國科會（大型/整合型）計畫撰寫分享

## 2030跨世代年輕學者方案

# 國際年輕傑出學者研究計畫

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寫計畫的心情就像面對颱風
氣象預報看十次　心裡劇場演十遍
來之前想太多~~颱風假~~
等的時候怕太多

但結束後才發現—我們都比自己想像得更強

**雨過天晴　就是下一步的開始**


# 年輕PI的奇幻漂流

夢想滿滿回國，
結果環顧四周—
空空的實驗室、
空空的帳戶、
空空的人手。

突然變成：「先活下去比較重要。」

| 項目 | 國外研究環境 | 國內研究環境 |
|---|---|---|
| **經費資源** | ✔ 經費多、管道多 | ✘ 經費較少，但效率高 |
| **合作與能見度** | ✔ 團隊大、跨領域成熟、能見度高 | ✘ 能見度需持續提升 |
| **研究成本** | ✘ 人事超貴（請博士後像請明星）<br>✘ 共儀更貴（開一次像在燒超跑油） | ✔ 研發成本低（同筆錢做三倍事）<br>✔ 儀器頂規、好借好用、CP值優 |
| **行政與流程** | ✘ 行政流程長、進度常延宕 | ✔ 決策快、執行穩定、人員流動小 |
| **整體體驗** | 像住五星級飯店：豪華但花費驚人 | 像住自己家：錢不多但好用 |

# 國科會年輕學者大型計畫比較表

| 面向 | 114年度「2030跨世代年輕學者方案」 | 115年度「青穗計畫」 | 115年度「優秀年輕學者計畫」 |
|---|---|---|---|
| **原始定位** | 含三類：新秀學者、優秀年輕學者、**國際年輕傑出學者** | **整併所有 2030 計畫 → 成為單一大型計畫** | **保留原本的「優秀年輕學者」類別，獨立成案** |
| **目的** | 培育跨世代人才：新秀、優秀、**國際鏈結** | 更聚焦**前瞻、跨域、國際、技術落地** | 支持年輕優秀學者強化研究能量 |
| **年齡限制** | 新秀：無明確限制但職涯 ≤5年優秀/<br>國際：**45 歲以下** | **45 歲以下** | **45 歲以下** |
| **主持人資格** | 新秀 & 國際：可無專題 PI 資格申請<br>優秀：需具 PI 資格 | 有 PI 資格即可申請（未具資格者須入職後取得） | 必須具 PI 資格才能申請 |
| **每年補助額度** | 新秀：≤ 500萬<br>優秀：依審查擇優給予<br>**國際：≤ 1,000萬** | **≤ 800 萬 / 每年**（新計畫以 50 件為原則） | **≤ 500 萬 / 每年** |
| **研究主持費** | 新秀：3萬/月<br>優秀：2萬/月<br>**國際：5萬/月** | **3萬 / 月** | **2.5萬 / 月** |
| **執行期間** | **最多 4 年** | 一期最多 4 年，<br>**可申請第二期 → 最多 8 年** | 最多 4 年 |
| **研究方向** | 無明確分類，但包含新興、跨域、國際合作 | **四大方向**：前瞻探索 / 國際鏈結 / 跨域合作 / 技術落地 | 基礎及應用研究，無特定方向要求 |
| **競爭強度** | **國際類補助 1,000 萬，件數少、競爭強** | 走大規模人才培育，件數較多（50 件） | 競爭度中等（件數未明訂） |

# 12月要投哪個國科會計畫呢?


| 您目前的狀況 | 適合的計畫 |
|---|---|
| **有亮眼成果 but 不算非常頂尖** | → 一般型國科會計畫 |
| **已累積一定能見度、發表穩定、具發展潛力** | → 優秀年輕學者 |
| **成果很強、具國際高度、有領域突破性** | → 青穗計畫（最競爭） |

**① 青穗計畫 Self-check（難度最高）**
如果您的答案大多數是 **Yes** → 青穗值得拼！
- ☑ 過去 3–5 年有頂尖期刊代表作 *(Top-tier)*
- ☑ 科研領域有「明確突破」或不可取代性
- ☑ 您能說出「我正在建立一個新方向 / 新平台」
- ☑ 有初步的國際合作或國際能見度
- ☑ 已經帶領過小團隊、產出穩定
- ☑ 寫計畫時可以回答：**「為什麼是我？」** → 很有說服力

如果您覺得您的 CV 拿去國外也能打，
那青穗就是您的主戰場。

**② 優秀年輕學者 Self-check（中等競爭）**
如果您符合以下，大多數人適合從這裡開始扎根：
- ☑ 過去幾年有不錯量與質的論文輸出
- ☑ 逐漸形成自己特色的研究主題
- ☑ 還沒有非常頂尖，但已具穩定成長軌跡
- ☑ 想打造團隊、需要資源、正在「從 0→1」
- ☑ 您可以回答：**「我有潛力，值得投資。」**

如果您覺得自己是「明日之星」，
但還沒到「今天就要火」——
這個計畫就是您的 VIP 包廂。

**③ 一般型國科會計畫 Self-check（穩健打法）**
如果您：
- ☑ 剛回國建立實驗室
- ☑ 產出還在累積
- ☑ 想先穩定基本盤
- ☑ 尚未大量發表
- ☑ 想先確保安全上壘

那就先投一般型，
**穩穩拿基本研究能量，明年再拼大的！**
先把血量補滿，再去打 Boss。

🎯 如果您要問**「我能不能活下去？」→ 一般型最穩**
🎯 如果您要問**「我夠不夠強？」→ 就先投優秀青年**
🎯 如果您要問**「我敢不敢拼？」→ 就投青穗**

# 如何創造研發經費永動機?

**國科會產學計畫(Pre育苗I)**：
發展標靶癌幹細胞之新創轉錄因子藥物 (111-2622-B-038-008-)(主持人)
期間：2022/08 ~ 2023/07
經費：100萬

**國科會產學計畫(大奈米)**：
新型癌症標靶治療：葡萄糖轉運子介導胞移之奈米藥物雛形品開發 (113-2124-MA49-006-)(共同主持人)
期間：2024/08/01 ~ 2027/07/31
經費：1,923萬

**業界產學計畫(長春藤)**：
研究幹細胞之代謝分選及其對癌幹細胞誘導分化之機制及應用 (A-109-084)(主持人)
期間：2021/12/01 ~ 2023/11/31
經費：420萬 (技轉金300萬)

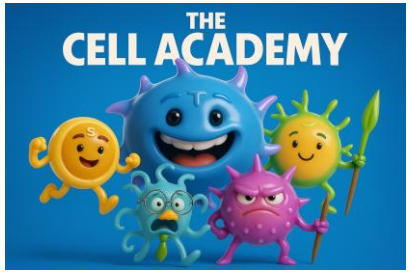
**業界產學計畫(啟新)**：
免疫細胞體外擴增培養基研究計畫 (A-113-062)(主持人)
期間：2024/08/01 ~ 2025/11/30
經費：150萬 (技轉金未定)

**國科會研究型計畫(跨世代國際年輕傑出學者)**：
以糖化奈米藥物扭轉代謝代償 及協同抑制轉錄活性作為胰臟癌幹細胞新穎治療策略 (113-2628-B-038-012-)(主持人)
期間：2024/08/01 ~ 2028/07/31
經費：3,200萬

**國衛院研究型計畫(IRG)**：
運用中孔洞二氧化矽奈米載體傳遞PBX1 抑制劑克服吉西他濱所誘導抗藥性胰臟癌之癌幹細胞特性 (NHRI-EX114-11404EI)(主持人)
期間：2025/01/01 ~ 2029/12/31
經費：760萬


**國科會產學計畫(萌芽)**：
癌幹細胞篩選技術平台暨細胞療法開發 (112-2823-8-038-001-)(主持人)
期間：2023/01/01 ~ 2023/12/31
經費：560萬

**國科會產學計畫(萌芽延續)**：
癌幹細胞篩選技術平台暨細胞療法開發之商業化應用 (113-2823-8-038-001-)(主持人)
期間：2024/01/01 ~ 2024/12/31
經費：745萬




**國科會產學計畫(科普製播)**：細胞學院 (主持人)
期間：2025/07/01 ~ 2026/06/31
申請經費：國科會830萬+廠商701萬 = 1,531萬

衍生新創

Enlighten 光合生醫

# 國科會與業界產學計畫期程


2022 2023 2024 2025 2026 2027 2028

**癌症新藥領域**

- 國科會產學計畫(Pre育苗I)
- 國科會研究型計畫(跨世代國際年輕傑出學者)
- 國衛院研究型計畫(IRG)
- 國科會產學計畫(大奈米)

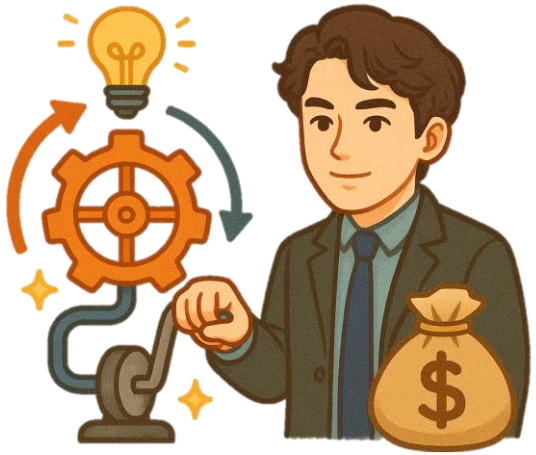
**細胞療法領域**

- 國科會產學計畫(萌芽)
- 國科會產學計畫(萌芽延續)
- 國科會產學計畫(科普製播)
- 業界產學計畫(長春藤)
- 業界產學計畫(啟新)

# 如何創造研發經費永動機?

- **永動機的核心概念**
  **用一筆經費 → 做出成果 → 讓成果帶來更多經費 → 再做更多成果 → 再獲更多經費**
  形成持續循環，而非一次性。

1. **建構自己的招牌平台（Signature Platform）：**專屬IP模型、平台或技術
2. **產出高價值研究成果：**高引述論文、跨領域突破
3. **多來源併行：**建立「三重經費引擎」
   A. 政府計畫（穩定基底）
   B. 產業合作（現金流來源）
   C. 國際資源（加速擴張）
4. **用小額經費做出初步成果 → 再申請大額（槓桿效應）**
   - **Step 1. 用校內種子經費（小額）**→ 做驗證、生成 preliminary data
   - **Step 2. 申請國科會專題（中額）**→ 擴大研究、產出 1–2 篇論文
   - **Step 3. 申請青穗/產學（大額）**→ 建立大型平台、實驗團隊
   - **Step 4. 再用成果申請國際計畫（超大額）**
5. **佈局合作網絡 →放大經費：**國內外產學團隊合作
6. **持續產生可以「再生經費」的研究資產：**可授權、可協同開發、可臨床驗證



# 臺灣生醫前瞻領域


**為何被視為「前瞻領域」？**

1. **技術快速演進** + 高影響力
2. 產業 + 經濟 + **國家競爭力關鍵**
3. 產學研整合 / **跨域整合**需求高
4. 社會 / 公共衛生**需求強烈**

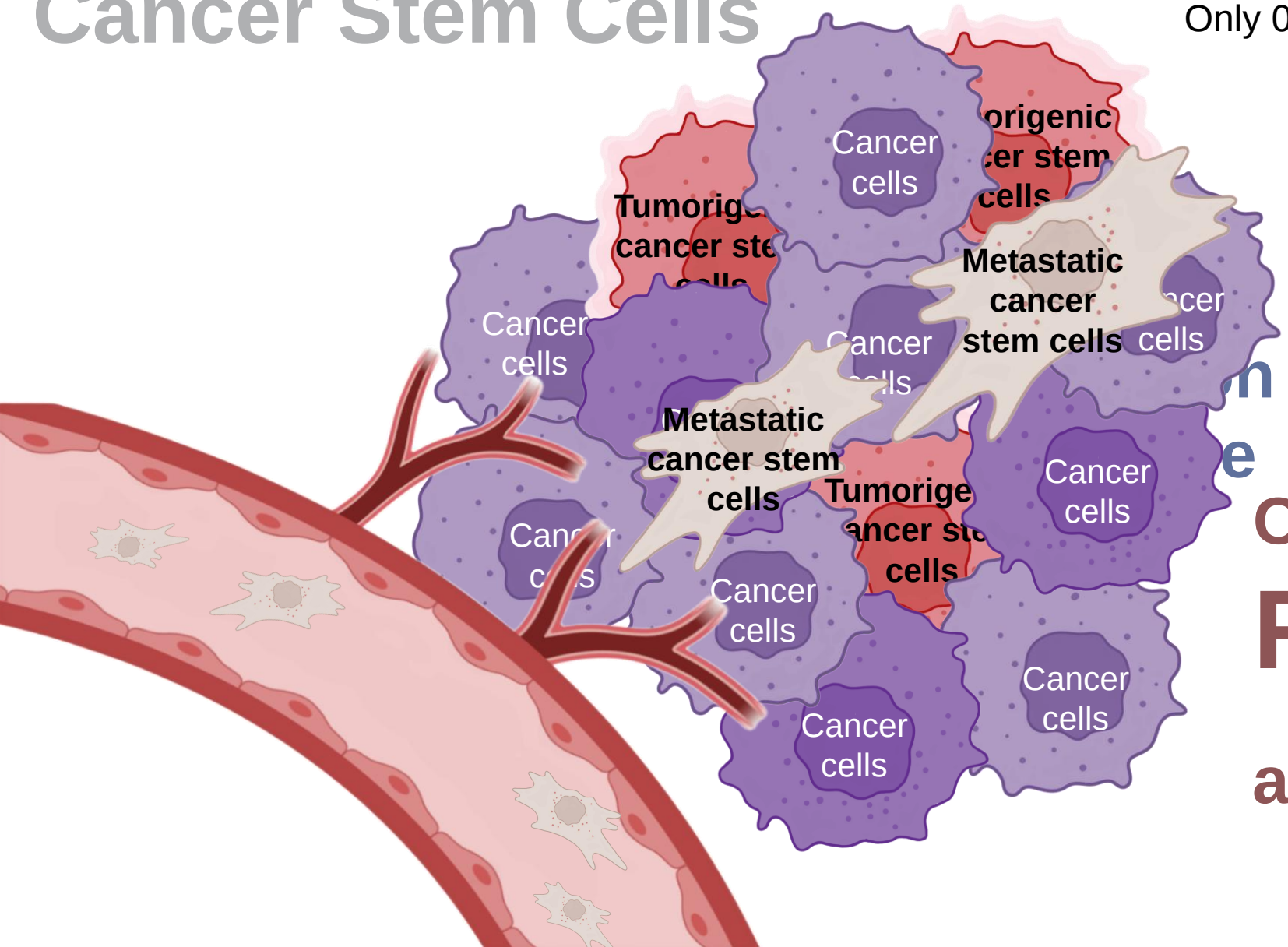
當您申請像是「年輕傑出學者」、「青穗計畫」等支持年輕學者的計畫時，
若主題屬於「生醫前瞻領域」，就有以下優勢：

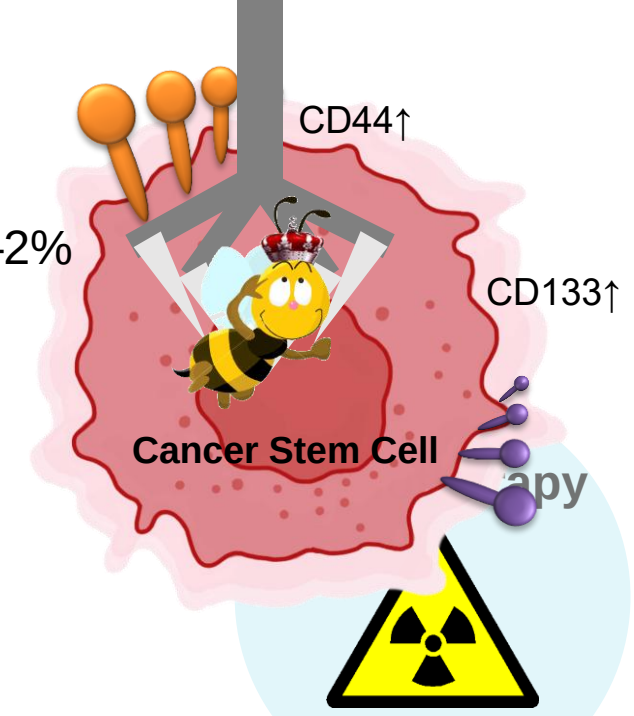
- **政策加分**：政府鼓勵前瞻科技，這樣的研究主題通常更容易**與國家科技發展戰略對齊**。
- **國際與跨域合作機會較多**：生醫前瞻領域本身要求**高技術整合、國際鏈結**，您可在申請中凸顯這一點。
- **資源與補助機會較好**：由於**為重點發展領域**，可能更容易獲得補助、資源支持。
- **產學研轉譯潛力強**：若研究具備**技術落地、產業合作、醫療應用前景**，能提升計畫的可行性與影響力。

Unmet medical need

## Current Therapies Cannot Eradicate

# Cancer Stem Cells




Only 0.01–2%

Causing Tumor

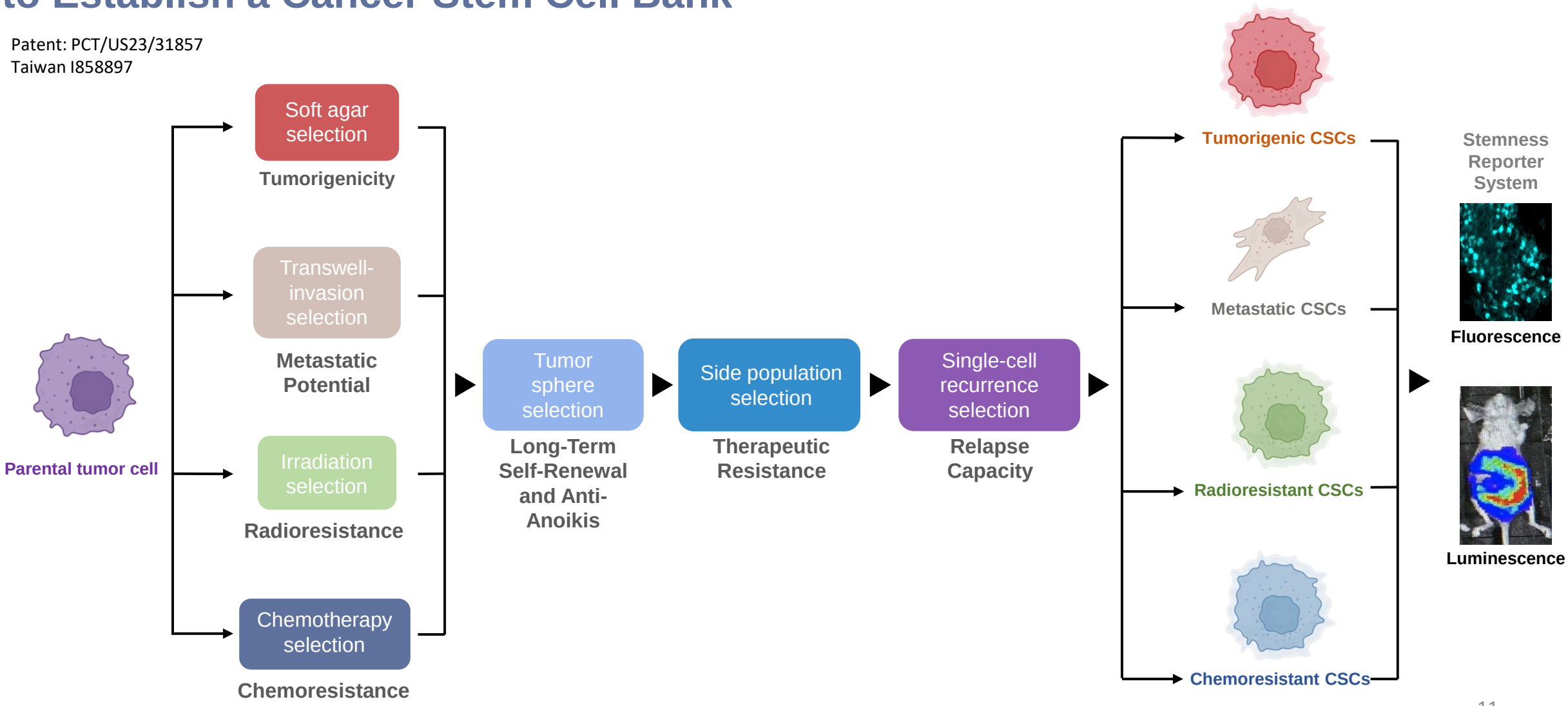
Chemotherapy

**Recurrence**

and **Metastasis!**

# Development of a Cancer Stem Cell Behavior Isolation Platform to Establish a Cancer Stem Cell Bank

Patent: PCT/US23/31857
Taiwan I858897



# Resolving the Pain Points of Clinical Treatment and Cancer Research

| | Conventional antibody selection method | | Cancer stem cell behavior isolation platform |
|---|---|---|---|
| Current technical challenges | • Costly<br>• Performed multiple times | → | • Exceptional quality<br>• 70% less expensive than antibody screening |
| | • Inconsistent CSC markers in different cancers | → | • Applicable to various solid or liquid tumors<br>• Applicable to cancers without knowing markers<br>• Can develop novel CSC surface antigen targets |
| | • Few CSCs can be isolated ($10^2$-$10^3$ cells)<br>• Unstable | → | • Billions of CSCs<br>• Stable expansion<br>• Maintaining high purity for several years |
| Current clinical challenges | Cancer • resistance<br>• recurrence<br>• metastasis | → | Development of targeted CSC drugs or therapies |

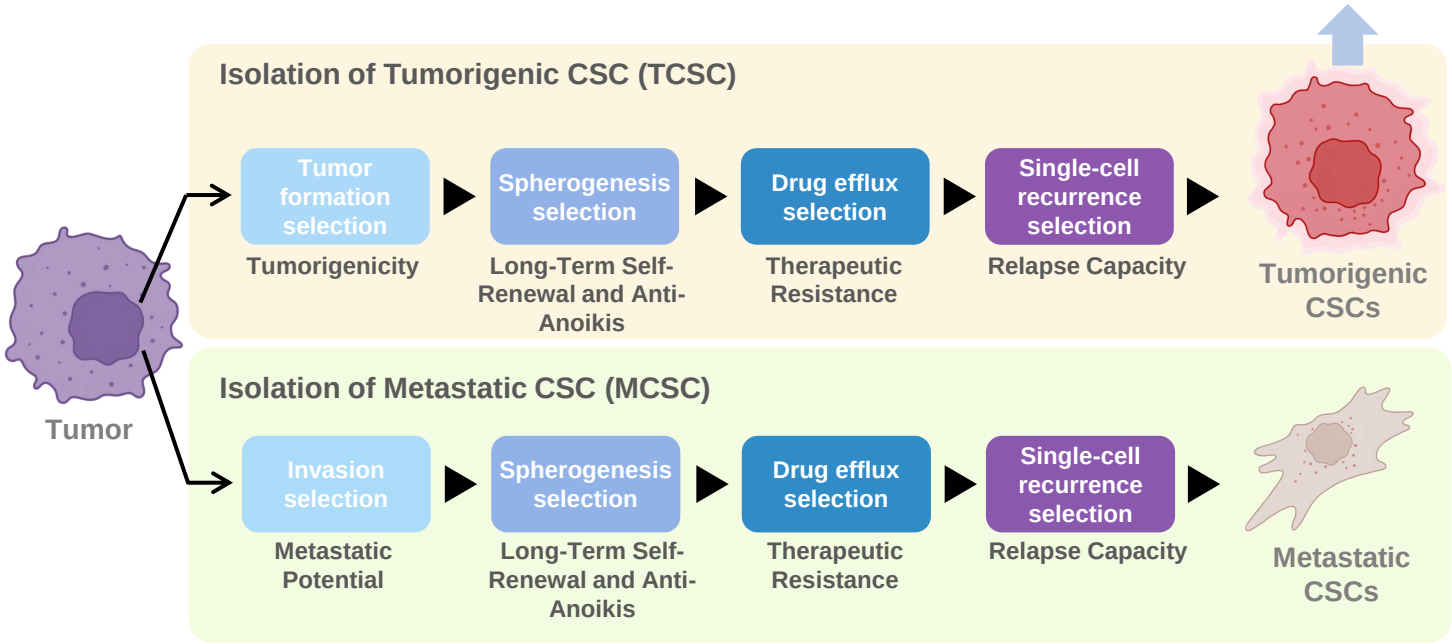
# CSC Behavior Selection

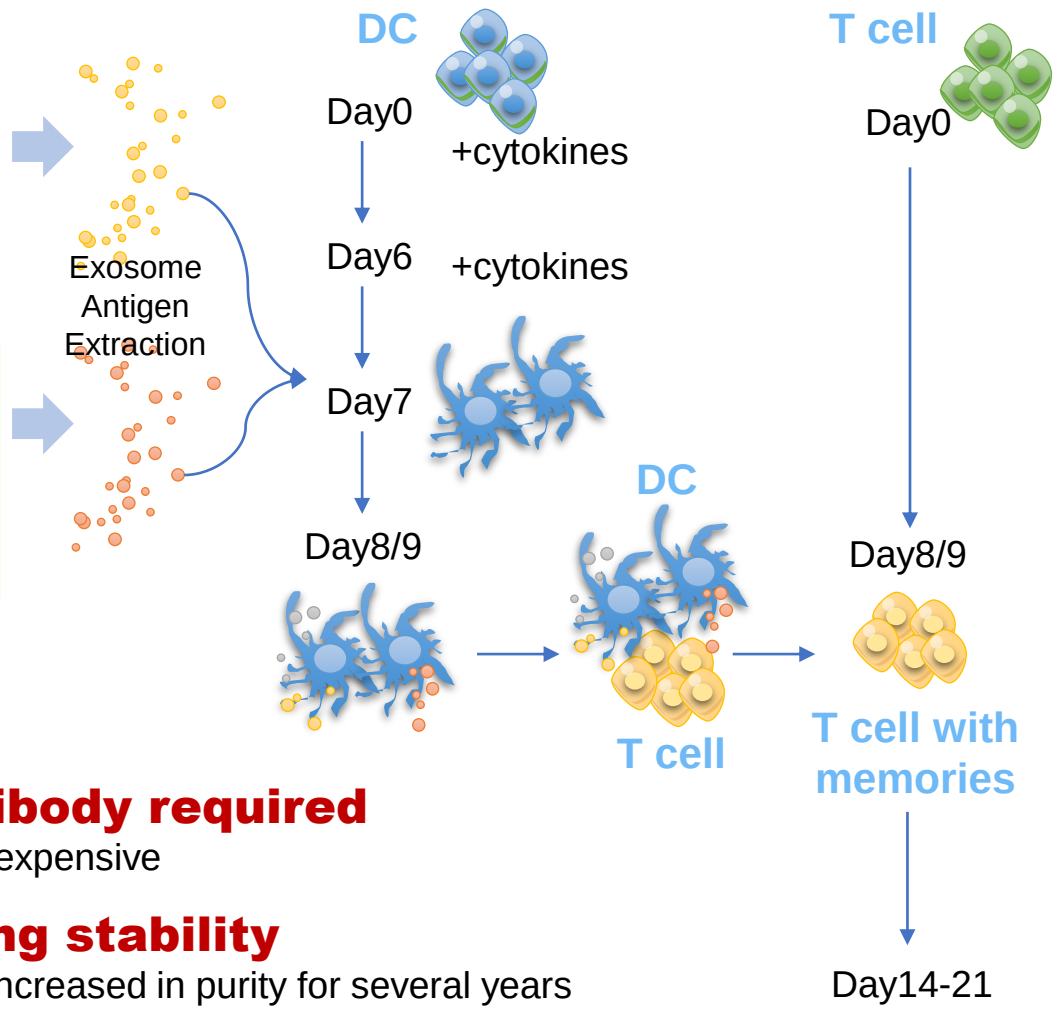
## 1 CSC Bank, Medium, Antigens

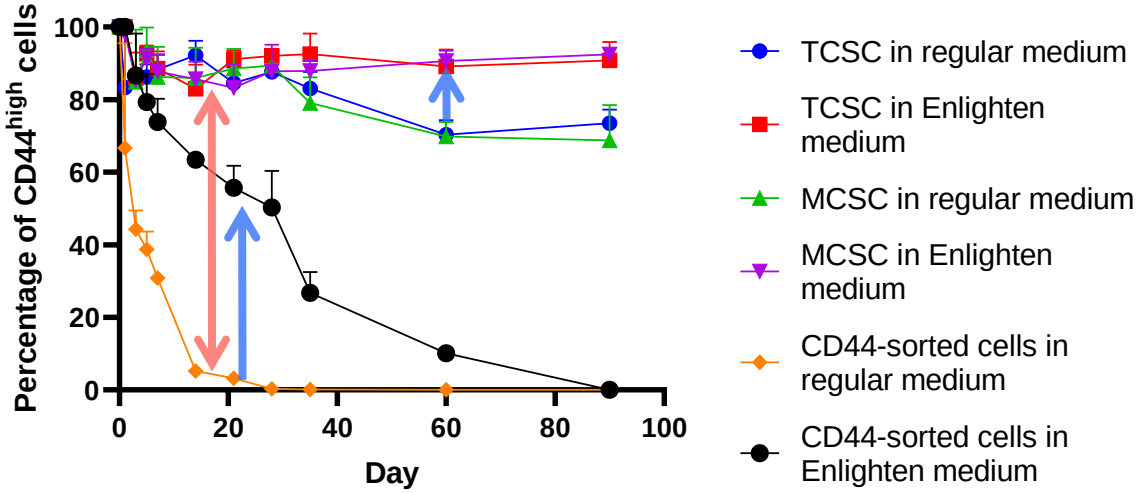
Patent: PCT/US23/31857
Taiwan I858897

## 2 Anti-CSC DC-T Cell Therapy

Patent: PCT/US24/55481
Taiwan 2110011TW



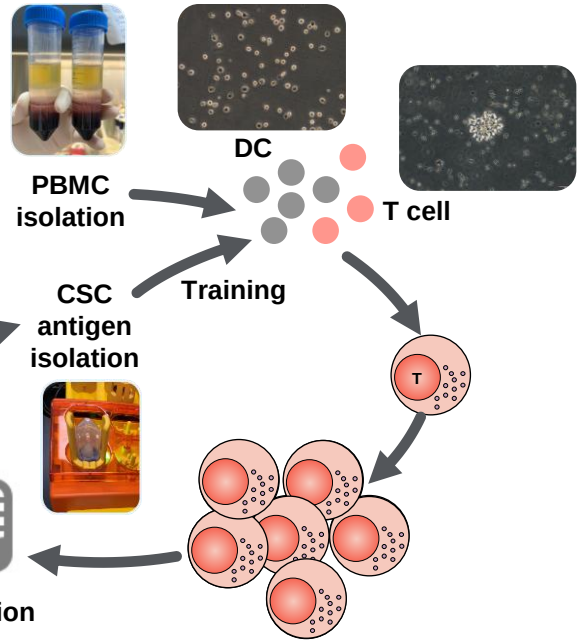



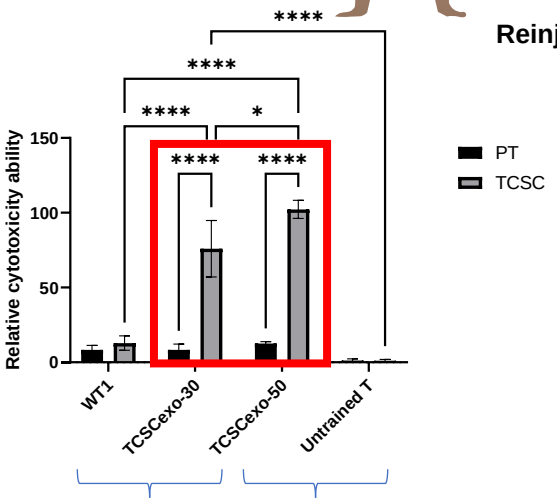

**No antibody required**
**70%** less expensive

**Enduring stability**
**50⁺ fold** increased in purity for several years

**Expandable**
**500⁺ fold** increased CSC quantity

# Anti-CSC DC-T Therapy




**6-8** fold increase

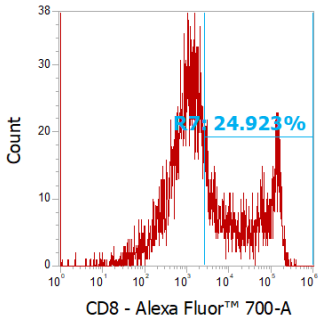
**76-102** fold increase

CSC Cytotoxicity

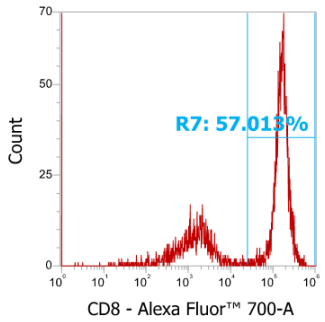
Cytotoxic T Cell

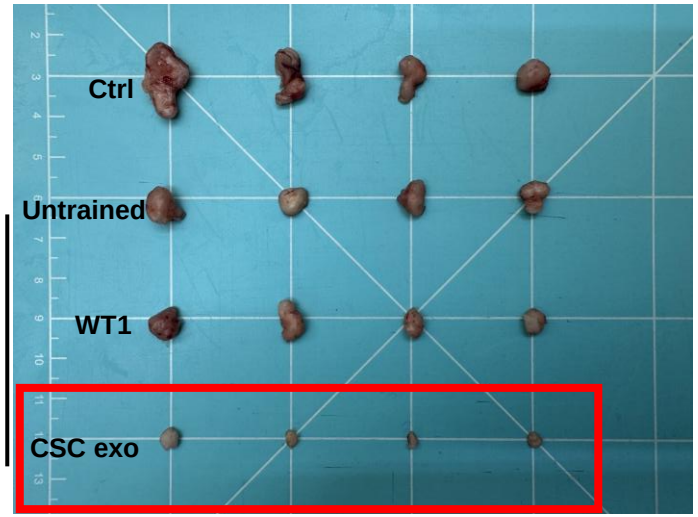
**2** fold increase

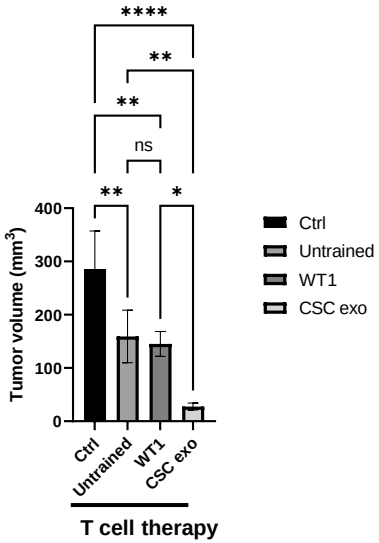
**Before training**




**After training**



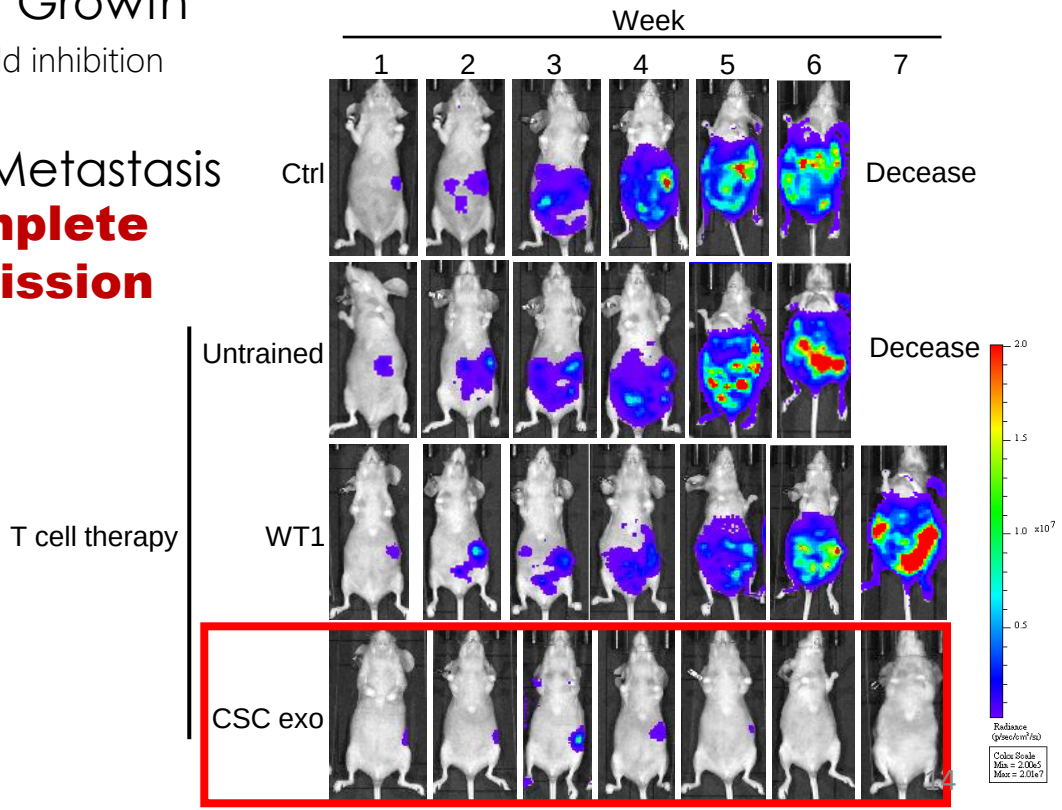




Tumor Growth

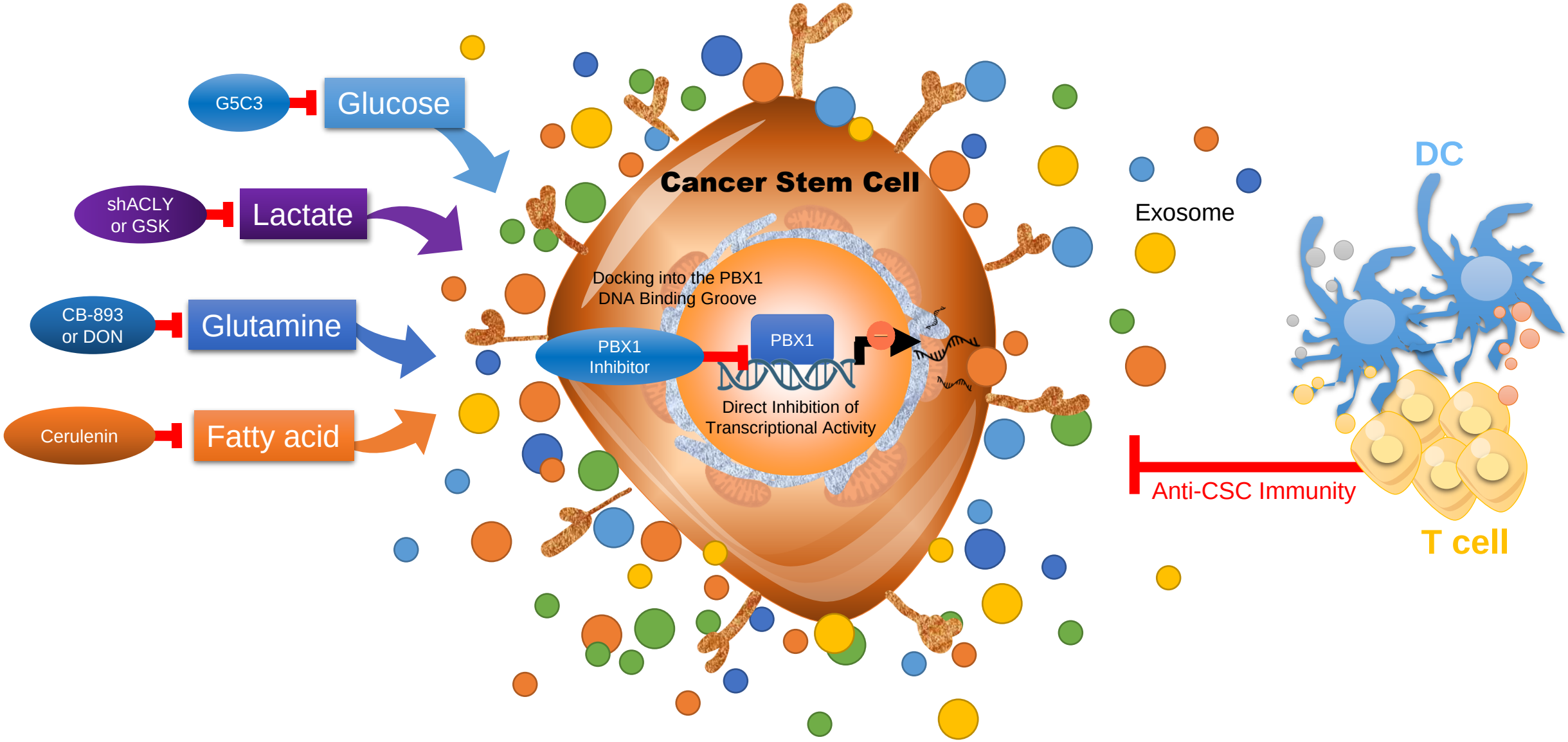
**15** fold inhibition

Tumor Metastasis

**complete remission**



# All-Out Attack on CSCs from Core to Surface

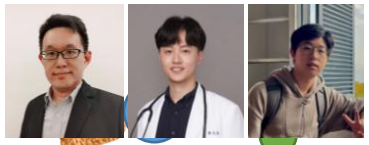


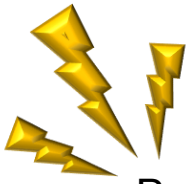
Prof. YAS
Entertain Every Possibility

YAS LAB
ENLIGHTENING PATHS IN CANCER STEM CELL RESEARCH

Vesicle: Luu, Jane

Neoantigen: George, Kyle, Cody





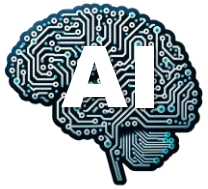
Pressure: Jack

**Cancer Stem Cell**

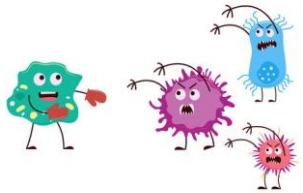
LncRNA: Asad

Transcription factor

Mito-ER Interaction: Xuan-Ru, Heidi



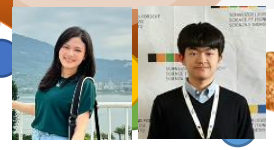
AI: Sharon, Melody, Kelly, Wan, Li-Min

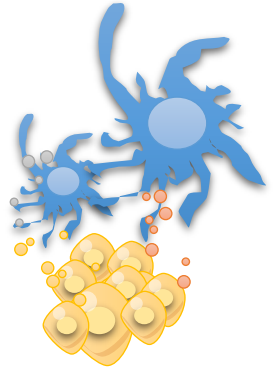


Microbiota: Dinesh

PBX1: Wan, Jamie, Mina, Tiffany, Angelia, Johanna, Andie

Metabolism: Liang-Yun, Albert





Herbal Medicine: Yuyu

Immune Cell Therapy: Tsai, Tobey, Nick, Eman, Eimen


# 恐怖12月 計畫動筆時

You say “I’m ready!”

Your brain says “Nope.”
Your proposal says “Good luck.”
Your ideas say “We’re on vacation.”

怎辦？如何讓計畫大喊：
「選我!!」「非我不可!!!」

## [輔導調查]113年國科會「2030跨世代年輕學者方案」，敬請於12/8惠覆，謝謝。 收件匣 ×

**iting0318, TMU** <iting0318@tmu.edu.tw> 2023年12月4日 週一 下午3:36
寄給 Sandy、 密件副本： 我

老師您好

經學院推薦您預計提出113年國科會「2030跨世代年輕學者方案」
研發處將於12月初至12月中安排後續專家輔導
若您有輔導需求敬請於12/8前回覆此信件

如有任何未盡事宜，煩請不吝隨時與我聯繫謝謝

怡婷敬上

## [會議通知]113年國科會「2030跨世代年輕學者方案」專家輔導會議112年12月19日(二)15:00-16:00 (視訊會議) External 收件匣 ×

**iting0318, TMU** <iting0318@tmu.edu.tw> 2023年12月13日 週三 下午3:10
寄給 裘正健、 我、 Sandy

113年國科會「2030跨世代年輕學者方案」專家輔導會議 (視訊會議)
時　　間：112年12月19日 (二) 15：00-16：00
視訊網址：https://meet.google.com/nsv-fmxy-guc
出席人員：裘正健教授　沈耀安助理教授

輔導計畫

國際年輕傑出學者
主持人： 醫學院醫學系沈耀安助理教授
計畫名稱：透過葡萄糖轉運蛋白1所調控之胞移作用雙靶向幹細胞轉錄活性及麩醯胺酸代謝作為新穎癌幹細胞治療策略

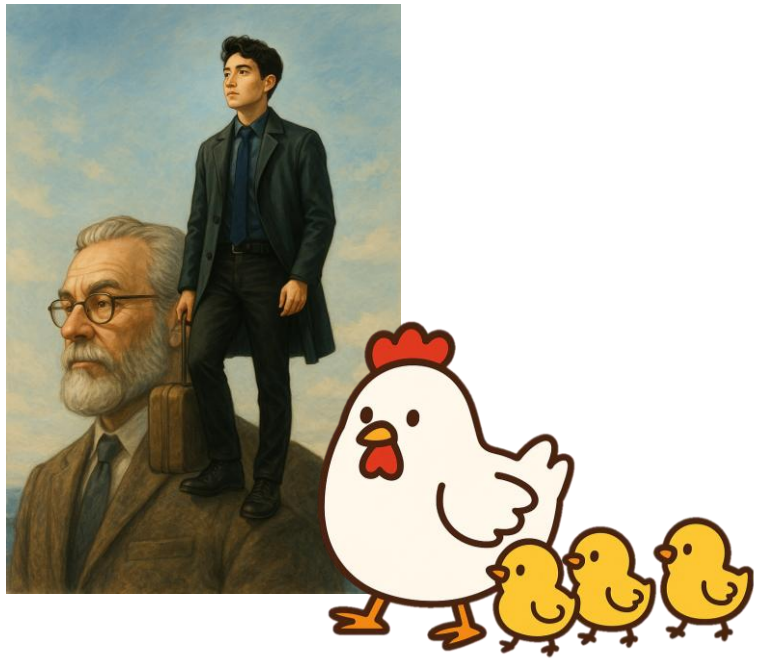
附上國科會113年度2030跨世代年輕學者方案徵求公告，請參閱

若有任何未盡事宜，煩請不吝隨時與我聯繫，謝謝您。

怡婷敬上

「巨人肩膀接力賽」

**Standing on giants.**
**Becoming a giant.**
**Raising the next giants.**



# 研究主題吸睛易懂

透過葡萄糖轉運蛋白1所調控之胞移作用雙靶向幹細胞轉錄活性及麩醯胺酸代謝作為新穎癌幹細胞治療策略

A Novel Cancer Stem Cell Therapy that Dual-Targets Stemness Transcriptional Activity and Glutaminolysis via Glucose Transporter 1-Mediated Transcytosis

太高深莫測，
連自己也看不懂？

精煉成

國際年輕傑出學者研究計畫主題

**以糖化奈米藥物扭轉代謝代償及協同抑制轉錄活性作為胰臟癌幹細胞新穎治療策略**

Utilizing Glucosamine-Labeled Nanodrugs as a Novel Pancreatic Cancer Stem Cell Therapy to Counteract Metabolic Compensation and Synergistically Inhibit Transcriptional Activity

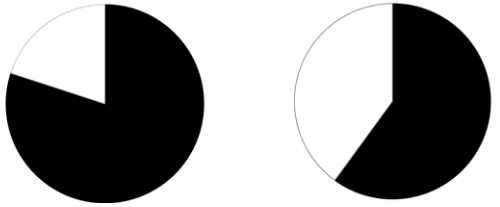
點出 痛點、解決策略、機制，

並 簡化 + 科普

# 研究背景

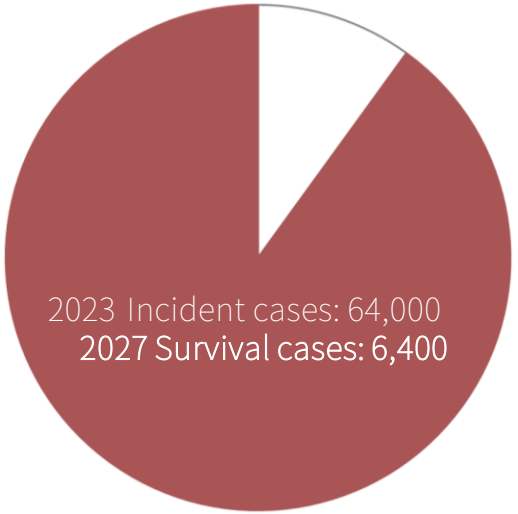
# US Pancreatic Cancer SOM by 2030 Is $145.4 M

| Relapse (Rate) | Stage IV (metastasis) |
|---|---|
| 80% | 60% |

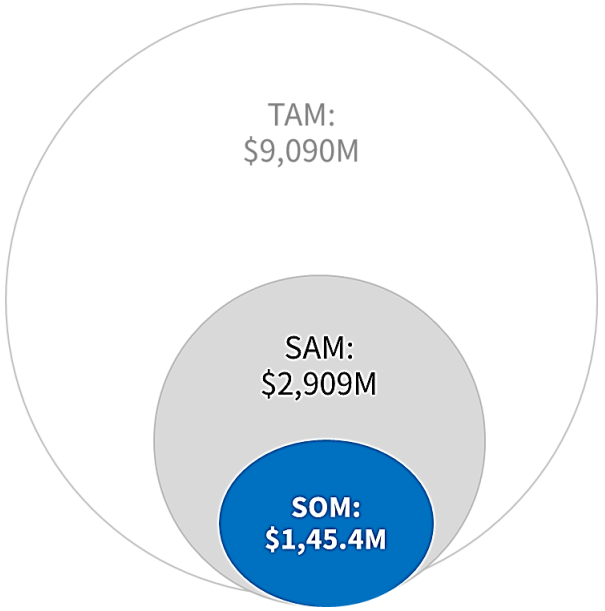


Mortality rate
(within 3 years)

**90%**

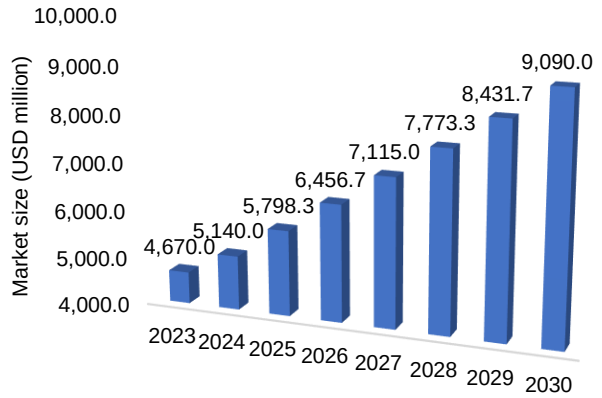



**Breakthrough therapy** for pancreatic cancer is in urgent need




CAGR
(2023~2030)

9.95%
($4,670 M~$9,090M )




## BTD

(Breakthrough Therapy Designation)

Applicable to treatments with preliminary clinical data demonstrating significant efficacy.

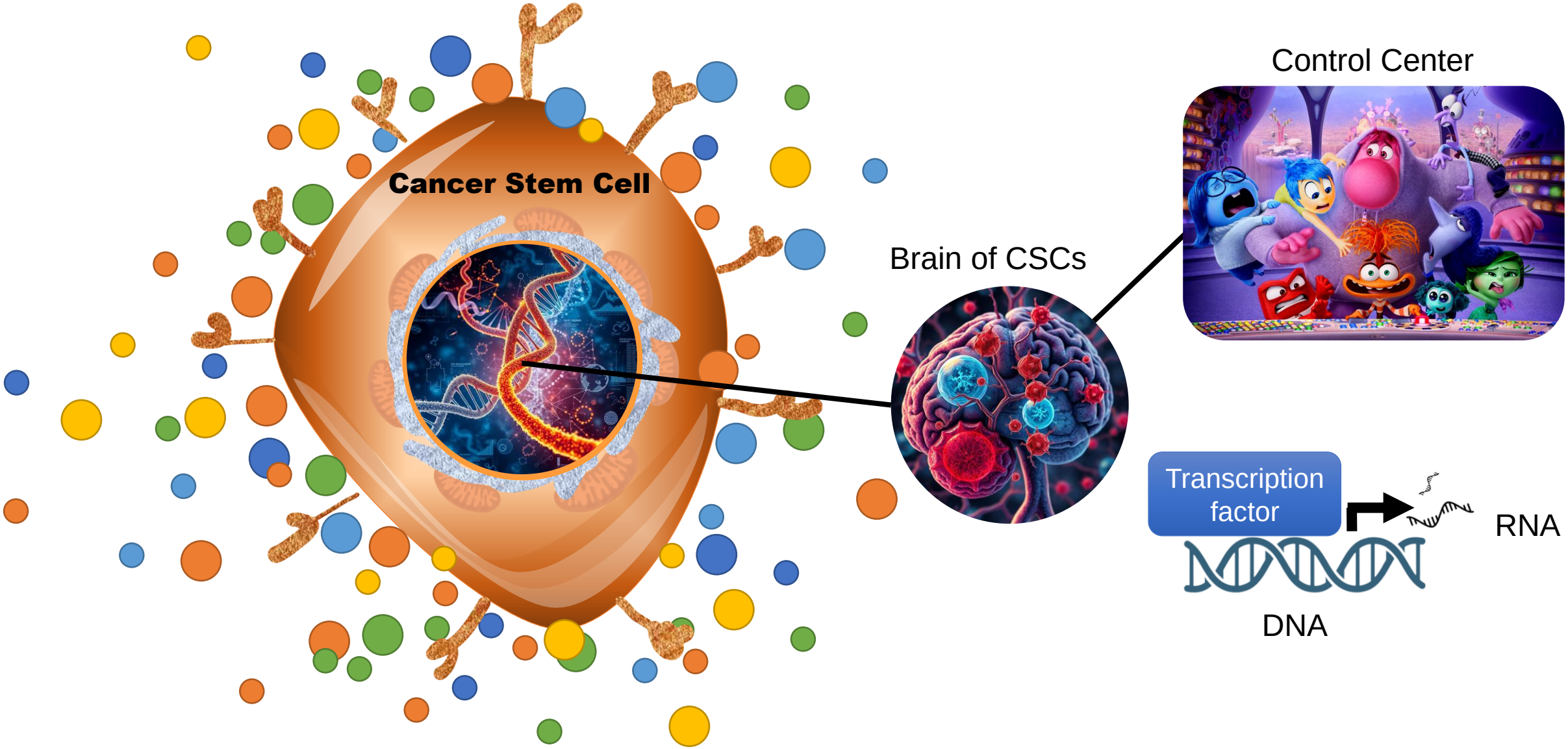
## ODD

(Orphan Drug Designation)

Targeting rare diseases, including certain cancers such as pancreatic cancer.

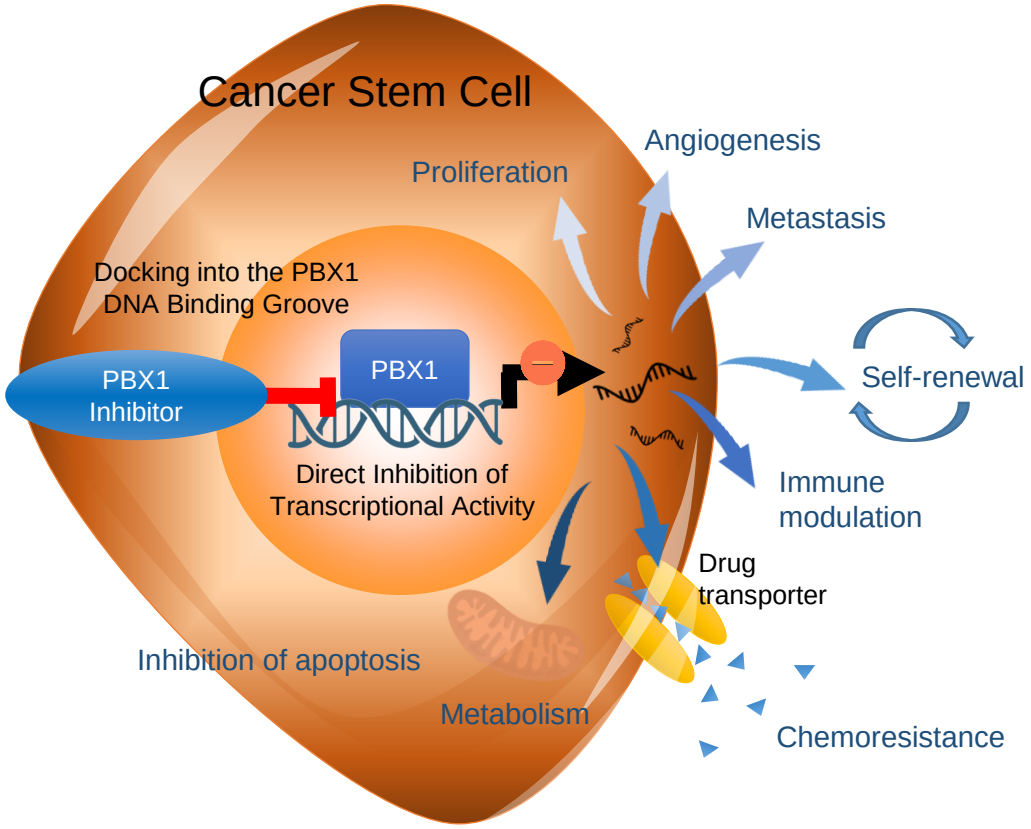
研究背景

# Blocking Transcription to Shut off CSCs

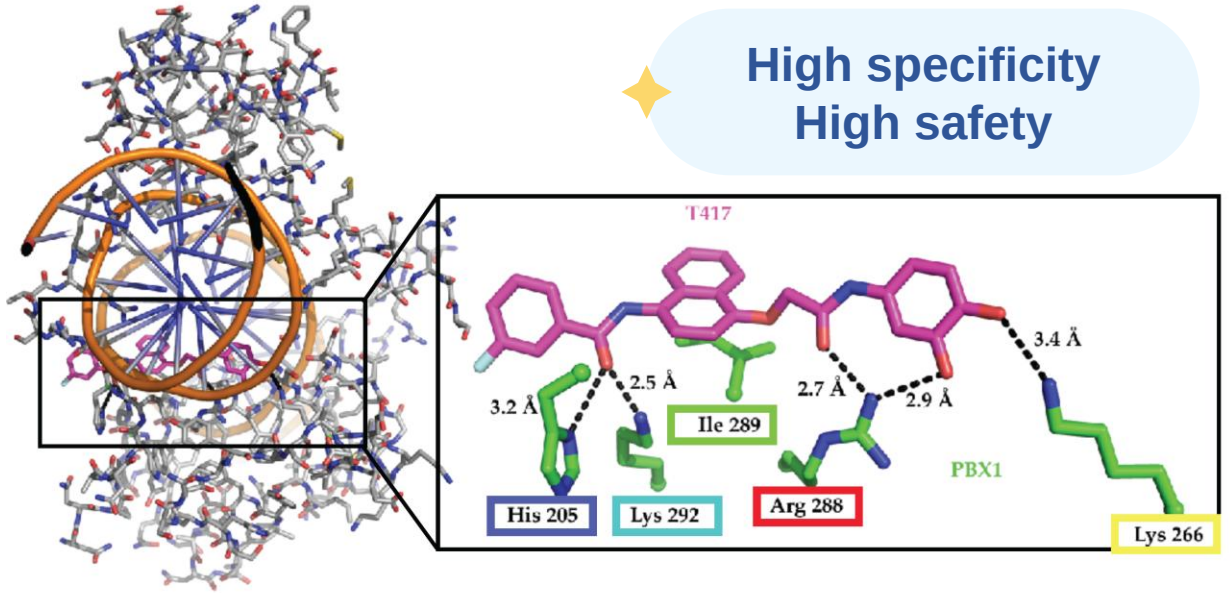


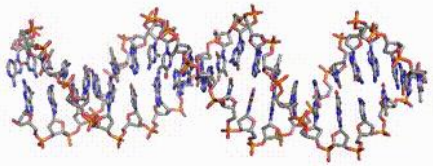
# Targeting PBX1 Stem Cell Transcriptional Network as Novel Cancer Therapeutics

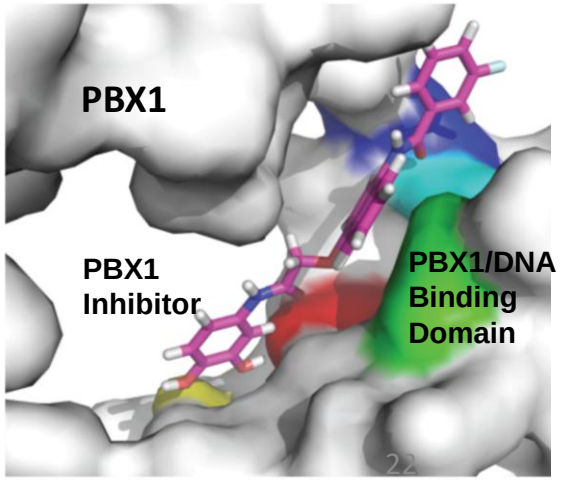
## Drugging the Undruggable Target




- First-in-Class MOA
- High specificity
  High safety






US patent:
US10800742B2

Blood. 2022 Mar 31;139(13):1939-1953.

iScience. 2021 Oct 15;24(11):103297.

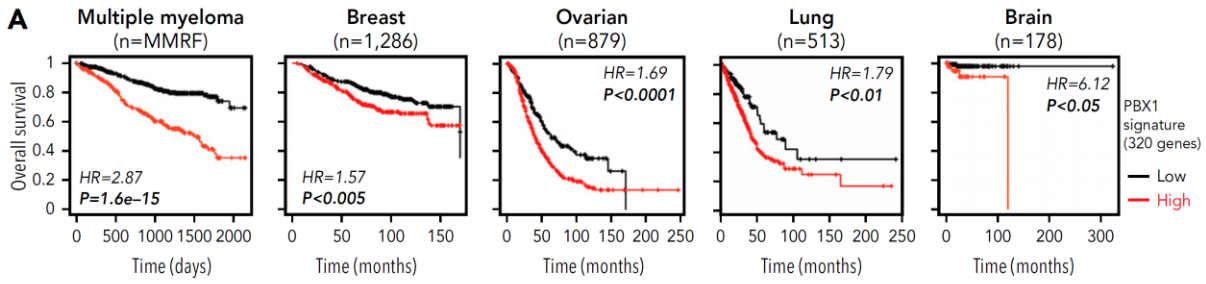
# PBX1與多癌種不良預後相關

轉錄因子與DNA結合導致腫瘤具有抗藥性及幹細胞特性

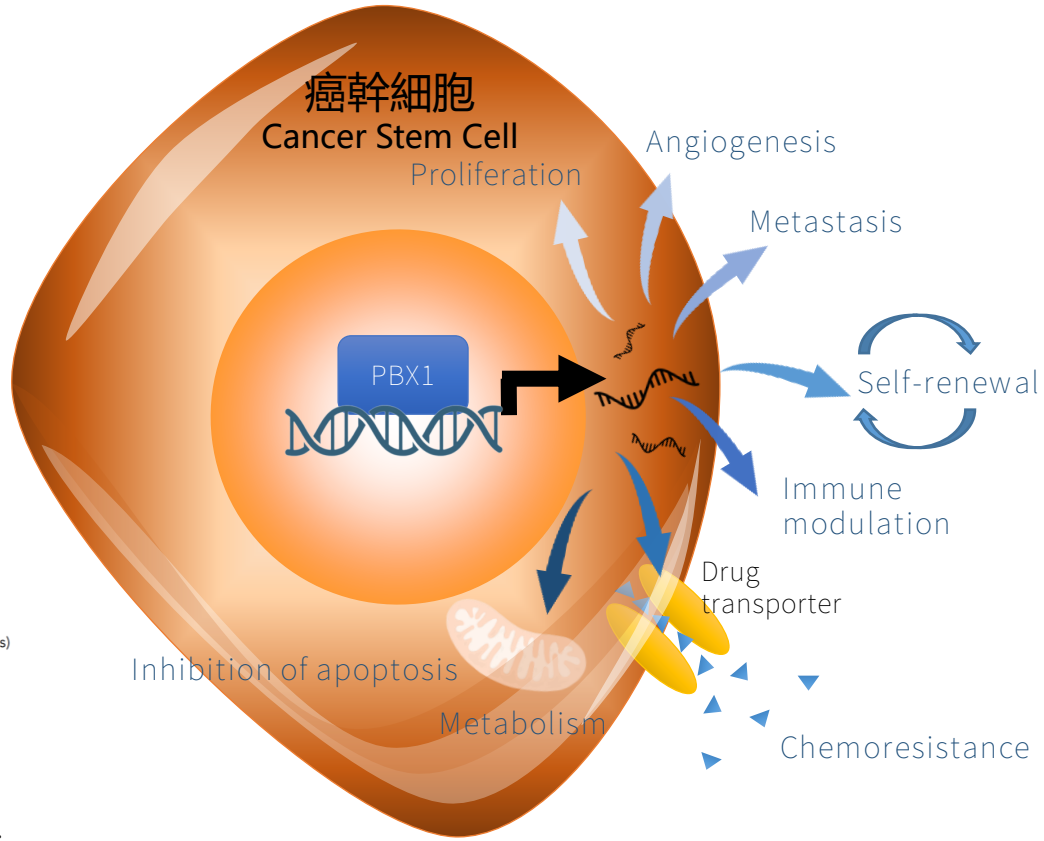
PBX1僅在癌症組織表現

**高**vs.低**存活率**最高降低 **6**倍

| 癌症種類 | **多發性骨髓瘤** | 乳癌 | 卵巢癌 | 肺癌 | **腦瘤** |
|---|---|---|---|---|---|
| 風險比值 (HR, hazard ratio ) | **2.9** | **1.6** | **1.7** | **1.8** | **6.1** |



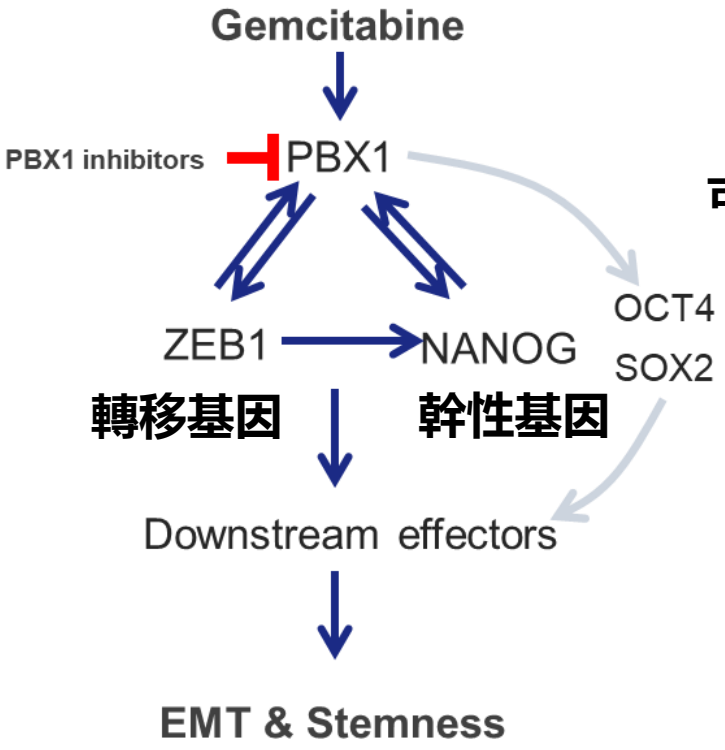

Blood. 2022 Mar 31;139(13):1939-1953.



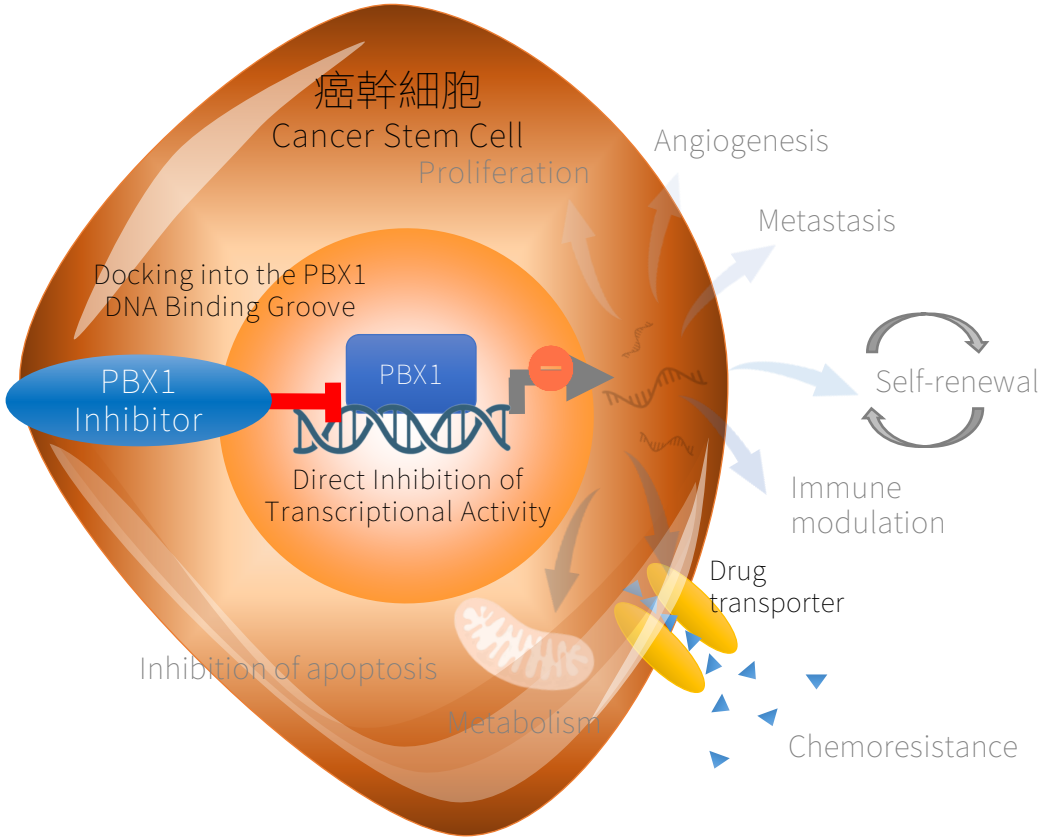
# 阻斷PBX1減少腫瘤抗藥性、復發與轉移

轉錄因子與DNA**無法**結合導致腫瘤**不**具有抗藥性及幹細胞特性

胰臟癌第一線用藥(Gemcitabine)
會促進抗藥性胰臟癌細胞
**誘發幹性及轉移相關基因**




**阻斷PBX1轉錄作用**
**可同時抑制正回饋循環**

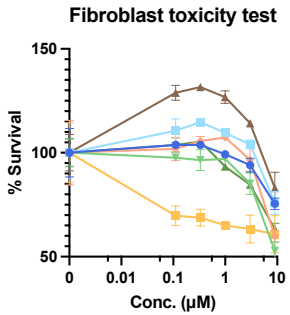


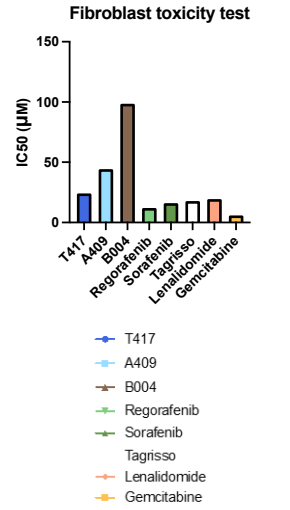

Blood. 2022 Mar 31;139(13):1939-1953.

# PBX1抑制劑100倍有效劑量仍無顯著毒性

斑馬魚模式中與其他抗癌藥物相比：未造成孵化、生長/型態異常

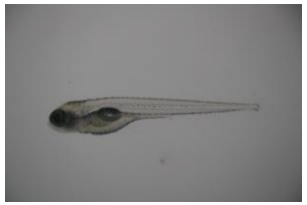
**Fibroblast toxicity test**




**Zebrafish embryo toxicity test**

Normal control

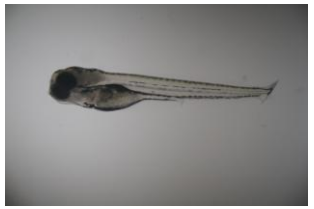


**T417 256 μM**
**normal gross apearance**

**A409 256 μM**
**normal gross apearance**

**B004 256 μM**
**normal gross apearance**

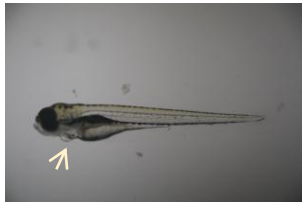
Reg 8 μM
craniofacial malformation,
disrupted caudal fin



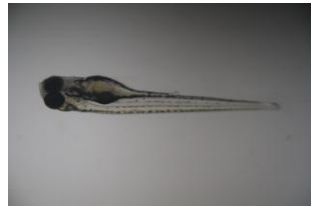
Len 64 μM
pericardial & yolk sac edema,
craniofacial malformation

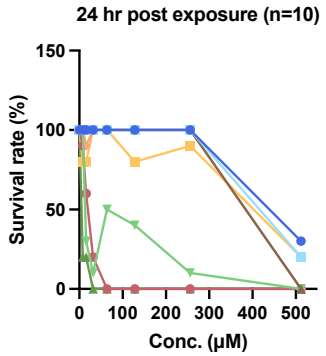
Tag 16 μM
scoliosis (dorsal view)

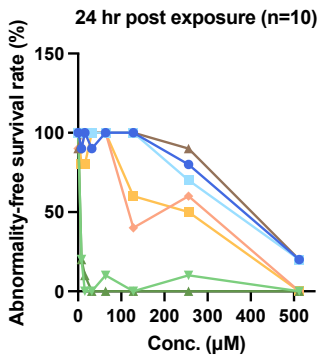
Gem 64 μM
scoliosis, pericardial edema



Sor 8 μM
scoliosis, swim bladder dysfunction





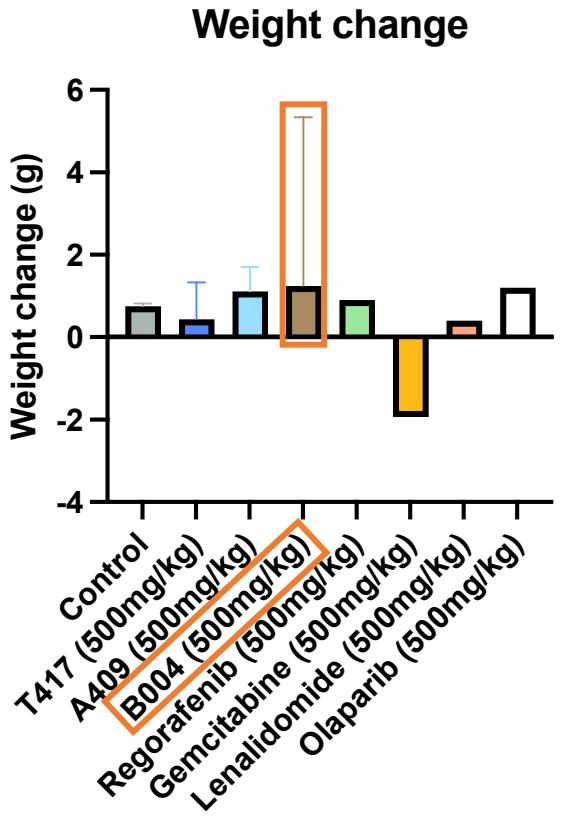

T417
A409
B004
Regorafenib
Sorafenib
Tagrisso
Lenalidomide
Gemcitabine

# PBX1抑制劑100倍有效劑量無顯著毒性

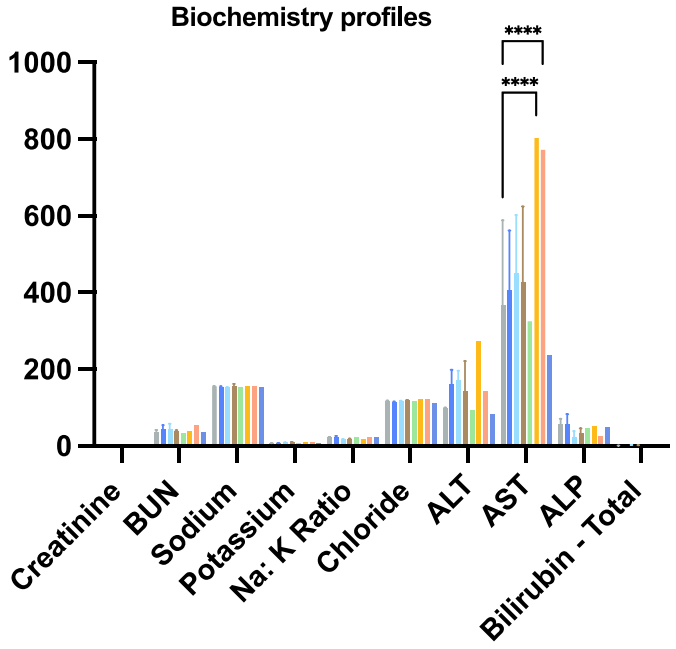
小鼠模式中與其他抗癌藥物相比：體重、生化值、血液指標皆正常

Murine maximum tolerated dose test

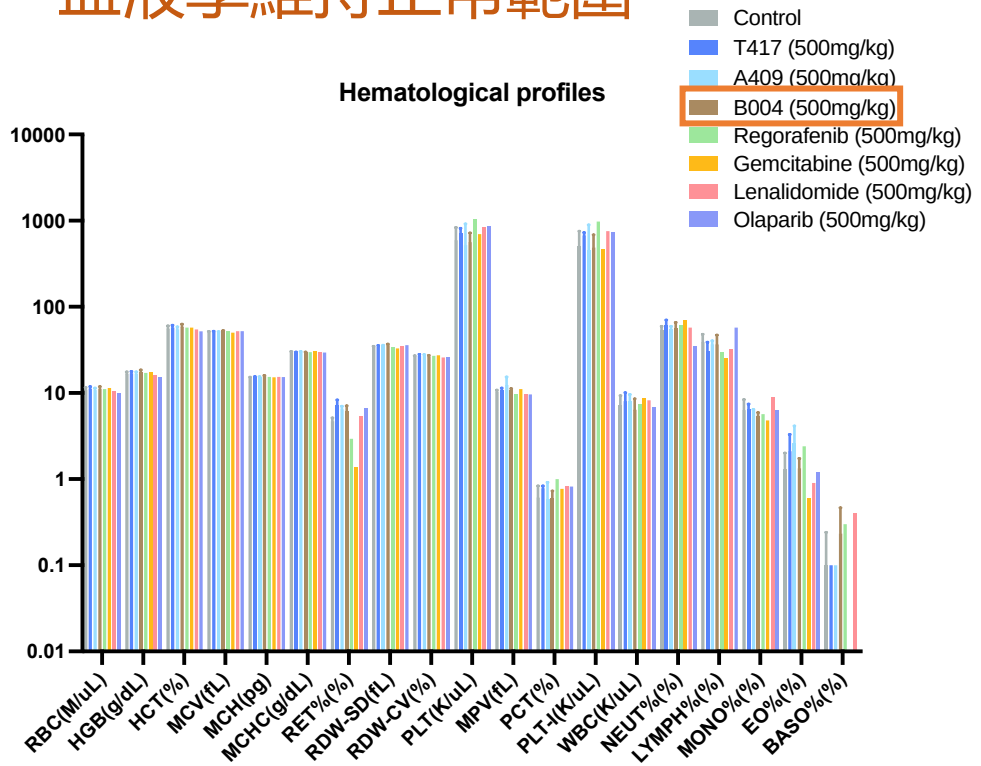
## 體重維持




## 生化值維持正常範圍



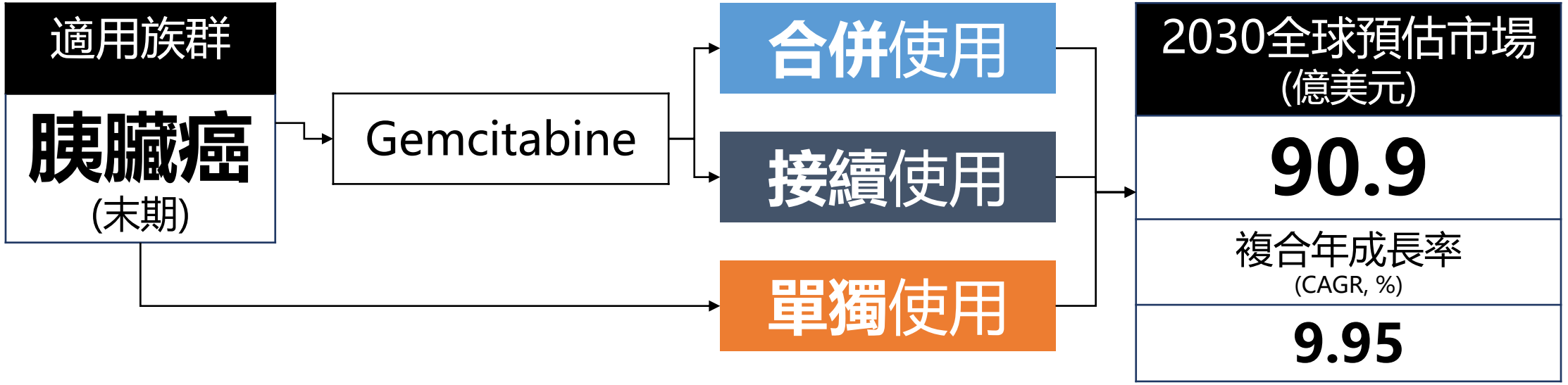

## 血液學維持正常範圍



# PBX1抑制劑瓦解癌幹細胞防禦機制

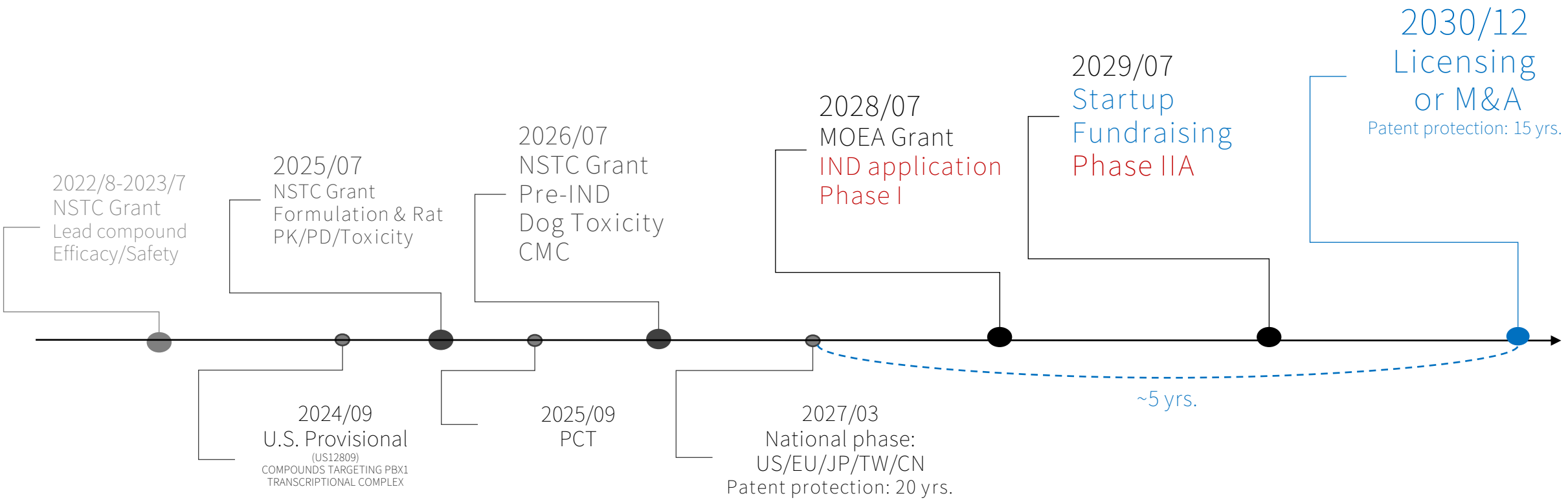
癌幹細胞小分子藥物輔助癌症治療減少抗性、轉移與復發

| 完全新創藥物<br>(First-in-Class) | 專一毒殺<br>腫瘤細胞 | 安全<br>無顯著副作用 |
|---|---|---|
| 突破過去**35年轉錄因子無法設計藥物(undruggable)**之困境。直接結合並阻擾PBX1與下游基因結合路徑**減少抗性與轉移**。 | 抑制**多種**癌症(抗性/轉移)細胞生長。並**可搭配其他化療藥物或標靶療法**做**結合治療(combination therapy)** | 動物實驗顯示**100有效倍劑量(ED)**下，此藥物**不具顯著毒性及副作用**，對正常細胞影響小。 |



# Licensing B004 Patents for 15 Years of Protection from 2030

## Expanding business and advancing B004 toward clinical trials for marketization




- For **pancreatic cancer as the first indication**, B004 is expected to be a standalone treatment or used with or following gemcitabine therapy.
- The global market is projected to reach **$9.09 billion** by 2030.

# Selective Cytotoxicity and Stemness Inhibition in CSCs by Glucosamine-Coated Liposomes (G5C3)

## A Trojan Horse capable of smuggling drugs direct into the nexus of CSCs

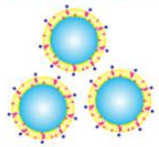
ACS NANO
www.acsnano.org
ARTICLE

### Glucose Transporter 1-Mediated Transcytosis of Glucosamine-Labeled Liposomal Ceramide Targets Hypoxia Niches and Cancer Stem Cells to Enhance Therapeutic Efficacy

Lu-Yi Yu,† Pei-Wei Shueng,† Hsin-Cheng Chiu,† Yu-Wei Yen, Tzu-Yu Kuo, Chieh-Ru Li, Ming-Wei Liu, Chia-Hsin Ho, Tzu-Hao Ho, Bo-Wei Wang, Cheng-En Li, Ming-Hung Chen, Yao-An Shen,* and Chun-Liang Lo*

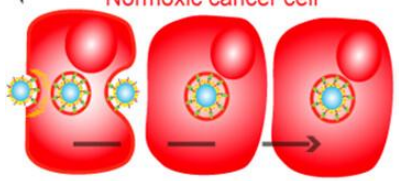


Glucosamide-labeled liposomal ceramide



Size : 81.0±3.8 nm
PDI : 0.16 ± 0.03
Zeta : -18.3±3.2 mV
Ceramide EE : 99±0.08 %

GLUT1-mediated endocytosis
Normoxic cancer cell

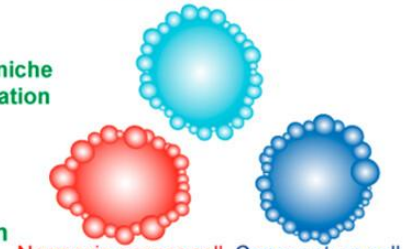


GLUT1-mediated transcytosis

Targeting tumor hypoxic niche
Enhancing drug accumulation

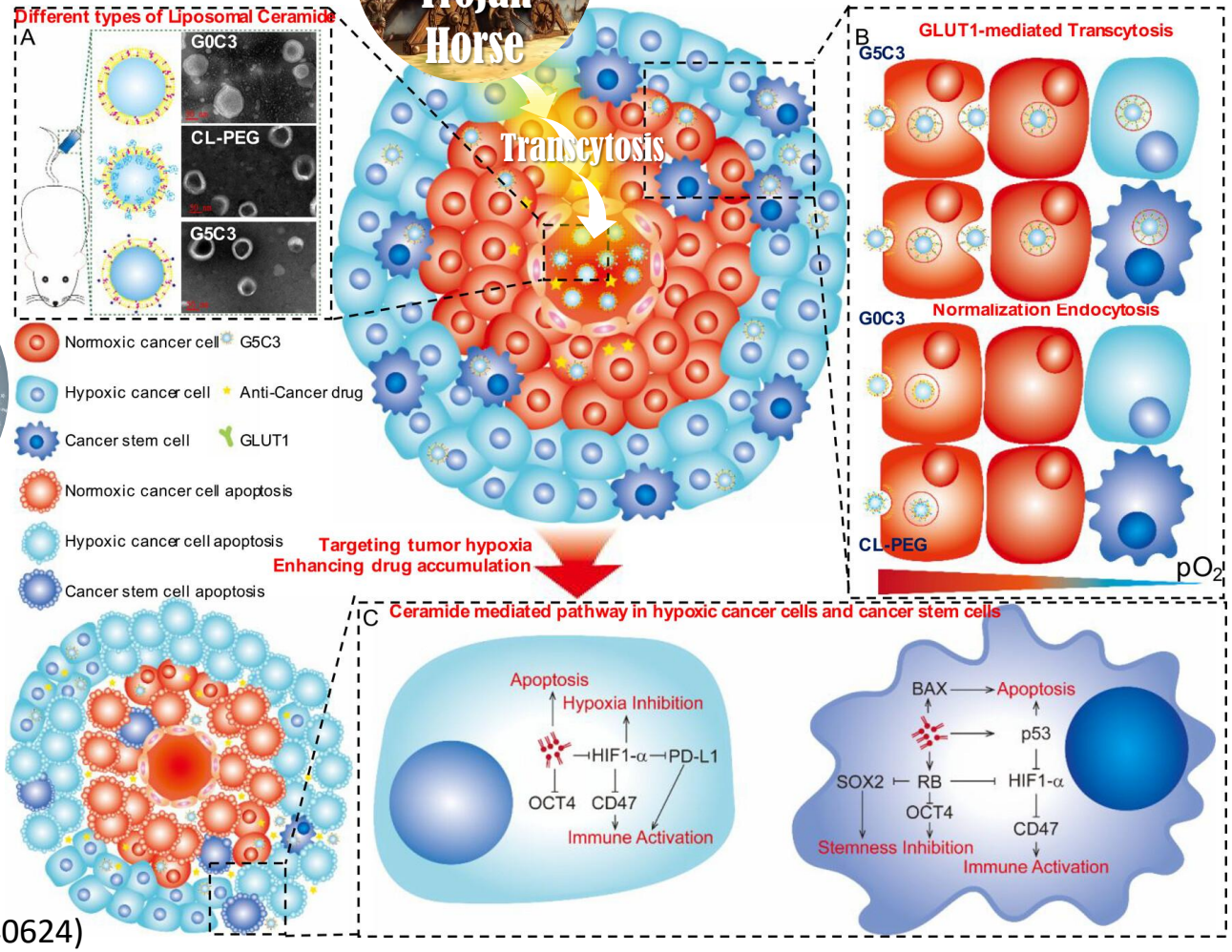
HIF-1α inhibition
Stemness inhibition

Hypoxic cancer cell



Normoxic cancer cell Cancer stem cell

Inducing cell apoptosis
Improving therapeutic efficacy


Patents: USA (US20220257514), Taiwan (TWI734987B), and China (CN113840624)

ACS Nano 2023, 17, 14, 13158–13175

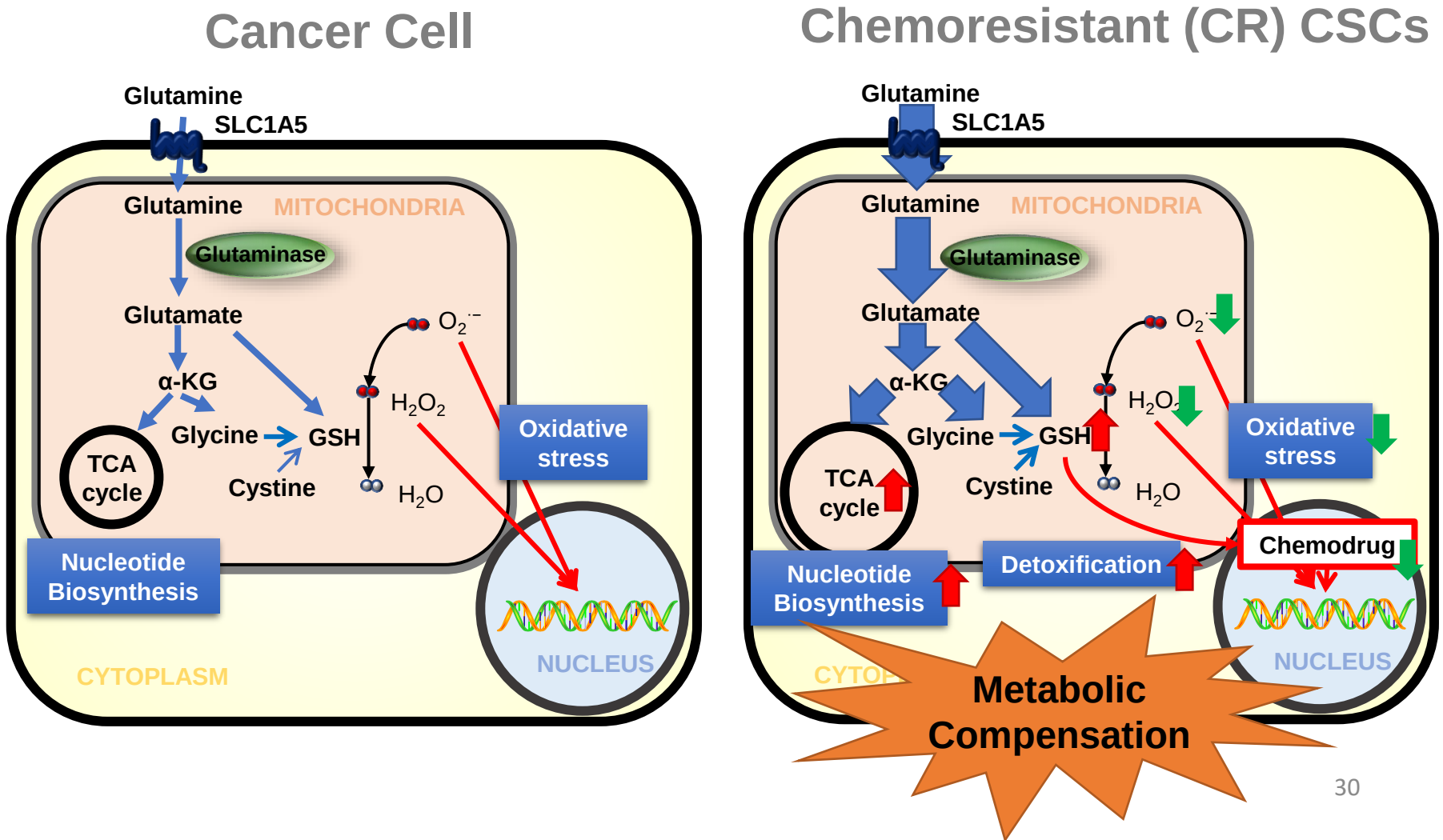
研究背景

# Metabolic Compensation

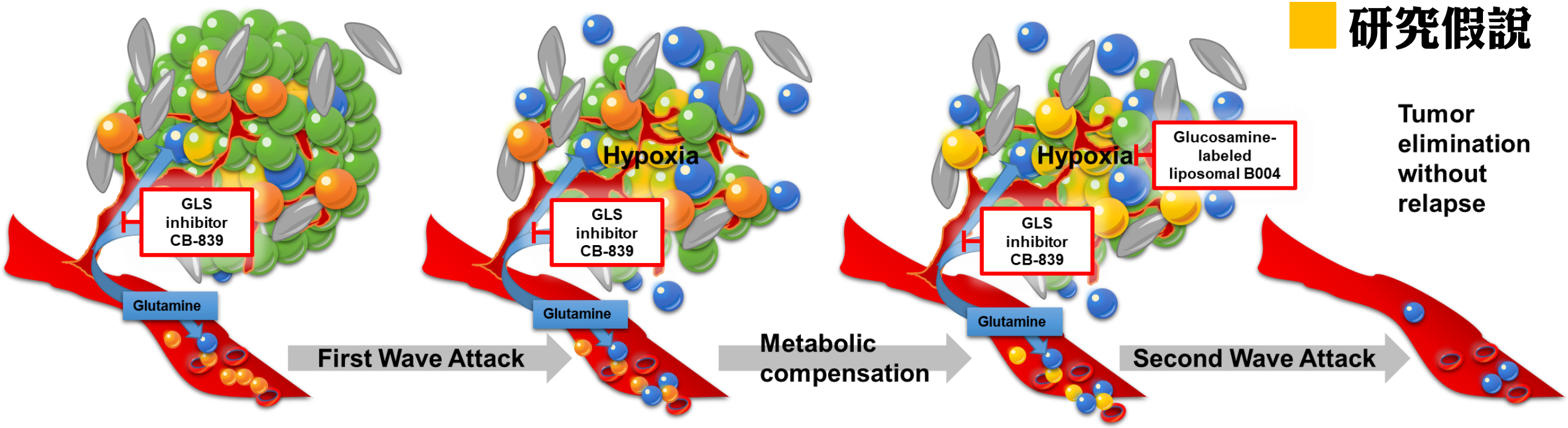
## Survival of the fittest

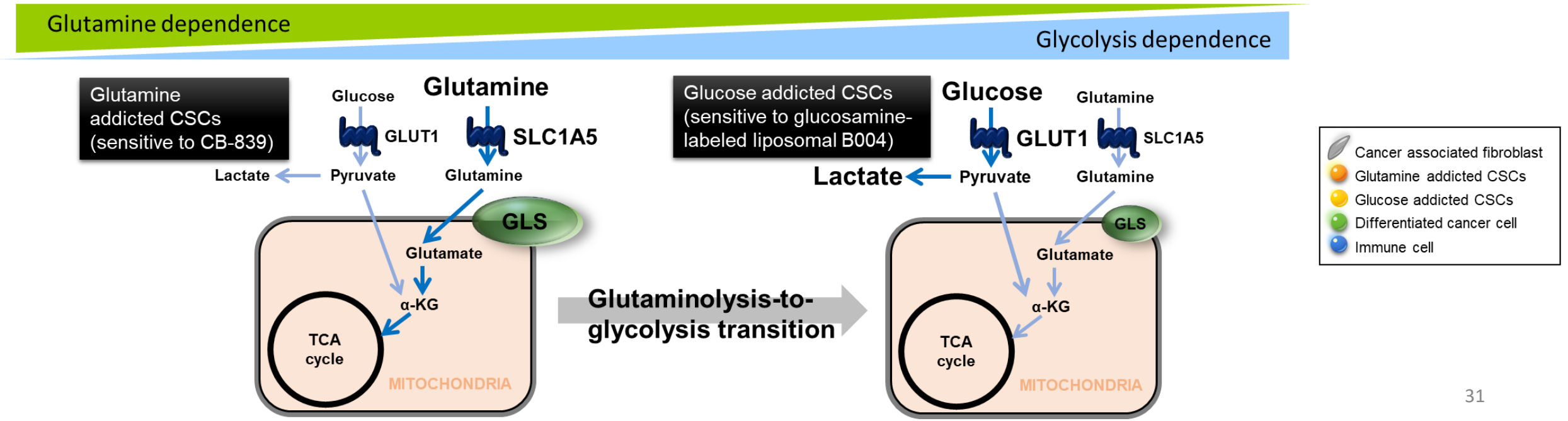
CANCER RESEARCH

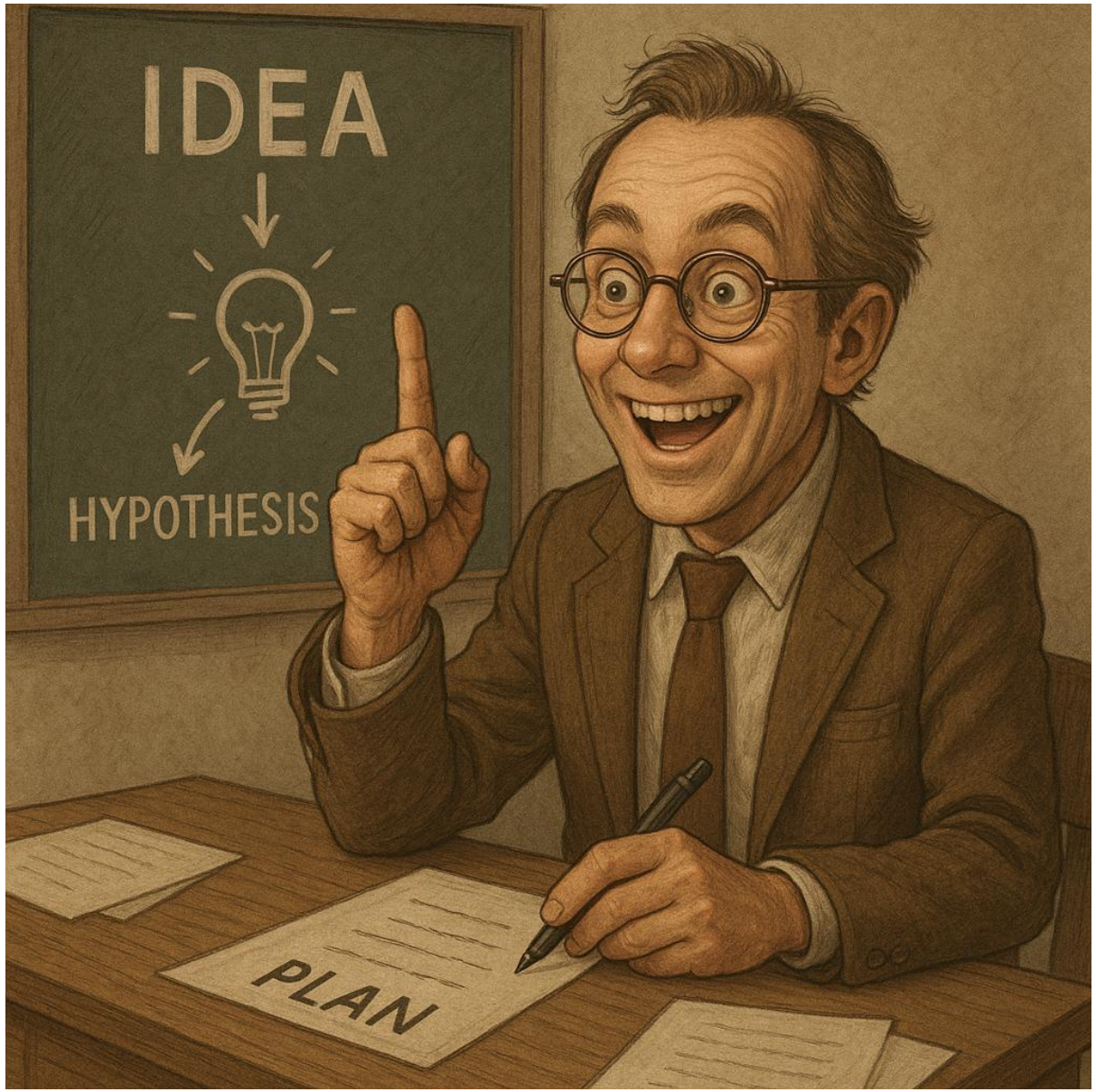
Shen et al. Cancer Res. 2020
Oct 15; 80(20): 4514–4526.



# 研究假說


GLS inhibitor CB-839
Glutamine
First Wave Attack
Hypoxia
GLS inhibitor CB-839
Glutamine
Metabolic compensation
Hypoxia
Glucosamine-labeled liposomal B004
GLS inhibitor CB-839
Glutamine
Second Wave Attack
Tumor elimination without relapse


Glutamine dependence
Glycolysis dependence
Glutamine addicted CSCs (sensitive to CB-839)
Glucose
Glutamine
GLUT1
SLC1A5
Lactate
Pyruvate
Glutamine
GLS
Glutamate
α-KG
TCA cycle
MITOCHONDRIA
Glutaminolysis-to-glycolysis transition
Glucose addicted CSCs (sensitive to glucosamine-labeled liposomal B004)
Glucose
Glutamine
GLUT1
SLC1A5
Lactate
Pyruvate
Glutamine
GLS
Glutamate
α-KG
TCA cycle
MITOCHONDRIA
Cancer associated fibroblast
Glutamine addicted CSCs
Glucose addicted CSCs
Differentiated cancer cell
Immune cell




**A real proposal needs:**

- **A pain point** worth **fighting**
- **A strategy** worth **trusting**
- **A battle plan** worth **funding**

**And then—**

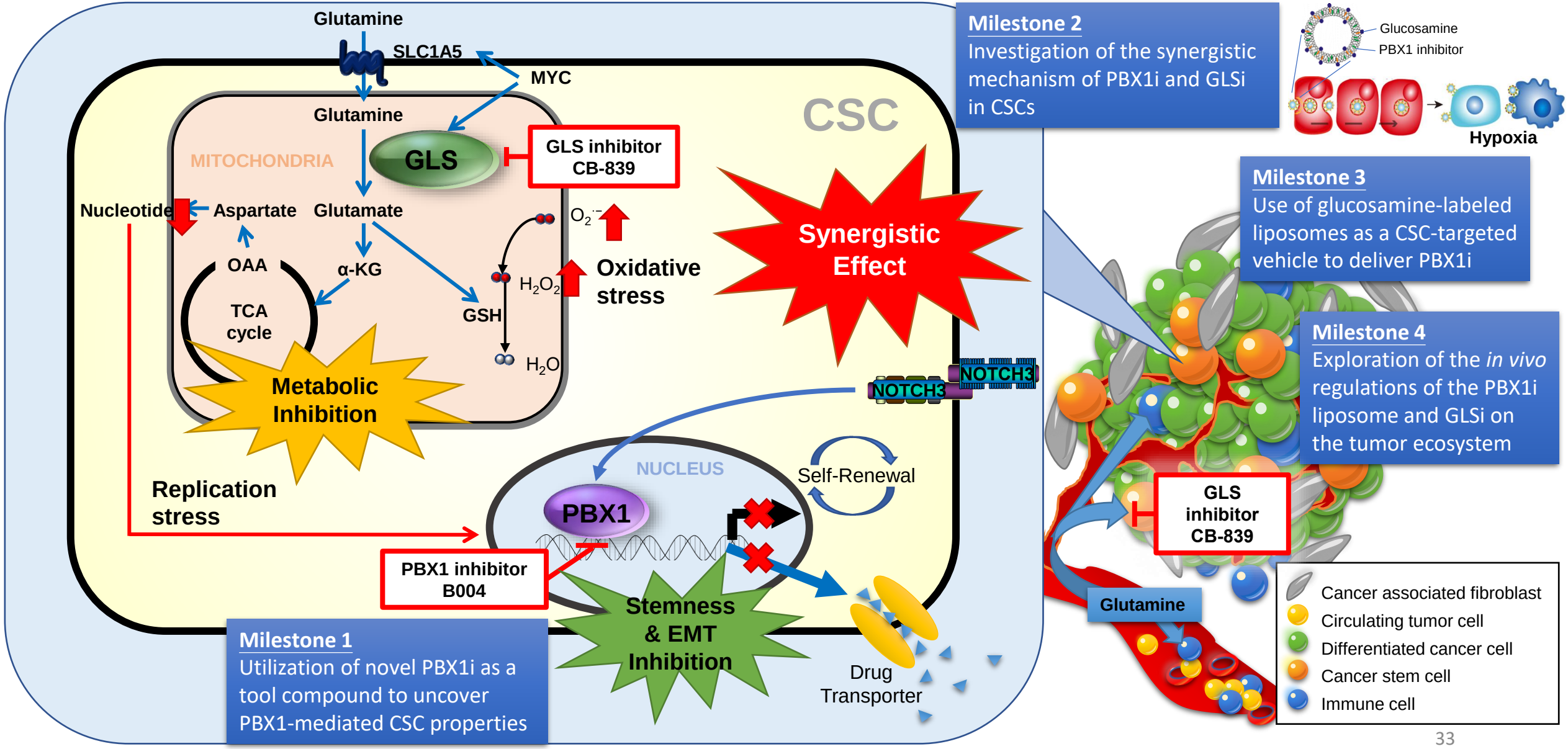
You grab your laptop like a warrior lifting a sword and say：

**“Let’s do this.**

Time To Write!!”

# 研究主軸

## Utilizing Glucosamine-Labeled Nanodrugs as a Novel Pancreatic CSC Therapy to Counteract Metabolic Compensation and Synergistically Inhibit Transcriptional Activity



# 摘要

**癌幹細胞**在腫瘤中只占0.01-2%，卻是**導致腫瘤抗性、復發及轉移的元凶**，我們因此在此計畫透過**功能性篩選擴增癌幹細胞之技術**建立不同類型之癌幹細胞，並發現其核內的**轉錄因子PBX1**及**粒線體麩醯胺酸酶(GLS)**為極具潛力的治療標的。許多**致癌轉錄因子**被認為是**難以製成藥物**，原因在於轉錄因子是透過與DNA結合而缺乏特定活性區可讓小分子藥物標靶，然而，我們所開發之**完全新創小分子**藥物能形成氫鍵穩定結合在PBX1蛋白的DNA結合位上，抑制PBX1與下游調控基因的啟動子結合，故抑制調控癌幹細胞特性之基因轉錄活性。另外，由於麩醯胺酸為血液中最豐沛的胺基酸，能被癌幹細胞大量攝取後以**麩醯胺酸代謝(glutaminolysis)對化療藥物產生抗性**，而GLS抑制劑可扭轉癌幹細胞的化療抗性。因此，我們將以**合成致死(synthetic lethality)的策略運用PBX1和GLS抑制劑雙重阻斷轉錄活性及麩醯胺酸代謝**，目前初步發現此兩種抑制劑在癌幹細胞中具有協同作用，在本計畫中將深入探討其機制及更精進其效果。由於癌幹細胞多位於腫瘤缺氧區，而缺氧區位於腫瘤深處因缺乏血管而難以將藥物送達，然而腫瘤缺氧會透過瓦氏效應(Warburg effect)高度表現葡萄糖輸送器1(GLUT1)，故我們將微脂體鑲嵌葡萄糖胺(glucosamine)，此**糖化奈米藥物可藉由癌細胞中GLUT1所調控的胞移作用(transcytosis)機制，有效地將PBX1抑制劑送達缺氧區**；此外，雖然GLS抑制劑可殺死高度仰賴麩醯胺酸的癌細胞及癌幹細胞，而殘存具有高度代謝可塑性的癌幹細胞仍可能會透過代謝代償(metabolic compensation)轉而使用糖解代謝而非麩醯胺酸代謝而逃脫GLS抑制劑；因此，在**給予GLS抑制劑時，我們將以糖化微脂體包裹PBX1抑制劑，引誘此類高度仰賴糖解且具有GLS抑制劑抗性的癌幹細胞**，攝取糖化奈米藥物並抑制其幹細胞特性相關基因之轉錄。本四年期計畫將從微觀至巨觀剖析研究，從**微觀3D腫瘤球模式**了解PBX1新藥對癌幹細胞特性及機制的調控、結合**代謝藥物及糖化奈米藥物**的協同作用機制探討，再**放大至動物活體單細胞核糖核酸定序及代謝體學之探究**，更深入了解此結合治療在**腫瘤與微環境之複雜生態系**的詳細調控機制，將可成為精準標靶癌幹細胞的新穎治療策略。

此領域背景（點出困境）

強化臨床痛點及商業痛點（痛到不行）

創新獨門秘技（痛點解方）

研究策略（新穎方法學）

# 國際年輕傑出學者計畫相關國際合作及學術表現

## 一、請簡述本計畫如何鏈結國際學術社群、建立國際研究團隊並促進臺灣與國外學術機構交流合作等（至多1頁）

申請人與美國約翰霍普金斯大學(Johns Hopkins University; JHU)的研究團隊維持長期夥伴關係，過去三年共帶領24位臺北醫學大學醫學生至約翰霍普金斯大學作暑期研習，除了學習最新的研究技術，也建立北醫和霍普金斯大學的研究交流機制，透過此合作平台，申請人持續將霍普金斯大學最新技術及研究經驗帶入北醫，霍普金斯的施教授和王教授也會定期蒞臨北醫講授最新研究進展，除了與北醫沈老師與藥學院劉景平院長合作之外，與病理科陳志榮教授、林修浩醫師、簡燕微醫師也有合作 Serous tubal intraepithelial carcinoma (STIC)的計畫，簡燕微醫師目前在施教授實驗室進行兩年 postdoc 的研究訓練；期許臺北醫學大學和約翰霍普金斯大學能透過學生、教職員及研究團隊間不斷交流，持續帶動北醫人才培育和跨國研究合作之能量。申請人除了平常與霍普金斯大學的視訊開會做研究討論，在暑期帶領醫學生前往研習的期間，申請人也會親自至霍普金斯的實驗室進行合作研究，主題包括：

1. 申請人與北醫藥學院劉景平院長、霍普金斯施教授和王教授合作開發新穎轉錄因子小分子抗癌藥物，轉錄因子過去被認為無法製成藥物，經由申請人與霍普金斯團隊持續合作下，成功開發一系列本計畫所提及的 PBX1轉錄因子抑制劑，能有效結合轉錄因子 DNA 結合位(DNA binding domain)與下游基因的啟動子(promoter)所調控之區域以阻斷其下游路徑。目前在北醫已經將第一代藥物 T417結構優化，第二代新藥 A409、B004有比 T417更強的腫瘤生長、轉移之抑制，及 PBX1下游基因表現之抑制，並在卵巢癌、肺癌、胰臟癌、大腸癌皆有相當優異的效果，正著手專利申請。
2. 抗藥性腫瘤細胞之代謝體(metabolomics)及代謝補償(metabolic compensation)分析技術，找尋抗藥性腫瘤的代謝標靶以結合化療藥物做組合治療(combination therapy)，這部分的研究除與 JHU 的施教授與王教授合作，亦與 JHU 的 Anne Le 教授進行合作，我們發現麩醯胺酸酶(GLS)為癌症代謝相當重要的標的，因此在本計畫詳細探討其機制。

在此四年計畫中，申請人欲進行 PBX1糖化奈米藥物的開發及麩醯胺酸酶(GLS)抑制劑的合併治療，將與約翰霍普金斯以下教授進行跨國合作：與 Jeff Wang 教授、Thomas Pisanic 教授合作探討奈米載體的技術精進及製程優化，並與 Daniele Gilkes 教授合作研究腫瘤缺氧區的 hypoxia memory 及 PBX1糖化奈米藥物在腫瘤缺氧區 Single-cell RNA sequencing 的機制探討，也將與 Sudipto Ganguly 教授研究 PBX1糖化奈米藥物與 GLS 抑制劑的合併治療對腫瘤免疫微環境之影響。除此之外，我們也將跟 James Berger 教授一同進行 x-ray crystallography 研究 PBX1藥物與 PBX1蛋白結合之結構，並在 JHU 的共儀進行 SPR、ITC、FA 等藥物和蛋白結合之穩定性分析；我們將與 Anne Le 教授合作體內和體外代謝體學分析，研究 PBX1糖化奈米藥物與 GLS 抑制劑的合併治療對腫瘤生態系之代謝體調控，尤其是腫瘤與免疫細胞之麩醯胺酸競爭效應。此外，由於 Stephanie Louise Gaillard 教授進行癌症藥物臨床試驗多年，我們將與她合作 PBX1糖化奈米藥物與 GLS 抑制劑臨床前試驗及未來臨床治療之規畫。

## 二、申請人(計畫主持人)過去國際學術交流、合作經驗及成果

申請人至今已與美國約翰霍普金斯大學、英國倫敦帝國學院 (Imperial College London)合作完成8篇國際文獻發表：Blood[1] (listed as 4th author), Cancer Research[2] (listed as 1st author), EbioMedicine[3] (listed as 3rd author), J Exp Clin Cancer Res[4] (listed as corresponding author), iScience[5] (listed as 1st author), Curr Opin Chem Biol.[6] (listed as 1st author), Genes Dis.[7] (listed as corresponding author), and Cell Reports[8] (listed as 13th author)；申請人藉國際合作，著重於轉譯醫學(translational medicine)的研究，戮力於將基礎研究從實驗室應用到病床邊(bench to bedside)，將研究重點主分為二大方向：1. 轉錄因子小分子抗癌藥物研發；2. 癌幹細胞及治療抗性癌細胞之代謝體(metabolomics)研究。

1. 轉錄因子小分子抗癌藥物研發：申請人與美國約翰霍普金斯大學Ie-Ming Shih教授、Tian-Li Wang教授和Stephanie Louise Gaillard教授合作癌症抗藥機制的研究，發現PBX1是NOTCH3下游重要調控轉錄因子，因此PBX1路徑可能是治療上的重要標的。然而，許多致癌轉錄因子如PBX1至今仍被認為是無法製成藥物(undruggable)，我們分析PBX1蛋白質結構與下游基因結合位(藥物可阻斷處)，成功開發了至今仍被認為無法製藥的完全新創(first-in-class)轉錄因子PBX1小分子抑制劑，能有效結合PBX1轉錄因子DNA結合位(DNA binding domain)與下游基因的啟動子(promoter)所調控之區域，以阻斷PBX1其下游路徑，因此抑制癌幹細胞特性及抗藥性運輸蛋白，有效逆轉化療抗性及癌幹細胞自我更新能力。目前在北醫已經將第一代藥物T417結構優化，衍生第二代A409、B004系列藥物，第二代藥物比T417具有更強的腫瘤生長與轉移之抑制，及PBX1下游基因表現之抑制效果，並在卵巢癌、肺癌、胰臟癌、肝癌、多發性骨髓瘤皆有相當優異的治療效果，正進行專利申請(PCT)。此研究陸續發表在Blood (T417應用在多發性骨髓瘤)和Cell新的子期刊iScience (T417應用在卵巢癌抗性腫瘤)。
2. 癌幹細胞及治療抗性癌細胞之代謝體研究：申請人與約翰霍普金斯大學的施教授、王教授、Anne Le教授進行合作，透過跨國雙邊合作，在北醫建置了癌幹細胞及抗性腫瘤細胞之代謝體及代謝補償(metabolic compensation)分析技術，找尋抗藥性腫瘤的代謝靶點以結合化療藥物做組合治療(combination therapy)，本成果發表於Cancer Research和Genes & Diseases。另外，由於腫瘤缺氧會透過瓦氏效應（Warburg effect）以葡萄糖輸送器1（GLUT1）的表現，我們與施教授、王教授探討腫瘤缺氧區的治療策略，並共同發表在J Exp Clin Cancer Res[4]，因此我們利用癌幹細胞中GLUT1所調控的胞移作用（Transcytosis）機制，開發了標靶腫瘤低氧區的奈米藥物。我們的實驗結果證實，可透過葡萄糖輸送器1有效地在腫瘤細胞之間運輸葡萄糖胺（Glucosamine）標記的神經醯胺（ceramide）微脂體，成功扭轉腫瘤缺氧之抗藥性問題，此研究發表於ACS Nano[9]。

**References**


1. Trasanidis N, Katsarou A, Ponnusamy K, et al. Systems medicine dissection of chr1q-amp reveals a novel PBX1-FOXM1 axis for targeted therapy in multiple myeloma. *Blood*. Jan 11 2022;doi:10.1182/blood.2021014391
2. Shen Y-A, Hong J, Asaka R, et al. Inhibition of the MYC-Regulated Glutaminase Metabolic Axis Is an Effective Synthetic Lethal Approach for Treating Chemoresistant Ovarian Cancers. *Cancer research*. 2020;80(20):4514-4526. doi:10.1158/0008-5472.Can-19-3971
3. Yu Y, Suryo Rahmanto Y, Shen YA, et al. Spleen tyrosine kinase activity regulates epidermal growth factor receptor signaling pathway in ovarian cancer. *EBioMedicine*. Sep 2019;47:184-194. doi:10.1016/j.ebiom.2019.08.055


**國合經驗**

羅列過去國際合作經驗，且合作關係是現在進行式

# 學術表現

不要客氣，必須說服委員有執行大計畫的能力


沈耀安

副教授

臺北醫學大學臨床醫學研究所
暨醫學系病理學科

博士後研究員 |
Johns Hopkins University


## 研究能力: 榮獲多項獎項及發表頂尖期刊

### 11項國際年輕科學家獎

- 美國、日本、韓國、新加坡、台灣等國際研討會年輕科學家獎
- 瑞典IAAM先進材料科學家獎章
- 獲選為Sigma Xi學會正式會員

**Blood** (血液學門第一名，IF: 25.476)

**ACS Nano** (IF: 18.027)

**Cancer Research** (IF: 13.312)

## 大型產學計畫經歷: 產出高商業價值專利

### 國科會科研創業計畫

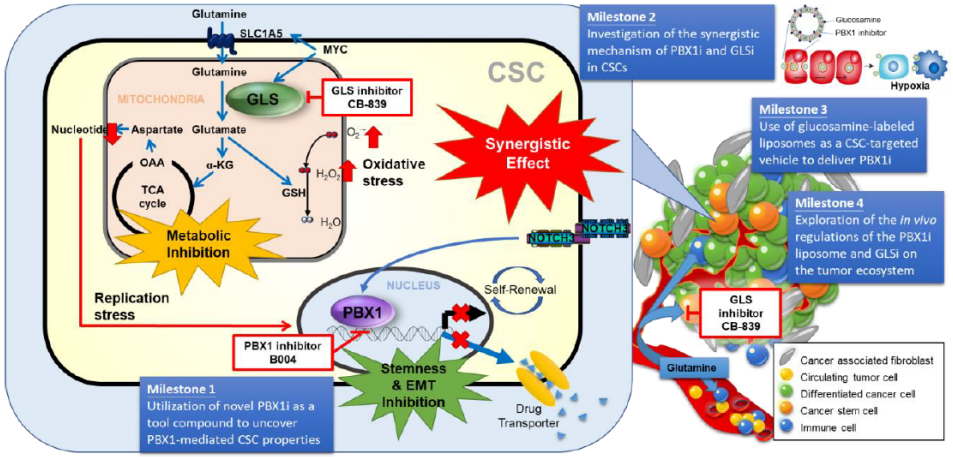
- 112年度國科會**萌芽計畫** – 癌幹細胞篩選技術平台暨細胞療法開發
- 113年度國科會**萌芽延續案** – 癌幹細胞篩選技術平台暨細胞療法開發之商業化應用

### 12項細胞療法及癌症新藥專利

- **單醣標記之奈米脂質體藥物**遞送系統，其製法及其作為藥物靶定遞送載體之應用 (美國、台灣、中國)
- **增強富含血小板血漿**及其製備方法與用途 (台灣與中國)
- **周邊血幹細胞**擴增方法 (台灣與中國)
- **循環腫瘤細胞**之擴增方法及其應用 (台灣與中國)
- **自然殺手細胞外泌體**在製備用於治療肝癌之藥物的用途 (台灣與中國)
- **恆定自然殺手T細胞**族群擴增方法及其應用 (台灣與中國)
- **細胞分選方法**、其在製備治療用製劑的應用以及挑選高細胞增殖能力的細胞的方法 (台灣與中國)
- **癌幹細胞之無血清專屬培養基，及其用於四階段篩選癌幹細胞株**的方法與分離的癌幹細胞株 (台灣、PCT)
- **可標靶癌幹細胞之樹突細胞及其與T細胞之結合體**、及其製備方法與用途 (台灣、PCT)
- COMPOUNDS TARGETING **PBX1 TRANSCRIPTIONAL COMPLEX** (U.S. Provisional)
- **金奈米蒲公英**增進百萬電子伏特光子及質子放射療效、及其製備方法與用途 (美國、台灣)
- **多功能細胞膜奈米囊泡**載藥平台及製備方法 (U.S. Provisional)

三、研究計畫內容（以中文或英文撰寫）：

（一） 研究計畫之背景。請詳述本研究計畫所要探討或解決的問題、研究原創性、重要性、預期影響性及國內外有關本計畫之研究情況、重要參考文獻之評述等。如為連續性計畫應說明上年度研究進度。

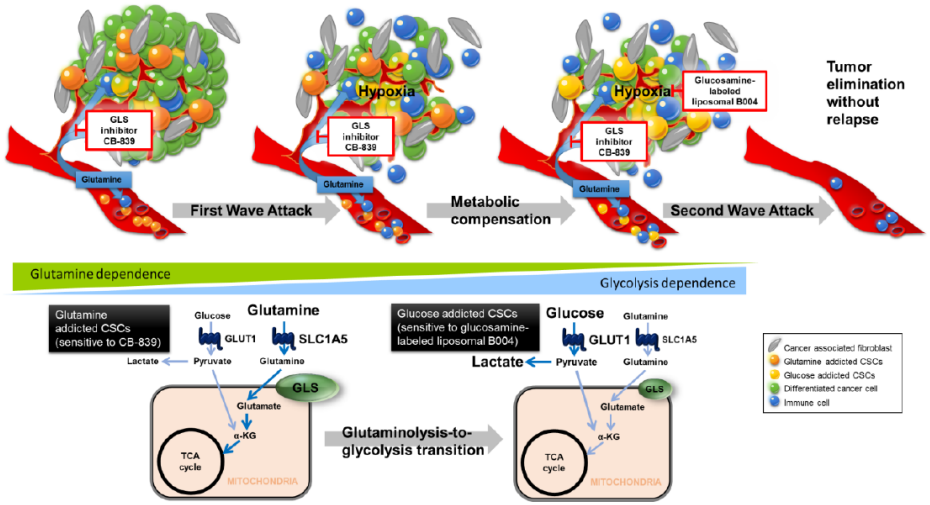



**SIGNIFICANCE AND SPECIFIC AIMS**

Given that cancer stem cell (CSC) is the quintessential driver of therapeutic resistance and metastasis, we strived to investigate the stemness pathway and discovered that PBX1, a stem cell reprogramming factor, plays a crucial role in mediating CSC properties[1]. PBX1, a homeodomain nuclear protein, heterodimerizes or homodimers with MEIS or HOX to form transcription factor complexes[2]. This protein binds to the consensus DNA motif 5'-ATCAATCAA-3' and functions within the complex by stimulating transcription[3]. In stem cells, PBX1 controls the self-renewal of hematopoietic stem cells[4]. In cancer, PBX1 expression is a prognostic biomarker in multiple myeloma, breast, ovarian, lung, and brain cancer[5,6]. PBX1 overexpression induces phenotypes characteristic of CSCs, such as an increase in resistance to platinum-based therapies[1]. Contrarily, PBX1$^{high}$ platinum-resistant cells were rendered more susceptible to platinum, and their stem-like characteristics diminished when PBX1 was silenced via RNA interference[1]. By impeding the interaction between PBX1 and HOX, a dominant negative PBX1 protein or HOX hexapeptide motif obstructs the growth of breast cancers and melanomas[7].

Oncogenic transcription factors have long been deemed "undruggable targets," primarily because they lack of defined small-molecule binding pockets[8]. Efforts have been undertaken to create pharmaceutical inhibitors that specifically target oncogenic transcription factors—such as PBX1, HIF, MYC, and β-Catenin – which regulate the expression of numerous genes and contribute to the advancement of tumors – but to date, none of these inhibitors have been developed into clinical practice[8]. However, in contrast to other transcription factors, we discovered that the DNA binding domains of PBX1 are relatively close to a particular location. We developed an array of small molecular PBX1 inhibitors (PBX1is) via *in silico* prediction; the lead compounds inhibit the interaction within PBX1 and downstream genes selectively and efficiently. Experiments utilizing biophysical techniques have validated the postulated mechanism of action of PBX1is, which entails the exact targeting of the DNA binding groove of the PBX1 protein[6,9]. The lead compound exhibited encouraging anti-tumor properties while causing minimal toxicity in seven different human tumor xenograft models[6,9]. The research for these models was undertaken at three distinct academic institutions – Imperial College London, Johns Hopkins University, and Taipei Medical University – and was published in the journals Blood and iScience[6,9]. PBX1i T417, A409, and B004 have the potential to develop into a groundbreaking class of innovative cancer therapeutics that target the oncogenic PBX1 signaling pathway. As a result, the mechanism of this first-of-its-kind PBX1i that overcomes the resistance of CSCs by targeting the PBX1 pathway is avidly anticipated to be elucidated in detail.

In terms of cancer metabolism, CSCs possess the capability to modify their metabolic processes in order to persist in perilous environments. We discovered that following chemotherapy treatment, CSCs might experience metabolic compensation by becoming more reliant on glutamine metabolism. These findings were published in Cancer Research[10], Curr Opin Chem Biol.[11], Genes Dis.[12], and Cell Reports[13]. CSCs, or resistant cells, exhibit increased expression of glutaminase (GLS) and rely primarily on glutamine to support anabolic growth dependent on the TCA cycle and to eliminate reactive oxygen species (ROS) through glutathione synthesis[10]. Cancer cells that manage to resist chemotherapy are typically more vulnerable to CB-839, an extremely potent small-molecule inhibitor of GLS (GLSi)[10]. CB-839 inhibits the synthesis of glutathione and nucleotides, resulting in concurrent redox imbalances and replication stresses[10]. Relieving glutamine from cancer cells, treatment with CB-839 can also transform active T-cells into highly activated cells[14]. By means of synthetic lethality, metabolic inhibition by GLSi may augment the effectiveness of stemness inhibition by PBX1i in a synergistic fashion.




CSCs typically appear in hypoxic environments with no blood vessels to transport drugs. As

# 計畫背景

- 善用卡通圖（委員可能只看這頁就決定是否要繼續往下看）
- 須點出：
  - 痛點
  - 原創性
  - 重要性

described in our prior publications in ACS Nano[15] and J Exp Clin Cancer Res[16], we developed glucosamine-labeled liposomes capable of facilitating drug delivery to the hypoxia region via GLUT1-mediated transcytosis, given that hypoxia tumor cells employ the Warburg effect to upregulate glucose transporter 1 (GLUT1). Although first waves of GLSi are effective at eliminating glutamine dependent cancer cells or CSCs, those that have managed to survive and exhibit considerable metabolic plasticity may utilize metabolic compensation to bypass the GLSi by switching from glutaminolysis to glycolysis. Glucosamine-labeled liposomes carrying PBX1is will be used in the context of the second wave of GLSi therapy to trick sugarholic CSCs with GLSi resistance to consume the liposomes, therefore reducing their transcription of genes associated with CSC characteristics. Throughout this 4-year endeavor, we intend to conduct micro-to-macroscopic investigations. To begin, we will use a microscopic 3D tumor spheroid model to learn how PBX1i regulates CSC traits and how metabolic drugs and glucosamine-labeled nanodrugs work together to regulate CSC features synergistically. By analyzing the single-cell transcriptome of the macroscopic tumor ecosystem, we will gain a deeper understanding of how drugs influence the interaction between the immune system and circulating tumor cells (CTCs). We have outlined a research endeavor spanning four years, which consists of the following four milestones:

1. Utilization of novel PBX1i as a tool compound to uncover PBX1-mediated CSC properties
2. Investigation of the synergistic mechanism of PBX1i and GLSi in CSCs
3. Use of glucosamine-labeled liposomes as a CSC-targeted vehicle to deliver PBX1i
4. Exploration of the *in vivo* regulations of the PBX1i liposome and GLSi on the tumor ecosystem

## PRELIMINARY RESULTS

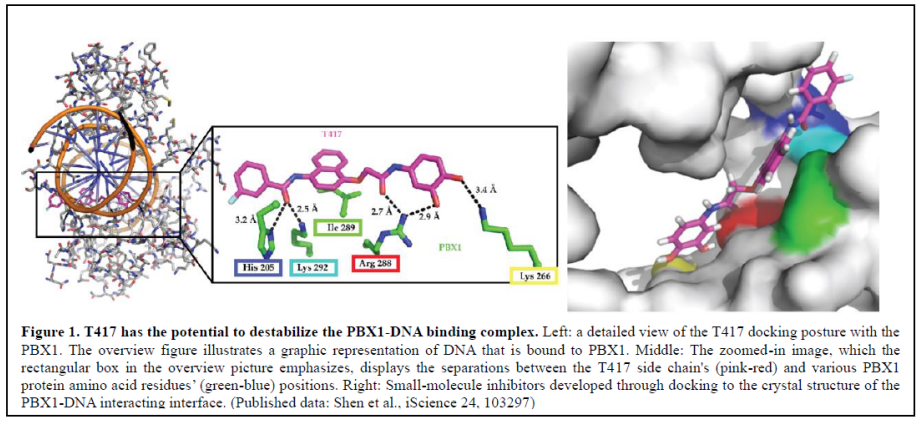



**Figure 1. T417 has the potential to destabilize the PBX1-DNA binding complex.** Left: a detailed view of the T417 docking posture with the PBX1. The overview figure illustrates a graphic representation of DNA that is bound to PBX1. Middle: The zoomed-in image, which the rectangular box in the overview picture emphasizes, displays the separations between the T417 side chain's (pink-red) and various PBX1 protein amino acid residues' (green-blue) positions. Right: Small-molecule inhibitors developed through docking to the crystal structure of the PBX1-DNA interacting interface. (Published data: Shen et al., iScience 24, 103297)

It was observed that ovarian cancer cells can be reprogrammed into a stem-like state through PBX1 overexpression, as evidenced by a greater proportion of the side population and the ALDH-high population[1]. Conversely, the properties of CSCs can be diminished by inhibiting PBX1[1]. Consequently, we formulate PBX1is as CSC-targeted therapies. Due to the fact that only a limited number of amino acid residues on the surface of the PBX1 protein are responsible for DNA

The preliminary results of this project yielded a total of 15 novel PBX1is. As illustrated in **Fig. 2A**, we preserved the hydrogen bonding sites with the PBX1 protein while modifying other regions of T417 to generate 3 derivatives. MPT1A409 exhibited enhanced cytotoxic effects and inhibited PBX1 signaling pathways (**Figs. 2B and 2C**). Subsequently, 12 additional derivatives were synthesized in accordance with the structure of MPT1A409. Among these, MPT1B004 exhibited the most effective anti-tumor characteristics and suppression of the PBX1 pathway (**Figs. 2D and 2E**). The luciferase reporter assay on the PBX1 downstream gene MEOX1 shows that, in contrast to T417, A409 and B004 exhibit a more pronounced suppression of PBX1 transcriptional activity (**Fig. 3A**). A synergistic effect has been noted when gemcitabine and B004 are administered concurrently to gemcitabine-resistant pancreatic cancer (**Fig. 3B**). B004, as illustrated in **Figs. 3C and 3D**, demonstrates a more conspicuous inhibitory impact on migration and invasion when compared to other inhibitors of PBX1. Spherogenesis is augmented in gemcitabine-resistant pancreatic cancer, which can be hampered by PBX1is (**Fig. 3E**). The gene set implicated in functions such as stemness, epithelial-mesenchymal transition (EMT), metastasis, proliferation, and immunological regulation, and which has been shown to be governed by the canonical PBX1 pathway, demonstrated a more pronounced level of inhibition in treatment groups A409 and B004 (**Fig. 3F**). The transcriptome analysis and CSC functional studies demonstrate that new generation of PBX1i A409 and B004 are capable of disrupting PBX1 transcriptional activity and dampening PBX1 downstream gene expression, thereby hindering the characteristics of CSCs.

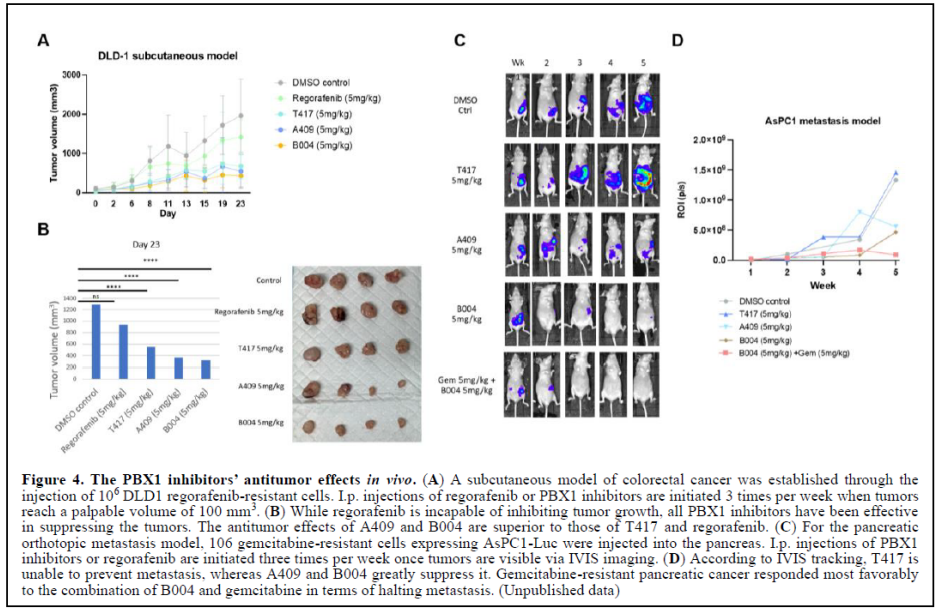



**Figure 4. The PBX1 inhibitors' antitumor effects *in vivo*.** (**A**) A subcutaneous model of colorectal cancer was established through the injection of $10^6$ DLD1 regorafenib-resistant cells. I.p. injections of regorafenib or PBX1 inhibitors are initiated 3 times per week when tumors reach a palpable volume of 100 $mm^3$. (**B**) While regorafenib is incapable of inhibiting tumor growth, all PBX1 inhibitors have been effective in suppressing the tumors. The antitumor effects of A409 and B004 are superior to those of T417 and regorafenib. (**C**) For the pancreatic orthotopic metastasis model, 106 gemcitabine-resistant cells expressing AsPC1-Luc were injected into the pancreas. I.p. injections of PBX1 inhibitors or regorafenib are initiated three times per week once tumors are visible via IVIS imaging. (**D**) According to IVIS tracking, T417 is unable to prevent metastasis, whereas A409 and B004 greatly suppress it. Gemcitabine-resistant pancreatic cancer responded most favorably to the combination of B004 and gemcitabine in terms of halting metastasis. (Unpublished data)

In the colorectal cancer subcutaneous model, $10^6$ regorafenib-resistant DLD1 cells were

# 初步數據

數據不用多，但關鍵數據能支撐每個里程碑（多年期每個里程碑都需要有支持數據，並非只支撐第一年里程碑）

# 研究方法

**Milestone 1: Utilization of novel PBX1i as a tool compound to uncover PBX1-mediated CSC properties**

- Establishment of CSCs to scrutinize the changes in CSC properties caused by PBX1 inhibitors
- Understanding PBX1i-induced single-cell transcriptome changes in the tumor microenvironment
- Dissecting the roles of PBX1-mediated signaling in regulating CSC properties

**Milestone 2: Investigation of the synergistic mechanism of PBX1i and GLSi in CSCs**

- Examination of alteration of metabolism upon single treatment with a PBX1 inhibitor
- Examination of stemness signaling upon single treatment with a GLS inhibitor
- Evaluation of the effects of synchronous and asynchronous treatment of PBX1i and GLSi in 3D models

**Milestone 3: Use of glucosamine-labeled liposomes as a CSC-targeted vehicle to deliver PBX1i**

- Examination of transcytosis of glucosamine-labeled liposomes in 3D models
- Assessment of the CSC properties upon treatment of glucosamine-labeled liposomes
- Understanding metabolic compensation caused by GLSi and its impact on glucosamine-labeled liposomes

**Milestone 4: Exploration of the *in vivo* regulations of the PBX1i liposome and GLSi on the tumor ecosystem**

- Validation of the *in vivo* antitumor effect and toxicity of PBX1i liposome and GLSi
- Single-cell transcriptomic profiling of *in vivo* tumors, circulating tumor cells, and immune cells
- Investigation of *in vivo* metabolomic regulations of PBX1i liposome and GLSi

## First Year

### Milestone 1: Utilization of novel PBX1i as a tool compound to uncover PBX1-mediated CSC properties

Our innovative PBX1i targets CSCs, therapeutically resistant cancer, and other human malignancies associated with PBX1. This novel class of small-molecule compounds targets PBX1, a homeodomain transcription factor and proto-oncogene that is upregulated genetically and epigenetically to promote carcinogenesis[18]. One or two of the most promising PBX1is, such as B004, will be chosen on the basis of their ability to inhibit PBX1 downstream targets and CSC properties. We will further dissect the effects of novel PBX1i on the tumor microenvironment through single-cell transcriptomics profiling. To elucidate the CSC properties mediated by PBX1, we propose the following interrelated milestones (**1a–1c**).

***1a. Establishment of CSCs to scrutinize the changes in CSC properties caused by PBX1 inhibitors***

Because PBX1 regulates stemness, EMT, and drug resistance[1], we will investigate whether the PBX1i can inhibit CSC features such as tumorgenicity, spherogenesis, drug resistance, and metastatic potential. To verify this hypothesis, we will isolate pancreatic tumorigenic (TCSCs), metastatic (MCSCs), radioresistant (RR), and chemoresistant (CR) CSCs using our quadruple functional selection approach (PCT/US23/31857).

(1) *CSC percentage analysis*: By employing either a flow cytometer or an ELISA reader, the quantity of eGFP fluorescence is quantified in the OCT4-GFP reporter assay. This value is proportional to the amount of OCT4-GFP activity (i.e., CSC percentage) in the cell population.

(2) *TOF-SIMS analysis*: To determine whether PBX1i can penetrate the nucleus and target the PBX1 transcription factor, a nuclear localization assay will be performed. Utilizing time-of-flight secondary-ion mass spectrometry (TOF-SIMS), the nuclear accumulation of PBX1i will be quantified. TOF-SIMS possesses the capacity to generate illustrative images of affected by B004, gene set enrichment analysis will be performed. Furthermore, a comparison will be made between the B004 transcriptomes and gene sets accessible through the Molecular Signature Database (Broad Institute), which comprise the embryonic stem (ES) cell signature, PBX1 target set, and stem cell factors such as NANOG, OCT4, SOX2, and MYC. The evaluation of this group of PBX1 target genes, as well as a number of stemness and EMT factors, in the transcriptomes under B004 regulation will provide additional proof that B004 inhibits the PBX1-mediated CSC transcriptional activity. We will then validate the pathways through chromatin immunoprecipitation (ChIP), qPCR, and Western blots. The rescue assay will be performed to ascertain the contribution of each PBX1-mediated signaling in orchestrating CSC properties as assessed in **Milestone 1a**.

**Pilot Study:** It was observed that pancreatic CSCs upon gemcitabine treatment upregulate stemness transcription factors (OCT4, NANOG, and BMI1), mesenchymal marker vimentin (VIM), EMT transcription factors (TWIST, SNAIL, ZEB1), and glutaminolysis-related genes (MYC, GLS, ME2) (**Fig. 7**). Conversely, the epithelial marker E-CAD was downregulated in response to gemcitabine treatment (**Fig. 7**). We will continue to employ PBX1i B004 as a tool compound to uncover PBX1-mediated CSC properties.

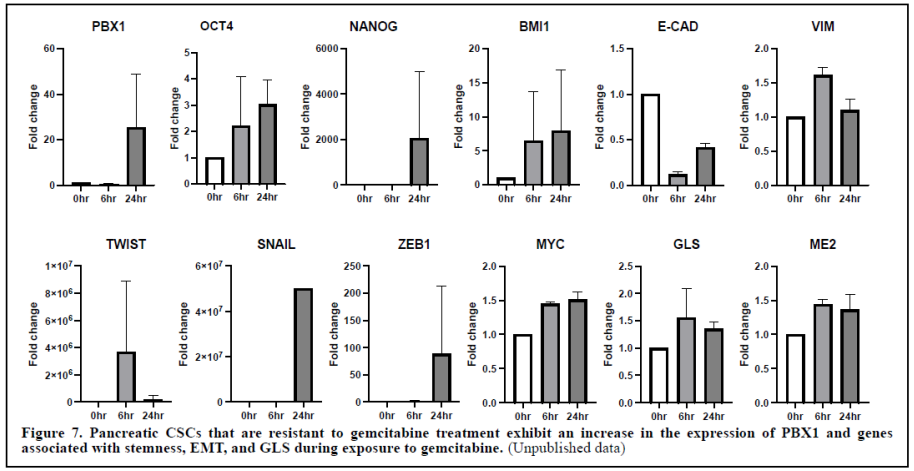



**Figure 7. Pancreatic CSCs that are resistant to gemcitabine treatment exhibit an increase in the expression of PBX1 and genes associated with stemness, EMT, and GLS during exposure to gemcitabine.** (Unpublished data)

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先導試驗
（呈現計畫可行性）

## Second Year

### Milestone 2: Investigation of the synergistic mechanism of PBX1i and GLSi in CSCs

In order to comprehend the synergistic effect of PBX1 and GLS inhibitors, as depicted in **Fig. 6C**, we will initially analyze their respective functions in the context of single-drug and combination therapies pertaining to the regulation of stemness and metabolism. The objective of this milestone is to ascertain whether the synergistic effects of these two medications are facilitated by a shared pathway or whether they operate independently through their own mechanisms.

***2a. Examination of alteration of metabolism upon single treatment with a PBX1 inhibitor***

PBX1 knockdown has been demonstrated to alter numerous genes implicated in cancer metabolism, according to our findings[3]. We are intrigued by the potential impact of PBX1i on

# 研究方法

By pursuing **Milestone 3a** and **3b**, it is possible to identify new regulatory mechanisms for PBXi and GLSi and determine whether they operate independently or through a shared mechanism in the stemness and metabolism pathway. If they share pathways in the regulation of stemness and metabolism, we will treat the CSCs with both drugs in order to compare the synergistic or additive effects in these pathways to single-drug therapy. If these two medications operate on distinct pathways in an independent manner, we shall utilize a rescue assay to investigate the role of these distinct pathways in coordinating the properties of CSCs. During drug treatment, the rescue assay entails the overexpression of downstream genes involved in PBX1 signaling, including STAT3, MEOX1, or NANOG[1], or the reintroduction of downstream metabolites of glutamine metabolism, such as α-KG[10].

**Pilot Study:** We construct a 3D spheroid model that simulates *in vitro* tumor growth to analyze the drug response and gain insight into the synergistic mechanism of PBX1i and GLSi in CSCs. A recurrence of gemcitabine-resistant CSCs was identified in this model, and concurrent treatment with B004 can prevent this recurrence (**Fig. 8**).

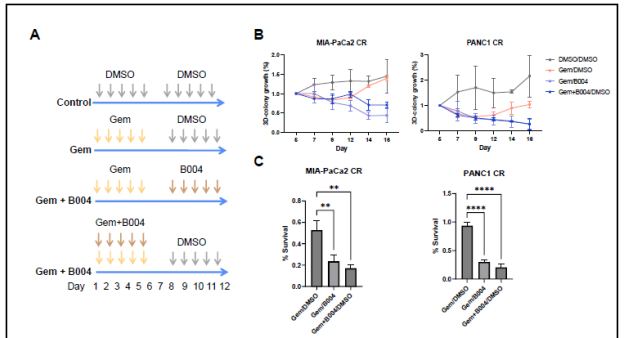



**Figure 8. Drug response in a 3D spheroid model.** After gemcitabine withdrawal, a recurrence was observed in pancreatic gemcitabine-resistant CSCs; this recurrence can be prevented by concurrent treatment with B004. (Unpublished data)

## Third Year

### Milestone 3: Use of glucosamine-labeled liposomes as a CSC-targeted vehicle to deliver PBX1i

***3a. Examination of transcytosis of glucosamine-labeled liposomes in 3D models***

It is challenging to administer drugs to tumor cells located in hypoxic regions due to the absence of blood vessels. The hypoxia tumor is resistant to chemotherapy, radiotherapy, and immunotherapy and exhibits stemness[19-22]. We established a tumor hypoxia-targeting nanomedicine by demonstrating that GLUT1-mediated transcytosis is possible in cancer cells, given that the Warburg effect induces cancer cells to upregulate the expression of GLUT1[15]. Our findings indicate that glucosamine-labeled liposomal ceramide nanomedicines, as opposed to PEG-modified nanomedicines, can be transcytosed from one cancer cell to another via GLUT1-mediated transport. Subsequently, these nanomedicines accumulate extensively in the hypoxic core of *in vitro* CSC spheroids and *in vivo* tumor xenografts[15].

In order to generate glucosamine-labeled liposomal PBX1i, a lipid thin film will be generated at room temperature through the rotary evaporation of DCM as described previously[15]. Following the addition of phosphate-buffered saline (PBS) to rehydrate the thin film, a 6-minute sonication was performed on the solution. A PVDF filter with a pore size of 0.1μm will be utilized to extrude peripheral blood. We will then use the MiCareo imaging system to track the glutamine flux across different peripheral blood cell subpopulations.

***4c. Investigation of in vivo metabolomic regulations of PBX1i liposome and GLSi***

To conduct an *in vivo* metabolomics study, tumors and immune cells were rapidly frozen using liquid nitrogen for subsequent extraction and analysis of metabolites. After homogenizing the tumors in an 80/20% methanol/water mixture, they will be centrifuged for 10 minutes at 14,000 g. The resultant supernatant was transferred to a fresh tube. The pellet will undergo a second extraction cycle in which it will be suspended in an 80/20% methanol/water mixture and centrifuged at 14,000 g for 10 minutes. The supernatant samples will undergo a drying process at a temperature of 37°C for a duration of 60 minutes using a Speed Vac® system. Subsequently, they will be subjected to lyophilization and kept at a temperature of -80°C for LC/MS analysis. The Metabolomics Core Facility at Taipei Medical University will utilize the Agilent 6470 LC-MS/MS technology to collect metabolomics data from samples. We will utilize our own compound standard databases to identify metabolites based on their retention times. Subsequently, we will employ MS/MS fragmentation data to verify the identity of these metabolites. In order to analyze the metabolic content of each sample, we will utilize the Agilent MassHunter, Agilent Mass Profiler Professional (MPP), and Agilent Qualitative and Quantitative Analysis Software programs. The concentration of proteins was used to normalize the peak intensities of metabolites.

**Pilot Study:** As the zebrafish model provides a rapid, reliable, and cost-effective approach for assessing the metastatic potential of CSCs, we analyze the metastatic pattern using PBX1is or gemcitabine. In line with prior findings that gemcitabine boosted EMT genes (**Fig. 7**), gemcitabine caused proximal metastasis to the head and distant metastasis to the tail, as well as reduced survival rates (**Fig. 10**). Conversely, A409 and B004 increase survival rates and substantially prevent metastasis (**Fig. 10**). This model will be utilized to pre-evaluate the combination dosage and

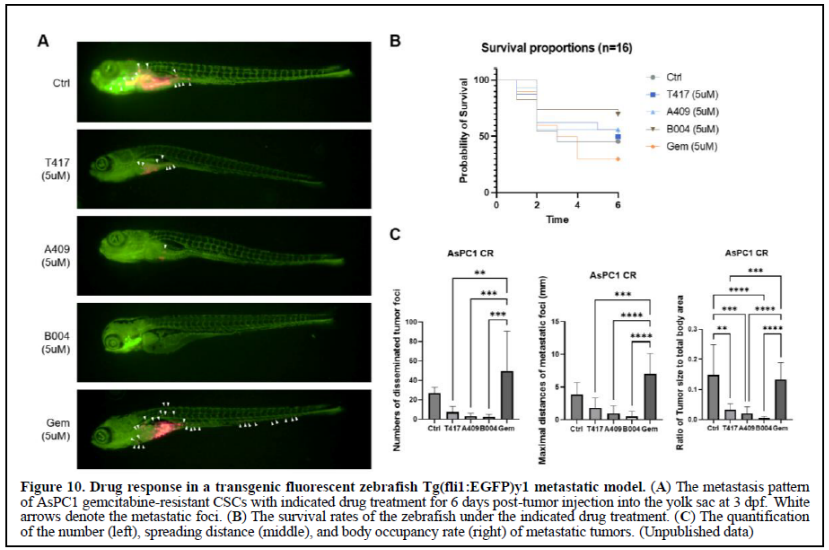



**Figure 10. Drug response in a transgenic fluorescent zebrafish Tg(fli1:EGFP)y1 metastatic model. (A)** The metastasis pattern of AsPC1 gemcitabine-resistant CSCs with indicated drug treatment for 6 days post-tumor injection into the yolk sac at 3 dpf. White arrows denote the metastatic foci. (B) The survival rates of the zebrafish under the indicated drug treatment. (C) The quantification of the number (left), spreading distance (middle), and body occupancy rate (right) of metastatic tumors. (Unpublished data)

★★★★★

第一年到第四年
**都有先導試驗證實可行性**（萬事俱備只欠東風）

# 困難解決

提出有對策解決的問題，勿提無解的困境（委員通常是看這頁寫Critique）

2. 預計可能遭遇之困難及解決途徑:

(1) ***Competition:*** Research indicates that our PBX1is, T417, A409, and B004, are unparalleled in comparison to other drugs. The most similar rival technique aims to manipulate the interaction between the PBX1-HOX heterodimer proteins. Using a computer-guided structural design technique, the competing strategy comprised docking 1,4-disubstituted naphthalenes to the binding pocket between the PBX-HOX protein-protein interaction interface[17], rather than the PBX1-DNA interaction interface where our drugs are deposited. A different research team has created peptide-based substances that operate as antagonists, imitating a particular HOX hexapeptide. These substances have the ability to compete with other homeobox proteins, such as PBX1[27], for interaction. However, because of their inadequate cellular penetration, potency, and solubility, the chemicals or peptides resulting from these methods can only be used *in vitro*[27,28], which leads to extremely disappointing outcomes. This is to be expected, given that protein-protein complexes frequently traverse numerous sites on each protein and involve substantial interfaces. Our new PBX1i analog exhibits superior solubility and anti-tumor potency compared to small-molecule-based agents and previously developed peptide-based PBX1i agents. As a result, we anticipate minimal commercial risk associated with competition from these agents. While ovarian, pancreatic, colon cancer, and multiple-myeloma therapies targeting alternative novel biomarkers may not be marketed as direct competitors to T417, A409, and B004, they are more likely to be utilized in combination therapy.

競爭者分析
（雖有競爭對手，
但不是我們的對手）

(2) ***Technical risks*:** Technical risks consist of formulation complications and unanticipated toxicity. In the event that the current PBX1i is required to be replaced, backup lead compounds such as PBX1i derivatives (produced in **Milestone 1**) are available for development.

技術瓶頸
（要是先導藥物行不通，
我們有一堆候選藥物）

3. 重要儀器之配合使用情形:

Taipei Medical University will provide the instruments below: Flow cytometry, HPLC, NMR, Seahorse XF Analyzers, Time-of-flight secondary-ion mass spectrometry (TOF-SIMS), Q-TOF mass spectrometer, Laser Confocal Microscope, TissueFAXS, 10x Genomics' single-cell RNA-seq (scRNA-seq); MiCareo Taiwan Co., Ltd: MiCareo Rare Cell Diagnostics (isolation of CTCs and immune cells from peripheral bloods)

頂尖設備秀Muscle
（工欲善其事，必先利其器，
北醫好棒棒!!）

4. 如為須赴國外或大陸地區研究，請詳述其必要性以及預期效益等:

My laboratory has established long-term collaborations with the following Johns Hopkins University (JHU) professors: Ie-Ming Shih, Tian-Li Wang, Stephanie Louise Gaillard, and Anne Le. I published 8 papers on Blood[6] (listed as 4th author), Cancer Research[10] (listed as 1st author), EbioMedicine[29] (listed as 3rd author), J Exp Clin Cancer Res[16] (listed as corresponding author), iScience[9] (listed as 1st author), Curr Opin Chem Biol.[11] (listed as 1st author), Genes Dis.[12] (listed as corresponding author), and Cell Reports[13] (listed as 13th author) with these JHU faculties. Furthermore, we engage in a collaborative effort with the research team at Imperial College London regarding the investigation of our PBX1i, which was recently published in Blood[6]. Our collaborative efforts persist in the pursuit of creating innovative small-molecule cancer therapeutics and combination treatment approaches. To extend global connections, we will begin collaborating with other Johns Hopkins University professors in the following disciplines: (1) Bioengineering – Professors Jeff Wang and Thomas Pisanic. (2) Hypoxia/Cancer metastasis – Professor Daniele Gilkes. (3) Cancer immunology – Professor Sudipto Ganguly.

In order to stay up-to-date with the latest technological developments, our research team will annually visit JHU to learn about the latest techniques and strategies for drug development and commercialization. It is vital for our research team to not only keep up with new technology but also to assess whether resources or collaborators will likely be accessible and supportable in the future.

(1) In the first year, our research team will travel to JHU to perform the Surface Plasmon Resonance (SPR) technology, which will be used to investigate the effect of each PBX1 mutation on PBXi binding. We will use biophysical and biochemical experiments to assess the interaction between PBX1i and PBX1. All of these approaches are utilized to validate and measure the binding of our drugs to the protein PBX1. Through our time at JHU, we will also acquire knowledge of the ITC and FA techniques.

(2) In the second year, we will use x-ray crystallography to identify the entire protein structure of PBX1 as well as the complex of PBX1-B004 variants. Dr. James Berger of Johns Hopkins University will teach us about x-ray crystallography. Dr. Berger specializes in x-ray crystallography, particularly with small molecules that bind to proteins.

(3) In the third year, we will learn how to do *in vitro* and *in vivo* metabolomics analyses to identify the effects of B004 on metabolism. Dr. Le's investigations using metabolomics technology resulted in ground-breaking discoveries showing various characteristics of cancer metabolism. Following the implementation of this innovative treatment, her team took additional steps to investigate the metabolic pathways in the drug-resistant tumor and determine which drugs would be most effective for combination synergistic therapy.

(4) Last year, we will visit Dr. Stephanie Louise Gaillard at Johns Hopkins University to learn about trial design for future clinical studies of PBX1i. Dr. Gaillard's research is focused on the design of clinical trials to improve results by adding promising novel biologic, targeted, and immunological drugs to current therapy regimens. We will visit FastForward at Johns Hopkins Technology Ventures to discuss the possible commercialization of PBX1i. In order to help businesses progress and bring their innovative inventions to market, FastForward may offer them financial assistance, mentorship, support services, cost-effective space, and education.

# ~~旅遊規劃~~出國規劃

## 移地研究及研討會規劃必須契合

## 每年研究方向 → 出國尋找資源 + 跨國合作

**十一、國外差旅費-執行國際合作與移地研究：**

(一) 計畫主持人及參與研究計畫之相關人員因計畫需要必須與國外合作研究、從事實驗、田野調查、採集樣本或使用國外研究設施等移地研究得申請本項經費。
(二) 請詳述預定各出國人員之出國行程、預估經費、天數及地點。部份「雙邊協議專案型國際合作計畫」經雙方協議議定由共同合作之國外計畫下負擔我方研究人員到訪之生活費者，不得於本表重覆編列。
(三) 生活費、機票費及其他費用之標準，請依照行政院頒布之「中央各機關（含事業機構）派赴國外進修、研究、實習人員補助項目及數額表」規定填列（網址 http://law.dgbas.gov.tw/LawContent.aspx?id=FL020312）。
(四) 請將所列各項費用換算為新臺幣，並註明估算匯率。
(五) 請分年列述。

第 1 年　　金額單位：新臺幣元

| 申請補助費用 | | |
|---|---|---|
| 經費類別 | 預估經費 | 詳述預定各出國人員之出國行程、預估經費、天數及地點 |
| 赴國外 | 100,000 | Our research team will travel to JHU to perform the Surface Plasmon Resonance (SPR) technology, which will be used to investigate the effect of each PBX1 mutation on PBXi binding. We will use biophysical and biochemical experiments to assess the interaction between PBX1i and PBX1. All of these approaches are utilized to validate and measure the binding of our drugs to the protein PBX1. Through our time at JHU, we will also acquire knowledge of the ITC and FA techniques. The estimated duration of a stay at JHU is one month. |
| 合　計 | 100,000 | |

第 2 年　　金額單位：新臺幣元

| 申請補助費用 | | |
|---|---|---|
| 經費類別 | 預估經費 | 詳述預定各出國人員之出國行程、預估經費、天數及地點 |
| 赴國外 | 100,000 | We will use x-ray crystallography to identify the entire protein structure of PBX1 as well as the complex of PBX1-B004 variants. Dr. James Berger of Johns Hopkins University will teach us about x-ray crystallography. Dr. Berger specializes in x-ray crystallography, particularly with small molecules that bind to proteins. The estimated duration of a stay at JHU is one month. |
| 合　計 | 100,000 | |

第 3 年　　金額單位：新臺幣元

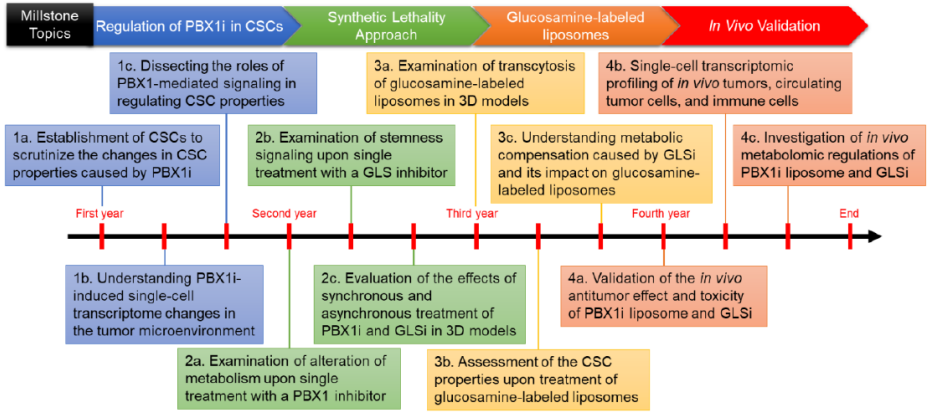
| 申請補助費用 | | |
|---|---|---|
| 經費類別 | 預估經費 | 詳述預定各出國人員之出國行程、預估經費、天數及地點 |
| 赴國外 | 100,000 | We will learn how to do in vitro and in vivo |

**十二、國外差旅費-出席國際學術會議：**

(一) 計畫主持人及參與研究計畫之相關人員參加國際學術會議得申請本項經費。
(二) 請詳述預定參加國際學術會議之性質、預估經費、天數及地點。
(三) 機票費、生活費及其他費用之標準，請依照行政院頒布之「國外出差旅費報支要點」規定填列（網址https://law.dgbas.gov.tw/LawContent.aspx?id=FL017584）。
(四) 請詳述計畫主持人近三年參加國外舉辦之國際學術會議論文之發表情形。（包括會議名稱、時間、地點、發表之論文題目、補助機構，及後續收錄於期刊或專書之名稱、卷號、頁數、出版日期）
(五) 請分年列述。

第 1 年　　金額單位：新臺幣元

| 出席國際學術會議 | | | |
|---|---|---|---|
| 出席國際學術會議人數 | 共 2 名 | 金　額 | 160,000 |
| 費用說明 | 1. 會議名稱：AACR Annual Meeting 2025<br>2. 會議時間：April 25-30, 2025<br>3. 會議地點：McCormick Place Convention Center, Chicago, Illinois, USA<br>4. 會議性質：AACR covers the latest discoveries across the spectrum of cancer research from population science, prevention, cancer biology, translational, and clinical studies from institutions all over the world.<br>5. 出國行程：共同主持人和博士後研究員將一同參展及洽談可能合作之學業界單位<br>6. 預估經費：80,000/人<br>7. 天數：14天(會後將拜訪當地藥廠或其他潛在合作單位)<br>8. 地點：Chicago, Illinois, USA | | |
| 近三年論文發表情形 | 1. 會議名稱：Healthcare Exo Taiwan; 時間：Dec 1, 2023; 地點：Taipei Nangang Exhibition Center, Taiwan; 發表之論文題目：Innovative Technique Platform Development for Cancer Stem Cell Isolation and Cell Therapy; 補助機構：Creative Biotechnology Inc., Taiwan<br>2. 會議名稱：AMWC Asia-TDAC 10th Taiwan Dermatology Aesthetics Conference; 時間：May 7, 2023; 地點：Taipei International Convention Center; 發表之論文題目：PRP-Plus Reprograms the Metabolism of Fibroblasts and Mesenchymal Stem Cells to Facilitate the Wound Healing and Anti-Aging; 補助機構：iCare Biotechnology Inc., Taiwan<br>3. 會議名稱：The 26th Taiwan Joint Cancer Conference (TJCC 2022); 時間：April 3, 2022; 地點：NTUH International Convention Center, Taiwan; 發表之論文題目：Preclinical Drug Development of Precision Medicine in Ovarian Cancer; 補助機構：Taiwan Clinical Oncology Society, TCOS<br>4. 會議名稱：Annual Cancer Research Retreat; 時間：June 5, 2020; 地點：Taipei Medical University Hospital, Taiwan; 發表之論文題目：Preclinical Drug Development of Precision Medicine; 補助機構：Taipei Medical University Hospital, Taiwan | | |




Throughout this four-year endeavor, our plan is to utilize PBX1 and GLS inhibitors to thwart both the transcription and glutaminolysis of CSCs as a paradigm of synthetic lethality. CSCs primarily inhabit hypoxic areas characterized by a deficiency of blood vessels, which hinders the effective delivery of medications. We will develop liposomes tagged with glucosamine that can transport PBX1is to the hypoxic area using GLUT1-mediated transcytosis. This is because tumor cells under hypoxia rely on the Warburg effect to produce substantial quantities of GLUT1. Furthermore, even though GLSis can eradicate glutamine-dependent cancer cells, or CSCs, those that have outlasted and have a high degree of metabolic flexibility might use metabolic compensation to circumvent the inhibitor by switching from glutaminolysis to glycolysis. Glucosamine-labeled liposomes carrying PBX1is will be used in the treatment of GLSis. These liposomes will attract sugarholic CSCs that are resistant to GLSis. By consuming the liposomal PBX1i, the transcription of genes related to CSC characteristics will be inhibited. Utilizing *in vivo* single-cell RNA sequencing and metabolomic analysis, a more thorough understanding of the intricate mechanisms that regulate the interaction within the complex tumor ecosystem may be acquired with regards to this combination therapy. This insight will facilitate the future advancement of an innovative treatment approach targeting pancreatic CSCs.

**First Year**

**Milestone 1: Utilization of novel PBX1i as a tool compound to uncover PBX1-mediated CSC properties**

***1a. Establishment of CSCs to scrutinize the changes in CSC properties caused by PBX1 inhibitors***

With or without treatment with PBX1is, CSCs will be subjected to soft agar colony formation, tumor sphere tests, drug-sensitive assays, migration, and invasion assays. This study is to dissect novel PBX1is that hinder to what extent the versatile capabilities of CSCs, such as their ability to form tumors, create spherical structures, develop resistance to drugs, and spawn metastasis.

***1b. Understanding PBX1i-induced single-cell transcriptome changes in the tumor microenvironment***

In the mouse model, scRNA-Seq is expected to show the complexity effects of PBX1is on tumor cells, TILs, CAFs, within different subpopulations and over time, at the single-cell level.

***1c. Dissecting the roles of PBX1-mediated signaling in regulating CSC properties***

We will analyze the transcriptomics controlled by CSC and compare it to transcriptomes influenced by B004. This analysis will allow us to identify the PBX1-mediated CSC transcriptional activity. To confirm the pathway, we will use ChIP, qPCR, and Western blots. The rescue test will be conducted to determine the role of PBX1-mediated signaling in coordinating CSC characteristics, as evaluated in **Milestone 1a.**

**Alternative plan:** We aim to discover novel PBX1-mediated signaling for regulating CSC properties at this milestone. We have already found that B004 can suppress critical stemness regulators such as OCT4, NANOG, and EMT regulators such as TWIST, SNAIL, and ZEB1, which have not been reported yet. In addition, we may also examine whether canonical PBX1 downstream gene sets control CSC properties. Their contribution to rescue assays of CSC functional assays will serve to justify these PBX1-mediated signalings.

**Second Year**

**Milestone 2: Investigation of the synergistic mechanism of PBX1i and GLSi in CSCs**

***2a. Examination of alteration of metabolism upon single treatment with a PBX1 inhibitor***

Given that the knockdown of PBX1 can modify several genes related to cancer metabolism[3], it is anticipated that the use of a PBX1i will impact the metabolic signatures of CSCs. The investigation will encompass a thorough examination of metabolic profiles, including: 1) assessment of mitochondrial respiration (function) and glycolytic flux; 2) classification of mitochondrial subtypes; 3) analysis of metabolomics; and 4) evaluation of mitochondrial dynamics.

***2b. Examination of stemness signaling upon single treatment with a GLS inhibitor***

The goal of this study is to find out how the GLSi affects the stemness pathway and the characteristics of CSCs that are linked to their ability to form tumors, spherogenesis, resistance to treatment, and ability to metastasize.

***2c. Evaluation of the effects of synchronous and asynchronous treatment of PBX1i and GLSi in 3D models***

A comparison will be made between the effects of synchronous and asynchronous therapy of PBX1i and GLSi in a 3D CSC spheroid model. The treatment regimen yielding the most favorable outcome will be chosen for subsequent mechanistic investigation. This approach will unveil the coordination networks or independent pathways that are governed by PBX and GLS inhibitors. The role of these pathways in orchestrating CSC characteristics will be assessed by a rescue examination.

**Alternative plan:** In the event that the synergistic effects of CB-839 and B004 do not occur at any dosage, alternative inhibitors of glutaminolysis such as DON, JHU-083, BPTES, or compound 968 may be utilized in place of CB-839, and other PBX1i, including T417, A409, or other members of the PBX1i series, may be utilized in place of B004. Furthermore, we intend to utilize synchronous

# 工作項目

按照里程碑的規畫擬出作戰計畫，每個規劃都有**預期結果**及**Plan B**

天有不測風雨，計畫總會遇到小意外。

失敗了？
沒關係—

我們不是只有Plan A，
我們有**一整套Plan A 到 Plan Z的「全餐組合」**

★★★★★

and asynchronous drug treatment time points for PBX1i and GLSi in 3D models.

**Third Year**

**Milestone 3: Use of glucosamine-labeled liposomes as a CSC-targeted vehicle to deliver PBX1i**

***3a. Examination of transcytosis of glucosamine-labeled liposomes in 3D models***

We will establish a 3D CSC spheroid model stained with a HP-1 hypoxia probe to verify whether glucosamine-labeled liposomes can be delivered to the hypoxia region. Through introducing chlorpromazine (an inhibitor of clathrin-mediated endocytosis), genistein (an inhibitor of caveolae-mediated endocytosis), and BAY-876 (an inhibitor of GLUT1) in a 3D CSC spheroid model, we are able to evaluate how glucosamine-labeled liposomes are taken by CSCs. We anticipate that CSCs may uptake glucosamine-labeled liposomes by ligand-mediated endocytosis, while liposomes lacking glucosamine-labeled are internalized into cells through caveolae-mediated endocytosis.

***3b. Assessment of the CSC properties upon treatment of glucosamine-labeled liposomes***

We will examine the effects of glucosamine-labeled liposomal PBX1i on PBX1-mediated signaling and CSC features, including tumor-forming ability, formation of spherical structures, resistance to drugs, and potential for metastasis. We will investigate the potential impact of glucosamine-labeled liposomal PBX1i on PBX1-mediated signaling, specifically its role in controlling CSC characteristics. The rescue examination will study the involvement of PBX1-downstream genes that are associated with CSC signaling.

***3c. Understanding metabolic compensation caused by GLSi and its impact on glucosamine-labeled liposomes***

In a 3D CSC spheroid model stained with 2-DG, we will evaluate if CB-839 induces the glutaminolysis-to-glycolysis transition of CSCs. We anticipate that CSCs that can escape CB-839 treatment will have an elevated glycolytic rate and a greater consumption of liposomes tagged with glucosamine. We will conduct a comparative analysis of cell viability and CSC functionality in a 3D spheroid model between the treatment of PBX1i liposomes and GLSi in combination and that of a single drug.

**Alternative plan:** In the event that the synergistic effects of CB-839 and liposomal B004 do not occur at any dosage, alternative inhibitors of glutaminolysis such as DON, JHU-083, BPTES, or compound 968 may be utilized in place of CB-839, and other liposomal PBX1i, including liposomal T417, A409, or other members of the PBX1i series, may be utilized in place of liposomal B004. Furthermore, we intend to utilize synchronous and asynchronous drug treatment time points for GLSi and liposomal PBX1i in 3D models or zebrafish models.

**Fourth Year**

**Milestone 4: Exploration of the *in vivo* regulations of the PBX1i liposome and GLSi on the tumor ecosystem**

***4a. Validation of the in vivo antitumor effect and toxicity of PBX1i liposome and GLSi***

The endpoints for the subcutaneous and orthotopic metastatic models are anticipated to be statistically significant differences between each group in the following: (i) tumor weight and volume at sacrifice; (ii) PBX1 signaling activities in tumors harvested at the end point as determined by qRT-PCR or western blot analysis; (iii) CSC percentage as identified by flow cytometry. Since normal tissues express PBX1 much less than tumors and PBX1 expression dictates a cell's sensitivity to PBX1is, prospective safety profiles of liposomal B004 or B004 are anticipated based on histopathology and clinical chemistry endpoints. The expected biodistribution and tumor accumulation of liposomes suggest that liposomes will mostly accumulate in tumors and, to a lesser extent, in the liver, with no significant accumulation observed in other organs.

***4b. Single-cell transcriptomic profiling of in vivo tumors, circulating tumor cells, and immune cells***

ScRNA-Seq will reveal transcriptomic alterations caused by the antagonistic, additive, or synergistic effects of liposomal PBXi and GLSi on many cell types, including CTCs, primary/metastatic tumor cells, TILs, and CAFs. This analysis will be conducted at the single-cell level, allowing for the investigation of diverse subpopulations and changes over time. MiCareo Rare Cell Diagnostics will quantify and isolate CTCs and immune cells from peripheral blood.

***4c. Investigation of in vivo metabolomic regulations of PBX1i liposome and GLSi***

Through the utilization of LC-MS-based metabolomic methods, we may get insight into the combined impact of liposomal PBXi and GLSi on the regulation of tumor and immune cell metabolism in living organisms.

**Alternative plan:** We will use the zebrafish model to pre-evaluate the combination dosage and effectiveness prior to the mouse model to reduce the risk of failure of the mouse model. If scRNA-seq does not have promising results, we will use qPCR, flow cytometry, and IHC to investigate the regulation of putative targets, which will be revealed in **Milestones 1b and 2c**.

**The mouse models employed in the project are outlined as follows**

| Milestone | Animal Model | Drug | Endpoint Analysis |
|---|---|---|---|
| 1b | scRNA-seq of orthotopic tumors (8 Balb/c) | B004 | scRNA-seq, tumors, TIL, etc. |
| 4a & 4c | Subcutaneous model (36 Nude) | CB-839+B004 lipo | Flow, qPCR, IHC, etc. |
| 4a & 4c | Orthotopic metastatic model (36 Nude) | CB-839+B004 lipo | IVIS, Flow, qPCR, IHC, etc. |
| 4a & 4c | Biodistribution and tumor accumulation of liposomes (24 Nude) | CB-839+B004 lipo | IVIS, confocal, etc. |
| 4b | scRNA-seq of orthotopic tumors (36 Balb/c) | CB-839+B004 lipo | scRNA-seq, CTC, immune, etc. |

Detailed descriptions of analyses are provided in each milestone

2.對於參與之工作人員，預期可獲之訓練。

We will train one postdoctoral fellow, two research assistants, two doctoral students, two to three master's students, and five undergraduate medical students (preparing them to become physician scientists) over the span of this four-year endeavor. Participants will gain knowledge and skills regarding the comprehensive process of translating therapeutic targets into clinical practice and the development of novel drugs. Experiments such as CSC analyses, drug-protein interactions, NGS analyses, biodistribution, and toxicity analyses, among others, will be taught to the

## 工作項目

按照里程碑的規畫擬出作戰計畫，每個規劃都有預期結果及Plan B

沒有動物實驗，就沒有 Proof of Concept。

臨床前驗證更是研究的「生死關卡」。

因此直接把動物實驗全盤整理、摺好、打包—

讓委員秒懂。

★★★★★

# 動物試驗

按照里程碑的規畫擬出詳細動物實驗設計儘早送IACUC審查

**The mouse models employed in the project are outlined as follows**

| Milestone | Animal Model | Drug | Endpoint Analysis |
|---|---|---|---|
| 1b | scRNA-seq of orthotopic tumors (8 Balb/c) | B004 | scRNA-seq, tumors, TIL, etc. |
| 4a & 4c | Subcutaneous model (36 Nude) | CB-839+B004 lipo | Flow, qPCR, IHC, etc. |
| 4a & 4c | Orthotopic metastatic model (36 Nude) | CB-839+B004 lipo | IVIS, Flow, qPCR, IHC, etc. |
| 4a & 4c | Biodistribution and tumor accumulation of liposomes (24 Nude) | CB-839+B004 lipo | IVIS, confocal, etc. |
| 4b | scRNA-seq of orthotopic tumors (36 Balb/c) | CB-839+B004 lipo | scRNA-seq, CTC, immune, etc. |

Detailed descriptions of analyses are provided in each milestone

## 第1組實驗設計內容

實驗內容名稱 * scRNA-seq of BALB/c-derived KPC orthotopic tumors (B004)

實驗分組 * 動物分組：實驗組1組+控制組1組=總共2組
每組使用數量：4隻
總共所需隻數為：2組x4隻/每組=8隻
Once tumors reached an average volume of 100 mm3, mice (n = 4) were randomized into 2 arms and treated with vehicle DMSO (1%) (i.p. injection) and B004 (i.p. injection) for 3–4 weeks.

實驗物質之投予、採樣方法及頻率 * B004 will be administered at 5 mg/kg and by i.p. injection or oral gavage three times a week. Upon reaching the designated endpoint, the breadth and length of each tumor burden will be assessed, along with the body weight. The tumor dimension was measured by a Vernier caliper every other day. Tumor burden is calculated as volume [mm3] = 0.52 × width2 × length. The endpoints will be statistically evaluated for the significant differences between each group in (i) tumor weight and volume at sacrifice, (ii) In order to ascertain the impact of B004 on single-cell transcriptome levels, single-cell RNA-sequencing (scRNA-seq) will be conducted on viable cells isolated from BALB/c-derived KPC orthotopic tumors using the 10x Genomics Chromium platform, identifying the genes and pathways that are perturbed by the PBX1i. The utilization of scRNA-seq permits the molecular and cellular characterization of hundreds of thousands of cells within the heterogeneous tumor masses on a cell-by-cell basis. At the single-cell level, we will examine the intricacy of the drug's effects on cancer-associated fibroblasts (CAFs), tumor-infiltrating lymphocytes (TILs), and tumor cells across subpopulations in mice treated with B004. We will compare the hematologic or clinical chemistry profiles of mice treated with the indicated drugs with those of animals treated with DMSO. We will also check to see if the mice have any unusual medical conditions, such as lethargy, weight loss, or serious physical problems. Necropsies will also be conducted to assess tissue damage or histological abnormalities in the brain, heart, lungs, liver, spleen, kidney, and intestine.

## 第2組實驗設計內容

實驗內容名稱 * Subcutaneous model

實驗分組 * 動物分組：實驗組5組+控制組1組=總共6組
每組使用數量：6隻
總共所需隻數為：6組x6隻/每組=36隻
A subcutaneous transplantation of 1×106 cells/0.1 mL of pancreatic CSCs will be performed onto the dorsal body surface of four-week-old female Balb-c/nude mice. Mice (n = 6) will be randomized into 6 arms and assigned to receive one of the following treatments: (i) vehicle DMSO (1%), (ii) B004 (5 mg/kg, i.p. injection), (iii) CB-839 (oral gavage), (iv) glucosamine-labeled liposomes with no drug (i.p. injection), (v) glucosamine-labeled liposomes with B004 (i.p. injection), or (vi) glucosamine-labeled liposomes with B004 (i.p. injection) combined with CB-839 (oral gavage).

實驗物質之投予、採樣方法及頻率 * B004 or glucosamine-labeled liposomes with B004 will be administered at a dosage of 5 mg/kg, three times per week. CB-839 will be administered at a dosage of 200 mg/kg, twice daily. The body weight, breadth, and length of each tumor burden will be evaluated once the designated endpoint has been reached. Every other day, the tumor's dimensions were determined using a Vernier calliper. The formula for calculating tumor burden is volume [mm3] = 0.52 × width2 × length. The statistical evaluation of the endpoints will focus on distinguishing significant differences between each group in the following ways: (i) tumor weight and volume at sacrifice; (ii) qRT-PCR or western blot analysis of PBX1 and GLS signaling activities in tumors harvested at the end point; and (iii) flow cytometry-based identification of OCT4-GFP activity for CSC percentage analysis in tumors harvested at the end point. A comparison will be made between the hematologic or clinical chemistry profiles of mice that were administered the specified drugs and those of mice that were treated with DMSO. Additionally, we will conduct an assessment to identify any atypical medical conditions exhibited by the mice, including but not limited to lethargy, weight loss, or severe physical ailments. In order to evaluate tissue damage or histological abnormalities in the liver, kidney, heart, lungs, brain, spleen, and intestine, necropsies will also be performed.

## 第3組實驗設計內容

實驗內容名稱 * Orthotopic metastatic model

實驗分組 * 動物分組：實驗組5組+控制組1組=總共6組
每組使用數量：6隻
總共所需隻數為：6組x6隻/每組=36隻
Based on the ability of PBX1 to modulate genes involved in EMT, it is conceivable to postulate that inhibiting PBX1 could potentially reduce the risk of cancer metastasizing. Our objective is to generate an orthotopic murine model of liver metastasis through the orthotopic injection of pancreatic CSCs. This will facilitate the evaluation of the drug's effectiveness in impeding the progression of metastasis. (i) Vehicle DMSO (1%), (ii) Glucosamine-labeled liposomes with no drug (i.p. injection), (iii) glucosamine-labeled liposomes with B004 (i.p. injection), (iv) CB-839 (oral gavage), (v) glucosamine-labeled liposomes with B004 (i.p. injection), or (vi) glucosamine-labeled liposomes with B004 (i.p. injection) combined with CB-839 (oral gavage) will be administered to mice (n = 6) beginning the second week after tumor injection.

實驗物質之投予、採樣方法及頻率 * The dosage of B004 or liposomes labeled with glucosamine containing B004 will be 5 mg/kg, three times weekly. The dosage of CB-839 to be administered is 200 mg/kg, twice daily. IVIS spectrum bioluminescence imaging was utilized to track the progression and metastasis of the tumor cells. The statistical evaluation of the endpoints will focus on distinguishing significant differences between each group in the following ways: (i) number of metastatic nodules on the liver surface at sacrifice; (ii) qRT-PCR or western blot analysis of PBX1 and GLS signaling activities in tumors harvested at the end point; and (iii) flow cytometry-based identification of OCT4-GFP activity for CSC percentage analysis in tumors harvested at the end point. A comparison will be made between the hematologic or clinical chemistry profiles of mice that were administered the specified medications and those of mice that were treated with DMSO. Additionally, we will conduct an assessment to identify any atypical medical conditions exhibited by the mice, including but not limited to lethargy, weight loss, or severe physical ailments. In order to evaluate tissue damage or histological abnormalities in the liver, kidney, heart, lungs, brain, spleen, and intestine, necropsies will additionally be performed.

## 第4組實驗設計內容

實驗內容名稱 * Biodistribution and tumor accumulation of liposomes

實驗分組 * 動物分組：實驗組3組+控制組1組=總共4組
每組使用數量：6隻
總共所需隻數為：4組x6隻/每組=24隻
The mice will be divided into 4 arms and allocated to one of the following treatments: (i) Cy5.5-labeled liposomes (i.p. injection), (ii) CB-839 (oral gavage) treatment for 1 week and combined with Cy5.5-labeled liposomes (i.p. injection) at day 6, (iii) CB-839 (oral gavage) treatment for 2 weeks and combined with Cy5.5-labeled liposomes (i.p. injection) at day 13, (iv) CB-839 (oral gavage) treatment for 3 weeks and combined with Cy5.5-labeled liposomes (i.p. injection) at day 20.

實驗物質之投予、採樣方法及頻率 * The dose of CB-839 will be 200 mg/kg, delivered twice daily. The optical images will be inspected 24 hours after the injection of liposomes tagged with Cy5.5. In order to analyze hypoxia in tumors, mice will receive an i.p. injection of HP-1 (Pimonidazole: 100□mg/kg; HPI Inc., Burlington, MA, USA) for a duration of 1 hour. The mouse organ will also be collected for organ accumulation examination. Following the analysis of the IVIS visuals, the tumors will be retrieved from the mice, preserved in PBS with 3.7% formaldehyde at a temperature of -20°C, and subsequently embedded in Tissue-Tek O.C.T. compound (Sakura, Tokyo, Japan). Immunohistochemical analysis will be performed on 5-μm-thick cryostat coronal slices. The sections were exposed to FITC-mAb (HPI Inc., Burlington, MA, USA) for 1 hour at room temperature. The confocal Zeiss 880 microscope (Carl Zeiss AG, Oberkochen, Germany) will be used to take the pictures.

## 第5組實驗設計內容

實驗內容名稱 * scRNA-seq of BALB/c-derived KPC orthotopic tumors (CB-839+B004 liposome)

實驗分組 * 動物分組：實驗組5組+控制組1組=總共6組
每組使用數量：6隻
總共所需隻數為：6組x6隻/每組=36隻
(i) Vehicle DMSO (1%), (ii) Glucosamine-labeled liposomes with no drug (i.p. injection), (iii) glucosamine-labeled liposomes with B004 (i.p. injection), (iv) CB-839 (oral gavage), (v) glucosamine-labeled liposomes with B004 (i.p. injection), or (vi) glucosamine-labeled liposomes with B004 (i.p. injection) combined with CB-839 (oral gavage) will be administered to mice (n = 6) beginning the second week after tumor injection.

實驗物質之投予、採樣方法及頻率 * The dosage of B004 or liposomes labeled with glucosamine containing B004 will be 5 mg/kg, three times weekly. The dosage of CB-839 to be administered is 200 mg/kg, twice daily. (1) Changes in subpopulations of CTCs and immune cells in the peripheral blood population, as well as their transcriptome profiles, will be analyzed in order to elucidate the impact of drugs on the interaction between CTCs and the immune system. Utilizing the rare cell isolation system of MiCareo to profile immune cells would yield more comprehensive information regarding the cellular response of each drug. By employing the imaging system of MiCareo to track PD1, TIM3, LAG3, and IFNγ staining, we will distinguish sixteen distinct subtypes of rare immune cells and determined their significance in relation to each drug treatment regimen. By utilizing the rare cell isolation system of a MiCareo in conjunction with the SelectChip Retrieval cartridge, CTCs and immune cells will be isolated in order to increase our understanding of the effects of drugs on cancer metastases. Using this cartridge, even more pure rare cells can be filtered and delivered directly into a microcentrifuge tube for subsequent scRNA-seq profiles. (2) We will conjugate glutamine with a fluorescent dye and inject it intraperitoneally into mice prior to drug treatments in order to observe the glutamine flux between CTCs and immune cells in peripheral blood. We will then use the MiCareo imaging system to track the glutamine flux across different peripheral blood cell subpopulations.

# 經費規劃

**按照里程碑的規畫擬出各項經費細節，包含儀器耗材購置及人力規劃**

## 五、申請補助經費：

（一）請將本計畫申請書之第七項(表CM07)、第八項(表CM08)、第九項(表CM09)、第十項(表CM10)、第十一項(表CM11)、第十二項(表CM12\CM12-1)所列費用個別加總後，分別填入「研究人力費」、「耗材、物品、圖書及雜項費用」、「國外學者來臺費用」、「研究設備費」、「國外差旅費-執行國際合作與移地研究」及「國外差旅費-出席國際學術會議」等欄內。

（二）管理費為申請機構配合執行本計畫所需之費用，其計算方式係依本會規定核給補助管理費之項目費用總和及各申請機構管理費補助比例計算後直接產生，計畫主持人不須填寫「管理費」欄。

（三）依據本會「補助延攬客座科技人才作業要點」規定提出博士級研究人員申請，請依各年度申請之名額填入下表，如於申請時一併提出「補助延攬博士級研究人員員額/人才進用申請書」（表CIF2101、CIF2102），若計畫核定僅核定名額者應於提出合適人選後，另向本會提出進用申請，經審查通過後，始得進用該名博士級研究人員。

（四）申請機構或其他單位（含國內外、大陸地區及港澳）補助項目，請檢附相關證明文件。

金額單位：新臺幣元

| 補助項目 \ 執行年次 | | 第一年（113年8月～114年7月） | 第二年（114年8月～115年7月） | 第三年（115年8月～116年7月） | 第四年（116年8月～117年7月） | 第五年 |
|---|---|---|---|---|---|---|
| **業務費** | | **6,567,521** | **8,230,760** | **8,282,222** | **8,756,841** | |
| 研究人力費 | | 3,768,771 | 3,823,410 | 3,874,872 | 3,935,991 | |
| 耗材、物品、圖書及雜項費用 | | 2,798,750 | 4,407,350 | 4,407,350 | 4,820,850 | |
| 國外學者來臺費用 | | 0 | 0 | 0 | 0 | |
| **研究設備費** | | **2,450,000** | **440,000** | **341,420** | **0** | |
| **國外差旅費** | | **260,000** | **260,000** | **260,000** | **260,000** | |
| 執行國際合作與移地研究 | | 100,000 | 100,000 | 100,000 | 100,000 | |
| 出席國際學術會議 | | 160,000 | 160,000 | 160,000 | 160,000 | |
| **管理費** | | **1,085,128** | **1,300,614** | **1,293,546** | **1,313,526** | |
| **合計** | | **10,362,649** | **10,231,374** | **10,177,188** | **10,330,367** | |
| 博士級研究人員 | 國內、外地區 | 共 1 名 | 共 1 名 | 共 1 名 | 共 1 名 | 共 名 |
| | 大陸地區 | 共 0 名 | 共 0 名 | 共 0 名 | 共 0 名 | 共 名 |

申請機構或其他單位（含國內外、大陸地區及港澳）補助項目（無配合補助項目者免填）

| 配合單位名稱 | 配合補助項目 | 配合補助金額 | 配合年次 | 證明文件 |
|---|---|---|---|---|
| | | | | |
| | | | | |

## 七、研究人力費：

（一）凡執行計畫所需研究人力費用，均得依本會「補助專題研究計畫研究人力約用注意事項」規定，按所屬機構自訂敘薪標準及職銜，就預估專任、兼任人員或臨時工需求填寫，並請述明該研究人力在本計畫內擔任之具體內容、性質、項目及範圍，以利審查。專任人員不限學歷，包含博士級人員。

（二）約用專任人員，請依其於專題研究計畫負責之工作內容，所應具備之專業技能、獨立作業能力、預期績效表現及相關學經歷年資等條件，綜合考量敘薪，並檢附各機構自訂之薪資支給依據，以為本會核定聘用助理經費之參考。

（三）請分年列述。

第 1 年　　金額單位：新臺幣元

| 類別 | 金額 | 請敘明在本計畫內擔任之具體內容、性質、項目及範圍（如約用專任人員，請簡述其於計畫內所應具備之專業技能、獨立作業能力、預期績效表現及相關學經歷年資等條件） |
|---|---|---|
| 專任人員 | 735,174 | 進行新藥開發實驗，包含藥物對癌幹細胞特性及機制分析、分生實驗如Western blot、QPCR、細胞培養，及負責計畫文書業務、論文文字修訂、定期實驗室整理、藥品器皿儀器訂購等。<br>735,174元(含月支費用、年終獎金、勞健保費雇主負擔部分、勞工退休金雇主負擔部分）x 1名 |
| 專任人員 | 1,209,597 | 計畫執行及報告撰寫，進行新藥開發實驗進行，包含：藥物對癌幹細胞功能性分析、single-cell RNA-sequencing、動物實驗、分生實驗如Western blot、QPCR、細胞培養，及負責計畫文書業務、論文文字修訂、定期實驗室整理、藥品器皿儀器訂購等。<br>1,209,597元(含月支費用、年終獎金、勞健保費雇主負擔部分、勞工退休金雇主負擔部分）x 1名 |
| 兼任人員(碩士生-學習範疇) | 540,000 | 進行新藥開發實驗，包含藥物對癌幹細胞功能性分析：tumorgenicity assay、spherogenesis assay、drug sensitivity assay、migration capacity assay、invasion capacity assay等。<br>(月支費用 15000.00元 x 12.00月）x 3名 |
| 兼任人員(大專生-學習範疇) | 384,000 | 實驗執行，包含：Western blot、QPCR、細胞培養，及負責計畫文書業務、論文文字修訂、定期實驗室整理、藥品器皿儀器訂購等。<br>(月支費用 8000.00元 x 12.00月）x 4名 |
| 兼任人員(博士生-學習範疇) | 900,000 | 進行新藥開發實驗，包含：CSC percentage analysis、TOF-SIMS analysis、tumorgenicity assay、spherogenesis assay等。<br>(月支費用 25000.00元 x 12.00月）x 3名 |
| 合計 | 3,768,771 | |

第 2 年　　金額單位：新臺幣元

| 類別 | 金額 | 請敘明在本計畫內擔任之具體內容、性質、項目及範圍（如約用專任人員，請簡述其於計畫內所應具備之專業技能、獨立作業能力、預期績效表現及相關學經歷年資等條件） |
|---|---|---|
| 專任人員 | 750,564 | 進行新藥開發實驗，包含藥物對癌幹細胞代謝分析、癌幹細胞特性及機制分析、分生實驗如Western blot、QPCR、細胞培養，及負責計畫文書業務、論文文字修訂、定期實驗室整理、藥品器皿儀器訂購等。<br>750,564元(含月支費用、年終獎金、勞健保費雇主負擔部分、勞工退休金雇主負擔部分）x 1名 |

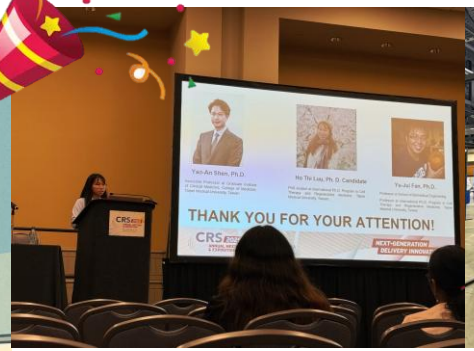
## 八、耗材、物品、圖書及雜項費用：

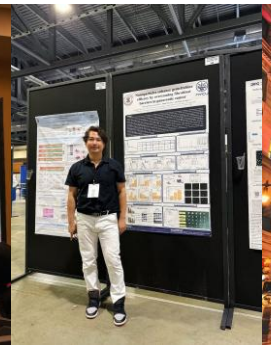
（一）凡執行研究計畫所需之耗材、物品(非屬研究設備者)、圖書及雜項費用，均可填入本表內。
（二）說明欄請就該項目之規格、用途等相關資料詳細填寫，以利審查。
（三）若申請單位有配合款，請於備註欄註明。
（四）請分年列述。

第 1 年　　金額單位：新臺幣元

| 項目名稱 | 說明 | 單位 | 數量 | 單價 | 金額 | 備註 |
|---|---|---|---|---|---|---|
| 消耗性器材 | 胎牛血清(FBS) | 瓶 | 20 | 10,000 | 200,000 | 培養細胞用 |
| 消耗性器材 | DMEM、RPMI 等培養基 | 盒 | 40 | 1,500 | 60,000 | 培養細胞用 |
| 消耗性器材 | 二合一抗生素 | 瓶 | 20 | 1,200 | 24,000 | 培養細胞用 |
| 消耗性器材 | 各式細胞培養盤（25 cm2 and 75 cm2 flasks） | 箱 | 10 | 5,000 | 50,000 | 培養細胞用 |
| 消耗性器材 | 拋棄式塑膠吸管（5 ml, 10 ml, and 25 ml pipets） | 箱 | 40 | 1,000 | 40,000 | 培養細胞及一般實驗用 |
| 消耗性器材 | 試劑過濾膜 | 箱 | 5 | 2,000 | 10,000 | 培養細胞及一般實驗用 |
| 消耗性器材 | 無菌滴管 | 箱 | 10 | 2,000 | 20,000 | 培養細胞及一般實驗用 |
| 消耗性器材 | 流式細胞儀專用鞘液 | 箱 | 4 | 2,000 | 8,000 | 流式細胞儀用 |
| 消耗性器材 | RNA萃取試劑組 | 組 | 10 | 10,000 | 100,000 | 檢測RNA表現量 |
| 消耗性器材 | 反轉錄套組 | 組 | 15 | 12,000 | 180,000 | 研究基因表現用 |
| 消耗性器材 | 蛋白質萃取相關試劑組 | 組 | 10 | 12,000 | 120,000 | 西方墨點用 |
| 消耗性器材 | 蛋白標準品試劑(BSA) | 瓶 | 8 | 2,500 | 20,000 | 西方墨點用 |
| 消耗性器材 | 西方墨點製膠及跑膠相關試劑 | 組 | 8 | 12,000 | 96,000 | 西方墨點用 |
| 消耗性器材 | PVDF雜交膜 | 盒 | 8 | 8,500 | 68,000 | 西方墨點用 |
| 消耗性器材 | 2D及3D細胞活性試劑組 | 組 | 10 | 18,000 | 180,000 | 測試藥物對細胞活性 |
| 消耗性器材 | ELISA檢測套組 | 組 | 6 | 15,000 | 90,000 | 檢測酵素活性 |
| 消耗性器材 | 一般性的化學藥品及溶劑 | 批 | 5 | 25,000 | 125,000 | 一般實驗用 |
| 消耗性器材 | 玻璃器皿（反應瓶、冷凝管、分液漏斗、試管、樣本瓶、冷凍乾燥瓶等） | 批 | 5 | 30,000 | 150,000 | 一般實驗用 |
| 消耗性器材 | 拋棄式塑膠用品（吸管尖、螢光比色管、濾膜、針 | 批 | 5 | 15,000 | 75,000 | 一般實驗用 |

# *Big grant secured!*


Controlled Release Society (CRS)


Harvard Medical School
Dr. Kun-Hsing Yu

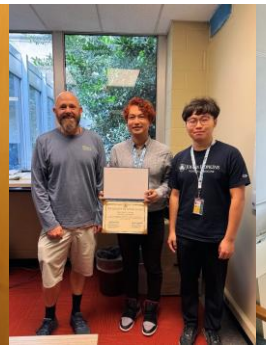
National Institute of Drug Abuse (NIDA)
Dr. Tsung-Pin Su



Johns Hopkins University

Dr. Ie-Ming Shih
Dr. Tian-Li Wang

Dr. Karen L. Reddy



Dr. Steven Claypool

Dr. Martin Alphonse

【國科會提醒您】請於5/31前繳交國際年輕傑出學者研究計畫期中進度報告，俾利後續辦理審查及下年度經費核定作業，謝謝您！ 收件匣 ×

**黃欣釧[NSTC]** <hhc105@nstc.gov.tw> 5月1日 週四 上午8:54

寄給 ijtsai@gate.sinica.edu.tw、chenic@ncku.edu.tw、wanghc@mail.ncku.edu.tw、emorypan@gmail.com、ycl@life.nthu.edu.tw、alenskchen@ntu.edu.tw、wlwu@ncku

計畫主持人您好：

提醒您，貴單位所執行之113年度國際年輕傑出學者研究計畫即將於114年7月31日屆期，
為辦理114年度計畫核定作業，
請協助於114年5月31日(六)前至「學術研發服務網(https://arspb.nstc.gov.tw/NSCWeb/slogin.jsp)」上傳期中進度報告，
俾利後續辦理審查及下年度經費核定作業。
非常感謝您的配合！

**國家科學及技術委員會補助專題研究計畫報告**

**以糖化奈米藥物扭轉代謝代償及協同抑制轉錄活性作為胰臟癌幹細胞新穎治療策略(1/4)**

報 告 類 別 ： 進度報告
計 畫 類 別 ： 個別型計畫
計 畫 編 號 ： NSTC 113-2628-B-038-012-
執 行 期 間 ： 113年08月01日至114年07月31日
執 行 單 位 ： 臺北醫學大學醫學系

計 畫 主 持 人 ： 沈耀安

本研究具有政策應用參考價值：■否 □是，建議提供機關
（勾選「是」者，請列舉建議可提供施政參考之業務主管機關）
本研究具影響公共利益之重大發現：□否 □是

中 華 民 國 114 年 05 月 31 日

***B004-Mediated PBX1 Inhibition Blocks EMT and Stemness Gene Expression in Chemoresistant Pancreatic CSCs***

In order to confirm the correlation between PBX1 and the upregulation of EMT and stemness markers, additional RT-PCR was conducted (Figs. 4A and 4B). The results indicated that all 13 EMT and stemness genes were upregulated in CR cells in comparison to their parental cell line. However, the effect was abolished by the inhibition of PBX1 via shPBX1, A409, or B004. The administration of T417 also partially reversed the effect, although the effect was less significant than that of A409 and B004. In CR, gemcitabine administration resulted in a substantial increase in the expression of PBX1, *SLUG*, *ZEB1*, *ZEB2*, and *KLF4* in comparison to CR that did not receive gemcitabine stimulation, as was observed in previous experiments. Nevertheless, the levels of *TWIST*, *SNAIL*, *OCT4*, *SOX2*, *MYC*, *NANOG*, and *CTNNB1* were not substantially elevated in the CR + gemcitabine group compared to CR only (Figs. 4A and 4B). This implies a positive correlation between PBX1 and the upregulated

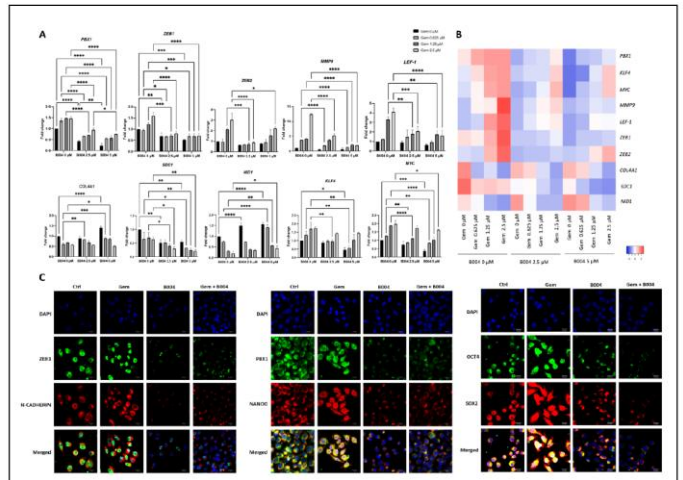


**Figure 5. B004 inhibits the gemcitabine-induced stemness and EMT.** (A) The expression levels of PBX1, metastasis-related genes, and stemness-related genes in MIA PaCa-2 CR-treated cells with the indicated drugs and dose were delineated by qPCR analysis. (B) Representative immunofluorescent images illustrating the expression and distribution of Zeb1 and N-cadherin proteins in MIA PaCa-2 CR cells treated with DMSO (control), 2.5 μM gemcitabine, 2.5 μM B004, or 2.5 μM gemcitabine + 2.5 μM B004.

resistant ($EpCAM^+/Vim^-$) populations in response to gemcitabine (Fig. 6E). The gemcitabine-induced stemness and EMT in both intrinsically resistant and non-resistant subpopulations are counteracted by the inhibition of PBX1.

***Disrupting the PBX1/ZEB1/NANOG Feedback Loop to Inhibit Stemness and Metastasis in Gemcitabine-Resistant Pancreatic Cancer***

The administration of gemcitabine in resistant pancreatic cancer results in an increase in metastasis and stemness features, as indicated by the aforementioned data. These effects may be facilitated by a network of interacting transcription factors that includes NANOG, ZEB1, and PBX1. Its activation triggers downstream effectors, creating an expression landscape that fosters stemness and metastasis. The GSEA analysis of the TCGA dataset yielded the *ZEB1* gene set from the ENCODE Transcription Factor Targets dataset (Fig. 7A). The *ZEB1* gene set was significantly enriched in cases of elevated *PBX1* expression in pancreatic cancer (Fig. 7A). The close association between PBX1 and other EMT regulators was also demonstrated by the TCGA database gene clustering analysis (Fig. 7B).

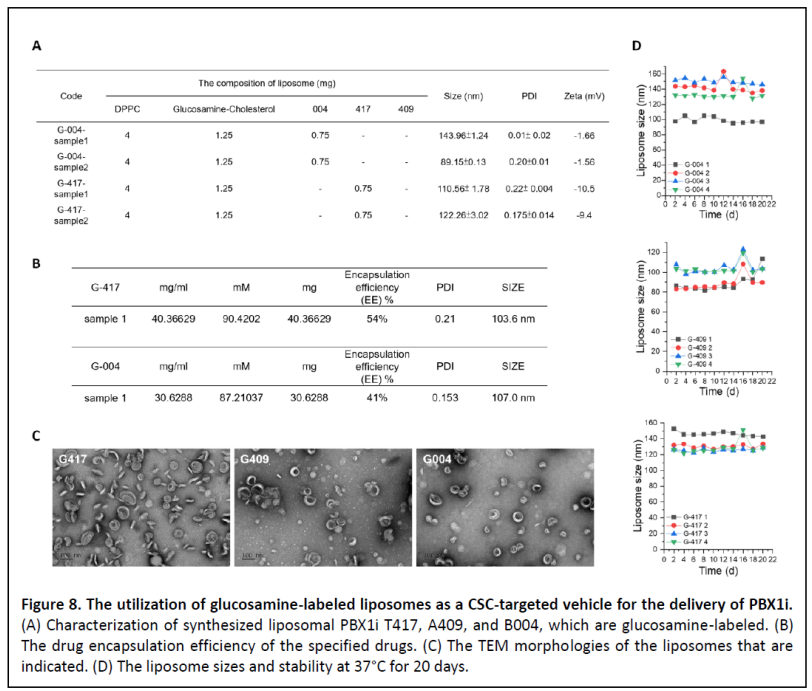



**Figure 8. The utilization of glucosamine-labeled liposomes as a CSC-targeted vehicle for the delivery of PBX1i.** (A) Characterization of synthesized liposomal PBX1i T417, A409, and B004, which are glucosamine-labeled. (B) The drug encapsulation efficiency of the specified drugs. (C) The TEM morphologies of the liposomes that are indicated. (D) The liposome sizes and stability at 37°C for 20 days.

【國科會生科處通知】請協助於114.11.7(五)下班前提供執行「113年度國際年輕傑出學者研究計畫」之執行成果報告(格式如附件)，感謝您！ 收件匣 ×

**0B3.生科處三科黃欣釧** 10月16日 週四 下午5:08

寄給 林懿雯、密件副本：我

計畫主持人 您好：

為辦理填報「2030跨世代年輕學者方案」績效評估作業，
惠請協助提供執行**「113年度國際年輕傑出學者研究計畫」之執行成果報告** (執行期間介於113/8/1~114/7/31者皆須填寫)，
報告格式詳如附件，說明如下：

1. **填寫內容** - 請儘量精簡、挑重點，如有無法填寫相關成果的部分，請填「無此項成果」即可。
2. **修改檔名** - 請於檔名最前面填上您的姓名+核定清單上的學門名稱。

請協助於**114年11月7日(五)下班前**回傳填報完成之報告word檔，俾利後續彙整。
如有相關問題，歡迎不吝與我聯繫。
非常感謝您！

## 113 年度國際年輕傑出學者研究計畫執行成果報告

### 一、計畫執行成果簡要說明

本計畫以「糖化奈米藥物調控代謝代償並協同抑制轉錄活性於膠臟癌幹細胞之新穎治療策略」為核心目標，在執行期間於科研成果、跨國合作、人才培育與技術轉移等面向皆獲得相當進展。在學術成果方面，已發表多篇高品質國際期刊論文，在癌幹細胞代謝調控領域包括探討麩醯胺酸酶（Glutaminase）在子宮內膜癌免疫抑制微環境之角色，以及 FASN/APP 軸向於肝癌幹細胞的新穎治療策略，亦證實 DNA 去甲基化酵素 TET1 能調控卵巢癌幹細胞的氧化磷酸化活性，並提升其對粒線體第一複合體抑制劑的治療敏感性，強化了表觀遺傳與代謝交互作用在癌幹細胞脆弱性中的重要性。除此之外，本團隊亦開展天然物抗癌研究，以細胞毒性導向的分離策略自 *Elatostema tenuicaudatum* 中鑑定六種新型 elatostemanosides，並揭示其對癌細胞具顯著的細胞毒活性，不僅大幅拓展蕁麻科植物的化學多樣性，也為天然物抗癌先導化合物的開發提供重要基礎。

同時，本計畫同步推動以 PBX1 為標的之轉錄調控研究，成功證實 PBX1 為膠臟癌幹細胞的核心轉錄調節因子，其活化與化療抗性、上皮細胞間質轉化（epithelial-mesenchymal transition, EMT）、代謝重塑及幹細胞性維持密切相關，並首次揭示 PBX1–ZEB1–NANOG 正回饋迴路在膠臟癌幹細胞存活與惡化中的關鍵角色。研究亦明確證實 PBX1 抑制劑（如 B004、A409、T417）或 PBX1 基因表現抑制（knockdown）均可阻斷此正回饋迴路、逆轉 EMT 與幹細胞性，並重新提高對 gemcitabine 之治療反應；此外，透過核糖核酸定序（RNA sequencing）、基因集富集分析（GSEA）及三維腫瘤球模式的整合，本計畫已成功描繪 PBX1 所介導的轉錄網絡與代謝路徑全景。本計畫亦於 CRS Annual Meeting、TMU–CWRU、UTS × UAAT 等國際與雙邊研討會中，以 PBX1 抑制策略、癌幹細胞代謝補償機制、及奈米載具專題進行口頭報告與壁報展示，顯著提升國際能見度。

在技術研發與智財布局方面，團隊已取得三項台灣專利（PRP-PLUS、癌幹細胞無血清培養基、循環腫瘤細胞擴增方法），並完成 PBX1 小分子藥物的美國專利臨時案申請。目前 PBX1 抑制劑不僅成功證明能直接阻斷 PBX1-DNA 結合界面，更在多種癌症模型中展現高度抑制腫瘤生長與轉移的效果，動物實驗在 100 倍劑量亦未觀察到明顯毒性，顯示其為具潛力的完全新創（first-in-class）轉錄因子抑制藥物，可望申請 FDA orphan drug designation 並推進 pre-IND 研究。

此外，本計畫亦在奈米藥物的研發上取得重大突破，成功建立以 GLUT1 介導胞移作用為基礎之葡萄糖胺標記奈米載體（glucosamine-labeled liposomal PBX1 inhibitors），可有效累積於腫瘤缺氧區，並解決癌幹細胞常因代謝代償（如由 glutaminolysis 轉向 glycolysis）而逃避免疫或藥物治療的困境。此奈米藥物策略具高穩定性、粒徑均一，並已證實能提升 PBX1 抑制劑於缺氧區的精準遞送效率，為後續結合 GLS 抑制劑之合成致死治療奠定基礎。

在跨國合作方面，本計畫已促成與美國哈佛大學、約翰霍普金斯大學、NIH 等多位教授展開合作洽談，並規劃多項移地研究與共同論文撰寫，逐步形成長期國際科研鏈結。在人才培育方面，本計畫共培訓國內外學生與研究人員超過二十名，包括大專生、碩博士生以及博士後研究員，並成功協助國際學生獲得國科會博士獎學金，展現本計畫在跨文化科研教育上的貢獻。此外，計畫主持人並獲得臺



| | |
|---|---|
| | 一、沈耀安副教授之癌幹細胞無血清培養技術與循環腫瘤細胞擴增方法，具高度臨床檢測市場價值，將衍生新創公司並完成技轉。<br><br>二、PRP-PLUS 技術已吸引國內再生醫學公司展開產學合作並授權，未來將推動於皮膚醫學、運動醫學及抗老化治療之商品化應用。<br><br>三、本計畫研發之癌幹細胞擴增與奈米藥物平台可降低檢測成本、縮短分析時間，未來若商品化可達成>30%成本下降，具顯著商業競爭力。 |
| 社會影響 | 請先敘明學者之任職單位、姓名：(1)媒體露出，請詳列年度、成果主題、媒體管道及則數統計；(2)擔任學術社群/社會重要職務，請說明社群及職務名稱、屆期年度，並例舉效益。諸如：<br><br>一、沈耀安副教授執行本計畫之癌幹細胞研究與國際合作成果，於臺北醫學大學研究新聞、健康科普平台與媒體消息多次曝光，有效將癌症精準醫療知識推廣至大眾。<br><br>二、研究成果可加速未來癌症檢測與治療之普及性，包括降低檢測成本、縮短分析時效，對臨床端與偏鄉醫療均具正面效益。<br><br>三、計畫期間培育多名國內外青年研究者，提升台灣癌症研究能量並強化社會整體科研人才結構。 |
| 國際合作 | 請先敘明學者之任職單位、姓名：(1)國際合作，請詳列合作對象名稱、合作年度、合作主題，並例舉對我國之效益；(2)獲邀擔任國際重要職務/成果發表，請說明職務/成果發表名稱、年度，並例舉對我國之效益。諸如：<br><br>一、沈耀安副教授於 2025 年與美國哈佛大學醫學院生醫資訊學系余坤興教授展開合作洽談，合作主題含癌症轉譯資訊學與新型生物標記物分析，對我國 AI 醫學合作具有策略性價值。<br><br>二、2025 年與美國約翰霍普金斯醫學院多位教授（Ie-Ming Shih、Tian-Li Wang、Gabrielson、Borahay、Kiemen）推動癌症發展機制與治療策略研究合作，並規劃移地研究，有助我國癌症學術研究能量提升。<br><br>三、受邀於 CRS Annual Meeting（2025, Philadelphia）發表技術成果，提升台灣在奈米醫學與癌症療法領域能見度。 |
| 人才培育 | 請先敘明學者之任職單位、姓名：(1)碩博士培育/研究團隊建立，請提供人數統計及統計年度區間；(2)課程開設，請說明開設年度、課程名稱/課程數，並例舉效益。諸如：<br><br>一、計畫期間（2024–2025）共培育國內大專生 14 名、國際碩士生 4 名、國際博士生 3 名及博士後研究員 2 名，總計超過 20 名研究人才。<br><br>二、指導學生於國內外學術會議發表研究成果，包括 CRS Annual Meeting、TMU–CWRU、UTS × UAAT 等國際研討會。<br><br>三、成功協助國際學生 Dinesh Kute 獲得國科會博士生研究獎學金，展現優異指導與跨國人才育成成效。 |
| 其他效益 | 請先敘明學者之任職單位、姓名，並補充效益年度。諸如：<br><br>一、透過本計畫建立癌幹細胞代謝與轉錄調控之研究平台，並整合多項專利技術形成精準治療分析系統，為後續跨國研究合作奠定基礎（2024–2025）。 |

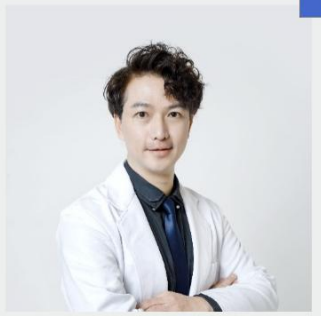
# 學者專區



年度 | 計畫別 | 領域別 | 請輸入關鍵字 | 搜尋

計畫別
愛因斯坦培植計畫
哥倫布計畫
2030跨世代年輕學者方案

113 生科



## 沈耀安

臺北醫學大學
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## 柯立偉

國立陽明交通大學
電控工程研究所

113 工程

## 陳奕廷

國立陽明交通大學
資訊工程學系

113 工程

## 劉振良

國立臺灣大學
材料科學與工程學系暨研究所


## 11/12活動議程

地點：臺大醫院國際會議中心4樓401室（臺北市中正區徐州路2號）

| 時間 | 議程 | |
|---|---|---|
| 13:00~13:30 | 報到暨活動交流 | |
| 13:30~13:40 | 開場致詞　國科會 吳主任委員誠文 | |
| 13:40~14:20 | 綜合座談暨大合影 國科會 吳主任委員誠文 | |
| 14:20~14:50 | 執行成果分享I | 1. 吳添立 / 國立陽明交通大學電子研究所 副教授<br>2. 張泰榕 / 國立成功大學物理學系 教授<br>3. 黃彥婷 / 國立臺灣大學大氣科學系暨研究所 副教授 |
| 14:50~15:50 | 茶敘暨成果交流 | |
| 15:50~16:20 | 執行成果分享II | 1. 李銘晃 / 國立清華大學動力機械工程學系 副教授<br>2. 何銘洋 / 國立臺灣大學生命科學系 副教授<br>3. 張書蓉 / 國立臺灣大學醫學院微生物學科(所) 助理教授 |
| 15:20~16:50 | 執行成果分享III | 1. 洪崇展 / 國立成功大學土木工程學系 特聘教授<br>2. 張景安 / 國立政治大學阿拉伯語文學系 副教授<br>3. 林盈仲 / 國立臺灣大學生命科學系 教授 |
| 16:50~ | 賦歸 | |

# 2030 跨世代年輕學者交流會


2030跨世代年輕學者交流會

問與答 9+ | 民意調查

**為何要從事研究職涯?** 80

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3. 滿足好奇心 56
6. Do something new 45
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2030跨世代年輕學者交流會

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1.Scientist 68
8.Dreamer 57
7.Communicator 54
3.Manager 41
4.Philosopher 38
5.Strategist 34
2.Engineer 30
6.Psychologist 25

2030跨世代年輕學者交流會

問與答 | 民意調查

**匿名** 7分鐘前 1

請問院長對於台灣產業較為偏重特地產業造成學生的群聚效應的影響與看法。

**匿名** 8分鐘前 0

如果一個年輕學者的領域在台灣是一個全新的領域，對於剛回台的年輕學者同時要做自己的研究，又要開拓與建立新領域的生態系統，不知道有什麼建議？ （已編輯）

**匿名** 20分鐘前 2

年輕的老師通常都要兼任行政，如何兼顧研究和教學等工作

**匿名** 22分鐘前 0

在台灣從事研究的優勢是什麼 & 該如何善用？

**匿名** 2小時前 1

您回台灣時，認為自己可以貢獻的社會貢獻研究是什麼？您現在這個時刻，認為中研院未來5年可能產生的社會貢獻是什麼？

2030跨世代年輕學者交流會

問與答 | 民意調查

**要研究什麼樣的問題?** 86

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2030跨世代年輕學者交流會

問與答 | 民意調查

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2030跨世代年輕學者交流會

問與答 | 民意調查

**你做的事是有急迫性(Urgency)還是有重要性(Importance)?** 71

2. 重要性(Importance) 61
1. 急迫性(Urgency) 22


這是一場馬拉松，不是短跑。
把該寫的寫好，把該努力的做到。
剩下的，就交給運氣與好心的審查委員吧。
祝大家申請順利，Good luck！

**Contact Information:**
**Prof. Yao-An Shen**
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Prof. YAS
Entertain Every Possibility

YAS LAB
Enlightening Paths in Cancer Stem Cell Research

# ACKNOWLEDGMENT

Enlighten
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- ***Development of Acid-Responsive Mesoporous Silica Nanoparticles for Delivery of PBX1 Inhibitors Targeting Cancer Stem Cell Transcriptional Activity*** (NHRI-EX114-11404E1)

Funding from **National Science and Technology Council (NSTC)**

- ***Utilizing Glucosamine-Labeled Nanodrugs as a Novel Pancreatic Cancer Stem Cell Therapy to Counteract Metabolic Compensation and Synergistically Inhibit Transcriptional Activity*** (NSTC 113-2628-B-038-012)
- ***Commercial Applications of Technique Platform Development for Cancer Stem Cell Isolation and Cell Therapy*** (NSTC 113-2823-8-038-001)
- ***Investigation on the Synergistic Effect of a Combination of PCSK9 Inhibitors and Hyperthermia in Hepatic Cancer Stem Cells*** (NSTC 112-2314-B-038-081)
- ***Technique Platform Development for Cancer Stem Cell Isolation and Cell Therapy*** (NSTC 112-2823-8-038-001)
- ***Development of First-in-class Transcription Factor Drug Targeting Cancer Stem Cells*** (NSTC 111-2622-B-038-008)
- ***Reversing Metabolic Compensation to Overcome Recurrence in Ovarian Cancer by Inhibition Of MYC/GLS Axis*** (MOST 109-2314-B-038 -021 -MY3)


# Thank You For Listening.

## Any Questions?

臺北醫學大學
TAIPEI MEDICAL UNIVERSITY