

STEM CELL dan METABOLIT : TEROBOSAN BARU TERAPI COVID-19

***(STEM CELL AND ITS METABOLITES:
A NEW BREAKTHROUGH FOR COVID-19 THERAPY)***

Rachmawati Noverina

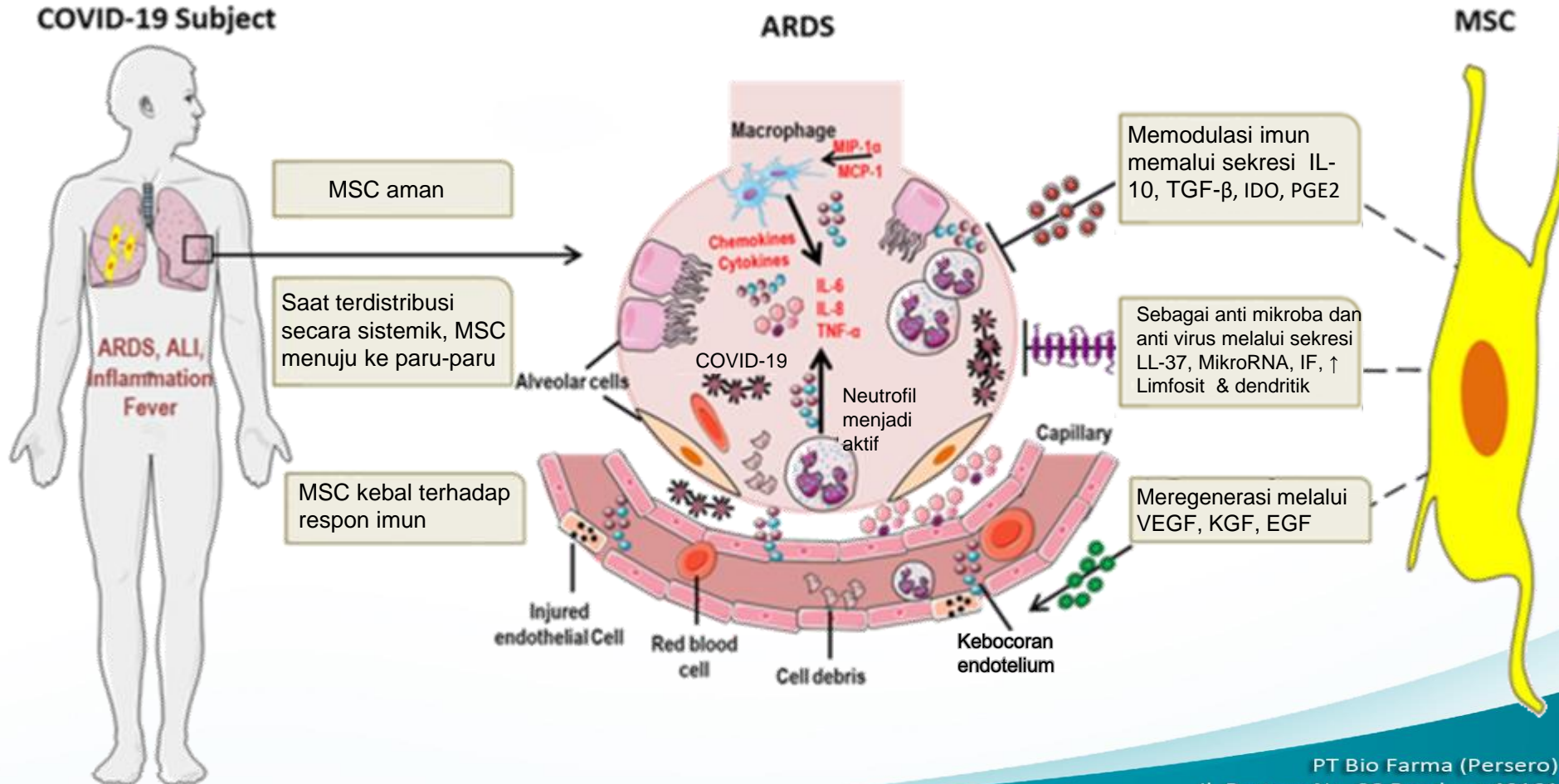
30 Agustus 2021

PT BIO FARMA (PERSERO)



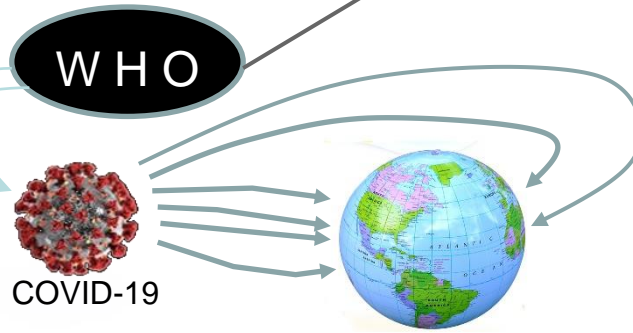


Stem Cell Therapy for SARS CoV 2 (COVID-19)



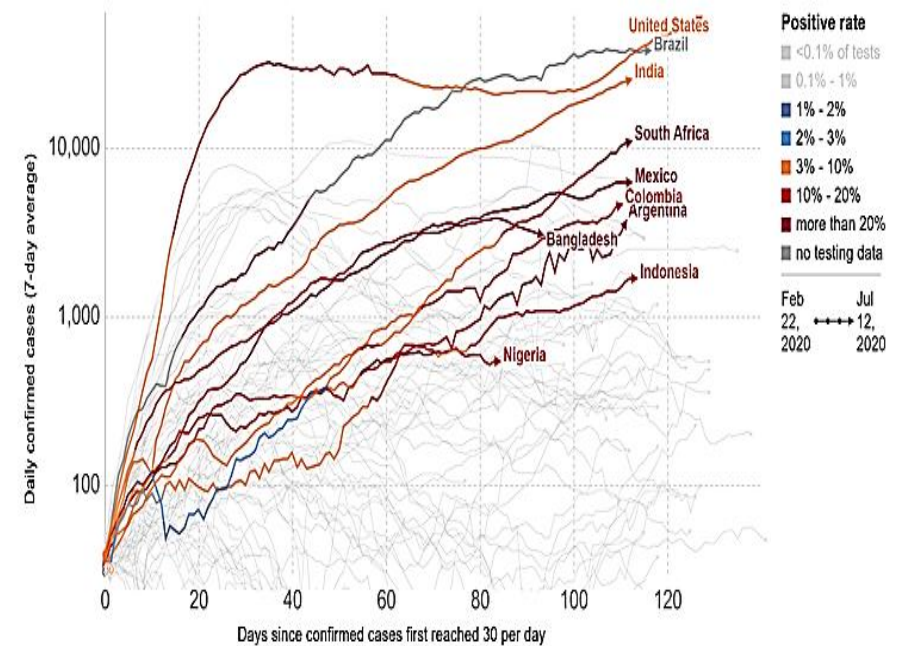
LATAR BELAKANG

Lonjakan pneumonia di Wuhan



Status **DARURAT** kesehatan global

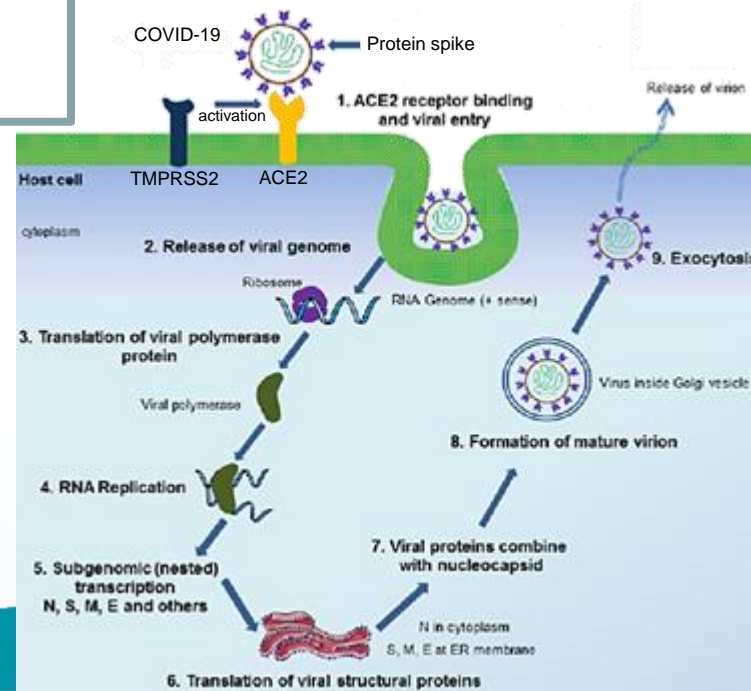
Penularan, Kematian



Karakteristik COVID-19

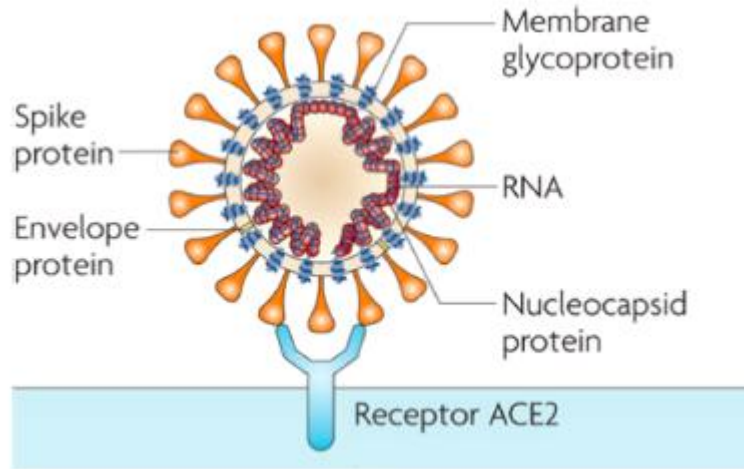
1. Virus RNA untai tunggal dari tipe baru β -coronavirus
2. Diameter sekitar 80-120 nm
3. Ukuran genome sekitar 29.9 kb yang mengkode 29 protein
4. Jalur masuk ke sel inang melalui ACE2 & TMPRSS2
5. Homologi 79% dari SARS-CoV 1

Punya afinitas Glikoprotein spike 10 -20 kali > SARS & MERS



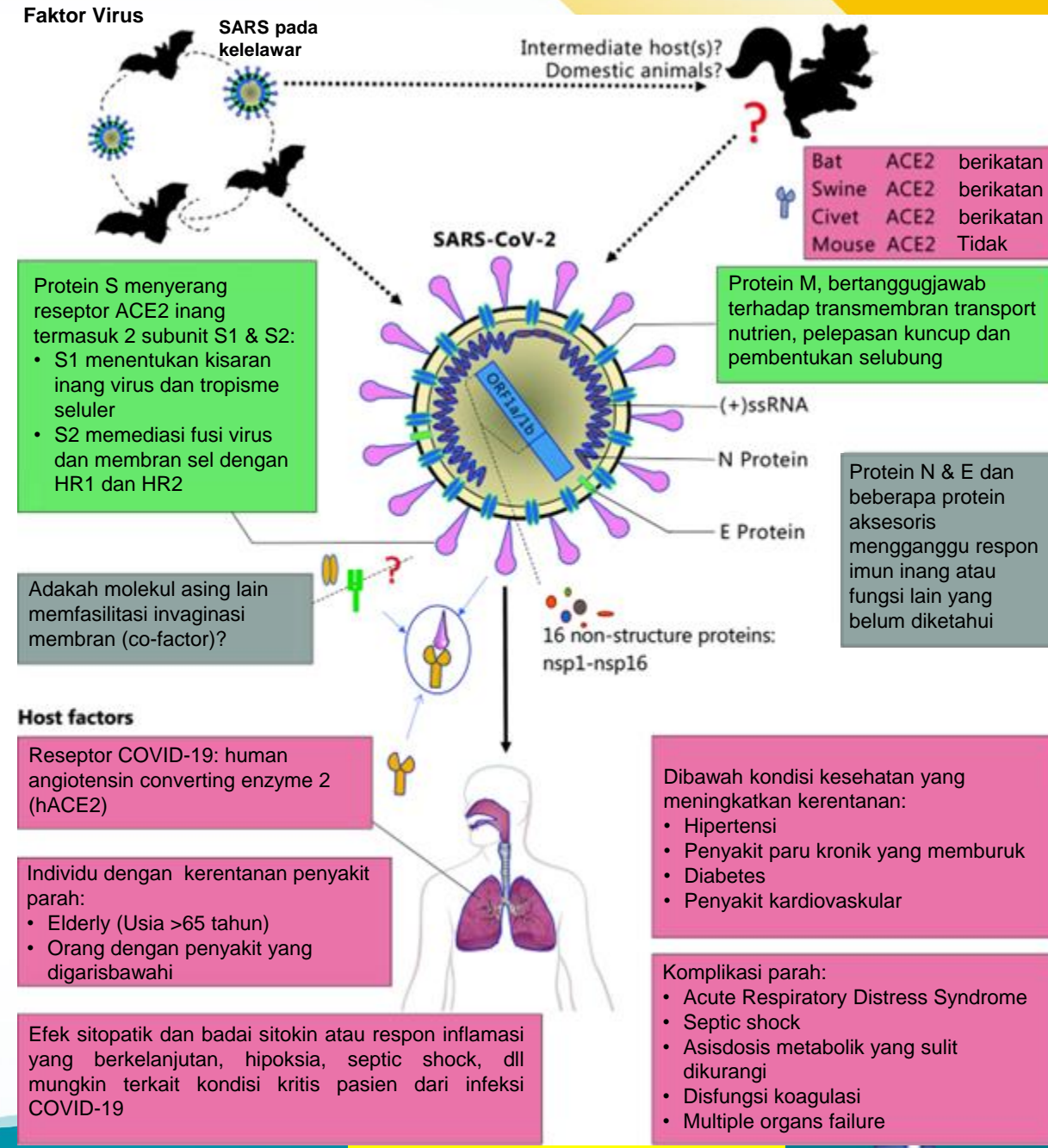
- Alpha (B117) asal Inggris,
- Beta (B1351) asal Afrika Selatan,
- Delta (B16172) asal India,
- Gamma (P1) asal Brasil,
- Zeta (P2) asal Brasil,
- Kappa (B16171) asal India,
- Theta (P3) asal Filipina,
- Iota (B1526) asal Amerika Serikat dan
- Epsilon (B1227/B1759) asal Amerika Serikat

Sifat Umum Virus Corona

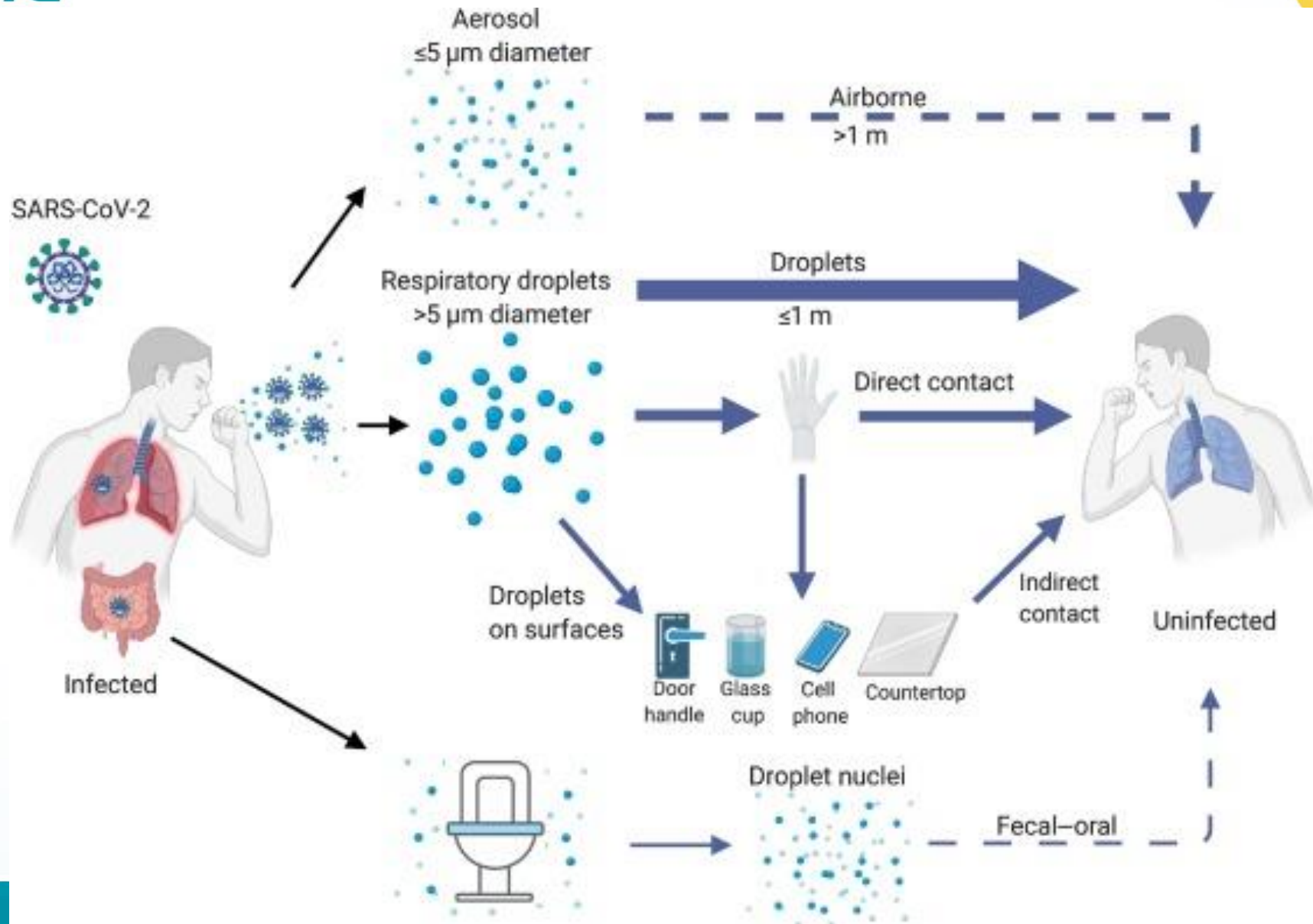


Liu, C., Zhou, Q., Li, Y., Garner, L. V., Watkins, S. P., Carter, L. J., ... & Albaiu, D. (2020). Research and development on therapeutic agents and vaccines for COVID-19 and related human coronavirus diseases.

- Corona = mahkota, ditandai adanya paku (spike) di permukaan virus
- Protein S (spike) berikatan dengan suatu reseptor di permukaan sel manusia yaitu angiotensin-converting enzyme 2 (ACE-2)



CARA PENYEBARAN COVID-19



OPSI TERAPI COVID-19

COVID-19

Pneumonia berat

Acute Lung Injury (ALI), ARDS, fibrosis paru

01

Antivirus

Azitromisin
Klorokuin fosfat/
Hidroksi klorokuin
Kortikosteroid



Tocilizumab (Actemra):
Antibodi monoklonal IL-6
mAb IL-1, Interferon,
hlg,

03

Convalescent Plasma



Plasma konvalesen :
Ab netralisasi virus,
sitokin (immunomodulatory)

04

Terapi kuratif : stem cell,
Sekretom (CT2),

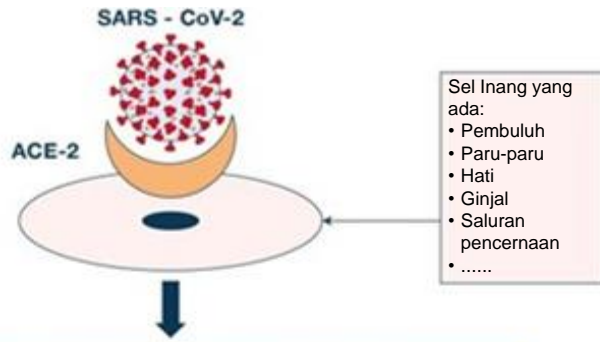
05

Terapi preventif :
Vaksin

menekan respon imun sehingga menekan respon inflamasi yang berlebihan saat terjadi badai sitokin

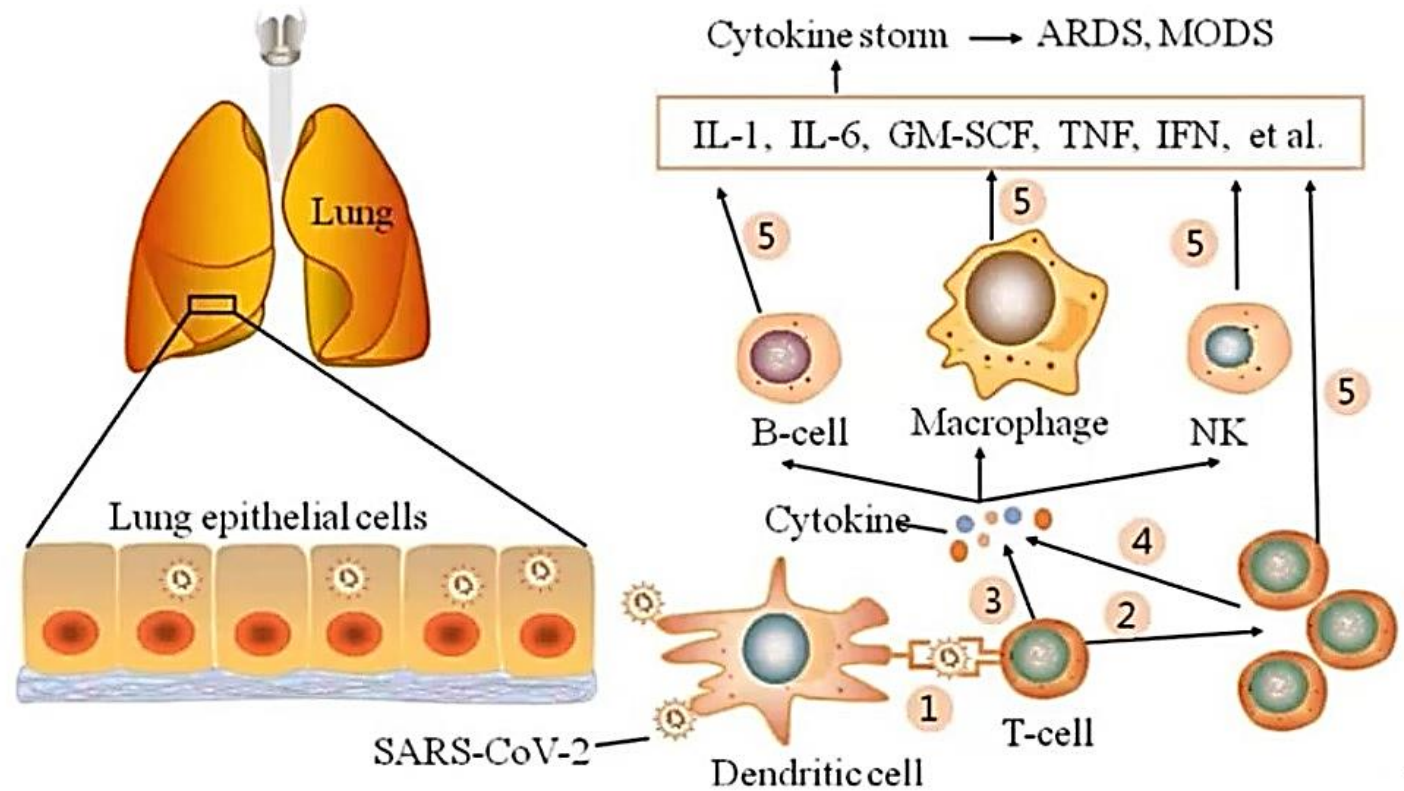
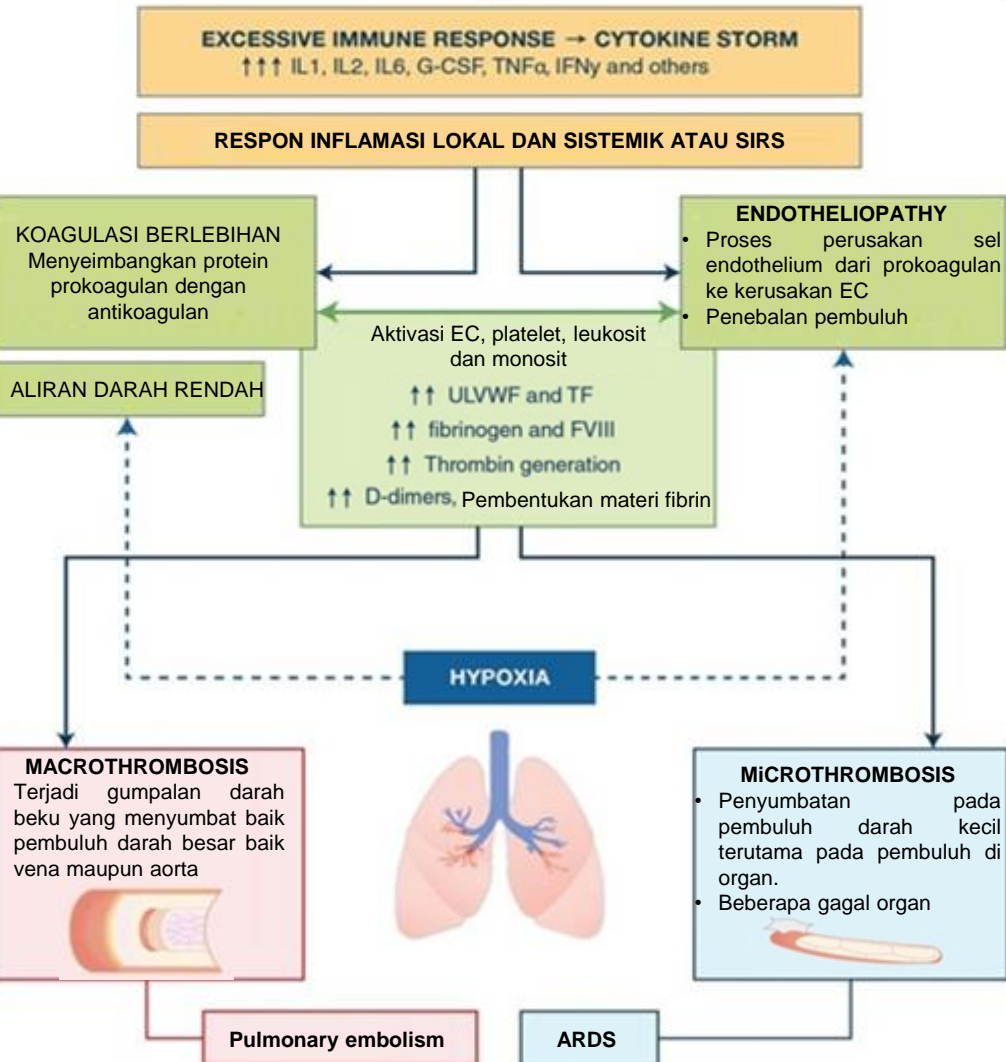
- Anti-inflamasi : menurunkan badai sitokin
- Immunomodulatory
- Pro-angiogenesis

Patofisiologi COVID-19

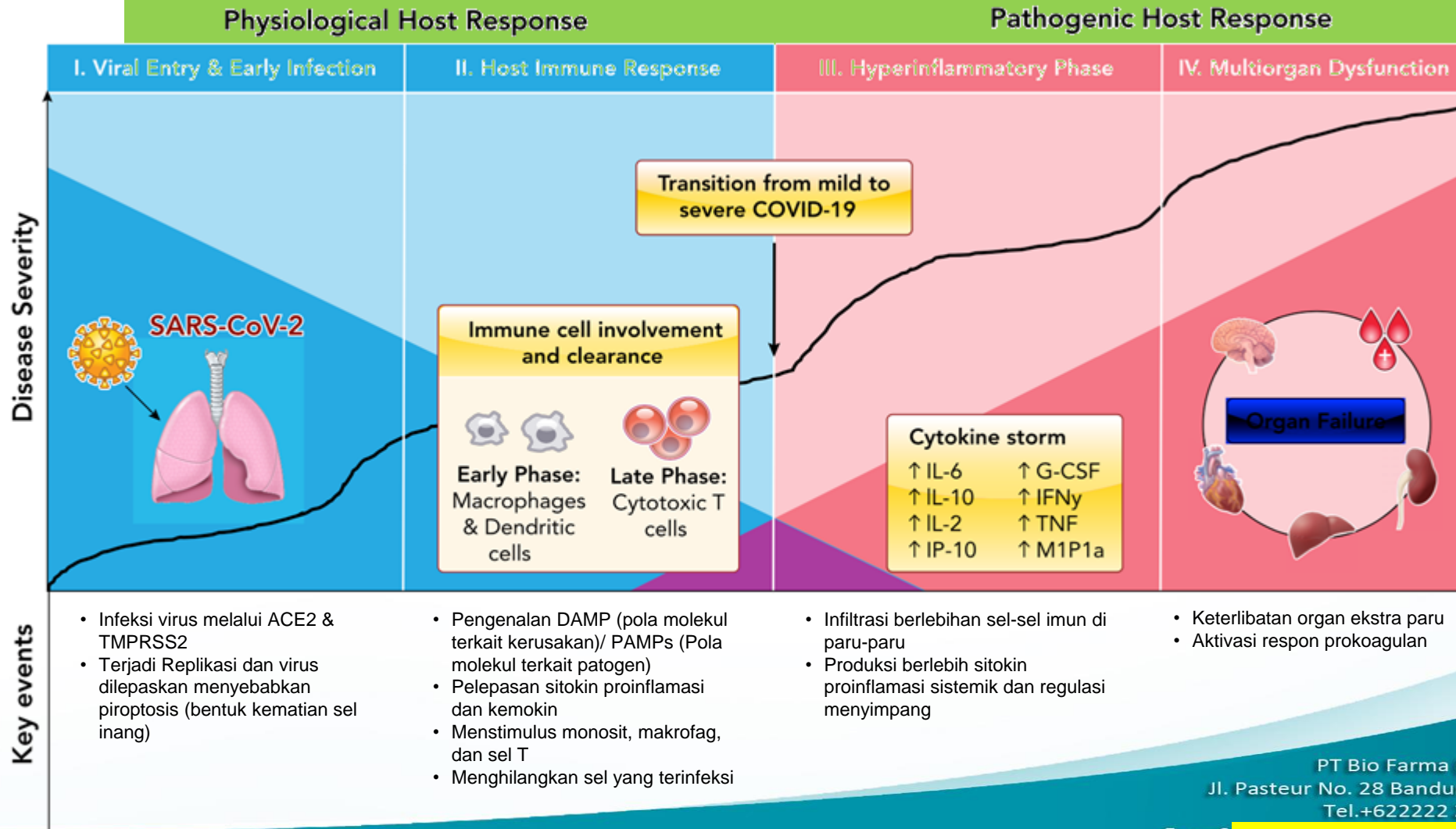


CORONA VIRUS DISEASE-19 (COVID-19) : global health issue

Cytokine Storm in Lung

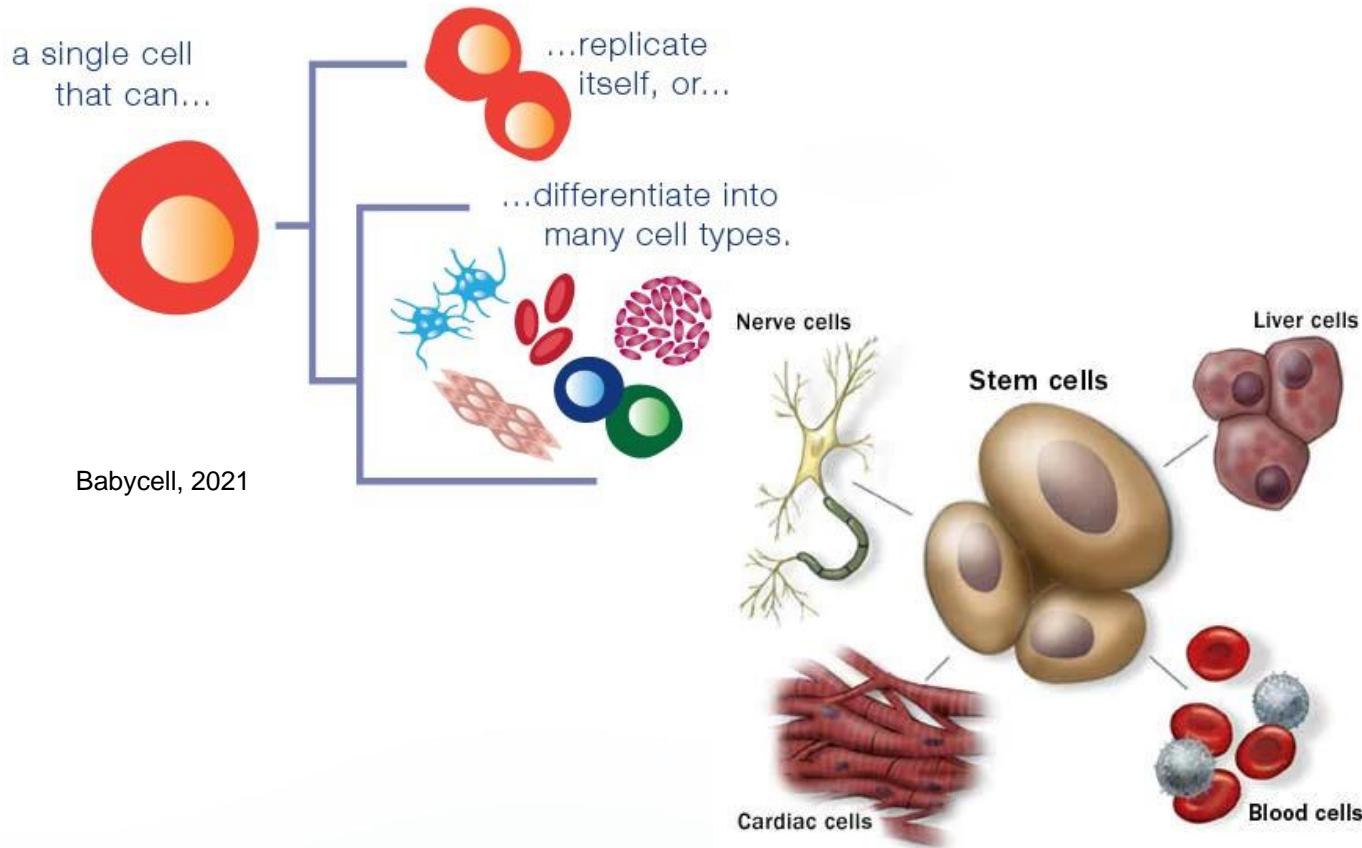


Characterization of Key Events in COVID-19 Disease Pathophysiological Progression



What is Stem cell



What is a Stem Cell?




Babycell, 2021

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Benefits :

Used to treat **over 80** diseases



Used in **22%** of all stem cell transplants



Used in **30,000** medical treatments worldwide in past 20 years



@infoimunisasi

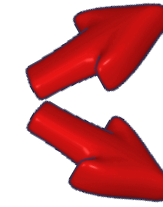


infoimunisasi

Stem Cell

Definition of Stem Cell

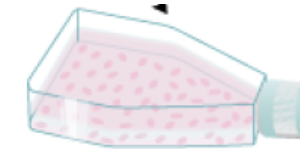
- I. Belum terspesialisasi
- II. Replicate it self like mother
- III. Self renewal
- IV. Differentiation : unipotent, totipotent, multipotent, pluripotent



MSC : CD105+,C90+,CD73+,CD34,CD45-, CD14-

I. Cell ← HLA Typing

II. Secretome



2 Dimensi



3 Dimensi

Secretome contain :

1. Solved protein: cytokine, chemokine, growth factor
2. Ekstraseluler vesicel : exosome, microvesicle

Stem cell therapy

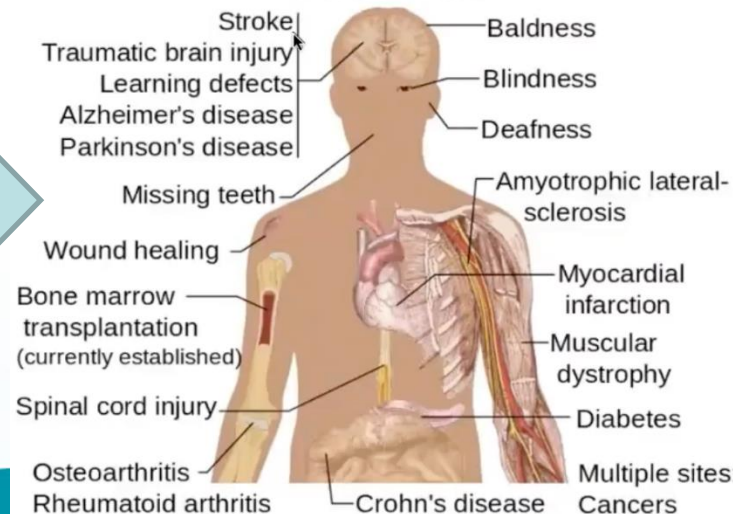


Permenkes
No 32/ 2018

Ethical approved : unipotent, multipotent

No Cure
No Hope
No Option → **5R : Regenerate**
Repair
Restore
Rejuvenate
Replace

Potential uses of Stem cells



STEM CELL DIFFERENTIATION

This cell
Can form the
Embryo and placenta

fertilised egg



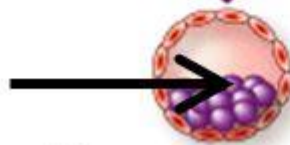
totipotent stem cells

Totipotent

No ethic



This cell
Can just form the
embryo



blastocyst containing
pluripotent stem cells

Pluripotent

No ethic

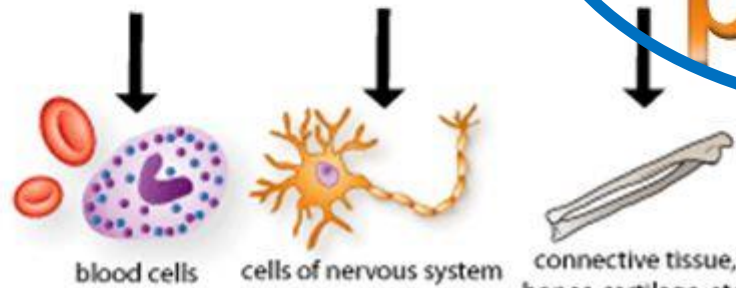
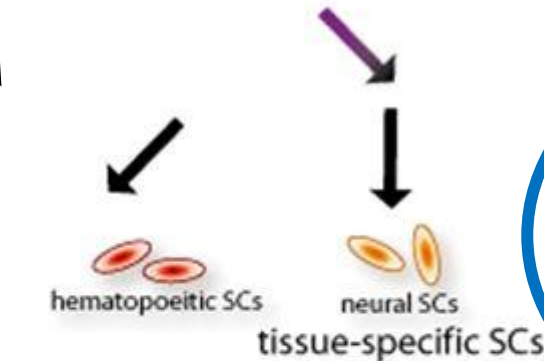
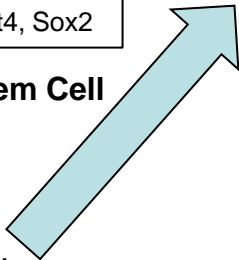


Reprogramming factor:
c-Myc, Klf4, Oct4, Sox2

Induced Pluripotent Stem Cell

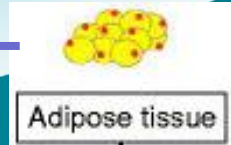
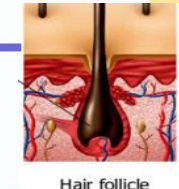
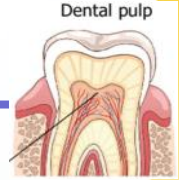
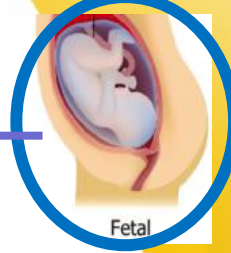
Tumorogenic

Somatic Cell



ethic
Multi-potent

Fully mature

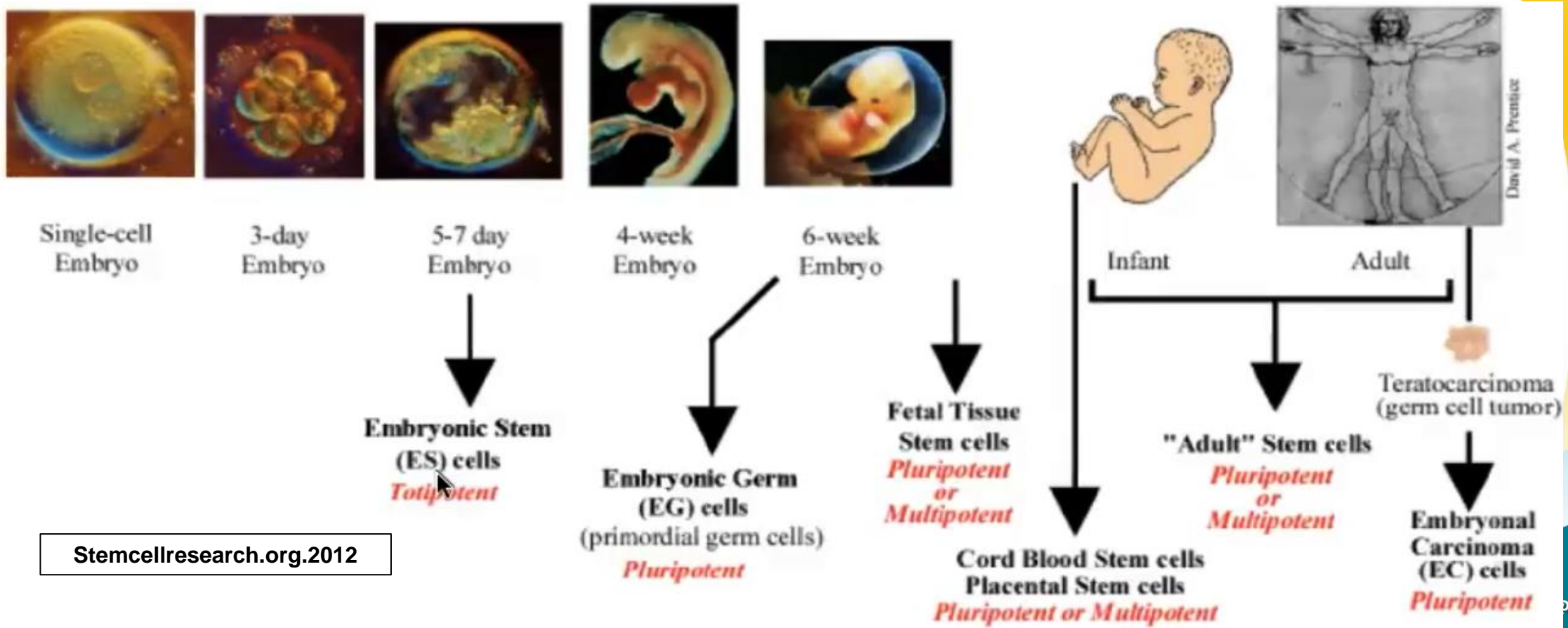


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JENIS STEM CELL

Human Developmental :



Stemcellresearch.org.2012

Autologous cell therapy

- No immune response
- Same environment as patient
- Manufacturing failure dependent
- Additional invasive procedure
- Delayed delivery

Quality control:

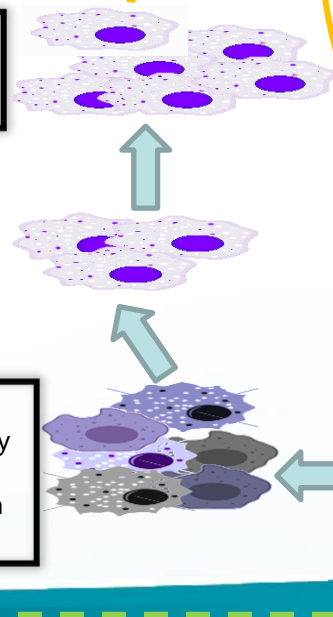
- Sterility
- Viability
- Differentiation or immunosuppression ability

Expansion:

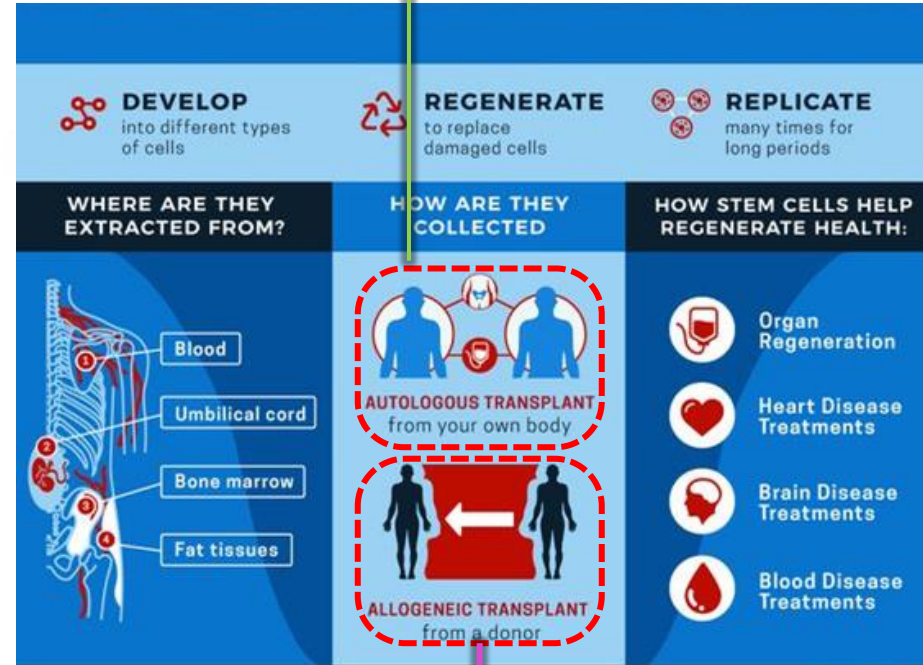
- 2-3 passages
- Characterization

Isolation:

- Gradient density centrifugation
- Plastic Adherence
- Trypsinization



AUTOLOGOUS VS ALLOGENIC



Donor eligibility:

- Sterility
- Viability
- Differentiation or immunosuppression ability

Isolation:

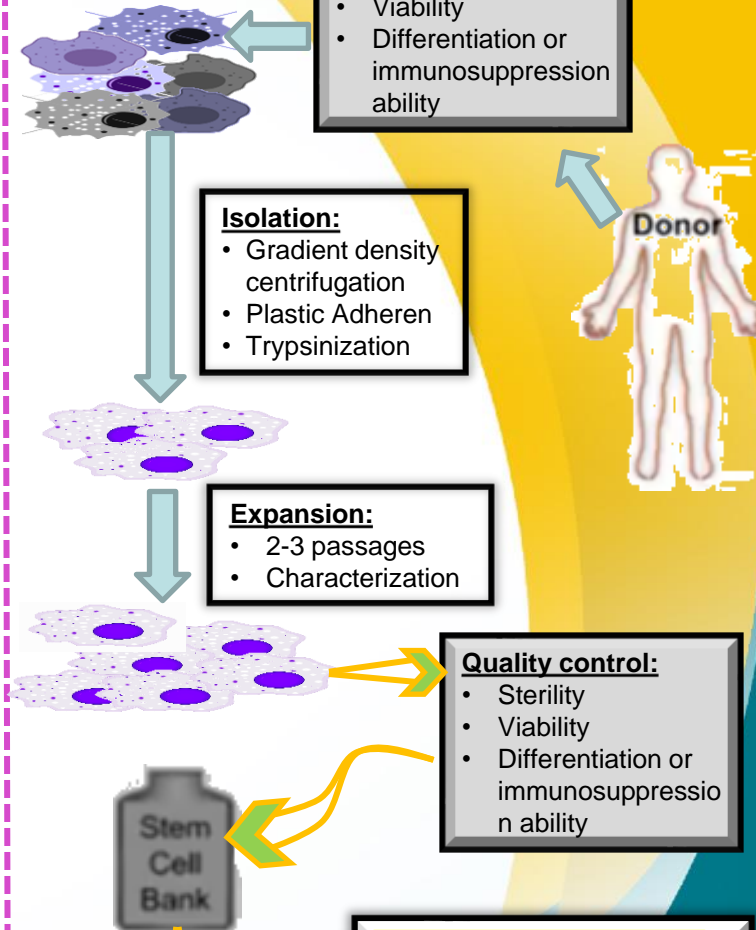
- Gradient density centrifugation
- Plastic Adherence
- Trypsinization

Expansion:

- 2-3 passages
- Characterization

Quality control:

- Sterility
- Viability
- Differentiation or immunosuppression ability



Allogeneic cell therapy

- Minimal Immune response
- Readily available
- Guaranteed dosage
- Young healthy donors
- No additional invasive procedure

Quality control:

- Sterility
- Viability
- Differentiation or immunosuppression ability

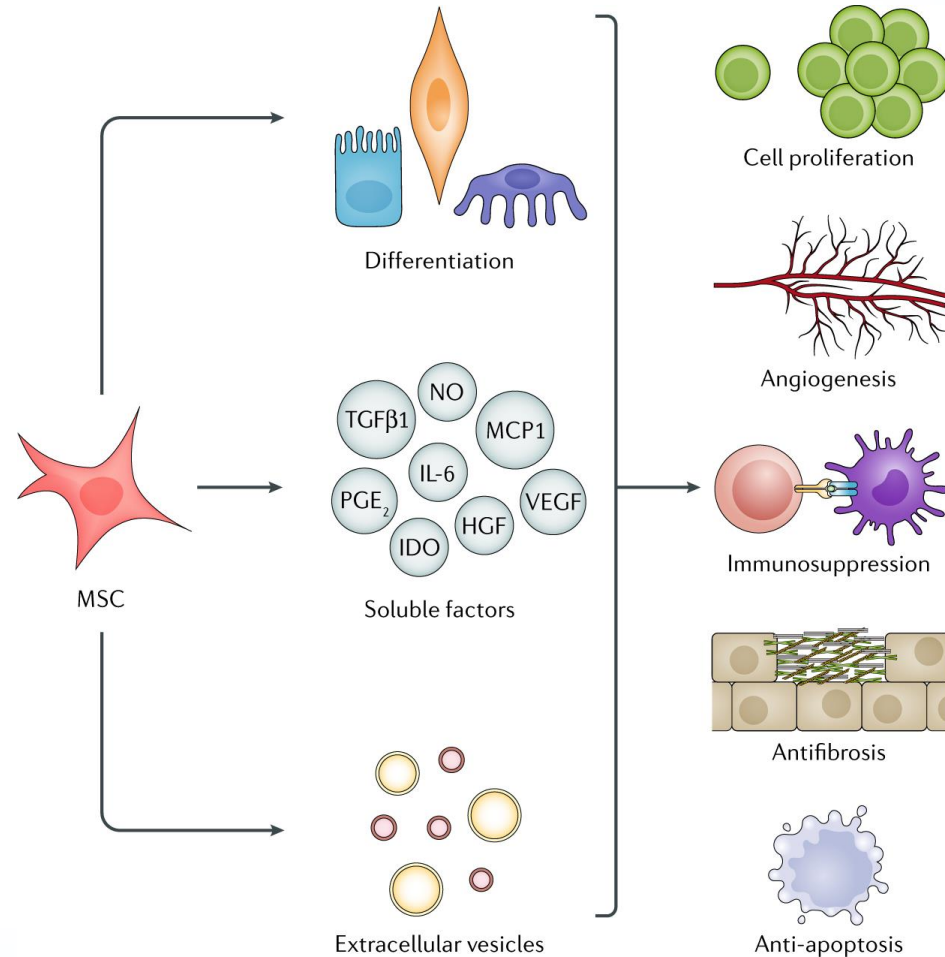
Turunan Stem Cell

(stem cell derivatives)



Stem cell

Skretom



Sekretom?

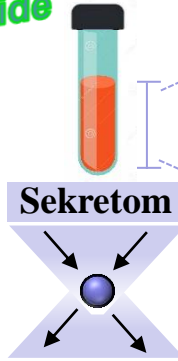
yaitu *small molecule* yang merupakan campuran kompleks antara protein terlarut (*cytokines, chemokines, growth factors*) dan vesikel ekstraseluler (*eksosom, microvesicles*).

Novel cell-free therapy : from bench to bedside

- Visible
- Kemandirian bangsa

1. Produk sekretom yang terbaik terstandarisasi
2. Kearifan lokal (UCB)
3. Limbah medis

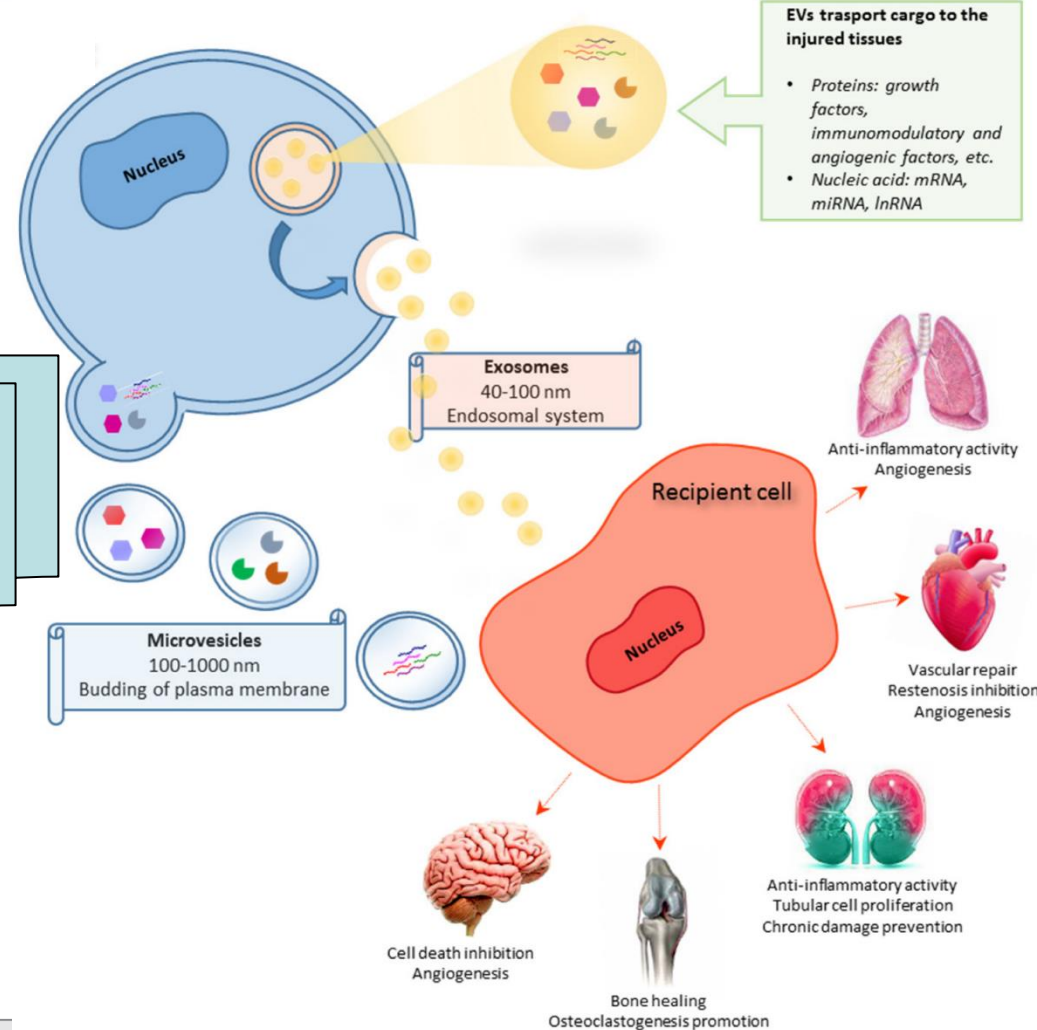
Sekretom



PATEN

1. Homogen = variasi
2. Massal
3. Reproducible
4. Stabil, biocompatibility, lower toxicity lower immunogenicity (Terriaca *et al*, 2021)

Sinergi (Sretome , Eksosome, Faktor terlarut)
Perbaiki lingkungan mikro dan perbaiki kerusakan

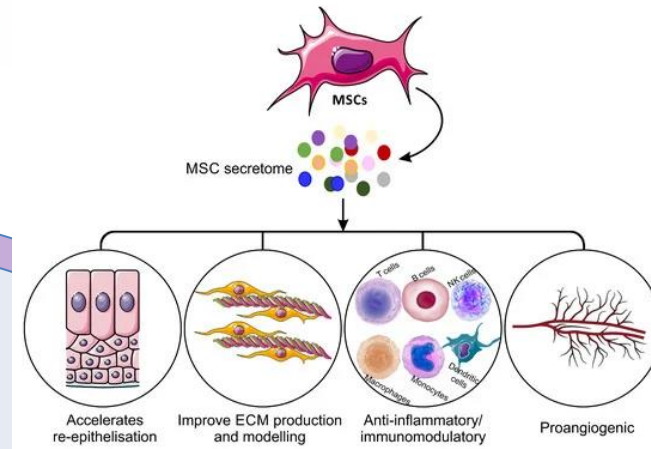
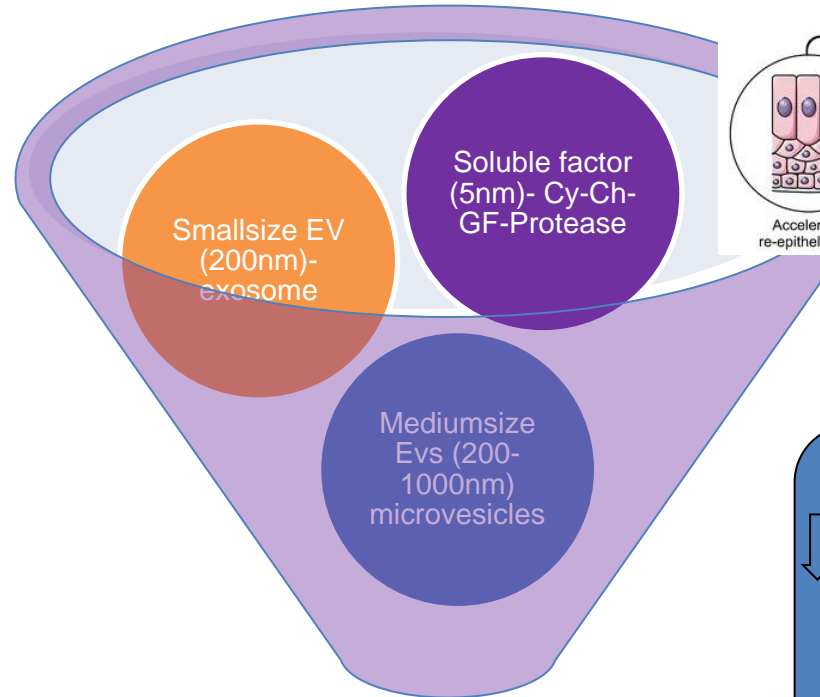


EVs transport cargo to the injured tissues

- Proteins: growth factors, immunomodulatory and angiogenic factors, etc.
- Nucleic acid: mRNA, miRNA, lncRNA

Characteristics	Exosomes	Microvesicles	Apoptotic Bodies
Origin [51]	Endosomal network	Plasma membrane	Plasma membrane
Size [1, 2]	50-150 nm	50-1000 nm	500-2000 nm
Markers [2, 21]	Tetraspanins (CD63, CD9), ESCRT components, Alix, TSG101, flotillin, MFGE8	Integrins, selectins, CD40 ligand	Extensive amount of phosphatidylserine
Morphology [21]	Cup-shaped	Irregular	Heterogeneous
Contents [2, 51]	mRNA, miRNA, cytoplasmic and membrane proteins, including receptors and MHC molecules	mRNA, miRNA, cytoplasmic and membrane proteins, including receptors	Histones, DNA, cell organelles

Skretom stem cell :

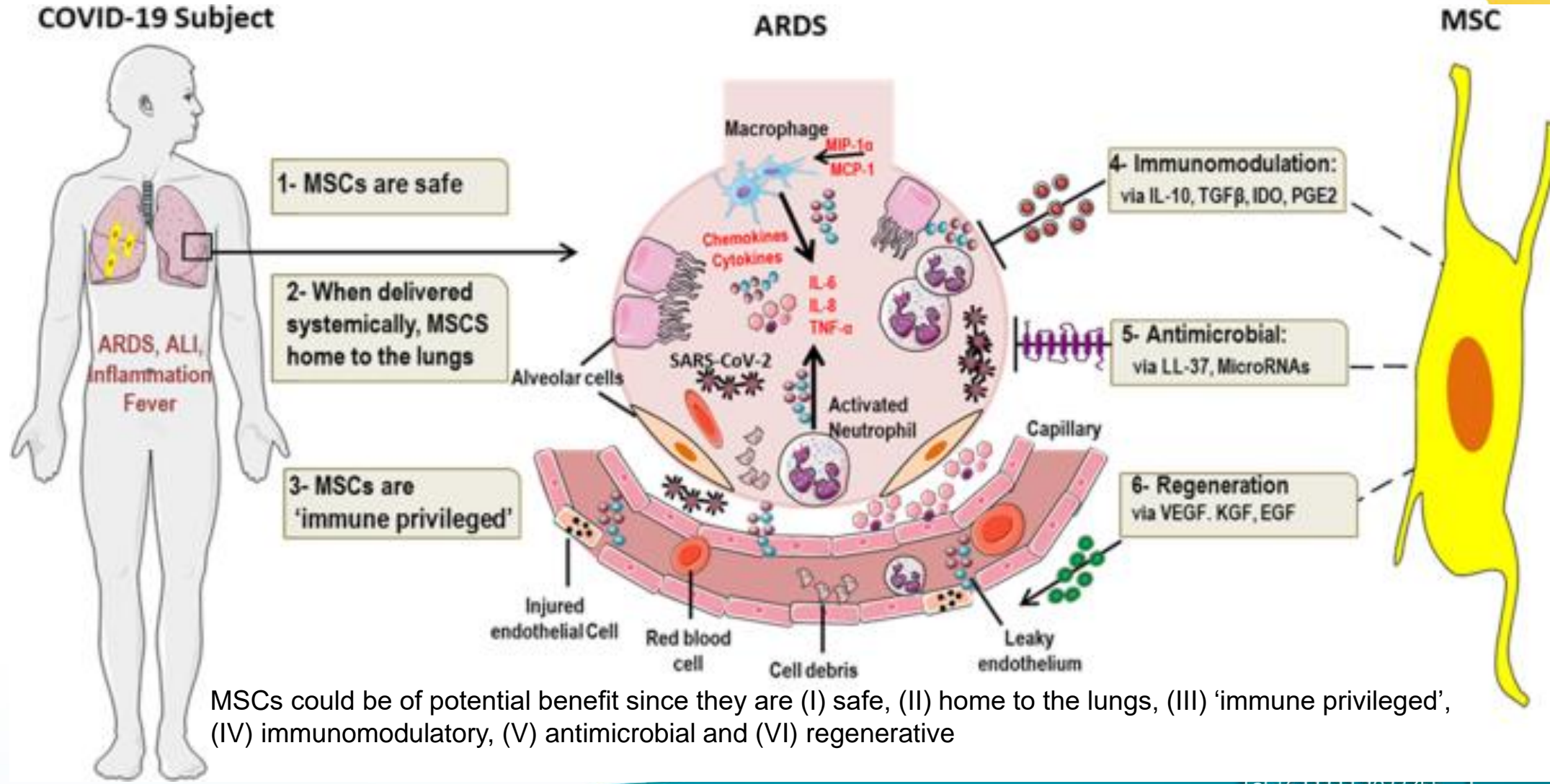


Covid-19:
 ↓ D-dimer, CRP,
 gambaran ground glass
 opacity

Skretome/Sceretome:

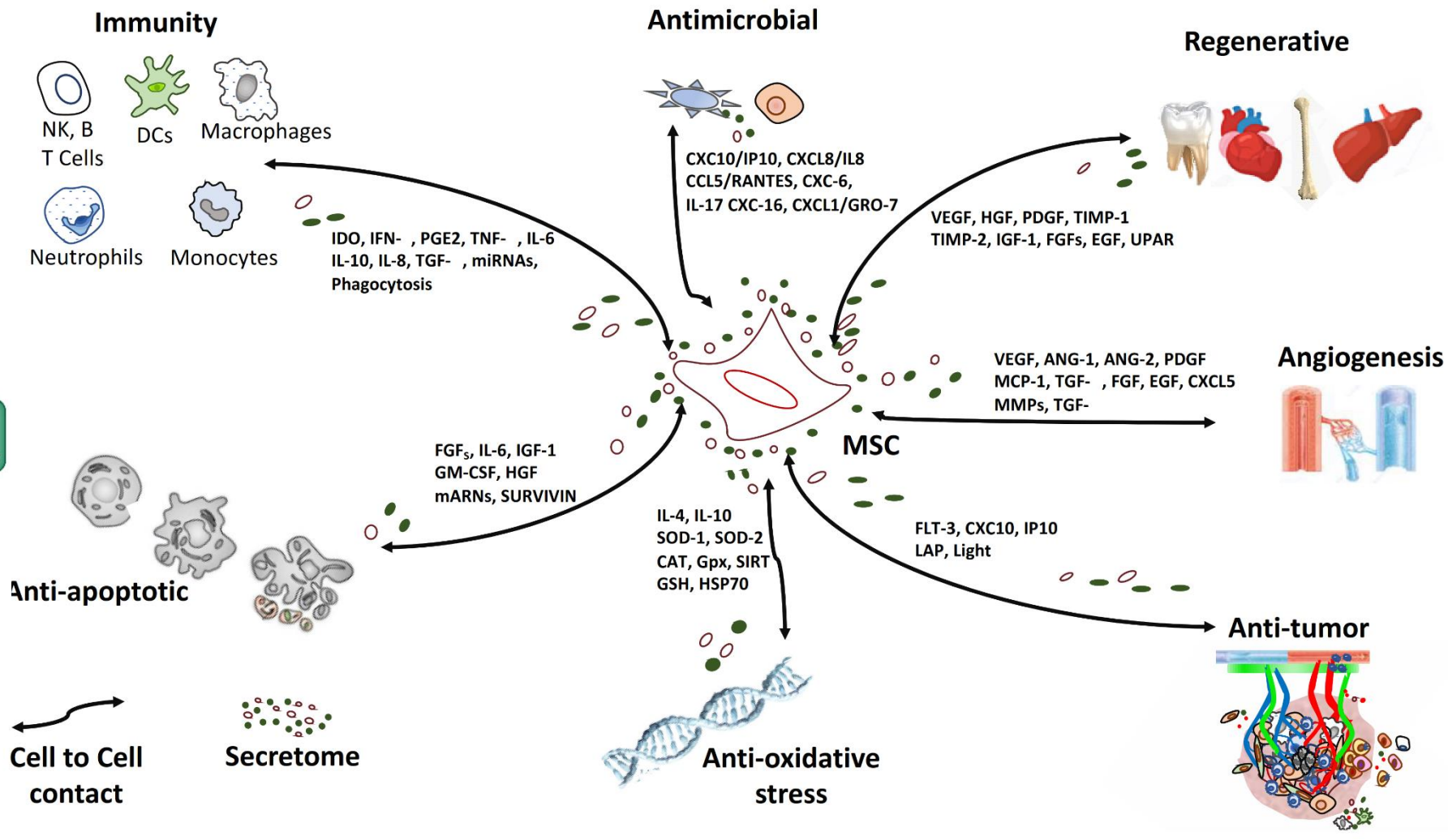
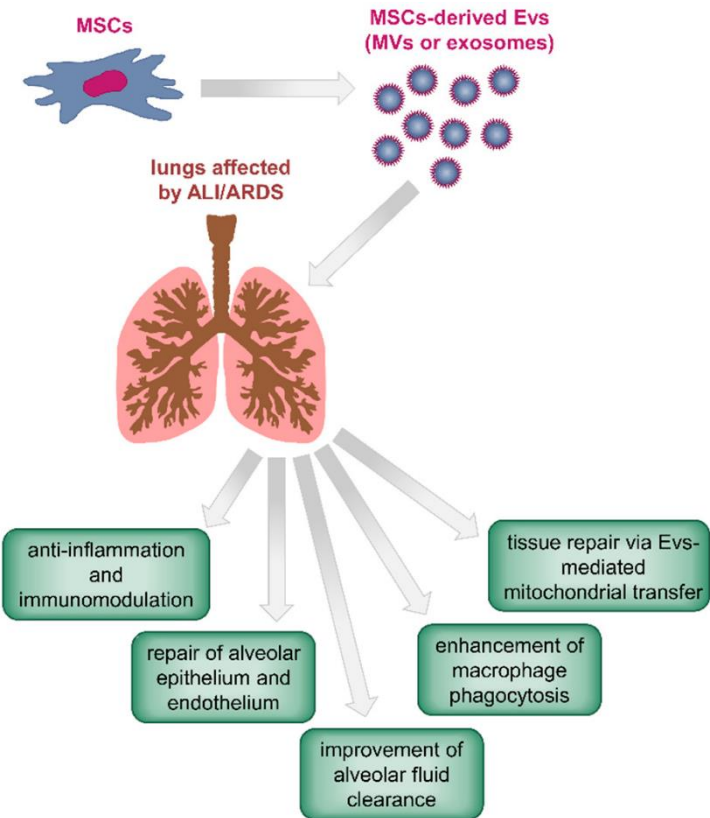
1. Bebas sel
2. Memperbaiki jaringan yang rusak

Stem Cell Therapy for COVID-19



MSCs could be of potential benefit since they are (I) safe, (II) home to the lungs, (III) 'immune privileged', (IV) immunomodulatory, (V) antimicrobial and (VI) regenerative

Mekanisme Stem Cell



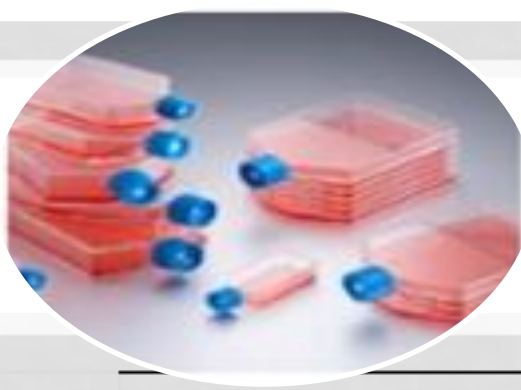


Industri Stem cell

Produksi massal stem cell dan metabolites
di Bio Farma

Kultur 2D vs 3D





2D VS 3 D:



Kondisi	2 Dimensi	3 Dimensi
Culture system	<i>opened</i>	<i>closed</i>
GMP system	<i>yes</i>	<i>yes</i>
Clinical grade	<i>yes</i>	<i>yes</i>
Risk of contamination	<i>high</i>	<i>low</i>
Surface per volume ratio	<i>low</i>	<i>high</i>
Control system	<i>Manually</i>	<i>Automatically</i>
Yield	<i>low</i>	<i>high</i>

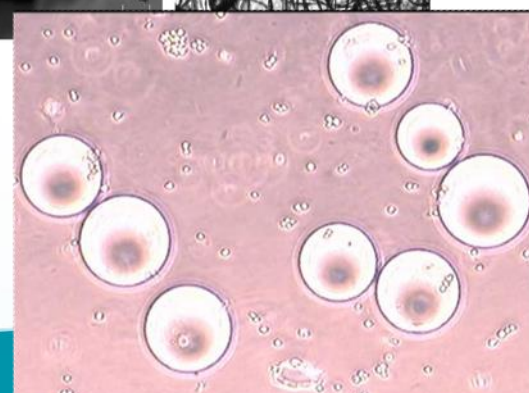
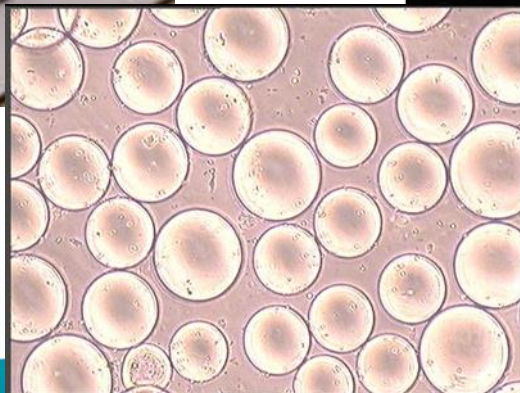
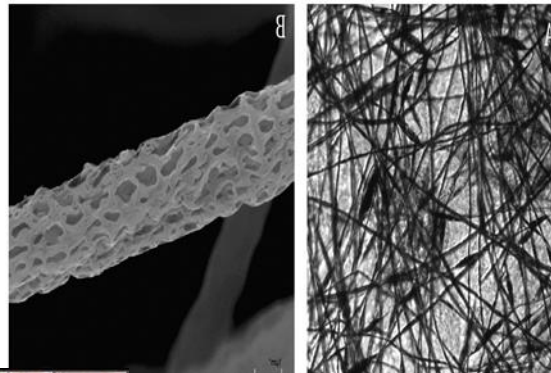
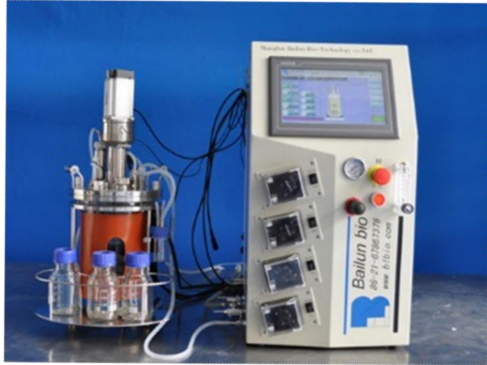
Karakteristik Sel	2 Dimensi	3 Dimensi
Shape	<i>spindle , plastic adherent, elasticity, 0.3µm</i>	<i>spheroids, aggregates, ellipsoidswith dimension 10-30 µm</i>
Environment	<i>50% exposed to other cells, 50% to surface</i>	<i>~100% exposed to other cells</i>
Behaviour	<i>unnaturally</i>	<i>naturraly and better</i>

Kultur Konvensional/Tradisional Metode 2 Dimensi (2D):

- Botol/cawan petri
 - botol bersusun/Cell factor
- Sel memanjang/stretch/besar
tidak natural/komunikasi 2 D
panen sedikit → lama



Kultur 3 Dimensi Bioreaktor



Types of Single Use Bioreactors

Stirrer Type

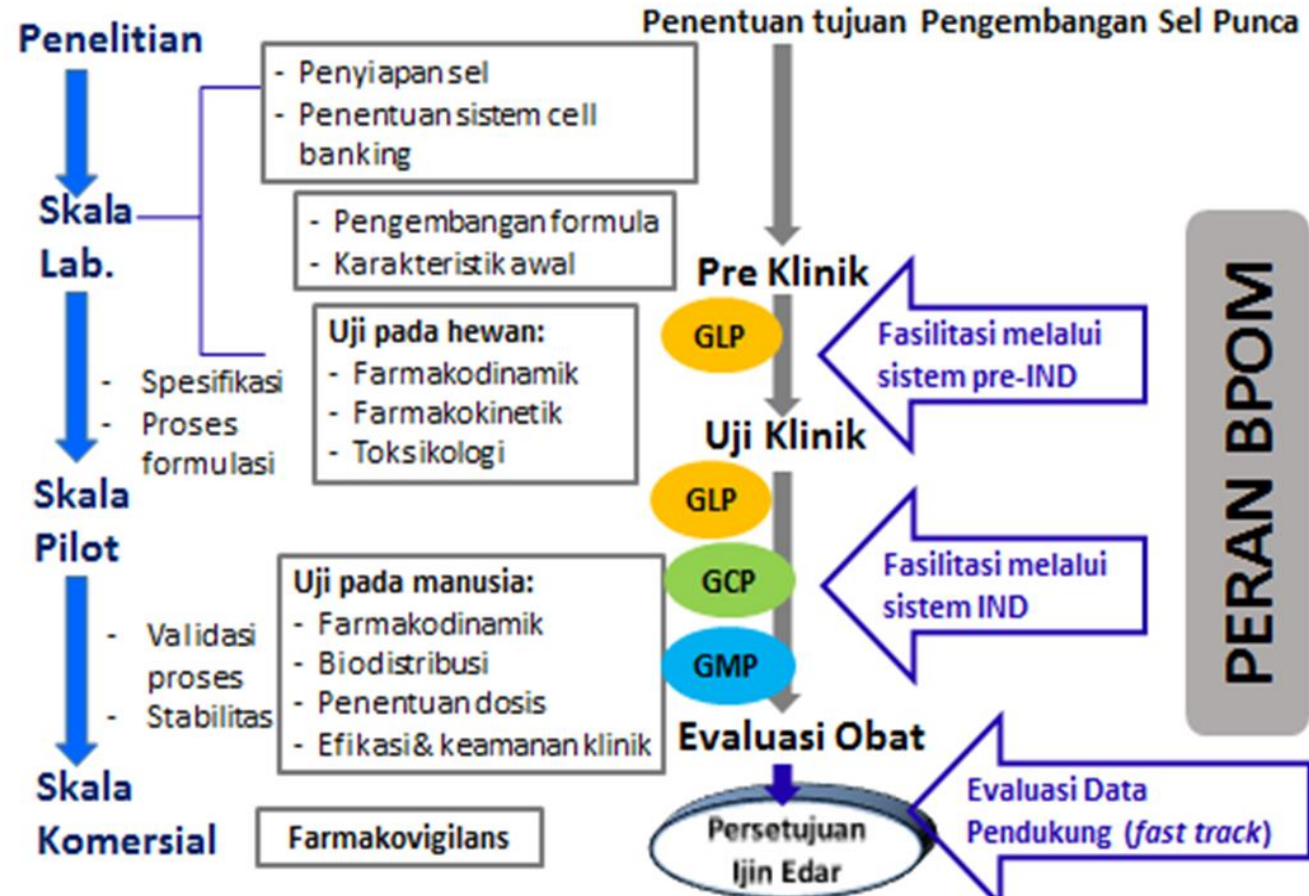


Rocking Motion Type



Produk Stem Cell (BPOM-RI)

Rencana Pelaksanaan Proyek



BIO FARMA
(INDUSTRI FARMASI)

B
A
L
A
N
C
E



biofo



?

Question



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