北京干细胞库 | Beijing Stem Cells Bank

Regulatory and Legal Frameworks for Offering Stem Cell Therapies in China

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Institute of Zoology
Chinese Academy of Sciences

Stem Cell Clinical Trials in The World

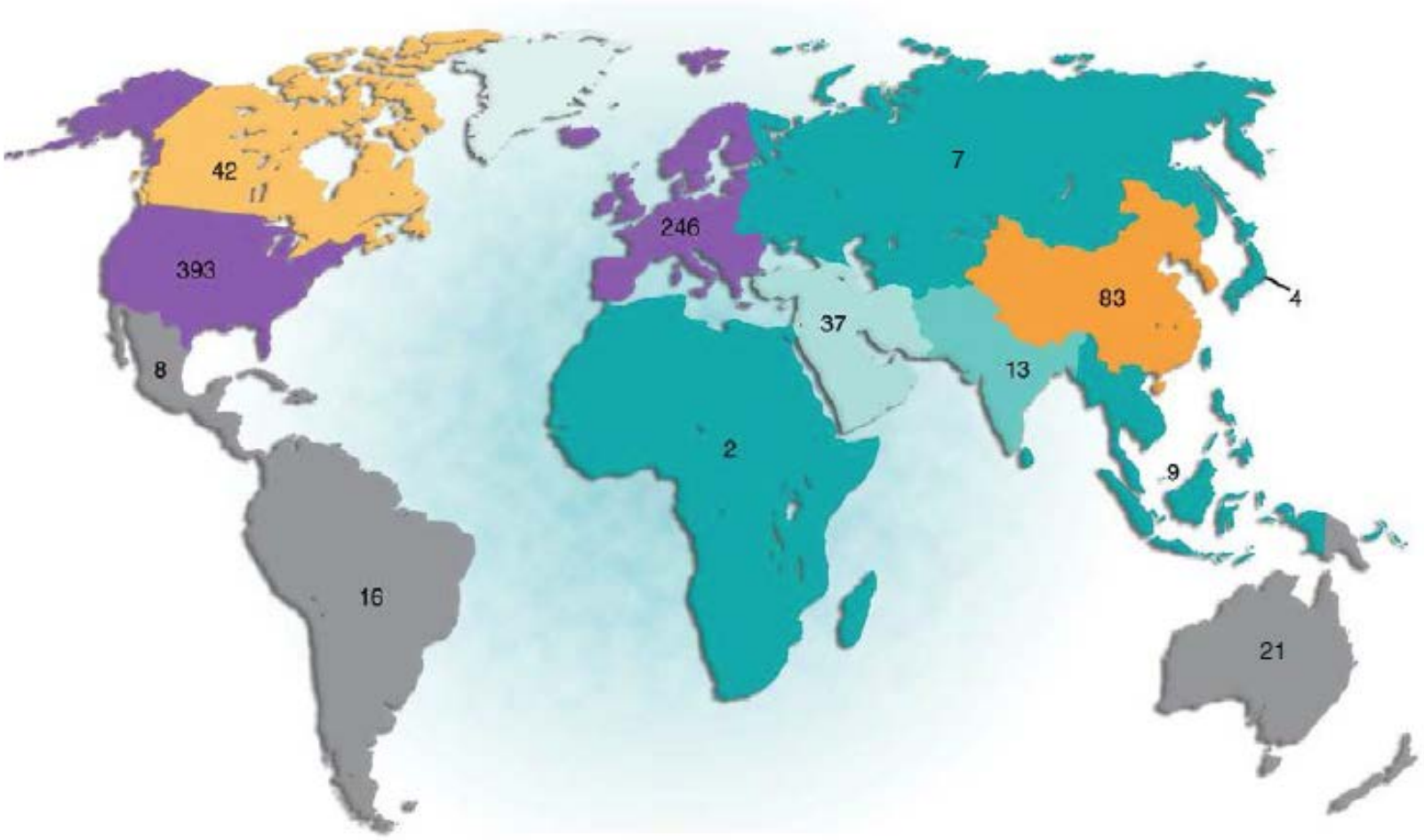

Figure 1. Geographic distribution of clinical trials that have been registered on ClinTrials.gov since January 2000 that are listed as involving stem cells as an interventional part of the therapy. Search criteria exclude gene therapy trials.

Cited from *World Stem Cell Report (2012)*

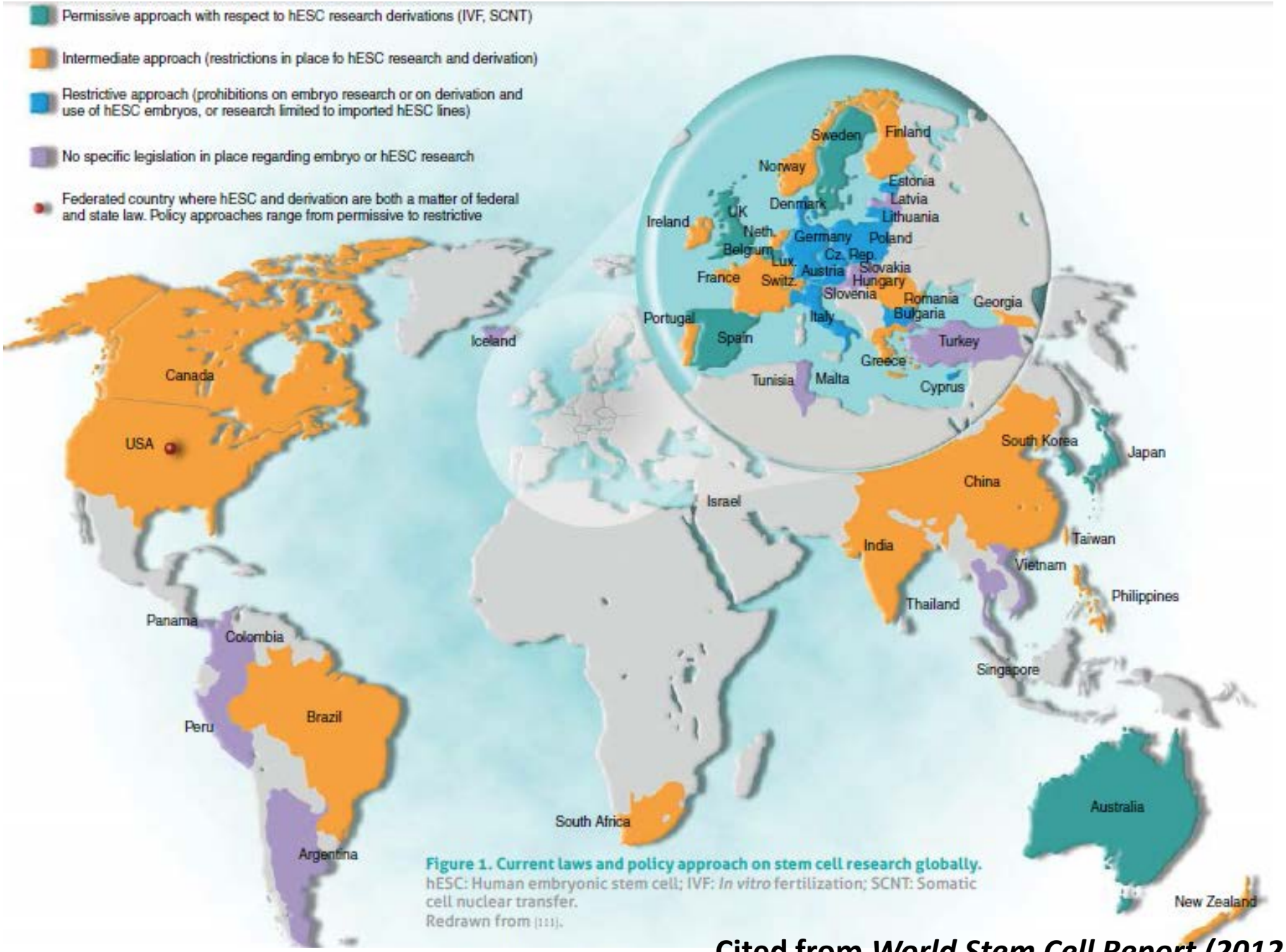

Figure 1. Current laws and policy approach on stem cell research globally.
hESC: Human embryonic stem cell; IVF: *In vitro* fertilization; SCNT: Somatic cell nuclear transfer.
Redrawn from [111].

Cited from *World Stem Cell Report (2012)*


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Holiday shopping: Y
Stem-cell therapy: Cure or hoax in China?
PATRICK WHITE
From Thursday's Globe and Mail
Published Thursday, Aug. 23, 2007 9:11AM EDT
Last updated Friday, Apr. 03, 2009 10:31AM EDT
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A
A
The website for Beike Biotechnology bursts with stories that can only be categorized as medical miracles: a paraplegic can move his legs again; a man with muscular dystrophy can carry a cup of water, a stroke victim can speak.
These tales of ailments treated come from all over the world - England, Hungary, Russia, Canada - and back the healing claims of a controversial Chinese treatment that purports to cure the incurable.
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NEWS

Overview of Stem Cell Researches in China

Development of stem cell research in China: Funding

MOST (Ministry of Science and Technology):
1.2 Billion RMB /5 yr (190 Million USD)

CAS (Chinese Academy of Science):
0.94 Billion RMB /5 yr (160 Million USD)

NSFC (National Science Foundation of China):
0.7 Billion RMB /5yr (110 Million USD)

Development of stem cell research in China: Innovation

CAS "Innovation 2020" Stem Cell Research Project

Chief scientist: Qi ZHOU

Major Objectives: from bench to bedside

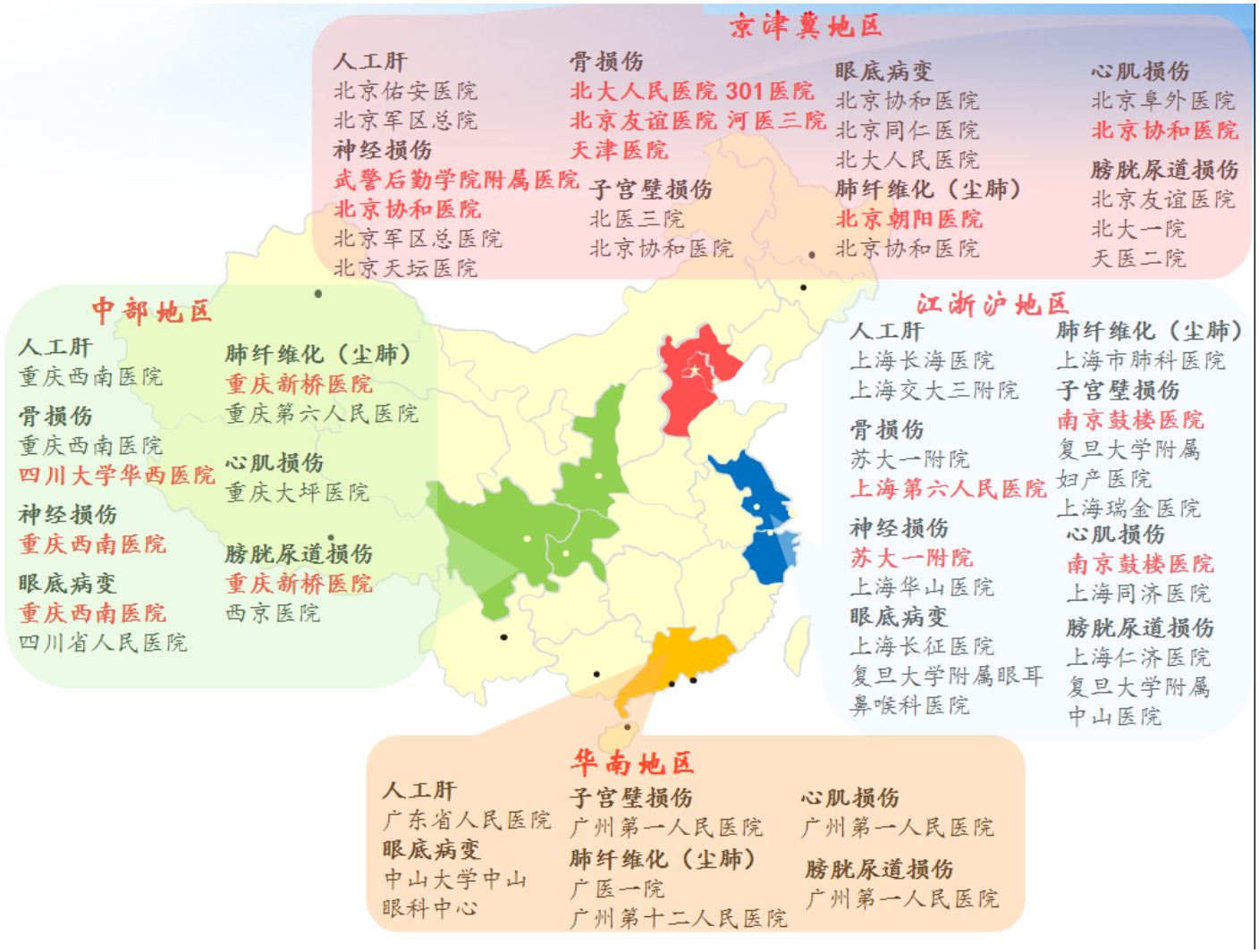
Duration: 2011-2020

Funding: 0.94 Billion RMB (2011-2016)

Participated Institutes: 18+11

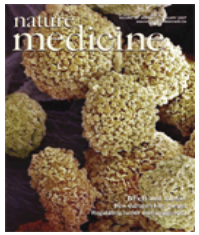
Participated Investigators: 110 PI+2800 staff+ Postdoc

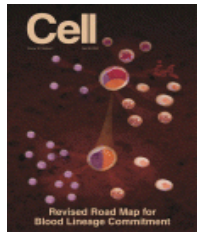
Development of stem cell research in China: Institutions and Clinical Bases

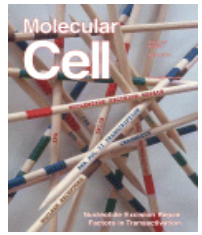


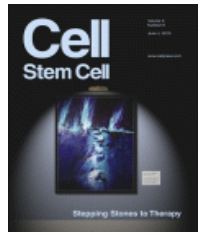
Development of stem cell research in China: Publications

Rank	Country	Paper in 2011	Country	Paper from 2001-2011
1	USA	7076	USA	50542
2	China	1983	Germany	13620
3	Germany	1863	Japan	12096
4	Japan	1453	UK	10348
5	UK	1243	China	8159
6	Italy	1115	Italy	8141
7	France	943	France	6720
8	Korea	806	Canada	5388
9	Canada	743	Korea	4149
10	Spain	634	Holland	4040



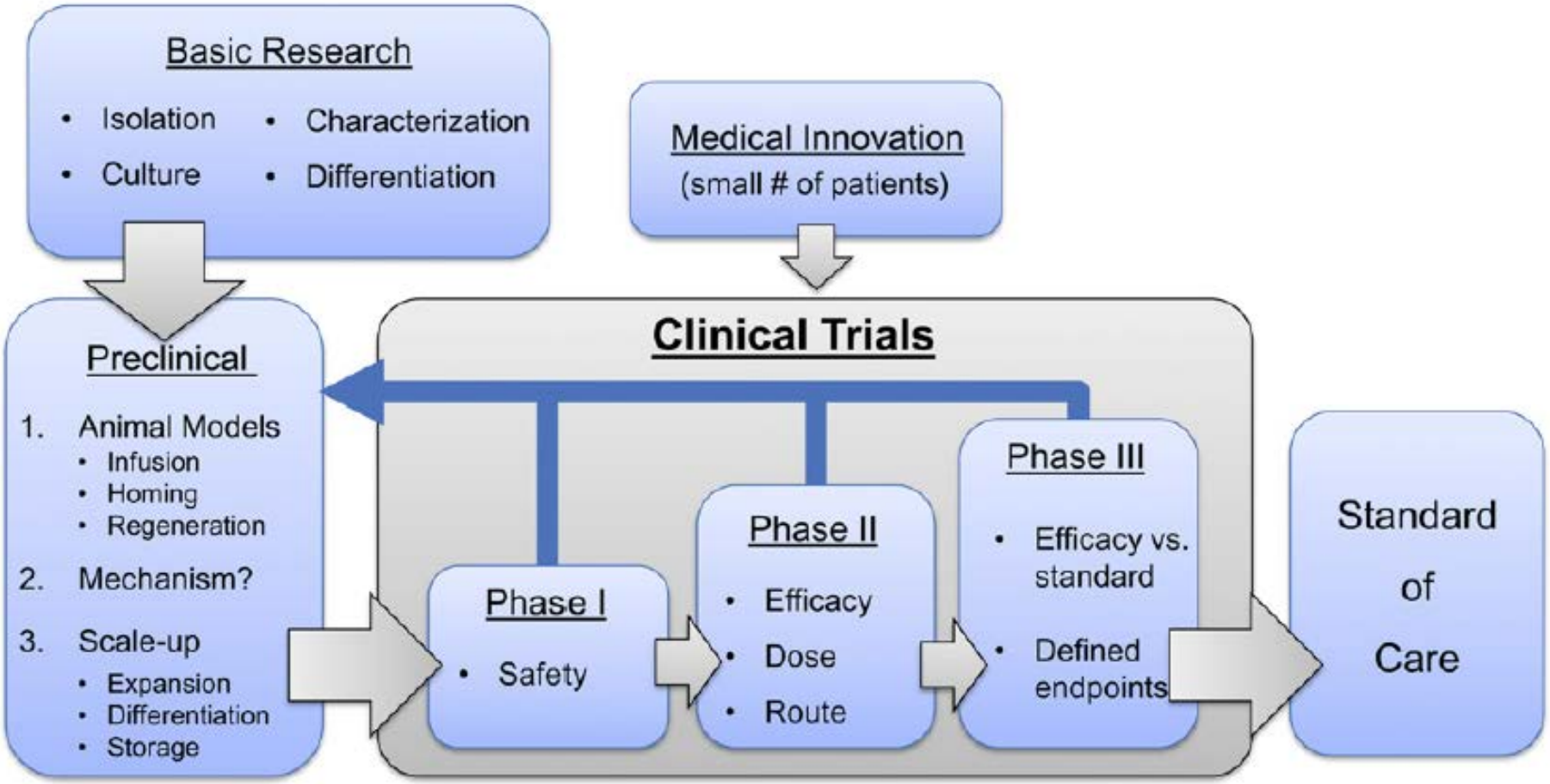






Regulations on Stem Cell Therapy in China

Community standards for stem cell clinical research



Regulations on stem cell therapy

Ethical Guideline & Regulations for Human ES Cell Research in China

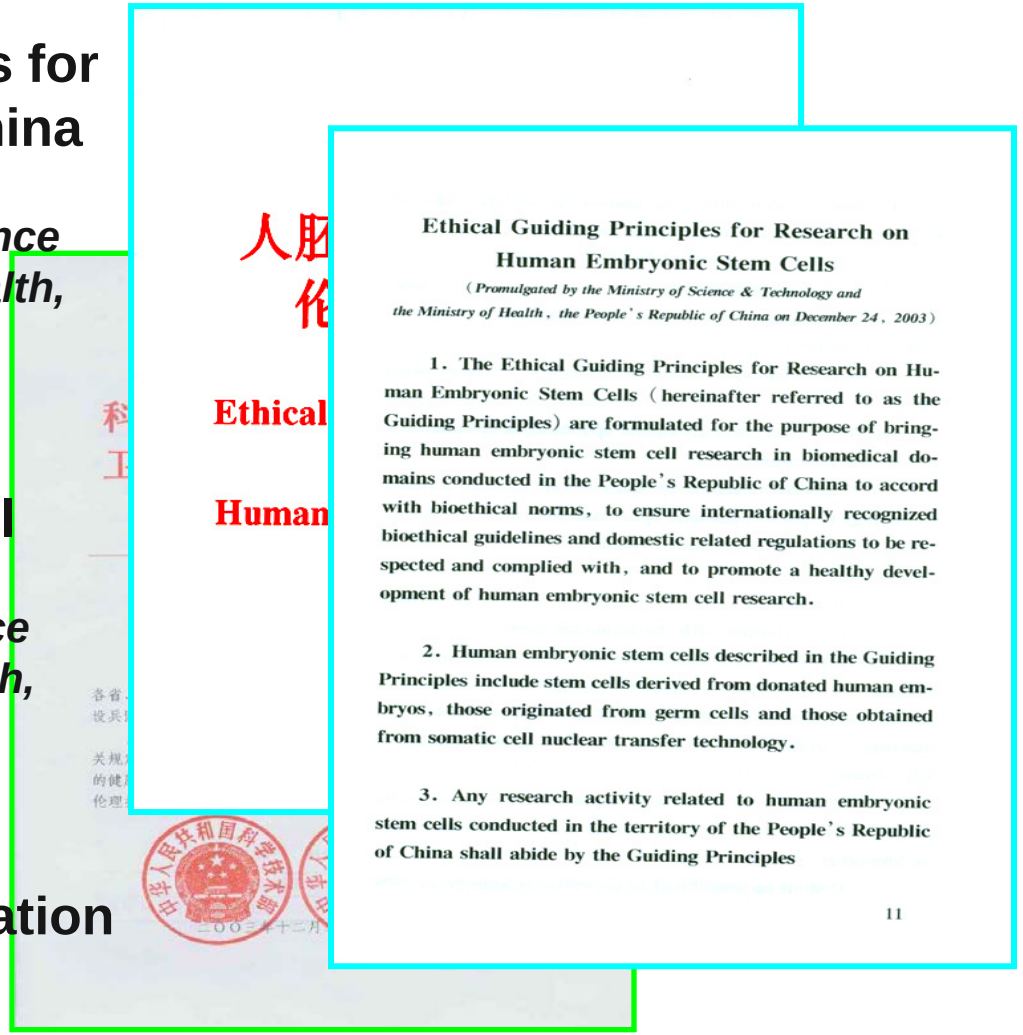
(Promulgated by the Ministry of Science & Technology and the Ministry of Health, Dec 24, 2003)

Regulations for Human ES Cell

(Promulgated by the Ministry of Science & Technology and the Ministry of Health, June, 2009)

Human ES Cell Research regulation in China

(Ministry of Health, Jan,12, 2012)



Ethical Guiding Principles for Research on Human Embryonic Stem Cells

(Promulgated by the Ministry of Science & Technology and the Ministry of Health, the People's Republic of China on December 24, 2003)

1. The Ethical Guiding Principles for Research on Human Embryonic Stem Cells (hereinafter referred to as the Guiding Principles) are formulated for the purpose of bringing human embryonic stem cell research in biomedical domains conducted in the People's Republic of China to accord with bioethical norms, to ensure internationally recognized bioethical guidelines and domestic related regulations to be respected and complied with, and to promote a healthy development of human embryonic stem cell research.

2. Human embryonic stem cells described in the Guiding Principles include stem cells derived from donated human embryos, those originated from germ cells and those obtained from somatic cell nuclear transfer technology.

3. Any research activity related to human embryonic stem cells conducted in the territory of the People's Republic of China shall abide by the Guiding Principles

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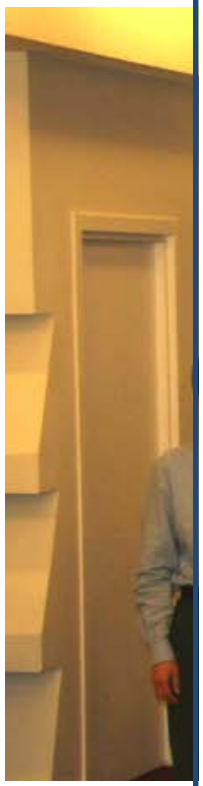
The ISFC Clinical Grade Stem Cell Banking Meeting



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

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.

Formation of National Stem Cell Research Supervision and Coordination Committee

October, 2011

Stem Cell and Regenerative Medicine Industrial Technology Innovation League

August, 2011

Guidelines on Quality Control and Preclinical Research of Stem Cell Preparations (Trial)

干细胞制剂质量控制及临床前研究指导原则

（试行）（征求意见稿）

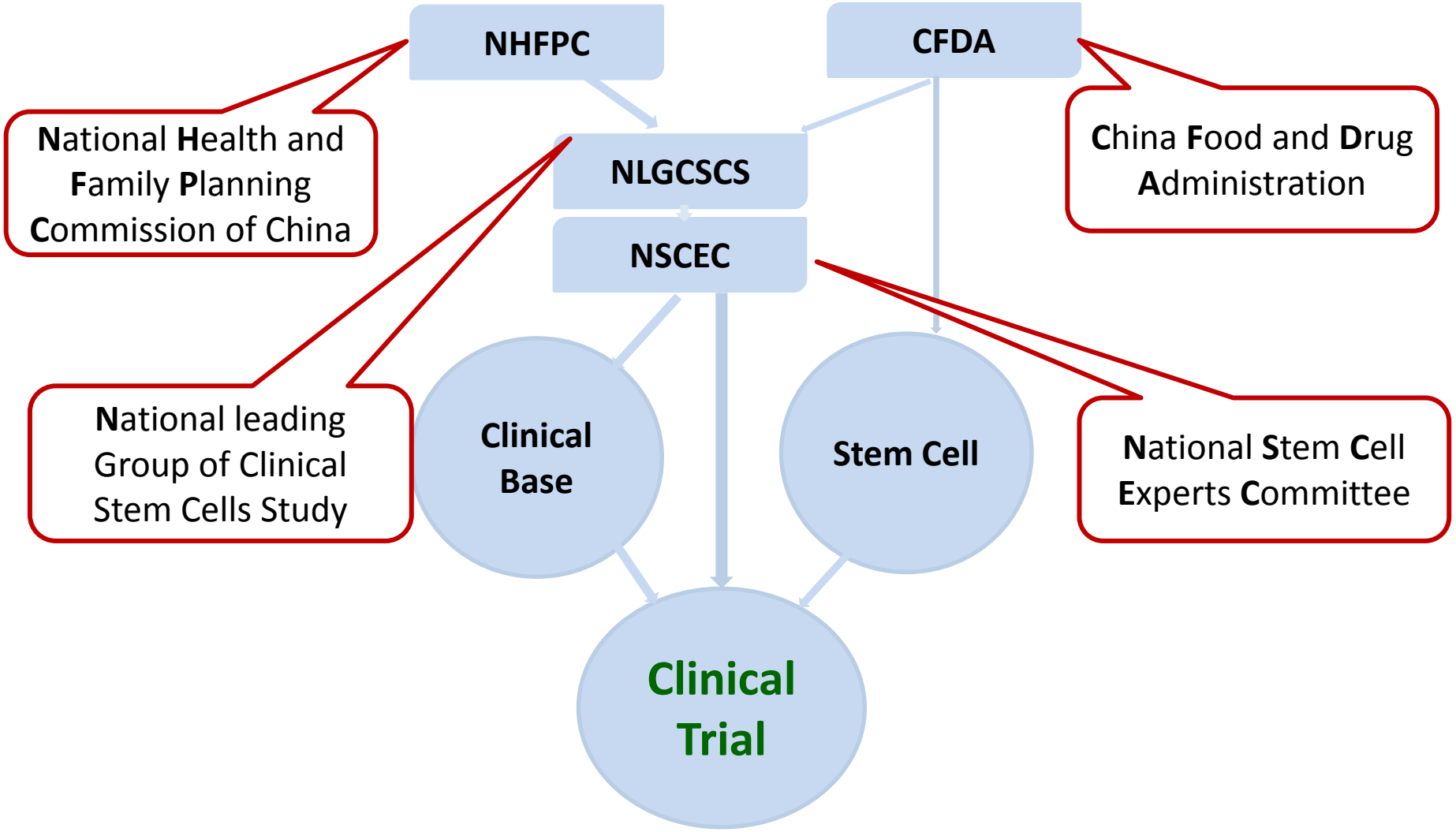
一、前言

干细胞是一类具有不同分化潜能，并在非分化状态下自我更新的细胞。干细胞治疗是指应用人自体或异体来源的干细胞经体外操作后输入（或植入）人体，用于疾病治疗的过程。这种体外操作包括干细胞的分离、纯化、扩增、修饰、干细胞（系）的建立、诱导分化、冻存和冻存后的复苏等过程。用于细胞治疗的干细胞主要包括成体干细胞、胚胎干细胞及诱导的多能性干细胞（iPSC）。成体干细胞包括自体或异体、胎儿或成人不同分化组织，以及发育相伴随的组织（如脐带、羊膜、胎盘等）来源的造血干细胞、间充质干细胞、各种类型的祖细胞或前体细胞等。

目前国内外已开展了多项干细胞（指非造血干细胞）临床应用研究，涉及多种干细胞类型及多种疾病类型。主要疾病类型包括骨关节疾病、肝硬化、移植物宿主排斥反应（GVHD）、脊髓损伤及退行性神经系统疾病和糖尿病等。其中许多干细胞类型，是从骨髓、脂肪组织、脐带血、脐带或胎盘组织来源的间充质干细胞，它们具有一定的多向分化潜能及抗炎和免疫调控能力等。

用于干细胞治疗的细胞制备技术和治疗方案，具有多样性、复杂性和特殊性。但作为一种新型的生物治疗产品，所有干细

Guidelines on Quality Control and Preclinical Research of Stem Cell Preparations (Trial)



Guidelines on Quality Control and Preclinical Research of Stem Cell (Trial)

Guideline Contents

Cell types：

ES/iPS/MSC/HSC/ others Progenitor cells or precursor cells

Manipulation process：

Isolation, Purification, Culture, Amplification, Modification, Differentiation, Cryopreservation and Resuscitation, *In vivo* Implantation

Others：

Resources: Autologous or allogeneic
Function :Treatment or prevention

Guidelines on Quality Control and Preclinical Research of Stem Cell Preparations (Trial)

Security evaluation

- Detection of bacteria and fungi
- Mycoplasma detection (direct culture method, DNA fluorescence staining)
- Detection of endogenous and exogenous viral agents
- Reagent detection

Validity evaluation

- Cell identification tests
- Pluripotency of ES(AS) cells
- Detection of ES(AS) cell-specific markers
- Cell activity assay
- Animal model

附件 2

干细胞临床试验研究基地管理办法（试行）（征求意见稿）

Conditions and Management of Clinical Base Application

第一章 总则

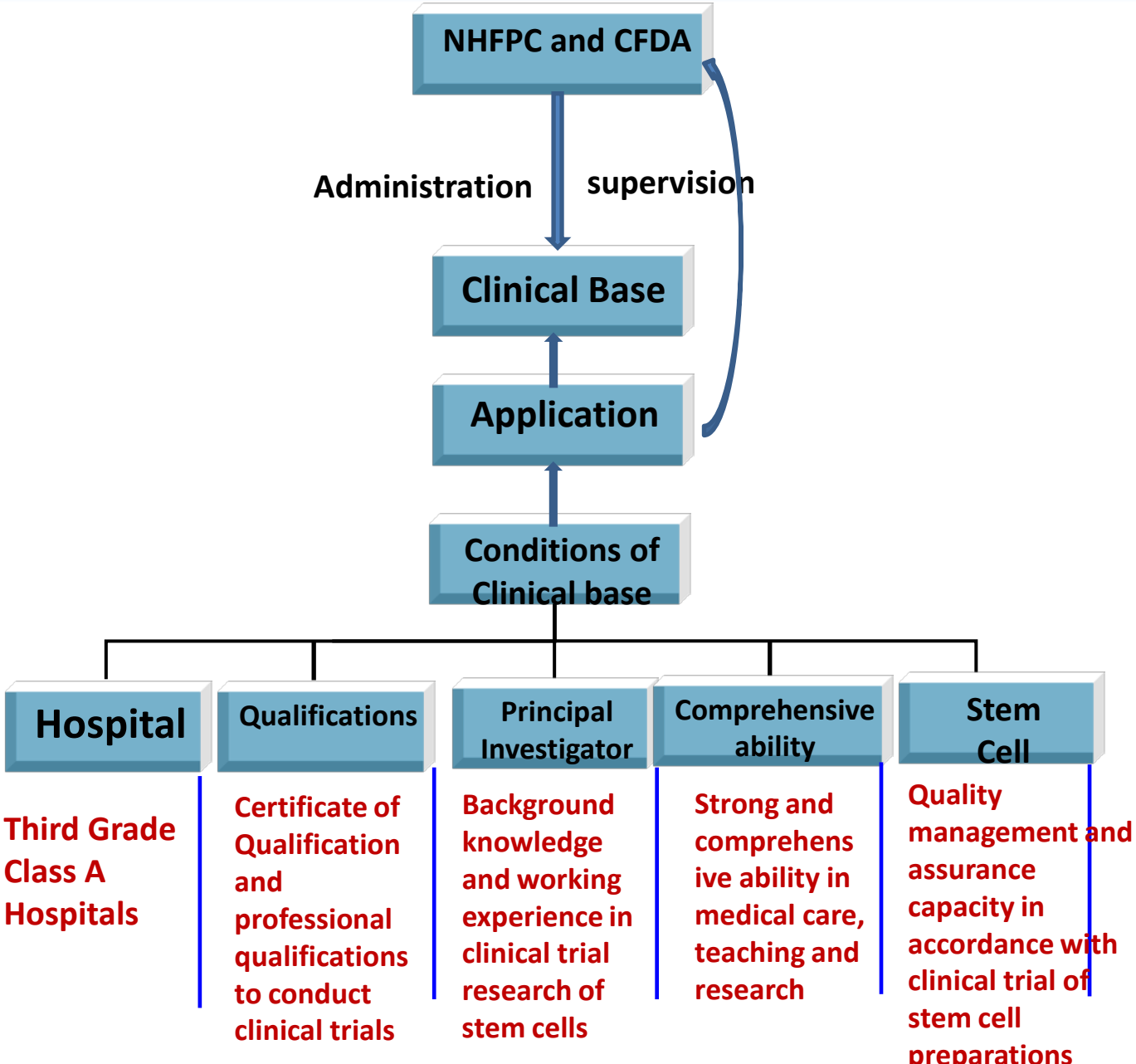
第一条 为加强干细胞临床试验研究的监督管理，根据《药物临床试验质量管理规范》、《药物临床试验机构资格认定办法（试行）》和《干细胞临床试验研究管理办法（试行）》，制定本办法。

第二条 干细胞临床试验研究必须在干细胞临床试验研究基地进行。

第三条 干细胞临床试验研究应当符合《药物临床试验质量管理规范》、《干细胞临床试验研究管理办法（试行）》和《干细胞制剂质量控制及临床前研究指导原则（试行）》的规定。

第四条 卫生部和国家食品药品监督管理局负责干细胞临床试验研究基地的确定工作。各省级卫生厅局、食品药

Conditions and Management of Clinical Base Application



干细胞临床试验研究管理办法（试行）
（征求意见稿）

Management of Stem Cell Clinical Trial Research

第一章　总则

第一条　为规范干细胞临床试验研究，保护受试者权益，根据《中华人民共和国药品管理法》、《中华人民共和国药品管理法实施条例》、《医疗机构管理条例》、《医疗技术临床应用管理办法》等相关法律法规，制定本办法。

第二条　本办法所指干细胞，是一类具有自我更新及不同分化潜能的细胞。干细胞临床试验研究，是指在临床前研究基础上，应用人自体或异体来源的干细胞经体外操作后回输（或植入）人体，用于疾病预防和治疗的临床试验研究。这种体外操作包括干细胞在体外的分离、纯化、培养、扩增、修饰、诱导分化、冻存及复苏等植入人体前的全部过程。用于干细胞治疗的干细胞主要包括成体干细胞、胚胎干细胞以及诱导的多能性干细胞。成体干细胞包括自体或异体不同组织来源的造血干细胞、间充质干细胞、各种类型的祖细胞或前体细胞等。

干细胞临床试验研究基地（以下简称“干细胞基地”）

第三条　干细胞临床试验研究必须具备充分的科学依据，其预防和治疗疾病的预期优于现有的手段，或用于尚无有效干预措施的疾病，优先考虑威胁生命和严重影响生存质量的重大疾病，以及重大医疗卫生需求。

第四条　干细胞临床试验研究应当按照《药物临床试验质量管理规范》要求，干细胞临床试验研究应当遵守以下原则：

（一）符合临床试验研究伦理原则，保护受试者、捐献者生命健康权益；

（二）符合技术安全性、有效性原则，即风险最小化；

（三）符合干细胞制剂质量要求的原则；

（四）认真履行有效知情同意的原则；

（五）有益于促进公众健康的原则；

（六）干细胞临床试验研究透明化原则；

（七）保护个人隐私的原则。

第五条　干细胞临床试验研究管理施行干细胞基地资格认定、项目备案监管的制度。

第六条　国家卫生和计划生育委员会与国家食品药品监督管理总局共同成立国家干细胞临床研究和应用规范整顿工作领导小组（以下简称“国家干细胞临床研究领导小

Management of Stem Cell Clinical Trial Research

- General Principles
- Qualification of clinical base
- Clinical trials approvals and records
- Clinical trials
- Rights and interests of donors and receivers
- Supervision and management
- Supplementary articles

《干细胞临床试验研究管理办法（试行）》实施细则（征求意见稿）

Management of Stem Cell Clinical Trial Research The detailed rules

总则

第一条 为做好干细胞临床试验研究管理工作，根据《干细胞临床试验研究管理办法（试行）》，制定本实施细则。

第二条 干细胞临床试验研究管理工作主要包括干细胞临床试验研究基地（以下简称“干细胞基地”）的资格认定、检查、评估，以及研究项目的立项、备案和评估、监管等。

第二章 干细胞基地资格认定

第一节 申请

第三条 申请干细胞临床试验研究基地资格的医疗机构（以下简称“申请机构”），按照国家干细胞临床研究领导小组办公室发布的干细胞基地申报指南要求，向所在地的省级干细胞临床研究领导小组办公室递交申请。

第四条 申请机构应当根据《干细胞临床试验研究管理办法》，主要准备以下申报材料：

（四）承担干细胞临床试验的组织管理机构图、责任人；

（五）承担干细胞临床试验的研究人员名单和简历；

（六）申请机构学术委员会和伦理委员会的人员组成及其工作制度和标准操作规范；

（七）干细胞临床试验研究的管理制度和标准操作规程；

（八）防范和处理干细胞临床试验风险的管理机制和措施；

（九）干细胞制剂的质量评价标准和相应的设备设施。

（十）承担的国家级干细胞或细胞相关研究课题任务书复印件。

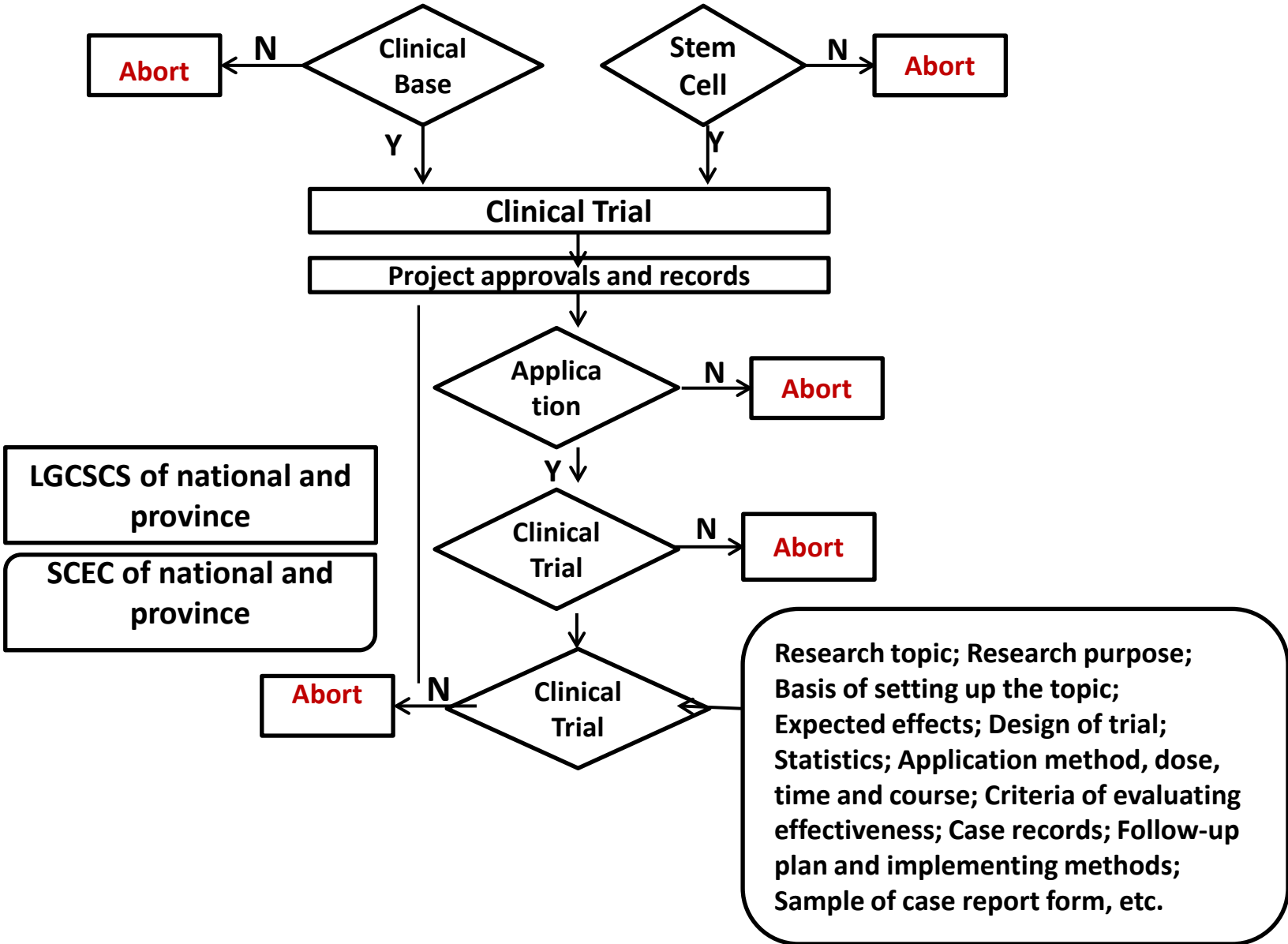
（十一）其他相关资料。

第二节 初审

第五条 申报材料由所在地的省级干细胞临床研究领导小组办公室进行初审。初审内容包括：

（一）医疗机构执业许可、医疗机构概况、申请资格认定的专业科室的卫生技术人员及其他相关技术能力与设施情况、承担的国家级干细胞或细胞相关研究情况、伦理委员会的资质和标准操作规范（SOP）建设情况等。

Procedure of Clinical Trial Research



Chinese government is banning illegal stem cell therapies

Case 1: CFDA notification on the illegal stem cell therapy conducted by a hospital in Jilin province

CFDA 国家食品药品监督管理总局
China Food and Drug Administration

关于吉林硅谷医院和吉林高新技术医院违法违规开展干细胞相关活动的通报

卫办医政发[2012]111号

Chinese government is banning illegal stem cell therapies

Case 2: News report on the illegal stem cell therapy conducted by a hospital in Shandong province

济南协和肝病医院DC疗法原是干细胞治疗 属违禁项目

大众网 2013-04-05 12:30:36

日前，有关济南某医院违规开展干细胞移植治疗致患者死亡的消息引起业界和主管部门的普遍关注。日前，记者接投诉称，济南协和肝病医院对外宣传的“新免疫靶向疗法”实际上就是自体干细胞移植术，属于卫生部明文规定禁止临床开展的限制性手术，存在巨大风险。

大众网济南4月3日讯 日前，有关济南某医院违规开展干细胞移植治疗致患者死亡的消息引起业界和主管部门的普遍关注。日前，记者接投诉称，济南协和肝病医院对外宣传的“新免疫靶向疗法”实际上就是自体干细胞移植术，属于卫生部明文规定禁止临床开展的限制性手术，存在巨大风险。

记者从济南协和肝病医院的官方宣传材料上看到，新免疫靶向疗法的作用机理是提取患者自身单个核细胞，然后诱导分化出DC细胞，并输入患者体内，DC就可将乙肝病毒的抗原信息传递给T淋巴细胞，从而发生免疫应答，并对病毒进行靶向性、主动式共计，最终清除病毒，实现乙肝转阴。

山东省某公立肝病医院的一张姓主任医师告诉记者，社会上一些肝病医院宣传的所谓的新型疗法，基本上都是自体干细胞移植术。目前这一治疗方法还处在临床研究状态，还没有临床应用。他表示：“目前，市场上自体干细胞移植术的开展非常混乱，这一疗法到底能达到怎样的效果还没有定性，但是一些医院就承诺治愈，这是对患者非常不负责任的引导。”

记者从山东省卫生厅了解到，目前，我国对于干细胞的临床应用已经有规范性文件，并列入第三类医疗技术管理的有脐带血造血干细胞治疗技术和造血干细胞（脐带血干细胞除外）治疗技术。其他类型的干细胞治疗目前国家暂无相应的技术规范，也不能开展正式的临床治疗。截至目前，山东省卫生厅尚未审批任何医疗机构开展其他类型的干细胞移植临床治疗。

Chinese government is banning illegal stem cell therapies

Report about the punishment on the hospital in case 2.

济南中医肝病医院：无资质进行干细胞移植被查处

来源：齐鲁网　　2012-04-20 09:23

我来说说(0)　复制链接

关键词：济南中医肝病医院　干细胞移植　无资质

[提要] ”在明知道自己医院没有干细胞移植手术资质的情况下，却硬是给我做了手术，这家医院的责任心、良心何在？”张先生气愤地告诉记者。...

Chinese government is banning illegal stem cell therapies

Case 3: News report about the punishment on the illegal stem cell therapy conducted by a clinic in Shanghai

上海一家门诊部给2名韩国人注射干细胞制剂被查处

2013年07月04日 10:01

来源：东方早报 作者：陈斯斯 李燕

0人参与 0条评论 分享到： 更多

原标题：韩国旅行团来沪注射干细胞

Our efforts on promoting stem cell therapy

Research Interests

- **Cell reprogramming and differentiation**
- **Mechanisms of pluripotency acquirement and maintenance**
- **Regenerative medicine**

Set Up Beijing Stem Cell Bank

Establishment of Embryonic Stem Cell Bank

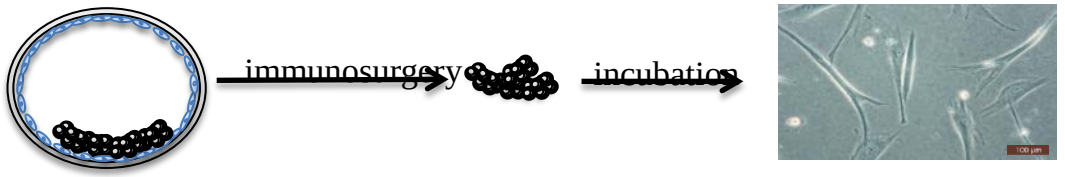
Cell types			No. of Strains
Human embryonic stem cell	Derived from fertilized embryos	Commonly used	2
		Self established	4
		Collected	9
	Parthenogenic cell line		3
	Pathogenic cell line		1
	Human iPS cell line		57
	Human disease derived iPS cell line		23
Rhesus monkey stem cell line			1
Macaca fascicularis stem cell	Embryonic stem cell		3
	iPS cell line		1
Rabit embryonic stem cell			1
Rat stem cell	Embryonic stem cell		10
	iPS cell line		10
	Haploid ES line		13
Mouse stem cell	Embryonic stem cell		21
	Nuclear transferred stem cell		26
	iPS cell line		251
	Haploid ES line		19

Clinical grade embryonic stem cells

Cell Type		No. of cell lines
Human embryonic stem cell	Embryonic stem cell	3
	Parthenogenic stem cell line	1
Human adult stem cell	Umbilical cord hemopoietic stem cell	5
	Adipose-derived stem cell	4
	Umbilical cord-derived mesenchymal stem cell	6
	Mesenchymal stem cells	1
Human differentiated cell	Human foreskin fibroblast	5

Generation of clinical grade pluripotent stem cells from blastocysts

A



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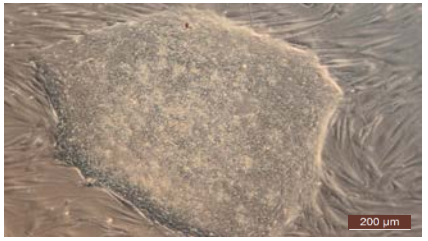

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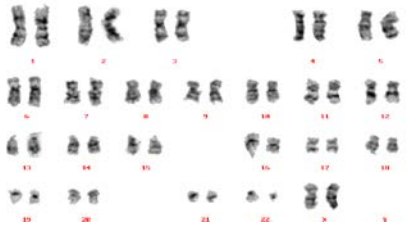

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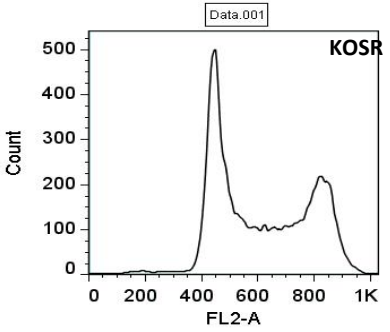

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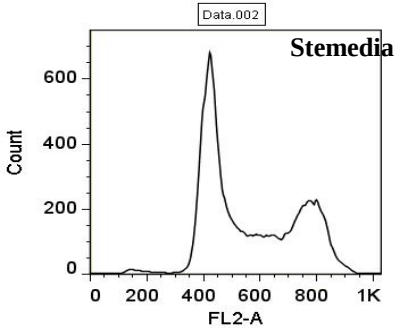
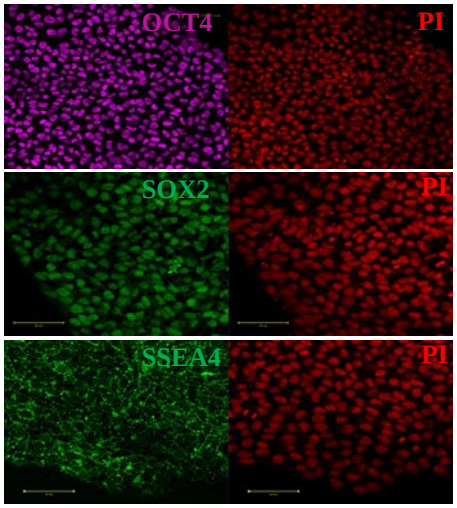


Characterization of xeno-free hESCs



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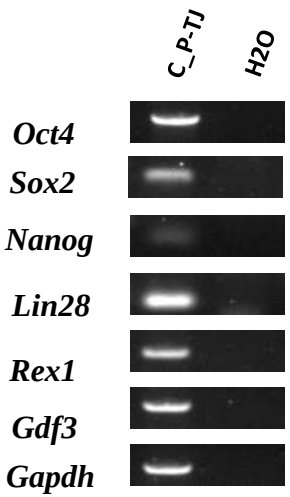

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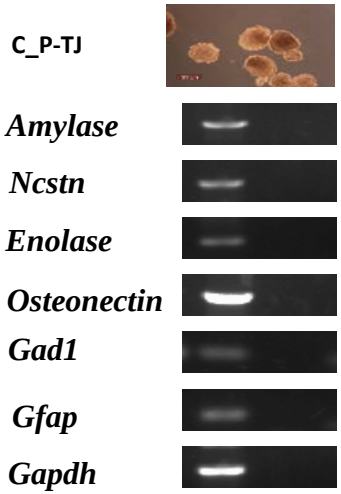

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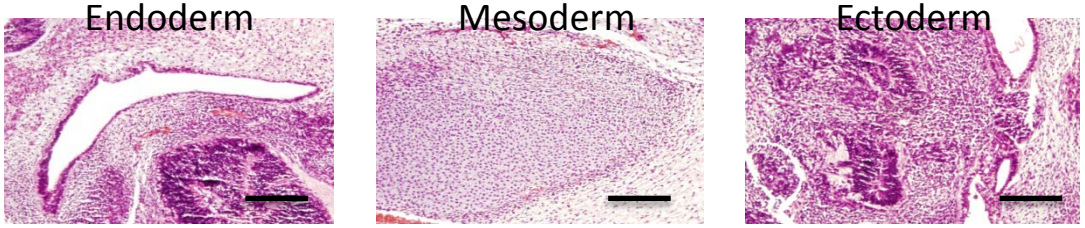

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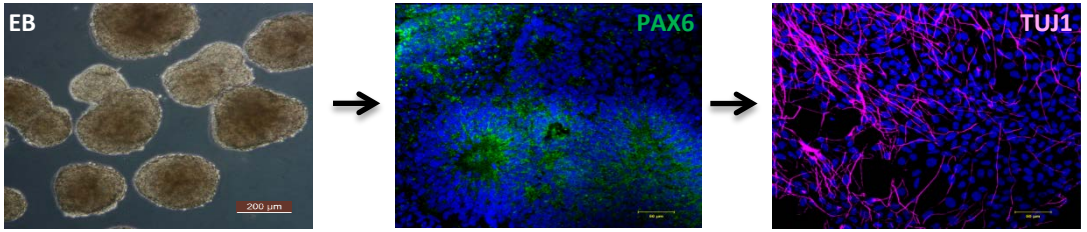


Sterility and pathogen testing

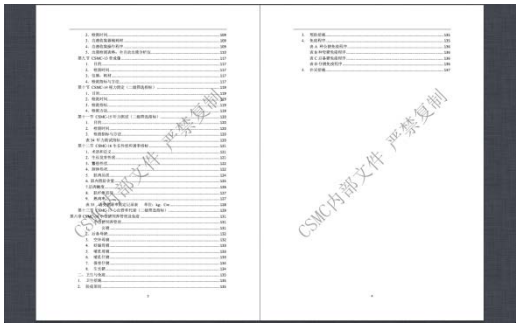
Virus Types	Virus Names	Report
	Gram staining	**-**
	Endotoxin	**-***
	Mycoplasma	**-**
	bovine virus	**-**
	porcine virus	**-**
	Human T-lymphotropic Virus I	**-**
	Human Immuno Deficiency Virus I	**-**
	Human Immuno Deficiency Virus II	**-**
	Human Hepatitus A Virus	**-**
	Human Hepatitus B Virus	**-**
	Human Hepatitis C virus	**-**
	Human polyomavirus (JCV)	**-**
	Human cytomegalovirus (HCMV)	**-**
	TEM	**-**

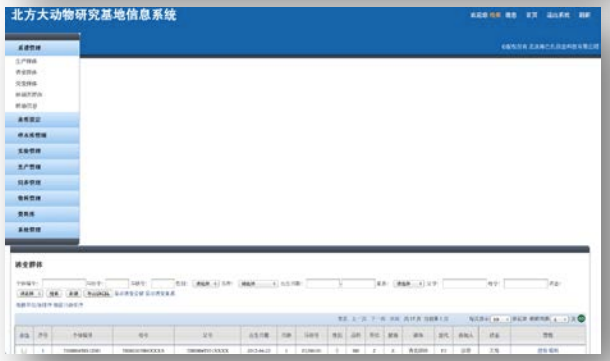
* Endotoxin was tested negative <0.5EU/L

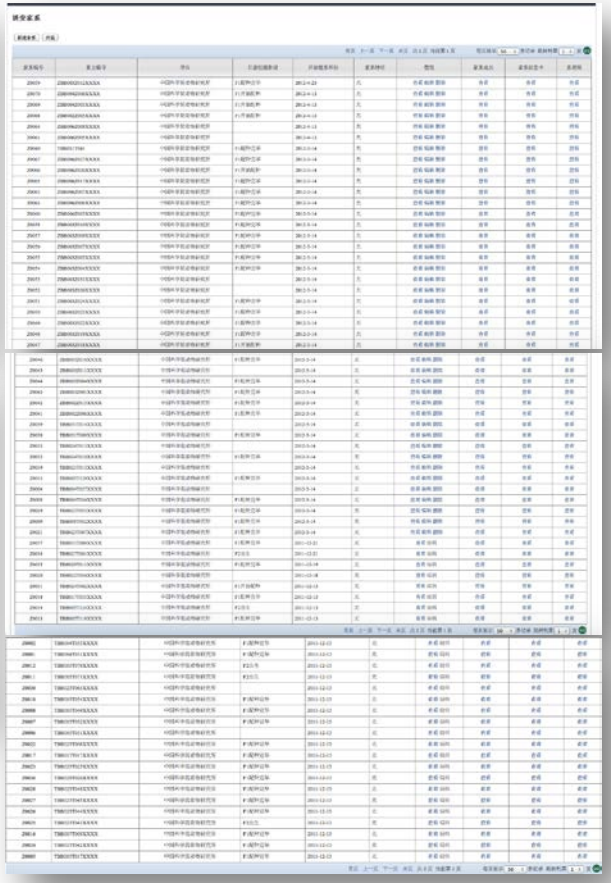
Establishment of clinical grade hES standard with CFDA

List of analysis	Embryonic stem (ES) cells		
		P40	P30
1. Cell identification tests			
1.1 Cell morphology	★		
1.2 Short Tandem Repeats (STRs)	★	★	
1.3 Isoenzyme analysis	★		
1.4 Cell markers (flow cytometry) positive: Oct4, SSEA-3, SSEA-4, TRA-1-60, TRA-1-81; negative: SSEA-1	★		
1.5 Species determination and detection of trophoblasts contamination	★		
1.6 Karyotyping (G-banding counting)	★		
2. Detection of bacteria and fungi	★		
3. Mycoplasma detection (direct culture method, DNA fluorescence staining)	★		
4. Detection of endogenous and exogenous viral agents			
4.1 Direct observation of cell culture	★		
4.2 In vitro culture of various passages of cells and hemadsorption test/hemagglutination test	★		
4.3 Animal innoculation	★		
4.3.1 Intracerebral and intraperitoneal injections in sukling mouse	★		
4.3.2 Intracerebral and intraperitoneal injections in mouse	★		
4.3.3 Intraperitoneal injection in guinea pig	★		
4.3.4 Intracutaneous and subcutaneous injections in rabbit	★		
4.4 Chicken embryo innoculation	★		
4.5 Detection of special human virus	★		
4.5.1 HIV (PCR)	★		
4.5.2 HBV (PCR)	★		
4.5.3 HCV (PCR)	★		
4.5.4 HCMV (PCR)	★		
4.5.5 EBV (PCR)	★		
4.5.6 Human parvovirus B19 (quantitative PCR, qPCR)	★		
4.5.7 Human herpesvirus 6 (qPCR)	★		
4.5.8 Human herpesvirus 7 (qPCR)	★		
4.5.9 Human papillomavirus (molecular hybridization)	★		
4.6 Detection of bovine virus contamination (three types of cell passages and immunofluorescence)	★		
4.7 Porcine virus detection (qPCR)	★		
4.8 Reverse transcriptase activity assay	★		
5. Detection of ES cell-specific markers			
5.1 Alkaline Phosphatase Staining	★	★	
5.2 Immunofluorescence detection of pluripotent gene expression: Sox2, Nanog	★	★	
5.3 PCR assay of pluripotent gene expression: Oct4, Sox2, Nanog, Rex1, Klf4	★	★	★
6. Pluripotency of ES cells			
6.1 Embryoid Body Differentiation			
6.1.1 Morphology of embryoid body		★	
6.1.2 Hematoxylin and eosin staining of embryoid body		★	
6.1.3 PCR analysis of expression of three germ layers differentiation genes (Gad1, Pax6, Enolase, Ostenectin, Ncstn, Afp) in embryoid body		★	
6.2 Teratoma Formation			
6.2.1 Morphology of teratoma		★	
6.2.2 Hematoxylin and eosin staining of the three germ layers cells in teratoma		★	
6.3 Ectoderm neural differentiation (Neural stem cells)			
6.3.1 Immunofluorescence of neural differentiation markers (PAX6、NESTIN)		★	★
6.3.2 PCR of neural differentiation specific genes (Pax6, Nestin, Otx2)		★	★
6.3.3 Cell telomerase detection after neural differentiation		★	★
6.4 Mesoderm cardiac Differentiation (cardiac muscle)			
6.4.1 Immunofluorescence of cardiac muscle differentiation markers (MESP1、ISL1)		★	
6.4.2 PCR of cardiac muscle differentiation specific genes (Mesp1, Isl1, Nkx2-5)		★	
6.4.3 Cell telomerase detection cardiac muscle differentiation		★	
6.5 Endoderm differentiation (liver)			
6.5.1 Immunofluorescence of liver differentiation markers (SOX17, HNF4A)		★	
6.5.2 PCR of liver differentiation specific genes (Sox17, Hnf4a, Afp)		★	
6.5.3 Cell telomerase detection after liver differentiation		★	
7. Cell activity assay			
7.1 Cell counting and cell viability		★	
7.2 Cell population doubling level and growth curve		★	
7.3 Cell cycle analysis		★	
7.4 Telomerase activity		★	★
8. Reagent detection			
8.1 Endotoxin detection	★	★	
8.2 Detection of bovine serum albumin residuals	★	★	

Establishment of pre-clinical and clinical trial management software





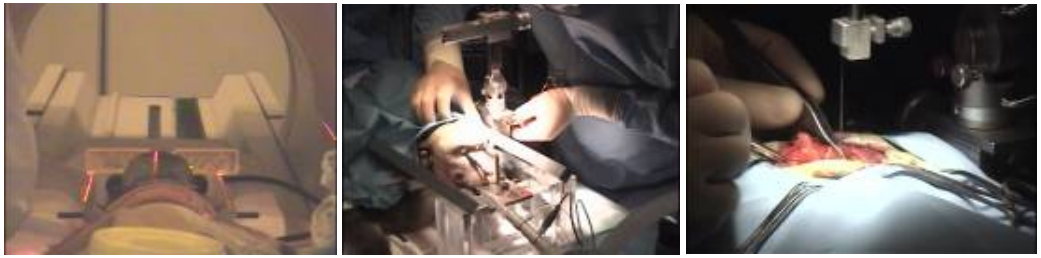


Pre-clinical animal model studies of clinical grade stem cells

- **Differentiate ES cells into different types of neuronal cells for Parkinson disease treatment**

Brain transplantation of ES cell differentiated neurons in rat

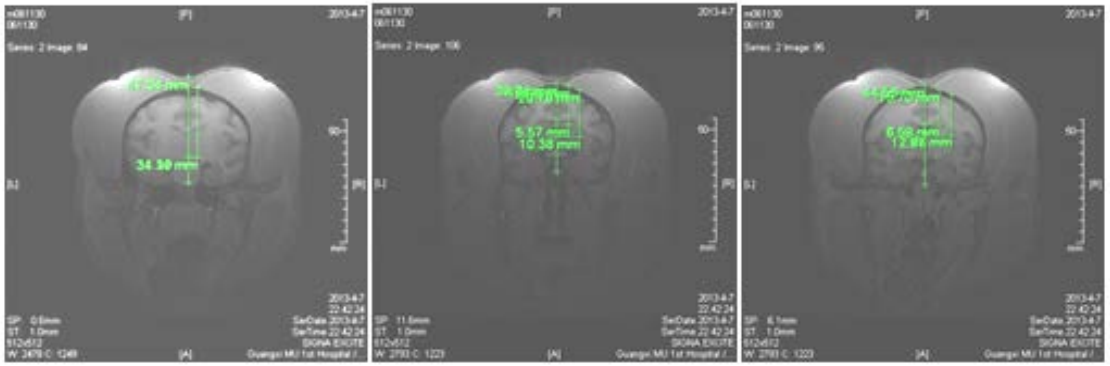
Brain transplantation of ES cell differentiated neurons in monkey



In vivo detection of implanted cells

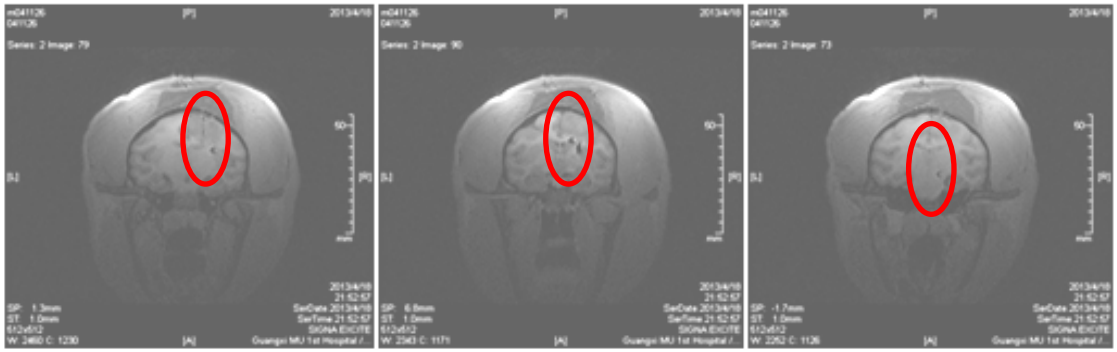
MRI images before implantation

A

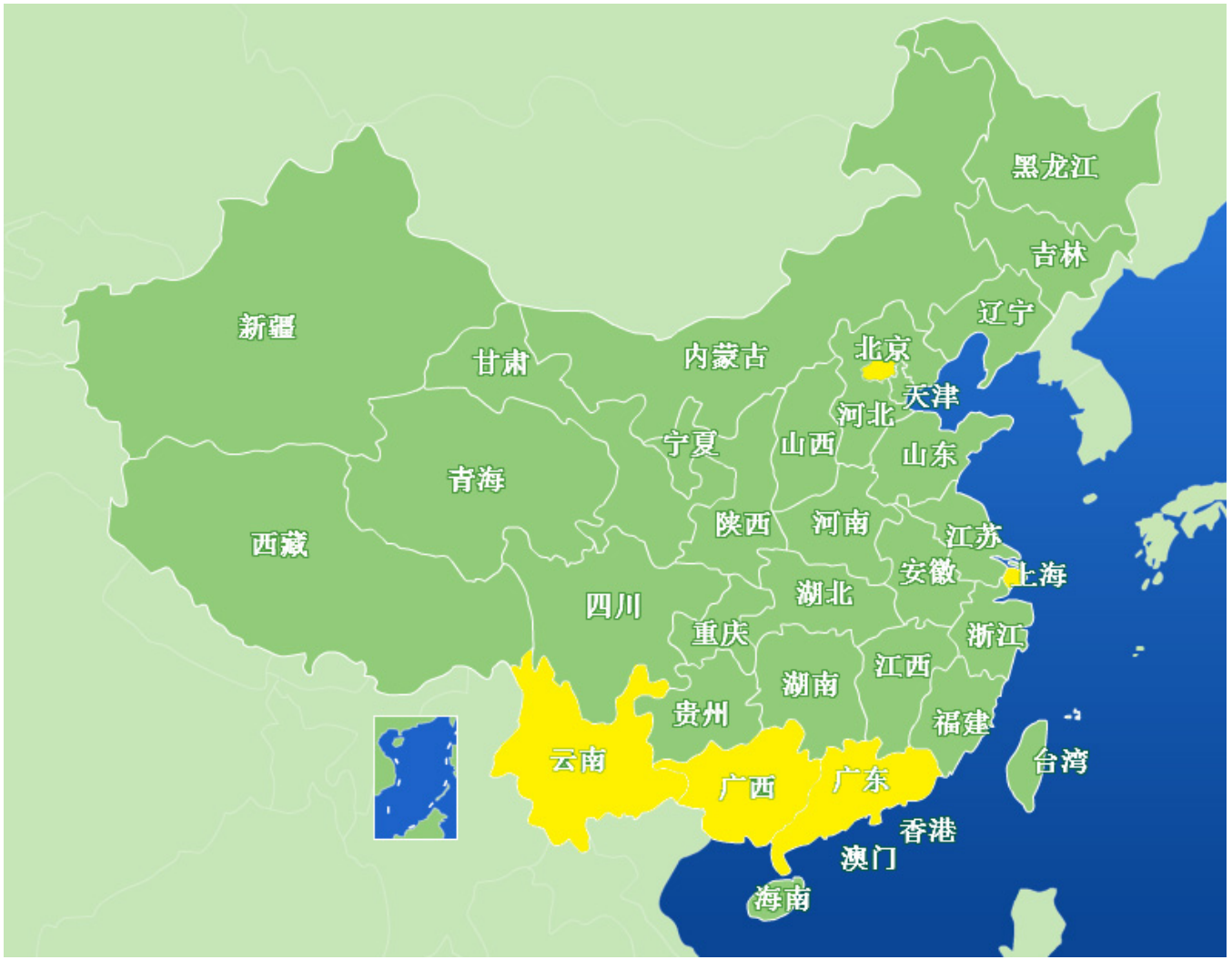


MRI images after implantation

B



Establishment of monkey models



Establishment of pig models

China would like to cooperate with the world to promote stem cell applications!