate transfer of basic science into U.S. economy. Universities gain right to own their federally-funded intellectual property and license it for commercial development.

**1981** Supreme Court case rules living organisms can be patented.

**1988** Human Genome Project explodes knowledge of gene interactions, has big implications for large-scale, federally-funded science & its oversight.

**1989** Smithies develops "knockout" mouse model. Technique becomes fundamental in identifying the genes involved in disease & development.



1970's  
Permissive environment for biotech  
Reproductive medicine takes off  
1980's  
1990's  
Aging population & introduction of new drugs & technologies increase demand. Cost of health care explodes

demand. Cost of health care explodes

# 1990's

**1993** President Clinton authorizes National Institutes of Health (NIH) to fund human embryo research. President nullifies requirement for EAB approval for federally-funded embryo research projects, ending moratorium begun in 1980.

**1988** Human Genome Project explodes knowledge of gene interactions, has big implications for large-scale, federally-funded science & its oversight.

**1989** Smithies develops "knockout" mouse model. Technique becomes fundamental in identifying the genes involved in disease & development.



**1995** Thomson (UW-Madison) isolates and cultures nonhuman primate embryonic stem cells.



**1995** Thomson discusses research with ethicists and notifies Institutional Review Board (IRB) about his research.

**1995** Geron and WARF fund Thomson's research on hESC.

**1995** WARF files patent on Thomson's discovery covering isolation and culture of primate embryonic stem cells. Files follow-on patent specifying human cells in 1998.

**1998** Biotech Advisory Committee (BAC) created at UW-Madison establishes guidelines in anticipation of hESC research. One of the first in U.S. Committee discussions are then addressed again at national level.

**1998** Thomson isolates and cultures stem cells from donated human embryos.



**1998** Gearhart (Johns Hopkins) isolates and cultures human embryonic germ cells from donated aborted fetus tissue.

**2001** President Bush signs executive order approving use of federal funds for hESC lines, but only those derived before August 9, 2001.

**2004** California Proposition 71 commits \$3 billion to stem cell research within state over 10 years. Other states begin to set own funding and oversight guidelines.

**2005** U.N. asks members to avoid all forms of human cloning, prohibit genetic engineering that may impact human dignity, ensure justice for resource-poor countries in development of regenerative medicine.

**2006** International Society for Stem Cell Research (ISSCR) issues international guidelines, considering cross-national collaborations and addressing human-animal mixtures.

**2007** Thomson and Yu (UW) and Yamanaka (Kyoto U) independently induce pluripotency in human fibroblasts, creating possible alternative to using embryos to derive cells (iPS cells). George Daley soon follows (Harvard). However, technique uses viral vectors that may cause cancer. Debates ensue about using the new iPS cells or continuing with lines made from embryonic stem cells.

**2008** WiCell Research Institute starts own cell bank to distribute non-federal registry lines. Begins by offering iPS lines from Thomson lab.

**1994** Congress creates Embryo Research Panel (ERP) to recommend guidelines for federally-funded embryo research.

**1995** Dickey-Wicker Amendment prohibits use of federal funds for research in which embryos are destroyed. Derivation of new human embryonic stem cells (hESC) now must be carried out with private money.



**1997** Dolly the sheep is first successful cloned mammal. Controversies surrounding possibility of human cloning ensue.

**1999** WiCell created as private, non-profit affiliate of WARF to support stem cell research at UW-Madison, allowing independence from federal funding policies.

**2000-01** Under President Clinton, NIH provides guidelines for federally-funded research on hESC. Guidelines are put on hold when President Bush takes office and withdrawn by him in 2001.

**2004** Wisconsin Initiative dedicates \$750 million to research in state, a portion for stem cell research.

**2005** National Stem Cell Bank (NSCB) established at UW-Madison to distribute approved cell lines worldwide.



**2005** National Academy of Sciences (NAS) recommends hESC guidelines for U.S. Includes creation of stem cell research oversight (SCRO) committees. Voluntary guidelines aim to provide consistency & address donation, derivation and research ethics.

**2005** President Bush vetoes Stem Cell Research Enhancement Act, his first veto during five years in office. He vetoes similar bill in 2007, which also would have allowed federal funding for hESC research. Congress is unable to override vetoes so no laws are enacted.

**2005** Hwang (Seoul National U) claims to create hESC by cloning. Results found to be fraudulent. Scandal raises questions about the ethical conduct of stem cell research.

**2007** Stem Cell & Regenerative Medicine Center founded at UW-Madison.

**2007** President Bush signs executive order significantly increasing funding for research from non-embryonic sources.

**2008** Jaenish (MIT) induces pluripotency in adult somatic cells without viral vectors, which may cause cancers. Key advance for using iPS cells in humans.

# 2000-2008

Increased public awareness

How will the landscape change?

# Human Embryonic Stem Cells, 1998

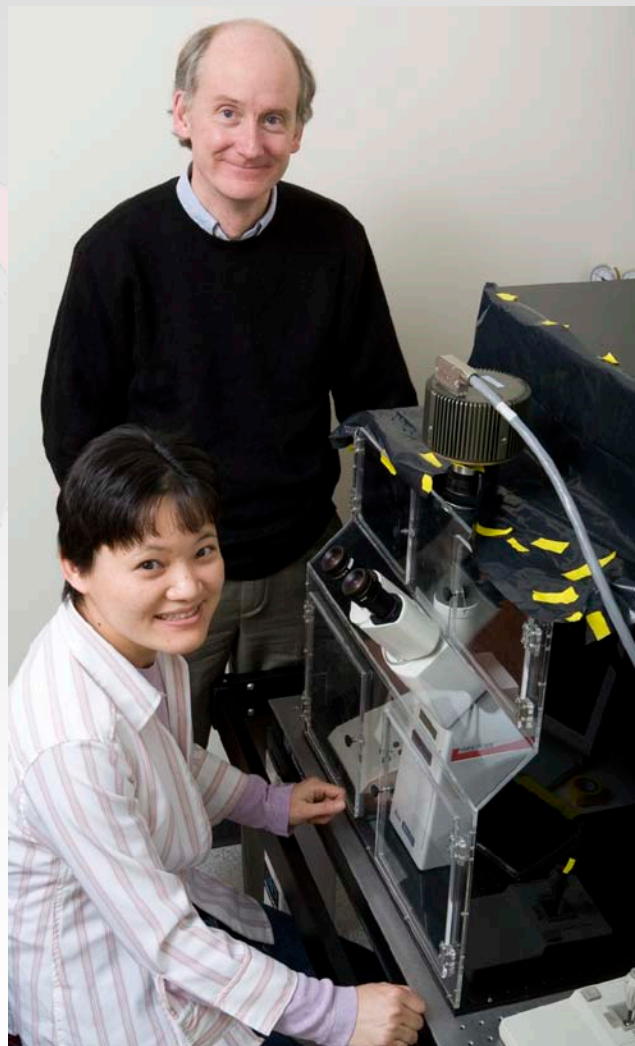
“The development of cell lines that may produce almost every tissue of the human body is an unprecedented scientific breakthrough. It is not too unrealistic to say that this research has the potential to revolutionize the practice of medicine and improve the quality and length of life”.

NIH Director Harold Varmus

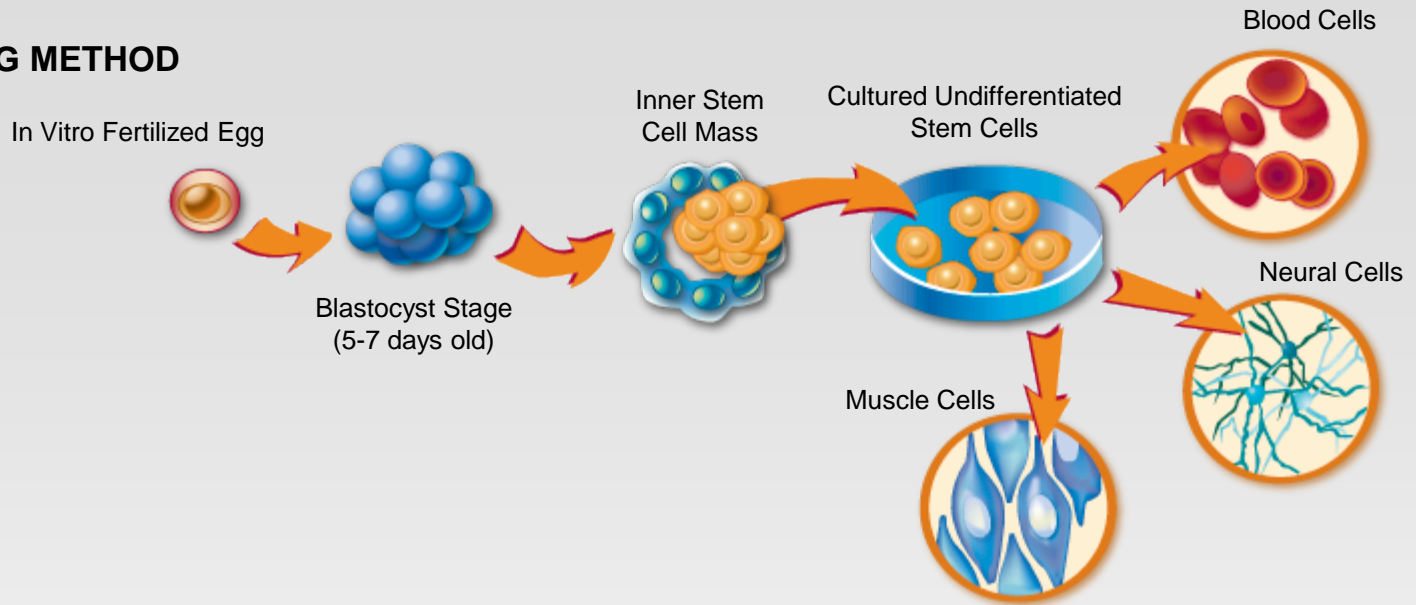
Before the United States Senate Subcommittee on Labor, Health, and Human Services, Education and Related Agencies, December 2, 1998.

The Isolation of Human Embryonic Stem Cells was listed among the most significant scientific advances of 1998 in *Science*, *Time*, *The London Times*, and *Discover Magazine*, and was featured in *Science*’s “Breakthrough of the Year” in 1999.

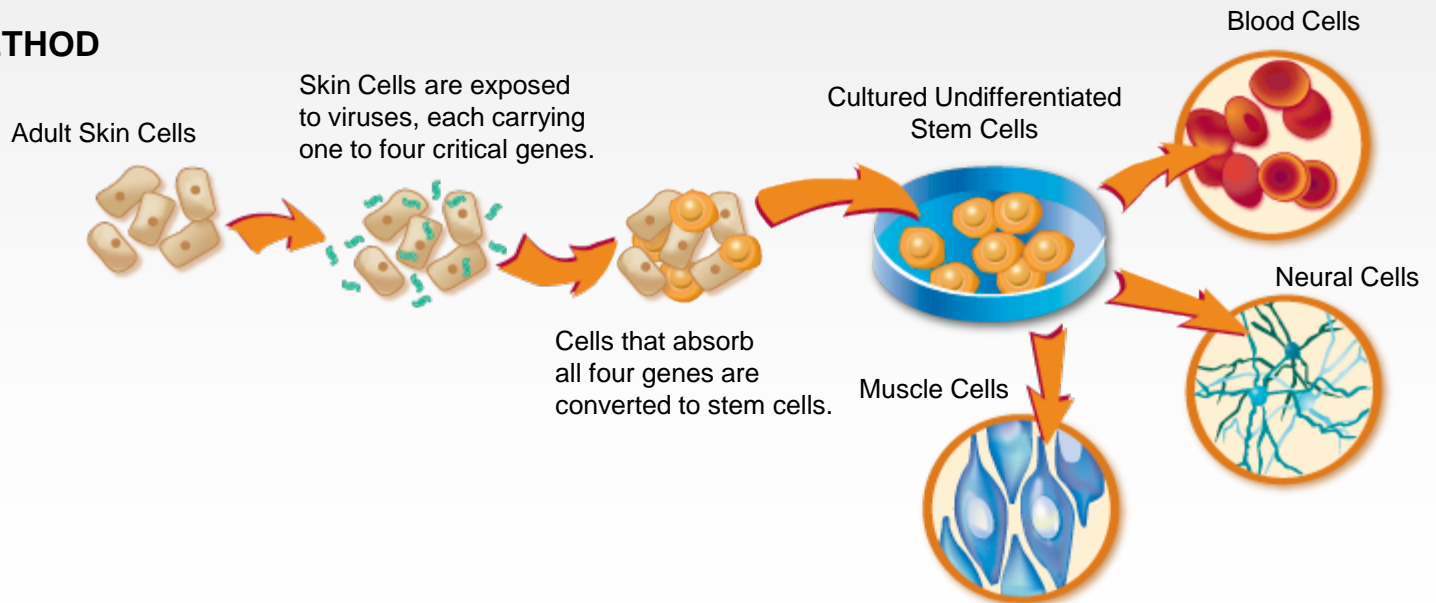
# Human iPS Cells, 2007



## EXISTING METHOD



## NEW METHOD



  
**MORGRIDGE**  
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WISCONSIN INSTITUTES FOR  
**DISCOVERY**

  
**WISCONSIN**  
INSTITUTE FOR DISCOVERY

PRIVATE

COLLABORATION

PUBLIC



Twin institutes under one roof on the UW-Madison campus



# MIR Discovery to Delivery Team

Susan Millar  
education research

Rock Mackie  
medical devices

Miron Livny, CTO

Paul Ahlquist  
virology/oncology

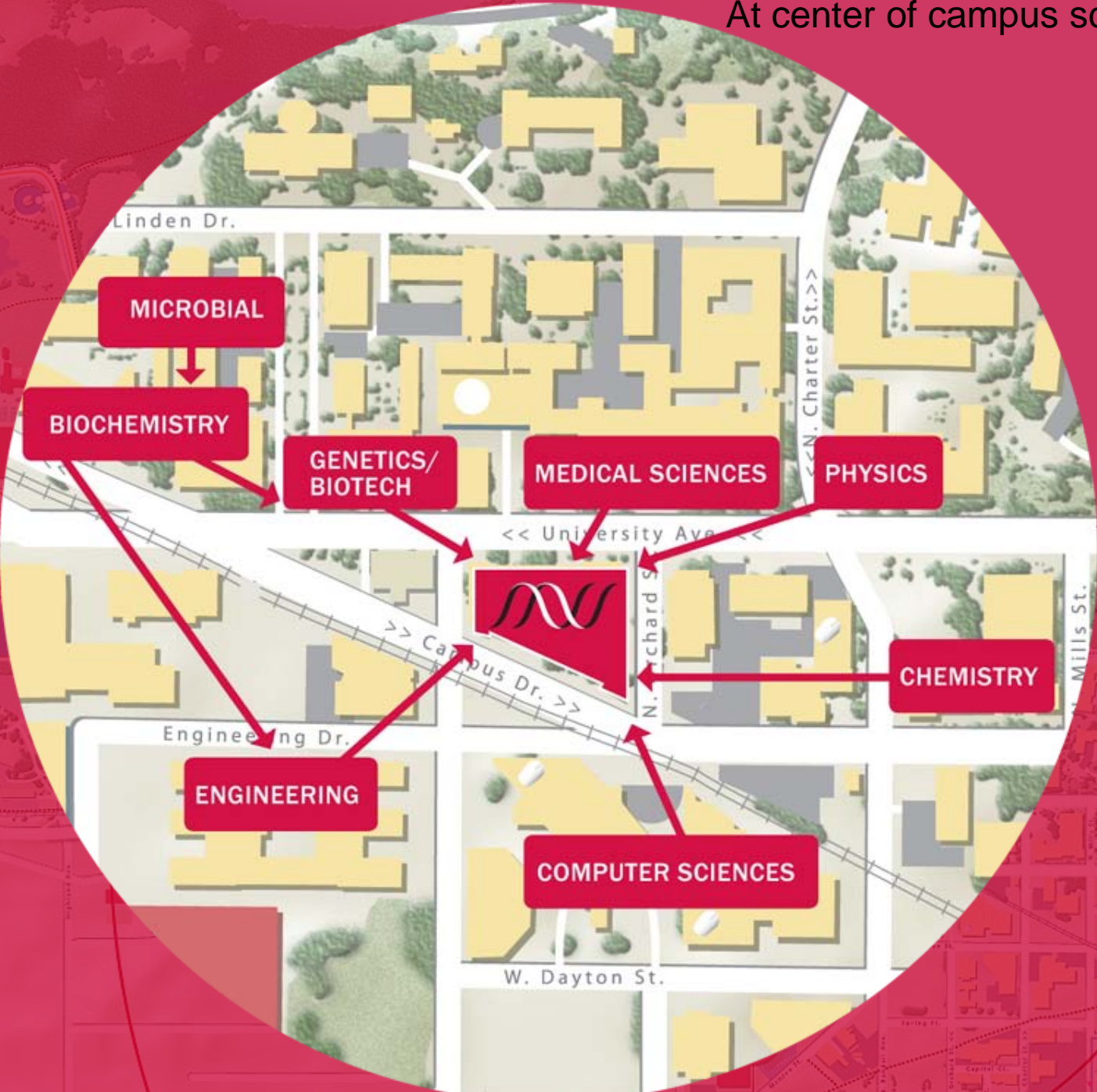


Rupa Shevde  
outreach experiences

Sang Kim  
pharma-informatics

Jamie Thomson  
regenerative biology

At center of campus science sites



WAISMAN CENTER

MEDICAL SCHOOL

SOCIAL SCIENCES

ARTS / HUMANITIES

MICROBIAL

BIOCHEMISTRY

GENETICS/  
BIOTECH

MEDICAL SCIENCES

PHYSICS

CHEMISTRY

ENGINEERING

COMPUTER SCIENCES

Linden Dr.

N. Charter St.

University Ave.

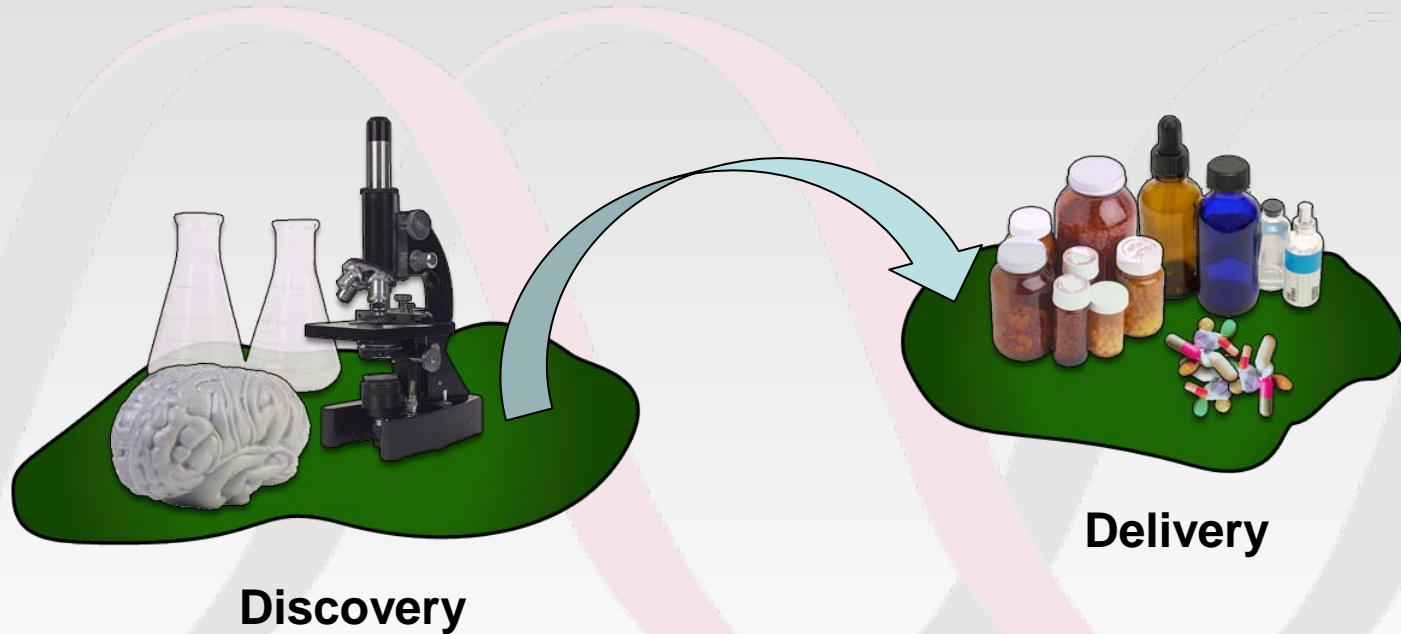
Campus Dr.

Engineering Dr.

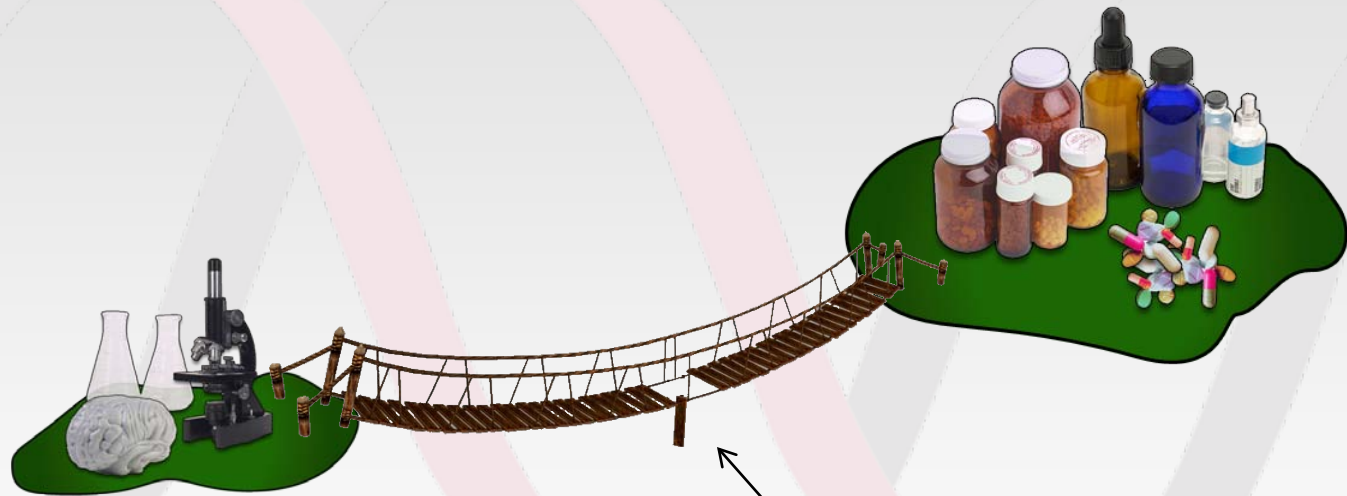
W. Dayton St.

Mills St.

# UW/WARF History: Discovery to Delivery



# Global Reality: the Past Decade



**Universities' IP portfolios  
decline in market value**

**Longer, riskier path**

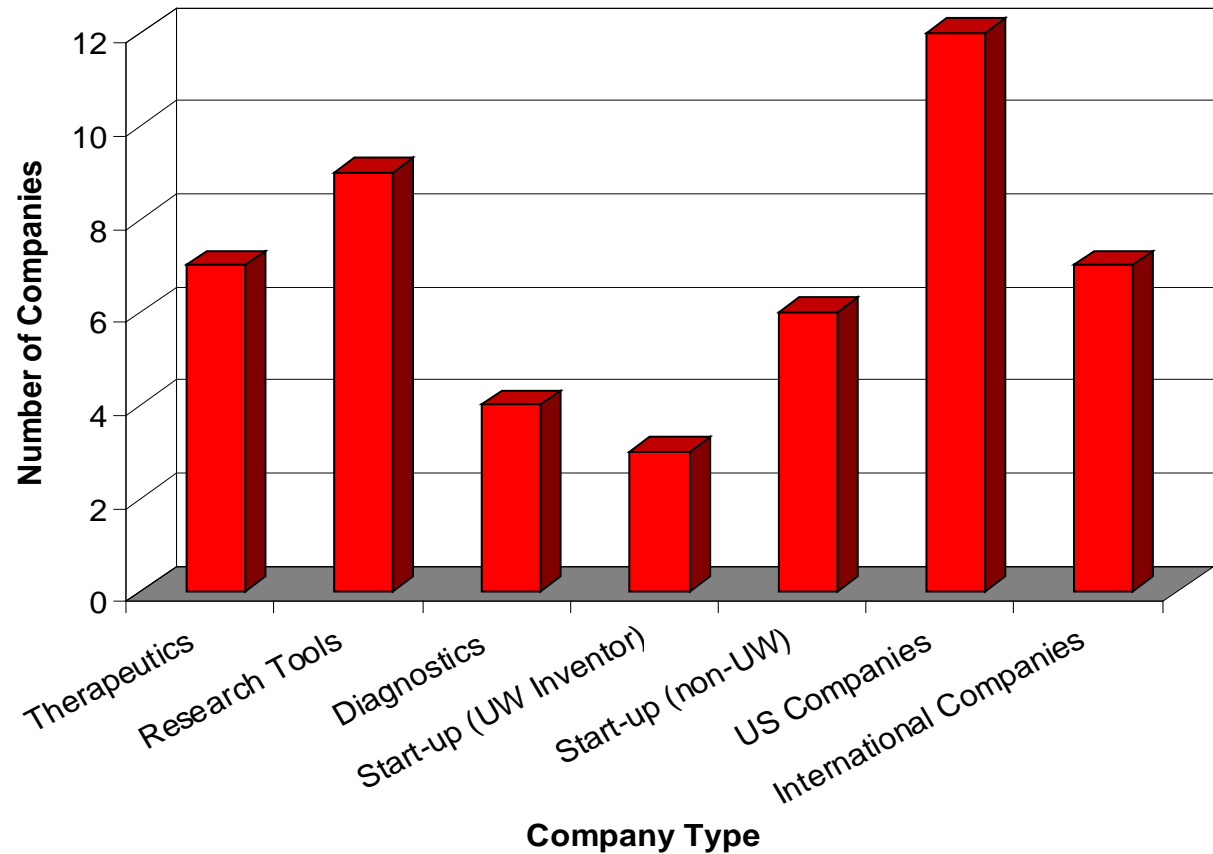
# MIR Vision: Discovery to Delivery



**IP portfolio grows in value, responding to market forces**

# Commercial Program Profile

## Commercial Licensee Stats



# Stem Cell Therapeutic Applications

- Immediate Applications
  - Diabetes
  - Cardiovascular Disease
  - Autoimmune Disease
  - Alzheimer's Disease
  - Parkinson's Disease
  - Spinal Cord Injury
- Other Applications
  - Osteoporosis
  - Cancer
  - Burns and Skin Grafts



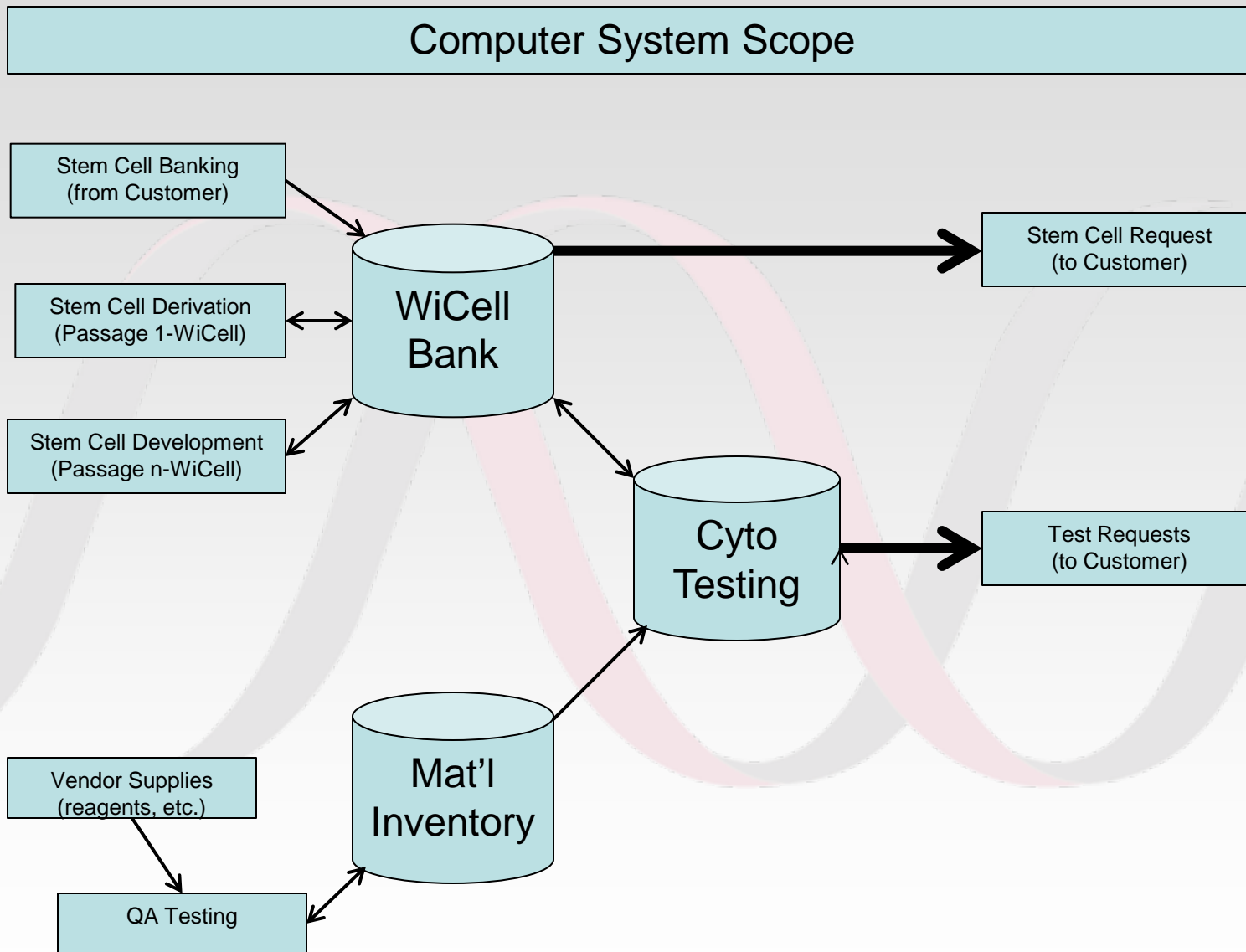
# Stem Cell Therapeutics Market

- Market expected to reach \$11.5B by 2015
- 50% growth rate over next ten years
- 116 companies involved in stem cell therapy
- *Need data provenance from the start – long before the clinical phases!*





# WiCell Process



# CytoGenetics Database (Dave Feryus)

Active Request	Accession	Fund/Proj	Cell Line	Label	From	Num Days	Rec Date	Harv	Drop	GBand	FISH	SKY	Fast Fish	RNA	DNA	CGH	STR	HLA	ABO	SNP
3490	1007735	/	HDFa-TK4 p35	-	Kristen Martins-Taylor(UCHC)	53	Jul22								Aug22	Subst				
3492	1007737	/	HDFa-TK7 p34	-	Kristen Martins-Taylor(UCHC)	53	Jul22								Aug22	Subst				
3495	1007542	000/221	WA07 p32	WISC9488	Lisa Kesler(WiCell Distribution)	52	Jul23	Jul23	Jul23	Aug05					Jul22					REC
3499	1007705	000/221	IPS(Foreskin)-4-WB0038 p20	WISC 5021	Lisa Kesler(WiCell Distribution)	45	Jul30	Jul30	Jul30	Aug09					Jul09					REC
3509	1007958	000/221	WA19 p10	WISC 8841	Lisa Kesler(WiCell Distribution)	35	Aug09	Aug09	Aug09	Aug15					Aug12					REC
3609	1008378	099/1230	WA22 (WISC 6081) p8	WISC 6081	Nicole George(WiCell Derivation)	18	Aug26	Aug27	Aug27	Sep02				Aug22	Aug26					REC
3627	1008521	000/221	IPS(IMR90)-3 p23+23(5)	WISC 6942	Lisa Kesler(WiCell Distribution)	18	Aug26								Aug26					REC
3637	1008376	000/221	WA22 (WISC 8432) p	WISC 8432	Dan Felkner(Distribution)	17	Aug27	Aug27	Aug27	Sep02				Aug22	Aug26					REC REC
3629	1008524	/	ECp1 p50/25	-	Rachel Lewis(CDI)	13	Aug31	Sep01	Sep01	Sep09										
3630	1008525	/	MB TeSR (1 control) p45	-	Sarah Burton(CDI)	13	Aug31	Sep03	Sep03	DIR										
3632	1008527	/	MB TeSR (3 +PEDF +bFGF) p45(11)	-	Sarah Burton(CDI)	13	Aug31	Sep03	Sep03	1 REV										
3633	1008528	/	6.1 p76(56)	-	Sarah Burton(CDI)	13	Aug31	Sep03	Sep03	1 REV										
3634	1008529	/	MB Other (1 control) p45(11)	-	Sarah Burton(CDI)	13	Aug31	Sep03	Sep03	1 REV										
3635	1008530	/	MB Other (2 +pleo) p45(11)	-	Sarah Burton(CDI)	13	Aug31	Sep03	Sep03	1 REV										
3636	1008531	/	MB Other (3 +PEDF +bFGF) p45(11)	-	Sarah Burton(CDI)	13	Aug31	Sep03	Sep03	1 REV										
3637	1008532	/	MRB Other (1 control) p51(12)	-	Sarah Burton(CDI)	13	Aug31	Sep03	Sep03	1 REV										
3638	1008533	/	MRB Other (2 +pleo) p51(12)	-	Sarah Burton(CDI)	13	Aug31	Sep03	Sep03	Sep09										
3639	1008534	/	MRB Other (3 +PEDF +bFGF) p51(12)	-	Sarah Burton(CDI)	13	Aug31	Sep03	Sep03	Sep09										
3640	1008535	/	MRB TeSR (1 control) p51(12)	-	Sarah Burton(CDI)	13	Aug31	Sep03	Sep03	DIR										
3641	1008536	/	MRB TeSR (2 +pleo) p51(12)	-	Sarah Burton(CDI)	13	Aug31	Sep03	Sep03	1 REV										
3642	1008537	/	MRB TeSR (3 +PEDF +bFGF) p51(12)	-	Sarah Burton(CDI)	13	Aug31	Sep03	Sep03	1 REV										
3643	1008538	000/221	WA15.02 p21	-	Marybeth Witkowski(Distribution)	12	Sep01						Sep09							
3644	1008543	000/221	WA15.02 p21	-	Marybeth Witkowski(Distribution)	12	Sep01						Sep09							
3645	1008604	/	hESC01 p14	-	Nick Strelchenko(Cybrid Cell Genetics )	11	Sep02	Sep03	Sep03	DIR										
3646	1008605	/	hESC31 p28	-	Nick Strelchenko(Cybrid Cell Genetics )	11	Sep02	Sep03	Sep03	DIR										
3647	1008606	/	OAT p11	-	Sara Howden(Thomson Lab)	11	Sep02							Sep02	Q287					
3648	1008607	/	OAT IPS 12.4 p18	-	Sara Howden(Thomson Lab)	11	Sep02							Sep02	Q287					
3649	1008608	/	IPS 6.1 p55/31/12	-	Christine Daigh(CDI)	11	Sep02	Sep03	Sep03	1 REV										
3650	1008679	099/1230	WA21-WB0006 p12	WISC 8421	Nicole George(WiCell Derivation)	10	Sep03	Sep03	Sep03	1 REV										
3651	1008691	/	6.1 p35/13	-	Rachel Lewis(CDI)	10	Sep03	Sep03	Sep03	1 REV										
3652	1008741	000/221	TE04-MCB-02 p45	WISC 0116	Marybeth Witowski(WiCell Distribution)	5	Sep08							Sep08						SNP
3653	1008743	/	2.008cd other +pleo p	-	Sarah Burton(Cellular Dynamics International)	5	Sep08	Sep10	Sep10	1 REV										
3654	1008744	/	2.008cd, other +PEDF +bFGF p	-	Sarah Burton(Cellular Dynamics International)	5	Sep08	Sep10	Sep10	1 REV										
3655	1008745	/	2.008cd, other, control p	-	Sarah Burton(Cellular Dynamics International)	5	Sep08	Sep10	Sep10	1 REV										
3656	1008746	/	2.008cd, TeSR, control p	-	Sarah Burton(Cellular Dynamics International)	5	Sep08	Sep10	Sep10	1 REV										
3657	1008747	/	2.008cd, TeSR, +Pleo p	-	Sarah Burton(Cellular Dynamics International)	5	Sep08	Sep10	Sep10	1 REV										
3658	1008748	/	2.008cd, TeSR +PEDF +bFGF p	-	Sarah Burton(Cellular Dynamics International)	5	Sep08	Sep10	Sep10	1 REV										
3659	1008813	/	H1 p59	-	Tania Hennessy(Stemcell Technologies)	4	Sep09	Sep10	Drop	-										
3660	1008785	000/210	WA01 p46(22)	-	Kim Leonhard(WiCell CytoGenetics)	3	Sep10						HybE							
3661	1008749	000/221	H9-hTnnT2-pGZ-D2 p40	WISC 3166	Lisa Kesler(WiCell Distribution)	3	Sep10	Sep10	Sep10	1 REV				Sep10						SNP
3661	1008788	/	MRB(5) mTeSR1 p65	-	Brian Riley(CDI)	3	Sep10	Sep10	Sep10	1 REV										
3662	1008789	/	MRB(6) TeSR 10F p45	-	Brian Riley(CDI)	3	Sep10	Sep10	Sep10	1 REV										
3663	1008800	/	H1-VP2 Clone 1 p6	-	Maksym Vodyanyk(CDI)	3	Sep10	Sep10	Sep10	1 REV										
3664	1008806	/	H1-VP2 Clone 2 p6	-	Maksym Vodyanyk(CDI)	3	Sep10	Sep10	Sep10	1 REV										
3666	1008814	099/1230	WA22 p	WISC 5971	Jeff Jones(WiCell Derivation)	0	Sep13	Sep13	DROP	-										

Returned 45 Rows

Active Request Pending=White Warning=Yellow Overdue=Red Complete=Date



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**Discovery** Regenerative Biology, Virology

**Delivery** Medical Devices, Pharmaceutical Informatics

**Personalized – Provenance**

Questions or Comments?

# Morgridge Institute Mission

## Accelerating Discovery to Delivery to Improve Human Health

- Move biomedical discoveries from benchtops of researchers to bedsides of patients . . . from point of discovery to application
- Impact society through new treatments, tools and scientific insight
- Scientific Areas

**Discovery** Regenerative Biology, Virology

**Delivery** Medical Devices, Pharmaceutical Informatics



# Stem Cell Research Tools

- Cell Culture Media
- ADME/Toxicology
- Cryopreservation
- Drug Discovery Assays
- Karyotyping
- hESC Characterization Kits
- Gene Expression Systems
- Differentiated Cell Characterization Kits



# Stem Cell Diagnostics

- Least developed market
- Will require enabling technologies (e.g. cost effective cell culture)
- Will compete with genetic and molecular diagnostics
- *Promising applications in personalized medicine*