外泌體的臨床應用與發展趨勢

黃奇英特聘教授兼副院長
國立陽明交通大學藥物科學院生物藥學研究所

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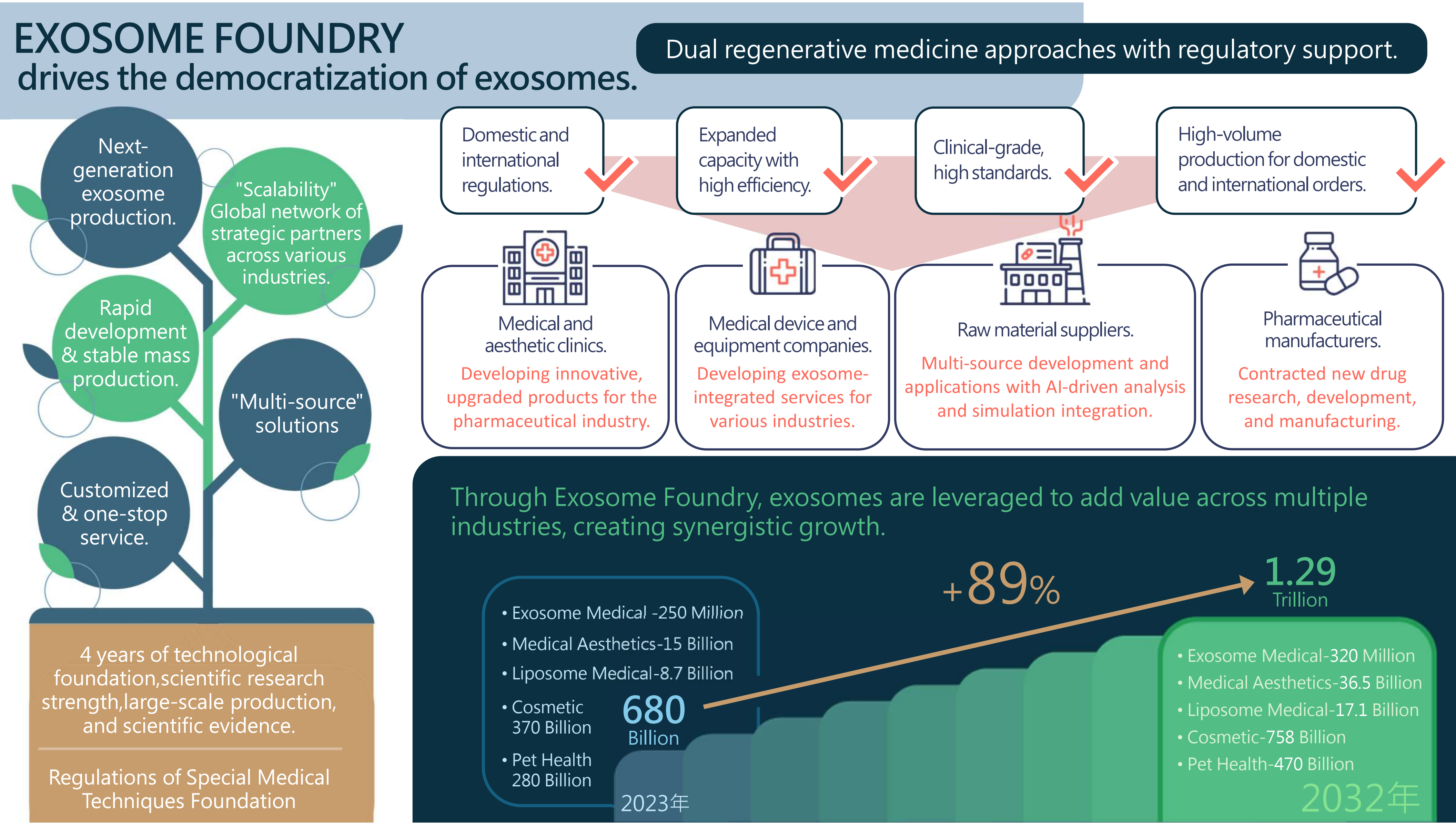

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• Exosome Medical -250 Million
• Medical Aesthetics-15 Billion
• Liposome Medical-8.7 Billion
• Cosmetic 370 Billion
• Pet Health 280 Billion
680 Billion
2023年
+89%
1.29 Trillion
• Exosome Medical-320 Million
• Medical Aesthetics-36.5 Billion
• Liposome Medical-17.1 Billion
• Cosmetic-758 Billion
• Pet Health-470 Billion
2032年

外泌體在台灣合法嗎?

“鑑於外泌體相關治療之臨床試驗多處於探索階段，尚未完成人體試驗以證療效，且目前國內尚未核准外泌體之治療行為，醫療機構執行新醫療技術人體試驗前,必須擬擬訂計畫，經中央主管機關申請核准才能執行外泌體相關治療。”

台灣衛福部於2024年3月21日宣布，可有條件將人類來源外泌體製作成保養品，需符合相關認證規定，以確保安全。

https://www.fda.gov.tw/tc/newsContent.aspx?cid=3&id=30445
https://celltherapy.mohw.gov.tw/education_page.htm?id=120

三類外泌體臨床產品的監管定位比較

產品型態	主管機關常見分類	代表法規依據	Note
天然 EV (未裝載重組核酸，僅純化分離)	生物製劑／再生醫療製劑	FDA〈Regulation of Exosomes〉; MFDS EV Guideline ; CDE EV 指導原則 CDE	• 依循細胞療法規範， • **橋接既有細胞治療臨床資料**
Optimized-culture / Minimal modification EV （改低氧/3D/藥物誘導處理）	生物製劑；屬「製程重大變更」	ICH Q5E ICH Database； PMDA comparability 指南 藥事醫療器械綜合機構	• 同天然 EV • 非基因療法 • 加註 comparability 及主要差異療效分子
核酸-loaded EV (電穿孔或融合載 mRNA/siRNA/CRISPR 等)	基因治療 **ATMP (**EU CAT) 或 GT 產品(US/JPN/KOR/TWN)	EMA ATMP 分類清單 European Medicines Agency (EMA)； FDA GT 定義(Potency Draft) U.S. Food and Drug Administration	• 依循基因治療規範 • 類LNP、AAV產品 • 外泌體視為載體，療效來自裝載之核酸藥物

外泌體療法不同途徑之法規與毒理要求

項目	外用（Topical）	局部注射（Local Injection）	全身注射（IV/IP）
適應症導向	創傷癒合、慢性傷口、炎症性皮膚病、EB等	骨關節炎、局部纖維化等	肝肺腎纖維化、神經退化、免疫疾病等
GLP 毒理測試要求	可依風險調整： ✓ 局部皮膚刺激 ✓ 皮膚吸收率 ✓ 潛在過敏性	✓ 局部組織毒性 ✓ 劑量耐受性 ✓ 局部發炎/免疫反應	需符合 ICH 指南： ✓ 單劑/重複劑毒性 ✓ 系統性毒性(肝腎) ✓ 免疫毒理學 ✓ 組織分佈與滯留
Biodistribution 試驗	免除、通常不需(如無系統吸收)	建議進行局部分析	必須進行(含主器官分佈)
Tumorigenicity / Genotoxicity	免除、通常不需 (依組成與宣稱)	免除、通常不需 (依組成與宣稱)	免除、通常不需 (依組成與宣稱)
免疫原性評估	視是否為異種/表面蛋白改變	需評估外泌體是否誘發免疫反應	為必要項目(特別是多次劑量)
毒理模型	單一物種 免疫正常鼠或兔，即可支撐前期臨床	單一物種 免疫正常鼠或兔，即可支撐前期臨床	建議使用兩物種
臨床試驗風險等級	最低風險(可爭取先行人體觀察)	中度風險	高風險(需全套非臨床支持)

外泌體開發為孤兒藥（Orphan Drug）

項目	孤兒藥可簡化
GLP毒理試驗	單一物種
致癌性/基因毒性	提出豁免
生殖毒性	提出豁免
Biodistribution（體內分佈）	不強制重複實驗
免疫毒性 / 免疫原性	體外數據支撐，可替代為 in vitro 宿主細胞免疫分析
大型動物試驗	免除或用人源化鼠替代
資料橋接	如利用外泌體為載體，可以現有病毒基因治療資料橋接

例如：

1. 外泌體治療遺傳性皮膚病 **EB(**泡泡龍症**)(**多國申請**)**：單物種毒理 + 縮短觀察期，多為topical use 或 IV 給藥，但已有HSV機轉數據支持，只做 GLP 小鼠毒性、豁免猴試驗、生殖毒性延後(Aegle Therapeutics 公司產品)

2. ExoFlo (MSC-EV for COVID-19)，快速IND通過，僅做短期毒性試驗(Direct Biologics公司產品)

Regulatory Comparison of Exosomes
Medical / Therapeutic vs. Skincare / Cosmetic

Market	Official Regulatory	Medical Use / Therapeutic	Cosmetic Use / Skincare
USA	FDA	■ Regulated as Biologics or Drugs. ■ Requires IND application. ■ GMP compliance. ■ clinical trials.	□ No mandatory classification under cosmetics □ INCI registration encouraged. □ Must not claim therapeutic effects.
EU	EMA	■ Classified as ATMP (Advanced Therapy Medicinal Products) or Medical Devices. ■ Requires GMP & risk/technical documentation.	□ Cosmetics must comply with INCI, GMP, and submit Product Information File (PIF) □ No therapeutic claims.
China	NMPA	■ Regulated under stem cell/biologic framework (no finalized exosome-specific law). ■ Subject to pilot zone principles.	□ Treated as cosmetics with case-by-case approval. □ Exosomes may fall under functional raw material list (draft stage).
Taiwan	TFDA	■ May fall under Medical Devices or New Drugs, depending on indication. ■ GMP and clinical review required.	□ Human-derived exosome products must submit safety dossier. □ Therapeutic claims prohibited.
South Korea	MFDS	■ Classified under "cell and tissue-based products", including exosome therapy. ■ Regulated as advanced biologics.	□ Established "Exosome Herbal Cosmetics" category in 2023. □ Classified based on source, formulation, and safety.
Japan	MFDA	■ Regulated as Regenerative Medical Products. ■ Each product must undergo review based on source, process, and safety.	□ Managed under cosmetic raw ingredient registration list. □ No therapeutic claims allowed.

U.S. Food and Drug Administration. (2019, December 6). *Public safety notification on exosome products*. https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/public-safety-notification-exosome-products

REACH24H Consulting Group. (2025, May 16). INCI Registration for Exosome Ingredients: A Global Compliance Guide. https://www.reach24h.com/en/news/inci-registration-for-exosome-ingredients-global-compliance-guide.html

ZMUni. (2024, April 1). *Monthly Collection | China International Cosmetic Regulatory Updates (Issue 8)*. ZMUni. https://www.zmuni.com/en/news/monthly-collection-china-international-cosmetic-regulatory-8/

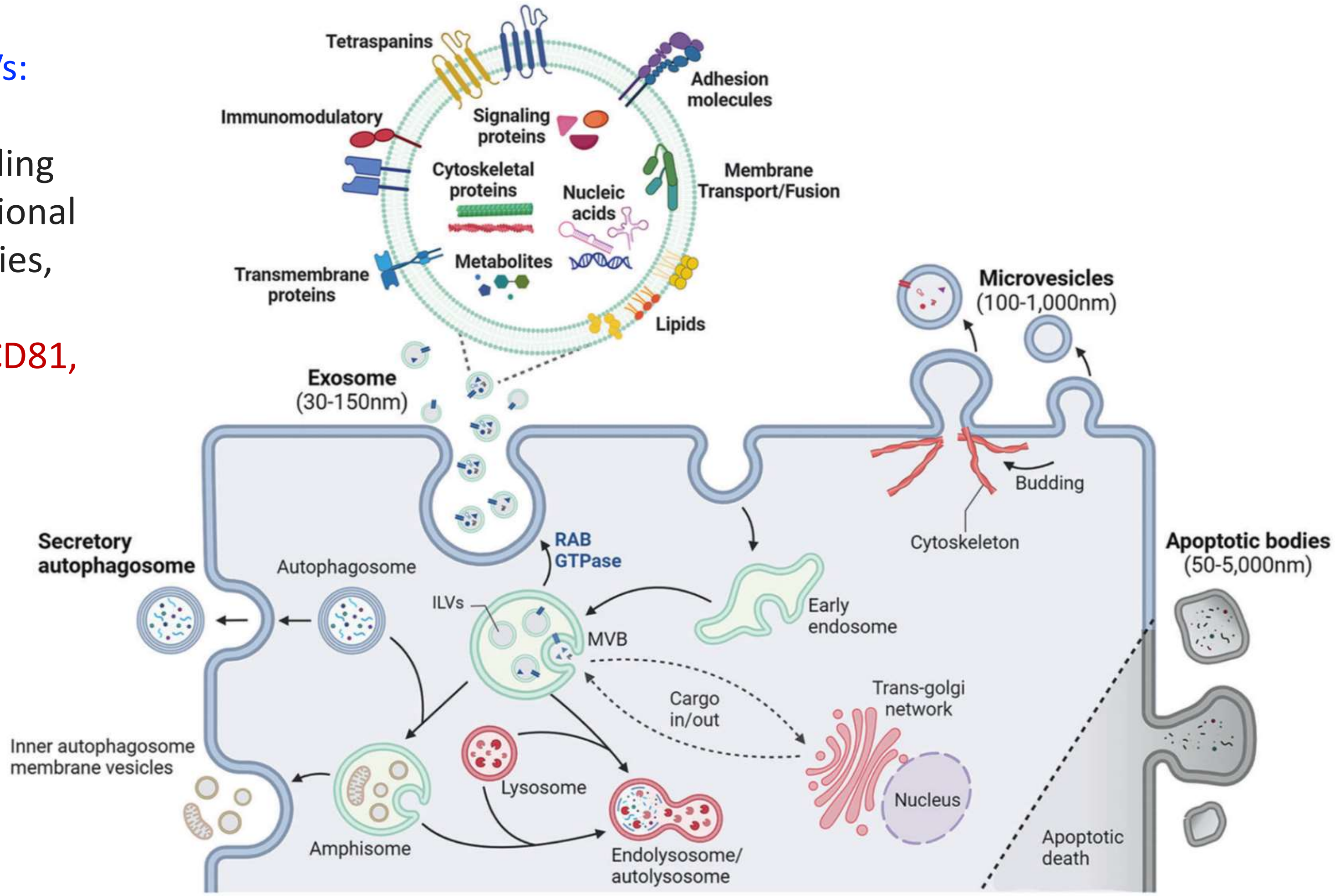
National Medical Products Administration. (2024, September 3). *關於公開徵求《化妝品原料使用目錄（2024年版）》意見的通知*. https://www.nmpa.gov.cn/zwgk/jyta/zhxta/20240903172653181.html

Yoon J, Lee S, Kim MJ, Kim JH. Brief summary of the regulatory frameworks of regenerative medicine therapies. Front Pharmacol. 2025 Jan 22;15:1486812. doi: 10.3389/fphar.2024.1486812.

Mechanisms of extracellular vesicle (EV) biogenesis and EV components

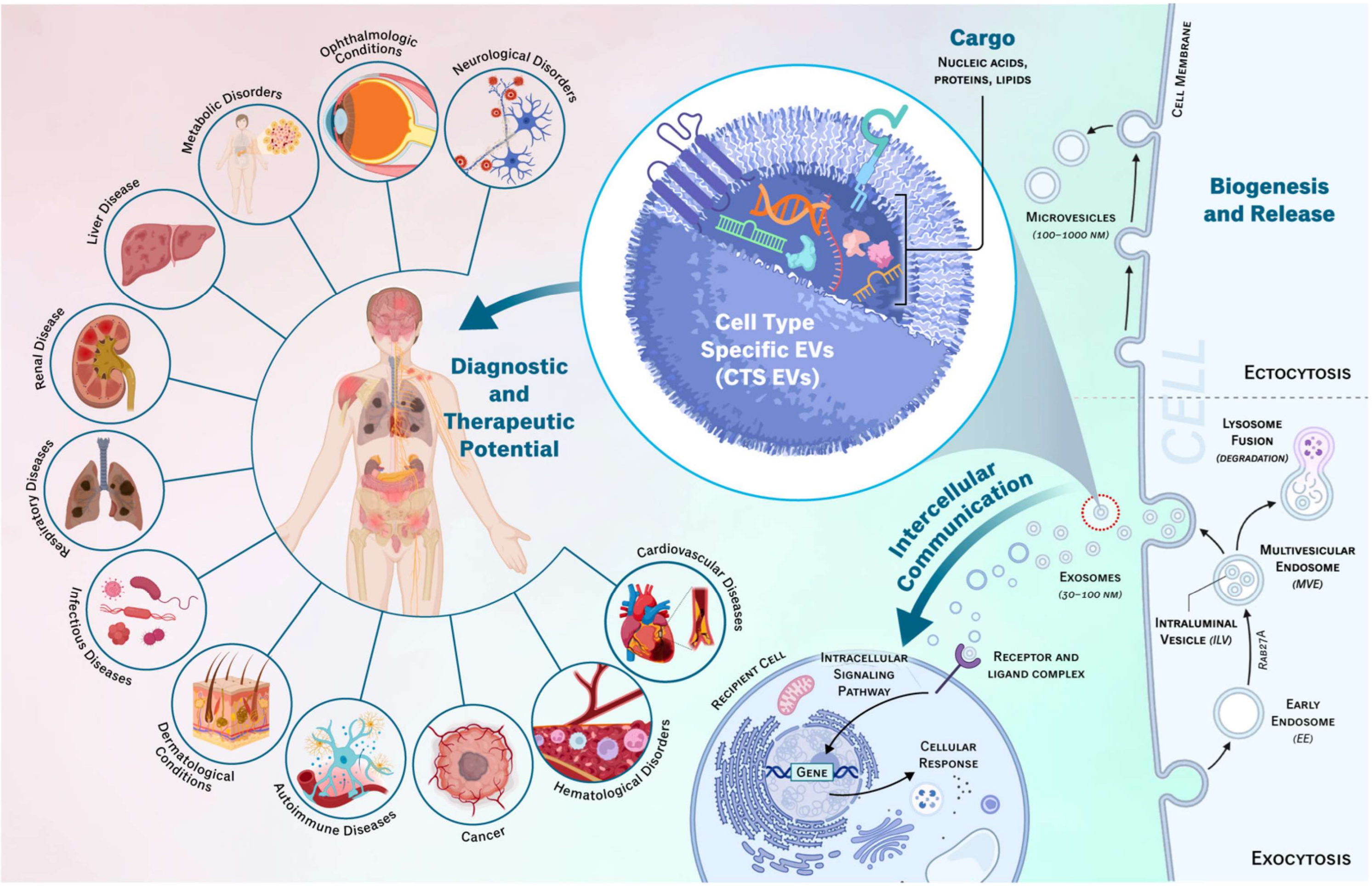
Characteristics of Exosomes/sEVs:

- Small Size & Lipid Bilayer
- Heterogeneous Cargo: including signaling proteins, transcriptional regulators, various RNA species, DNA, and lipids.
- Surface Markers: e.g., CD9, CD81, CD63
- Natural Targeting Ability



Experimental & Molecular Medicine (2024) 56:877 – 889

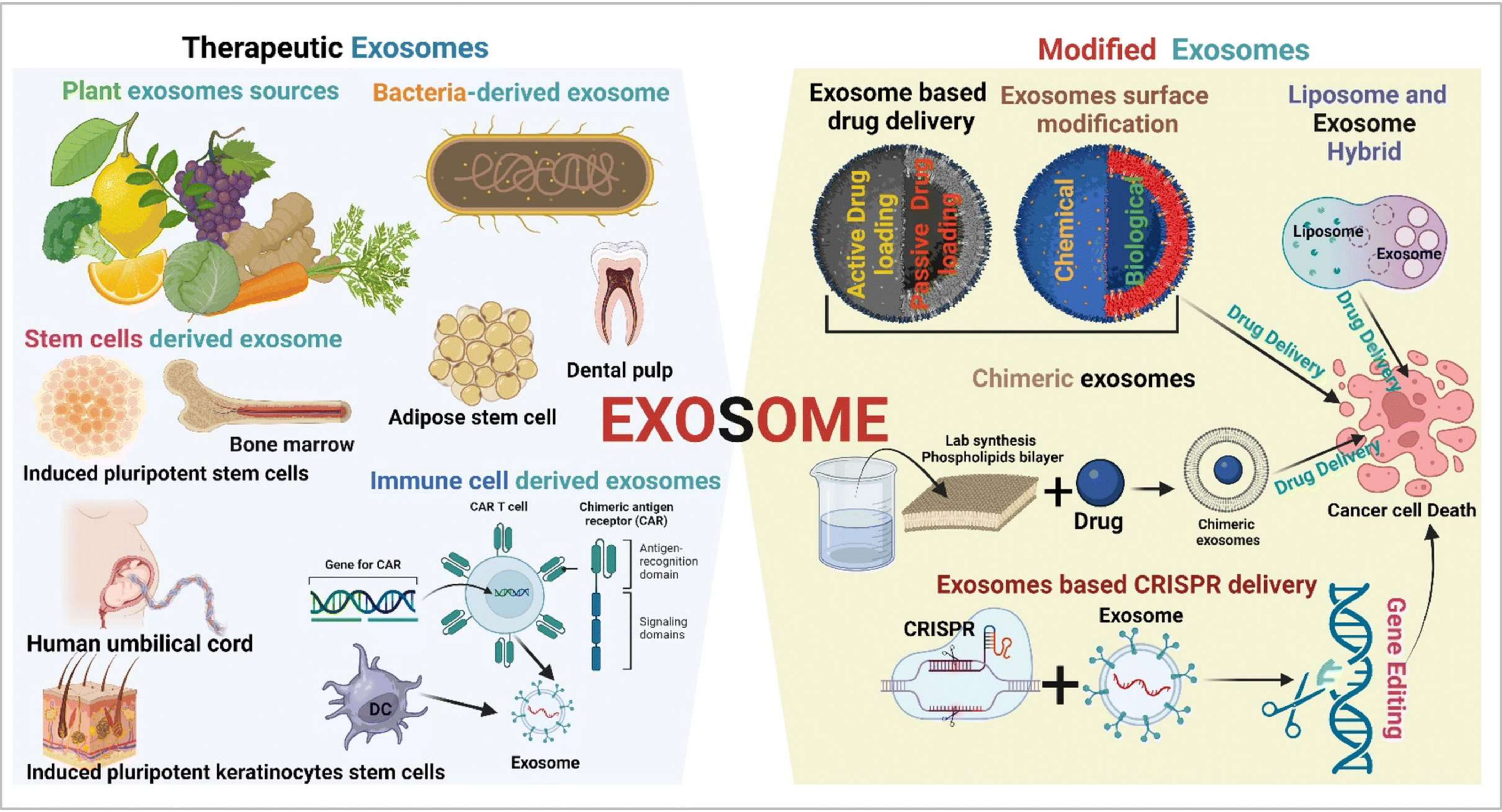
The potential of Exosomes/sEVs



Benefits in Clinical Applications:

- Natural Delivery System
- Low immunogenicity
- Crossing Biological Barriers
- Biomarkers
- Targeted Therapy
- Customizable
- Regenerative Medicine
- Diagnostic procedures can be non-invasive (e.g., liquid biopsy).

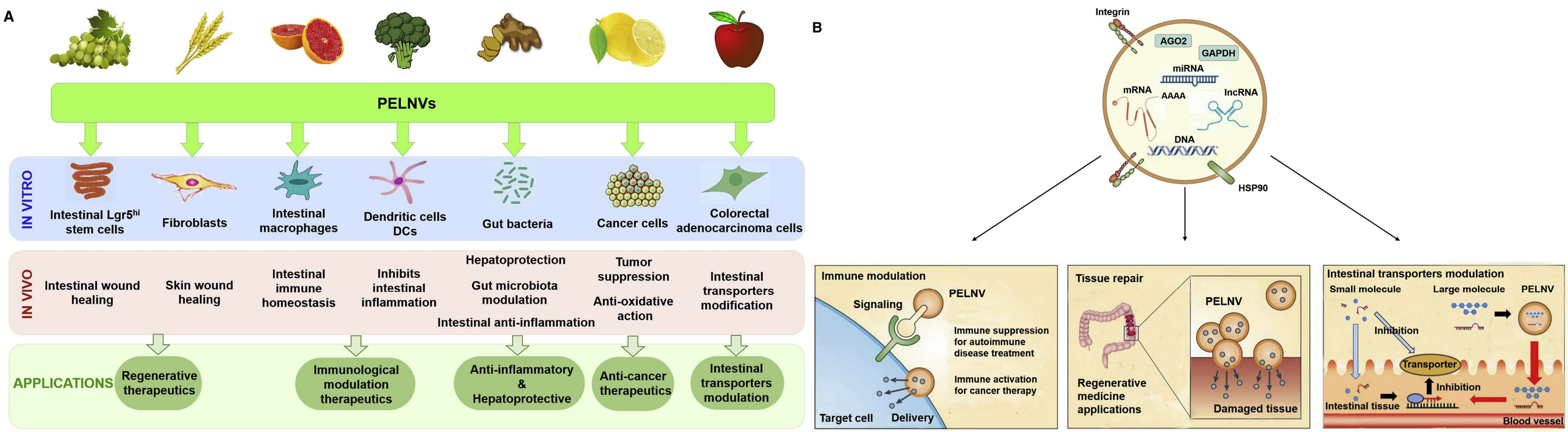
Int. J. Mol. Sci. (2024) 25(5): 2730



(Divya Mirgh, RSC Advances,2024)

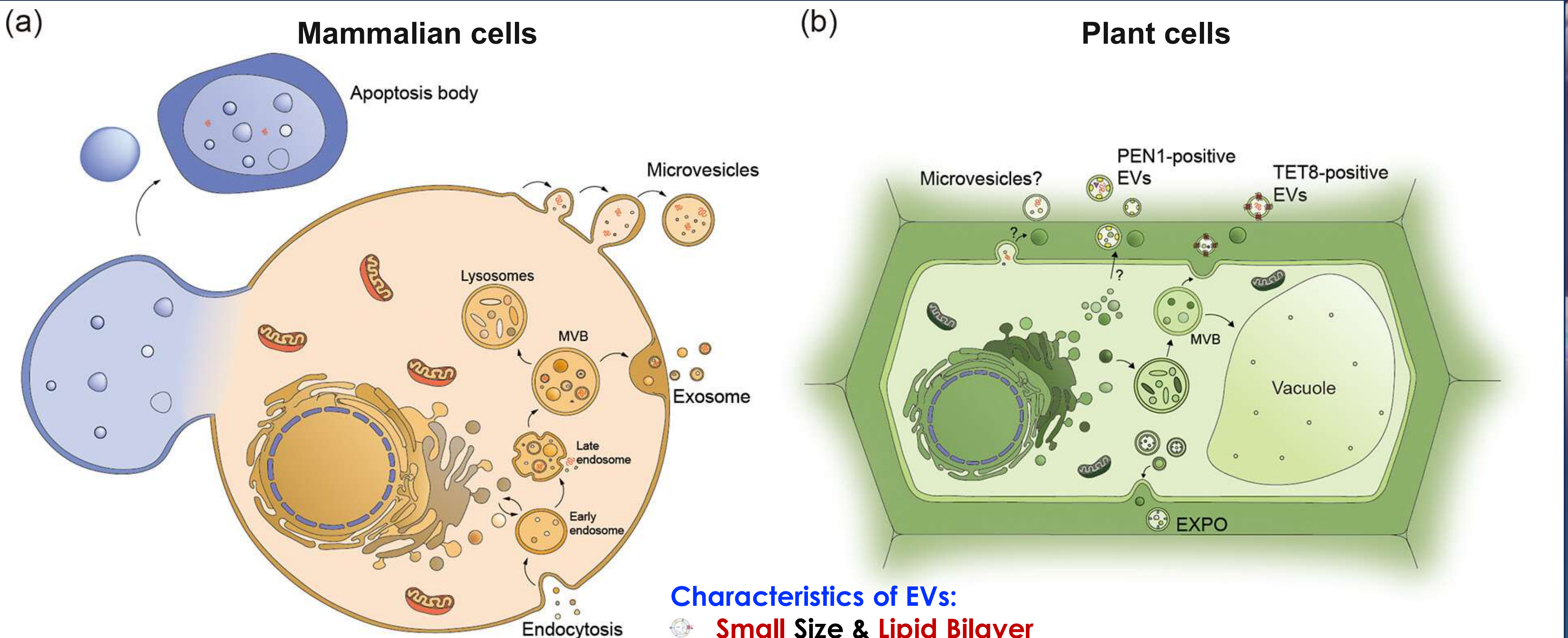
Biological Functions of Plant-EVs from a Variety of Plant Sources and Their Translation into Therapeutic Applications

- Plant-EVs, are naturally **non-immunogenic** and **free from zoonotic or human pathogens**, ensuring **safety** and **extended circulation**.
- These traits give plant-EVs an advantage over mammalian EVs in **bioavailability** and **immune evasion**.



(Haseeb Anwar Dad, Molecular Therapy, 2021)

Biogenesis of Extracellular Vesicles (EVs) in Mammalian and Plant Cells

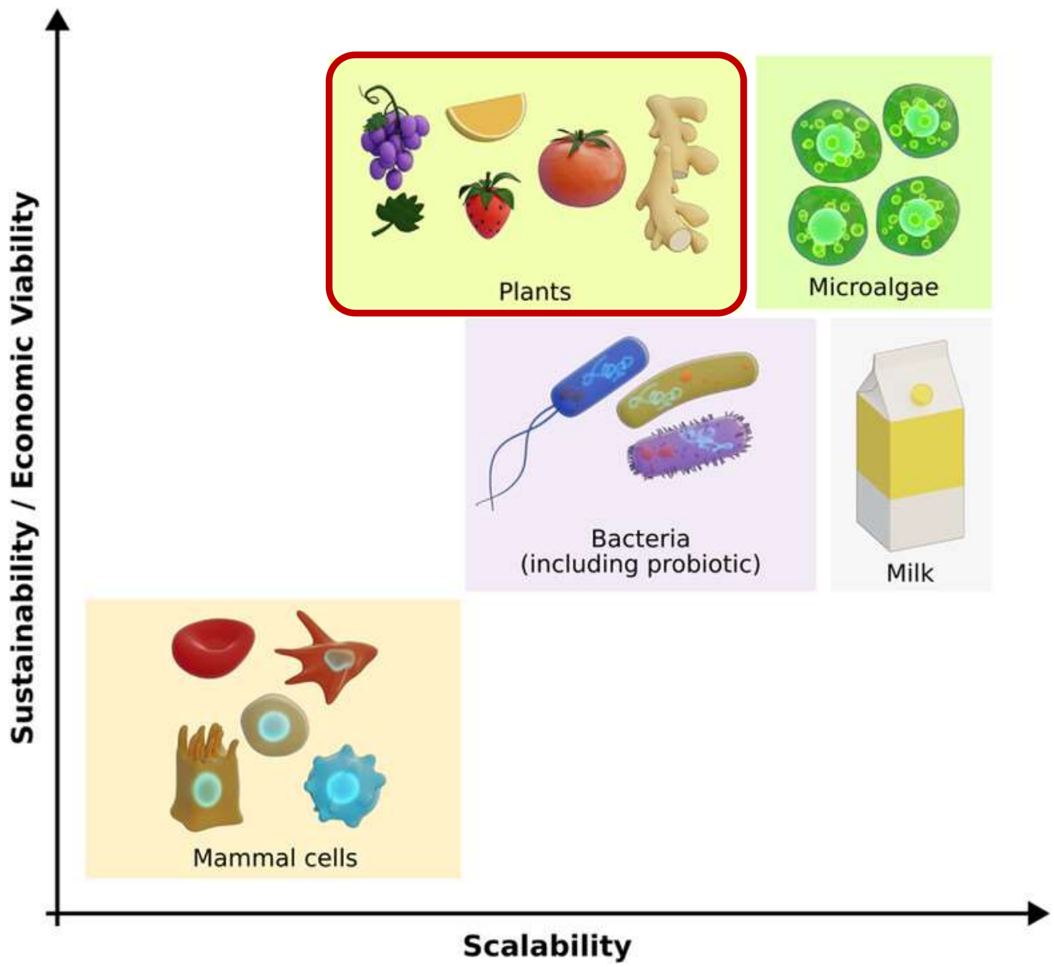


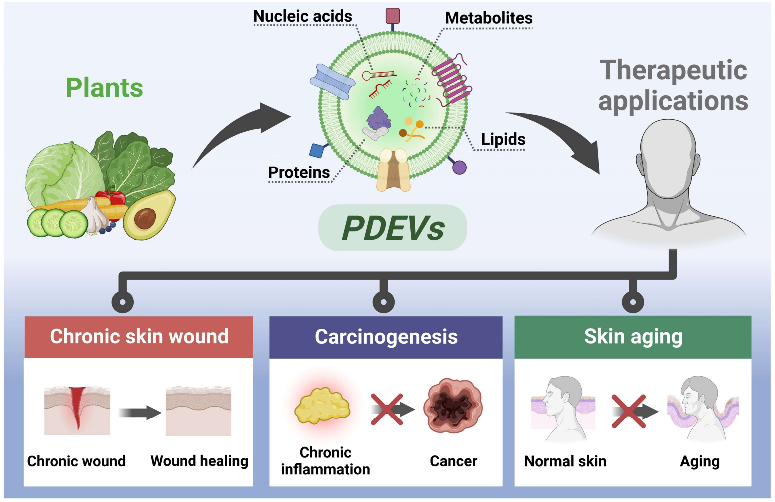
Characteristics of EVs:

- **Small Size & Lipid Bilayer**
- **Heterogeneous Cargo**
- **Surface Markers: e.g., CD9, CD81, and CD63 (Mammalian Cells)**
  e.g., TET8/9, PEN1, and EXPO (Plant Cells)

Journal of agricultural and food chemistry 72.6 (2024): 2853-2878.

The Benefits of Plant-derived EVs in Therapeutic Applications

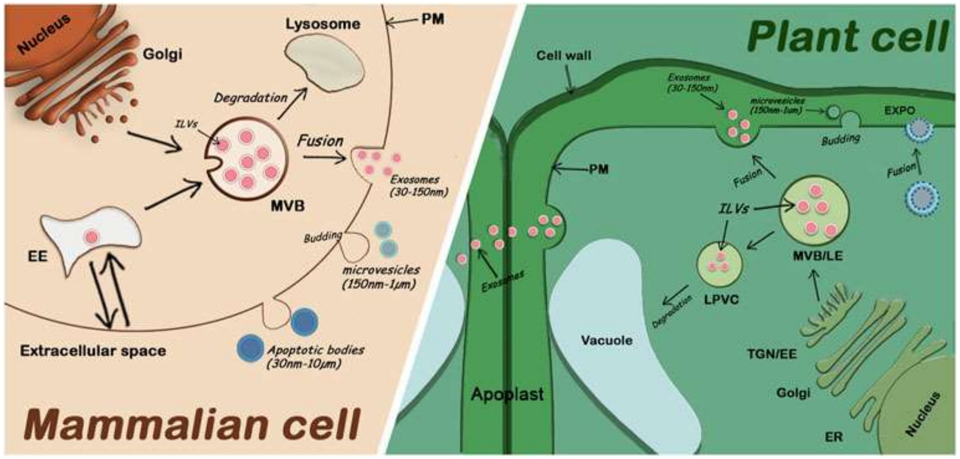




- Enhanced safety
- High sustainability and scalability
- Anti-inflammatory and antioxidant properties

Journal of extracellular vesicles 11.12 (2022): 12283.
Antioxidants 12.6 (2023): 1286.

Comparison of MSC-Derived EVs and Plant-Derived EVs



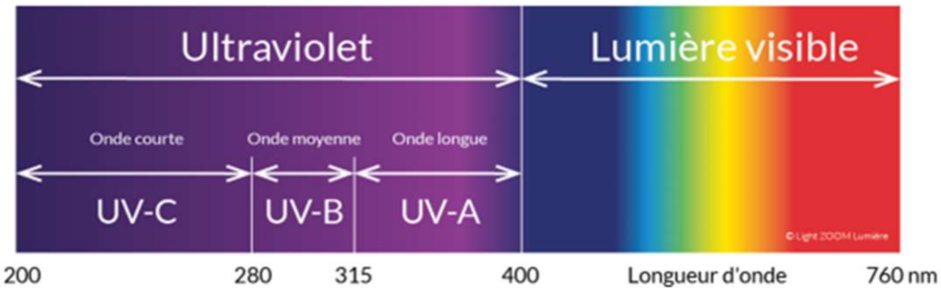
Front Cell Dev Biol. 2022 Jun 1;10:883841

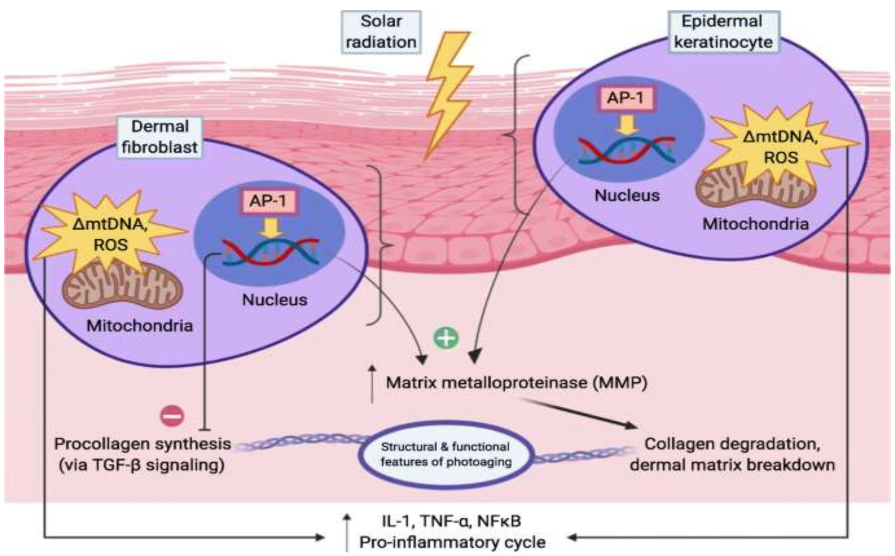
- **Key Similarities**:
- Both types of EVs facilitate intercellular communication.
- They possess therapeutic potential and can be engineered for drug delivery.

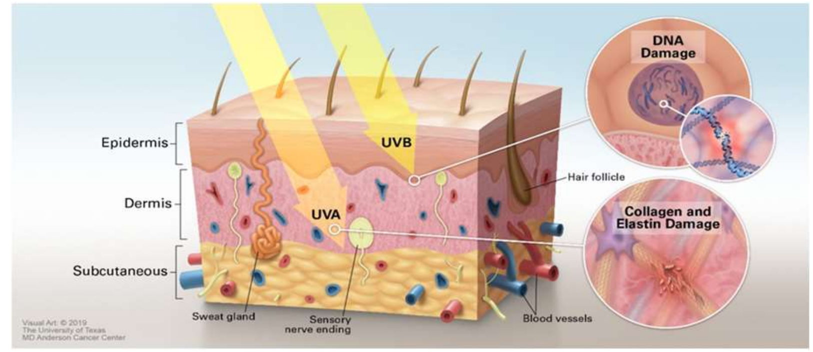
- **Key Differences**:
- **Source**: MSC-EVs come from complex cell cultures, whereas plant-EVs are extracted from readily available plant materials.
- **Cargo Composition**: MSC-EVs carry mammalian-specific proteins and nucleic acids, while plant-EVs contain plant-specific components and metabolites.
- **Production and Cost**: MSC-EVs are more expensive and challenging to produce; plant-EVs are scalable and cost-effective.
- **Regulation**: MSC-EVs face stricter regulatory requirements as biologics, while plant-EVs often fall under dietary supplement or cosmetic regulations.

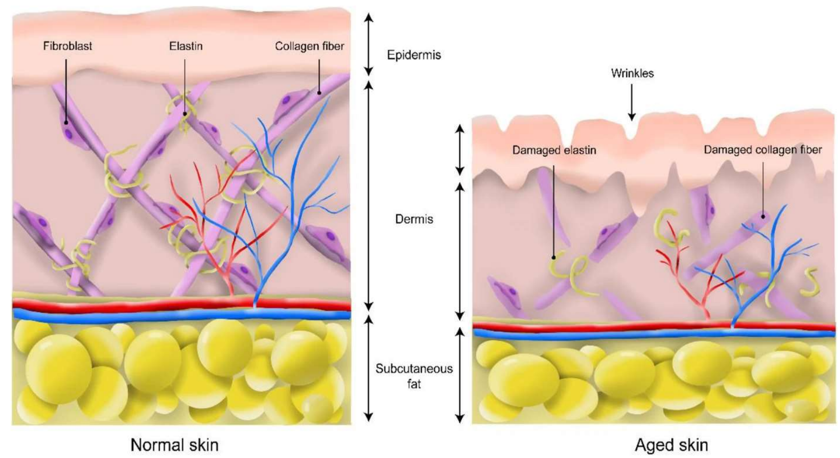
Aspect	MSC-EVs	Plant-EVs
Source	Mesenchymal stem cells (human/animal)	Edible plants (e.g., ginger, grapefruit)
Key Markers/ Proteins	CD9, CD63, CD81, growth factors, cytokines	Plant-specific proteins and lipids
Size	50–150 nm (exosomes); 100–1000 nm (microvesicles)	100–500 nm
Nucleic Acids	Mammalian mRNAs and miRNAs	Plant miRNAs, siRNA, and other RNAs
Additional Cargo	-	Antioxidants and flavonoids
Primary Applications	Regenerative medicine, immunotherapy	Nutraceuticals, cosmetics, drug delivery
Cost	High	Low
Immunogenicity	Low (if autologous; potential issues with allogeneic)	Generally low; potential allergenic risks

UVB-induced Photoaging of Dermal Fibroblasts





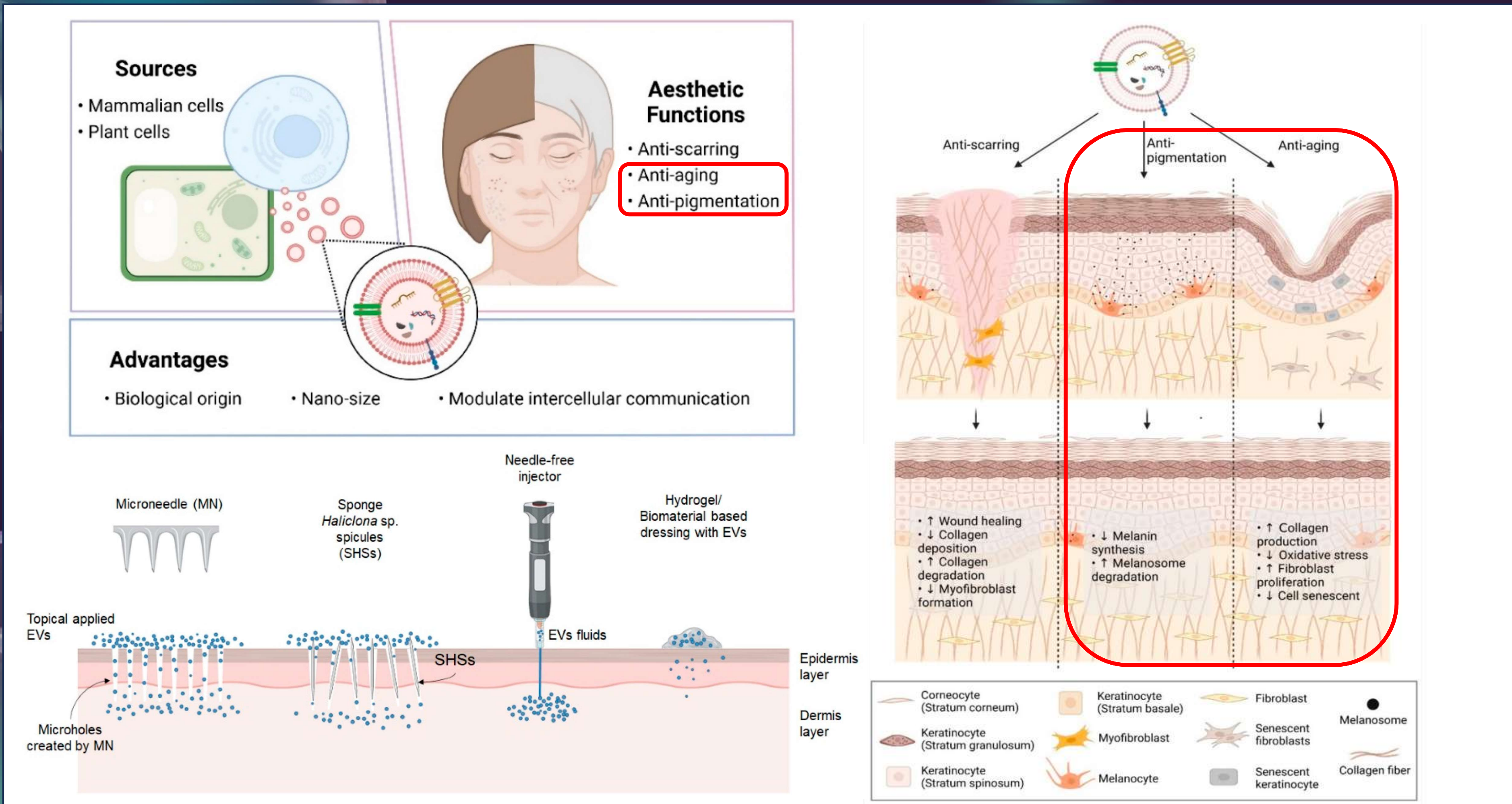




- **UVB-induced damage leads to decreased structural integrity, characterized by the loss of collagen and elastin.**

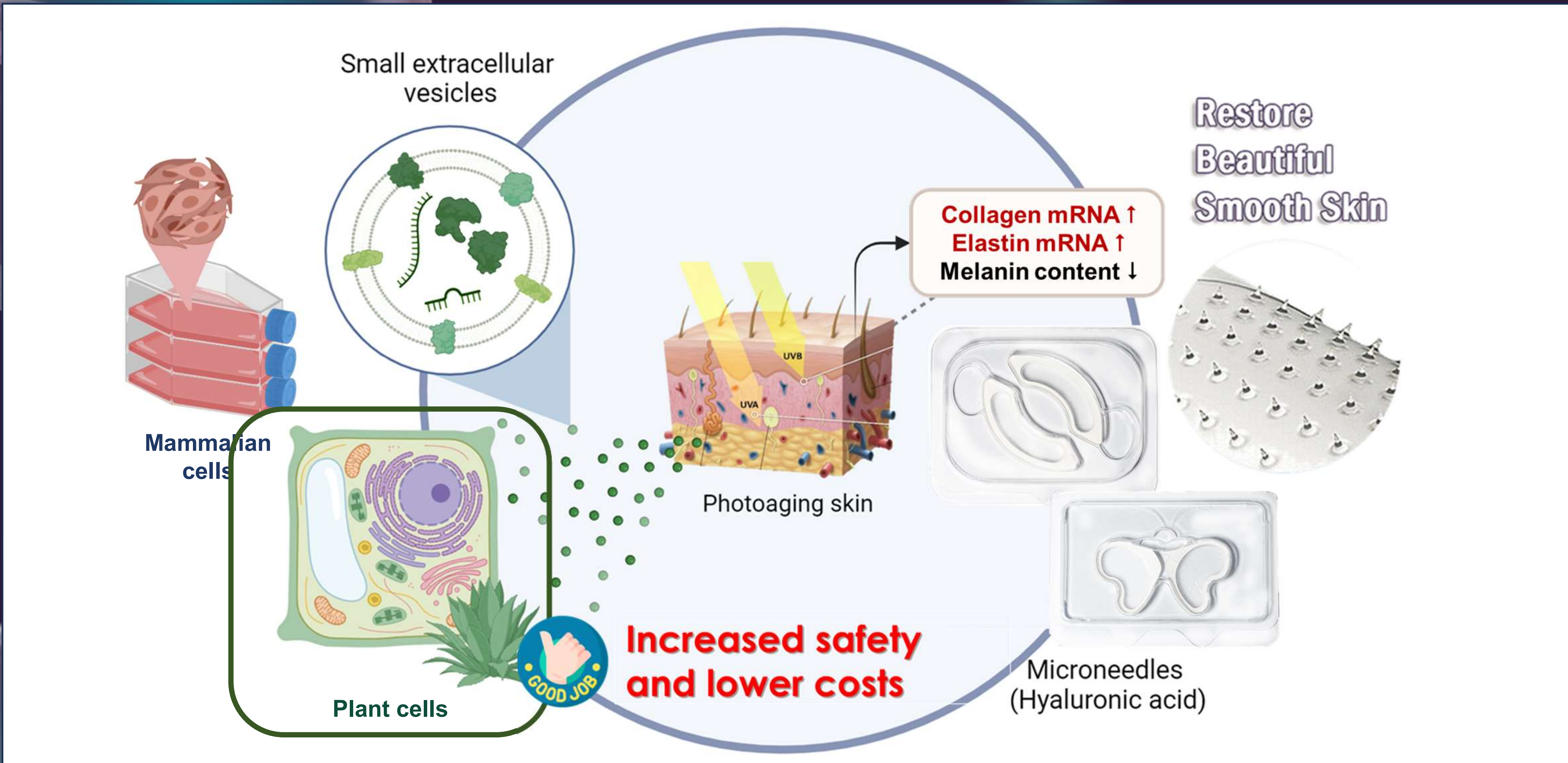
Current Dermatology Reports 9 (2020): 22-29.

Applications of Extracellular Vesicles in Facial Aesthetics



International Journal of Molecular Sciences 23.12 (2022): 6742.

Overall Scheme of Plant-Derived Extracellular Vesicles in Cosmetics-Skin Photoaging



Applications of Plant-Derived Extracellular Vesicles in Cosmetics-Skin Photoaging

Biomaterials Research
A SCIENCE PARTNER JOURNAL

Biomaterials Research 28 (2024): 0098.

RESEARCH ARTICLE

Polygonum multiflorum Extracellular Vesicle-Like Nanovesicle for Skin Photoaging Therapy

Junjia He[1,2†], Luoqin Fu[2†], Yeyu Shen[1,2], Yan Teng[1], Youming Huang[1], Xiaoxia Ding[1], Danfeng Xu[1], Hong Cui[1], Mingang Zhu[3], Jiahao Xie[4], Yue Su[4], Ting Li[5], Weitao Huang[2], Xiaozhou Mou[2*], Qiong Bian[2*], and Yibin Fan[1*]

[1]Center for Plastic & Reconstructive Surgery, Department of Dermatology, Zhejiang Provincial People's Hospital, Affiliated People's Hospital, Hangzhou Medical College, Hangzhou, Zhejiang 310014, China. [2]Clinical Research Institute, Zhejiang Provincial People's Hospital, Affiliated People's Hospital, Hangzhou Medical College, Hangzhou, Zhejiang 310014, China. [3]Department of Dermatology, the First People's Hospital of Jiashan, Jiaxing, Zhejiang 314100, China. [4]The Second Clinical Medical College, Zhejiang Chinese Medical University, Hangzhou, Zhejiang 310014, China. [5]College of Bioengineering, Zhejiang University of Technology, Hangzhou, Zhejiang 310014, China.

*Address correspondence to: fanyibin@hmc.edu.cn (Y.F.); bianqiong@zju.edu.cn (Q.B.); mouxz@zju.edu.cn (X.M.)
†These authors contributed equally to this work.

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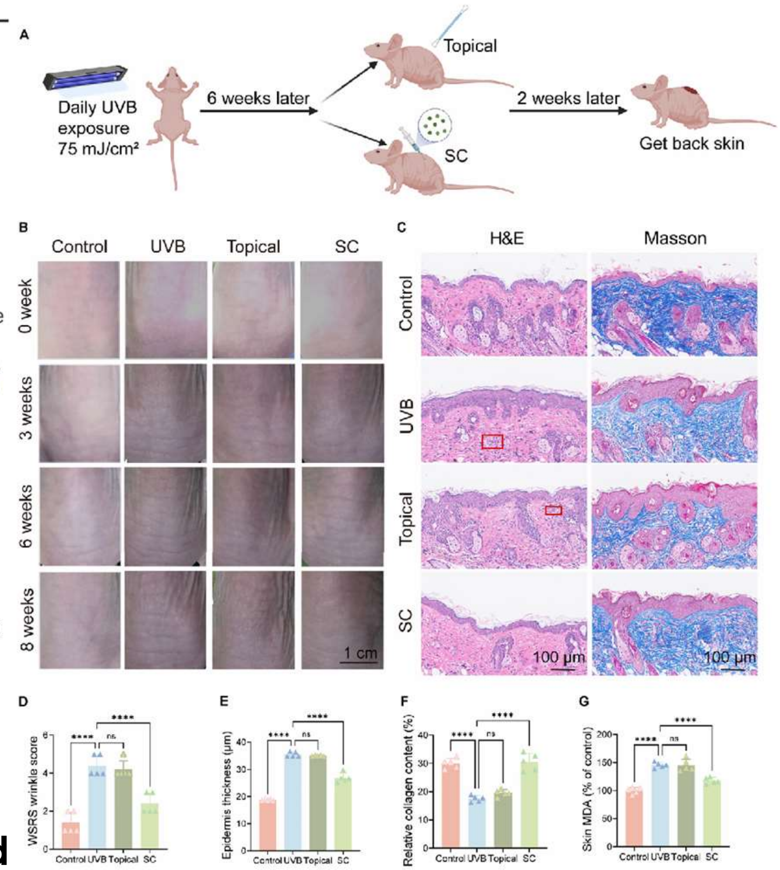


P. multiflorum **extracellular vesicle-like nanovesicles (PMELNVs) demonstrate potential anti-photoaging effects when administered via subcutaneous injection.**

SC, subcutaneous injection

Applications of Plant-Derived Extracellular Vesicles in Skin Disorders

Table 2 The Role of PELNs in Chronic Wound Healing

International Journal of Nanomedicine (2024): 11293-11303.

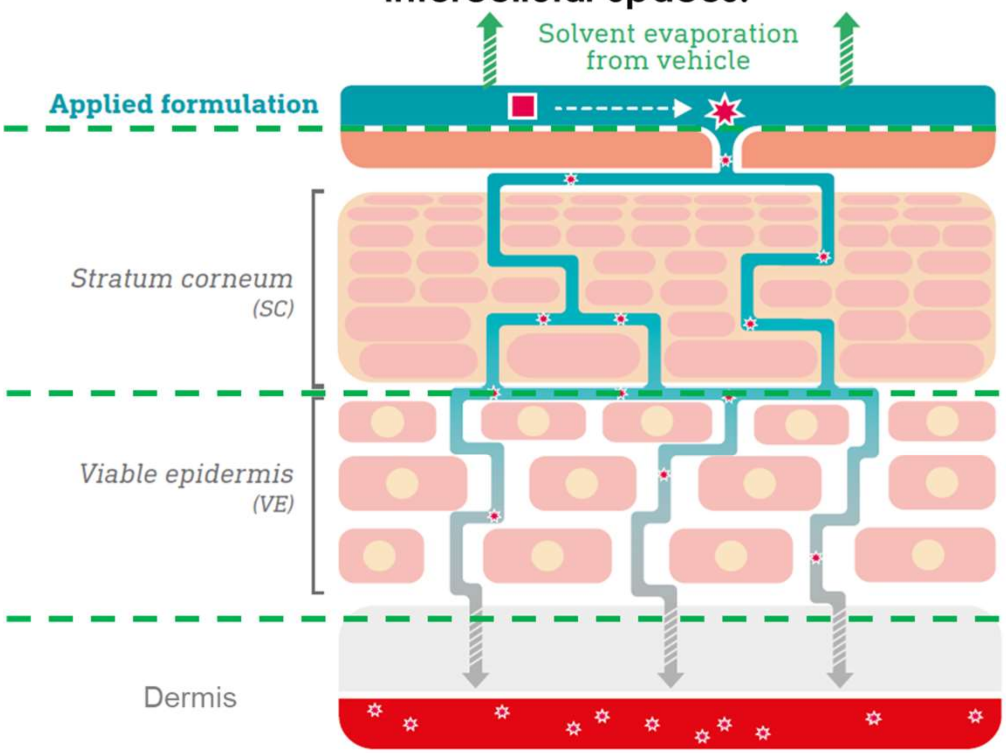
Mechanisms of role	Plant Sources	In Vitro and (or) Vivo	Effects	References
Promotion of healing	*Physalis peruviana*	HDF	Elevated HDF proliferation and migration; Upregulated collagen I	[59]
	Aloe	HDF; HaCaT	Reduced ROS levels in HaCaT; Enhanced migration ability of HaCaT and HDF	[79]
	Tomato	HaCaT; mouse fibroblasts (NIH-3T3)	Increased cell migration of HaCaT and NIH-3T3	[80]
	Grapefruit	HaCaT	Increased cell migration of HaCaT	[81]
Anti-inflammatory effects	*Aloe*	RAW264.7 macrophages; HaCaT	Anti-inflammatory potential in macrophages and keratinocytes; Decreased the secretion of pro-inflammatory cytokines TNFα, IL-1β, and IL-6.	[43]
	Pomegranate	Monocytic cell (THP-1); Intestinal cell (Caco-2)	Anti-inflammatory effects in vitro cultures of THP-1 and Caco-2 cell lines	[82]
	Dendrobium	C57BL/6J mice	Suppressing IL-1β expression	[83]
Promotion of angiogenesis	*Grapefruit*	HUVECs	Increased the tube formation capabilities of HUVECs	[81]
	Aloe	HUVECs	Enhanced tube formation in HUVECs	[50]
	Wheat	HUVECs	Increased tube-like structure formation of the HUVECs	[84]
	Ginseng	HUVECs; ICR mice	Enhanced the migration and angiogenesis in HUVECs; Facilitated skin wound healing in mouse	[85]
Modulating the immune response	*Catharanthus roseus*	RAW264.7 macrophages; primary spleen lymphocytes; BALB/c mice	Promoted the polarization of macrophages and lymphocyte proliferation; Alleviated white blood cell reduction and bone marrow cell cycle arrest in immunosuppressive mice	[86]
	Pueraria lobata	Peritoneal macrophages	Promote M2 macrophage polarization	[60]
	Turmeric	RAW 264.7 macrophages; C57BL/6J mice	Regulate macrophage polarization and advance the healing process	[87]
Antibacterial activity	*Dandelion*	Staphylococcus aureus; mouse RBCs; ICR mice	Binding to Staphylococcus aureus exotoxins; Showing detoxification effect in vivo	[88]

Abbreviations: PELNs, plant-derived exosome-like nanovesicles; HDF, human dermal fibroblast; HaCaT, Human keratinocytes; HUVECs, Human umbilical vein endothelial cells; RBCs, red blood cells; ROS, reactive oxygen species; TNFα, tumor necrosis factor α; IL-1β, interleukin-1β; IL-6, interleukin-6.

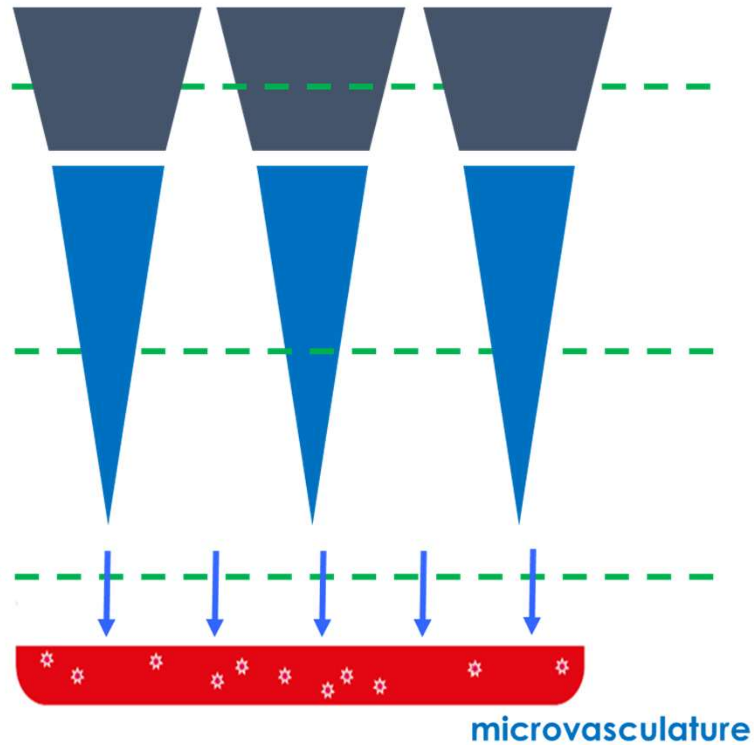
Microarray Patch Platform Technology in Cosmetics

The key advantage over traditional skincare products:
Permeation efficiency!

- Topical formulation: slowly and minimally permeates into the microvasculature through intercellular spaces.



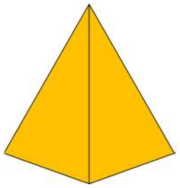
- Microneedle patch: penetrates the stratum corneum, dissolves in interstitial fluid, and rapidly permeates into the microvasculature in large quantities.



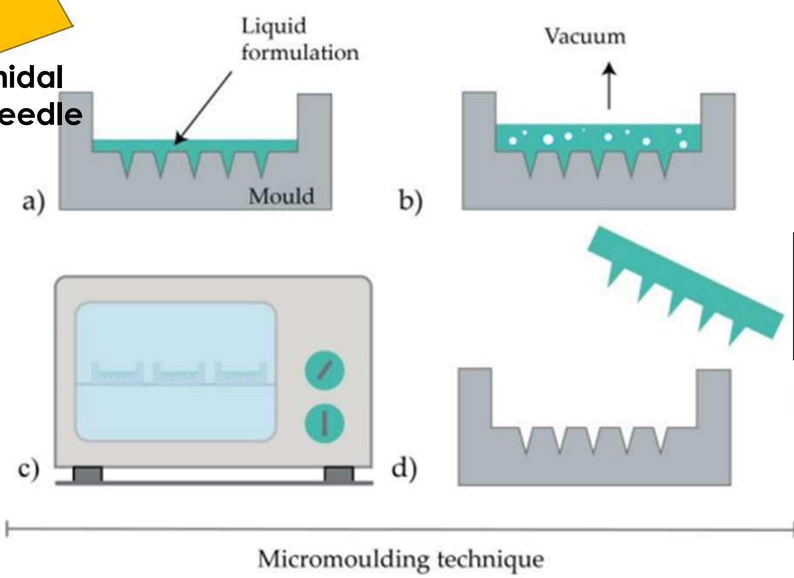
Microarray Patch Platform Technology in Cosmetics

健喬信元 synmosa

- ► An array composed of hundreds of crystals (microneedles) made from biocompatible, absorbable polymer materials (such as hyaluronic acid).
- ► Each crystal has a length of no more than 1,000 μm, allowing it to penetrate the skin and release active ingredients without touching nerves.

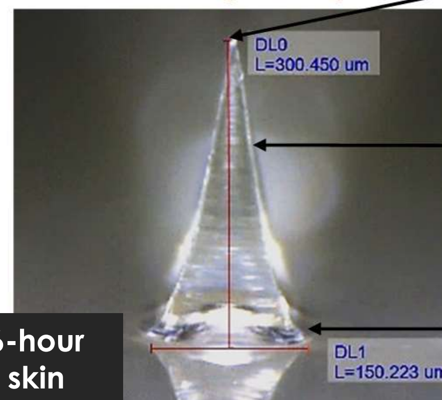


Pyramidal Microneedle



Precision Coating& Molding Method

Needle length: 300 μm
Needle tip: < 30 μm

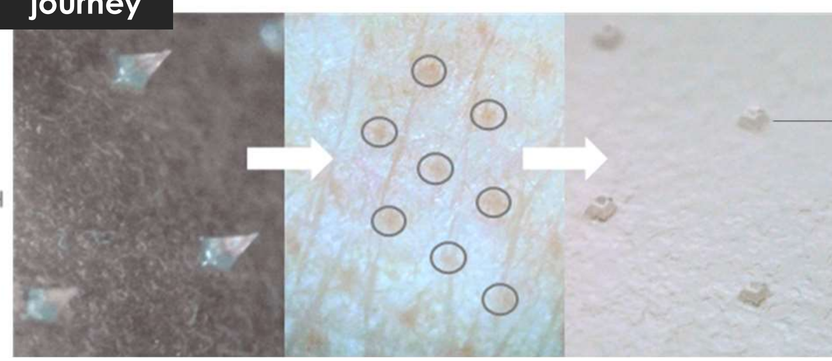


Sharp Tip

Straight & Solid Structure with Sufficient Active Ingredients

Strong Base to Ensure Effective Penetration

6-hour skin journey



The top layer of hyaluronic acid reaches the target within 30 minutes, leaving the basal layer for sustained action.

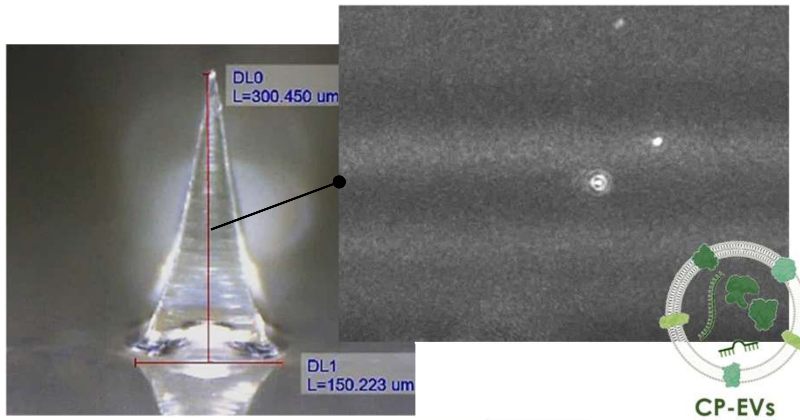
Microneedle Patch Prototype with *Carica papaya* (CP)-Derived Extracellular Vesicles

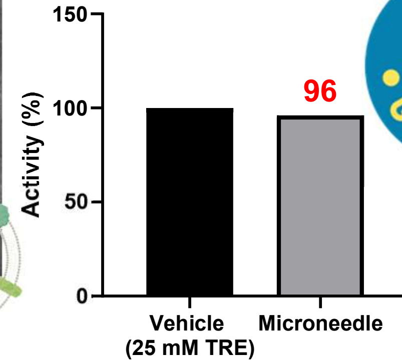
健喬信元 synmosa

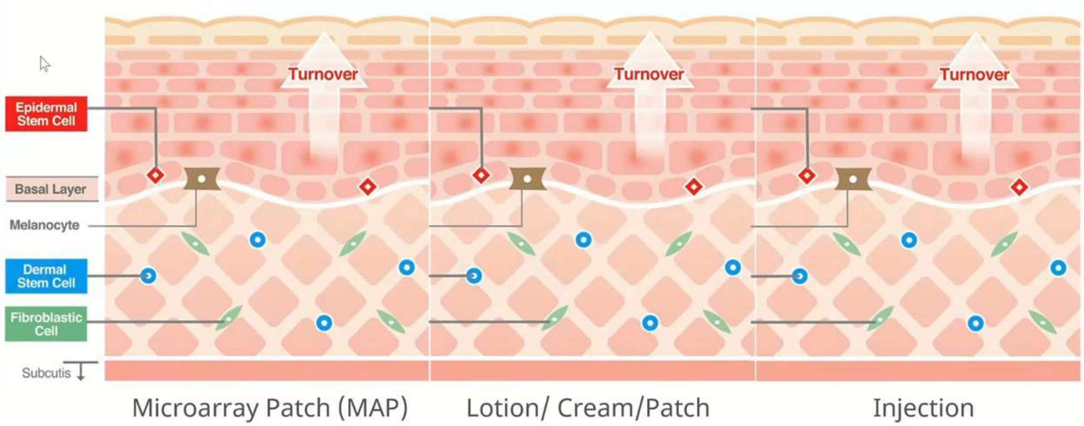
- CP-EVs **retained their functionality** following the dissolution of a microneedle patch at 37°C for 30 minutes, making it a promising candidate for final product development.

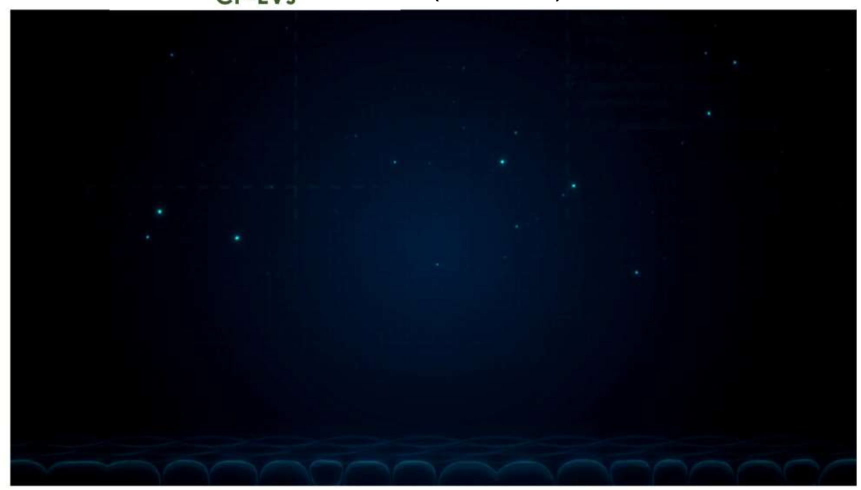
Containing 2.68E+11 CP-EVs!!!

CP-EVs

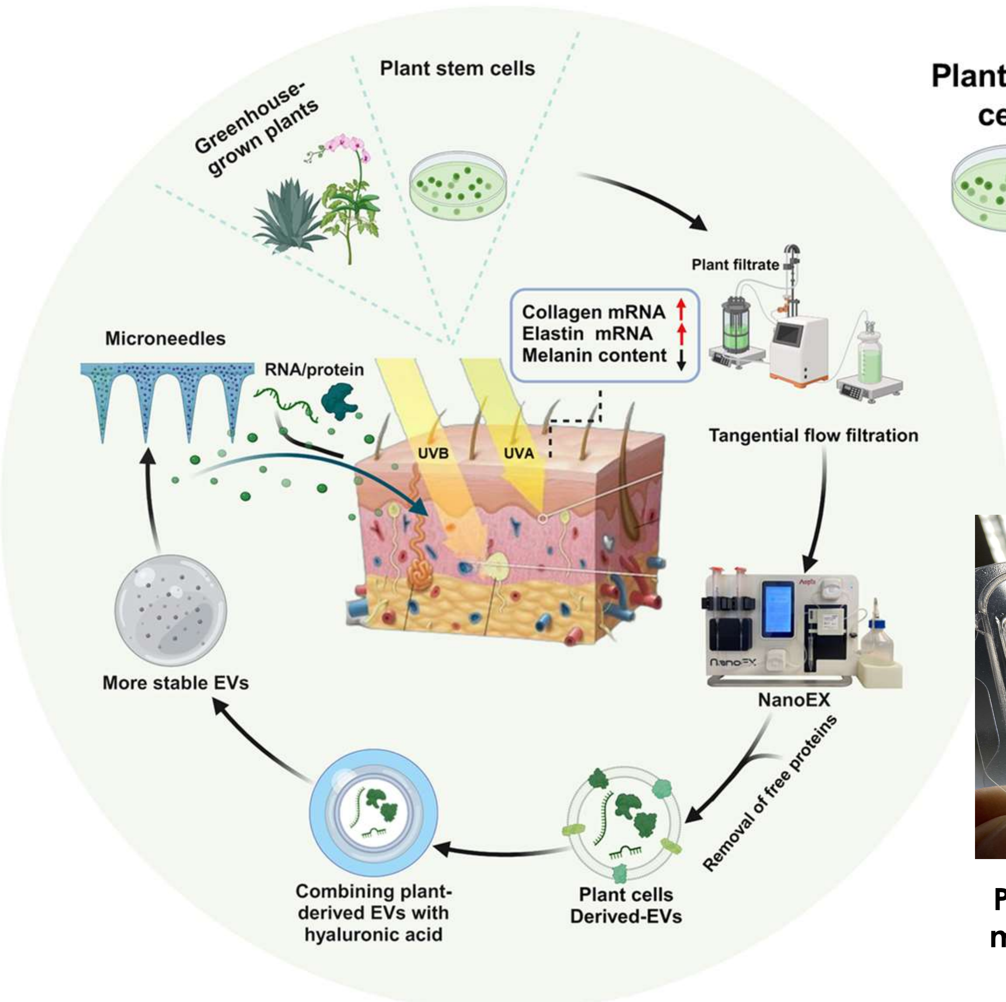




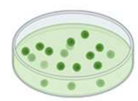




Plant-Derived Extracellular Vesicles in Cosmetics



Plant stem cells



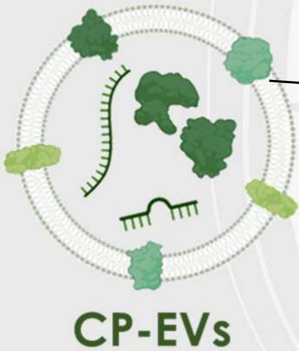
- *Carica papaya cv. Red lady (木瓜紅妃)*

Prototype of CP-EV microneedle patch

- Reversed cell viability after UVB induction
- Anti-pigmentation effects
- DPPH radical scavenging capacity
- Increased safety and lower costs

Proposed Plan 1 for Cosmetic Applications

Containing bioactive CP-EVs!!!



Restore Beautiful Smooth Skin

Generated using the OpenAI platform

Proposed Plan 2 for Cosmetic Applications

Generated using the OpenAI platform

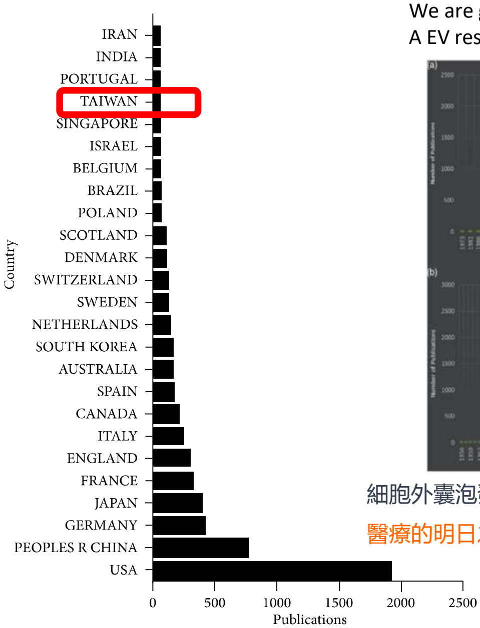
創新的研究主題

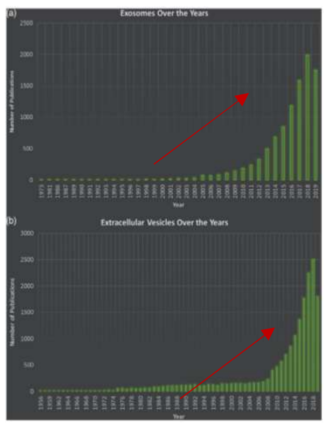
The Ohio State University

此特色領域中心是台灣在細胞外囊泡領域
不可缺少的急迫需求

台灣細胞外囊泡相關發世界排名第22名

We are good, but not good enough.
A EV research center should be established.





細胞外囊泡發表數逐年增加，此領域為再生醫療的明日之星，逐台灣不能錯過或落後!

Bin Wang et al., BioMed Research International. 2019.
Akhil Srivastava et al., Wiley Interdiscip Rev Nanomed Nanobiotechnol. 2020;12(4):e1621.

Fields of specialty:
nanobiotechnology,
gene delivery,
liquid biopsy

李利 (L. James Lee)

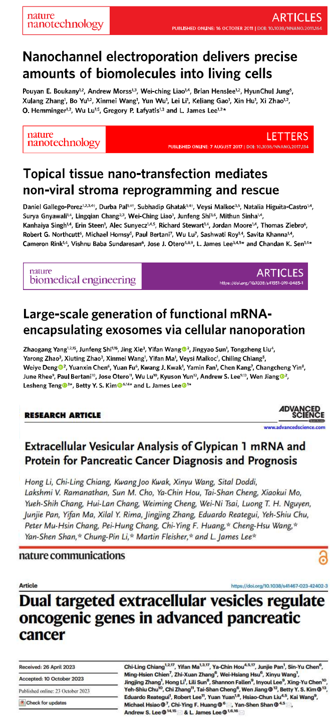
THE OHIO STATE UNIVERSITY
- William G. Lowrie Department of Chemical and Biomolecular Engineering
- Helen C. Kurtz Chair Emeritus
- Founder and leader of the NSF Nanoscale Science and Engineering Center for Affordable Nanoengineering of Polymeric Biomedical Devices (CANPBD)

NATIONAL YANG MING CHIAO TUNG UNIVERSITY
- Institute of Biopharmaceutical Sciences
- Jade Mountain Scholar

延攬玉山學者（2018-2025）
帶領台灣接軌世界!

- Research interests: nanobiotechnology, drug delivery, gene therapy, and liquid biopsy.
- >460 refereed journal articles, >25,000 citations, ***h*-index: 82**
- >40 patents and patent applications.
- 14 book chapters.
- He was elected as a Fellow of the American Institute for Medical and Biological Engineering in 2006.
- External research grants (more **than $120 million**)

He received the following awards:
- 2008 Malcolm E. Pruitt Award from the Council of Chemical Research.
- 2010 International Award from the Society of Plastic Engineers.
- 2016 Lifetime Achievement Award from the Society of Advanced Molding Technology.



胞外體
創新精準醫療

臺美團隊研發「外泌體生物晶片」抽血即驗小細胞肺癌

撰文 | 記者 吳培安　Advanced Science. e2416711 (2025)　日期 | 2025-04-29

陽明交大領軍高長、亞東 聚焦急性肺損傷開發胞外體核酸藥物

撰文 | 記者 吳培安　Journal of Biomedical Science 31:30 (2024)　日期 | 2024-03-26

《Nature》子刊：陽明交大、成大「核酸藥+胞外體」創新療法 精準攻擊胰臟癌

撰文 | 記者 吳培安　Nature Communications 14:6692 (2023)　日期 | 2023-10-25

臺美研究：胞外囊泡GCP1為胰臟癌早期發現、化療預後評估指標

撰文 | 記者 吳培安　Advanced Science 11:e2306373 (2024)　日期 | 2024-01-12

見 微 知著 –
單胞外體檢測晶片

矢無虛發 –
雙重靶向胞外體基因療法

https://news.gbimonthly.com/

研究成果

1) **Advanced Science: e2416711 (2025) (IF=14.3)**
2) **Advanced Science 11:e2306373 (2024) (IF=14.3)**
3) **Journal of Biomedical Science 31:30 (2024) (IF=9)**
4) **Nature Communications 14:6692 (2023) (IF=14.7)**

nature communications

Article https://doi.org/10.1038/s41467-023-42402-3

Dual targeted extracellular vesicles regulate oncogenic genes in advanced pancreatic cancer

Received: 26 April 2023
Accepted: 10 October 2023
Published online: 23 October 2023
Check for updates

Chi-Ling Chiang[1,2,17], Yifan Ma[1,3,17], Ya-Chin Hou[4,5,17], Junjie Pan[1], Sin-Yu Chen[6], Ming-Hsien Chien[7], Zhi-Xuan Zhang[6], Wei-Hsiang Hsu[6], Xinyu Wang[1], Jingjing Zhang[1], Hong Li[1], Lili Sun[8], Shannon Fallen[9], Inyoul Lee[9], Xing-Yu Chen[10], Yeh-Shiu Chu[10], Chi Zhang[11], Tai-Shan Cheng[6], Wen Jiang[12], Betty Y. S. Kim[13], Eduardo Reategui[1], Robert Lee[11], Yuan Yuan[1,8], Hsiao-Chun Liu[4,5], Kai Wang[9], Michael Hsiao[7], Chi-Ying F. Huang[6], Yan-Shen Shan[4,5], Andrew S. Lee[14,15] & L. James Lee[1,6,16]

Chen *et al.*
Journal of Biomedical Science (2024) 31:30
https://doi.org/10.1186/s12929-024-01019-4

NSTC 國家科學及技術委員會 National Science and Technology Council

Journal of Biomedical Science

RESEARCH Open Access

Engineered extracellular vesicles carrying *let-7a-5p* for alleviating inflammation in acute lung injury

Sin-Yu Chen[1†], Yi-Ling Chen[2,3†], Po-Chen Li[1], Tai-Shan Cheng[1,4], Yeh-Shiu Chu[5], Yi-Shan Shen[4,6], Hsin-Tung Chen[1], Wei-Ni Tsai[1], Chien-Ling Huang[1], Martin Sieber[7], Yuan-Chieh Yeh[8,9], Hsiao-Sheng Liu[10,11,12], Chi-Ling Chiang[13,14], Chih-Hung Chang[15,4], Andrew S. Lee[16], Yen-Han Tseng[17], Ly James Lee[1,13,16*], Hsiu-Jung Liao[1,18*], Hon-Kan Yip[19,2,20,21,3*] and Chi-Ying F. Huang[1,22*]

RESEARCH ARTICLE

ADVANCED SCIENCE Open Access
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Extracellular Vesicular Analysis of Glypican 1 mRNA and Protein for Pancreatic Cancer Diagnosis and Prognosis

Hong Li, Chi-Ling Chiang, Kwang Joo Kwak, Xinyu Wang, Sital Doddi, Lakshmi V. Ramanathan, Sun M. Cho, Ya-Chin Hou, Tai-Shan Cheng, Xiaokui Mo, Yueh-Shih Chang, Hui-Lan Chang, Weiming Cheng, Wei-Ni Tsai, Luong T. H. Nguyen, Junjie Pan, Yifan Ma, Xilal Y. Rima, Jingjing Zhang, Eduardo Reategui, Yeh-Shiu Chu, Peter Mu-Hsin Chang, Pei-Hung Chang, Chi-Ying F. Huang, Cheng-Hsu Wang,* Yan-Shen Shan,* Chung-Pin Li,* Martin Fleisher,* and L. James Lee**

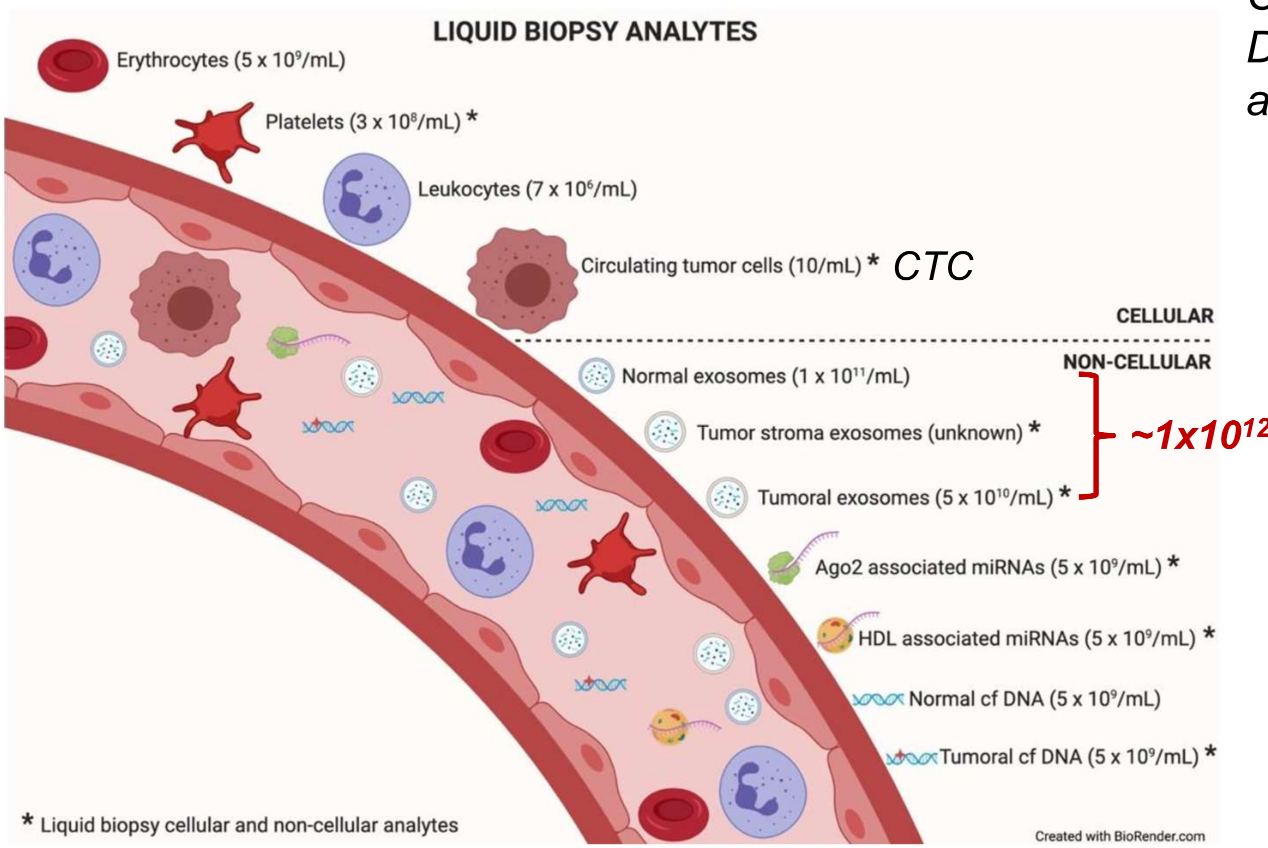
RESEARCH ARTICLE

ADVANCED SCIENCE Open Access
www.advancedscience.com

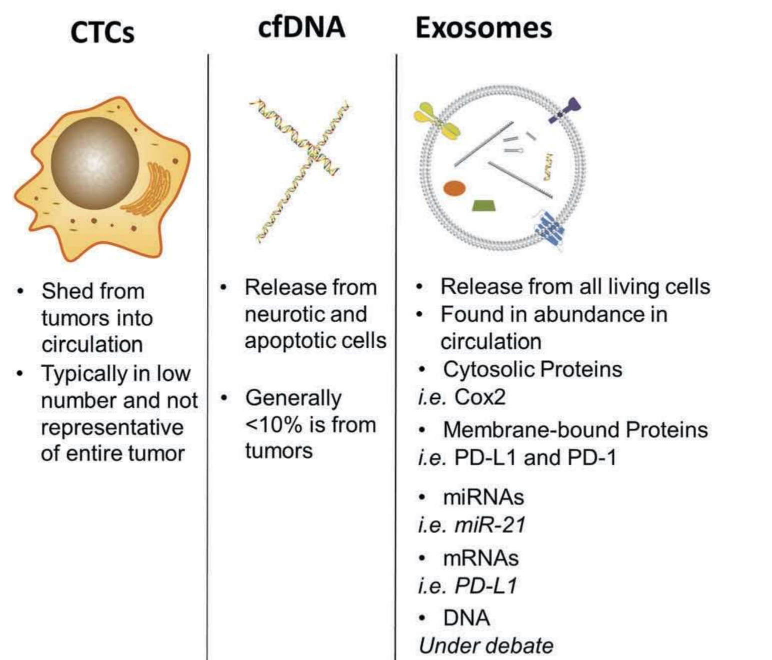
Extracellular Vesicular Delta-Like Ligand 3 and Subtype Transcription Factors for Small Cell Lung Cancer Diagnosis

Hong Li, Chi-Ling Chiang, Kwang Joo Kwak, Hsin-Lun Lee, Xinyu Wang, Giulia Romano, Michela Saviana, Robin Toft, Tai-Shan Cheng, Yuehshih Chang, Bi-Da Hsiang, Guan-Wan Liu, Xiaokui Mo, Yifan Ma, Junjie Pan, Xilal Y. Rima, Truc Nguyen Kim, Eduardo Reategui, Chia-Ning Shen, Yeh-Shiu Chu, Carlo Croce, Peter Mu-Hsin Chang, Yi-Chen Yeh, David P. Carbone, Chi-Ying F. Huang,* Chi-Lu Chiang,* Patrick Nana-Sinkam,* and L. James Lee**

Liquid Biopsy for Cancer Detection



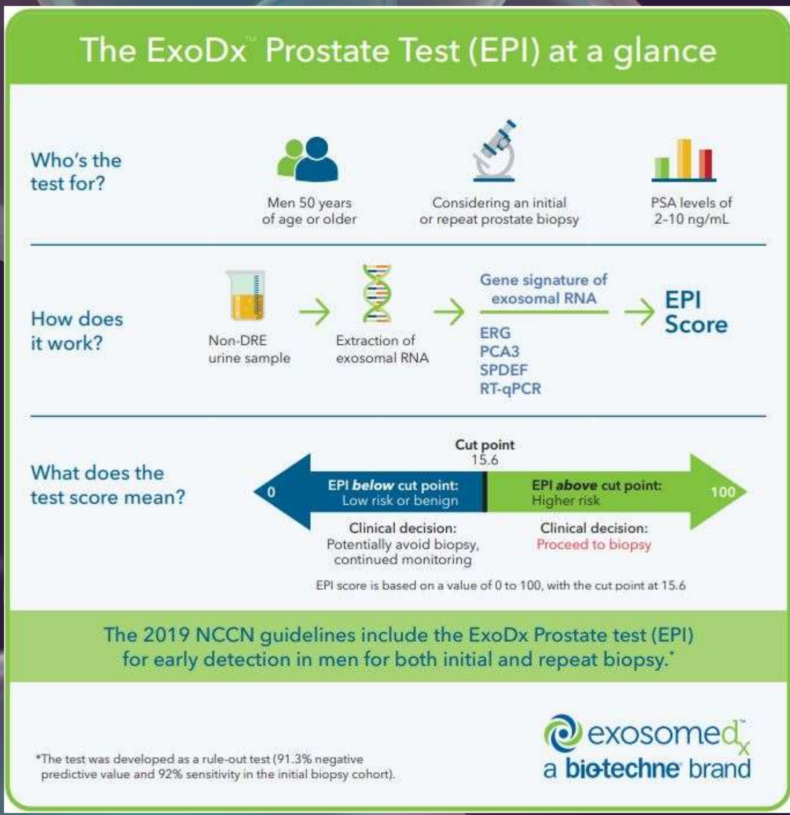
*Circulating tumor cells (**CTCs**), cell-free DNA (**cfDNA**) and **exosomes** are known as the "**troika**" of liquid biopsy.*



Cancers (**2021**) 13:2147.
Signal Transduction and Targeted Therapy (**2020**) 5:144
Expert Rev Mol Diagn. (**2020**)20:1.

ExoDx Prostate(IntelliScore)

https://www.exosomedx.com/gsa-award



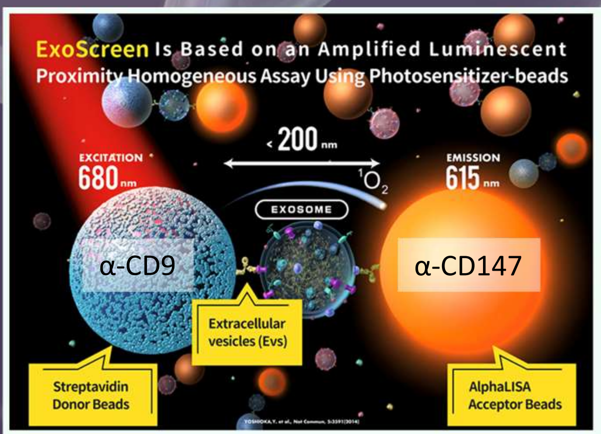
ExoDx™ 攝護腺 (IntelliScore) 測試 (EPI) 是一項在美國提供的非侵入性尿液檢測，旨在評估男性高等級前列腺癌的風險。此檢測尤其適用於根據 PSA 水平考慮是否進行前列腺活檢的患者。**該測試未獲FDA批准，但可在符合 CLIA 規定下作為LDTs提供。**

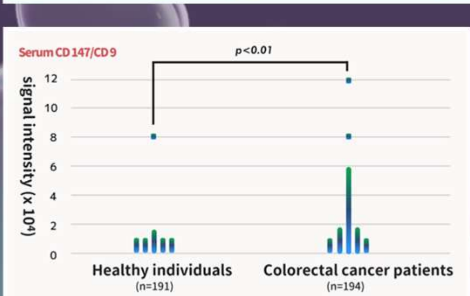
測試費用通常介於600至800美元之間。

檢測過程中，需要在直腸指檢後收集首次尿液樣本。該檢測分析尿液中的前列腺細胞衍生外泌體RNA，測量三種生物標記（ERG、PCA3 和 SPDEF）的表達水平，並通過演算法計算出預測高級別前列腺癌風險的 IntelliScore 分數。

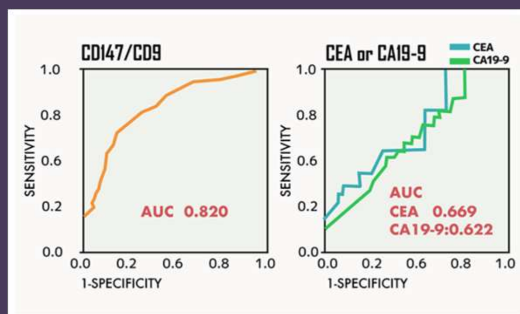
此分數有助於臨床醫生和患者就是否進行前列腺活檢做出更明智的決策。高分數提示可能需要活檢，而低分數則可能建議持續觀察。**ExoDx 檢測的主要優點是能夠減少不必要的侵入性活檢。**

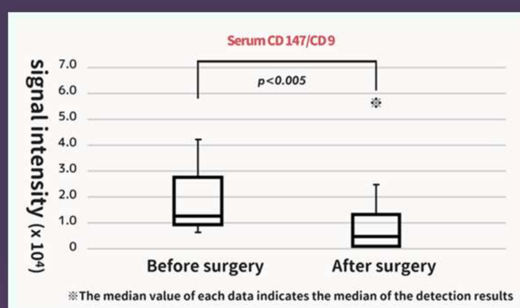
ExoScreen uses the AlphaLISA measurement system to quantify exosomes, specifically cancer-derived exosomes. It does this by detecting light emitted when beads approach **exosomes with specific surface antigens.**





CRC screening





- Theoria Science於2012年成立於日本
- 2023/12/1開始使用外泌體診斷技術建立癌症預防和治療方法
- 已經確定了14種癌症衍生的外泌體，並從胰腺癌開始，爲結直腸癌、胃癌、食道癌、膽囊癌和肝癌提供早期診斷服務

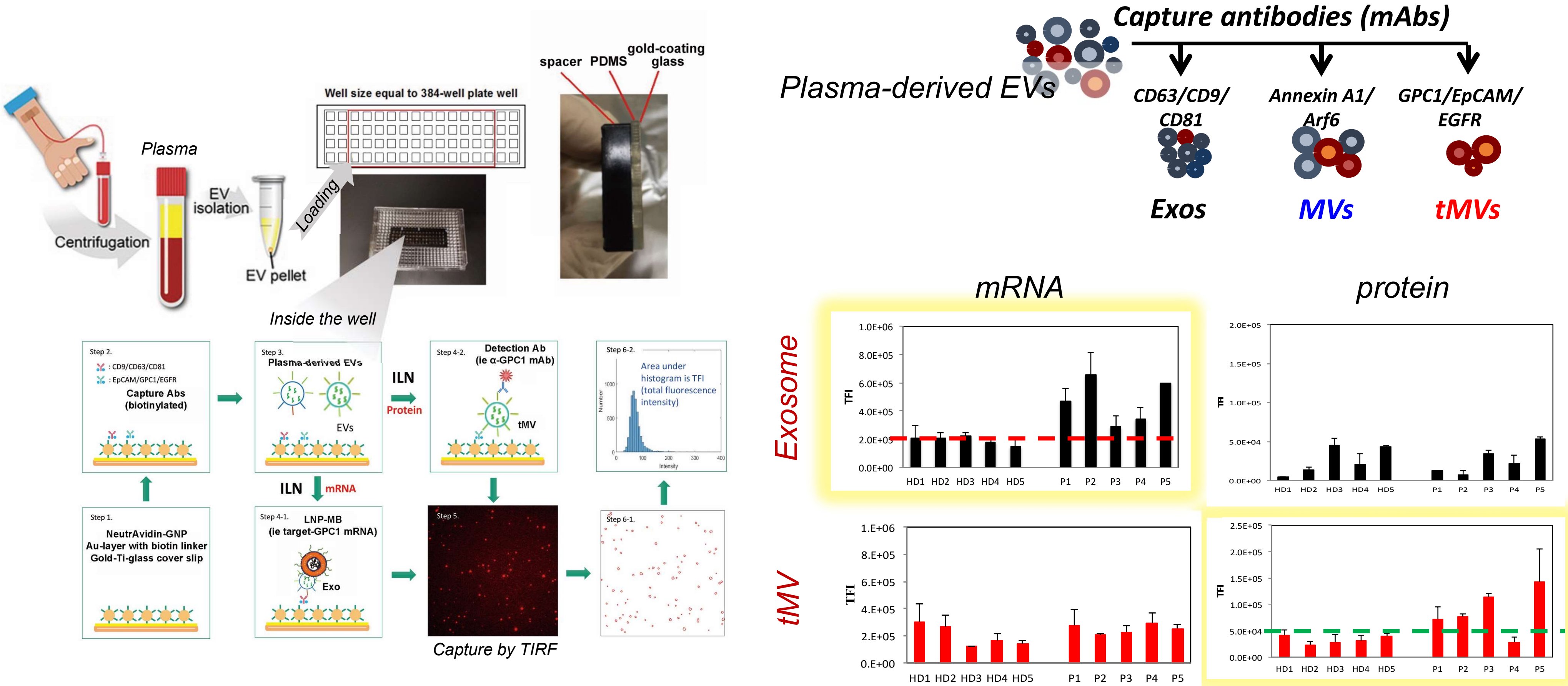
Normal **Cancer**

PDAC Biomarker:
EPS8 & GPRC5C

CRC Biomarker:
CD147

https://en.theoria.co.jp

Immune Lipoplex Nanoparticle (ILN) assay



RESEARCH ARTICLE

ADVANCED SCIENCE
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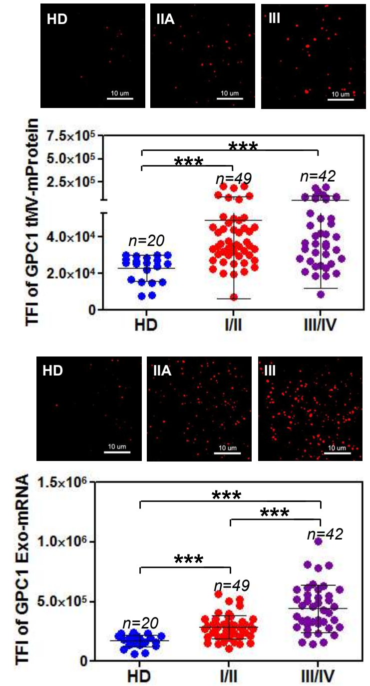
www.advancedscience.com

Extracellular Vesicular Analysis of Glypican 1 mRNA and Protein for Pancreatic Cancer Diagnosis and Prognosis

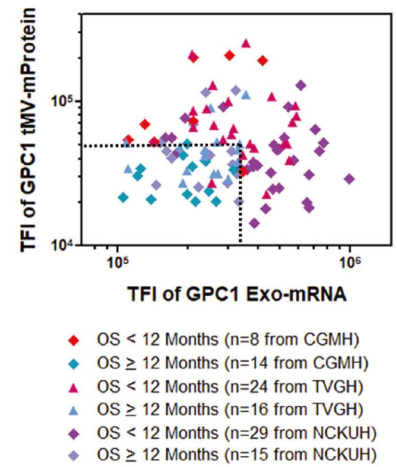
Hong Li, Chi-Ling Chiang, Kwang Joo Kwak, Xinyu Wang, Sital Doddi, Lakshmi V. Ramanathan, Sun M. Cho, Ya-Chin Hou, Tai-Shan Cheng, Xiaokui Mo, Yueh-Shih Chang, Hui-Lan Chang, Weiming Cheng, Wei-Ni Tsai, Luong T. H. Nguyen, Junjie Pan, Yifan Ma, Xilal Y. Rima, Jingjing Zhang, Eduardo Reategui, Yeh-Shiu Chu, Peter Mu-Hsin Chang, Pei-Hung Chang, Chi-Ying F. Huang, Cheng-Hsu Wang,* Yan-Shen Shan,* Chung-Pin Li,* Martin Fleisher,* and L. James Lee**

Ohio State University, and Memorial Sloan Kettering Cancer Center, USA
National Yang Ming Chiao Tung University, National Cheng Kung University, National Cheng Kung University Hospital, Chang Gung University, Keelung Chang Gung Memorial Hospital, and Taipei Veterans General Hospital, Taiwan

Early Diagnosis



Complementary Diagnostics



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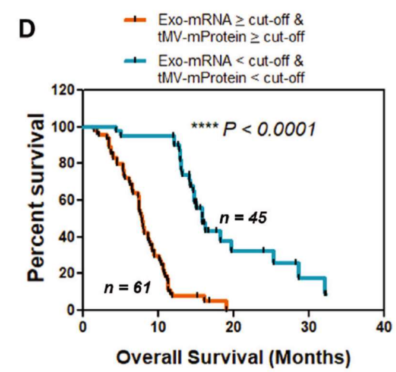
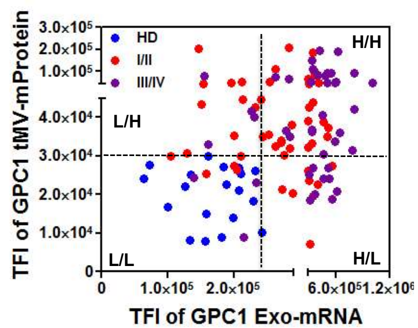
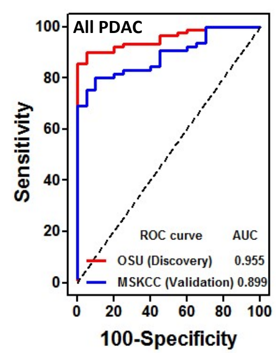


GPC1-ILN assay vs. CA 19-9 ELISA in PDAC

PDAC Stage	IA/IB	IIA	IIB	III	IV
Number of patients	9	18	36	42	51
GPC1 Exo-mRNA	0.672	0.908	0.858	0.957	0.862
GPC1 tMV-mProtein	0.850	0.896	0.858	0.855	0.850
GPC1 Exo-mRNA/ GPC1 tMV-mProtein	0.889	0.953	0.926	0.986	0.935
CA19-9 protein * (number of patients)	0.735 (n=5)	0.668 (n=18)	0.740 (n=117)	0.729 (n=11)	0.788 (n=41)



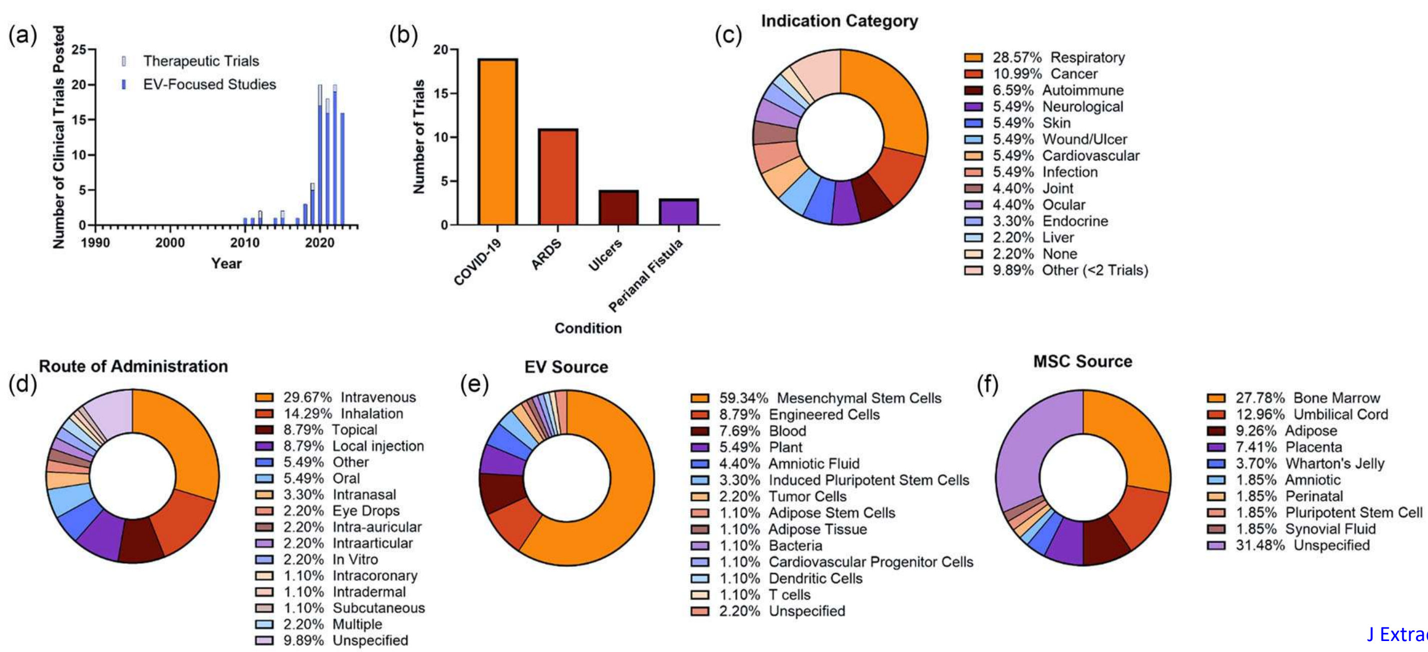


Adv Sci. (2024) 11(11):e2306373.

Nature 439,66
3–664 (2006)

Summary of EV-related therapeutic clinical trials

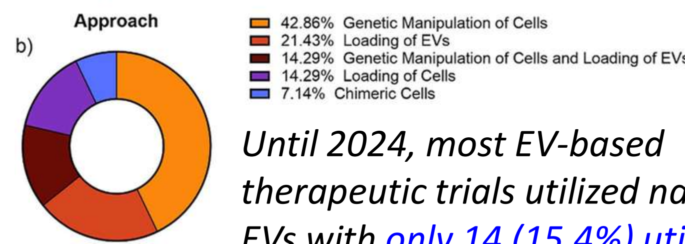
- The first clinical trial for extracellular vesicles (EVs) was in 2010, with consistent trials starting in 2017.
- **The trials targeted 61 diseases, primarily COVID-19 and ARDS.**
- Respiratory illnesses were the most frequently studied (28.6%), followed by cancer (11.0%) and autoimmune diseases (6.6%).
- Intravenous was the most common route of administration (29.7%).
- Most trials (59.3%) used EVs derived from mesenchymal stem cells (MSCs), often sourced from bone marrow or umbilical cord.
- About 35.2% of trials reported dosing strategies, mostly using the number of EV particles.



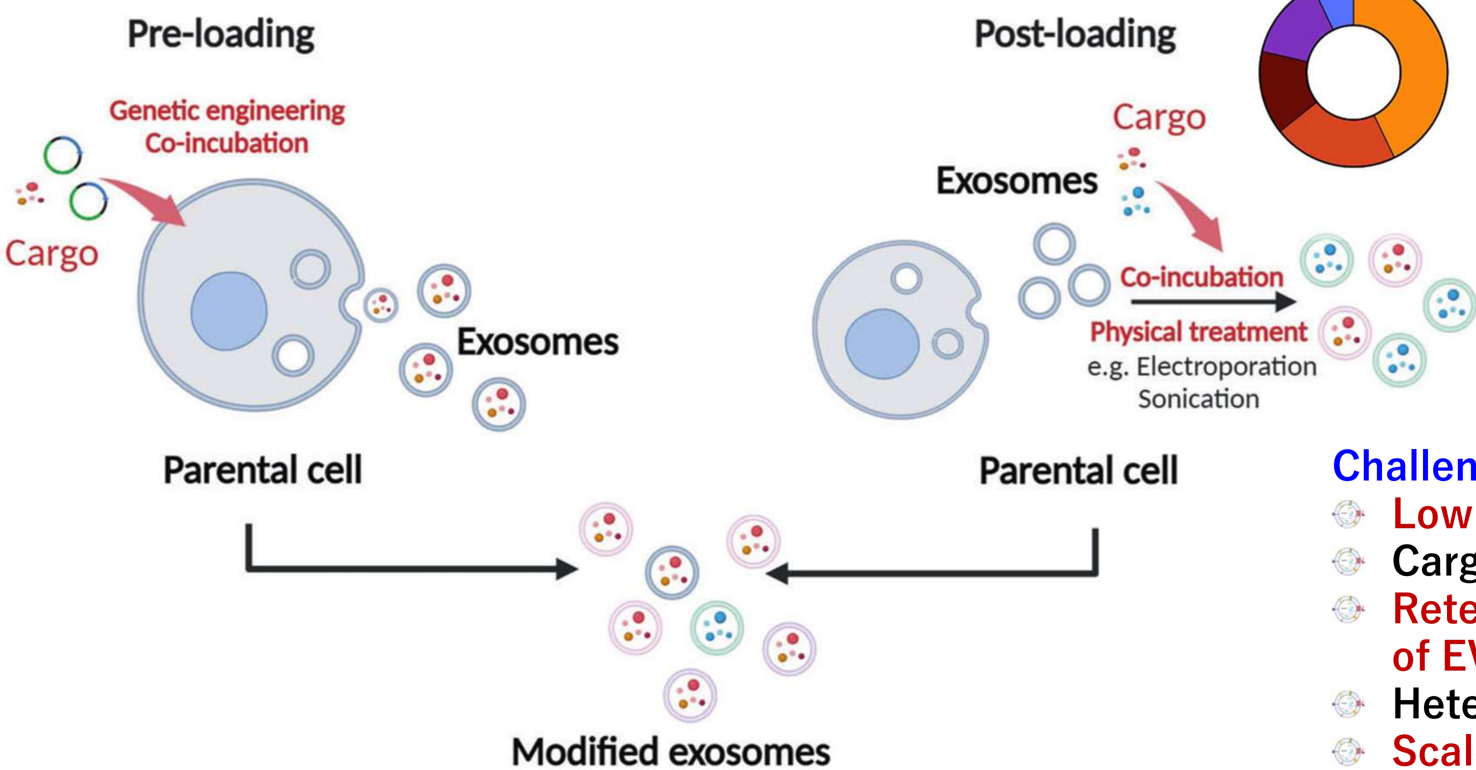
J Extracell Vesicles. (2024)13:e12510.

Exosome engineering strategies for loading therapeutic cargo into exosomes

Summary of engineered EVs in EV-related therapeutic trials



Until 2024, most EV-based therapeutic trials utilized native EVs with only 14 (15.4%) utilizing engineered EVs.

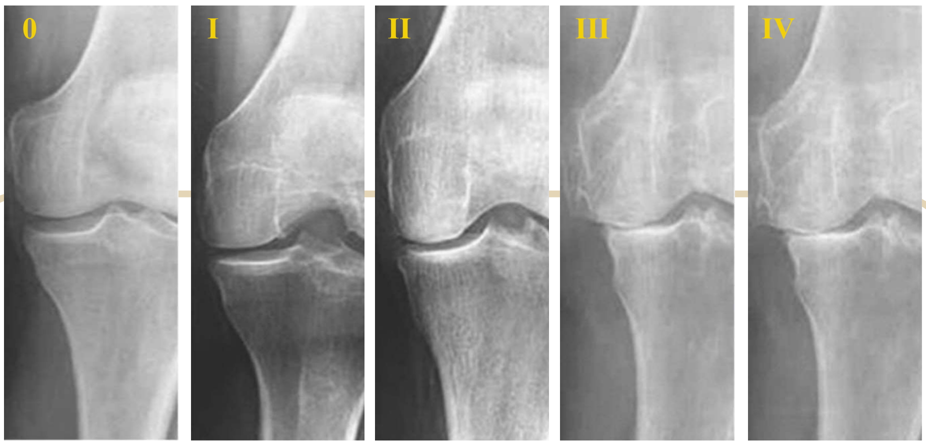


Challenges

- Low Efficiency
- Cargo Stability
- Retention of Functional Integrity of EVs
- Heterogeneity
- Scalability

Experimental & Molecular Medicine (2024) 56:877 – 889
J Extracell Vesicles. (2024)13:e12510

OSTEOARTHRITIS (OA) is the second most common musculoskeletal and is a leading cause of disability



There is a lack of available **disease-modifying osteoarthritis drugs (DMOADs)**, resulting in treatment options being confined to pain relief in the early stages and resorting to surgical joint replacement in advanced cases.

	Mild OA	Moderate OA	Severe OA
1st Line	• None-pharmacological intervention (physical therapy) • Lifestyle Modification: exercise, weight loss	• Oral analgesics • Topicals	• **Opioids** • **IA injections** • **Cell therapy**
2nd Line	• NSAIDs • COX-2 inhibitors	• NSAIDs • COX-2 inhibitors	• **Osteotomy**
3rd Line	• Opioids • Intra-articular (IA) injections	• **Opioids** • **IA injections** • **Cell therapy**	• **Surgery (total Knee arthroplasty, TKA)**

IA injections: hyaluronic acid (HA) or corticosteroid

Naive EV on knee OA

Source of EV	Animal Model	EV Concentration and Protocol	Effects	Measures	References
hUC-MSCs-Exos	**Male SD Rat** (ACLT + MMx)	10^{11}particles/ml, 100 µl twice/week for 4 week (5th~ 8th week)	OARSI: 3→1 **2**	IHC: Col2a1, Mmp-13	Li P et al. *Ann Transl Med.* 2022; 10(18): 976.
hBMSCs-EVs	**Male SD Rat** (ACLT + MMx)	100 µg/100 µl 100 µl/week for 8 weeks (0~7th week)	OARSI: 2→1 **1**		Jin Y et al. *J Cell Mol Med.* 2021; 25(19): 9281-9294.
mBMSCs-EVs	**Male SD Rat** (ACLT + MMx)	10^{10} particles/ml 10 µl /3 days for 4 weeks (5th~ 8th week)	OARSI: 3→1.5 **1.5**	Micro CT; IHC: Col2a1,Colx	Zhang J et al. *Aging (Albany NY).* 2020; 12(24): 25138-25152.
mBMSCs-EVs	**Male SD Rat** (Sodium iodoacetate Induced)	40 µg 100 µl /week for 5 weeks (1st~ 6th week)	OARSI: 4→3 **1**	IHC: Col2a1, Mmp-13	He L et al. *Stem Cell Res Ther.* 2020; 11(1): 276.
hUC-MSCs-Exos	**Male C57BL/6 mice** (ACLT + MMx)	10^{11} particles/ml 10 µl twice/week for 6 weeks (3rd day + forced exercise)	OARSI:4.5→3 **1.5**	Micro CT; IHS: Col2a1, Aggrecan, Adamts5, Mmp-13	Zhou H et al. *Stem Cell Res Ther.* 2022; 13(1): 322.
Antler Stem Cells-Exos	**Male C57BL/6 mice** (ACLT)	10^{8} particles/ml 10 µl/week for 8 weeks (2nd week)	OARSI: 3→2 **1**	Grip strength, Bone density	Lei J et al. *Protein Cell.* 2022; 13(3): 220-226.
hADMSCs-Exos	**Male C57BL/6 mice** (DMM)	10^{8} particles/ml 6 µl/week for 6 weeks (5th~ 11st week)	OARSI: 5→2.5 **2.5**	IHC: Mmp-13, NITEGE	Woo CH et al. *J Extracell Vesicles.* 2020; 9(1): 1735249.
hIPFP-MSCs-Exos	**Male C57BL/6 mice** (DMM)	10^{10} particles/ml 10 µl twice/week for 4 weeks (5th~ 8th week)	OARSI: 4→2 **2**	IHC: Col2a1, Adamts5, Mmp-13	Wu J et al. *Biomaterials.* 2019; 206: 87-100.
hBMSCs-EV hADSCs-EV	**Female BALB/c Mice** (Ciprofloxacin-induced)	100 µg/ml 25 µl/week for 3 weeks (4th ~ 6th week)	OARSI: 4.5→2 **2.5** OARSI: 4.5→3 **1.5**	IHC: Col2a1	Fazaeli H. et al. *Biomed Res Int.* 2021; 27:9688138.

Mean: 1.65

胞外體
創新精準醫療

見微知著–
單胞外體檢測晶片

矢無虛發–
雙重靶向胞外體基因療法

陽明交大領軍高長、亞東 聚焦急性肺損傷開發胞外體核酸藥物

撰文 | 記者 吳培安　　日期 | 2024-03-26

《Nature》子刊：陽明交大、成大「核酸藥+胞外體」創新療法 精準攻擊胰臟癌

撰文 | 記者 吳培安　　日期 | 2023-10-25

臺美研究：胞外囊泡GCP1為胰臟癌早期發現、化療預後評估指標

撰文 | 記者 吳培安　　日期 | 2024-01-12

https://news.gbimonthly.com/

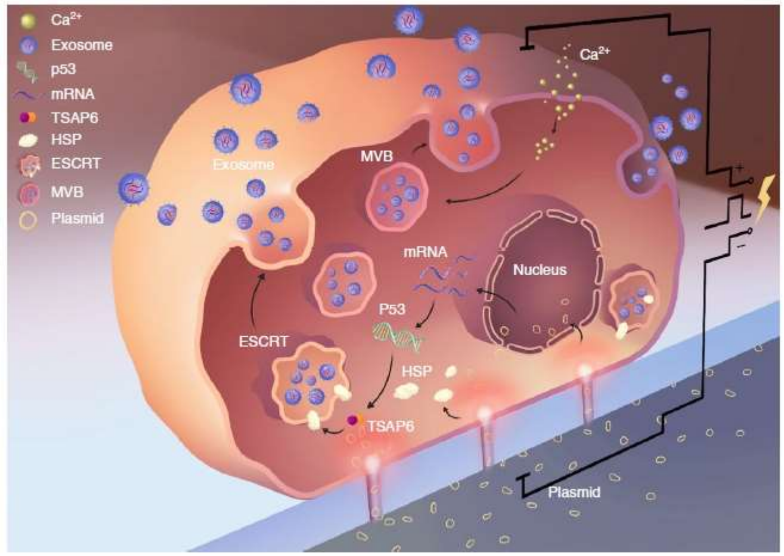
Nanochannel electroporation (Cellular nanoporation, CNP)

Prof. LJ Lee
Chaired Professor Emeritus at OSU,
Jade Mountain Scholar at NYCU,
and key inventor of the CNP

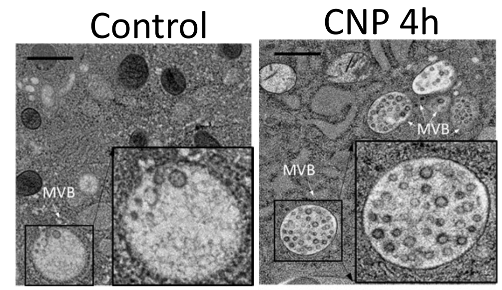
nature biomedical engineering ARTICLES
https://doi.org/10.1038/s41551-019-0485-1

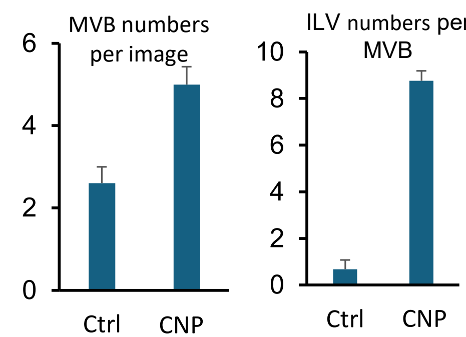
Large-scale generation of functional mRNA-encapsulating exosomes via cellular nanoporation

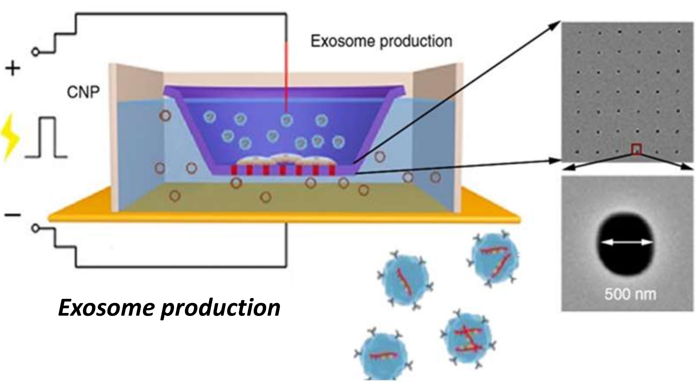
Zhaogang Yang[1,2,15], Junfeng Shi[1,15], Jing Xie[3], Yifan Wang[2], Jingyao Sun[1], Tongzheng Liu[4], Yarong Zhao[3], Xiuting Zhao[3], Xinmei Wang[1], Yifan Ma[1], Veysi Malkoc[1], Chiling Chiang[5], Weiye Deng[2], Yuanxin Chen[6], Yuan Fu[6], Kwang J. Kwak[1], Yamin Fan[1], Chen Kang[7], Changcheng Yin[8], June Rhee[9], Paul Bertani[10], Jose Otero[11], Wu Lu[10], Kyuson Yun[12], Andrew S. Lee[9,13], Wen Jiang[2], Lesheng Teng[3*], Betty Y. S. Kim[6,14*] and L. James Lee[1*]



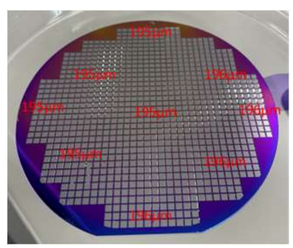
Nature Biomedical Engineering.Zhaogang Yang, Junfeng Shi, [...]L. James Lee., 2019)







Exosome production



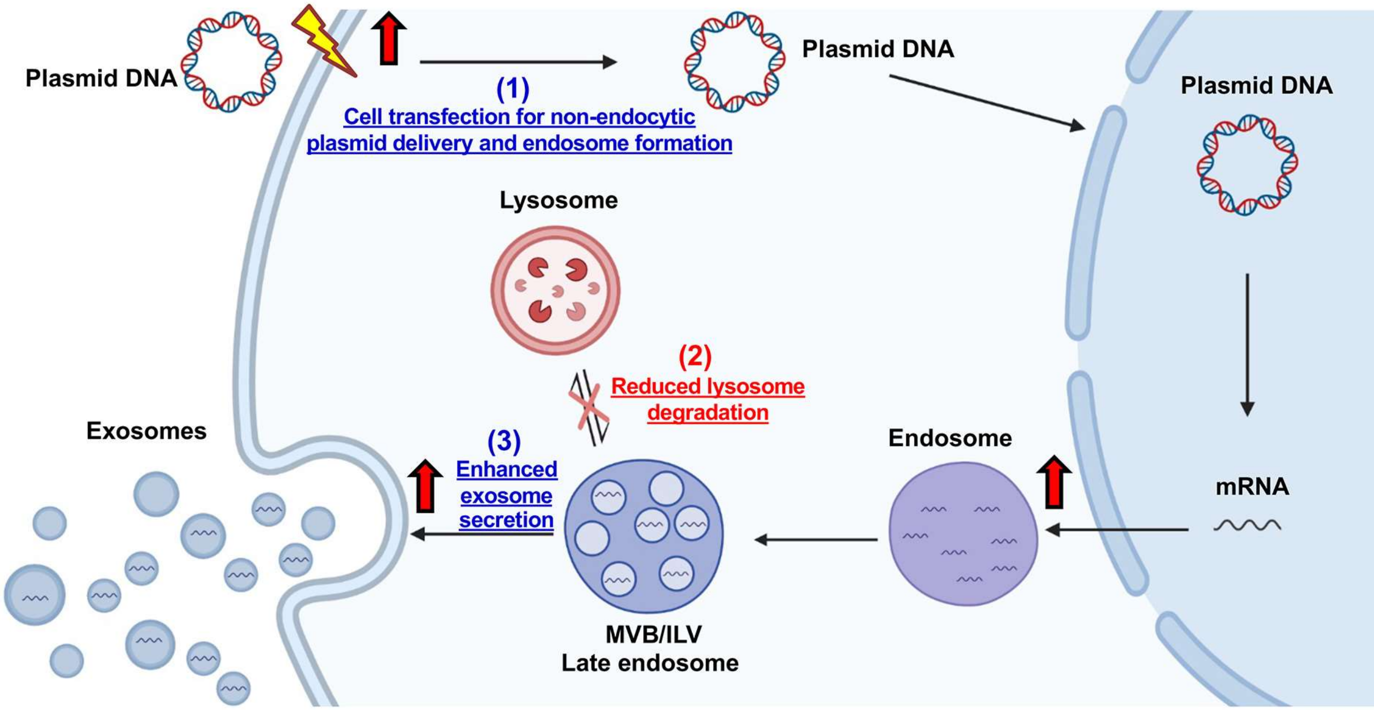
Advantage 1
＊High transfection efficiency.
＊Lower cell death.

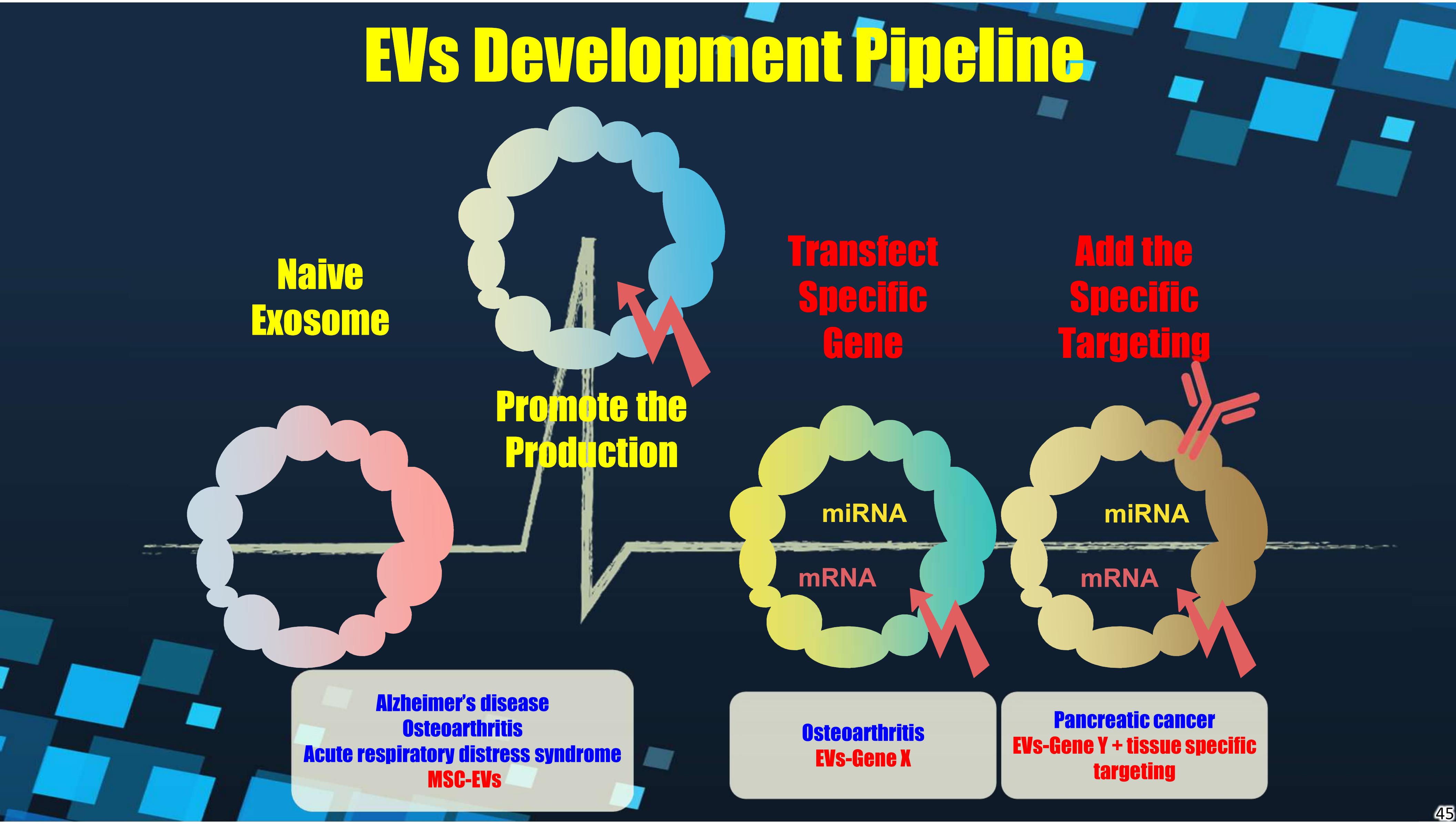
Advantage 2
＊Promote exosome secretion.
＊Exosome decoration. (By deliver special plasmid)

Advantage 3
＊ Provide QC target
＊ Provide consistency

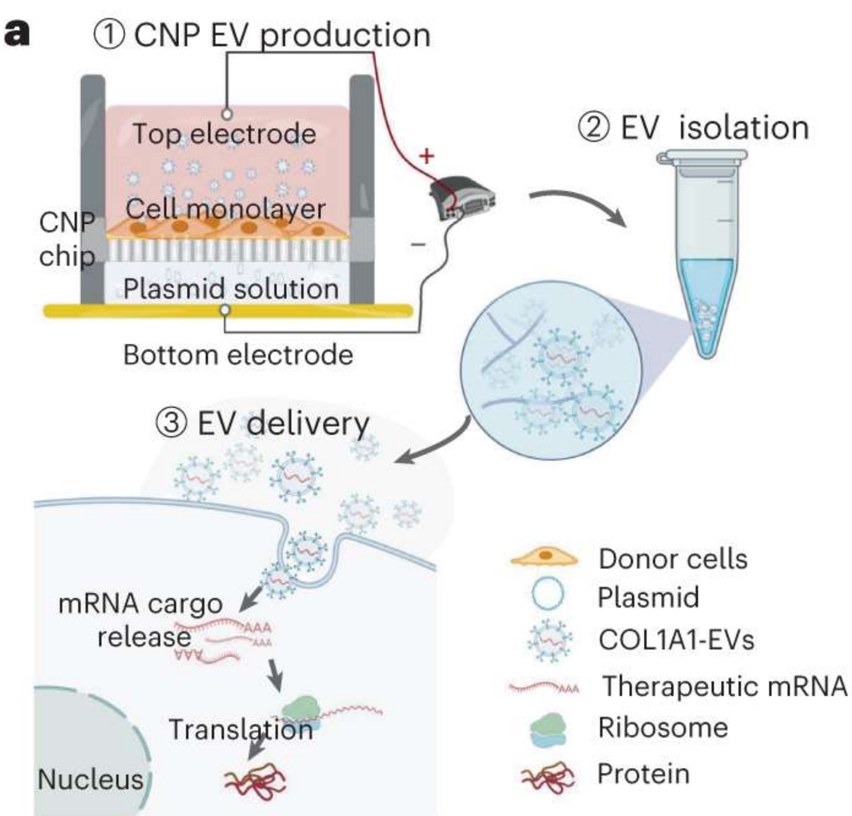
How Nanochannel Electroporation Boosts EV Production and Efficient Cargo Loading

- Efficient delivery of plasmid DNAs into cells results in a high transcription rate, leading to the production of significant quantities of endogenous, albeit non-native, mRNAs within the cytosol.
- It is crucial that any cellular damage caused by nanopores remains non-lethal to enable membrane repair and inhibit lysosomal activity. Additionally, changes in the activity of cytosolic ion channels may occur.
- Activate the exosome secretion pathway.




EVs Development Pipeline
Naive Exosome
Promote the Production
Transfect Specific Gene
Add the Specific Targeting
miRNA
mRNA
miRNA
mRNA
Alzheimer's disease
Osteoarthritis
Acute respiratory distress syndrome
MSC-EVs
Osteoarthritis
EVs-Gene X
Pancreatic cancer
EVs-Gene Y + tissue specific targeting
45

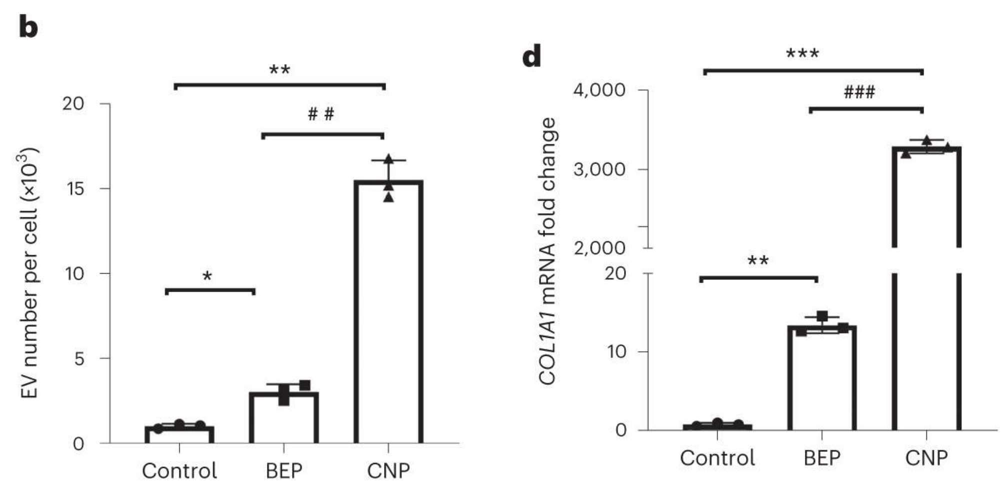
Collagen replacement therapy: Collagen I mRNA enriched-EVs



nature biomedical engineering

Article https://doi.org/10.1038/s41551-022-00989-w

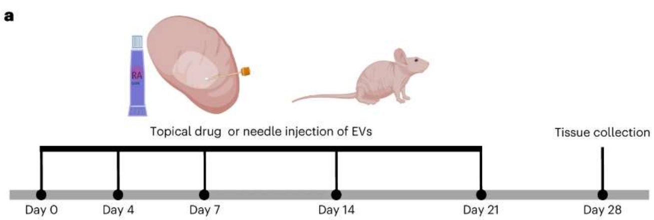
Intradermally delivered mRNA-encapsulating extracellular vesicles for collagen-replacement therapy

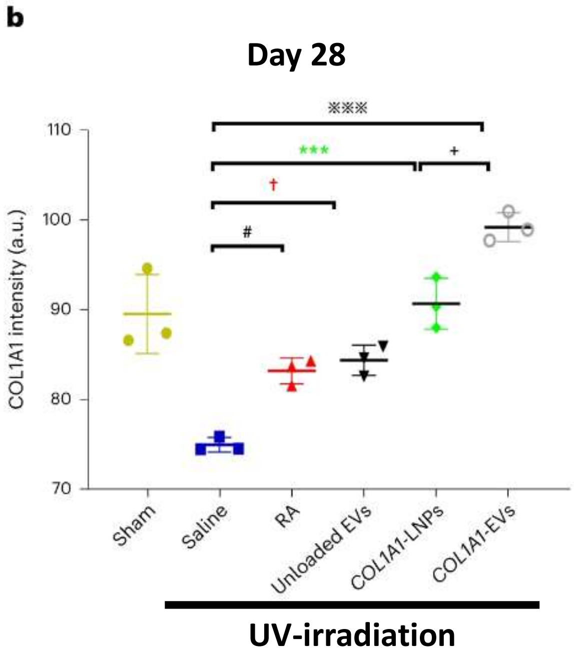


CNP generates large quantities of EVs loaded with *COL1A1* mRNA.

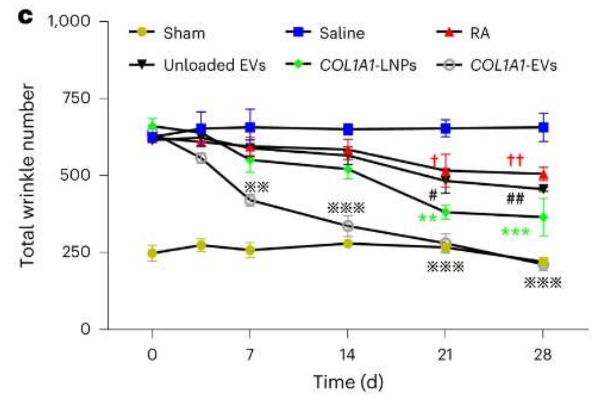
Nature Biomedical Engineering (2023) 7: 887-900

COL1A1-EV mRNA delivery successfully improves UV-irradiation photoaging

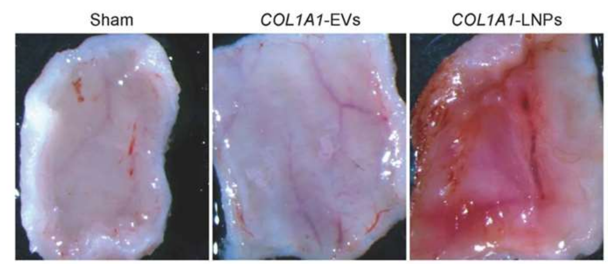




Increase COL1A1 protein expression



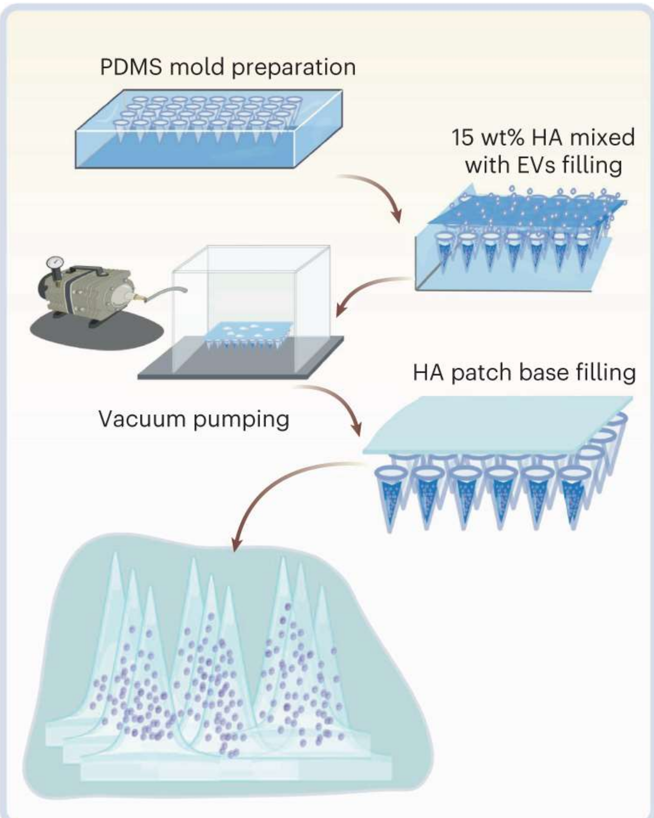
Reduce dermal wrinkles



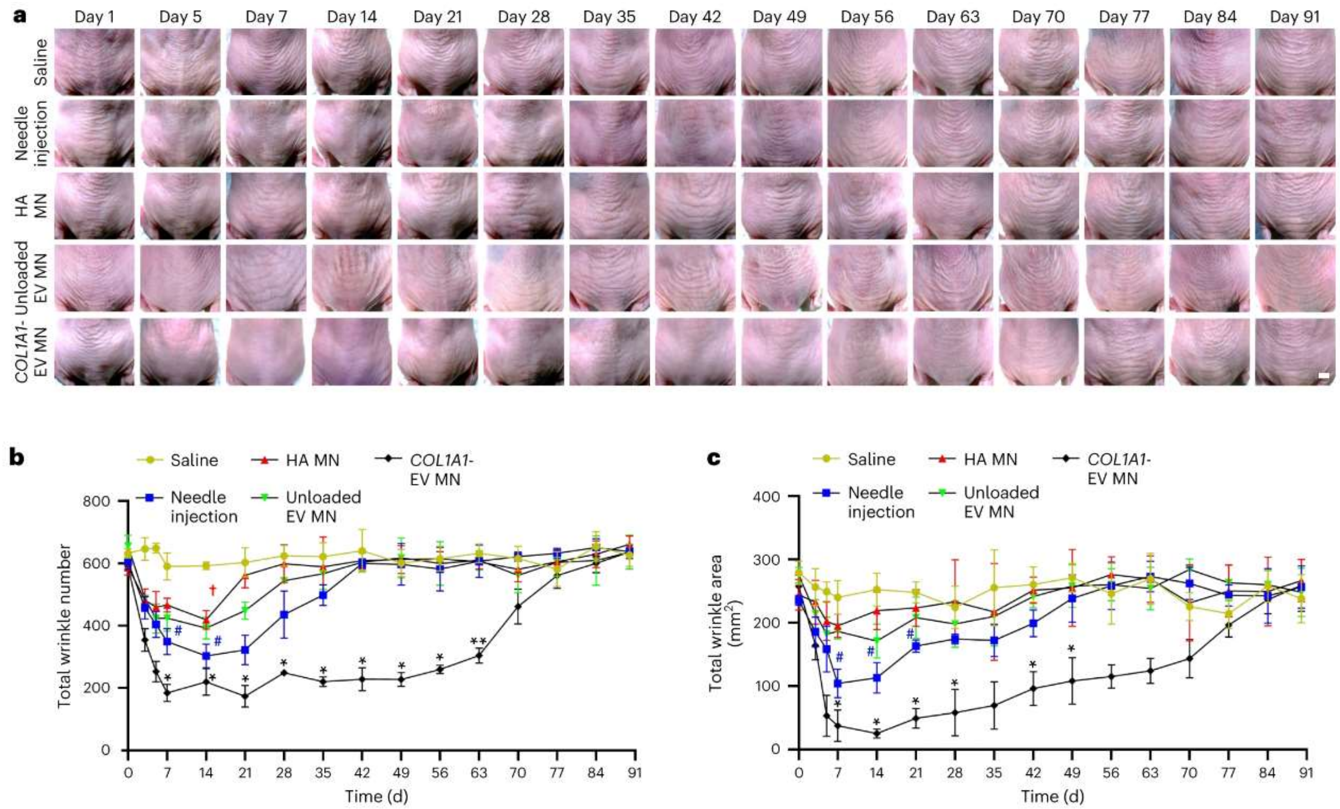
No immunogenic side effects

Nature Biomedical Engineering (2023) 7: 887-900

COL1A1-EV delivery via microneedle improves long-term treatment of photoaged skin



Schematic illustration of microneedle fabrication



Nature Biomedical Engineering (2023) 7: 887-900

Novel anti-cancer therapy: Dual-targeted shKRAS/TP53 EVs

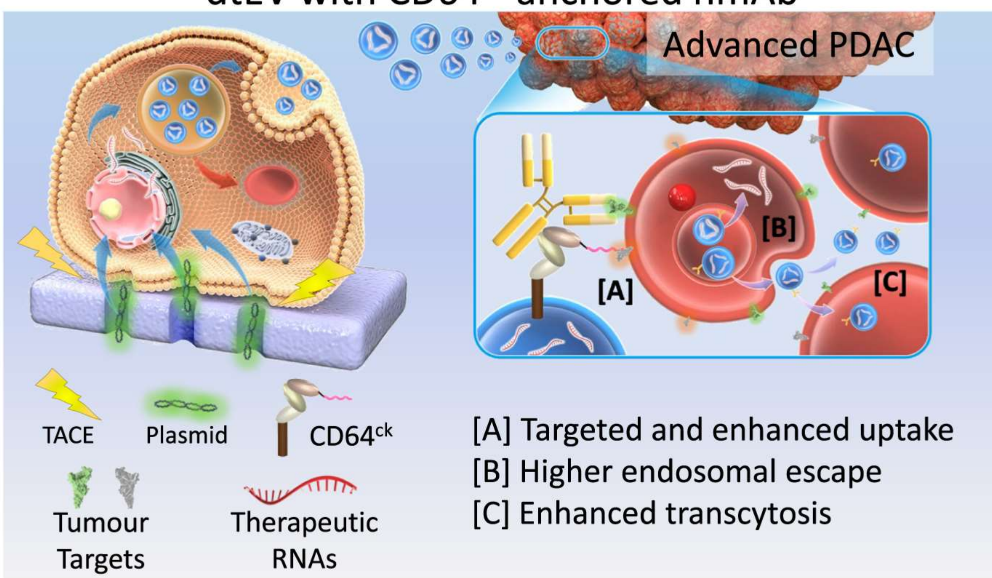
nature communications

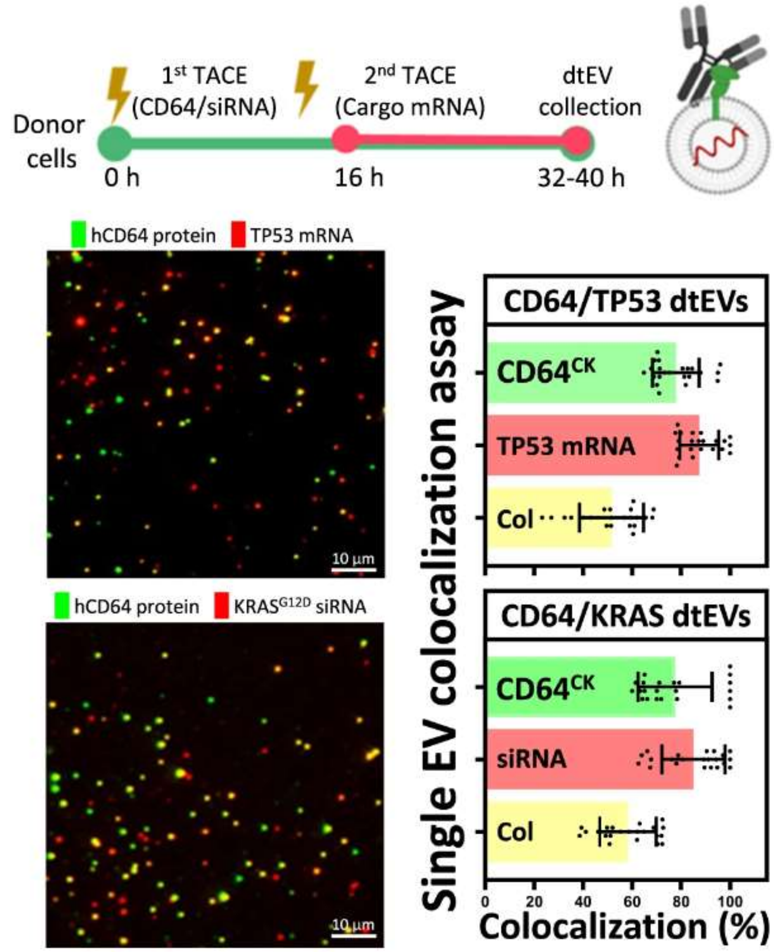
Article

https://doi.org/10.1038/s41467-023-42402-3

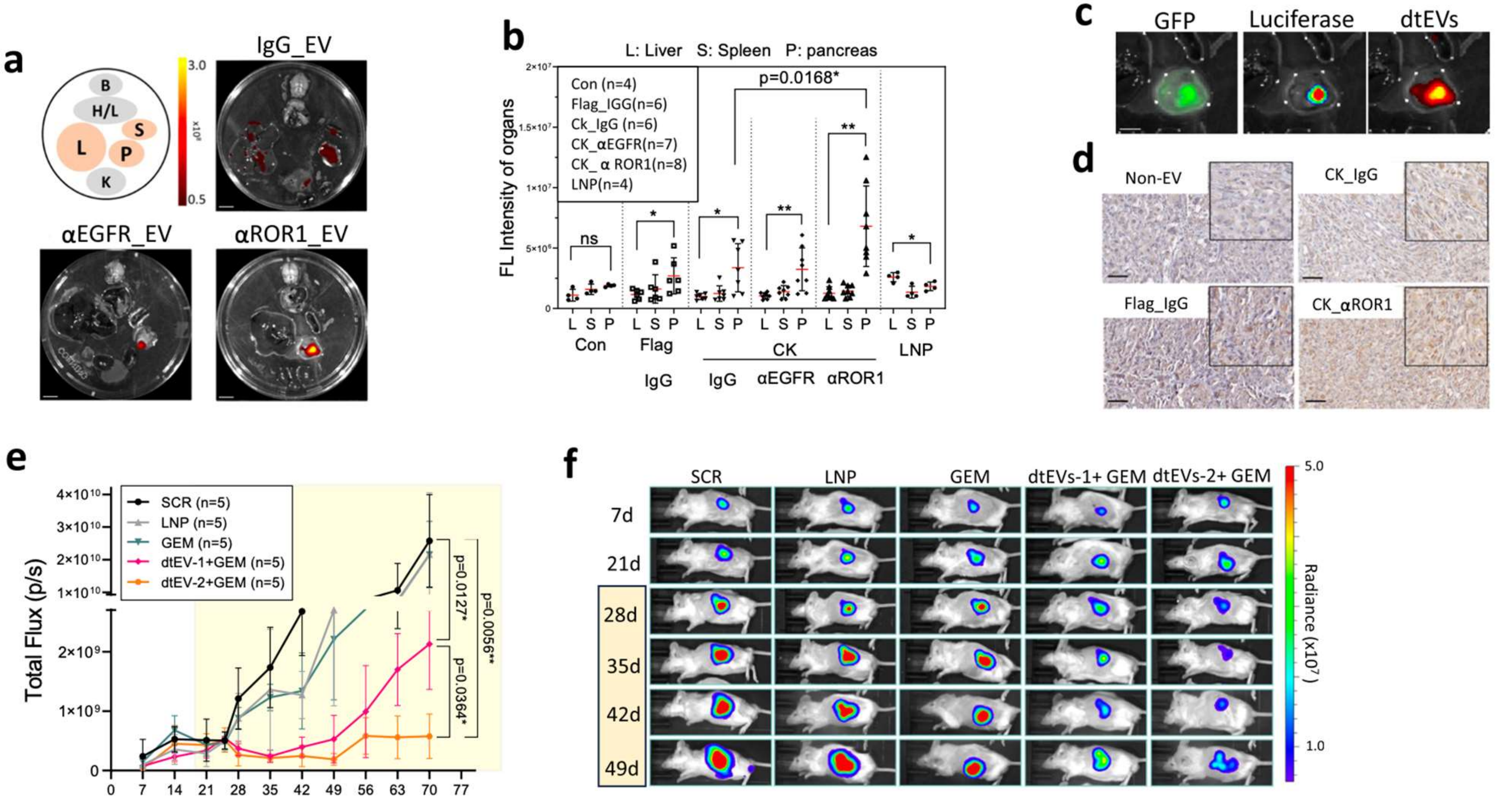
Dual targeted extracellular vesicles regulate oncogenic genes in advanced pancreatic cancer

dtEV with CD64^{ck} anchored hmAb

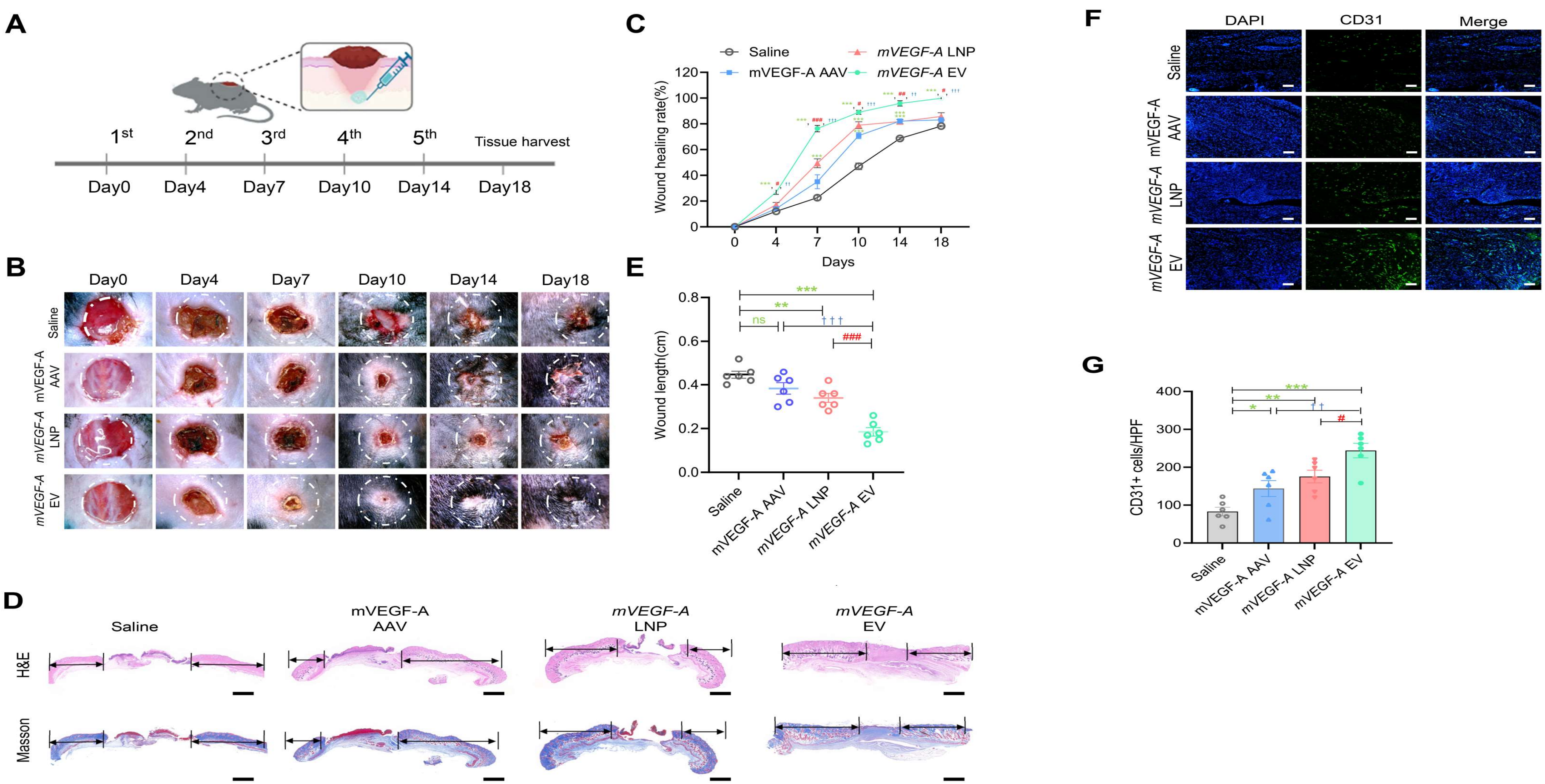




Targeting and therapeutic efficacy of dtEVs in mice bearing orthotopic PANC-1 tumors

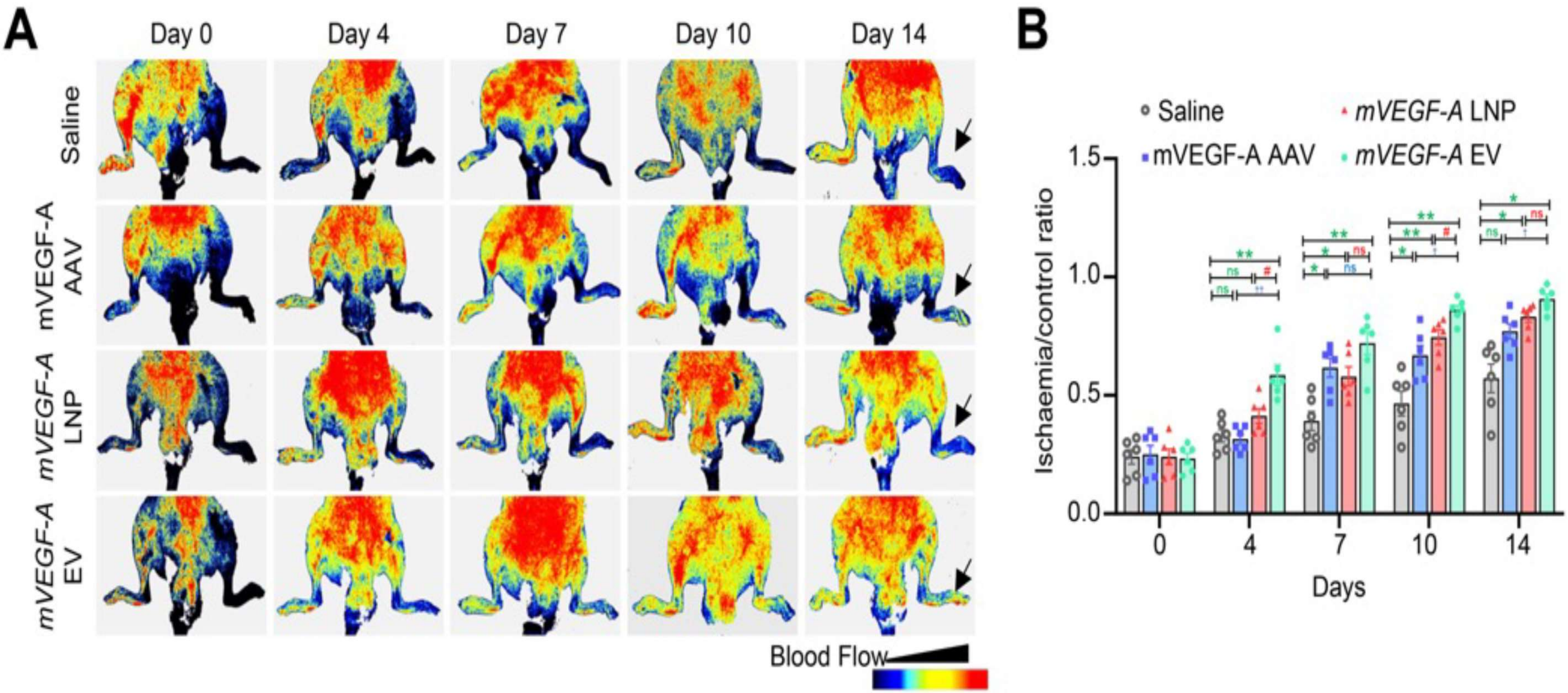


Repeated Intradermal Administrations of *mVEGF-A* EVs Promote Cutaneous Wound Healing and Angiogenesis in Immunocompetent Mice



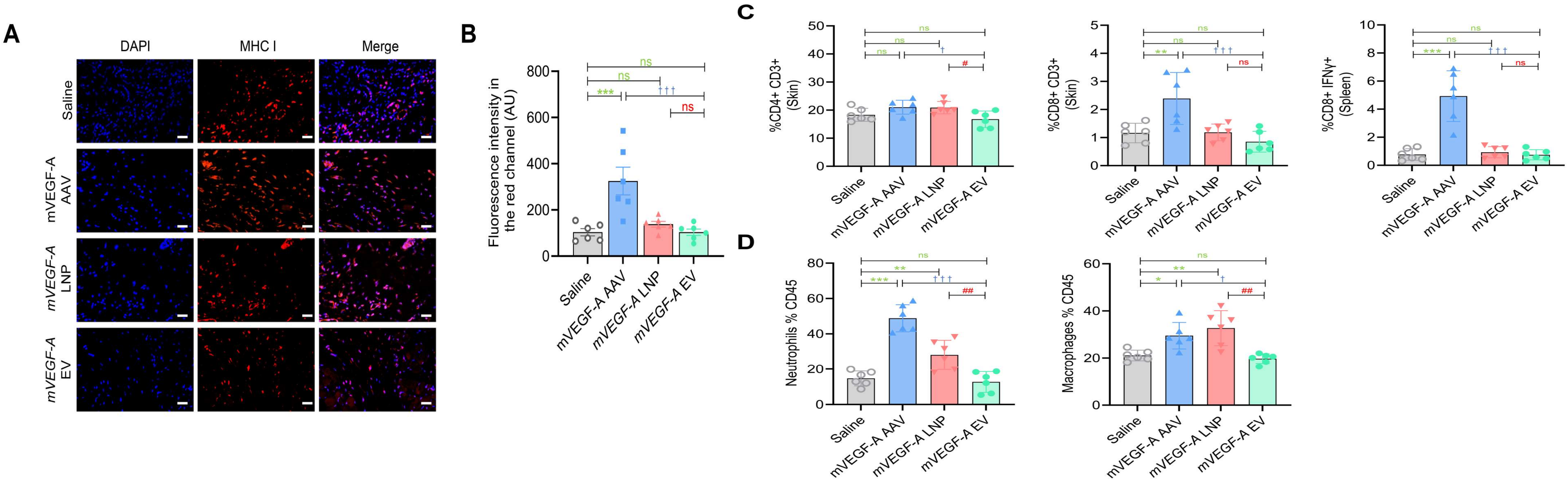
Y. You ,et al., L.J. Lee, et al,. European Heart Journal, 2025

Limb Perfusion and Immune Responses after Intramuscular Delivery of *mVEGF-A* EVs in Immunocompetent Mice with Femoral Artery Ligation



Y. You ,et al., L.J. Lee, et al,. European Heart Journal, 2025

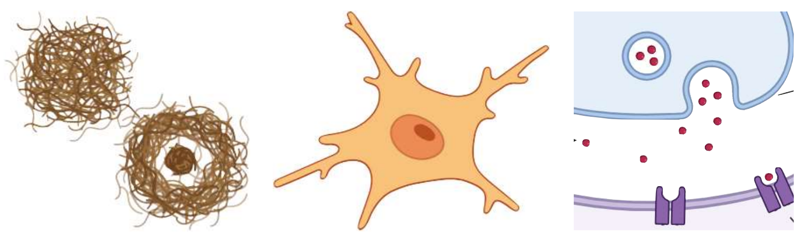
Immunogenic Response in Skin and Skin Cells after Serial Cutaneous Injections (5 times in 18 days) of mVEGF-A AAVs, *mVEGF-A* LNPs, and *mVEGF-A* EVs in Immunocompetent Mice



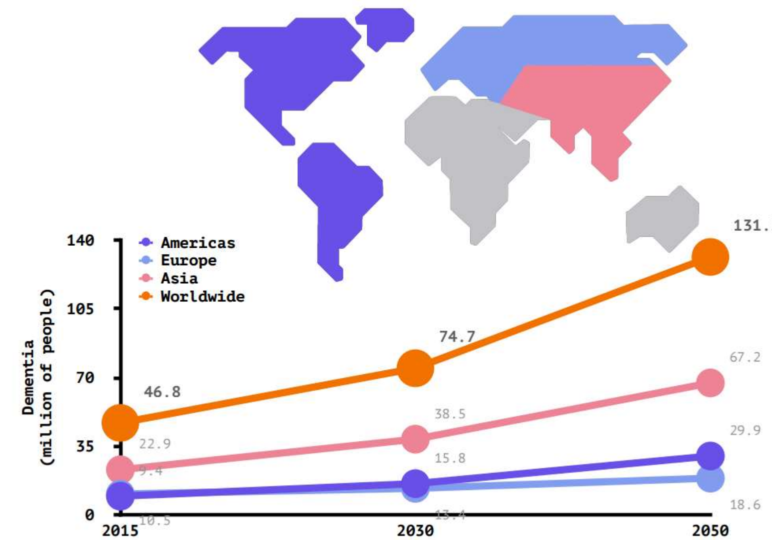
Y. You ,et al., L.J. Lee, et al,. European Heart Journal, 2025

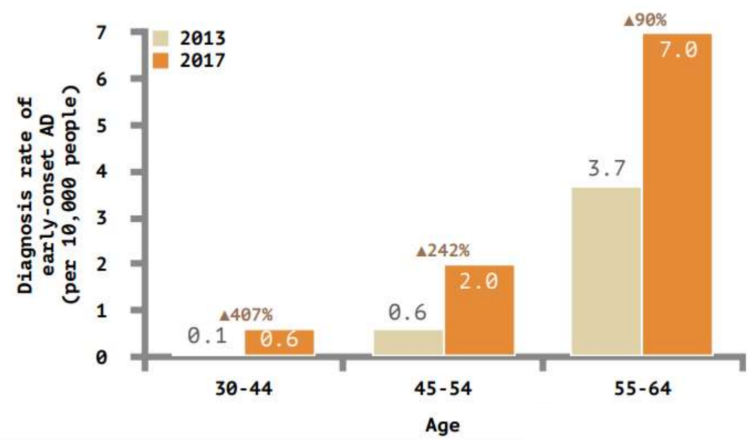
Alzheimer's Disease (AD)

- Alzheimer's disease (AD) is a kind of neurodegenerative disorder that accounts for 60-80% of dementia cases.
- Its significance as a social problem is growing due to the <u>aging population</u>.
- Risk factors such as <u>high blood pressure, high blood sugar (type 2 diebetes), and stress</u> can also increase the likelihood of developing and worsening the disease.
- The <u>early-onset</u> Alzheimer's disease (< 65 y/o) has grown by 131%.



Toxic senile plaque (Aβ/tau) | Inflammation | Signal transduction

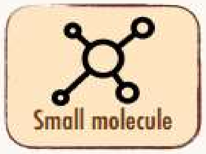




The Lancet. Neurology. 2019;18(1), 88–106.
Cheong et al. Pharmaceuticals 2022

FDA Approved Drug for AD Therapy

Cholinergic System | Neurotransmitters | Other function



1995 **Tacrine** (discontinued) Liver toxicity

2003 **Memantine** NMDA receptor antagonist

1997 **Rivastigmine**

2008-2010 **Rivastigmine patch** (patch overdose)

2000 **Galantamine**

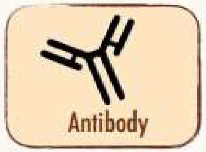
2006 **Donepezil**

2020 **Suvorexant** Only for sleep

2022 **Donepezil patch**

2023 **Brexpiprazole** Serotonin/dopamine activity modulator

1990 | 2000 | ... | 2010 | 2020



2004 PiB amyloid PET

2005-2012 Bapineuzmab Ph2/3

2013 AV1451 (flortaucipir) tau PET

2018 Plasba Aβ (IPMS)

2020 Plasma P-tau181 and 217

2009-2017 Solanezumab Ph3 (x3)

2012-2019 Aducanumab Ph1

2012-present DIAN-TU

2013-2023 API Crenezumab prevention trial

2014-2023 Solanezumab (A4) prevention trial

2015-2019 Multiple Ph3 beta secretase trials

2015-2019 Aducanumab Ph3 (x2)

2016-2019 Crenezumab Ph3 (x2)

2017-2021 Donanemab Ph2

2017-2022 Tau ASO (BIIB080) Ph1

2018-2022 Gantenerumab Ph3 (x2)

2019-2022 Lecanemab Ph3

2020-2023 Donanemab Ph3

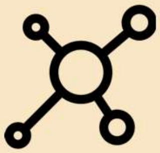
2020-present AHEAD 3-45 (Lecanemab)

2022-present Aducanumab Ph3/4

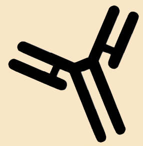
	Aduhelm (Aducanumab)	**Leqembi** (Lecanemab)	**Kisunla** (Donanemab)
FDA	2021.6 (accelerated approval)	**2023.7 (traditional approval)**	**2024.7 (traditional approval)**
Target	$A\beta_{42}$ oligomers	Aβ soluble protofibrils	Aβ p3-42 (amyloid plaques)
Side effect	**edema, bleeding, infusion-related reactions in the brain (ARIA).**		
Efficiency	Only for slow down in mild stage.		-
Yearly cost	USD$~~56,000~~ 28,000	USD$26,500	USD$32,000

Boxer et al. Cell 2023
Alzforum: Therapeutics
DrugBank

Unmet Clinical Need of Alzheimer's Disease



Small molecule



Monoclonal antibody

Cell therapy (include exosome)

- No target for multifactorial disease
- No effect on disease progression

- Severe side effects (ARIA/inflammation)
- Limited for mild-stage

Stem cell application on AD

Benefit

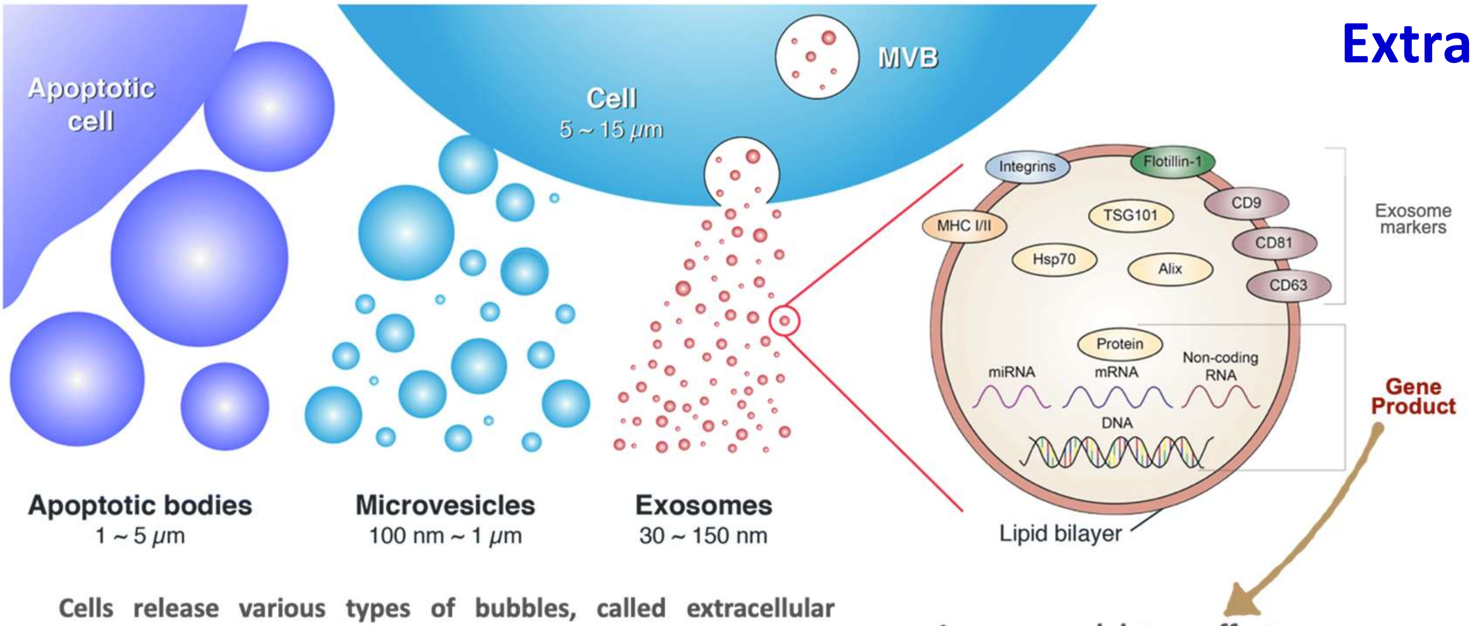
- Possess neuroprotective and immunomodulatory properties which promote tissue repair and regeneration
- Capable of homing back to the side of injury to initiates endogenous repair
- Absence of cell replacement evidence; trophic effects likely induce transient recovery
- Generally well-accepted with no serious adverse effects such as infection or tumour
- Easily obtained (MSC from adult) and Rapidly expanded

Limitation

- Must successfully **overcome the BBB** in order to exert therapeutic effects in the brain
- Homing potential is influenced by the **delivery method**
- Sufficient numbers of cells reaching the target site are necessary to exert a therapeutical effect
- Treatment outcome may be affected by various factors including the donor's age, host tissue, and growth regulators expressed by recipient tissue

Chia et al. Stem Cells Int 2020

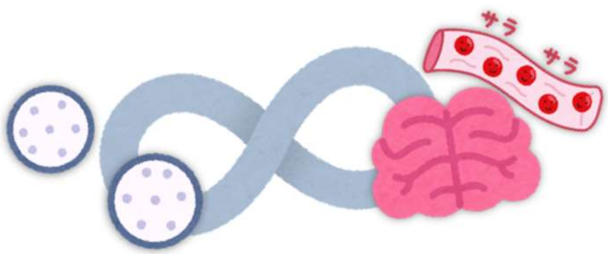
Extracellular Vesicles (EVs)
& Super Donor

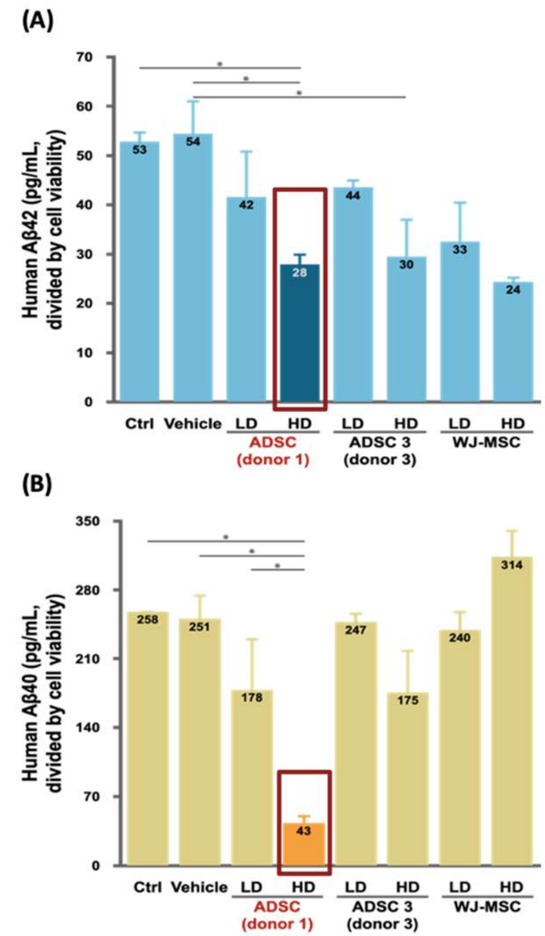


Cells release various types of bubbles, called extracellular vesicles (EVs). EVs are the key role of intercellular communication.

Exosomes are a kind of EVs, which <u>carry several molecules from host cells</u>, including DNA, RNA, and proteins. Because of the lipid layer outside, exosomes can <u>pass through the blood-brain barrier</u>.

- ➡ ***Immunomodulatory effects***
- ➡ ***Neuroprotective effects***
- ➡ ***Neuro-regeneration***
- ➡ ***Promote Aβ degradation***

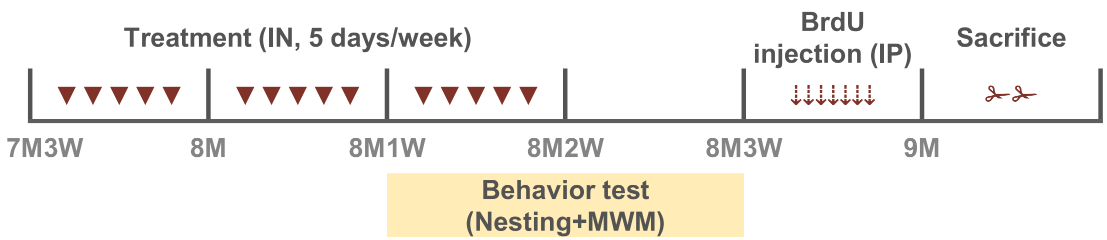




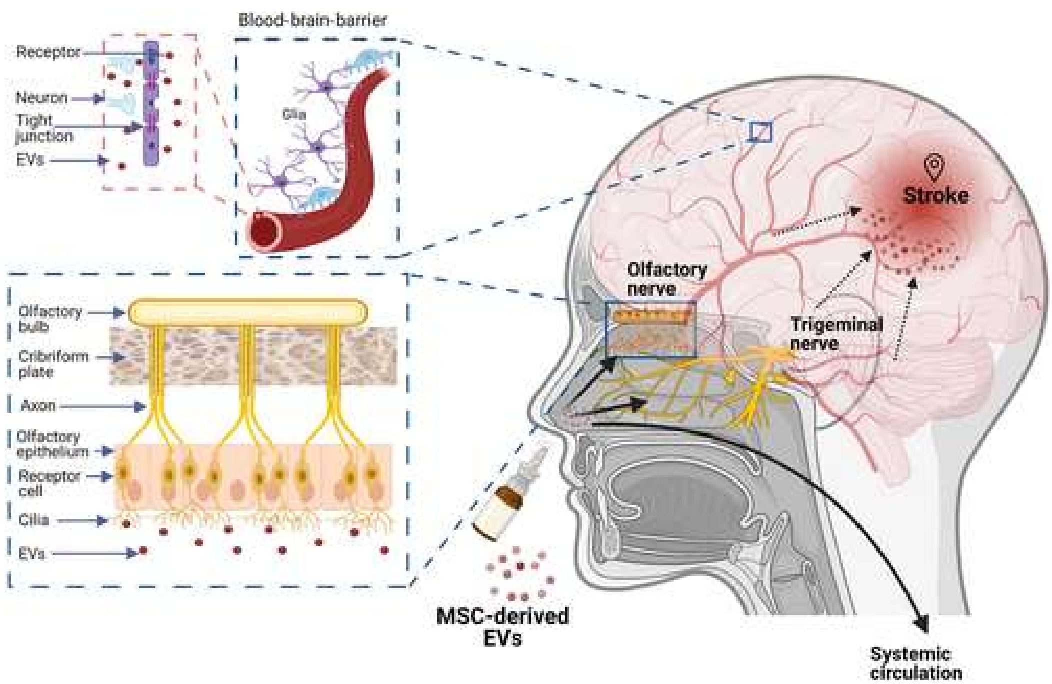
*presented as the mean ± SD values. Analyzed with One-way ANOVA, *p < 0.05, **p < 0.01.*

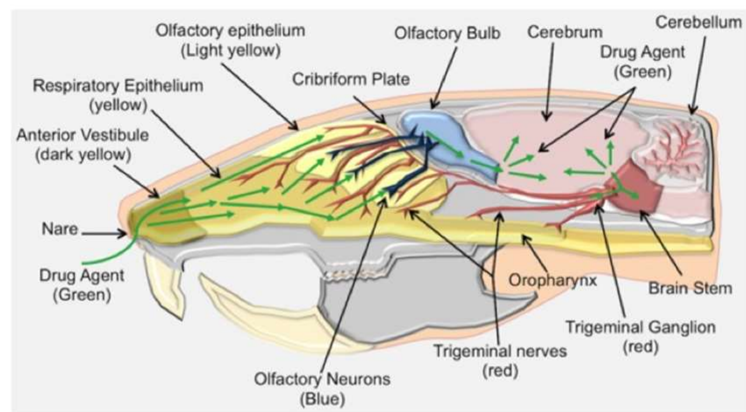
Lab. 2017;17(21), 3558–3577.
Molecchipular cancer. 2019;18(1), 52.
Neuroimmune Pharmacol. 2020
Cell Prolif. 2016;49(1):3-13.
Alzheimers Res Ther. 2020;12(1):109.

In vivo Design & Intranasal Administration



Strain	C57BL/6	APP/PS1	
Group	WT	AD	AD+Exo
Treatment	20 µl PBS		1E8-1E9 ADSC (donor 1)-Exos
n	3	9	16





Stem Cells. 2021;39(12):1589-1600.

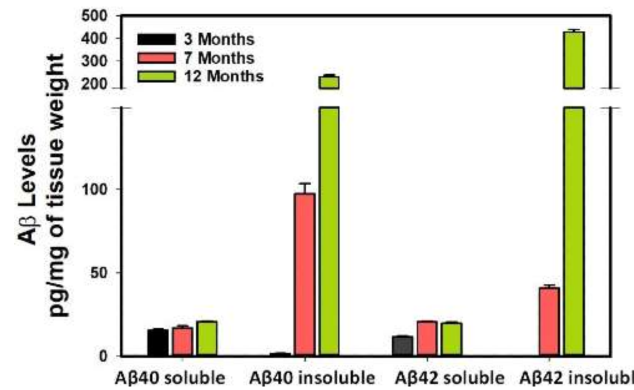
AD Mice model

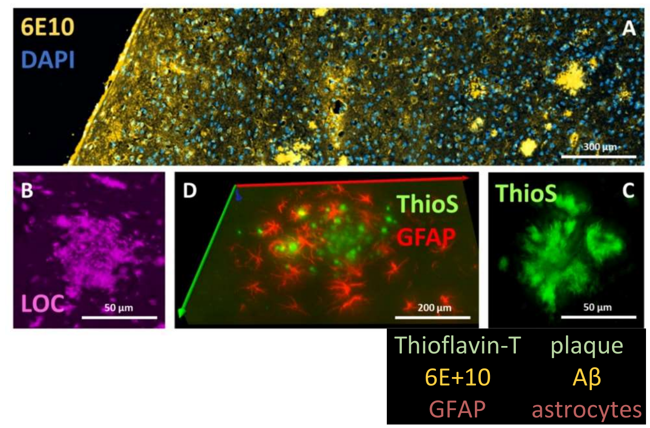
APP/PS1

Human amyloid precursor protein (Mo/HuAPP695swe)

Human presenilin 1 (PS1-dE9)

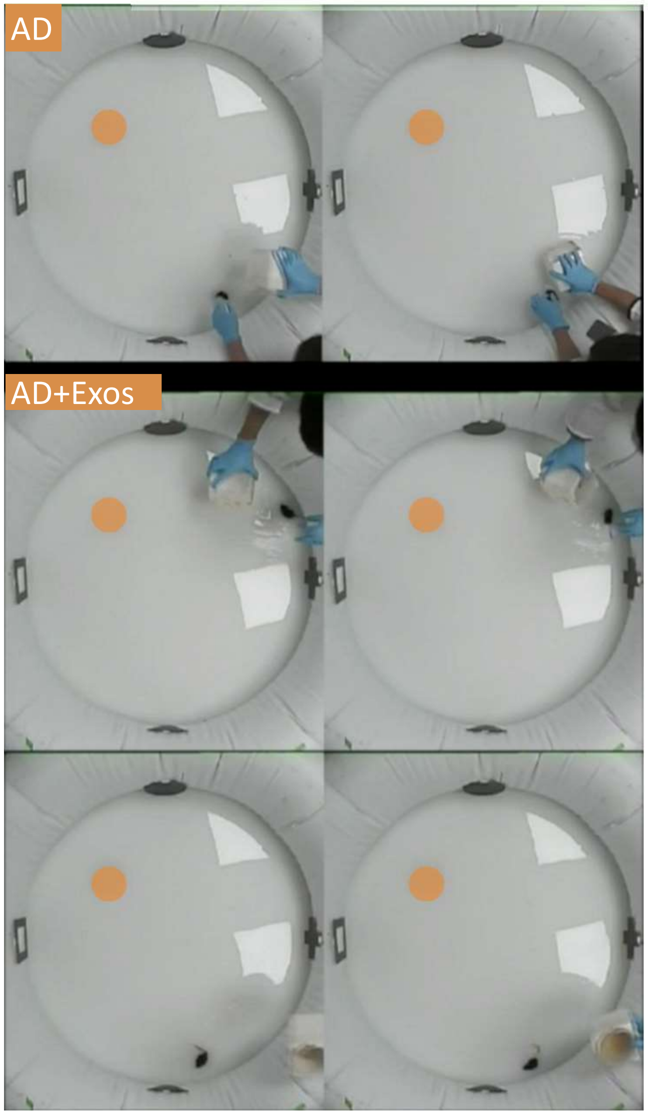
Plaques	Amyloid plaques begin to emerge in the cortex at about 4 months of age and in the hippocampus at about 6 months.
Tangles	Not observed.
Neuronal Loss	Neuron loss has not been observed in mice up to 12 months of age.
Gliosis	Plaque-associated astrogliosis and microgliosis are evident by 4 and 8 months, respectively.
Synaptic Loss	Synapse loss in the hippocampus occurs by 4 months.
Changes in LTP/LTD	No data.
Cognitive Impairment	Deficits in the Morris water maze emerge between 6 and 10 months and worsen with age.

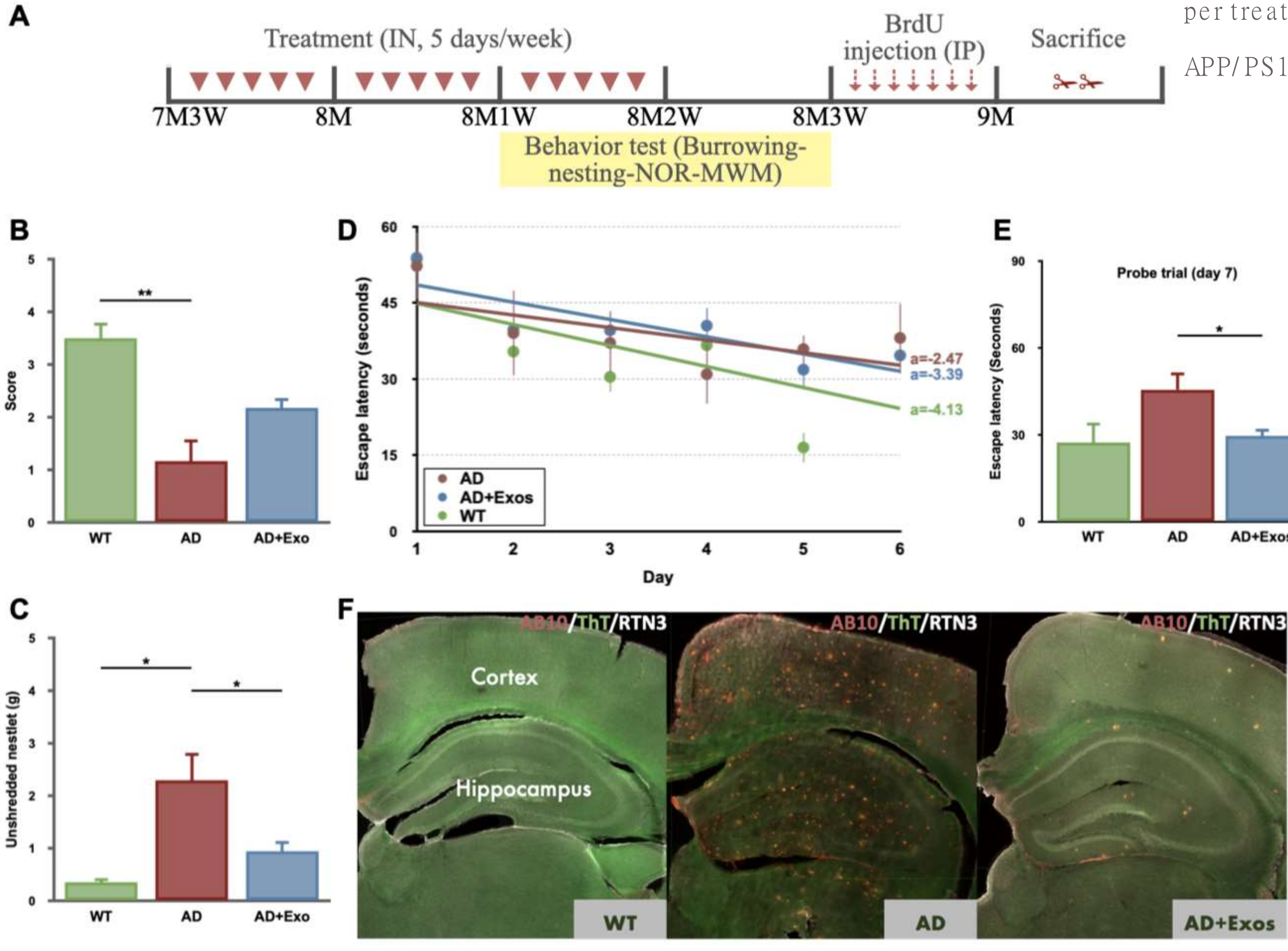




Web: APP/PS1 Amyloidosis Mouse Model of Alzheimer's Disease (captured 2023)
Med Sci Monit. 2018;24:5635-5644

Therapeutic effect of ADSC-Exos by intranasal administration



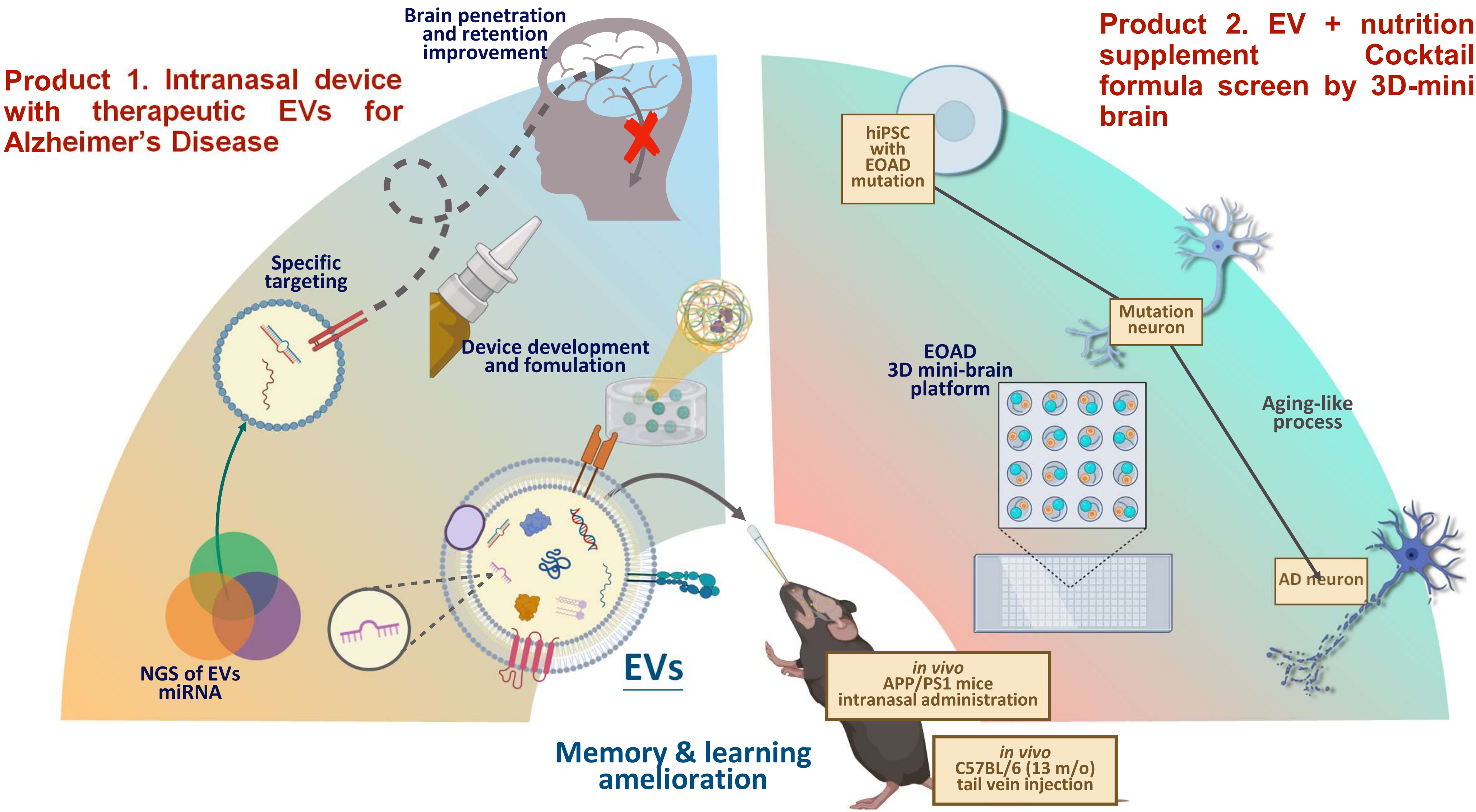


Dosage:
1E8-1E9 EVs
per treat

APP/PS1

presented as the mean ± SEM values. Analyzed with One-way ANOVA, * $p < 0.05$, ** $p < 0.01$.

Corder et al. PLoS One 2018
Lehtonen et al. Philos Trans R Soc Lond B Biol Sci 2023



Product 1. Intranasal device with therapeutic EVs for Alzheimer's Disease
Brain penetration and retention improvement
Specific targeting
Device development and fomulation
NGS of EVs miRNA
EVs
Memory & learning amelioration
in vivo
APP/PS1 mice
intranasal administration
in vivo
C57BL/6 (13 m/o)
tail vein injection
Product 2. EV + nutrition supplement Cocktail formula screen by 3D-mini brain
hiPSC with EOAD mutation
Mutation neuron
EOAD 3D mini-brain platform
Aging-like process
AD neuron

團隊

葉漢根醫師
高雄長庚
Group leader
Medical expert

李利教授
陽明交大玉山學者
Co-founder & CTO
of SPOT Biosystems
Manufacturing expert

張學嘉教授
陽明交大玉山學者
Co-founder & CTO
of Aopia Biosciences
Bioengineering expert

測略合作公司

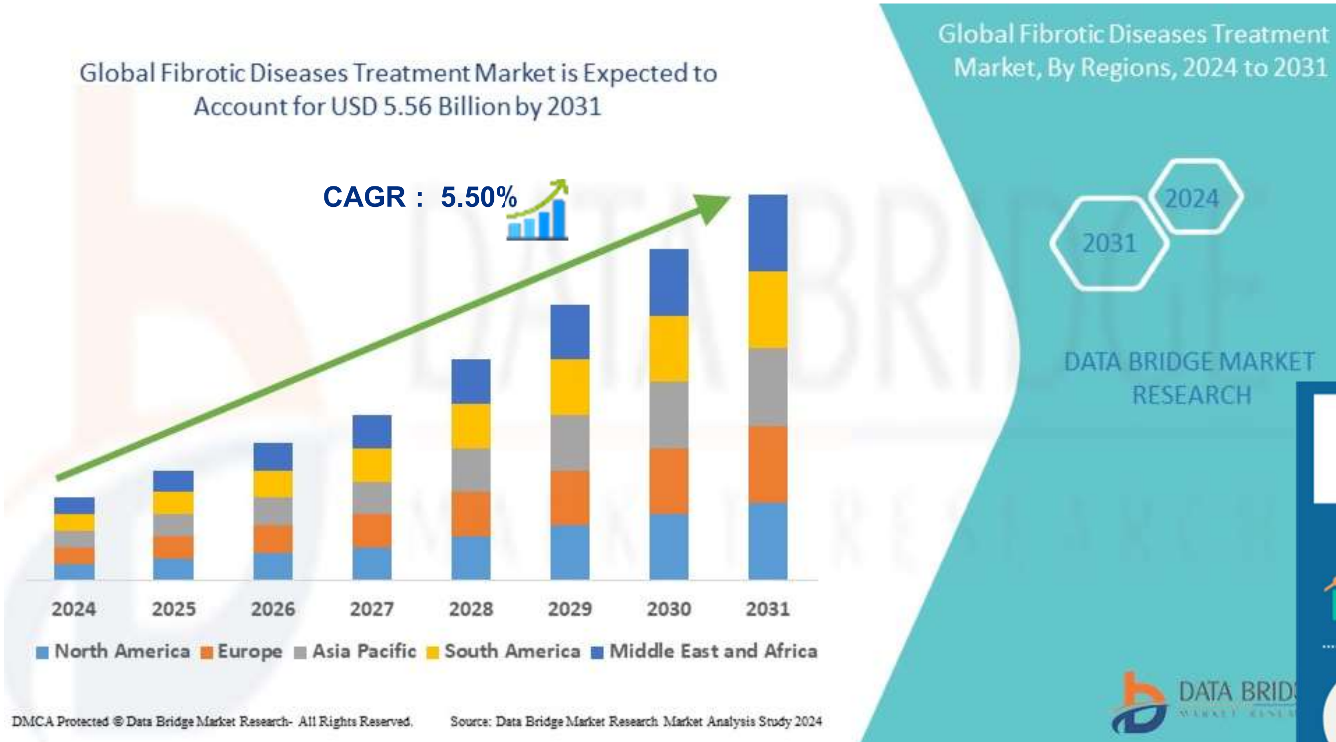
BiONET THERAPEUTICS 訊 聯 細 胞 智 藥

SPOT BIOSYSTEMS

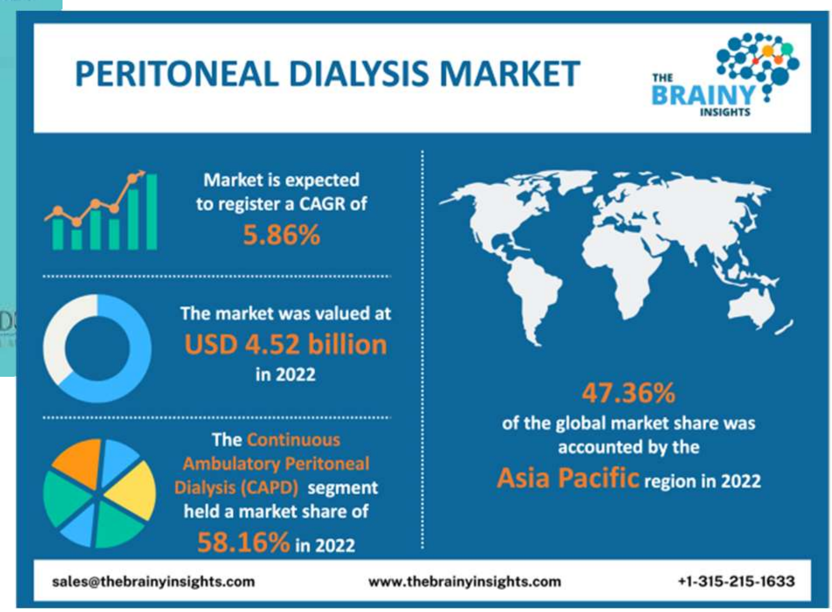
Aopia

tstbio 嘉碩生醫

Fibrosis, whether in the lungs, heart, liver, kidneys, or other organs, is indeed a major clinical challenge in aging societies.



https://www.databridgemarketresearch.com/reports/global-fibrotic-diseases-treatment-market?srsltid=AfmBOoqpRC9c74zjUD7yHJ4JuMj7BIcWzJhH4zlPee7OI1jhXVzQD43H



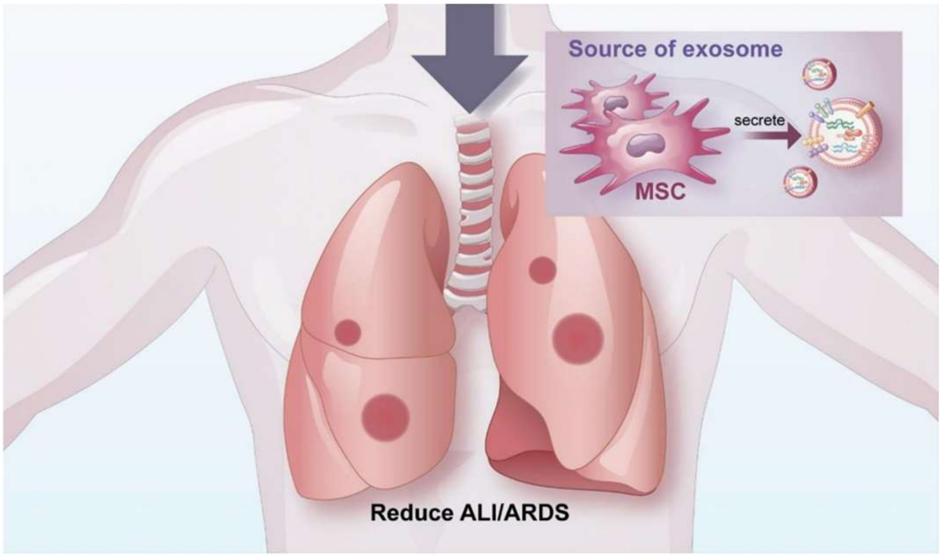
https://www.thebrainyinsights.com/report/peritoneal-dialysis-market-13236

Summary of clinical trials involving MSC exosomes in ALI/ARDS patients

NCT04602104 (Phase 1, 2) — Human MSC

NCT04493242 (Phase 2), **NCT04657458 (Phase 2)** — Bone marrow MSC

NCT04276987 (Phase 1) — Adipose-derived MSC



- **Anti-inflammation**
- **Anti-fibrosis**
- **Cell regeneration**

MSC-derived exosomes show great potential for the treatment of ALI/ARDS and are expected to be effective therapeutic options

Frontiers in Immunology. (2022) 13:971189.
Tissue Engineering and Regenerative Medicine. (2022) 19(4):659-673.

What could be the potential therapy/target for acute lung injury?

Herbal medicine

Honeysuckle

PG2

Virofree

YQ1

Stem cell therapy

Human Umbilical Cord-Derived Mesenchymal Stem Cells for Acute Respiratory Distress Syndrome

Hon-Kan Yip, MD[1–5]; Wen-Feng Fang, MD[6–8]; Yi-Chen Li, PhD[1]; Fan-Yen Lee, MD[9,10]; Chen-Hsiang Lee, MD[11,12]; Sung-Nan Pei, MD[13]; Ming-Chun Ma, MD[13]; Kuan-Hung Chen, MD, PhD[14]; Pei-Hsun Sung, MD[1]; Mel S. Lee, MD, PhD[15]

Phase II in Taiwan

Let-7a-5p

EV therapy

Year	Title	Exo Source	Disease	Stage	Administration	Dosage	
2020	NCT04602104	MSCs	ARDS	Phase 1	**Aerosol Inhalation**	7 times 2.0-16.0x10^8 at D1-D7.	China
				Phase 2		7 times 1/4-1 MTD/day at D1-D7.	
2022	NCT05387278	UC-MSCs	COVID-19 ARDS	Phase 1	**Intravenous**	EV-Pure™ and WJ-Pure™	USA
2020	NCT04493242	BM-MSCs	Covid19 ARDS Pneumonia, Viral	Phase 2	**Intravenous**	1 time of 8-12x10^{11} particles of exosomes	USA

Clinical observation and prediction

frontiers in Molecular Biosciences

ORIGINAL RESEARCH

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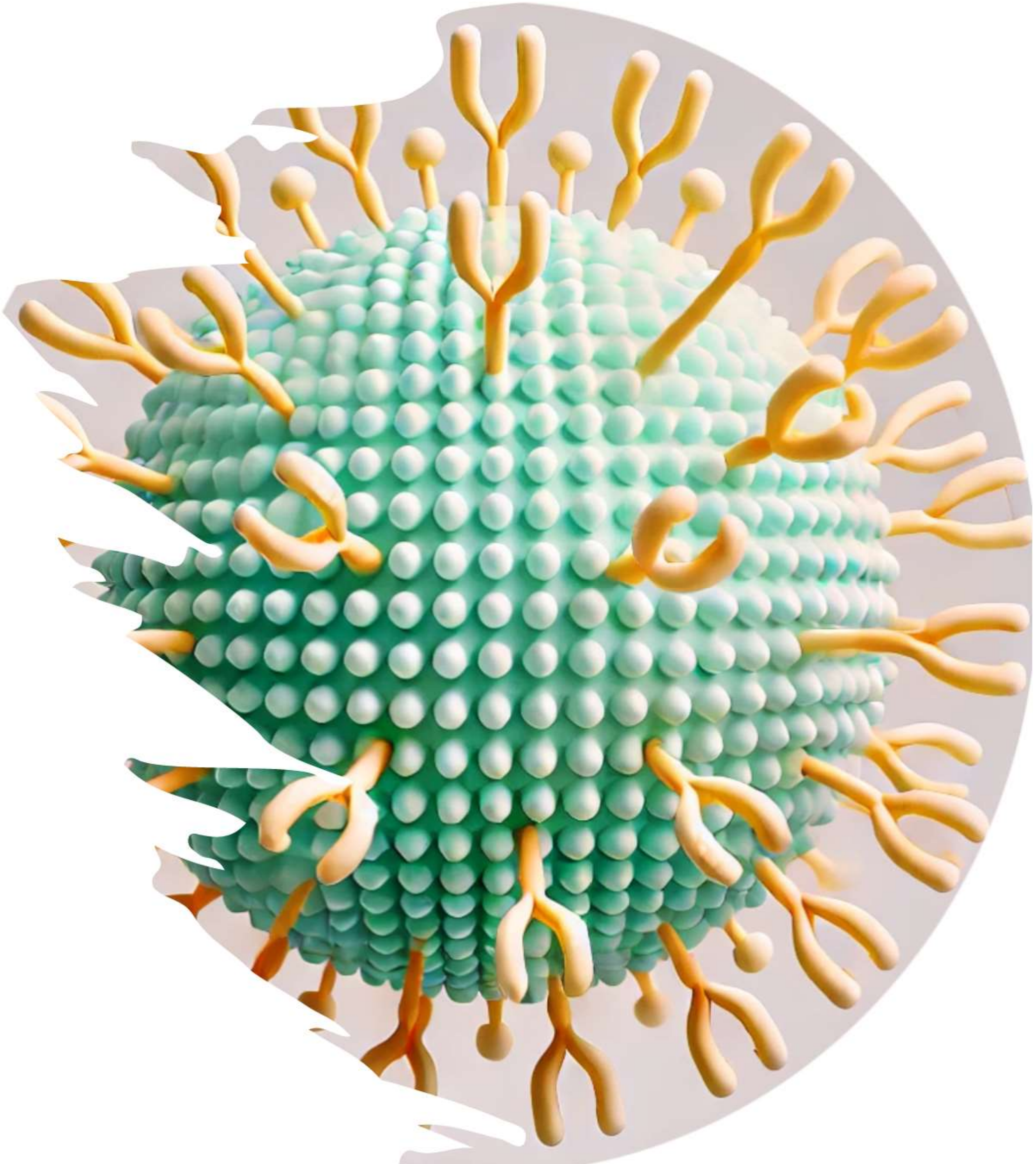
A Blood Exosomal miRNA Signature in Acute Respiratory Distress Syndrome

Gilles Parzibut[1], Monique Henket[2], Catherine Moermans[2], Ingrid Struman[3], Edouard Louis[4,5], Michel Malaise[5,6], Renaud Louis[2,5], Benoît Misset[1], Makon-Sébastien Njock[2,4,5,6]* and Julien Guiot[1,2,5]

Reference:

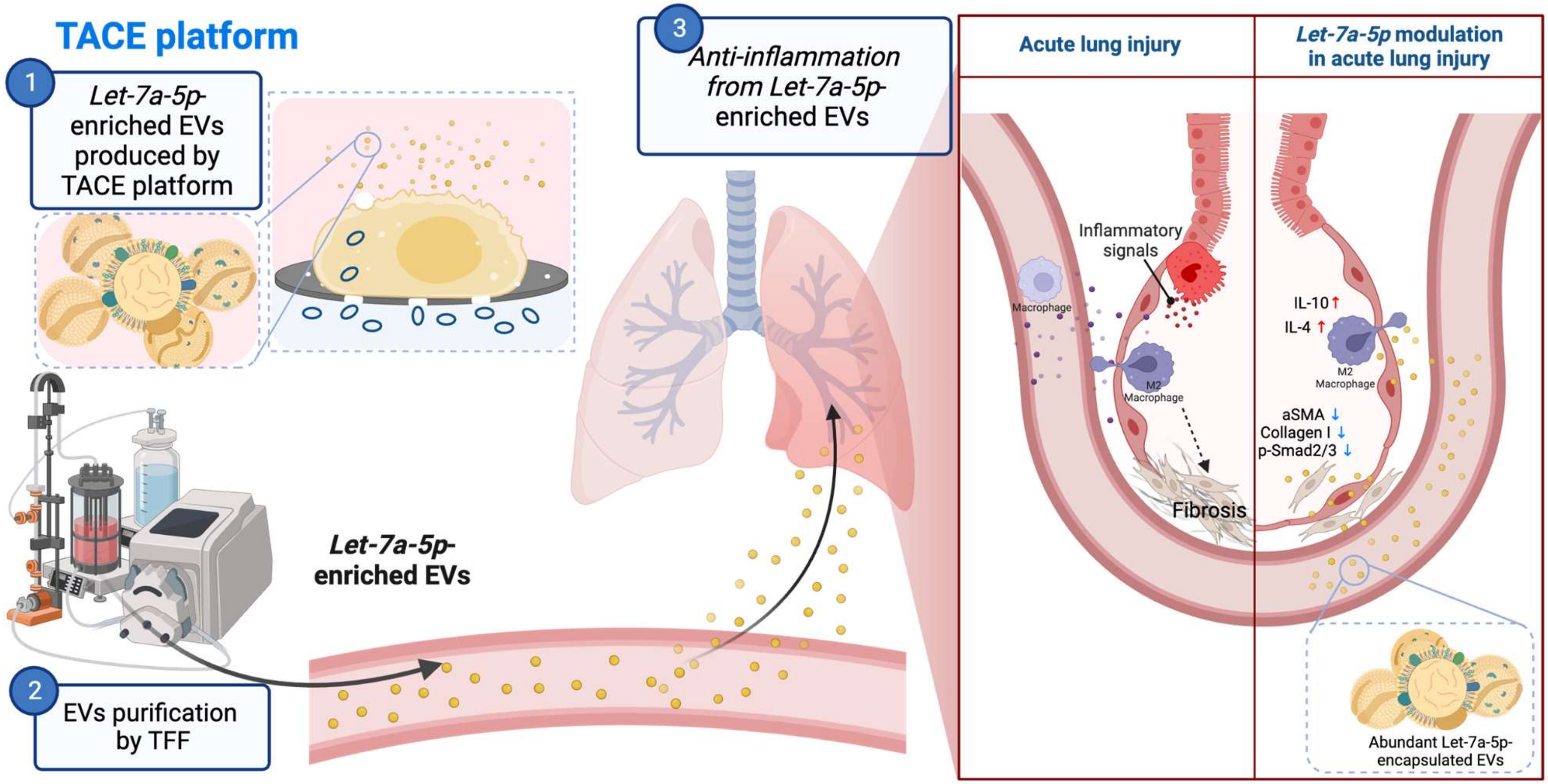
Lee, C.-Y., Chi-Ying F. Huang et al. Viruses 2023, 15, 641.
Yuan-Chieh Yeh, Chi-Ying F. Huang et al. Front Pharmacol. 2022 Mar 25:12:765553.
Hon-Kan Yip, Mel S Lee et al. Crit Care Med. 2020 May;48(5):e391-e399.



Let-7a-5p-enriched EVs

Engineering EVs for Therapeutic Applications

- The distinct technical advantages we offer



Take home message

(1) Deliver nucleic acid platform
(2) High EV production rate

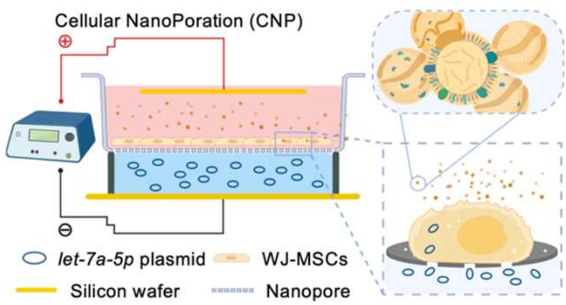
(3) Easy scale-up TFF system

(4) Let-7a-5p is potential RNA therapeutics for acute lung injury

J Biomedical Science (2024) 31:30

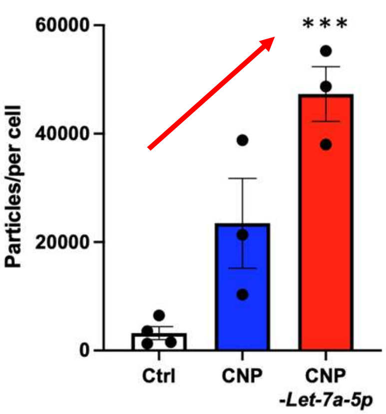
Methods for Large-Scale Production of High-Purity EVs

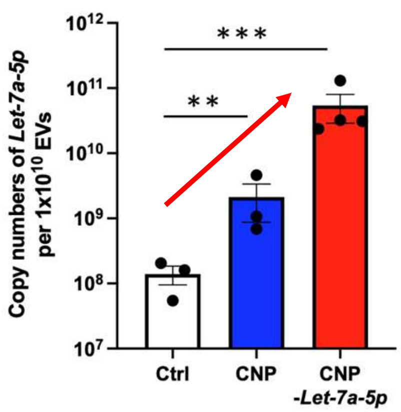
Massive EV production & Nucleic acid encapsulation platform

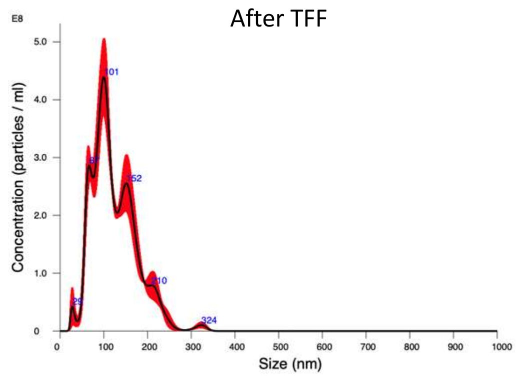


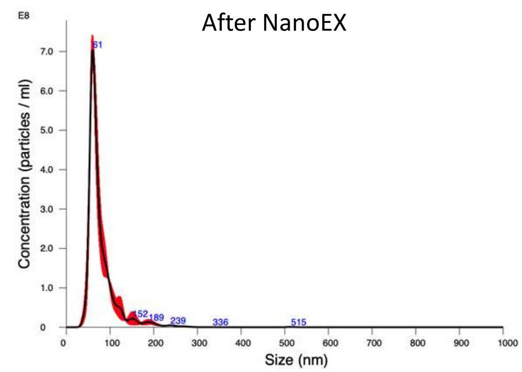
EV purification by TFF

Further concentrated by NanoEX to remove >99.99% of free proteins

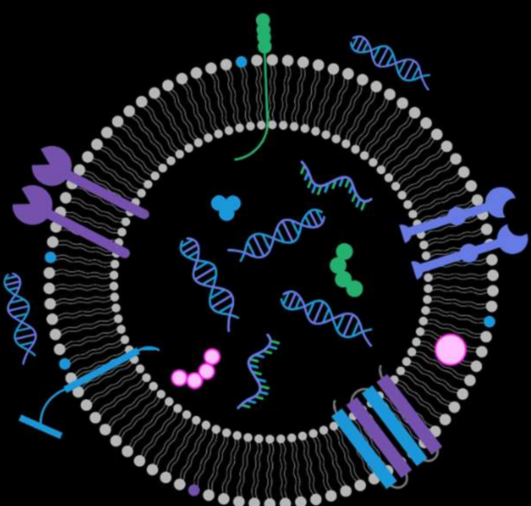






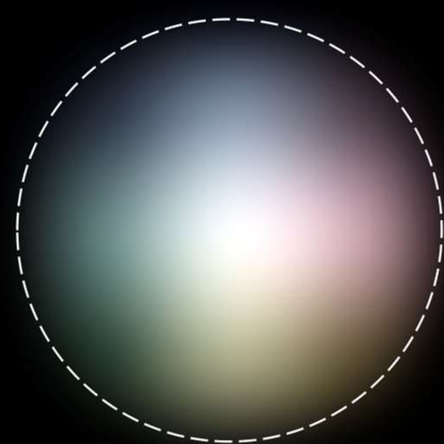


Super-resolution imaging of EVs



100 nm

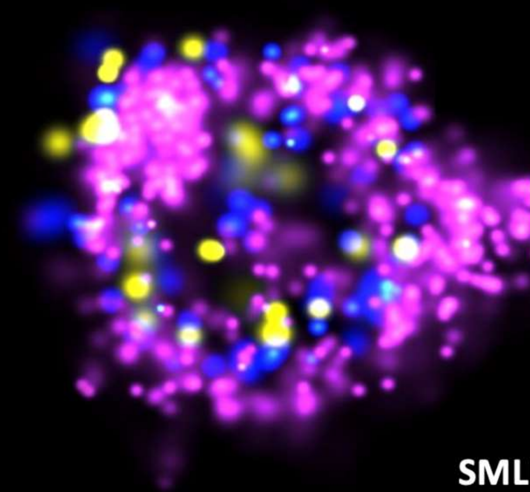
With **Standard** Microscope



Widefield

300 nm

With **Nanoimager**



WGA-AF647 (membrane)

Anti-CD63 (AF555)

Anti-CD81 (Atto488)

SMLM (dSTORM)

100 nm

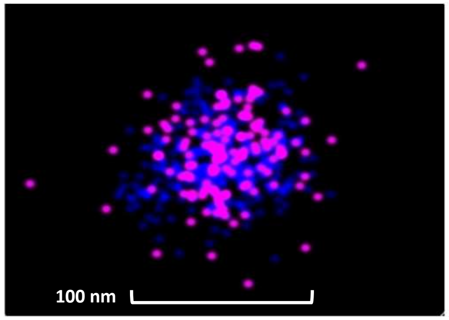
Key advantages

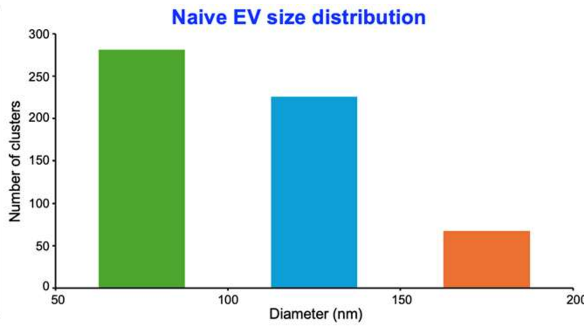
- Achievable resolution below 20nm
- Simultaneous visualization of multiple biomarkers
- Multi-factor characterization – Size, biomarker distribution & number
- Single-molecule detection
- High sensitivity

ONI

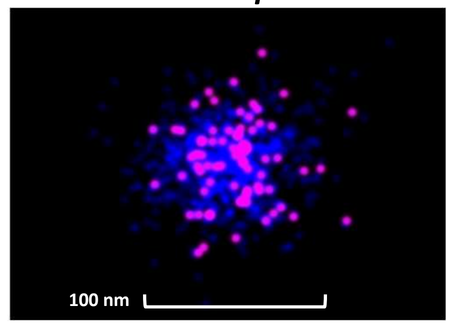
Effects of CNP on EV Size Distribution

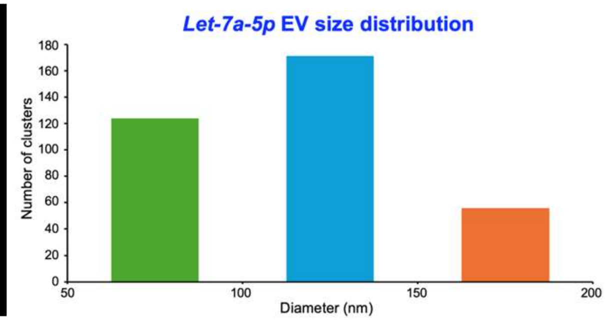
Naive EV



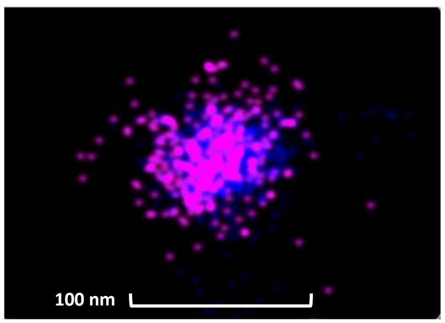


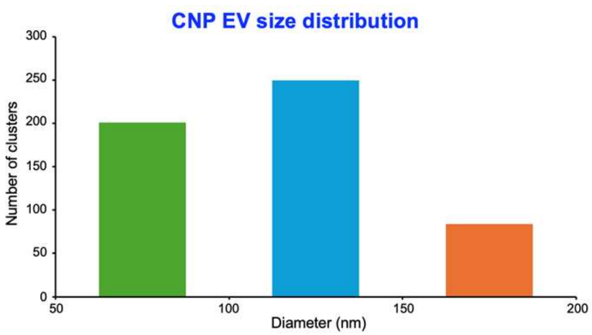
***Let-7a-5p* EV**

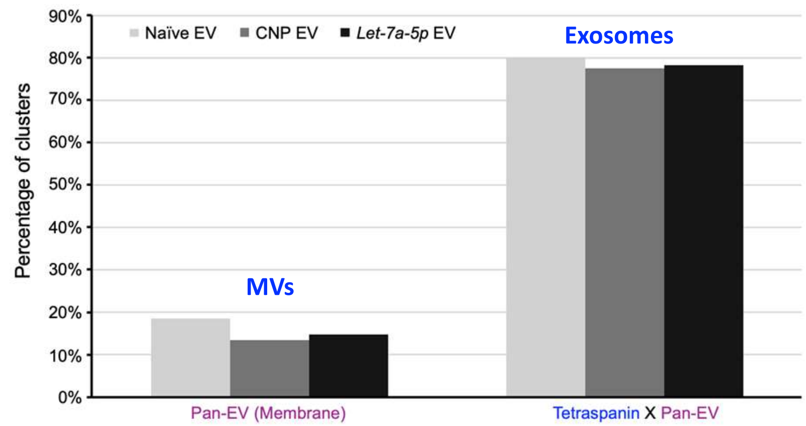




CNP EV



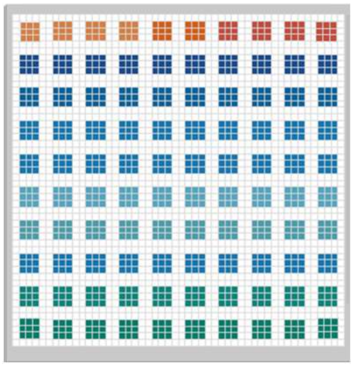




Blue: Tetraspanin (CD9+CD63+CD81)
Purple: Pan-EV (Membrane)

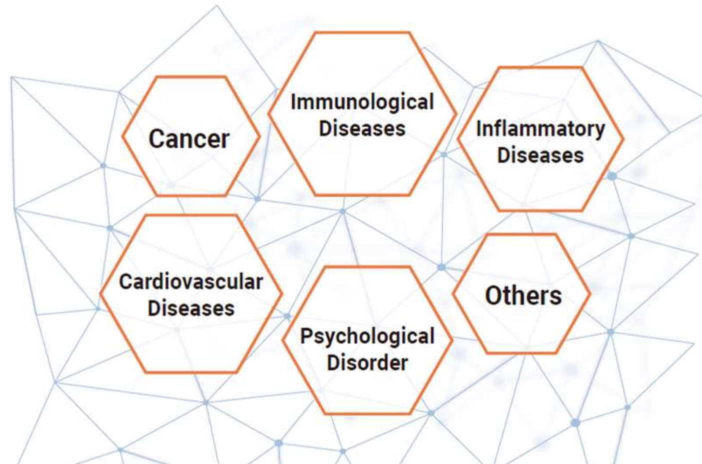
CNP stimulation increases the proportion of EVs exceeding 100 nm, while EV subpopulations remain unchanged. This suggests that CNP can be utilized as a strategy for EV production.

mirSCAN^{TM} miRNA Profiling Tool

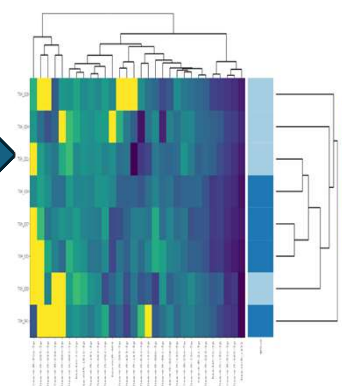


89 miRNAs qPCR screening
- Selected from publications
- Expressed in body fluids

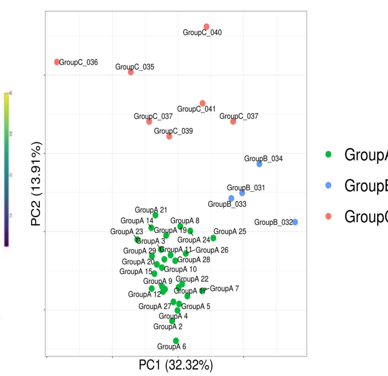
Exogeneous Controls
- Extraction Spike-in Control
- RT Spike-in Control
- qPCR Spike-in Control



Sample Types
- Tissue / Cell line
- Cell-free samples
  - Blood (serum/plasma)
  - EV

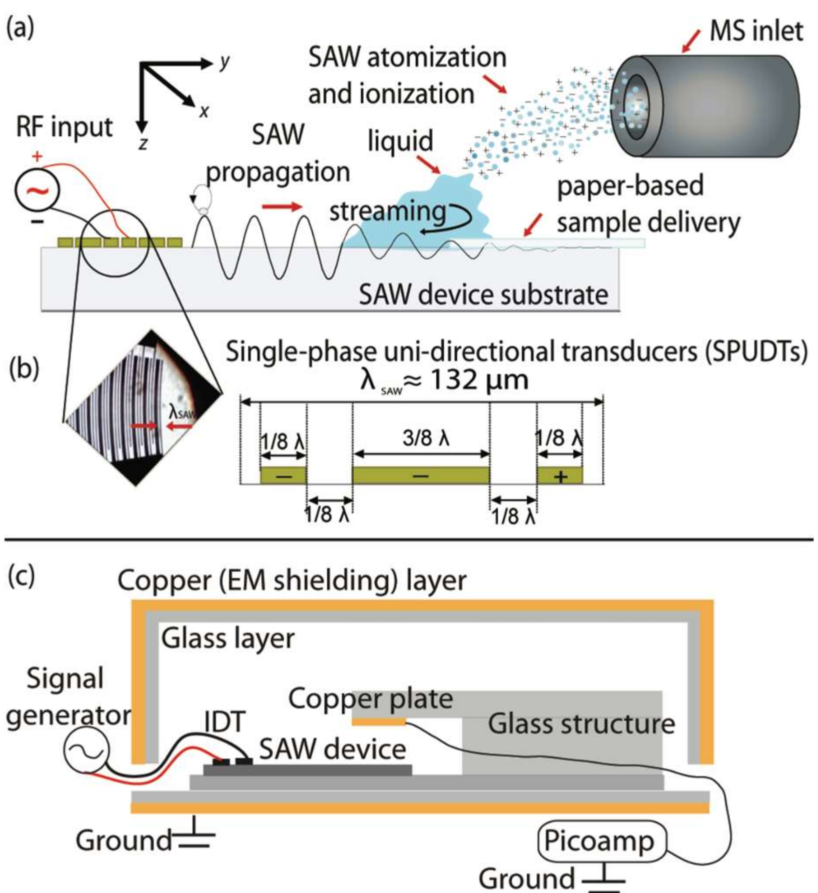


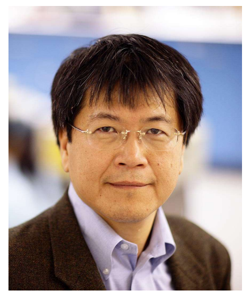
Cq profiling



PCA analysis

Aerosolized EV therapeutics for lung disease-Microfluidic Surface Acoustic Wave Sample Delivery





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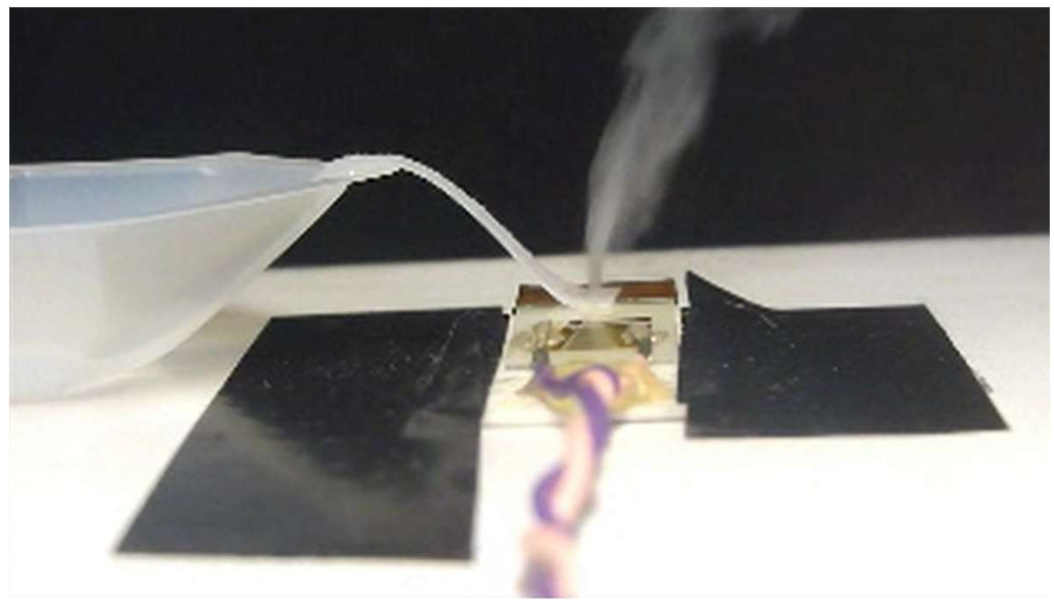
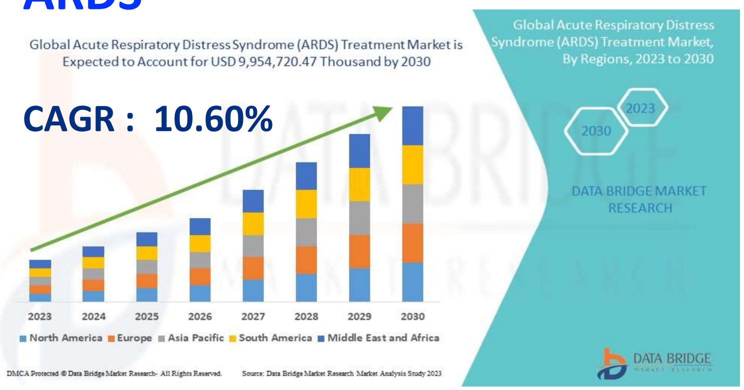


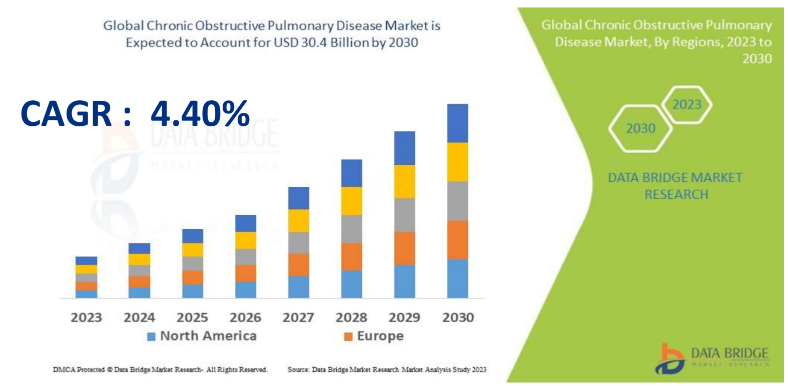
Future Marketing

ARDS



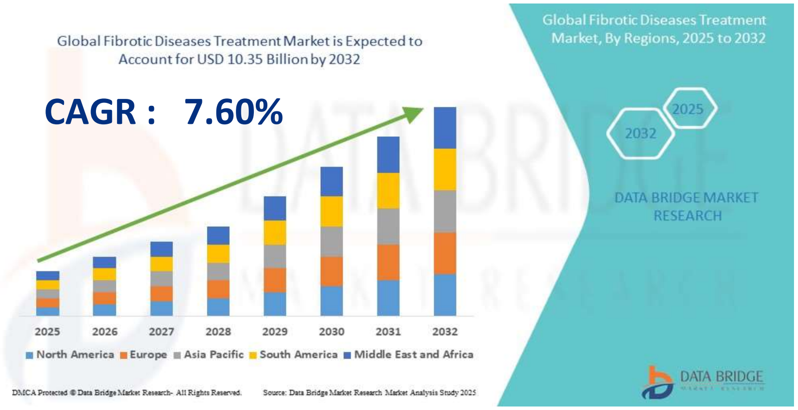
https://www.databridgemarketresearch.com/reports/global-acute-respiratory-distress-syndrome-ards-treatment-market

COPD



https://www.databridgemarketresearch.com/reports/global-chronic-obstructive-pulmonary-disease-market

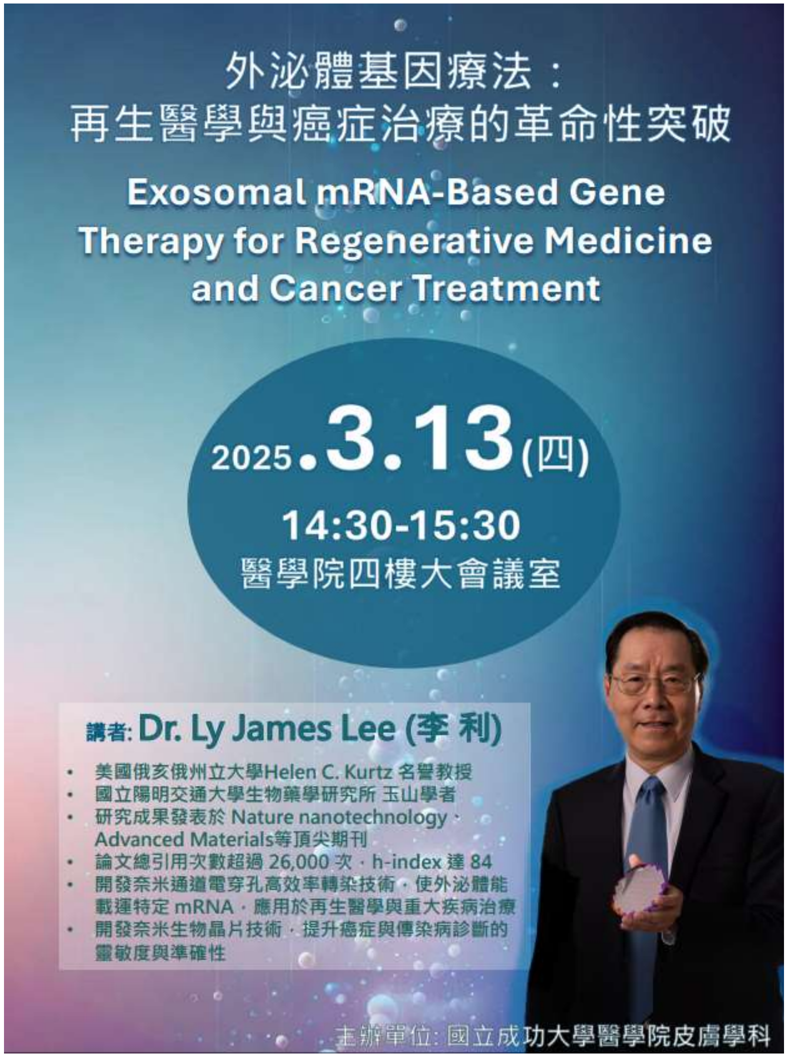
Global Fibrotic Diseases



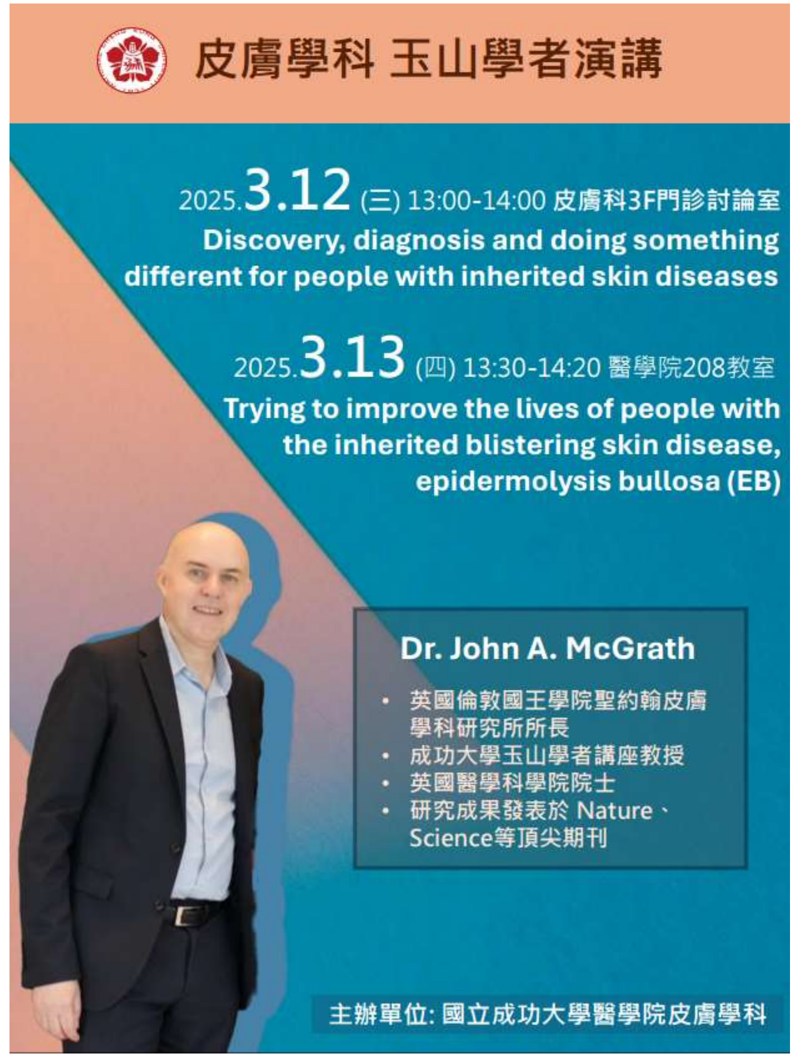
https://www.databridgemarketresearch.com/reports/global-fibrotic-diseases-treatment-market

- Acute lung injury surge drives ARDS market amid multifactorial risks.
- Global COPD surge: tobacco, healthcare spending, R&D fuel market growth.
- Global fibrotic diseases are rising due to aging, lifestyle changes, and chronic conditions.
- Increased patient numbers drive demand for effective antifibrotic drugs and biologics.

Nature 439,663–664 (2006)



外泌體基因療法：
再生醫學與癌症治療的革命性突破
Exosomal mRNA-Based Gene Therapy for Regenerative Medicine and Cancer Treatment
2025.3.13(四)
14:30-15:30
醫學院四樓大會議室
講者: Dr. Ly James Lee (李 利)
美國俄亥俄州立大學Helen C. Kurtz 名譽教授
國立陽明交通大學生物藥學研究所 玉山學者
研究成果發表於 Nature nanotechnology、Advanced Materials等頂尖期刊
論文總引用次數超過 26,000 次，h-index 達 84
開發奈米通道電穿孔高效率轉染技術，使外泌體能載運特定 mRNA，應用於再生醫學與重大疾病治療
開發奈米生物晶片技術，提升癌症與傳染病診斷的靈敏度與準確性
主辦單位: 國立成功大學醫學院皮膚學科



皮膚學科 玉山學者演講
2025.3.12 (三) 13:00-14:00 皮膚科3F門診討論室
Discovery, diagnosis and doing something different for people with inherited skin diseases
2025.3.13 (四) 13:30-14:20 醫學院208教室
Trying to improve the lives of people with the inherited blistering skin disease, epidermolysis bullosa (EB)
Dr. John A. McGrath
英國倫敦國王學院聖約翰皮膚學科研究所所長
成功大學玉山學者講座教授
英國醫學科學院院士
研究成果發表於 Nature、Science等頂尖期刊
主辦單位: 國立成功大學醫學院皮膚學科

Acknowledgement