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**Future landscape on post-COVID19  
oncology product development**

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CSO & President @ Xylonix

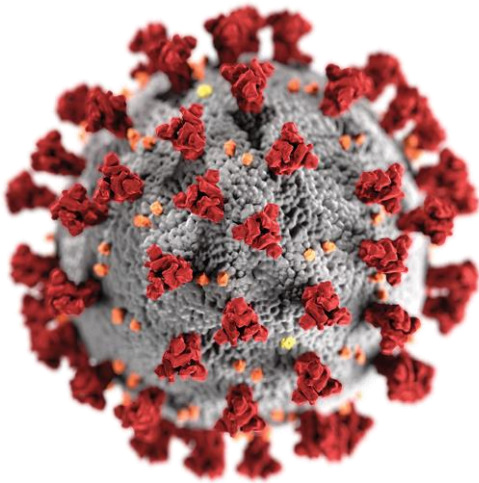
2021.11.16 21:10 Taipei Time

## Summary

- **Xylonix is a Singapore company developing chemo-immune agents for treating solid cancers**
- **COVID19 pandemic caused lasting damages to current & developing cancer treatments**
  - Clinical sites (hospitals) stretched thin – diagnosis and treatments disrupted
  - Escalated risk of COVID19 deaths in cancer patients – expanding trial contamination from COVID19
  - COVID-reprogramming of immunity suspected to reduce cancer treatment effectiveness and patient survival
- **Xylonix view and strategy on the COVID19 pandemic**
  - Pipeline change-up to C010DS-Zn-liposome to effectively treat cancer patients with COVID history
  - R&D logistics up to Phase 2a consolidated between TW and SG to minimize cross-border risks
  - PET-CT-based companion diagnostic to enable Phase 0 in-human PK study : shortened-minimized trial risk
  - Pandemic clinical risk further reduced by Accessible-Clarified-Shortened-Minimized (ACSM) early trial design



# Post-COVID19 oncology R&D : what changed?



December 2019 –SARS-CoV-2

Now being **made into ENDEMIC**

## Negative (-) changes



### Distress on R&D logistics

- Unpredictable site lockdowns
- Supply chain / shipping disruptions
- Main disruptions in clinical operations

### Approach

- Reduce cross-border ops
- Supply chain consolidation



### Distress at clinical sites (US data)<sup>1,2</sup>

- Healthcare resources drained to the pandemic
- Hospital and patient access challenges – trial disruptions
- Declining patient interest / participation in trials

### Approach details on pg.4



### Aggravated cancer post-COVID19

- ↑ tumor burden at initial mCRC diagnosis<sup>3</sup> / ↑ brain metastasis in NSCLC<sup>4</sup>
- ↑ risk of death in COVID19-recovered cancer patients (2020Jan-2021Feb) <sup>7</sup>
- COVID19-reprogrammed immunity suspected as a cause<sup>5,6</sup>

### Approach details on pg.5

## Positive (+) changes



### Aggressive uptake on new technologies

- mRNA drugs
- Liposome formulations
- Set precedents of accelerated drug approvals / global harmonization
- Better acceptance of novel science
- Improved novel drug production / distribution capacity



# Distress at clinical sites – based on US and UK data

nature

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NEWS | 28 June 2021

## The COVID pandemic’s lingering impact on clinical trials

Medical researchers are beginning to shift their focus away from COVID-19 – but the pandemic could continue to affect studies focused on other diseases.

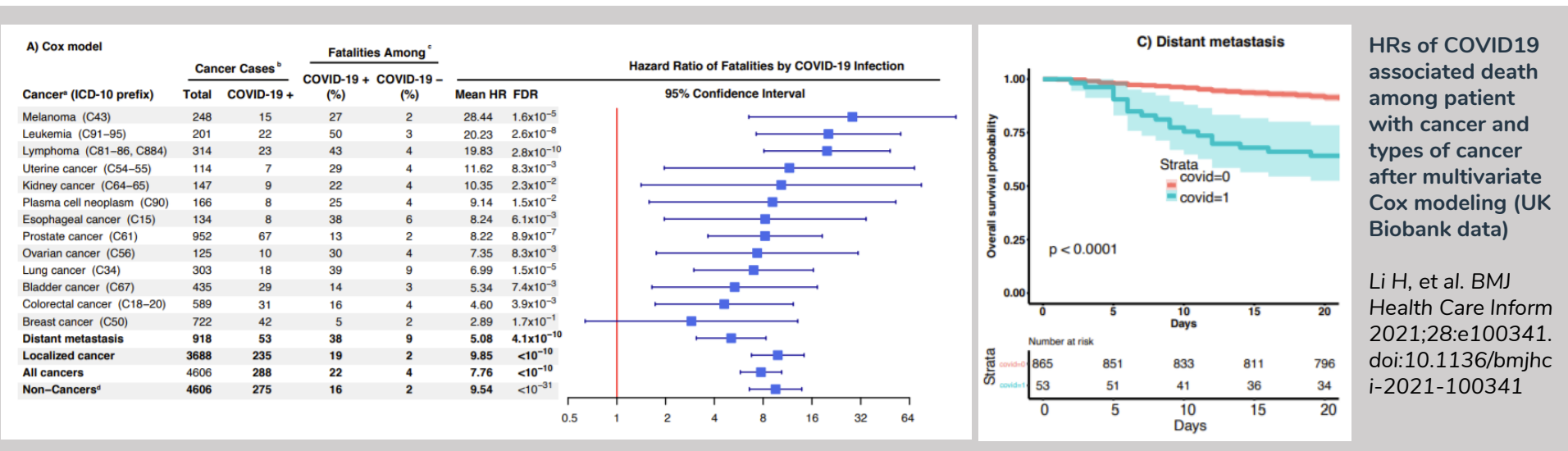
*“It is like time stopped” – Dr. Emilia Bagiella*

### COVID19 impact on clinical trials in US

- Diagnostic – treatment disruptions from overwhelmed hospitals
- **43% less** oncology US clinical trials in 2020 (mainly early trials)<sup>1</sup>
- **20% reduction** in patient trial participation- slower patient uptake<sup>2</sup>
- **8X COVID19 deaths** in cancer patients - overall HR 7.76, (95%CI:5.78-10.40). Worse for hematological and metastatic cancer<sup>7</sup>

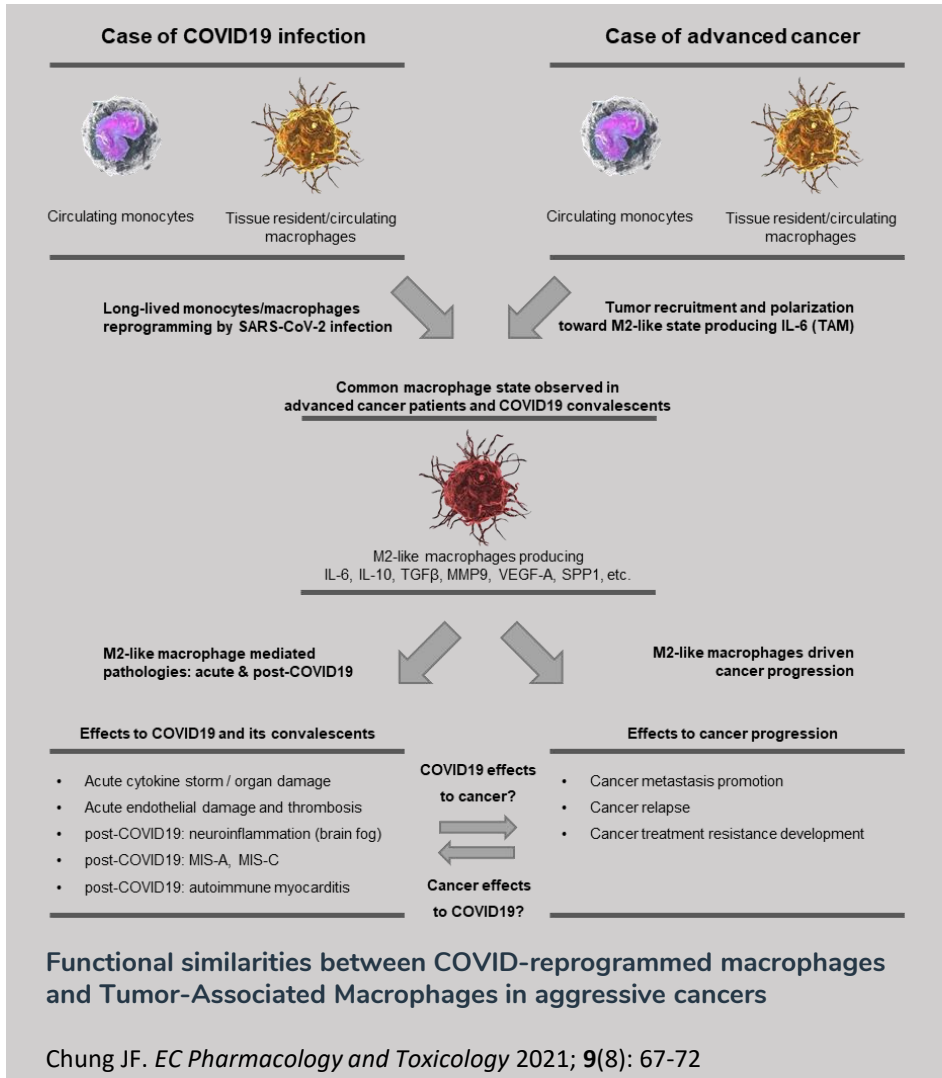
### Approach

- Simplify clinical trial designs - minimize actions/interventions
- Adopt formulations for less frequent dosing (ER, liposomes, etc.)
- Early trials – design with smaller size & shorter follow-up
- Late-phase trials - delay entry until further COVID19 discoveries





# Aggravated cancer post-COVID19



## Aggravated cancer post-COVID19

- 6.9x Increased tumor burden at initial diagnosis of metastatic CRC vs pre-pandemic<sup>3</sup>
- 40% brain metastasis in S4 NSCLC patients at diagnosis, up from 25% historical<sup>4</sup>
- 76% Increased death risk in COVID-recovered cancer patients during the 1-year study (HR 1.76, adj for sex, age, comorbidities, tumor characteristics, cancer treatment, and COVID19 severity)<sup>8</sup>
- COVID-reprogrammed macrophages/neutrophils suspected as a cause<sup>5,6</sup>

## Approach

- Assume ↑ cancer aggressiveness – aim for higher potency
- Countermeasure for the COVID-reprogrammed immunity aggravating cancer progression
- Consider macrophage-relating biomarkers in development data sets
- Late-phase trials - delay entry until further COVID19 discoveries

**“This virus will find you - it will infect you eventually”**  
 – Michael Osterholm

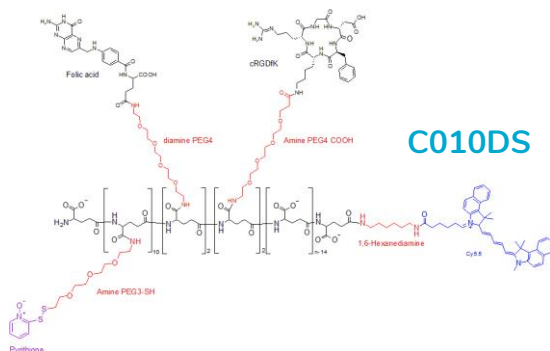
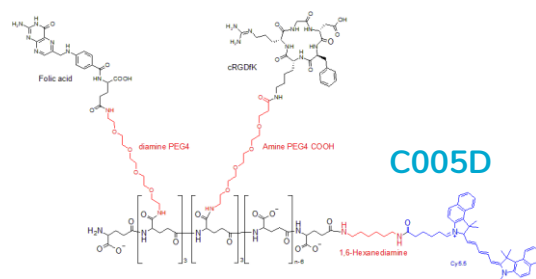
# Pandemic ride out @Xylonix



- Singapore incorporated & operated
- Focus: 1<sup>st</sup>-in-class chemo-immuno cancer drugs
- Lead pipelines: C005D-Zn, C010DS-Zn-lipo
- Techs involved: immunology, polymer, liposome, metals

## Xylonix capture on the pandemic challenges

- **Consolidate & Integrate**  
Minimize development risks from cross-border R&D
- **Drastically improve PK for less frequent dosing & higher potency**  
Minimize hospital/patient load during clinical trials
- **Early trials must be Accessible – Clarified – Shortened – Minimized**  
Minimize site risks & pandemic effect contamination



## Xylonix strategy around COVID19 pandemic – Duke-NUS/CITI Programme

- **Liposome formulation** development for improved PK  
Less frequent dosing, and improved drug delivery to solid tumor sites
- **Pipeline change-up from C005D-Zn to C010DS-Zn-lipo**  
For anti-macrophage activity & higher potency (req. for liposome formulation)
- **PET-CT-based companion diagnostic (cDX) - radiolabeled 010DS-Zn-lipo**  
Enabling Phase 0 – in-human PK study strategy: eliminate early trial risks,  
New indication strategy built-into cancer diagnosis
- **One-stop development through P0, P1, and P2a trials in Singapore**  
Easy and reliable medical access for patients + working regulatory relationship



# R&D logistics consolidation @Xylonix

## Pre-pandemic ( - 2020)

API synthesis  
Taiwan

建誼生技股份有限公司 + main reagent from China  
KriSan Biotech Co., Ltd.

Formulation  
Korea

**SAMSUNG BIOLOGICS**

In vitro tests  
China / Singapore

**CrownBio**  
CONNECTING SCIENCE TO PATIENTS

**INVITROCUE®**  
Transforming bioanalytics

In vivo tests  
US / Singapore

**CHAMPIONS ONCOLOGY**

Agency for Science, Technology and Research  
SINGAPORE

IND data workup  
China

康龙化成  
PHARMARON

Clinical  
US P1

US party  
undecided

## Pandemic (2020 - )

API synthesis  
Taiwan

建誼生技股份有限公司 + main reagent sourcing within Taiwan  
KriSan Biotech Co., Ltd.

Formulation  
Singapore

**BioSpectrum**  
ASIA EDITION

Singapore to revolutionise therapeutics for cancer & infectious diseases  
14 October 2021 | News

In vitro tests  
Singapore



Scientists from Duke-NUS Medical School have partnered with Singapore biotechnology company Xylonix to optimise liposome drug formulations and develop companion diagnostics for Xylonix's novel cancer immunity drug, called 010DS-Zn.

In vivo tests  
Singapore

**DukeNUS**  
Medical School

National Cancer Centre Singapore  
SingHealth

IND data workup  
Singapore

### CANCER IMMUNOTHERAPY IMAGING "CITI" PROGRAMME

"A fully integrated platform for development, GMP-formulation, radiolabel, and clinical study"

Clinical  
SG P0, P1, P2a



# Pipeline improvements targeting post-COVID cancer @Xylonix

NEWS • Daily News

## Autopsy Study Finds Most COVID-19 Patients Have Macrophages in Myocardium

More studies will be needed to understand what the white blood cells are doing and whether they pose long-term risk.

by L.A. McKeown | OCTOBER 02, 2020

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**Multisystem Inflammatory Syndrome in Children (MIS-C) Interim Guidance**

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- Toxic shock syndrome-like features with hemodynamic instability and poor heart function. Cytokine storm/**macrophage activation** or hyperinflammatory features.

EMBO Molecular Medicine

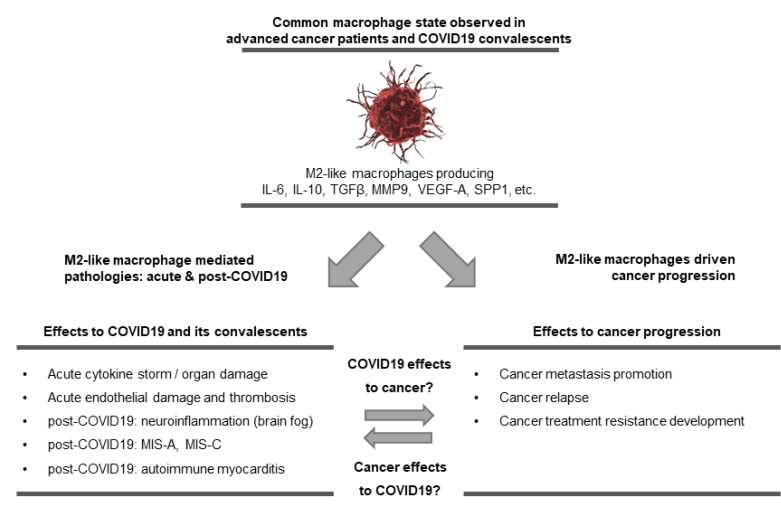
CURRENT ISSUE ABOUT INFORMATION ARCHIVE ALERTS

Article | 16 June 2021

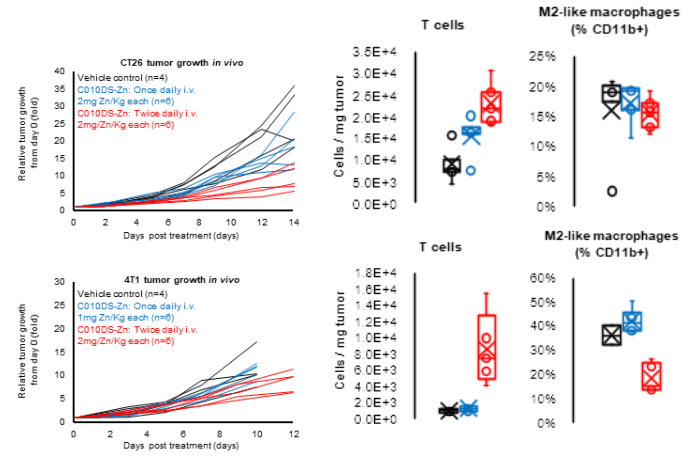
## Long-lived macrophage reprogramming drives spike protein-mediated inflammasome activation in COVID-19

Sebastian J Theobald, Alexander Simonis, Theodoros Georgomanolis,  
EMBO Mol Med (2021) 13: e14150  
<https://doi.org/10.15252/emmm.202114150>

## Post-COVID macrophages in M2-like state with cancer-promoting potential



## C010DS-Zn : anti-tumor & anti-macrophage agent for post-COVID cancer







# De-risked cDX-guided clinical development strategy @Xylonix

Performing body

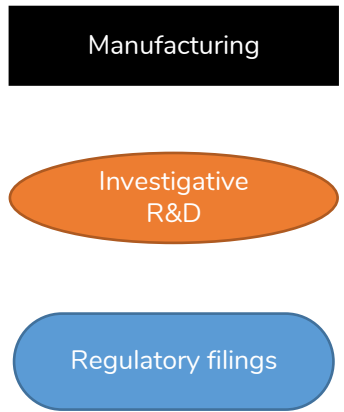
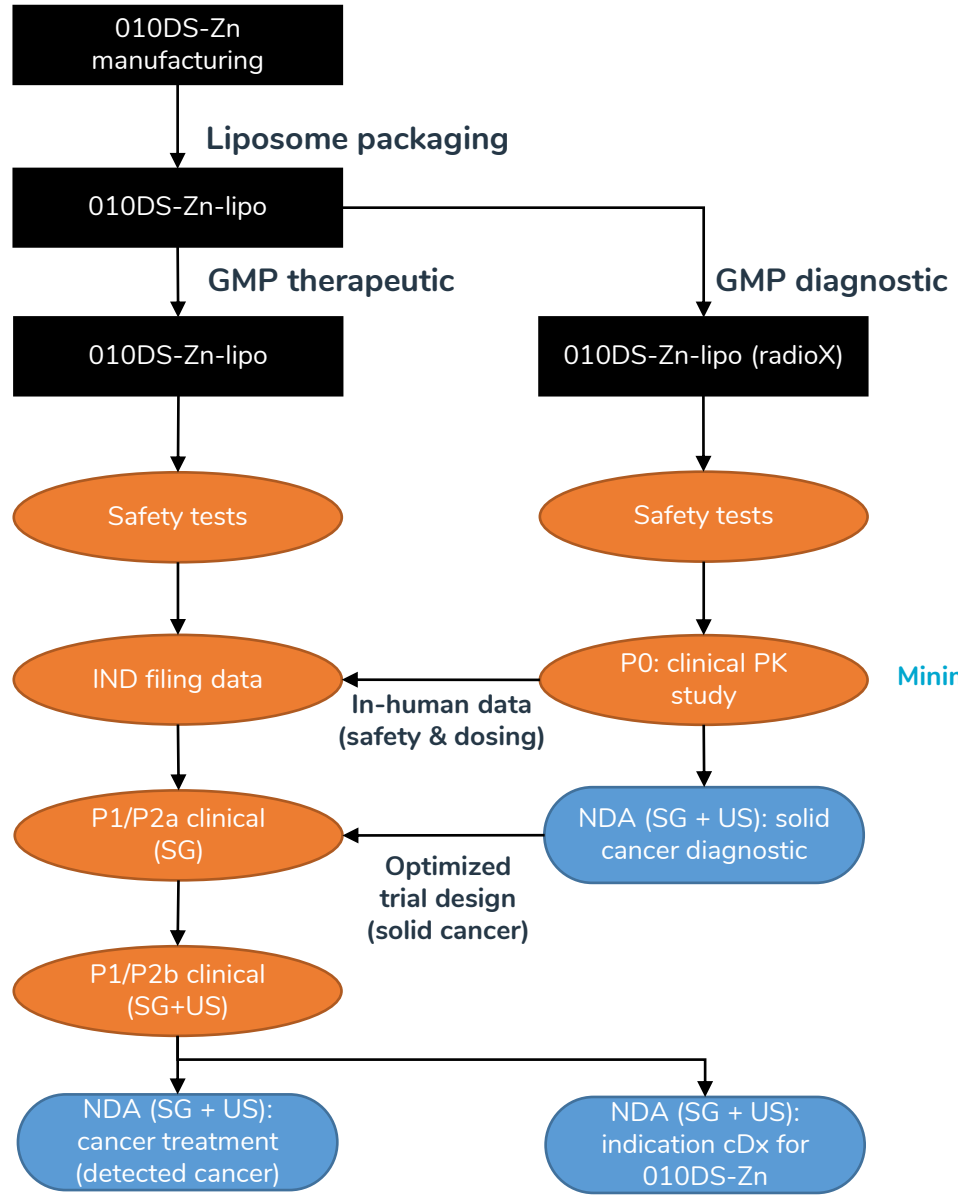
TW: KRISAN Biotech

SG: Duke-NUS/CITI Program

US: TBD

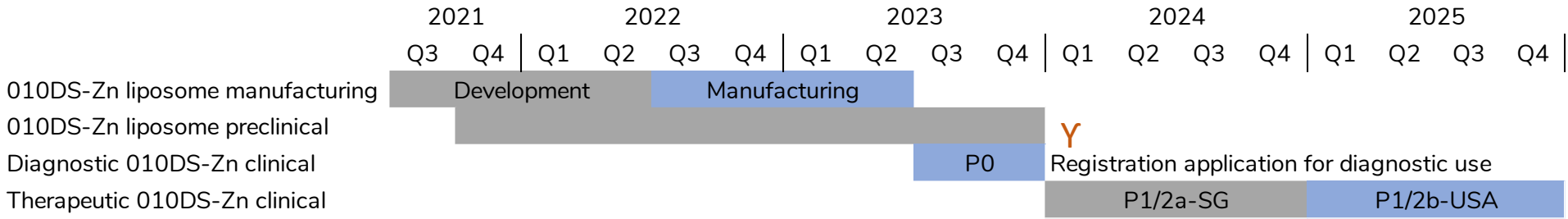
Development tasks

Legend

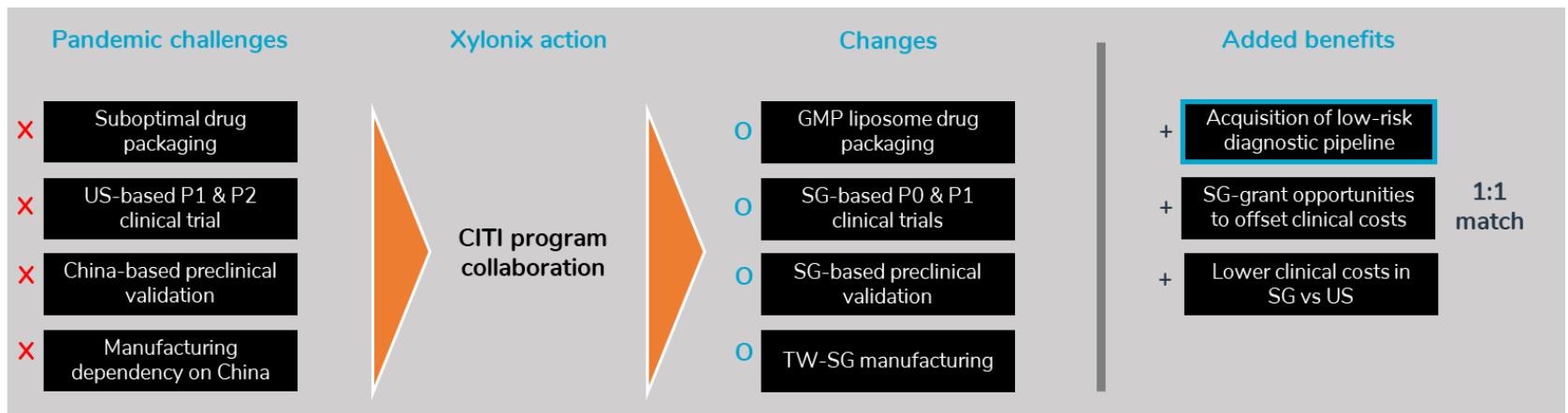


Minimized single-injection study

# Graphic summary of pandemic response @Xylonix



↑ Updated COVID19 vaccine rollout  
 COVID19 ending – US/EU trial site stabilization



## Made possible by the aggressive uptake on pandemic developments

- Liposome formulations
- Set precedents of accelerated drug approvals / global harmonization
- Better acceptance of novel science
- Improved novel drug production / distribution capacity

# Very special thanks

Xylonix pandemic response made possible by

- KRISAN Biotech (Tainan, Taiwan) – Complex polymer conjugation
- Duke-NUS/CITI Programme – Fully integrated preclinical-clinical translation platform



## CANCER IMMUNOTHERAPY IMAGING “CITI” PROGRAMME

- |                      |                    |                                 |                       |
|----------------------|--------------------|---------------------------------|-----------------------|
| ▪ GM Dr. Yu Pei Wang | Special provisions | ▪ Prof. Ann-Marie Chacko        | Program co-chair      |
| ▪ Dr. Bret Wu        | Synthesis science  | ▪ Prof. Subramanian Venkatraman | Liposome science      |
| ▪ Mr. Elvis Yu       | API dev/synthesis  | ▪ Dr. Su Yin Chaw               | Formulation / testing |
| ▪ Dr. Tina Yen       | KSB-X2 Liason      |                                 |                       |

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## More on our COVID19 pandemic forecast

Mini Review

Volume 9 Issue 11 - 2021

### COVID19 Vaccine's Delta Paradox and Dangers of Further Viral Evolution

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Abstract

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### Abstract

Despite the rapid deployment of effective COVID19 vaccines that were designed against the original Wuhan strain of SARS-CoV-2, viral mutations that led to the Delta and other variants are now fueling another round of global pandemic. As the world seeks to find an exit scenario from the pandemic, better understanding on the viral evolution that shaped the Delta variant and its possible future course would be invaluable. Of particular significance, vaccinated individuals have been reported to mainly experience milder or asymptomatic infection by the Delta variant with paradoxically high viral titers at similar level to those without vaccination. Analysis on this paradox of symptomatic reduction without viral neutralization raises worrisome possibilities of its future evolution into becoming a chronic macrophage-inhabiting pathogen in the likes of HIV. Careful considerations are required in adopting endemic or with-COVID approaches, as the infection case number is the driver of the viral evolution, and since the measures remove the initial contact barrier to the public in the event of another lethal variant emergence. Anti-pandemic measures need to focus more on the case number reduction for preventing further pandemic risks.

**Keywords:** COVID19; Macrophage; Endemic; Vaccine; Immunity; Delta with-COVID

<https://www.ecronicon.com/ecpt/pdf/ECPT-09-00670.pdf>

# End

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