

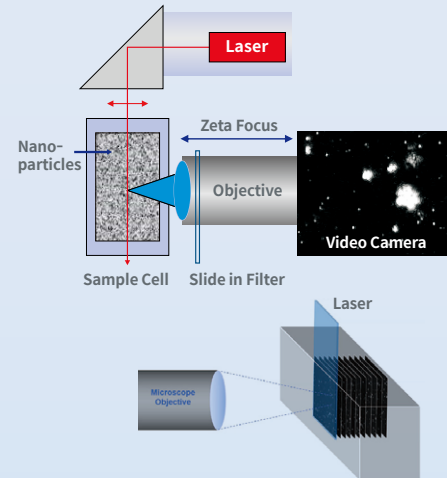
Zetaview®

F-NTA 나노 입자 추적 분석기

Fluorescence Nano particle Tracking Analyzer



- Size
- Concentration
- Zeta Potential
- Sub-populations
- Fluorescence

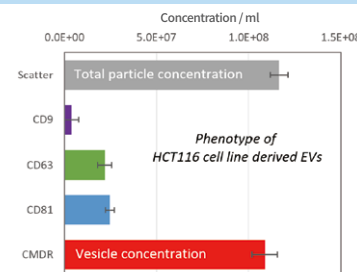
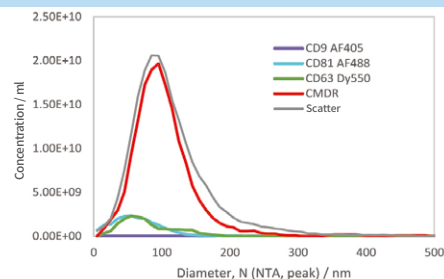


Models	Laser	wavelength	Filter	
• PMX-120 1 Laser	405 nm		410 LP	• NTA(Nano particle Tracking Analysis)
• PMX-220 2 Lasers 최대 2개 레이저 동시 장착	488 nm		500 LP	• 15nm ~ 1µm, 10 ⁵ ~10 ⁹ particles/ml
• PMX-420 4 Lasers 최대 4개 레이저 동시 장착	520 nm		550 LP	• Auto Alignment and Focus
	640 nm		660 LP	• 11 positions 스캐닝 분석
				• Anti Bleaching Technology
				• Sample Cell 자동 세척 (Pump Control)
				• 1 Click 레이저, 형광 필터 Change

Applications

Extracellular Vesicles(EVs) Exosomes Liposomes Nanobubbles Nanometals Viruses

Purity & Phenotyping of EVs



KSEV 2021 Annual meeting

Extracellular vesicles : Small is beautiful for the bigger world

Extracellular vesicles :

Small is beautiful for the bigger world

2021.11.28. SUN - 11.30. TUE

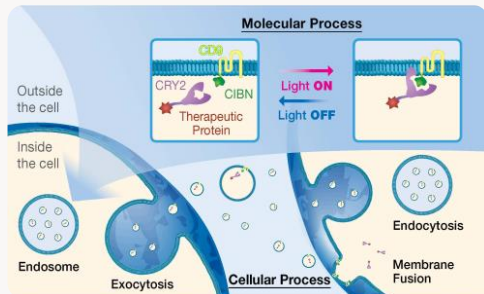
Hotel Nongshim,
Busan

KSEV 2021 Annual Meeting



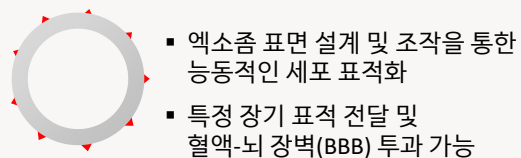
ILIAS Platform Technologies

EXPLOR® 빛을 이용해 엑소좀 내부에 고분자 약물 단백질을 탑재하는 기술



- 단백질 모듈을 활용한 엑소좀 내 단백질 약물 탑재
- ▶ 세계 최초로 엑소좀 내부에 **Free Form 상태로** 치료용 단백질 탑재
- 엑소좀을 매개로 약리물질을 세포 내부로 전달, 직접적인 Intracellular Targeting 약물 개발
- ▶ 근본적인 **세포 내 질병 원인 기전**을 효과적으로 타겟

Exo-Target® 능동적인 표적 세포 타겟팅 기술



▶ 약물 효율 증대 및 **off-target effect 감소**

Pure-Exo® 대용량 & 고순도 엑소좀 의약품 생산 기술



- Scalable 생산공정으로 clinical-grade 엑소좀 시료 생산
- 고순도 & 고수득률의 엑소좀 신약 생산

▶ 고순도 엑소좀 신약의 **대량 생산** 가능

Founding Year

2015

Employees

70+

Funding Stage

Series B (2020)
Series A (2018)

Therapeutic Areas

염증성 질환(Inflammatory disease)
종양(Oncology)
중추신경계(CNS) 질환

Exosome은 세포에서 분비되는 나노 크기의 소포체로 세포 간 커뮤니케이션을 위한 메신저 역할을 합니다. 우수한 생체 적합성과 안전성 등으로 약물전달에 적합해 차세대 첨단 의약품으로 개발되고 있습니다.

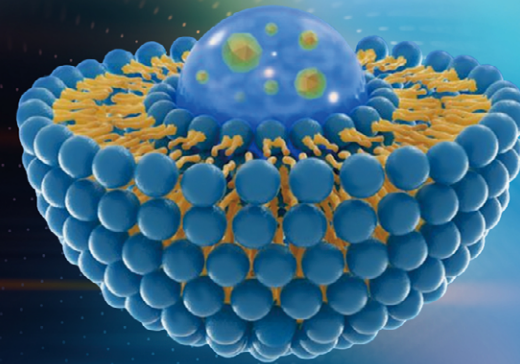
www.iliasbio.com

본사
대전광역시 유성구 테크노6로 40-20
서울사무소
서울특별시 강남구 삼성로100길 24-2 B동 6층(오피스빌딩)
미국법인
ILIAS Therapeutics, Inc. NY., USA.

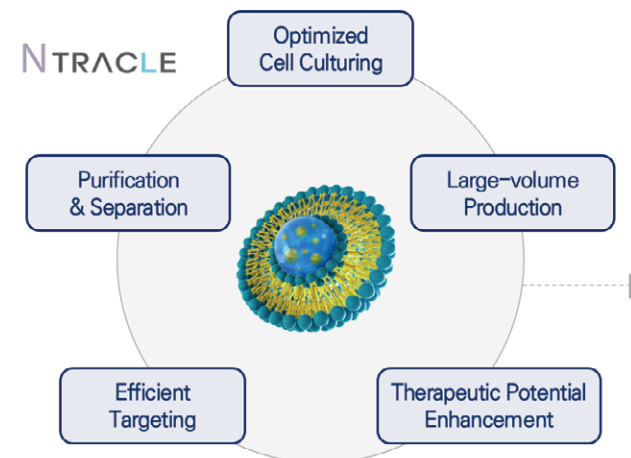


NUMAIS

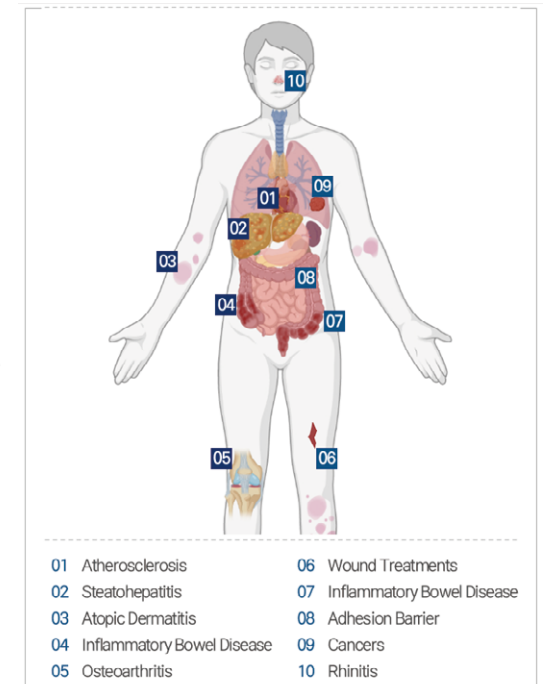
Improving your Quality of life



(주)뉴메이스는 줄기세포유래 나노베지클 진단치료제 및 온도감응성 생분해성 하이드로겔 플랫폼에 대한 세계 최고 수준의 기술력을 보유하고 있으며, 최첨단 제조 및 공정 테크닉을 구축하여 나노베지클 진단치료제 및 약물전달 시스템이 최대의 효과를 안정적으로 낼 수 있도록 노력하고 있습니다. 각종 염증성 질환을 앓고 있는 환자들을 위한 삶의 질 향상과 함께, 세계인의 건강한 삶을 구현하는 (주)뉴메이스가 될 수 있도록 많은 관심과 성원 부탁드립니다.



Ntracle Core Technology



www.numais.com



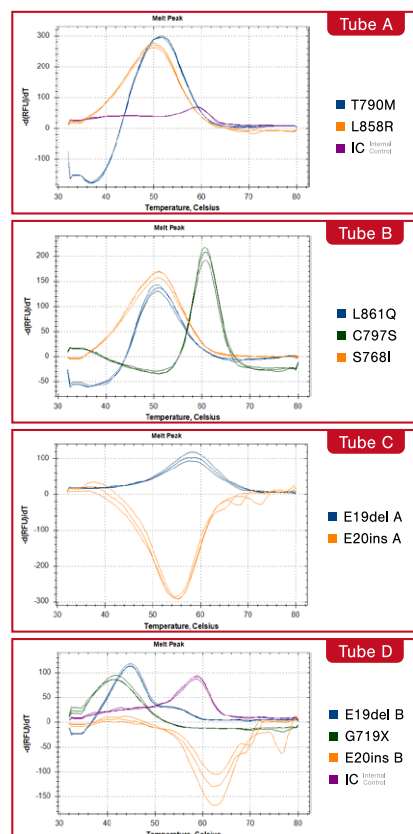
info@numais.com

UPCOMING PRODUCTS

NEW PANAMutyper™ R EGFR (ver. 2)



Ver. 1	Ver. 2
<p>7 detectable targets</p> <ul style="list-style-type: none"> G719X Exon 19 deletion S768I Exon 20 insertion T790M L858R L861Q <p>6 reactions per test</p>	<p>8 detectable targets</p> <ul style="list-style-type: none"> G719X Exon 19 deletion S768I Exon 20 insertion T790M L858R L861Q + C797S <p>4 reactions per test</p>



NEW PANA RealTyper™ TB-MDR/XDR (Drug-resistant tuberculosis)



Detect 48 genotypes related to drug resistance
* Specification may changed before launch

MDR (Multi-drug resistant)

RIF-resistance

rpoB gene mutations (25 genotypes)

INH-resistance

katG gene mutations (4 genotypes)
 inhA gene mutations (4 genotypes)
 ahpC gene mutations (2 genotypes)

XDR (Extensively drug resistant)

Fluoroquinolone-resistance

gyrA gene mutations (7 genotypes)

Injectable drug-resistance

rrs gene mutations (3 genotypes)
 eis gene mutations (3 genotypes)

What Science can do

Oncology combination therapy (종양학 표적 요법)

AstraZeneca는 암 치료를 위해
 생물학과 소분자 요법의 조합을 연구하고 있습니다.
 이러한 조합은 종양을 직접 표적하며
 일부는 신체의 면역 체계를 강화해
 종양 세포 사멸을 유도하는 데 도움이 됩니다.



thePLANB

부산광역시 해운대구 APEC로 55, BEXCO 제 1전시장 3층 354호
문의: 051-742-8407 | theplanb@planbgroup.org



 Bristol Myers Squibb™

**Extracellular
vesicles :**

**Small is beautiful
for the bigger world**

**KSEV 2021
Annual Meeting**



012	Program at a glance
014	Greeting
015	KSEV 2021 Board Members
016	General information
019	TUTORIAL SESSION
020	현경아 (연세대학교) Microfluidic strategy to isolate extracellular vesicle
022	오재원 (경희대학교) Quantitative Analysis of Exosome Protein Marker based on Mass Spectrometry for Exosome Quality-Control
025	PLENARY SESSION I
026	이계영 (건국대학교병원) EV-based liquid biopsy in lung adenocarcinoma
029	PARALLEL SESSION I 기초/임상
030	최동식 (순천향대학교 의과대학) Single extracellular vesicle analysis by nano-flow cytometry
032	류성호 (순천향대학교 의과대학) Exosomal multi-omics approaches in Precision diagnosis
034	최용준 (아주대학교 의과대학) Apoptotic cell-derived exosomes: messages from dying cells
036	오연목 (서울아산병원) Studies of extracellular vesicles in COPD
039	PARALLEL SESSION I 임상
040	김현구 (고려대학교 구로병원) Exosomal Biomarker at Tumor Draining Blood in Lung Cancer Patients
042	김태범 (서울아산병원) Multiomics-based precision medicine in asthma
044	김한상 (연세대학교 암병원) Extracellular Vesicle and Particle Biomarkers Define Multiple Human Cancers
046	김진국 (건국대학교병원) Clinical feasibility as biomarker of EV from nasal secretion
049	PLENARY SESSION II
050	박재성 (포스텍) Exosome-Engineering in Diagnosis and Therapy

053	PARALLEL SESSION II 분리/진단
054	박종민 (강원대학교) Immunomagnetic Electrochemical Sensor for Extracellular Vesicle Analysis in Human Body Fluids
056	심상준 (고려대학교) Nanoplasmonic biosensor for diagnosis of the incurable disease using exosome-derived biomarkers
058	이원종 (인천대학교) Simple and Efficient Extracellular Vesicle Concentration Using Super Absorbent Polymer Beads and Its Applications
061	PARALLEL SESSION II 분리/진단/치료
062	김필남 (KAIST) 폴리페놀을 이용한 액체생검 내 exosomal RNA 추출/분석 기술
064	백문창 (경북대학교) Novel immunotherapeutic approach using engineered T-cell derived extracellular vesicles
066	박재형 (성균관대학교) Surface-modified exosomes for targeted therapy
069	PLENARY SESSION III
070	방오영 (삼성서울병원) 임상 관점에서 본 소포외소포체 연구
073	PARALLEL SESSION III 임상/치료
074	성학준 (연세대학교병원) Cell-derived nanovesicles for theranostic programing
076	박중훈 (서울대학교) Therapeutic approaches of exosomes and exosome-mimetics
078	홍성희 (고려대학교) A diagnostic and therapeutic value of exosome and its derivatives in the incurable diseases
080	장윤실 (삼성서울병원) Mesenchymal stem cell-derived extracellular vesicles for the treatment of neonatal intractable disorders
083	PARALLEL SESSION III 영상/치료
084	조윤경 (UNIST) Programmed Exosome Fusion For Artificial Organelles
086	조용우 (한양대학교) Taking Stem Cell EV Therapeutics From Bench to Bed Side
088	김현철 (서강대학교) Highly stable microbubbles for enhanced cancer diagnosis and therapy through exosome hybridization
090	홍장원 (경북대학교) Neutrophil-derived trail is a proinflammatory subtype of neutrophil-derived extracellular vesicles
093	KSEV 2021 POSTER SESSION

Program at a glance

Day 1		11월 28일(일)
HALL A		크리스탈홀
14:00-16:00	Registration	
TUTORIAL SESSION		
16:00-16:50	현경아 (연세대학교) Microfluidic strategy to isolate extracellular vesicle	
16:50-17:00	BREAK	
17:00-17:50	오재원 (경희대학교) Quantitative Analysis of Exosome Protein Marker based on Mass Spectrometry for Exosome Quality-Control	
18:00-18:15	Opening Ceremony	
18:15-20:00	이사회 및 초청연사 만찬	

Day 2		11월 29일(월)			
HALL A		크리스탈홀	HALL B	에메랄드홀	
PLENARY SESSION I				고용승 (포스텍)	
09:00-09:50	이계영 (건국대학교병원) EV-based liquid biopsy in lung adenocarcinoma				
09:50-10:00	BREAK				
PARALLEL SESSION I					
	좌장: 문지숙 (차의과학대학교)		좌장: 허재영 (건국대학교병원)		
10:00-10:30	최동식 (순천향대학교 의과대학) Single extracellular vesicle analysis by nano-flow cytometry		김현구 (고려대학교 구로병원) Exosomal Biomarker at Tumor Draining Blood in Lung Cancer Patients		
10:30-11:00	류성호 (순천향대학교 의과대학) Exosomal multi-omics approaches in Precision diagnosis		김태범 (서울아산병원) Multiomics-based precision medicine in asthma		
11:00-11:30	최용준 (아주대학교 의과대학) Apoptotic cell-derived exosomes: messages from dying cells		김한상 (연세대학교 암병원) Extracellular Vesicle and Particle Biomarkers Define Multiple Human Cancers		
11:30-12:00	오연목 (서울아산병원) Studies of extracellular vesicles in COPD		김진국 (건국대학교병원) Clinical feasibility as biomarker of EV from nasal secretion		
LUNCHEON SEMINAR					
12:00-12:30	(주)제이씨바이오 Bioreactor를 이용한 Exosome 수득		(재)씨젠의료재단		
12:30-13:30	LUNCH BREAK				
PLENARY SESSION II					홍종욱 (한양대학교)
13:30-14:20	박재성 (포스텍) Exosome-Engineering in Diagnosis and Therapy				
14:20-14:30	BREAK				

구두 발표		양유수 (KIST), 김선화 (KIST)	
14:30-14:40	문연주 (서울대학교병원) Plasma-derived extracellular vesicles miR-512-3p from moyamoya disease is regulated tubule formation ability of endothelial colony-forming cells through targeting ARHGEF3		
14:40-14:50	박준수 (고려대학교) ExoCAS-2: Rapid and Pure Isolation of Exosomes by Anionic Exchange Using Magnetic Beads		
14:50-15:00	유하은 (연세대학교) Integrated Microfluidic Platform for Serial Enrichment and Isolation of Extracellular Vesicles		
15:00-15:10	윤석환 (취스페바이오) Efficient Production of Extracellular Vesicles using Cell Spheroids		
15:10-15:20	임영갑 (서울대학교) Heterogeneity of Extracellular Vesicles Derived from THP-1 Macrophages Infected with Tannerella forsythia		
15:20-15:30	정소연 (삼성서울병원) Brain-derived neurotropic factor mediates neuroprotection of mesenchymal stem cell-derived extracellular vesicles against severe intraventricular hemorrhage in newborn rats		
15:30-15:40	이채은 (UNIST/IBS) EGFR Mutation Detection of Non-Small Cell Lung Cancer Patients by Analyzing Bronchial Washing derived EVs using Exodisc		
15:40-15:50	안정신 (이대목동병원) Association between breast cancer and Firmicutes/Bacteroidetes ratio		
15:50-16:00	김찬호 (성균관대학교) A Macitentan loaded Nanoparticle for Biogenesis Inhibition and Enhanced Immune Checkpoint Blockade		
16:00-16:10	BREAK		
PARALLEL SESSION II			
	좌장: 최연호 (고려대학교)		좌장: 정효일 (연세대학교)
16:10-16:40	박종민 (강원대학교) Immunomagnetic Electrochemical Sensor for Extracellular Vesicle Analysis in Human Body Fluids		김필남 (KAIST) 폴리페놀을 이용한 액체생검 내 exosomal RNA 추출/분석 기술
16:40-17:10	심상준 (고려대학교) Nanoplasmonic biosensor for diagnosis of the incurable disease using exosome-derived biomarkers		백문창 (경북대학교) Novel immunotherapeutic approach using engineered T-cell derived extracellular vesicles
17:10-17:40	이원종 (인천대학교) Simple and Efficient Extracellular Vesicle Concentration Using Super Absorbent Polymer Beads and Its Applications		박재형 (성균관대학교) Surface-modified exosomes for targeted therapy
17:40-18:00	총회		

Day 3		11월 30일(화)	
HALL A		크리스탈홀	HALL B
		에메랄드홀	
PLENARY SESSION III		김광표 (경희대학교)	
09:00-09:50	방오영 (삼성서울병원) 임상 관점에서 본 소포외소포체 연구		
09:50-10:00	BREAK		
PARALLEL SESSION III			
	좌장: 박지호 (KAIST)	좌장: 노태영 (포스텍)	
10:00-10:30	성학준 (연세대학교병원) Cell-derived nanovesicles for theranostic programming	조윤경 (UNIST) Programmed Exosome Fusion For Artificial Organelles	
10:30-11:00	박중훈 (서울대학교) Therapeutic approaches of exosomes and exosome-mimetics	조용우 (한양대학교) Taking Stem Cell EV Therapeutics From Bench to Bed Side	
11:00-11:30	홍성희 (고려대학교) A diagnostic and therapeutic value of exosome and its derivatives in the incurable diseases	김현철 (서강대학교) Highly stable microbubbles for enhanced cancer diagnosis and therapy through exosome hybridization	
11:30-12:00	장윤실 (삼성서울병원) Mesenchymal stem cell-derived extracellular vesicles for the treatment of neonatal intractable disorders	홍장원 (경북대학교) Neutrophil-derived trail is a proinflammatory subtype of neutrophil-derived extracellular vesicles	
12:00-12:30	Closing Ceremony		

Greeting



한국세포박소포체 (KSEV) 회원 및 세포박소포체 (Extracellular Vesicles) 연구자 여러분, 안녕하세요!
 2020년 1월 한국세포박소포체학회는 Covid-19 pandemic으로 인한 어려움을 극복하고
 2020 KSEV를 성공적으로 개최한 바 있습니다.
 변이바이러스의 창궐로 인해 우리나라는 물론 전세계적으로 어려운 시간을 보내고 있지만,
 머지않아 정상 생활로 복귀할 수 있다는 희망찬 메시지가 들려오는 시점에
 오는 11월 28일(일) - 30일(화) 3일간 부산에서 2021 KSEV를 개최한다는 사실을 알게 되어 기쁘게 생각합니다.
 학술활동 및 연구가 시류를 벗어날 수는 없기에,
 지난 2년간 Biomedical Research News의 중심에는 covid-19이 차지하고 있었지만,
 최근 세포박소포체 연구에 쏟아지는 학계 및 산업계의 관심과 스포트라이트를 생각해 볼 때
 이제는 세포박소포체 연구가 세상으로 나아갈 시점이 아닌가 생각하며, 그 중심에 KSEV가 있다고 생각합니다.
 다행히 2021년 5월 KSEV가 사단법인으로 정식 발족하였습니다.
 이를 위해 노력해주신 김광표 전임 회장님과 여러 운영위원 선생님들께 감사의 말씀을 드리며,
 이번 2021 KSEV는 이를 축하하는 자리가 될 것 입니다.
 금번 2021 KSEV의 catchphrase는 "Extracellular Vesicles : small is beautiful for the bigger world"로
 선정하였습니다. 세포박소포체가 가지고 있는 상징성과 함께 생물학적, 의학적 의미를 함축적으로 표현해주는
 표제가 아닌가 생각합니다. 나노 크기의 극미한 존재이지만 세포박소포체 연구가 밝혀줄 미지의 세계는
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 이러한 의미에서 보다 많은 세포박소포체 연구자 선생님들이 이번 2021 KSEV에 참가해 주셔서 자리를 빛내
 주시고 학문적 성과를 공유하고 교류하는 축제의 한마당이 되었으면 하는 바람과 함께
 사단법인 한국세포박소포체학회의 새로운 출범을 축하해 주시기를 진심으로 부탁드립니다.
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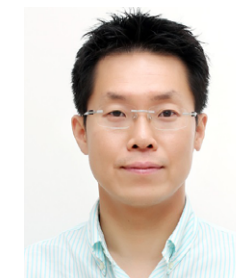
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정효일 | 연세대학교



총무이사
홍종욱 | 한양대학교



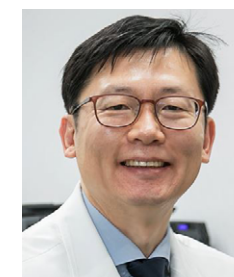
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기획이사
강지윤 | KIST



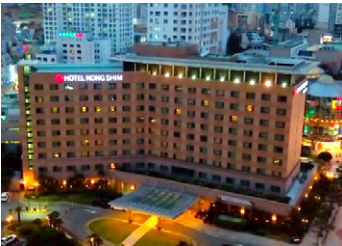
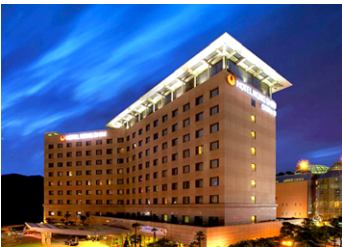
기획이사
박재성 | 포스텍

General information

Overview

제목	2021년도 한국세포막소포체학회 정기 학술 대회 (KSEV 2021)
주제	Extracellular vesicles: Small is beautiful for the bigger world
기간	2021년 11월 28일 (일)- 11월 30일 (화), 3일간
장소	부산 호텔농심 2F 크리스탈홀, 에메랄드홀
주최/주관	한국세포막소포체학회

Venue



크리스탈홀 HALL A

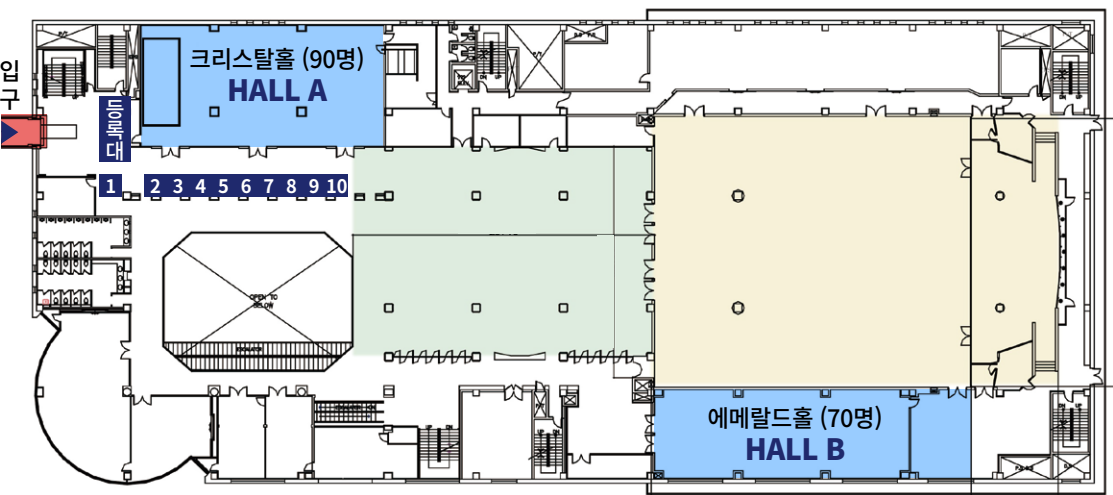


에메랄드홀 HALL B

Program

11월 28 (일)	Tutorial Session, Opening Ceremony, 이사회 및 초청연사 만찬
11월 29 (월)	Plenary Session I-II, Parallel Session I-II, Luncheon Seminar, 구두 발표, 포스터 세션, 업체 전시, 총회
11월 30 (화)	Plenary Session III, Parallel Session III, Closing Ceremony

Floor Plan



NO.	BOOTH	NO.	BOOTH
1	한국로슈진단(주)	6	주식회사 엑소퍼트
2	(주)파나진	7	에스엘사이언스
3	(주)마이크로젠타스	8	Quantum Design Korea
4	보령제약(주)	9	(주)제이씨바이오
5	ILIAS Biologis Inc.	10	위드인스트루먼트



KOREAN SOCIETY FOR
EXTRACELLULAR
VESICLES

KSEV 2021 Annual Meeting 연구상



학술상

탁월한 연구 업적과 헌신적인 학술 활동을 통해
학회 발전에 큰 기여를 한 연구자

박재성 | 포스텍



신진 연구자상

박사학위를 취득 후 세포박소포체 분야에서
10년 이내에 탁월한 연구업적을 성취한 연구자

양유수 | KIST

TUTORIAL SESSION

Microfluidic strategy to isolate extracellular vesicle

현경아 | 연세대학교

Quantitative Analysis of Exosome Protein Marker based on Mass Spectrometry for Exosome Quality-Control

오재원 | 경희대학교



Kyung-A Hyun

Affiliation Department of mechanical engineering, Yonsei University

E-mail hyunkkuplus@gmail.com

Educational Background & Professional Experience

2017-present	Research Professor	Department of mechanical engineering, Yonsei University
2016-2017	Senior researcher	BioNano Health Guard Research Center

Research Interests

Extracellular vesicle purification; Microfluidic platform

List of Major Publications

1. M. W. Kim, et al. Multi-miRNAs panel of tumor-derived extracellular vesicles as promising diagnostic biomarkers of early-stage breast cancer. Cancer Science 2021; doi.org/10.1111/cas.15155.
2. J. Park, et al. Microfluidic recapitulation of circulating tumor cell-neutrophil clusters via double spiral channel-induced deterministic encapsulation. Lab on a Chip 2021; 18, 3483-3497.
3. H. Gwak, et al. Microfluidic chip for rapid and selective isolation of tumor-derived extracellular vesicles for early diagnosis and metastatic risk evaluation of breast cancer. Biosensors and Bioelectronics 2021; 192, 113495.
4. L. Kashefi-Kheyabadi, et al. Detachable microfluidic device implemented with electrochemical aptasensor (DeMEA) for sequential analysis of cancerous exosomes. Biosensors and Bioelectronics. 2020; 169, 112622.

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Republic of Korea*

Microfluidic strategy to isolate extracellular vesicle

Extracellular vesicles (EVs) are nanometer-sized lipid bilayer vesicles secreted by cells for intercellular communication. EVs have been emerging as a crucial biomarker for disease diagnosis and strategy establishment of treatment through liquid biopsy because it contains information of origin cells and is present in most biological fluids. Conventional isolation methods for EVs, such as ultracentrifugation and size exclusion chromatography, suffer from time-consuming processes, low isolation efficiencies, and a lack of selectivity from disease-related EVs. Microfluidic strategy can be an alternative that can overcome the limitations of the aforementioned EVs separation technology. Microfluidic technology is to manipulate fluids using micrometer dimensioned channels. It is attracting attention as a technology for processing micro-nanometer biomarkers because of the advantages such as separation and detection with high resolution and high sensitivity, short times for analysis, and a small footprint for the analytical devices. At this conference, I will outline and present the microfluidic devices for the rapid and selective isolation of EVs.



Jae Won Oh

Affiliation Kyung Hee university, Macrogen

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Educational Background & Professional Experience

2019-present	Researcher	Macrogen
2015-	Ph D integrated course	Department of Applied Chemistry, College of Applied Sciences, Kyung Hee University
2011-2015	Bachelor degree	Deapartment of molecular biotechnology, Konkuk university

Research Interests

Proteomics, Genomics, Multi-omics, Extracellular Vesicle, Mass Spectrometry

List of Major Publications

1. Discovery of plasma biomarkers for predicting the severity of coronary artery atherosclerosis by quantitative proteomics BMJ Open Diabetes Res Care. 2020 Apr, DOI: 10.1136/bmjdr-2019-001152.
2. IRT5 Probiotics Changes Immune Modulatory Protein Expression in the Extraorbital Lacrimal Glands of an Autoimmune Dry Eye Mouse Model Invest Ophthalmol Vis Sci. 2020 Mar 9, DOI: 10.1167/iovs.61.3.42.
3. Mass spectrometry-based proteome profiling of extracellular vesicles and their roles in cancer. Exp Mol Med. 2019 Mar, DOI: 10.1038/s12276-019-0218-2.
4. Changes in Human Tear Proteome Following Topical Treatment of Dry Eye Disease: Cyclosporine A Versus Diquafosol Tetrasodium 2019 Dec, Investigative Ophthalmology & Visual Science 60(15):5035
5. Integrated proteomic and phosphoproteomic analyses of cisplatin-sensitive and resistant bladder cancer cells reveal CDK2 network as a key therapeutic target. Cancer Lett. 2018 Aug, DOI: 10.1016/j.canlet.2018.08.014.
6. Altered Proteome of Extracellular Vesicles Derived from Bladder Cancer Patients Urine. Mol Cells. 2018 Mar, DOI: 10.14348/molcells.2018.2110
7. Proteomic analysis of human lacrimal and tear fluid in dry eye disease Scientific reports. 2017 Oct, DOI: 10.1038/s41598-017-13817-y
8. Proteomic analysis of human follicular fluid in poor ovarian responders during in vitro fertilization Proteomics. 2017 Jan, DOI: 10.1002/pmic.201600333
9. Single-electron-transfer strategy for reductive radical cyclization: Fe(CO)5 and phenanthroline system Org Lett. 2016 Oct, 18(198):4900-4903
10. An automated high-throughput sample preparation protocol for LC-MS/MS analysis of glycopeptides Current Proteomics. 2016 Mar, 13(1):55-60

Jae Won Oh¹,
Jae Sung Park^{2*},
Kwang Pyo Kim^{1*}

¹Department of Applied Chemistry, College of Applied Sciences, Kyung Hee University, Yongin-si, Gyeonggi-do, Republic of Korea, ²School of Interdisciplinary Bioscience and Bioengineering, POSTECH, 77, Cheongam-Ro, Pohang, Gyeongbuk 37673, Republic of Korea

Quantitative Analysis of Exosome Protein Marker based on Mass Spectrometry for Exosome Quality-Control

Exosome is one of the subgroups of extracellular vesicles that possesses significant signal molecules such as multiple proteins, nucleic acids, metabolites and more. Several references suggest that exosomes participate in intercellular communication and regulation of several pathological processes. Therefore, many researchers started to study the exosome to conceal how they work for potential marker or regulator of specific signalling in diseases. As the isolation of exosome is time consuming and difficult because of its characteristics, thus, various isolation methods based on different principles are developed. However, various isolation methods cause doubt in the purity of exosome. There should be multiple validation methods such as electron microscopy, size distribution analysis, and antibody-based analysis. Even though multiple validation methods are presented, none of a single method can confirm the quality of exosomes. To check the quality of exosome, we adopted proteomic quantitative analysis based on mass spectrometry. It is true that a protein can does not represent a signalling or a function of molecule, but several protein expressions can represent their molecular function and cellular compartment. We qualified the exosomes with positive and negative markers from in-sillico database including Evpedia and Exocarta. The algorithm designed to detect positive marker and negative marker candidates is based on known exosome functional annotations and markers. Finally, we quantified total 56 positive markers and hope the markers to help the quality control of exosome.

PLENARY SESSION

Chair 고용승 | 포스텍

EV-based liquid biopsy in lung adenocarcinoma

이계영 | 건국대학교병원



Kye Young Lee

Affiliation Precision Medicine Lung Cancer Center, Konkuk University Medical Center
E-mail kyleemd@kuh.ac.kr

Educational Background & Professional Experience	2005-Present	Professor	College of Medicine, Konkuk University
	1997-1999	Post-doc Research Fellow	School of Medicine, Stanford University
	1988-1997	MS and PhD	School of Medicine, Seoul National University
	1979-1985	BS	School of Medicine, Seoul National University
Research Interests	Lung Cancer, Molecular diagnosis, Liquid biopsy, Extracellular vesicles		
List of Major Publications	<div>1. Hur JY, Lee KY. Characteristics and Clinical Application of Extracellular Vesicle-Derived DNA. Cancers (Basel). 2021 Jul 29;13(15):3827.</div> <div>2. Kim IA, Hur JY, Kim HJ, Lee SA, Hwang JJ, Kim WS, Lee KY. Targeted Next-Generation Sequencing Analysis Predicts the Recurrence in Resected Lung Adenocarcinoma Harboring EGFR Mutations. Cancers (Basel). 2021 Jul 20;13(14):3632</div> <div>3. Seung Eun Lee, Ha Young Park, Jae Young Hur, Hee Joung Kim, In Ae Kim, Wan Seop Kim, Kye Young Lee. Genomic profiling of extracellular vesicle-derived DNA from bronchoalveolar lavage fluid of patients with lung adenocarcinoma. Transl Lung Cancer Res. 2021 Jan; 10(1): 104-116</div> <div>4. Hur JY, Lee JS, Kim IA, Kim HJ, Kim WS, Lee KY. Extracellular vesicle-based EGFR genotyping in bronchoalveolar lavage fluid from treatment-naive non-small cell lung cancer patients. Transl Lung Cancer Res. 2019 Dec;8(6):1051-1060</div> <div>5. Hur JY, Lee JS, Kim IA, Kim HJ, Kim WS, Lee KY. Extracellular vesicle-based EGFR genotyping in bronchoalveolar lavage fluid from treatment-naive non-small cell lung cancer patients. Transl Lung Cancer Res. 2019 Dec;8(6):1051-1060</div> <div>6. Hur JY, Kim HJ, Lee JS, Choi CM, Lee JC, Jung MK, Pack CG, Lee KY. Extracellular vesicle-derived DNA for performing EGFR genotyping of NSCLC patients. Mol Cancer. 2018 Jan 27;17(1):15.</div>		

Kye Young Lee, MD,PhD

Precision Medicine Lung Cancer Center, Konkuk University Medical Center, Seoul, Republic of Korea

EV-based liquid biopsy in lung adenocarcinoma

Blood liquid biopsy is introduced to overcome the clinical limitations of rebiopsy in T790M mutation detection, the acquired resistance mutation to EGFR-tyrosine kinase inhibitor (TKI). It has many merits including repeatability and non-invasiveness, but with a relatively low sensitivity rate of 50-60%, it currently only works as a supplemental test and cannot replace tissue biopsy. Circulating tumor DNAs (ctDNAs) used in the blood liquid biopsy are passive products of fragmented DNA released from tumor cell death. Low sensitivity arises from the instability with half-life, which makes increasing sensitivity fundamentally difficult to meet the requirements for a clinical use. Extracellular vesicles (EVs) make an ideal cancer biomarker as the contents of EV from tumor cells reflect molecular and genetic composition of parental cells and are secreted in higher abundance compared to EVs of normal cells. In addition, EV-derived DNA (EV DNA) consists of big-sized genomic DNAs and tumor-specific oncogenic mutant DNAs unlike the fragmented ctDNA. For these reasons, liquid biopsy using EV can be beneficial in overcoming small biopsy issue from tissue shortage often seen in lung cancer patients and can be applied to EGFR mutations testing and next-generation sequencing. Higher sensitivity can be achieved when EV DNAs obtained from bronchoalveolar lavage fluid (BALF) are used than those from blood. BALF, obtained within close proximity to the tumor site, is a promising liquid biopsy tool as it enables gathering of both cellular and non-cellular fractions of tumor microenvironment (TME) and can be a better alternative to blood for increased sensitivity. Key Words: Lung adenocarcinoma; Liquid biopsy; Extracellular vesicles; EV-based EGFR genotyping; BALiquid biopsy

PARALLEL SESSION I

기초/임상

Chair 문지숙 | 차의과학대학교

Single extracellular vesicle analysis by nano-flow cytometry

최동식 | 순천향대학교 의과대학

Exosomal multi-omics approaches in Precision diagnosis

류성호 | 순천향대학교 의과대학

Apoptotic cell-derived exosomes: messages from dying cells

최용준 | 아주대학교 의과대학

Studies of extracellular vesicles in COPD

오연목 | 서울아산병원



Dongsic Choi

Affiliation Department of Biochemistry, Soonchunhyang University, College of Medicine

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Educational Background & Professional Experience

2021-Present	Assistant Professor	Department of Biochemistry, Soonchunhyang University
2015-2021	Postdoctoral Fellow	The Research Institute of the McGill University Health Centre
2012-2015	Postdoctoral Fellow	Department of Life Sciences, POSTECH
2012-2015	Ph. D.	Department of Life Sciences, POSTECH
2002-2006	B. S.	Department of Life Sciences, POSTECH

Research Interests

Proteomics; EV uptake; Oncogene; Diagnosis

List of Major Publications

1. Choi D et al., Oncogenic RAS drives the CRAF-dependent extracellular vesicle uptake mechanism coupled with metastasis, *Journal of Extracellular Vesicles* 2021;10:e12091.
2. Choi D, Rak J, Gho YS, Isolation of Extracellular Vesicles for Proteomic Profiling, *Methods Mol Biol.* 2021;2261:193-206.
3. Choi D et al., Quantitative proteomic analysis of trypsin-treated extracellular vesicles to identify the real-vesicular proteins, *Journal of Extracellular Vesicles* 2020;9(1):1757209.
4. Choi D et al., Mapping subpopulations of cancer cell-derived extracellular vesicles and particles by nano-flow cytometry. *ACS Nano.* 2019;13(9):10499-10511.
5. Choi D et al., Oncogenic regulation of extracellular vesicle proteome and heterogeneity, *Proteomics* 2019;19(1-2):e1800169.
6. Choi D et al., The impact of oncogenic EGFRvIII on the proteome of extracellular vesicles released from glioblastoma cells, *Mol Cell Proteomics* 2018;17(10):1948-1964.

Dongsic Choi

*Department of Biochemistry,
Soonchunhyang University,
College of Medicine, Cheonan,
Chungcheongnam, 31151, Republic
of Korea*

Single extracellular vesicle analysis by nano-flow cytometry

Cells project their molecular contents via the lipid bilayer vehicles, known as extracellular vesicles (EVs), exhibiting the multipotent functionality in multicellular organism. The elusive complexity of these membranous EV populations released from various cellular sources contains clues as to their biological functions and diagnostic utility. In this study, we employed the optimized multicolor nano-flow cytometry, structured illumination (SIM), and atomic force microscopy (AFM) to bridge sensitive detection at the single EV level and high-throughput analysis of cancer cell secretomes. We applied these approaches to EVs released from intact cells driven by several different transforming mechanisms or to cells under therapeutic stress imposed by pharmacological inhibition of their oncogenic driver EGFR. We demonstrate a highly heterogeneous distribution of biologically relevant elements of the EV cargo, including oncoproteins (EGFR), clotting factors (tissue factor), pro-metastatic integrins (ITGA6, ITGA4), tetraspanins (CD63), and genomic DNA across the entire particulate secretome of cancer cells. Nano-flow cytometry enables quantification of these changes across the entire particular EV subsets. We observed that targeting EGFR activity with irreversible kinase inhibitors (dacomitinib) triggers emission of DNA containing EV subpopulations. Moreover, we analyzed the impact of EGFRvIII on the profile of glioma EVs using isogenic tumor cell lines, in which this oncogene EGFRvIII exhibits a strong transforming activity. Using quantitative proteomic analysis, we identified the selective sorting of pro-invasive proteins (CD44, BSG, CD151) into EGFRvIII-cell derived EVs. By nano-flow cytometry, we revealed that the EV output from individual glioma cell lines was highly heterogeneous, such that only a fraction of vesicles contained specific proteins (including EGFRvIII). Notably, glioma cells expressing EGFRvIII released EV subpopulation with double positive for CD44/BSG, and these proteins also colocalized in cellular filopodia. Thus, our study illustrates the potential of nano-flow cytometry to explore the cancer-related EV landscape.



Seongho Ryu

Affiliation Soonchunhyang Institute of Med-bio Science (SIMS), Soonchunhyang University
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Educational Background & Professional Experience

2018-Present	Associate Professor	Soonchunhyang Institute of Med-bio Science (SIMS), Soonchunhyang University
2014-2018	Assistant Professor	Soonchunhyang Institute of Med-bio Science (SIMS), Soonchunhyang University
2008-2013	Postdoctoral fellow	Weill Cornell Medical College
2003-2008	PhD	New York University (NYU)

Research Interests

Bioinformatics, Exosomes, Precision diagnosis, miRNA, Epigenetics, Cancer, Metastasis

List of Major Publications

1. Shira Yomtoubian, Sharrell B Lee, Akanksha Verma, Franco Izzo, Geoffrey Markowitz, Hyejin Choi, Leandro Cerchietti, Linda Vahdat, Kristy A Brown, Eleni Andreopoulou, Olivier Elemento, Jenny Chang, Giorgio Inghirami, Dingcheng Gao, Seongho Ryu*, Vivek Mittal*. Inhibition of EZH2 Catalytic Activity Selectively Targets a Metastatic Subpopulation in Triple-Negative Breast Cancer. Cell Reports. 2020 Jan 21;30(3):755-770.e6. (*Corresponding author)

2. Choi C, Thi Thao Tran N, Van Ngu T, Park SW, Song MS, Kim SH, Bae YU, Ayudthaya PDN, Munir J, Kim E, Baek MJ, Song S, Ryu S*, Nam KH*. Promotion of tumor progression and cancer stemness by MUC15 in thyroid cancer via the GPCR/ERK and integrin-FAK signaling pathways. Oncogenesis. 2018 12;7(11):85. (*Corresponding author)

3. Bongseo Choi, Hyojin Moon, Sung Joon Hong, Changsik Shin, Yoonkyung Do, Seongho Ryu* , Sebyung Kang*. Effective Delivery of Antigen-Encapsulin Nanoparticle Fusions to Dendritic Cells Leads to Antigen-Specific Cytotoxic T Cell Activation and Tumor Rejection. ACS Nano. 2016 Jul 8, 10:7339-7350. (*Corresponding author)

4. Fischer KR, Durrans A, Lee S, Sheng J, Li F, Wong ST, Choi H, El Rayes T, Seongho Ryu, Troeger J, Schwabe RF, Vahdat LT, Altorki NK, Mittal V, Gao D. Epithelial-to-mesenchymal transition is not required for lung metastasis but contributes to chemoresistance. Nature. 2015 Nov 26;527(7579):472-6.

5. Changsik Shin, Jae-A Han, Hyein Koh, Bongseo Choi, Yongbin Cho, Hyeongmin Jeong, Jea-Sun Ra, Pil Soo Sung, Eui-Cheol Shin, Seongho Ryu*, Yoonkyung Do*. CD8α(-) Dendritic Cells Induce Antigen-Specific T Follicular Helper Cells Generating Efficient Humoral Immune Responses. Cell Reports. (2015) Jul 30;11(12):1929-40. (*Corresponding author)

6. Seongho Ryu, Kevin McDonnell, Hyejin Choi, Dingcheng Gao, Mary Hahn, Natasha Joshi, Sun Mi Park, Raul Catena, Yoonkyung Do, Jacqueline Brazin, Linda T. Vahdat, Randi B. Silver, and Vivek Mittal. Suppression of miRNA-708 by polycomb group promotes metastases by calcium-induced cell migration. Cancer Cell (2013) 23:63-76.

Seongho Ryu

Soonchunhyang Institute of Medi-
biosciences (SIMS)
Department of Integrated
Biomedicine
Soonchunhyang University

Exosomal multi-omics approaches in Precision diagnosis

Complications of diabetes mellitus, commonly known as diabetes, may affect many organ systems either rapidly (acute) or over time (chronic). The complications of diabetes can dramatically impair quality of life and cause disability and death. Nevertheless, the efficient biomarker for early diagnosing complication of diabetes are not available yet. Recently, many studies have demonstrated that exosomal miRNA and proteomics in serum can be useful as a biomarker for several types of diseases including cancers and diabetes. However, multi-omics data have not been used to diagnosis complication of diabetes due to the limitation of serum sampling and lack of bioinformatics tool. The overall objective of this study is to develop and evaluate a totally new model of integration of multi-omics datasets had been obtained from serum exosomes in order to predict diabetic complications.



Yong-Joon Chwae

Affiliation Department of Microbiology, Ajou University School of Medicine

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Educational Background & Professional Experience

2013-Present	Assistant Professor	Department of Microbiology, Ajou University School of Medicine
2008-2013	Assistant Professor	Department of Microbiology, Ajou University School of Medicine
1995-2002	PhD	Department of Medicine, Yonsei University College of Medicine
1986-1995	MD & BD	Department of Medicine, Yonsei University College of Medicine

Research Interests

Apoptotic cell-derived exosomes

List of Major Publications

1. Hur J, et al. Role of Gasdermins in the Biogenesis of Apoptotic Cell-Derived Exosomes. <https://doi.org/10.1101/2021.04.27.441709>
2. Kakarla R, et al. Apoptotic cell-derived exosomes: messages from dying cells. *Exp Mol Med* 2020 Jan;52(1):1-6
3. Park SJ, et al. Molecular mechanisms of biogenesis of apoptotic exosome-like vesicles and their roles as damage-associated molecular patterns. *Proc Natl Acad Sci USA* 2018 Dec 11;115(50):E11721-E11730
4. Yoon S, et al. Caspase-dependent cell death-associated release of nucleosome and damage-associated molecular patterns. *Cell Death Dis* 2014 Oct 30;5(10):e1494

Da Ae Choi^{1,2},
Dae Wook Kang^{1,2},
Jaeyoung Kim^{3,4},
Sk Abrar Shahriyar^{1,2},
Tamanna Mustajab^{1,2},
Junho Kim^{1,2},
Yong-Joon Chwae^{1,2}

¹Department of Microbiology, Ajou University School of Medicine, Suwon, Gyeonggi-do 16499, South Korea; ²Department of Biomedical Science, Graduate School of Ajou University, Suwon, Gyeonggi-do 16499, South Korea; ³Department of Medicine, Graduate School of Ajou University, Suwon, Gyeonggi-do 16499, South Korea; ⁴CK-Exogene Inc., Seoul 54853, South Korea

Apoptotic cell-derived exosomes: messages from dying cells

Apoptosis, a type of programmed cell death that plays a key role in both healthy and pathological conditions, releases extracellular vesicles such as apoptotic bodies and microvesicles, but exosome release due to apoptosis is not yet commonly accepted. Here, we'd like to introduce the exomes derived from apoptotic cells (ApoExos) encompassing physical characteristics and specific markers. According to our researches, the ApoExos begin to be synthesized from the endosomes formed by sphingosine-1-phosphate receptor 1/3 signals at the early apoptotic phase, which would be matured into multi-vesicular endosomes by gasdermins-mediated endosomal Ca²⁺ influx and subsequent recruitment of ESCRT-III complex. In the point of functional properties, the ApoExo have shown to induce inflammation in macrophages and play a role as danger-associated molecular patterns, supported by the recent reports. Conclusively, apoptosis is not just a 'silent' type of cell death but an active form of communication from dying cells to live cells through exosomes.



Yeon-Mok Oh

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Educational Background & Professional Experience

2002–Present Professor (assistant to full) University of Ulsan College of Medicine		
2017–2020	Head	Department of Pulmonary and Critical Care Medicine, Asan Medical Center
2015–2020	Director	Stem Cell Center, Asan Medical Center
2014–2016	Head	Department of Convergence Medicine, Asan Medical Center

Research Interests

Airway diseases, Stem cell, Regeneration

List of Major Publications

1. Kim YS, Kim JY, Cho R, Shin DM, Lee SW, Oh YM. Adipose stem cell-derived nanovesicles inhibit emphysema primarily via an FGF2-dependent pathway. *Exp Mol Med*. 2017 Jan 13;49(1):e284.
2. Cho RJ, Kim YS, Kim JY, Oh YM. Human adipose-derived mesenchymal stem cell spheroids improve recovery in a mouse model of elastase-induced emphysema. *BMB Rep*. 2017 Feb;50(2):79–84
3. Hong Y, Kim YS, Hong SH, Oh YM. Therapeutic effects of adipose-derived stem cells pretreated with pioglitazone in an emphysema mouse model. *Exp Mol Med*. 2016 Oct 21;48(10):e266.
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5. Park JS, Cho R, Kang EY, Oh YM. Effect of Slit/Robo signaling on regeneration in lung emphysema. *Exp Mol Med*. 2021 May;53(5):986–992.

Yeon-Mok Oh

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Studies of extracellular vesicles in COPD

Chronic obstructive pulmonary disease, COPD is one of the top leading causes in morbidity and mortality worldwide. Until recently, many studies have shown that extracellular vesicles (EVs) have an important role in the pathogenesis of COPD. Among the studies, we will discuss indoor dust EVs as a new etiology for the COPD development. Because more than thirty percent of COPD patients are a non-smoker in South Korea, we should find out the etiology for the non-smoker COPD patients. As a possible etiology for the non-smoker COPD, the indoor dust EVs were proposed by YK Kim, et al. They demonstrated that bacterial EVs from the indoor dusts induce the development of COPD pathology, airway inflammation and emphysema. This demonstration was supported by human data with the case-control study of COPD patients and non-COPD subjects. In addition, we will discuss several studies showing that EVs from macrophages, epithelial cells, and endothelial cells in the pathogenesis of cigarette smoke-induced COPD. Cigarette smokes increase macrophage- and epithelial cell-induced EVs which contain proinflammatory mediators. Circulating EVs from endothelial cells increase in smoker COPD patients compared to non-COPD subjects and even more increase when they are exacerbated. Finally, we will discuss our studies showing that artificial nanovesicles from stem cells have a therapeutic potential in the regeneration of the destroyed emphysema lung in COPD.

PARALLEL SESSION I

임상

Chair 허재영 | 건국대학교병원

Exosomal Biomarker at Tumor Draining Blood in Lung Cancer Patients

김현구 | 고려대학교 구로병원

Multomics-based precision medicine in asthma

김태범 | 서울아산병원

Extracellular Vesicle and Particle Biomarkers Define Multiple Human Cancers

김한상 | 연세대학교 암병원

Clinical feasibility as biomarker of EV from nasal secretion

김진국 | 건국대학교병원



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Educational Background & Professional Experience

2015-Present	Professor	Department of Thoracic and Cardiovascular Surgery, Korea University, College of medicine
2000-2004	Ph.D.	College of Medicine, Korea University
1998-2000	M.S.	College of Medicine, Korea University
1988-1996	B.S.	College of Medicine, Korea University

Research Interests

Liquid biopsy; Lung cancer biomarker; Exosome; circulating tumor cells; Image guided surgery

List of Major Publications

1. Jiyun Rho. et al. Fluorescent and Iodized Emulsion for Preoperative Localization of Pulmonary Nodules. Annals of Surgery 2021; 273(5):989-996

2. Kyeong Cheol On. et al. Tumor-Targeting GlycolChitosan Nanoparticles for Image-Guided Surgery of Rabbit Orthotopic VX2 Lung Cancer. Pharmaceutics 2020;12(7):621

3. YuHuaQuan. et al. Evaluation of Intraoperative Near-Infrared Fluorescence Visualization of the Lung Tumor Margin With Indocyanine Green Inhalation. JAMASurgery 2020;155(8):732-740

4. Hyunku Shin. et al. Early-stage lung cancer diagnosis by deep learning based spectroscopic analysis of circulating exosomes. ACS NANO 2020;14(5)5435-5444

5. Hark Soo Choi. et al. Multispectral image-guided surgery in patients. NATURE BIOMEDICAL ENGINEERING 2020;4(3)245-246

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Exosomal Biomarker at Tumor Draining Blood in Lung Cancer Patients

Lung cancer is a leading cause of cancer-related death globally. Early diagnosis is associated with a better prognosis, and surgical resection results in improved survival rates. Tumor draining pulmonary vein blood (TDPV) is more abundant in cancer-associated molecules than peripheral blood. We previously reported that TDVP derived exosomes were increased than the periphery, and GRIP and coiled-coil domain containing 2 (GCC2) in exosomes act as potential lung adenocarcinoma biomarkers. We hypothesized that the analysis of TDPV derived exosomes GCC2 could provide more reliable pathologic information in patients with underwent surgery. Rabbit animal models and 60 human subjects (30 control and 30 patients) were used in this study. The blood samples were collected via the peripheral vein from all groups, and pulmonary was collected intraoperatively, except the human control. Plasma exosomes were isolated by size exclusion chromatography and analyzed by nanoparticle tracking assay, western blot, TEM, enzyme-linked immunosorbent assay. The concentration of exosome GCC2 from TDPV significantly increased comparing to periphery in both rabbit cancer models and patients. As a result of ROC analysis of peripheral and TDPV-derived exosome GCC2, TDPV showed higher AUC, sensitivity, and specificity than peripheral. The increasing trend of exosome GCC2 in TDPV identified a significantly higher correlation with pathological stages than that of the periphery (periphery: p < 0.05 and TDPV: p < 0.0001). This study provides evidence that exosome GCC2 in TDPV higher significant correlation with pathological stages and accurate AUC value than the periphery. Exosome GCC2 in TDPV might be a promising and clinically informative biomarker for lung cancer patients who received surgery.



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Educational Background & Professional Experience	2019-present	Professor	Department of Allergy & Clinical Immunology, Asan Medical Center, University of Ulsan College of Medicine
	2012-2014	Visiting Scholar	Brigham & Women's Hospital, Harvard Medical School, Boston, USA
	2004-2006	Ph.D	Graduate School, College of Medicine, Seoul National University
	2002-2004	M.S	Graduate School, College of Medicine, Seoul National University
	1993-1997	B.S	College of Medicine, Seoul National University

Research Interests Asthma; drug hypersensitivity; multi-omics

List of Major Publications

1. Pragmatic Randomized Controlled Trial for Stepping Down Asthma Controller Treatment in Patients Controlled with Low-Dose Inhaled Corticosteroid and Long-Acting β 2-Agonist: Step-Down of Intervention and Grade in Moderate Asthma Study. J Allergy Clin Immunol Pract. 2021
2. Genome-wide association study in Korean Asthmatics: A comparison with UK asthmatics. Allergy Asthma Immunol Res. 2021
3. Discontinuation of inhaled corticosteroids in patients with controlled asthma: The DISCO study. Ann Allergy Asthma Immunol. 2021
4. Extracellular vesicle-derived microbiome obtained from exhaled breath condensate in patients with asthma. Ann Allergy Asthma Immunol. 2021
5. Serum folliculin is related to lower pulmonary function in patients with asthma. Allergy Asthma Immunol Res. 2021
6. A Randomized, Noninferiority Trial Comparing ICS + LABA with ICS + LABA + LAMA in Asthma-COPD Overlap (ACO) Treatment: The ACO Treatment with Optimal Medications (ATOMIC) Study. J Allergy Clin Immunol Pract. 2021
7. Clinical importance of work-exacerbated asthma: Findings from a prospective asthma cohort in a highly industrialized city in Korea. Allergy Asthma Immunol Res. 2021
8. Cost-Effectiveness of Tiotropium in Elderly Patients with Severe Asthma Using Real-World Data. J Allergy Clin Immunol Pract. 2021
9. Serum Eosinophil-Derived Neurotoxin Better Reflect Asthma Control Status Than Blood Eosinophil Counts. J Allergy Clin Immunol Pract. 2020
10. Clinical significance of serum MRGPRX2 as a new biomarker in allergic asthma. Allergy. 2020
11. Relationship between age and bronchodilator response at diagnosis in adult-onset asthma. Respir Res. 2020
12. Association between obesity and lung function changes by sex and age in adults with asthma. J Asthma. 2020

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Multi-Omics Based Precision Medicine in Asthma

Asthma is one of major clinical unmet needs causing deterioration in quality of life and socioeconomic burden. Although deeper understanding in pathophysiology of asthma led to development of biologic agents targeting T2 inflammation, therapeutic responses vary between patients.

Introduction of omics technologies, including transcriptomics, epigenetics, metagenomics, metabolomics, and proteomics, provided a research platform to identify molecular markers which are not readily detected in usual diagnostic tests in clinics. The 'Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes (U-BIOPRED)' consortium has reported the novel molecular markers in severe asthma based on proteomic, transcriptomic, and metabolomic data generated from blood, sputum, airway epithelial cells, as well as exhaled breath. Further, cluster analysis of sputum transcriptomics identified three clusters of severe asthma, which were characterized by eosinophilic phenotype, inflammasome, and metabolic/mitochondrial pathway, respectively. The Cohort for Reality and Evolution of Adult Asthma in Korea (COREA) is a nation-wide prospective asthma cohort in Korea that has maintained serial follow-up of patients for more than 16 years. COREA investigators have conducted several multi-omics researches as well as clinical studies. In addition, we have recently performed a multi-omics study, named Precision Medicine Intervention in Severe Asthma (PRISM) study collaborated with UK investigators, to examine whether molecular phenotypes will be a better biomarker of best therapeutic response to biologics than conventional markers such as blood eosinophil counts, sputum eosinophils, Fractional Exhaled nitric oxide (FeNO). The ultimate aim of the study is to find molecular phenotype of severe asthma by analyzing multi-omics data including genomics, epigenetics, transcriptomics, proteomics, metagenomics, and metabolomics. The results of the study may give clues for upcoming omics researches as well as identify molecular pathways which is essential for precision medicine of asthma.



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Educational Background & Professional Experience	2020~Present	Assistant Professor	Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Korea
	2019	Clinical Assistant Professor	Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Korea
	2018	Clinical Fellow	Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Korea
	2018	Ph.D.	Graduate School, Yonsei University, Seoul, Korea
	2008~2013	Intern / Residency	Severance Hospital, Seoul, Korea
	2008	M.D.	Yonsei University College of Medicine, Seoul, Korea
Research Interests	Cancer Metastasis, Colorectal Cancer, Premetastatic Niche		
List of Major Publications	1. Hoshino A*, Kim HS*, Linda Bojmar*, Gyan*, Jones D, Matei I, Jarnagin WR, Lyden D et al. Extracellular Vesicle and Particle Biomarkers Define Multiple Human Cancers. Cell 2020. E-pub. *co-first		
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Extracellular Vesicle and Particle Biomarkers Define Multiple Human Cancers

There is an unmet clinical need for improved tissue and liquid biopsy tools for cancer detection. We investigated the proteomic profile of extracellular vesicles and particles (EVPs) in 426 human samples from tissue explants (TEs), plasma, and other bodily fluids. Among traditional exosome markers, CD9, HSPA8, ALIX, and HSP90AB1 represent pan-EVP markers, while ACTB, MSN, and RAP1B are novel pan-EVP markers. To confirm that EVPs are ideal diagnostic tools, we analyzed proteomes of TE- (n = 151) and plasma-derived (n = 120) EVPs. Comparison of TE EVPs identified proteins (e.g., VCAN, TNC, and THBS2) that distinguish tumors from normal tissues with 90% sensitivity/94% specificity. Machine-learning classification of plasma-derived EVP cargo, including immunoglobulins, revealed 95% sensitivity/90% specificity in detecting cancer. Finally, we defined a panel of tumor-type-specific EVP proteins in TEs and plasma, which can classify tumors of unknown primary origin. Thus, EVP proteins can serve as reliable biomarkers for cancer detection and determining cancer type.



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Educational Background & Professional Experience	2009–Present	Professor	Department of Otorhinolaryngology-Head and Neck Surgery, Konkuk University School of Medicine
	2007–2009	Postdoctoral fellowship	NIEHS(National Institute of Environmental & Health Science, Research Triangle Park, NC, USA)
	1999	Clinical fellow	Department of Otorhinolaryngology, Yonsei University College of Medicine
	1995–1999	Residency	Department of Otorhinolaryngology, Konkuk University College of Medicine
Research Interests	Sinusitis; Olfactory and taste disorders		
List of Major Publications	<div>1. Min JY, Kin YM, Kim DW, Kim JW, Kim JK, Mo JH, Shin JM, Cho KS, Kwak S, Shin SH. Risk Model Establishment of Endoscopic Sinus Surgery for Patients with Chronic Rhinosinusitis: a Multicenter Study in Korea. J Korean Med Sci. 2021 Oct 18;36(40):e264.</div> <div>2. Park JY, Kim YS, Kim JK, Cho JH. Cost-Effectiveness Analysis of Immunotherapy in Patient with Allergic Rhinitis. Korean J Otorhinolaryngol-Head Neck Surg 2021;64(8):554–62</div> <div>3. Noh H, Choi BY, Jeong H, Moon WJ, Kim JK. Diagnosis of isolated congenital anosmia using simultaneous functional magnetic resonance imaging and olfactory event-related potentials: Our experience in six patients. Clin Otolaryngol. 2021 Cover Image.</div> <div>4. Noh H, Choi BY, Jeong H, Moon WJ, Kim JK. Diagnosis of isolated congenital anosmia using simultaneous functional magnetic resonance imaging and olfactory event-related potentials: Our experience in six patients. Clin Otolaryngol. 2021 Jul;46(4):906–910.</div> <div>5. Cha S, Seo EH, Lee SH, Kim KS, Oh CS, Moon JS, Kim JK. MicroRNA Expression in Extracellular Vesicles from Nasal Lavage Fluid in Chronic Rhinosinusitis. Biomedicines. 2021 Apr 26;9(5):471.</div> <div>6. Jeong H, Choi BY, Lee J, Kim KS, Min SJ, Kim JK. Prevalence and characteristics of S-point bleeding compared to non S-point bleeding in severe epistaxis. Braz J Otorhinolaryngol. Jul-Aug 2021;87(4):462–468.</div> <div>7. Choi BY, Jeong H, Noh H, Park JY, Cho JH, Kim JK. Effects of Olfactory Training in Patients With Postinfectious Olfactory Dysfunction. Clin Exp Otorhinolaryngol 2021 Feb;14(1):88–92.</div> <div>8. Noh H, Park JY, Jung T, Kim JK. Two Cases of Recalcitrant Chronic Rhinosinusitis Treated with Endoscopic Maxillary Mega-Antrostomy in Primary Ciliary Dyskinesia . Korean J Otorhinolaryngol-Head Neck Surg 2021; 64(5): 350–353.</div> <div>9. Lee J, Kim JK, Cho JH. Current Status and Future Forecast of the Number of Otolaryngologists in Korea. Korean J Otorhinolaryngol-Head Neck Surg 2021; 64(2): 77–85.</div> <div>10. Han K, Lee J, Choi BY, Jeong H, Cho JH, Kim JK. Does Improved Attention Induced by Caffeine Intake Affect Olfactory Function? Clinical and Experimental Otorhinolaryngology 2020; 13(1): 52–57.</div> <div>11. Kim JK. Can Olfactory Tests Help to Diagnose Parkinson Disease?. Clinical and Experimental Otorhinolaryngology 2019 May;12(2):105–106.</div> <div>12. Moon WJ, Park M, Hwang M, Kim JK. Functional MRI as an Objective Measure of Olfaction Deficit in Patients with Traumatic Anosmia. American Journal of Neuroradiology 2018 Dec;39(12):2320–2325</div>		

Jin Kook Kim

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Clinical feasibility as biomarker of EV from nasal secretion

Chronic rhinosinusitis (CRS) is characterized by chronic inflammation of the sinonasal mucosa. Chronic rhinosinusitis without nasal polyps (CRSsNP) and chronic rhinosinusitis with nasal polyps (CRSwNP) are two different CRS phenotypes. Advances in our understanding of CRS pathophysiology have led to adoption of the endotype paradigm of disease characterization. The main goal of CRS research is to understand its etiopathology and significant prognostic information for personalized CRS treatment. Identifying pathways that allow CRS to be expressed is fundamental to improving preventative strategies, developing diagnostic tools, and designing therapies. Extracellular vesicles (EVs) are nanovesicles of endocytic origin released by cells and found in human bodily fluids including nasal secretion. EVs contain both mRNA and microRNA (miRNA), which can be shuttled between cells, indicating their role in cell communication. We investigated whether nasal secretions contain EVs and whether these EVs contain RNA and EV miRNA expression was different in the chronic rhinosinusitis without nasal polyp (CRSsNP) and chronic rhinosinusitis with nasal polyp (CRSwNP) groups. In this lecture, based on various information obtained from nasal secretions, we would like to share opinions on the potential as a biomark for the diagnosis, prognosis, and treatment of nasal diseases.

PLENARY SESSION II

Chair 홍종욱 | 한양대학교

Exosome-Engineering in Diagnosis and Therapy

박재성 | 포스텍



Jaesung Park

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Educational Background & Professional Experience	2021~Present	Visiting Professor	University of Michigan
	2021~	Senior Vice President	The Society of Micro- and Nano systems
	2018~	CTO	Co-Founder of Exosome Plus. Inc
	2007~	Assistant Professor, Associate Professor,	Mechanical Engineering/ Interdisciplinary Bioscience and Bioengineering
	2002-2007	Research Associate / PostDoc	Harvard Medical School
	2002		PhD. University of Wisconsin-Madison, Mechanical Engineering
	1997		MS, Seoul National University, Mechanical Engineering
	1995		BS, Pohang University of Science and Technology (Postech), Mechanical Engineering
Research Interests	Extracellular vesicle-based diagnosis /Single extracellular vesicle analysis/ Exosome therapy		
List of Major Publications	<div>1. S Cho, J Yi, Y Kwon, H Kang, C Han, J Park," Multifluorescence Single Extracellular Vesicle Analysis by Time-Sequential Illumination and Tracking," ACS nano 15 (7), 11753-11761</div> <div>2. C Han, H Kang, J Yi, M Kang, H Lee, Y Kwon, J Jung, J Lee, J Park , "Single-vesicle imaging and co-localization analysis for tetraspanin profiling of individual extracellular vesicles," Journal of Extracellular Vesicles 10 (3), e12047</div> <div>3. J Kim, C Han, W Jo, S Kang, S Cho, D Jeong, YS Gho, J Park," Cell-Engineered Nanovesicle as a Surrogate Inducer of Contact-Dependent Stimuli," Advanced Healthcare Materials, doi.org/10.1002/adhm.201700381, 2017</div> <div>4. J Kim, H Shin, J Park," RNA in Salivary Extracellular Vesicles as a Possible Tool for Systemic Disease Diagnosis," Journal of Dental Research, 0022034517702100, 2017</div> <div>5. J Yoon, W Jo, D Jeong, J Kim, H Jeong, J Park, "Generation of nanovesicles with sliced cellular membrane fragments for exogenous material delivery," Biomaterials 59, 12-20, 2015</div> <div>6. H Shin, C Han, JM Labuz, J Kim, J Kim, S Cho, YS Gho, S Takayama, J Park, "High-yield isolation of extracellular vesicles using aqueous two-phase system," Scientific reports 5. doi:10.1038/srep13103, 2015</div>		

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Siwoo Cho²,
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Siwoo Cho², Junho Kim¹,
Wonju Jo²,
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Exosome Engineering in Diagnosis and Therapy

Extracellular vesicles (EVs) are known to mediate intercellular communications, and have drawn wide attention due to their potential potency in therapy and diagnostics. Although the results in therapy and diagnostics with EVs are promising, there have been inconsistencies in the findings. To overcome the inconsistencies, more reliable methods for EV isolation and analysis are needed.

In this seminar, critical issues of isolation and analysis of EVs will be discussed. 1) For isolation of EVs, density-gradient ultracentrifugation is widely used, but the recovery efficiency is estimated to be much less than 20%. Although several methods have been tried to overcome this poor recovery, the results have not been satisfactory in terms of recovery and purity. Conventional methods for isolation of EVs will be discussed and compared.

Two new methods for the analysis of EVs will be introduced: drying droplet and single EV analysis. 1) The first method uses the coffee-ring effect to perform size-based chromatography of EVs. In drying droplet, Marangoni recirculation allows size-sorting EVs with ~50 nm resolution. The smallest EVs are deposited at outer edge of the drying droplet, and larger EVs are deposited further inside. Using this method, the correlation between the size and EV-specific markers (CD9, CD63, CD81) has been investigated. This method has been further extended to investigate the correlation between the size, specific markers, and cancer-associated markers as well; the findings of this work will be presented. 2) Currently most EV studies are based on ensemble of EVs even though EVs are heterogeneous. To understand the heterogeneity of EVs, single EV analysis is required. However, the size of EV (~100nm) is below the diffraction limit, and phase-contrast microscopes cannot be used to observe EVs properly. Additionally, the fluorescence of EVs labeled with markers quenches very rapidly because the small size of EVs limits the number of fluorescence molecules on EVs. To overcome this technical challenge, a system for visualization of single EVs has been developed; the results obtained with this system will be discussed. Not like ensemble analysis methods, this system is able to count the number of EVs and type EVs simultaneously.

PARALLEL SESSION II

분리/진단

Chair 최연호 | 고려대학교

Immunomagnetic Electrochemical Sensor for Extracellular Vesicle Analysis
in Human Body Fluids

박종민 | 강원대학교

Nanoplasmonic biosensor for diagnosis of the incurable disease using
exosome-derived biomarkers

심상준 | 고려대학교

Simple and Efficient Extracellular Vesicle Concentration Using Super
Absorbent Polymer Beads and Its Applications

이원종 | 인천대학교



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Educational Background & Professional Experience

2018-Current	Assistant Professor	Kangwon National University
2015-2018	Research Fellow	Harvard Medical School
2012-2014	Postdoctoral Fellow	Seoul National University
2006-2012	Ph.D.	Seoul National University
2001-2005	B.S.	Seoul National University

Research Interests

Liquid Biopsy, Electrochemistry, Extracellular Vesicle Analysis, Chemical Biology

List of Major Publications

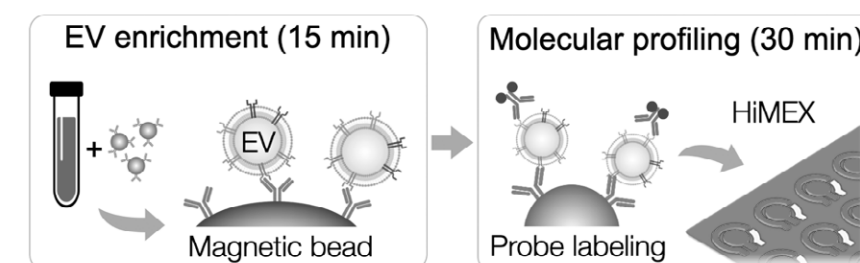
1. Park, J.+, Lin, H.+, Assaker, J. P.+, Jeong, S., Huang, C. -H., Kurdi, A., Lee, K., Fraser, K., Min, C., Eskandari, S., Routray, S., Tannous, B., Abdi, R., Riella, L., Chandraker, A., Castro, C. M., Weissleder, R., Lee, H., Azzi, J. Integrated kidney exosome analysis for the detection of kidney transplant rejection. *ACS Nano*. 2017, 11, 11041-11046.
2. Park, J.+, Im, H.+, Hong, S., Castro, C. M., Weissleder, R., Lee, H. Analyses of Intravesicular Exosomal Proteins Using a Nano- Plasmonic System. *ACS Photonics* 2018, 5, 487-494.
3. Kim, S.M.+, Park, J.+, Kim, M.S., Song, H., Jo, A., Park, H, Choi, S.H., Park, S. B. Phenotypic discovery of an anti-virulence agent against vibrio vulnificus via modulation of quorum-sensing regulator SmcR. *ACS Infect. Dis.* 2020, 6, 3076-3082.
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5. Ha, J., Park, H., Park, J.*, Park, S. B.* Recent Advances in Identifying Protein Targets in Drug Discovery. *Cell Chem. Biol.* 2021, 28, 394-423.

Jongmin Park

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Immunomagnetic Electrochemical Sensor for Extracellular Vesicle Analysis in Human Body Fluids

Extracellular vesicles, including exosomes, are nanoscale membrane particles that carry molecular information on parental cells. They are being pursued as biomarkers of various diseases, especially cancer that are difficult to detect or serially follow. To solve this issue, we developed a compact sensor technology for rapid, on-site exosome screening. The sensor is based on an integrated magneto-electrochemical assay: exosomes are immunomagnetically captured from patient samples and profiled through electrochemical reaction. By combining magnetic enrichment and enzymatic amplification, the approach enables (i) highly sensitive, cell-specific extracellular vesicle detection and (ii) sensor miniaturization and scale-up for high-through put measurements. We demonstrated this system to screen extracellular vesicles in human body fluids such as plasma or urine samples from patients with ovarian cancer^{1,2}, kidney transplant rejection³ and colorectal cancer patients⁴. The sensor allowed for the simultaneous profiling of multiple protein markers within an hour, outperforming conventional methods in assay sensitivity and speed.



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3. Park, J.+, Lin, H.+, Assaker, J. P.+, Jeong, S., Huang, C. -H., Kurdi, A., Lee, K., Fraser, K., Min, C., Eskandari, S., Routray, S., Tannous, B., Abdi, R., Riella, L., Chandraker, A., Castro, C. M., Weissleder, R., Lee, H., Azzi, J. Integrated kidney exosome analysis for the detection of kidney transplant rejection. *ACS Nano*. 2017, 11, 11041-11046.
4. Park, J.+, Park, J. S.+, Huang, C., Jo, A., Cook, K., Wang, R., Lin, H- Y., Deun, J. V., Li, H., Min, J., Yoon, G., Choi, G- S., Castro, C. M., Weissleder, R., Lee, H. Magneto-electrochemical system enables rapid and high-throughput profiling of extracellular vesicles. *Nat. Biomed. Eng.* 2021, 5, 678-689.



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Educational Background & Professional Experience

2011-Present	Professor	Department of chemical and biological engineering, Korea University
2002-2011	Associate Professor	Department of Chemical Engineering, Sungkyunkwan University
1996 -2002	Senior Research Scientist	Korea Institute of Science and Technology (KIST)

Research Interests

Chip Development and nanobiotechnology, Bio-Micro Electro Mechanical Systems (MEMS), Nanoplasmonic biosensor for diagnostic of incurable disease

List of Major Publications

1. Min Sun Song et al., "Real-time, sensitive, and specific detection of promoter-polymerase interactions in gene transcription using a nanoplasmonic sensor", *Advanced Materials*, 2013;25(9), 1265-1269.
2. Xingyi Ma et al., "Gold nanocrystals with DNA-directed morphologies", *Nature Communications* 2016;7, 12873.
3. Xingyi Ma et al., "Single gold-bridged nanoprobe for identification of single point DNA mutations," *Nature Communications* 2019;10, 836.
4. Jong Uk Lee et al., "Quantitative and Specific Detection of Exosomal miRNAs for Accurate Diagnosis of Breast Cancer Using a Surface-Enhanced Raman Scattering Sensor Based on Plasmonic Head-Flocked Gold Nanopillars," *Small* 2019;15(17), 1804968.
5. 4. Hong Il Choi et al., "Augmented CO2 tolerance by expressing a single H⁺-pump enables microalgal valorization of industrial flue gas", *Nature Communications* 2021;12, 6049.

Sang Jun Sim¹

¹Department of Chemical and Biological Engineering, Korea University, 145, Anam-ro, Seongbuk-gu, Seoul 02841, Republic of Korea

Nanoplasmonic biosensor for diagnosis of the incurable disease using exosome-derived biomarkers

Biomarkers in exosomes (exosome-derived biomarkers) have attracted increased attention as incurable disease biomarkers for early diagnosis and prognosis owing to their stability in body fluids. Since strong association exists between exosome-derived biomarkers expression levels and incurable diseases, the development of effective methods that can monitor exosome-derived biomarkers expression both over broad concentration ranges and in ultralow amounts is critical. Here, a nanoplasmonic based sensing platform is developed for the qualitative and quantitative determination of exosome-derived biomarkers. Ultrasensitive exosome-derived biomarker detection with biomolecule-probe specificity is obtained from enhanced optical signals from a uniform plasmonic nanoparticles and nanosubstrates, which generates multiple hotspots and enables specific binding between exosomal biomarkers. The proposed nanoplasmonic biosensor shows an extremely low detection limit without any amplification process, a wide dynamic detection range, multiplex sensing capability. Furthermore, this nanoplasmonic biosensor allows reliable observation of exosome-derived biomarker expression patterns and can represent indicators for evaluation of clinical diagnostic significance. The results suggest that this biosensor can be used for universal diagnosis of incurable diseases and further biomedical applications through the qualitative and quantitative measurement of exosomal biomarker in bodily fluids.



Won Jong Rhee

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Educational Background & Professional Experience

2021-Present	Professor	Division of Bioengineering, Incheon National University
2012-2021	Assistant/Associate Professor	Division of Bioengineering, Incheon National University
2010-2012	Senior Scientist	LG Life Sciences
2005-2010	Postdoctor	Georgia Institute of Technology
1993-2004	BS(1997), MS(1999), PhD(2004)	Seoul National University

Research Interests

Liquid biopsy, biologics development, drug delivery, extracellular vesicle isolation

List of Major Publications

1. Yang HC, et al. Single-step equipment-free extracellular vesicle concentration using super absorbent polymer beads. *Journal of Extracellular Vesicles* 2021;10:e12074
2. Hong SH, et al. Inhibition of tumor progression and M2 microglial polarization by extracellular vesicle-mediated microRNA-124 in a 3D microfluidic glioblastoma microenvironment. *Theranostics* 2021;11:9687-9704
3. You JY, et al. Isolation of cabbage exosome-like nanovesicles and investigation of their biological activities in human cells. *Bioactive Materials* 2021;6:4321-4332
4. Cao TGN, et al. Safe and targeted sonodynamic cancer therapy using biocompatible exosome-based nanosonosensitizers. *ACS Applied Materials & Interfaces* 2021;13:25575-25588
5. Jeong K, et al. Exosome-mediated microRNA-497 delivery for anti-cancer therapy in a microfluidic 3D lung cancer model. *Lab on a Chip* 2020;20:548-557
6. Cho S, et al. Simultaneous multiplexed detection of exosomal microRNAs and surface proteins for prostate cancer diagnosis. *Biosensors and Bioelectronics* 2019;146:111749

Won Jong Rhee

Simple and Efficient Extracellular Vesicle Concentration Using Super Absorbent Polymer Beads and Its Applications

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Extracellular vesicles (EVs), nano-sized particles, are promising biomaterials for the delivery of therapeutic molecules. Also, EVs contain various biomarkers originating from their parental cells that can be used for liquid biopsy. Accordingly, an efficient concentration method is necessary for large-scale production or high-throughput isolation of EVs from bulk liquid samples, including culture medium and body fluids, to achieve their biomedical applications. However, current EV concentration methods are severely limited with respect to efficiency, cost, and centrifugation time. This study presents the simple and efficient EV concentration method using super absorbent polymer (SAP) beads. SAP beads absorbed small molecules, including water, via nano-sized channels but expel and thereby concentrate EVs. Consequently, the beads drastically enriched EVs by reducing the solution volume in a single step, without affecting EV characteristics. Moreover, the concentrated EV solution purity was high due to the absorption of protein impurities by SAP beads. The versatility of the method was demonstrated by investigating that SAP beads successfully enrich EVs in human urine samples, culture medium, and plant juices enabling better isolation performance than conventional ultrafiltration. I believe the developed approach and insight gained in this study will facilitate the use of EVs as prominent biomaterials for disease diagnosis and therapy.

PARALLEL SESSION II

분리/진단/치료

Chair 정효일 | 연세대학교

폴리페놀을 이용한 액체생검 내 exosomal RNA 추출/분석 기술
김필남 | KAIST

Novel immunotherapeutic approach using engineered T-cell derived extracellular vesicles
백문창 | 경북대학교

Surface-modified exosomes for targeted therapy
박재형 | 성균관대학교



Pilnam Kim

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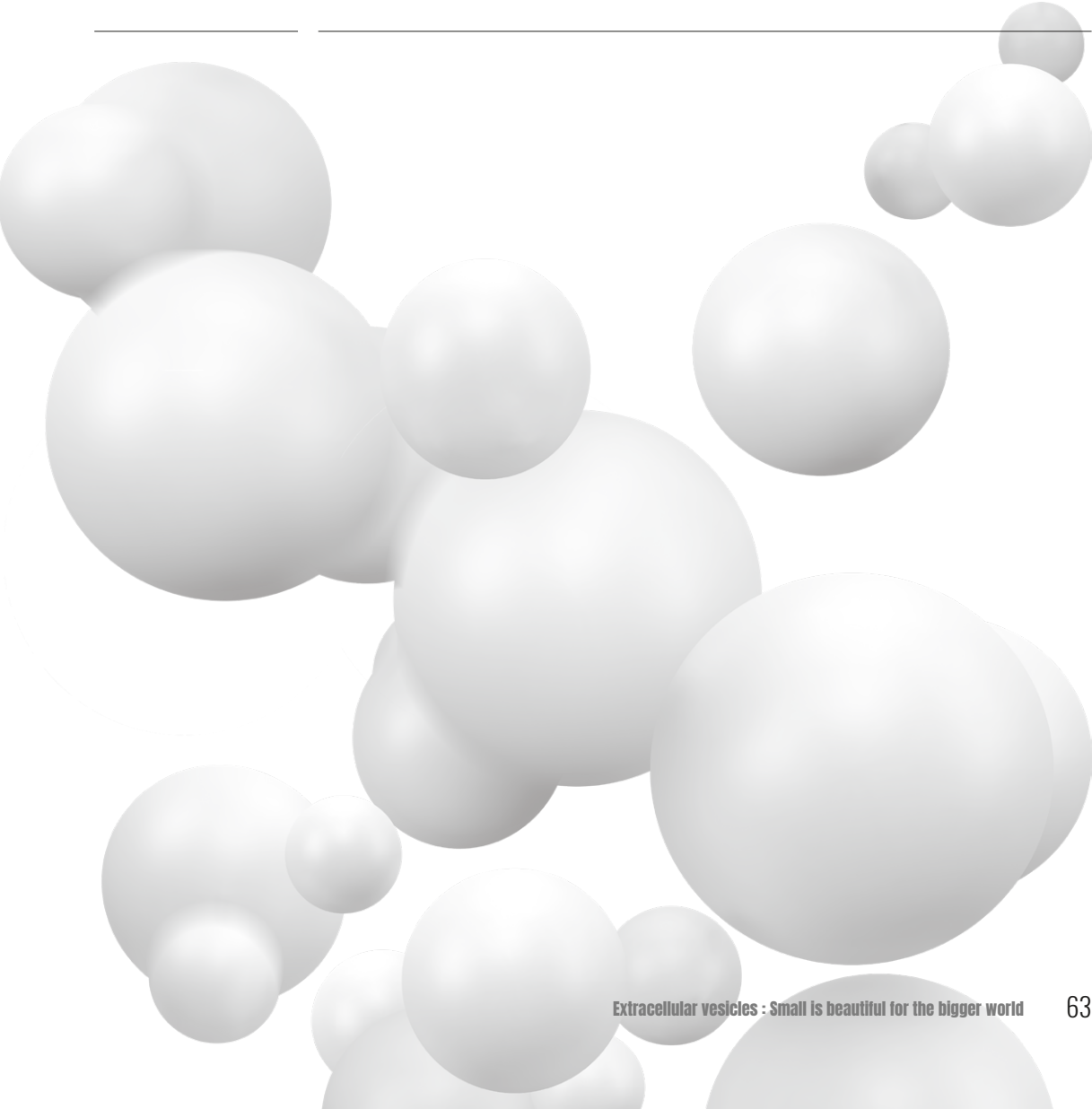
Educational Background & Professional Experience	2017-Present	Associate Professor	Dept. Bio and Brain Engineering, KAIST
	2012-2017	Assistant Professor	Dept. Bio and Brain Engineering, KAIST
	2009-2011	Post-doc	ME, Princeton University
	2004-2009	PhD	ME, Seoul National University
Research Interests	Tissue Engineering, Organoids, Tumor microenvironment		
List of Major Publications	<div>1. M. Jang, J. An, S. W. Oh, J. Y. Lim, J. Kim, J. K. Choi*, J.-H. Cheong*, P. Kim*, "Matrix stiffness epigenetically regulates the oncogenic activation of the Yes-associated protein in gastric cancer", Nature Biomedical Engineering, 5, 114-123(2021, 1)</div> <div>2. E. Lim, S. Kim, Y. Oh, Y. Suh, N. Kaushik, J. Lee, H. Lee, M. Kim, M. Park, R. Kim, J. Cha, S. Kim, J. Shim, J.Choi, J. Chang, Y. Hong, Y. Huh, P. Kim*, S. Kang*, S. Lee*, "Crosstalk between GBM cells and mesenchymal stem-like cells promotes the invasiveness of GBM through the C5a/p38/ZEB1 axis", Neuro-Oncology, 22, 1452-1462 (2020, 03)</div> <div>3. M. Jang, G. Choi, Y. Y. Choi, J. E. Lee, S. W. Oh, D. H. Han, H. Lee, J.-H. Cheong, P. Kim*, "Extracellular vesicles (EVs)-bioadhesives nanoaggregates for microRNA-based cancer diagnosis", NPG Asia Materials, 11:79 (2019, 12)</div> <div>4. J. Cha, P. Kim*, "Time series assessment of the effects of hypoxic stress on glioma tumorsphere development within engineered microscale niches", Biomaterials, 194, 171 (2019, 01)</div> <div>5. H. N. Kim*, K.-J. Jang, J.-Y. Shin, D. Kang, S. M. Kim, I. Koh, Y. Hong, S. Jang, M. S. Kim, B.-S. Kim, H. E. Jeong, N. L. Jeon, K.-Y. Suh, and P. Kim* "Artificial Slanted Nanocilia Array as a Mechanotransducer for Controlling Cell Polarity", ACS Nano, (2017.1)</div>		

Pilnam Kim

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폴리페놀을 이용한 액체생검 내 exosomal RNA 추출/ 분석 기술

Small extracellular vesicles (EVs), including exosomes, in body fluids have important applications in the noninvasive liquid biopsy-based diagnosis of cancer. Current EV-based diagnostic techniques still face practical challenges, such as inefficient EV isolation. Here, we report an efficient, resource-free pre-enrichment approach using (-)-epigallocatechin3-gallate (EGCG), a polyphenolic biomolecule, to isolate and detect exosomal microRNAs (miRNAs) in human blood plasma samples. Our system comprises three steps: (1) EGCG-mediated EV aggregation, (2) filter-based EV isolation, and (3) molecular beacon-based detection of target miRNA in EVs. Using blood samples from cancer patients with gastric cancer or hepatocellular carcinoma, we constructed an EGCG-assisted miRNA diagnostic system. For both cancers, the levels of target miRNAs (miR-21, -27a, and -375) in EVs were strongly correlated with those in the publicly available GEO database. Our approach, an easy-to-use method for efficient EV isolation and the detection of miRNA in clinical samples, is applicable for molecular diagnostics in precision medicine.





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Educational Background & Professional Experience

2005-present	Professor	Department of Molecular Medicine, School of Medicine, KNU
2012-2013	Visiting Scholar	Dept. of Chemical Physiology, The Scripps Research Institute, La Jolla, USA
1998-2002	Post-Doc	Department of Biological Chemistry & Molecular Pharmacology, Harvard Medical School, Boston, USA
1994-1997	Ph. D.	College of Pharmacy, Seoul National University, Seoul, Korea

Research Interests

Extracellular vesicles, Cancer therapeutics, Immune checkpoint blockade, exosome purification, liquid biopsy, Cancer early diagnosis

List of Major Publications

1. Kim DK, et al. Mastocytosis-derived extracellular vesicles deliver miR-23a and miR-30a into pre-osteoblasts and prevent osteoblastogenesis and bone formation, Nat Commun. 2021 May 5;12(1):2527.
2. Im EJ, et al. Sulfisoxazole inhibits the secretion of small extracellular vesicles by targeting the endothelin receptor A. Nat Commun. 2019 Mar 27;10(1):1387.
3. Lee CH, et al. Discovery of a diagnostic biomarker for colon cancer through proteomic profiling of small extracellular vesicles. BMC Cancer. 2018 Nov 1;18(1):1058.
4. Cho YE et al. Exogenous exosomes from mice with acetaminophen-induced liver injury promote toxicity in the recipient hepatocytes and mice. Sci Rep. 2018 Oct 30;8(1):16070.
5. Cho YE et al. Extracellular vesicles as potential biomarkers for alcohol- and drug-induced liver injury and their therapeutic applications. Pharmacol Ther. 2018 Jul;187:180-194.

Moon-Chang Baek

Exosome Convergence Research Center (ECRC), Department of Molecular Medicine, School of Medicine, Kyungpook National University, Daegu, Republic of Korea.

Novel immunotherapeutic approach using engineered T-cell derived extracellular vesicles

Antibody blockade of PD-L1 has shown effectiveness against many cancers, including melanoma and non-small-cell lung cancer. However, only small portion of patients respond to anti-PD-L1/PD-1 therapy. Recently, it has been reported that activated CD8+ T cell-derived extracellular vesicles (EVs) inhibit fibroblastic stroma-mediated tumor progression. Additionally, elevation of exosomal PD-L1 from cancer cells is one of reasons for resistance of anti-PD-L1/PD-1 therapy. It suggests that inhibition of exosomal PD-L1 may overcome the resistance of this immunotherapy. In this study, we tried to find endogenous cytokines which suppress exosomal PD-L1 from cancer cells and further develop engineered T-cell derived exosomes containing the cytokine. This engineered T cell-derived exosomes would show two characteristics, immune modulation and inhibition of exosomal PD-L1 from cancer cells. We used a lentivirus-based cytokine library to screen for cytokines that inhibit the secretion of metastatic cancer cell derived exosomes and finally identified a cytokine. Next, we used membrane bound cytokine (MBC) platform. This platform is composed of the transmembrane domain of the cytokine-linker-PDGF receptor. We engineered T cells which express the cytokine on the surface of T cells. The engineered immune exosomes are evaluated using western blot and enzyme linked immunosorbent assay. Immune exosomes reduced the secretion of exosomes from metastatic melanoma cells and suppressed PD-L1 expression on the exosomes. Furthermore, by the immune exosomes, cytotoxic T cell activity was enhanced as shown in increase of interferon gamma, granzyme B and perforin. In this study, we first identify an endogenous cytokine which could reduce the exosomal PD-L1 in cancer cells, and engineered T cell derived therapeutic exosomes lead the increase of anti-cancer effects on melanoma. This new strategy would become a new technological breakthrough to overcome the limitation of anti-PD L1 immunotherapies.



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Educational Background & Professional Experience

2011.9.~Present	Professor	School of Chemical Engineering, Sungkyunkwan University
2005.4.~2011.8.	Associate Professor	Department of Chemical Engineering, Kyung Hee University
2004.3.~2005.3.	Postdoc	Departments of Pharmaceutics and Biomedical Engineering, Purdue University
2002.3.~2004.2.	Postdoc	Biomedical Research Center, KIST
1998.3.~2002.2.	Ph.D.	Department of Materials Science and Engineering, Gwangju Institute of Science and Technology

Research Interests

Nanomedicine, polymeric conjugates for cancer immunotherapy, therapeutic exosomes

List of Major Publications

1. Son S, Shin JM, Shin S, Kim CH, Lee JA, Ko H, Lee ES, Jung JM, Kim J, Park JH*, Repurposing macitentan with nanoparticle modulates tumor microenvironment to potentiate immune checkpoint blockade. Biomaterials 2021;276:121058.
2. You DG, Lim GT, Kwon S, Um W, Oh BH, Song SH, Lee J, Jo DG, Cho YW, Park JH*. Metabolically engineered stem cell-derived exosomes to regulate macrophage heterogeneity in rheumatoid arthritis. Sci Adv 2021;7:eabe0083.
3. Lim GT, You DG, Han HS, Lee H, Shin S, Oh BH, Pramod Kumar EK, Um W, Kim CH, Han S, Lee S, Lim S, Yoon HY, Kim K, Kwon IC, Jo DG, Cho YW, Park JH*. Bioorthogonally surface-edited extracellular vesicles based on metabolic glycoengineering for CD44-mediated targeting of inflammatory diseases. J Extracell Vesicles 2021;10:e12077.
4. Jeon J, You DG, Um W, Lee J, Kim CH, Shin S, Kwon S, Park JH*. Chemiluminescence resonance energy transfer-based nanoparticles for quantum yield-enhanced cancer phototheranostics. Science Adv 2020;6:eaz8400.
5. Um W, Ko H, You DG, Lim S, Kwak G, Shim MK, Yang S, Lee J, Song Y, Kim K, Park JH*. Necroptosis-inducible polymeric nanobubbles for enhanced cancer sonoimmunotherapy. Adv Mater 2020;32:1907953.

Jae Hyung Park

School of Chemical Engineering,
Sungkyunkwan University, Suwon
16419, Republic of Korea

Surface-modified exosomes for targeted therapy

Extracellular vesicles (EVs) are essential mediators in intercellular communication that have emerged as natural therapeutic nanomedicines for the treatment of intractable diseases. Their therapeutic applications, however, have been limited by unpredictable in vivo biodistribution after systemic administration. To control the in vivo fate of EVs, their surfaces should be properly edited, depending on the target site of action. Herein, based on bioorthogonal copper-free click chemistry (BCC), surface-edited EVs were prepared by using metabolically glycoengineered cells. First, the exogenous azide group was generated on the cellular surface through metabolic glycoengineering (MGE) using the precursor. Next, PEGylated hyaluronic acid, capable of binding specifically to the CD44-expressing cells, was labelled as the representative targeting moiety onto the cell surface by BCC. The surface-edited EVs effectively accumulated into the target tissues of the animal models with rheumatoid arthritis and tumour, primarily owing to prolonged circulation in the bloodstream and the active targeting mechanism. Overall, these results suggest that BCC combined with MGE is highly useful as a simple and safe approach for the surface modification of EVs to modulate their in vivo fate.

PLENARY SESSION III

Chair 김광표 | 경희대학교

임상 관점에서 본 소포외소포체 연구
방오영 | 삼성서울병원



Bang Oh Young

Affiliation CEO, S&E Bio, Department of Neurology, Samsung Medical Center

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Educational Background & Professional Experience

2019-Present	대표	(주)에스엔이바이오
2006-Present	교수	성균관대학교 의과대학 신경과
2000-2006	조교수	아주대학교 의과대학 신경과
1992		연세대학교 의과대학 졸업

Research Interests

1. Neuroimaging and artificial intelligence - Clinical studies
2. Stem cells and exosome therapeutics - Preclinical and clinical studies
3. Stroke risk factors and biomarkers - Clinical studies

List of Major Publications

1. Lee J, Chang WH, Chung JW, Kim SK, Lee JS, Sohn SI, Kim YH, Bang OY; STARTING-2 Collaborators. Efficacy of Intravenous Mesenchymal Stem Cells for Motor Recovery After Ischemic Stroke: A Neuroimaging Study. Stroke. 2021 Sep 29;STROKEAHA121034505.
2. Chung JW, Chang WH, Bang OY, Moon GJ, Choi EH, Kim SJ, Kim SK, Lee JS, Sohn SI, Kim YH, as STARTING-2 collaborators. Efficacy and safety of intravenous mesenchymal stem cells for ischemic stroke. Neurology, 2021 Feb 16;95(7) e1023
3. Bang OY, Kim EH. Mesenchymal Stem Cell-Derived Extracellular Vesicle Therapy for Stroke: Challenges and Progress. Front Neurol. 2019 Mar 12;10:211.
4. Moon GJ, Sung JH, Kim DH, Kim EH, Cho YH, Son JP, Cha JM, Bang OY. Application of Mesenchymal Stem Cell-Derived Extracellular Vesicles for Stroke: Biodistribution and MicroRNA Study. Transl Stroke Res. 2018 Oct 19.
5. Chung JW, Cho YH, Ahn MJ, Lee MJ, Kim GM, Chung CS, Bang OY. Association of Cancer Cell Type and Extracellular Vesicles With Coagulopathy in Patients With Lung Cancer and Stroke. Stroke. 2018 May;49(5):1282-1285
6. Cha JM, Shin EK, Sung JH, Moon GJ, Kim EH, Cho YH, Park HD, Bae H, Kim J, Bang OY. Efficient scalable production of therapeutic microvesicles derived from human mesenchymal stem cells. Sci Rep. 2018 Jan 19;8(1):1171.
7. Cha JM, Park H, Shin EK, Sung JH, Kim O, Jung W, Bang OY, Kim J. A novel cylindrical microwell featuring inverted-pyramidal opening for efficient cell spheroid formation without cell loss. Biofabrication. 2017 Aug 14;9(3):035006
8. Cha JM, Park H, Shin EK, Sung JH, Kim O, Jung W, Bang OY, Kim J. A novel cylindrical microwell featuring inverted-pyramidal opening for efficient cell spheroid formation without cell loss. Biofabrication. 2017 Aug 14;9(3):035006
9. Lee JS, Hong JM, Moon GJ, Lee PH, Ahn YH, Bang OH, for the STARTING collaborators. A long-term follow-up study of intravenous autologous mesenchymal stem cell transplantation in patients with ischemic stroke. Stem Cells. 2010 Jun;28(6):1099-106.

Bang Oh Young

CEO, S&E Bio, Inc.

Professor, Samsung Medical Center,
Sungkyunkwan University

A journey of exosome research as a clinical scientist

임상 관점에서 본 소포외소포체 연구

Stroke is the leading cause of death and physical disability among adults. Over the past 20 years, major clinical trials of therapeutic agents for stroke have failed. Accordingly, new strategies to overcome the limitations of current therapeutics are required. The importance of the use for biomarkers for selection of optimal candidate patients and demonstration of molecular mechanisms of the treatment and the need for neuroprotective agents with multiple therapeutic mechanisms have emerged in the stroke field. Recently the diagnostics and therapeutics of extracellular vesicle (EV) have been introduced. Therefore, I have conducted biomarker researches using circulating EVs in stroke patients and tested the efficacy of the application of stem cell-derived EVs in animal models of stroke. In this talk, I would like to briefly discuss my research journey, results of recent researches, and the efforts for commercialization of EV theranostics.

PARALLEL SESSION III

임상/치료

Chair 박지호 | KAIST

Cell-derived nanovesicles for theranostic programming

성학준 | 연세대병원

Therapeutic approaches of exosomes and exosome-mimetics

박중훈 | 서울대학교

A diagnostic and therapeutic value of exosome and its derivatives in the incurable diseases

홍성희 | 고려대학교

Mesenchymal stem cell-derived extracellular vesicles for the treatment of neonatal intractable disorders

장윤실 | 삼성서울병원



Hak-Joon Sung

Affiliation Dept. of Medical Engineering, Yonsei University College of Medicine

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Educational Background & Professional Experience

2018-Present	Professor (*21-Chair)	Dept. Of Medical Engineering, Yonsei University College of Medicine
2016-2018	Distinguished Professor	Yonsei University College of Medicine
2009-2018	Faculty member	School of Engineering/College of Medicine, Vanderbilt University
2006-2009	R&D team leader	NJ Center for Biomaterials, Princeton

Research Interests

Cell-derived theranostic; Shape memory medical polymer & device; Implantable Biochip

List of Major Publications

1. (Corresponding) "Cancer Patient Tissueoid with Self-Homing Nano-Targeting of Metabolic Inhibitor." 2021 Adv Sci. 2021 Oct 18;e2102640. doi: 10.1002/advs.202102640.
2. (Corresponding) "Cell-Membrane-Derived Nanoparticles with Notch-1 Suppressor Delivery Promote Hypoxic Cell-Cell Packing and Inhibit Angiogenesis Acting as a Two-Edged Sword" 2021 Advanced Materials. 2021; 33(40): 2101558. DOI: 10.1002/adma.202101558
3. (Corresponding) Dilation-Responsive Microshape Programing Prevents Vascular Graft Stenosis, 2021 Small, Epub 17 March 2021, <https://doi.org/10.1002/sml.202007297>.
4. (Corresponding) Hormone Autocrination by Vascularized Hydrogel Delivery of Ovary Spheroids to Rescue Ovarian Dysfunctions. 2021 Science Advances 2021;7(18):eabe8873.
5. (Corresponding) "Anti-Atherogenic Effect of Stem Cell Nanovesicles Targeting Disturbed Flow Sites" 2020 Small, 2020 April; 16(16): 2000012
6. (Corresponding) "Microchannel network hydrogel induced ischemic blood perfusion connection." 2020 Nature Communication 2020; 11: 615.

Hak-Joon Sung

Department of Medical Engineering,
Yonsei University College of Medicine

Cell-derived nanovesicles for theranostic programining

Cell-derived nanovesicles (NVs) serve as a reliable platform for theranostic programining because i) their cell membrane-like properties at a nanoscale can prolong the systemic circulation time and thereby enhance endocytosis or membrane fusion-mediated intracellular delivery; ii) Specific cell-derived components reduce inflammatory dysfunctional activities^[29] and avoid host immune rejection, thereby supporting their potential as therapeutic and delivery vehicles, respectively; iii) concern regarding the possible differentiation of stem cells can be avoided using NVs; and iv) NVs preserve transfection signatures from source cells. These advantages were utilized to validate the anti-atherogenic effect of stem cell NVs targeting disturbed flow target (*15 ACS Nano; *20 Small). However, since therapeutic power and side effects due to internal vesicular contents (e.g. miRNA) can be conteroversal, the concepts of global positioning system (GPS) and multi-organ targeting with touch-on activation of therapeutic signaling were applied to operate the ideal vascular nanotheranostics by displaying a peptide as a potent theranostic power (under review). On the other hand, NVs were used as a membrane-derived mediator to promote cell-cell interactions by bridging membrane-membrane contacts. The nanoscale size allowed for tight bridging of two membranes to promote cell-cell packing; membrane characteristics to express cell-cell adhesion molecules (e.g., cadherin) for executing the bridging function at a high resolution; and the membrane could be modified to display a functional molecule, allowing additional functions to be programmed. Displaying anti-angiogenic peptide to NVs executed a two-edged sword function of inducing hypoxic cell-cell packing, followed by suppressing angiogenesis to promote laryngeal cancer death and chondrogenesis simultaneously (*21 Advanced Materials). Lastly, since cancer cells are capable of targeting their own type of cells, the breakthrough strategy of self-homing nano-targeting was approached using the reciprocal interaction of cell membranes as a key mediator of cancer cell-cell interactions. This function was potentiated using cancer cell-derived nanovesicles (CaNV), owing to i) the same membrane characteristics as target cancer cells; ii) inanimation to prevent living cell-mediated side effects; and iii) effective systemic delivery similar to exosomes. Moreover, the loading of anti-cancer drugs into CaNV represented a "Trojan horse" strategy to inhibit cancer action synergistically with the self-homing nano-targeting approach (*21 Advanced Science).



Joonghoon Park

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Educational Background & Professional Experience	2016	Principal Investigator	LG Life Sciences
	2009	PhD	University of Connecticut
	2000	MS	Seoul National University
	1998	BS	Seoul National University
Research Interests	Systems pharmacology lab is focusing on a systematic understanding of the function of genes on metabolic phenotypes and conducts research on the discovery and evaluation of novel pharmacological perturbagens to control them.		
List of Major Publications	<div>1. Zhang et al. PROKR1 delivery by cell-derived vesicles restores the myogenic potential of Prokr1-deficient C2C12 myoblasts. Nanomedicine. 2021 Oct;37:102448</div> <div>2. Kim et al. Cellhesion VP enhances the immunomodulating potential of human mesenchymal stem cell-derived extracellular vesicles. Biomaterials. 2021 Apr;271:120742</div> <div>3. Mok et al. Prokineticin receptor 1 ameliorates insulin resistance in skeletal muscle. FASEB J. 2021 Feb;35(2):e21179</div> <div>4. Park et al. 8-OxoG in GC-rich Sp1 binding sites enhances gene transcription in adipose tissue of juvenile mice. Sci Rep. 2019 Oct 30;9(1):15618</div> <div>5. Park et al. Connectivity mapping of angiotensin-PPAR interactions involved in the amelioration of non-alcoholic steatohepatitis by Telmisartan. Sci Rep. 2019 Mar 8;9(1):4003</div> <div>6. Park et al. Disruption of G0/G1 switch gene 2 (G0S2) reduced abdominal fat deposition and altered fatty acid composition in chicken. FASEB J. 2019 Jan;33(1):1188-1198</div> <div>7. Choi et al. Integrative analysis of oncogenic fusion genes and their functional impact in colorectal cancer. Br J Cancer. 2018 Jul;119(2):230-240</div>		

Eun Seo Kim¹, Chunjuan Zhang¹, Jongsoo Mok², Yeonwoo Seong², Seo Yeon Jo¹, Katsuhiko Kida³, Tatsuro Kanaki³, Masato Horikawa³, Hui-Chong Lau⁴, Dayeon Kim⁴, Junsik Yoon⁴, Seung Wook Oh⁴, Kyung-Hee Kim⁵, Tae Min Kim^{1,2}, Tae Sub Park^{1,2}, Joonghoon Park^{1,2}

¹Department of International Agricultural Technology, Graduate School of International Agricultural Technology, Seoul National University, Republic of Korea, ²Institute of GreenBio Science and Technology, Seoul National University, Republic of Korea, ³Nissan Chemical Corporation, Japan, ⁴Biodrone Research Institute, MDimune Inc., Republic of Korea, ⁵Proteomics Core Facility, Research Core Center, Research Institute, National Cancer Center, Republic of Korea

Therapeutic approaches of exosomes and exosome-mimetics

Mesenchymal stem cell (MSC) transplantation is a promising therapy for regenerative medicine. However, MSCs grown under two-dimensional (2D) culture conditions differ significantly in cell characteristics from those in the body, with downregulated stemness genes and differential secretion of paracrine factors. We evaluated the effect of 3D culture using Cellhesion VP, a water-insoluble material composed of chitin-based polysaccharide fibers, on the characteristics of human Wharton's jelly-derived MSCs (hMSCs). Cellhesion VP significantly increased cell proliferation after retrieval. Transcriptome analyses suggested that genes involved in cell stemness, migration ability, and extracellular vesicle (EV) production were enhanced by 3D culture. Subsequent biochemical analyses showed that the expression levels of stemness genes including OCT4, NANOG, and SSEA4 were upregulated and migration capacity was elevated in 3D-cultured hMSCs. In addition, EV production was significantly elevated in 3D cells, which contained a distinct protein profile from 2D cells. Gene and drug connectivity analyses revealed that the 2D and 3D EVs had similar functions as immunomodulators; however, 3D EVs had completely distinct therapeutic profiles for various infectious and metabolic diseases based on activation of disease-associated signaling pathways. Therefore, EVs from Cellhesion VP-primed hMSCs offer a new treatment potential for immune and metabolic diseases. However, the low yield and inconsistent composition of active ingredients in EVs are challenges to be resolved to facilitate clinical applications of them. Cell-derived vesicles (CDVs) have been investigated as an alternative to EVs. We generated CDVs from Prokineticin receptor 1 (PROKR1) overexpressing HEK293T cells using micro-extrusion. More than 60 billion PROKR1-enriched CDV (PROKR1tg CDVs) particles with canonical exosome properties were recovered from 107 cells. With 25 µg/mL of PROKR1tg CDVs, we observed delivery of PROKR1 proteins, significant reduction of apoptosis, and myotube formation in C2C12Prokr1-/- myoblasts that have lost their myogenic potential but underwent apoptosis following myogenic commitment. Expression levels of early and late myogenic marker genes and glucose uptake capacity were restored to equivalent levels with wild-type control. Furthermore, PROKR1tg CDVs were accumulated in soleus muscle comparable to the liver without significant differences. Therefore, CDVs obtained from genetically engineered cells appear to be an effective method of PROKR1 protein delivery and offer promise as an alternative therapy for muscular dystrophy. EVs or CDVs have differentiated strengths from existing drugs in that they can induce the therapeutic effects by reconstituting signaling pathways or cellular networks through delivery of a set of signaling molecules beyond a single active ingredient. Therefore, EVs/CDVs with improved yield and safety promise high potential as a new type of therapeutics.



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Educational Background & Professional Experience

2021-Present	Dean	College of Health Science, Korea University
2015	Visiting Professor	Department of Genetics, Yale School of Medicine
2009-Present	Professor	School of Biosystems and Biomedical Sciences, Korea University
2004-2008	Post-Doctor	Harvard Medical School

Research Interests

Development of the therapeutics for cancers and neurodegenerative diseases using exosomes, exosome-derivatives and neural stem cells

List of Major Publications

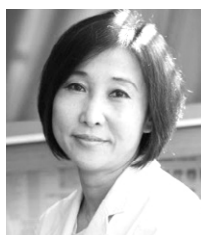
1. Jeong H et al. GCC2 as a New Early Diagnostic Biomarker for Non-Small Cell Lung Cancer. *Cancers* 2021, 13, pp-pp.
2. Shin, H et al. Early-Stage Lung Cancer Diagnosis by Deep Learning-Based Spectroscopic Analysis of Circulating Exosomes. *Acs Nano* 2020, 14, 5435-5444.
3. Choi KA et al. Tissue inhibitor of metalloproteinase proteins inhibit teratoma growth in mice transplanted with pluripotent stem cells. *Stem Cells* 2019, 38, 516-529.
4. Park, J et al. Exosome Classification by Pattern Analysis of Surface-Enhanced Raman Spectroscopy Data for Lung Cancer Diagnosis. *Anal. Chem.* 2017, 89, 6695-6701.
5. Park HS et al. Generation of induced pluripotent stem cells without genetic defects by small molecules. 2015. *Biomaterials* 39, 47-58.

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Seulbee Lee¹, Jik-han Jung⁵,
Hyunku Shin⁶, Ka-Won Kang⁷,
Yu Hua Quan^{4,9}, Jewon Yu⁸,
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A diagnostic and therapeutic value of exosome and its derivatives in the incurable diseases

No specific markers have been identified to detect non-small cell lung cancer (NSCLC) cell-derived exosomes circulating in the blood. Here, we report a new biomarker that distinguishes between cancer and non-cancer cell-derived exosomes and its knockdown inhibited the tumorigenicity of lung cancer. Exosomes isolated from patient plasmas at various pathological stages of NSCLC, NSCLC cell lines, and human pulmonary alveolar epithelial cells using size exclusion chromatography were characterized. The GRIP and coiled-coil domain-containing 2 (GCC2) protein, involved in endosome-to-Golgi transport, was identified by proteomics analysis of NSCLC cell line-derived exosomes. GCC2 protein levels in the exosomes derived from early-stage NSCLC patients were higher than those from healthy controls. Receiver operating characteristic curve analysis revealed the diagnostic sensitivity and specificity of exosomal GCC2 to be 90 % and 75 %, respectively. A high area under the curve of 0.844 confirmed that GCC2 levels could effectively distinguish the exosomes. Notably, shRNA-mediated GCC2 knockdown altered mesenchymal-to-epithelial gene expression levels, in vitro cancer cell growth, motility, and death, as well as in vivo suppression of tumor formation. These results demonstrate GCC2 as a promising early diagnostic biomarker for NSCLC and a therapeutic target for cancer treatment. Furthermore, since stem cell derived exosomes has emerged as a new strategy for treating immune disorders accompanying acute inflammatory reactions, we examined their possibility as a biomaterial source for immune modulating therapy using stem cell-derived exosomes. Our results show that exosomes can act as potential mediators to inhibit the inflammatory reactions, suggesting that the stem cell-derived exosomes could be used as a new therapeutic biomaterial for the immune-mediated inflammatory diseases, such as autoimmune disorders, cerebrovascular diseases and cancers.



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Sungkyunkwan University School of Medicine

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Educational Background & Professional Experience

2019-Present	Director	Stem Cell & Regenerative Medicine Institute, Samsung Medical Center
2012-Present	Professor	Samsung Advanced Institute for Health Sciences & Technology, Sungkyunkwan University
2009-Present	Professor	Sungkyunkwan University School of Medicine
2004	Visiting Scholar	University of California, San Francisco(UCSF), USA
1995/1996-Present	Fellow/Staff	Samsung Medical Center
1989/1990/1994	Intern/Resident/Fellow	Seoul National University Hospital

Research Interests

Mesenchymal stem cells, Extracellular vesicles, Exosome,
Newborn infant, Premature infant, Rare or incurable diseases

List of Major Publications

1. Ahn SY et al. Stem cell restores thalamocortical plasticity to rescue cognitive deficit in neonatal intraventricular hemorrhage. *Exp Neurol* 2021;342:113736
2. Ahn SY et al. BDNF-overexpressing engineered mesenchymal stem cells en-hances their therapeutic efficacy against severe neonatal hypoxic ischemic brain injury. *Int J Mol Sci* 2021;22:11395
3. Kim S et al. Reactive microglia and astrocytes in neonatal intraventricular hemorrhage model are blocked by mesenchymal stem cells. *Glia* 2020;68:178-192
4. Ahn SY et al. Mesenchymal stem cell therapy for intractable neonatal disorders. *Pediatr Neonatol.* 2021;62 Suppl 1:S16-S21
5. Ahn SY et al. Vascular endothelial growth factor mediates the therapeutic efficacy of mesenchymal stem cell-derived extracellular vesicles against neonatal hyperoxic lung injury. *Exp Mol Med* 2018;50(4):1-12

Yun Sil Chang,
So Yoon Ahn,
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Won Soon Park

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Medical Center, Sungkyunkwan
University School of Medicine,
Stem Cell and Regenerative Medicine
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Seoul, Korea*

Mesenchymal stem cell-derived extracellular vesicles for the treatment of neonatal intractable disorders

Previously, we have reported that the MSCs could be a therapeutic option for the various neonatal disorders such as braonchopulmonary dysplasia and severe intraventricular hemorrhage, which are devastating and intractable neoontal disorders especially in tiny preterm infants. On the other hand, recent studies have shown that mesenchymal stem cell (MSC)-derived extracellular vesicles (EVs) could recapitulate the therapeutic efficacy of parent MSCs in various disorders such as cardiovascular disease, lung injury, acute kidney injury through the transfer of mRNA, miRNA, and proteins. therefore, we have recently shown that the use of MSC-derived EVs is a promising new therapeutic modality since this therapy is cell-free and thus may bypass concerns associated with viable MSC treatmen through direct transport extracellular messages and mediate cell-to-cellcommunication. Here, we will present the preclinical data regarding therapeutic efficacy and its mechanisms of MSC-EVs in bronchoupulmonary dysplasia and intraventricular hemorrhage in the neonatal animal model.

PARALLEL SESSION III

영상/치료

Chair 노태영 | 포스텍

Programmed Exosome Fusion For Artificial Organelles

조윤경 | UNIST

Taking Stem Cell EV Therapeutics From Bench to Bed Side

조용우 | 한양대학교

Highly stable microbubbles for enhanced cancer diagnosis and therapy through exosome hybridization

김현철 | 서강대학교

Neutrophil-derived trail is a proinflammatory subtype of neutrophil-derived extracellular vesicles

홍장원 | 경북대학교



Yoon-Kyoung Cho

Affiliation Biomedical Engineering, UNIST, Center for Soft and Living Matter, IBS

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Educational Background & Professional Experience

2015 - Present	Group leader	Center for soft and Living Matter, IBS
2008 - Present	Assist., Assoc., Full Prof.	Biomedical Engineering, UNIST
1999 - 2008	Senior Researcher	Samsung Advanced Institute of Technology (SAIT)
1994 - 1999	Ph.D.	Materials Sci. & Eng. Univ. of Illinois at Urbana- Champaign (UIUC), USA

Research Interests

Liquid biopsy; Lab-on-a-disc; ExoDisc; EV engineering; Tumor microenvironment; Extracellular biomarkers; System analysis of cellular communication. <http://fruits.unist.ac.kr>

List of Major Publications

1. Sumit Kumar, et al. "Programmed exosome fusion for energy generation in living cells", Nature Catalysis, 4, 763-774 (2021) Journal Cover
2. Junyoung Kim, et al. "Three-dimensional Human Liver-chip Emulating Pre-metastatic Niche Formation by Breast Cancer-derived Extracellular Vesicles", ACS Nano, 14, 11, 14971-14988, (2020) Journal cover, BRIC Top 5 research award
3. Vijaya Sunkara, et al. "Fully automated, label-free isolation of extracellular vesicles from whole blood for cancer diagnosis and monitoring", Theranostics, 9, 1851-1863, (2019)
4. Sumit Kumar, et al. Human platelet membrane functionalized microchips with plasmonic codes for cancer detection, Advanced Functional Materials, 1902669, (2019) Journal cover
5. Hyun-Kyung Woo, et al. "Exodisc for rapid, size-selective, and efficient isolation and analysis of nanoscale extracellular vesicles from biological samples, ACS Nano, 11 (2), 1360-1370, (2017)

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Mamata Karmacharya^{1,3},
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Yongjun Choi^{1,2},
Junyoung Kim^{1,2}, InUn Kim¹,
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¹Center for Soft and Living Matter, Institute for Basic Science (IBS), Ulsan 44919 (South Korea), ²Department of Biomedical Engineering, Ulsan National Institute of Science and Technology (UNIST), Ulsan 44919 (South Korea), ³Department of Chemical Engineering, Ulsan National Institute of Science and Technology (UNIST), Ulsan 44919 (South Korea)

Programmed Exosome Fusion For Artificial Organelles

Despite tremendous efforts to create artificial organelles as cellular implants, their application in live cells and tissues are very few owing to the limitations in terms of delivery, cellular uptake, stability, biocompatibility and biodegradability of the synthetic materials. The natural analogues of nanoreactors made of biomembranes, such as exosomes, play an active role in intercellular communication and are recognized as a promising source of diagnostic biomarkers and therapeutic agents. In this study, we used exosomes as a natural compartment that allowed encapsulation of multiple exogenous reagents to facilitate enzymatic reaction within the cell. Using supramolecular chemistry-based fusion of exosomes enabled in cell-sized droplet microreactors, we could demonstrate controlled fusion of exosomes that act as nanoreactors for biocatalytic cascade reactions. Furthermore, we engineered the exosome membrane proteins and encapsulated multiple reagents and enzymes to form a minimal electron transport chain capable of energy generation (ATP production) for many hours after uptake into living cells. The artificial organelle made of all-natural ingredients showed efficient penetration into the core of tissue spheroids and supplied ATP and reduced ROS levels. We believe that our study makes a significant contribution to the literature because this strategy could be used to develop new biomaterials, synthetic cell networks, miniaturized bioreactors, implanted theragnostic devices, and responsive soft-matter microsystems by bridging the bottom-up synthetic biology and bio-inspired engineering area.



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Educational Background & Professional Experience	2006–Present	Professor	Hanyang University ERICA
	2016–Present	CEO	ExoStemTech, Inc
	2005–2006	Research Assistant Professor	University of Ulsan College of Medicine
	1996–2000	PhD	Seoul National University
Research Interests	Extracellular vesicles, exosomes, drug delivery systems, tissue engineering, nanobiotechnology		
List of Major Publications	<div>1. Extracellular vesicles from adipose tissue-derived stem cells alleviate osteoporosis through osteoprotegerin and miR-21–5p. J. Extracell Vesicles, 10 (12), e12152, 2021.</div> <div>2. Metabolically engineered stem cell-derived exosomes to regulate macrophage heterogeneity in rheumatoid arthritis. Sci. Adv., 7 (23), eabe0083, 2021.</div> <div>3. Cell reprogramming using extracellular vesicles from differentiating stem cells into white/beige adipocytes. Sci. Adv., 6 (13), eaay6721, 2020.</div> <div>4. Small extracellular vesicles from human adipose-derived stem cells attenuate cartilage degeneration. J. Extracell. Vesicles 9 (1), 1735249, 2020.</div> <div>5. Human adipose stem cell-derived extracellular nanovesicles for treatment of chronic liver fibrosis, J. Control. Release, 320, 328–336, 2020.</div>		

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²ExoStemTech Inc., Ansan 15588, Republic of Korea

Taking Stem Cell EV Therapeutics From Bench to Bed Side

Loss or damage of tissues that result from traumatic injury and tumor resection need reconstructive approaches, such as cell/tissue transplantation or tissue engineering. Although stem cell-based therapies have clear beneficial effects on tissue regeneration, there are still a number of concerns, such as limited survival and the reduced regenerative capacity of engrafted stem cells, as well as immune-mediated rejection. Stem cells secrete exosomes containing various proteins and genetic materials, which could act as critical signals of cell-to-cell communication for tissue regeneration. Stem cell exosomes provide a cell-free therapeutic approach for regeneration of various tissues. Exosomes were isolated from conditioned media during proliferation or differentiation of human adipose derived stem cells (hASC) into adipogenesis, chondrogenesis, or osteogenesis. The tissue regeneration potency of exosomes was analyzed in different animal models. Exosomes contained various cytokines and microRNAs related to each tissue development. New tissue formations were observed in the exosome injection sites of animal models. Based on the results from our laboratory in Hanyang University ERICA, we founded ExoStemTech Inc. in 2016. ExoStemTech is now developing several exosome therapeutics for treatment of various human diseases such as osteoarthritis, liver/lung fibrosis, osteoporosis, diabetes/obesity etc. We are about to enter clinical trials of some exosome products. In this presentation, we hope to discuss several important issues for entry to clinical trials of exosome therapy such as mass production, quality control, CMC documentation, pre-clinical experiments, etc.

References

1. Cell reprogramming using extracellular vesicles from differentiating stem cells into white/beige adipocytes, Sci. Adv., 6, eaay6721, 2020.
2. Small extracellular vesicles from human adipose-derived stem cells attenuate cartilage degeneration, J. Extracell. Vesicles, 9, 1, 1735249, 2020.
3. Human adipose stem cell-derived extracellular nanovesicles for treatment of chronic liver fibrosis, J. Control. Release, 320, 328–336, 2020.
4. Functional recovery in photo-damaged human dermal fibroblasts by human adipose-derived stem cell extracellular vesicles, J. Extracell. Vesicles, 8, 1, 1565885, 2019.

Keywords

Exosomes, Extracellular vesicles, Stem cells, Cell-free therapy, Osteoarthritis, Liver fibrosis



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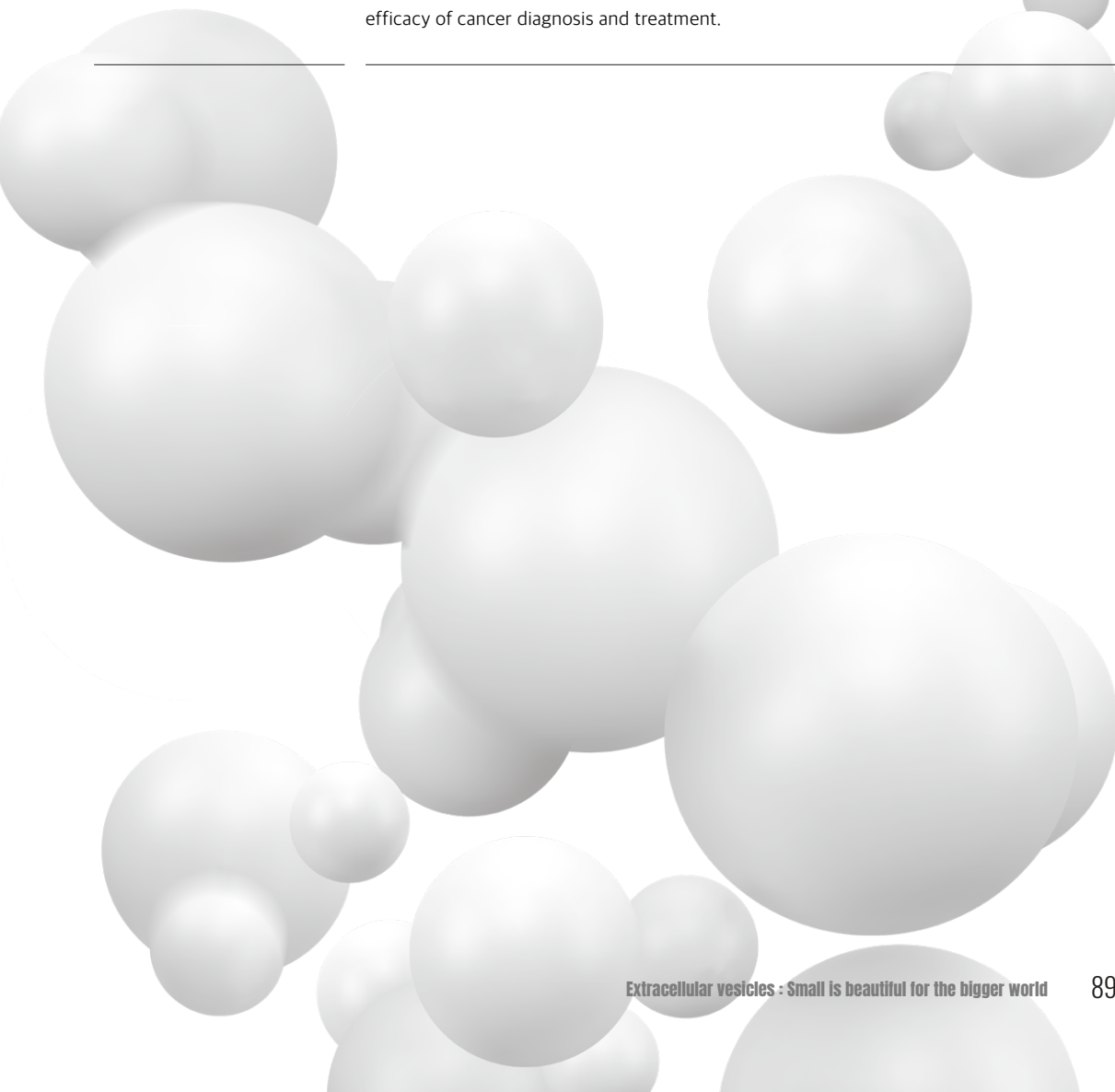
Educational Background & Professional Experience	2009–Present	Professor	Department of Chemical and Biomolecular Engineering, Sogang University
	2016–2018	Visiting Scholar	Biomedical Engineering, University of Texas–Austin
	2007–2009	Research Assistant Professor	Duke University Medical Center
	2004–2007	Postdoctoral Fellow	National Institutes of Health
Research Interests	Drug Delivery System, Gene Therapy		
List of Major Publications	1. Han H, et al. Focused ultrasound-triggered chemo–gene therapy with multifunctional nanocomplex for enhancing therapeutic efficacy. J Control Release 2020;322:346–356		
	2. Jang Y, et al. Exosome–based photoacoustic imaging guided photodynamic and immunotherapy for the treatment of pancreatic cancer. J Control Release 2021;330:293–304		
	3. Kim D, et al. Development and evaluation of an ultrasound-triggered microbubble combined transarterial chemoembolization (TACE) formulation on rabbit VX2 liver cancer model. Theranostics 2021;11:79–92		
	4. Lee H, et al. Development and evaluation of a CEACAM6–targeting theranostic nanomedicine for photoacoustic–based diagnosis and chemotherapy of metastatic cancer. Theranostics 2018;8:4247–4261		

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¹Department of Chemical and Biomolecular Engineering, Sogang University, 35 Baekbeom-ro, Mapo-gu, Seoul 04107, South Korea
²Department of Electronic Engineering, Sogang University, 35 Baekbeom-ro, Mapo-gu, Seoul 04107, South Korea
³Biomedical Research Institute & Department of Radiology, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul, 03080, Republic of Korea
⁴Department of Biomedical Engineering, Sogang University, 35 Baekbeom-ro, Mapo-gu, Seoul 04107, South Korea

Highly stable microbubbles for enhanced cancer diagnosis and therapy through exosome hybridization

Microbubbles (MBs) are widely used as ultrasound contrast agent and has recently been actively investigated as drug delivery carriers. However, the short half-life in blood system due to the low stability of MBs is a bottleneck in ultrasound diagnosis and drug delivery using MBs. The exosome, a type of extracellular vesicles released from all kinds of cells, has a stable membrane and a preferentially targeting ability for its original cell. In this study, exosome-embedded microbubbles (Exo-MBs) were developed to overcome the limitation mentioned above by embedding the exosome membrane proteins into MBs. As a result, the stability of Exo-MBs is improved over the conventional MBs. On the same principle that microbubbles arecavitated and self-assembled into liposomes under the exposure of ultrasound, Exo-MBs are also self-assembled into exosome-embedded liposomes (Exo-Lipos) at ultrasound irradiation. The Exo-Lipos showed favorable accumulation properties for the target cells because of the enhanced stability from embedded exosome membrane proteins. As a result, the improved stability and targeting ability of Exo-MBs enhanced the efficacy of cancer diagnosis and treatment.





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Educational Background & Professional Experience

2021-Present	Associate Professor	Kyungpook National University
2016-2021	Assistant Professor	Kyungpook National University
2012-2016	Research Professor	College of Medicine, Hallym University
2009-2011	Medical officer, captain	The Armed Forces Medical Research Center
2007-2011	PhD in pharmacology	College of Medicine, Hallym University
2005-2007	MS in pharmacology	College of Medicine, Hallym University
1998-2005	MD in medicine	College of Medicine, Hallym University

Research Interests

Neutrophils are the most abundant leukocytes and comprise the first line of defense in the innate immune system. Neutrophils circulate in blood vessels and play a role in immune surveillance by recognizing and neutralizing invading pathogens. Our lab is interested in the phenotype and function of neutrophils in various immunologic environments.

List of Major Publications

1. Jun-Kyu Kim, Young-Jin Youn, Yu-Bin Lee, Sun-Hwa Kim, Dong-Keun Song, Min-Sang Shin, Hee Kyung Jin, Jae-sung Bae, Sanjeeb Shrestha, Chang-Won Hong*, Development of drug-delivery system using dHL-60-derived extracellular vesicles, Scientific reports, 11, 8289 (2021), *corresponding author

2. Young-Jin Youn, Yu-Bin Lee, Sun-Hwa Kim, Hee Kyung Jin, Jae-sung Bae, Chang-Won Hong, Nucleocapsid and spike proteins of SARS-CoV-2 drive neutrophil extracellular trap formation, Immune Network, 23;21(2):e16 (2021) *corresponding author

3. Young-Jin Youn, Sanjeeb Shrestha, Yu-Bin Lee, Jun-Kyu Kim, Jee Hyun Lee, Keun Hur, Nanda Maya Mali, Sung-Wook Nam, Sun-Hwa Kim, Dong-Keun Song, Hee Kyung Jin, Jae-sung Bae, Chang-Won Hong*, Neutrophil-derived trail is a proinflammatory subtype of neutrophil-derived extracellular vesicles, Theranostics, 2021; 11(6):2770-2787, *corresponding author

4. Chang-Won Hong, Extracellular vesicles of neutrophils, Immune Netw. 2018 Dec 7;18(6):e43

5. So Young Park, Sanjeeb Shrestha, Young-Jin Youn, Jun-Kyu Kim, Shin-Yeong Kim, Hyun Jung Kim, So-Hee Park, Won-Gyun Ahn, Shin Kim, Myung Goo Lee, Ki-Suck Jung, Yong Bum Park, Eun Kyung Mo, Yousang Ko, Suh-Young Lee, Yونسuck Koh, Myung Jae Park, Dong-Keun Song, Chang-Won Hong*, Autophagy primes neutrophils for neutrophil extracellular trap formation during sepsis, Am J Respir Crit Care Med. 2017 Sep 1;196(5):577-589. *corresponding author

Young-Jin Youn¹, Sanjeeb Shrestha¹, Yu-Bin Lee¹, Jun-Kyu Kim¹, Jee Hyun Lee², Keun Hur², Nanda Maya Mali³, Sung-Wook Nam⁴, Sun-Hwa Kim¹, Sunwoong Lee⁴, Dong-Keun Song⁵, Hee Kyung Jin^{6,7}, Jae-sung Bae^{1,7}, Chang-Won Hong¹

¹Department of Physiology, School of Medicine, Kyungpook National University, Daegu, 41944, Republic of Korea. ²Department of Biochemistry and Cell Biology, School of Medicine, Kyungpook National University, Daegu, 41944, Republic of Korea. ³Department of Anatomy, School of Medicine, Kyungpook National University, Daegu, 41944, Republic of Korea. ⁴Department of Molecular Medicine, School of Medicine, Kyungpook National University, Daegu, 41944, Republic of Korea. ⁵Department of Pharmacology, College of Medicine, Hallym University, Chuncheon, 24252, Republic of Korea. ⁶Department of Laboratory Animal Medicine, College of Veterinary Medicine, Kyungpook National University, Daegu, 41944, Republic of Korea. ⁷Stem Cell Neuroplasticity Research Group, Kyungpook National University, Daegu, 41944, Republic of Korea.

Neutrophil-derived trail is a proinflammatory subtype of neutrophil-derived extracellular vesicles

Extracellular vesicles (EVs) are membrane-derived vesicles that mediate intercellular communications. Neutrophils produce different subtypes of EVs during inflammatory responses. Neutrophil-derived trails (NDTRs) are generated by neutrophils migrating toward inflammatory foci, whereas neutrophil-derived microvesicles (NDMV) are thought to be generated by neutrophils that have arrived at the inflammatory foci. However, the physical and functional characteristics of neutrophil-derived EVs are incompletely understood. In this study, we aimed to investigate the differences between NDTRs and NDMVs. The generation of neutrophil-derived EVs were visualized by live-cell fluorescence images and the physical characteristics were further analyzed using nanotracking analysis assay, scanning electron microscopic analysis, and marker expressions. Functional characteristics of neutrophil-derived EVs were analyzed using assays for bactericidal activity, monocyte chemotaxis, phenotype polarization of macrophages, and miRNA sequencing. Finally, the effects of neutrophil-derived EVs on the acute and chronic inflammation were examined in vivo. Both EVs share similar characteristics including stimulators, surface marker expression, bactericidal activity, and chemoattractive effect on monocytes via MCP-1. However, the integrinmediated physical interaction was required for generation of NDTRs whereas NDMV generation was dependent on PI3K pathway. Interestingly, NDTRs contained proinflammatory miRNAs such as miR-1260, miR-1285, miR-4454, and miR-7975, while NDMVs contained anti-inflammatory miRNAs such as miR-126, miR-150, and miR-451a. Although both EVs were easily uptaken by monocytes, NDTRs enhanced proinflammatory macrophage polarization whereas NDMVs induced anti-inflammatory macrophage polarization. Moreover, NDTRs showed protective effects against lethality in a murine sepsis model and pathological changes in a murine chronic colitis model. These results suggest that NDTR is a proinflammatory subtype of neutrophil-derived EVs distinguished from NDMV.

KSEV 2021 POSTER SESSION

기초 P01 - P19
진단 P20 - P26
치료 P27 - P28

P 01

Sunyoung Park¹, Nilsu Donmez¹,
[Yonghyun Kwon¹](#), Haeun Yu¹,
Kyung-A Hyun¹, Hogyong Gwak¹,
Hyo-Il Jung^{1*}

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University, Seoul, Korea

Multi-detection of immune-mediated
extracellular vesicle and microRNA for
personalized immunotherapy of breast cancer

Understanding personalized immunity has grown essential not only to inform on tumor diagnosis and prognosis but also to drive therapeutic decisions. The new personalized diagnosis has expanded the spectrum of immunotherapies on exosomes. Exosome-containing microRNAs can contribute the most beneficial information as a promising biomarker for either early detection or monitoring. However, the compelling challenges facing the commonly used detection methods consist of sensitivity and throughput of breast cancer immunotherapy regarding multiple detections. Herein, we investigated the breast cancer diagnosis strategy achieved multi detection of cancer-cell-derived exosomal microRNA. The exosome-specific microRNA, MiR-21, and PD-L1 as an extracellular vesicle protein were simultaneously monitored by fluorescent dye-conjugated antibodies. Our simultaneous recognition approach provides an accurate and high-sensitivity diagnosis method for breast cancer.

Keywords: Extracellular vesicle, microRNA, PD-L1, Companion diagnosis, molecular beacon

P 02

[Dong Young Kim¹](#), Jea-Yong Lee,
Dae Han Lee, Hee-Jin Ahn,
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Republic of Korea,*

Analysis of Pneumonia Inhibition Efficacy of
Extracellular Vesicles Secreted by Umbilical
Cord Blood Mesenchymal Stem Cell

Pneumonia can be treated with antibiotics and antivirals that remove bacteria and viruses, but overexpression of inflammation cytokines by pneumonia contributes to acute lung injury and acute dyspnea syndrome. Therefore, the development of non-antibiotic pneumonia therapeutic agents having lung injury and anti-inflammatory effects is urgent. Mesenchymal stem cells having excellent anti-inflammatory and tissue regeneration functions can be obtained from bone marrow, adipocytes, cord blood etc. However, since the cell engraftment rate of a cell therapy agent utilizing mesenchymal stem cells differs depending on the patient, the efficacy may differ and there is a concern about side effects. The treatment of extracellular vesicles (EVs) is attracting attention as a new therapeutic method because it can reduce the shortcomings and concerns of the cell therapeutic agent while maintaining the therapeutic mechanism of the cell therapeutic agent. In this study, umbilical cord blood - mesenchymal stem cells(UCB-MSC) EV reduced inflammation-induced cytotoxicity, reduced infectious disease mediator expression levels and infectious cytokine levels, and increased autophagy activation associated with inflammasome regulation. In parallel, UCB-MSC EV promotes M2 macrophages polarization and increases the concentration of regenerative factors secreted by M2 macrophages. As results, UCB-MSC EV modulated the inflammasome by activating autophagy in inflammation-induced lung cells(B2B) to reduce the expression of pro-inflammatory mediators. In addition, tissue regeneration was promoted by regulating macrophages polarization and increasing expression of regenerative factors. Therefore, UCB-MSC EVs may be an effective strategy for non-antibiotic treatment of pneumonia.

Key words: Pneumonia, Umbilical cord blood mesenchymal stem cells, Exosome, Anti-inflammation, Lung regeneration

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²Department of Biomedical Engineering, Sungkyunkwan University, Republic of Korea
³Xcell Therapeutics, Republic of Korea

Improved production and regenerative activity of MSC-derived EVs cultured with chemically defined media

A serum-free condition (starvation) has been required to isolate extracellular vesicles (EVs; exosomes) produced from the cell of interests with excluding the unknown influence of serum-derived EVs. Serum-free culture media have recently been suggested as replacements for serum-supplemented media, allowing MSCs to proliferate while maintaining their original properties in a serum-free environments. Due to the different properties of the EVs representing the states and characteristics of the origin cells, a study is needed to compare the properties of the cell-derived EVs according to the cell culture media. Human umbilical cord mesenchymal stem cells (UCMSCs) were cultured with two different media, serum-containing medium, 10% FBS supplemented DMEM (NM), and serum-free chemically defined medium, CellCor™ CD MSC (CDM), to compare the characteristics of EVs depending on cell culture media. To eliminate FBS-derived EVs from UCMSC cultured with NM, the medium was changed with FBS-free DMEM for starvation during EVs isolation. Even though starvation promoted EVs production of the cell, we could get about 25 times more EVs from CDM than from NM. And, the surface characteristics and internal cytokines were used to classify the subpopulations of EVs. EVs derived from UCMSC cultured with CDM (EXOSC-CDM) were high in regeneration related factors including EGF and PDGF-AB/BB, whereas EVs produced from UCMSC cultured with NM were high in pro-inflammatory cytokines like IL-6 and IL-8 (EXOSC-NM). Accordingly, compared to EXOSC-NM, EXOSC-CDM has improved wound healing and angiogenic effects due to a higher level of regeneration-related cytokines and less pro-inflammatory cytokines. From these results, we would recommend the newly developed serum-free media (CDM) for culturing MSC to isolate highly purified and functional EVs.

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Hong-Hee Kim^{2,5}, Bong-Kyu Choi^{1,*}

¹Department of Oral Microbiology and Immunology, School of Dentistry, Seoul National University, Seoul, Republic of Korea, ²Department of Cell and Developmental Biology, School of Dentistry, Seoul National University, Seoul, Republic of Korea, ³Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea, ⁴Department of Life Sciences, Pohang University of Science and Technology (POSTECH), Pohang, Republic of Korea, ⁵Dental Research Institute, Seoul National University, Seoul, Republic of Korea

Extracellular Vesicles Derived from the Periodontal Pathogen Filifactor alocis Induce Systemic Bone Loss through Toll-like receptor 2

Periodontitis is an inflammatory disease induced by local infection in tooth-supporting tissue. Periodontitis is associated with systemic bone diseases, but little is known about the mechanism of the causal effect of periodontitis on systemic bone resorption. Bacteria-derived extracellular vesicles (EVs) act as natural carriers of virulence factors that are responsible for systemic inflammation. In this study, we investigated the role of EVs derived from Filifactor alocis, a Gram-positive, anaerobic periodontal pathogen, in systemic bone loss and osteoclast differentiation. F. alocis EVs accumulated in the long bones of mice after intraperitoneal administration. These EVs induced pro-inflammatory cytokines, osteoclastogenesis, and bone resorption via Toll-like receptor 2 (TLR2). The phase separation of F. alocis EVs showed that amphiphilic molecules were responsible for the induced bone resorption and osteoclastogenesis. The osteoclastogenic effects of F. alocis EVs were reduced by lipoprotein lipase. Proteomic analysis of the amphiphilic molecules identified seven lipoproteins. Our results indicate that lipoprotein-like molecules in F. alocis EVs may contribute to systemic bone loss via TLR2.

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Extracellular Vesicles Introduced in Three-Dimensional Human Liver-Chip to Mimic Breast Cancer Metastasis

The liver is the most common organ regarding tumor metastasis, and EVs have emerged as important intercellular messengers and prominent initiators in forming the pre-metastatic niche. To understand tumor metastasis, we studied tumor-derived secretion including the interaction of extracellular vesicles(EVs) and the tumor cells in the microenvironment. Herein, we present an in vitro microfluidic platform for investigating the effect of primary breast cancer-derived EVs on the liver microenvironment. The platform consists of a flow-injected top channel with human LSECs and a bottom channel with human hepatocytes and liver fibroblasts divided by a thin porous polydimethylsiloxane (PDMS) membrane. We measured albumin secretion and urea synthesis in the liver chip with higher values than hepatocyte monoculture, indicating that the liver chip can functionally recapitulate the liver in vivo. Breast cancer EVs were isolated with a size-based enrichment method involving the centrifugal microfluidic platform Exodisc. Under different EV treated conditions, MDA cell adhesion was analyzed. Enhanced adhesion of MDAs was found only upon MDAEV treatment. The liver chips that were pretreated with Nocodazole showed reduced adhesion of adhered tumor cells exposed to MDAEVs. Therefore, it can be suggested that tumor-derived EVs participate in the progression of liver metastasis. In conclusion, to study the interaction between tumor cells and microenvironment at metastatic sites, we utilized liver-on-a-chip to mimic the formation of a pre-metastatic niche and adhesion of breast cancer cells on the liver microenvironment by breast cancer-derived EVs. Furthermore, this liver microenvironment chip can be utilized to study the mechanisms underlying the secondary cancer metastasis to the liver.

Acknowledgement: The work is supported by a grant given to Center for Soft and Living Matter, Institute for Basic Science (IBS-R020-D1), funded by the Korean Government and the National Research Foundation of Korea(NRF), under 2021 Project BK21 Four.

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Plant-Derived Extracellular Vesicles for Drug Delivery Carrier Using Grapefruit

Exosomes are nanosize modulator of intercellular communications as subgroup of Extracellular Vesicles (EVs) secret from cells. Recently, exosomes are considered as a novel drug carrier with membrane modification due to their biocompatibility, biodistribution and low immune response, but there were still some challenges including stability and homogeneity of exosomes, and large-scale manufacturing To address with these limitations, artificial EV like vesicles using cell membranes or liposomes formation using various lipids have been studied for drug delivery system. However, there are some issues still need to be improved in terms of efficacy, efficiency and side effects. To overcome these shortcomings, we studied feasibility of plant-derived extracellular vesicle(pEV) as drug delivery carriers that can replace mammalian cell exosomes and liposomes. The pEVs are known as non-toxic, easily internalized into mammalian cells, and they are beneficial for mass-production with high yield. We use grapefruit as an origin of pEVs which are isolated by ultracentrifugation and size exclusion chromatography. Then they were characterized using DLS, NTA, and Cryo-EM. grapefruit derived EV's whose size were 170±12 nm and 1.96x10¹² particles/ml of concentration was obtained with total volume 3 ml from a grapefruit. The stable size distribution was maintained at 4°C for 4 weeks. Drug loading (doxorubicin) and DiO labeling to pEVs were confirmed by confocal microscopy through colocalized fluorescence. Cell uptake study was also conducted using U87MG (glioblastoma) and PC12 cell line with DiO labeled PEV and we confirmed uptake of PEVs by cells. We expect the results of our study would be helpful to overcome the limitations of exosomes and liposomes as drug carriers because in terms of stability and mass productivity.

P 07

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Plasma-derived extracellular vesicles miR-512-3p from moyamoya disease is regulated tubule formation ability of endothelial colony-forming cells through targeting ARHGEF3

Moyamoya disease (MMD) is a chronic occlusive cerebrovascular disease known to be a major cause of stroke in children. Emerging evidence suggests that circulating extracellular vesicles (EVs) containing miRNAs in cerebrovascular disease plays an important role in intercellular communication by delivering RNA cargo involved in biological processes. This study aimed to investigate the specific miRNAs loaded into MMD plasma-derived EVs, followed by identification of their roles and mechanisms. Plasma-derived EVs were isolated from healthy volunteers (normal control) and MMD patients. Characterization of EVs were determined using TEM, NanoSight, ExoView and western blot. Profiling of miRNAs in EVs were determined using NanoString nCounter miRNAs analysis system and validated using ExoView and RT-qPCR. Endothelial colony forming cells (ECFCs) from MMD were isolated and the miR-512-3p inhibitor was transfected to assess the cell viability, tubule formation, GTPase activity. There was no significantly difference in size and distribution of EVs between normal and MMD EVs. However, the total number was higher, with CD81 and CD9 were lower and CD63 was higher in MMD EVs. miRNA profiling demonstrated that miR-512-3p were significantly upregulated in MMD EVs. Target prediction analysis of miR-512-3p showed downregulated ARHGEF3 which is metabolism regulation GTPase can be targeted in MMD ECFCs. Inhibition of miR-512-3p in ECFCs reduced miR-512-3p in both EVs as well as ECFCs, and increased ARHGEF3. The increase in ARHGEF3 through the inhibition of upregulated miR512-3p in MMD EVs, which can restore tubule formation dysfunction by activation of GTPase. Our study imply that MMD EV miR-512-3p is correlated with the metabolism of ECFCs and may affect angiogenesis disorder in MMD patients.

구두 발표 14:30 - 14:40 HALL A(크리스탈홀)

P 08

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ExoCAS-2: Rapid and Pure Isolation of Exosomes by Anionic Exchange Using Magnetic Beads

Extracellular vesicles (EVs) are considered essential biomarkers in liquid biopsies. Despite intensive efforts aimed at employing EVs in a clinical setting, workable approaches are currently limited owing to the fact that EV-isolation technologies are still in a nascent stage. This study introduces a magnetic bead-based ion exchange platform for isolating EVs called ExoCAS-2 (exosome clustering and scattering). Owing to their negative charge, exosomes can easily adhere to magnetic beads coated with a polycationic polymer. Owing to the features of magnetic beads, exosomes can be easily processed via washing and elution steps and isolated with high purity and yield within 40 min. The present results confirmed the isolation of exosomes through analyses of size distribution, morphology, surface and internal protein markers, and exosomal RNA. Compared with the commercially available methods, the proposed method showed superior performance in terms of key aspects, including operation time, purity, and recovery rate. This highlights the potential of this magnetic bead-based ion exchange platform for isolating exosomes present in blood plasma.

구두 발표 14:40 - 14:50 HALL A(크리스탈홀)

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ExoCAS-2: Rapid and efficient bulk isolation of exosomes from cell culture media

As exosome-based therapeutic technologies are developed exponentially, it is becoming increasingly important to isolate exosomes from cell culture media. However, isolation of exosomes from these bulk media still requires new and innovative techniques.

ExoCAS-2 (exosome clustering and scattering), which was recently developed by our research team, is an innovative technology that separates exosomes with magnetic beads coated with positively charged materials. In this study, high-capacity exosome isolation performance in cell culture was studied using ExoCAS-2 technology. The whole process was completed within 40 minutes for 20 mL of cell culture medium. In the present study, ExoCAS-2 yielded 3 times higher exosomes than other products, whereas the purity was nearly same as others. Through Western blot analysis, ExoCAS-2 yielded the highest intensity of exosomal protein compared to other products. Also, it was confirmed that ExoCAS-2 extracted the most nucleic acids through housekeeping gene analysis. These results confirmed that ExoCAS-2 can most efficiently and quickly extract exosomes from a large-capacity cell culture medium.

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Quorum Sensing Inhibitors D-Galactose and D-Arabinose Affect the Biological Activity of Tannerella forsythia Outer Membrane Vesicles in monocytes

Tannerella forsythia is among the major pathogens which are involved in periodontitis, a chronic inflammation. Outer membrane vesicles (OMVs) released from the cell envelope of Gram-negative bacteria play an important role in bacteria-host interaction. OMVs contain bioactive molecules including DNA, RNA, lipopolysaccharides, proteins, toxins, and peptidoglycan. Quorum sensing (QS) is mediated by small signaling molecules that are secreted from bacteria. QS molecules induce bacterial virulence and biofilm formation. However, there are no reports that QS molecules regulate production and virulence of T. forsythia OMVs. In this study, we purified OMVs from T. forsythia in the absence or presence of quorum sensing inhibitors (QSIs, D-galactose and D-arabinose) and investigated their biological activity in monocytes. Highly purified OMVs isolated using density gradient ultracentrifugation were measured for their size using Nanoparticle tracking analysis (NTA). qPCR array analysis showed that mRNA expression of proinflammatory cytokines (IL-6 and IL-1 β) was significantly reduced by OMVs of T. forsythia treated with QSIs (D-galactose and D-arabinose) than OMVs of T. forsythia without QSIs. Human cytokine array analysis showed that the expression of IL-1 β , IL-6, IL-8 and TNF- α was significantly reduced by OMVs of T. forsythia treated with D-galactose (Tf D-gal OMVs) than OMVs of T. forsythia without D-galactose (Tf OMVs) in monocytes at the gene and protein expression level. T. forsythia OMVs activated NF- κ B and MAPK signaling pathway via TLR2, which are less activated by Tf D-gal OMVs compared to Tf OMVs. Our results indicate that QSIs regulate the inflammatory activity of T. forsythia OMVs.

Keyword : Tannerella forsythia, Outer membrane vesicles, Quorum sensing, Inflammatory response

P 11

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Comparison of Surface Functionalization of PLGA Composite to Immobilize Extracellular Vesicles

Mesenchymal stem cell (MSC)-based approaches have been established as a potential therapy in regenerative medicine. Especially, extracellular vesicles (EVs) derived from MSCs have regenerative and anti-inflammatory properties emerged as key mediators for the therapeutic effects. Although previous studies have focused on enhancing regenerative and anti-inflammatory properties through the immobilization of EVs onto the surface of biodegradable scaffolds, comparative studies of effective surface modification have not been reported yet. Here, we implemented a comparative study on the surface modification of poly(lactide-co-glycolide) (PLGA)-based composites to graft mesenchymal stem cell-derived extracellular vesicles (MSC-EVs) using three different bond strengths of ligand-receptor interaction, ionic bond, and covalent bond, which have different materials, namely, fibronectin (FN), polyethylenimine (PEI), and polydopamine (PDA), respectively. Further in vitro analysis exhibited that MSC-EVs released from all modified films sustainably, but the MSC-EVs grafted onto the surface coated with PEI are more effective than other groups in increasing angiogenesis and reducing the inflammatory responses in endothelial cells. Collectively, these results demonstrated that PEI is a desirable coating reagent for the immobilization of MSC-EVs with ionic bonding on the surface of biodegradable implants.

P 12

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Integrated microfluidic platform for serial enrichment and isolation of extracellular vesicles

Extracellular vesicles(EVs) are small particles derived from cells with a size of 50-200 nm. They refelect cellular characteristics and are used for intercellular communication. Due to these features, EVs can be used as biomaterials for disease diagnosis and therapeutics. However, ultracentrifugation, which is considered the golden standard method for EVs isolation, is time-consuming, poor in purity, and has tedious steps. So we developed an integrated microfluidic chip for rapid EVs enrichment and isolation with high yields. This chip is composed of two parts: the horseshoe-shaped orifice micromixer (HOMM) and fish trap-shaped microfilter (FiTrapter). The HOMM chip serves as a micromixer that increases the collisions between EVs and microbeads immobilized with EV-specific antibodies to generate EVs-microbeads complex.. By injecting the elution buffer into the FiTrapter chip, pure EVs can be harvested at outlet of the chip while the microbeads remain on the chip. As a result, 1x10⁸ particles/ml EVs can be harvested in 1 ml of cell culture medium. After that, the isolated EVs can be tested for the possibility of diagnosis of disease or treatment as a therapeutic agent. In addition, these two chips can be used individually or as a modular chip, rapidly conjugating EVs or harvesting EVs. We hope that this study from the probe will pave the way for research based on EVs such as prompt diagnosis and efficacy as therapeutic agents.

구두 발표 14:50 - 15:00 HALL A(크리스탈홀)

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Efficient Production of Extracellular Vesicles using Cell Spheroids

Cell-derived extracellular vesicles(EVs) contain miRNA, mRNA, and various proteins, and many studies have been conducted on the therapeutic potential due to their intracellular communication capabilities. However, for commercial use, it is necessary to improve the production efficiency and quality control standards of existing EV production technology. Here, we have developed EV production technology using cell aggregates/spheroids to improve EV production efficiency. Since the EV production environment changes according to the size of the cell spheroid used for EV production, we developed cell spheroid production automation technology to produce uniform cell spheroids. The production of EVs derived from cell spheroids significantly increased the production index of number of EVs per cell(# of EVs/cell) compared to the conventional 2D cell culture, and a change in productivity was confirmed depending on the size. The results of this study could suggest mass production technology for EV commercialization.

구두 발표 15:00 - 15:10 HALL A(크리스탈홀)

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The Wound Healing Effect of Exosome Secreted by Umbilical Cord Blood Mesenchymal Stem Cells

Exosomes are secreted from cells in the form of small vesicles, and contain various substances (genes, proteins, lipids, etc.) of secreted cells. It is used in the area of disease diagnosis through substance analysis in exosome, and recently, the development of treatments for various diseases has been actively carried out by utilizing the changing properties of cells that accept exosome. In this study, the possibility of developing a wound treatment using umbilical code blood - mesenchymal stem cells(UCB-MSC) secreted exomes was explored. Basic characterization (morphology, size, CD markers, surface proteins) was performed on exosomes secreted by UCB-MSC, and only exosomes were purely secured through the purification process. When exosomes were treated on human dermal fibroblast, it was confirmed that they were harmless without inducing apoptosis. In order to confirm the effectiveness of wound healing effect of exosomes, cell growth, cell mobility, cell protection in an inflammatory environment, inflammation suppression efficacy, and scar generation control ability were analyzed using human dermal fibroblast and human keratinocyte. After establishing an animal model for wound disease using the experimental animal rat, it was confirmed that dermal tissue regeneration was significantly promoted and the wound was quickly cured in the exosome treatment group. Through various dyeing methods using the internal tissue, it was confirmed that tissue regeneration proceeds stably and quickly by exosomes. Through these results, it was confirmed that UCB-MSC derived exosomes have the effect of wound healing. In addition, the results of this study suggest that it is possible to develop drugs for various diseases that require inflammation suppression and tissue regeneration.

Key words: Exosome, Umbilical cord blood mesenchymal stem cells, Anti-inflammation, Tissue regeneration, Wound healing

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Orbicularis oculi muscle stem cell-derived
extracellular vesicles can be used to prepare
skin whitening, antioxidant, anti-wrinkle, anti-
aging, and wound healing agents

Extracellular vesicles (EVs) are paracrine factors that mediate stem cell therapeutics. We evaluated the possible therapeutic applications of orbicularis oculi muscle stem cell-derived EVs (OOM-SC-EVs) which were prepared from the waste human facial tissue-derived OOM-SCs. Initially, OOM-SCs were isolated from the ocular tissue that was discarded after upper eyelid blepharoplasty or epiblepharon surgeries, and their stem cell properties were compared with other mesenchymal stem cells (MSCs) such as Wharton’s jelly-MSCs, adipose-derived MSCs, and urine-derived stem cells. OOM-SCs showed a spindle-like morphology with trilineage differentiation capacity, positive expression of CD105, CD 90, and CD73, and negative expression of CD45 and CD34. We purified the natural OOM-SC-EVs via ultracentrifugation and filtration of cell culture supernatants. OOM-SC-EVs possessed an apparent inhibitory effect on melanin synthesis in B16F10 cells by blocking tyrosinase activity. OOM-SC-EV treatment led to a significant attenuation of senescence-associated changes, a decrease in reactive oxygen species generation, and upregulation of antioxidant gene expression. We demonstrated the role of OOM-SC-EVs in in vitro wound healing of normal human dermal fibroblasts and upregulation of anti-wrinkle-related genes and confirmed the potential of OOM-SC-EVs in healing of the experimental wound mouse model. Our study provides novel OOM-SC-EVs with potential therapeutic applications in melanogenesis suppression, anti-wrinkle process, and in vitro and in vivo wound healing, for application in esthetic and clinical reconstructive fields.

Keywords: waste orbicularis oculi muscle tissue; OOM-SC extracellular vesicles; anti-senescence; antioxidant; whitening; wound healing

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Heterogenicity of Extracellular Vesicles
Derived from THP-1 Macrophages Infected with
Tannerella forsythia

Extracellular vesicles (EVs) are nano-sized vesicles secreted from all kinds of living cells. EVs can modulate physiological status of recipient cells since EVs carry various molecules of originated cells, such as proteins, lipids, nucleic acids, and metabolites. Several studies have figured out that EVs derived from host cells infected with several pathogens contain pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) which can induce the immune response in non-infected recipient cells. Therefore, we investigated immunogenicity of EVs derived from THP-1 macrophages infected with Tannerella forsythia, one of periodontal pathogens, and identified PAMPs and DAMPs of those EVs. The EVs were isolated by size exclusion chromatography combined with iodixanol density gradient ultracentrifugation. Density gradient ultracentrifugation separated the EVs into three distinct components, low- and middle-density vesicles and high-density amorphous aggregates. The low-density vesicles were host EVs since they contained host EVs markers such as CD9, CD63, and alix. The middle-density vesicles were T. forsythia outer membrane vesicles (OMVs) since they were highly enriched with T. forsythia antigens but were negative for host EVs markers. The amorphous aggregates were composed of various proteins of host and T. forsythia. Proteomic analysis revealed that T. forsythia infection increased the amount of interleukin (IL)-8, IL-1β, and tumor necrosis factor (TNF)-α in host EVs compared with non-infected host EVs. Treatment of T. forsythia OMVs to THP-1 cells induced the expression of pro-inflammatory cytokines, including TNF-α, IL-1β, IL-6, and IL-8. Amorphous aggregates and host EVs also induced expression of pro-inflammatory cytokines from THP-1 cells but their expression was lower than T. forsythia OMVs. These results suggest that EVs derived from THP-1 macrophages infected with T. forsythia were composed of host EVs and T. forsythia OMVs. In addition, immunogenicity of T. forsythia OMVs was much stronger than host EVs.

구두 발표 15:10 - 15:20 HALL A(크리스탈홀)

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Brain-derived neurotropic factor mediates neuroprotection of mesenchymal stem cell-derived extracellular vesicles against severe intraventricular hemorrhage in newborn rats

Brain-derived neurotropic factor (BDNF), which is secreted by mesenchymal stem cells (MSCs), protects against severe intraventricular hemorrhage (IVH)-induced brain injuries. Although the paracrine protective effects of MSCs are mediated primarily by extracellular vesicles (EVs), the therapeutic efficacy of MSC-derived EVs and the role of the BDNF in the EVs have not been studied. This study aimed to determine whether MSC-derived EVs attenuate severe IVH-induced brain injuries, and if so, whether this protection is mediated by BDNF transfer. We compared the therapeutic efficacy of MSCs, MSC-derived EVs with or without BDNF knockdown, and fibroblast-derived EVs in vitro in rat cortical neuronal cells challenged with thrombin and in vivo in newborn rats by injecting 200 µL of blood at postnatal day (P) 4 and transplanting 1 × 10⁵ MSCs or 20 µg of EVs at P6. The MSCs and MSC-derived EVs, but not the EVs derived from BDNF-knockdown MSCs or fibroblasts, significantly attenuated in vitro thrombin-induced neuronal cell death and in vivo severe IVH-induced brain injuries such as increased neuronal cell death, astrogliosis, and inflammatory responses; reduced myelin basic protein and neurogenesis; led to progression of posthemorrhagic hydrocephalus; and impaired behavioral test performance. Our data indicate that MSC-derived EVs are as effective as parental MSCs in attenuating severe IVH-induced brain injuries, and this neuroprotection is primarily mediated by BDNF transfer via EVs.

구두 발표 15:20 - 15:30 HALL A(크리스탈홀)

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Panax ginseng-Derived Extracellular Vesicles Facilitate Anti-Senescence Effects in Human Skin Cells: An Eco-Friendly and Sustainable Way to Use Ginseng Substances

Ginseng is a traditional herbal medicine in eastern Asian countries. Most active constituents in ginseng are prepared via fermentation or organic acid pretreatment. Extracellular vesicles (EVs) are released by most organisms from prokaryotes to eukaryotes and play central roles in intra- and inter-species communications. Plants produce EVs upon exposure to microbes; however, their direct functions and utility for human health are barely known, except for being proposed as delivery vehicles. In this study, we isolated EVs from ginseng roots (GrEVs) or the culture supernatants of ginseng cells (GcEVs) derived from Panax ginseng C.A. Meyer and investigated their biological effects on human skin cells. GrEV or GcEV treatments improved the replicative senescent or senescence-associated pigmented phenotypes of human dermal fibroblasts or ultraviolet B radiation-treated human melanocytes, respectively, by downregulating senescence-associated molecules and/or melanogenesis-related proteins. Based on comprehensive lipidomic analysis using liquid chromatography mass spectrometry, the lipidomic profile of GrEVs differed from that of the parental root extracts, showing significant increases in 70 of 188 identified lipid species and prominent increases in diacylglycerols, some phospholipids (phosphatidylcholine, phosphatidylethanolamine, lysophosphatidylcholine), and sphingomyelin, revealing their unique vesicular properties. Therefore, our results imply that GEVs represent a novel type of bioactive and sustainable nanomaterials that can be applied to human tissues for improving tissue conditions and targeted delivery of active constituents.

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Extracellular vesicle (sEV) protein profiling study for biomarker discovery of breast cancer

Small extracellular vesicle (sEV) proteomic profiling studies are advantageous for early detection of breast cancer (BC) and discovery of novel biomarkers for targeted therapy. It can also be used to enable diagnostics in a patient's blood through a non-invasive approach. We compared and analyzed sEV proteomics in several breast cancer cell lines using the sEV marker CD63 and the cancer cell specific markers EpiCAM & CD49f. A total of 3,700 proteins were identified, and as a result of GO analysis of 474 unique proteins from sEV isolated by CD63, it was confirmed that proteins related to sEV production and transport such as exocytosis and endocytosis, which are characteristic of sEV, appeared. On the other hand, GO analysis showed that 389 proteins expressed only in EpiCAM & CD49f, which are cancer cell-specific markers, are related to signal transduction and RNA metabolism. This can be considered to be closely related to the generation of miRNA in sEV, which shows a specific expression difference in breast cancer patients. Finally, as a result of comparative analysis of sEV proteome extracted from the blood of triple-negative breast cancer (TNBC) patients and normal persons, 179 out of 389 proteins that appear only in EpiCAM & CD49f were identified, and it was confirmed that 103 proteins (about 57.5%) showed significant differences. In particular, as a result of GO analysis of different proteins, autophagosome-related proteins characteristically appearing in TNBC patients could be identified. Biomarkers found through more proteomic analysis in the future will be available for early diagnosis and targeted treatment of breast cancer.

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Collection and analysis of exosomes in exhaled breath using a mask: comparison between healthy control and lung cancer

Extracellular vesicles (EVs) obtained from blood has been intensively investigated for an early diagnosis of cancer. Recently, analysis of EVs obtained from exhaled breath, so-called breath biopsy, is being alternatively attempted. The present study adopted face mask for collecting EVs from exhaled breath and conducted analysis of concetration and purity of exosomes, Western blot and miRNA. From the face mask worn by healthy controls, the amount of exosomes increased linearly with the mask wearing time. The amount of exosomes extracted from the mask worn for 3 hours was the same as that from 1 mL of plasma. Comparing exosomal miRNA, it was confirmed that 97% coincident results between plasma and face mask. In addition, there were also apparent difference in miRNA between healthy control mask and non-small cell lung cancer (NSCLC) patient mask. Though the present study, we confirmed that there were plenty of exosomes in exhaled breath and breath biopsy would be equivalent to blood-based liquid biopsy.

Keywords: non-small cell lung cancer, screening, face mask, breath biopsy, exhaled breath

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MicroRNAs signature of circulating tumor-derived EV as a potential diagnostic biomarker for early-stage of breast cancer

Liquid biopsy is an emerging technology with a potential role in the screening and early detection of breast cancer. However, the potential circulating biomarker for early detection in breast cancer remains challenging. Tumor-derived EVs (TDEs) have been emerging circulating biomarkers, which carry oncogenic microRNAs (miRNAs). Therefore, we validated seven-candidate miRNAs from the TDEs in 82 plasma samples of breast cancer by using a novel microfluidic device, which rapidly and selectively isolates cancerous EVs within two minutes. Among seven-candidate miRNAs, four miRNAs (miR-9, miR-16, miR-21, and miR-429) from the EVs were highly elevated in early-stage breast cancer patients compared with healthy donors. The combination of significant miRNAs from specific EVs has high sensitivities of 0.90, 0.86, 0.88, and 0.84 of AUC in each subtype (luminal A, luminal B, HER-2, and triple-negative) of early-stage breast cancer. Our results suggest that the combination of four miRNA signatures of TDEs can open a door to enable the early diagnosis of breast cancer using liquid biopsy.

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Molecular Analysis using Extracellular Vesicles from Urine of Patients with Prostate Cancer

Extracellular vesicles (EVs) are composed of a lipid bilayer membrane that protects the enclosed materials. EVs carry information such as DNA, mRNA, microRNA (miRNA), long non-coding RNA, proteins, and lipids from the host cell from where they are originated and deliver the information to their neighboring or distant sites. Thus, EVs can be used as diagnostic, prognostic, and predictive biomarkers for diseases. EVs are present in various biofluids such as urine, plasma, and cerebrospinal fluid. Among them, urine samples can be easily obtained from a human body without using invasive methods. Therefore, EV from urine samples is a promising source of novel biomarkers for prostate cancer. Here, to screen the prostate cancer biomarkers, exodisc2 was used to isolate EVs in urine from 11 patients with benign prostatic hyperplasia (BPH) and 13 patients with prostate cancer (PCa). EVs are characterized by bicinchoninic acid (BCA) assay for protein concentration, enzyme-linked immunosorbent assay (ELISA) for EV representative markers, and nanoparticle tracking analysis (NTA) for particle concentration and size distribution. According to the result of ELISA, the OD value of CD63 was higher than that of CD9 and CD81. And there was no significant difference between the two groups regarding the number of particle and protein concentrations. The total RNA was extracted from EVs using miRNeasy micro kit. When measuring the RNA concentration by Fragment analyzer before the Nanostring experiment, the RNA concentration of BPH group was slightly higher than that of PCa. Nanostring analysis of both miRNA and mRNA results also showed differences between BPH group and PCa group.

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EGFR mutation detection of non-small cell lung cancer patients by analyzing bronchial washing derived EVs using Exodisc

Lung cancer is a fatal disease and one of the leading causes of death in South Korea. Non-small cell lung cancer (NSCLC) is the most common type of lung cancer. The epidermal growth factor receptor (EGFR) mutation has been widely used as a diagnostic marker for drug selection of NSCLC patients. Tissue biopsy is the standard way to detect EGFR mutation from the patients. However, it has some limitations in that the procedure for biopsy is invasive, painful for patients, and hard to monitor the prognosis of patients according to the medication routinely. In this study, we showed the EGFR mutation detection using bronchial washing (BW) sample, which is less invasive compare to tissue biopsy, and can be done routinely in a clinic for lung cancer patients. EVs are isolated using Exodisc, and the EGFR mutations, including L858R, 19del, and T790M were analyzed. The detection rate of T790M was compared with the results derived from tissue samples and plasma-derived cfDNA. Among 55 BW samples from the patients, the detection sensitivity was 89.7% and 31.0% for EV-DNA, EV excluded cfDNA, respectively, with a specificity of 100% 2. Also, the detection rate of T790M in 13 samples was 61.5%, 10.0%, and 30.8% from BW-derived EV-DNA, plasma-derived cfDNA, and tissue samples, each. Interestingly, the longitudinal study of BW-derived EVs showed an excellent correlation with the disease progression measured by CT images. Therefore, our study suggests that the EGFR mutations can be successfully detected in BW-derived EVs, and could reflect the cancer mutation prognosis of patients. Also, the EV-DNA shows better results compared to EV excluded cfDNA, and it might be because of the protection of nucleic acids by EV membrane. This study suggests the potential usage of BW-derived EVs as clinical liquid-biopsy samples, and the EGFR mutation detection from BW-derived EVs can be helpful for cancer monitoring and precision medicine for NSCLC patients.

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Ultra-sensitive ELISA detection of oligomer Abeta in exosome from plasma using Automated Photooxidation-Induced Fluorescence Amplification (PIFA) Machine

The number of people with AD has increased every year, and it is expected to be continued to increase in the future. As there is no appropriate treatment for AD patients, early diagnosis of AD is important. Currently, widely used diagnostic methods for AD include Aβ assay from CSF biopsy sample, MMSE score, and PET imaging, but these methods have disadvantages including high cost and inaccuracy. To resolve these limitations, a number of blood-based diagnostic methods have been developed to detect of Aβ from plasma exosomes that require low concentration protein measurement. To enable low-concentration protein measurement, various methods have been developed such as digital ELISA, plasmon ELISA, and SPR. However, it takes a long time and requires manual labour that has to use microbeads or metal surfaces such as Au or Ag. To overcome these shortcomings, we developed an automated ELISA machine for PIFA to detect Aβ in exosomes extracted from plasma. AR is converted into a fluorescent product, RSF, by the HRP labeled detection antibody. By monitoring the change in fluorescence intensity of RSF under the continuous light exposure, the sensitivity of the assay can be enhanced compared to conventional ELISA that relies on end-point signal analysis. It took less than an hour to assay one sample with PIFA based ELISA, and the LOD for determining dimer Aβ40 levels was less than 1 pg/mL. Then, it was used to detect oligomeric Aβ amount in exosomes from plasma of clinical samples (60 AD & 61 NC). The sensitivity and specificity were nearly 80% and the AUC was 0.872. The measurement of oligomeric Aβ levels in plasma exosomes using the automated PIFA machine is expected to be used for the pre-screening of AD patients in general medical institutions with small sample volume and low cost.

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Association between breast cancer and Firmicutes/Bacteroidetes ratio

Breast cancer is associated with postmenopausal obesity which is considered as a risk factor of breast cancer. Obesity is known to correlate with the microbiome. This study investigated the relationship among breast cancer, body mass index (BMI), and dietary habits by comparing the microbiome of breast cancer patients and normal healthy controls. The symbiotic bacteria secrete extracellular vesicles into the blood and lymphatic fluid. And these vesicles contain bacterial nucleic acids and metabolites. We extracted blood extracellular vesicles and analyzed the blood microbiome of 95 female breast cancer patients and 192 healthy controls by NGS using a universal bacterial primer of 16S rDNA. This study investigated the Firmicutes/Bacteroidetes (F/B) ratio in normal controls and breast cancer patients and observed that the F/B ratio in the control group was 2.6-fold higher than in breast cancer group. In the control group, Firmicutes were 5-fold higher than Bacteroidetes. Among Firmicutes, Staphylococcus and Bacillus were especially higher. Bacteroidetes levels in the breast cancer patients were elevated, particularly Bacteroides and Parabacteroides levels were increased. In breast cancer patients, the F/B ratio was 1.3-fold higher in patients with high BMI (BMI>30) compared to patients with normal BMI (BMI 20-24). The F/B ratio was the highest in breast cancer patients of meat-eater (F/B ratio: 2.3), followed by vegetarian patients(F/B ratio: 2.0), and omnivorous patients (F/B ratio: 1.8). Menopause had no considerable impact on the F/B ratio. Changes in F/B ratio of microbiome that are affected by BMI and dietary status may be related to the breast cancer.

구두 발표 15:40 - 15:50 HALL A(크리스탈홀)

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Novel Biomarkers for Isolation of Brain Derived Extracellular Vesicles in Plasma for Accurate Diagnosis of Alzheimer’s Diseases

Neurodegenerative disease is diagnosed after brain function is irreversible. Therefore, diagnosing at incipient disease and predicting the disease stage are imperative for prevention and effective treatment. Unfortunately, early and accurate diagnosis are still challenging due to difficult to detect biomarkers such as beta amyloid and Tau proteins secreted from the brain, not other organs. Recently, capture of neuronally derived extracellular vesicle (NDEV) using L1CAM has been suggested as a new diagnostic technology for detection of brain derived biomarkers. However, L1CAM has limitations in isolation of NDEV. Here, we present new markers that can replace L1CAM. In this study, we have further demonstrated in detail the process of selecting novel markers and present evidence that the new markers, X1 and X2, are more sensitive and accurate for isolation of neuron-enriched EVs than L1CAM as well as early biomarkers of Alzheimer’s Disease. In addition, we verified the potential of captured EV by X1 and X2 from human plasma through analysis of EV RNA. Our results demonstrate that X1 and X2 are more sensitive and specific biomarkers for isolating neuron-enriched EVs. Furthermore, our results suggest usefulness as a diagnostic platform for early diagnosis of neurodegenerative diseases through a combination of X1 and another specific neuronal marker such as X2. This research was financially supported by the Ministry of Trade, Industry, and Energy (MOTIE), Korea, under the “Regional Innovation Cluster Development Program (OpenLab, P0004793)” supervised by the Korea Institute for Advancement of Technology (KIAT) and the Bio & Medical Technology Development Program of the National Research Foundation (NRF) 2019M3A9H1103765.

구두 발표 15:50 - 16:00 HALL A(크리스탈홀)

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A macitentan loaded nanoparticle for biogenesis inhibition and enhanced immune checkpoint blockade

Tumor microenvironment (TME) including a variety of cells functions as barrier for cytotoxic T lymphocytes (CTLs). Within TME, cancer-associated fibroblasts (CAFs) have been known to release cytokines for establishing immune suppressive environment. Also, several studies reported that cancer cells secrete the exosomes which stimulated the differentiation of stromal cells into CAFs. To overcome these immune suppressive strategies, macitentan, an endothelin receptor antagonist for the pulmonary arterial hypertension, was repurposed to inhibit biogenesis of tumor derived exosomes. To improve biocompatibility of macitentan, we encapsulated them in poly(ethyleneglycol)-poly(lactic-co-glycolic acid) (PEG-PLGA) nanoparticles. In murine orthotopic tumor model, it was revealed that macitentan in polymeric nanoparticles (M-NPs) can impede the secretion of tumor derived exosomes resulting in modulating TME. Additionally, when we treated the tumor bearing mouse using M-NPs with aPD-1 antibody, the therapeutic efficacy was more enhanced than only aPD-1 treatment. These results suggested that the M-NPs potentiate reorganizing the TME, consequently, have synergistic antitumor effects in combination with immune checkpoint blockade therapy.

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Tumor-Targeted Membrane Fusion Delivery for Deep Tissue Penetration and Synergistic Chemotherapy

Nanoparticle-based drug delivery has been widely used for effective anti-cancer treatment. However, a key challenge restricting the efficacy of nanotherapeutics is limited tissue penetration within solid tumors. Here, we report the advanced membrane fusogenic liposomes (AMFL), which can target tumor tissues and assist in the infiltration of hydrophobic drugs into the internal region of tumors. The AMFLs exhibited selective binding affinity with cancerous cells and delivered hydrophobic compounds to cell membranes and extracellular vesicles secreted from the cells engineered with liposomes. Surface modification of liposomes with tumor-targeting peptides, CGKRK, provided the increase in blood circulation time, tumor accumulation and penetration of drugs. The anti-tumor therapeutic efficacy of AMFL was evaluated using a hydrophobic apoptotic drug, thapsigargin(Tg). Tg-loaded AMFL allowed the effective inhibition of tumor growth in CT26 mouse model. Furthermore, combination treatment of Tg-loaded AMFL with Doxil exhibited augmented therapeutic effects. These results demonstrate that membrane fusogenic liposome-mediated drug delivery has great potential for exceptional drug delivery and deep penetration to tumor tissues, thereby expecting remarkable therapeutic efficacy.

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