Genovate Biotechnology Co., Ltd.
健亞生物科技股份有限公司

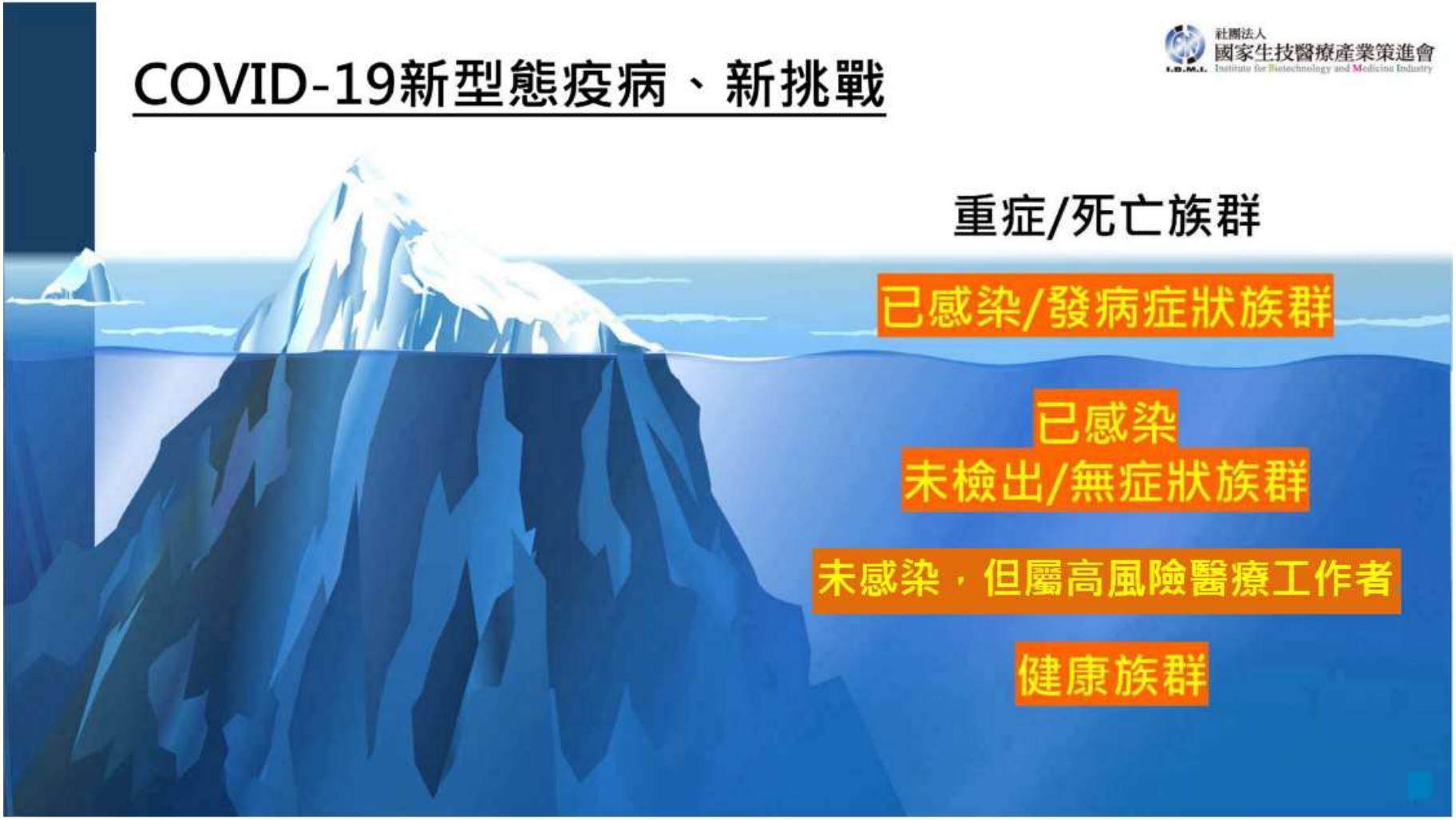
13 July 2020

Company Overview

- Genovate is a fully integrated specialty pharmaceutical company focusing on new drug development and equipped with PIC/S GMP manufacturing, marketing and distribution capabilities.
- Major Investors:
  - National Development Fund, Executive Yuan (26.54%)
  - Chinachem Group (HK) (7.93%)
- Established: 1993
- Number of Employees: 175
- Paid-in Capital: NT$1,058M
- Revenue: NT$465.8M (2019)
- Profit before tax: NT$40.7M (2019)

COVID-19新型態疫病、新挑戰

社團法人
國家生技醫療產業策進會
I.B.M.I. Institute for Biotechnology and Medicine Industry



NIH begins clinical trial of hydroxychloroquine and azithromycin to treat COVID-19

14 May 2020

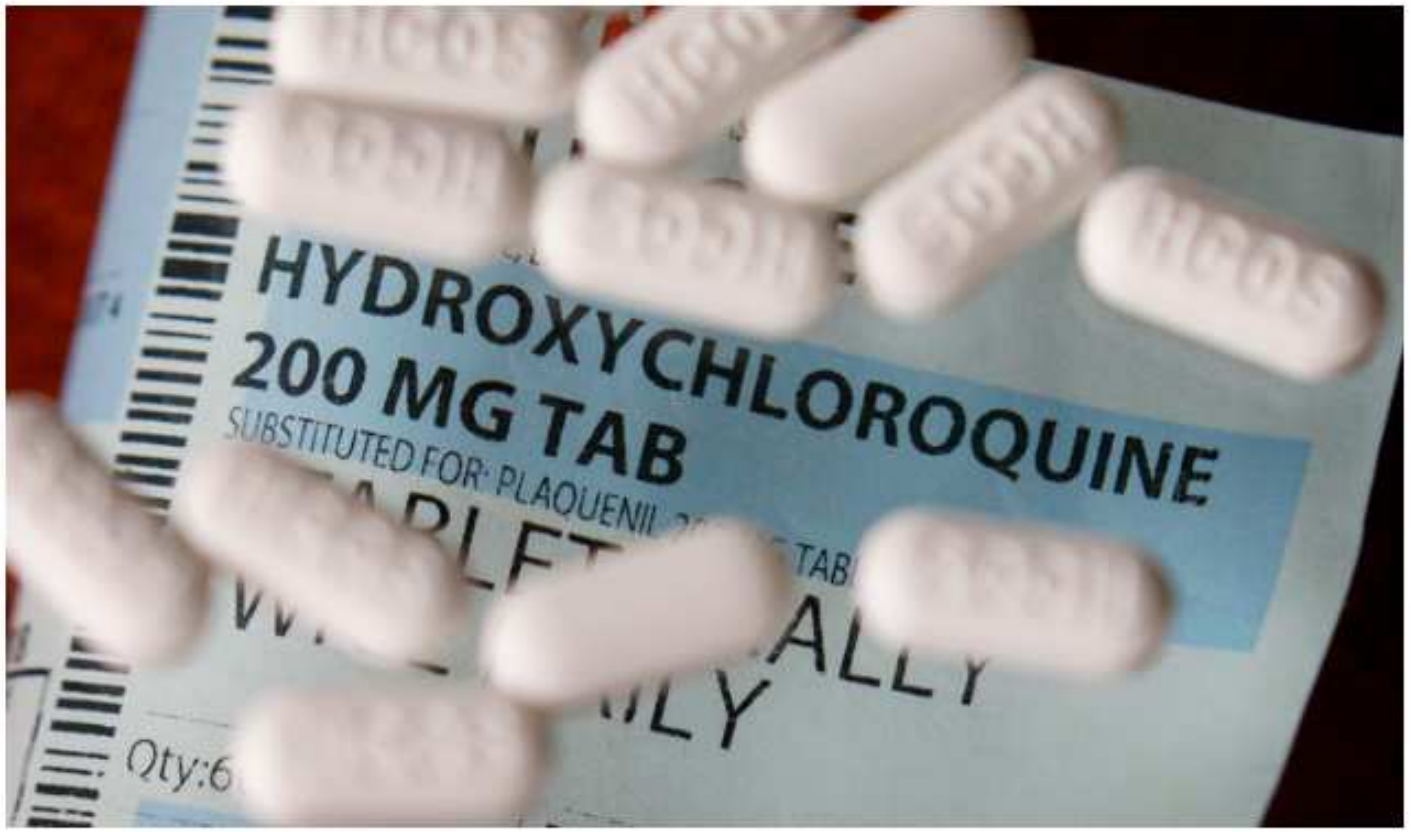
- NIH begins a clinical trial of hydroxychloroquine and azithromycin to treat adults with mild to moderate COVID-19 in the United States since May 2020.
- Participants must have confirmed infection with SARS-CoV-2, the virus that causes COVID-19, and be experiencing fever, cough and/or shortness of breath. The investigators anticipate that many of those enrolled will be 60 years of age or older or have a comorbidity associated with developing serious complications from COVID-19, such as cardiovascular disease or diabetes.
- "We urgently need a safe and effective treatment for COVID-19. Repurposing existing drugs is an attractive option because these medications have undergone extensive testing, allowing them to move quickly into clinical trials and accelerating their potential approval for COVID-19 treatment," said NIAID Director Anthony S. Fauci, M.D.".
- The main objective of the study is to determine whether hydroxychloroquine and azithromycin can prevent hospitalization and death due to COVID-19.
- Teva Pharmaceuticals is donating medications for the study.

Source: NIH news release, 14 May 2020. (NCT04358068)

Hydroxychloroquine drug trial set for high-risk healthcare workers

20 May 2020

The first gold standard Australian clinical trial to determine whether the drug can help prevent COVID-19 is now open.



COVID-SHIELD FAQs

- The COVID-SHIELD is exclusively looking at hydroxychloroquine as a preventative therapy for COVID-19. The trial is not using the drug in people who have tested positive for COVID-19 or as a treatment for people who are sick with COVID-19.
- There are several examples of drugs that are effective in preventing diseases but less effective in treating them, such as antiretroviral drugs used for pre-exposure prophylaxis (PrEP) to HIV and neuraminidase inhibitor drugs (oseltamivir (Tamiflu®) and zanamivir (Relenza®)) used for influenza.
- Hydroxychloroquine has been in clinical use for decades and is currently being taken by thousands of Australians for rheumatic conditions. Like any medication, hydroxychloroquine has certain side effects, but fortunately these are well known and quite uncommon.
- There is currently no evidence from randomised, double-blinded clinical trials to suggest that hydroxychloroquine will either work or not work as a pre-exposure preventative agent in healthy people, which is why this trial is being pursued.

Source: The Walter and Eliza Hall Institute of Medical Research website. (ACTRN12620000501943)

COPCOV: Hydroxychloroquine trial to restart

30 Jun 2020

- The COPCOV trial will see chloroquine, hydroxychloroquine or a placebo given to more than 40,000 healthcare workers from Europe, Africa, Asia and South America.
- One of the lead researchers, Prof Sir Nicholas White from the University of Oxford, said: "Hydroxychloroquine could still prevent infections, and this needs to be determined in a randomised controlled trial."
- Co-investigator Prof Martin Llewelyn, from the Brighton and Sussex Medical School, said: "Although rates of coronavirus are low just now in the UK, healthcare workers are still being affected across the NHS and a second wave of infection this winter is widely expected.
- Although studies suggest hydroxychloroquine is not a life-saver for people who are already ill with coronavirus, researchers are keen to continue exploring whether it might prevent infections.
- UK regulators say hydroxychloroquine and a similar drug chloroquine can be given to healthcare workers in a clinical study to test the theory. Recruitment to the COPCOV trial had been paused amid concerns about side-effects raised by other research that has since been discredited.

Source: BBC news, 30 Jun 2020. (NCT04303507)

Risk of QT Interval Prolongation Associated With Use of Hydroxychloroquine With or Without Concomitant Azithromycin Among Hospitalized Patients Testing Positive for Coronavirus Disease 2019 (COVID-19)

JAMA Cardiol. Published online **May 1, 2020**.

Findings In a cohort study of 90 hospitalized patients with coronavirus disease 2019, use of hydroxychloroquine with or without azithromycin for treatment of COVID-19 was associated with frequent QTc prolongation, and those taking hydroxychloroquine and azithromycin had greater QT prolongation than those taking hydroxychloroquine alone.

Meaning Clinicians should carefully weigh risks and benefits if considering hydroxychloroquine and azithromycin, with close monitoring of QTc and concomitant medication usage.

GV17 - HCQ 2.0 進階版

COVID-19, Chloroquine Repurposing, and Cardiac Safety Concern: Chirality Might Help

by Giovanni Lentini [1,*], Maria Maddalena Cavalluzzi [1] and Solomon Habtemariam [2]

Molecules 2020, *25*(8), 1834; https://doi.org/10.3390/molecules25081834

Received: 20 March 2020 / Revised: 14 April 2020 / Accepted: 15 April 2020 / Published: 16 April 2020

Abstract

The desperate need to find drugs for COVID-19 has indicated repurposing strategies as our quickest way to obtain efficacious medicines. One of the options under investigation is the old antimalarial drug, chloroquine, and its analog, hydroxychloroquine. Developed as synthetic succedanea of cinchona alkaloids, these chiral antimalarials are currently in use as the racemate. Besides the ethical concern related to accelerated large-scale clinical trials of drugs with unproven efficacy, the known potential detrimental cardiac effects of these drugs should also be considered. **In principle, the safety profile might be ameliorated by using chloroquine/hydroxychloroquine single enantiomers in place of the racemate.**

GV17 對心臟影響較小

- 心肌的收縮舒張乃是經過內外離子電位差去極化及再極化作用而完成。
- **HCQ及CQ這類藥物會阻斷hERG基因控制的鉀離子通道，使心肌細胞活動電位持續的時間（QTc）延長（QTc prolongation），擾亂心臟正常的收放電活動，從而導致潛在的惡性心律不整。**

2020.05 健亞 hERG 離子通道試驗（IonChannelProfiler™HEK hERG Manual Patch Clamp Assay）

結果：

GV17對鉀離子通道有較低的阻隔性，其對心臟預期安全性為CQ的11倍、HCQ和R-HCQ的2.5倍以上。

GV17 - HCQ 2.0 FOR LUPUS

- Patented (S)-(+)-hydroxychloroquine sulfate, the active ingredient of GV17 is targeted for the treatment of moderately-to-severely active cutaneous lupus erythematosus (CLE) or systemic lupus erythematosus (SLE) with active skin manifestations.
- The market size of HCQ was USD 978.745 million in 2019.
- Preclinical studies showed that comparing to HCQ, GV17 had
  - Higher survival rate and better control of skin lesions in MRL/lpr mice
  - Higher safety (> 2.5 folds IC50 for hERG inhibition)

GV17 作為COVID-19預防性藥物選項

與知名學府國際級病毒專家合作，評估**GV17**：

- 確認**GV17**具抗病毒活性。
- 以用藥時間在細胞株感染前（預防性）與感染後（治療性）之分析，觀察到其在「感染前」的抗病毒活性較「感染後」的抗病毒活性為佳。

- 文獻資料：抗**SARS-CoV-2**病毒活性測試結果

Compound	Antiviral activity (IC50)	Toxicity (EC50)
ROC-325	3.275 μM	> 15 μM
Chloroquine	2.007 μM	> 3 μM
Hydroxychloroquine	4.469 μM	> 30 μM
Remdesivir	7.036 μM	> 30 μM

Source: ResearchGate May , 2020

Enantiomers of Chloroquine and Hydroxychloroquine Exhibit Different Activities Against SARS-CoV-2 *in vitro*, Evidencing S-Hydroxychloroquine as a Potentially Superior Drug May, 2020for COVID-19

bioRxiv, May, 2020 (NOT CERTIFIED BY PEER REVIEW)

- In all of the clinical trials for COVID-19 conducted thus far and among those ongoing involving chloroquine or hydroxychloroquine, the drug substance used has invariably been chloroquine (CQ) diphosphate or hydroxychloroquine (HCQ) sulfate, i.e., the phosphoric or sulfuric acid salt of a racemic mixture of R- and S-enantiomer (50/50), respectively.
- S-chloroquine (S-CQ) and S-hydroxychloroquine (S-HCQ) were found to be 27% and 60% more active against SARS-CoV-2, as compared to R-CQ and R-HCQ.
- we recommend that future clinical studies should employ S-HCQ as a potentially superior drug substance for the treatment of COVID-19 for improved therapeutic index.

GV17-具開發潛力的利基新藥

- 與**HCQ**比較

項目	GV17	HCQ
血中濃度穩定性	高	低
藥效	高	低
安全性	高	低
對心臟影響	低	高

- 可依需要，開發為**Lupus** 相關疾病的**505b2**新藥與**COVID-19**預防性（**PrEP**或**PEP**）藥物選項。
- 完成多項專利申請。
- 已申請美國 **FDA**的**pre-IND meeting**，規劃臨床設計與開發策略。

新藥/新醫材產品進度

計畫/開發階段	IND	Ⅰ	Ⅱ	Ⅲ	NDA	合作夥伴
Mycocep™ （狼瘡腎炎）					台灣上市	五年專賣權 自行銷售
PMR （間歇性跛足）				美國 Pre-NDA會議 已完成		美國先上市
GBL121 （糖尿病）			中國臨床Ⅲ期計畫書 已批准試驗啟動中			1. 永信、中化、 南光、信東、 東洋、健亞 2. 中國石藥集團
NF02 （阿茲海默症）		澳洲臨床計畫書 倫委會審查中				浩宇生醫 （聚焦超音波）
GV17 （自體免疫疾病）	美國 Pre IND 會議申請已送件					華宇藥品

New Formulation New Drug PMR

- **Patented "once-a-day" extended-release of Cilostazol for the treatment of Intermittent Claudication (IC).**
- **The global market of IC treatments is over US$500M and about US$18B for antiplatelet treatments. The global sales of Cilostazol is about US$250M.**
- **Taiwan pharmacokinetic study showed that in comparison to Cilostazol bid, PMR had**
  - **Lower Cmax**
  - **Lower Cmax/Cmin ratio**
- **Taiwan PhII study nicely demonstrated the trend of better efficacy and safety profile (including less headache, diarrhea and palpitation, the leading causes of treatment discontinuation) comparing to Cilostazol bid.**
- **US FDA's written responses dated 23 Mar 2020 to the Pre-NDA meeting request were received.**

DPP4 Inhibitor GBL121

- A novel and patented DPP4 inhibitor with better efficacy and safety profiles against Januvia in preclinical evaluation.
- China market rights licensed to China Shijiazhuang Pharma Company (CSPC) which is listed in Hong Kong and a top three pharma in China. The Golden Technology Transfer Award of 2015 Bio Taipei Awards was granted to our collaboration with CSPC.
- PhIa and PhIb studies completed under US IND;

  PhI and PhII completed, PhIII ongoing in China by CSPC.
- As a late-comer into DPP4 inhibitors market, GBL121 is positioned as a "friendly" anti-diabetic drug for Chinese patients.

GMP Manufacturing

- Development and manufacture of proprietary products
  - New drugs, such as Genetaxyl™ (patented new formulation of Paclitaxel), Robatrol™ (Ribavirin capsule marketed by Roche), Linicor™ (Niacin ER/Lovastatin marketed by TSH), Mycostatin™ (Nystatin powder for oral solution).
  - Niche generic drugs, injectable preparation such as Atracurium, Rocuronium, and Cisatracurium as adjunct to general anaesthesia.
- Professional contract manufacturing services
  - Major clients including DSTW, TSH, etc.
- Professional contract development and manufacturing services
  - Major clients including SyneuRx (NaBen®), UIC Group (Bowklean™ - Sodium Picosulfate/Magnesium Oxide/Anhydrous Citric Acid), etc.
- Drug export to Korea and southeast Asia since 2003.

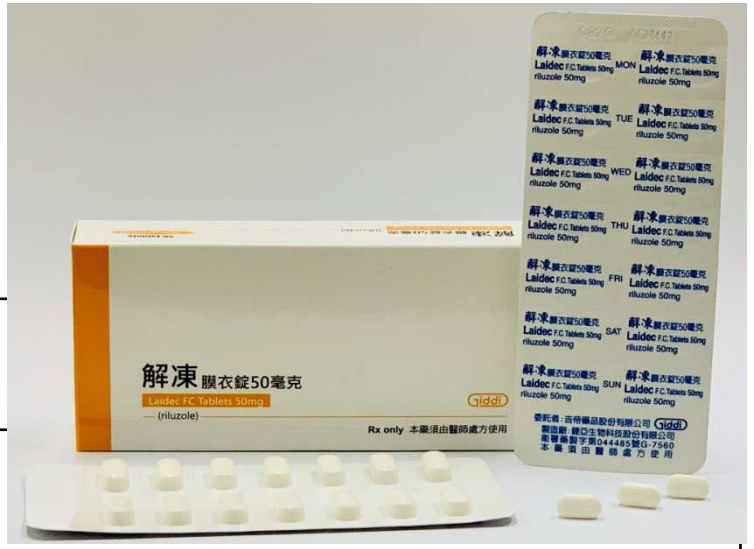
Linicor「理脂」（降血脂治療藥）

藥品證號	衛署藥製字第057216號
成份	**lovastatin 20mg, niacin 500mg**
適應症	高血脂症，且適合同時使用 **Niacin** 及 **lovastatin** 治療者。患者在接受 **Linicor** 治療之前應採用標準之低膽固醇飲食療法，並且在 **Linicor** 治療期間仍應持續進行這種飲食療法。
產品市況	是目前唯一**niacin**複方治療藥物。健保價為**9.1**元。 **2018**年已有**1200**萬顆的健保銷售量。

Bowklean「保可淨」（大腸鏡檢查用藥）

藥品證號	衛署藥製字第**034904**號
成份	**magnesium oxide, picosulfate sodium, citric acid anhydrous**
適應症	成人大腸鏡檢查前之清腸劑
產品市況	第一個台灣核准國人自行研發的新複方新藥。 市場唯一雙效的第三代清腸劑。

Laidec「解凍」（漸凍症治療藥）



藥品證號	衛署藥製字第**044485**號
成份	**riluzole 50mg**
適應症	肌萎縮脊髓側索硬化症。
產品市況	台灣每年新增病患至少 **100**人，以盛行率 **0.5-0.6/100,000** 來看，總罹病人數可能在 **1,000** 人。 **riluzole**是目前台灣唯一治療漸凍症的藥物成分 ，台灣僅**2**家藥品上市。健保價皆為**142**元。 **2018**年**riluzole**的健保用量已有**34**萬顆。

研發策略之股權投資（1/2)

持有之公司	營業項目	持股比例	健亞合作項目
昌達生化科技	醫藥研發與技術委辦服務之公司(CRO)	**6.326%**	臨床委託
心悅生醫 **(興櫃/6575)**	中樞神經系統新藥開發	**4.600%**	劑型開發與生產製造
瑞寶基因 **(興櫃/6479)**	動物疫苗	**2.973%**	無
生控基因 **(興櫃/6567)**	子宮頸癌與B肝治療型疫苗	**0.486%**	**HPV Vx** 中國開發
Purapharm **(HKEX/1498)**	中藥研究生產與銷售	**0.521%**	多醣體研發

研發策略之股權投資（2/2)

持有之公司	營業項目	持股比例	健亞合作項目
Medeor Therapeutics	免疫細胞治療	**3.379%**	亞洲換肝
Soleno Therapeutics (NASDAQ/SLNO)	開發治療小胖威力症候群	**0.467%**	區域市場
華宇藥品 **(興櫃/6621)**	護肝新藥與高階醫療器材	**17.661%**	劑型開發與生產製造
浩宇生醫	聚焦式超音波腦部藥物釋放系統	**13.511%**	神經退化（區域）

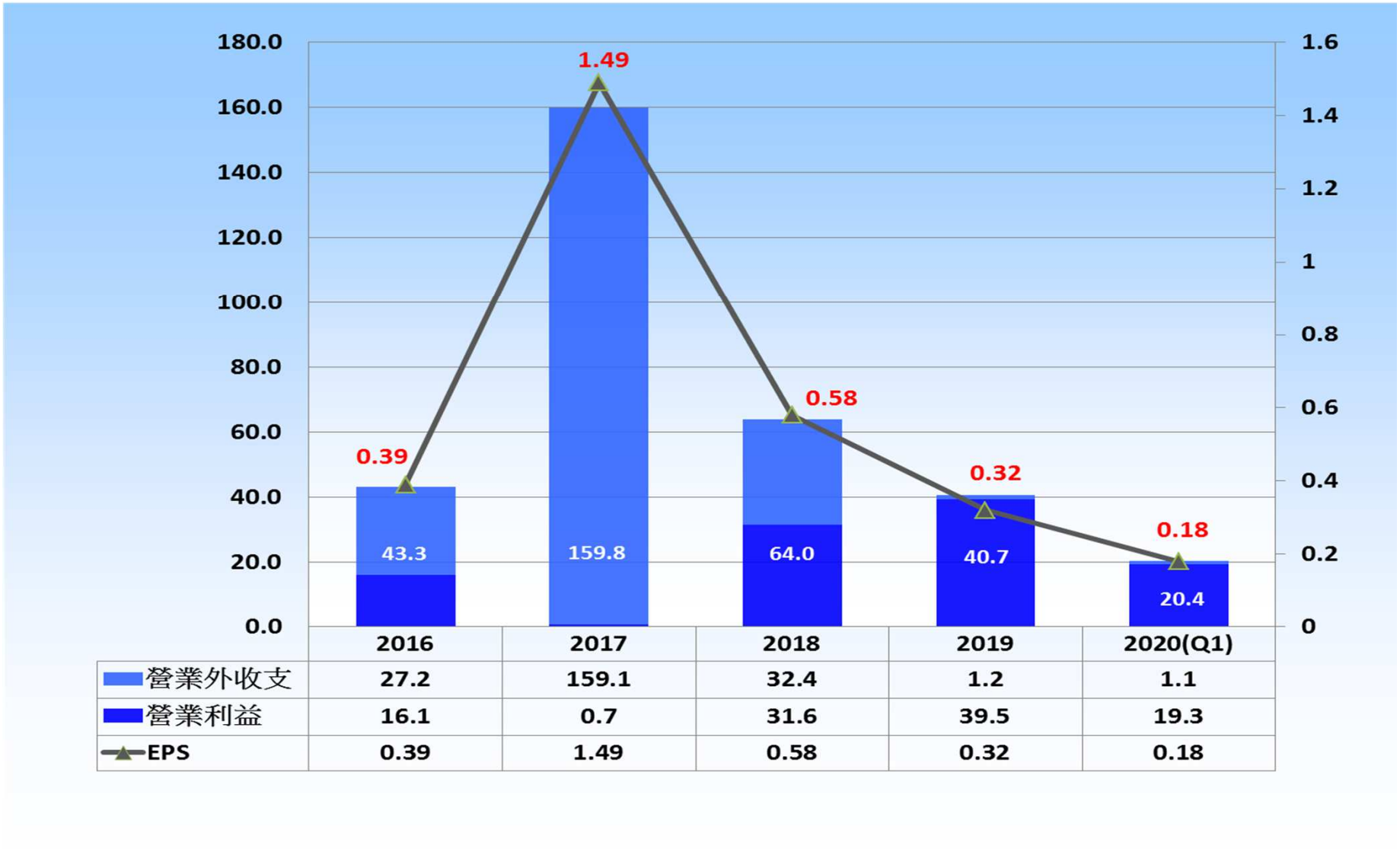
核心優勢與策略佈局

- 核心優勢
  - 核心技術：劑型改良、配合工廠生產（心悅、華宇）
  - 優勢利基：選題靈活、搭配投資、取得合作商機（心悅、浩宇）
  - 市場應用：經臨床驗證後，進行區域授權或市場銷售（**GBL121**、**Mycocep**）
  - 國際競爭力：依各計畫屬性，規劃不同的開發策略（**Soleno**、**Medeor**）
- 策略佈局
  - **PMR**：**2020**美國**NDA**，成功後尋求國際授權。
  - 心悅：全力配合兩個「**BTDs**」計畫的時程，提供**CMC**相關專業。
  - 浩宇：合作開發**CNS**疾病新療法。
  - **Soleno**：評估區域市場，銷售合作。
  - 華宇：共同合作**GV17**新藥計畫。

營業收入 (2016～2020Q1-Q2)

資料來源：公開資訊觀測站/合併營收

稅前淨利 (2016～2020Q1)



	2016	2017	2018	2019	2020(Q1)
營業外收支	27.2	159.1	32.4	1.2	1.1
營業利益	16.1	0.7	31.6	39.5	19.3
EPS	0.39	1.49	0.58	0.32	0.18

Genovate

附件

NaviFUS Clinical Trial I： BBB opening/ rGBM

- Planning
  - NaviFUS System initiated, IDE safety/ feasibility clinical trial
  - 2018.01 TFDA approval
  - 2018.04 IRB approval
  - 2019.04 6th patient recruited for level III
  - BBB opened and closed in 6 pts, No AEs
  - 2020.01 GCP monitoring and close the trial in March

- Schedules

NaviFUS

Breaking Down Barriers

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NaviFUS Clinical Trial I-a : BBB opening/ rGBM/TW

- Planning:
  - rGBM, Avastin+FUS, CGMH, Taiwan
  - Increased Frequency, Drug and Tissue Volume
  - 8 pts
  - IRB approval on 12/12/2019
  - TFDA IDE approved on 03/30/2020
  - IRB contract to be done in 05/2020
  - Kick-off the trial in 07/2020
  - Sponsored by FUS foundation

NaviFUS

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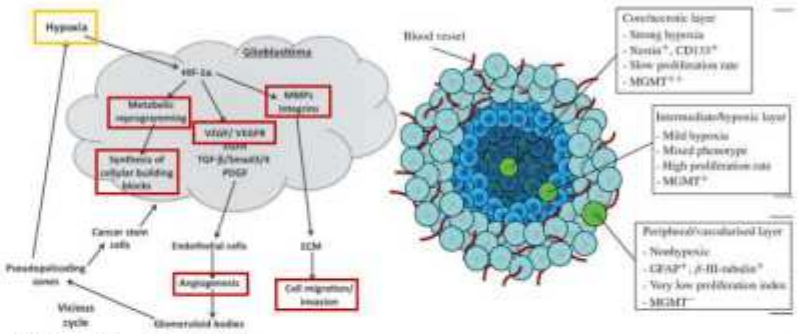
NaviFUS Clinical Trial I-b： BBB Opening/rGBM/USA

- Planning:
  - Study Titles:
    - Avastin+FUS
  - Investigator-initiated IDE in Stanford University Hospital, USA
  - 6 rGBM pts
  - IDE consultant: Greenleaf, USA
  - 2020/07/28 IDE Pre-submission T-conf with FDA
  - Kick-off the trial in Q4/2020

Clinical Trial I-c : FUS+RT Therapy / rGBM

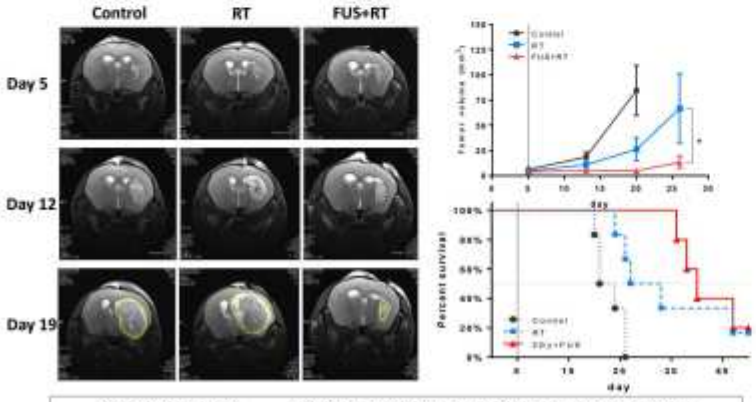
- Planning:
  - Study Titles:
    - RT+FUS to treat primary GBM patients
  - Investigator-initiated IDE in CGMH
  - Pt Group: rGBM
  - Device Only
  - 6 pts
  - 2020Q2 TW/CDE submission

Molecular mechanisms happen in hypoxia region



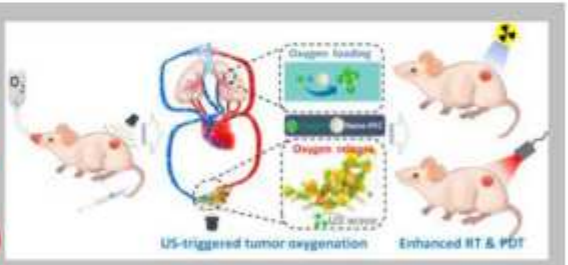
HUANG et al., Oncology letter (2016)

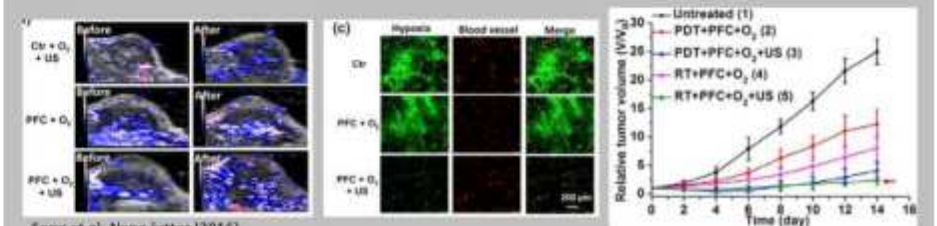
In vivo assay shows FUS enhances RT and significantly reduces tumor growth.



RT dose: 2Gy, 1 dose **FUS parameter:** 400KHz, duty 1%, PRF 1Hz, electric power 2W

2. Oxygenate the tumor microenvironment by ultrasound and Perfluorocarbon (PFC)





Song et al. Nano letter (2016)

NaviFUS

Breaking Down Barriers

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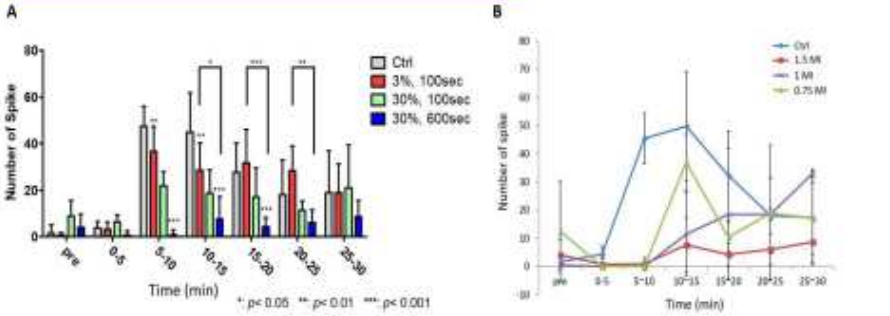
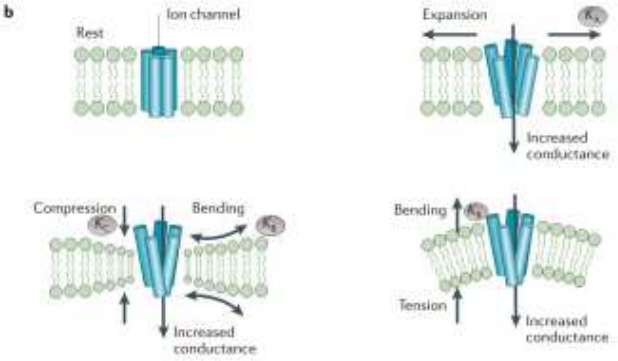
2. Clinical application to Neuromudulation: Epilepsy

- The use of focused ultrasound to transcranially modulate neuron activity via the alternation of gating kinetics on neuronal cell membrane of many voltage – gated ion channels or mechanosensitive channels.
- Indications: Epilepsy, Parkinson Disease
- FUS treatment can reduce the seizure spike No. to 90%-- Brain Stimulation, 2019

Good Pre-clinical Outcomes

Brain Stimulation, 2019





NaviFUS Clinical Trial II：Neuromodulation/Epilepsy

- Milestones
  - 2018.11.15 VGH IRB approval
  - **2019.02 TFDA approval**
  - 2019.05 SIV
  - 2020.01.02 the 2nd Pt recruited
  - 2020.03.11 DSMB approved!
  - 2020.05 3rd Pt ready for FUS treatment