Stem Cell and Cancer Research
Medical Faculty of UNISSULA

Secretome of Hypoxia-Mesenchymal Stem Cells in Controling Cytokine Storm COVID-19

Assoc.Prof.DR.dr. Agung Putra, MSi, Med

Director of SCCR (Stem Cell & Cancer Research) Indonesia

Chairman of PERSEPSI (Perkumpulan Peneliti Sel Punca Indonesia)

PERSONAL DETAILS

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Faculty of Medicine UNISSULA, Semarang.
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NIP/NIDN : 210199050 / 0607067102

Date of Birth : Juni 7th, 1971

Nationality : INDONESIA

POSITIONS

POSITION	AFFILIATION	DURATION
Director	Stem Cells and Cancer Research (SCCR) Medical Faculty of UNISSULA	Since 2012
Guest Lecturer / Co-promotor PhD	Doctoral Program of Faculty Medicine (PhD Program) Sumatera Utara University	Since 2019
Co-promotor PhD	Doctoral Program of Faculty Medicine (PhD Program) Diponegoro University (UNDIP)	Since 2020
Co-promotor PhD	Doctoral Program of Faculty Medicine (PhD Program) Sebelas Maret University (UNS)	Since 2020
International PhD Examiner	PhD Program of Biotechnology, SNMV College of Arts and Sciences, Coimbatore, India	Since 2020
Chairman	Perkumpulan Peneliti Sel Punca Indonesia (PERSEPSI)	Since 2020

RESEARCH PUBLICATION INTERNATIONAL / NATIONAL

SCOPUS
H-Index : 4
ID : 57197818079
: https://www.scopus.com/authid/detail.uriauthorId=57197818079

ORCHID
ID : 0000-0003-4261-9437
: http://orcid.org/0000-0003-4261-9437

SINTA
SCORE : 8,39
ID : 6200121
: http://sinta.ristekbrin.go.id/authors/detail?id=6200121&view=overview

PROFESIONAL SERVICE

INTERNATIONAL REVIEWER

NO	POSITION	INSTITUTION	DURATION
1	International Reviewer	Cytokine Elsevier (Scopus Q1)	Since 2020
2	International Reviewer	F1000 Research (Scopus Q1)	Since 2020
3	International Reviewer	Folia Medika Bulgaria (Scopus Q2)	Since 2020
4	International Reviewer	Biocell (Scopus Q4)	Since 2020

NATIONAL REVIEWER

NO	POSITION	INSTITUTION	DURATION
1	National Reviewer	Research of Ministry Research, Technology and Higher Education	Since 2019
2	National Reviewer	Majalah Kedokteran Bandung	Since 2019
3	National Reviewer	IJCC UGM	Since 2020

NO	TITLE	VOLUME (NO) YEAR	JOURNAL
1	MSCs Released TGFβ1 Generate $CD4^+CD25^+Foxp3^+$ in T-reg Cells of Human SLE PBMC	120 (1) 2020	**SCOPUS Q1 :** Journal of Formosan Medical Association https://www.sciencedirect.com/science/article/pii/S0929664620302886
2	MSCs Regulate PDGF and VEGF Levels in Inflammation and Remodeling Phases Diabetes Islet Cell Regenaration	Accepted / 2020	**SCOPUS Q2 :** Folia Medica Bulgaria
3	Intravenous Administration of Mesenchymal Stem Cells is The Best Route for Improving Liver Function Enzyme during Acute Liver Failure	62 (1) 2020	**SCOPUS Q2 :** Folia Medica Bulgaria https://www.researchgate.net/publication/340316864_Intravenous_Administration_is_the_Best_Route_of_Mesenchymal_Stem_Cells_Migration_in_Improving_Liver_Function_Enzyme_of_Acute_Liver_Failure
4	MSC-released TGF-β regulate α-SMA expression of myofibroblast during wound healing	16 (2) 2020	**SCOPUS Q2 :** Journal of Stem Cells & Reegenerative Medicine (JSRM)
5	Thyphonium flagelliforme Extract Induce Apoptosis in Breast Cancer Stem Cells by Suppressing Survivin	16 (6) 2020	**SCOPUS Q2:** Journal of Cancer Research and Therapeutics https://www.cancerjournal.net/article.asp?issn=0973-1482;year=2020;volume=16;issue=6;spage=1302;epage=1308;aulast=Putra

KOMISI ETIK PENELITIAN KESEHATAN
HEALTH RESEARCH ETHICKS COMMITTEE
RUMAH SAKIT BETHESDA YOGYAKATYA
BETHESDA HOSPITAL YOGYAKARTA

KETERANGAN LAYAK ETIK
DESCHRIPTION OF ETHICAL APPROVAL
" ETHICAL APPROVAL "

No. 91/KEPK-RSB/VI/20

Protokol penelitian yang diusulkan oleh:
The research protocol proposed by

Peneliti utama : Dr. dr. Agung Putra, M.Si., Med
Principal in Infestigator

Nama Institusi : Stem Cell and Cancer Recearch
Name of the Istitution

Dengan judul :
Title
" PENGARUH PEMBERIAN ISOLATE SECRETOME MESENCHYMAL STEM CELI HYPOXIA TERHADAP PERBAIKAN PENDERITA COVID 19 "

Dinyatakan layak etik sesuai 7 (tujuh) Standar WHO 2011, yaitu1) Nilai Sosial, 2) Nilai Ilmiah, Pemerataan Beban dan Manfaat, 4) Risiko, 5) Bujukan/Eksploitasi, 6) Kerahasiaan dan Privacy, Persetujuan Setelah Penjelasan, yang merujuk pada Pedoman CIOMS 2016, Hal ini seperti ya ditunjukkan oleh indikator setiap standar.

Declared to be ethical appropriate in sccordance to 7 (seven) WHO 2011 Standars, 1) Social Values, Scientific Values, 3) Equitable Assesment and Benefits, 4) Risk, 5) Persuasion/Exploitation, Confidentiality, 7) Informed Consent, referring to the 2016 CIOMS Guidelines. This is as indicated by fulfilment of the indicator of each standard.

Pernyataan Laik Etik ini berlaku selama kurun waktu tanggal 8 Juni 2020 sampai dengan tanggal 8 Ju 2021.
This Declaration of ethics applies during the period Juni 8, 2020 until Juni 8, 2021.

LOKASI PENELITIAN:
1. RSUP Dr. Kariadi Semarang
2. RSUP Dr. Moewardi Surakarta
3. RS Khusus Dadi Propinsi Sulawesi Selatan
4. RS Bhayangkara Makasar
5. RSPAD Gatot Soebroto Jakarta
6. RS AU Esnawan Antariksa, Halim Perdana Kusuma Jakarta
7. RSI Sultan Agung Semarang
8. RS Martha Friska Multatuli Sumatarea Utara
9. RS PKU Muhammadiyah Gamping Yogyakarta

Juni 8, 2020
Professor And Chairperson

Dr. T.A. Meriel Kusumosih, Sp.OG

KEMENTERIAN KESEHATAN REPUBLIK INDONESIA
BADAN PENELITIAN DAN PENGEMBANGAN KESEHATAN
Jalan Percetakan Negara No. 29 Jakarta 10560 Kotak Pos 1226
Telepon (021) 4261088 Faxsimile (021) 4243933
Laman : www.litbang.depkes.go.id Surat Elektronik : sesban@litbang.depkes.go.id

Nomor : LB.02.01/II/2791/2020 13 Juli 2020
Hal : Penetapan Rumah Sakit sebagai Lokasi Penelitian

Yth. *Principal Investigator* (PI) Penelitian MSC *Hypoxia*
Stem Cell and Cancer Research (SCCR)
Jalan Kaligawe Raya Km. 4
Gedung IBL Unissula
Semarang

Berdasarkan surat Saudara Nomor: 10/SCCR/VI/2020 tertanggal 22 Juni 2020 hal Permohonan Penunjukan Senter, sebagai tindak lanjut hasil audiensi Tim Peneliti dengan Menteri Kesehatan, maka bersama ini ditunjuk rumah sakit:
1. RSPAD Gatot Subroto Jakarta;
2. RSAU Esnawan Antariksa-Halim Perdana Kusuma Jakarta;
3. RSUP Dr. Kariadi Semarang;
4. RSUD Dr. Moewardi Surakarta;
5. RS Khusus Dadi Provinsi Sulawesi Selatan;
6. RS Bhayangkara Makassar;
7. RSI Sultan Agung Semarang;
8. RS Martha Friska Multatuli Sumatera Utara;
9. RS PKU Muhammdiyah Gamping, Yogyakarta;

sebagai senter penelitian yang berjudul "PENGARUH PEMBERIAN ISOLATE SECRETOME MESENCHYMAL STEM CELLS HYPOXIA TERHADAP PERBAIKAN PENDERITA COVID-19."

Atas perhatian dan kerja sama Saudara, kami ucapkan terima kasih.

Plt. Kepala Badan Litbangkes,

dr. Slamet, MHP.
NIP 196304081990111001

Tembusan:
1. Kepala RSPAD Gatot Soebroto Jakarta
2. Kepala RSAU Esnawan Antariksa-Halim Perdanakusuma Jakarta
3. Direktur Utama RSUP Dr. Kariadi Semarang
4. Direktur RSUD Dr. Moewardi Surakarta
5. Direktur RS Khusus Daerah Dadi Provinsi Sulawesi Selatan
6. Kepala RS Bhayangkara Makassar
7. Direktur Utama RSI Sultan Agung Semarang
8. Direktur Utama RS Martha Friska Multatuli Sumatera Utara
9. Dikretur Utama RS PKU Muhammadiyah Gamping Yogyakarta

PANGLIMA TNI

Nomor : B/2783 · IS/8/1/81/Bang Kes Jakarta, 7 Agustus 2020
Klasifikasi : Biasa
Lampiran : -
Perihal : Dukungan uji klinik penelitian

Dasar:

a. Surat *Principal Investigator Stem C* Nomor 17/SCCR/VII/2020 tanggal 10 J klinik penelitian "Pengaruh Pemberian *Hypoxia* terhadap Perbaikan Penderita C

b. Lembar Disposisi Panglima TNI N Juli 2020 tentang tanggapan permohon Pemberian *Isolate Secretome Mesenchy* Penderita Covid-19"; dan

c. Pertimbangan Pimpinan dan Staf M

Sesuai dasar tersebut di atas, dengan erkenan memberikan dukungan pelaksana *ecretome Mesenchymal Stem Cells Hypoxia* SPAD Gatot Soebroto dan RSAU dr. Esnawa

Demikian mohon dimaklumi.

mbusan:

Kasum TNI
Kabais TNI
Asintel, Aspers Panglima TNI
Kapuskes TNI

PUSAT KEDOKTERAN DAN KESEHATAN POLRI
RUMAH SAKIT BHAYANGKARA TK. I R. SAID SUKANTO
Jalan Raya Kramatjati Jakarta Timur 13510 Jakarta, 8 September 2020

Nomor : B/ 3910 /IX/2020/Rs Bhay. Tk. I
Klasifikasi : BIASA
Lampiran : -
Perihal : Permohonan keikutsertaan dalam penelitian uji klinis

Kepada

Yth. Dr. dr Agung Putra, M.Si, Med
Principal Investigator

di

Semarang

1. Rujukan:
   a. Keputusan Menteri Kesehatan Republik Indonesia Nomor :HK.01.07/MENKES/104/2020 tanggal 04 Februari 2020 tentang Penetapan Infeksi novel corona virus (infeksi 2019-nCoV) sebagai penyakit yang dapat menimbulkan wabah dan upaya penanggulangannya;
   b. Keputusan Menteri Kesehatan Republik Indonesia Nomor HK.01.07/Menkes/169/2020 tentang Penetapan Rumah Sakit Bhayangkara Tk. I R. Said Sukanto sebagai Rumah Sakit Rujukan Penanggulangan Penyakit Infeksi Emerging Tertentu di wilayah DKI Jakarta.

2. Sehubungan dengan rujukan tersebut di atas, bersama ini disampaikan bahwa sebagai salah satu Rumah Sakit Rujukan Covid-19 di wilayah DKI Jakarta, Rumah Sakit Bhayangkara Tk.I R. Said Sukanto telah merawat pasien covid-19 dengan kriteria sedang, berat dan kritis, dengan semakin meluasnya penyebaran wabah covid-19 di Indonesia, diperlukan langkah cepat dan sinergis dalam riset dan inovasi, untuk itu mohon kiranya Rumah Sakit Bhayangkara TK.I R. Said Sukanto dapat bergabung dalam penelitian uji klinis dengan judul "**Pengaruh Pemberian Isolate *scretome mesenchymal stem hypoxia* Terhadap perbaikan penderita Covid-19**" yang telah dilakukan.

3. Besar harapan kami dapat bergabung dalam penelitian multimeter tersebut diatas. Atas perhatian dan berkenannya diucapkan terimakasih.

KEPALA RUMAH SAKIT BHAYANGKARA TK. I R. SAID SUKANTO

dr. ASEP HENDRADIANA, Sp. An. KIC, M.Kes
BRIGADIR JENDERAL POLISI

Tembusan:
Kapusdokkes

Stem Cell and Cancer Research
Medical Faculty of UNISSULA

PRINCIPAL INVESTIGATOR:
Assoc.Prof.DR. Dr. Agung Putra, M.Si.Med

INVESTIGATOR MEMBERS

1. Dr. Agus Widyatmoko, Sp.PD, M.Sc.
2. Dr. Sugeng Ibrahim, M.Biomed (AAM)
3. Kolonel Kes. dr. Mukti Arja Berlian, Sp.PD
4. Kombes Pol. dr. Farid Amansyah, Sp.PD. FINASIM
5. Mayjend CKM. dr. Nana Sarnadi, Sp.OG
6. AKBP. Pol. dr. Fajar Amansyah, Sp.PD. FINASIM
7. Dr. Rita Agustina, M.Kes
8. Dr. Bayu Tirta Dirja, Ph.D.
9. Dr. Zenitalia Pasongka, M.Biomed (AAM)
10. Kolonel CKM. dr. Gunawan Dwiprayitno, Sp.OG (K)FER
10. Dr. Dwi Antono, Sp.THT-KL(K)
11. Dr. Franciscus Ginting, M.Ked (PD), Sp.PD KPTI
12. Dr. dr. Adi Muradi Muhar, Sp.B KBD
13. Dr. Ken Wirastuti, Sp.S, KIC M.Kes.
14. Dr. dr. Imelda Rey, M.Ked (PD), Sp.PD, K-GEH
15. Dr. Dedy Hermansyah Sp.B(K)Onk
16. Dr. dr. Dodik Tugasworo Pramukarso, Sp.S(K)
17. Dr. Rivan Danuaji, M.Kes, Sp.S
18. Dr. Danu Soesilowati, Sp.An. KIC
19. Dr. dr. Retnaningsih, Sp.S(K), KIC
20. Dr. Bhirau Wilaksono
21. Dr.Friska. SpPK

U.S. National Library of Medicine

ClinicalTrials.gov

Trial record **1 of 8** for: secretome

Previous Study | Return to List | Next Study

Treatment of Severe COVID-19 Patients Using Secretome of Hypoxia-Mesenchymal Stem Cells in Indonesia

Sponsor:
Stem Cell and Cancer Research Indonesia

Collaborator:
Provincial Government of Central Java, Indonesia

Information provided by (Responsible Party):
Agung Putra, Stem Cell and Cancer Research Indonesia

Study Details | Tabular View | No Results Posted | Disclaimer | How to Read a Study Record

Study Description

Go to

Brief Summary:
In this randomized controlled trial (RCT), severe cases of COVID-19 infection will be treated with secretome of hypoxia-mesenchymal stem cells. The improvement in clinical, laboratory, and radiological manifestations will be evaluated in treated patients compared with the control group.

Indonesia

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Charlie Hospital — **Recruiting**
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RS PKU Muhammadiyah Yogyakarta — **Recruiting**
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Contact: Flora Eka Sari, MD, Sp.P +62821-1447-7473 floraeka86@gmail.com
Sub-Investigator: Sugeng Ibrahim, MD, M.Biomed (AAM)

Information from the National Library of Medicine NIH NLM

To learn more about this study, you or your doctor may contact the study research staff using the contact information provided by the sponsor.

Please refer to this study by its ClinicalTrials.gov identifier (NCT number): ***NCT04753476***

Stem Cell and Cancer Research
Medical Faculty of UNISSULA

Secretome stem cell SCCR published in Internasional jurnal Scopus Q1

F1000Research F1000Research 2021, 10:228 Last updated: 13 JUL 2021

Check for updates

CLINICAL PRACTICE ARTICLE

Case series of the first three severe COVID-19 patients treated with the secretome of hypoxia-mesenchymal stem cells in Indonesia [version 1; peer review: 1 approved, 1 approved with reservations]

Agung Putra[1-3], Agus Widyatmoko[4], Sugeng Ibrahim[1,5], Fajar Amansyah[6], Farid Amansyah[6], Mukti Arja Berlian[7], R Retnaningsih[8], Zenitalia Pasongka[9], Flora Eka Sari[10], Basuki Rachmad[11]

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[5]Department of Molecular Biology, Faculty of Medicine, Universitas Katholik (Unika) Soegijapranata, Semarang, Central Java, Indonesia
[6]Department of Internal Medicine, Bhayangkara Hospital, Makassar, South Sulawesi, Indonesia
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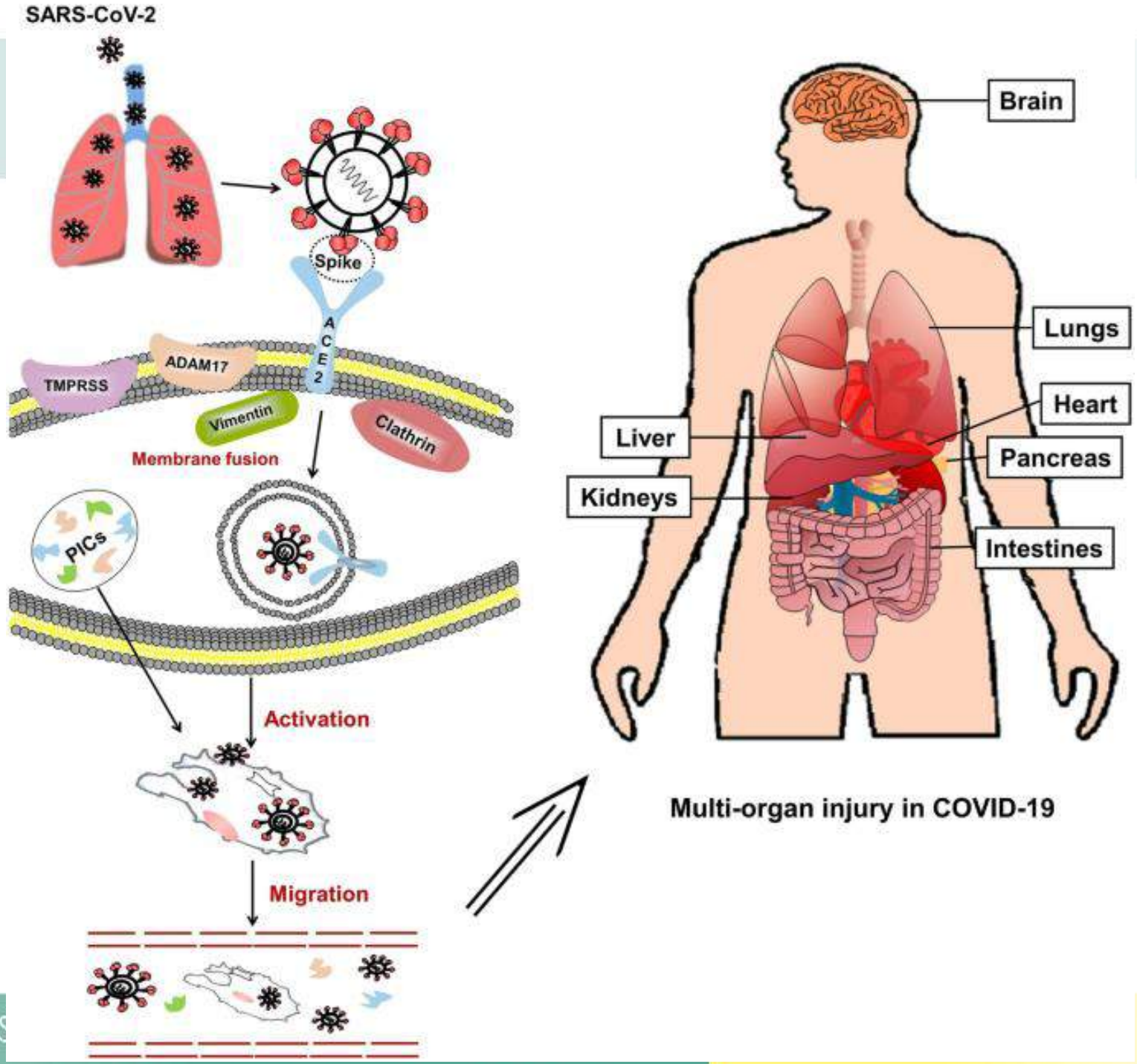
[8]Department of Neurology and Intensive Care Unit, Kariadi Hospital, Universitas Diponegoro, Semarang, Central Java, Indonesia
[9]Faculty of Medicine, Universitas Udayana, Denpasar, Bali, Indonesia
[10]Department of Pulmonary Medicine, Dr. Esnawan Antariksa Air Force Hospital, Jakarta, Jakarta, Indonesia
[11]Department of Intensive Care Unit, Gatot Soebroto Army Hospital, Jakarta, Jakarta, Indonesia

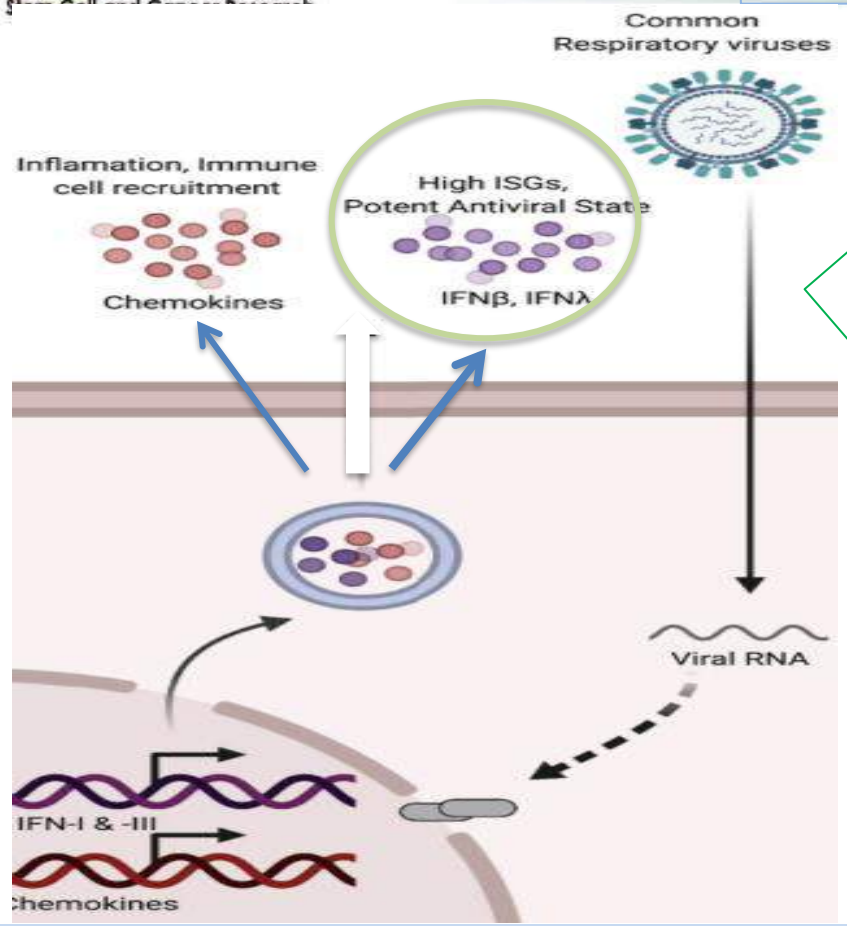
Tampilkan semua

Stem Cell and Cancer Research
Medical Faculty of UNISSULA

ACE2 Receprtor Distribution (Gejala Covid19 bervariasi)

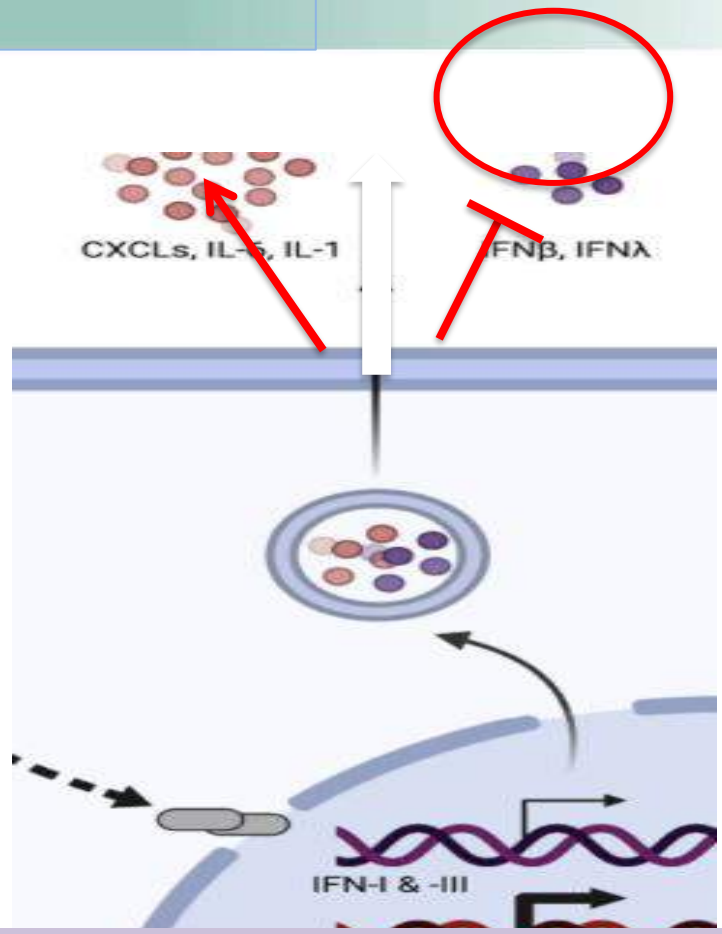


SARS COV-2 is Unique Virus



INFO!

Interferon (**IFN**) adalah molekul **perusak virus SARS CoV-2**



Virus flu sejenis:
Tubuh masih mampu stimulasi IFN sehingga virus SARS Co-V mudah di-eliminasi

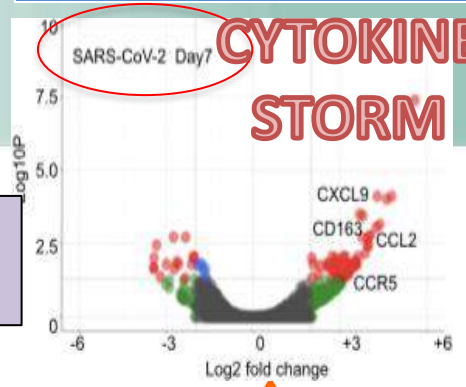
SARS-COV2:

- **Menghambat produksi IFN** sehingga tubuh sulit mengeliminasi virus secara cepat
- **Melepas chemokine** untuk mengatraksi (memanggil) berbagai sel radang untuk berkumpul di area paru

COMMON CORONA VIRUS VS SARS COV-2

SARS COV-2 (COVID-19)

CYTOKINE STORM



Pulmonary Intravascular Coagulation (PIC)

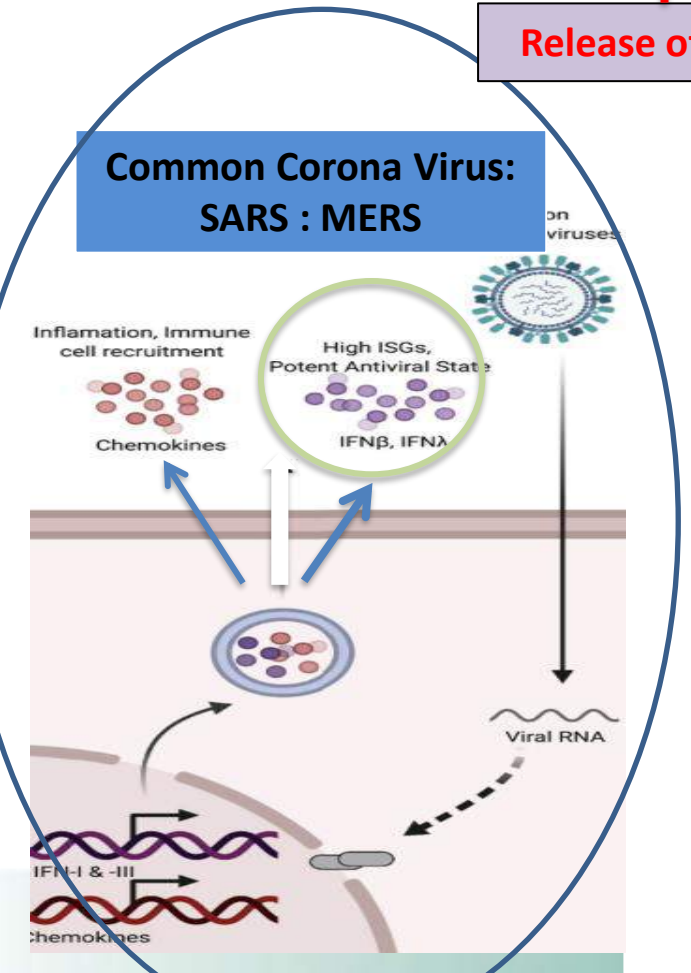
Release of Tissue factor

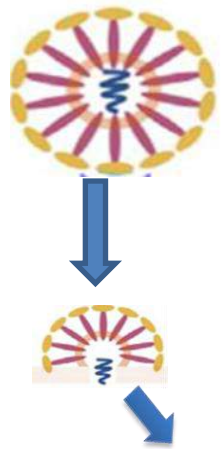
Inflammation chemokine

Limited antiviral state

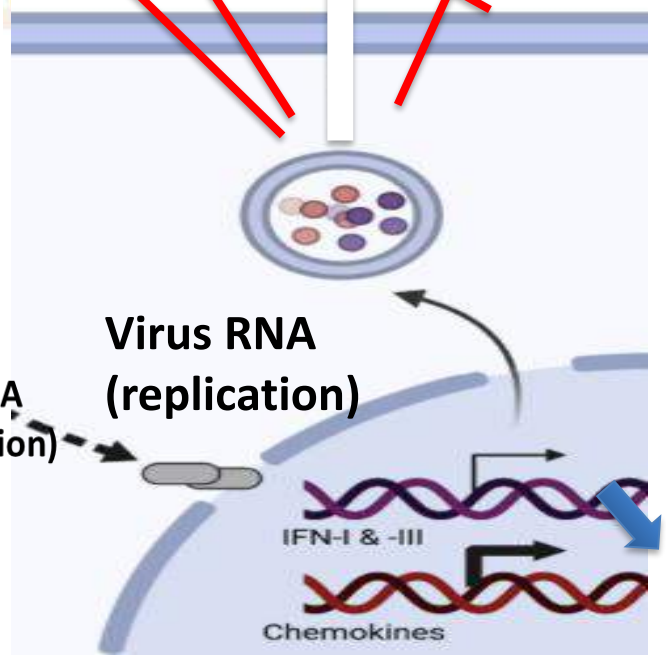
Cytokine Storm

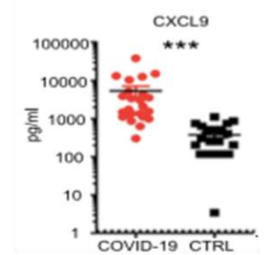
Significant increase in circulating IL-6, IL1RA, CCL2, CCL8 CXCL2, CXCL8, CXCL9, and CXCL16 levels



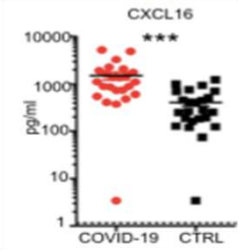


Virus RNA (replication)

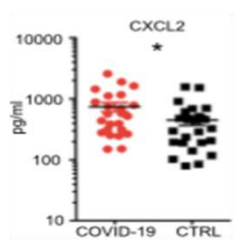




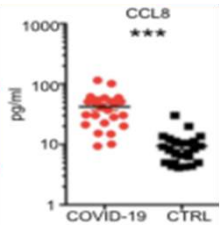
Elevation of CXCL9 for chemoattractant T cell



Elevation of CXCL16 for chemoattractant NK cell

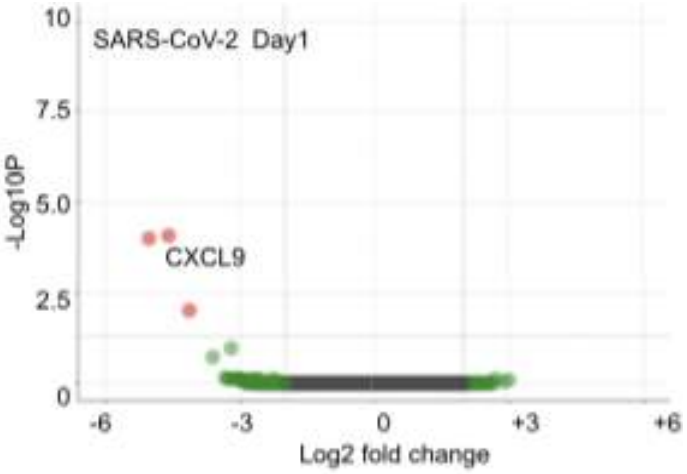


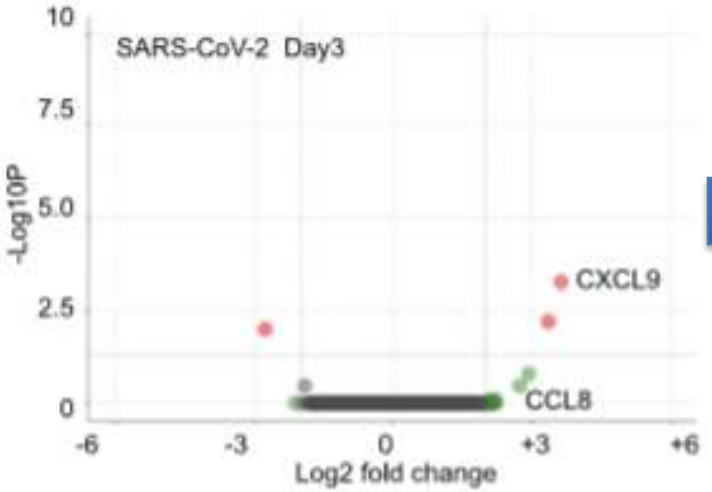
Elevation of CXCL2 for chemoattractant monocy

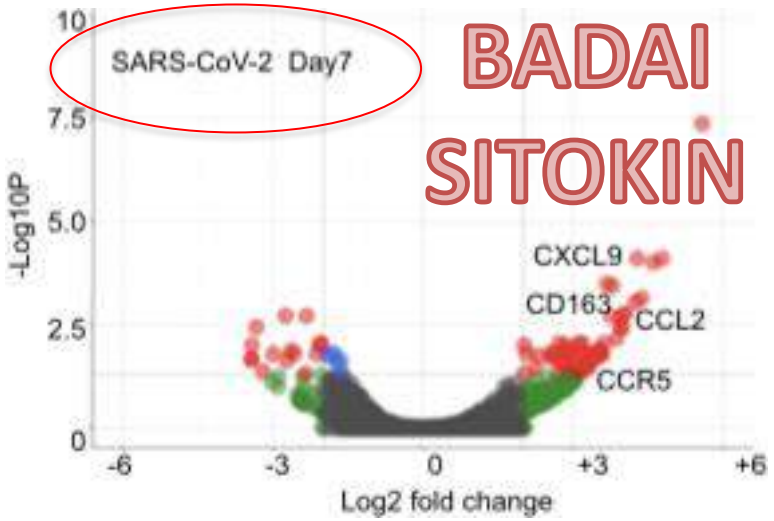


Elevation of CXCL8 for chemoattractant neutrophil

FASE INFEKSI SARS COV-2







Badai sitokin akibat infeksi SARS COV2 dimulai pada hari ke 9-12 setelah infeksi

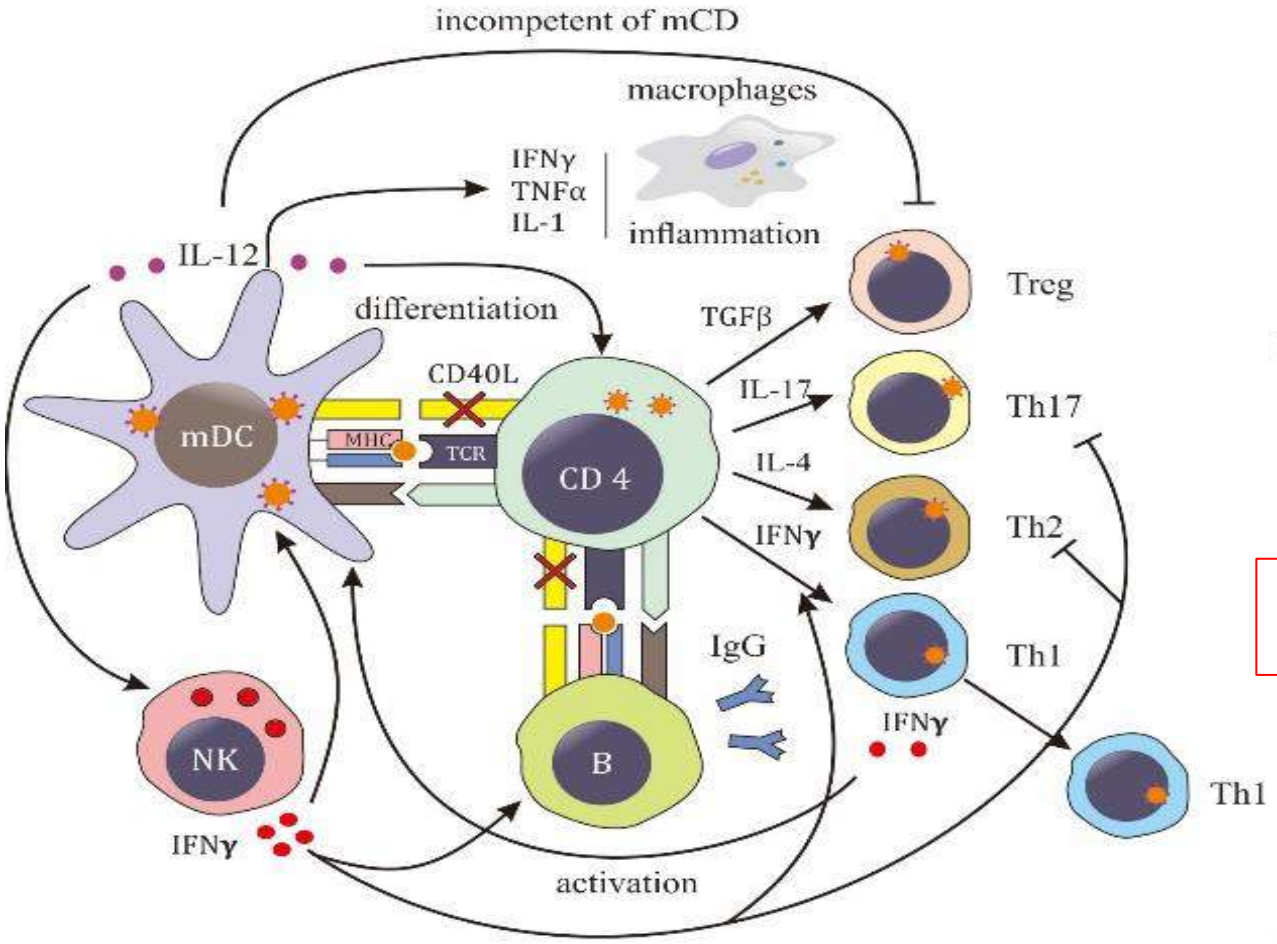
PENTING!

Meredakan badai sitokin pada fase awal dapat mencegah kerusan paru dan meningkatkan survival

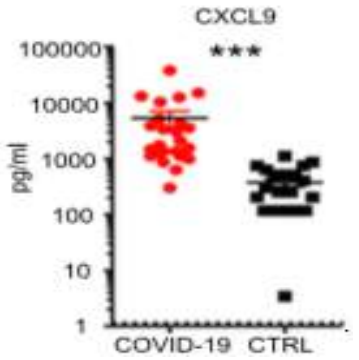
Early-Moderate Phase

Primary driver of the signature pathology observed in COVID-19 patients

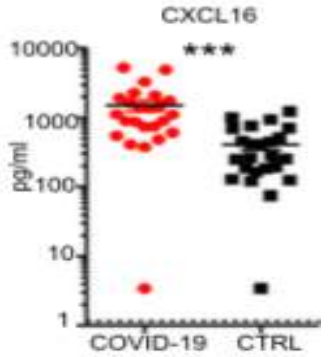
Incompentency pDC is the key point for SARS-Cov-2 infected T cells



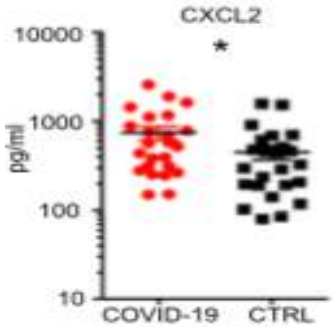
Significant increase in circulating IL-6, IL1RA, CCL2, CCL8 CXCL2, CXCL8, CXCL9, and CXCL16 levels



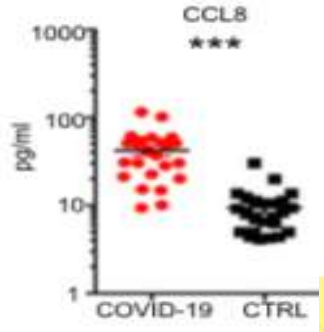
Elevation of CXCL9 for chemoattractant T cell



Elevation of CXCL16 for chemoatractant NK cell



Elevation of CXCL2 for chemoattractant monocyte

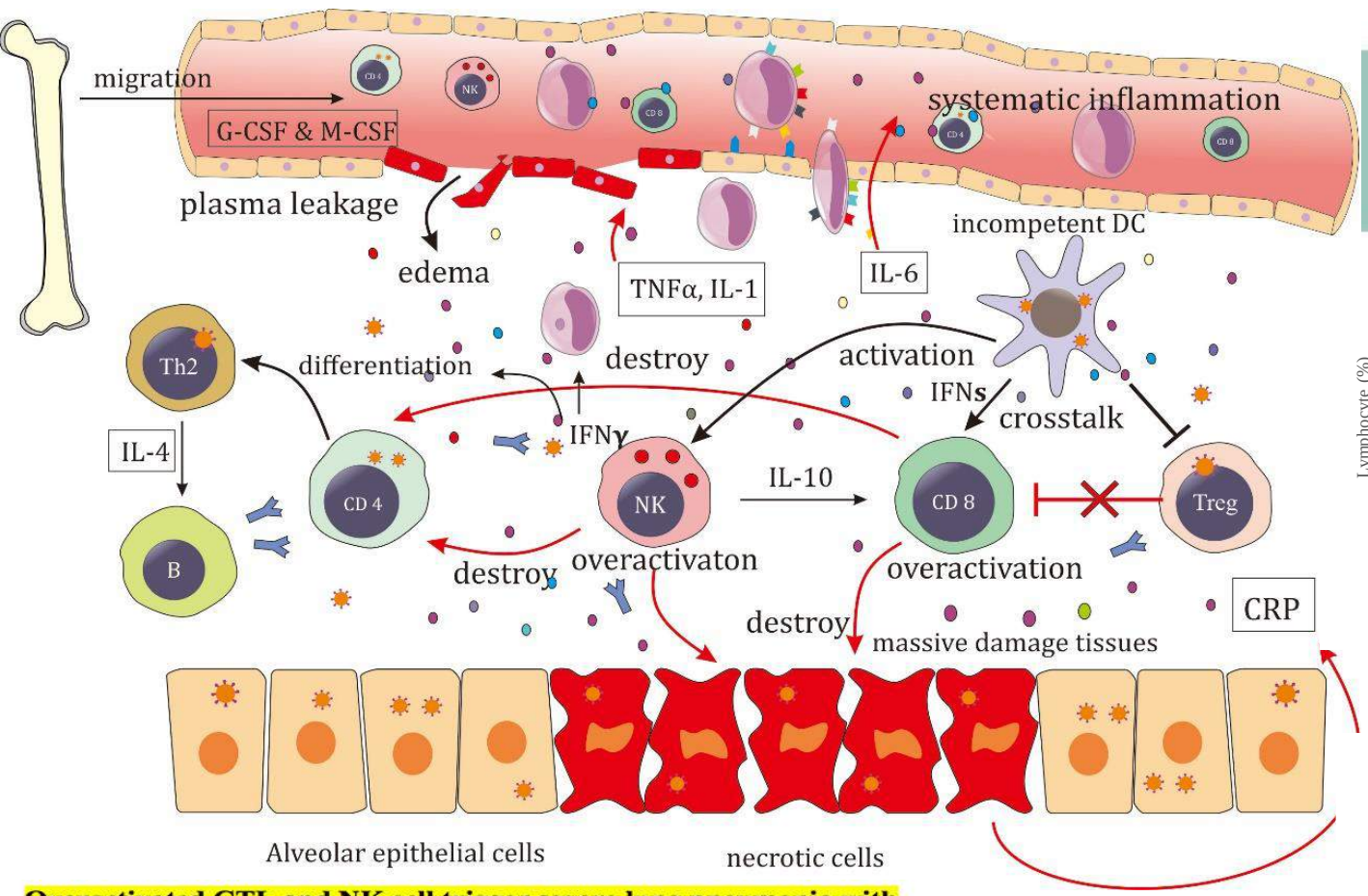


Elevation of CXCL8 for chemoattractant neutrophil

Source: Agung Putra,et ll, 2020 (In review)

Citation: Daniel Blanco-Melo, Cell, 2020

Massive Inflamation leads to Cytokine Storm



Overactivated CTL and NK cell trigger severe lung pneumonia with the cytokine storm in patients with Covid-19

Agung Putra[1,2,3*] Adi Muradi Muhar[4], Bayu Tirta Dirja[5], Retnaningsih[6]

[1]*Stem Cell and Cancer Research (SCCR), Faculty of Medicine, Sultan Agung Islamic University (UNISSULA), Semarang, Indonesia*
[2]*Department of Postgraduate Biomedical Science, Faculty of Medicine, Sultan Agung Islamic University (UNISSULA), Semarang, Indonesia*
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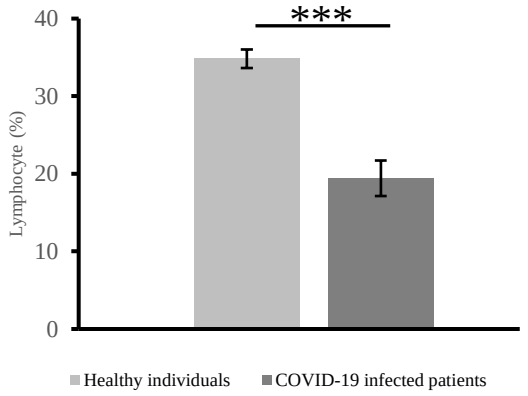
[4]*Departement of Surgery, Faculty of Medicine, Universitas Sumatera Utara, Medan Indonesia*
[5]*Department of Microbiology, Faculty of Medicine, Universitas Mataram, Mataram, Indonesia*
[6]*Department of Neurology and Intensive Care Unit, Kariadi Hospital, Diponegoro University, Semarang, Indonesia*

Corresponding author: Agung Putra, Stem Cell and Cancer Research (SCCR) Laboratory, Faculty of Medicine, Islamic Sultan Agung University, Semarang, Jl. Raya Kaligawe Km. 4 Semarang, Jawa Tengah, Indonesia, 50112; E-mail: dr.agungptr@gmail.com; Tel.: +628164251646. Orcid ID: https://orcid.org/0000-0003-4261-9437

Source: Agung Putra,et ll, 2020 (In review)



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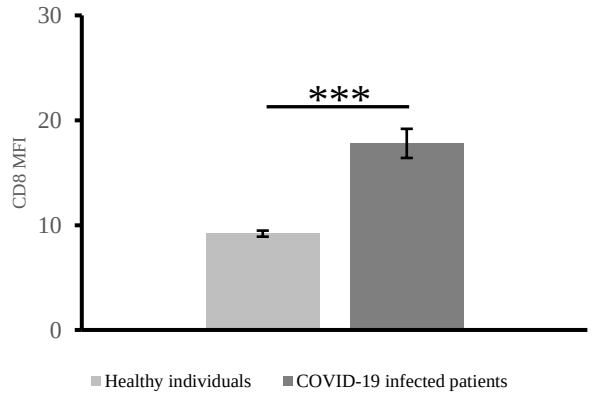

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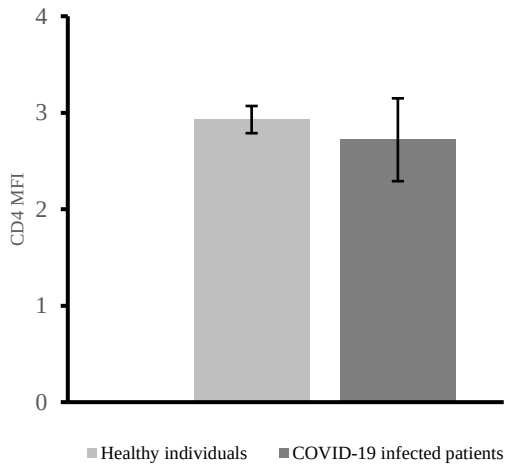

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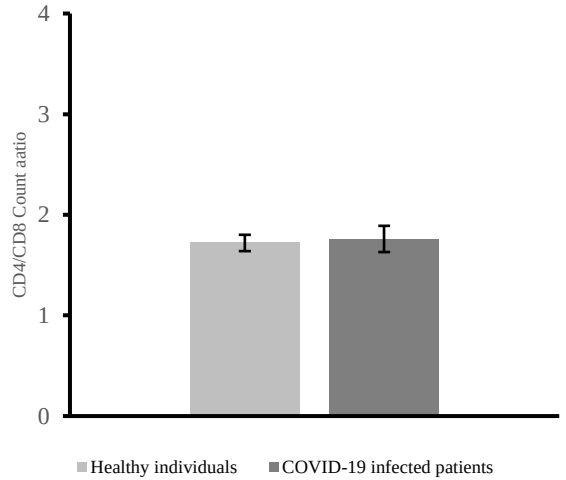
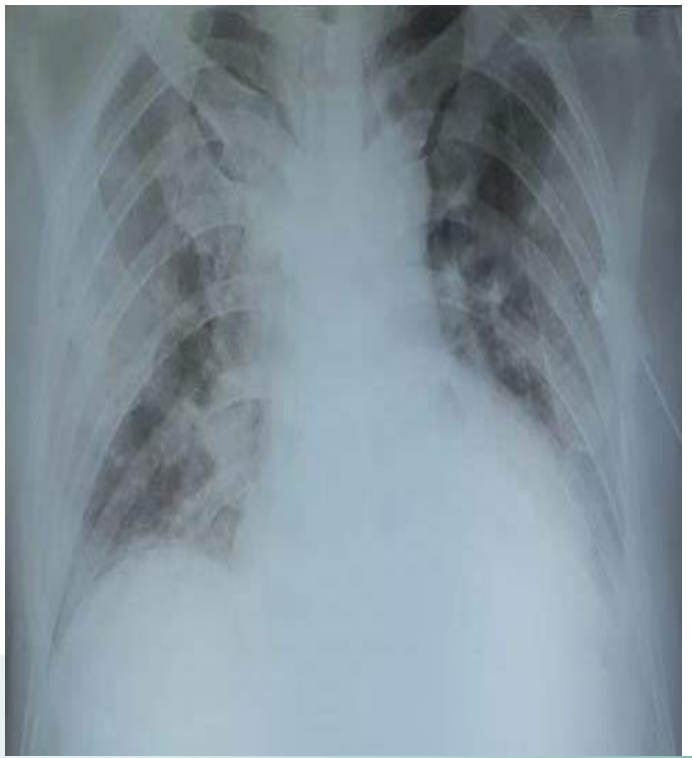


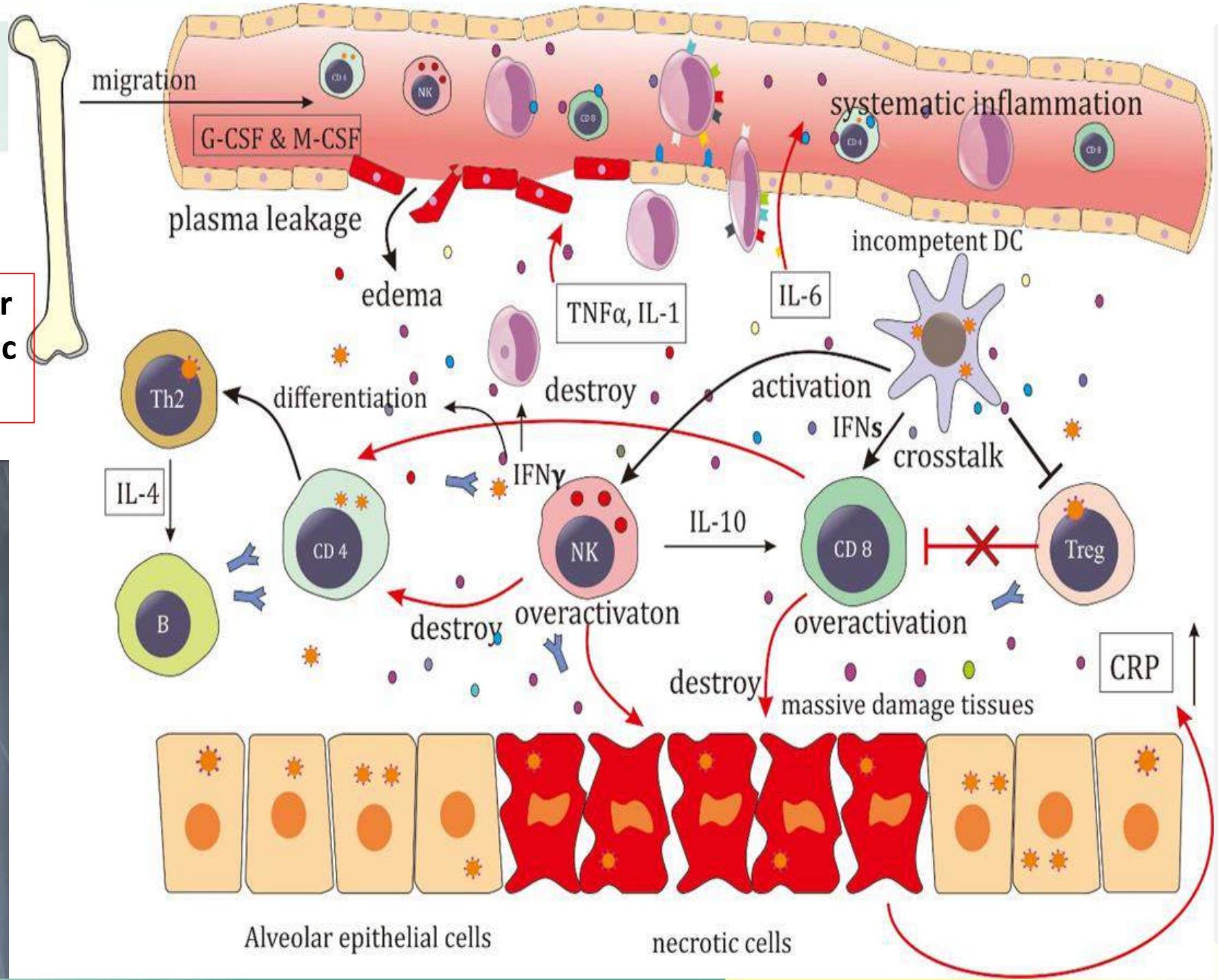
d

Ganji A, Farahani I, Khanarinejad B, Ghazavi A, Mosayebi G. Increased expression of CD8 marker on T-cells in COVID-19 patients. Blood Cells Mol Dis. 2020;83:102437.

SCCR
Stem Cell and Cancer Research
Medical Faculty of UNISSULA

Cytokine Storm Mechanism for Exudation procees and Sistemic Inflamation





Is the ventilator needed in severe patient covid-19 ?

Vascular microthrombi formation

Lung immunothrombosis

containment of bacterial infection

Inhibiting the spread of microorganism

Viral infection ???

Mechanical ventilation in patients progressing to ARDS,

Positive pressure ventilation

Driving factor to release of viral SARS-CoV-2 across damaged alveolar endothelial cell barriers

Immunothrombosis

Potential iatrogenic contributor

Need research to analysis marker PIC vs Ventilator

Poor outcomes

Citation: Dennis et all, The lancet, 2020

Stem Cell and Cancer Research
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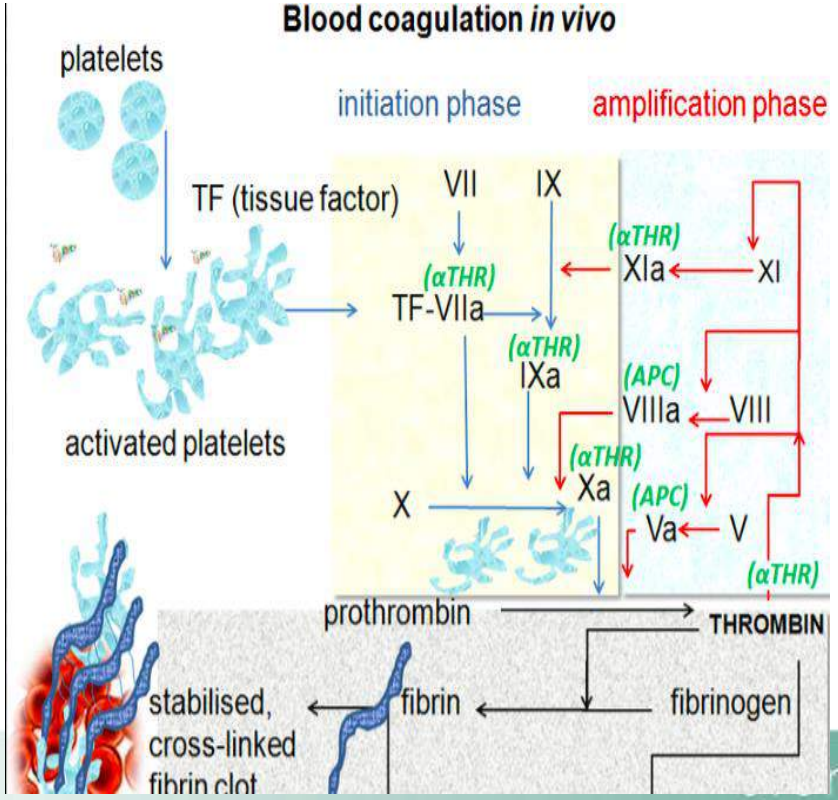
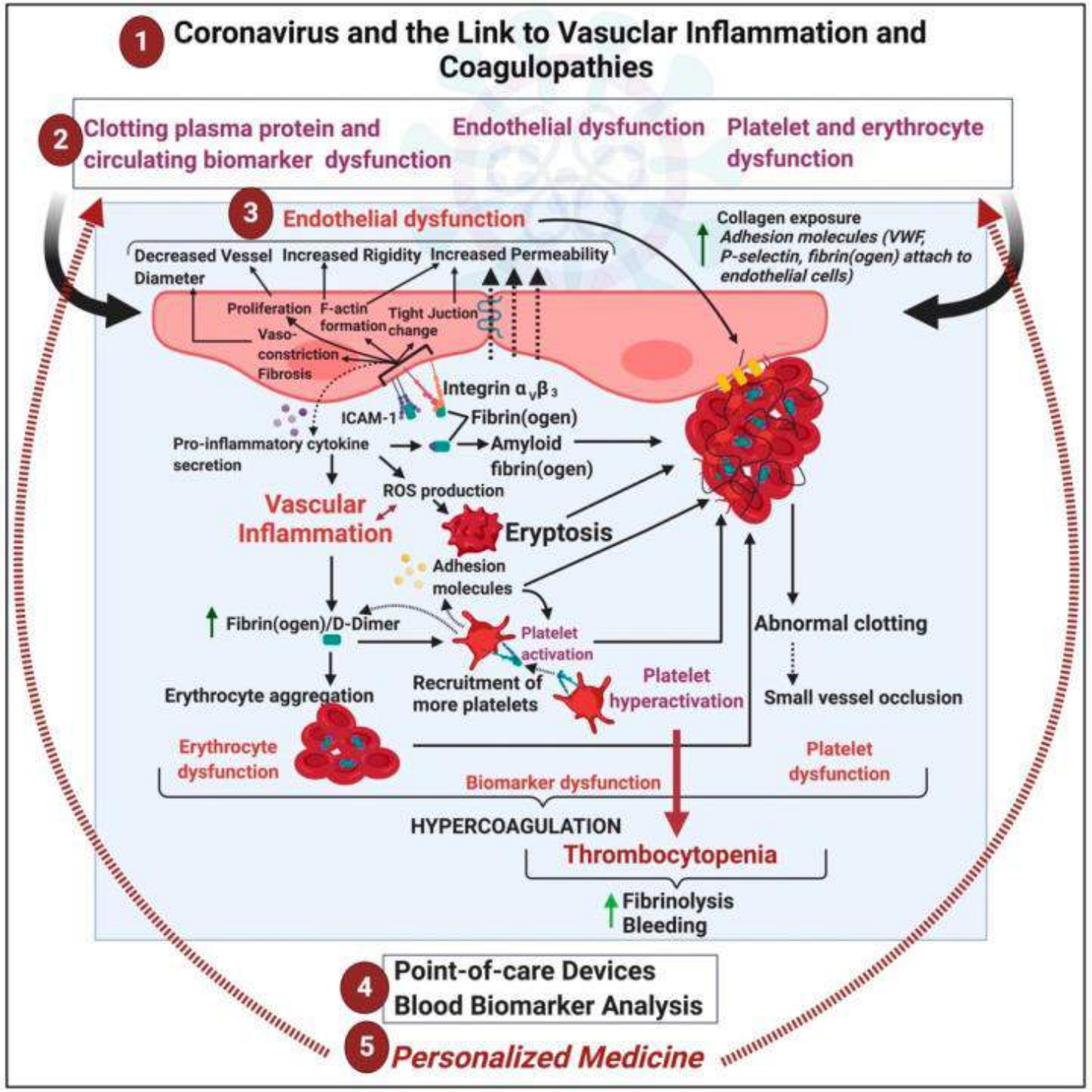
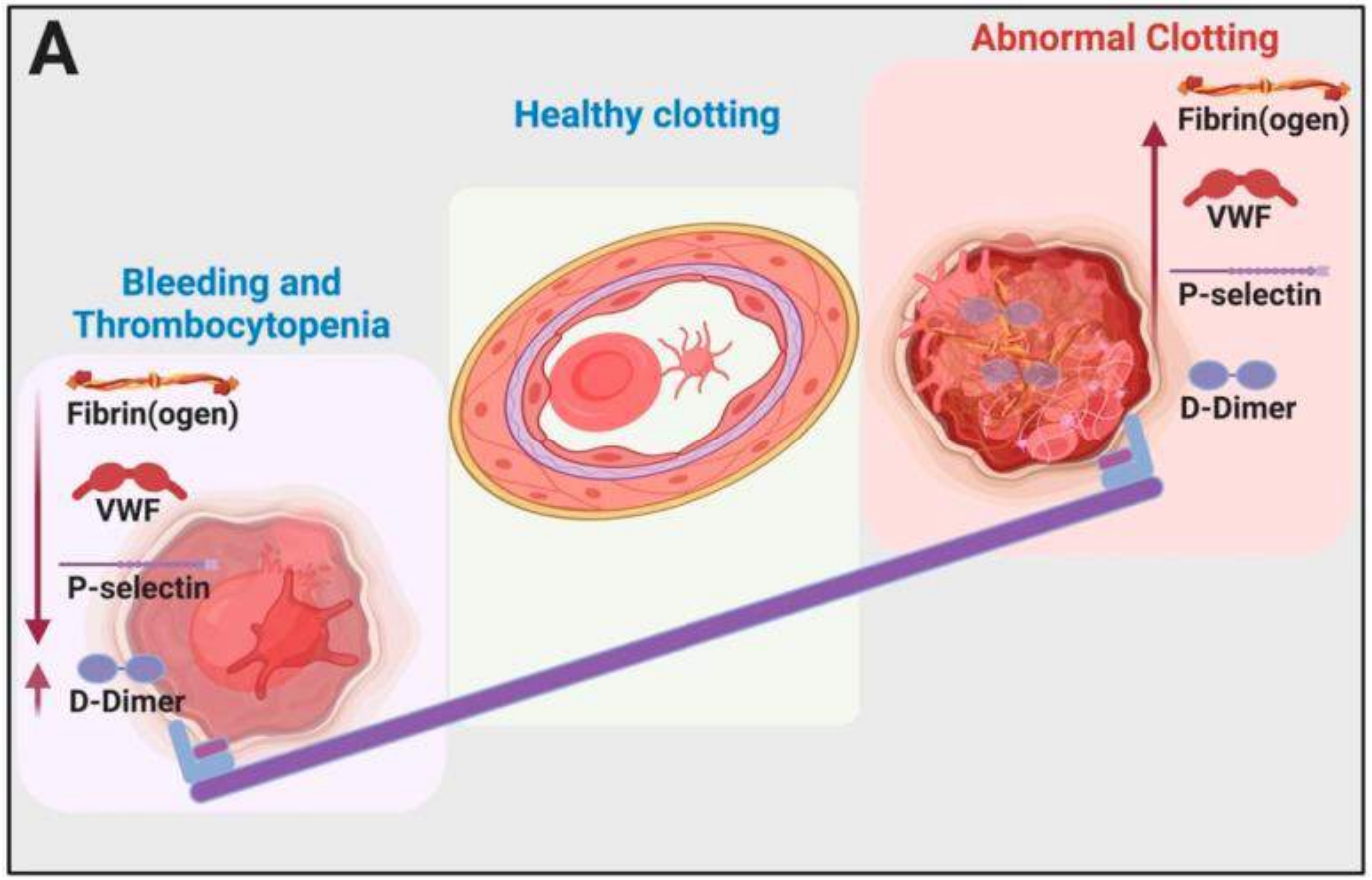
Cytokine Mechanism for Coagulation Mechanism on Covid-19





Bleeding-Clotting on Covid19



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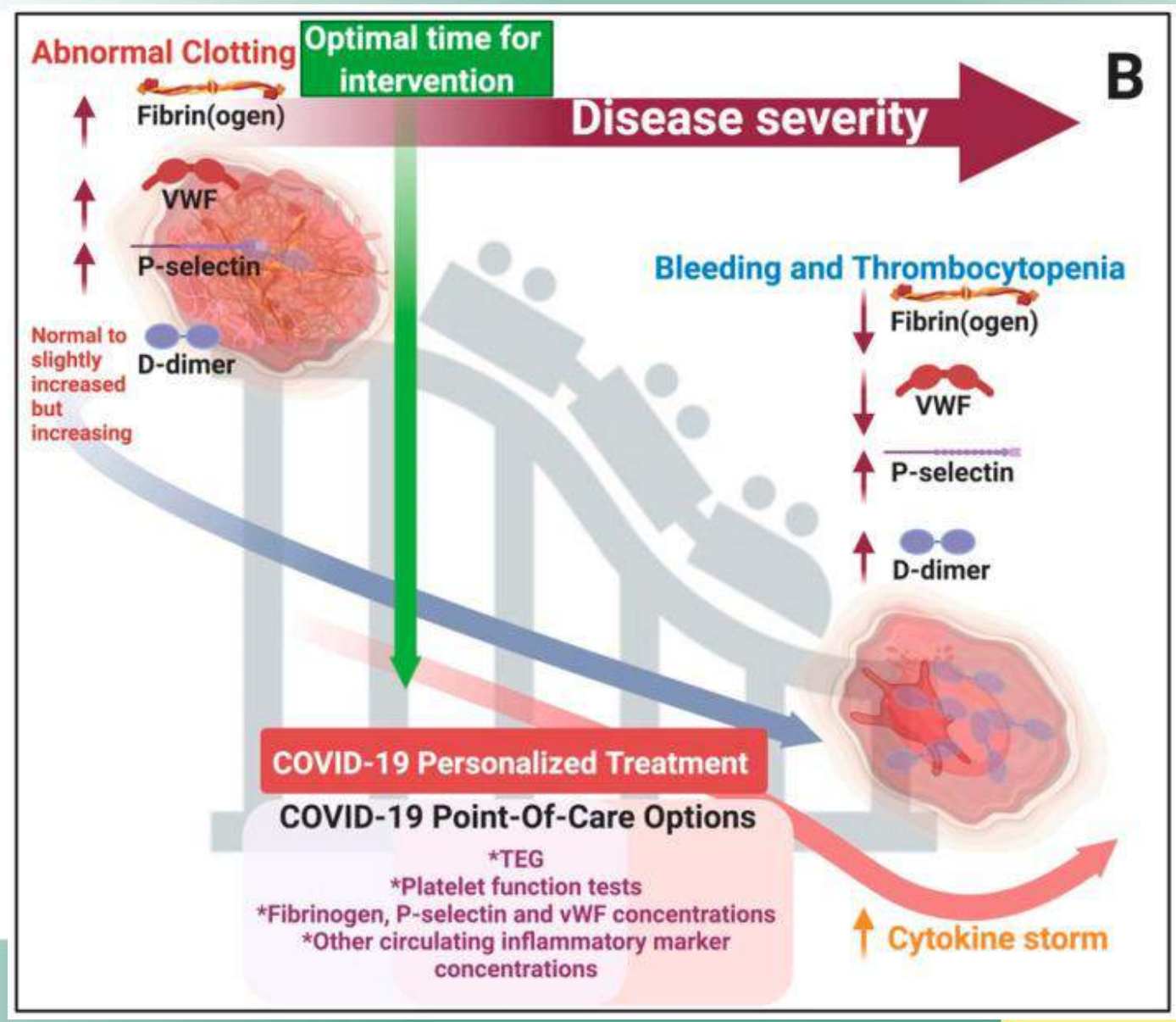
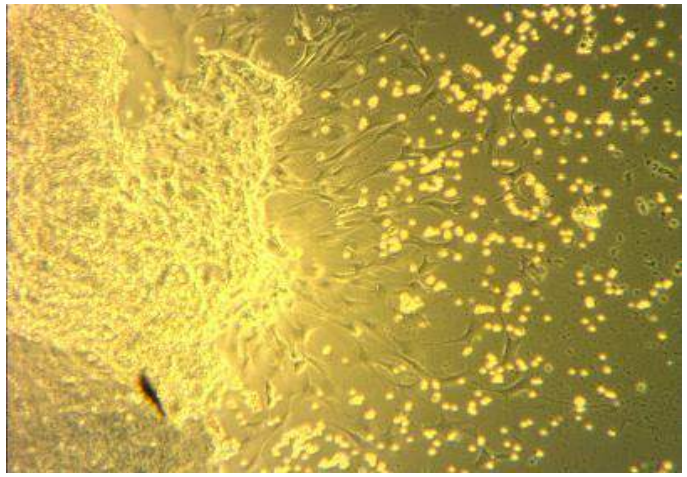
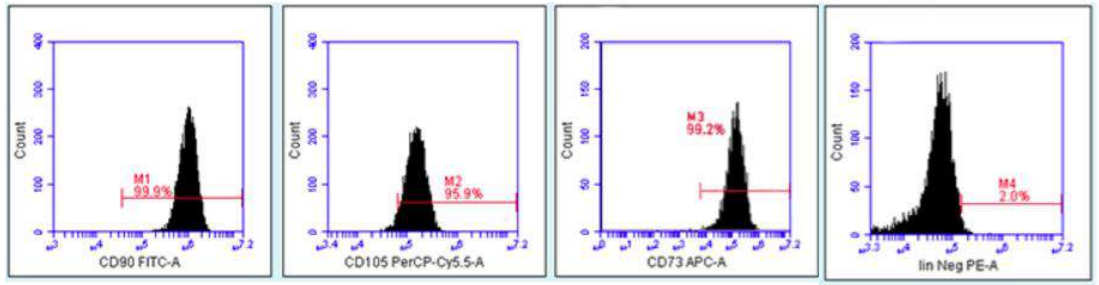
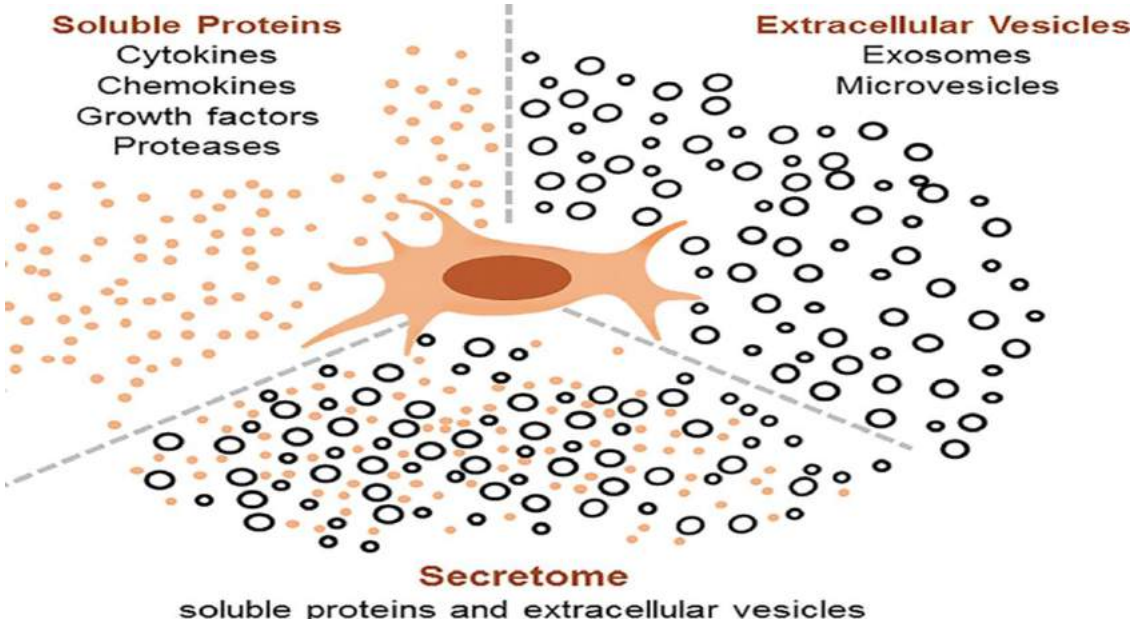
Optimal Time for Intervention of Covid19 stage



Secretome Stem Cell Isolation







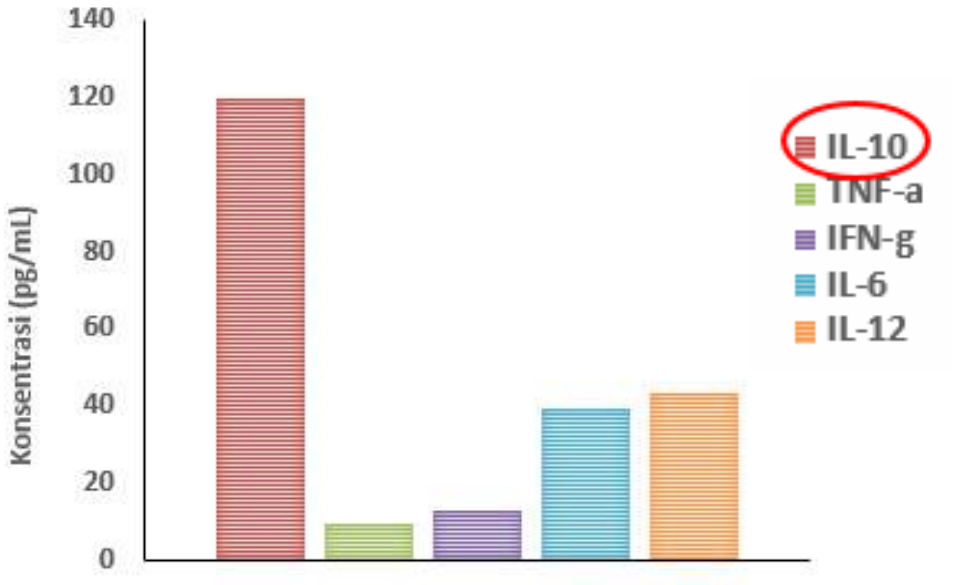
Medium S-MSCs

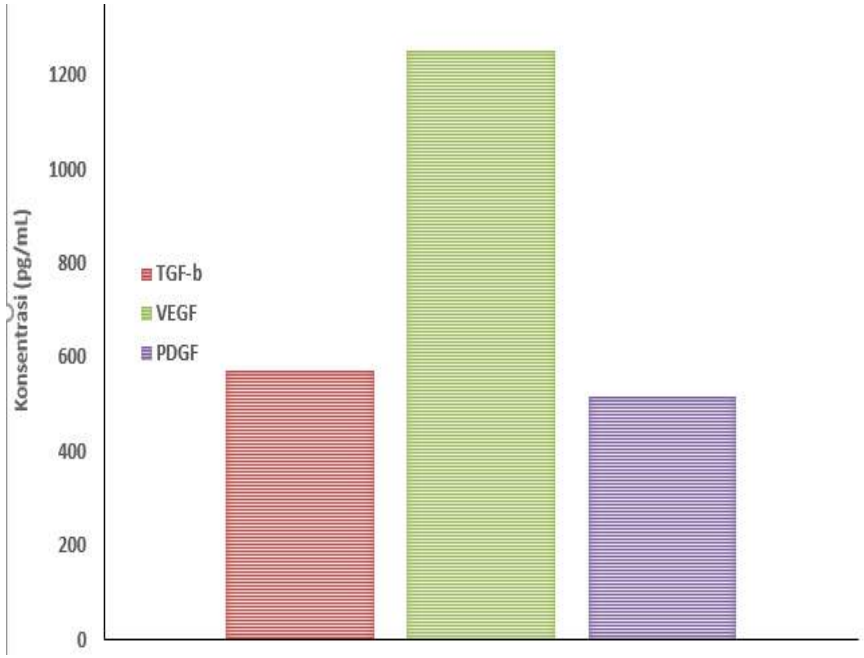
Metode
Utrafiltration
Tangensial flow filtration

Setelah filtrasi

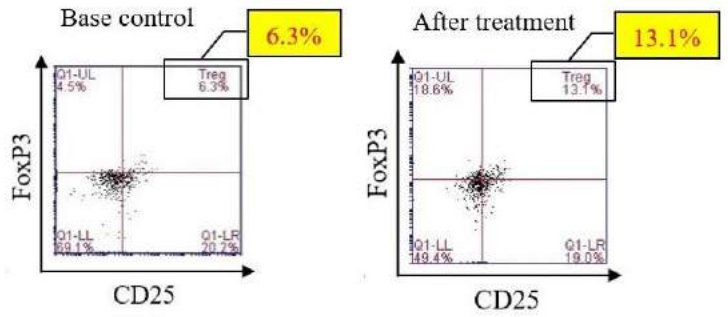
Sekretom MSC-s
5 - 50 Kd

Secretome Stem Cell Compound



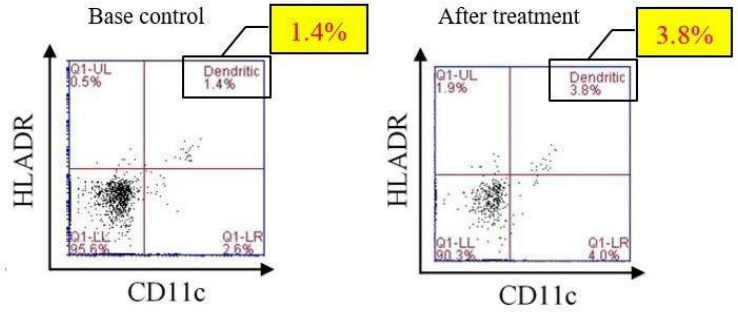


Treg cells after Secretome of Stem Cells for immune booster compared to base control



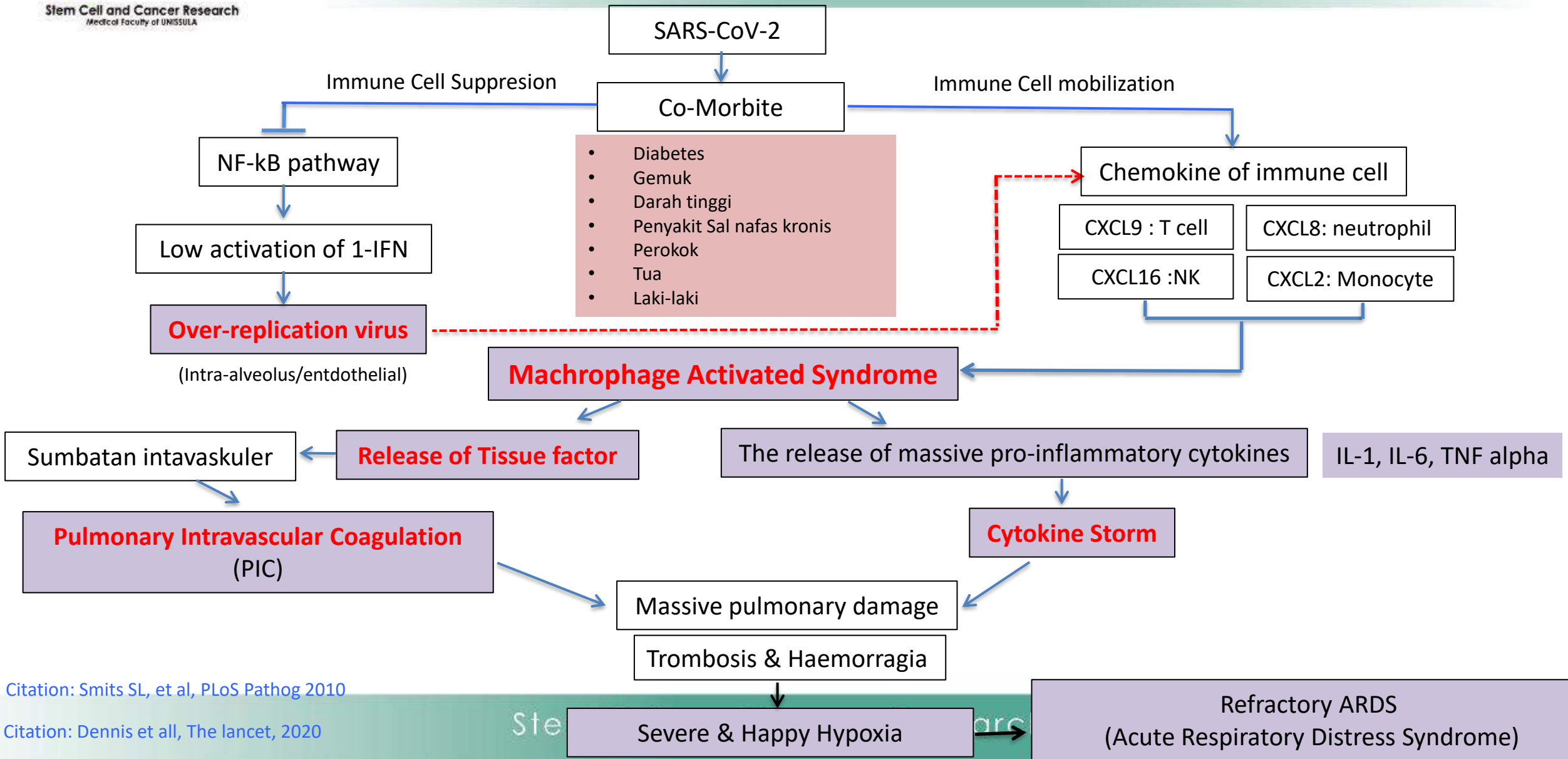
Research by SCCR

Dendritic cells after Secretome of Stem Cells for immune booster compared to base control



Research by SCCR

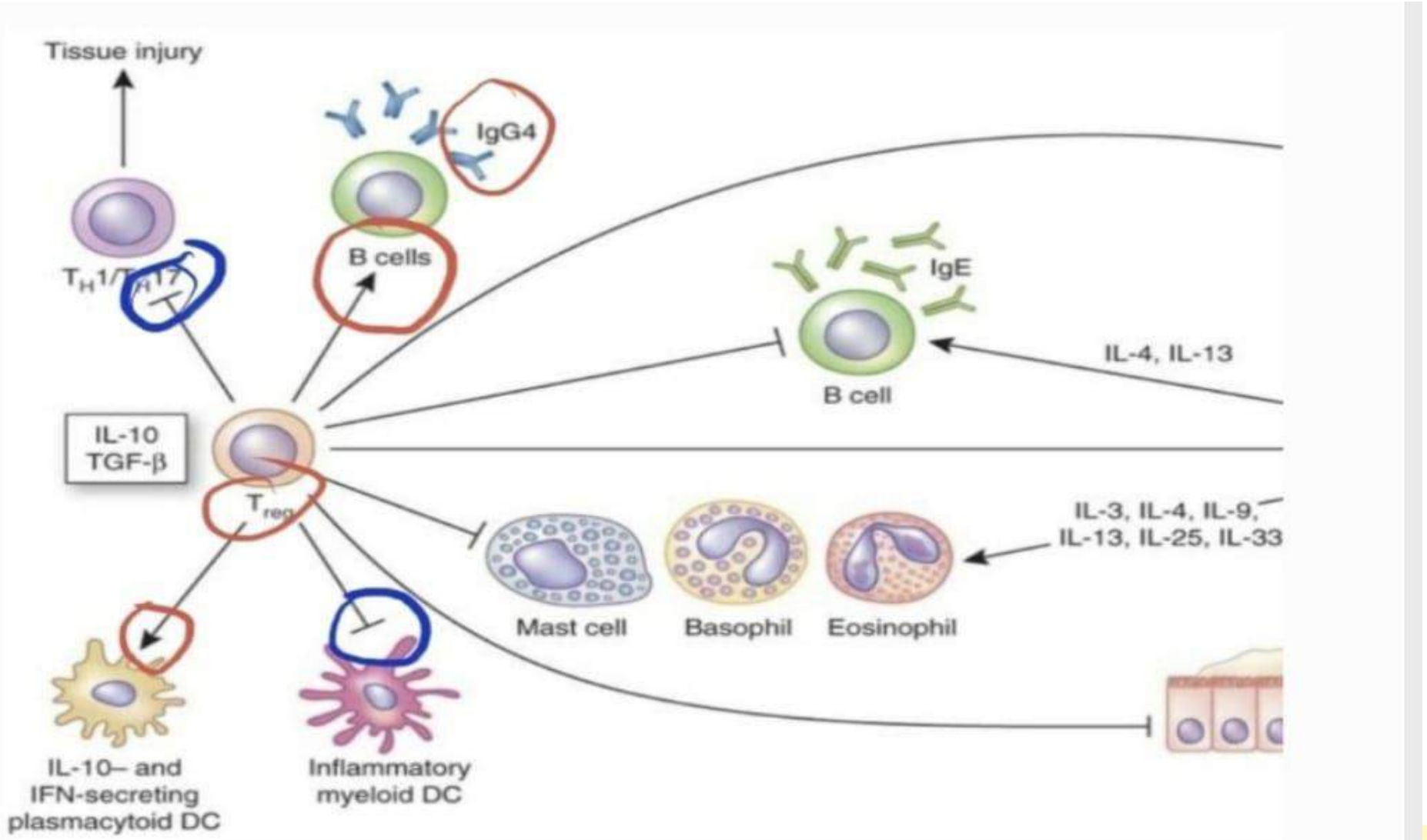
Mekanisme Molekuler SARS-CoV-2 dalam menginduksi ARDS-Death



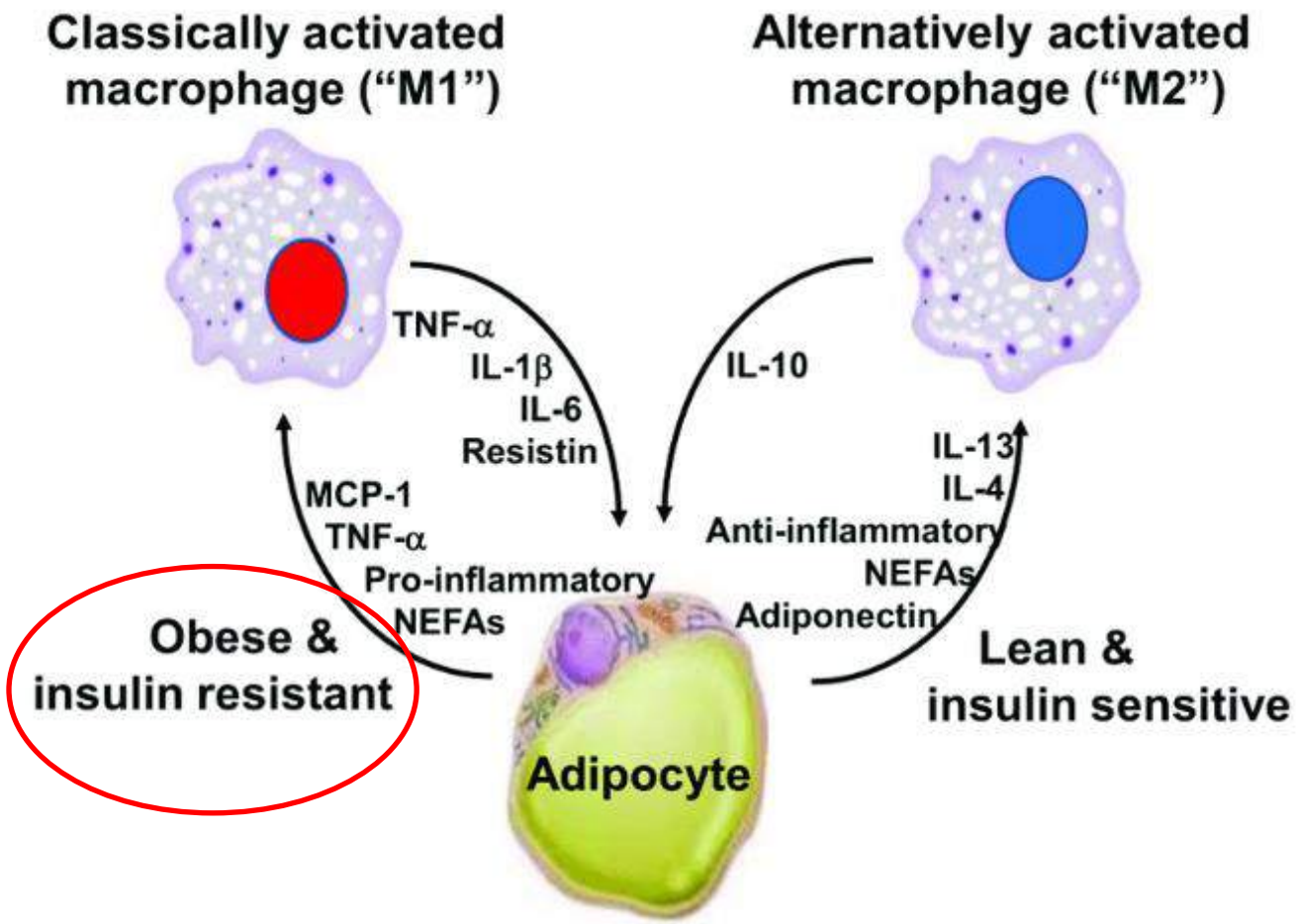
Citation: Smits SL, et al, PLoS Pathog 2010

Citation: Dennis et all, The lancet, 2020

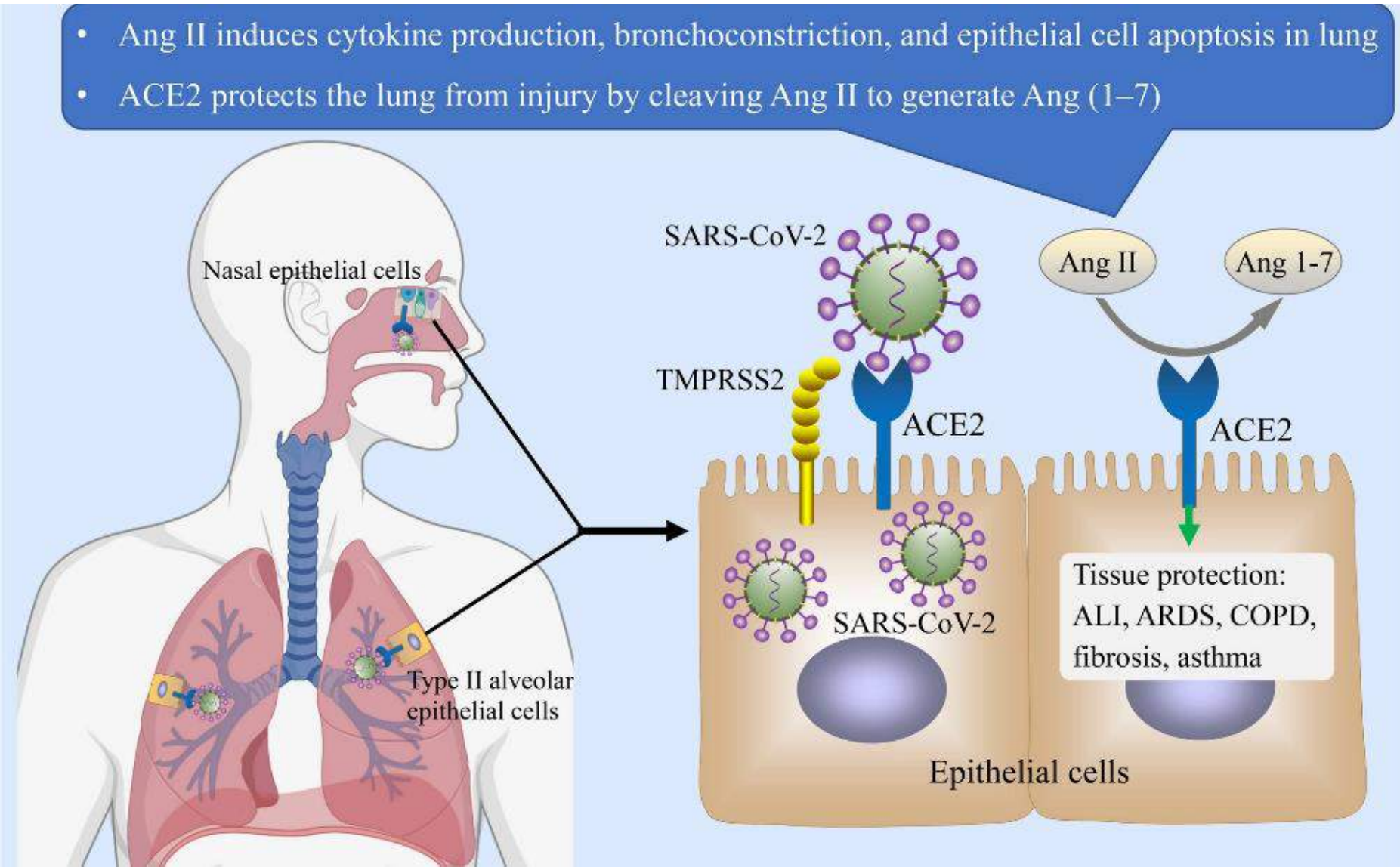
Secretome Immunomodulator mechanism



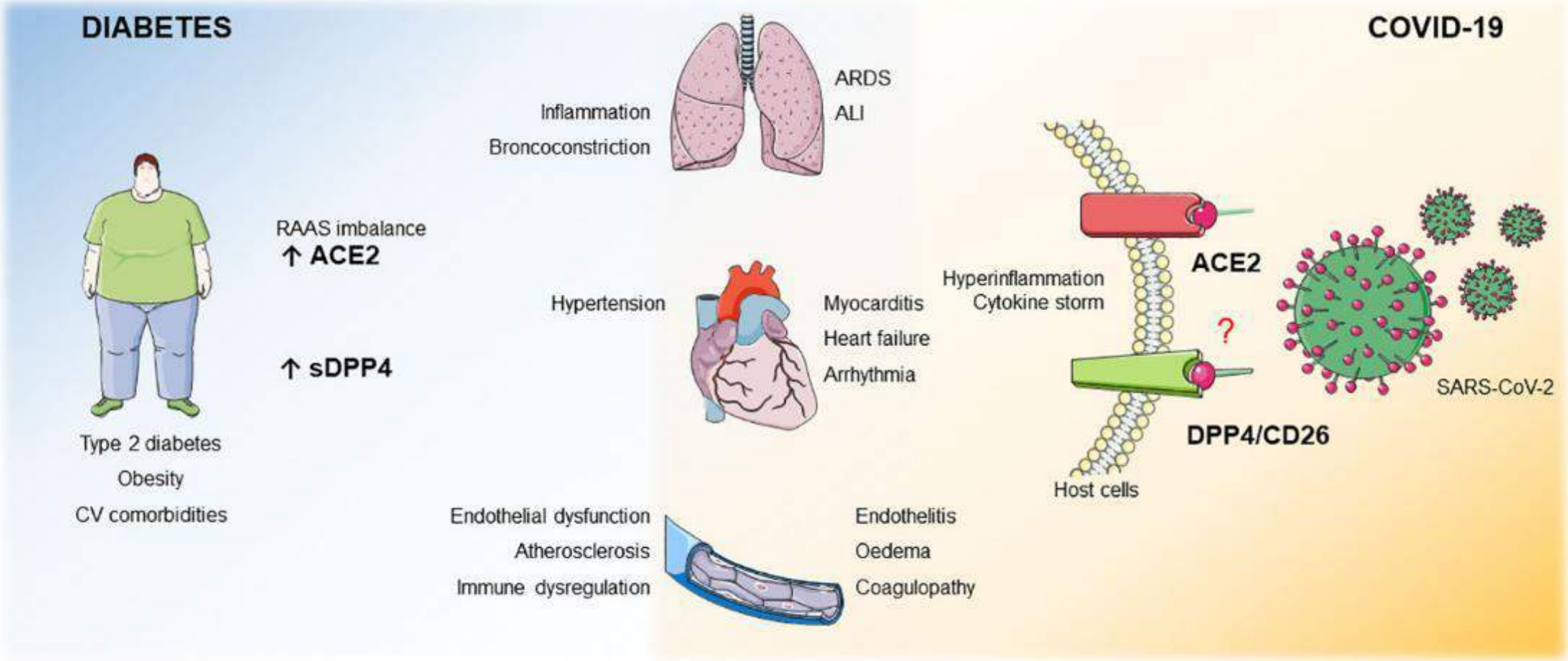
Resiko Comorbid : Obesitas



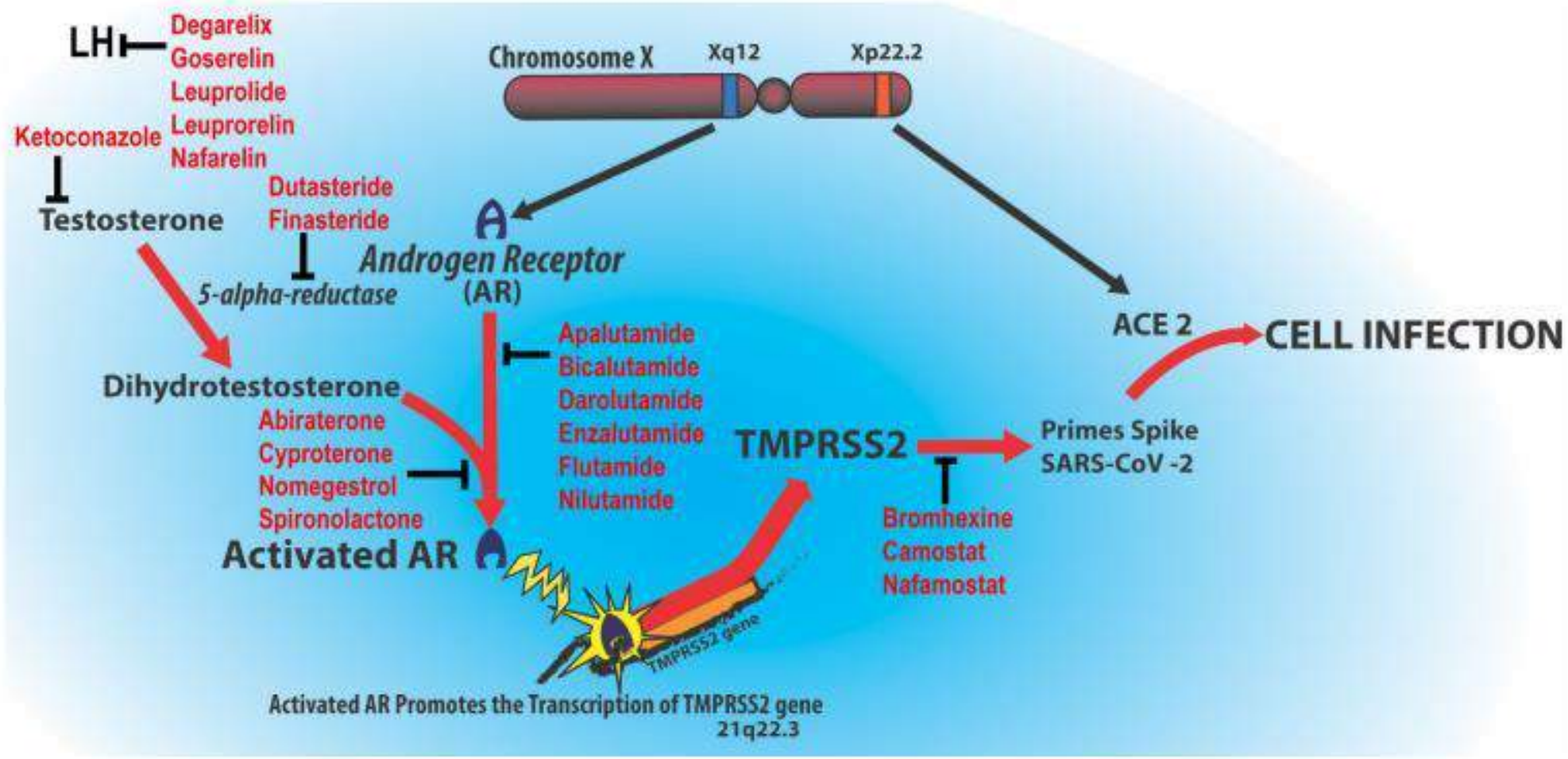
Resiko Comorbid : Gangguan Pernafasan



Resiko Comorbid : Diabetes



Resiko Comorbid : Laki-Laki



Internasional Scopus Jurnal: Plasma convalense is not significant

PLASMA COVALESVENS GAGAL MENYELAMATKAN PASIEN COVID19

ORIGINAL ARTICLE

A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia

Ventura A. Simonovich, M.D., Leandro D. Burgos Pratx, M.D., Paula Scibona, M.D., María V. Beruto, M.D., Marcelo G. Vallone, M.D., Carolina Vázquez, M.D., Nadia Savoy, M.D., Diego H. Giunta, M.D., M.P.H., Ph.D., Lucía G. Pérez, M.D., Marisa del L. Sánchez, M.D., Andrea Vanesa Gamarnik, Ph.D., Diego S. Ojeda, Ph.D., et al., for the PlasmAr Study Group*

CONCLUSIONS

No significant differences were observed in clinical status or overall mortality between patients treated with convalescent plasma and those who received placebo. (PlasmAr ClinicalTrials.gov number, NCT04383535.)

In our trial, the use of convalescent plasma therapy in addition to standard treatment in patients with severe pneumonia due to Covid-19 did not reduce mortality or improve other clinical outcomes at day 30 as compared with placebo. We believe the use of convalescent plasma as a standard of care in such patients should be reevaluated. Further studies regarding antibody therapy may be best focused on other populations or on interventions with other types of preparations, such as intravenous immunoglobulin or anti–SARS-CoV-2 monoclonal antibodies.

Internasional Scopus Jurnal Reporting

JAMA | Original Investigation

Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19
A Randomized Clinical Trial

Ling Li, MD, PhD; Wei Zhang, MD; Yu Hu, MD, PhD; Xunliang Tong, MD, PhD; Shangen Zheng, MD; Juntao Yang, PhD; Yujie Kong, MD; Lili Ren, PhD; Qing Wei, MD; Heng Mei, MD, PhD; Caiying Hu, MD; Cuihua Tao, MD; Ru Yang, MD; Jue Wang, MD; Yongpei Yu, PhD; Yong Guo, PhD; Xiaoxiong Wu, MD; Zhihua Xu, MD; Li Zeng, MD; Nian Xiong, MD; Lifeng Chen, MD; Juan Wang, MD; Ning Man, MD; Yu Liu, PhD; Haixia Xu, MD; E. Deng, MS; Xuejun Zhang, MS; Chenyue Li, MD; Conghui Wang, PhD; Shisheng Su, PhD; Linqi Zhang, PhD; Jianwei Wang, PhD; Yanyun Wu, MD, PhD; Zhong Liu, MD, PhD

IMPORTANCE Convalescent plasma is a potential therapeutic option for patients with coronavirus disease 2019 (COVID-19), but further data from randomized clinical trials are needed.

OBJECTIVE To evaluate the efficacy and adverse effects of convalescent plasma therapy for patients with COVID-19.

DESIGN, SETTING, AND PARTICIPANTS Open-label, multicenter, randomized clinical trial performed in 7 medical centers in Wuhan, China, from February 14, 2020, to April 1, 2020, with final follow-up April 28, 2020. The trial included 103 participants with laboratory-confirmed COVID-19 that was severe (respiratory distress and/or hypoxemia) or life-threatening (shock, organ failure, or requiring mechanical ventilation). The trial was terminated early after 103 of a planned 200 patients were enrolled.

CONCLUSION AND RELEVANCE Among patients with severe or life-threatening COVID-19, convalescent plasma therapy added to standard treatment, compared with standard treatment alone, did not result in a statistically significant improvement in time to clinical improvement within 28 days. Interpretation is limited by early termination of the trial, which may have been underpowered to detect a clinically important difference.

TRIAL REGISTRATION Chinese Clinical Trial Registry: ChiCTR2000029757

JAMA. doi:10.1001/jama.2020.10044
Published online June 3, 2020.

JAMA | Original Investigation

Association of Convalescent Plasma Treatment With Clinical Outcomes in Patients With COVID-19

A Systematic Review and Meta-analysis

Perrine Janiaud, PhD; Cathrine Axfors, MD, PhD; Andreas M. Schmitt, MD; Viktoria Gloy, PhD; Fahim Ebrahimi, MD, MSc; Matthias Hepprich, MD; Emily R. Smith, ScD, MPH; Noah A. Haber, ScD; Nina Khanna, MD; David Moher, PhD; Steven N. Goodman, MD, PhD; John P. A. Ioannidis, MD, DSc; Lars G. Hemkens, MD, MPH

Editorial page 1159

Supplemental content

IMPORTANCE Convalescent plasma is a proposed treatment for COVID-19.

OBJECTIVE To assess clinical outcomes with convalescent plasma treatment vs placebo or standard of care in peer-reviewed and preprint publications or press releases of randomized clinical trials (RCTs).

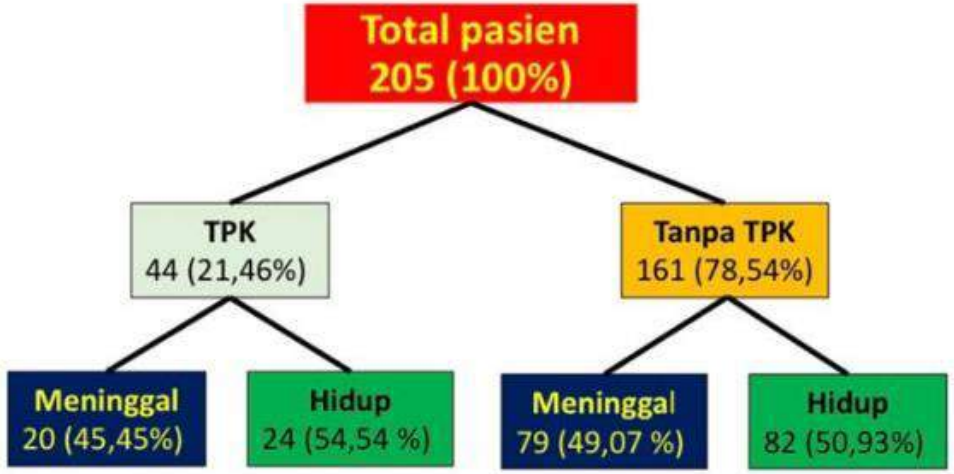
DATA SOURCES PubMed, the Cochrane COVID-19 trial registry, and the Living Overview of Evidence platform were searched until January 29, 2021.

due to imprecision for both outcomes. Limited data on clinical improvement, clinical deterioration, and serious adverse events showed no significant differences.

CONCLUSIONS AND RELEVANCE Treatment with convalescent plasma compared with placebo or standard of care was not significantly associated with a decrease in all-cause mortality or with any benefit for other clinical outcomes. The certainty of the evidence was low to moderate for all-cause mortality and low for other outcomes.

STUDI DI INDONESIA

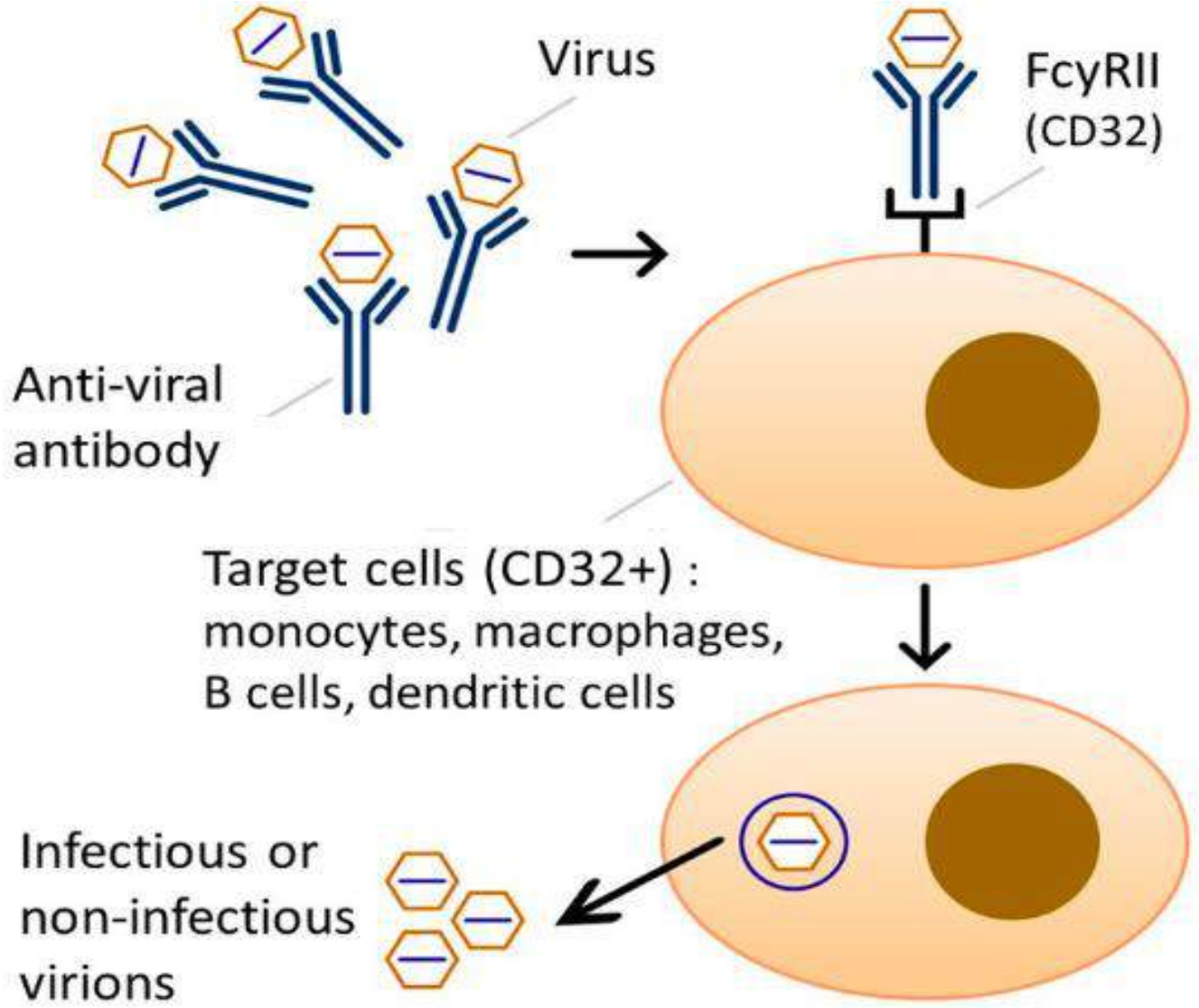
Interim Analysis
TPK RSUD Dr Soetomo



Chi-square 0,1807; P-value 0,670752 ($p < 0,05$)

(Tidak Signifikan)

ANTIBODY KILL VIRUS ???
If Not The virus use the Antibody as Trojen Horse



- Disease enhancement
- A phenomenon in which binding of a virus to suboptimal antibodies enhances its entry into host cells, followed by its replication.
- Antiviral antibodies promote viral infection of target immune cells by exploiting the phagocytic FcγR or complement pathway.

The virus “deceives” the process of phagocytosis of immune cells and uses the host's antibodies as a Trojan horse.

- After interaction with the virus the antibody binds Fc receptors (FcR) expressed on certain immune cells or some of the complement proteins.
- Phagocytosis is accompanied by the virus degradation, however, if the virus is not neutralized (either due to low affinity binding or targeting to a non-neutralizing epitope), antibody binding might result in a virus escape and therefore, enhanced infection.
- Thus, phagocytosis can cause viral replication, with the subsequent death of immune cells.

ADE occur due

1. The non-neutralizing characteristic of the antibody, which bind viral epitopes other than those involved in a host cell attachment and entry.
2. The presence of sub-neutralizing concentrations of antibodies (binding to viral epitopes below the threshold for neutralization).

- This phenomenon might lead to both increased virus infectivity and virulence.
- The viruses that can cause ADE frequently share some common features such as antigenic diversity, abilities to replicate and establish persistence in immune cells

Actemra Treatmentfor Covid19: Induce Systemic Inflamatory Respose

synthesis can lead to an acute severe systemic inflammatory response known as "cytokine storm", which is related to disease severity [157]. This strategy may also be effective at reducing COVID-19 mortality in older patients since IL-6 is the most prominent cytokine of the senescence-associated secretory phenotype (SASP) [12, 158]. Following this reasoning, another alternative drug for the control of cytokine release syndrome associated to COVID-19 is the humanized monoclonal antibody tocilizumab, which it targets IL-6 receptor [159]. In fact, there are several U. S. Food and Drug Administration (FDA)-approved clinical trials that are ongoing or recruiting patients to assess whether tocilizumab is therapeutic for COVID-19 patients [160–164]. Unfortunately, it was demonstrated that tocilizumab induces a pro-inflammatory profile in lipopolysaccharide (LPS)-stimulated dendritic cells with increased expression and secretion of IL-6 receptors, explaining its negligible effects in some patients with chronic inflammatory diseases [165]. This data suggests its use may pose a risk for patients with systemic inflammatory response.

Strategies focusing on reversing dendritic cell dysfunction and/or depletion during COVID-19 related sepsis may improve the survival of patients [108, 112, 113]. Molecules that have been shown to be targets for improving dendric cell function and survival during sepsis include high mobility group protein 1

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia

I.O. Rosas, N. Bräu, M. Waters, R.C. Go, B.D. Hunter, S. Bhagani, D. Skiest, M.S. Aziz, N. Cooper, I.S. Douglas, S. Savic, T. Youngstein, L. Del Sorbo, A. Cubillo Gracian, D.J. De La Zerda, A. Ustianowski, M. Bao, S. Dimonaco, E. Graham, B. Matharu, H. Spotswood, L. Tsai, and A. Malhotra

ABSTRACT

BACKGROUND

Coronavirus disease 2019 (Covid-19) is associated with immune dysregulation and hyperinflammation, including elevated interleukin-6 levels. The use of tocilizumab, a monoclonal antibody against the interleukin-6 receptor, has resulted in better outcomes in patients with severe Covid-19 pneumonia in case reports and

van Elteren test). In the safety population, serious adverse events occurred in 103 of 295 patients (34.9%) in the tocilizumab group and in 55 of 143 patients (38.5%) in the placebo group. Mortality at day 28 was 19.7% in the tocilizumab group and 19.4% in the placebo group (weighted difference, 0.3 percentage points (95% CI, −7.6 to 8.2; nominal P=0.94).

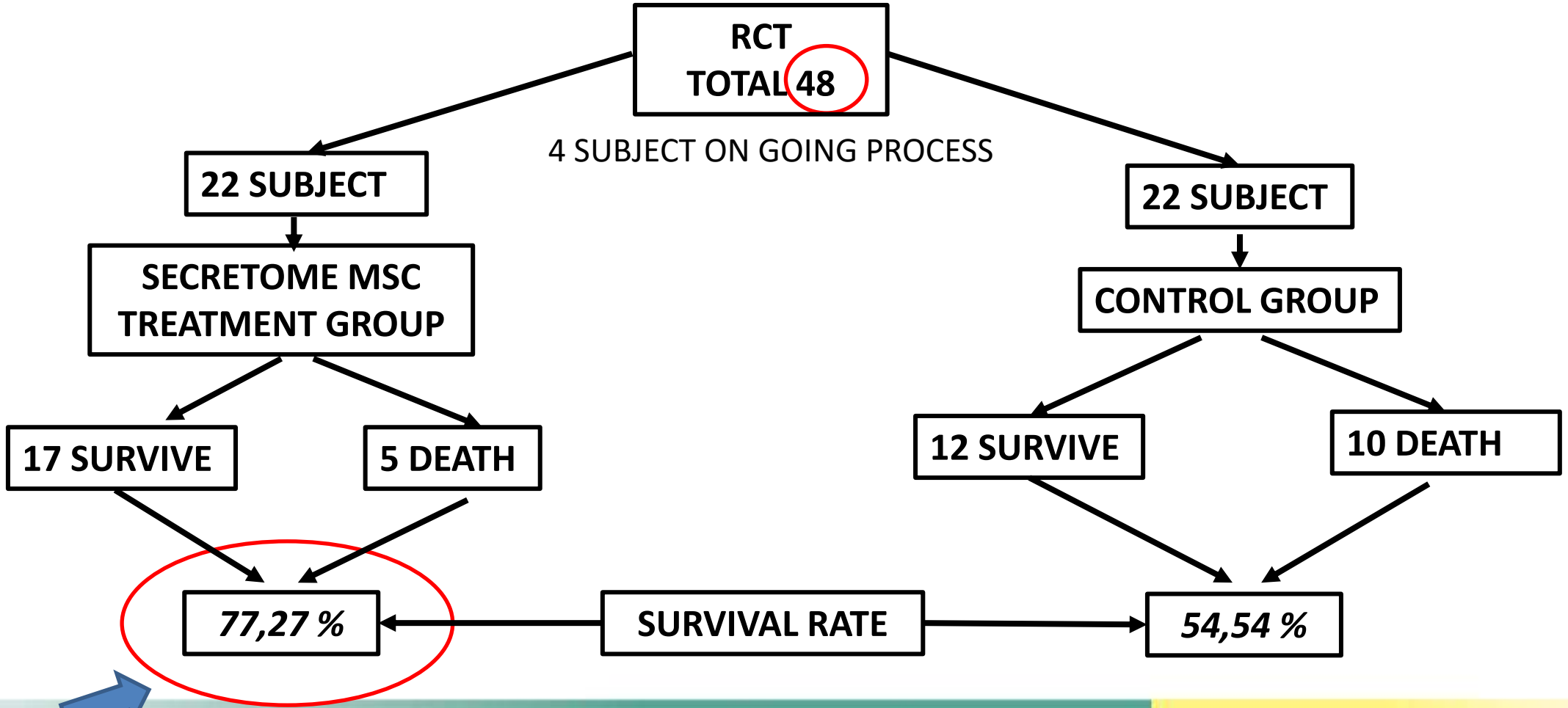
CONCLUSIONS

In this randomized trial involving hospitalized patients with severe Covid-19 pneumonia, the use of tocilizumab did not result in significantly better clinical status or lower mortality than placebo at 28 days. (Funded by F. Hoffmann–La Roche and the Department of Health and Human Services; COVACTA ClinicalTrials.gov number, NCT04320615.)

GRAND DESIGN

SCORING RANDOMIZED CONTROL TRIAL (Sementara)

SECRETOME STEM CELL-SCCR TO SEVERE COVID-19



SECRETOME STEM CELL CASE REPORT
Clinical and moleculer Improvement

Pasien 1 RSAU Dr. Esnawan Antariksa

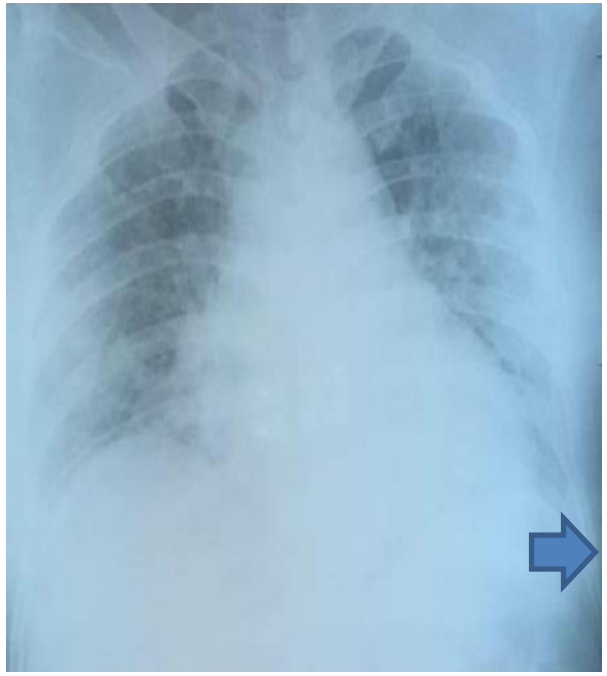
Pria 54 tahun

28/8/20 : MRS (ICU) dengan batuk dan kesulitan bernapas.
T:200/100, N: 102x/menit, P: 32/min, S: 36,5oC
(Covid-19+, Hipertensi berat)

10/9/20 : Covid-19 neg, pulang

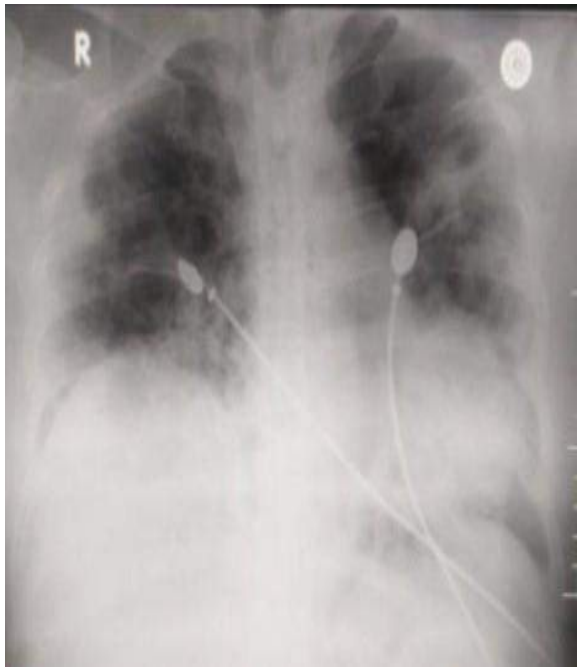
Clinical Factor	Before S-MSCs Treatment	After S-MSCs Treatment
CRP	61.7	0.37
D-dimer	1540	384
Lymphocyte	15	20
SO_2	80.6	99.6

29/8/20



X ray: bronchopneumonia with bilateral GGOs and cardiomegaly

10/9/20



X ray: absorption of bilateral GGOs with no both bronchopneumonia and cardiomegaly

SECRETOME STEM CELL CASE REPORT
Clinical and moleculer Improvement

Pasien 2 RSPAD Gatot Soebroto

Pria 53 tahun

17/11/20 : MRS (ICU) dengan batuk, sesak, nyeri dada dan lemas.

TD : 132/88, N : 60, P:24, S : 36,3

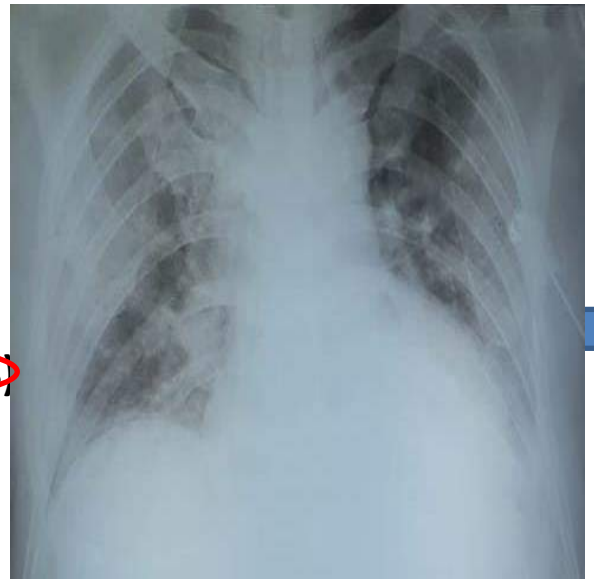
(Covid-19 +, hipertensi, DM Type-2-GDS: 398)

19/11/20 : Pindah ICU dengn ARDS.

28/12/20 : Covid-19 neg, pulang.

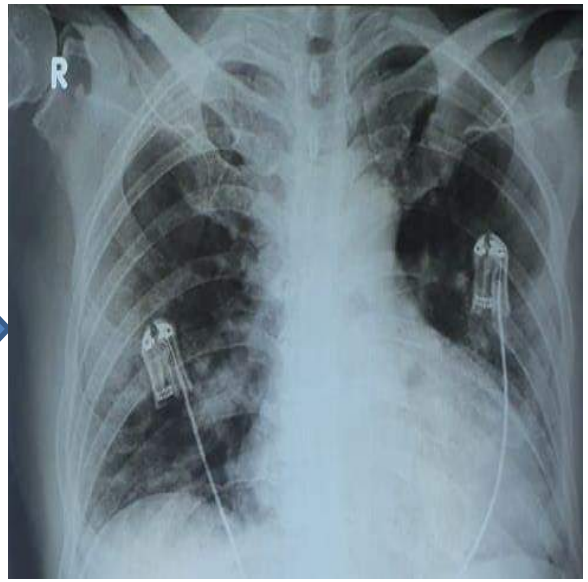
Clinical Factor	Sebelum S-MSCs	Setelah S-MSCs
CRP	160	5.12
D-dimer	880	660
Lymphocyte	10	27
SO_2	90.6	95.9

19/11/20:



X-ray : cardiomegaly, lung edema, aorta elongation and aorta atherosclerosis

22/11/20:



X-ray improvement with minimum infiltrate on pulmonalis dextra and sinistra

SECRETOME STEM CELL CASE REPORT
Clinical and moleculer Improvement

Pasien 3 Bayangkara Makassar

Pria 72tahun

16/12/20 : MRS (ICU) dengan Batuk, nyeri perut, diare, anosmia.

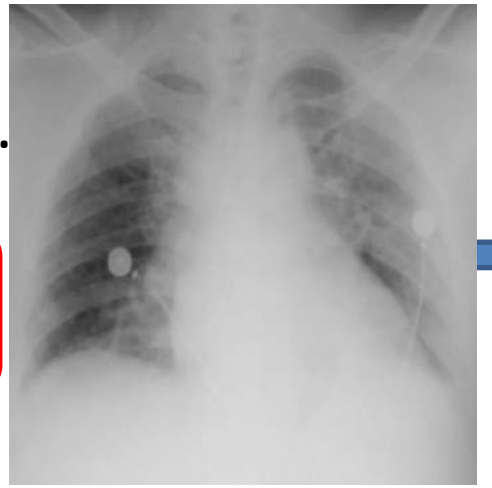
- **T: 140/90 mmHg N: 82/min P: 24/min S: 37,3°C**

(Covid-19+, Hipertensi, liver failure, long-term sequelae of stroke and thalassemia minor)

6/1/21 : Covid-19 neg, pulang.

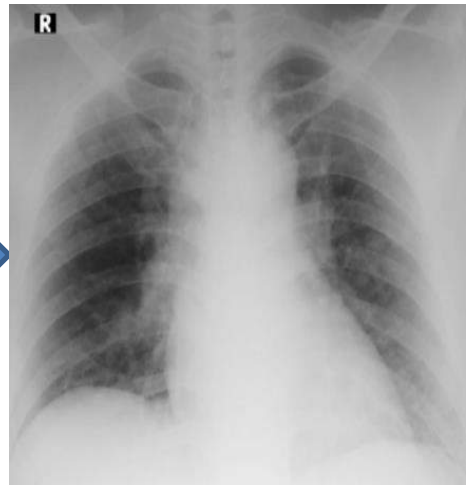
Clinical Factor	Before S-MSCs treatment	After S-MSCs treatment
CRP	118	8.5
D-dimer	235	87
Lymphocyte	11.7	25.8
SO_2	85	98

23/12/20:



X-ray : worsened bilateral GGOs with cardiomegaly and aortic atherosclerosis

28/12/20:

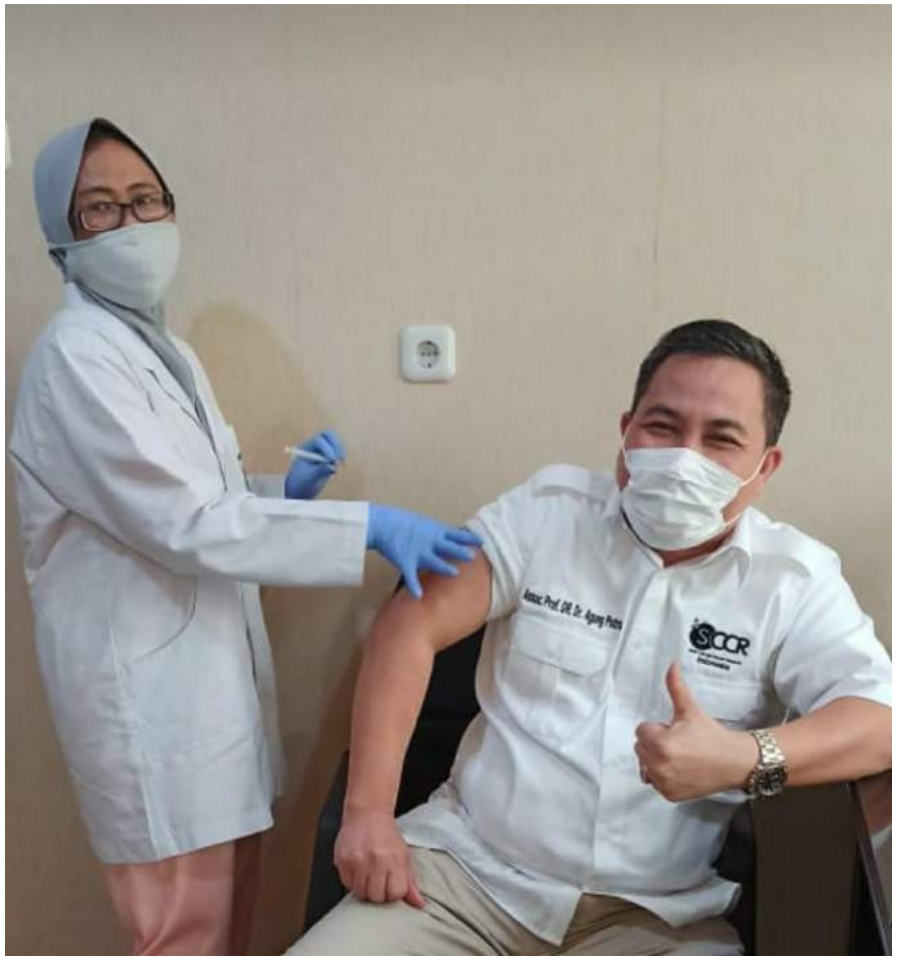


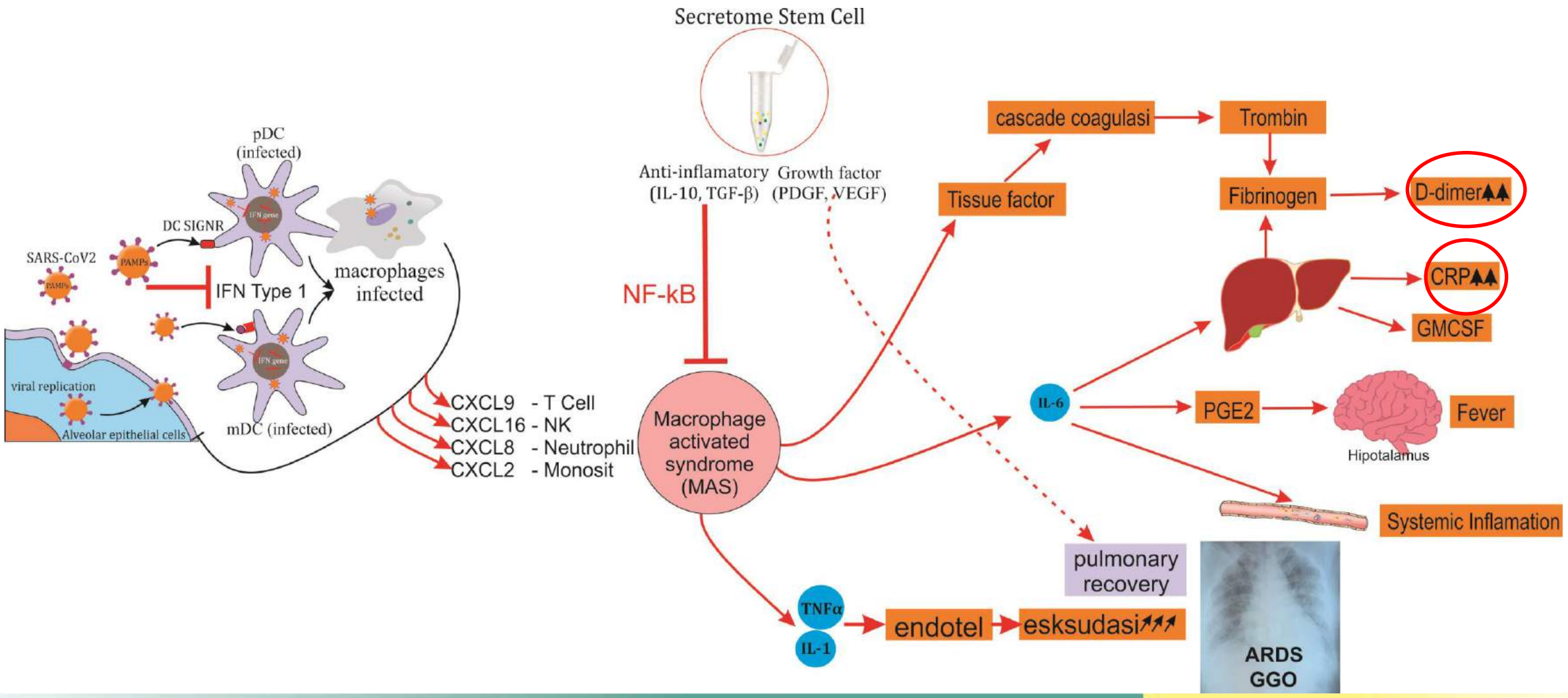
showed decreased bilateral GGOs, cardiomegaly and aortic elongation.

Secretome stem cell for Moderate cases

	Kadar CRP, IL6, PO2, SO2 Before S-MSCs Treatment	Kadar CRP, IL6, PO2, SO2 After S-MSCs Treatment
Pasien 1	CRP: 68 IL-6: 31,88 PO2: 68 SO2: 94	CRP: 0,9 IL-6: 17,14 PO2: 90 SO2: 97
Pasien 2	CRP: 109,36 IL6: 163,4 PO2: 69 SO2: 94	CRP: 11,4 IL6: 30,1 PO2: 106 SO2: 98
Pasien 3	CRP: 78,7 PO2: 56 SO2: 91	CRP: 3 PO2: 70 SO2: 95
Pasien 4	CRP: 286,1 PO2: 80 SO2: 96	CRP: 47,8 PO2: 132 SO2: 99
Pasien 5	CRP: 81,26 IL6: 66 PO2: 72 SO2: 92	CRP: 3,2 IL6: 9 PO2: 104 SO2: 99

SECRETOME STEM CELL FOR IMMUNO-MODULATOR




Secretome Stem Cell
Anti-inflamatory (IL-10, TGF-β)
Growth factor (PDGF, VEGF)
pDC (infected)
DC SIGNR
SARS-CoV2
PAMPs
IFN Type 1
macrophages infected
viral replication
Alveolar epithelial cells
mDC (infected)
NF-kB
CXCL9 - T Cell
CXCL16 - NK
CXCL8 - Neutrophil
CXCL2 - Monosit
Macrophage activated syndrome (MAS)
cascade coagulasi
Trombin
Tissue factor
Fibrinogen
D-dimer
CRP
GMCSF
IL-6
PGE2
Fever
Hipotalamus
Systemic Inflamation
pulmonary recovery
TNFα
IL-1
endotel
esksudasi
ARDS
GGO

Conclusion

1. **Tinggi Molekul Anti Badai Sitokin**
2. **Tinggi Molekul Regenerasi**
3. **Aman, tidak mengandung racun**
4. **Mampu menghentikan badai sitokin**
5. **Mampu mempercepat regenerasi jaringan rusak pasca COVID19**

Mampu mempercepat pemulihan pasien COVID19

REPUBLIK INDONESIA
MENTERIAN HUKUM DAN HAK ASASI MANUSIA

RTIFIKAT PATEN SEDERHANA

dan Hak Asasi Manusia atas nama Negara Republik Indonesia berdasarkan Undang-Undang Nomor 13 Tahun 2016 tentang Paten, memberikan hak atas Paten Sederhana kepada:

Nama dan Alamat Pemegang Paten	: Dr. dr. Agung Putra, M.Si., Med. Jl. Candi Prambanan Utara Raya Kav. 1135-1136 Kel. Kalipancur Kec. Ngaliyan, Semarang, INDONESIA
Untuk Invensi dengan Judul	: METODE OPTIMALISASI *SECRETOME* HASIL METABOLIT SEL PUNCA MESENKIMAL DENGAN RUANG HIPOKSIK 5% O_2
Inventor	: Dr. dr. Agung Putra, M.Si., Med.
Tanggal Penerimaan	: 21 Desember 2018
Nomor Paten	: ID S000003030
Tanggal Pemberian	: 19 Mei 2020

Perlindungan Paten Sederhana untuk invensi tersebut diberikan untuk selama 10 tahun terhitung sejak Tanggal Penerimaan (Pasal 23 Undang-Undang Nomor 13 Tahun 2016 tentang Paten).

Sertifikat Paten Sederhana ini dilampiri dengan deskripsi, klaim, abstrak dan gambar (jika ada) dari invensi yang tidak terpisahkan dari sertifikat ini.

a.n. MENTERI HUKUM DAN HAK ASASI MANUSIA
DIREKTUR JENDERAL KEKAYAAN INTELEKTUAL

Dr. Freddy Harris, S.H., LL.M., ACCS.
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Wassalamualaikum wr.wb

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SCCR Director

Dr. dr. Agung Putra, M.Si Med

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Currently serving as head of the anatomy pathology department of FK UNISSULA, chair of the SCCR Laboratory, teaching staff at the postgraduate program in biomedical medicine at FK UNISSULA and actively guiding doctoral program students

Dr. Dr. Agung Putra, M.Si.Med., actively involved in stem cell research that has been published in reputed and nationally accredited national journals.

Dr. Dr. Agung Putra, M.Si.Med. won superior research grant programs from Higher Education Institutions, fundamental grants and competed DIKTI to support research in the field of stem cells

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