股號：6492

生華生物科技股份有限公司

次世代DDR與HH/IO抗癌與抗病毒新藥

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A worldwide opportunity for Silmitasertib (CX-4945) as a COVID-19 targeted therapy

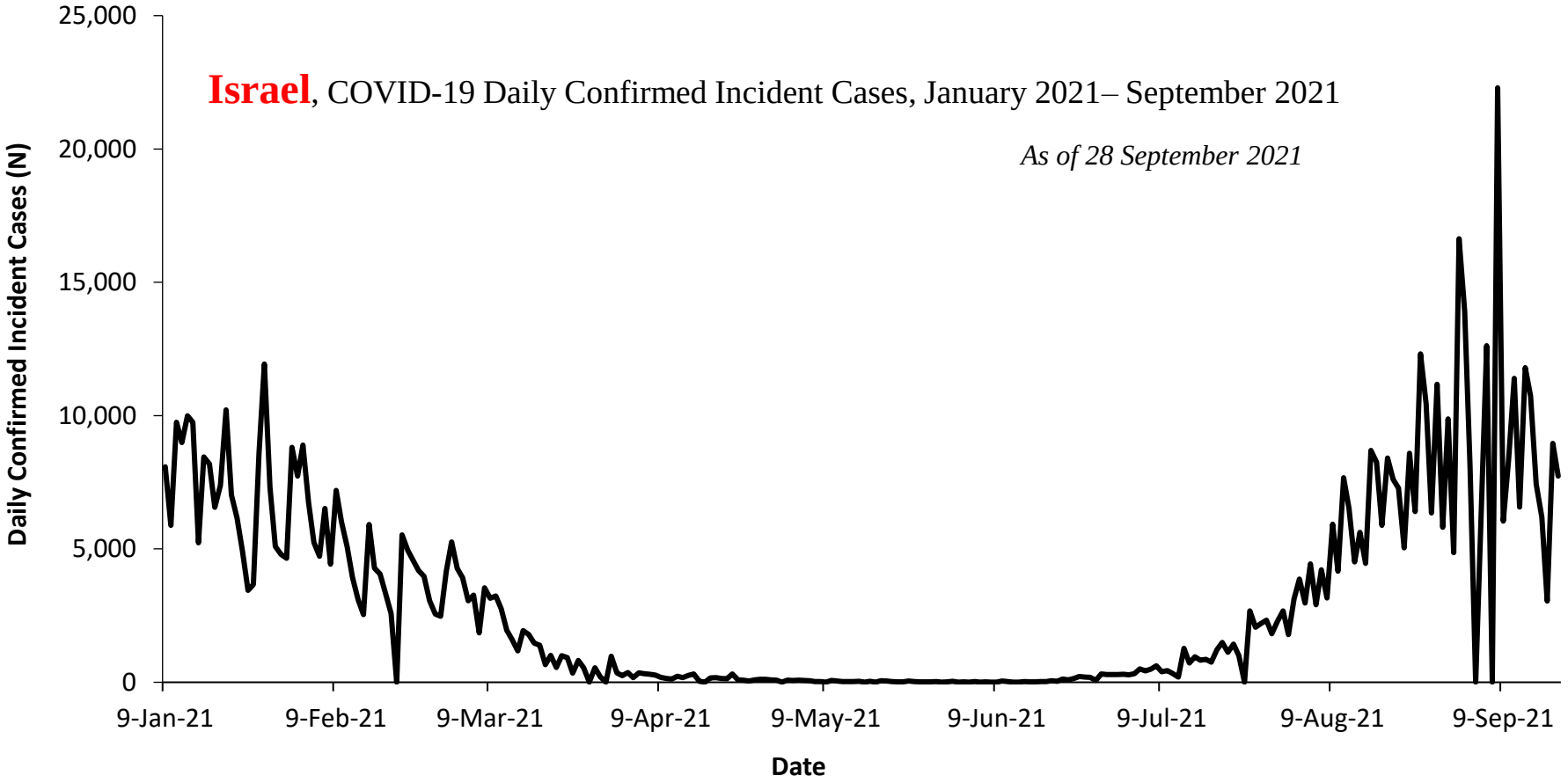
抗新冠病毒藥研發難度非常大

1. 病毒感染初期複製快，典型感染者每天產生至少100萬病毒粒子
2. 新冠病毒變種太快，變得快的病毒會產生耐藥性
3. 對抗新冠病毒，藥物作用不但要能跟人體免疫系統協同清除病毒，且也需要降低造成免疫風暴及肺部發炎反應的因子 **(IL-6, TNF-α)**、進而改善症狀、使人體盡快回復正常功能。

Source: 董宇紅博士, 歐洲病毒學及傳染學專家演講

新冠病毒變種造成突破性感染

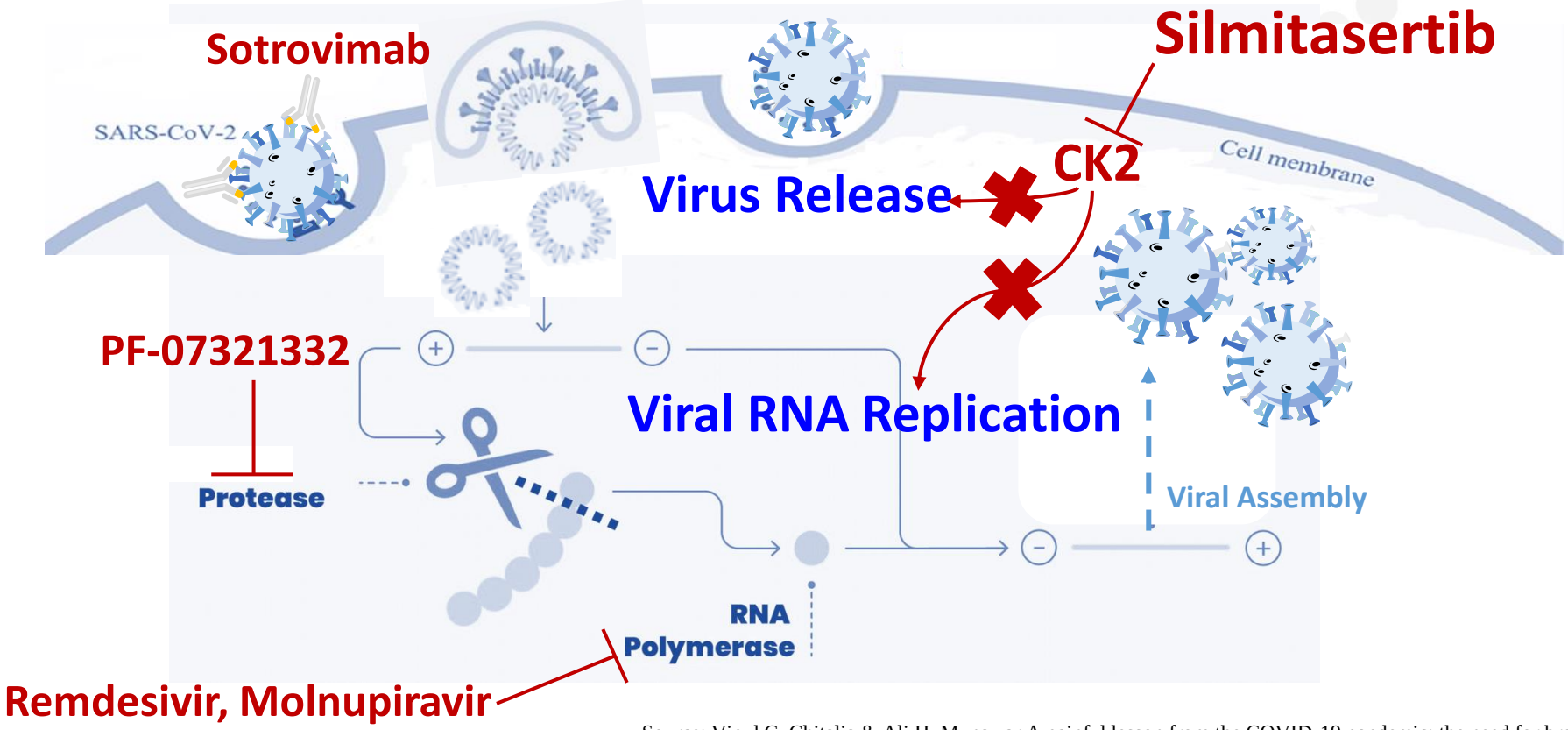
雖有疫苗接種仍迫切需要新冠治療藥物



Source: GlobalData Analysis

需要宿主導向的新冠藥物

新冠病毒變種太快，容易產生耐藥性



Source: Vipul C. Chitalia & Ali H. Munawar A painful lesson from the COVID-19 pandemic: the need for broad-spectrum, host-directed antivirals. Journal of Translational Medicine volume 18, Article number: 390 (2020)
Yu-Wen Zhou. REVIEW ARTICLE OPEN Therapeutic targets and interventional strategies in COVID-19: mechanisms and clinical studies . Signal Transduction and Targeted Therapy (2021) 6:317

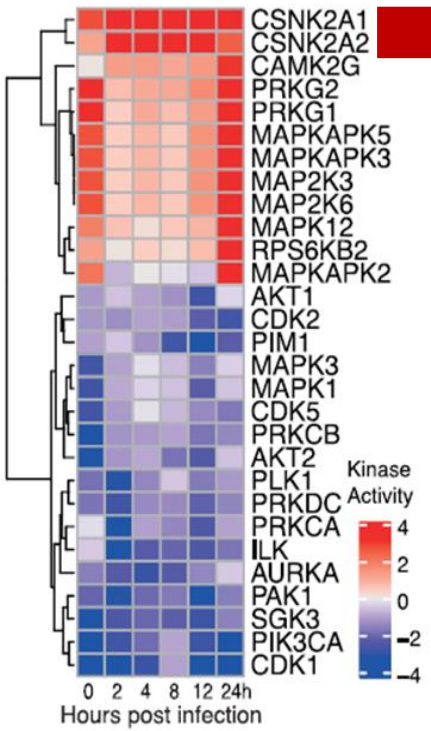
CK2宿主細胞蛋白驗證為終結新冠病毒的標靶

- **CK2為美國QBI-UCSF科學團隊研究發現SARS-CoV-2 在細胞中進行複製所依賴之最關鍵且不可或缺的宿主細胞蛋白激酶**

- **Silmitasertib藉由抑制CK2阻斷病毒複製、阻止 SARS-CoV-2 離開細胞，從而防止感染傳播。由於 CK2 蛋白激酶不會發生突變，因此不受病毒變異影響機制**

- **CIGB-325胜肽類靜脈注射藥物，在古巴完成的二期研究也顯示臨床效益。CIGB-325與Silmitasertib的二期臨床均驗證CK2是治療新冠病毒的關鍵標的。**

Signaling Changes in Host Cells in Response to SARS-CoV-2 Infection. Kinases depicting a strong change in activity upon infection.



CK2

"Achilles heel of SARS-CoV-2"

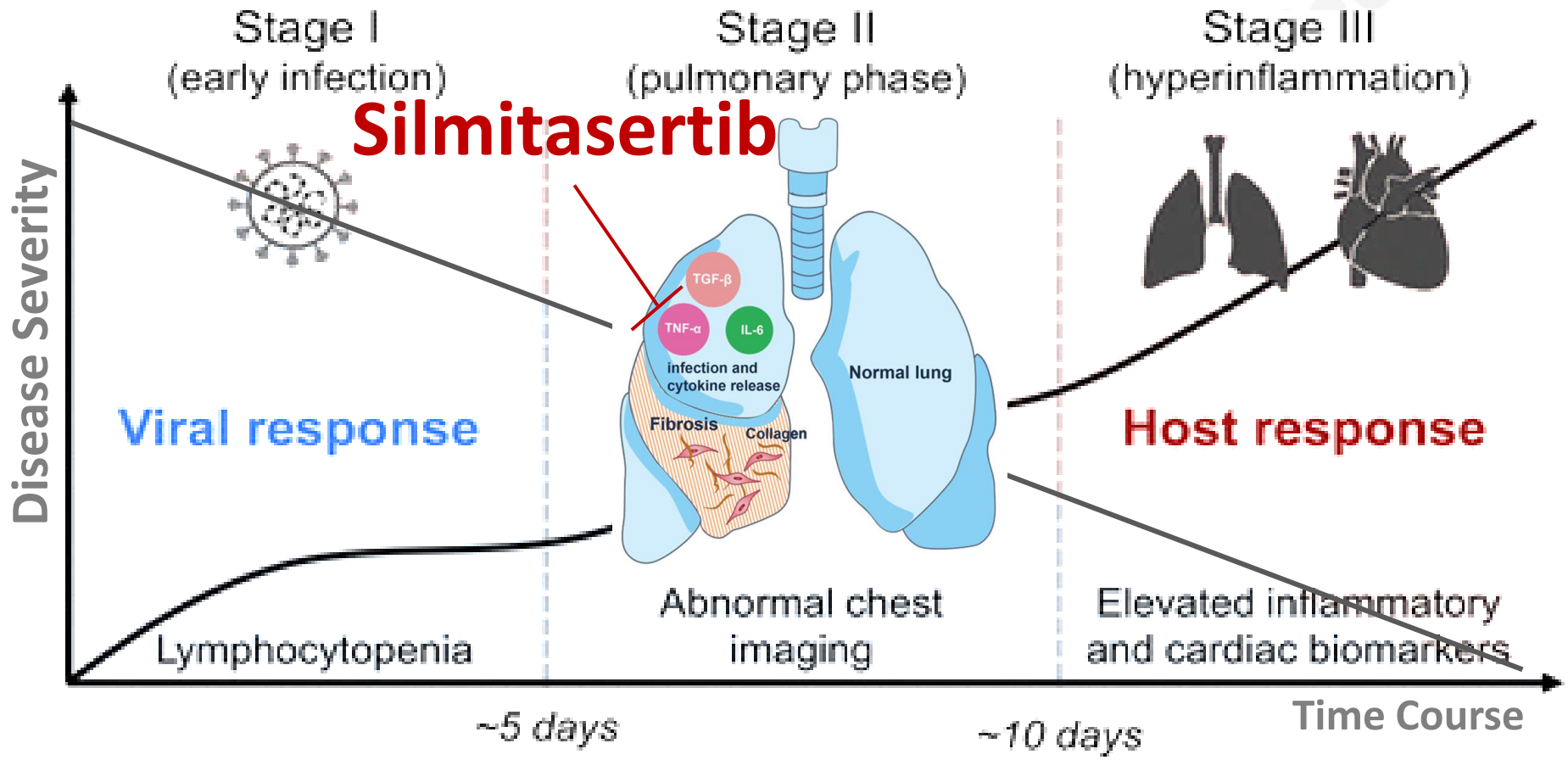
UCSF

"It totally makes sense there's an overlap in anticancer drugs and an antiviral effect," said Prof. Krogan, who added that cancers, HIV and SARS-CoV-2 are all searching for the "Achilles heel of the cell."

Source: Bouhaddou M, Memon D, Meyer B, et al. The Global Phosphorylation Landscape of SARS-CoV-2 Infection. Cell. Published online 2020. doi:10.1016/j.cell.2020.06.034
https://www.cell.com/cell/fulltext/S0092-8674(20)30811-4

開發具抗病毒及抗發炎的新冠藥物

對抗新冠病毒要針對呼吸系統、減緩肺部發炎反應



Silmitasertib 抗新冠臨床療效驗證

【Fail Fast-藥物快速驗效】策略

- 本二期新冠臨床設計採用大型製藥公司為加速藥物開發會採取的“藥物快速驗效” 策略
- 生華採此策略，旨在開發與對照組相比具臨床優勢高於一倍以上的藥物。因試驗設計採高標準，若此藥物臨床療效具統計上顯著意義，此藥物具高機會成為重磅藥物(blockbuster)
- 生華團隊期待藉由這項20 名受試者的二期臨床試驗快速驗證Silmitasertib是否為有效治療COVID-19的重磅藥物

【藥物快速驗效】策略－有效率地找出重磅藥物

臨床樣本數量

- 藥物快速驗效策略，其設計透過樣本小的試驗，快速篩選具開發成為重磅藥物的潛力藥物
- 如開發藥物在小樣本試驗中展現顯著臨床效益並具統計意義時，此結果可被視為進一步開發的重要依據。
- 生華目標開發出與對照組相比具臨床優勢高於一倍以上的重磅藥物

雙盲或開放式試驗

- 由於陸續有新的療法因取得EUA加入標準療法 (SOC)，且多為靜脈注射，本公司試驗藥物為口服劑型，在藥物快速驗效的策略下，毋須雙盲設計
- **經數據分析，10位試驗組患者在療程中都僅接受Silmitasertib單藥治療，並未接受其他同步性療法**
- **試驗結果可視為Silmitasertib大幅優於採標準療法(SOC)/最佳支持療法(best supportive care)對照組中的EUA藥物**

統計分析方式

- 本試驗採單側、1 型誤差 (Type 1 error) alpha 0.2 的統計分析，常見於 臨床2期試驗（初步療效評估）
- 如已上市癌症藥物愛寧達 (Alimta)，其 2 期臨床試驗即以單側 、alpha 0.2 進行統計分析
- 此試驗相關數據分析，當 p 值 < 0.2 ，即達統計上顯著差異。

COVID-19臨床應依不同病程設計臨床試驗

Severity	Description (NIH)
Mild	• Individuals who have any of the various signs and symptoms of COVID 19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain) without shortness of breath, dyspnea, or abnormal chest imaging.
Moderate	• Individuals who have evidence of lower respiratory disease by clinical assessment or imaging and a saturation of oxygen (SpO2) ≥94% on room air at sea level.
Severe	• Individuals who have respiratory frequency >30 breaths per minute, SpO2 <94% on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mmHg, or lung infiltrates >50%.
Critical	• Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.

- **COVID-19分輕、中、重、危重症四個病程階段，臨床症狀也不相同**
- **輕症多為典型症狀。中重症發生在下呼吸道及肺部發炎感染**
- **臨床試驗設計依不同病程納入相對應之患者，其試驗指標也隨不同設計而異**
- **國際藥廠新冠臨床設計多以Mild to Moderate (輕至中症)、Moderate (中症)、Severe (重症)、Critical (危重症)為收案區隔**

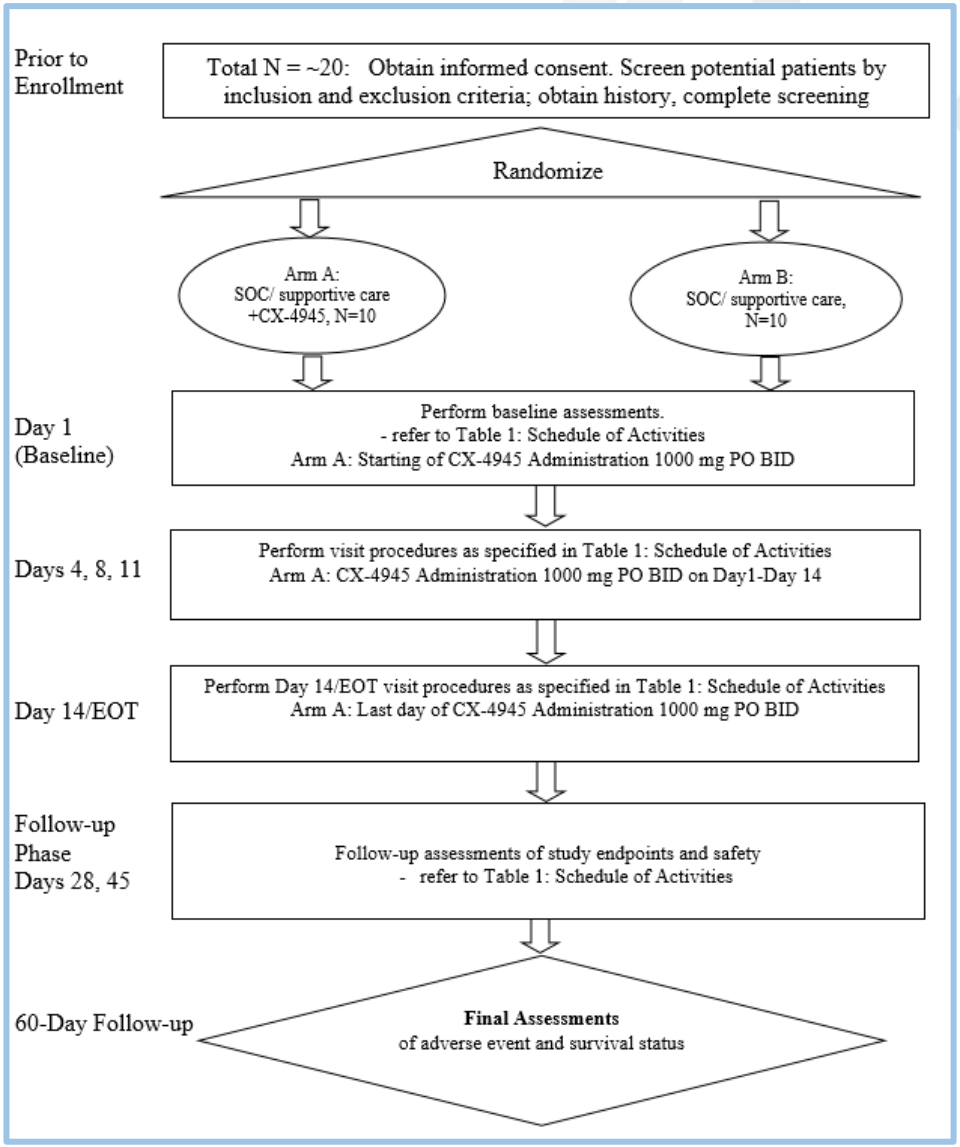
Silmitasertib 治療 COVID-19 中症患者：

一項隨機、開放性臨床二期試驗

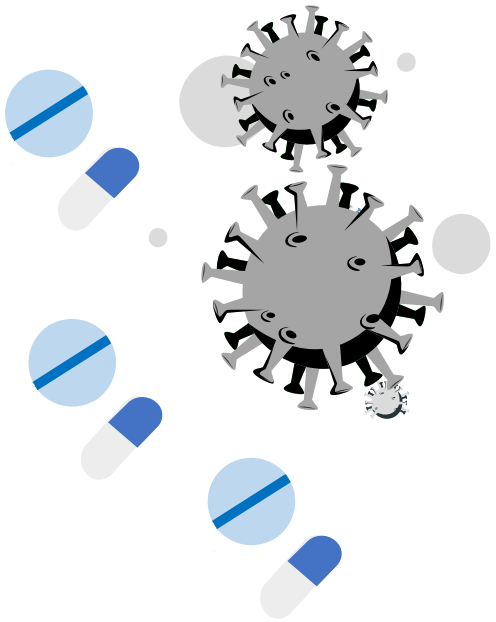
試驗方式:

- 招募 20 名新冠肺炎確診且出現中度體徵或症狀患者，並以 1:1 隨機分配進入試驗組或對照組
- 試驗組接受每日兩次、各1,000 mg 口服Silmitasertib加上標準治療/最佳支持療法，療程為14天
- 對照組接受標準治療/最佳支持療法14天

試驗模式:



"With the current therapeutic options available are infused and require access to healthcare facility, treatments that can be taken at home are critically needed. We are very encouraged by the results from this study and hope Silmitasertib can make a profound impact in controlling the pandemic"



- Dr. Chris Recknor, Center for Advanced Research and Education (CARE) in Gainesville, Georgia

新冠2期臨床試驗證明：

Silmitasertib 對 COVID-19 中症患者具顯著療效

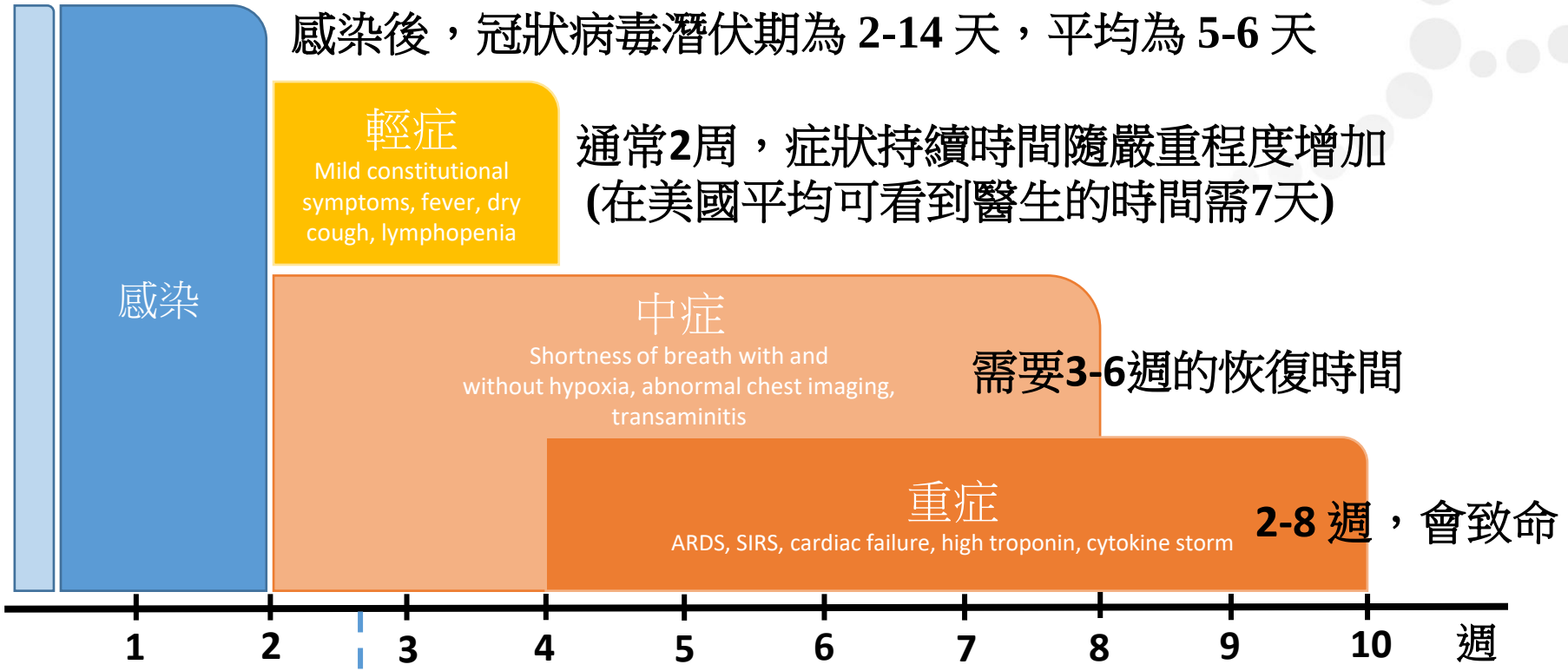
- 試驗結果顯示Silmitasertib與對照組相比具統計和臨床意義，可大幅加速患者康復時間(time to recovery)和臨床體徵正常化時間(time to normalization of clinical sign)等
- 10位試驗組患者在療程中都僅接受Silmitasertib單藥治療，並未同步接受其他EUA藥物治療
- 安全性 - 未顯示任何與 Silmitasertib 相關的嚴重不良事件 (SAE)
- 此2期試驗達到作為Silmitasertib治療COVID-19的臨床概念驗證(Clinical Proof-of-Concept)。

Silmitasertib 和 Molnupiravir 臨床試驗比較

	Silmitasertib (二期臨床試驗)	Molnupiravir (三期臨床期中分析)
藥物機制	宿主細胞蛋白導向的抗病毒/CK2抑製劑 (沒有致癌風險)	RNA聚合酶/病毒複製抑製劑 (有致癌風險)
疾病程度	COVID-19 中症	COVID-19 輕中症
給藥時機	COVID-19 檢測呈陽性後 7 天內	COVID-19 檢測呈陽性/ 出現症狀後 5 天內
試驗組	Silmitasertib 口服給藥、一天兩次， 與SOC併用 (然此組病患並未接受其他EUA藥物療法)	Molnupiravir 口服給藥、一天兩次
對照組	標準治療/最佳支持性護理 （醫生可用美國 任何EUA藥物治療患者）	安慰劑
治療時間	14天	5天
臨床結果	與標準療法/最佳支持療法相比，Silmitasertib 的療效具統計和臨床意義，大幅改善： • 更快達到COVID-19 相關臨床症狀改善時間 • 更快達到 EQ-5D-5L Q6 ≥ 90%的時間 • 更快達到COVID-19 相關臨床體徵正常化的時間	與安慰劑組相比住院率減少 50% (Molnupiravir 7.3% vs Placebo 14.1%)

Source: Shuntai Zhou, et al. β-d-N4-hydroxycytidine Inhibits SARSCoV-2 Through Lethal Mutagenesis But Is Also Mutagenic To Mammalian Cells. The Journal of Infectious Diseases, Brief Report

COVID-19 病程表：從感染到康復或死亡



Molnupiravir 需要在出現症狀後 5 天內服用

Silmitasertib

Silmitasertib 治療區間較廣且具單用或和其他不同機制藥物併用潛力

Source: https://elemental.medium.com/from-infection-to-recovery-how-long-it-lasts-199e266fd018

Silmitasertib 對於新冠肺炎治療優勢

優異臨床療效
(COVID-19中症)

- 與標準療法(SOC)/最佳支持療法相比 (best supportive care)，Silmitasertib 的療效具統計和臨床意義，大幅改善：
  - 更快達到COVID-19 相關臨床症狀改善時間
  - 更快達到 EQ-5D-5L Q6 ≥ 90%的時間
  - 更快達到COVID-19 相關臨床體徵正常化的時間
- 顯示可抑制多種導致免疫風暴的細胞激素因子 (IL-6)
- 具與其他不同機制的藥物併用治療COVID-19的潛力

口服方便使用

- 口服藥不但方便且具成本效益, 更可以減少患者就診次數，有利公共衛生，中症之前治療可防止進展到住院和危重症階段，以減輕醫療資源負擔
- 小分子藥物製程相對大分子穩定。藥物可室溫儲存方便使用

宿主細胞機制

- Silmitasertib利用冠狀病毒依賴宿主蛋白激酶CK2進行複製的特性，藉由抑制CK2阻斷病毒複製，阻止 SARS-CoV2 離開細胞，從而防止感染傳播。

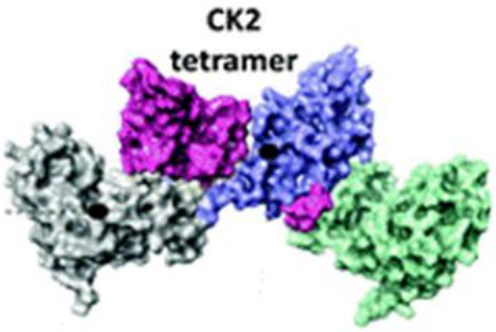
抵抗病毒變異

- 由於 CK2 蛋白激酶不會發生突變，因此不受病毒變異影響機制

良好安全性

- COVID-19二期試驗未顯示任何與 Silmitasertib 相關的嚴重不良事件 (SAE)
- 於多個一期和二期臨床試驗，逾200 多名受試者中驗證安全性和耐受性

Target Validation



Clinical Proof-of-Concept

Collaboration Opportunity

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