China's Policy on Stem Cell research and application

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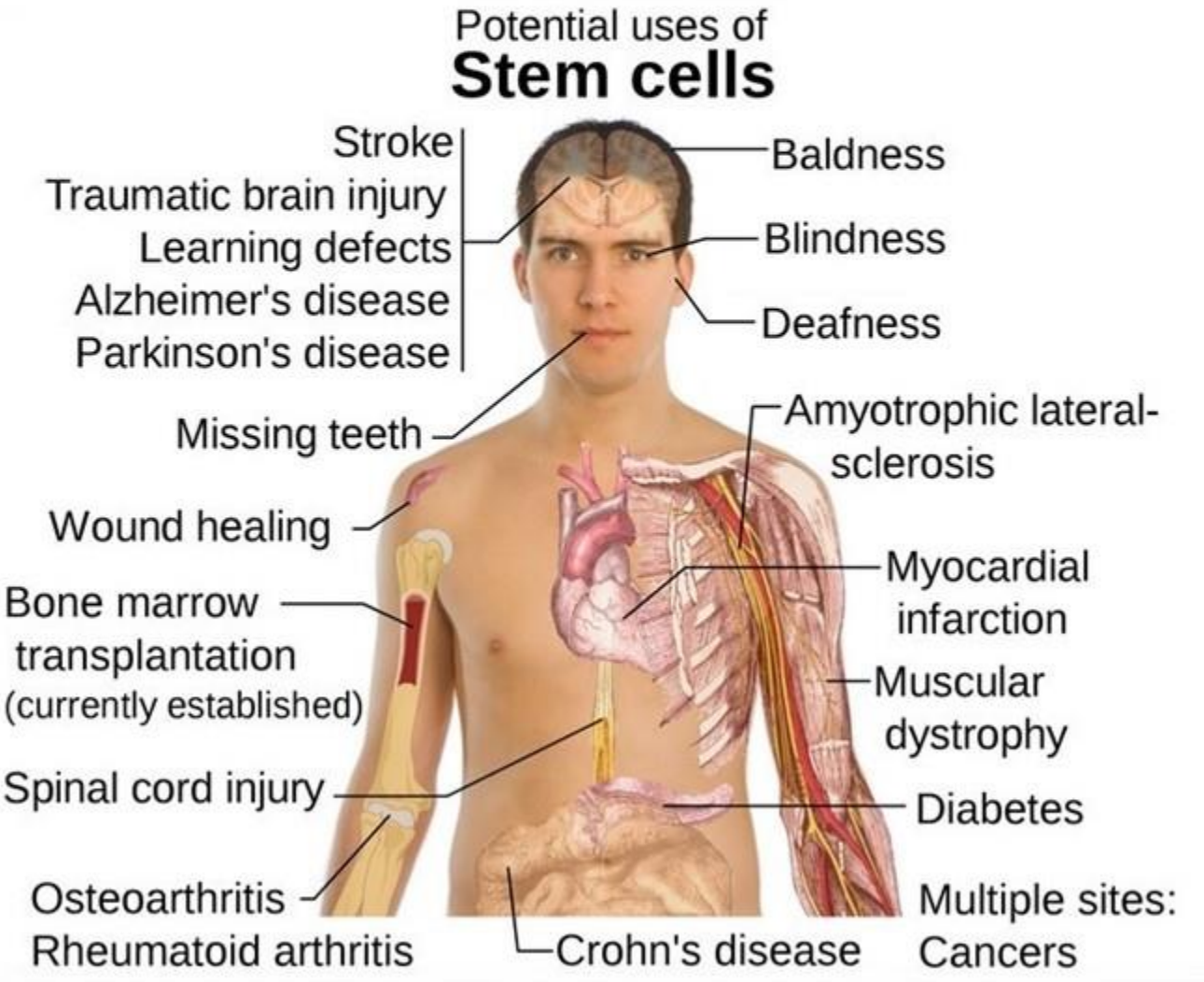
Stem Cell and Regenerative Medicine



Policy, National Regulation Related to Human Genetic Research

Dec 24 — **Ethics Guidelines of Human Embryonic Stem Cell Research（MOH/MOST）**

Jan 6 — **Notification on Self-Evaluation and Self-Correction regarding Clinical Stem Cell Research and Applications（MOH/CFDA）**

1998 | **2003** | **2009** | **2012** | **2015**

Jun 18 — **Interim Measures for the Administration of Human Genetic Resources(MOH/MOST)**

March 2 — **Regulations on Clinical Use of Medical Technologies（MOH）**

Jul 20 — **Regulations on Stem Cell Clinical Research *(Trial)*（NHFPC/CFDA）**

* The Ministry of Health (MOH), The Ministry of Science and Technology (MOST)
China Food and Drug Administration (CFDA), National Health and Family Planning Commission(NHFPC)

Policy, National Regulation Related to Human Genetic Research

- **Ethics Guidelines of Human Embryonic Stem Cell Research, 2003, MOH and MOST**

-- To prescribe **the basic principles** that should be followed in carrying out **human embryonic stem cell research**, including scope of research activity, research content of embryonic stem cell that should be allowed and forbidden to carry out, "Informed consent" and so on.

- **Regulations on Clinical Use of Medical Technologies, 2009, MOH**

-- To establish **medical technology access and management system**, which **stem cell transplant technology** was grouped into **category III** medical technology, which included technologies considered as risky, ethically controversial and in need of clinical verification.

Policy, National Regulation Related to Human Genetic Research


国家卫生计生委科技教育司

关于印发干细胞临床研究管理办法（试行）的通知

国卫科教发〔2015〕48号

各省、自治区、直辖市卫生计生委、食品药品监管局，新疆生产建设兵团卫生局、食品药品监管局，国家卫生计生委直属有关单位，食品药品监管总局直属有关单位：

为规范并促进我国干细胞临床研究，国家卫生计生委与食品药品监管总局共同组织制定了《干细胞临床研究管理办法（试行）》（可从国家卫生计生委、食品药品监管总局网站下载），现印发给你们，请遵照执行。

国家卫生计生委 食品药品监管总局
2015年7月20日

干细胞临床研究管理办法（试行）

第一章 总 则

第一条 为规范和促进干细胞临床研究，依照《中华人民共和国药品管理法》、《医疗机构管理条例》等法律法规，制定本办法。

第二条 本办法适用于在医疗机构开展的干细胞临床研究。

干细胞临床研究指应用人自体或异生来源的干细胞经体外操作后输入（或植入）人体，用于疾

- **Regulations on Stem Cell Clinical Research (NOT Trial), 2015, NHFPC and CFDA**

-- The **main responsibilities** of stem cell clinical trial research unit, ethics committee, expert committee and national and provincial health administration and food and drug regulatory authorities; clearly stipulated **the declaration and record** of stem cells, clinical research, rights and interests protection of donor and subject, report, supervision and punishment.


国家卫生计生委科技教育司

关于印发干细胞制剂质量控制及临床前研究指导原则（试行）的通知

国卫办科教发〔2015〕46号

各省、自治区、直辖市卫生计生委，食品药品监管局，新疆生产建设兵团卫生局，食品药品监管局，国家卫生计生委直属有关单位，食品药品监管总局直属有关单位：

为加强我国干细胞制剂和临床研究质量管理，国家卫生计生委与食品药品监管总局根据《干细胞临床研究管理办法（试行）》，共同组织制定了《干细胞制剂质量控制及临床前研究指导原则（试行）》（可从国家卫生计生委或食品药品监管总局网站下载），现印发给你们，请遵照执行。

国家卫生计生委办公厅
食品药品监管总局办公厅
2015年7月31日

干细胞制剂质量控制及临床前研究指导原则
（试行）

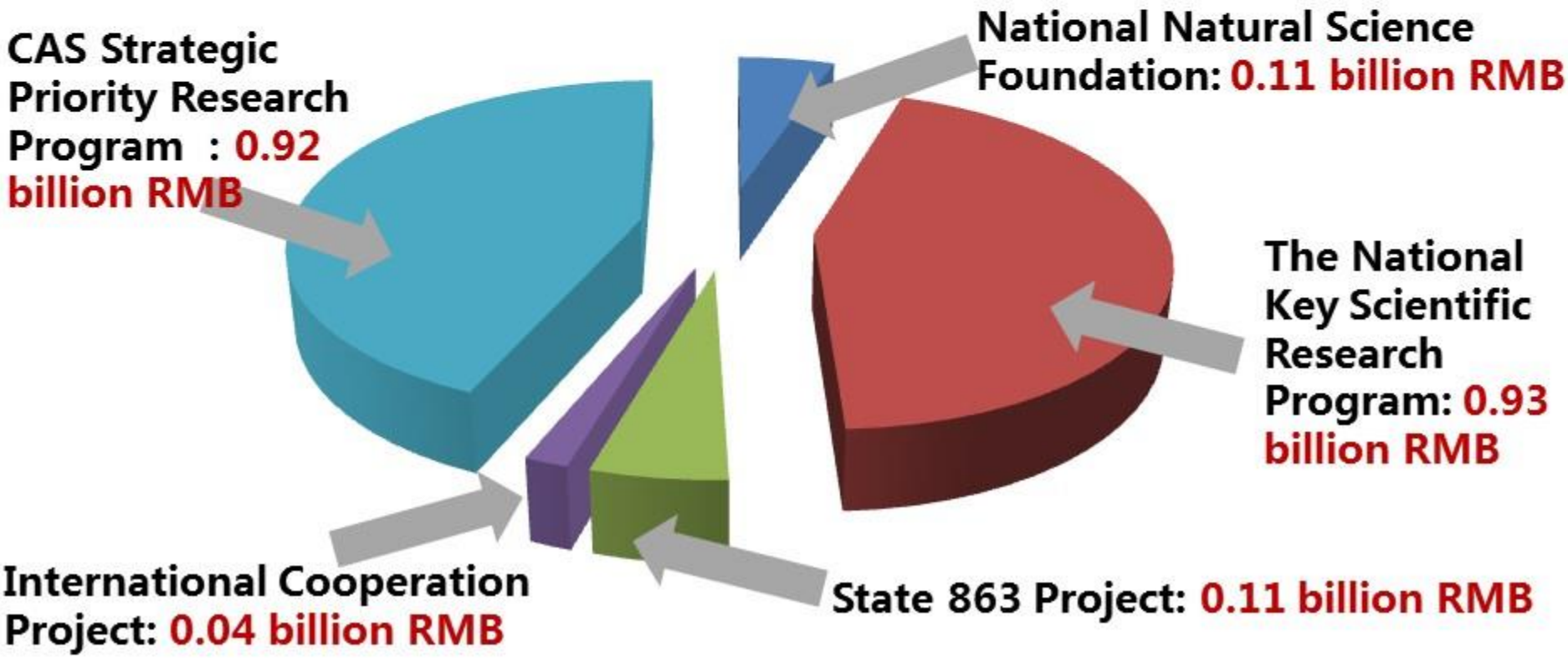
一、前言
二、干细胞制剂的质量控制
（一）干细胞的来源，分离及干细胞（系）的建立
（二）干细胞制剂的制备
（三）干细胞制剂的检验
（四）干细胞制剂的质量研究
三、干细胞制剂的临床前研究
（一）安全性评价
（二）有效性评价
名词解释

- **Guidelines of Stem Cell Preparations Quality Control and Preclinical Research(Trial), 2015, NHFPC and CFDA**

-- For **stem cell products quality control** (collection, separation, and establishment of stem cell lines; preparation, inspection, and quality research of stem cell products) and **preclinical research** (the research and evaluation of stem cell product safety and effectiveness in preclinical stage).

Blooming stem cell research in China

According to incomplete statistics, the total stem cell field research funding is about 2 billion RMB (300 million USD) during 2010-2015.



Blooming stem cell research in China

In the next five years (2016-2020), there will be 2.7 billion RMB(450million USD) funding for stem cell research in China.

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中华人民共和国科学技术部
Ministry of Science and Technology of the People's Republic of China

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当前位置：科技部门户 > 新闻中心 > 通知通告

www.most.gov.cn

【字体：大 中 小】

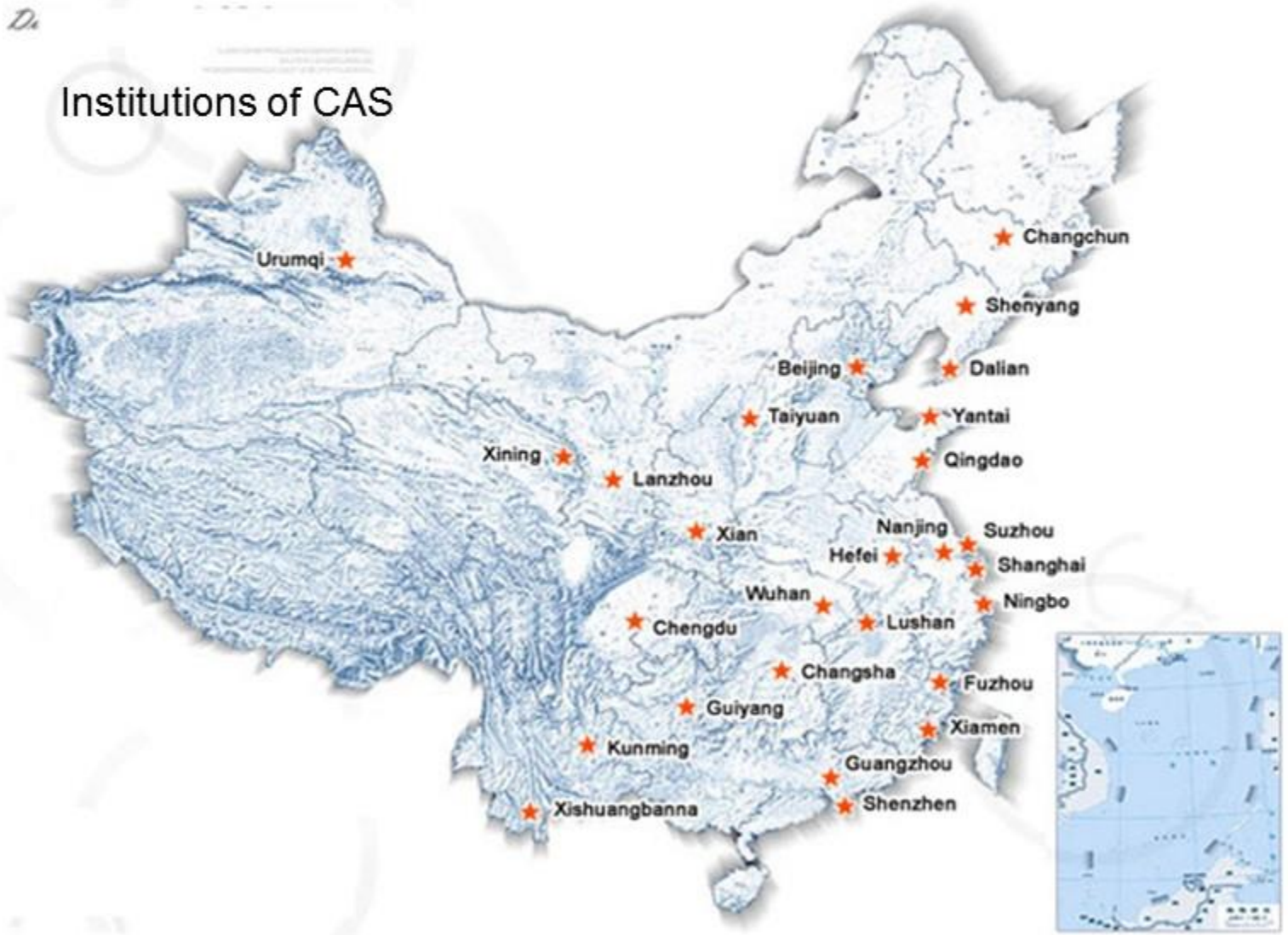
干细胞与转化医学重点专项实施方案征求意见

日期：2015年02月26日　　来源：科技部

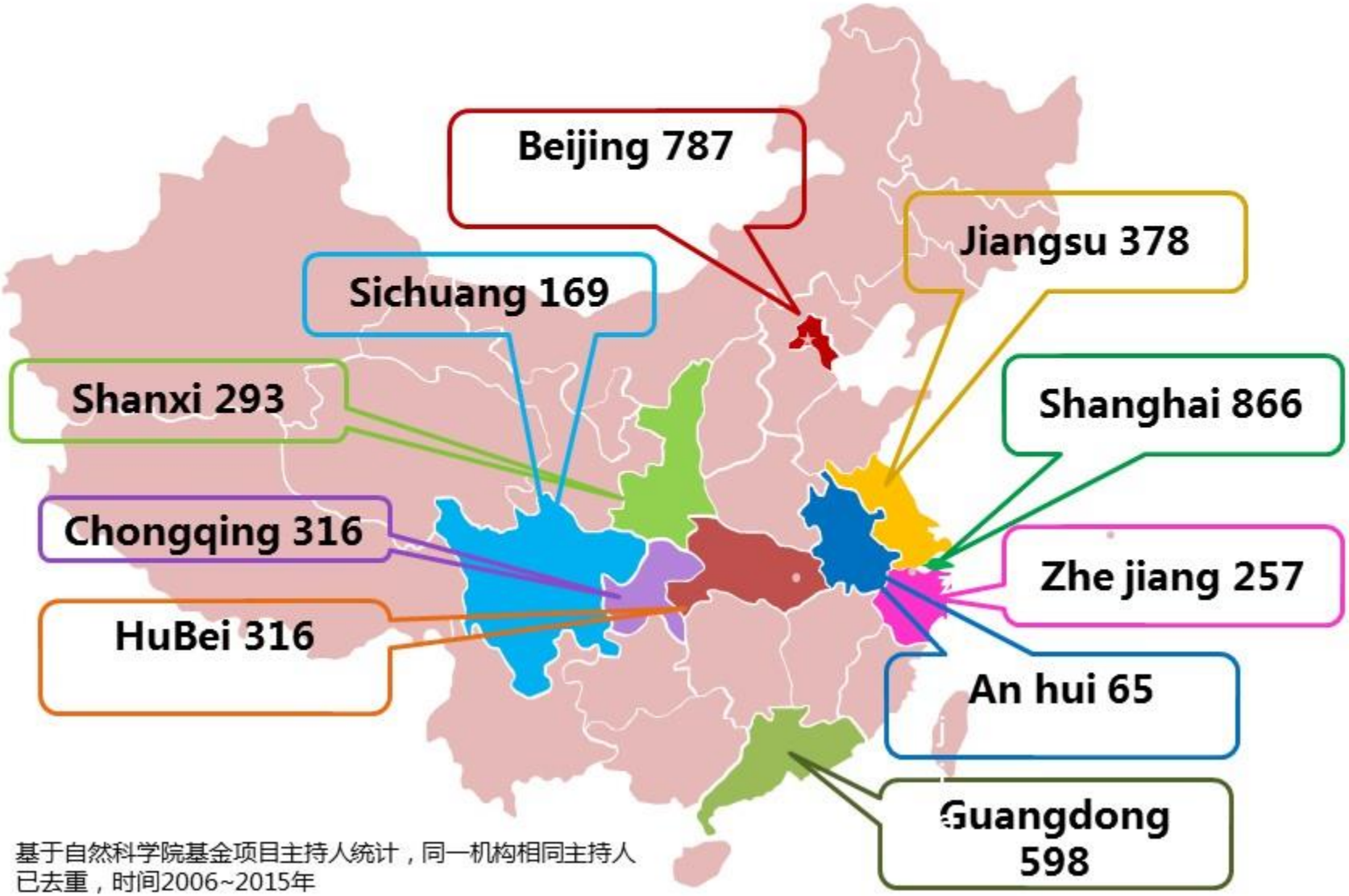
根据国务院《关于深化中央财政科技计划（专项、基金等）管理改革的方案》总体要求，科技部将会同有关部门，启动国家重点研发计划“干细胞与转化医学”重点专项试点工作。

目前，“干细胞与转化医学”重点专项已进入实施方案编制阶段。实施方案主要包括重点专项实施的重要性、发展趋势、现有基础、总体目标、主要任务等。现就重点专项实施方案（征求意见稿，见附件）向社会征求意见和建议，请发电子邮件至gxbyj@most.cn，反馈截止日期为2015年3月5日。

China: face for the new challenges



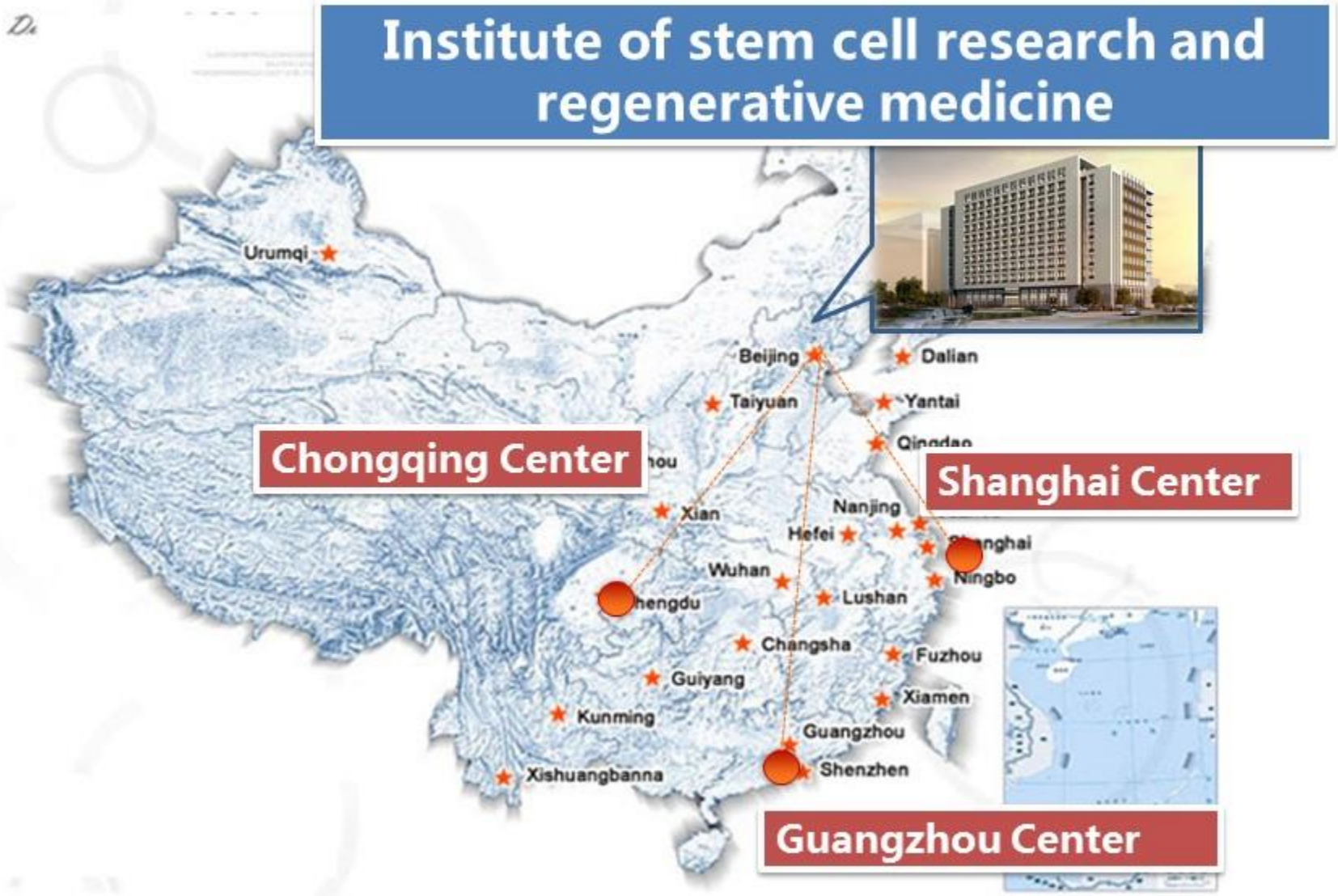
China: face for the new challenges



基于自然科学院基金项目主持人统计，同一机构相同主持人已去重，时间2006~2015年

China: face for the new challenges

CAS: face for the new challenges



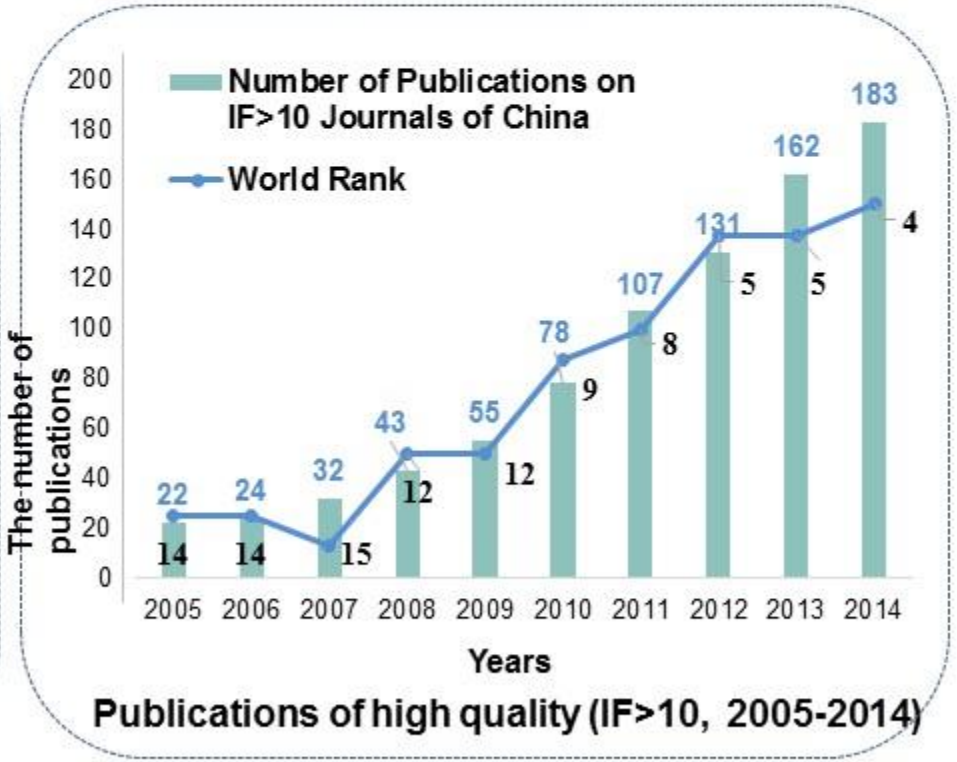

A 座
Building A
STEMCELL
中国干细胞第六届年会
The 6th Annual Meeting of CSSCR

"“As a stem cell research professional, I promise to dedicate myself to build a healthy environment for stem cell research and its application, and will follow rules and regulations such as those set by '*the Administration of Stem Cell-based Clinical Research*' and '*Quality Control of Stem Cell-based Medicinal Products and Preclinical Stem Cell Research Guidelines*'. I will restrain myself from unapproved stem cells or relevant procedures for any therapeutic purpose."

China's stem cell research publication

- China is ranked 2nd of total publications indexed by SCI since 2010
- China is ranked 4th of publications on IF>10 journals in 2014

Publications indexed by SCI (2005-2014)



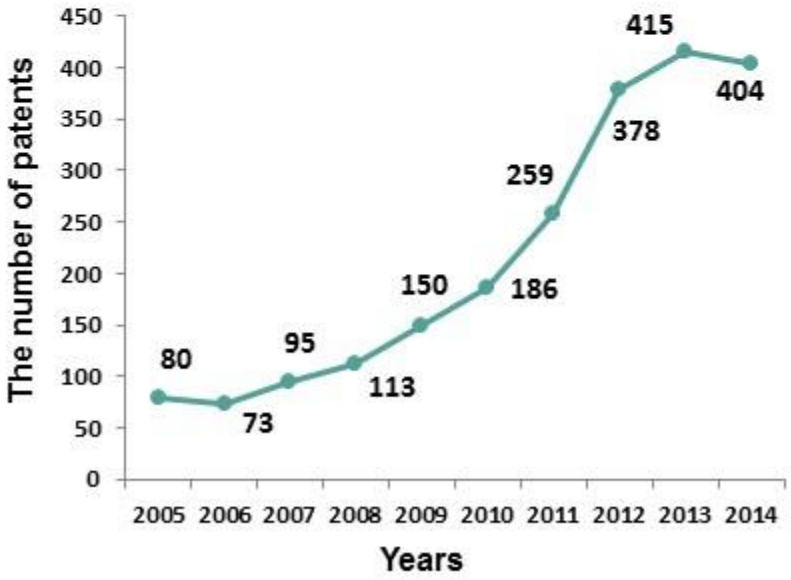
Publications of high quality (IF>10, 2005-2014)

Both quantity and quality increase steadily

China's stem cell research patent

- China is ranked 2nd with a total of 2153 patents in 2005-2014
- China is ranked 6th with a total of 57 PCT patents in 2005-2014

No. of patent (family) applications in the field of stem cells contributed by China



* Data Source: Derwent Innovation Index

No. of PCT applications and country distribution

Rank	Country/ Region	No. of PCT applications	Proportion of PCT applications /%
1	USA	690	10.7
2	Canada	257	15.2
3	Korea	134	7.0
4	Australia	82	25.2
5	Japan	72	4.4
6	**China**	**57**	**2.5**
7	UK	10	3.2
8	Russia	8	3.1
9	Germany	6	3.2

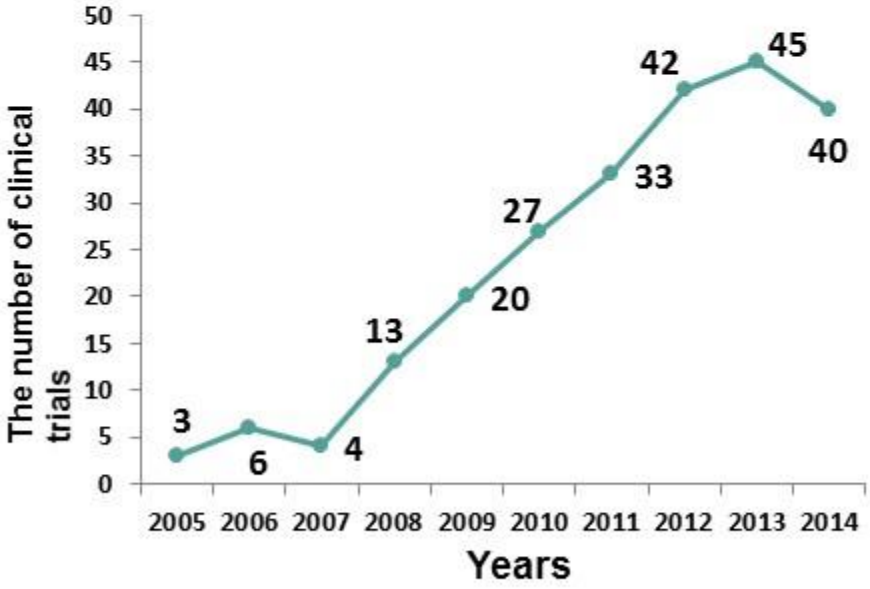
China's stem cell research clinical trials

- Over **6000** studies of clinical trials related to stem cell research worldwide

Country ranking by No. of clinical trials in the field of stem cell research

Rank	Country/Region	Number
1	USA	3383
2	Germany	382
3	France	349
4	Canada	328
5	Italy	286
6	**China**	**268**
7	UK	229
8	Spain	223
9	Korea	192
10	Australia	161

No. of clinical trials in China in the field of stem cell research



* Data Source: Clinical Trials. gov

China's stem cell industrialization developme

- Dozens of related enterprises are engaged in stem cell industry

Osiris THERAPEUTICS, INC.
3.09
own the first approved stem cell drug

geron
3.05
pioneer of embryonic stem cell treatment

ACT
1.43
achieve adult stem cell transplant clone for the first time

STEMCELLS
0.39
leading in the field of neural stem cells

BIOHEART
unlisted
focus on the stem cell therapies of cardiovascular diseases

中源协和 VCANBIO
15.19
overall planning for the stem cell industry chain

金卫医疗科技
1.59
runs stem cell storage business

CBMG Cellular Biomedicine Group 西比曼生物科技
0.8
China's first stem cell company on NASQAQ

冠昊生物 GRANDHOPE BIOTECH
0.06
mainly in stem cell therapy

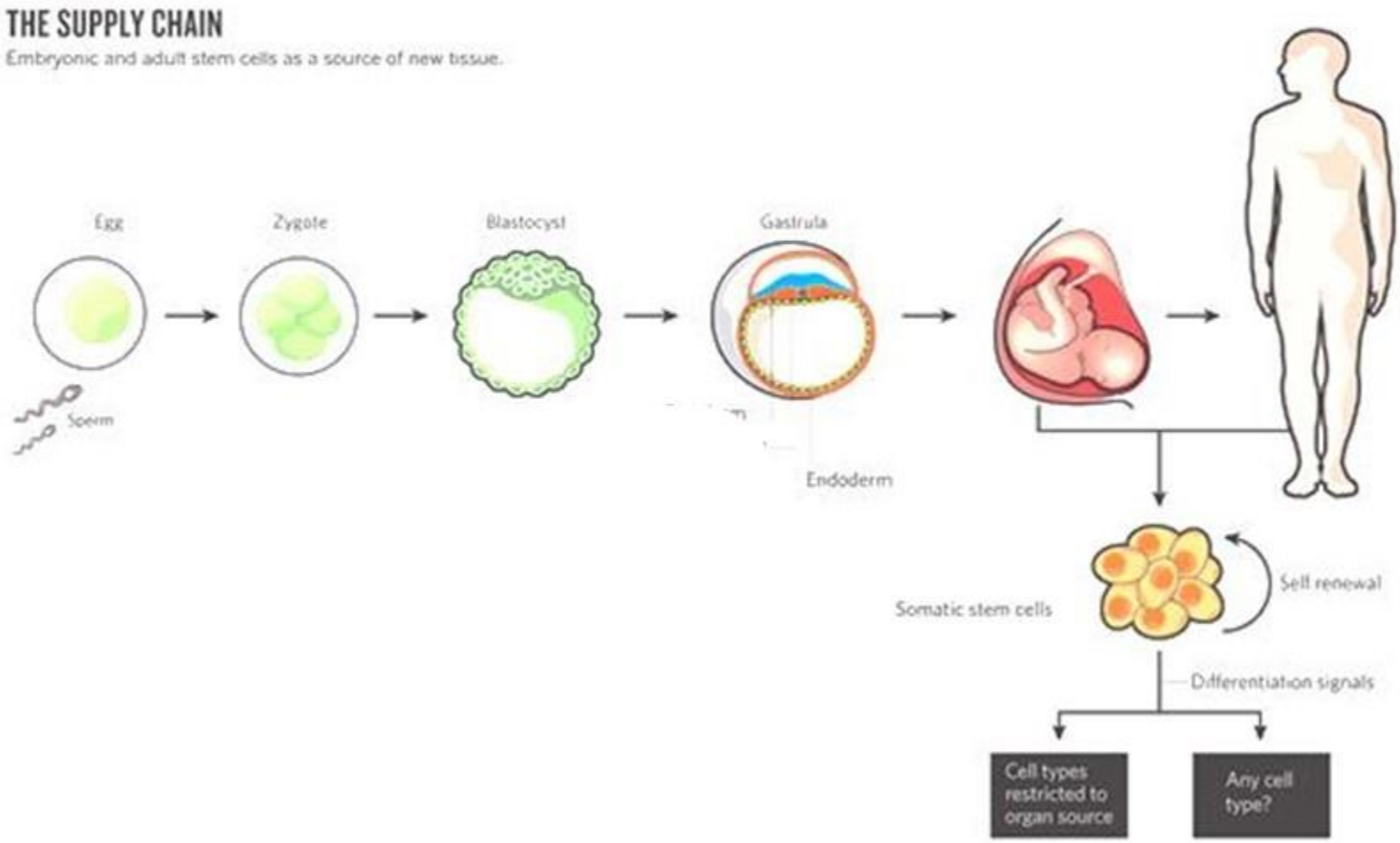
北科生物 Beike Bio-Tech
unlisted
strong research capabilities

博雅干细胞 BOYALIFE
unlisted
relying on the government to establish the largest comprehensive stem cell bank in the world

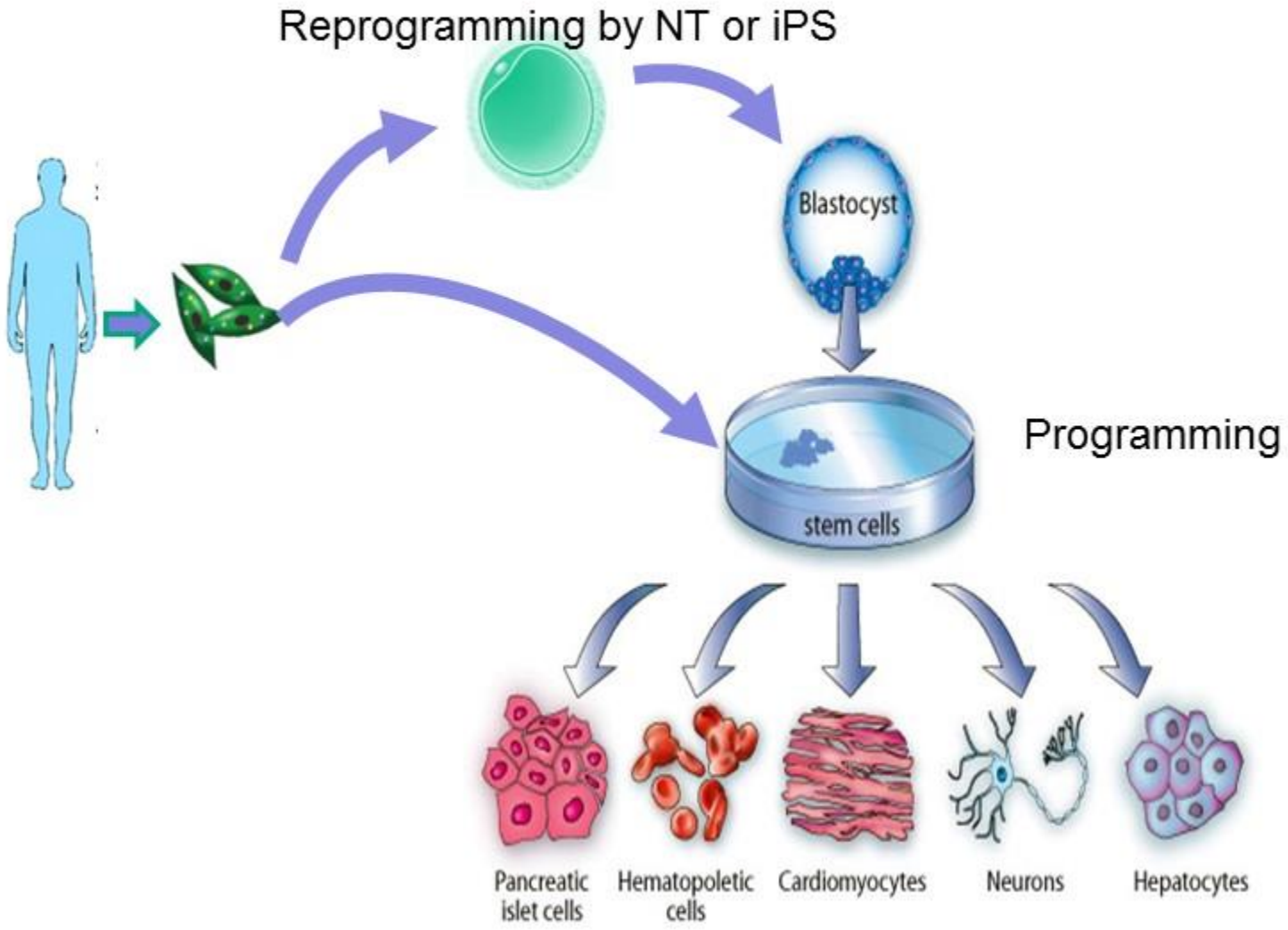
Over 20 billion RMB investment by 2015

* market value by 2015 / billion RMB

Stem Cell and Regenerative Medicine

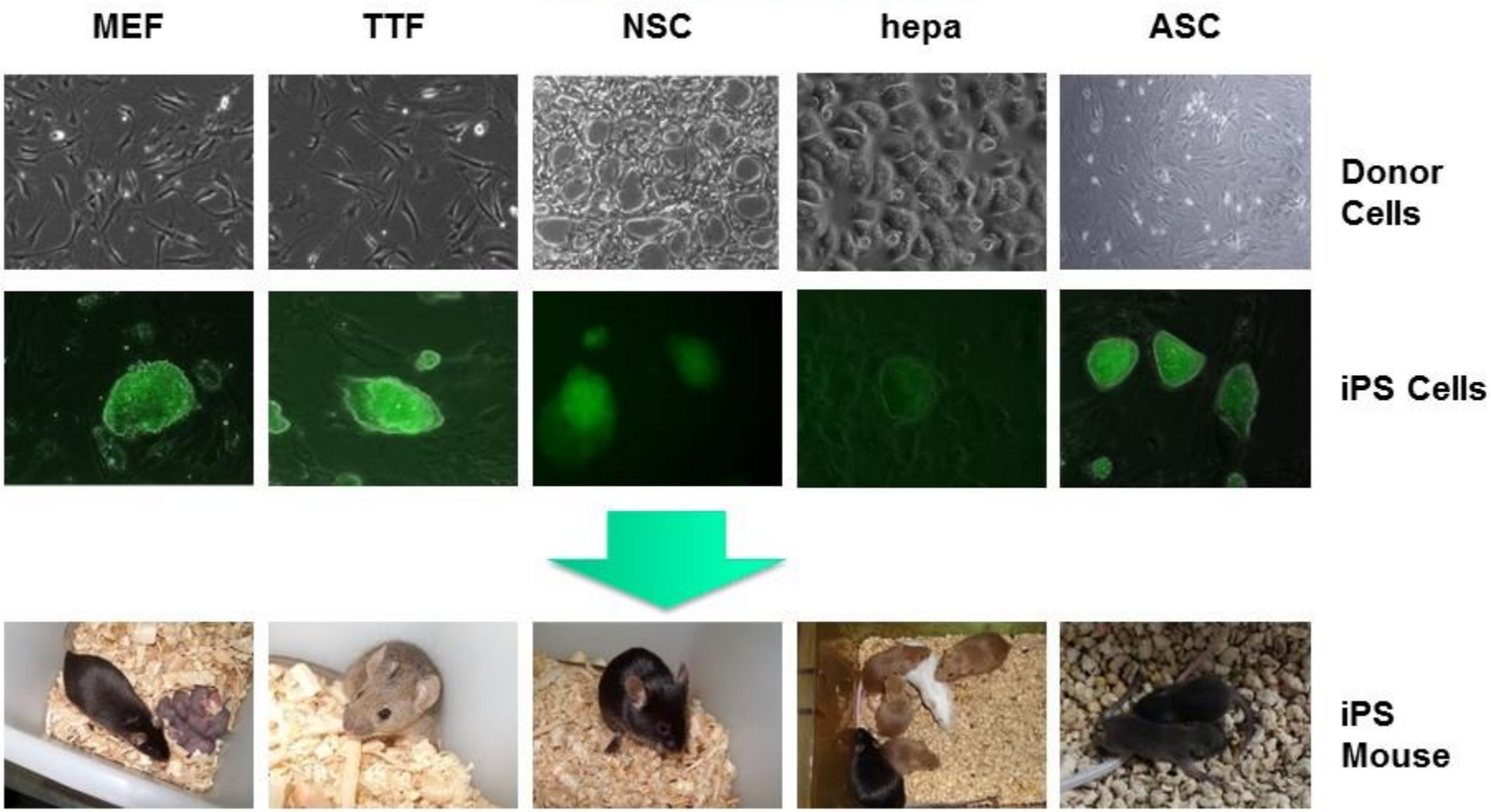


Stem Cell and Regenerative Medicine



Stem Cell and Regenerative Medicine

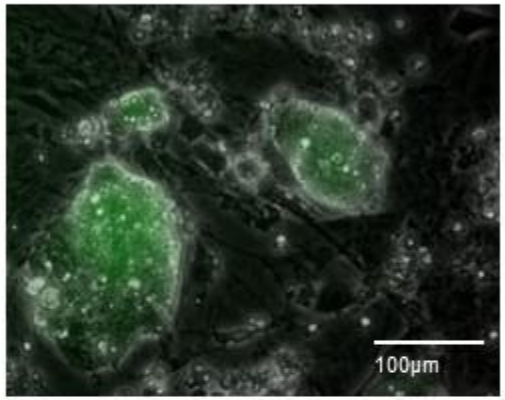
Full Pluripotent iPS Cells Generated From different Tissue



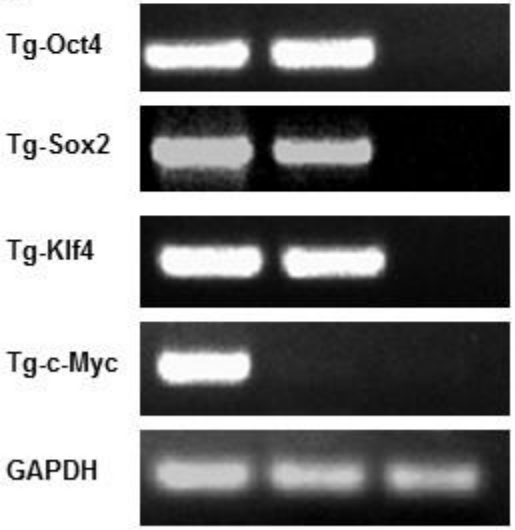
Zhao et al. Nature (2009)
Zhao et al. Cell Research (2010)
Zhao et al. Nature Protocol (2010)

Full Pluripotent iPS Cells Generated Without c-Myc

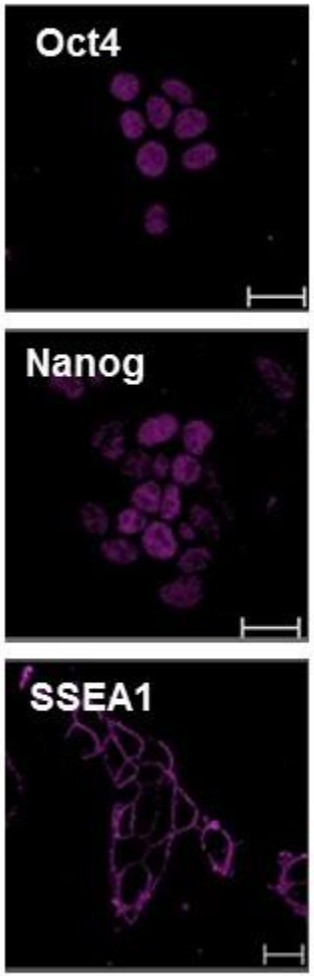
A



B



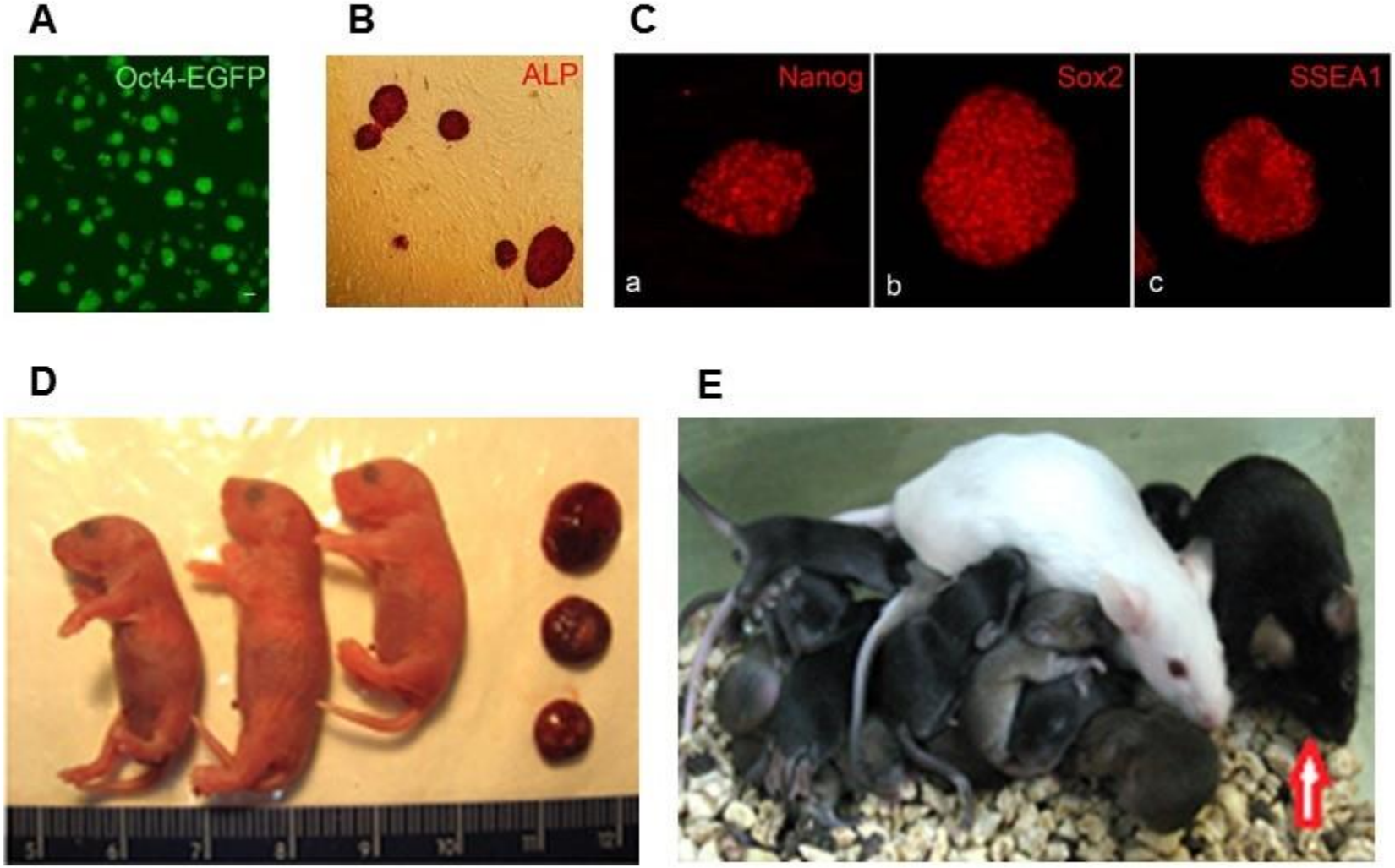
C



D

Li et al. Cell Research (2011)

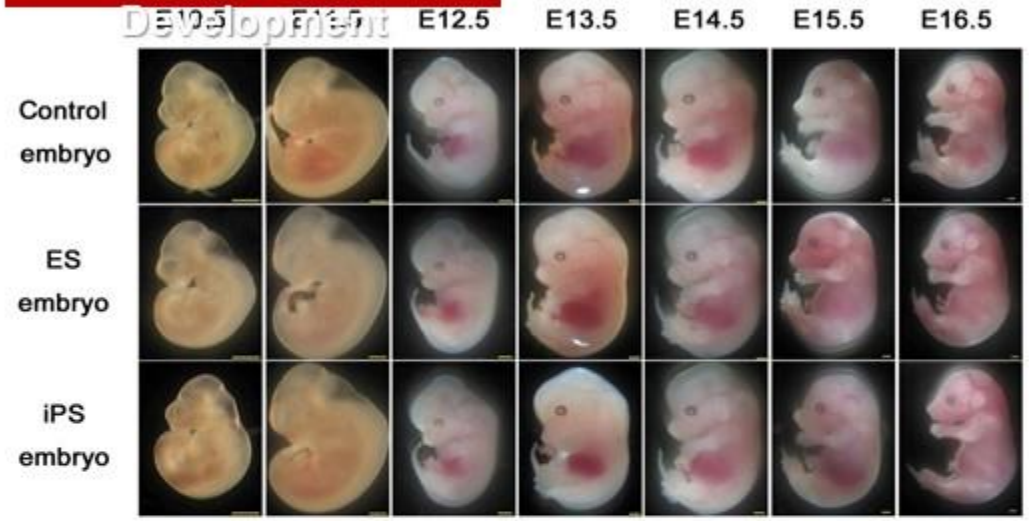
Full Pluripotent iPS Cells Generated With Oct4 and Small Molecule



Yuan et al. Stem Cells (2011)

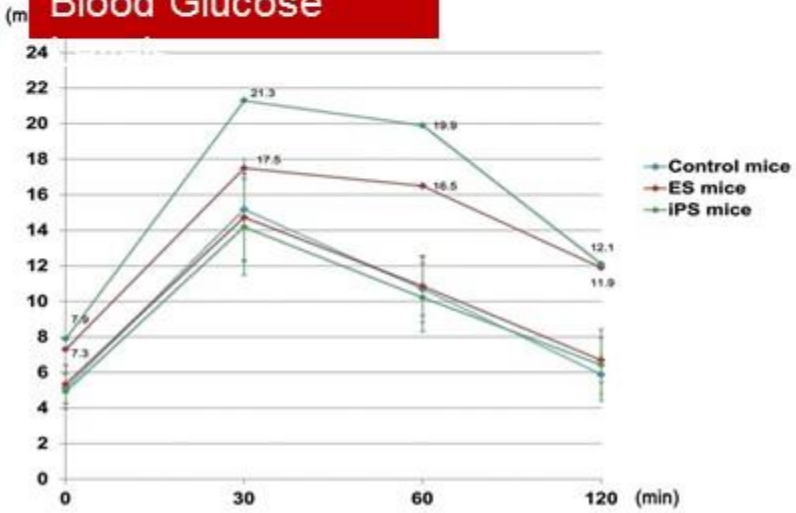
Safety Evaluation of iPS cells with full Development Potential

Embryonic

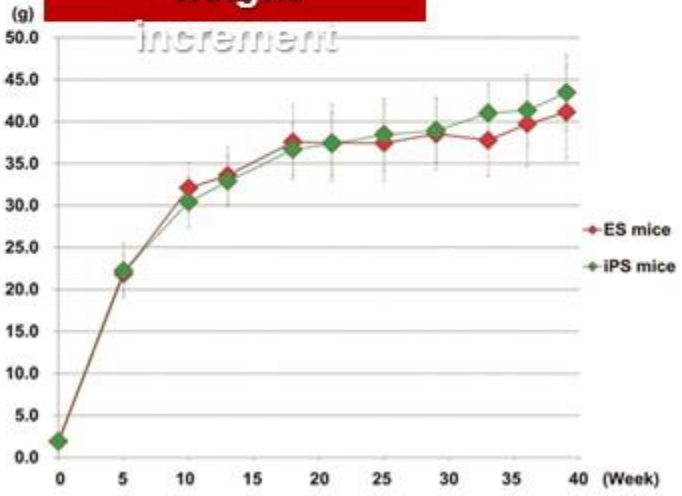


Adult iPS mice behaved normally, and were indistinguishable from ES mice in terms of intelligence test and clinical hematological analysis.

Blood Glucose



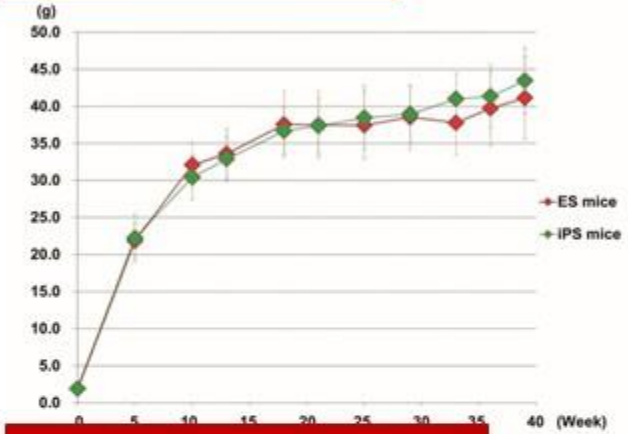
weight



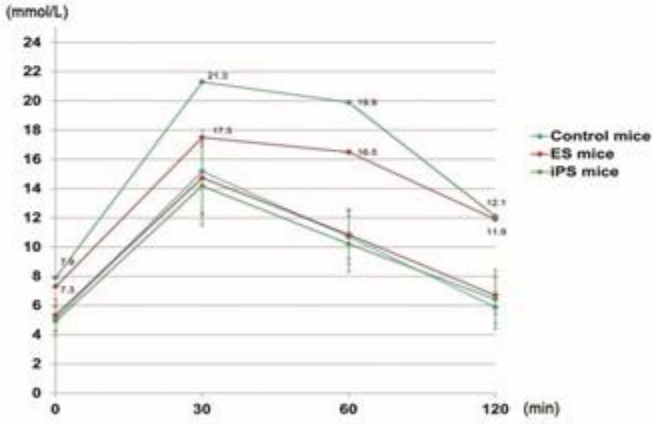
Tong et al. Cell Research (2011)

Are these fully iPS cell animals normal ?

growth



Blood glucose levels

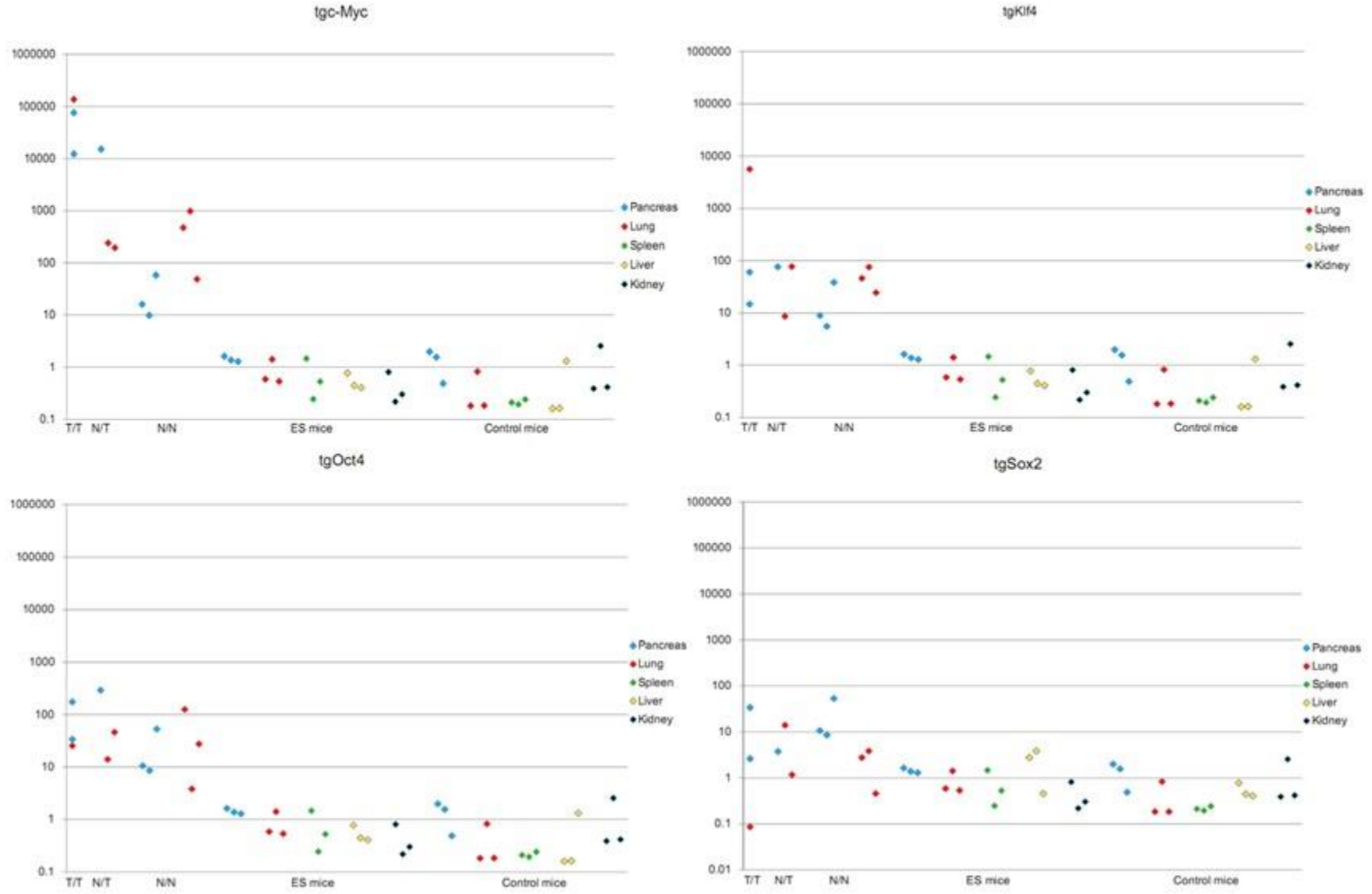


Tumor formation

Mouse	Age (Weeks)	Tumorigenesis (%)	Tumor Type	Tumor grade	Primary tumor tissue	Metastatic tumor tissue
Control mice	38-40	0/7[a]	---	---	---	---
ES F0 mice	38-40	0/7[a]	---	---	---	---
iPS F0 mice	38-40	3/13 (23.1%)[b]	0405-2#: Papillary adenocarcinoma	Tumor grade I	Pancreas	---
			0405-4#: Papillary adenocarcinoma	Tumor grade I	Pancreas	---
			583#: Osteosarcoma	Tumor grade I	Rib	Lung
iPS F1 mice	38-40	3/23 (13.0%)[b]	0117-1#: Papillary adenocarcinoma	Tumor grade I	Lung	---
			0117-5#: Malignant tumor	Tumor grade III	Pancreas	---
			0201-9#: Malignant tumor	Tumor grade III	✧ Neck, pancreas, kidney, spleen	

Tong et al, Cell Research, 2011

Expression of transgenic c-Myc, Klf4 and Oct4 in both tumorous and normal tissues of the iPS mice



Diploid parthenogenetic ES cells as a new tool for functional studies

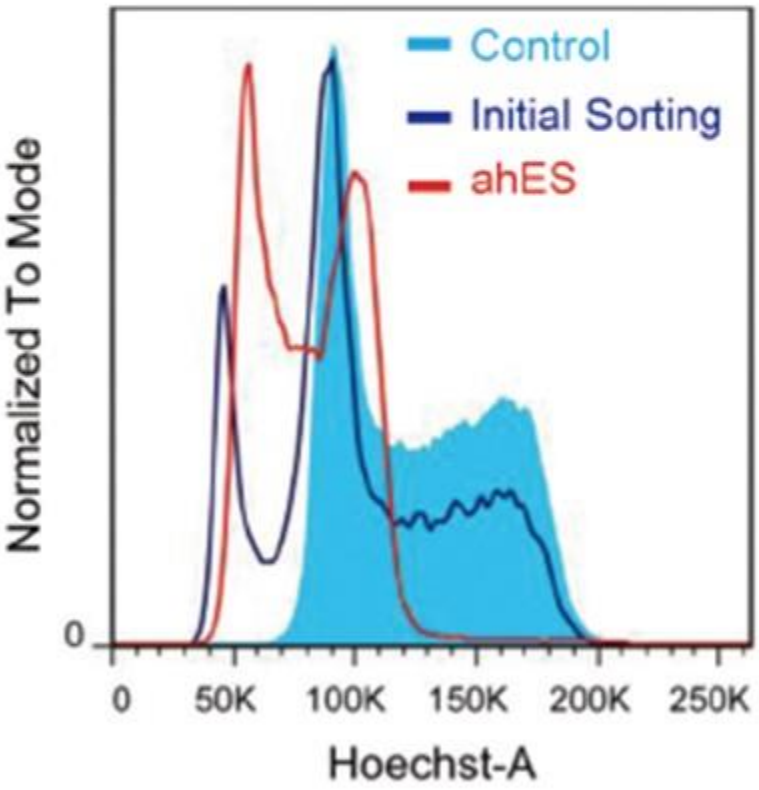
Generating haploid ES cells?

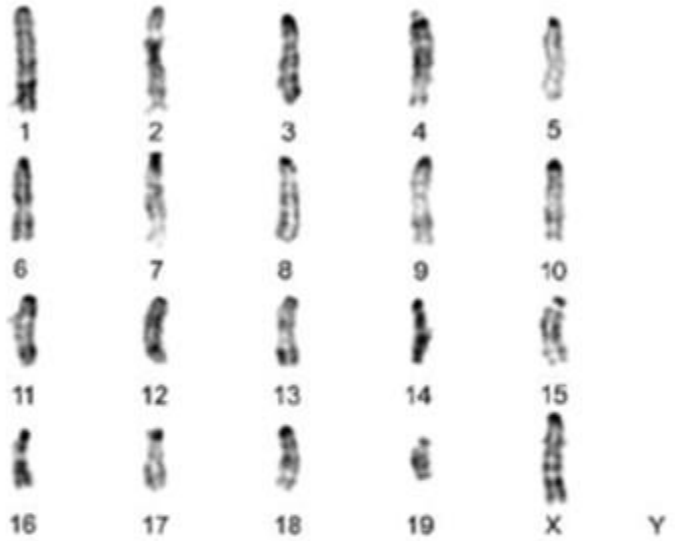
Inbred mouse

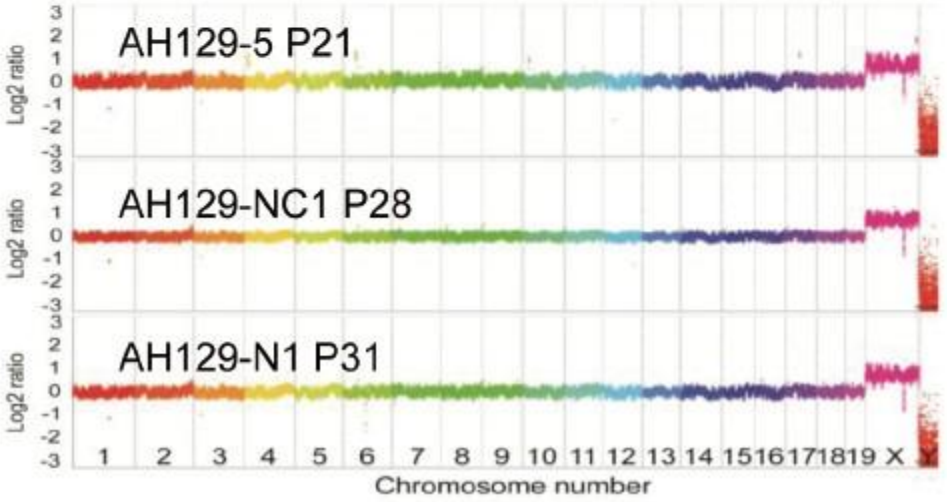
Predominant homozygous in any genomic locus

Good for functional studies of recessive genes

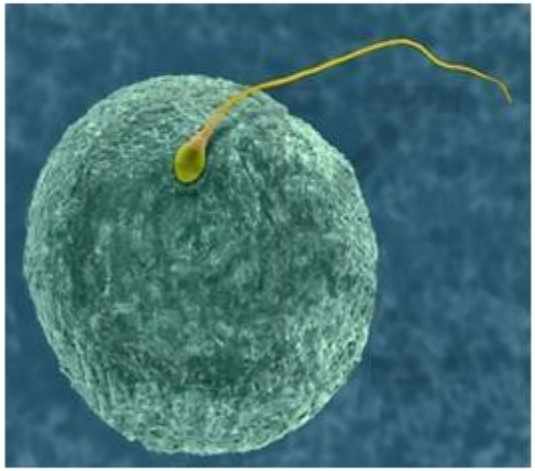
Haploidy test of mouse ahES cells





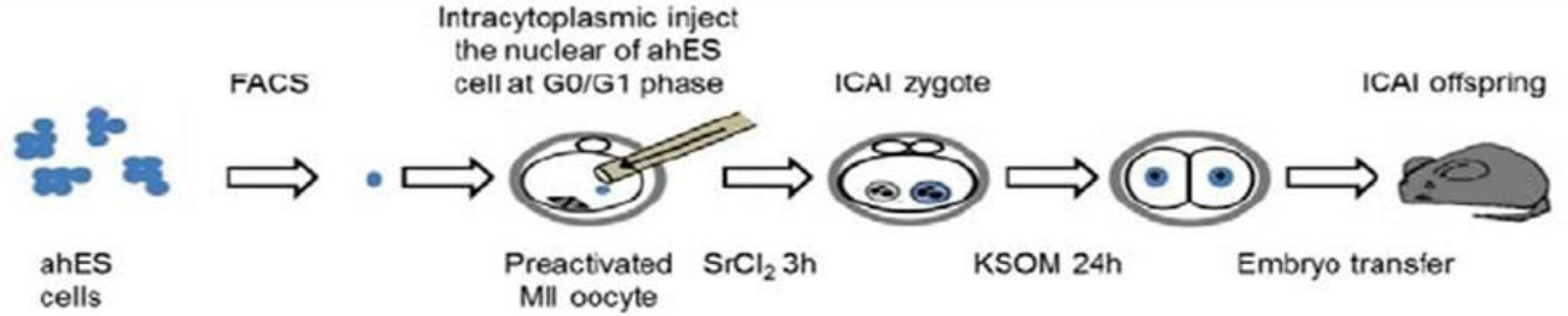


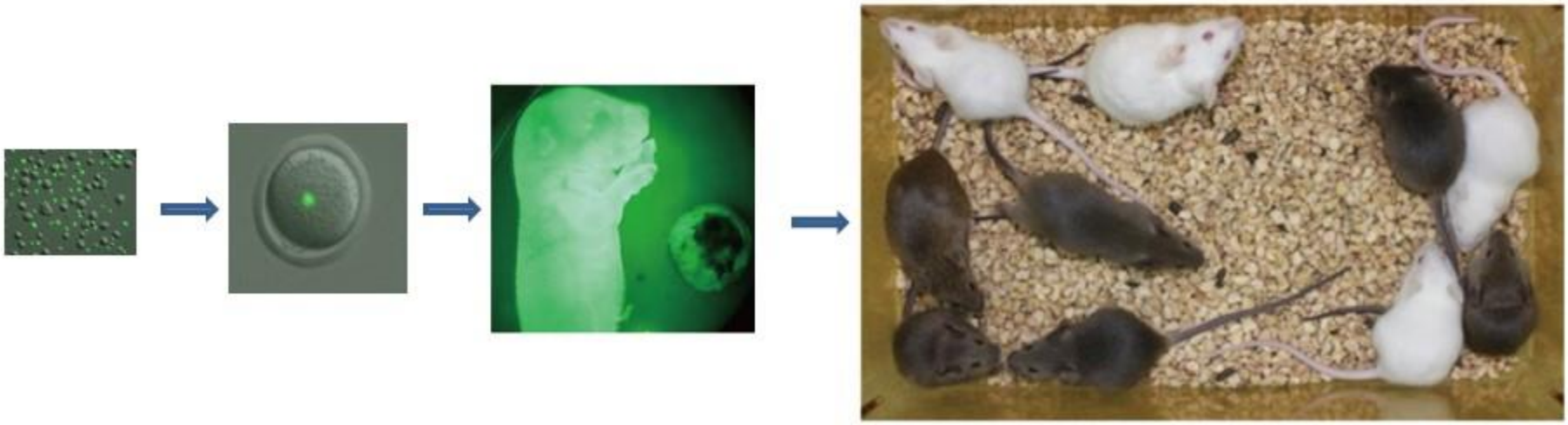
Can ahES cells take the place of sperm to support full-term development ?



Intracytoplasmic injection

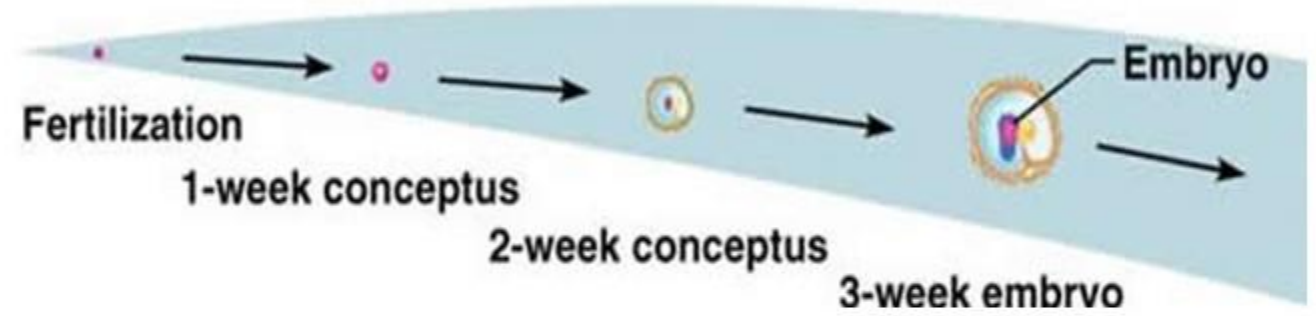
ahES cells produce fertile mice via intracytoplasmic injection into oocytes

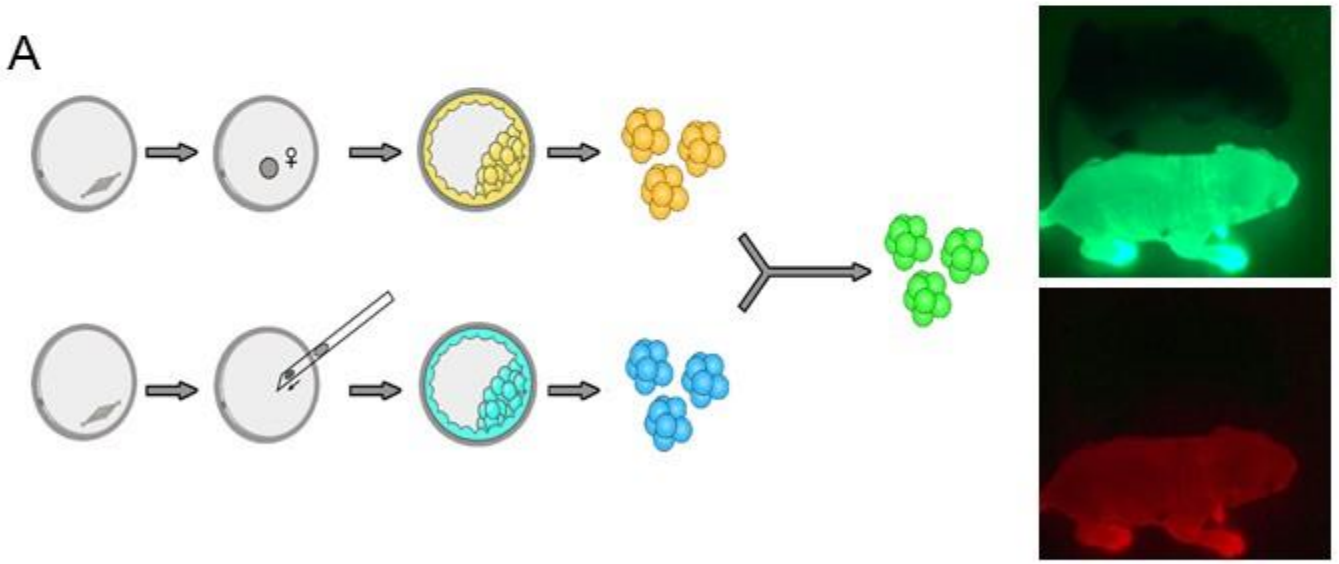




Nature, 2012.

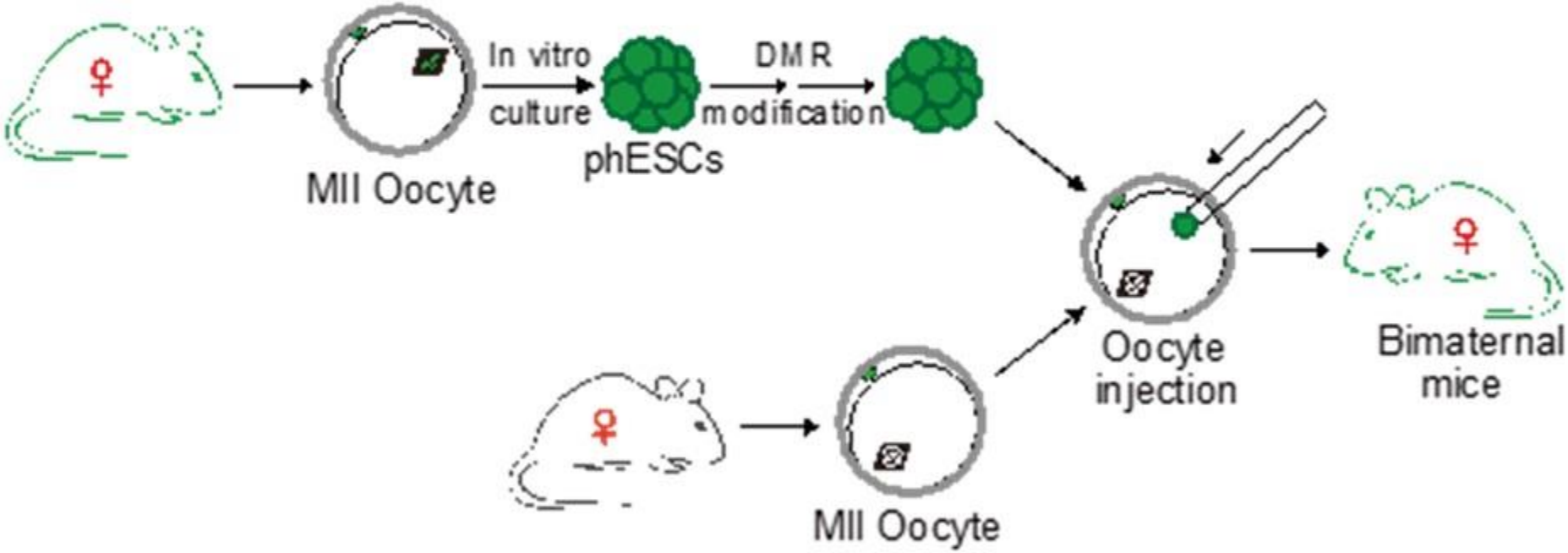
Is fertilization necessary?



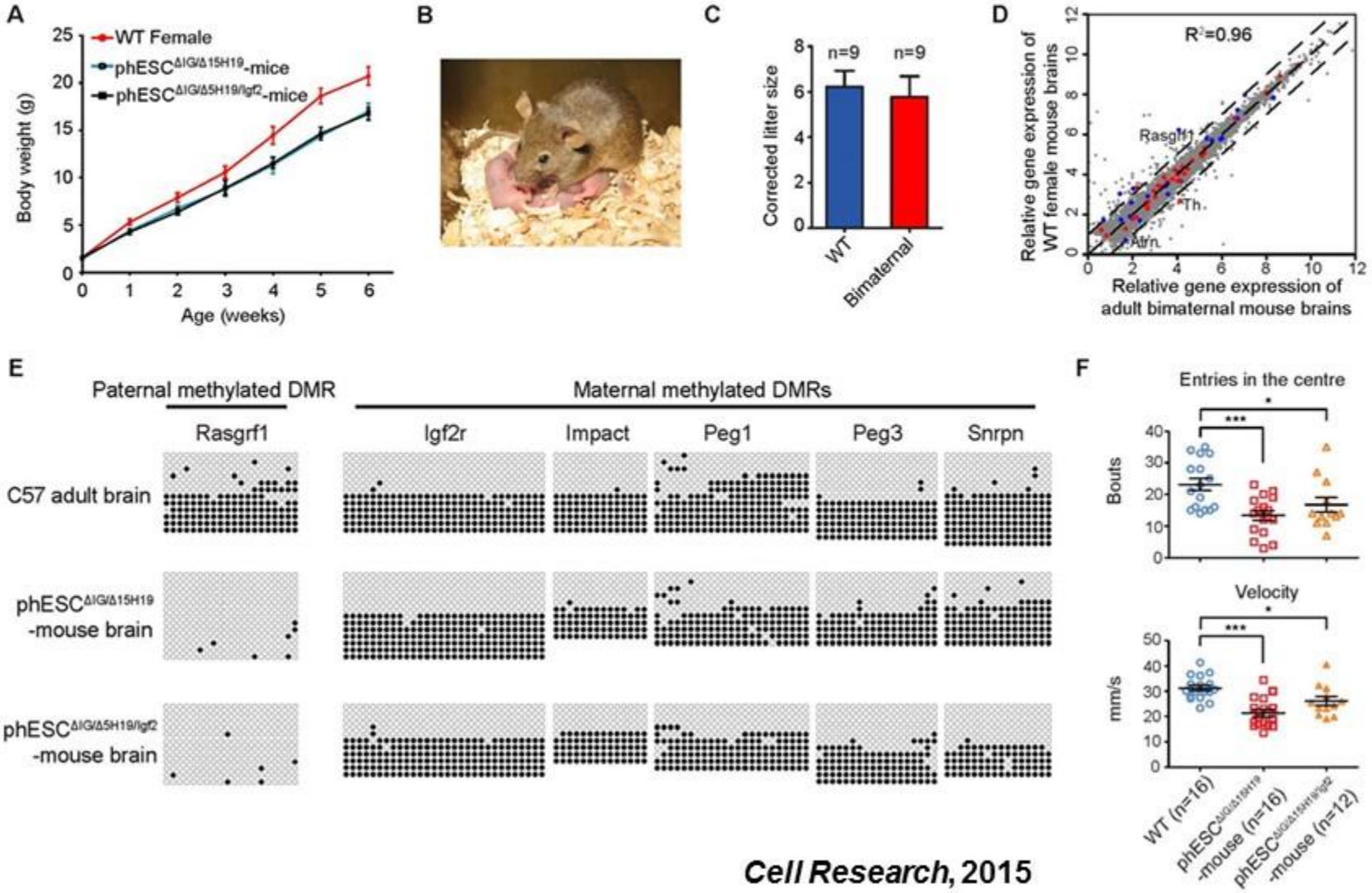


CellResearch，2013；JMCB, 2015; Cell Stem Cell, 2016

Generation of bi-maternal mice from phESCs by imprinting modifications ?



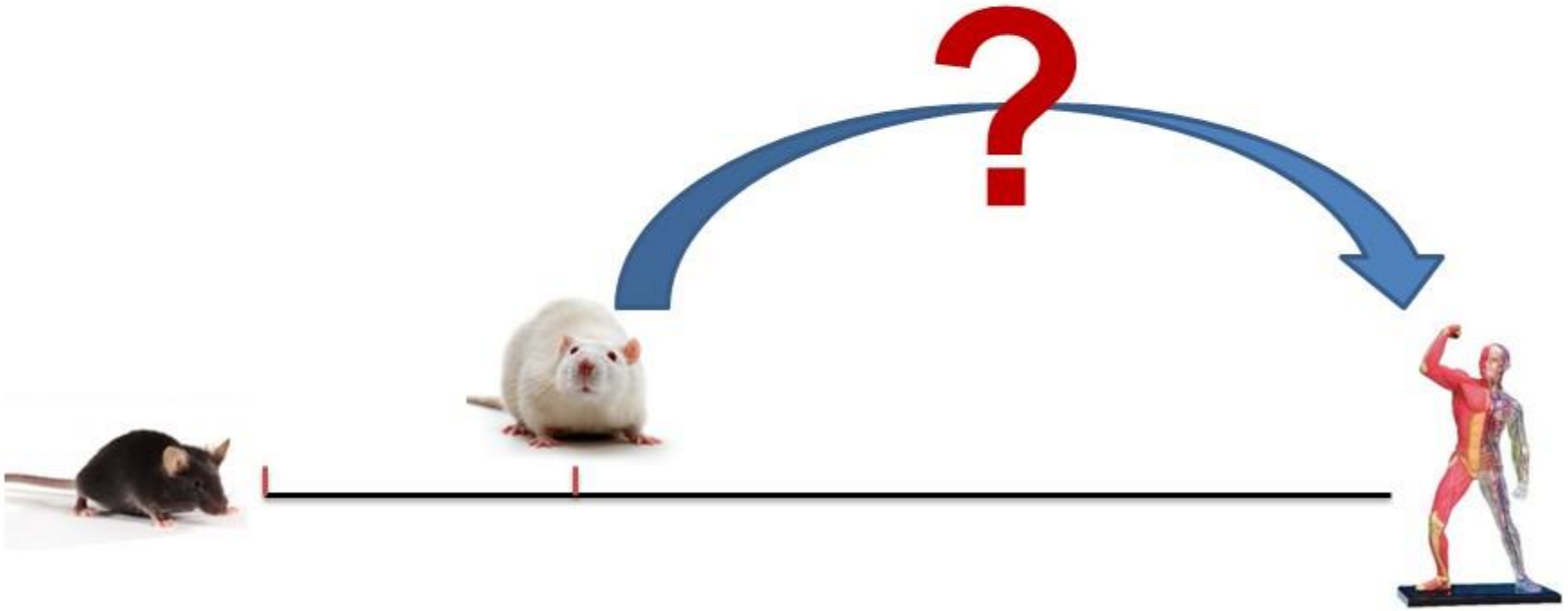
The bi-maternal mice had normal fertility, gene expression and methylation profiling, yet Rasgrf1 was aberrantly expressed



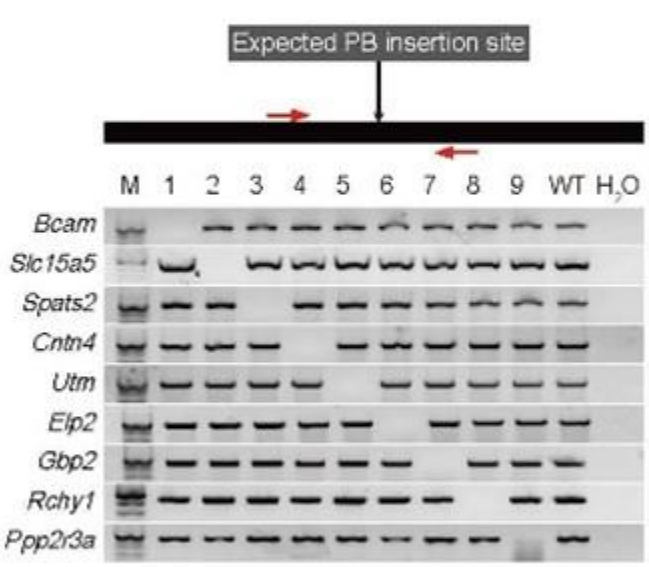
Cell Research, 2015

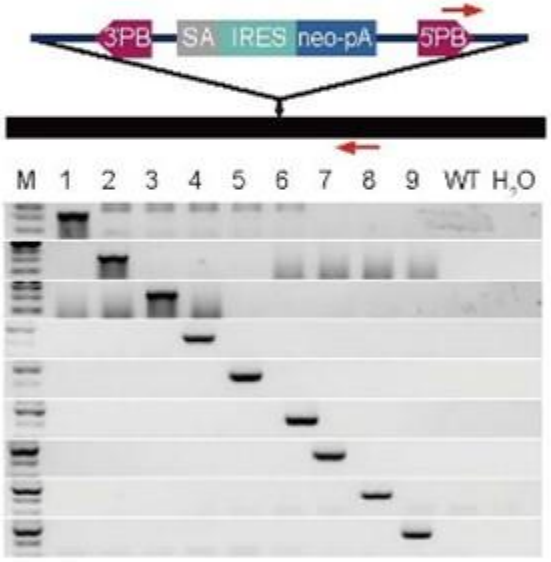
★★Derivation and application of haploid ES cells in other mammals？

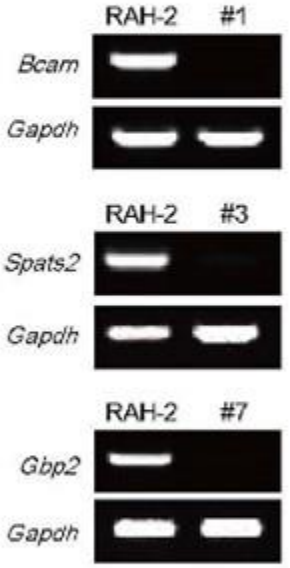
★★Expand the application scope of haploid ES cells ？



Generation of Genome-wide mutational ES cell libraries

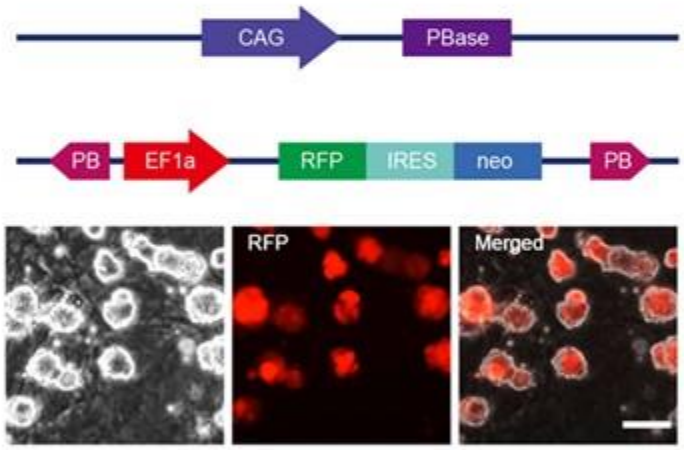


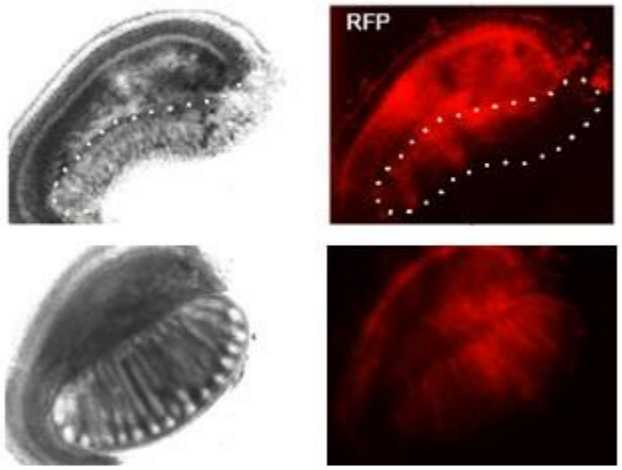




Cell Stem Cell, 2014

RahES cells produce transgenic rats via germline transmission

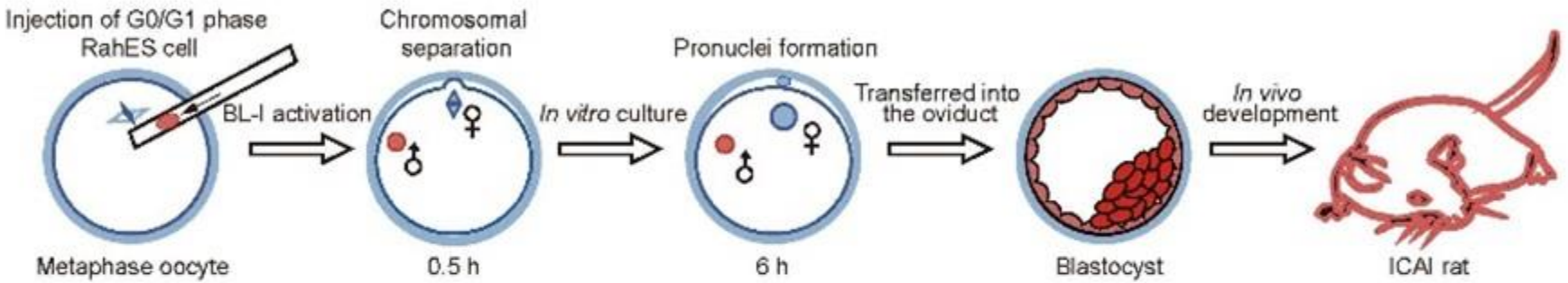




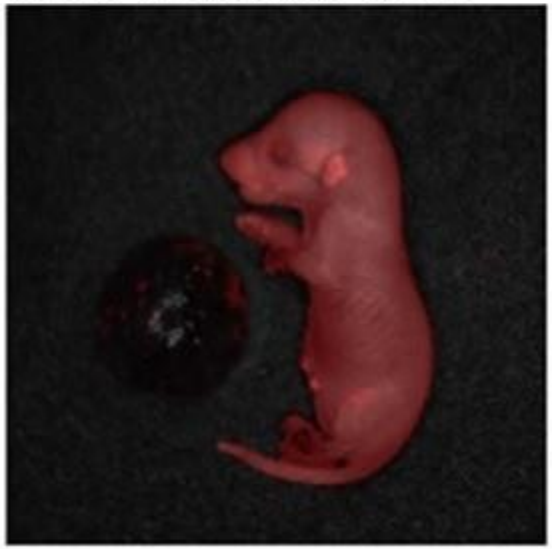
Germline contribution

Cell Stem Cell, 2014

RahES cells produce transgenic rats via oocyte intracytoplasmic injection



One step from cellular level to animal level



Generated rats are fertile

Cell Stem Cell, 2014

Cell

Volume 164, Issues 1–2, 14 January 2016, Pages 279–292

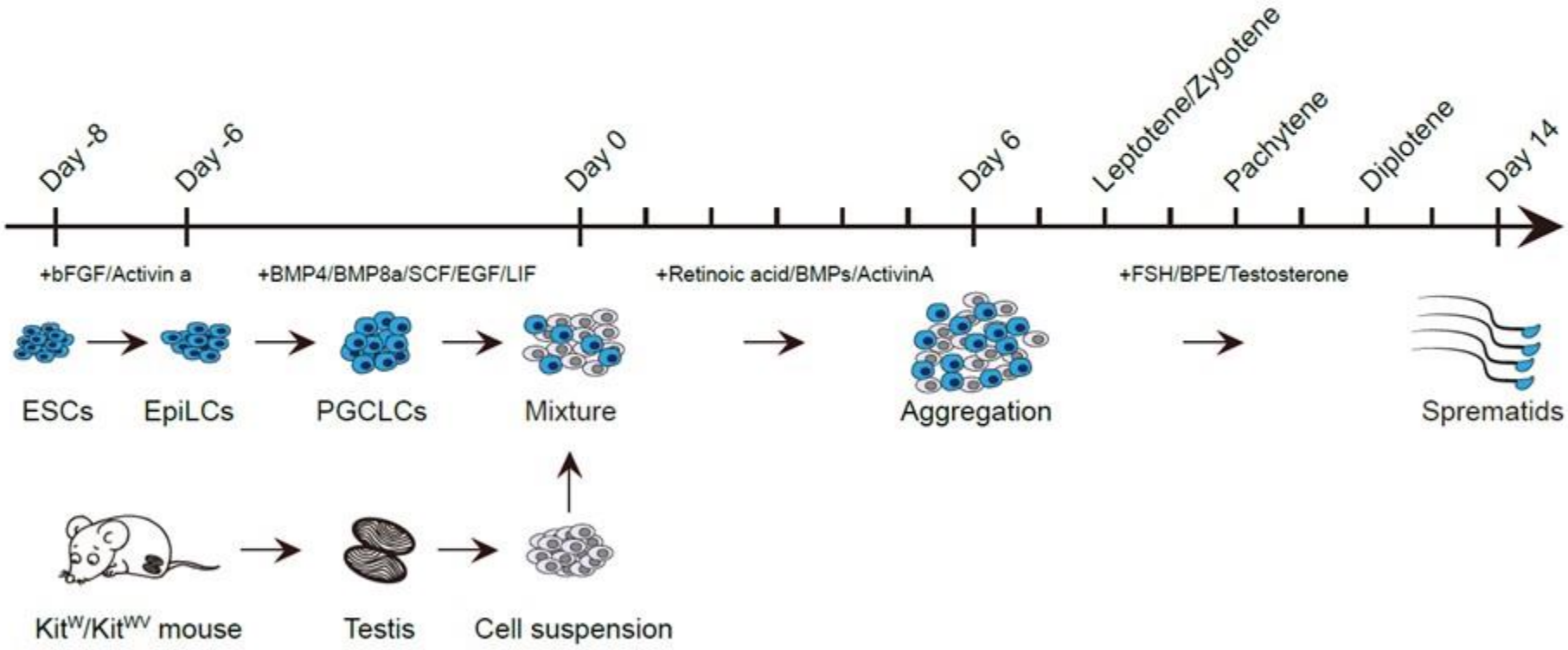
Generation and Application of Mouse-Rat Allodiploid Embryonic Stem Cells

Xin Li[1,5], Xiao-Long Cui[1,4,5], Jia-Qiang Wang[1,3,5], Yu-Kai Wang[1], Yu-Fei Li[1], Le-Yun Wang[1,3], Hai-Feng Wan[1], Tian-Da Li[1], Gui-Hai Feng[2], Ling Shuai[1], Zhi-Kun Li[1], Qi Gu[1], Jie Hao[1], Liu Wang[1], Xiao-Yang Zhao[1], Zhong-Hua Liu[3], Xiu-Jie Wang[2], Wei Li[1,*], Qi Zhou[1,*]

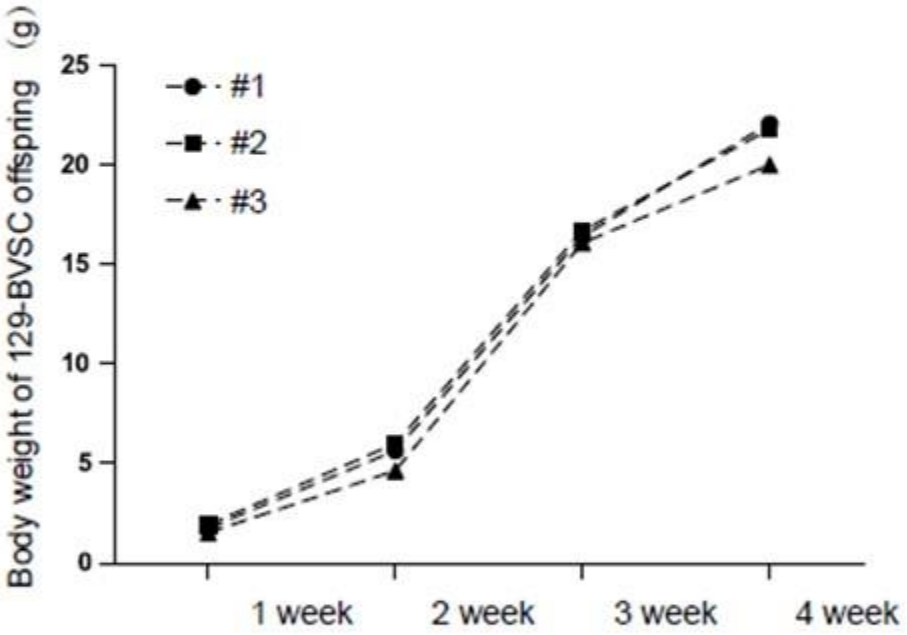
Highlights

- The mouse-rat AdESCs are genetically stable and pluripotent
- The AdESCs exhibit mid-parent and species-biased gene expression patterns
- Mouse-specific X inactivation in allodiploid cells reveals Xi-escaping genes
- The AdESCs provide a tool to study the species-specific pluripotency maintenance

Complete in vitro meiosis from embryonic stem cell-derived primordial germ cells by co-culture with neonatal testicular somatic cells and sequential exposure to morphogens and sex hormones.



In-vitro derived male gametes are functional to produce viable offspring in mice



Cell Stem Cell

Volume 18, Issue 3, 3 March 2016, Pages 330–340

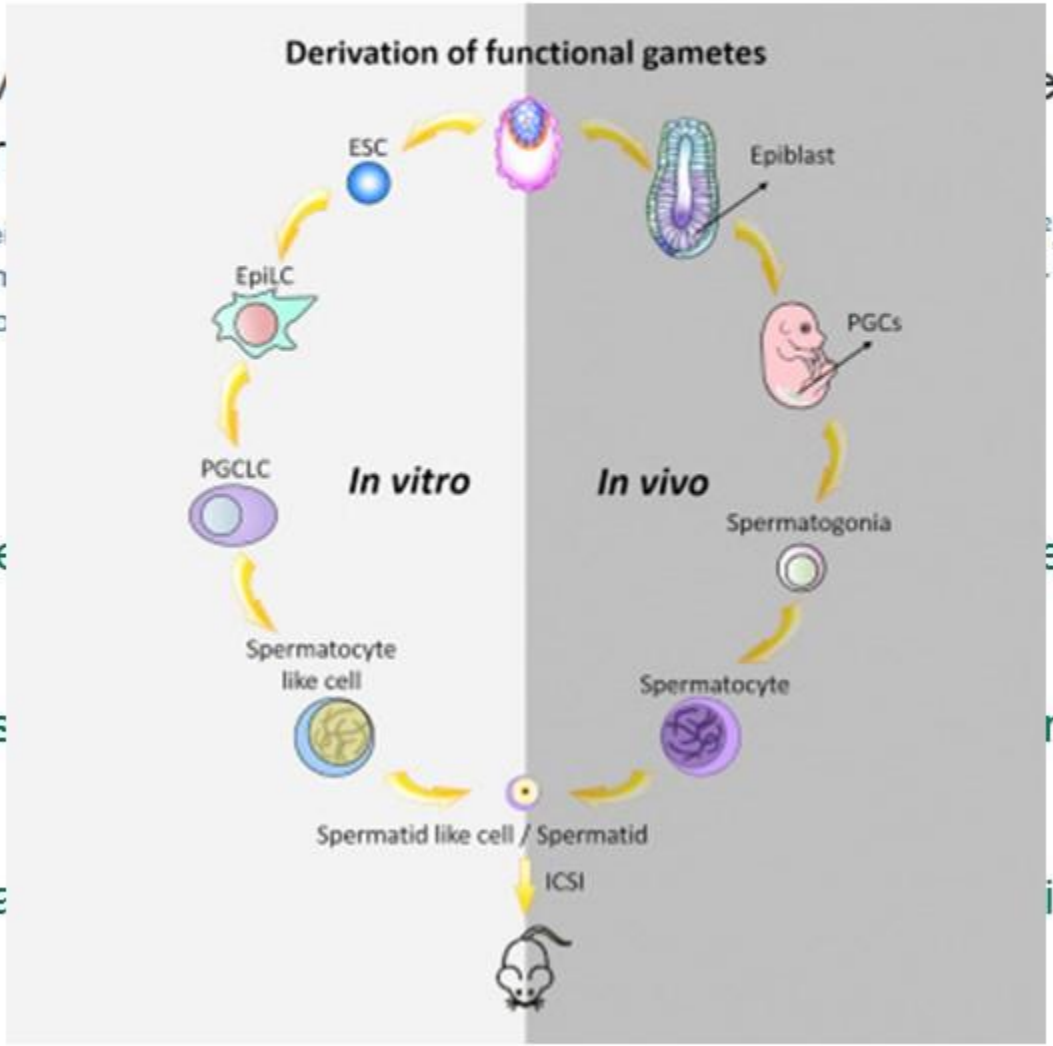
Article

Complete M ed Germ Cells In Vitr

Quan Zhou[1, 2, 8], Me , Mingming Xie[2, 5], Mingxi Liu[1], Xuejian , Jiahao Sha[1,], Qi Zho

Highlights

- Haploid spe e differentiation of ESCs
- This proces ng meiotic hallmarks
- Intracytopla ile offspring



干细胞与再生医学领域发展现状

2012年美国FDA批准干性黄斑变性神经干细胞疗法的临床试验

Cell Stem Cell

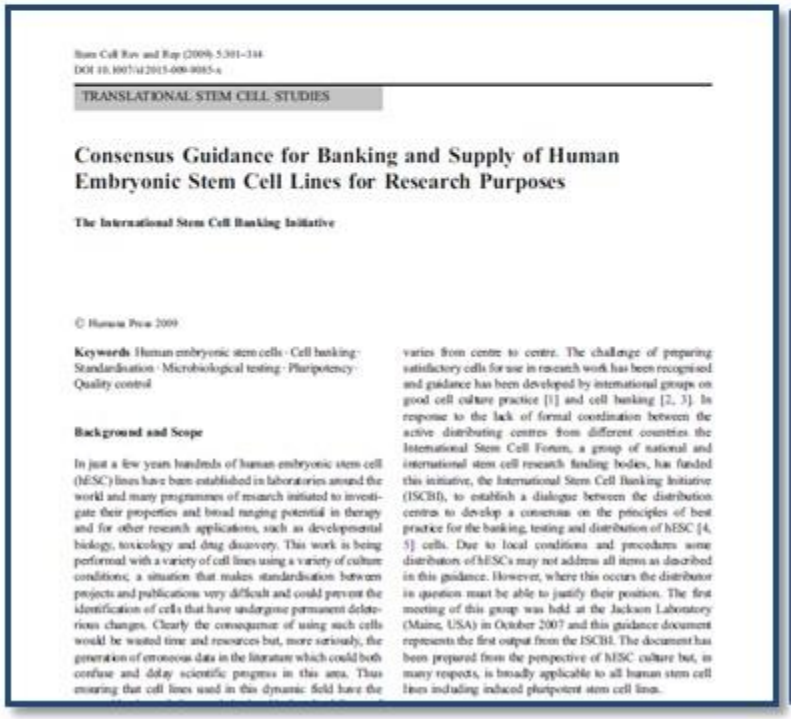
Many of the stem cell lines used by academics and registered with the U.S. National Institutes of Health (NIH) would not be eligible for commercialization because they don't pass muster with the Food and Drug Administration (FDA).

Cell Stem Cell, 14:139-40, 2014

International Stem Cell Consortium
Establishment of Standards for Clinical Embryonic Stem cells

Best Western Olympic Beijing Hotel, Beijing, China
April 16-18, 2008, Beijing

- **17 countries participated, including governors and representatives fromWHO, FDA, NIH, etc.**



Stem Cell Rev and Rep (2009) 5:301–314
DOI 10.1007/s12015-009-9085-x

TRANSLATIONAL STEM CELL STUDIES

Consensus Guidance for Banking and Supply of Human Embryonic Stem Cell Lines for Research Purposes

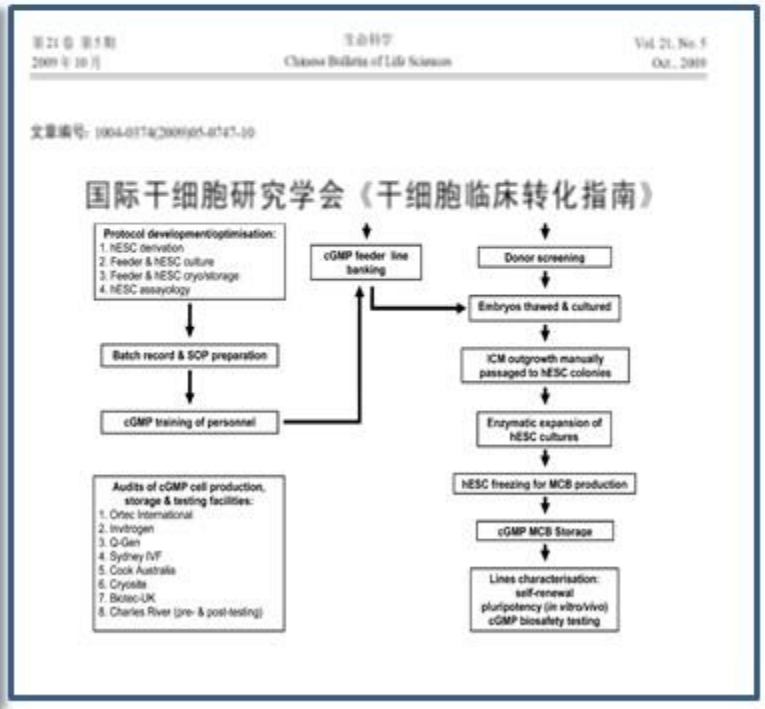
The International Stem Cell Banking Initiative

© Humana Press 2009

Keywords Human embryonic stem cells · Cell banking · Standardisation · Microbiological testing · Pluripotency · Quality control

Background and Scope

In just a few years hundreds of human embryonic stem cell (hESC) lines have been established in laboratories around the world and many programmes of research initiated to investigate their properties and broad ranging potential in therapy and for other research applications, such as developmental biology, toxicology and drug discovery. This work is being performed with a variety of cell lines using a variety of culture conditions; a situation that makes standardisation between projects and publications very difficult and could prevent the identification of cells that have undergone permanent deleterious changes. Clearly the consequence of using such cells would be wasted time and resources but, more seriously, the generation of erroneous data in the literature which could both confuse and delay scientific progress in this area. Thus ensuring that cell lines used in this dynamic field have the varies from centre to centre. The challenge of preparing satisfactory cells for use in research work has been recognised and guidance has been developed by international groups on good cell culture practice [1] and cell banking [2, 3]. In response to the lack of formal coordination between the active distributing centres from different countries the International Stem Cell Forum, a group of national and international stem cell research funding bodies, has funded this initiative, the International Stem Cell Banking Initiative (ISCBI), to establish a dialogue between the distribution centres to develop a consensus on the principles of best practice for the banking, testing and distribution of hESC [4, 5] cells. Due to local conditions and procedures some distributors of hESCs may not address all items as described in this guidance. However, where this occurs the distributor in question must be able to justify their position. The first meeting of this group was held at the Jackson Laboratory (Maine, USA) in October 2007 and this guidance document represents the first output from the ISCBI. The document has been prepared from the perspective of hESC culture but, in many respects, is broadly applicable to all human stem cell lines including induced pluripotent stem cell lines.



Chinese Bulletin of Life Sciences

Vol. 21, No. 5
Oct., 2009

国际干细胞研究学会《干细胞临床转化指南》

Protocol development/optimisation:
1. hESC derivation
2. Feeder & hESC culture
3. Feeder & hESC cryostorage
4. hESC assaysology

cGMP feeder line banking

Donor screening

Embryos thawed & cultured

ICM outgrowth manually passaged to hESC colonies

Enzymatic expansion of hESC cultures

hESC freezing for MCB production

cGMP MCB Storage

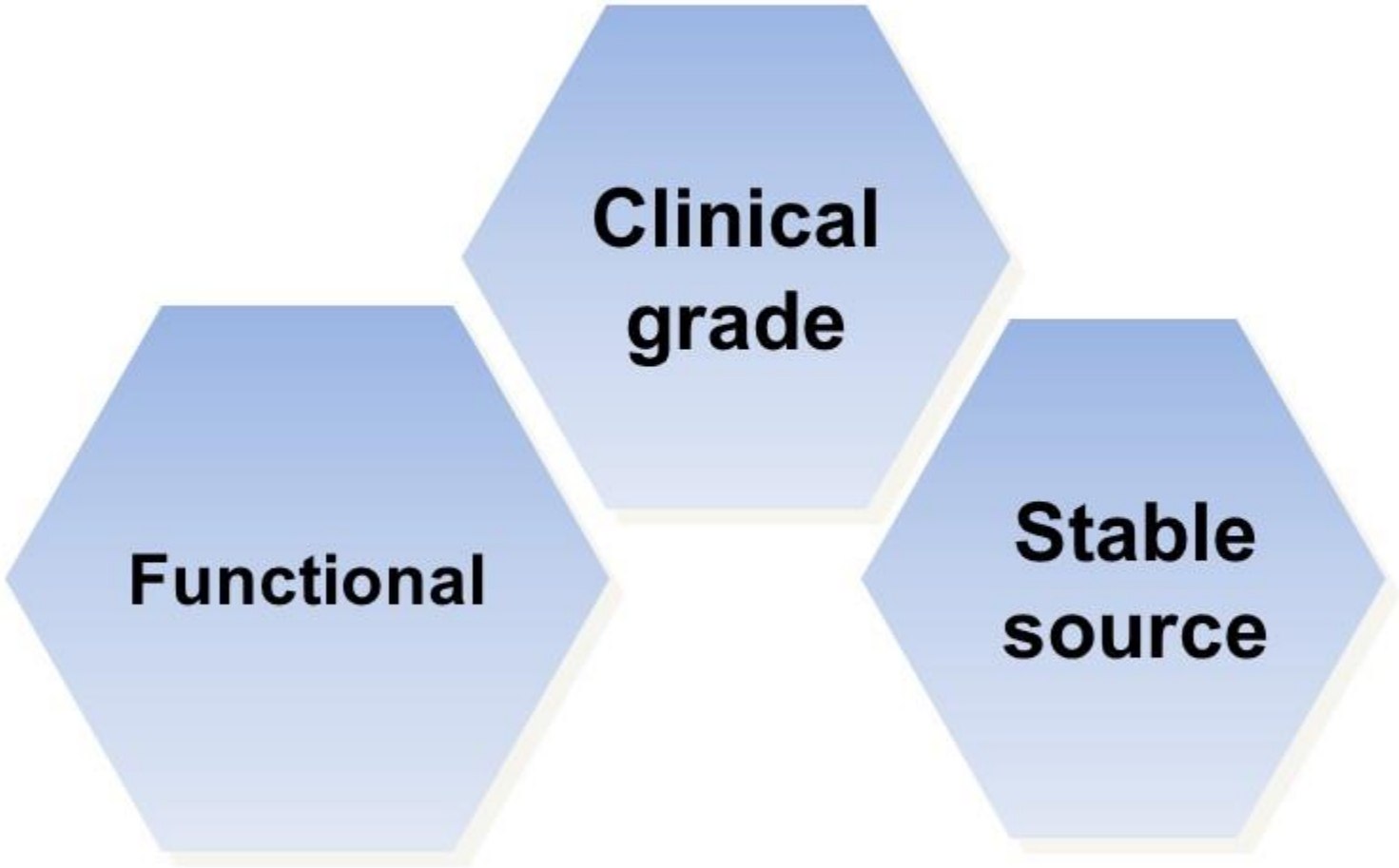
Lines characterisation: self-renewal pluripotency (in vitro/vivo) cGMP biosafety testing

Batch record & SOP preparation

cGMP training of personnel

Audits of cGMP cell production, storage & testing facilities:
1. Ortec International
2. Invitrogen
3. Q-Gen
4. Sydney IVF
5. Cook Australia
6. Cryosite
7. Biotec-UK
8. Charles River (pre- & post-testing)

Requirements of clinical grade cells



Blooming stem cell research in China

Clinical grade human stem cell bank (Beijing stem cell Bank)

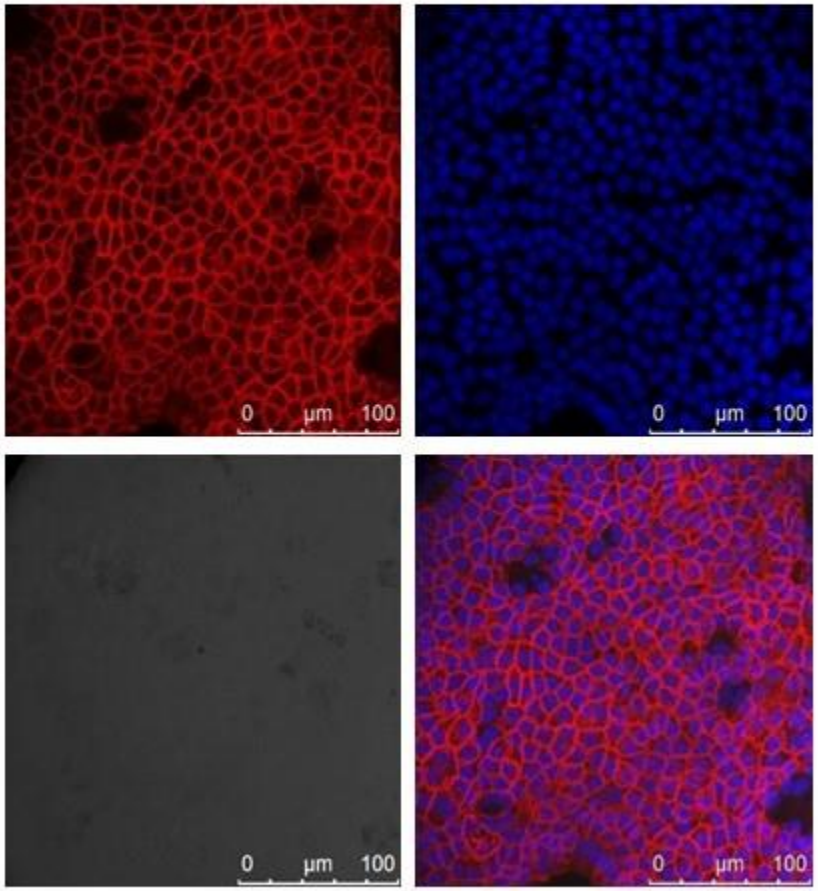
Blooming stem cell research in China

RPE for the treatment of age-related macular degeneration

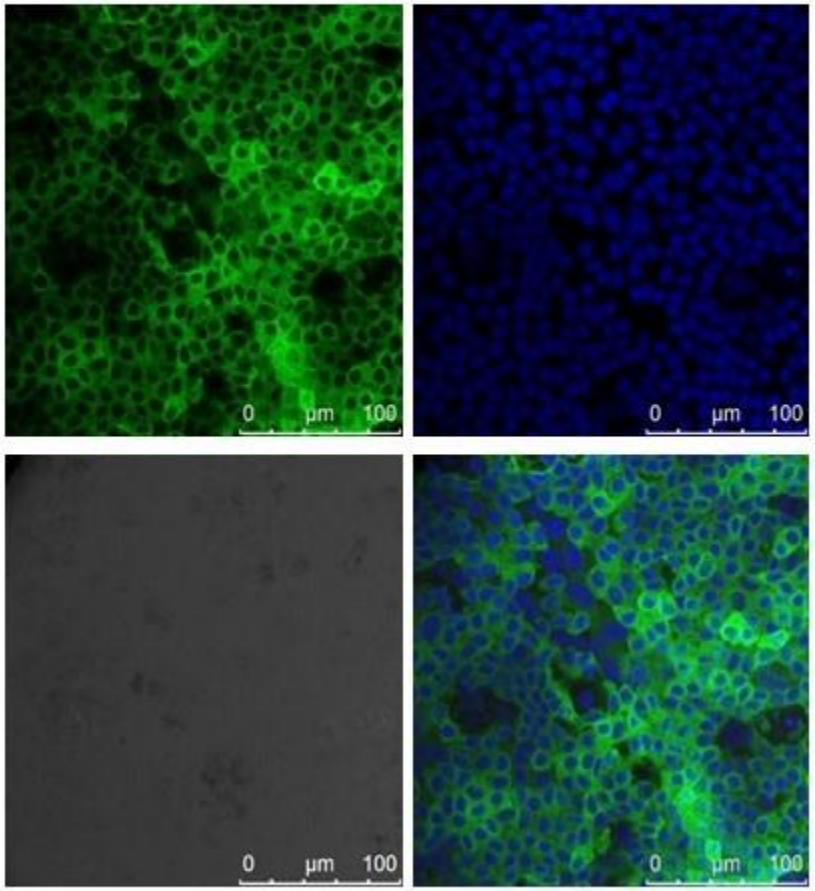
Assessments of safety and efficacy are crucial before human ESC (hESC) therapies can move into the clinic. Two important early potential hESC applications are the use of retinal pigment epithelium (RPE) for the treatment of age-related macular degeneration and Stargardt disease

Blooming stem cell research in China

RPE for the treatment of age-related macular degeneration



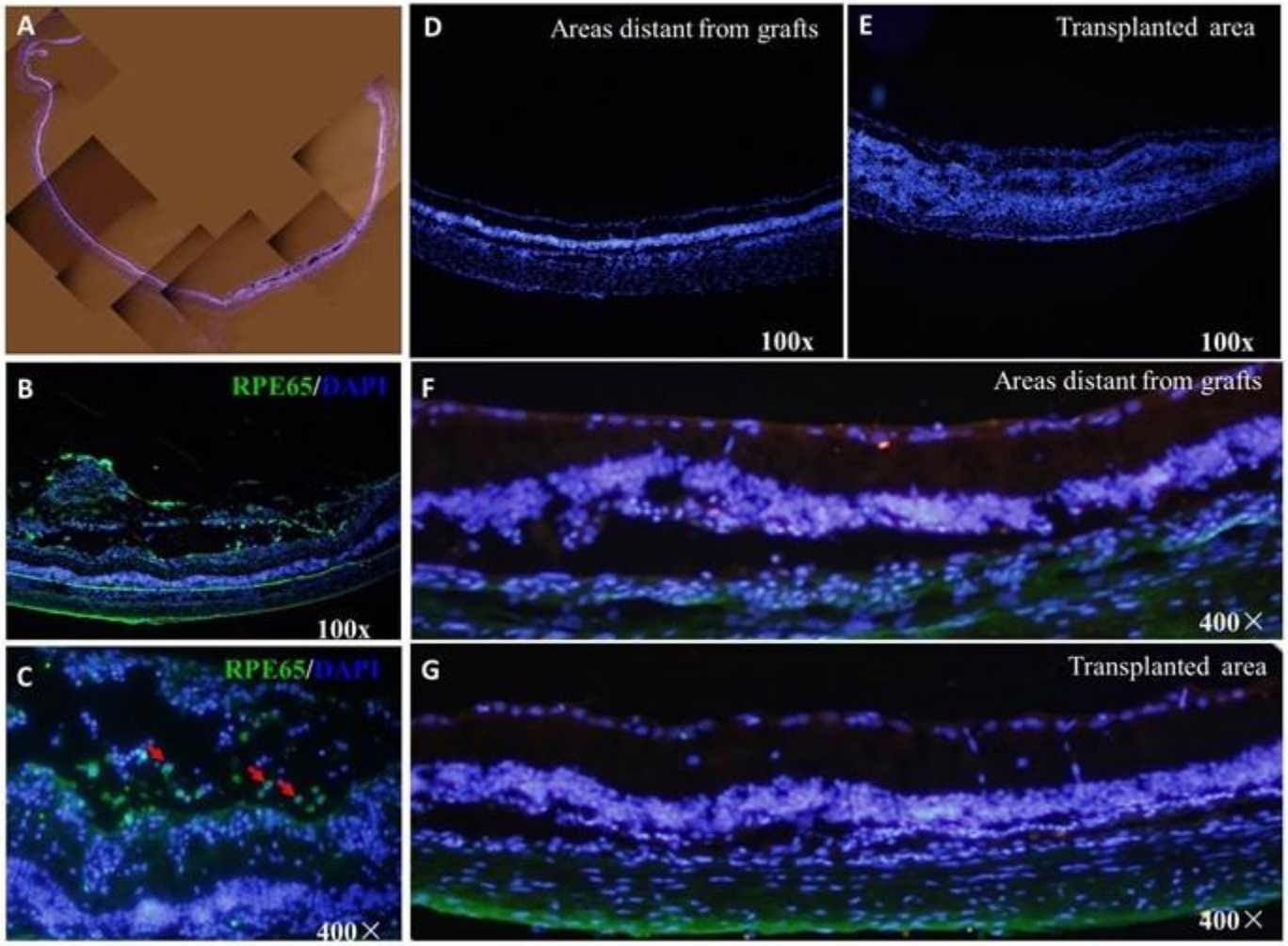
Bestrophin/DAPI/Pigment



Cralbp/DAPI/Pigment

Blooming stem cell research in China

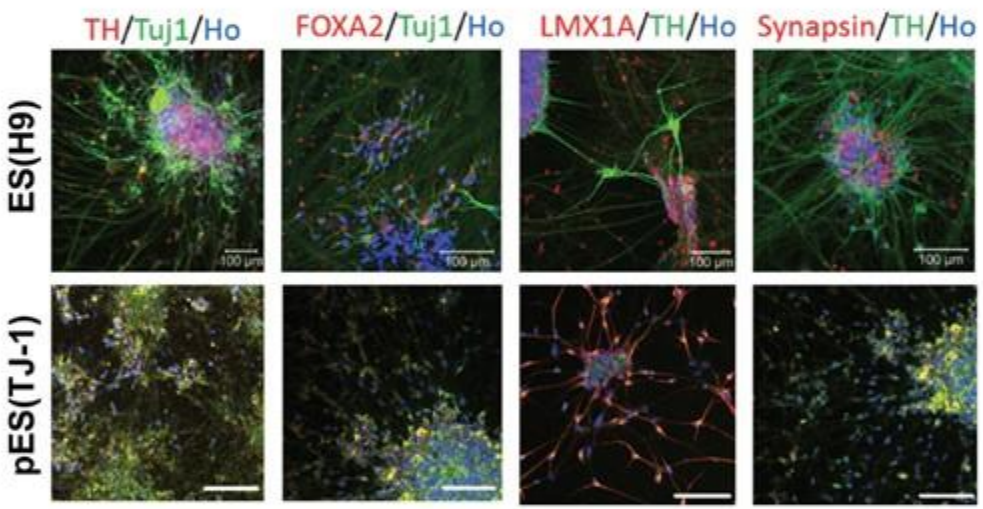
RPE for the treatment of age-related macular degeneration

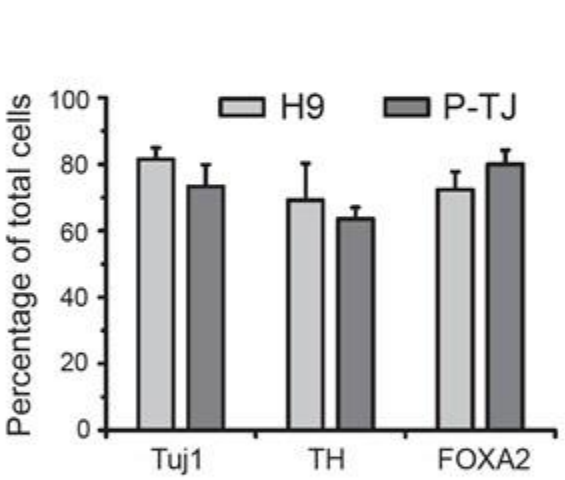


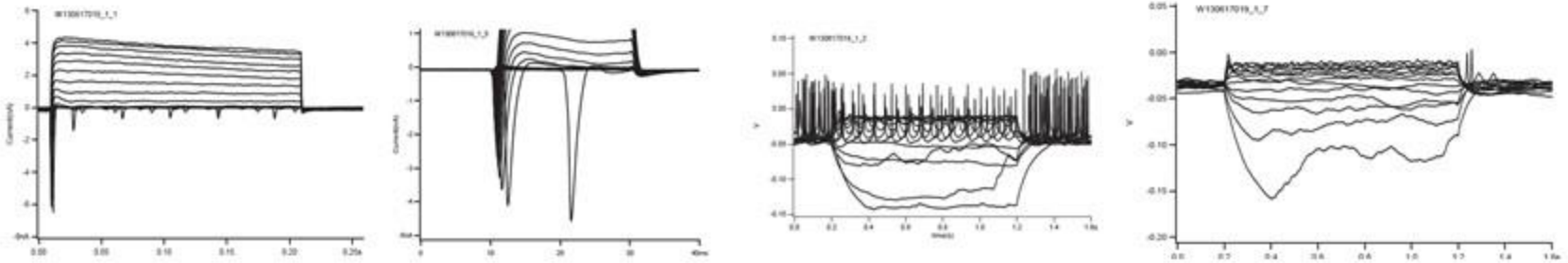
Blooming stem cell research in China

Parkinson Disease, the cell therapy in animal models

DA neurons from Clinical grade hESC







Clinical Rating

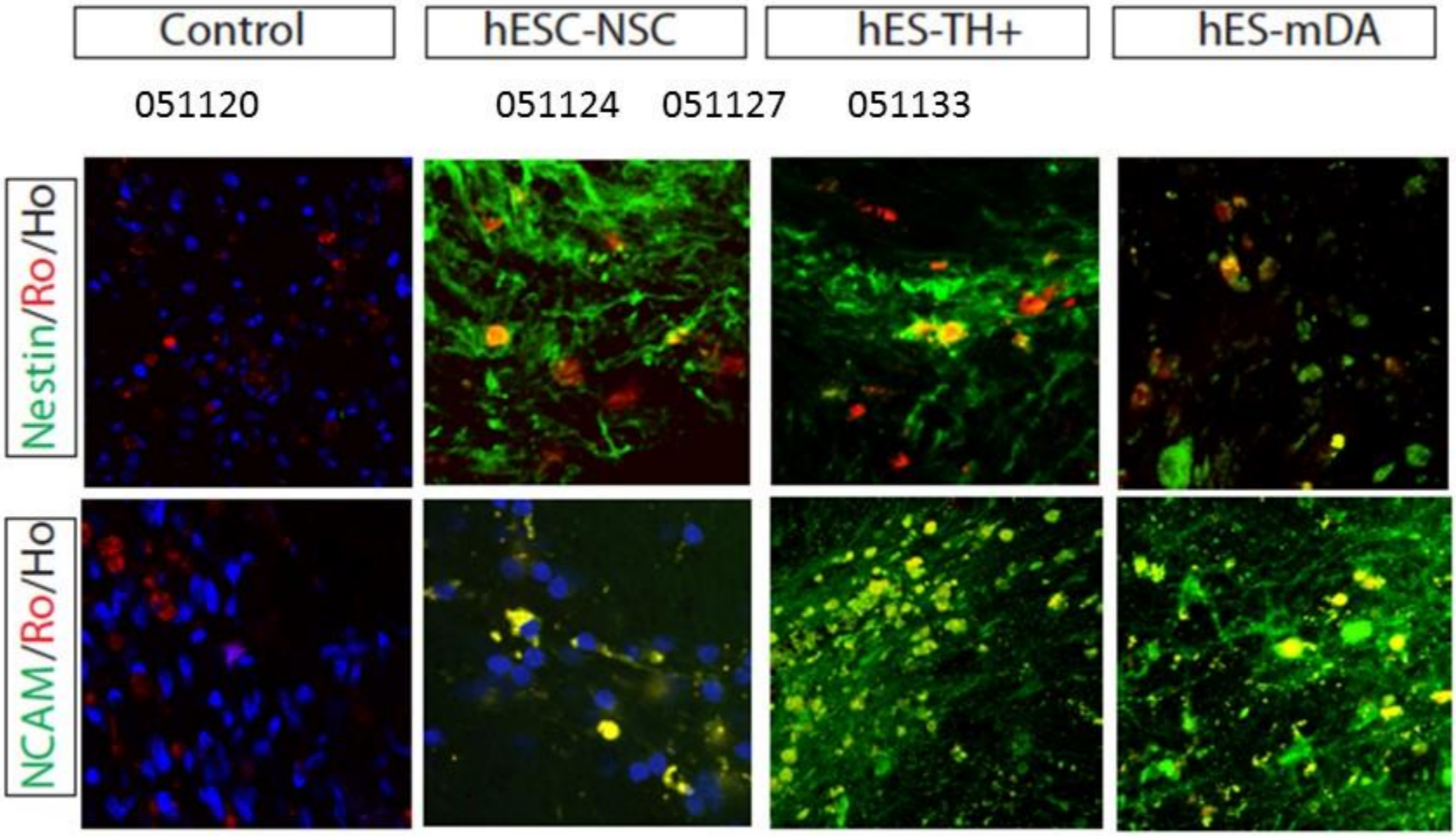
1. Tremor	R	0-3
	L	0-3
2. Posture		0-2
3. Gait		0-5
4. Bradykinesia geneneralized		0-5
5. Balance		0-2
6. Motor Skills upper	R	0-4
	L	0-4
7. Defense Reaction		0-2
8. Freezing		0-2

Left arm

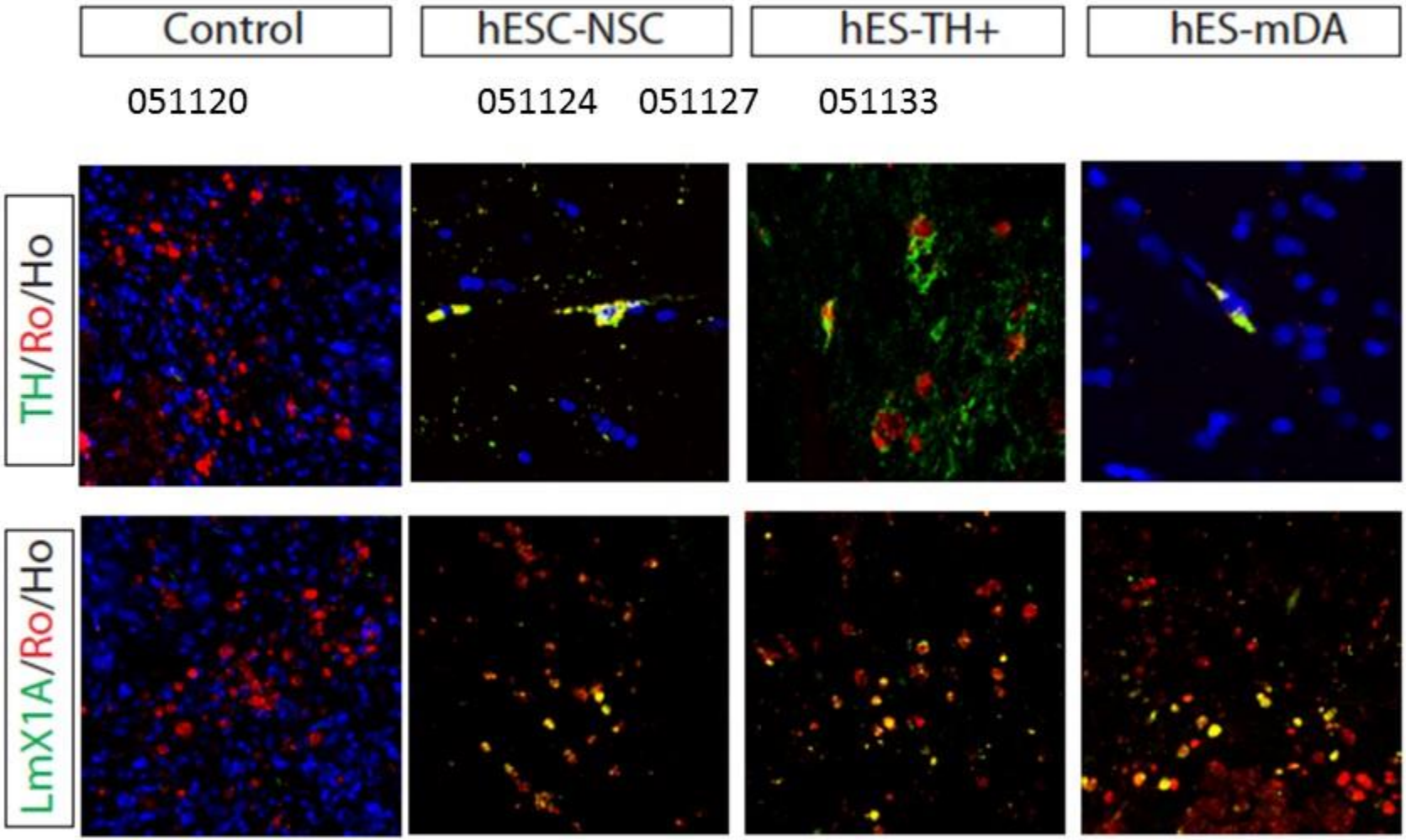
similar to the symptoms of PD patients

PD models and transplantation

Maturation of grafted cells



Integration of grafted DA neurons

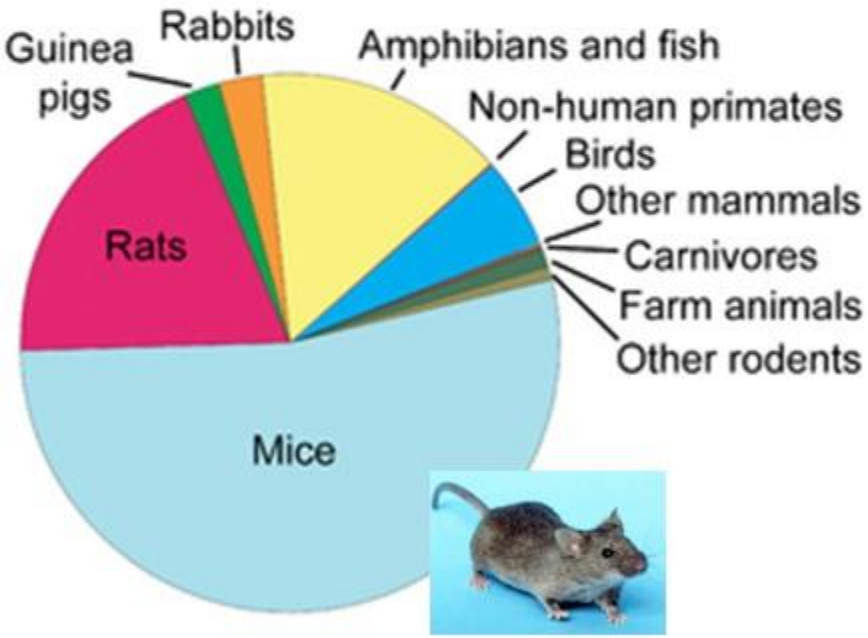


The clinical research: PD cell therapy

Animal Models：the Bottleneck of Regenerative Medicine

Why we need rodents and large animals?

Animal models used in FDA drug developmnet



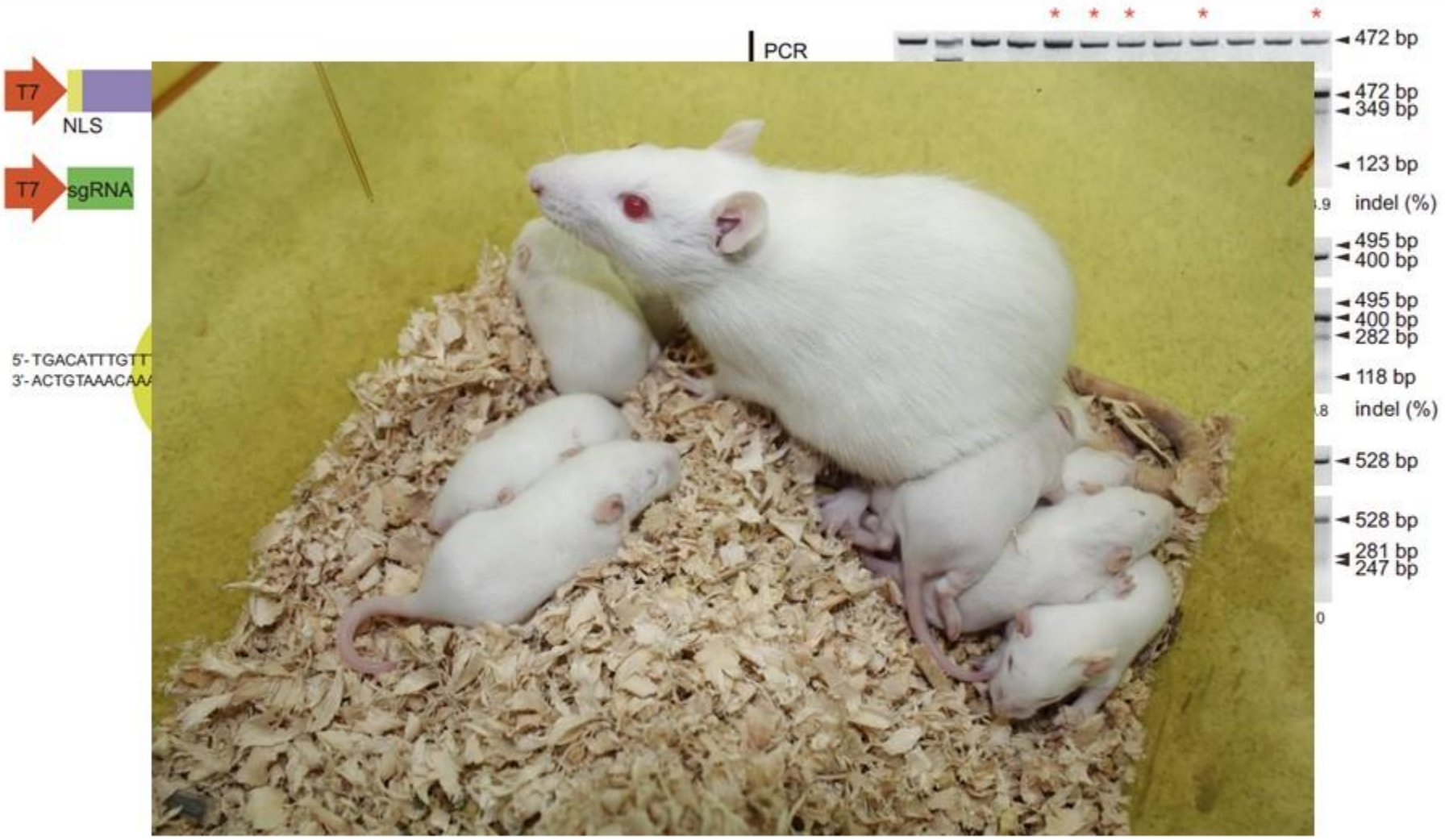
Even after animal studies suggest that a treatment will be safe and effective, more than 80% of potential therapeutics fail when tested in people.

Mouse is good, but is definitely not enough.

Why we need other rodents and large animals?

- Physiology
- Genomics
- Anatomy
- Immune reactions
- ……

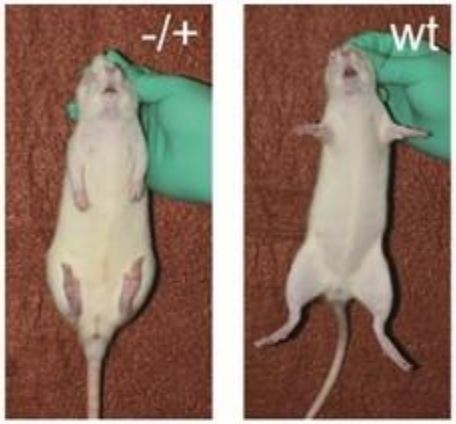
Multiple gene mutations in rat using CRISPR-Cas systems



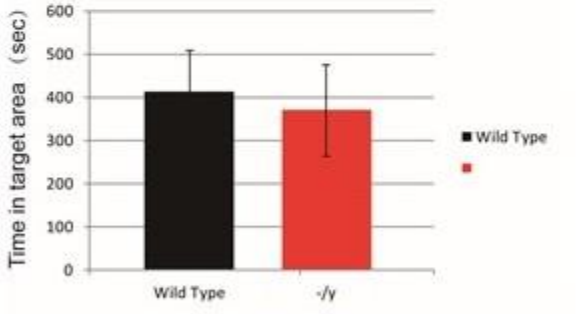
Nature Biotechnology, 2013

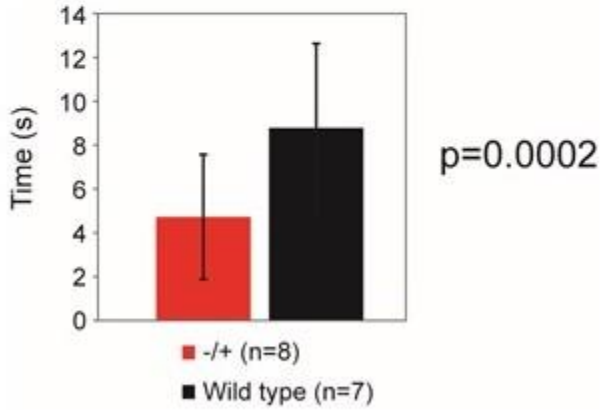
Rett syndrome rat: Mecp2 knockout

Male (8-9 weeks age)



Female (7-8 weeks age)





Compromised motor and learning abilities

unpublished

One-step generation of knockout pigs by zygote injection of CRISPR/Cas system

Cell Research, 2014

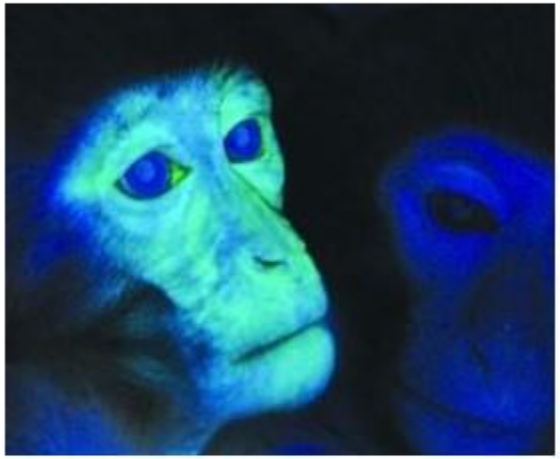
Establishment of experiental min-pig research framework

Establishment of Monkey research framework

Development of transgenic models in non-human primates

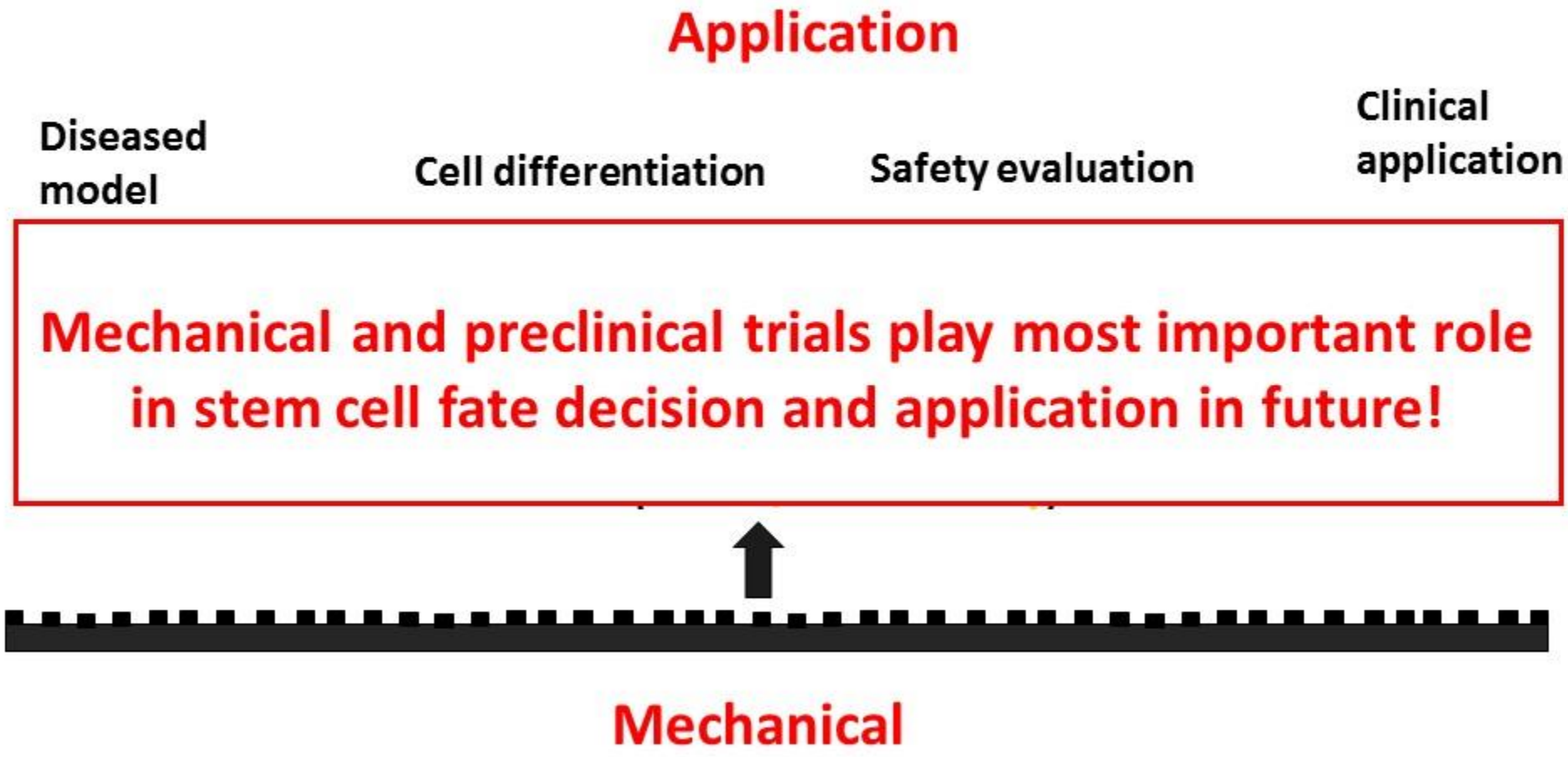
2001, USA

2009, Japan



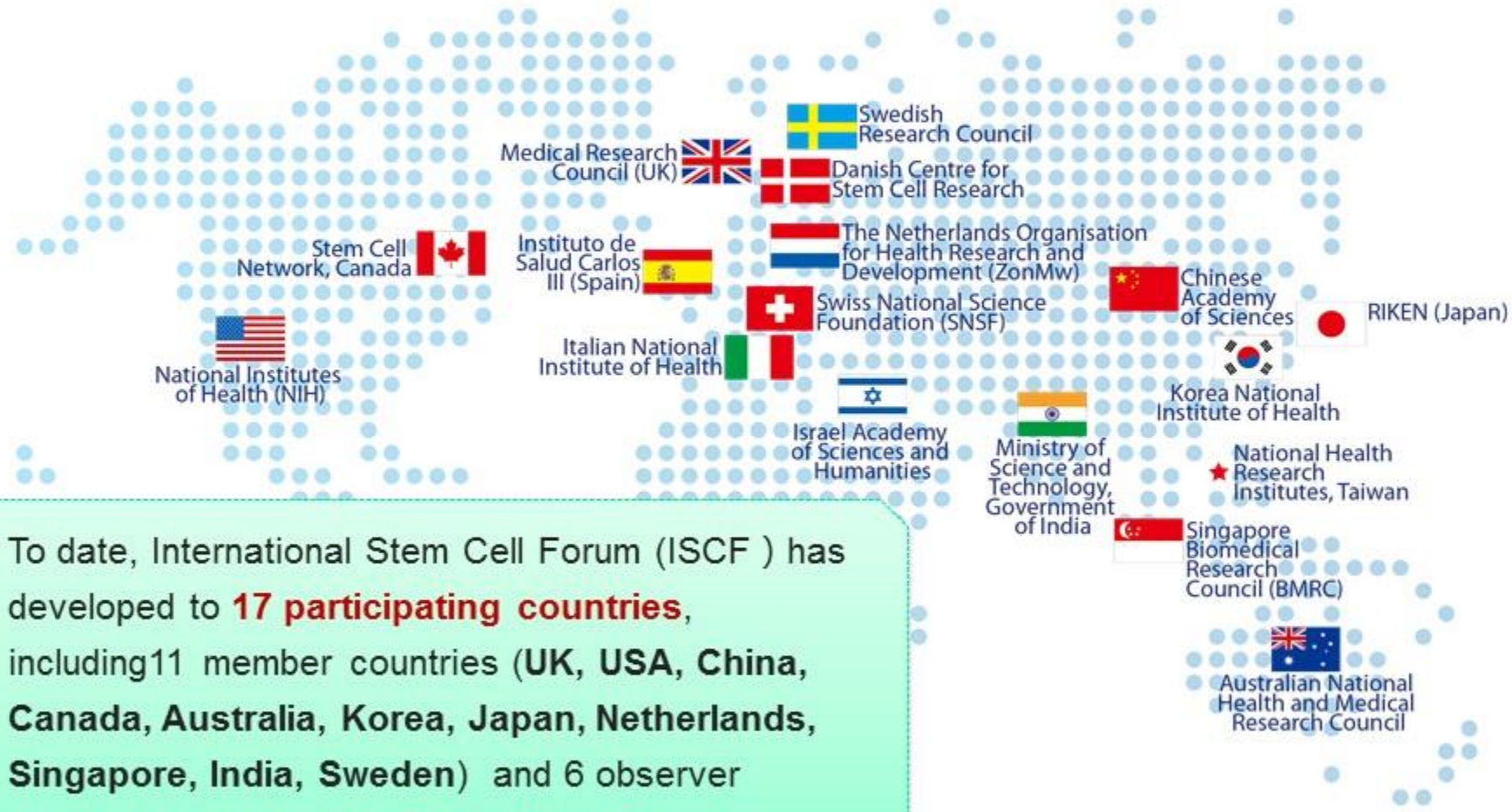
2010, China,

Bedside to Bench



International Stem Cell Forum

INTERNATIONAL STEM CELL FORUM

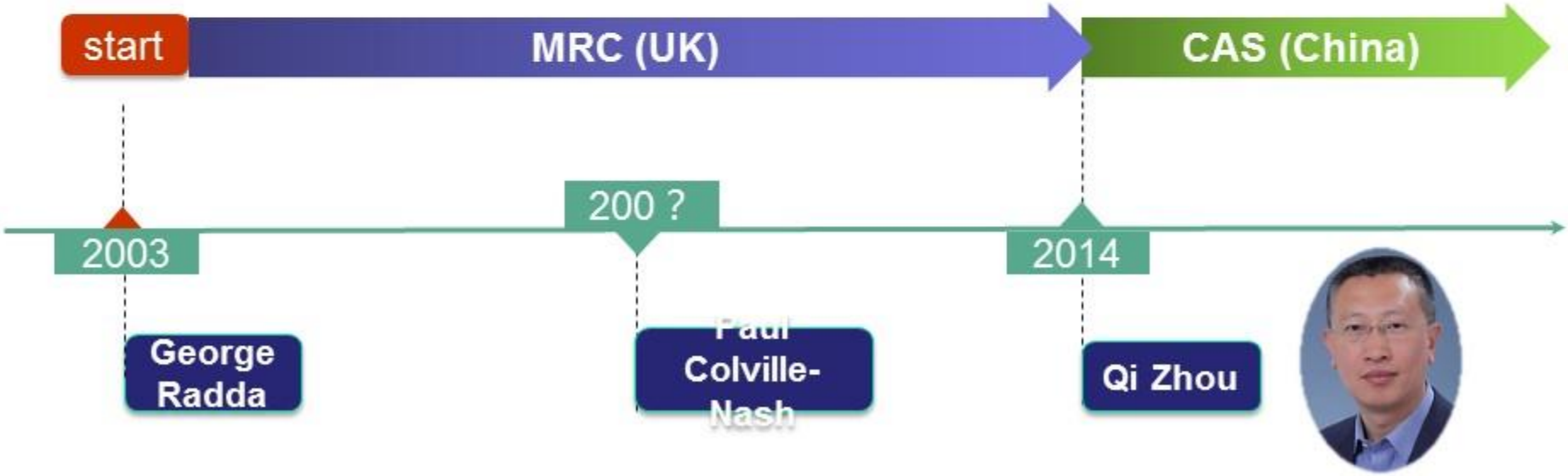


To date, International Stem Cell Forum (ISCF) has developed to **17 participating countries**, including11 member countries (**UK, USA, China, Canada, Australia, Korea, Japan, Netherlands, Singapore, India, Sweden**) and 6 observer countries / regions (**Denmark, Israel, Taiwan, Swiss, Italy, Spain**).

International Stem Cell Forum

INTERNATIONAL STEM CELL FORUM

The International Stem Cell Forum (ISCF) is made up of funders of stem cell research from around the world. It was founded in January **2003** to encourage international collaboration and funding support for stem cell research, with the overall aim of promoting global good practice and accelerating progress in this vitally important area of biomedical science.



China-Korea Joint Research Program

Government sponsored Korea-China Joint Research Project:

Cooperative development of stem cell based therapeutics for Asian population

Acquisition and banking of clinically useful stem cells

- Pluripotent stem cells derived therapeutic cells (C)
- Direct conversion-based therapeutic cells (K)

Quality control and pre-clinical evaluation

- Development of large animal models and long-term evaluation(C)
- Development of small rodent models and evaluation (K)

complementary strength

Production and evaluation of clinical grade stem cells

- Human pluripotent stem cell-derived cells as a model case (C)
- Human cord-blood-derived stem cells as a model case(K)

Development of bi-national collaborative platform

- Exchange scholar/students and training program(C/K)
- Regular joint symposiums on relevant important topics(C/K)

MERCI

THANK YOU