EV-based BALF liquid biopsy (ExoBAL) in peripheral pulmonary lesions (PPLs)

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Disclosure

- Founder and CEO : Exosignal, Inc.
- Research Funds :
  - YuHan corporation
  - Chong Kun Dang pharmaceutical corporation
  - Samyang Biopharm
  - MSD
  - Seasun Biomaterials, Inc.

PPLs (peripheral pulmonary lesions)

- Focal radiographic opacities not detectable beyond the visual segmental bronchi by flexible bronchoscopy
- **Nodules**
  - *solid*
  - *subsolid : pure GGN, psGGN*
  - *cystic or cavitary*
- **Consolidation-type or pneumonic type**

Table 1. Comparison of navigation technologies for PPLs.

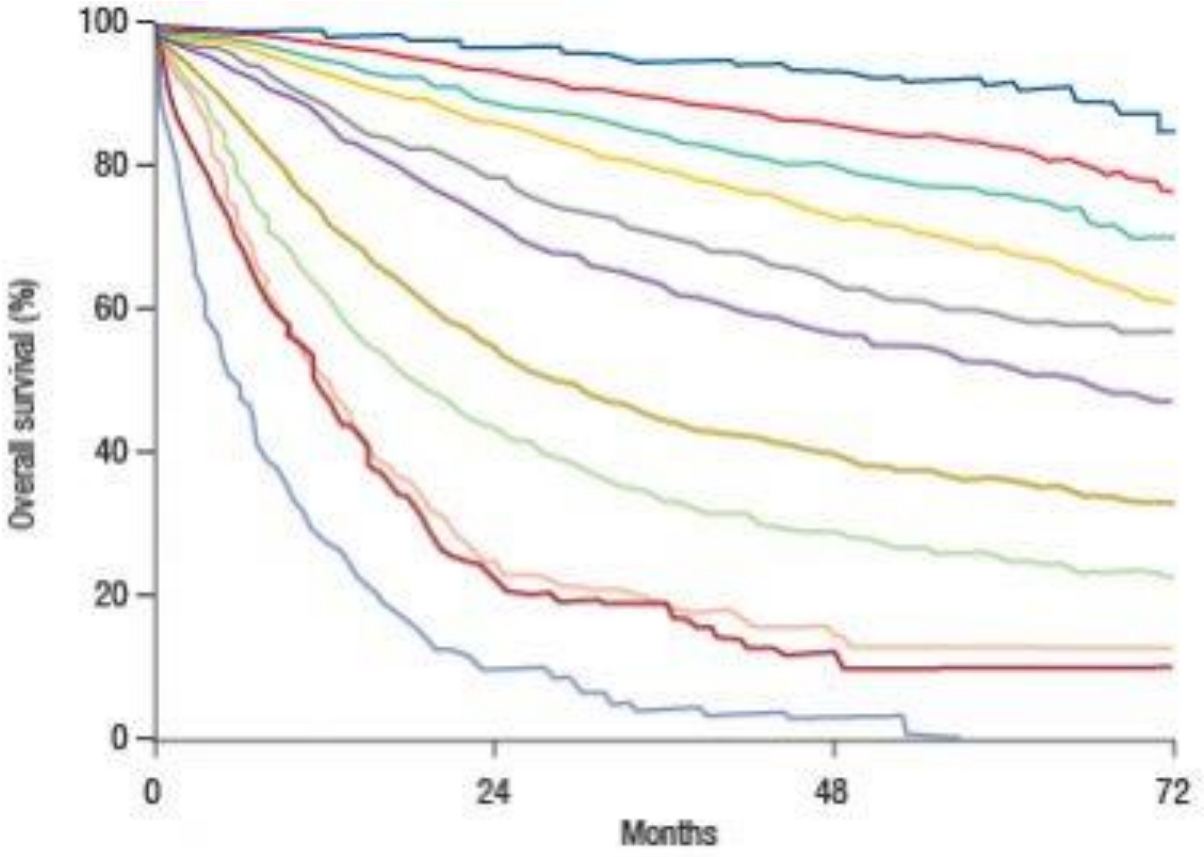
Method	Advantages	Disadvantages
Ultrathin bronchoscopy	• Affordable • Easily introduced into an already-established clinical practice	• Operator-dependent tip stability • Small working channel
RP-EBUS	• Affordable • Easily introduced into an already-established clinical practice	• Need to interpret artifacts • No real-time guidance during sampling
Virtual navigation bronchoscopy	• Active navigation correction according to preprocedural planning • BTPNA	• CT-to-body divergence • Absence of real-time position correction by fluoroscopy
EMN	• Active navigation correction according to preprocedural planning • Ability to associate real-time navigation correction with fluoroscopy • Real-time guidance during sampling	• CT-to-body divergence • Interference with metallic objects and other magnetic fields
Shape-sensing navigation	• Operator-independent tip stability	• Expensive in terms of acquisition (at present only within robotic bronchoscopy technology)
Augmented fluoroscopy	• Real-time navigation correction with fluoroscopy	• Expensive in terms of acquisition
CBCT	• The gold standard for tool-in-lesion confirmation	• Expensive in terms of acquisition • Non-negligible radiation exposure
Robotic bronchoscopy	• Integration of a navigation system within an articulating catheter that can be used for multiple purposes	• Expensive both in terms of acquisition and consumables • Technical demanding • Requires general anesthesia • CT-to-body divergence

RP-EBUS, radial-probe endobronchial ultrasound; BTPNA, bronchial transparenchymal nodule access; EMN, electromagnetic navigation; CBCT, cone-beam computed tomography.

Lung Biopsy Issues in PPLs

- *Diagnostic procedure : invasive and potential complications*
- *Small biopsy issue : "Tissue is the issue" in the era of precision medicine*
- *High cost and under general anesthesia : robotic brochoscopy*
- *Operator dependent : no clear-cut guideline*
- *Surgical biopsy w/o pre-op evaluation in stage 1 lung cancer*
- *15% of surgical biopsy : benign diseases*
- *The matter of Dx delay : increase post-op recurrence rate*

Staging and survival of lung cancer : the 8th TNM classification



Staging	60-month overall survival (%)
IA1	92
IA2	83
IA3	77
IB	68
IIA	60
IIB	53
IIIA	36
IIIB	26
IIIC	13
IVA	10
ICB	0

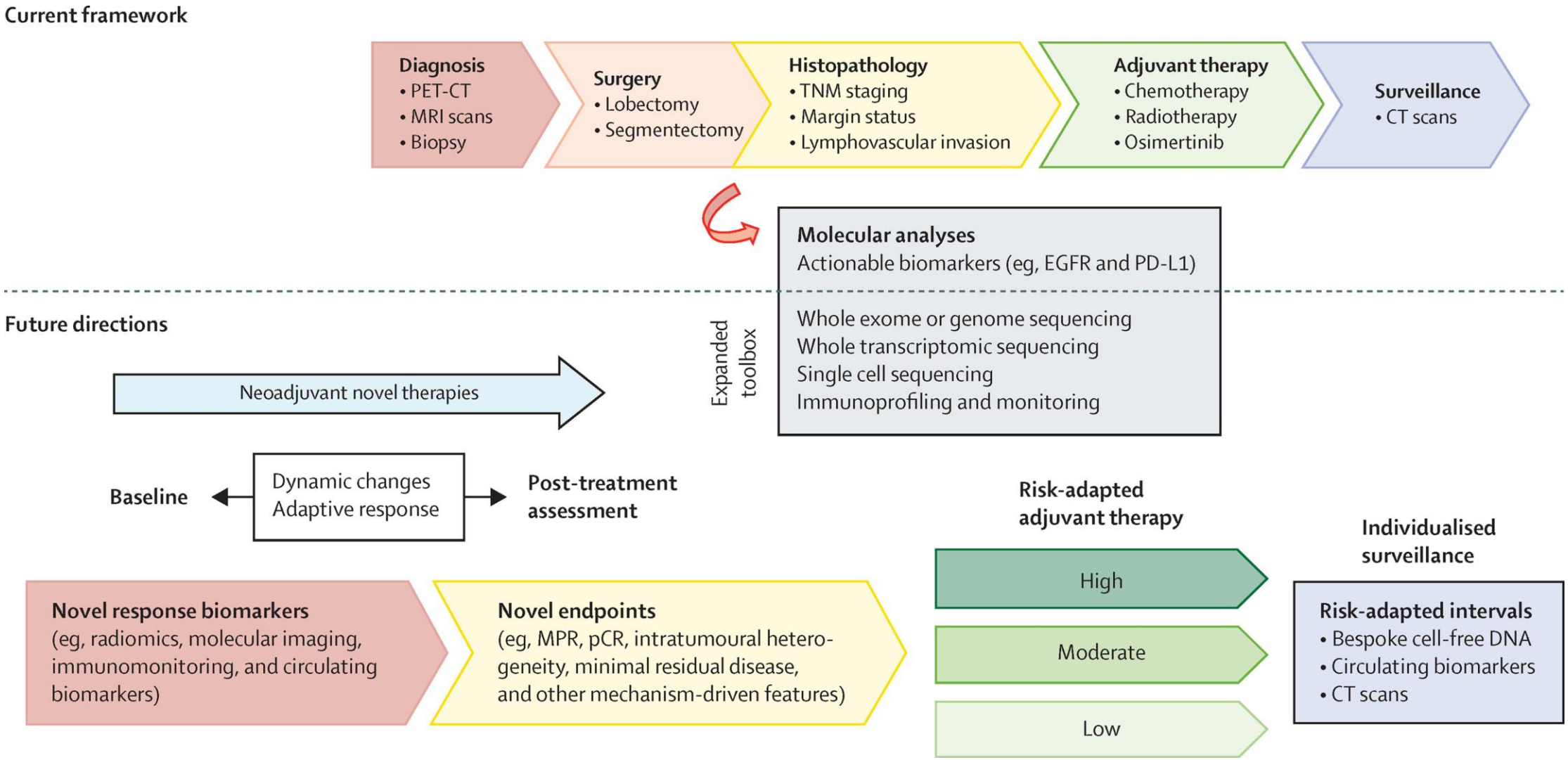
비소세포폐암 5년 생존율 (%)

	1기				2기		3기			4기	
Type	IA1	IA2	IA3	IB	IIA	IIB	IIIA	IIIB	IIIC	IVA	IVB
임상 병기	92	83	77	68	60	53	36	26	13	10	0
최종 병기	90	85	80	73	65	56	41	24	12	-	-

진단시 병기별 환자 분포	25-30%	5-6%	25%	40%

- 수술 가능 1,2기 초기 폐암이 적고, 전이성 4기가 절대적으로 많다.
- 수술 후 재발율이 높다.

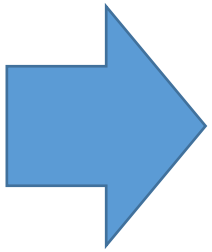
- **조기폐암 진단율 향상**
- **수술 후 재발 방지 전략**



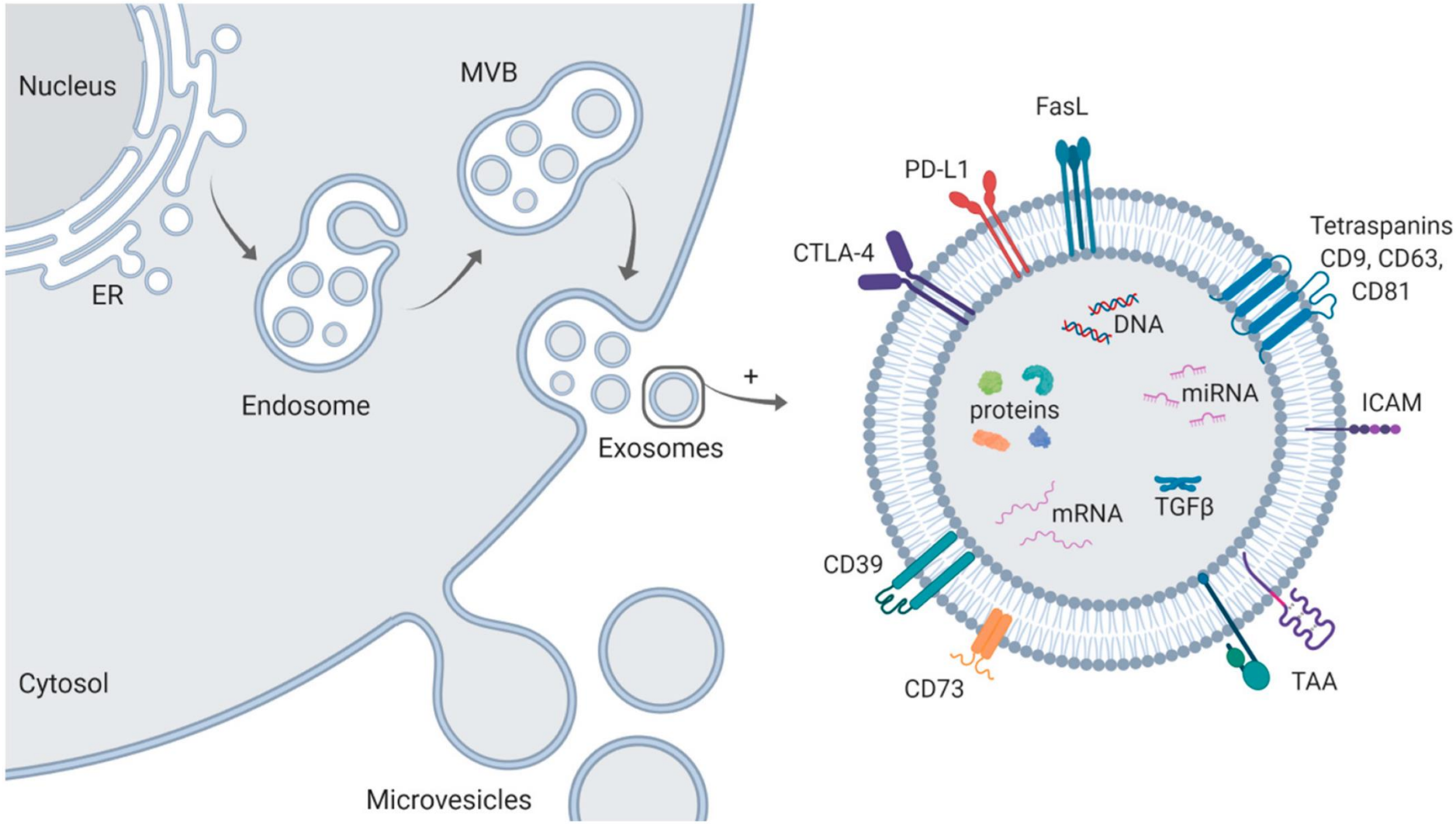
Neoadjuvant treatment of early-stage NSCLC with an adaptive approach

(Stephanie P L saw, et al. Lancet Oncol 2021)

Paradigm shift of early lung cancer diagnosis (from tissue biopsy to liquid biopsy)

Cell-based Dx  *Gene/Molecular Dx*

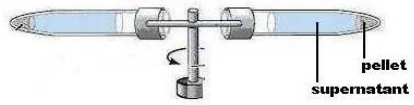
Exosomes/Extracellular Vesicles : The Messengers of Cancer Cells



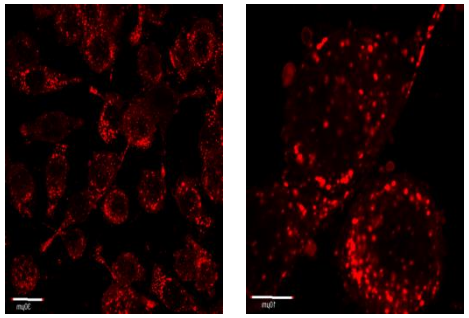
Extracellular vesicles contain cell-specific mutant oncogenic DNA

- **PC9 cells** : EGFR exon19 mutant cells – gefitinib sensitive
- **PC9/GR cells** : exon 19 del + T790M 2nd mutation – gefitinib resistant
- **H1975 cells** : exon 21 L858R + T790M de novo mutation

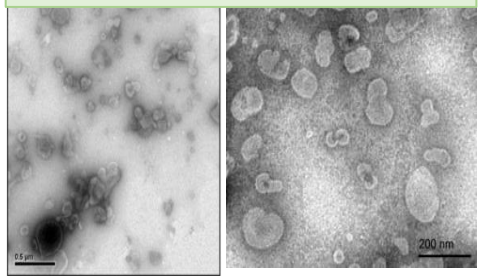
- Isolation of EVs by ultracentrifuge from culture supernatant



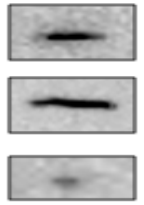
- Charaterization of EV



Electron Microscopy



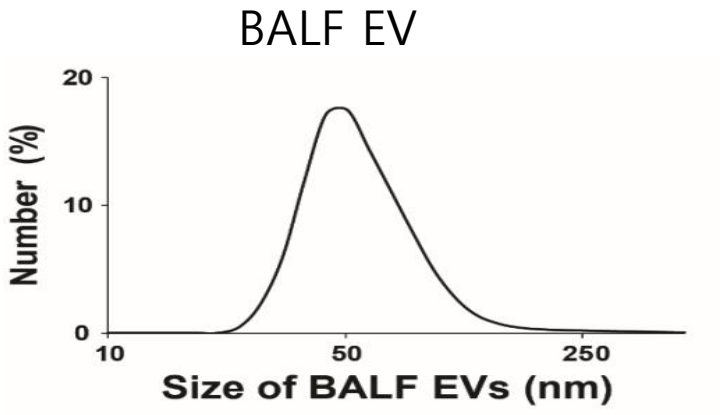
Western Blotting

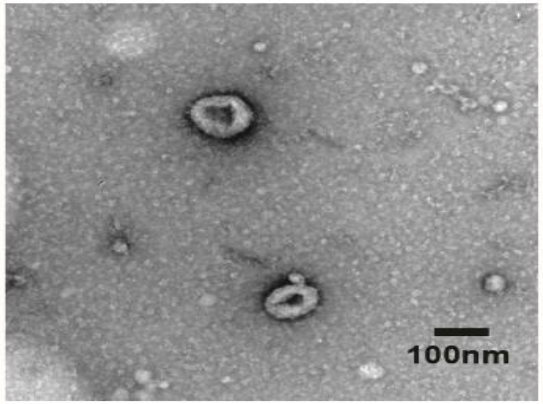


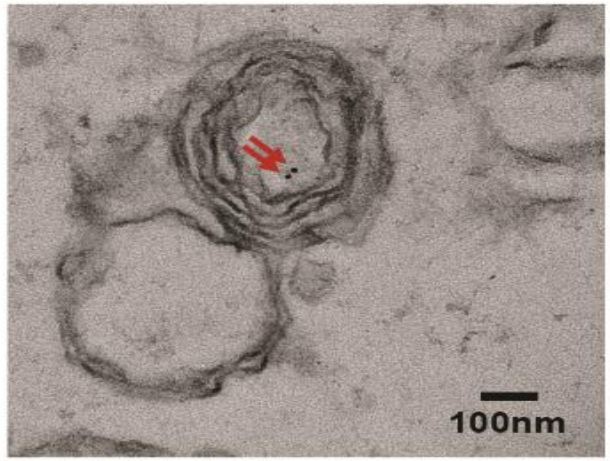
- EV DNA extraction and EGFR genotyping

	Cellular DNA	EV DNA
PC9 cells	19 del	19 del
PC9/GR cells	19 del + T790M	19 del + T790M
H1975 cells	L858R + T790M	L858R + T790M

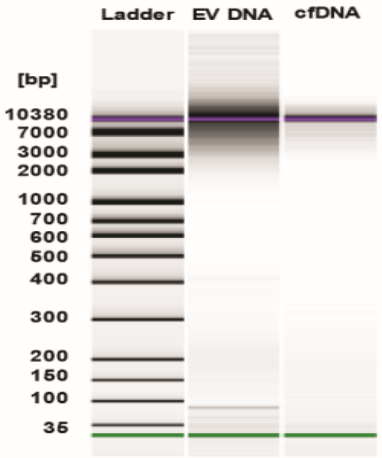
Detection of oncogenic dsDNA in EVs isolated from BALF of EGFR-mutated NSCLC patients

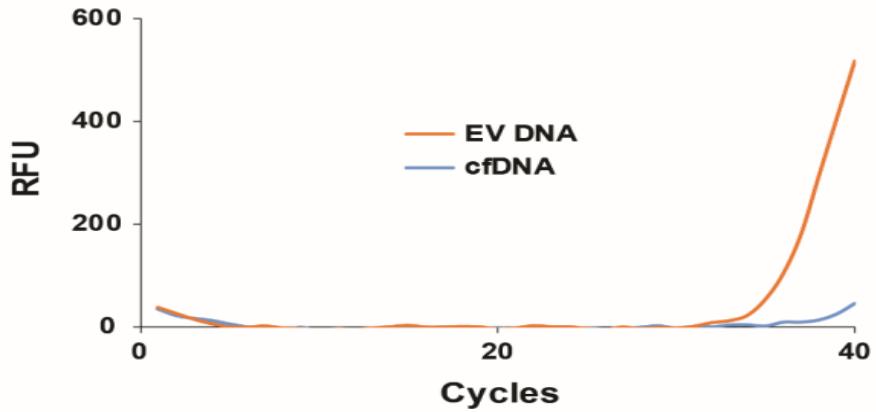






Immuno-EM by anti-dsDNA Ab



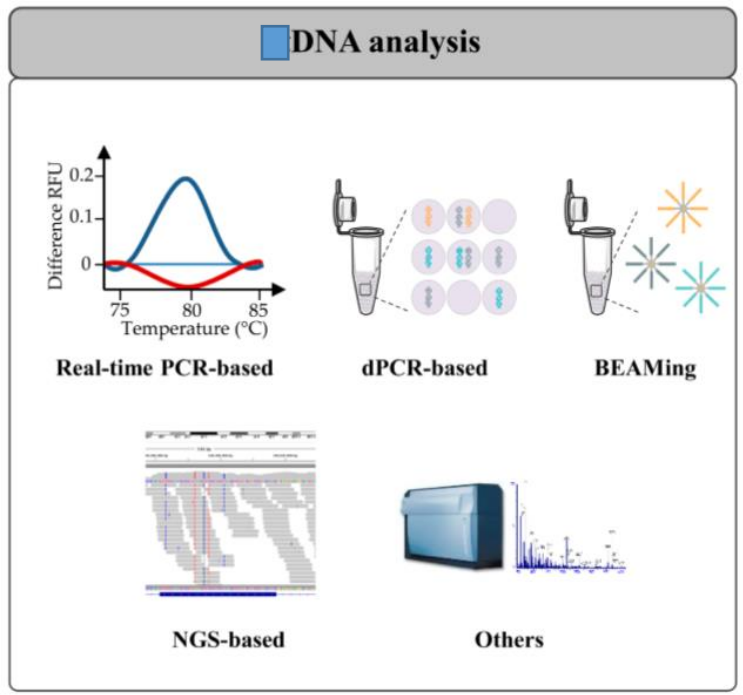


(JY Hur, KY Lee, et al. Molecular Cancer in 2018)

Table 1. Comparison of EV DNA and cfDNA

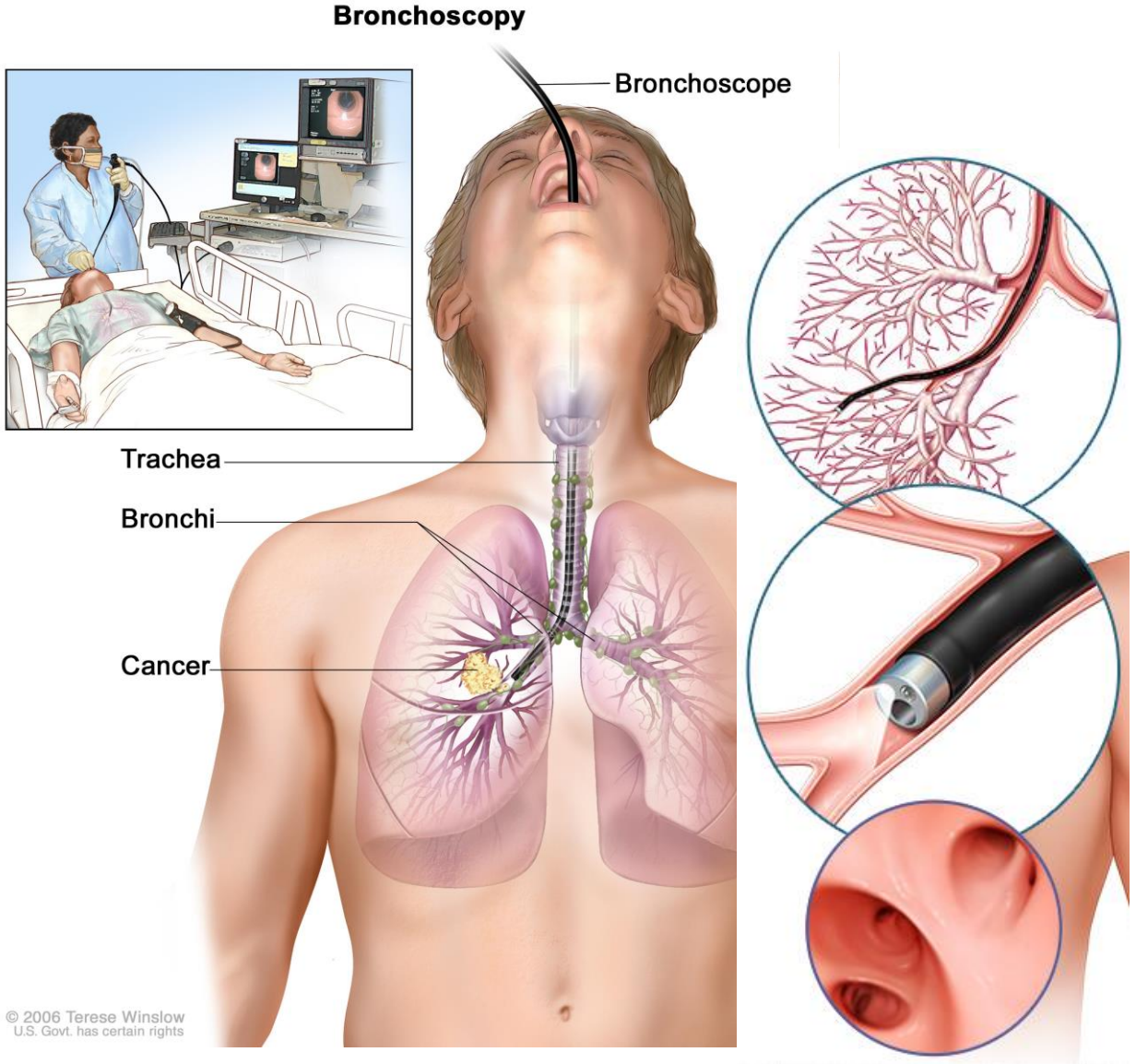
	EV DNA	cfDNA
Origin	Actively shed or secreted by cancer cells	Passive product of cell death
Size	Long (~10 kb)	~200 bp
Stability	High stability due to protection by double layered membrane	Short half-life (2–2.5 hr)
Isolation	Technically sophisticated	Easy and convenient

EV, extracellular vesicle; cfDNA, cell-free DNA.



Exosome-based BALF Liquid Biopsy (ExoBAL)

- Relatively noninvasive procedure
- Just endoscopy under sedation
- **Unique accessible way to tumor and or TME site without biopsy**
- 100-300 ml saline infusion and retrieval of BALF by gentle negative pressure
- Bronchoalveolar lining cells and noncellular components containing EV shed from TME
- **Highly enriched tumor cell released EV**
- **Advantage in peripheral lung tumor, especially adenocarcinoma**



Performance of EV-based BALF liquid biopsy for EGFR mutation testing in advanced non-squamous NSCLC

EGFR genotype	Tissue	BALF (n=224)		Tissue	plasma (n=110)	
		Mutant type	Wild type		Mutant type	Wild type
Mutant type	93	91	2	66	32	34
Wild type	131	3	128	44	6	38
Sensitivity	**97.8%**(91/93) (95% CI, 92.4-99.7)			**48.5%** (32/66) (95% CI, 36.6-61.1)		
Specificity	**96.9 %** (128/131) (95% CI, 93.5-99.5)			**86.3%** (41/49) (95% CI, 72.6-94.8)		
PPV	**96.8%**(91/94)			**84.2%** (32/38)		
NPV	**98.4%** (128/130)			**52.7%** (38/72)		
Concordance rate	**97.7%** (91+128)/224			**63.6%** (32+38)/110		

PPV, positive predictive value; NPV, negative predictive value;

(*IA KIM, et al. Cancers 2022*)

Turnaround time(TAT)

Table 4. Comparison of the turnaround time of EGFR mutation testing using BALF vs. tissue samples.

Sample Type	Mean (Days)	Median (Days)	*p*-Value
BALF	2.6 ± 2.03	2	<0.001
Tissue	13.9 ± 12.4	12	

Original Article

A prospective phase 2 study of expeditious *EGFR* genotyping and immediate therapeutic initiation through extracellular vesicles (EV)-based bronchoalveolar lavage fluid (BALF) liquid biopsy in advanced NSCLC patients

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Contributions: (I) Conception and design: IA Kim, HJ Kim, KY Lee; (II) Administrative support: IA Kim, HJ Kim, WS Kim; (III) Provision of study material or patients: All authors; (IV) Collection and assembly of data: IA Kim, JY Hur, HJ Kim, KY Lee; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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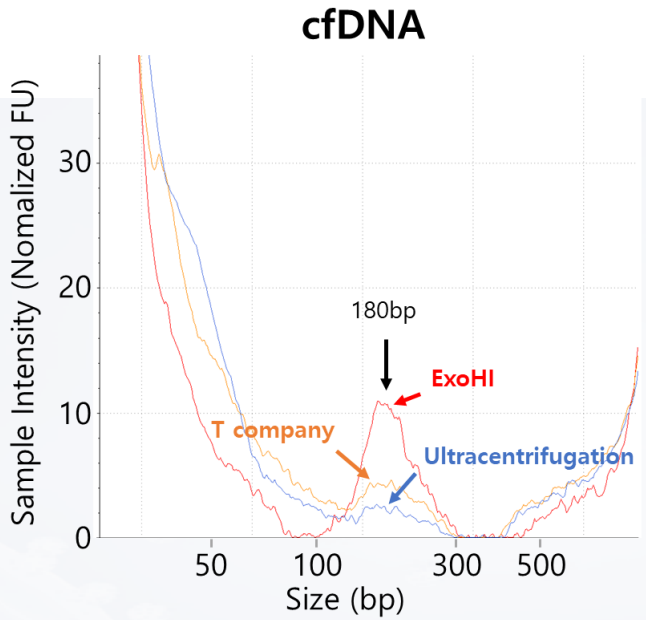
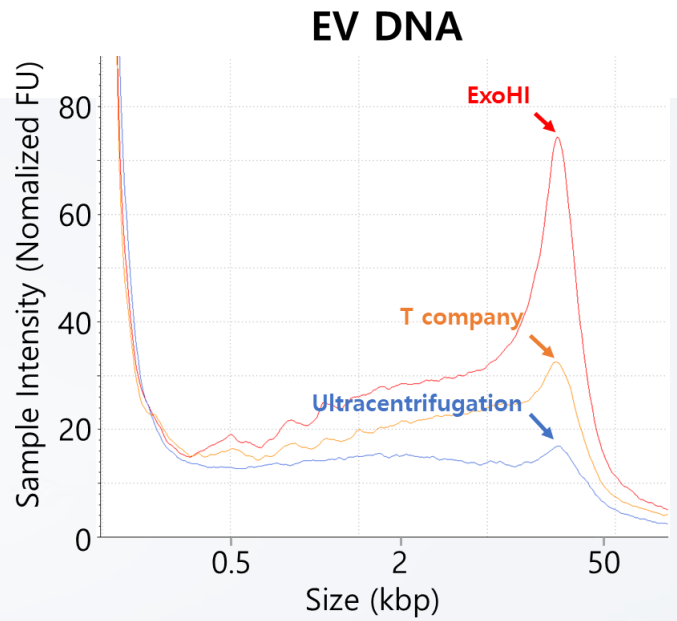
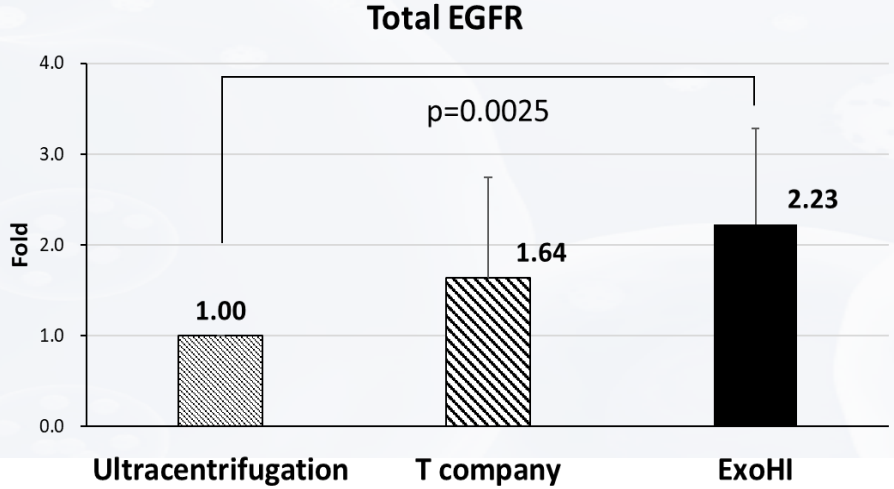
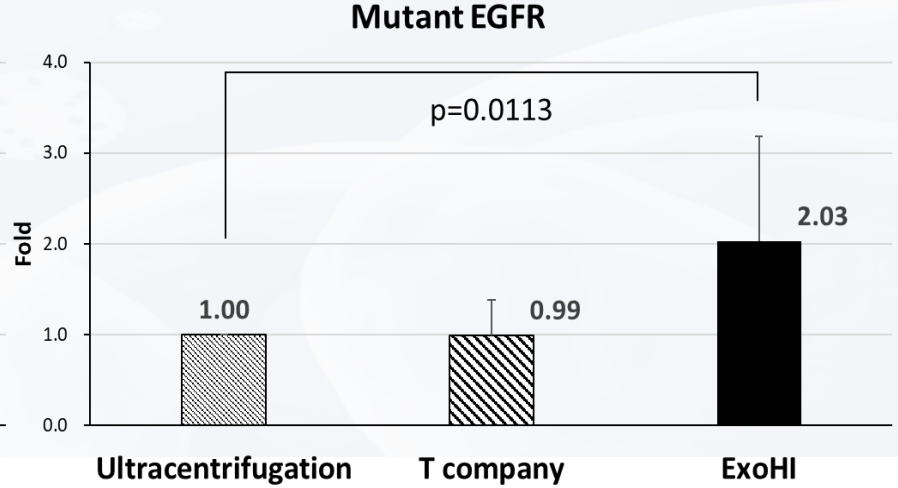
BALF 전용 DNA Prep 키트

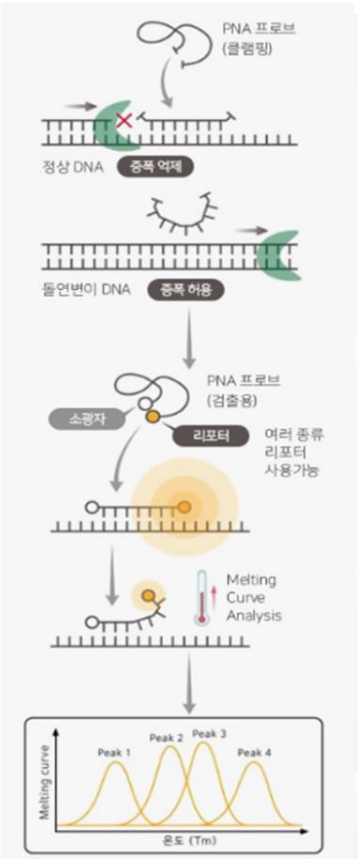




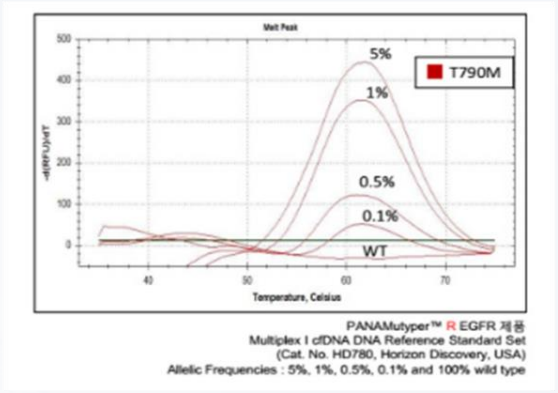




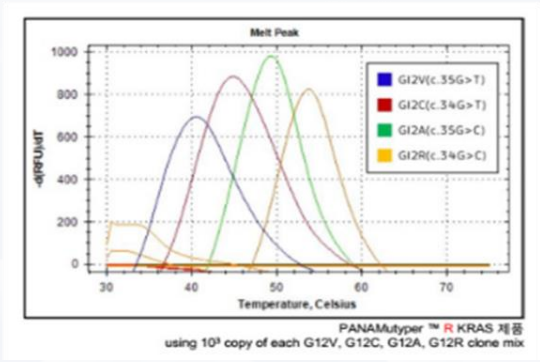
BALF 전용 EGFR 돌연변이 검출 키트



0.1 % 수준의 미량 돌연변이 검출 가능



돌연변이 유전자 genotyping 가능 (Tm)



- 획기적인 Turnaround time(TAT) 단축

Table 4. Comparison of the turnaround time of EGFR mutation testing using BALF vs. tissue samples.

Sample Type	Mean (Days)	Median (Days)	*p*-Value
BALF	2.6 ± 2.03	2	<0.001
Tissue	13.9 ± 12.4	12	

- **Real time PCR 기반의 유전자 증폭 기술로 편의성, 보급성, 신속성, 정확성이 우수함**
- **EGFR 유전자 돌연변이에서 KRAS, BRAF, HER2 등으로 유전자 범위를 확대할 예정**

EGFR 변이 양성 진행성 비소세포폐암 환자 검출에 대한 ExoBAL™ EGFR mutation Test의 진단능 평가와 1차 Lazertinib의 유효성을 평가하기 위한 다기관, 단일군 2상 연구

A multicenter, single-arm phase 2 study to evaluate the diagnostic performance of ExoBAL™ EGFR mutation test and efficacy of first-line Lazertinib in advanced non-small cell lung cancer patients harboring EGFR mutations

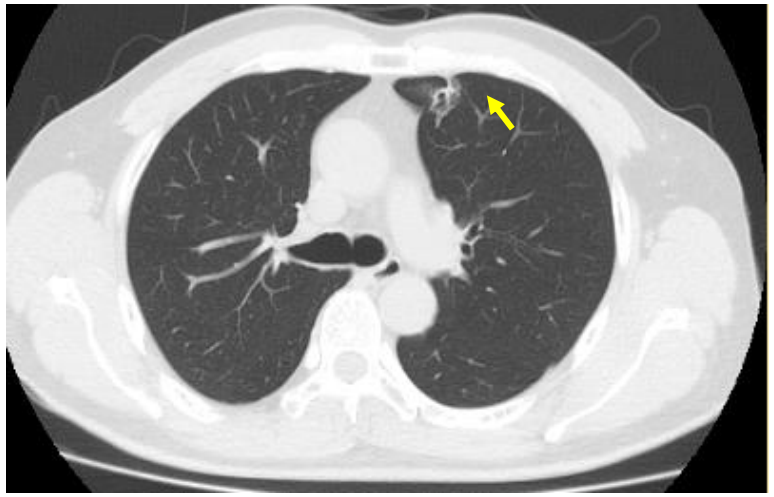
(1L-Laz-BAL study)

Application of ExoBAL in PPLs

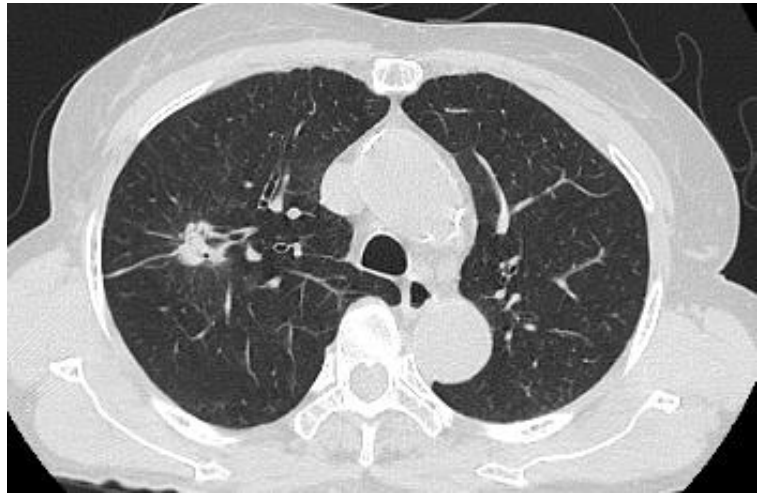
: *DDX of early stage lung cancer w/o tissue biopsy*

Early stage mEGFR adenocarcinoma cases detected by ExoBAL w/o tissue biopsy

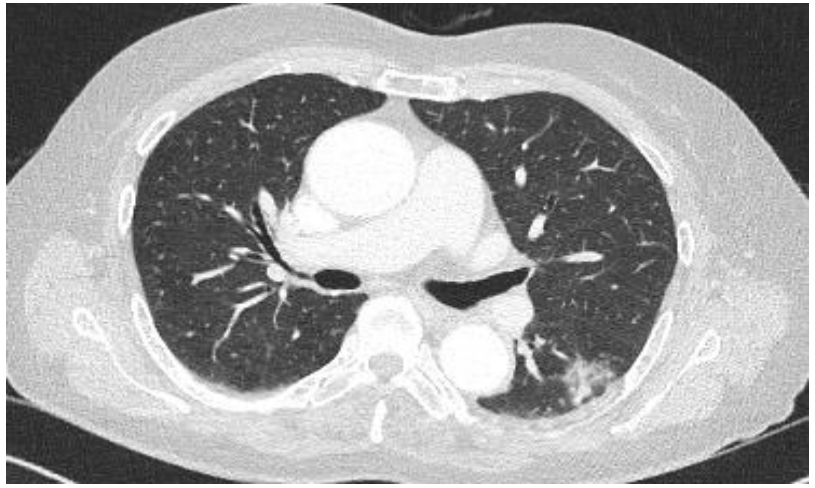
46/M never smoker : ExoBAL L858R



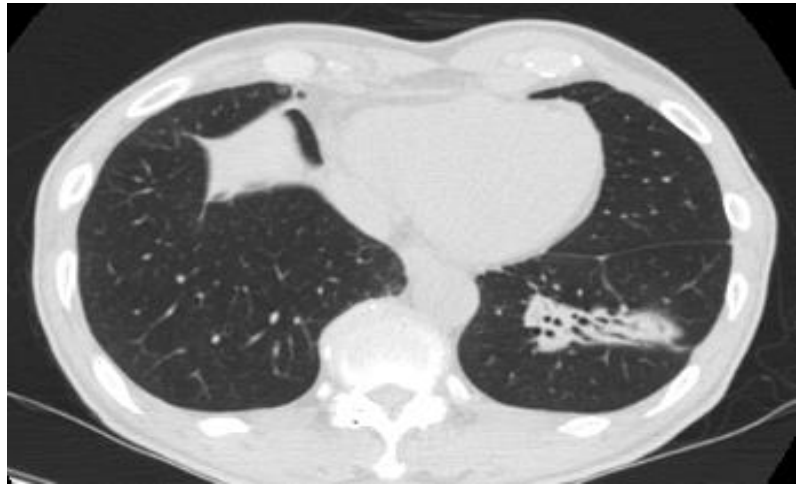
70/F never smoker : ExoBAL L858R



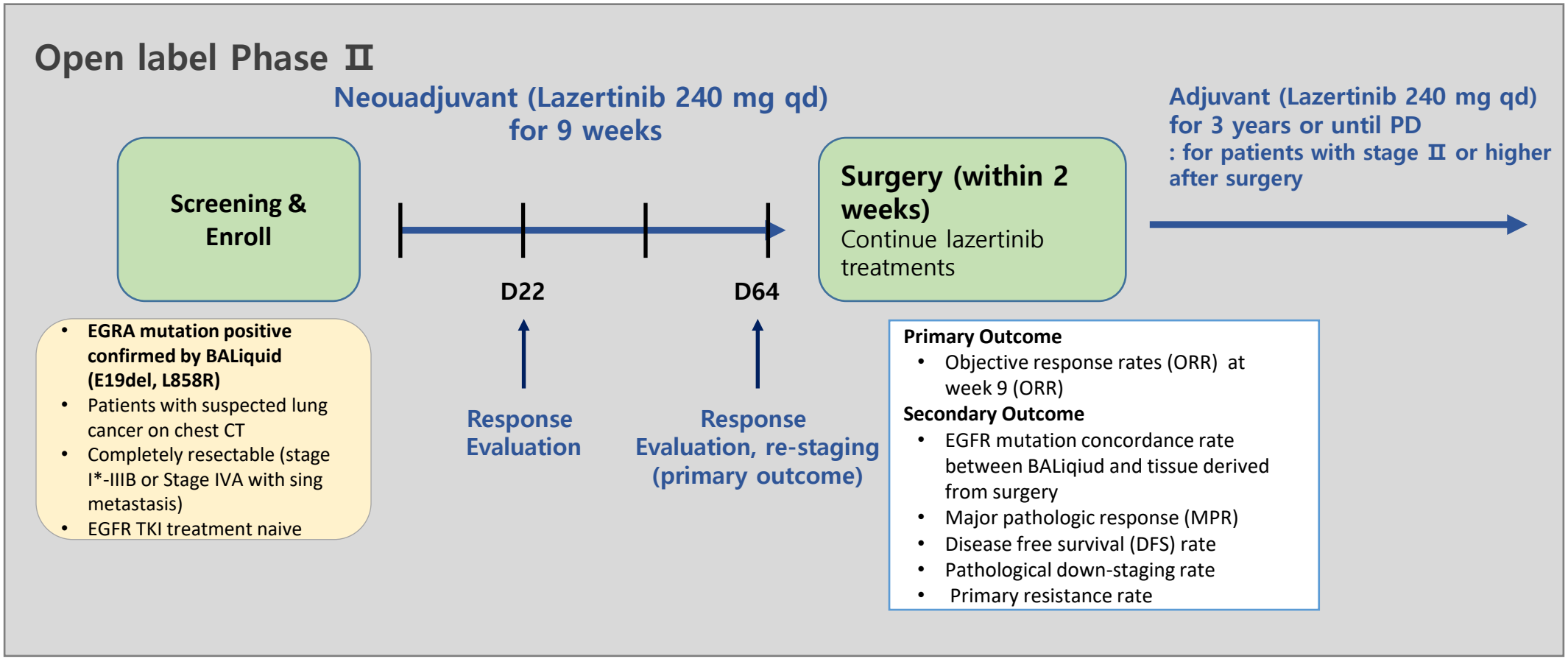
73/F never smoker : ExoBAL L861Q



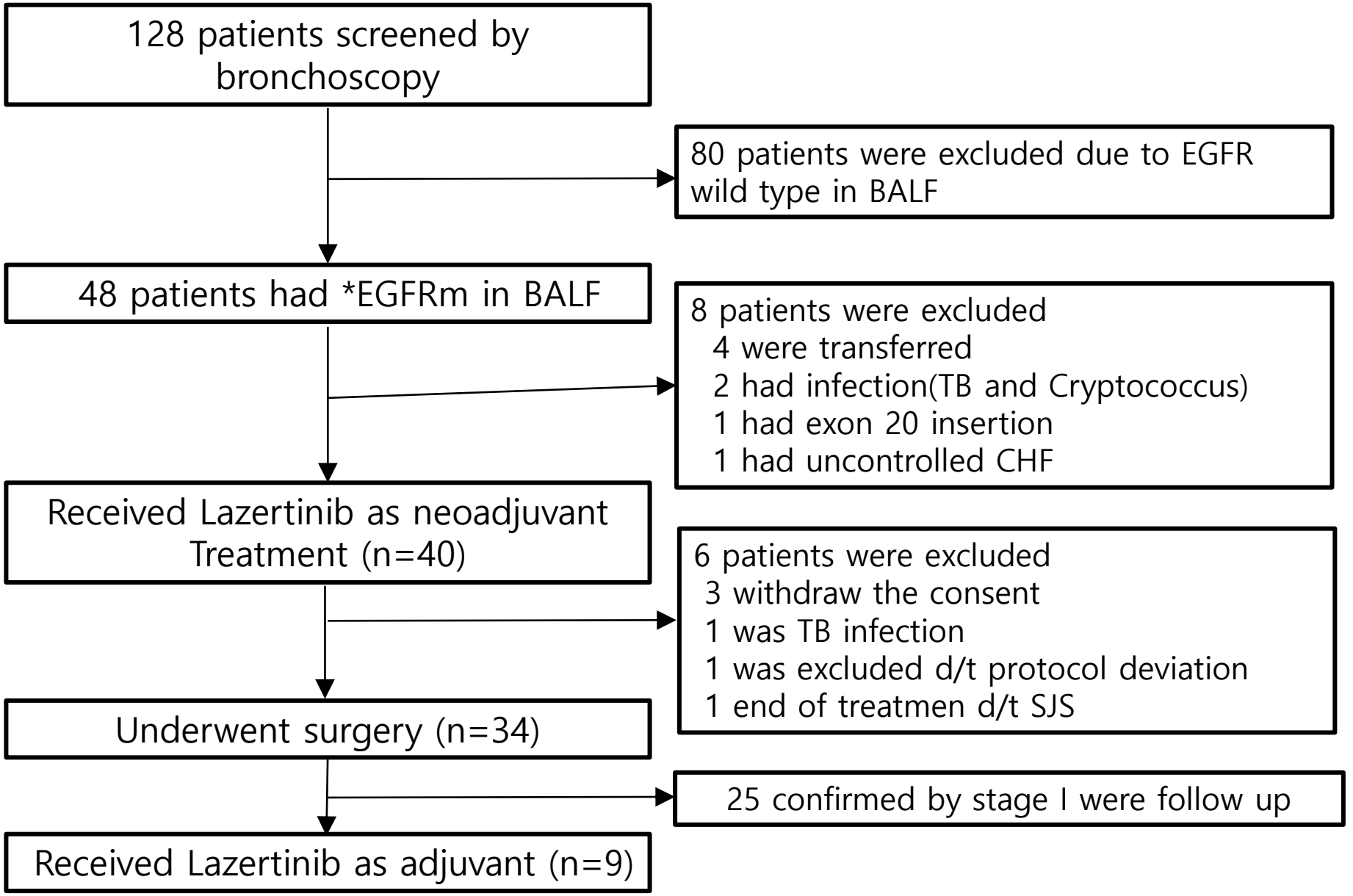
76/M never smoker : ExoBAL E19del



A Phase 2, Single Center, Single Arm, Prospective Study of Neoadjuvant Lazertinib Therapy in Resectable EGFR-Mutation Positive Lung Adenocarcinoma Patients Detected by Bronchoalveolar lavage fluid(BALF) Liquid Biopsy (NCT 05469022 : NeoLazBAL)



Study Flow



*Sensitive EGFR mutation(EGFRm) had 21L858R or E19Del or rare mutation combination.
Abbreviation: BALF, bronchoalveolar lavage; SCLC, small cell lung cancer.

Characteristics	N (%)
All patients	34
Age (Median)	
<65 years	11 (34.2)
≥65 years	23 (65.8)
Sex	
male	15 (45.7)
Female	19 (54.3)
Smoking history	
Never-smoker	24 (68.5)
Ex-smoker	7 (20.0)
Current smoker	3 (11.5)
Clinical stage	
I	19 (54.3)
II	5 (14.3)
III	9 (25.7)
IVA	1 (2.9)
Pathological stage	
I	24 (70.6)
II	4 (11.8)
III	5 (14.3)
IVA	1(2.9)

Histology	N(%)
Adenocarcinoma	33 (97.2)
Adenosquamous car.	1(2.8)
EGFR type (BAL)	
19 del	20 (60.0)
21 L858R	14 (40.0)
EGFR type (Tissue)	
19 del	19 (57.2)
21 L858R	14 (40.0)
WT	1 (2.8)
Operative procedure	
Lobectomy	31 (91.4)
Segmentectomy	1 (2.8)
Wedge resection	2 (5.7)

Primary outcome : Objective response rate

Response	N =34, N (%)
Partial response	19 (55.8%)
Stable disease	15 (44.2%)
ORR (CR+PR)	19/34 (55.8%)
DCR (CR+PR+SD)	34/34 (100%)

Concordance rate of EGFR mutation in tissue and BALF

EGFR genotype	Tissue	BALF (n=83)	
		Mutant type	Wild type
Mutant type	44	34	10
Wild type	39	1	38
Sensitivity	**77.3 %** (34/44)		
Specificity	**97.4 %** (38/39)		
PPV	**97.1 %** (34/35)		
NPV	**79.1 %** (38/48)		
Concordance rate	**84.1 %** (31+38)/82		

Down-staging rate

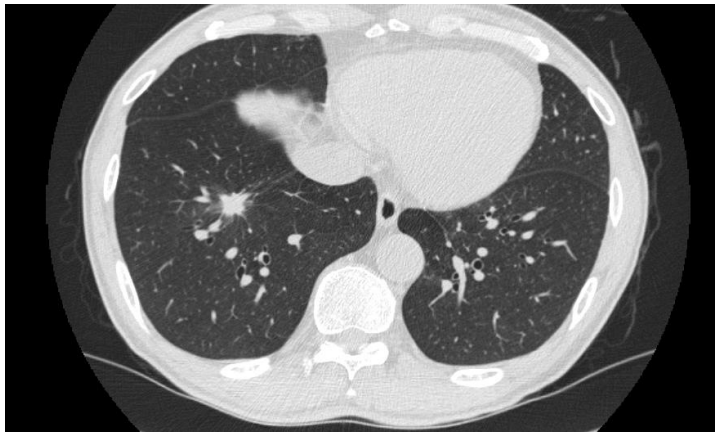
Clinical stage	Pre tissue (N)	Down stage (N)	%
I	19	4	21%
II	5	4	80%
III	9	6	75%
IVA	1	1	100%
Total	34	15	**44.1%**

Summary of NeoLazBAL study

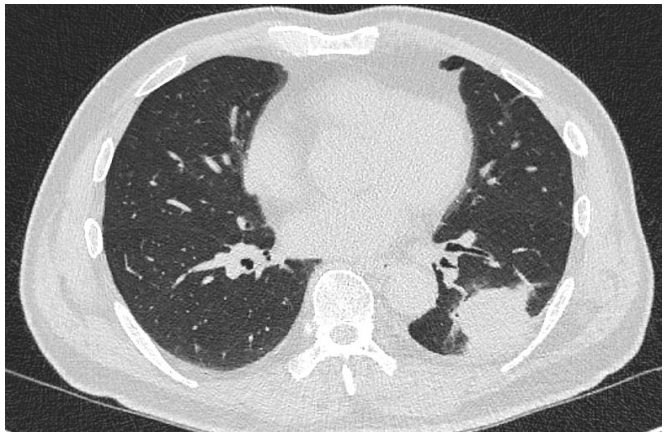
- Screen :128 pts
- Enroll : 40 pts
- RR : 55.6%
- Stage down rate : 47%
- Surgery : 35 pt
- MPR rate : 6 of 35 (17.1 %)

mKRAS adenocarcinoma cases detected by ExoBAL KRAS w/o tissue biopsy

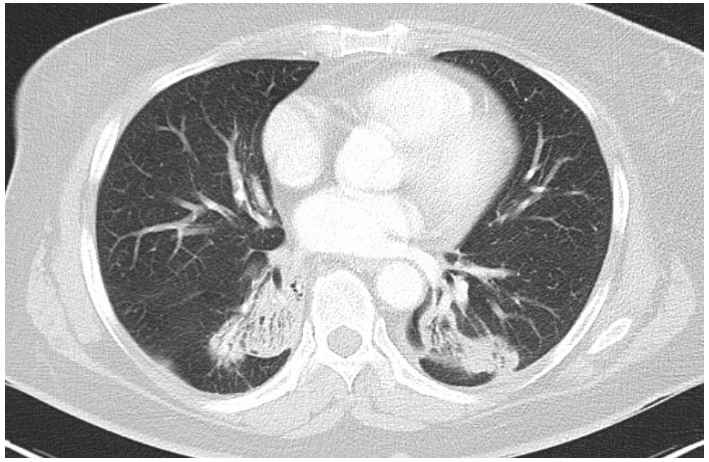
M/62 smoker ExoBAL G12C



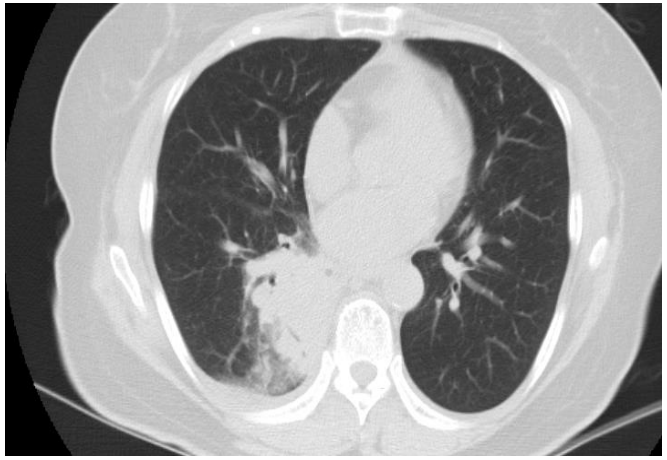
M/66 smoker ExoBAL G12V



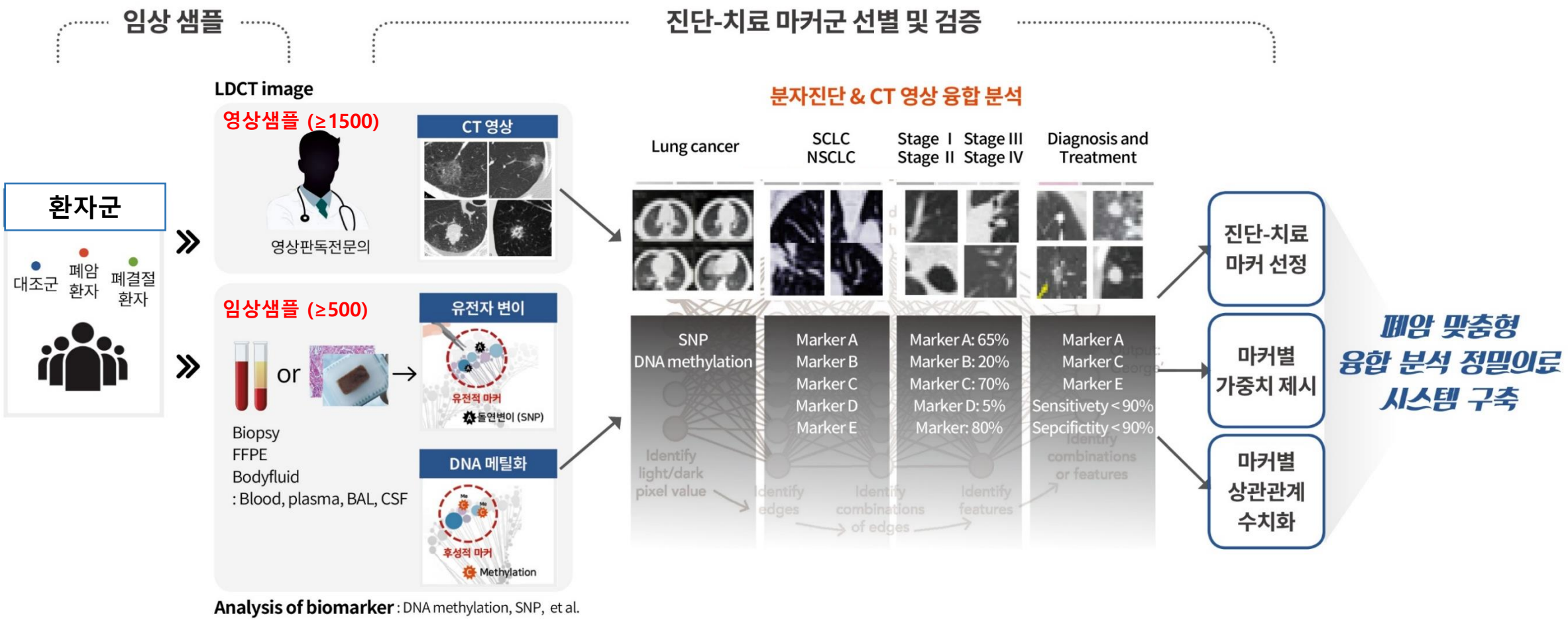
F/62 never smoker ExoBAL G12D

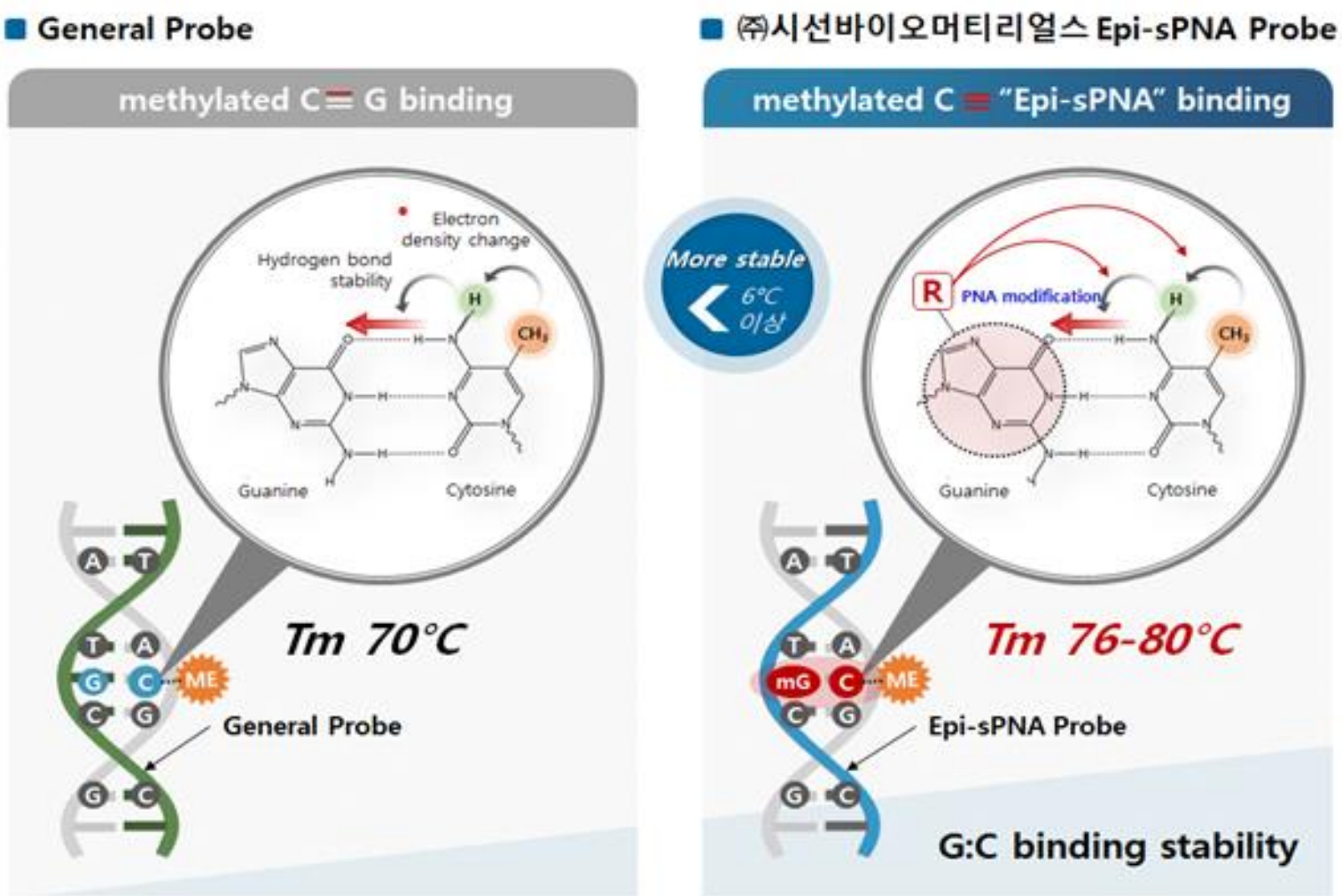


F/57 never smoker ExoBAL G12D



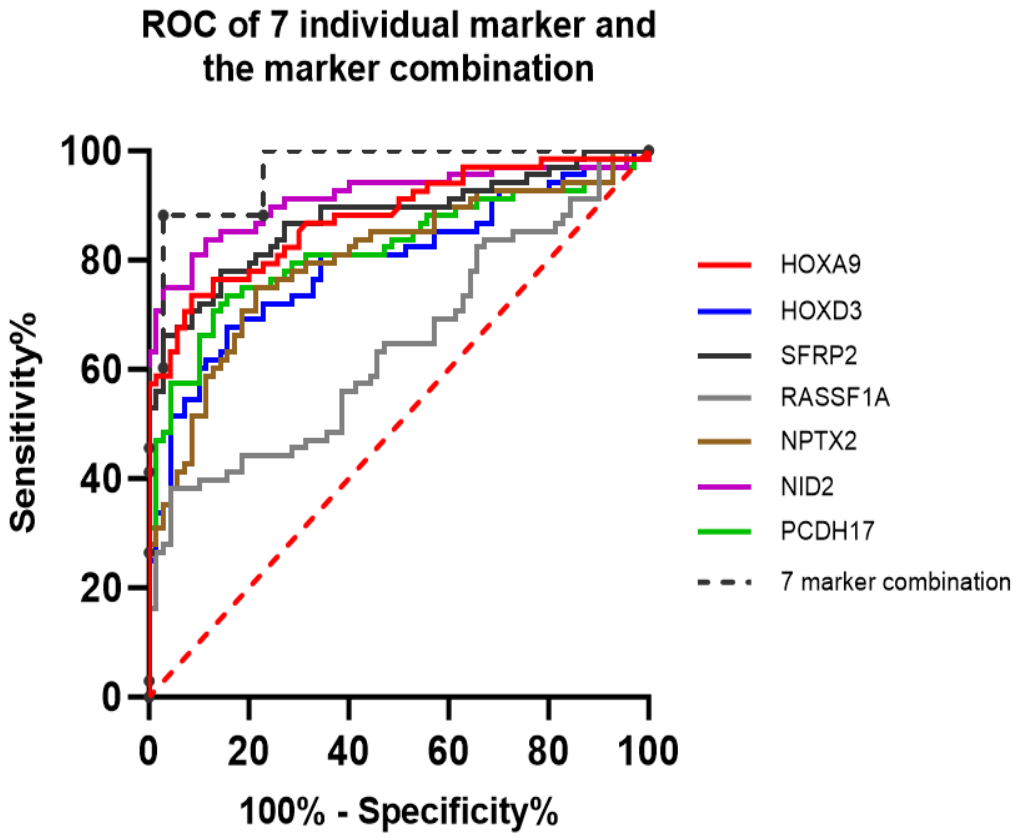
“저선량 흉부 CT 와 DNA 메틸화 통합분석을 통한 폐암 선별 및 예후예측 모델 개발 ”





Epi-sPNA probe기반 Epi-TOP™ DNA 메틸화 검출 원천기술

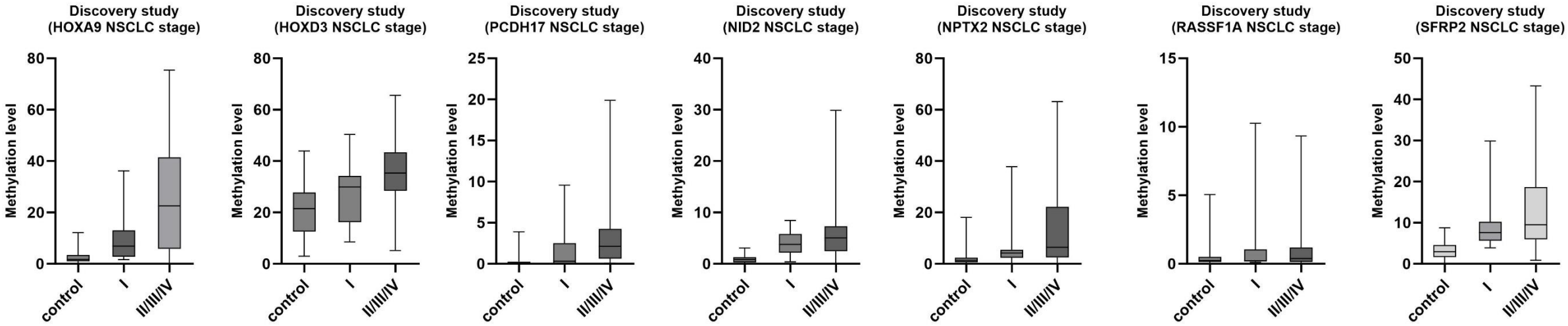
Discovery cohort: Selection of Lung cancer specific epigenetic biomarkers



#	Gene	Sensitivity (%)	Specificity (%)	AUC (p<0.0001)
1	HOXA9	73.53	91.43	0.88
2	HOXD3	80.88	65.71	0.79
3	PCDH17	73.53	84.29	0.82
4	NID2	83.82	88.57	0.91
5	NPTX2	75.00	77.14	0.80
6	RASSF1A	38.24	95.71	0.64
7	SFRP2	77.94	85.71	0.87
8	**7 gene combined panel**	**88.24**	**97.14**	**0.97**

- DNAs extracted from 138 clinical BALF exosome samples (70 lung benign disease (control) and 68 lung cancer) underwent the real-time PCR methylation assay targeting tumor suppressor gene promoters which are linked to early lung cancer development
- 7 genes which have been showed highest discrimination rate between lung cancer and non-cancer group were selected, and lung cancer prediction model was constructed using logistic regression

Discovery cohort: Mean Methylation Level of each marker in per NSCLC early and advanced stages

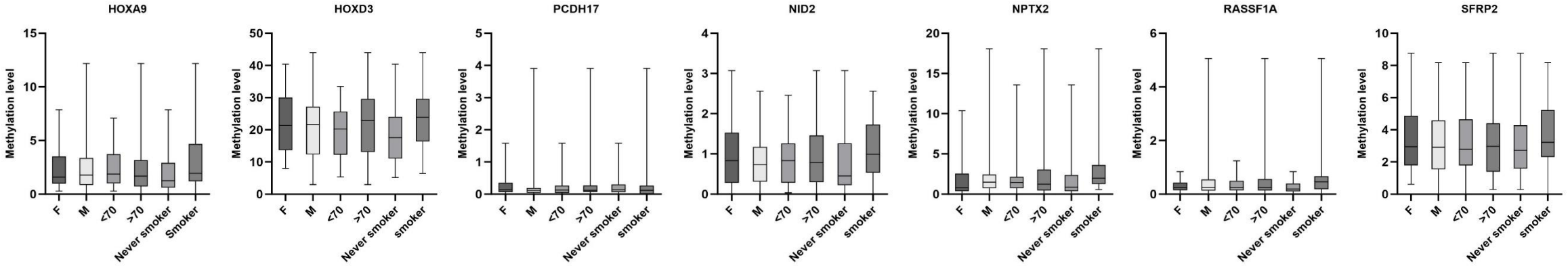


Gene	Control (n=70)	Stage I (n=13)			Stage II/III/IV (n=39)		
		I	Fold change	P value	II/III/IV	Fold change	P value
HOXA9	2.505	10.16	4.06	<0.0001	26.72	10.67	<0.0001
HOXD3	20.8	27.75	1.33	0.0717*	34.70	1.67	<0.0001
PCDH17	0.2722	1.74	6.39	0.0005	3.71	13.61	<0.0001
NID2	0.9007	4.13	4.59	<0.0001	6.81	7.56	<0.0001
NPTX2	2.255	6.31	2.80	0.0094	14.77	6.55	<0.0001
RASSF1A	0.4033	1.21	3.01	0.0433	1.27	3.16	0.0015
SFRP2	3.279	9.30	2.84	<0.0001	12.98	3.96	<0.0001

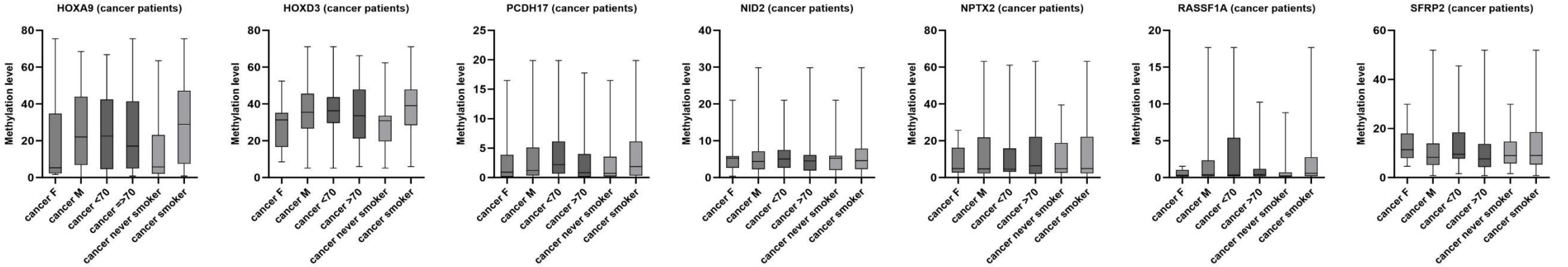
All seven markers showed higher Mean Methylation Level (MML) fold changes in NSCLC advanced stages (II, III, IV) than early stage (I) when comparing with the methylation level of control group

Discovery cohort: Methylation Level distributions among patient's age, sex and smoking history

Non cancer



Cancer

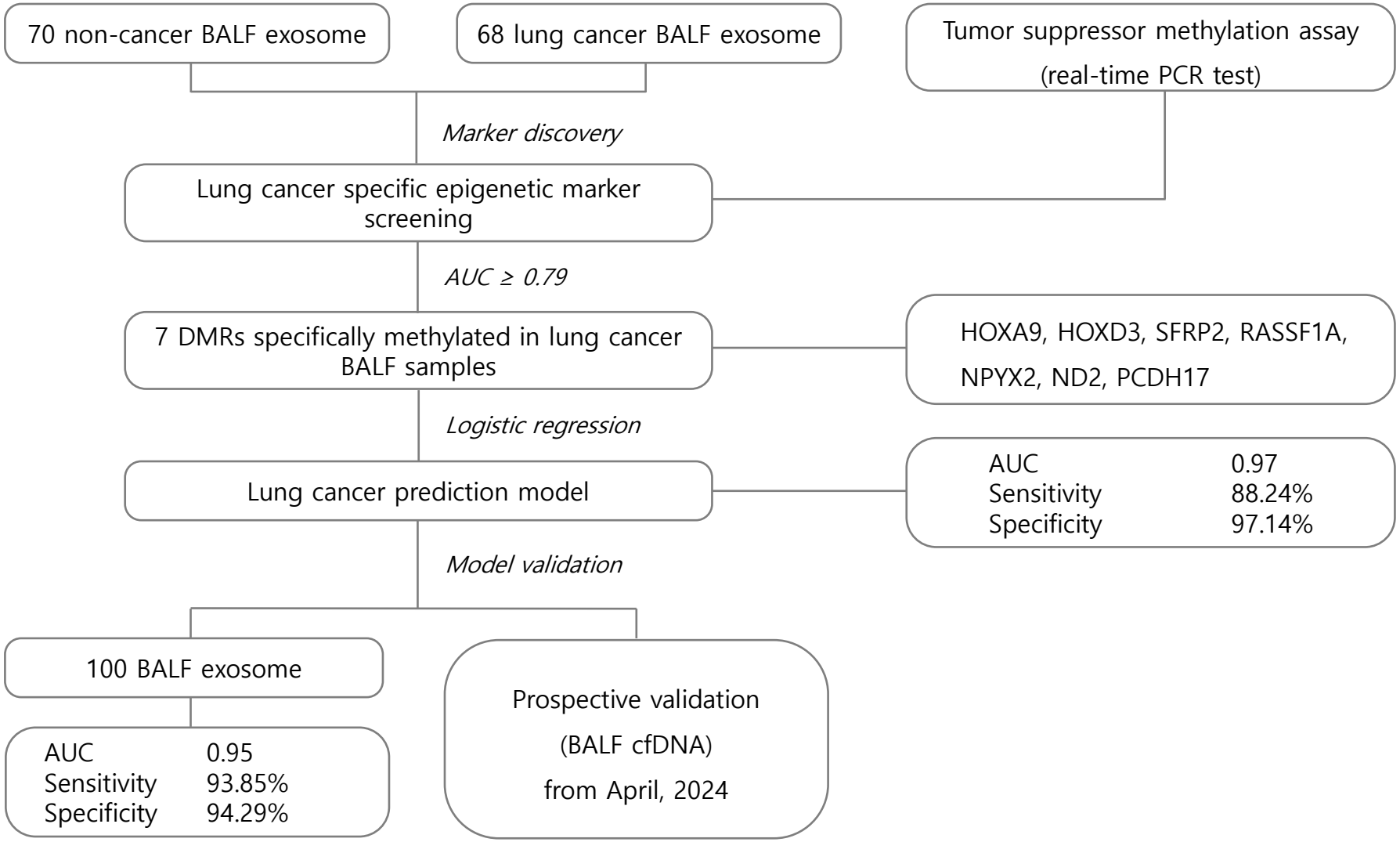


Mean methylation level of each 7 biomarker were found to be moderately elevated with increasing patient age and smoking history, irrespective of patient sex

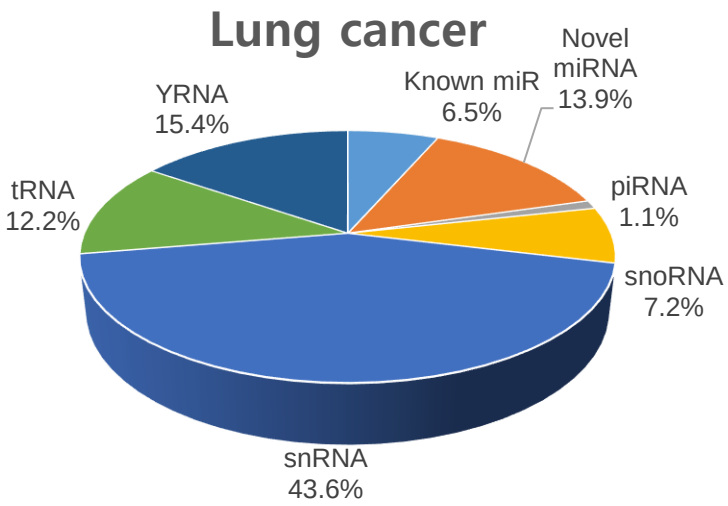
Validation cohort result

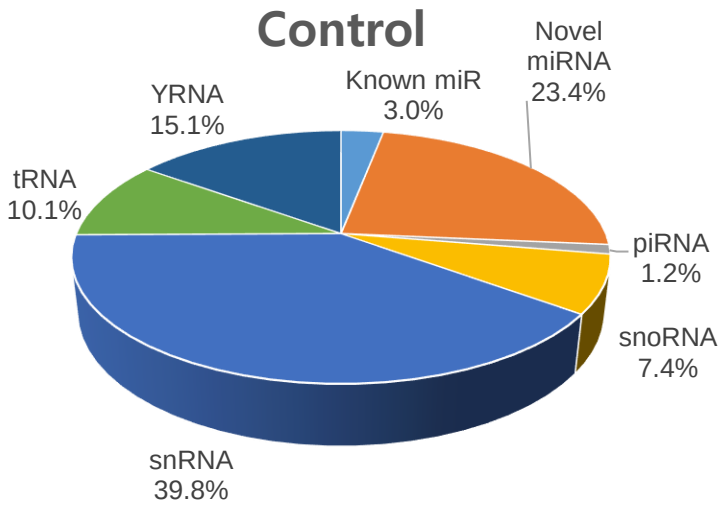
Markers	Test group (cancer stage)	Clinical performance			AUC (95% CI) P<0.0001
		Sensitivity% (95% CI)	Specificity% (95% CI)	Accuracy% (95% CI)	
7 epigenetic biomarker model	Total cancer samples	93.85 (84.99-98.30)	94.29 (80.84-99.30)	94.00 (87.40-97.77)	0.95 (0.89-0.99)
	NSCLC Stage I	88.00 (70.04-95.83)		91.67 (81.61-97.24)	0.91 (0.83-0.99)
	NSCLC Stage II-IV	97.37 (86.19-99.93)		95.89 (88.46-99.14)	0.96 (0.91-1.00)
7 epigenetic biomarker model + smoking history	Total cancer samples	95.38 (87.10-99.04)	94.29 (80.84-99.30)	95.00 (88.72-98.36)	0.95 (0.91-1.00)
	NSCLC Stage I	92.00 (73.97-99.02)		93.33 (83.82-98.15)	0.96 (0.91-1.00)
	NSCLC Stage II-IV	97.37 (86.19-99.93)		95.89 (88.46-99.14)	0.96 (0.92-1.00)

Workflow


70 non-cancer BALF exosome
68 lung cancer BALF exosome
Tumor suppressor methylation assay
(real-time PCR test)
Marker discovery
Lung cancer specific epigenetic marker screening
AUC ≥ 0.79
7 DMRs specifically methylated in lung cancer BALF samples
HOXA9, HOXD3, SFRP2, RASSF1A, NPYX2, ND2, PCDH17
Logistic regression
Lung cancer prediction model
AUC 0.97
Sensitivity 88.24%
Specificity 97.14%
Model validation
100 BALF exosome
AUC 0.95
Sensitivity 93.85%
Specificity 94.29%
Prospective validation
(BALF cfDNA)
from April, 2024

BALF EV Small RNA sequencing - RNA composition



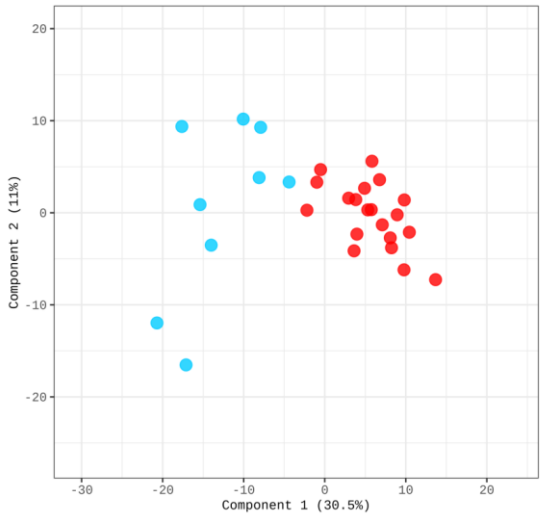


	%		p-value
	Lung cancer (n=20)	Control (n=20)	Ung cancer vs Control
miRNA	20.4	26.4	0.1
piRNA	1.1	1.2	0.2
snoRNA	7.2	7.4	0.4
snRNA	43.5	39.8	0.2
tRNA	12.2	10.1	0.2
YRNA	15.4	15.1	0.5

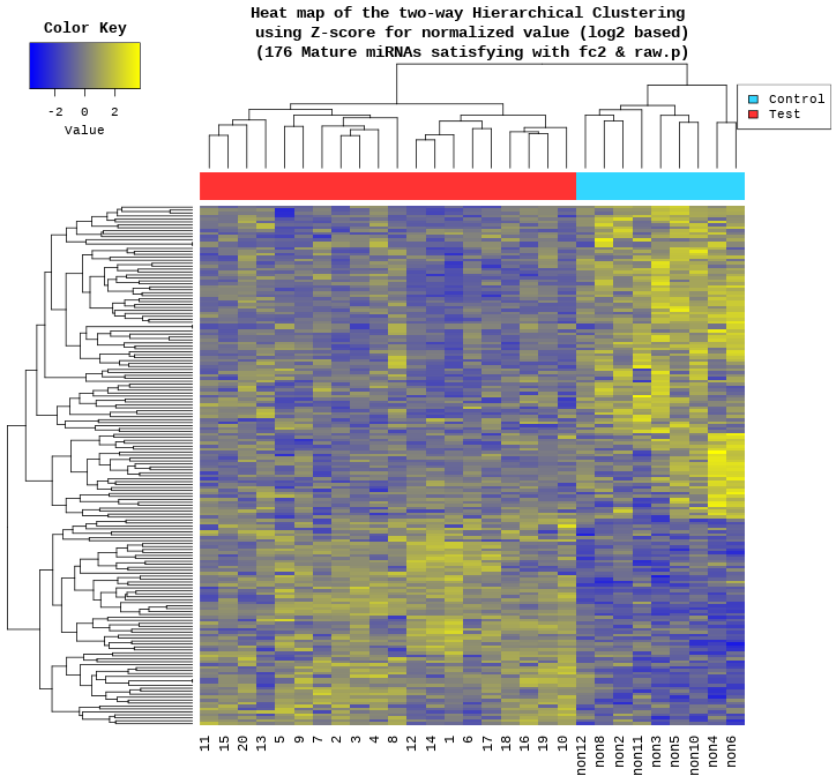
	Lung cancer	Control	Lung cancer vs Control
Known miR	6.5	3.0	0.005
Novel miRNA	13.9	23.4	0.014

Cancer /BLD miRNA

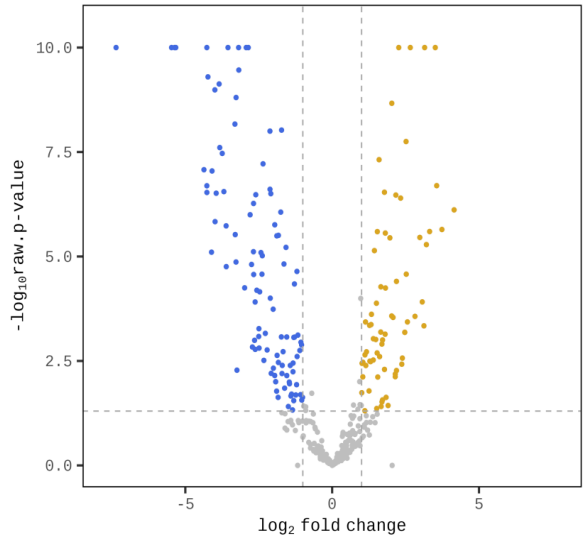
MDS plot



BLD
Cancer

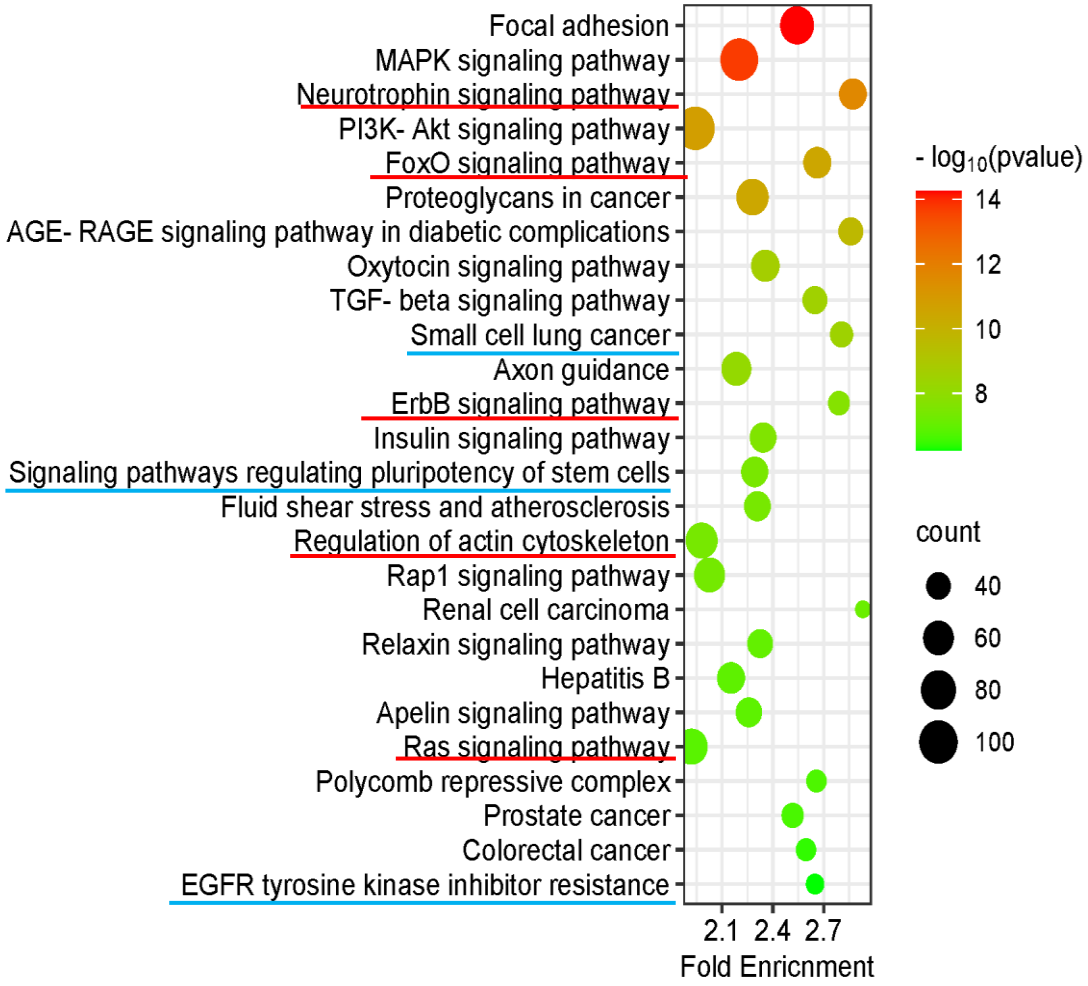


Volcano plot



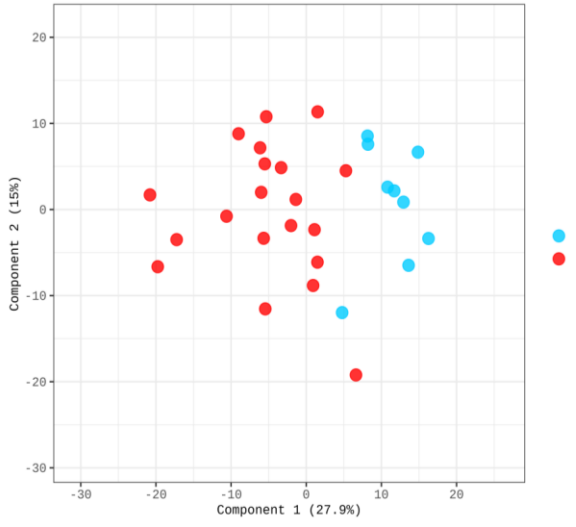
FC>=2, p<0.05
FC<=-2, p<0.05

Pathway- miRNA (Cancer/BLD)

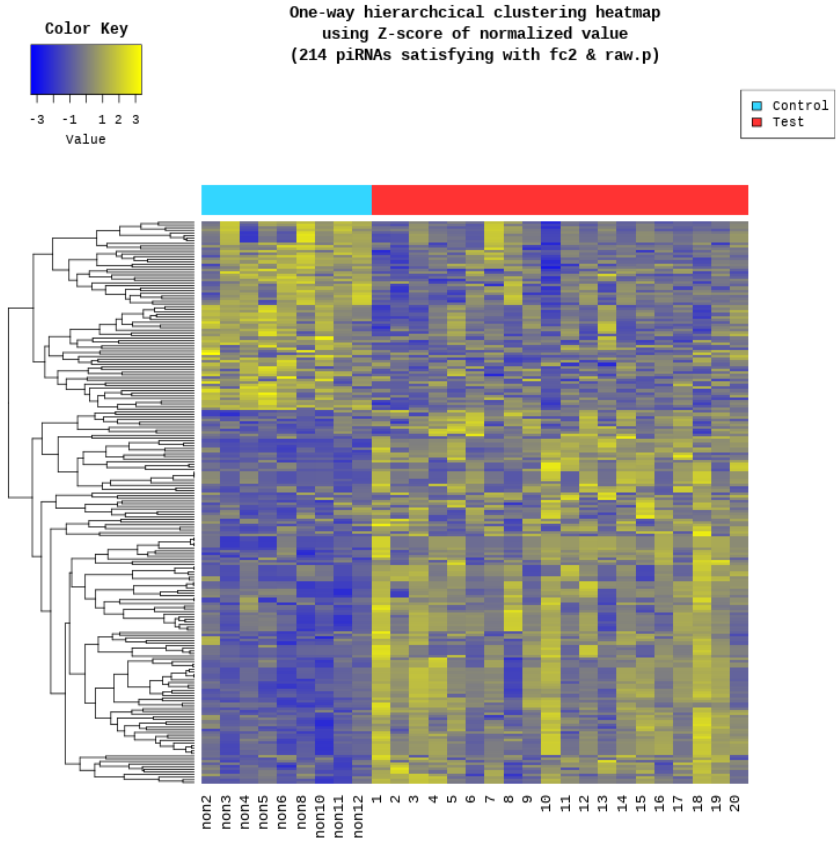


Cancer /BLD piRNA

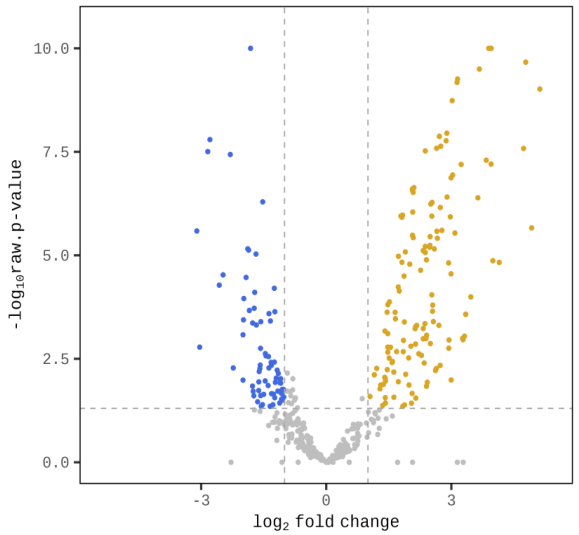
MDS plot



BLD
Cancer



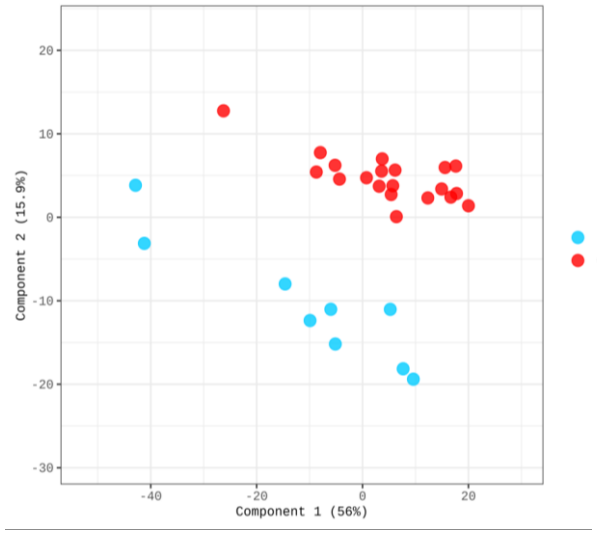
Volcano plot



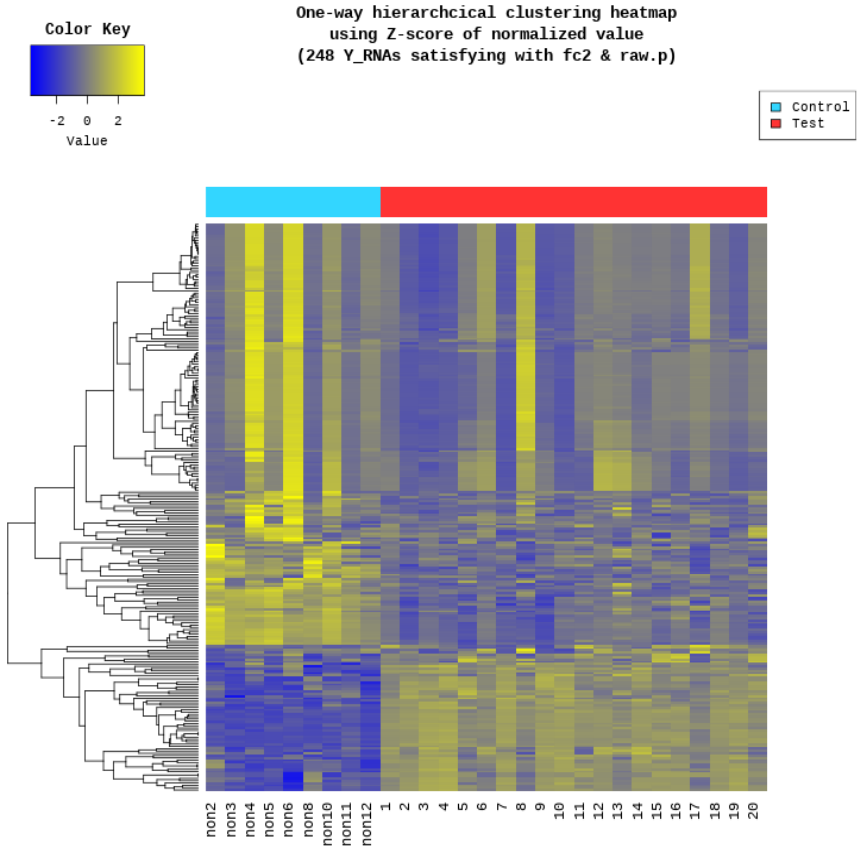
FC>=2, p<0.05
FC<=-2, p<0.05

Cancer /BLD YRNA

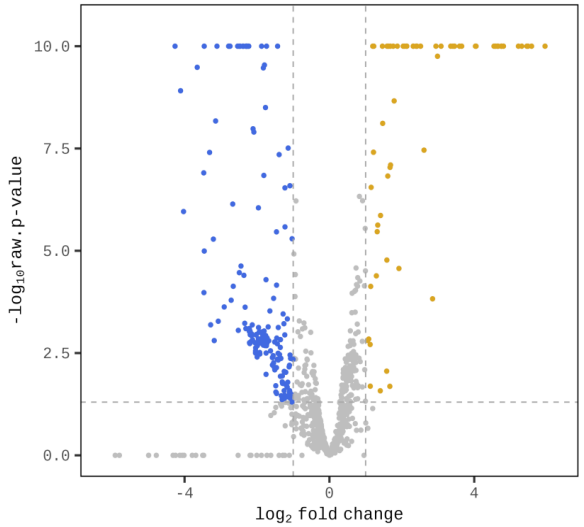
MDS plot



BLD
Cancer



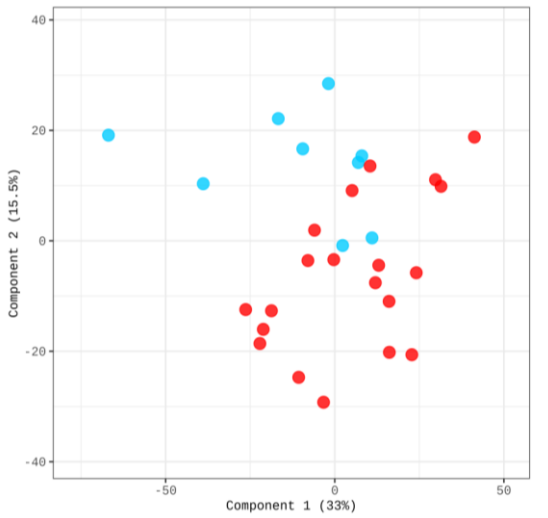
Volcano plot



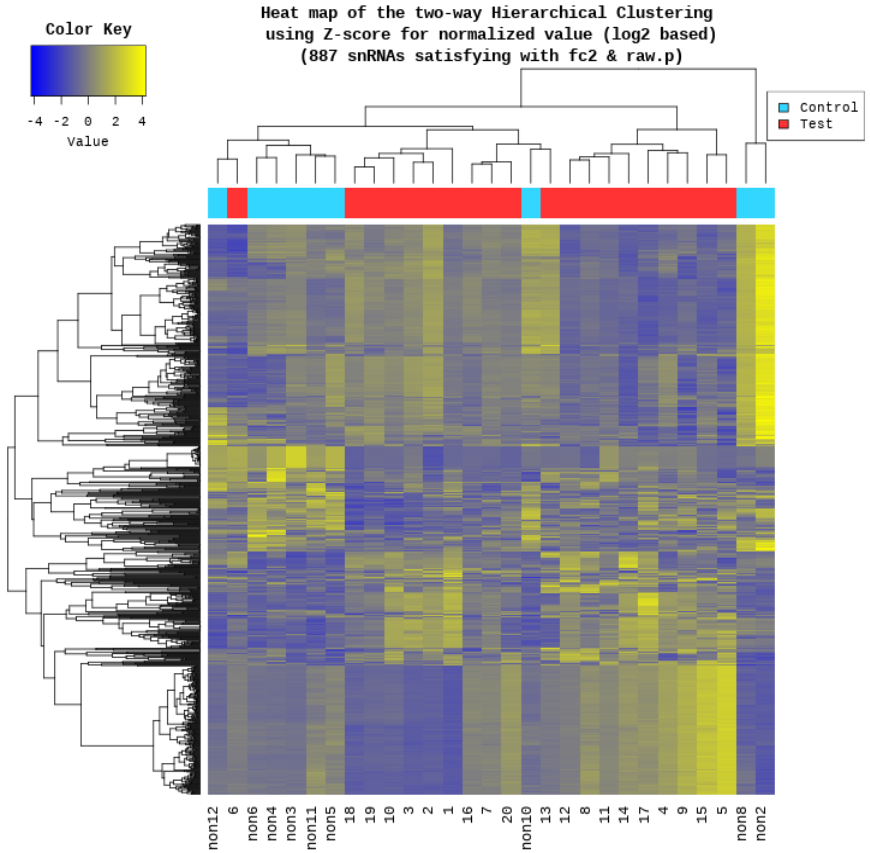
FC>=2, p<0.05
FC<=-2, p<0.05

Cancer /BLD snRNA

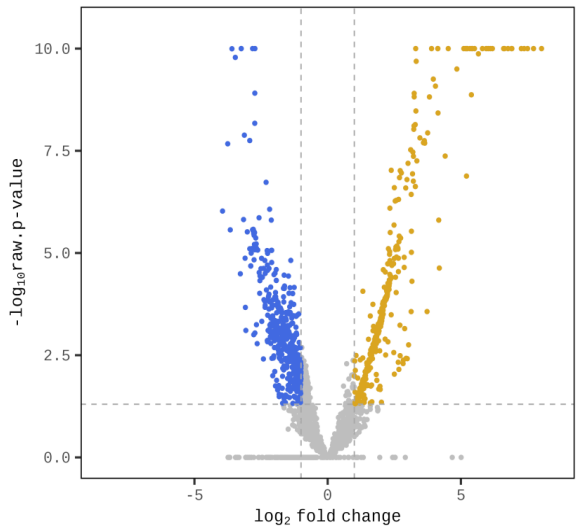
MDS plot



BLD
Cancer



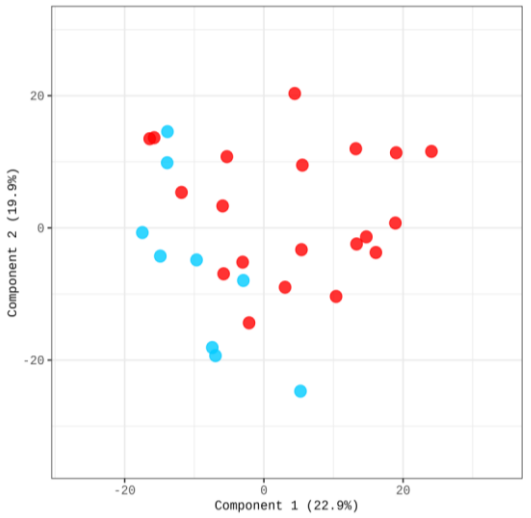
Volcano plot



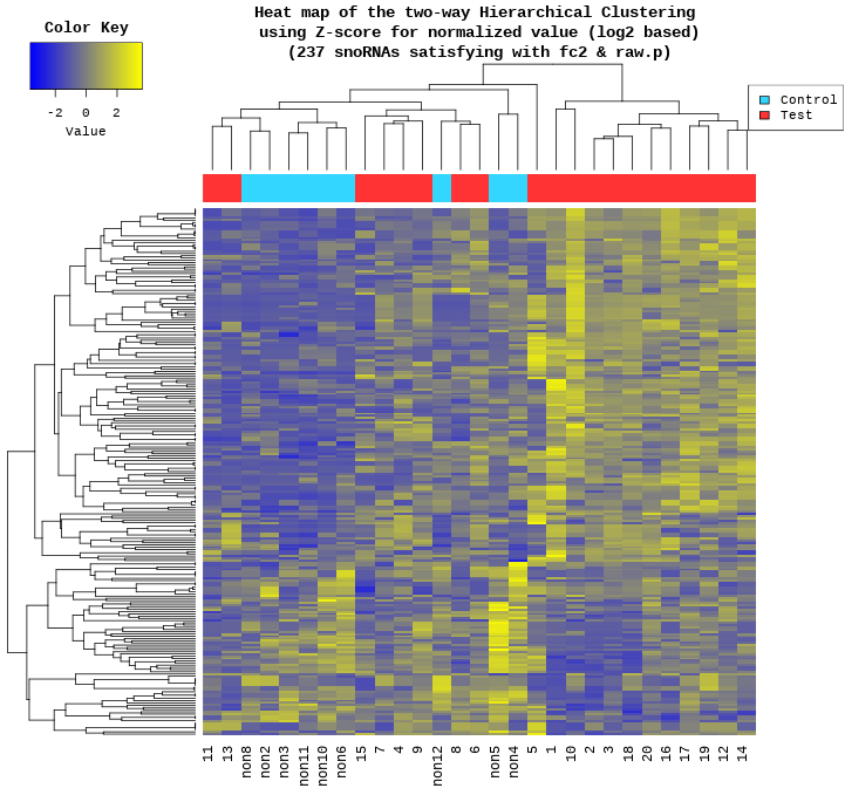
FC>=2, p<0.05
FC<=-2, p<0.05

Cancer /BLD snoRNA

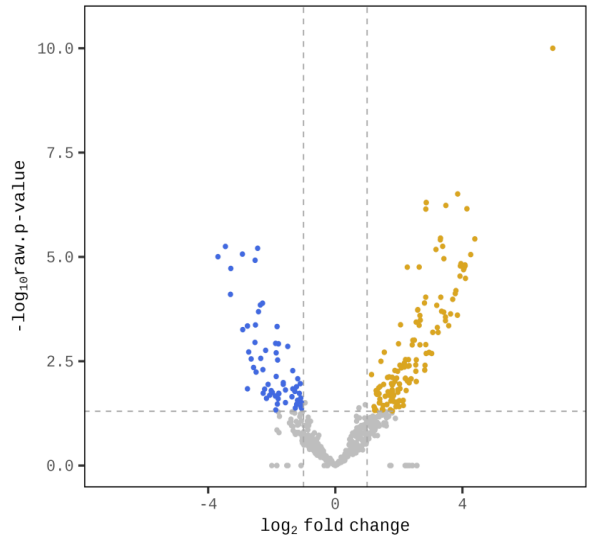
MDS plot



BLD
Cancer



Volcano plot



FC>=2, p<0.05
FC<=-2, p<0.05

NGS using BALF EV DNA

Original Article

Genomic profiling of extracellular vesicle-derived DNA from bronchoalveolar lavage fluid of patients with lung adenocarcinoma

Seung Eun Lee[1#], Ha Young Park[2#], Jae Young Hur[1,3#], Hee Joung Kim[3,4], In Ae Kim[3,4], Wan Seop Kim[1], Kye Young Lee[3,4#]

[1]Department of Pathology, Konkuk University School of Medicine, Seoul, Korea; [2]Department of Pathology, Busan Paik Hospital, Inje University College of Medicine, Gimhae, Korea; [3]Precision Medicine Lung Cancer Center, Konkuk University Medical Center, Seoul, Korea; [4]Department of Internal Medicine, Konkuk University School of Medicine, Seoul, Korea

Contributions: (I) Conception and design: JY Hur, SE Lee, HY Park, KY Lee; (II) Administrative support: WS Kim, KY Lee; (III) Provision of study materials or patients: WS Kim, KY Lee; (IV) Collection and assembly of data: JY Hur, SE Lee, HY Park, IA Kim, HJ Kim; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

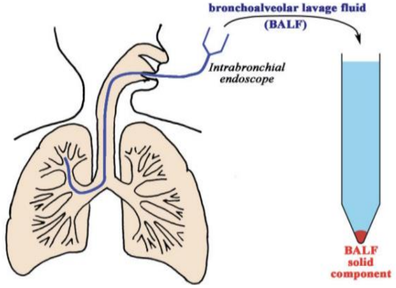
[#]These authors contributed equally to this work.

Correspondence to: Prof. Kye Young Lee, MD, PhD. Precision Medicine Lung Cancer Center, Konkuk University Medical Center and Department of Pulmonary Medicine, Konkuk University School of Medicine, 120-1 Hwayang-dong, Gwangjin-Gu, Seoul 05030, Korea. Email: kyleemd@kuh.ac.kr.

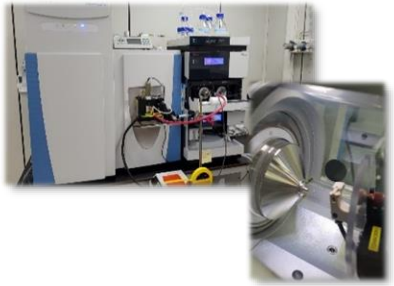
(SE Lee, et al. 104-116, 10, 2021 Trans Lung Cancer Research)

Workflow of proteomic analysis

BALF_Cell & EV

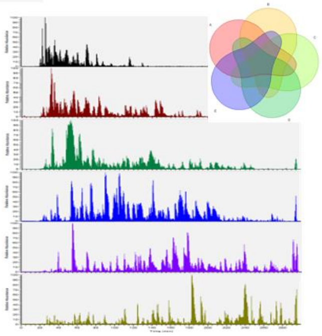


HR-LC-MS/MS Analysis



Proteome (Spectral) Library Construction

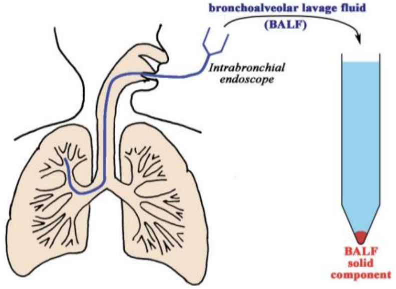
BALF EV Proteome



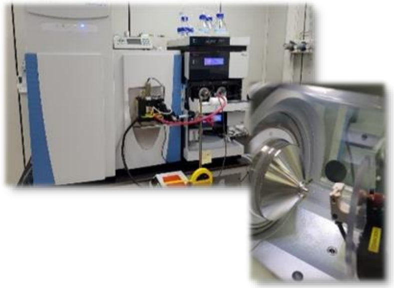
Identified unique proteins (6,013)

시료별 안정적 정량정보 추출

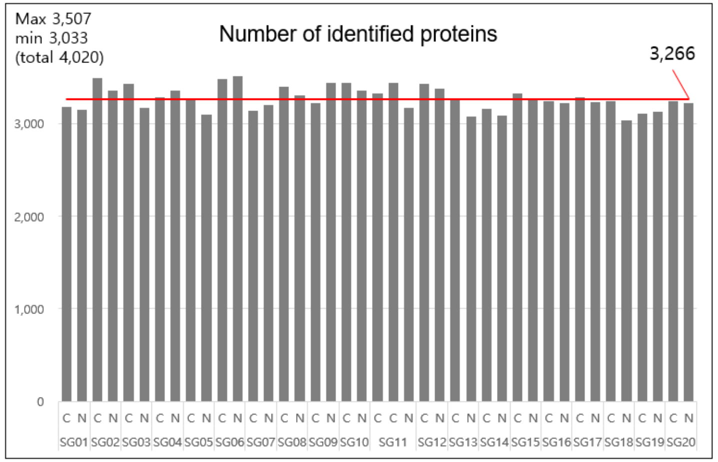
BALF_EV



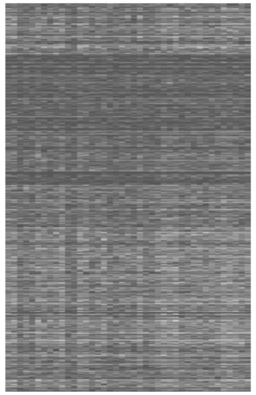
HR-LC-MS/MS Analysis



DIA (개별시료 정량결과: 40 Early lung cancer samples)

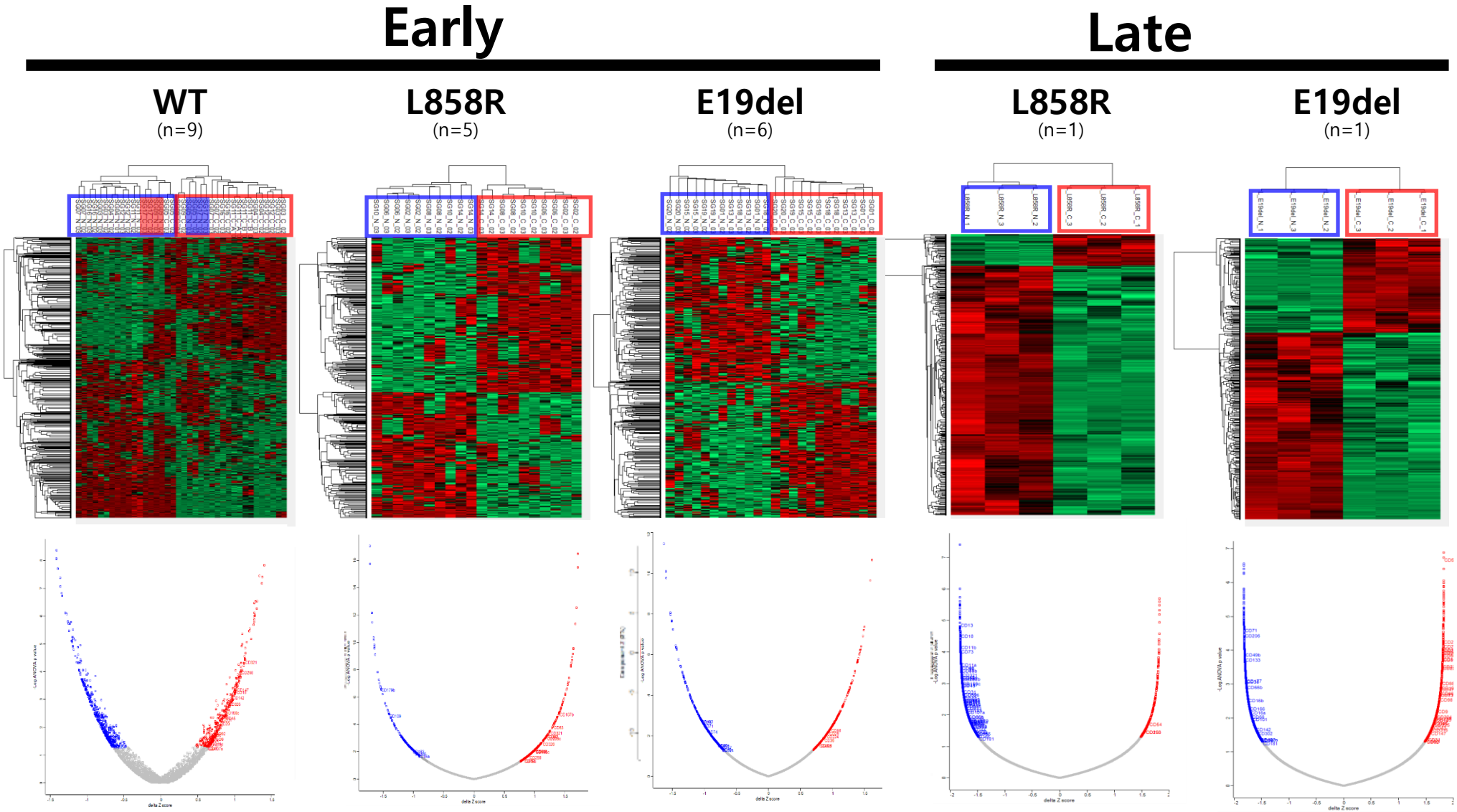


Missing value 18.8%



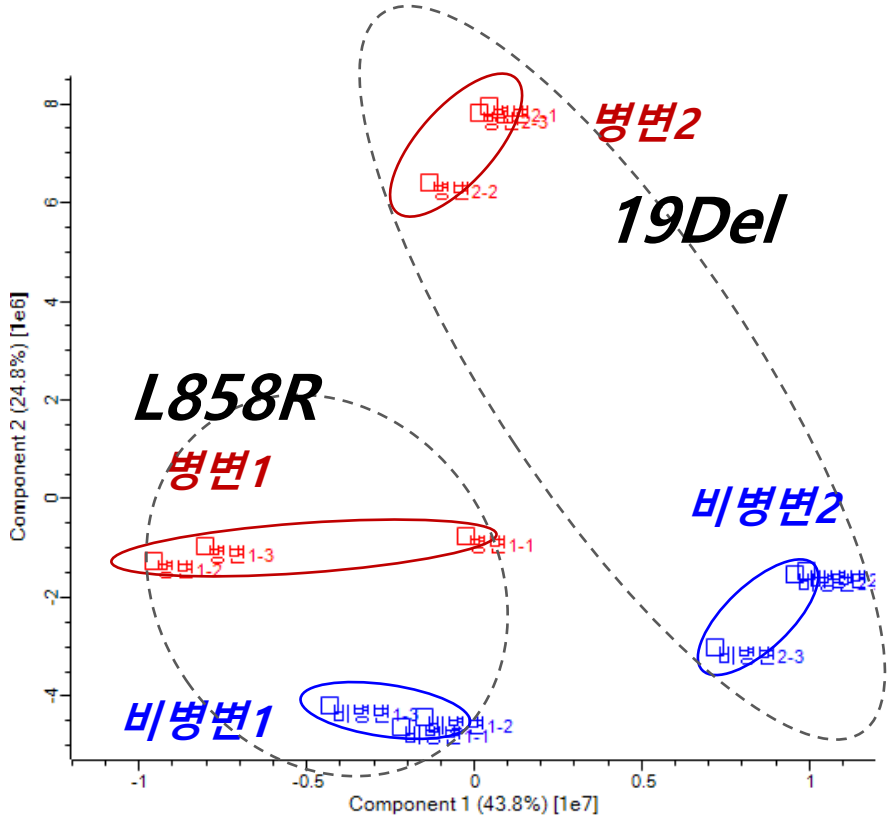
(cf) 4 samples: missing value ≈ 7.9%

Protein Profile Heatmaps of BALF EV proteomes

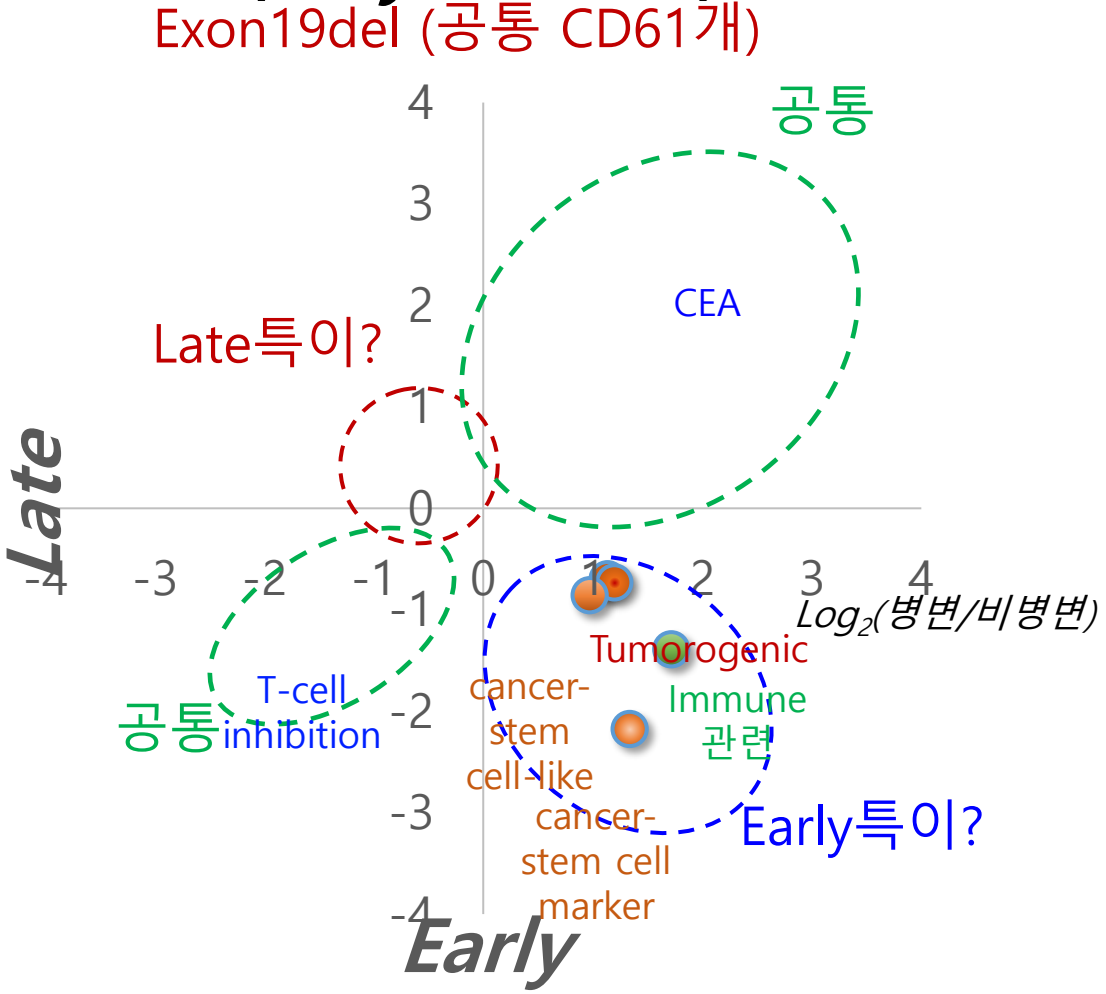


Further Analysis of Proteomic Results

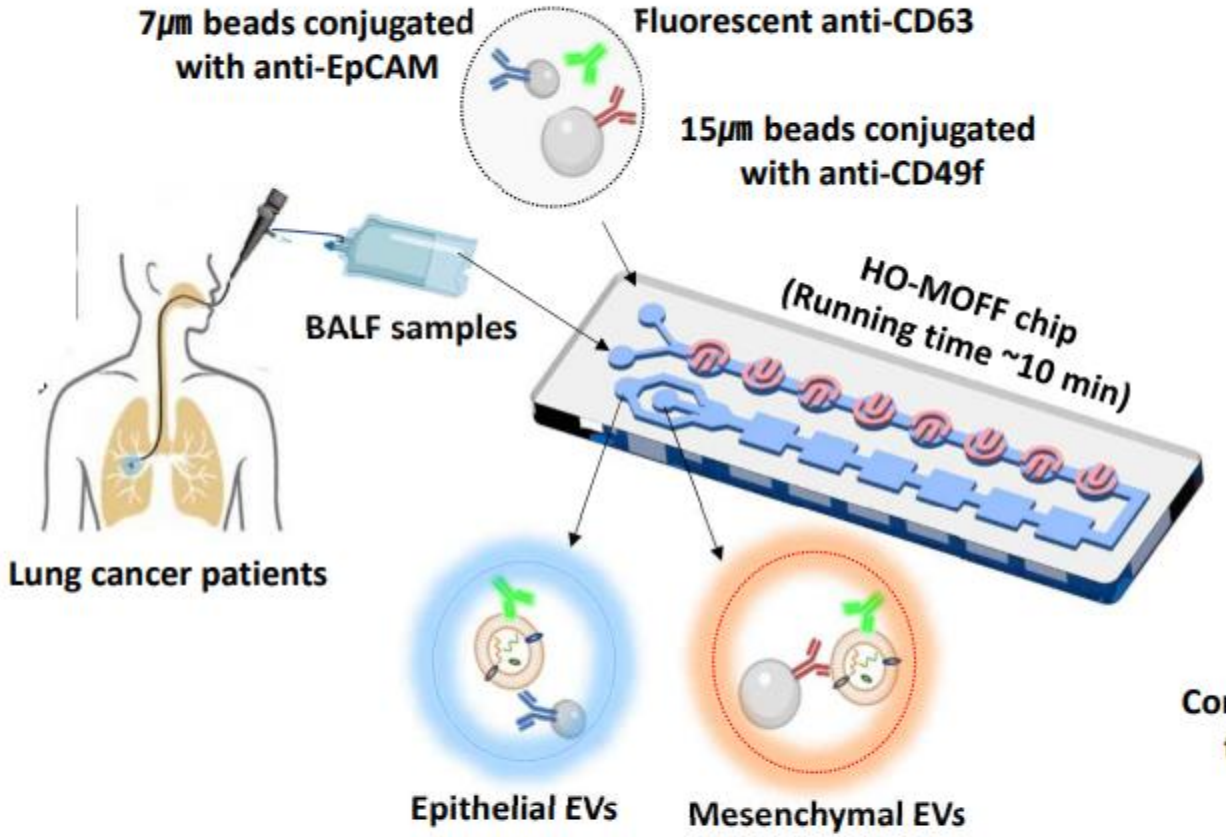
Principle Component Analysis (Late Cancer Only)



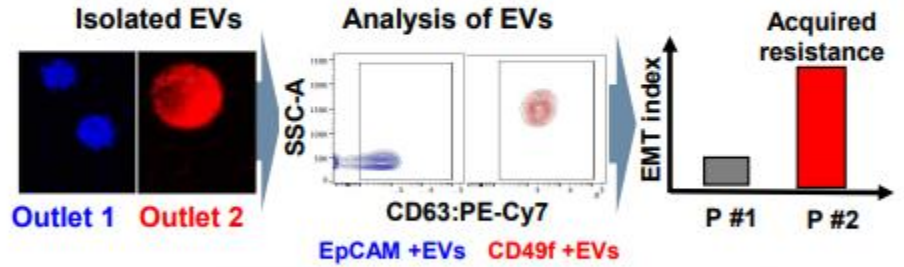
Comparison of Expression Levels of CD molecules in Exon19del patients (Early and Late)



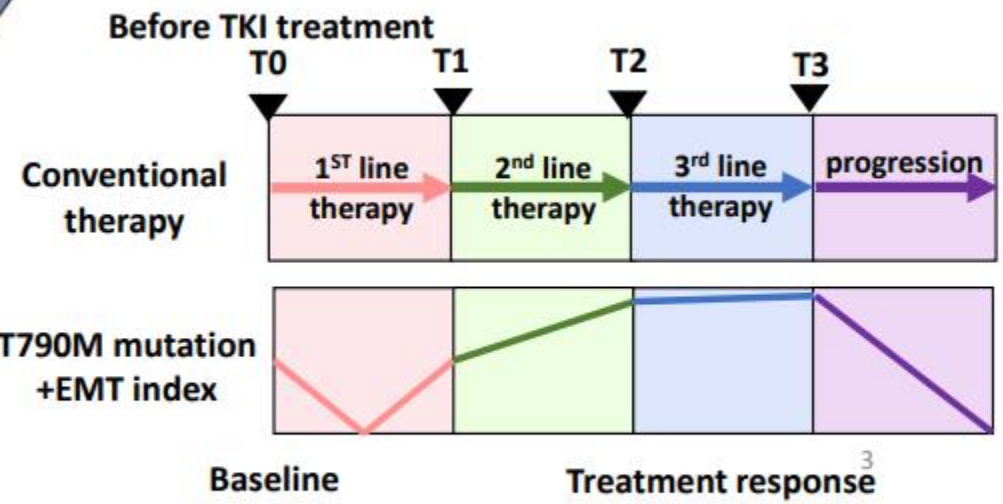
Microfluidic strategies for detection of EMT status in BALF sample of NSCLC patient



Generation of EMT index

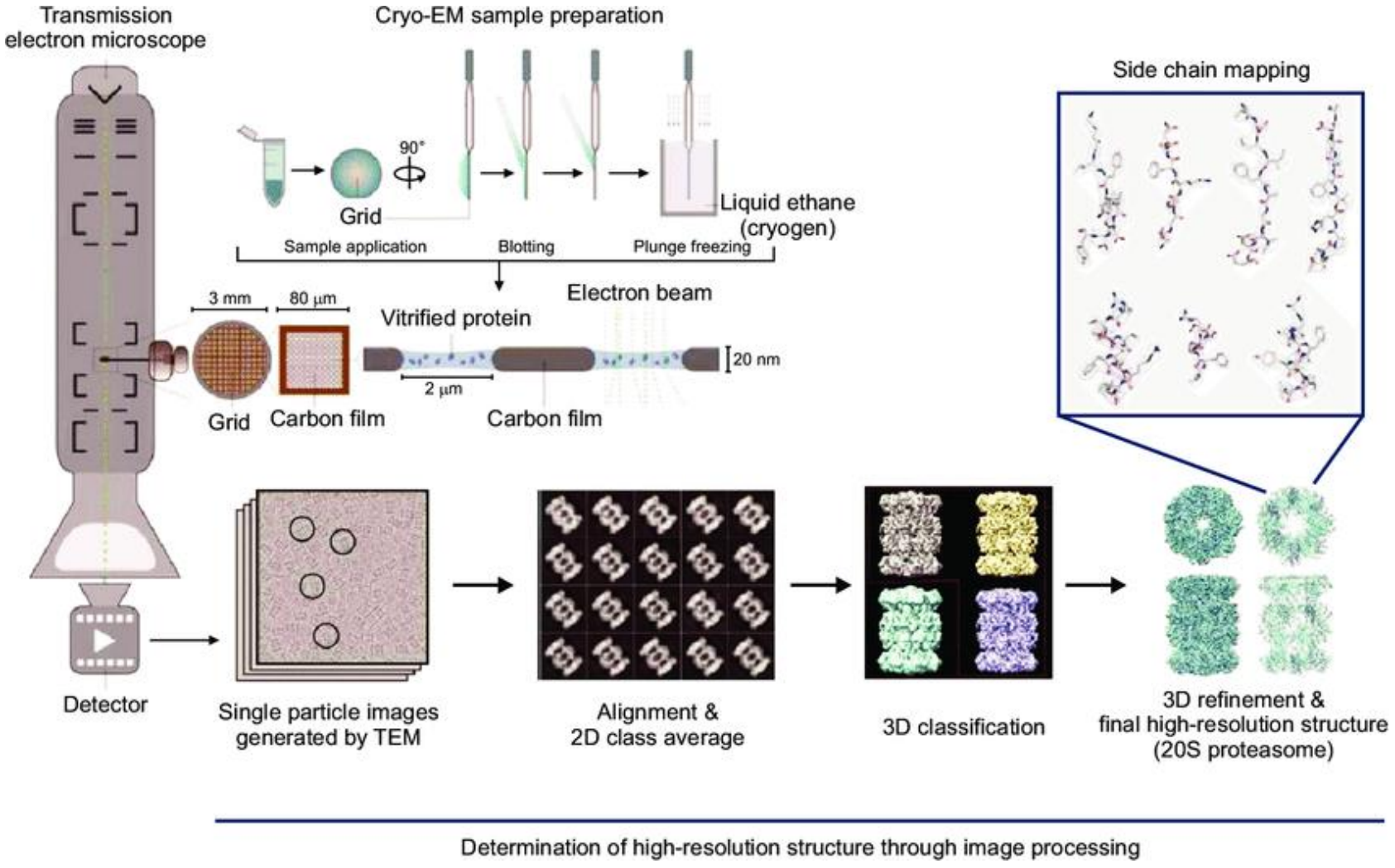


Prediction of EGFR-TKIs resistance for establishment of therapeutic strategies



연세대학교 바이오칩 연구실
Lab of Biochip Technology
LBT

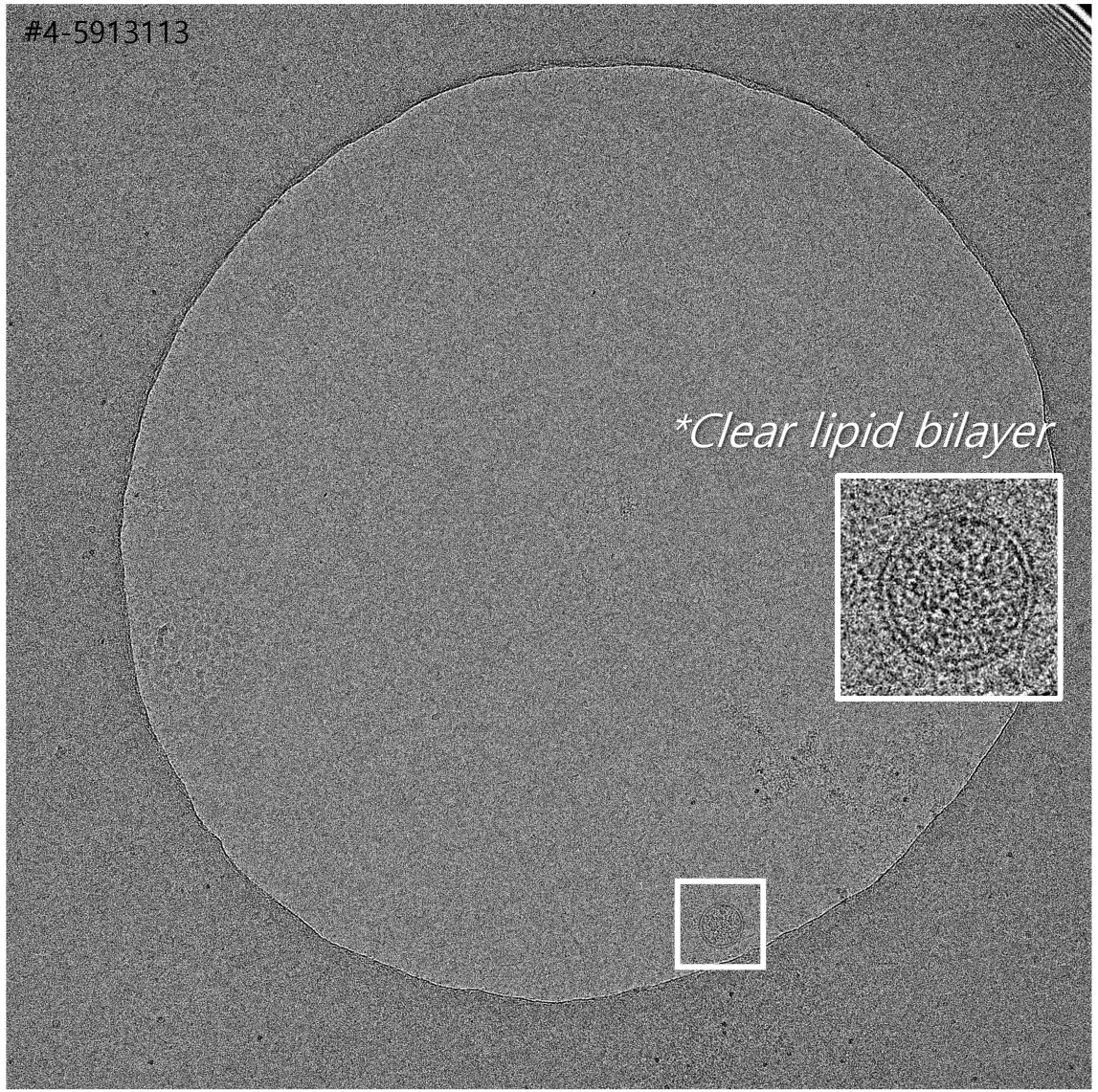
Cryo-EM Images of BALF EV in NSCLC Pt

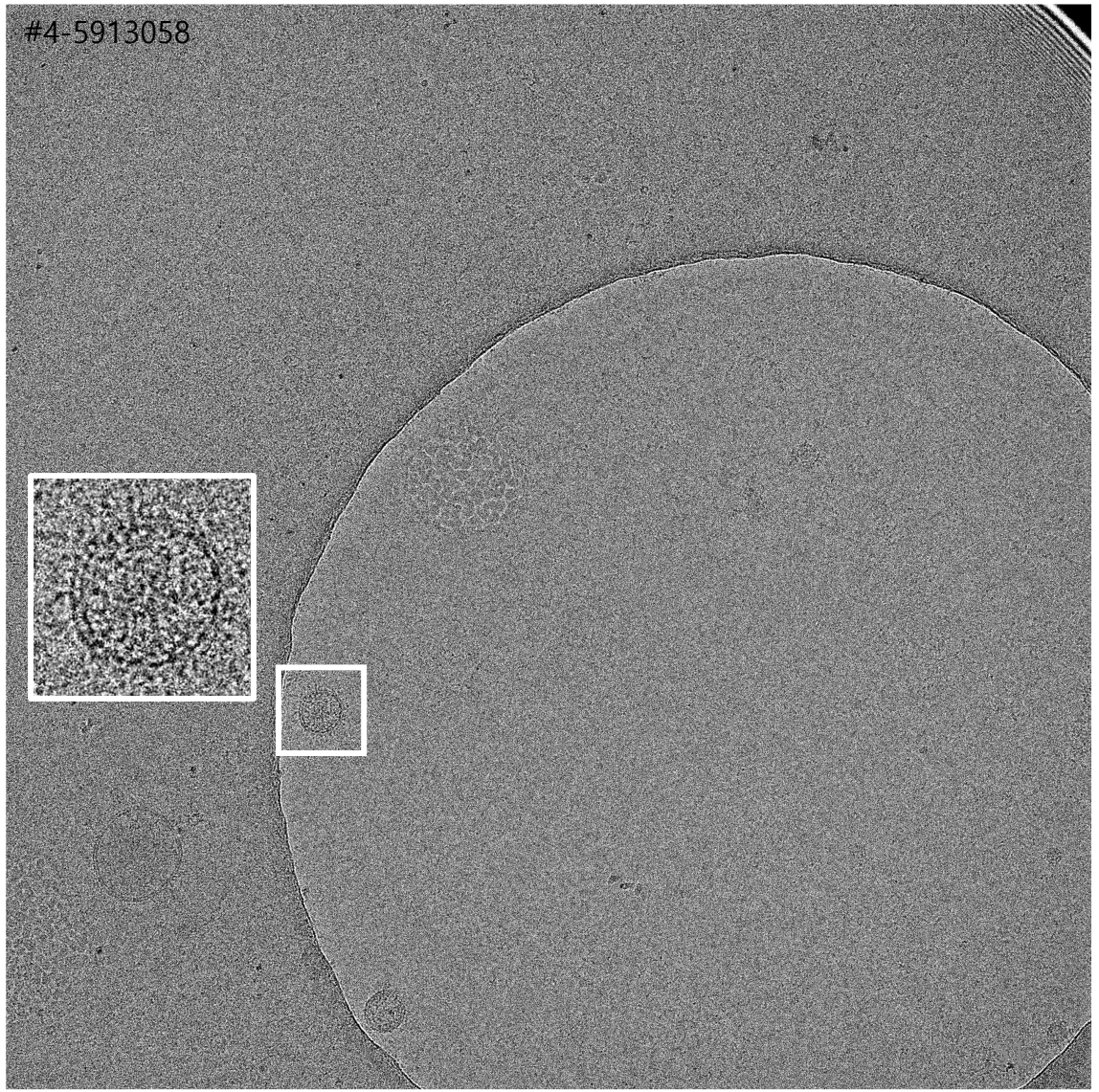


Determination of high-resolution structure through image processing

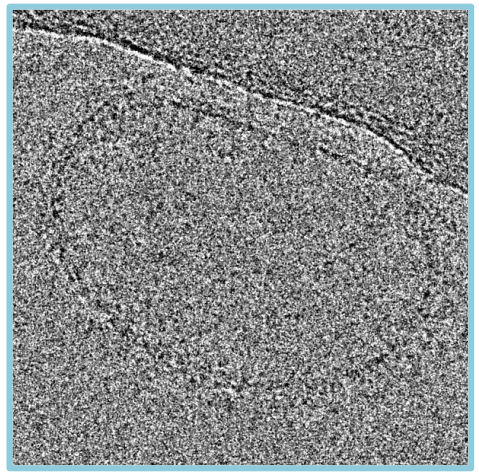
1 Cryo-EM images of BALF EV isolated by ultracentrifuge

Glacios, ~5 $e^{-}Å^{-2}$, DV -1~-2um

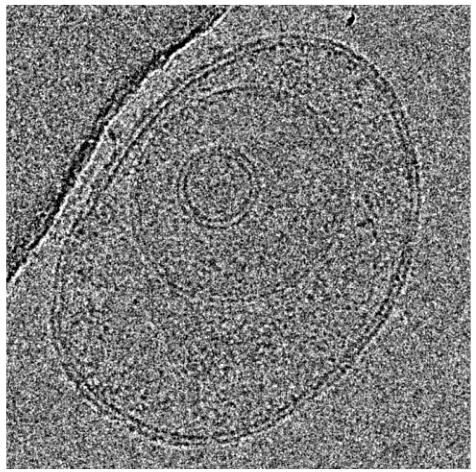




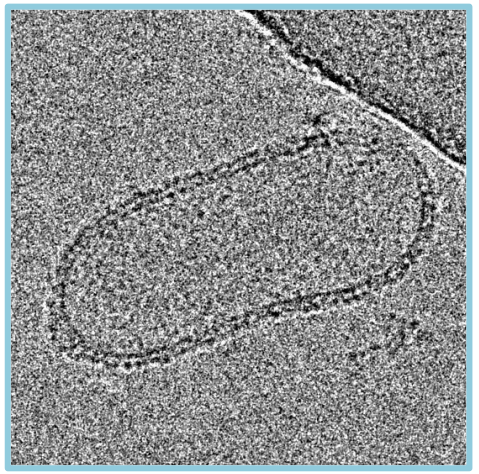
Brush-like membrane

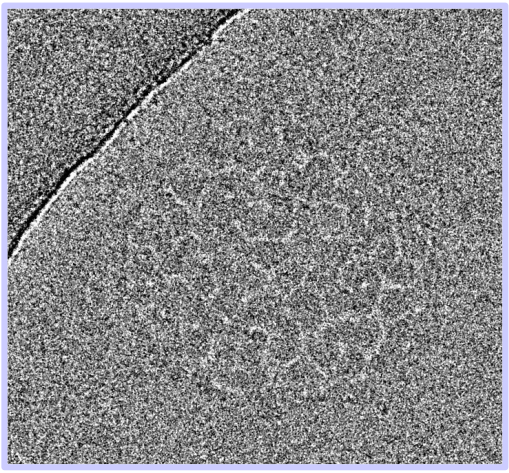


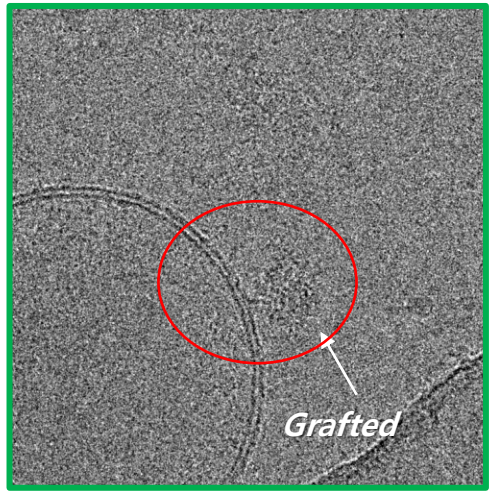
Clear lipid bilayer

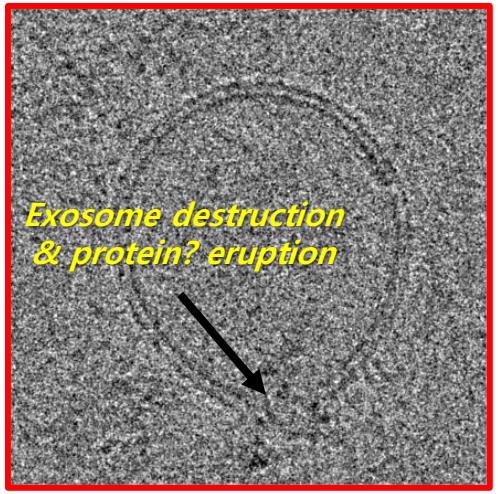


Irregular membrane thickness

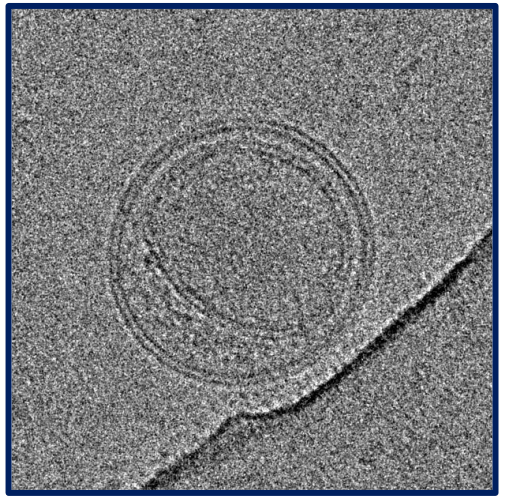




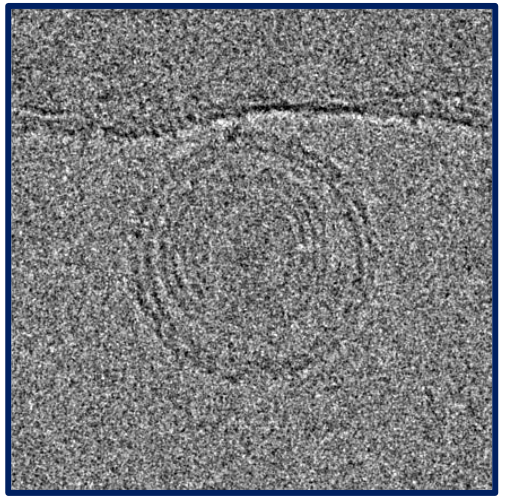




Multi-vesicle type

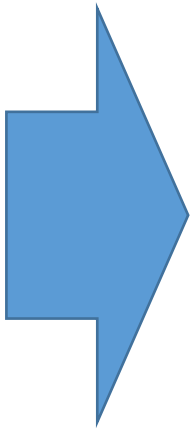


Multi-vesicle type



Multiomic EV-based BALF liquid biopsy in PPLs

- **Routine-based ExoBAL™ EGFR kit**
- **Developing ExoBAL KRAS kit**
- **ExoBAL Epi-TOP MPP assay**
- **ExoBAL miRNA/piRNA panel**
- **ExoBAL proteomics/Glycomics**
- **ExoBAL Microfluidic chip**
- **ExoBAL NGS : targeted, WES, WGS**



95% sensitivity, 95% specificity

- **Stage 1 cancer discrimination**
- **Genotyping for Neoadj Tx**
- **Selection of high risk for post-op recurrence**
- **Prediction of lung cancer development near future**

Acknowledgements

- 건국대학교병원 정밀의학폐암센터
  - 호흡기내과 :김영환, 김희정, 김인애 교수
  - 병리과 : 김완섭, 이승은 교수
  - 흉부외과 : 황재준, 이송암 교수
- Exosignal, Inc.
  - 허재영, 이현정, 배윤위 박사
  - 김경화, 이승윤, 박정경 연구원
- HLB Panagene, Inc.
- Seasun Biomaterils, Inc.
  - 김도원 박사
  - Chinbayar Bat-Ocir, PhD
  - 조은지 연구원
- 씨젠의료재단
  - 백제현 박사
- 서울공대 박정원 교수 Lab
- ㈜펜타메딕스
  - 노승재박사
  - 최정균 교수
- 연세공대 정효일 교수 Lab
  - 박선영 박사
  - 현경아 박사

Thank you for attention!!!