Minimal information for studies of extracellular vesicles (MISEV2023): from basic to advanced approaches

Info and outreach slides

Logos

Links

MISEV2018: https://onlinelibrary.wiley.com/doi/10.1080/20013078.2018.1535750
MISEV2014: https://onlinelibrary.wiley.com/doi/full/10.3402/jev.v3.26913
ISEV: https://www.isev.org/
JEV link: https://onlinelibrary.wiley.com/journal/20013078
JExBio link: https://onlinelibrary.wiley.com/toc/27682811/current

The beginnings of MISEV2023: MISEV2014, then...

MISEV2018 in J Extracellular Vesicles: a community effort

JOURNAL OF EXTRACELLULAR VESICLES
2018, VOL. 00, 1535750
https://doi.org/10.1080/20013078.2018.1535750

Minimal information for studies of extracellular vesicles 2018 (MISEV2018): a position statement of the international society for extracellular vesicles and update of the MISEV2014 guidelines

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Minimal information for studies of extracellular vesicles (MISEV2023): from basic to advanced approaches.

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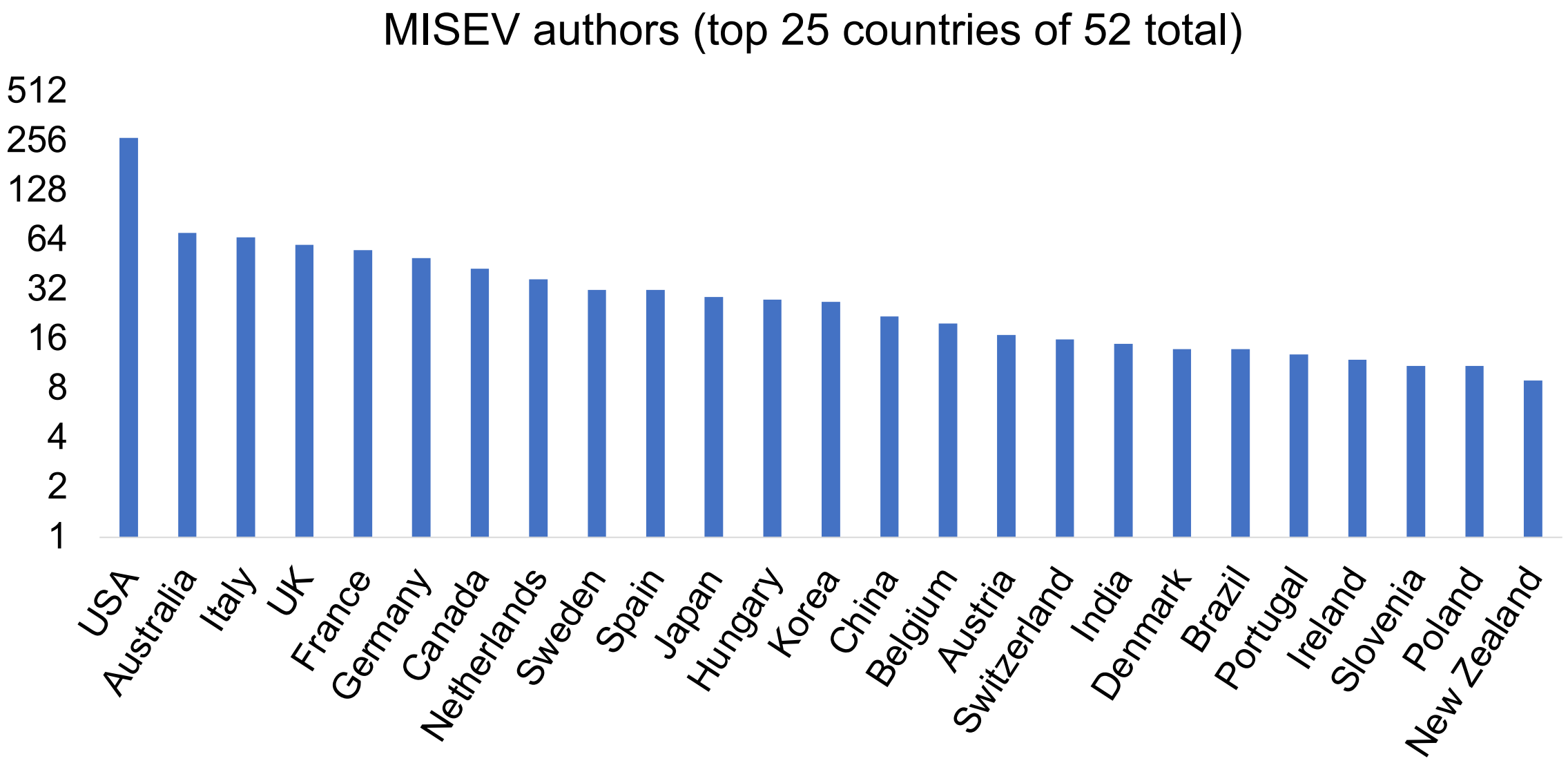
~60 drafting authors list here; 1045 total co-authors

R2 accepted by JEV, December 2023

MISEV2023 was a three-year effort

- 2020 pre-MISEV survey (See the summary article: https://onlinelibrary.wiley.com/doi/10.1002/jev2.12182)
- ISEV board assigned a five-author committee (Welsh, Goberdhan, O'Driscoll, Théry, Witwer)
- Drafts and refinements with ISEV board input and invited drafting authors
- 2022 co-author survey with >1000 responses
- Revisions based on the survey
- Internal review and additional invited contributions/revisions; style "unification"
- Journal pre-submission review and three post-submission reviews
- Co-author confirmation and consensus survey

MISEV2023: 1045 co-authors in 52 countries



MISEV2023: domains

Nomenclature: communication of concepts. How to approach Non-Vesicular Extracellular Particles

Collection and pre-processing: pre-analytical variables: EV sources including bacteria, biofluids, tissue

EV separation and concentration

EV characterization

Technique-specific reporting for EV characterization

EV release and uptake

Functional studies

In vivo EV studies

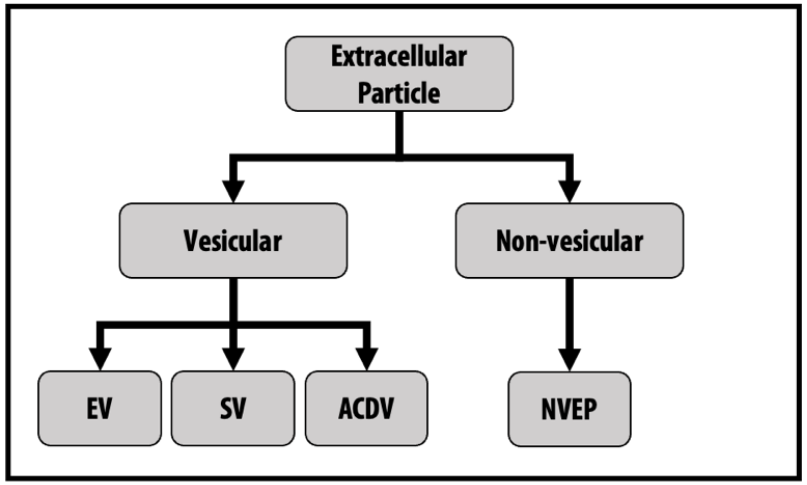
red = new in MISEV2023

Overall co-author agreement with the MISEV2023 sections (%, of 998 co-author confirmation survey responses considered complete and valid)

Percentage of 998 co-author confirmation survey responses considered complete and valid

	Agree		Disagree		
Section	Completely	Mostly	Mostly	Completely	No opinion/ expertise
1. Intro	89.3	10.7	0	0	0
2. Nomenclature	79.5	19.9	0.4	0	0.2
3. Pre-processing	70.4	28.5	0.1	0	1
4. Separation/Concentration	74.4	24.8	0.1	0	0.6
5. Characterization	72.3	27	0.3	0	0.4
6. Technique-specific	70.6	27.5	0.4	0	1.5
7. Release/Uptake	69.6	24.3	0.4	0	5.8
8. Functional studies	71.1	25.1	0.3	0.1	3.4
9. In vivo	65.5	21.6	0.1	0	12.7

Figures 1 and 2: EP nomenclature and separation/concentration methods



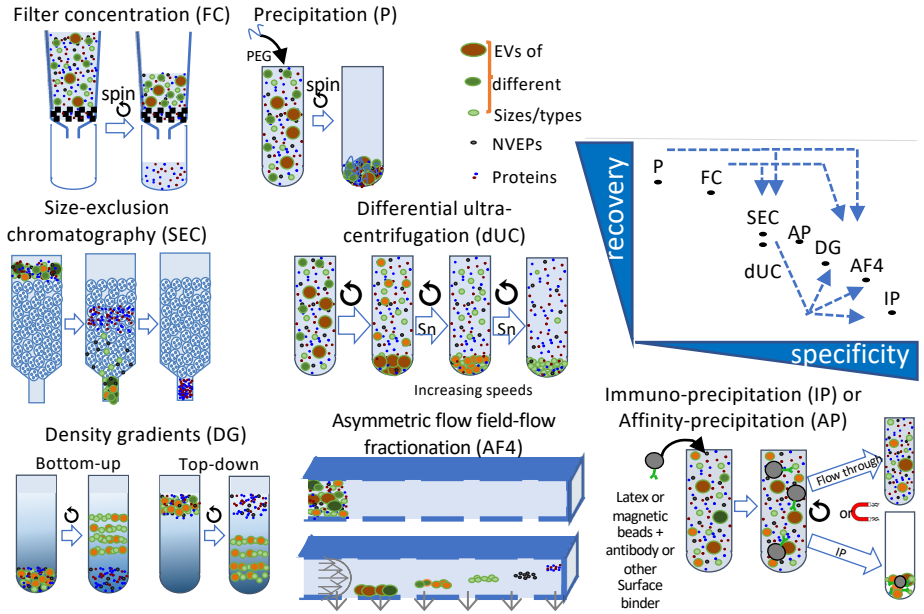


Table 3: characterization
Table 4: In vivo studies (organisms)

Table 2: quick reference on EV terms

Term	Definition	Usage
Extracellular vesicles (EVs)	Particles that are released from cells, are delimited by a lipid bilayer, and cannot replicate on their own.	Recommended
Non-vesicular extracellular particles (NVEPs)	Multimolecular assemblies that are released from cells and do not have a lipid bilayer (non-vesicular extracellular particle fraction).	Recommended
Extracellular particles (EPs)	Umbrella term for all particles outside the cell, including EVs and NVEPs.	Recommended
EV mimetic	EV-like particles that are produced through direct artificial manipulation. This term is preferred over “exosome-like vesicles” and similar terms that imply specific biogenesis-related properties.	Recommended
Artificial cell-derived vesicles (ACDVs)	EV mimetics that are produced in the laboratory under conditions of induced cell disruption, such as extrusion.	Recommended
Synthetic vesicles (SVs)	EV mimetics that are synthesized de novo from molecular components or made as hybrid entities, e.g., fusions between liposomes and native EVs.	Recommended
Small EVs (operational term)	Based on the diameter of the separated particles, small EVs are often described as <200 nm in diameter. However, measured diameter is related to the specific characterization method.	Recommended, but caution required
Large EVs (operational term)	Based on the diameter of the separated particles, large EVs are often described as >200 nm in diameter. However, measured diameter is related to the specific characterization method.	Recommended, but caution required
Other ‘operational terms’	Physical characteristics: e.g., diameter: small extracellular vesicles (sEVs), large EVs (lEVs), density: low, medium, high (defined ranges). Biochemical composition: e.g., contains a specific (macro)molecule, such as a protein. Cellular origin and/or conditions under which EVs were generated: terms that highlight specific aspects of biogenesis such as molecular mechanisms, energy-dependence (or lack thereof), and functional state of the parent cell related to stress or death.	Recommended, but caution required
Exosome	Biogenesis-related term indicating origin from the endosomal system. Unless subcellular origin can be demonstrated, it is likely that a broad population of EVs is being studied, not exosomes specifically. Exosomes represent a subtype of small EVs: the diameter of intraluminal vesicles of endosomes is generally smaller than 200 nm.	Discouraged unless subcellular origin can be demonstrated
Ectosome	Biogenesis-related term indicating origin from the plasma membrane. Unless subcellular origin can be demonstrated it is likely that a broad population of EVs is being studied, not ectosomes specifically. Ectosomes can have a wide range of sizes, including sizes similar to those of exosomes.	Discouraged unless subcellular origin can be demonstrated
Microvesicle	Biogenesis-related term indicating origin from the plasma membrane. However, historically, the term has often been used to designate large EVs or all EVs, whatever their subcellular origin. This term can therefore lead to confusion.	Discouraged
Exosome-like vesicles	As ‘exosome’ is a biogenesis-related term indicating origin from the endosomal system, this and similar terms are discouraged for synthesized EV mimetics.	Discouraged

What MISEV is NOT…or should not be…

- An unreasonable barrier to field entry
  - Rather, a guide to doing rigorous and publishable science
- An attempt to stifle innovation
  - See the MISEV2018 section on “exceptions”; MISEV2023 “IS NOT” section
- Irrelevant to non-mammalian EV studies
  - Principles of good definitions, markers, and controls are relevant to all EV sources. The exact markers and procedures will vary.
- Irrelevant to clinical studies: biomarkers, therapeutics

What other rigor and reproducibility initiatives does ISEV have?

ISEV Rigor and Standardization Subcommittee

Rienk Nieuwland
University of Amsterdam, The Netherlands

Juan-Manuel Falcon Perez
CIC bioGUNE, Spain

https://www.isev.org/rigor-standardization

ISEV/ISAC/ISTH: MIFlowCyt-EV *(Welsh, JEV 2020)*

Task forces (selected...see https://www.isev.org/taskforces)

- Blood EVs (*Clayton et al JEV 2019, Lucien et al JEV 2023*)
- Reference Materials (*Welsh, et al, JEV 2020*)
- Regulatory Affairs and EV Therapeutics (e.g. *publications on COVID-19 and EVs: Börger et al Cytotherapy 2020; Lim et al, Cell Stem Cells 2020*)
- Urinary EVs (*Erdbruegger et al, JEV, 2021*)
- Milk, saliva, cerebrospinal fluid (*Sandau et al, JEV, 2023*), synovial fluid, solid tissue, *CCM (Shekari et al, JExBio, 2023*), bacteria

Keep an eye on evolution of recommendations:
Specific biofluids, techniques
MISEV2023
Do you have a suggestion?
Want to join? Contact us!

INTERNATIONAL SOCIETY for EXTRACELLULAR VESICLES

ISEV position papers

Title	Year	Ref
Standardization of sample collection, isolation and analysis methods in extracellular vesicle research	2013	Witwer et al. 2013
ISEV position paper: extracellular vesicle RNA analysis and bioinformatics	2013	Hill et al. 2013
Minimal experimental requirements for definition of extracellular vesicles and their functions: a position statement from the International Society for Extracellular Vesicles	2014	Lotvall et al. 2014
Applying extracellular vesicles-based therapeutics in clinical trials – an ISEV position paper	2015	Lener et al. 2015
Obstacles and opportunities in the functional analysis of extracellular vesicle RNA – an ISEV position paper	2017	Mateescu et al. 2017
Minimal information for studies of extracellular vesicles 2018 (MISEV2018): a position statement of the International Society for Extracellular Vesicles and update of the MISEV2014 guidelines	2018	Thery et al. 2018
Biological membranes in EV biogenesis, stability, uptake, and cargo transfer: an ISEV position paper arising from the ISEV membranes and EVs workshop	2019	Russell et al. 2019
MIFlowCyt-EV: a framework for standardized reporting of extracellular vesicle flow cytometry experiments	2020	Welsh, Van Der Pol, Arkesteijn, et al. 2020
Urinary extracellular vesicles: A position paper by the Urine Task Force of the International Society for Extracellular Vesicles	2021	Erdbrügger et al. 2021

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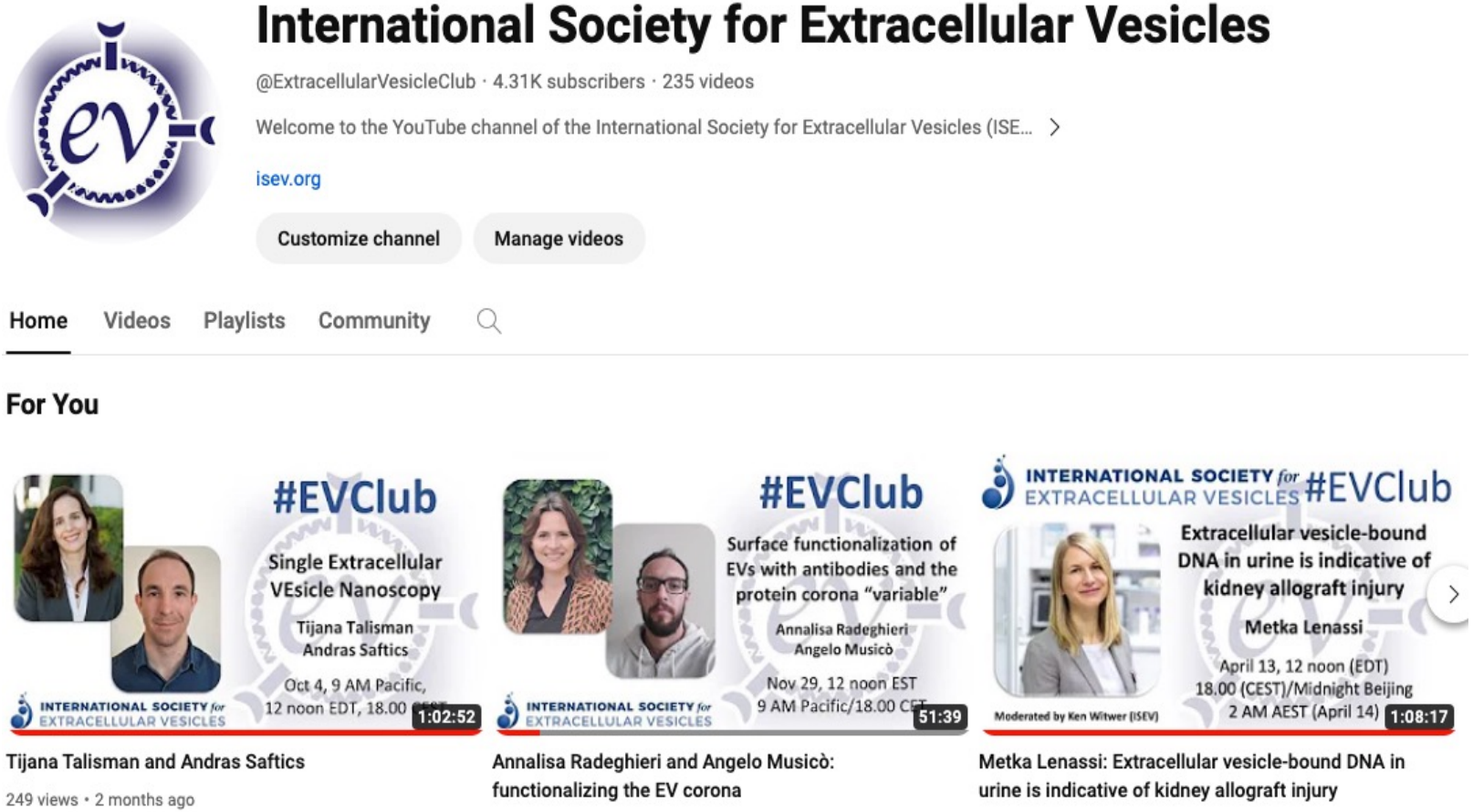

ISEV on YouTube:

https://www.youtube.com/@ExtracellularVesicleClub

>4300 subscribers

Educational videos

Plenary talks, ISEV2023

MOOC3

#EVClub

>180 weekly online sessions

30-300 live participants

5000 sign-ups

https://www.surveymonkey.com/r/EVClubISEV

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