HKUMed discovered beta-amyloid deposition to be a novel disease mechanism for Biliary Atresia

港大醫學院發現β-澱粉樣蛋白異常沉積是膽道閉塞的新發病機制

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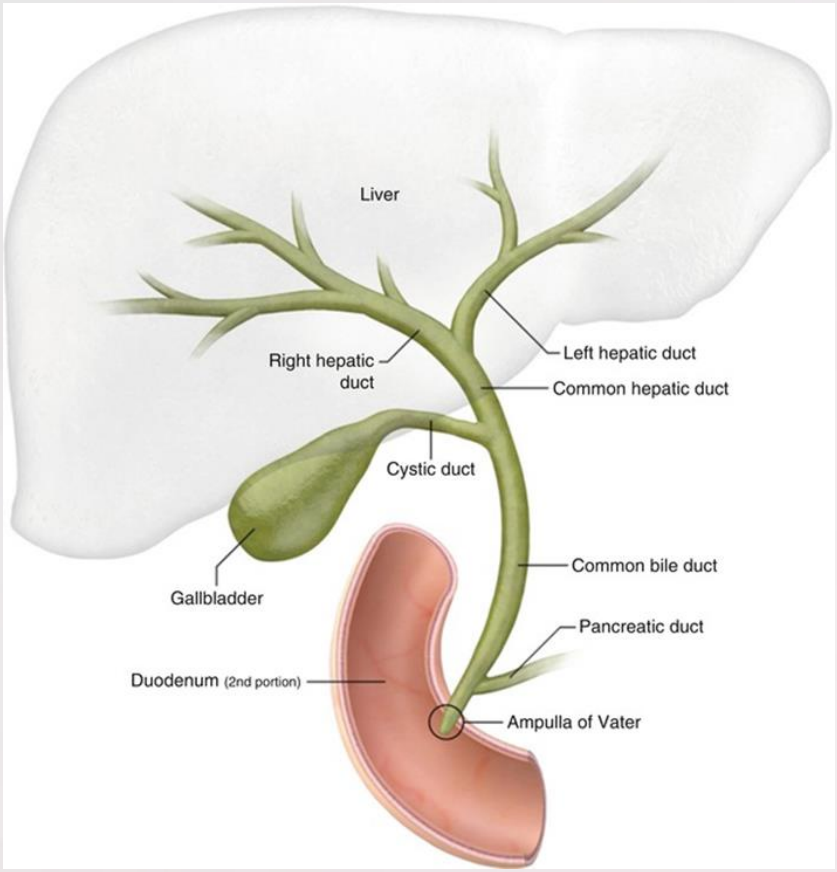
Biliary atresia (BA) 膽道閉塞

- Congenital cholangiopathy resulting in biliary stasis
- Commonest cause of neonatal obstructive jaundice
- Aetiology unknown
- Liver failure if left untreated

- 膽管先天性畸型疾病，膽汁無法引流至十二指腸
- 最常見新生兒膽汁排出障礙的原因
- 至今仍未能充分掌握導致該罕見病的成因
- 如未能及時治療可導致肝衰竭

Clinical Symptoms
臨床症狀

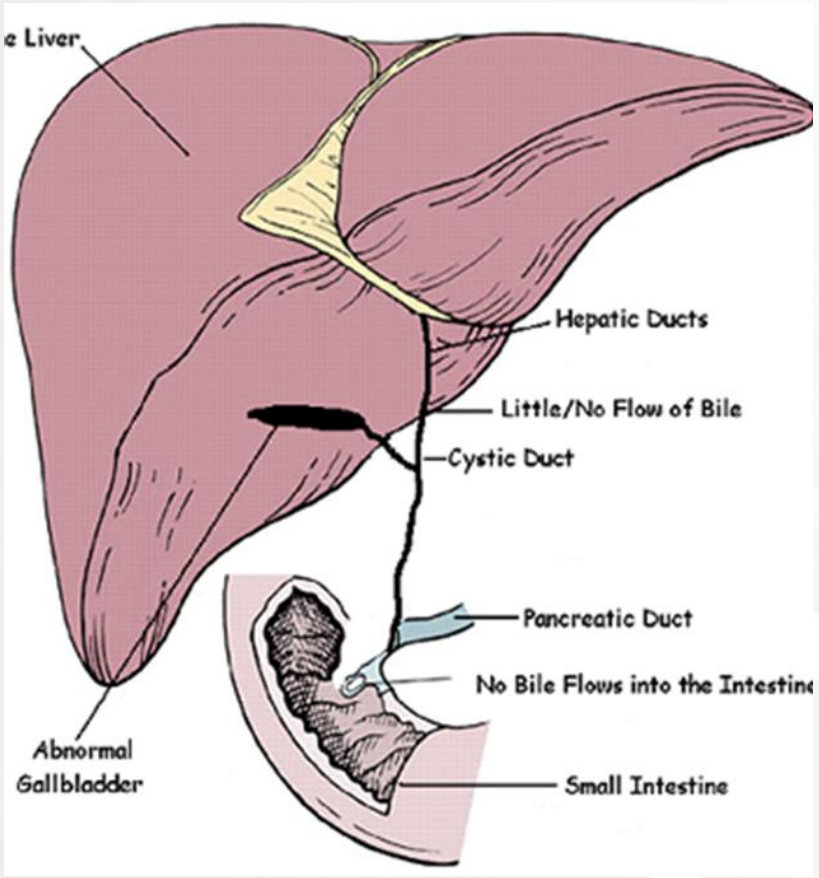
Normal bile duct 正常膽管



radiologykey.com

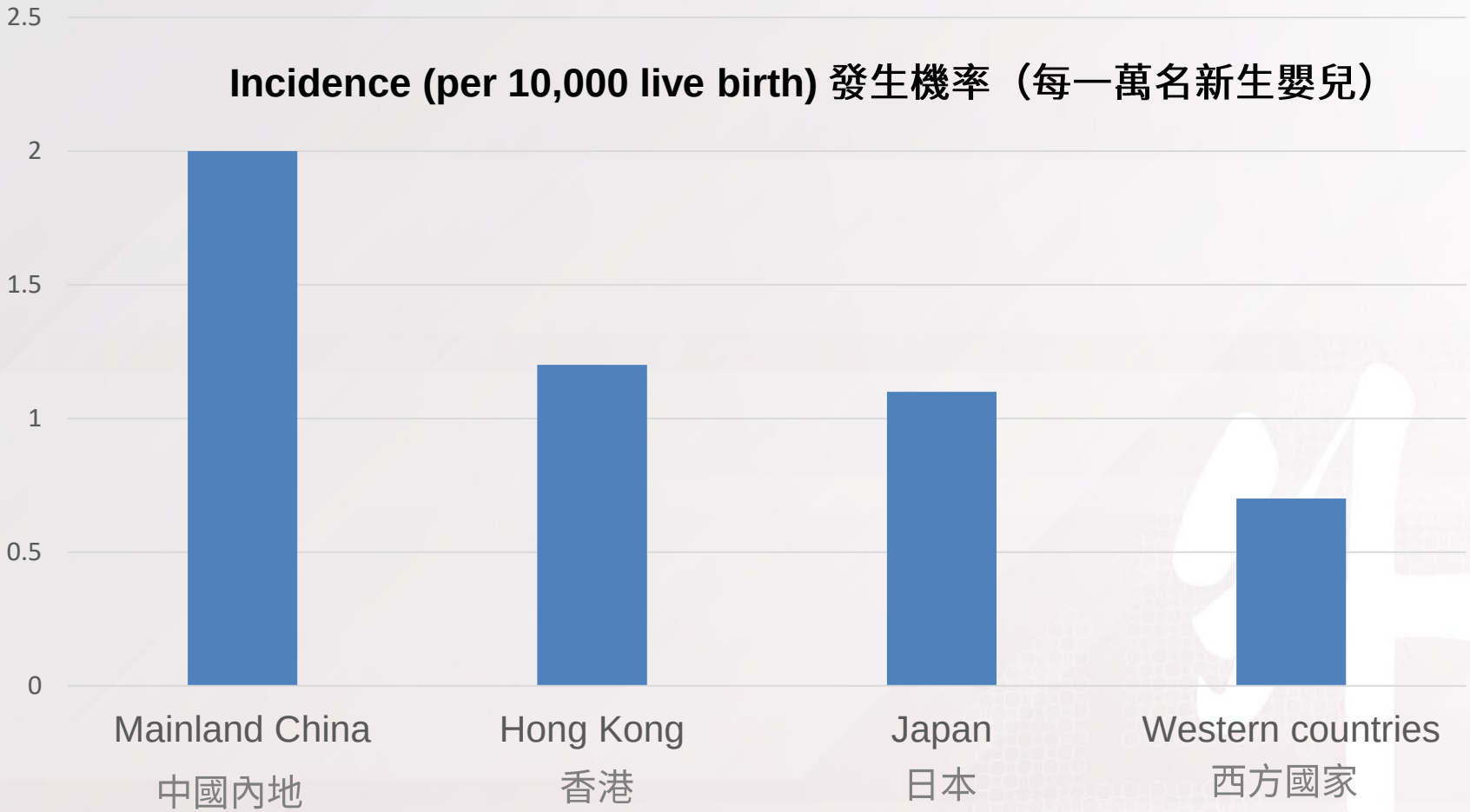
Biliary Atresia 膽道閉塞

膽管受纖維化發炎摧毀而阻塞



Kasai M et al. Shujutsu, 1959

BA is especially common among Asians
膽道閉塞於亞洲特別常見



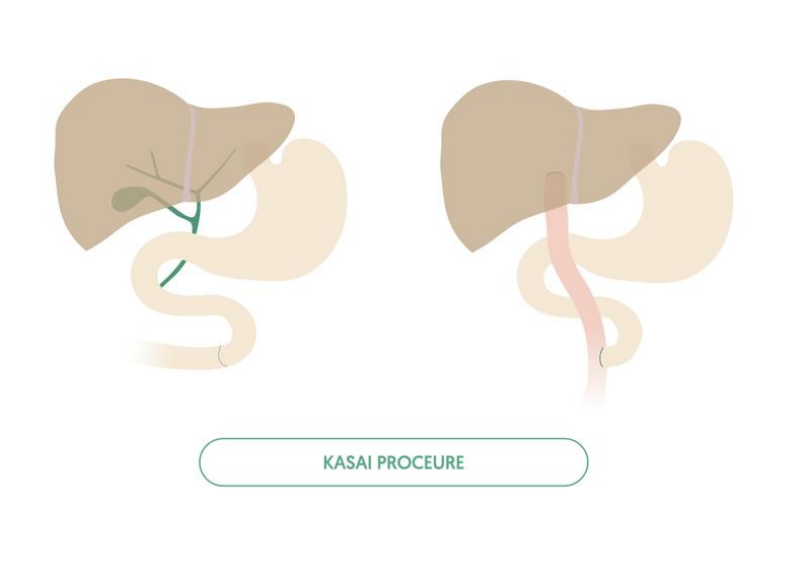
Data extracted from Chung et al. Semin Pediatr Surg, 2020

Kasai portoenterostomy restores bile drainage in only 60-70%

肝門空腸吻合手術（「葛西手術」）後只有六至七成病人可恢復排出膽汁

- Only treatment for BA is Kasai surgery: excision of extrahepatic fibrous cord and bilio-enteric anastomosis

  治療膽道閉塞唯一方法是「葛西手術」：切除纖維化肝門組織，接駁肝門與小腸

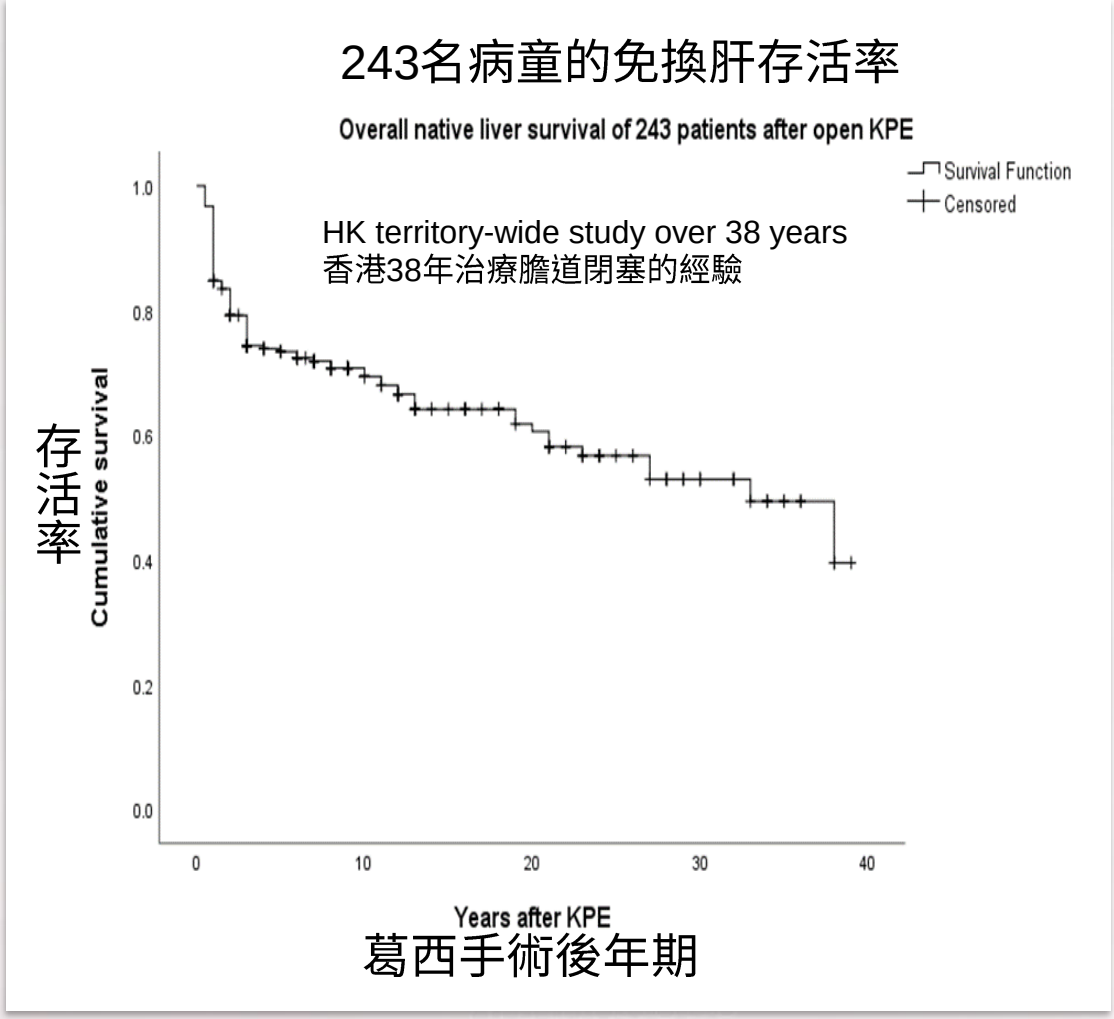


Reported outcome of Kasai operation
世界各地「葛西手術」的成效

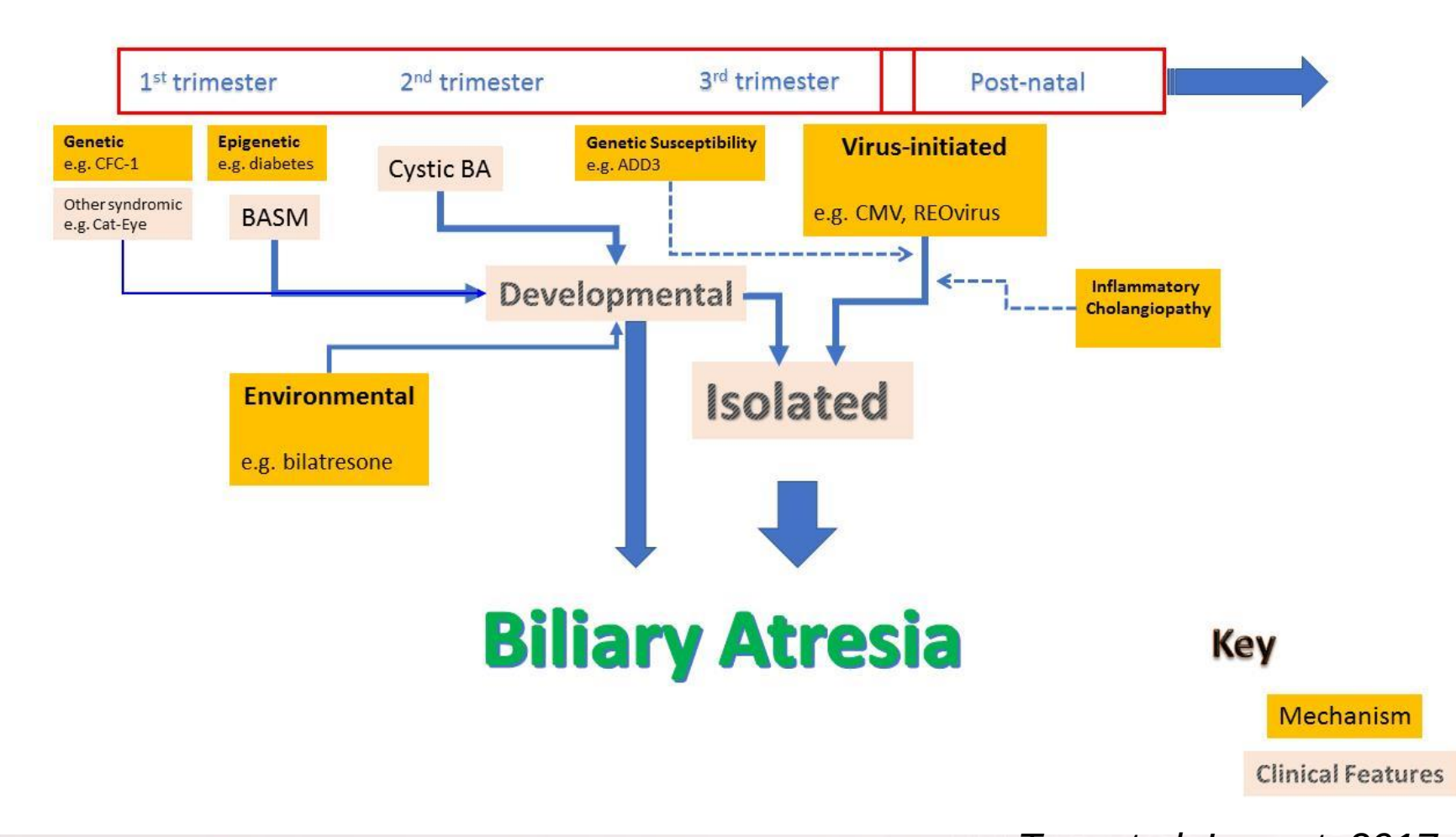
	Japan 日本	China 中國內地	Hong Kong 香港	United Kingdom 英國	France 法國	Canada 加拿大
Long term native liver survival 免換肝存活率	20 years: 49%	20 years: 29%	**20 years: 61%**	10 years: 44%	10 years: 36%	10 years: 26%

Residual problems after Kasai portoenterostomy
膽道閉塞兒童病患接受「葛西手術」的後遺症

- Recurrent cholangitis (bile duct infection)
  膽管炎：50%
- Progressive liver failure
  逐漸肝臟衰竭：50%
- Growth impairment
  生長遲緩：40%
- Portal hypertension
  肝門靜脈高壓：60%-70%
  - Oesophageal varices
    食道靜脈曲張
  - Hypersplenism 脾臟腫大



Aetiology of BA is unknown
膽道閉塞的成因未明



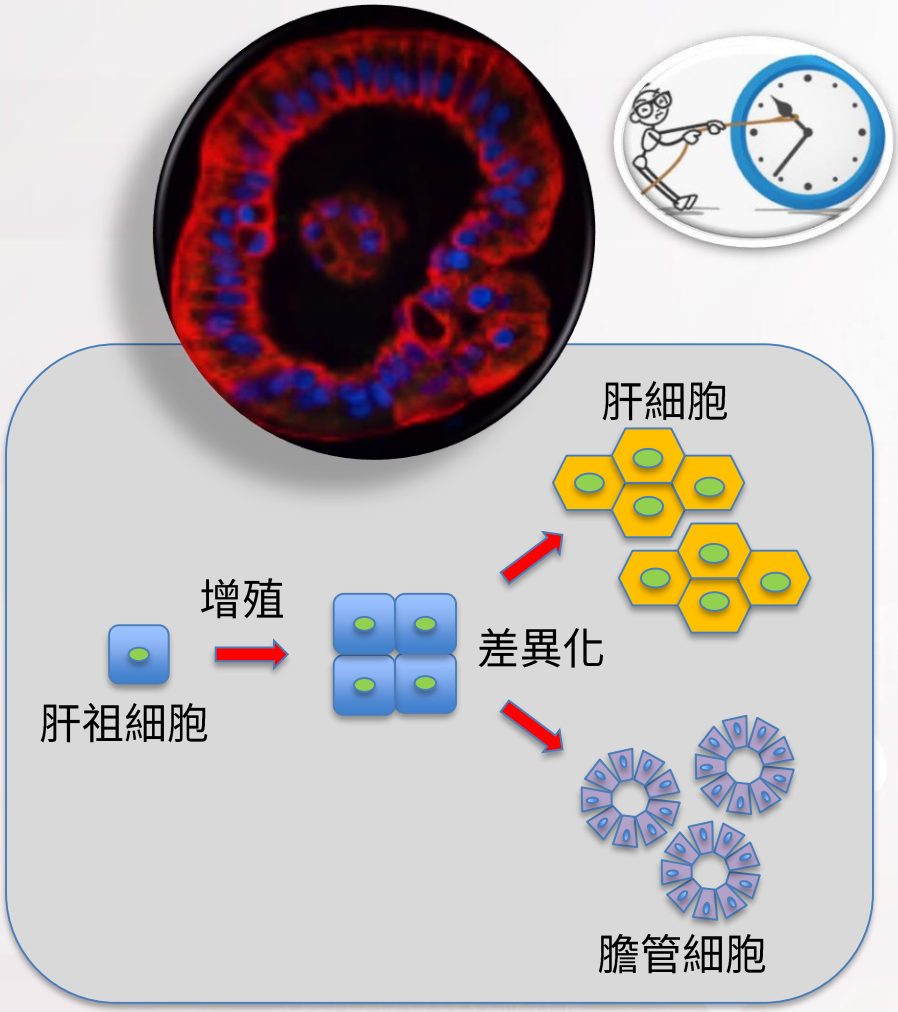
Tam et al. Lancet, 2017

Any new treatment to improve the outcome?

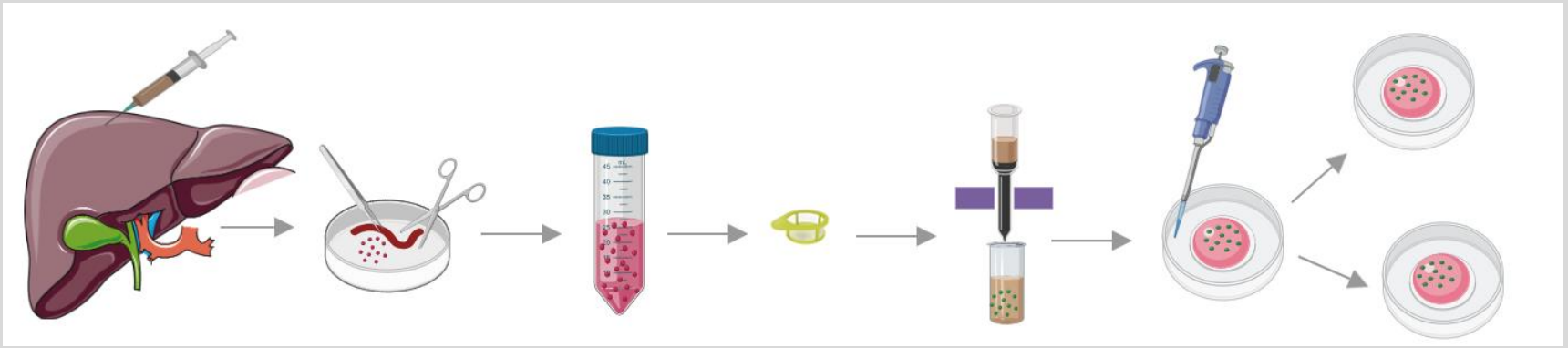
有改善膽道閉塞治療成效的新方法嗎？

Liver Organoids 肝臟類器官

- A cell/tissue-derived culture system that can mimic a real-life liver (*in vivo*) development “in a dish”
  以細胞/組織培植技術，在培植皿上模擬真實肝臟（體內）發育環境
- Turn the biological clock back to investigate the development of bile duct cells & liver cells “in a dish”
  把生物時鐘撥至早期的發育階段，以研究膽管細胞和肝細胞的發育
- None has successfully developed BA organoids
  未有團隊成功培植膽道閉塞肝臟類器官



港大譚廣亨教授團隊首次成功培植膽道閉塞肝臟類器官



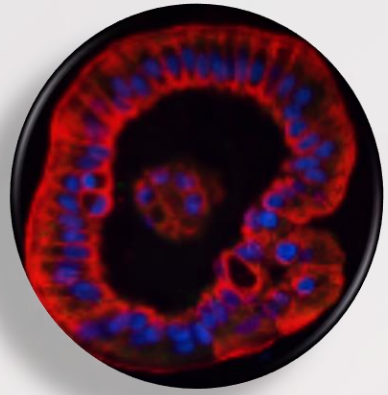
BA & Control Liver
膽道閉塞及對照組病人肝臟

BA & Control Liver Organoid
培植膽道閉塞及對照組肝臟類器官

- Novel human BA liver organoid allows dissection of hitherto unknown disease pathways
  利用膽道閉塞肝臟類器官，剖析該疾病未知的發病機制
- Experimental validation of the key biological findings in settings closely replicating the clinical situation
  在實驗室模擬臨床環境，以驗證箇中所發現的關鍵生物學信息

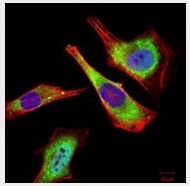
Utilisation of BA organoids 利用膽道閉塞肝臟類器官

BA & Control Liver Organoid
膽道閉塞及對照組肝臟類器官

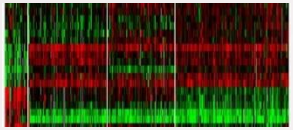


Morphology
形態學

Cell Biology
細胞生物學

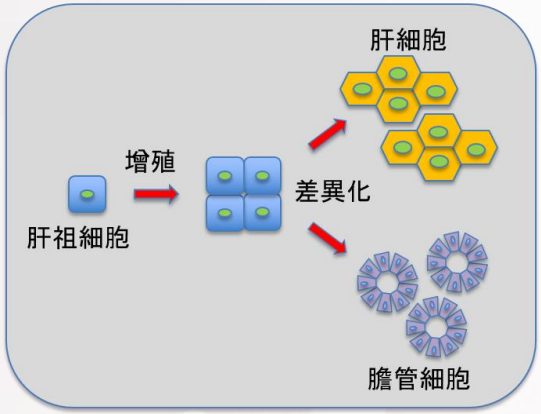


RNA sequencing
基因表達分析



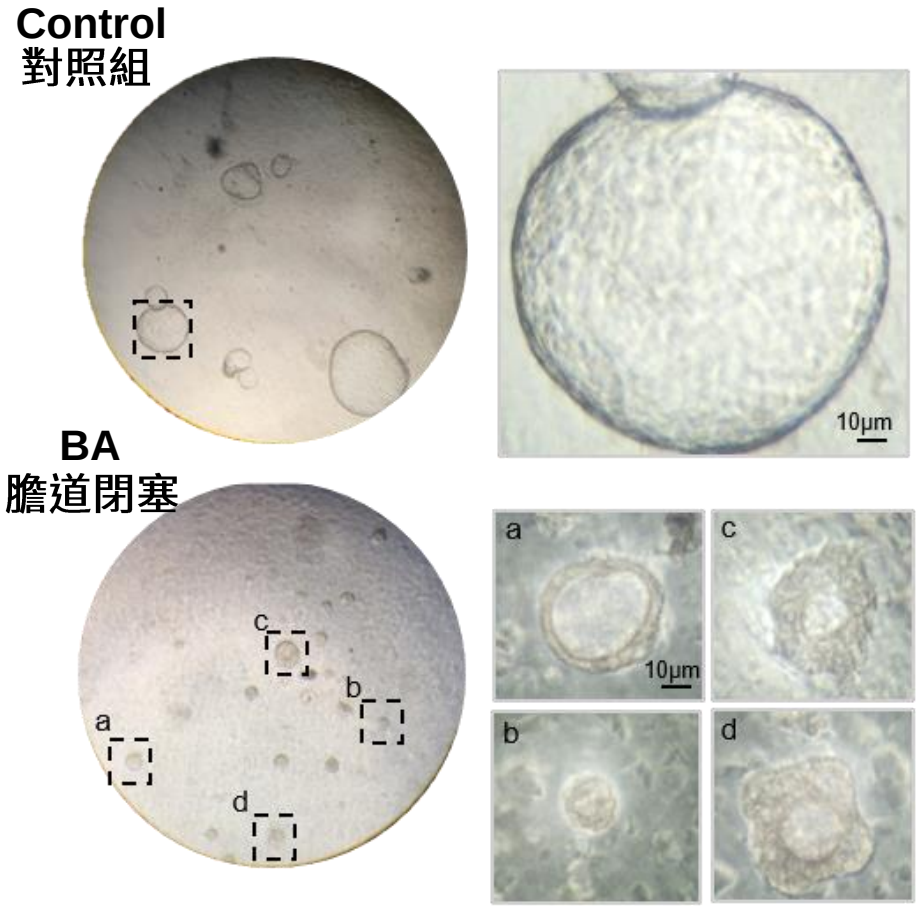
Bioinformatics
生物信息學

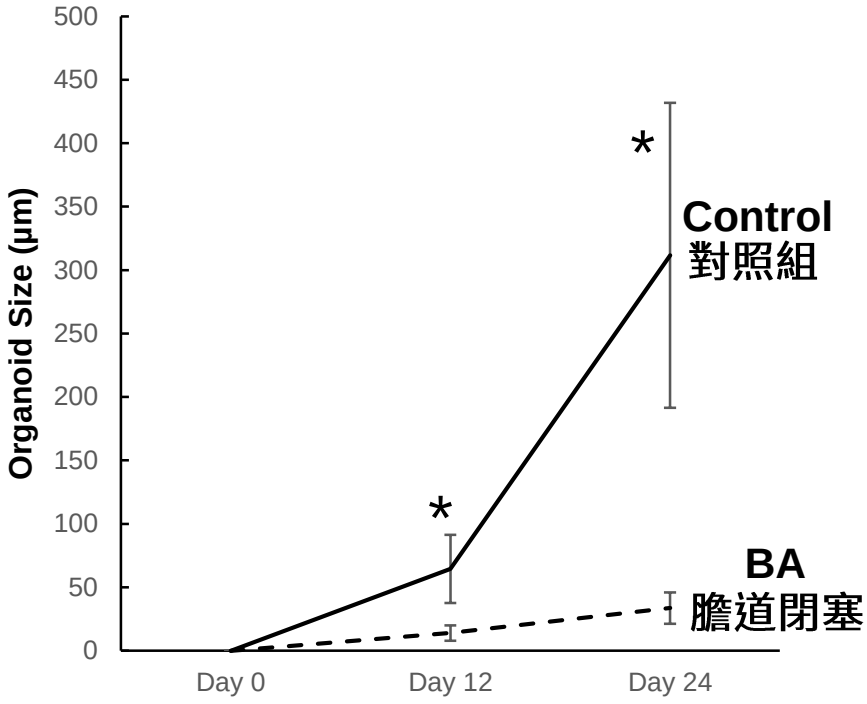
BA vs Control
膽道閉塞與對照組



- Unknown disease pathways
  未知的發病機制
- Experimental validation
  進行驗證

BA organoids display abnormal morphology & retarded growth
膽道閉塞肝臟類器官呈現生長阻滯、結構形態異常

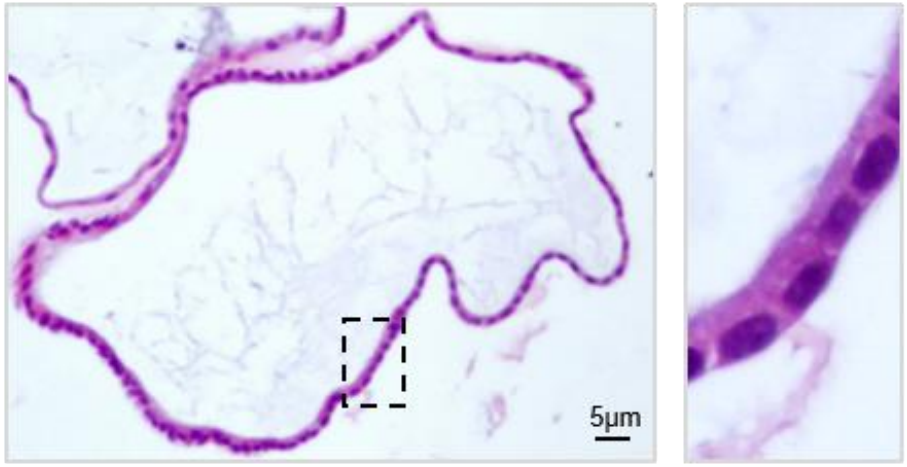


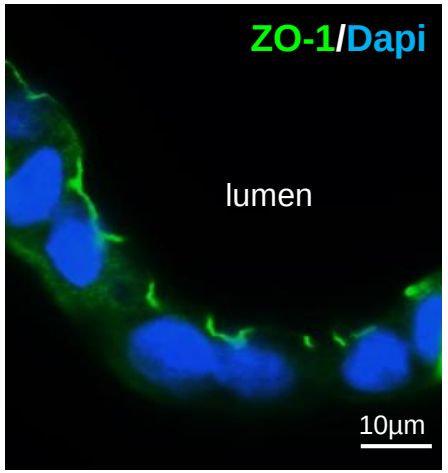


BA organoids display disturbed cell organisation & polarity (apex-base orientation)

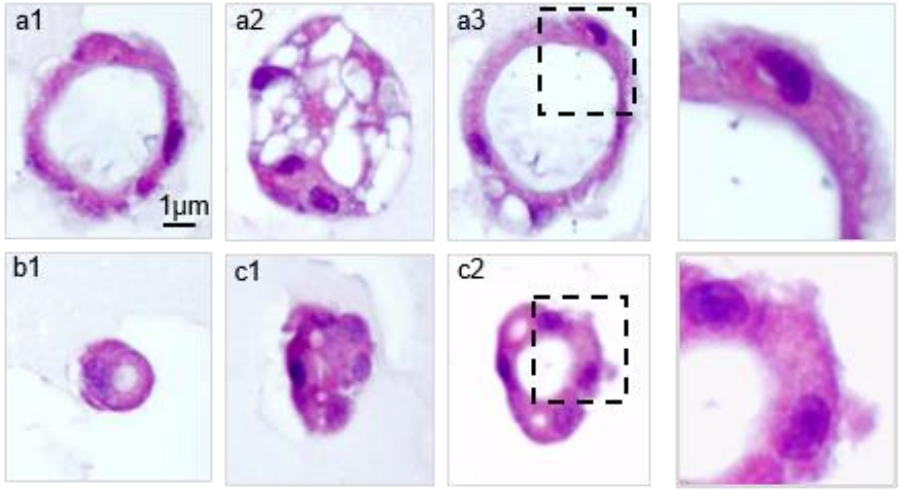
膽道閉塞肝臟類器官呈現組織及細胞紊亂（頂-底極性逆轉）特徵

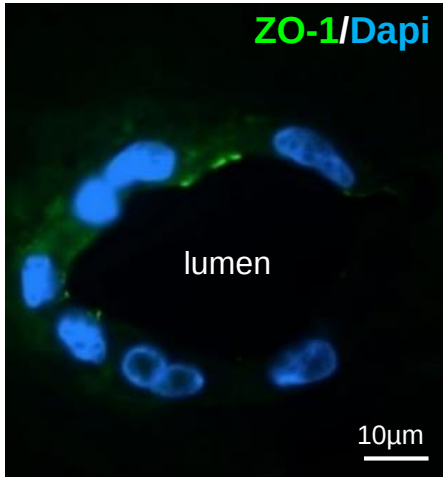
Control
對照組



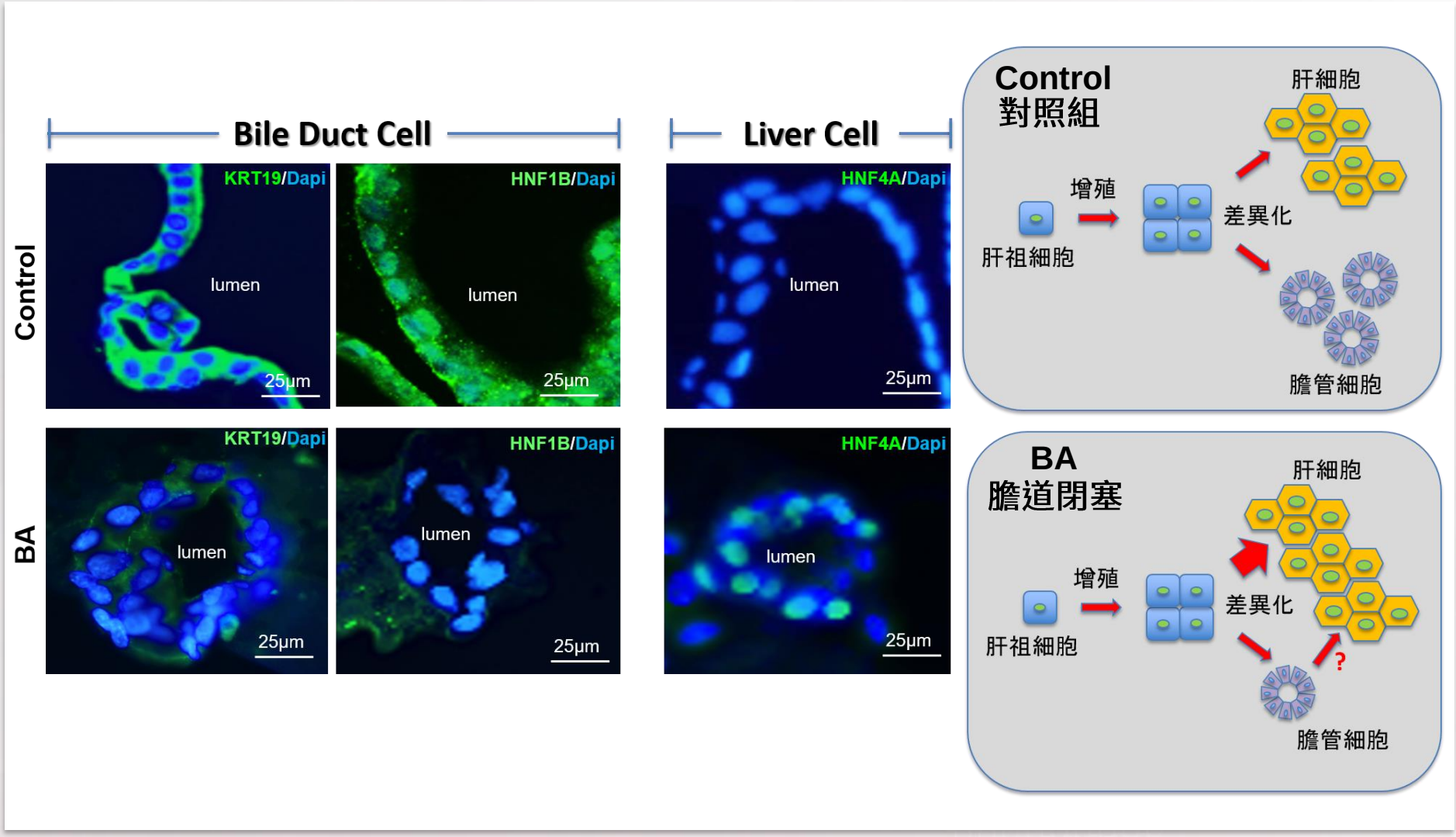


BA
膽道閉塞

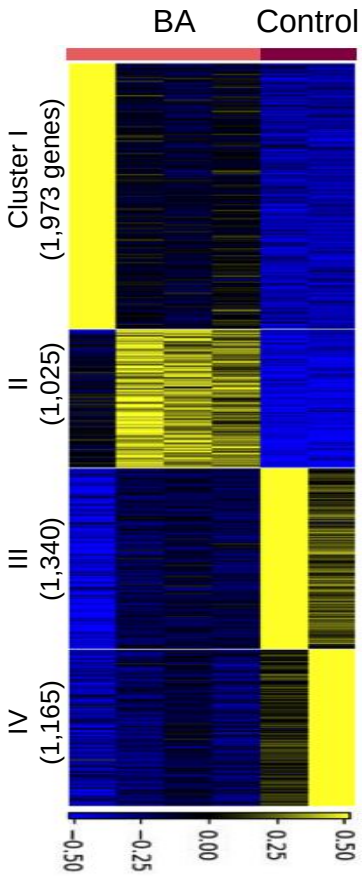


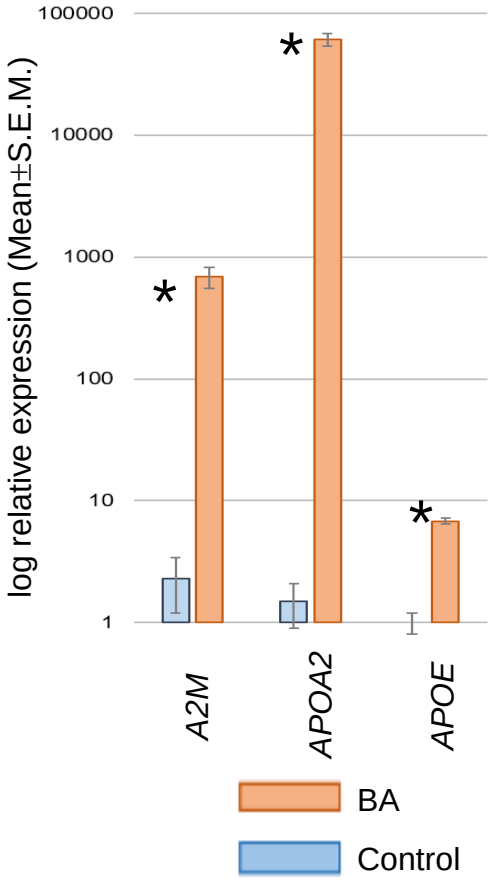


BA organoids display a developmental shift from bile duct cells to liver cells
膽道閉塞肝臟類器官原本發育成膽管細胞的幹細胞轉化為肝細胞



Altered expression of beta-amyloid genes in BA liver organoids
膽道閉塞肝臟類器官呈現β-澱粉樣蛋白相關基因的表達異常

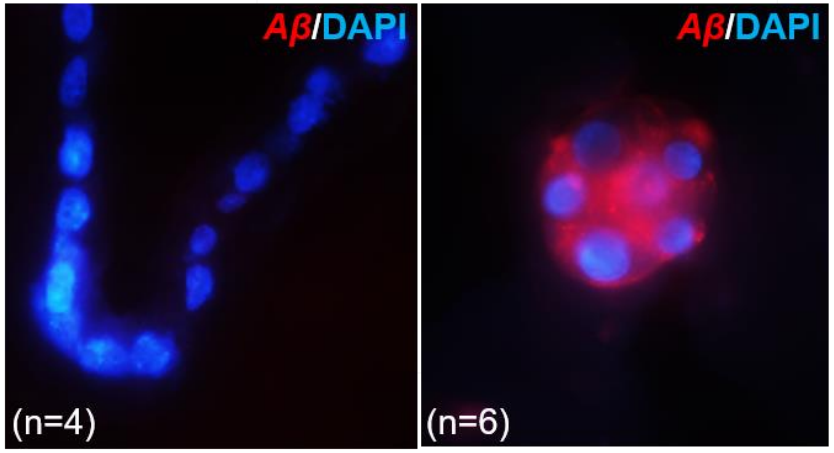




Organoids 肝臟類器官

Control
對照組

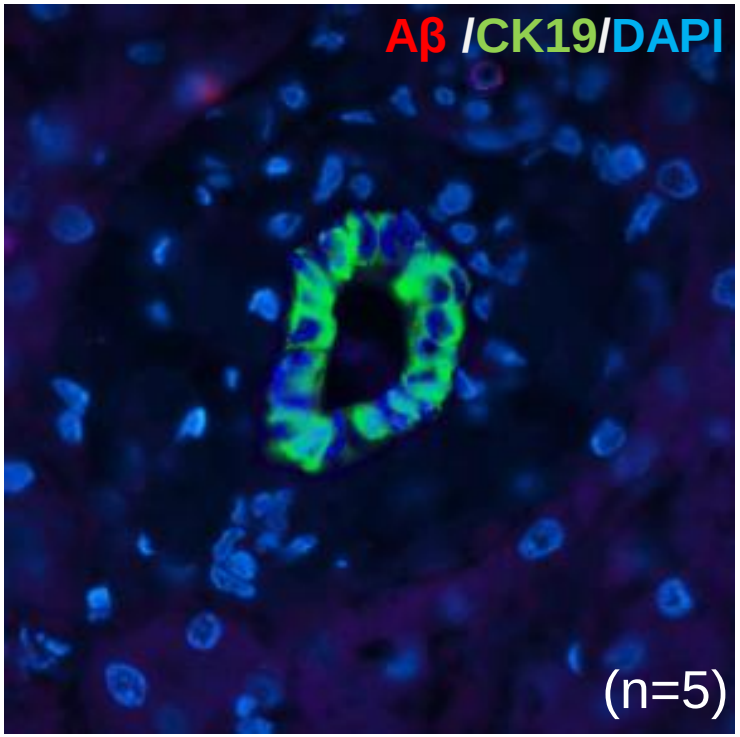
BA
膽道閉塞



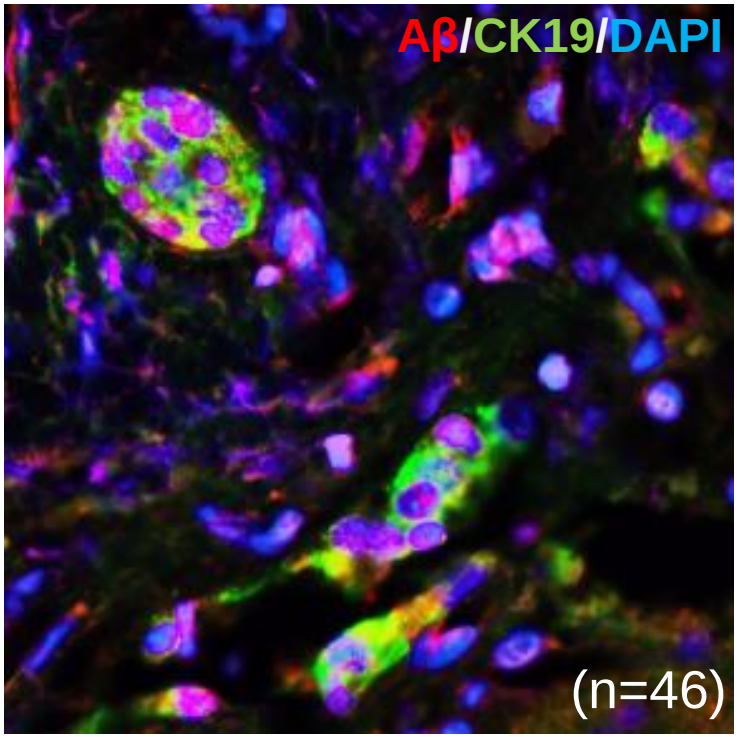
Deposition of Aβ in BA livers
膽道閉塞病人肝臟活體樣本同樣發現膽管周圍存在β-澱粉樣蛋白沉積

肝臟活體樣本（Liver Biopsies）

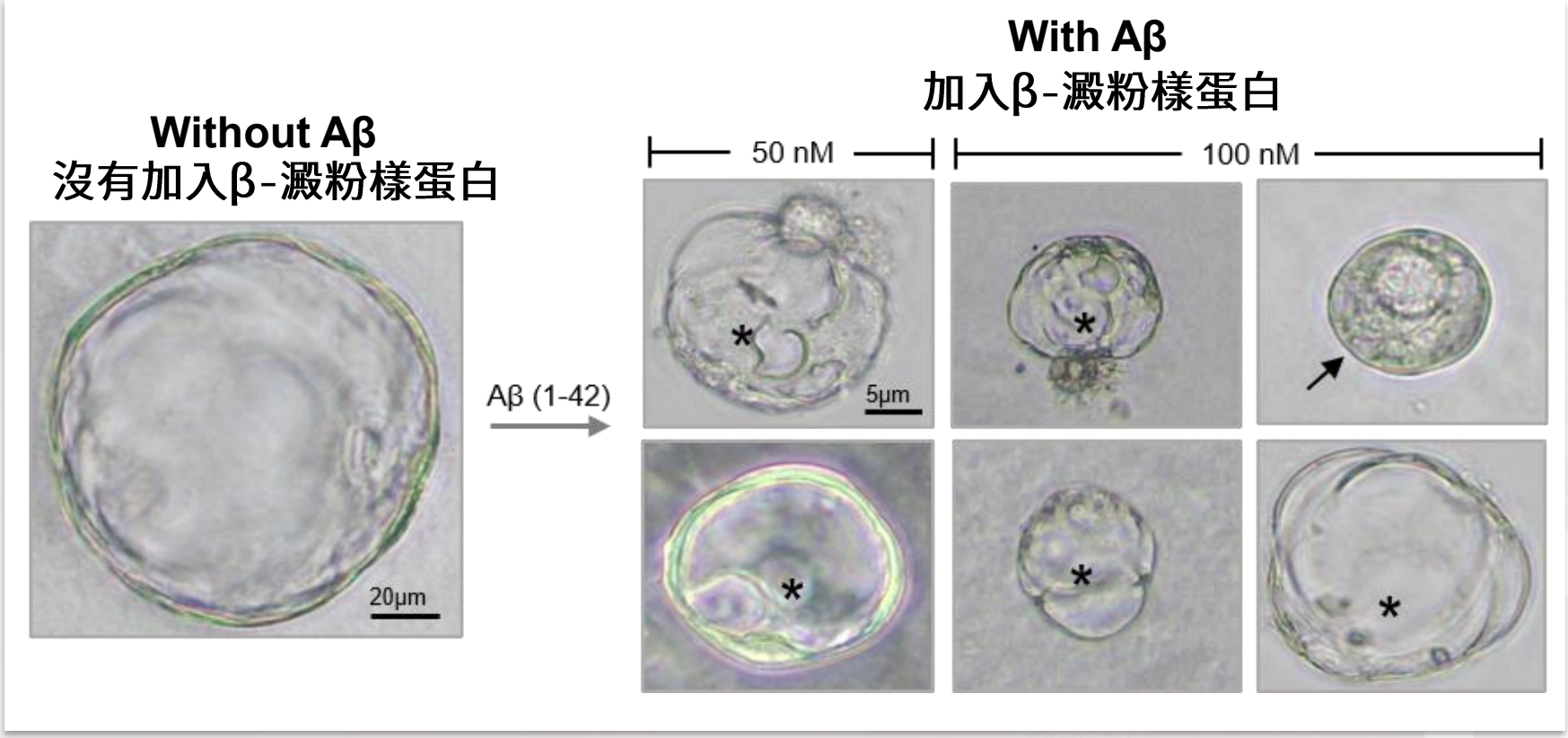
Control
對照組



BA
膽道閉塞



Aβ induces BA features in normal organoids
加入β-澱粉樣蛋白引致正常肝臟類器官產生膽道閉塞特異性細胞形態



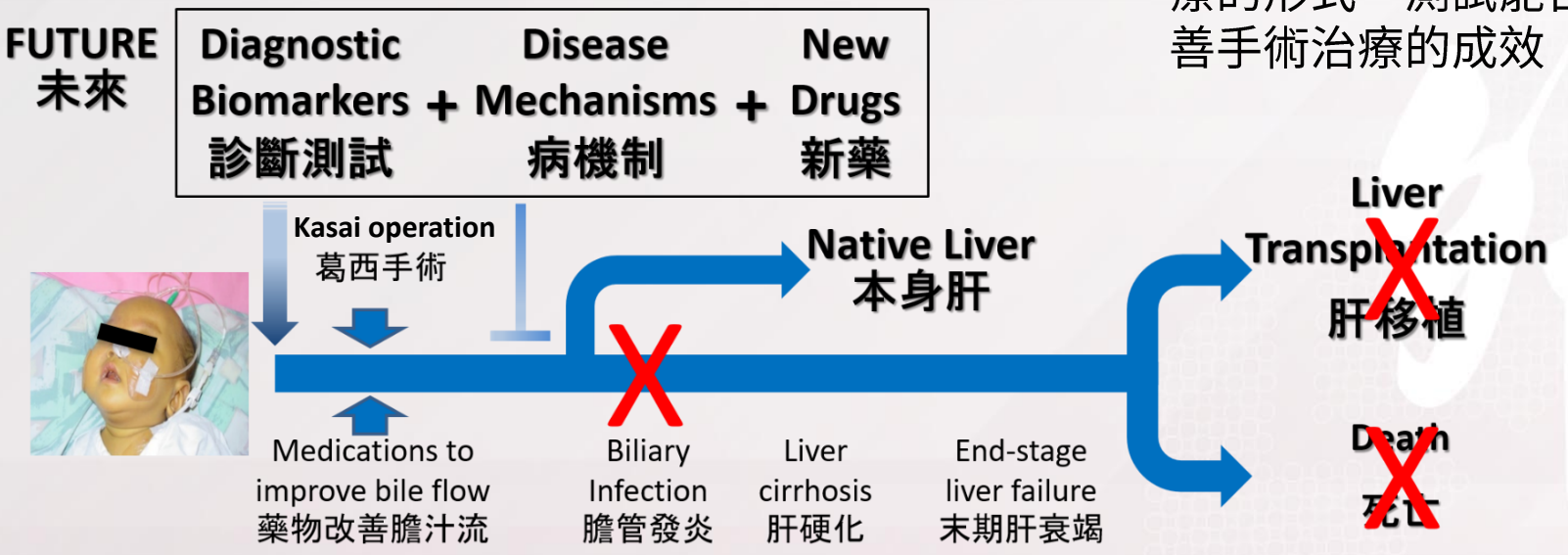
Summary 總結

- HKUMed research team is the first to successfully develop liver organoids for BA study
  團隊首次成功研發肝臟類器官並對膽道閉塞進行相關研究
- Identify beta-amyloid deposition
  發現膽道閉塞膽管周圍有β-澱粉樣蛋白沉積
- Beta-amyloid deposition is also the main pathological feature of Alzheimer's disease and Cerebral Amyloid Angiopathy
  β-澱粉樣蛋白是阿茲海默症及大腦澱粉樣血管病的主要病理特徵
- The finding of a novel disease mechanism for BA paves the way for innovative diagnostic and therapeutic strategies to radically improve treatment outcome
  這一研究發現揭示膽道閉塞的新發病機制，為創新的診斷及治療策略提供發展方向，有助大幅改善治療成效

Implications 研究意義

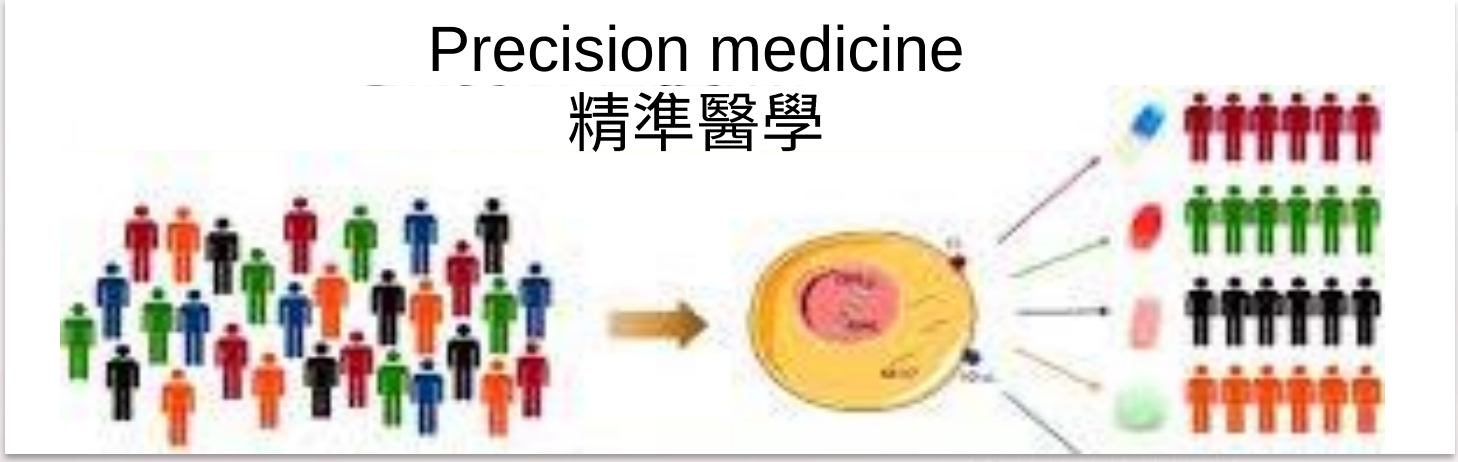
- Beta-amyloid may be used as a biomarker for early detection of BA, thus offering an opportunity to prevent or ameliorate the inflammatory-fibrotic pathology before the disease process becomes well advanced.
- Anti-beta amyloid and related therapies already in clinical trials for Alzheimer's disease may be tested as adjunct treatment to improve surgical outcome for BA.

- β-澱粉樣蛋白日後或可用作膽道閉塞的生物標記，以助及早診斷，在此疾病形成及惡化前進行干預，以預防甚至逆轉膽管因纖維化發炎致閉塞的情況
- 用以治療阿茲海默症的抗β-澱粉樣蛋白藥物及相關治療已達臨床試驗階段，可以輔助性治療的形式，測試能否進一步改善手術治療的成效



Implications 研究意義

- HKUMed's unique 'patient-based' BA organoid faithfully replicates patient-specific pathobiology to advance precision medicine
- 這獨特的「以病人為基礎」的膽道閉塞肝臟類器官可複製個別病人的特異性病理生物學情況，以用作精準醫學



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