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GADJAH MADA

Kajian :

Biologi Molekul Virus dari Tanaman ke COVID-19

Peran struktur protein virus dalam biofarmasi

Widhi Dyah Sawitri

27 Juni 2020

Karakter spesifik partikel virus berhubungan dengan mekanisme molekuler dalam menginfeksi sel

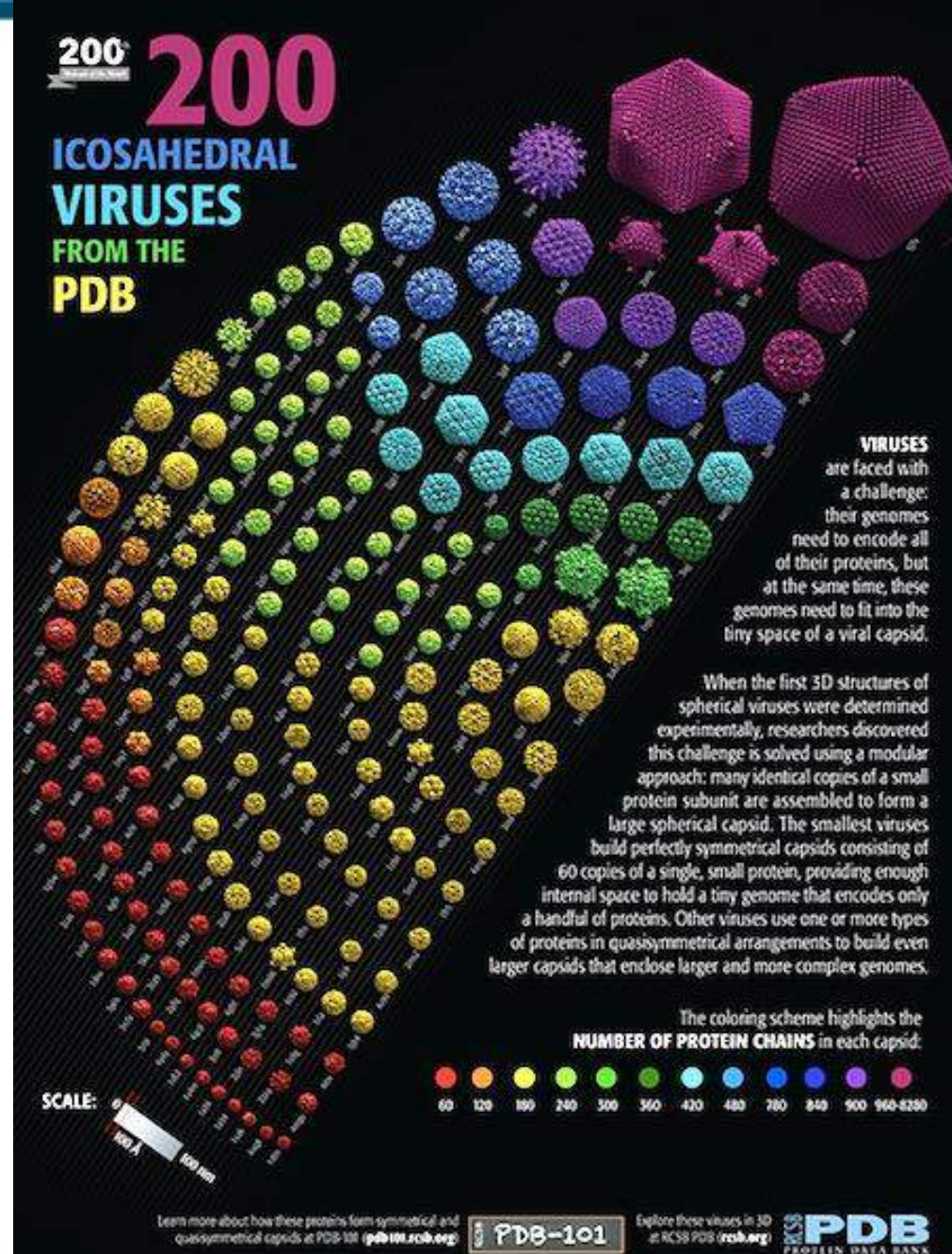


- ❑ Karena partikel virus berukuran kecil, sehingga ukuran genom virus kecil dan protein yang diproduksi sedikit
- ❑ Virus menggunakan prinsip “*genetic economy*” yang artinya virus memiliki banyak protein yang identik

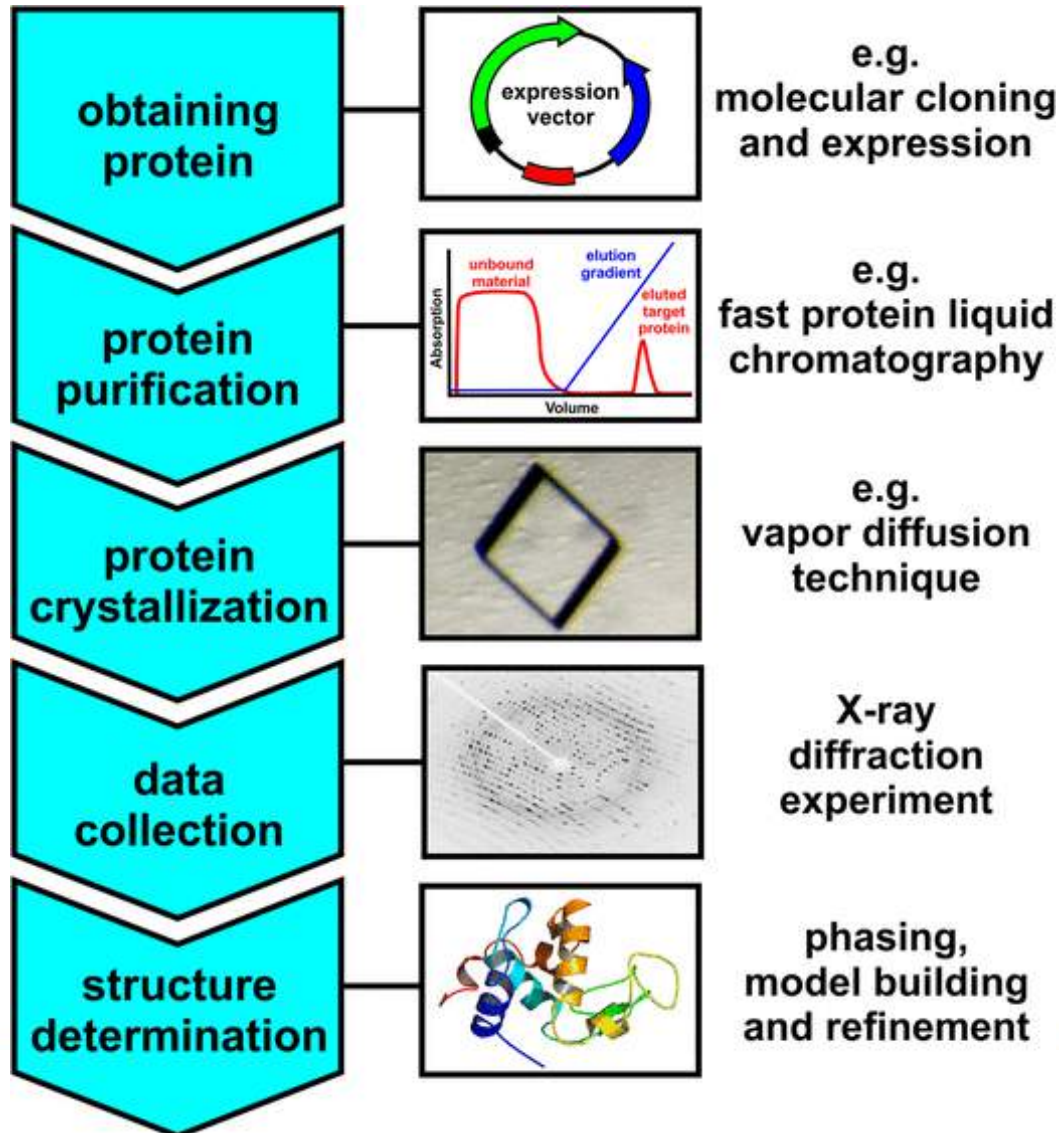
Ukuran virus umumnya dalam bentuk **Angstrom (Å)** → karena unit yang biasa digunakan untuk interaksi kimia

Contoh :

Ukuran virus 700 Å = 70 nm
(sekitar 1×10^{-6} dari bola tenis)



Metode analisis 3D struktur atom dengan resolusi tinggi :



X-Ray crystallography

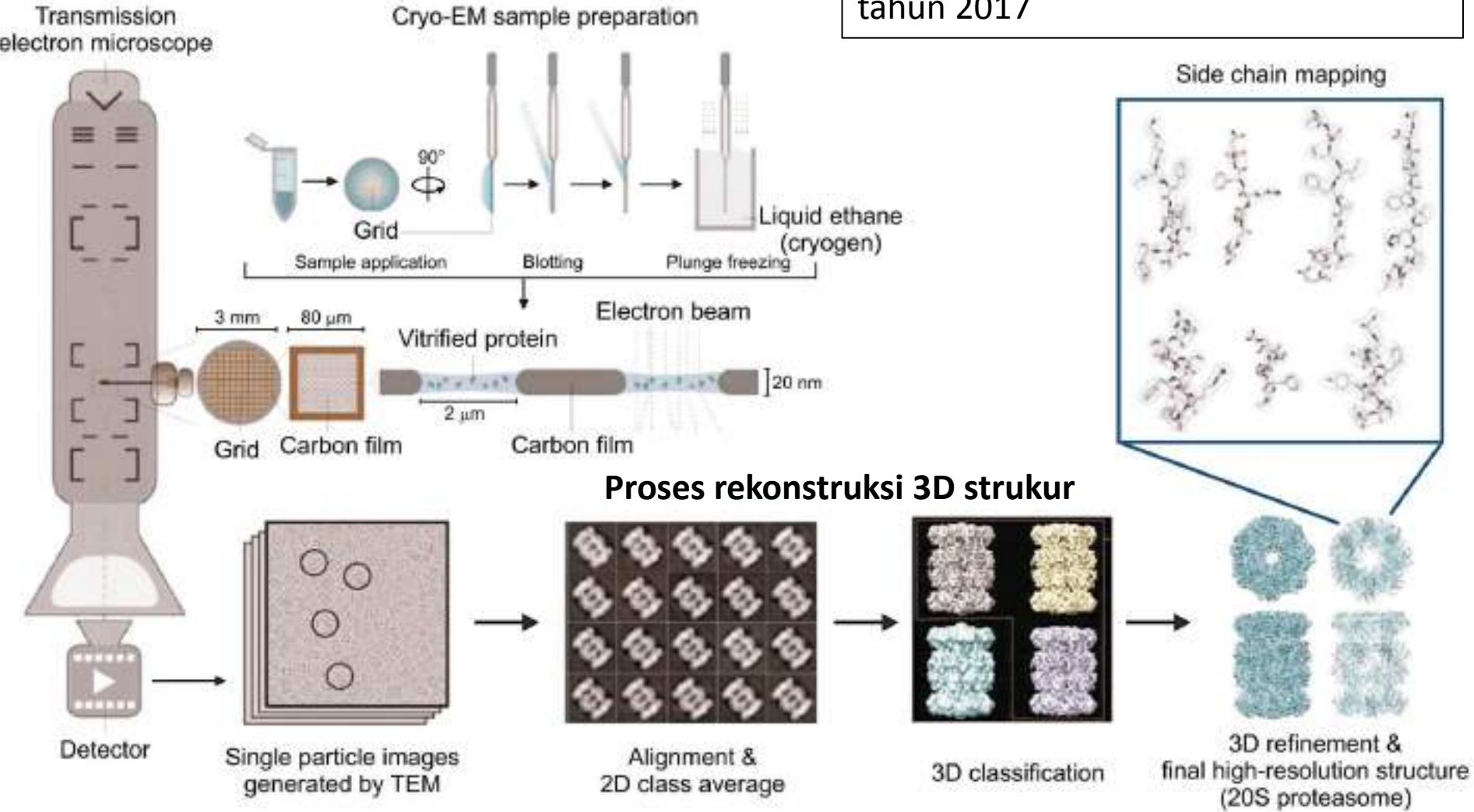
- ❖ Pertama kali kristalisasi virus oleh Wendell Stanley (1935), yaitu Tobacco Mosaic Virus.
- ❖ Pada tahun 1946, Wendell Stanley mendapatkan Nobel Prize in Chemistry

Deposit the structures to :



Cryo-EM High Resolution

Dr. Joachim Frank, Dr. Jacques Dubochet, dan Dr. Richard Henderson, mendapat Nobel Prize in Chemistry tahun 2017

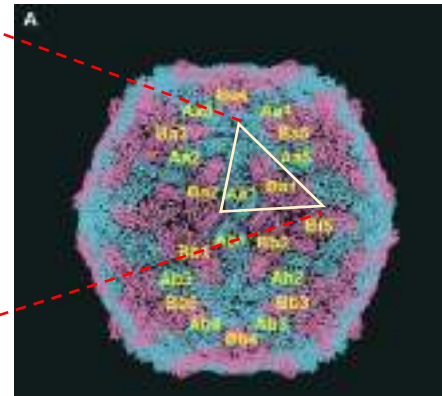
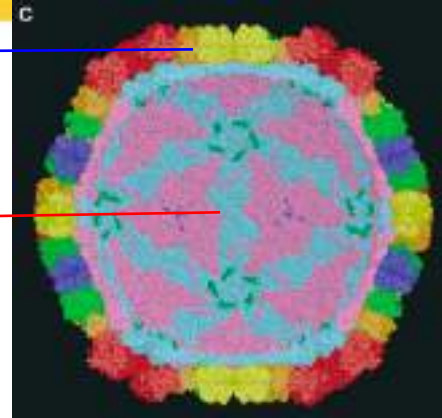


Rice Dwarf Virus (RDV)

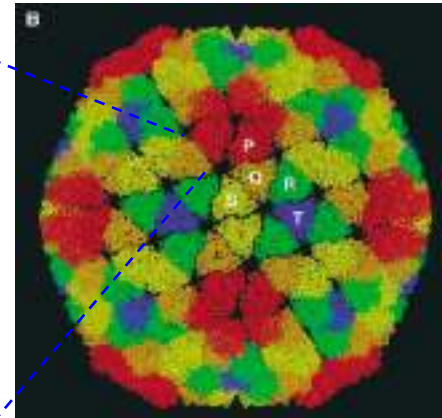
- ❑ Struktur virus dari *X-Ray crystallography* (3.5 Å)
- ❑ Berbentuk icosahedral, ukuran diameter 700 Å

The outer shell protein

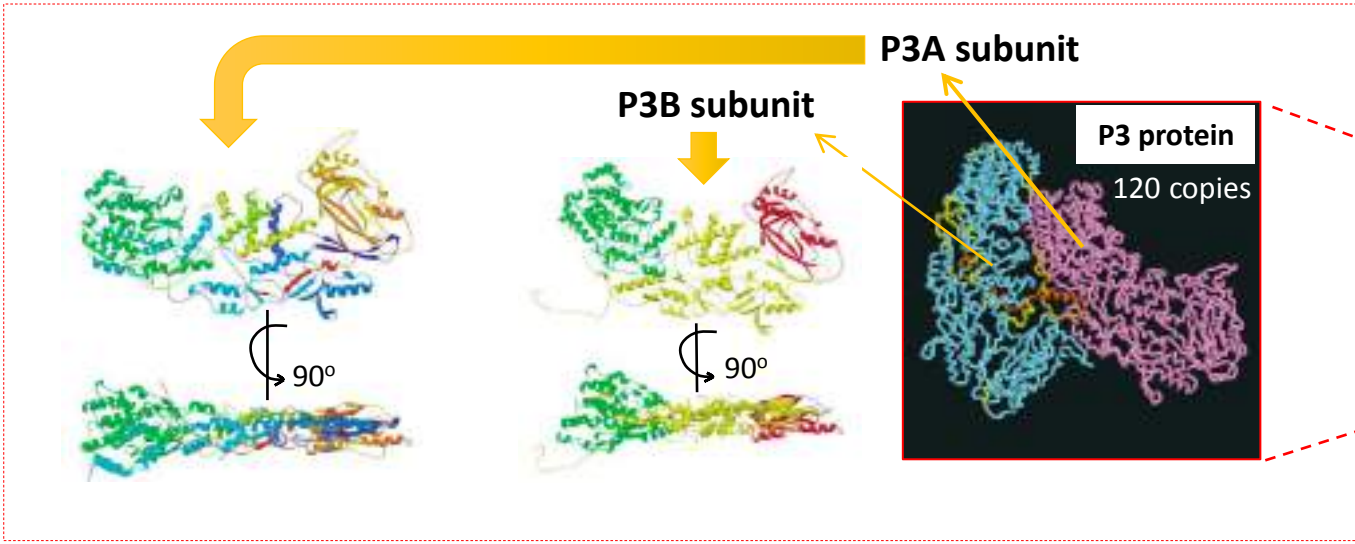
The core protein



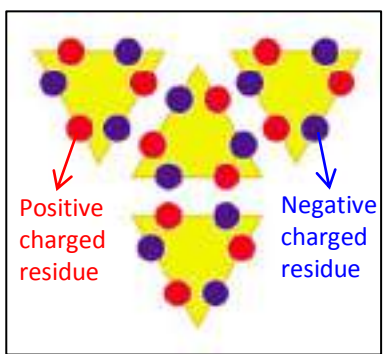
The core protein (P3)



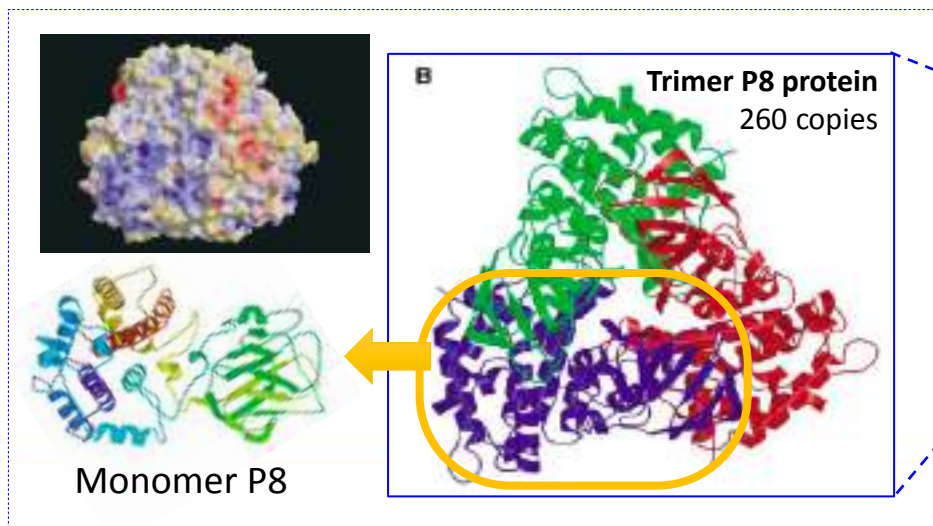
The outer shell protein (P8)



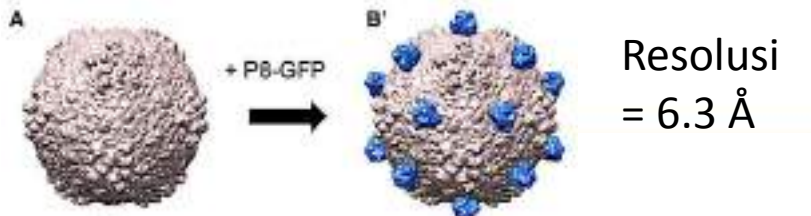
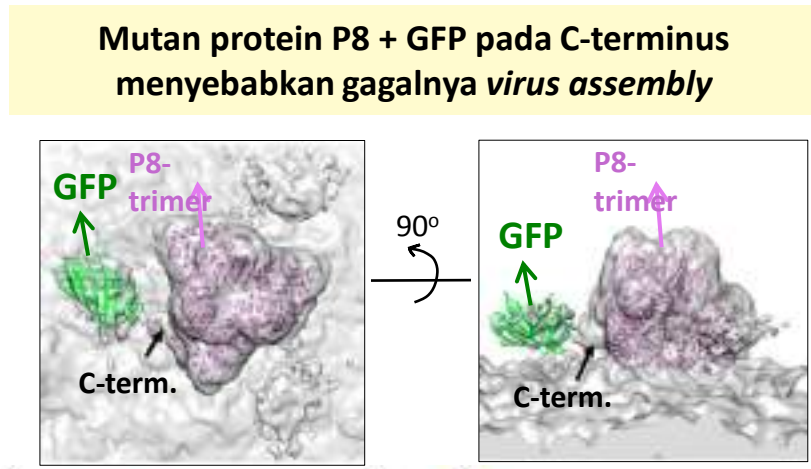
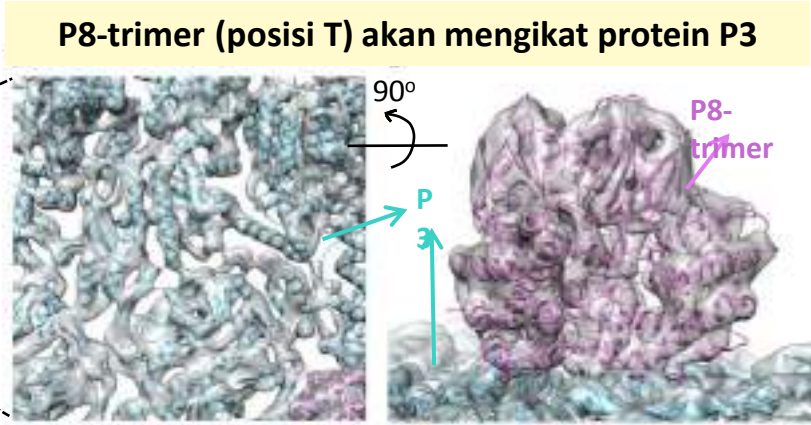
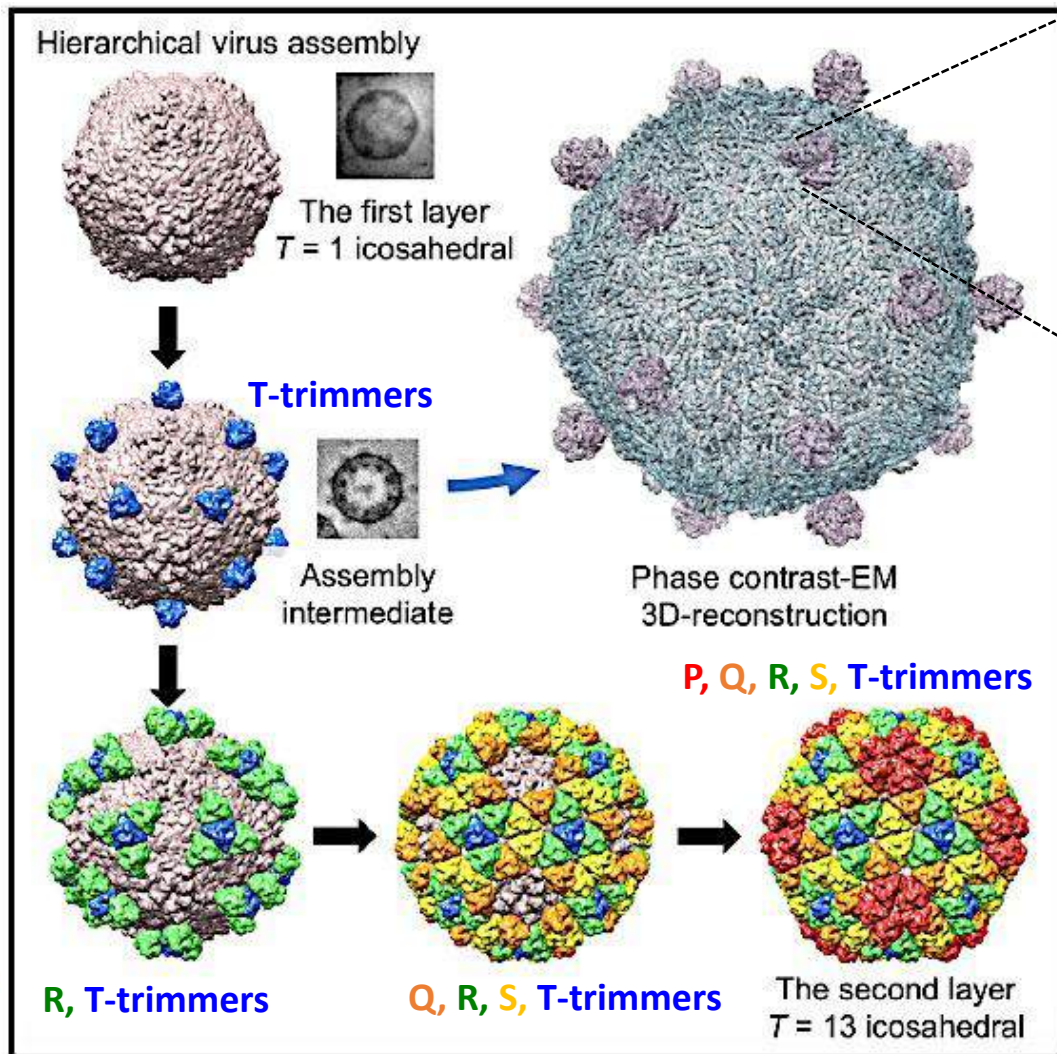
Model interaksi trimer P8



(Nakagawa, 2003)

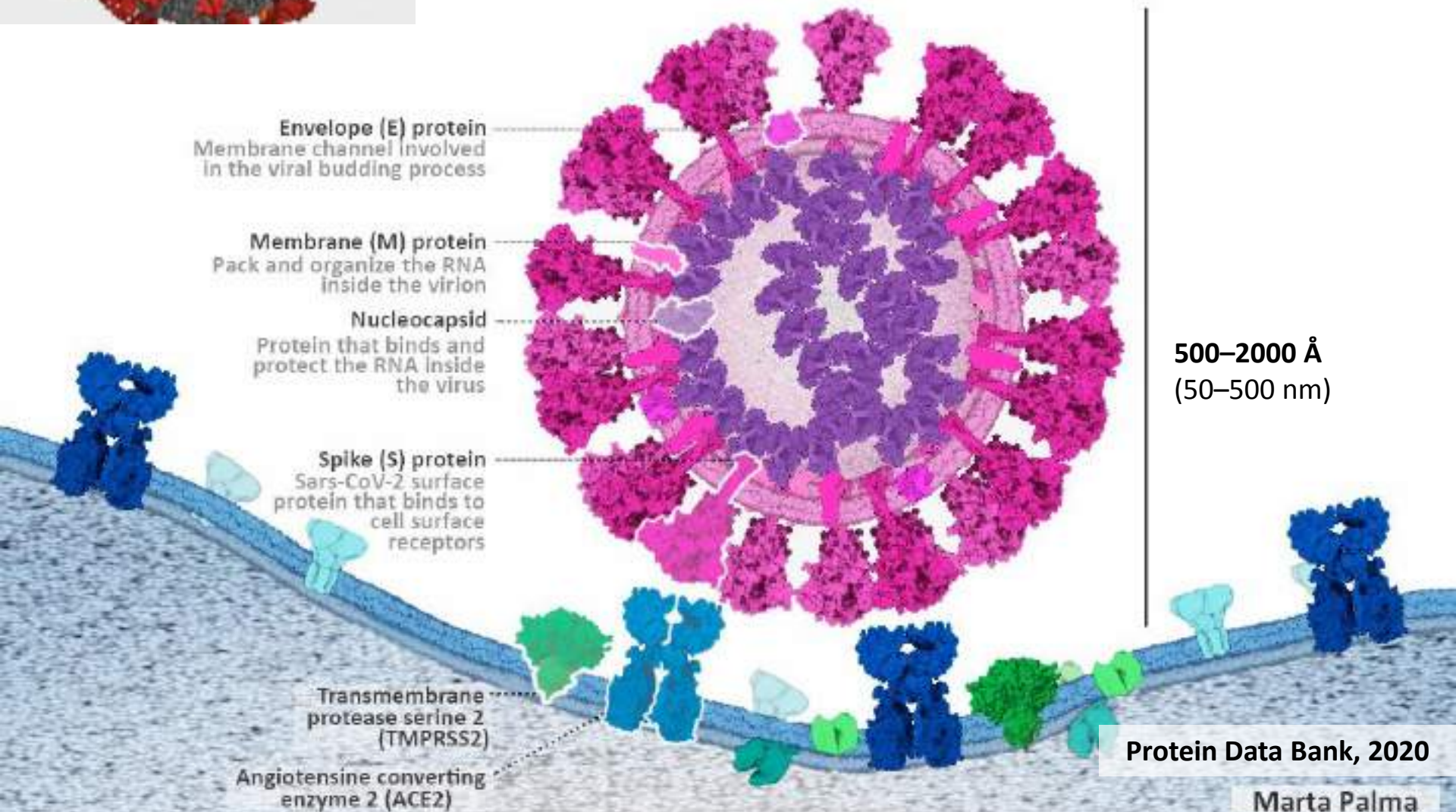
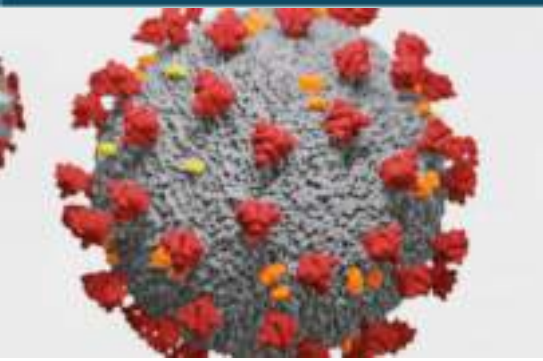


An Assembly Intermediate Structure of Rice Dwarf Virus Reveals a Hierarchical Outer Capsid Shell Assembly Mechanism



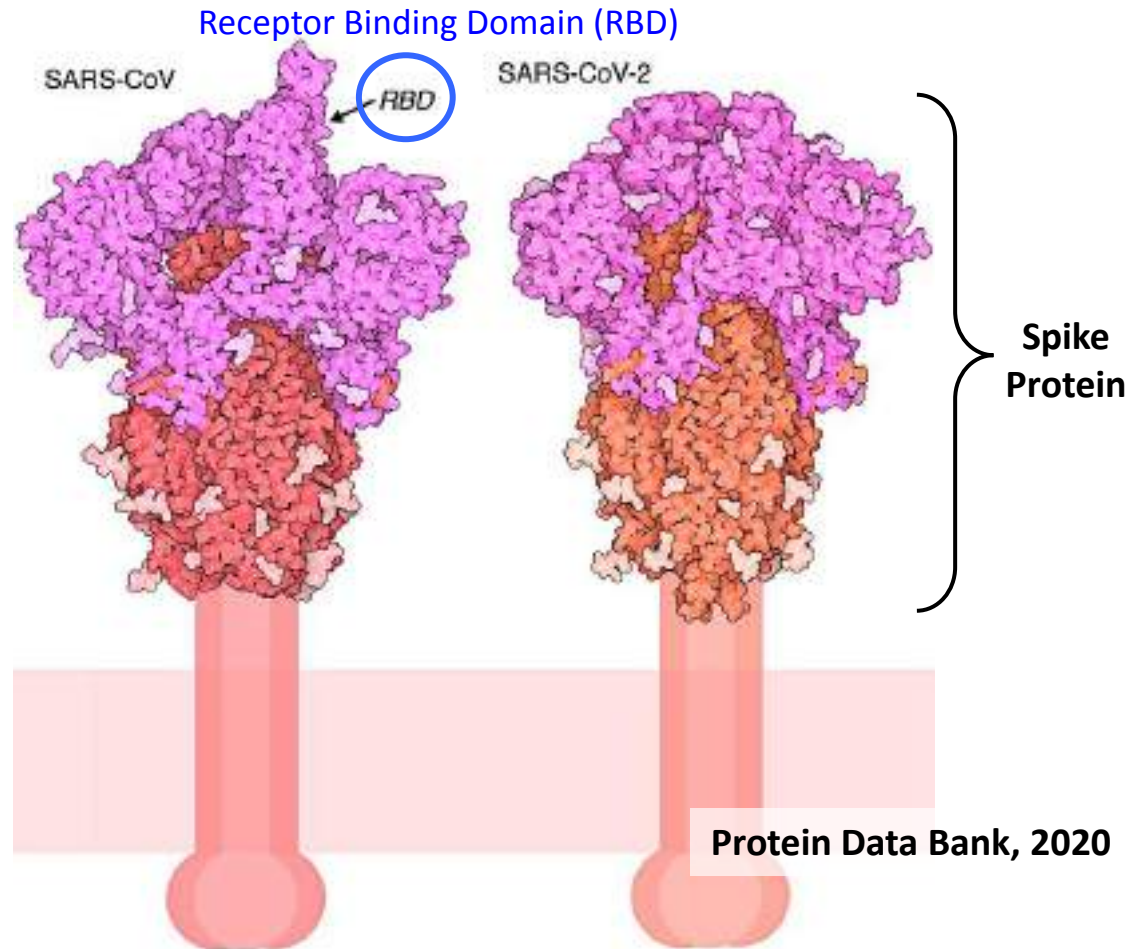
Coronavirus Disease 2019 (SARS-CoV-2)

Salah satu cara untuk menangani penyakit COVID-19 adalah mengetahui mekanisme virus mengenali sel inang (manusia)



Spike Glycoprotein (S protein) pada Virus Corona

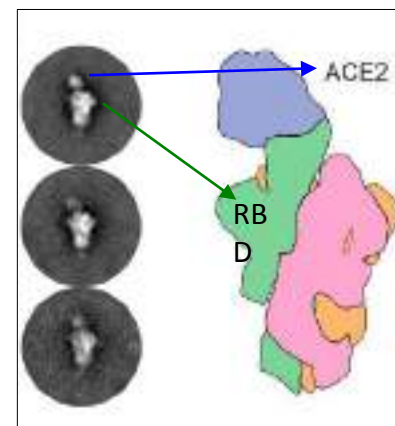
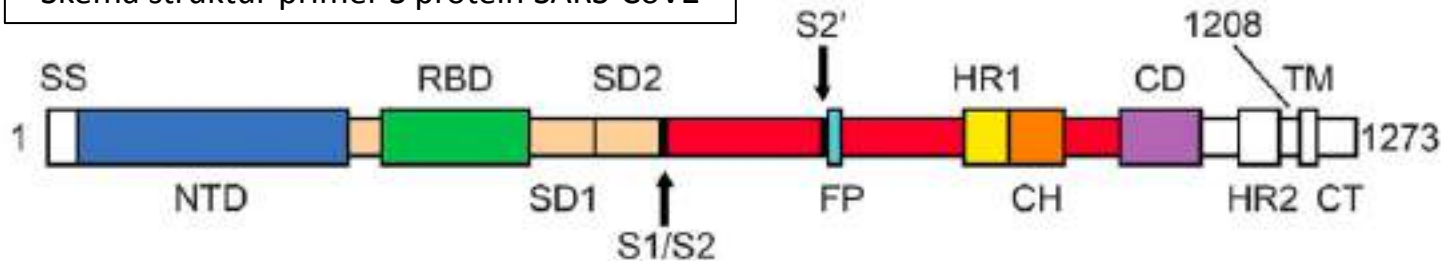
Oleh karena S protein pada SARS-CoV telah terbukti memiliki interaksi dengan reseptor ACE2 pada manusia, sehingga SARS-CoV2 **diprediksi** memiliki interaksi yang sama dengan SARS-CoV



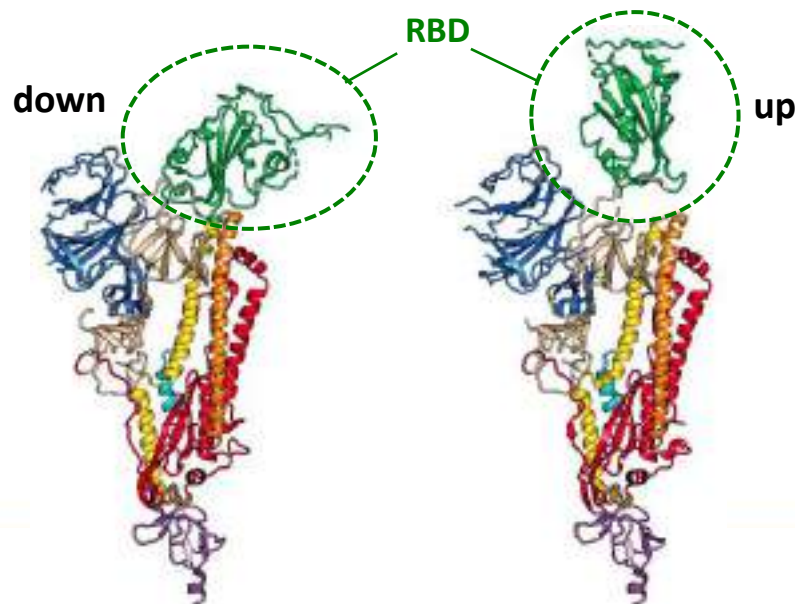
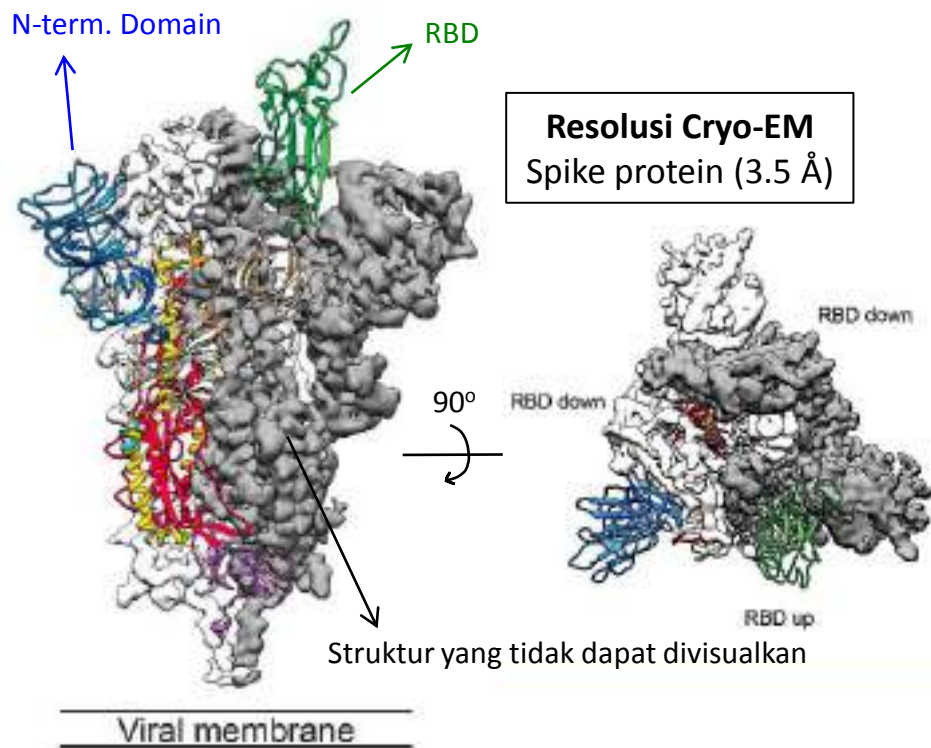
Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation

Interaksi S protein SARS-CoV2 dengan ACE2 melalui negatif stain EM

Skema struktur primer S protein SARS-CoV2



Pada posisi konformasi struktur RBD yang bagaimana agar dapat berinteraksi dengan ACE2 ?



Structural basis of receptor recognition by SARS-CoV-2

Jian Shang^{1,3}, Gang Ye^{1,3}, Ke Shi^{2,3}, Yushun Wan^{1,3}, Chuming Luo¹, Hideki Aihara², Qibin Geng¹, Ashley Auerbach¹ & Fang Li^{1,2}

Nature | Vol 581 | 14 May 2020

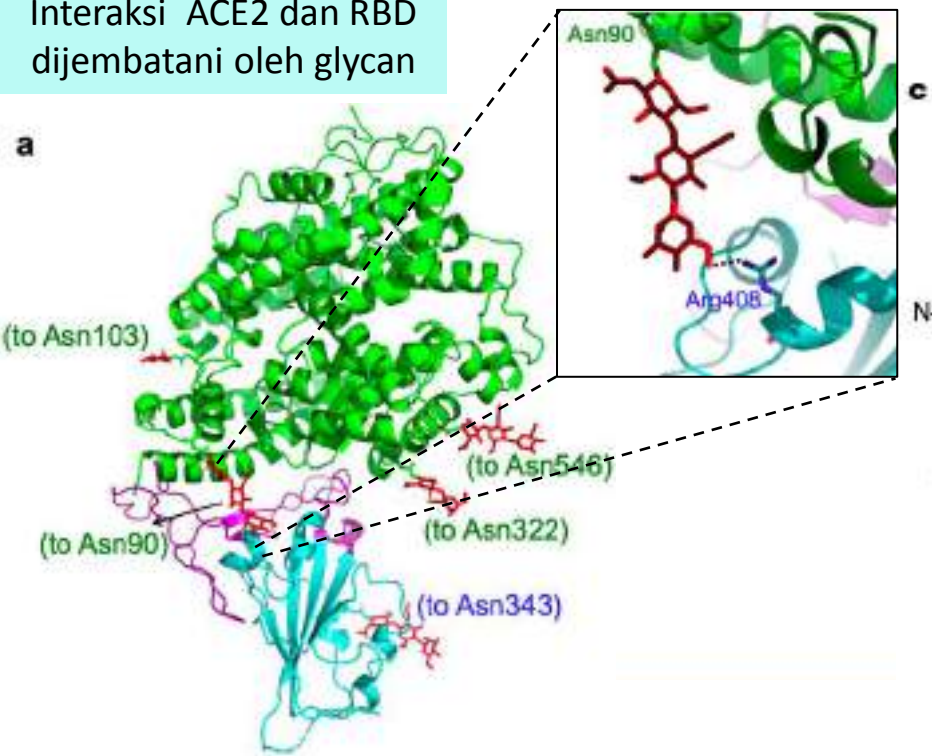
Resolusi *crystal structure* = 2.68 Å

Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor

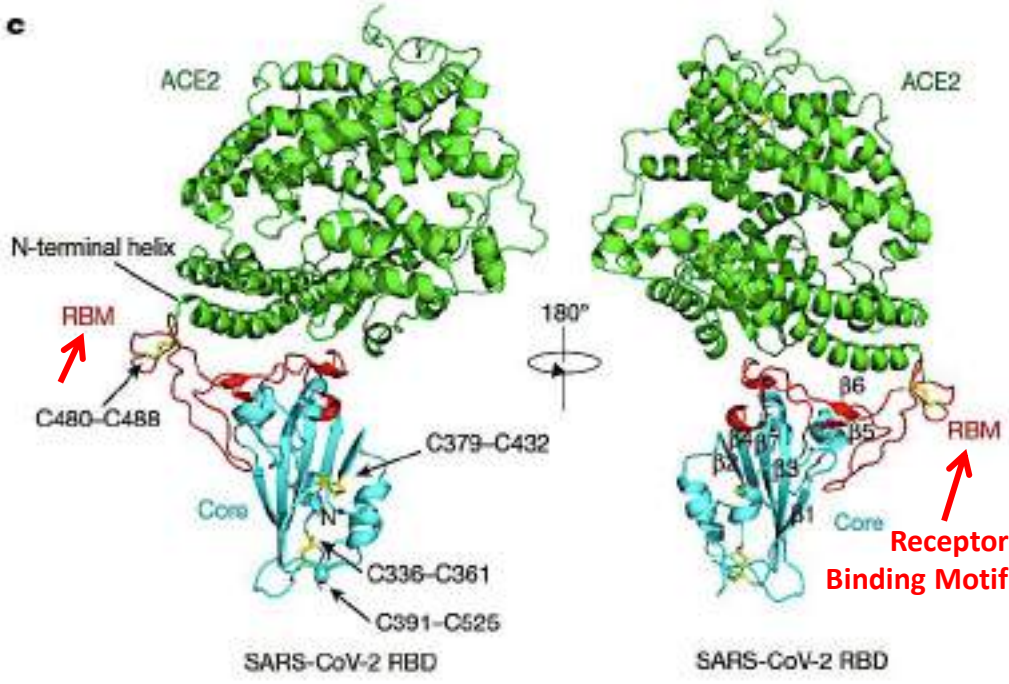
Jun Lan^{1,4}, Jiwan Ge^{1,4}, Jinfang Yu^{1,4}, Sisi Shan^{2,4}, Huan Zhou³, Shilong Fan¹, Qi Zhang², Xuanling Shi², Qisheng Wang³, Linqi Zhang² & Xinquan Wang¹

Resolusi *crystal structure* = 2.45 Å

Interaksi ACE2 dan RBD dijembatani oleh glycan

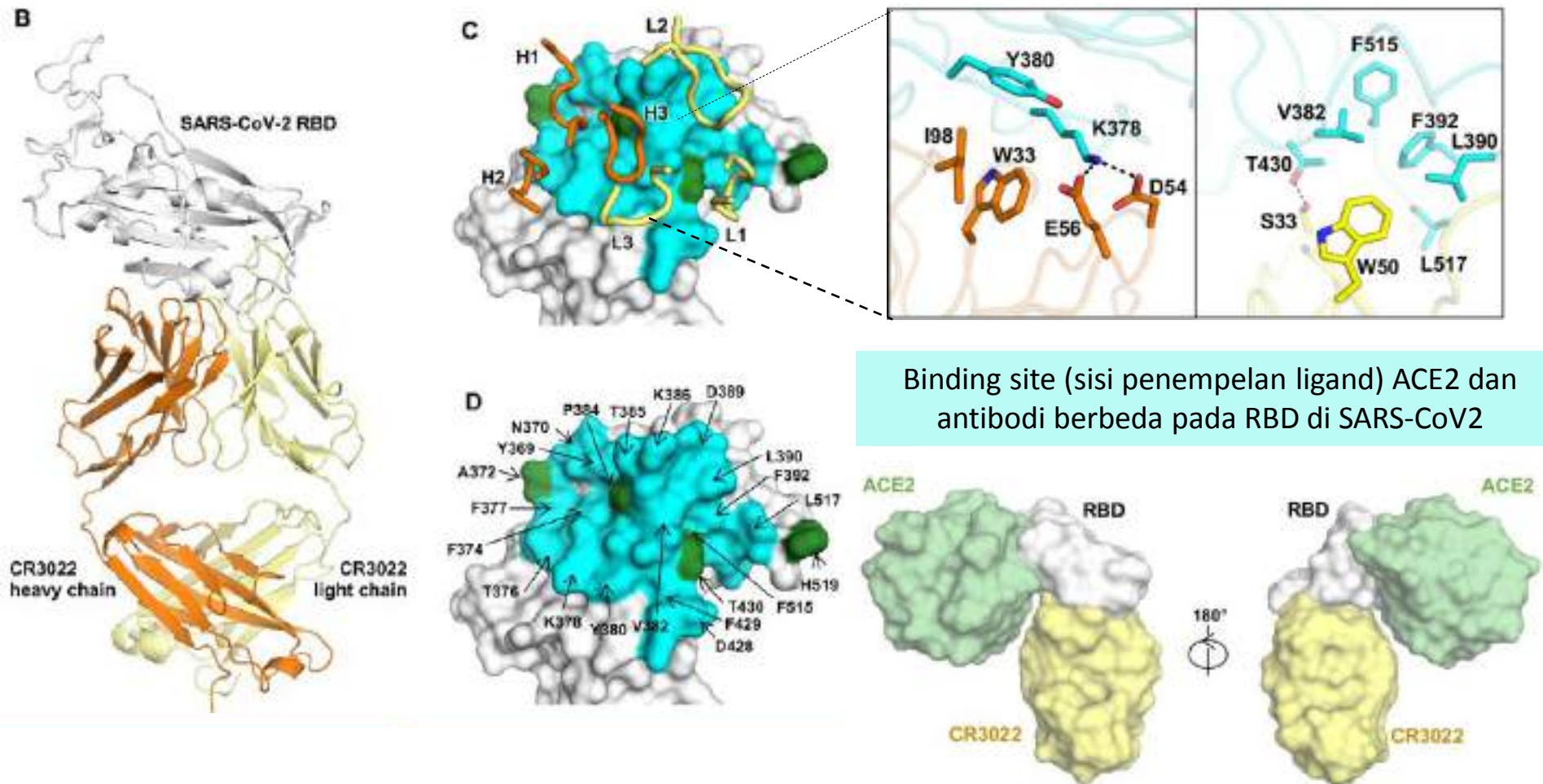


Receptor Binding Motif (RBM) pada SARS-CoV2 yang berikatan dengan ACE2



A highly conserved cryptic epitope in the receptor-binding domains of SARS-CoV-2 and SARS-CoV

Crystal structure kompleks RBD dari Spike Protein SARS-CoV2 dengan CR3022 (*neutralizing antibody* yang sebelumnya telah diisolasi dari pasien SARS) dengan resolusi = 3.1 Å



Apakah ada target protein lain selain Spike Protein?

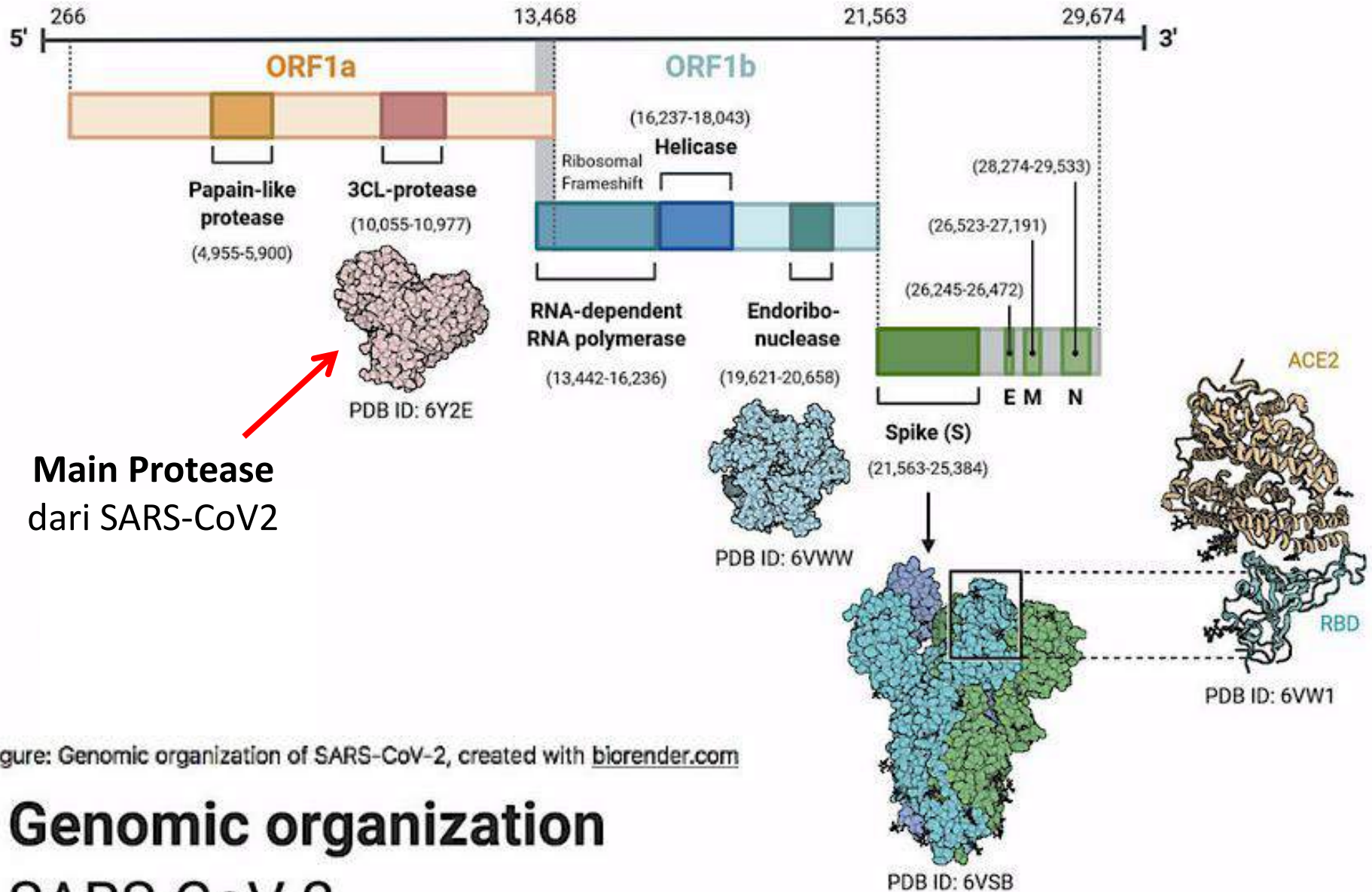
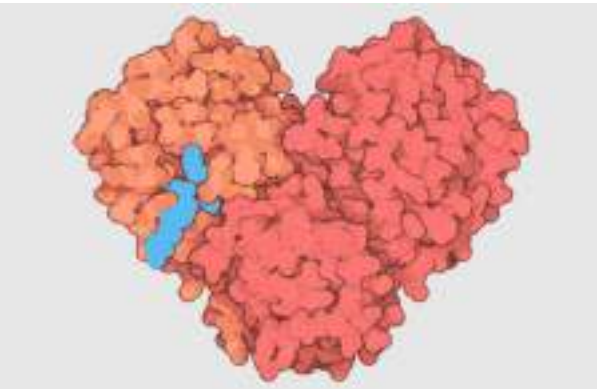


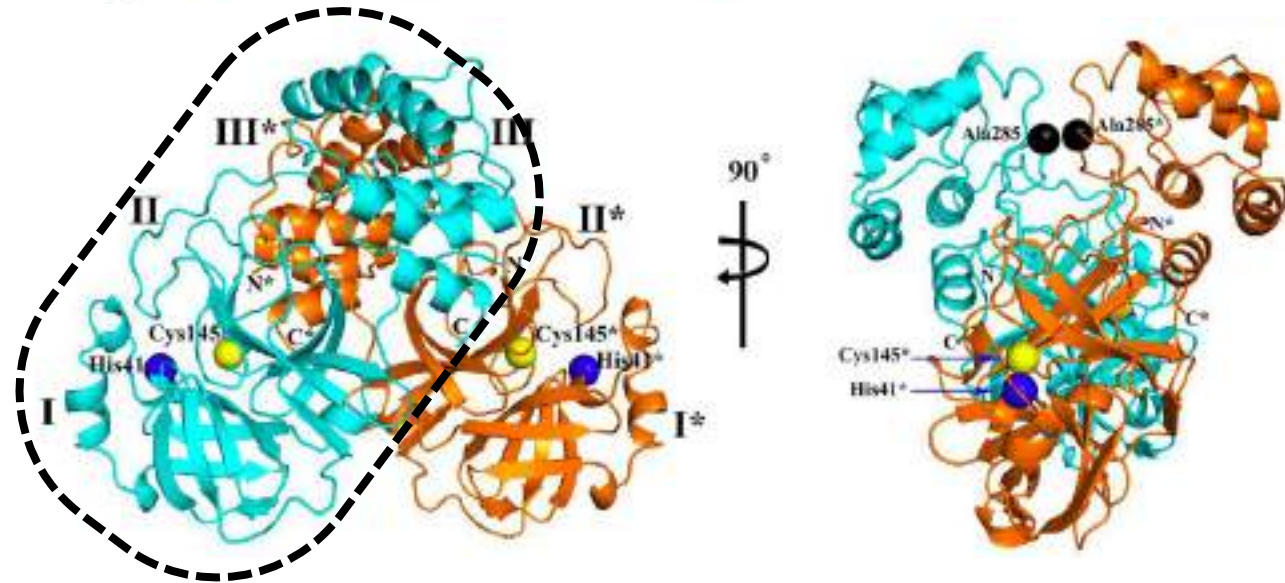
Figure: Genomic organization of SARS-CoV-2, created with biorender.com

Genomic organization SARS-CoV-2

Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved α -ketoamide inhibitors



Main Protease
berbentuk dimer



- Struktur didapatkan dari **X-Ray crystallography** (1.75 Å)
- Main Protease** penting untuk memproses protein yang telah ditranslasikan dari RNA virus (memotong bagian protein SARS-CoV2 menjadi banyak protein virus)
- Strategi: menghambat aktifitas Main Protease sehingga dapat mem-*block* replikasi virus → **Antiviral Drug Design**

Update struktur protein SARS-CoV2 di PDB



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RCSB PDB 165550 Biological Macromolecular Structures Enabling Breakthroughs in Research and Education

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- Severe acute respiratory syndrome coronavirus 2 (260)
- Homo sapiens (21)
- synthetic construct (13)
- Lama glama (5)
- Foot-and-mouth disease virus (2)
- Mus musculus (2)
- Severe acute respiratory syndrome-related coronavirus (1)
- Streptomyces exfoliatus (1)
- Streptomyces roseus (1)
- saltans group (1)

TAXONOMY Clear

- Riboviria (260)
- Eukaryota (26)
- artificial sequences (13)
- Bacteria (2)

EXPERIMENTAL METHOD Clear

- X-RAY DIFFRACTION (234)
- ELECTRON MICROSCOPY (25)
- SOLUTION NMR (1)

POLYMER ENTITY TYPE Clear

- Protein (260)
- RNA (0)



3D View

7C22

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Crystal structure of the C-terminal domain of SARS-CoV-2 nucleocapsid protein

Zhou, R.J., Zeng, R., Lei, J.

To be published

Released 2020-05-20
Method X-RAY DIFFRACTION 2 Å
Organisms Severe acute respiratory syndrome coronavirus 2
Macromolecule Nucleoprotein (protein)
Unique Ligands ACT, PEG



3D View

6YB7

Download File View File

SARS-CoV-2 main protease with unliganded active site (2019-nCoV, coronavirus disease 2019, COVID-19)

Owen, C.D., Lukacik, P., Strain-Damerell, C.M., Douangamath, A., Powell, A.J., Fearon, D., Brandao-Neto, J., Crawshaw, A.D., Aragao, D., Williams, M., Flaig, R., Hall, D.R., McAuley, K.E., Mazzorana, M., Stuart, D.J., von Delft, F., Welsh, M.A.

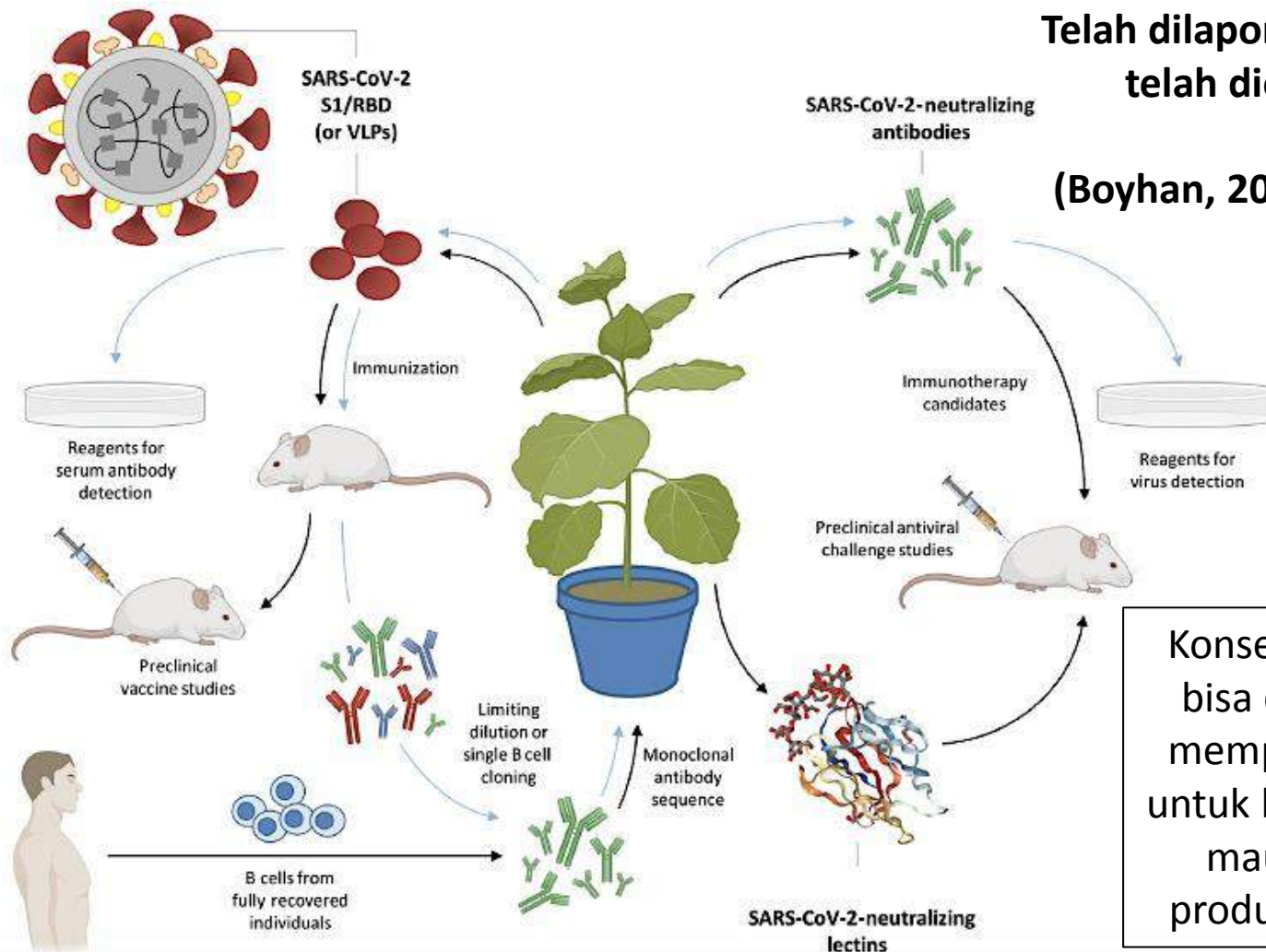
To be published

Released 2020-03-25
Method X-RAY DIFFRACTION 1.25 Å
Organisms Severe acute respiratory syndrome coronavirus 2
Macromolecule Replicase polyprotein 1ab (protein)
Unique Ligands DMS

Opinion

Potential Applications of Plant Biotechnology
against SARS-CoV-2Teresa Capell,^{1,6} Richard M. Twyman,^{2,6} Victoria Armario-Najera,¹
Julen K.-C. Ma,^{3,4} Stefan Schillberg,^{4,*} and Paul Christou^{1,5,*}Peran *Plant Biotechnologist* ?

Telah dilaporkan *low-cost* proinsulin
telah diekspresikan di kloroplas
tobacco dan lettuce
(Boyhan, 2011) - *Plant Biotechnol J.*



Konsep **Molecular Farming**
bisa dikembangkan untuk
memproduksi protein virus
untuk kepentingan diagnostic
maupun antigen untuk
produksi vaksin SARS-CoV2



I was captured for life by chemistry
and by crystals.

— *Dorothy Hodgkin* —

**Nobel Prize in Chemistry (1964),
Determining the structure of Insulin**

Thank you