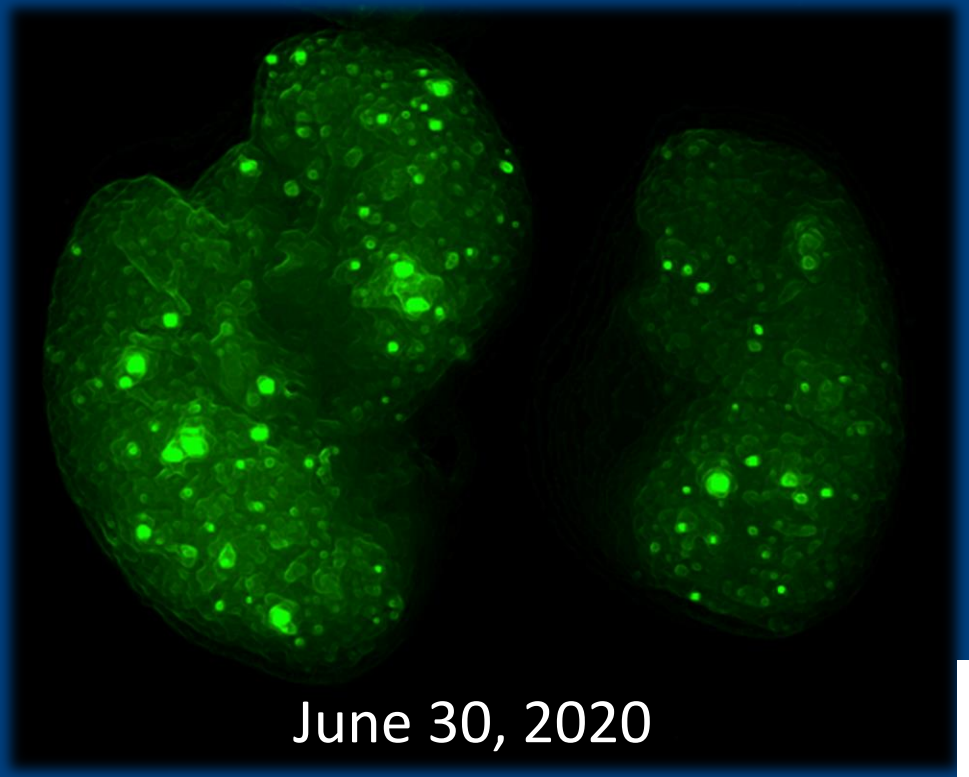
NCI EDRN
Breast/GYN Collaborative Group Meeting

Exosome Proteomics For Early Cancer Detection



June 30, 2020

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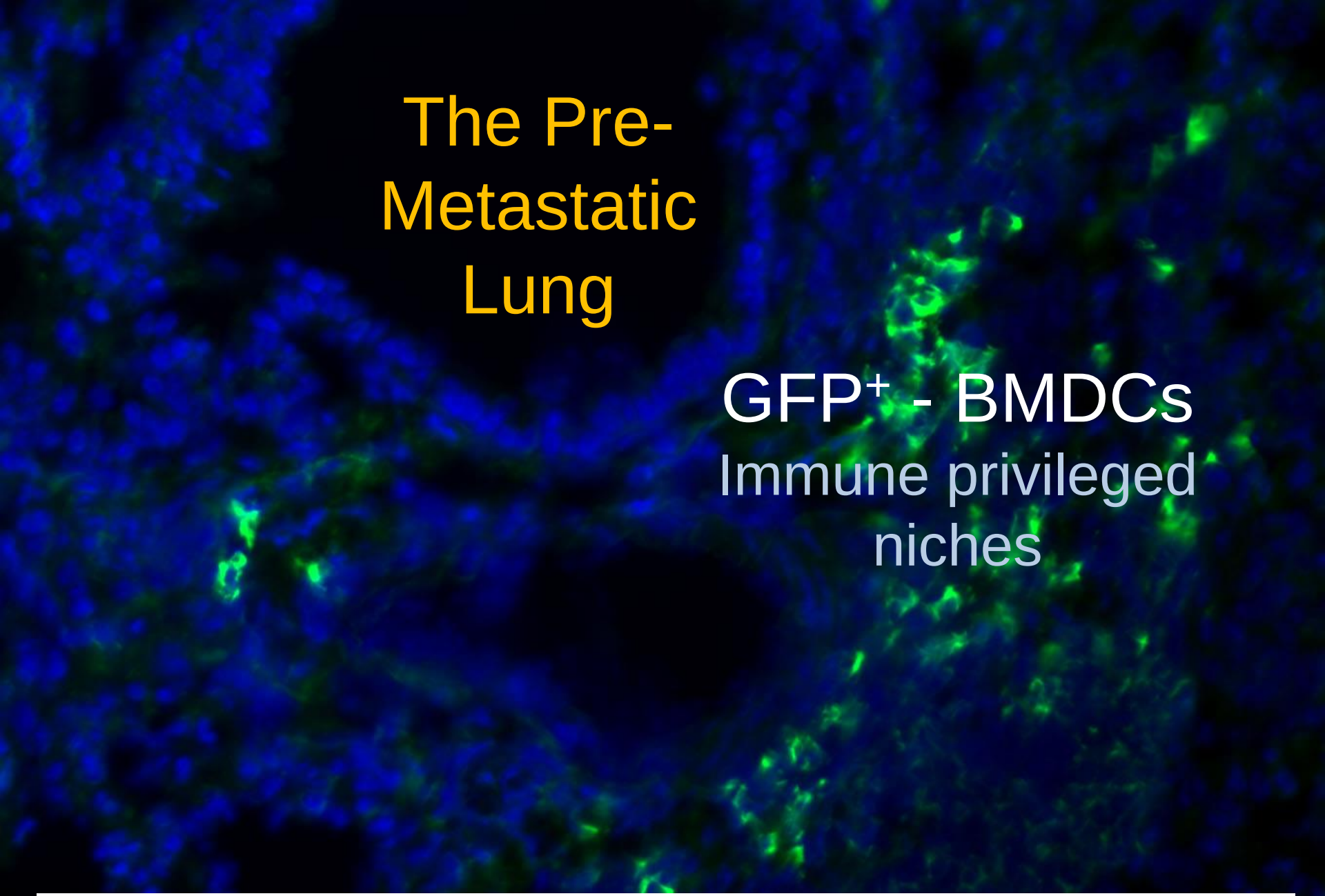

Rosie Kaplan, Stergios Zacharoulis, et. al.
Nature, 2005

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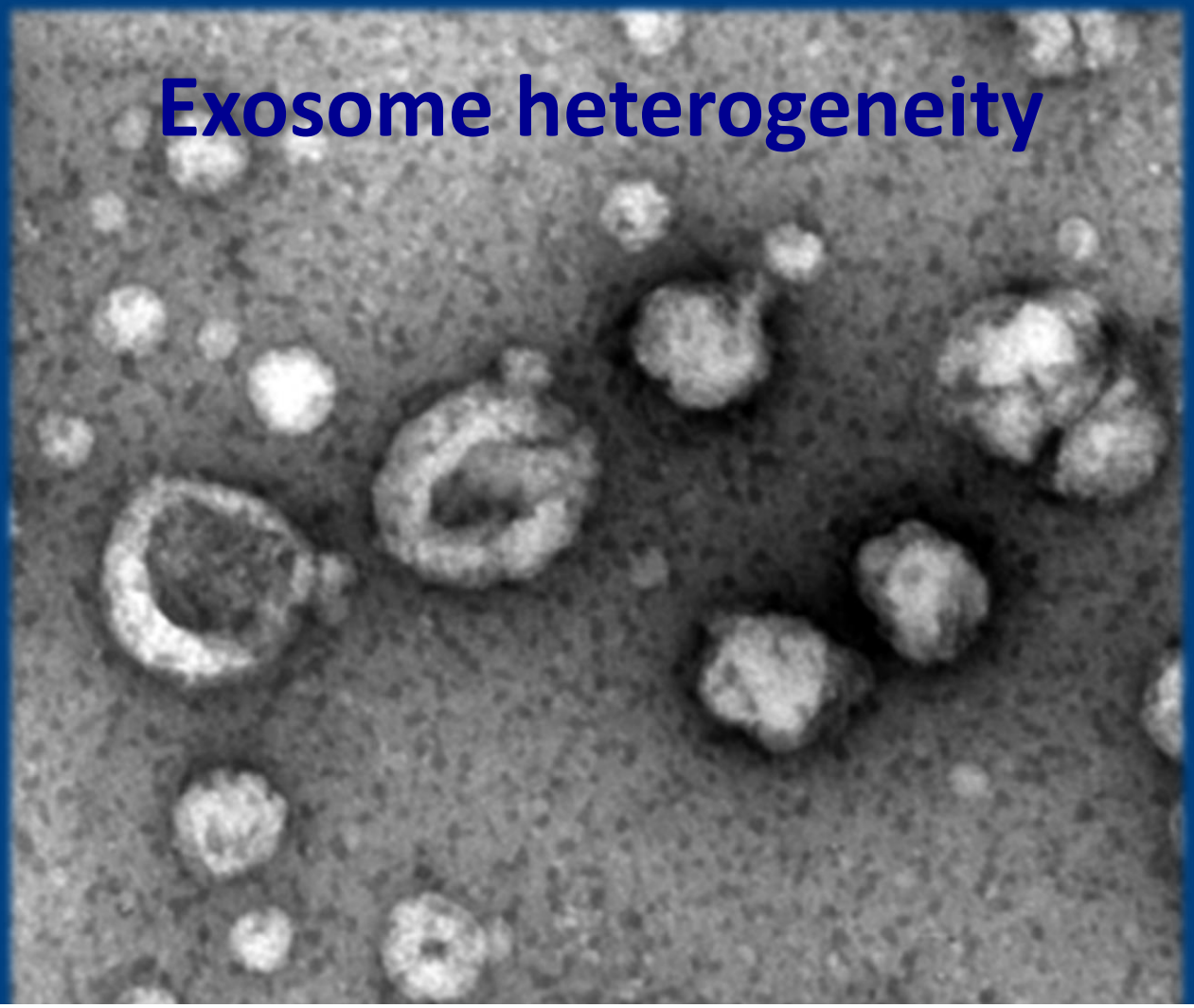
Exosomes: In Primary Tumors, In Circulation and at Pre-Metastatic Sites



Haiying Zhang, et. al.,
Nature Cell Biology, 2018

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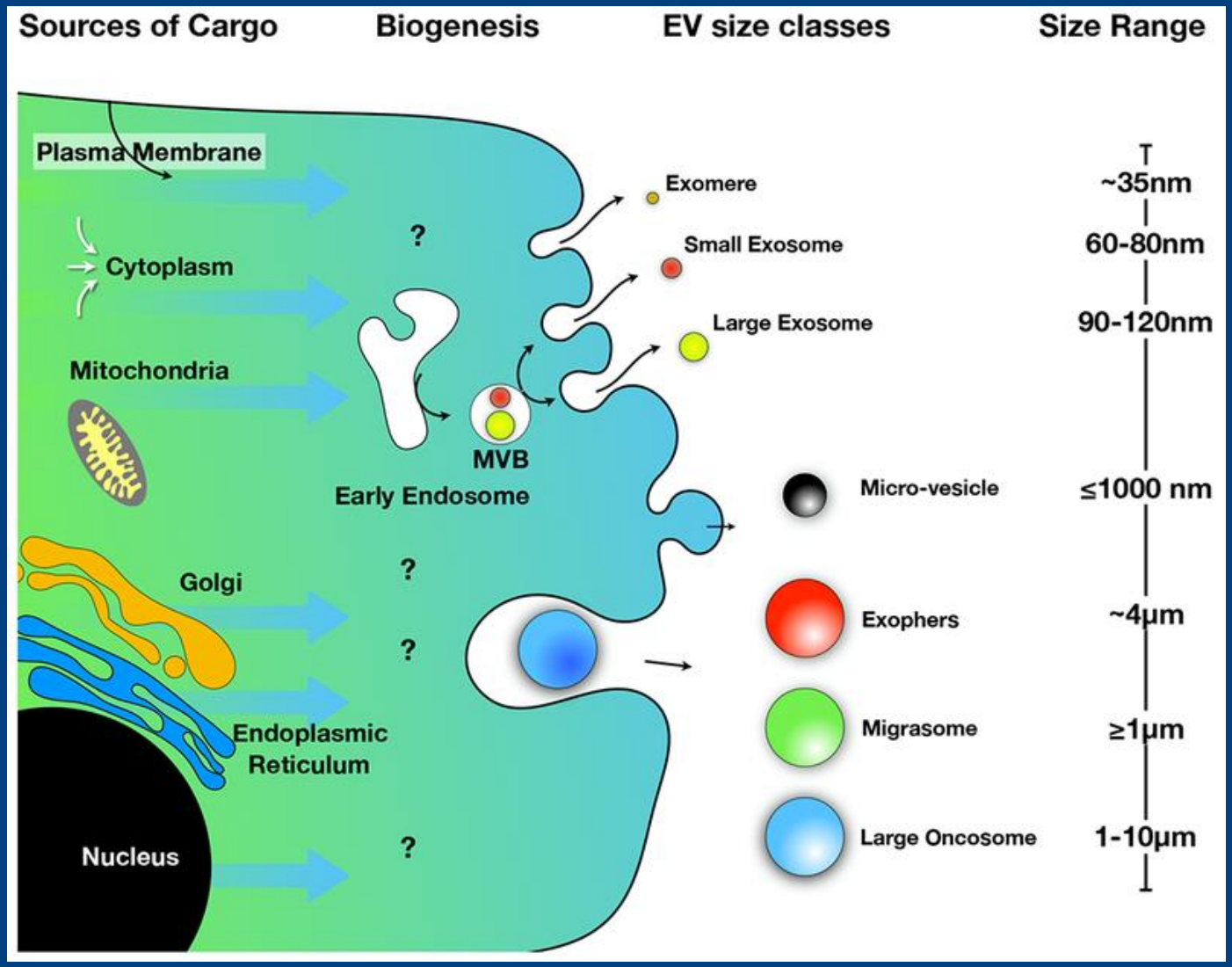
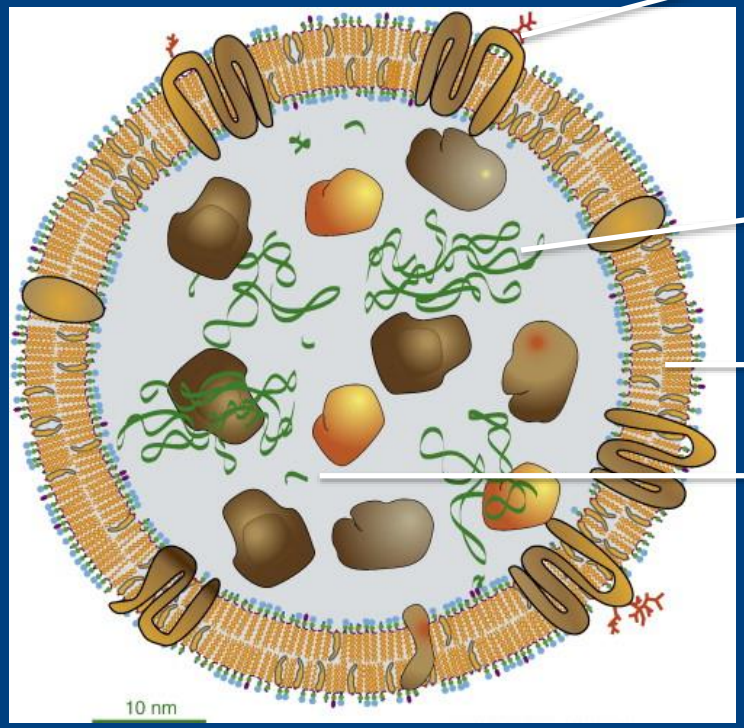
Distinct Classes of Microvesicles and Microparticles



Zijlstra et al NCB 2018

Biomarkers Found in Exosomes Biological Properties: Adhesion, Fusion, and Genomic Transfer



Proteins (membrane receptors, oncoproteins…)
Peinado et al., *Nature Medicine* 2012;
Costa-Silva et al., *NCB* 2015; Hoshino et al., *Nature* 2015

RNA (mRNA, miRNA, rRNA…)

Lipids

DNA
Thakur et al., *Cell Research* 2014

New Prognostic Markers and Therapeutic Targets

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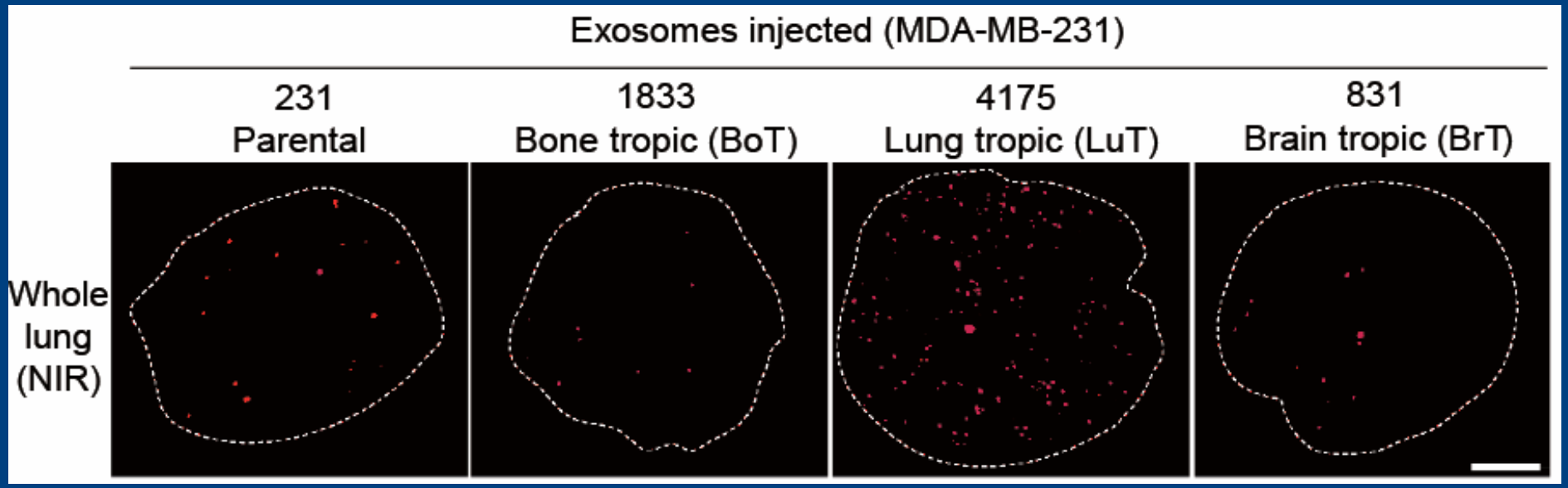
Exosomes from MDA-MB-231 Sub-lines Exhibit Organ Tropism



Ayuko Hoshino, et. al.,
Nature, 2015

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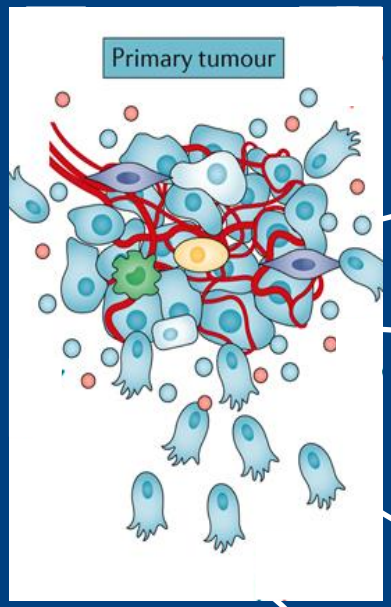
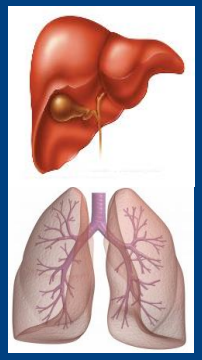
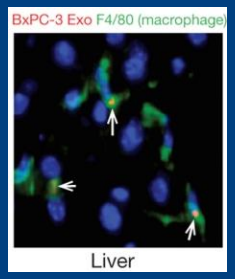
Tissue- and Cell-Specific Exosome Uptake and Education

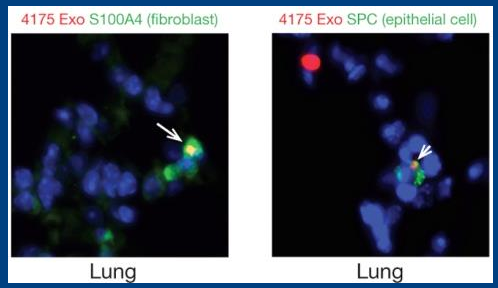


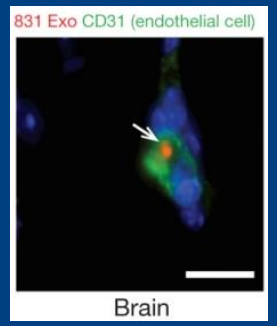


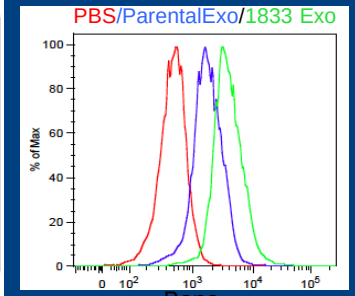
Integrin/ECM DEPENDENT

Integrin/ECM INDEPENDENT i.e. CEMIP









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Various technologies to isolate EVs

- Differential ultracentrifugation
- Density gradient
- Immuno-affinity capture
- Ultrafiltration
- Size-exclusion chromatography
- Polymer-based precipitation
- Microfluidics
- Asymmetric flow field flow fractionation (AF4)

Exosome Heterogeneity

I. Exosome subpopulations

II. Non-exosomal nanoparticles

William Jarnagin
Jacqueline Bromberg
Mary Sue Brady
Katia Manova

Haiying Zhang, et. al.,
Nature Cell Biology, 2018
Haiying Zhang, et al.,
Nature Protocols, 2019

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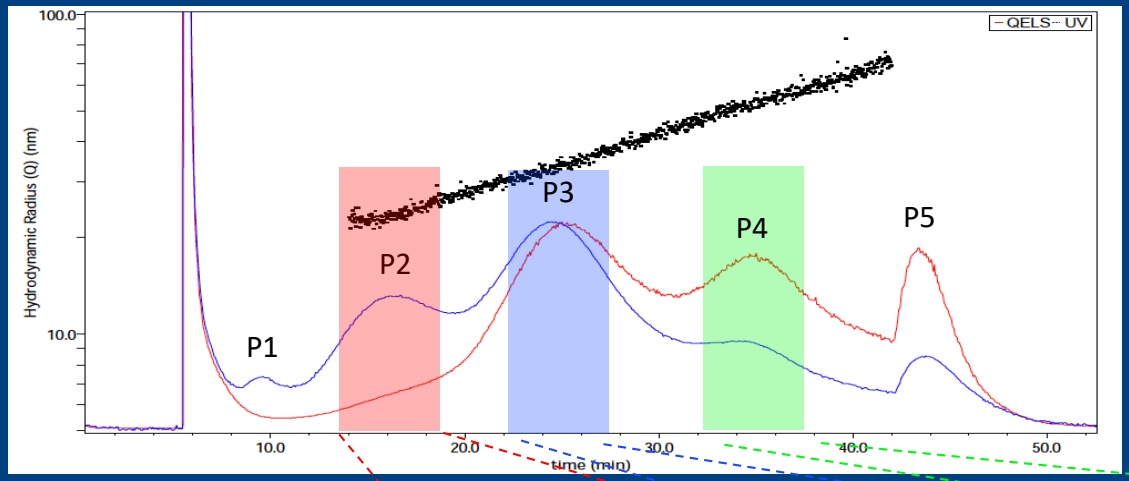
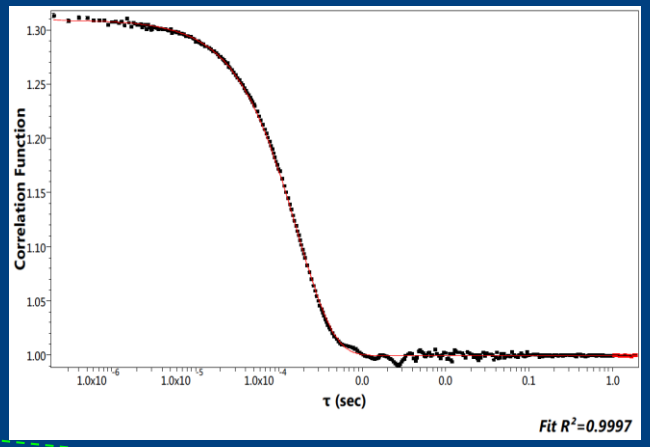
Identification of different subsets of exosomes by AF4 analysis

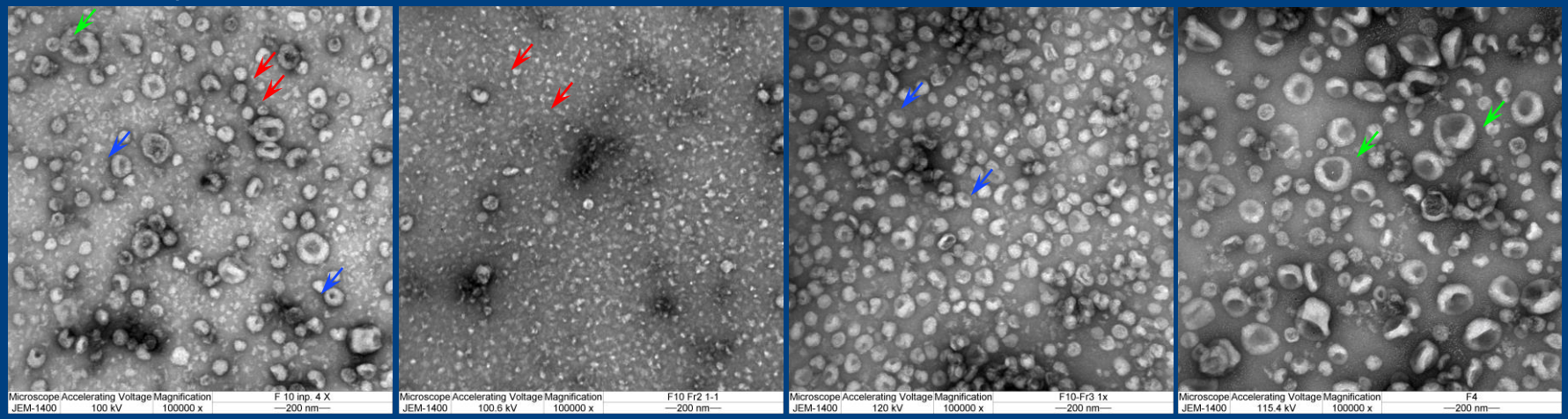
A Hydrodynamic Radius (Rh) vs. time



B Correlation Function (P3)



C



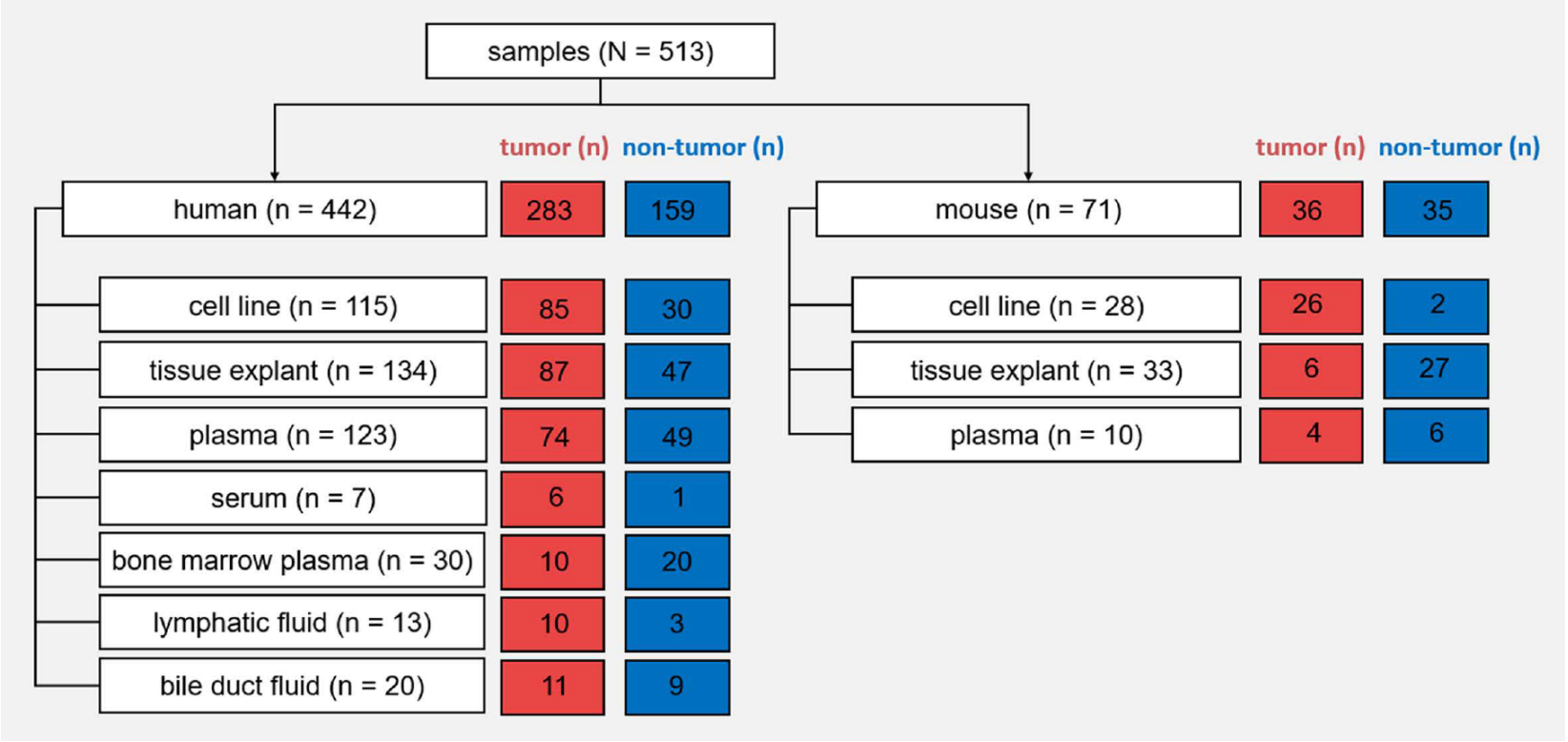
Exomeres and Exosomes Promote Metastasis and Systemic Diseases

Exomeres → Organ failure, and wasting (i.e. Cachexia)

Exo-S → Distant metastasis

Exo-L → Lymph node metastasis, immune dysfunction

Exosome proteomic data on human samples
Over 440 human samples



Goals:

1. **To define common human exosome markers from different sources (i.e. cell line, tissue, plasma, etc.)**
2. **To identify tumor-specific exosome markers**
3. **To classify primary tumor of unknown origin using exosome signature**

Unpublished data

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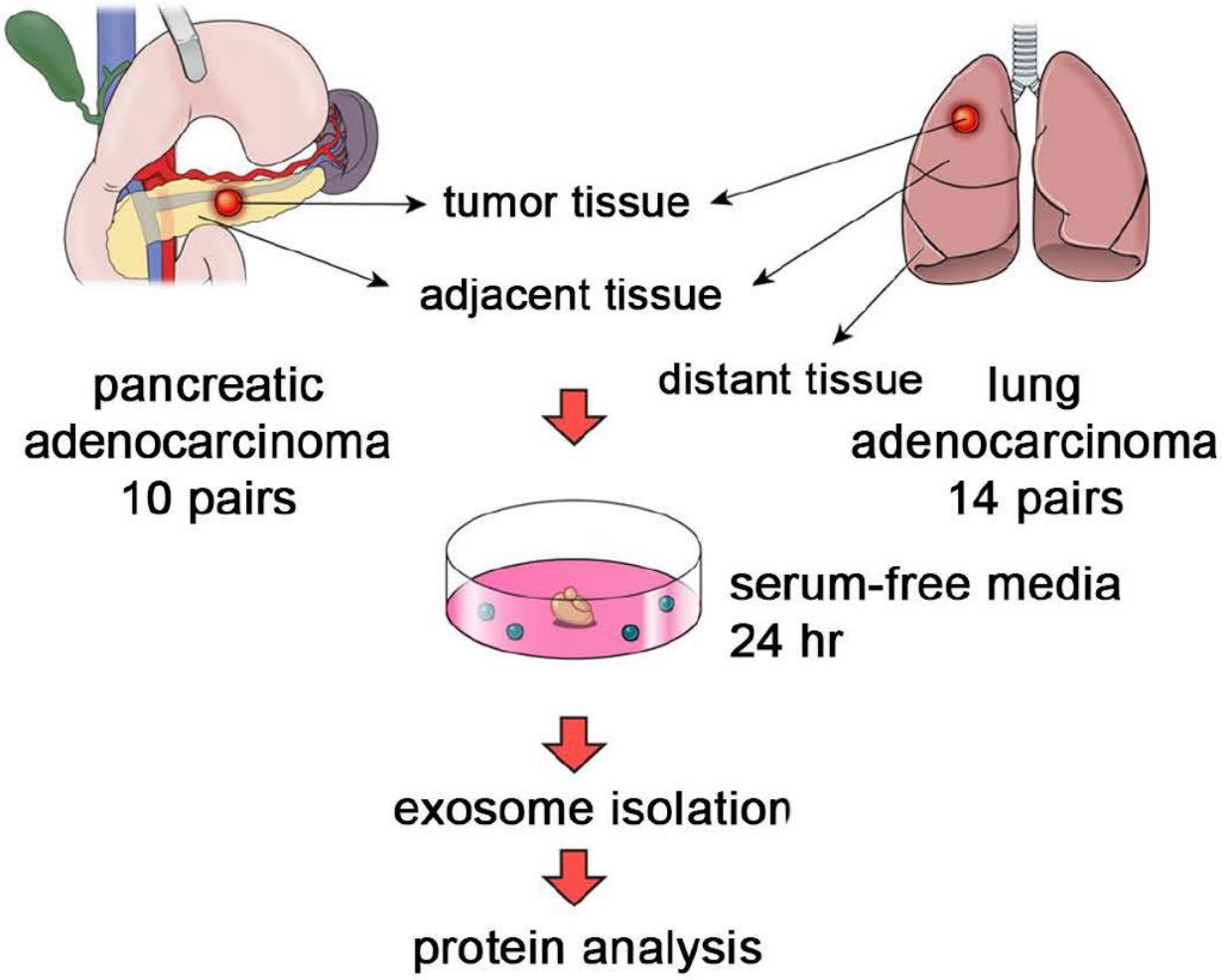
Identification of tumor-specific protein cargo in human lung and pancreatic cancer tissue explant



Unpublished data

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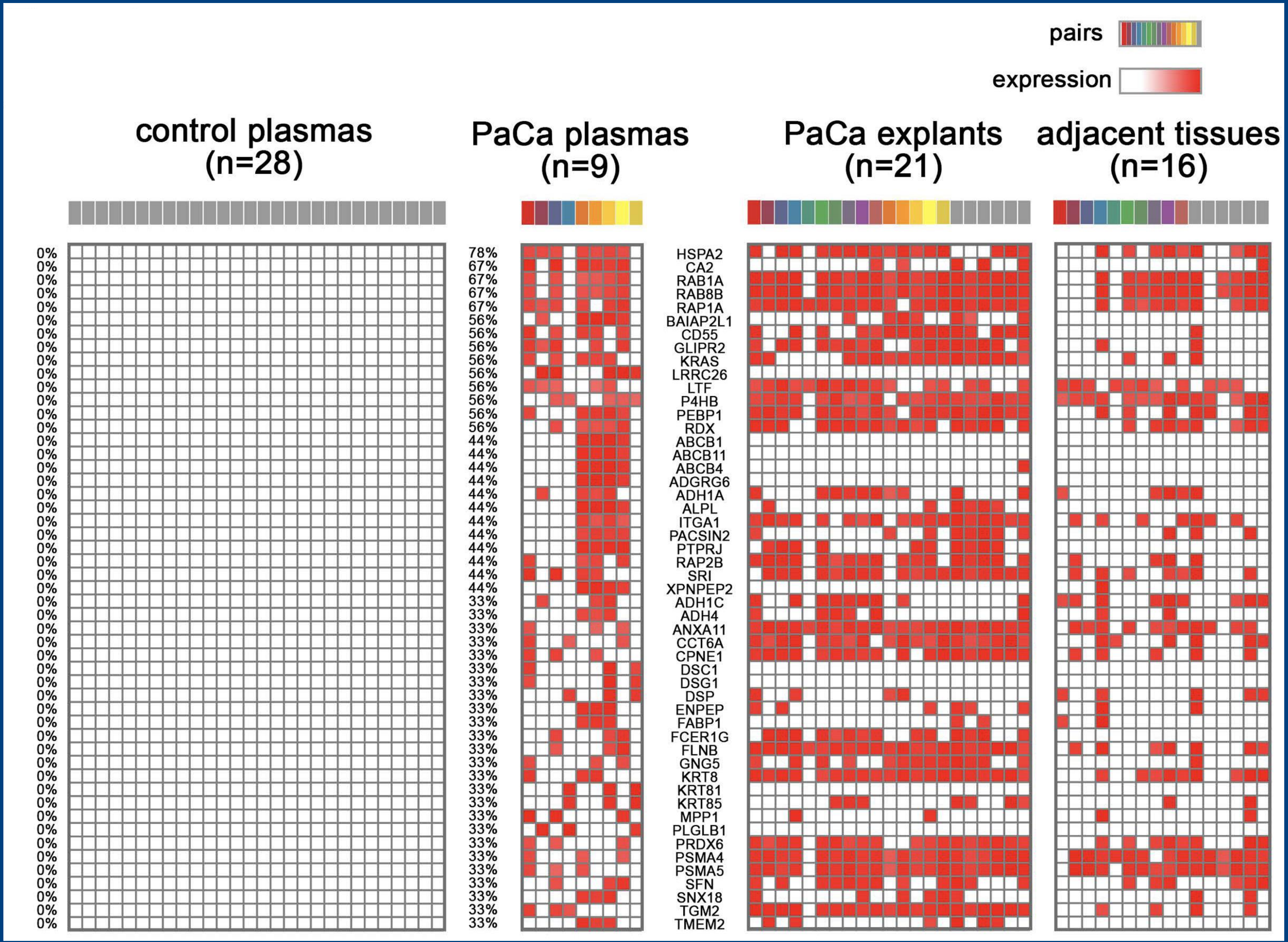
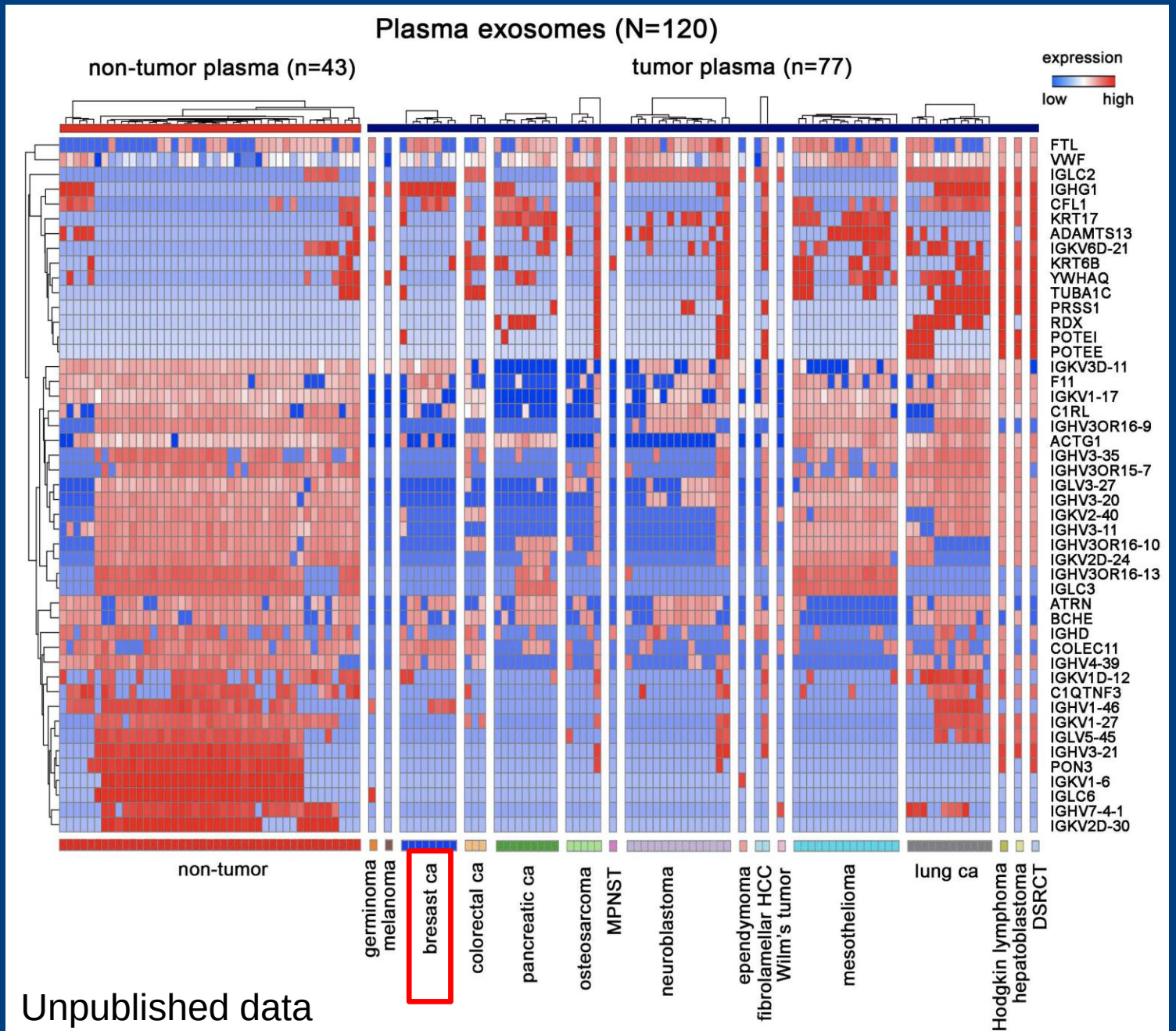
Plasma-derived Exosomal Proteins in Stage I/II PDAC Patients



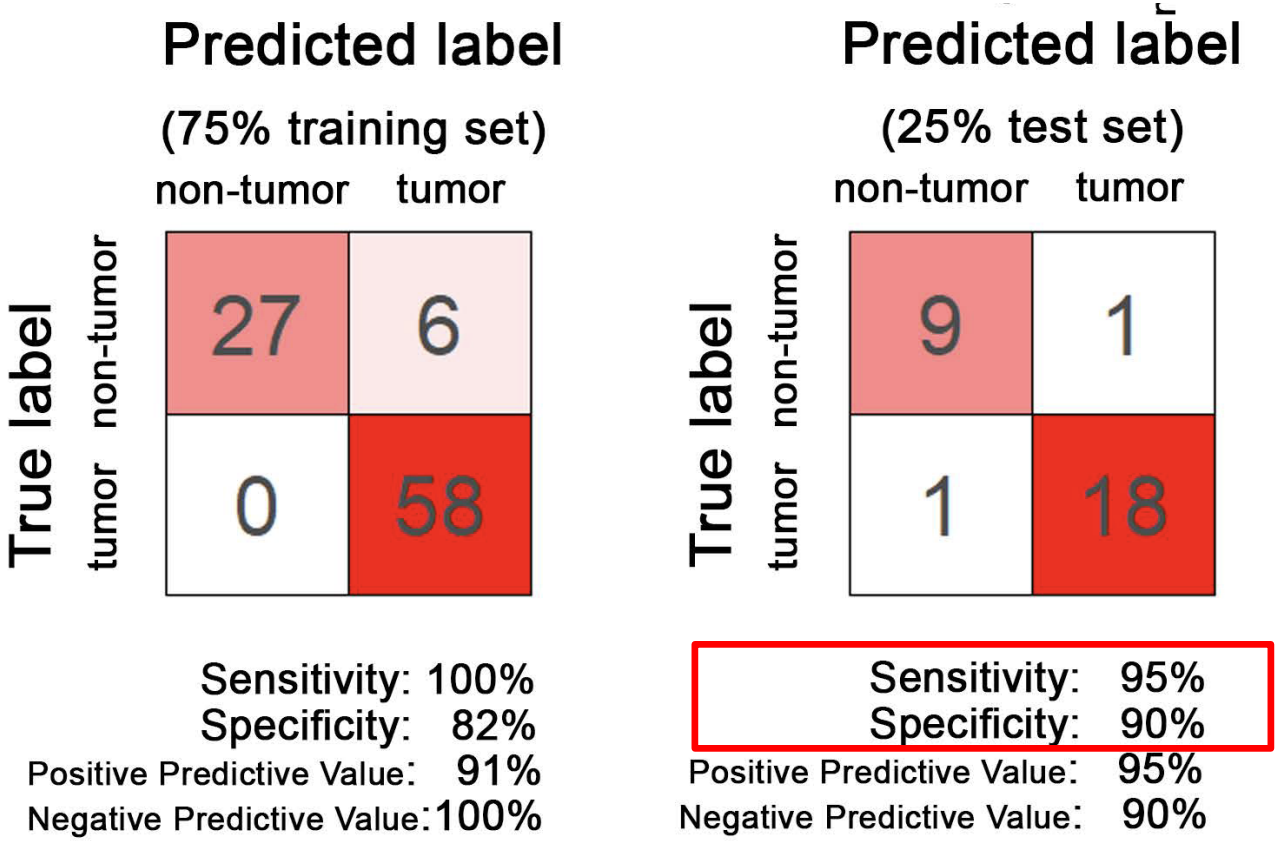
Unpublished data

Pan-Cancer Exosomal Proteins in Plasma



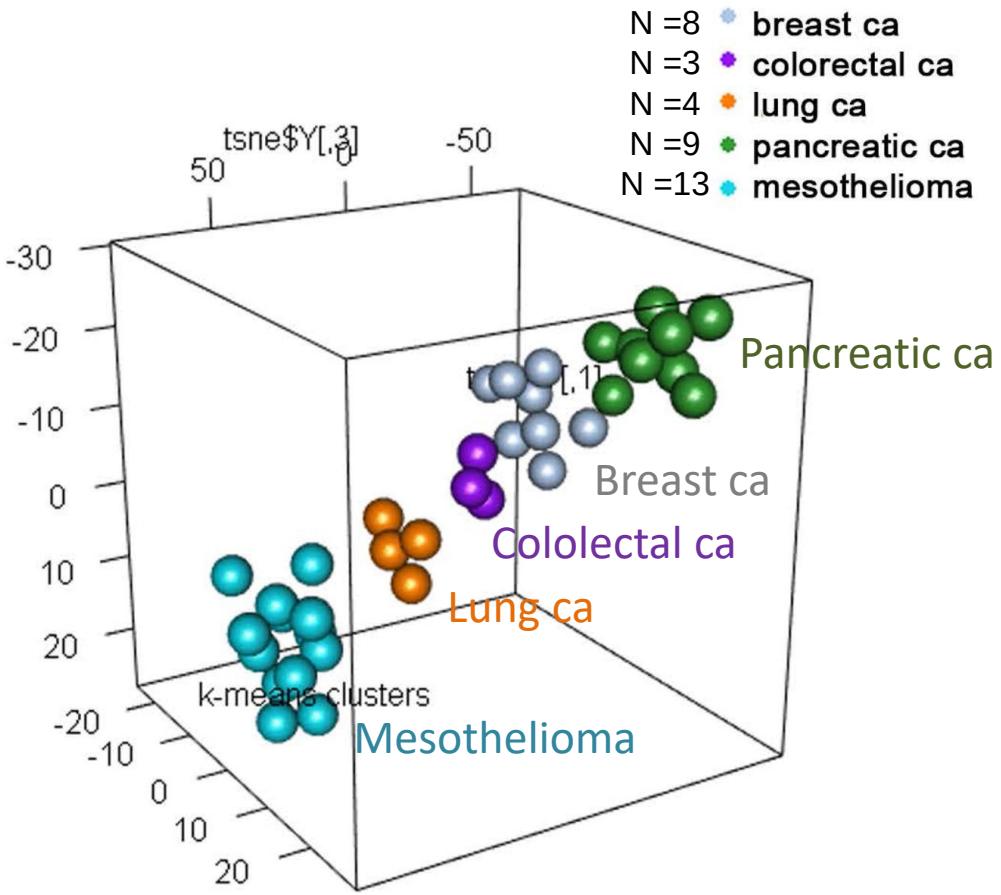
Unpublished data

Liquid biopsy biomarker:
Tumor plasma-derived exosomes vs non-tumor plasma-derived exosomes



Unpublished data

28 Plasma-derived exosome profiles classify primary tumors of unknown origin



Unpublished data

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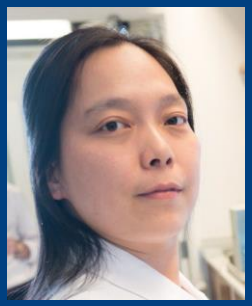
In Conclusion:

- Tissue- and plasma-derived exosome and exomere proteins may serve as biomarkers representing tumor formation (even in early stages), progression and metastasis
- Exosome and exomere proteomics may identify specific proteins and molecular pathways to target
- Exosome proteomic–based drug development will avoid unwanted side effects of targeting normal tissues

Lyden Lab

Lab Members

- **Haiying Zhang , PhD – Assistant Professor**
- **Irina Matei, PhD – Assistant Professor**
- **Ayuko Hoshino, PhD– Instructor**
- **Han Sang Kim, MD – Research Fellow**
- **Candia Kenific, PhD – Postdoctoral Fellow**
- **Linda Bojmar, PhD – Postdoctoral Fellow**
- **Fanny Vatter, PhD – Postdoctoral Fellow**
- **Michele Cioffi, PhD – Postdoctoral Fellow**
- **Shani Dror, PhD – Postdoctoral Fellow**
- **Inbal Wortzel, PhD – Postdoctoral Fellow**
- **Gang Wang, PhD – Postdoctoral Fellow**
- **Serena Lucotti, PhD – Postdoctoral Fellow**
- **Samer Hanna, PhD – Postdoctoral Fellow**
- **Gonçalo Rodrigues – Graduate Student**
- **Kofi Ennu Gyan – Graduate Student**
- **Pernille Lauritzen – Research Technician**
- **Jean Wang – Research Technician**
- **Sham Rampersaud – Research Technician**
- **Yanshen Liu, MD– Visiting research fellow**
- **Fenbo Zhao, MD – Visiting research fellow**
- **Amy Xu, MD, PhD – Research Fellow**
- **Kayleen Bailey, MD – Research Fellow**
- **Tammy Hennika, MD – Research Fellow**
- **Ashton Harris– Research Program Associate**
- **Ines Castarede – Graduate Student**



Collaborators

- Thompson Family Foundation collaborators
- Mina Bissell, PhD
- Celso Reis, PhD
- Jackie Bromberg, MD
- William Jarnagin, MD
- Tony Hollingsworth, Ph.D
- Paul Grandgenett, Ph.D
- Surinder K Batra, Ph.D
- Maneesh Jain, Ph.D
- David Pisapia, MD
- Cyrus M. Ghajar, PhD
- Yibin Kang, PhD
- Tanya Trippett, MD
- Michael Berger, PhD
- Robert Schwartz, MD, PhD
- John Blenis, PhD
- Todd Heaton , MD
- Scott Blanchard, PhD
- Tang-long Sheng, PhD

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