Certificate

PERHIMPUNAN DOKTER
ANTI PENUAAN, WELLNESS, ESTETIK
DAN REGENERATIF INDONESIA

This Certificate is awarded to

DR. dr. Ago Harlim, MARS, SpKK

as **SPEAKER**

IntAAC
International Anti Aging Conference 2.0
July 14-16th 2017
Hotel Grand Sahid Jaya - Jakarta

in **SYMPOSIUM**

"Challenges and Opportunities of Anti-aging Medicine in AEC Era"

SK Symposium
PB IDI No. : **01239/PB/A.4/07/2017**
Participant : 10 SKP, Speaker : 12 SKP,
Moderator : 4 SKP, Committee : 2 SKP

SK Workshop
PB IDI No. : **01240/PB/A.4/07/2017**
Participant : 5 SKP, Speaker : 12 SKP,
Moderator : 4 SKP, Committee : 2 SKP

President of PERDAWERI

Prof. DR. Dr. Abdul Razak Thaha, Msc, SpGK
NPA IDI : 48.390

Chairman of Committee

Dr. Putro Setyobudyo Muhammad
NPA IDI : 133.806

IntAAC 2.0
International Anti Aging Conference
"Tantangan dan Peluang Anti Aging Medicine Pada Era MEA"
Jakarta, 14 - 16 July 2017
PERDAWERI
Sekretariat : Jl. Dr. Samratulangi No. 29 Jakarta Pusat (10350) Indonesia,
Telp/Fax : 021-31937910 , 3155260. email: intaac2017@gmail.com

Jakarta, 16 Juni 2017

No. : 027/InTAAC/F.3/06/2017
Lamp :
Hal : **Permohonan Kesediaan sebagai Pembicara**

Kepada Yth.
DR. Dr. Ago Harlim, MARS, SpKK
di
Tempat

Dengan hormat,

International Anti Aging Conference (InTAAC) merupakan satu agenda kegiatan tahunan yang diselenggarakan oleh Perhimpunan Dokter Anti Penuaan, *Wellness*, Estetik & *Regeneratif* Indonesia (Perdaweri). Tahun ini merupakan tahun ke-2 pelaksanaan InTAAC 2017, yang bertemakan "***Challenges and Opportunities of Antiaging Medicine in AEC Era***", dan akan diselenggarakan pada tanggal 14 - 16 Juli 2017 di Hotel Sahid Jaya Jakarta.

Sehubungan dengan InTAAC ke-2, bersama ini kami mohon kesediaan sejawat menjadi pembicara dalam kegiatan yang akan dilaksanakan pada:

Hari/Tanggal	: Minggu, 16 Juli 2017 (Simposium)
Pukul	: 10.30-11.20 WIB
Topik 1 (20 menit)	: The Difference of Stemcell Product
Topik 2 (20 menit)	: Immunology Behind The Filler

Demikian kami sampaikan surat permohonan sebagai pembicara. Kiranya sejawat bersedia sebagai pembicara dalam kegiatan ini. Kami lampirkan formulir kesediaan, dan lembar kesediaan dapat dikirimkan melalui email intaac2017@gmail.com sebelum 28 Juni 2017.

Hormat kami,

Panitia InTAAC 2017

Dr. Putro Setyobudyo Muhammad
Ketua Panitia

Konfirmasi Kesediaan ke Sekretariat Panitia:
Ibu Iyek (08561938327) atau Evi (08567907503)

LEMBAR KESEDIAAN

Yang bertanda tangan dibawah ini:

Nama : Dr. dr. Ago Harlim MARS, Sp.KK

Institusi : Fakultas Kedokteran Universitas Kristen Indonesia

Jabatan : Kepala Bagian Kulit & Kelamin

Email : agoharlim@yahoo.com

No Telp/HP : 0816854083

1. Bersedia/tidak bersedia menjadi Pembicara dalam kegiatan ilmiah ***International Anti Aging Conference (InTAAC)*** **Perdaweri** yang ke 2 tahun 2017.
2. Memberikan CV
3. Memberikan materi presentasi

Mohon surat kesediaan ini ditandatangani dan diemail ke intaac2017@gmail.com

Jakarta, 17 Juni 2017

(Dr. dr. Ago Harlim MARS, Sp.KK)

Konfirmasi Kesediaan ke Sekretariat Panitia:
Ibu Iyek (08561938327) atau Evi (08567907503)

IntAAC 2.0
International Anti Aging Conference
"Tantangan dan Peluang Anti Aging Medicine Pada Era MEA"
Jakarta, 14 - 16 July 2017

PERDAWERI

Sekretariat : Jl. Dr. Samratulangi No. 29 Jakarta Pusat (10350) Indonesia,
Telp/Fax : 021-31937910 , 3155260. email: intaac2017@gmail.com

Jakarta, 28 Juni 2017

No. : 053/InTAAC/F.3/06/2017
Lamp : Rundown Acara
Hal : **Permohonan Power Point dan Abstrak Materi Pembicara**

Kepada Yth.
DR. dr. Ago Harlim, MARS, SpKK
di
tempat

Dengan hormat,

Sehubungan dengan semakin dekatnya waktu pelaksanaan **International Anti Aging Conference - InTAAC ke-2**, bersama ini kami mohon kesediaan sejawat untuk dapat memberikan power point dan abstrak materi pembicara, yaitu dengan jadwal dan topik sebagai berikut:

Hari/Tanggal : Minggu, 16 Juli 2017

Tempat : Hotel Sahid Jaya, Jakarta

Waktu (Sesi) : 09.30 – 10.20 WIB (Simposium Sesi 6)

Topik 1 (20') : The Difference of Stemcell Products

Topik 2 (20') : Immunology Behind The Filler

Demikian kami sampaikan surat permohonan power point dan abstrak materi pembicara serta informasi update susunan acara terbaru. Kiranya sejawat bersedia mengirimkan materi tersebut sebelum Rabu, 5 Juli 2017 melalui email intaac2017@gmail.com dan menginformasikannya kepada sekretariat InTAAC 2017 dengan Sdri Evi (08567907503) atau Sdri Sri Handayani (08561938327). Atas perhatian dan kerjasamanya kami ucapkan terima kasih.

Hormat kami,

Panitia InTAAC 2017

Dr. Putro Setyobudyo Muhammad
Ketua Panitia

Konfirmasi Kesediaan ke Sekretariat Panitia:
Ibu Iyek (08561938327) atau Evi (08567907503)

2nd International Antiaging Conference IntAAC 2017
RUNDOWN SIMPOSIUM Day 1
SABTU, 15 JULI 2017
HOTEL SAHID JAYA JAKARTA

Sesi /Jam		Tema
08.00 - 08.30		Registrasi Peserta
Sesi 1 (08.30-09.20)		**Nutraceuticals**
		Moderator : dr. Henti Widowati, M.Biomed (AAM)
08.30 - 08.50	20'	Personalized Nutrition for Healthy Condition & Rejuvenation
		Prof.DR.dr. Nurpudji Astuti Taslim, MPH, SpGK(K)
08.50 - 09.10	20'	Nutraceuticals for Anti Aging
		DR.med. Dr. Maya Surjadjaja, M.Gizi, SpGK
09.10 - 09.20	10'	Discussion
Coffee Break (09.20-09.30)		**Coffee Break**
Pembukaan (09.30-10.25)		**Pembukaan**
09.30 - 09.35	5'	Menyanyikan lagu Indonesia Raya
09.35 - 09.40	5'	Sambutan Ketua Panitia
09.30 - 09.40	10'	Sambutan Ketua Perdaweri
09.40 - 09.55	15'	Sambutan Ketua PB IDI
09.55 - 10.25	30'	Pembukaan dan Keynote Speech Menteri Kesehatan
		Kebijakan Pemerintah dalam Upaya Pengembangan Antiaging Medicine and Health Tourism di Indonesia pada Era MEA
Panel (10.25-12.05)		**Panel : Future Challenges for Anti Aging Physicians**
		Moderator : Dr. dr. Supriyantoro, Sp.P, MARS
10.25 - 10.45	20'	Konsep dan Implementasi Pemberian Kewenangan Tambahan oleh Ketua KKI
		Prof. Dr. Sukman Tulus, SpA
10.45 - 11.05	20'	Peluang dan Tantangan Pengembangan Antiaging/Aesthetic Health Tourisme di Indonesia
		Perdaweri
11.05 - 11.25	20'	Peran Wellness and Health Tourisme Khususnya Aesthetic Health Tourism dalam Mendukung Destinasi Wisata
		Kementerian Pariwisata RI
11.25 - 11.45	20'	Diskusi
Lunch & Prayer (11.45 - 13.00)		**Lunch & Prayer**
Sesi 2 (13.00 - 13.50)		**Rejuvenation**
		Moderator : Dr. Freddy Wilmana, MFPM, SpFK
13.00 - 13.20	20'	Hormone Therapy for rejuvenation
		Dr. Anoop Chaturvedi, BSc, MBBS, DA, MD, PhD
13.20 - 13. 40	20'	Update on telomerases
		DR. Drs. Andi Wijaya, Apt
13. 40 - 13. 50	10'	Discussion
Sesi 3 (13.50-14.40)		**New Modalities In Antiaging and Aesthetic**
		Moderator : Dr. Djauhery
13.50 - 14.10	20'	Metformin Update in Anti-Aging
		Dr. Freddy Wilmana, MFPM, SpFK
	5	Discussion
14.15 - 14.35	20'	Sculptra & Combination Treatment
		Dr. Darryl Chew
14.35 - 14.40	5	Discussion
Coffee break (14.40 - 15.00)		**Coffee break**
Sesi 4 (15.00-15.50)		**Silent Inflammation**
		Moderator : dr. Rita Lahirin
15.00 - 15.20	20'	SAMe nutrient for antiaging (detoxification and neurotransmitter balancing)
		DR. Dr. Gaga Irawan Nugraha, M.Gizi, SpGK
15.20 - 15.40	20'	Anti-Inflammation Diet Plan and Supplementation
		Dr. Siti Nur Fatimah, MS, SpGK
15.40 -15.50	10'	Discussion

2nd International Antiaging Conference IntAAC 2017

RUNDOWN SIMPOSIUM Day 2

MINGGU, 16 JULI 2017

HOTEL SAHID JAYA JAKARTA

Sesi/Jam	Jam	Tema
08.00 - 08.30		Registrasi
Plenary (08.30-09.30)		**Plenary**
08.30 - 08. 50	**20'**	Medical Ethics (MKEK IDI)
		Dr. M. Nasser, Sp.KK, LLM DLaw
08. 50 - 09. 10	**20'**	Patient Safety (PB IDI)
		PB IDI
09. 10 - 09.30	**20'**	Complement and Alternative Medicine in Indonesia
		Dr. Merdias Almatsier (Ketua Pokja Kemkes ttg CAM)
Sesi 5 (09.30 - 10.20)		**Antiaging : Economic Perspective**
		Moderator : Dr. Dyah Agustina Waluyo
09.30 - 09.55	25'	Entrepreneurship: Anti Aging as The New Startup Frountier
		dr. Bayu Prawira Hie
09.55 - 10.15	20'	Antiaging Lab Test
		Dr. George A. Mantiri, MLM, SpPK
10.15 - 10.25	10'	Discussion
Coffee Break (10.25-10.30)		**Coffee Break**
Session 6 (10.30-11.20)		Stemcell
		Moderator: dr. Henti Widowati, M.Biomed (AAM)
10.30 - 10.50	20'	The Difference of Stemcell Products
		DR.dr. Ago Harlim.MARS., SpKK
10.50 - 11.10	20'	Immunology Behind The Filler
		DR.dr. Ago Harlim.MARS., SpKK
11.10-11.20	10	Discussion
Sesi 7 (11.20 -12.10)		**Lifestyle Modification**
		Moderator: Dr. Putro S Muhammad
11.20 - 11. 40	**20'**	Management Obesity: Fight Obesity for Healthy Life
		DR.med, Dr. Maya Surjadjaja, M.Gizi, SpGK
11.40-12.00	20'	The Miracles of Aloe Vera
		Dr. Freddy Wilmana, MFPM, SpFK
12.00-12.10	10'	Discussion
Lunch & Prayer (12.10 - 13.00)	**50'**	**Lunch & Prayer**
Sesi 8 (13.00-13.50)		**Lifestyle Selection**
		Moderator : Dr. Siti Nur Fatimah, MS, Sp.GK
13.00 - 13.20	20'	Lifestyle for Uterine Cervical Health
		Prof. Dr. Antonius Kurniawan, Sp.PA (K)
13.20 - 13.40	20'	Rational Use of Probiotics in Daily Practice
		Dr. Abdullah Firmansah, SpGK. Mkes
13.40 - 13.50	10'	Discussion
Sesi 9 (13.50 - 14.40)		**Better Neurologic life style**
		Moderator : Dr. Kishanty Hardaningtyas
13.50 - 14.10	20'	Specific Exercise for Relax
		Dr. Grace Tumbelaka, SpKO
14.10 - 14.30	20'	Melatonin Contribution in Sleep and Quality of life
		Dr. Widya Murni, MARS
14.30 - 14.40	10'	Discussion
(14.40 - 15.10)	20'	**Coffee Break & Medikamentoring**
Sesi 10 (15.10-16.00)		**Hormone Therapy**
		Moderator : Dr. Yenni Zuharini, M. Gizi, Sp.GK
15.10 - 15.30	20'	Hormonal Changes & Sexual Function in Aging Women
		Dr. Widya Murni, MARS
15.30 - 15.50	20'	Climacteric & Post Menopause Symptoms and Management
		Dr. Prima Progestian, SpOG
15.50 - 16.00	10'	Discussion
Closing ceremony (16.00-16.15)		**Closing ceremony, doorprize**

INTAAC 2017

Permohonan Power Point dan Abstrak Materi Pembicara InTAAC 2017

To: Dr hadim sl al al. Cc: Freddy Wilmana, Maya Surjadjaja, Andalusia Adnar, [illegible], Yanni Rufadi, siti fatimah

30 June 2017 17.03

Details

Jakarta, 28 Juni 2017

No. : 053/InTAAC/F.3/06/2017
Lamp : Rundown Acara
Hal : **Permohonan Power Point dan Abstrak Materi Pembicara**

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Topik 1 (20') : The Difference of Stemcell Products

Topik 2 (20') : Immunology Behind The Filler

2nd International Anti Aging Conference IntAAC 2017
Jumat,14 Juli 2017
Hotel Sahid Jaya Jakarta
RUNDOWN WORKSHOP

WORKSHOP I		**Update in Fat Loss Management**
(09.00 - 11.00)		**Moderator: Prof. Dr. Antonius Kurniawan, Sp.PA (K)**
09.00 - 09.30	30'	Hunger Craving Weight Gain its all in The Brain
		Dr. Anoop Chaturvedi, BSc, MBBS, DA, MD, PhD
09.30 - 10. 00	30'	Hormone Diet: How To Do a Good Hormonal Diet
		DR.med, Dr. Maya Surjadjaja, M.Gizi, SpGK
10.00 - 10.30	30'	Bioidentical Hormones for Fat Loss
		Dr. Anoop Chaturvedi, BSc, MBBS, DA, MD, PhD
10.30-11.00	30'	Q n A
11.00-11.15		**Coffee Break dan Registrasi WS II**
WORKSHOP II		**Dysbiosis Fact – Relationship of Gut with Skin Health**
11. 15 - 12.15		**Moderator: Dr. Freddy Wilmana, MFPM, SpFK**
11.15 - 11.45	30'	Overview of Gut-Brain-Immune
		Dr. Anoop Chaturvedi, BSc, MBBS, DA, MD, PhD
11.45 - 12. 15	30'	Intestinal Barrier Dysfunction (Leaky Gut)
		DR. Dr. Aris Wibudi, SpPD
12.15 - 13.00		**ISHOMA**
WORKSHOP II (lanjutan)		**Dysbiosis Fact – Relationship of Gut with Skin Health**
13.00 - 14.00		**Moderator: Dr. Freddy Wilmana, MFPM, SpFK**
13.00 - 13.30	30'	Relevance of Hormonal Therapy with Dysbiosis
		Dr. Anoop Chaturvedi, BSc, MBBS, DA, MD, PhD
13.30 - 14.00	30'	Q n A
14.00-14.15		**Coffee Break dan Registrasi WS III**
WORKSHOP III		**Update On Minimal Invasive Acne Management**
14.30 - 16.30		**Moderator : Dr. Erdina Pusponegoro, SpKK**
14.30 - 15.00	30'	Etiopatogenesis Acne
		DR. Dr. Irma Bernadette, SpKK(K) FINS DV
15.00 - 15.30	30'	Update on Acne Treatment (Management Akne Update di Indonesia)
		Dr. Lili Legiawati, SpKK(K) FINSDV FAADV
15.30 - 16.00	30'	Managemen HPA dan SPA update
		Dr.Lilik Norawati, SpKK FINSDV FAADV
16.00 - 16.30	30'	Q n A

IntAAC
International Anti Aging Conference 2.0

&

4th NATIONAL CONGRESS OF
PERDAWERI

SYMPOSIUM

Ago Harlim

SPEAKER

The Different of Stem Cells Product

Ago Harlim

inTAAC 2017

Abstract

There were a lot of stem cell products in the market. They used word “stem cell” for increase their marketing, but we are not sure there is a real stem cell. Some product only contains growth factors. Patients need to know what the stem cell is? We need to know how it work in our body. We have to know the difference between stem cell, stromal vascular fraction and growth factor. Therefore, we can use the product accord to the problem and matching with our expectation. The two defining characteristics of a stem cell are perpetual self-renewal and the ability to differentiate into a specialized adult cell type. There are two major classes of stem cells: pluripotent that can become any cell in the adult body, and multipotent that are restricted to becoming a more limited population of cells. Cell sources, characteristics, differentiation and therapeutic applications are discussed. Stem cells have great potential in tissue regeneration and repair but much still needs to be learned about their biology, manipulation and safety before their full therapeutic potential can be achieved.

Introduction

Stem cells have the ability to build every tissue in the human body, hence have great potential for future therapeutic uses in tissue regeneration and repair. In order for cells to fall under the definition of “stem cells,” they must display two essential characteristics. First, stem cells must have the ability of unlimited self-renewal to produce progeny exactly the same as the originating cell. This trait is also true of cancer cells that divide in an uncontrolled manner whereas stem cell division is highly regulated. Therefore, it is important to note the additional requirement for stem cells; they must be able to give rise to a specialized cell type that becomes part of the healthy animal.[1]

The general designation, “stem cell” encompasses many distinct cell types. Commonly, the modifiers, “embryonic,” and “adult” are used to distinguish stem cells by the developmental stage of the animal from which they come, but these terms are becoming insufficient as new research has discovered how to turn fully differentiated adult cells back into embryonic stem cells and, conversely, adult stem cells, more correctly termed “somatic” stem cells meaning “from the body”, are found in the fetus, placenta, umbilical cord blood and infants.[2] Therefore, this review will sort stem cells into two categories based on their biologic properties - pluripotent stem cells and multipotent stem cells. Their sources, characteristics, differentiation and therapeutic applications are discussed.

Pluripotent stem cells are so named because they have the ability to differentiate into all cell types in the body. In natural development, pluripotent stem cells are only present for a very short period of time in the embryo before differentiating into the more specialized multipotent stem cells that eventually give rise to the specialized tissues of the body (Figure 1) . These more limited multipotent stem cells come in several subtypes: some can become only cells of a particular germ line (endoderm, mesoderm, ectoderm) and others, only cells of a particular tissue. In other words, pluripotent cells can eventually become any cell of the body by differentiating into multipotent stem cells that themselves go through a series of divisions into even more restricted specialized cells.

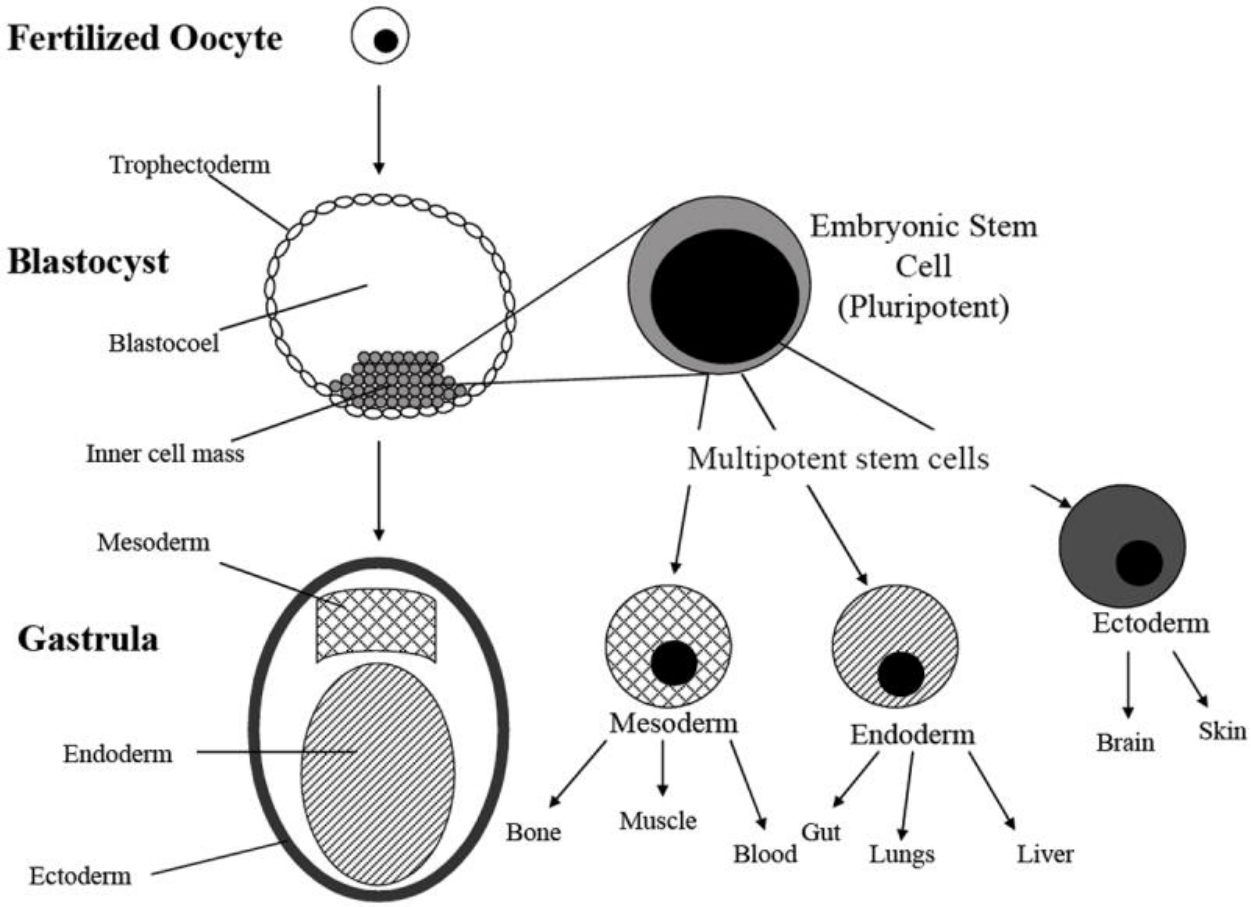

Figure 1.
Derivation of Stem Cells

During natural embryo development, cells undergo proliferation and specialization from the fertilized egg, to the blastocyst, to the gastrula during natural embryo development (left side of panel). Pluripotent, embryonic stem cells are derived from the inner cell mass of the blastoctyst (lightly shaded). Multipotent stem cells (diamond pattern, diagonal lines, and darker shade) are found in the developing gastrula or derived from pluripotent stem cells and are restricted to give rise to only cells of their respective germ layer.

Result and discussion

4.1 Stem cell fates

Based on the two defining characteristics of stem cells (unlimited self-renewal and ability to differentiate), they can be described as having four outcomes or fates[3] (Figure 2) A common fate for multipotent stem cells is to remain quiescent without dividing or differentiating, thus maintaining its place in the stem cell pool. An example of this is stem cells in the bone marrow that await activating signals from the body. A second fate of stem cells is symmetric self-renewal in which two daughter stem cells, exactly like the parent cell, arise from cell division. This does not result in differentiated progeny but does increase the pool of stem cells from which specialized cells can develop in subsequent divisions. The third fate, asymmetric self-renewal, occurs when a stem cell divides into two daughter cells, one a copy of the parent, the other a more specialized cell, named a somatic or progenitor cell. Asymmetric self-renewal results in the generation of differentiated progeny needed for natural tissue development/regeneration

while also maintaining the stem cell pool for the future. The fourth fate is that in which a stem cell divides to produce two daughters both different from the parent cell. This results in greater proliferation of differentiated progeny with a net loss in the stem cell pool.

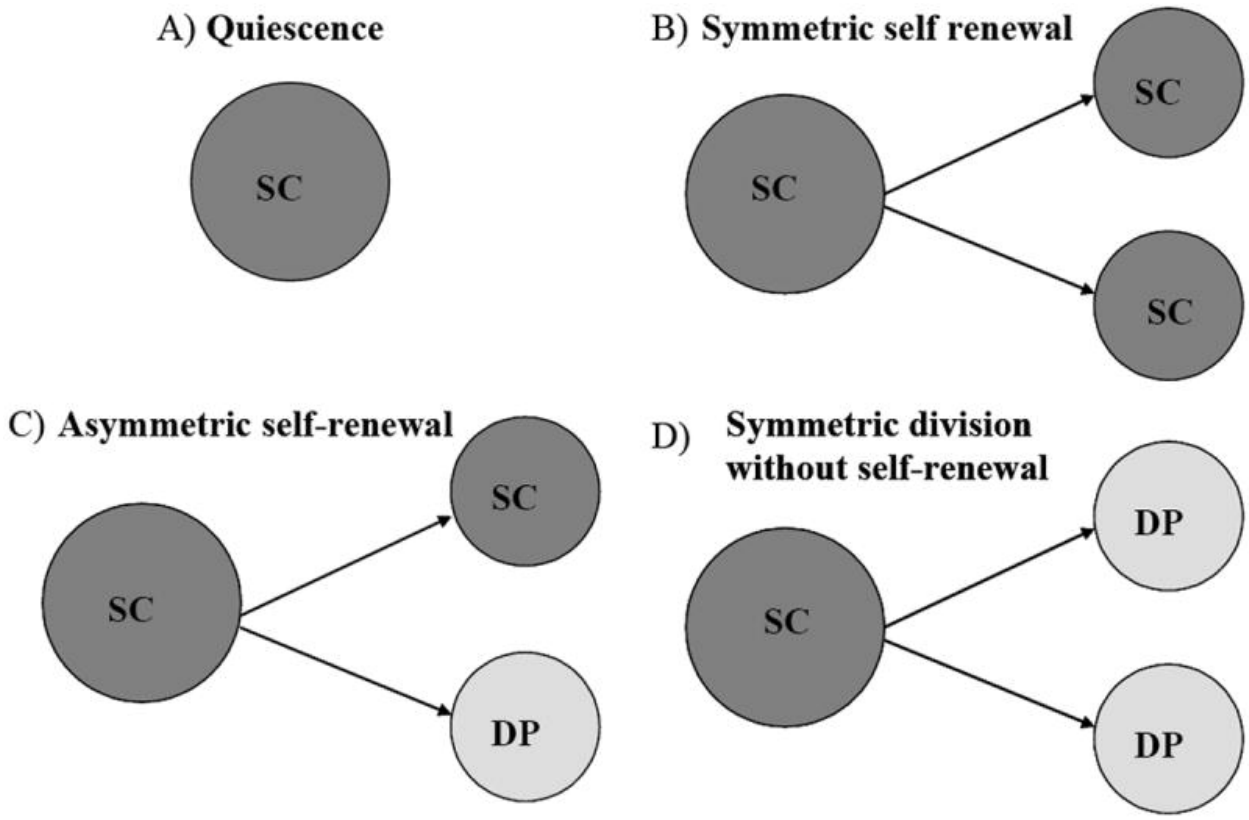

Figure 2
Stem Cell Fates

Four potential outcomes of stem cells. A) Quiescence in which a stem cell does not divide but maintains the stem cell pool. B) Symmetric self-renewal where a stem cell divides into two daughter stem cells increasing the stem cell pool. C) Asymmetric self-renewal in which a stem cell divides into one differentiated daughter cell and one stem cell, maintaining the stem cell pool. D) Symmetric division without self-renewal where there is a loss in the stem cell pool but results in two differentiated daughter cells. (SC- Stem cell, DP-Differentiated progeny)

4.2 Sources of stem cells

Pluripotent

Pluripotent stem cells being used in research today mainly come from embryos, hence the name, “embryonic stem cells”. Pre-implantation embryos a few days old contain only 10-15% pluripotent cells in the “inner cell mass”. Those pluripotent cells can be isolated, then cultured on a layer of “feeder” cells which provide unknown cues for many rounds of proliferation while sustaining their pluripotency.

Recently, two different groups of scientists induced adult cells back into the pluripotent state by molecular manipulation to yield "induced pluripotent stem cells" (iPS) that share some of the same characteristics as embryonic stem cells such as proliferation, morphology and gene expression (in the form of distinct surface markers and proteins being expressed).[4-8] Both groups used retroviruses to carry genes for transcription factors into the adult cells. These genes are transcribed and translated into proteins that regulate the expression of other genes designed to reprogram the adult nucleus back into its embryonic state. Both introduced the embryonic transcription factors known as Sox2 and Oct4. One group also added Klf4 and c-Myc[4] and the other group added Lin28 and Nanog.[6] Other combinations of factors would probably also work, but, unfortunately, neither the retroviral carrier method nor the use of the oncogenic transcription factor c-Myc are likely to be approved for human therapy. Consequently, a purely chemical approach to deliver genes into the cells, and safer transcription factors are being tried. Results of these experiments look promising.[9]

Multipotent stem cells may be a viable option for clinical use. These cells have the plasticity to become all the progenitor cells for a particular germ layer or can be restricted to become only one or two specialized cell types of a particular tissue. The multipotent stem cells with the highest differentiating potential are found in the developing embryo during gastrulation (day 14-15 in humans, day 6.5-7 in mice). These cells give rise to all cells of their particular germ layer, thus, they still have flexibility in their differentiation capacity. They are not pluripotent stem cells because they have lost the ability to become cells of all three germ layers. On the low end of the plasticity spectrum are the unipotent cells that can become only one specialized cell type such as skin stem cells or muscle stem cells. These stem cells are typically found within their organ and although their differentiation capacity is restricted, these limited progenitor cells play a vital role in maintaining tissue integrity by replenishing aging or injured cells. There are many other sub-types of multipotent stem cells occupying a range of differentiation capacities. For example, multipotent cells derived from the mesoderm of the gastrula undergo a differentiation step limiting them to muscle and connective tissue; however, further differentiation results in increased specialization towards only connective tissue and so on until the cells can give rise to only cartilage or only bone.

Multipotent stem cells found in bone marrow are best known, because these have been used therapeutically since the 1960's[10] (their potential will be discussed in greater detail in a later section). Recent research has found new sources for multipotent stem cells of greater plasticity such as the placenta and umbilical cord blood.[11] Further, the heart, until recently considered void of stem cells, is now known to contain stem cells with the potential to become cardiac myocytes.[12] Similarly, neuro-progenitor cells have been found within the brain.[13]

The cardiac stem cells are present in such small numbers, that they are difficult to study and their function has not been fully determined. The second review in this series will discuss their potential in greater detail.

4.3 Characteristic that identify Stem cells

Pluripotent

Since Federal funding for human embryonic stem cells is restricted in the United States, many scientists use the mouse model instead. Besides their ability to self-renew indefinitely and differentiate into cell types of all three germ layers, murine and human pluripotent stem cells have much in common. It should not be surprising that so many pluripotency traits are conserved between species given the shared genomic sequences and intra-cellular structure in mammals. Both mouse and human cells proliferate indefinitely in culture, have a high nucleus to cytoplasm ratio, need the support of growth factors derived from other live cells, and display similar surface antigens, transcription factors and enzymatic activity (i.e. high alkaline phosphatase activity).[14] However, differences between mouse and human pluripotent cells, while subtle, are very important. Although the transcription factors mentioned above to induce pluripotency from adult cells (Oct3/4 and Sox2) are shared, the extracellular signals needed to regulate them differ. Mouse embryonic stem cells need the leukemia inhibitory factor and bone morphogenic proteins while human require the signaling proteins Noggin and Wnt for sustained pluripotency.[15] Surface markers used to identify pluripotent cells also differ slightly between the two species as seen in the variants of the adhesion molecule SSEA

(SSEA-1 in mouse, SSEA-3 & 4 in humans).[16] Thus, while pluripotency research in mouse cells is valuable, a direct correlation to the human therapy is not likely.

Last, but certainly not least, a big difference between mouse and human stem cells are the moral and ethical dilemmas that accompany the research. Some people consider working with human embryonic stem cells to be ethically problematic while very few people have reservations on working with the mouse models. However, given the biological differences between human and mouse cells, most scientists believe that data relevant for human therapy will be missed by working only on rodents.

Multipotent

Cell surface markers are typically also used to identify multipotent stem cells. For example, mesenchymal stem cells can be purified from the whole bone marrow aspirate by eliminating cells that express markers of committed cell types, a step referred to as lineage negative enrichment, and then further separating the cells that express the sca-1 and c-Kit surface markers signifying mesenchymal stem cells. Both the lineage negative enrichment step and the sca-1/c-Kit isolation can be achieved by using flow cytometry and is discussed in further detail in the following review. The c-Kit surface marker also is used to distinguish the recently discovered cardiac stem cells from the rest of the myocardium. A great deal of recent work in cardiovascular research has centered on trying to find which markers indicate early multipotent cells that will give rise to pre-cardiac myocytes. Cells with the specific mesodermal marker, Kdr, give rise to the progenitor cells of the cardiovascular system including contracting cardiac myocytes, endothelial cells and vascular smooth muscle cells and are therefore considered to be the earliest cells with specification towards the cardiovascular lineage.[17] Cells at this early stage still proliferate readily and yet are destined to become cells of the cardiovascular system and so may be of great value therapeutically.

4.4 Differentiation

Pluripotent

Scientists are still struggling to reliably direct differentiation of stem cells into specific cell types. They have used a virtual alphabet soup of incubation factors toward that end (including trying a variety of growth factors, chemicals and complex substrates on which the cells are grown), with, so far, only moderate success. As an example of this complexity, one such approach to achieve differentiation towards cardiac myocytes is to use the chemical activin A and the growth factor BMP-4. When these two factors are administered to pluripotent stem cells in a strictly controlled manner, both in concentration and temporally, increased efficiency is seen in differentiation towards cardiac myocytes, but still, only 30% of cells can be expected to become cardiac.[18]

Multipotent

Multipotent cells have also been used as the starting point for cell therapy, again with cocktails of growth factors and/or chemicals to induce differentiation toward a specific, desired lineage. Some recipes are simple, such as the use of retinoic acid to induce mesenchymal stem cells into neuronal cells,[19] or transforming growth factor-β to make bone marrow-derived stem cells express cardiac myocyte markers.[20] Others are complicated or ill-defined such as addition of the unknown factors secreted by cells in culture. Physical as well as chemical cues cause differentiation of stem cells. Simply altering the stiffness of the substrate on which cells are cultured can direct stem cells to neuronal, myogenic or osteogenic lineages.[21] Cells evolve in physical and chemical environments so a combination of both will probably be necessary for optimal differentiation of stem cells. The importance of physical cues in the cell's environment will be discussed in greater detail in the final review of this series. Ideally, for stem cells to be used therapeutically, efficient, uniform protocols must be established so that cells are a well-controlled and well-defined entity.

4.5 Stem cells therapy

Pluripotent stem cells

Pluripotent stem cells have not yet been used therapeutically in humans because many of the early animal studies resulted in the undesirable formation of unusual solid tumors, called teratomas. Teratomas are made of a mix of cell types from all the early germ layers. Later successful animal studies used pluripotent cells modified to a more mature phenotype which limits this proliferative capacity. Cells derived from pluripotent cells have been used to successfully treat animals. For example, animals with diabetes have been treated by the creation of insulin-producing cells responsive to glucose levels. Also, animals with acute spinal cord injury or visual impairment have been treated by creation of new myelinated neurons or retinal epithelial cells, respectively. Commercial companies are currently in negotiations with the FDA regarding the possibility of advancing to human trials. Other animal studies have been conducted to treat several maladies such as Parkinson's disease, muscular dystrophy and heart failure.[18,22,23]

Scientists hope that stem cell therapy can improve cardiac function by integration of newly formed beating cardiac myocytes into the myocardium to produce greater force. Patches of cardiac myocytes derived from human embryonic stem cells can form viable human myocardium after transplantation into animals,[24] with some showing evidence of electrical integration.[25,26] Damaged rodent hearts showed slightly improved cardiac function after injection of cardiac myocytes derived from human embryonic stem cells.[21] The mechanisms for the gain in function are not fully understood but it may be only partially due to direct integration of new beating heart cells. It is more likely due to paracrine effects that benefit other existing heart cells (see next review).

Multipotent stem cells

Multipotent stem cells harvested from bone marrow have been used since the 1960's to treat leukemia, myeloma and lymphoma. Since cells there give rise to lymphocytes, megakaryocytes and erythrocytes, the value of these cells is easily understood in treating blood cancers. Recently, some progress has been reported in the use of cells derived from bone marrow to treat other diseases. For example, the ability to form whole joints in mouse models[27] has been achieved starting with mesenchymal stem cells that give rise to bone and cartilage. In the near future multipotent stem cells are likely to benefit many other diseases and clinical conditions. Bone marrow-derived stem cells are in clinical trials to remedy heart ailments. This is discussed in detail in the next review of this series.

Pluripotent vs. Multipotent

Pluripotent and multipotent stem cells have their respective advantages and disadvantages. The capacity of pluripotent cells to become any cell type is an obvious therapeutic advantage over their multipotent kin. Theoretically, they could be used to treat diseased or aging tissues in which multipotent stem cells are insufficient. Also, pluripotent stem cells proliferate more rapidly so can yield higher numbers of useful cells. However, use of donor pluripotent stem cells would require immune suppressive drugs for the duration of the graft[28] while use of autologous multipotent stem cells (stem cells from ones' self) would not. This ability to use one's own cells is a great advantage of multipotent stem cells. The immune system recognizes specific surface proteins on cells/objects that tell them whether the cell is from the host and is healthy. Autologous, multipotent stem cells have the patient's specific surface proteins that allow it to be accepted by the host's immune system and avoid an immunological reaction. Pluripotent stem cells, on the other hand, are not from the host and therefore, lack the proper signals required to stave off rejection from the immune system. Research is ongoing trying to limit the immune response caused by pluripotent cells and is one possible advantage that iPS cells may have.

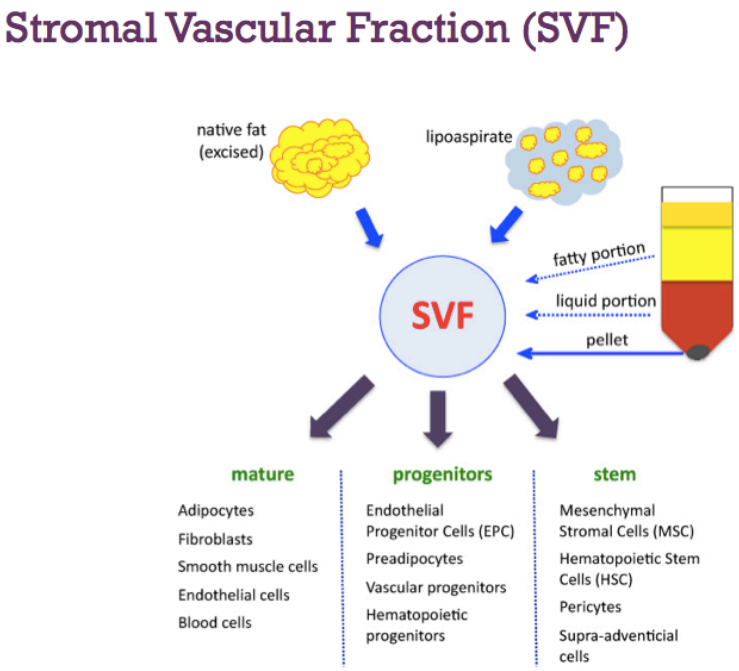

Figure 3. Stromal Vascular Fraction (SVF)

Stem cell

- Cell culture : 2-4 weeks.
- 1st phase, 2nd phase, 3rd phase dst.

SVF

- Stem cell and other cells.

Growth Factor

PDGF, IGF-1, EGF, and TGF-β , etc.

Conclusion

The promises of cures for human ailments by stem cells have been much touted but many obstacles must still be overcome. First, more human pluripotent and multipotent cell research is needed since stem cell biology differs in mice and men. Second, the common feature of unlimited cell division shared by cancer cells and pluripotent stem cells must be better understood in order to avoid cancer formation. Third, the ability to acquire large numbers of the right cells at the right stage of differentiation must be mastered. Fourth, specific protocols must be developed to enhance production, survival and integration of transplanted cells. Finally, clinical trials must be completed to assure safety and efficacy of the stem cell therapy. When it comes to stem cells, knowing they exist is a long way from using them therapeutically.

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