NIH Common Fund’s Extracellular RNA Communication Program

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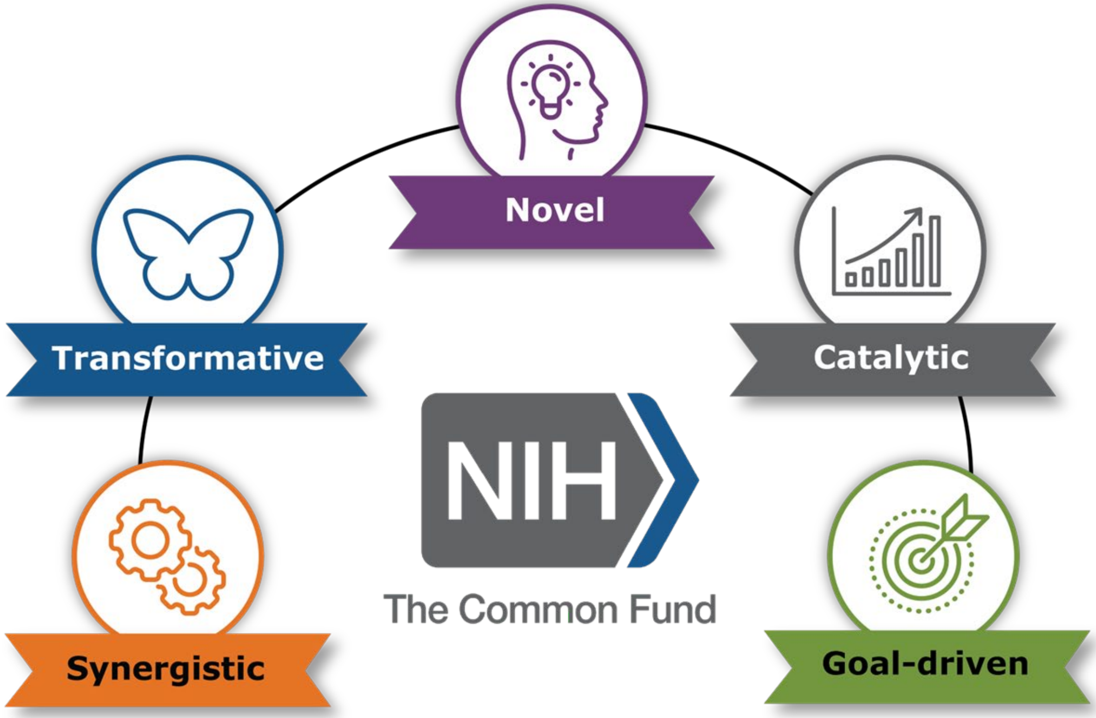
Extracellular RNA Communication Program

- **Breaking traditional thinking:**
  - In the past, RNA was only viewed as functioning ***within cells.***
  - Cell-to-cell communication occurs primarily through proteins, peptides, or hormones secreted into the extracellular spaces between cells or tissues.
- A **paradigm shift** occurred when RNA was observed to be ***released from cells*** into various body fluids carrying information and facilitating cell-to-cell communication.



Extracellular RNA Communication Program

This paradigm shift sparked intense scientific interest, posing critical questions:

- What type of cellular RNAs are released as exRNAs?
- How are exRNAs protected outside the source cell to impact target cells in distant organs?
- What is the impact of exRNAs in health and disease states?
- Can we harness the potential of exRNA communication for diagnosis and treatment?

ExRNAs are transported by encapsulation in extracellular vesicles and other carriers

The **NIH Common Fund's Extracellular RNA Communication Program** was designed to unravel the fundamental biological principles how exRNAs are produced, transported, how they function in both healthy and diseased states, and their potential for clinical utility.

NIH Common Fund Extracellular RNA Communication Program

Goal-driven

Stage 1 Initiatives

- ExRNA biogenesis & function
- Human exRNA reference profiles
- ExRNAs as biomarkers
- ExRNAs as therapeutics
- Data coordination & analysis

Stage 2 Initiatives

- Separation technologies
- Single EV isolation technologies
- Data coordination & analysis

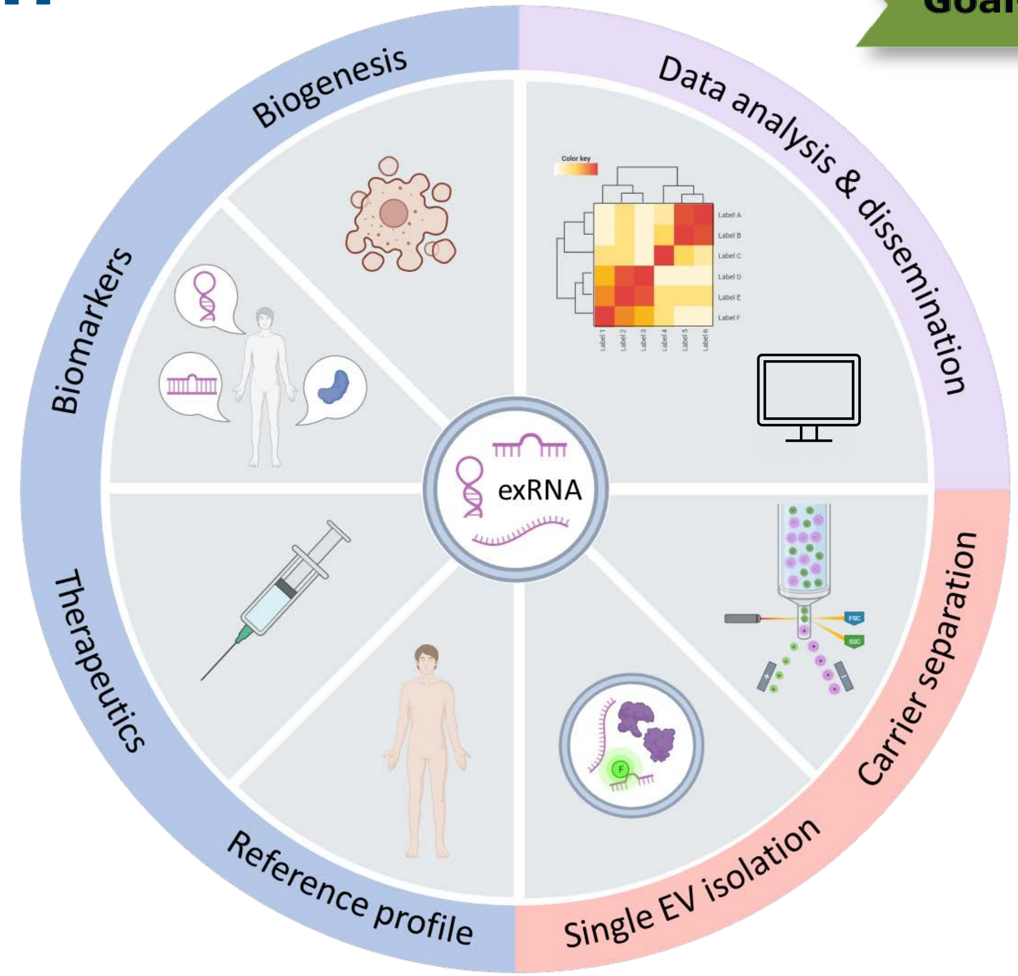


Image modified from: Amolegbe, Sara M *et.al.* (2025), *Journal of extracellular vesicles* vol. 14, 1. https://doi.org/10.1002/jev2.70016

NIH ExRNA Communication Program Timeline

Goal-driven

Kickoff Sept. 2013

Joint ISEV Meeting 2015

Cell pkg 2019

Launch Sept. 2019

COVID-19

Funding Complete Aug. 2022

Program Closeout 2025

Stage 1

Stage 2

Stage 1 Awards

- 30 awards across 5 initiatives
- 8 awards to support scientific conferences (R13 awards)

Stage 2 Awards

- 12 awards across 3 initiatives
- 3 awards to support scientific conferences (R13 awards)

Deliverables and Scientific Impact From Stage 1

Novel

Developed ontology to standardize language of emerging field

Identified diverse classes of circulating small RNAs from different biofluids

Demonstrated that exRNAs can be used as biomarkers for a variety of diseases

Demonstrated protective and regenerative properties of some exRNAs in exosomes

Resolved controversy that food-derived miRNA causes disease

Stage 2 of Extracellular RNA Communication Consortium (ERCC) Charts Next-Generation Approaches for Extracellular RNA Research

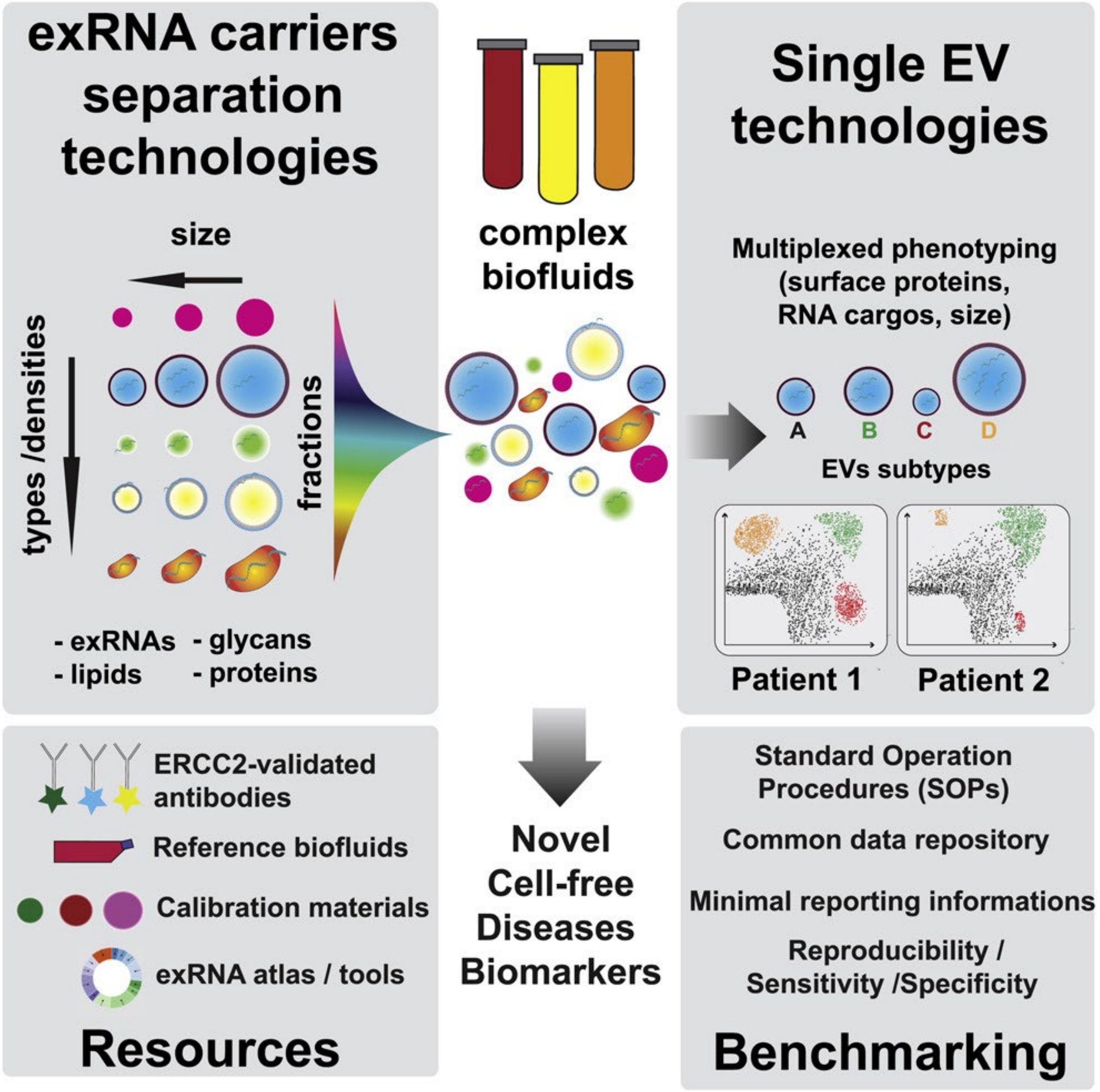
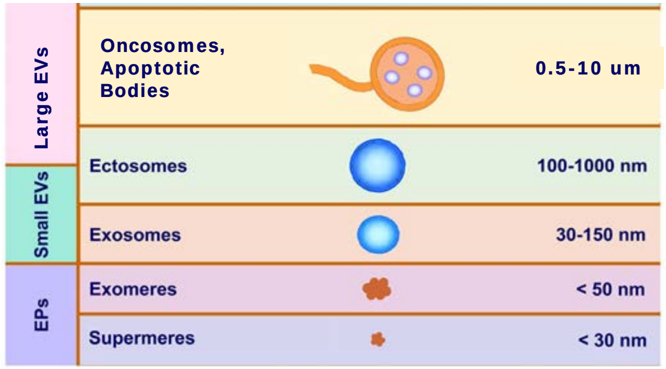


Image modified from: Mateescu, *et. al. (*2022) *iScience*, 25(8), 104653. https://doi.org/10.1016/j.isci.2022.104653

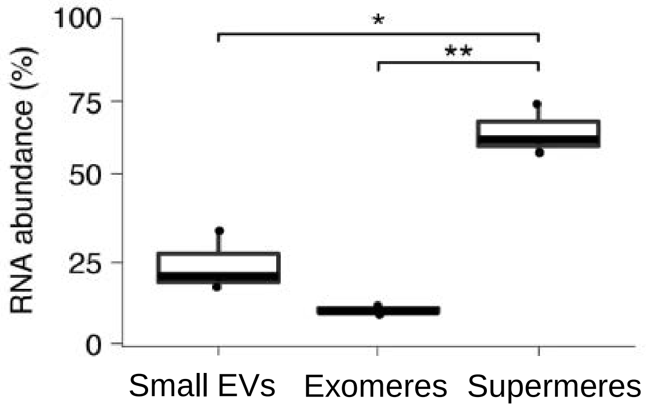
Deliverables and Scientific Impact From Stage 2

Novel



Discovered distinct types of exRNA carriers and that different carriers transport specific types of exRNA cargo

Identified supermeres as a major carrier of exRNA



Developed advanced tools for isolating and analyzing exRNA carriers, such as microfluidics-based purification and single EV analysis

Developed analytical tools and computational analysis of exRNA profiling data

Top: Image modified from Lorite et al., (2024) *Int. J. Mol. Sci. 26*(1), 189; https://doi.org/10.3390/ijms26010189
Bottom: From Zhang, Q., *et al.* (2021) *Nat Cell Biol* **23**, 1240–1254. https://doi.org/10.1038/s41556-021-00805-8

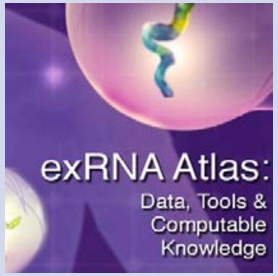
ExRNA Resources

exRNA RESEARCH PORTAL

exrna.org

Transformative

Data



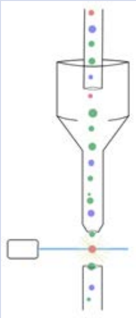
EV Antibody Database

Software

exRNA Atlas API

exceRpt

GENBOREE



Nanoflow Repository

Protocols

miRDaR

ExRNA Protocols Decision Tree

Reagents

ERCC Resource Catalog

Virtual Bio Repository

ExRNA Program Achievements: By the Numbers

Transformative

950+ Publications
Cited **100,000+** times

25 Unique Inventions
50+ Patent Applications

exRNA Atlas
Contains **>10K** human exRNA profiles
550,000+ downloads in **55** countries

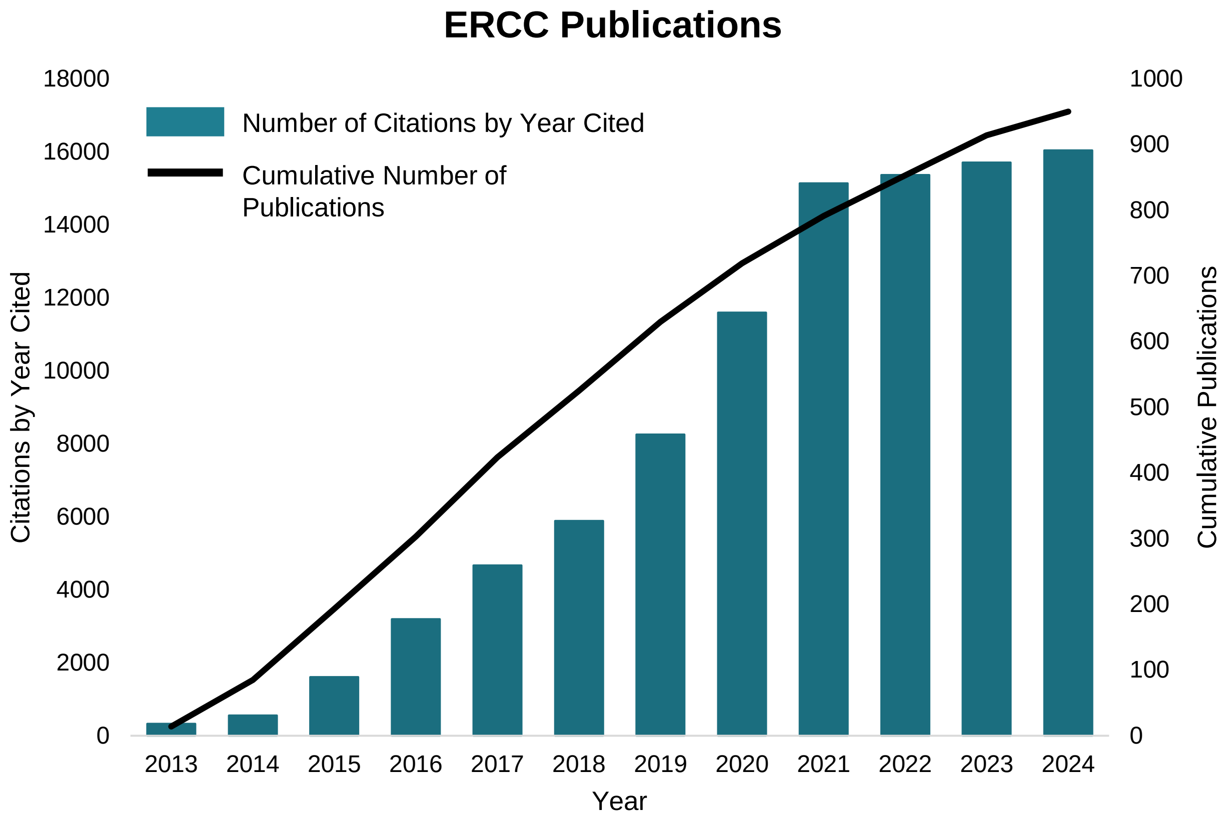
exceRpt Tool
143,420 samples processed & analyzed
91% submitted by non-ERCC users

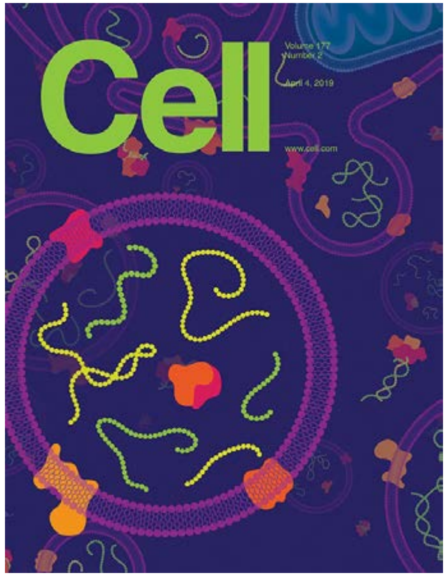
EV Antibody Database
Accessed 8,880+ times since 2020 launch

miRDaR Resource
Accessed 1,487 times since 2019 launch

A Decade of NIH Common Fund Support Illuminates ExRNA Biology

Catalytic



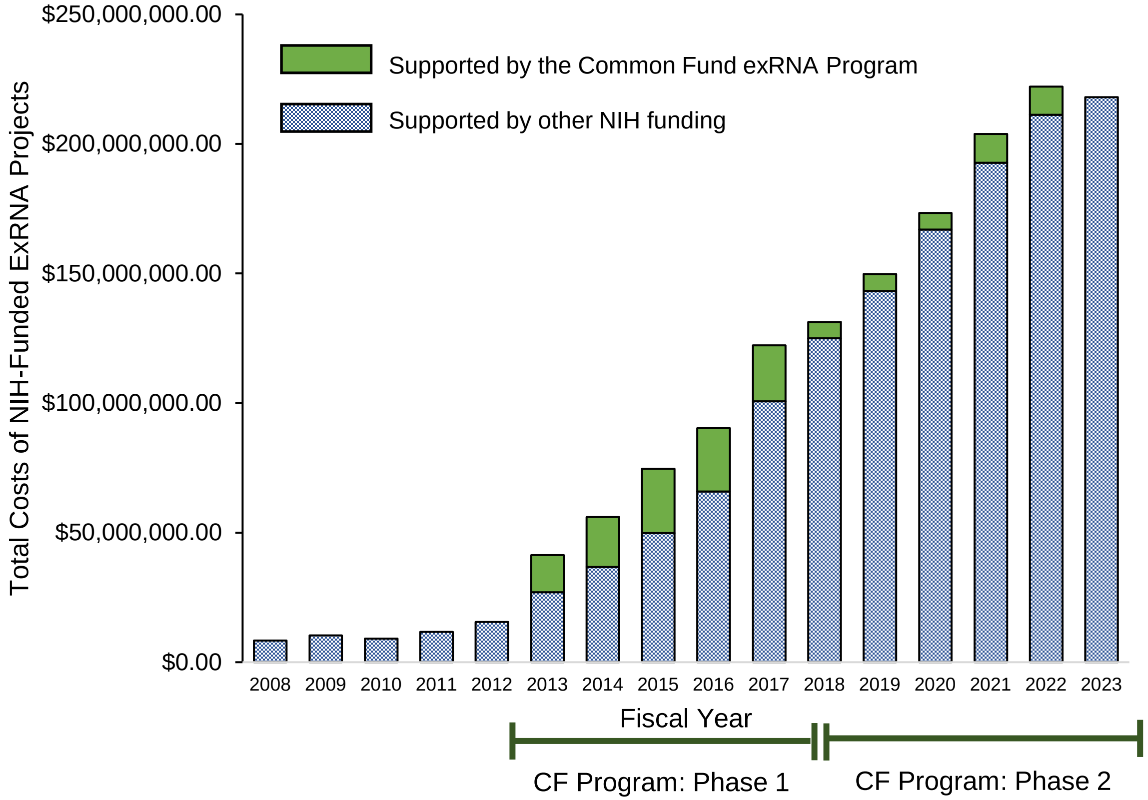


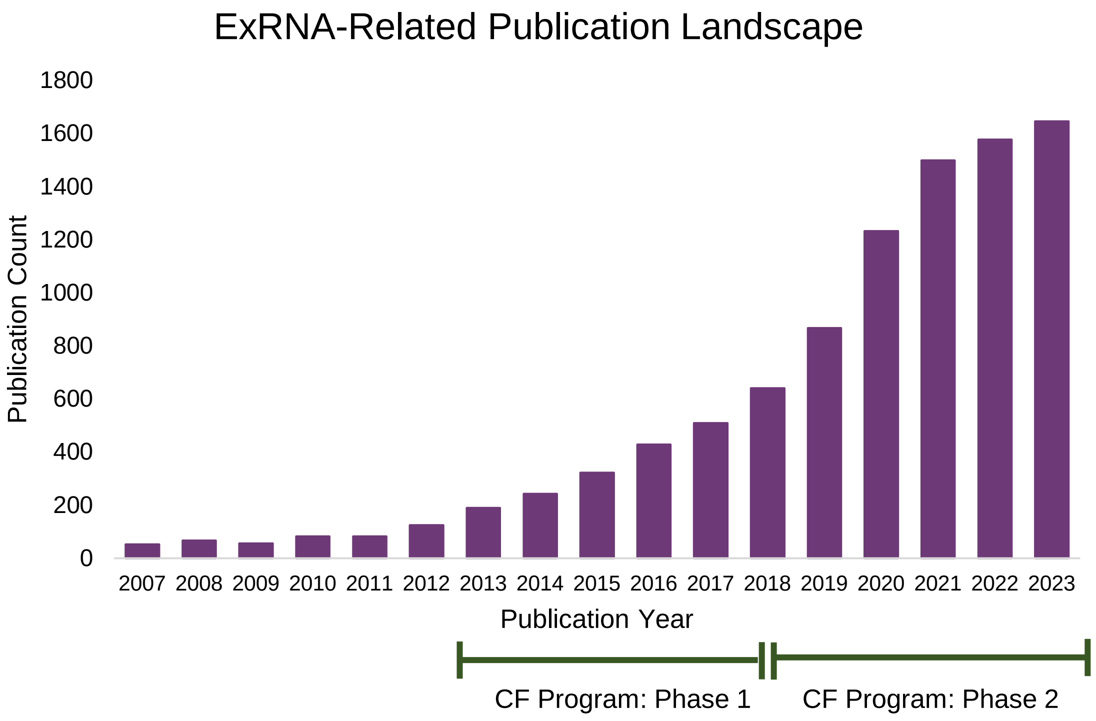
- 2019 Cell publication package, Insights from the Extracellular RNA Communication Consortium, featured over 30 articles
- Cell Genomics publication package in progress
- Coming soon: Methods in Molecular Biology, 16 chapters on exRNA and carriers

Amolegbe SM, *et.al.* (2025) *Journal of extracellular vesicles* vol. 14, 1. https://doi.org/10.1002/jev2.70016

A Catalytic Investment: Supporting the Acceleration of the Field

Catalytic

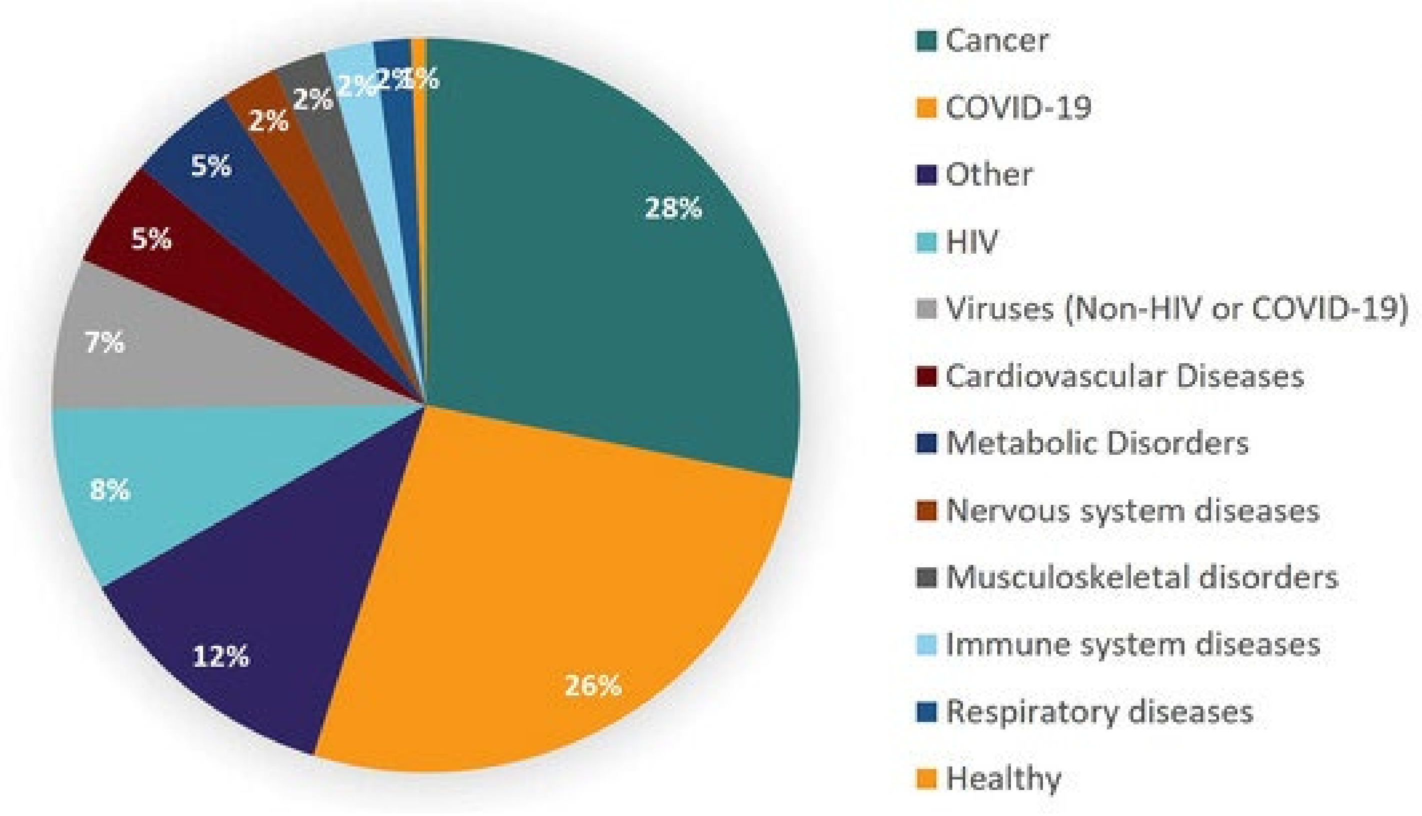




Amolegbe SM, *et.al.* (2025) *Journal of extracellular vesicles* vol. 14, 1. https://doi.org/10.1002/jev2.70016

Clinical Application of ExRNA-Related Research

Catalytic



RADx-rad: Exosome-based Technologies Towards Multi-Parametric and Integrated Approaches for SARS-CoV-2 virus detection

4 Awardees under RFA-OD-20-018

- >32 publications
- 14 patents filed
- 1 FDA EUA received, 1 FDA EUA application in progress, 4 pre-EUA applications submitted.

Amolegbe SM, *et.al.* (2025) *Journal of extracellular vesicles* vol. 14, 1. https://doi.org/10.1002/jev2.70016

ExRNA Communication Program Key Accomplishments

Helped establish exRNA as intercellular communicators	Potential for exRNA as novel therapeutics	Discovered vesicular and non-vesicular carriers with distinct exRNA cargo	ExRNAs from liquid biopsies are a source of biomarkers
Developed methods to separate and characterize exRNA carriers	Helped develop diagnostic tests for COVID-19 using exRNA carriers	Helped dispel role for food-derived miRNA impacting human health	Potential for exRNA as drug delivery vehicles

NIH Common Fund ExRNA Communication Program Working Group (past and present)

Synergistic

Co-Chairs:
Christopher P. Austin, M.D. (NCATS)*
Joni Rutter, Ph.D. (NCATS)
Story Landis, Ph.D. (NINDS)*
Dinah S. Singer, Ph.D. (NCI)

Common Fund Program Leader:
Patricia Labosky, Ph.D. (OD)

Working Group Coordinators:
T. Kevin Howcroft, Ph.D. (NCI)
Danilo A. Tagle, Ph.D. (NCATS)

Key Initiative Program Officers:
John Satterlee, Ph.D. (NIDA)
Pothur R. Srinivas, Ph.D., M.P.H. (NHLBI)

*Reflects affiliations during tenure on the Working Group

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Christine Happel, Ph.D. (NCATS)
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Thank you!

Questions?

ExRNA-Related NIH Programs

- NIDA — RFA-DA-25-073 “Exploratory Studies to Investigate Mechanisms of HIV infection, Replication, Latency, and/or Pathogenesis in the Context of Substance Use Disorders” (R01)
- NIAID — NOT-AI-24-007 “Notice of Special Interest (NOSI): RNA Delivery Technologies to Allow Specific Tissue Target Homing (RNA-DASH)”
- NCATS — PAR-25-157 / PAR-23-177 “Awards Supporting Cutting-Edge Technologies for Translational Science (ASCETTS)" (R21)
- NCATS — PAR-23-267 / PAR-23-268 “Industrialization and Translation of Extracellular Vesicles for use in Regenerative Medicine” (U43/U44) SBIR/STTR
- NIDA — PAR-20-147 / PAR-20-148 “Extracellular RNA carrier subclasses in processes relevant to Substance Use Disorders or HIV infection” (R01/R21)
- NCI — PAR-20-053 “Program to Assess the Rigor and Reproducibility of Extracellular Vesicle-Derived Analytes for Cancer Detection" (R01)
- OD — RFA-OD-20-018 “RADx-rad: Exosome-based Technologies Towards Multi-Parametric and Integrated Approaches for SARS-CoV-2” (U18)

Publications demonstrating progress towards exRNA *Communication* program goals

Amolegbe SM, *et.al.* (2025), *Journal of extracellular vesicles* vol. 14, 1. https://doi.org/10.1002/jev2.70016

Publications	PMID
exRNA Data and Resources	
Murillo *et al*. exRNA Atlas Analysis Reveals Distinct Extracellular RNA Cargo Types and Their Carriers Present across Human Biofluids. Cell. 2019 Apr 4;177(2):463-477.e15.	30951672
Rozowsky *et al*. exceRpt: A Comprehensive Analytic Platform for Extracellular RNA Profiling. Cell Syst. 2019 Apr 24;8(4):352-357.e3.	30951672
LaPlante *et al*. exRNA-eCLIP intersection analysis reveals a map of extracellular RNA binding proteins and associated RNAs across major human biofluids and carriers. Cell Genom. 2023 Apr 20;3(5):100303.	37228754
Advances in ExRNA Biology	
Freedman *et al*. Diverse human extracellular RNAs are widely detected in human plasma. Nat Commun. 2016 Apr 26;7:11106.	27112789
Godoy *et al*. Large Differences in Small RNA Composition Between Human Biofluids. Cell Rep. 2018 Oct 30;25(5):1346-1358.	30380423
Zhang *et al*. Supermeres are functional extracellular nanoparticles replete with disease biomarkers and therapeutic targets. Nat Cell Biol. 2021 Dec;23(12):1240-1254.	34887515
Enabling Technologies	
Andronico *et al*. Sizing Extracellular Vesicles Using Membrane Dyes and a Single Molecule-Sensitive Flow Analyzer. Anal Chem. 2021 Apr 13;93(14):5897-5905.	33784071
Gu *et al*. Acoustofluidic centrifuge for nanoparticle enrichment and separation. Sci Adv. 2021 Jan 1;7(1):eabc0467.	33523836
Wang *et al*. Slowing down DNA translocation through solid-state nanopores by edge-field leakage. Nat Commun. 2021 Jan 8;12(1):140.	33420061

References

- Freedman, J.E.; Gerstein, M.; Mick, E.; Rozowsky, J.; Levy, D.; Kitchen, R.; Das, S.; Shah, R.; Danielson, K.; Beaulieu, L.; et al. Diverse human extracellular RNAs are widely detected in human plasma. Nat Commun 2016, 7, 11106, doi:10.1038/ncomms11106.
- Godoy, P.M.; Bhakta, N.R.; Barczak, A.J.; Cakmak, H.; Fisher, S.; MacKenzie, T.C.; Patel, T.; Price, R.W.; Smith, J.F.; Woodruff, P.G.; et al. Large Differences in Small RNA Composition Between Human Biofluids. Cell Rep 2018, 25, 1346-1358, doi:10.1016/j.celrep.2018.10.014.
- Mateescu, B.; Jones, J.C.; Alexander, R.P.; Alsop, E.; An, J.Y.; Asghari, M.; Boomgarden, A.; Bouchareychas, L.; Cayota, A.; Chang, H.C.; et al. Phase 2 of extracellular RNA communication consortium charts next-generation approaches for extracellular RNA research. *iScience* **2022**, *25*, 104653, doi:10.1016/j.isci.2022.104653.
- Zhang, Q.; Jeppesen, D.K.; Higginbotham, J.N.; Graves-Deal, R.; Trinh, V.Q.; Ramirez, M.A.; Sohn, Y.; Neininger, A.C.; Taneja, N.; McKinley, E.T.; et al. Supermeres are functional extracellular nanoparticles replete with disease biomarkers and therapeutic targets. Nat Cell Biol 2021, 23, 1240-1254, doi:10.1038/s41556-021-00805-8.
- Murillo, O.D.; Thistlethwaite, W.; Rozowsky, J.; Subramanian, S.L.; Lucero, R.; Shah, N.; Jackson, A.R.; Srinivasan, S.; Chung, A.; Laurent, C.D.; et al. exRNA Atlas Analysis Reveals Distinct Extracellular RNA Cargo Types and Their Carriers Present across Human Biofluids. *Cell* **2019**, *177*, 463-477 e415, doi:10.1016/j.cell.2019.02.018.
- Rozowsky, J.; Kitchen, R.R.; Park, J.J.; Galeev, T.R.; Diao, J.; Warrell, J.; Thistlethwaite, W.; Subramanian, S.L.; Milosavljevic, A.; Gerstein, M. exceRpt: A Comprehensive Analytic Platform for Extracellular RNA Profiling. *Cell Syst* **2019**, *8*, 352-357 e353, doi:10.1016/j.cels.2019.03.004.
- LaPlante, E.L.; Sturchler, A.; Fullem, R.; Chen, D.; Starner, A.C.; Esquivel, E.; Alsop, E.; Jackson, A.R.; Ghiran, I.; Pereira, G.; et al. exRNA-eCLIP intersection analysis reveals a map of extracellular RNA binding proteins and associated RNAs across major human biofluids and carriers. *Cell Genom* **2023**, *3*, 100303, doi:10.1016/j.xgen.2023.100303.
- Andronico, L.A.; Jiang, Y.; Jung, S.R.; Fujimoto, B.S.; Vojtech, L.; Chiu, D.T. Sizing Extracellular Vesicles Using Membrane Dyes and a Single Molecule-Sensitive Flow Analyzer. *Anal Chem* **2021**, *93*, 5897-5905, doi:10.1021/acs.analchem.1c00253.
- Gu, Y.; Chen, C.; Mao, Z.; Bachman, H.; Becker, R.; Rufo, J.; Wang, Z.; Zhang, P.; Mai, J.; Yang, S.; et al. Acoustofluidic centrifuge for nanoparticle enrichment and separation. *Sci Adv* **2021**, *7*, doi:10.1126/sciadv.abc0467.
- Wang, C.; Sensale, S.; Pan, Z.; Senapati, S.; Chang, H.C. Slowing down DNA translocation through solid-state nanopores by edge-field leakage. *Nat Commun* **2021**, *12*, 140, doi:10.1038/s41467-020-20409-4.