ELBS

WG CTC Technologies

Evi Lianidou & Nick Stoecklein

WG CTC Technologies – Long Term Goals

Networking & Scientific Exchange

- Open platform for discussion of technologies and related issues
- Exchange between users and technology providers

Ring trials and technology assessment

- Organization and frequency of ring trials
- “Pre-competitive arena” for companies
- Cross comparisons between technologies

Promoting development of assays with clinical utility

- “wish-list” from Clinical WG for clinically relevant assays
- Development and/or standardization of “wish-list assays”

Working towards accreditation and reimbursement

- Markers of immediate interest for ISO15189 certification
- Establishment of a validation pipeline
- Distribution of protocols and support for certification

WG CTC Technologies – 2022

Networking & Scientific Exchange:

- ✓ **Active online-platform to facilitate long-term goals and enable scientific exchange and communication**

Ring trial & Technology Assessment:

- ✓ **inventory of all technologies, analytes and biomarkers used in the labs of ELBS members**
- ✓ **Starting to organize method-specific working groups**
- ✓ **Starting activities to validate novel technologies in terms of sensitivity, specificity and robustness with the platforms established within CANCER-ID (e.g. BioRad)**

WG CTC Technologies – 2022

Regular CTC Technologies Meetings – Content

- **address/raise a discussion point/question concerning CTC-technologies** Format: 2-5 min introduction followed by open discussion

- **present a recently published/accepted/pre-published paper** OR **novel methodological development** Format: presentation 15-20 min followed by a 10-15 min discussion (academic groups AND industry partners)

- **present an idea for a ring study** (to test a protocol, add weight to a publication, etc.) to identify collaborators from the ELBS group → Format: presentation 15 min followed by 10-15 min discussion

- **four meetings per year** (Wednesdays) for max 2 hrs

WG CTC Technologies – 2022

We had 6 CTC-Technologies meetings in 2021-2022

- **May 26th 2021**
- **September 15th 2021**
- **November 10th 2021**
- **February 2nd 2022**
- **June 1st 2022**
- **September 7th 2022**

All meetings with >60 participants!

WG CTC Technologies – 2022

Regular CTC Technologies Meetings – Content

Topics/Discussions covered so far :

- Ring trials and technology assessment
- Harmonization with the clinical group
- Working towards standardization (ISO)
- Forming working groups based on survey
- **Development of CTC reference material**
- **Pre-analytical variables**
- **Novel technologies from companies**
- **Novel technologies used by academic ELBS member**

WG CTC Technologies – 2022

Upcoming ELBS CTC Technology meetings in 2022

Wednesdays 2-4 pm CEST

14.12.2022

→ We will ask you for an update on your technologies

Exact dates for 2023 TBD
March, June, September, December

WG CTC Technologies – 2022

Networking & Scientific Exchange:

- ✓ **Active online-platform to facilitate long-term goals and enable scientific exchange and communication**

Ring trial & Technology Assessment:

- ✓ **inventory of all technologies, analytes and biomarkers used in the labs of ELBS members**
- ✓ **Starting to organize method- and biomarker-specific working groups**
- ✓ **Starting activities to validate novel technologies in terms of sensitivity, specificity and robustness with the platforms established within CANCER-ID (e.g. BioRad)**

CTC Technologies – Goals for 2023

1. Assay-specific groups (CellSearch, Parsortix, VyCAP, ISET, etc....)

ELBS

It‘s a pleasure to be part of this active WG!

Thank you!

Many thanks to Claudia!!!!

THE EUROPEAN LIQUID BIOPSY SOCIETY

Update ctDNA technology working group

General Assembly 28.11.2022
Montpellier, France

Patrizio Giacomini, Ellen Heitzer, Ed Schuuring, Michael Speicher

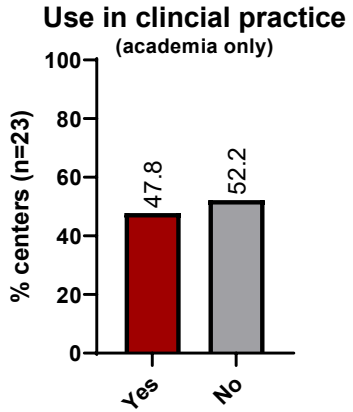
THE EUROPEAN LIQUID BIOPSY SOCIETY

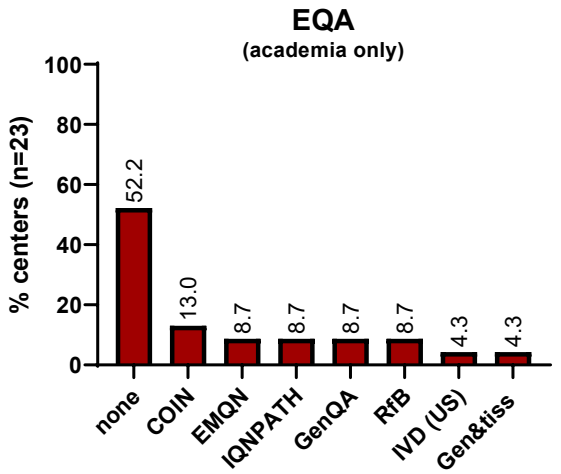
1st ctDNA technology working group meeting (1 of 1)

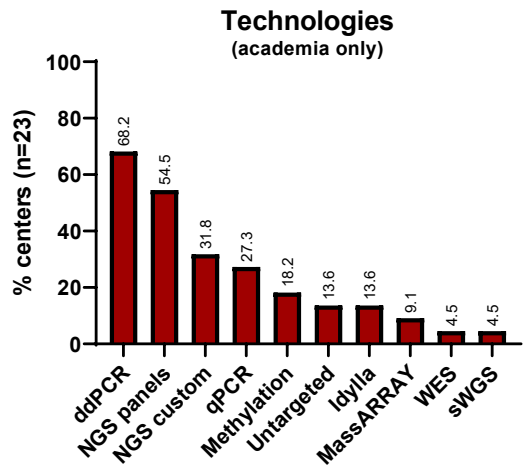
16:00 – 17:00	**Opening Presentations** **Moderation by Ellen Heitzer and Ed Schuuring**
16:00 – 16:10	Opening by Klaus Pantel
16:10 – 16:35	Opening presentation by Ellen Heitzer • Overview on technologies, workflows, existing activities and guidelines
16:35 – 16:50	Presentation by Ed Schuuring • Summary of survey questions • Efforts at harmonization by the COIN consortium
16:50 – 17:00	Discussion of the frequency and structure of future ctDNA meetings
17:00 – 17:50	**Suggested Topics and Discussion Rounds** **Moderation by Michael Speicher**
10min	• A consensus is needed on which methodologies may provide the best answers at various stages of the patient journey.
10min	• External Quality Assessment (EQA) participation should be recommend/mandatory for labs offering ctDNA test in clinical routine.
10min	• The interpretation of low VAF variants is the most challenging aspect of reliably reporting ctDNA.
10min	• When large panels are used PBMCs should be sequenced to correct for CH-related variants.
10min	• A ctDNA molecular report should include as much as information as possible (overall ctDNA level, the allelic fraction, absolute quantification of mutation (in copies / ml plasma), assay uncertainty and methodology and minimal QC metrics such as coverage, read depth primary driver mutations and aberrations, recent clinical studies/potential off-label treatment, targets that are not fully validated, a clinical interpretation).
17:50 – 18:00	**Closing Statements and Next steps** **Moderation by Klaus Pantel**
17:50 – 18:00	Summary of next steps: • Additional ideas, comments, and suggestions • Closing remarks

December 6th 2021

TOPIC:
ctDNA use in clinical practice







THE EUROPEAN LIQUID BIOPSY SOCIETY

2nd ctDNA technology working group meeting (1 of 2)

15:00 – 16:20	**Presentations on the topic of EQA** **Moderation by Ed Schuuring**
15:00 – 15:10	**Prof. Dr. Ed Schuuring** for the COIN consortium (*Netherlands*)
15:10 – 15:20	**Prof. Dr. Ellen Heitzer** for CancerID (*Europe*)
15:20 – 15:30	**Prof. Dr. Etienne Rouleau**, CLCC Institut Gustave Roussy and **Prof. Dr. Marc Denis**, directeur Pôle "Biologie-Pathologie" (*France*)
15:30 – 15:40	**Dr. Simon Patton**, Managing Director, EMQN CIC
15:40 – 15:50	**Prof Dr. Sandi Deans**, Consultant Clinical Scientist, Director of GenQA, member of UK NEQAS consortium
15:50 – 16:00	**Prof Dr. Claus Lindbjerg Andersen**, Group Leader and Director of the National Danish ctDNA Research Center (*Denmark*)
16:00 – 16:10	**Prof Dr Hege G. Russnes**, head, Experimental Pathology and Research Support, Oslo University Hospital (*Norway*)
16:10 – 16:20	**Dr. Lora Dimitrova**, Project manager, LB Proficiency Test, QuIP (*Germany*)
16:20 – 17:00	**Discussion** **Moderation by Ellen Heitzer**

March 23th 2022

TOPIC:
A sum-up of previous and ongoing EU-wide efforts in ctDNA EQA - major challenges ahead

Highlights:

- Results of pilot EQA testing in EU
- Minimal requirements for ctDNA/EQA
- Main focus was on Lung cancer (in the past)

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2nd ctDNA technology working group meeting (2 of 2)

March 23th 2022

15:00 – 16:20	**Presentations on the topic of EQA** **Moderation by Ed Schuuring**
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TOPIC:
A sum-up of previous and ongoing EU-wide efforts in ctDNA EQA - major challenges ahead

Conclusions:

- EQA provider use different reference materials
- Most EQA target VAFs >1%
- High variability in cfDNA recovery and cfDNA concentrations
- High number of FN and FP
- ctDNA-grade bioinformatics pipelines and errors in variant calling
- Reporting of results is not yet covered with EQA

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3rd ctDNA technology working group meeting (1 of 3)

16:00 – 17:20	**Presentations on the topic of ctDNA reference materials** **Moderation by Ed Schuuring**
16:00 – 16:05	Welcome by the ctDNA steering committee
16:05 – 16:20	**Dr. Leandro Lo Cascio**, Principal Investigator, Genome Engineering; NIBSC - National Institute for Biological Standards and Control (UK) *An International reference material to help the harmonisation of ctDNA diagnostics*
16:20 – 16:35	**David Chi**, Senior Product Manager; Thermo Fisher Scientific *Development of an In-Kit cfTNA Control for an NGS Liquid Biopsy Workflow*
16:35 – 16:50	**Dr. Mila Pavlova,** Senior Scientist; Horizon Discovery - a Perkin Elmer Company *High Quality Reference Materials for the Analysis of ctDNA and Liquid Biopsy*
16:50 – 17:05	**Dr. Krystyna Nahlik**, Senior Field Applications Scientist; LGC Clinical Diagnostics *Challenging the Limit of Detection in Liquid Biopsy Assays with Seraseq ctDNA Reference Materials*
17:05 – 17:20	**Dr. Björn Nowak**, Managing Director; SensID *cfDNA reference materials and uses thereof*
17:20 – 18:00	**Discussion** **Moderation by Ellen Heitzer**

July 5th 2022

Reference materials

Highlights:

- NIBSC - WHO effort
  - ds Oligo-nt
  - 'Natural' ctDNA mimics – mnDNA (cell lines to assess MSI, TMB, mutations)
  - Non-profit use
- Thermo:
  - In-kit control to monitor performance
  - Genomic background GIAB GM24385, RNA and DNA alterations

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3rd ctDNA technology working group meeting (2 of 3)

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17:20 – 18:00	**Discussion Moderation by Ellen Heitzer**

July 5th 2022

Reference materials

Highlights:

- Horizion
  - Fragmented DNA (160-170 bp), multiple mutations
- LGC
  - Biosynthetic spike-ins
  - Patient-like materials
  - Genomic background GIAB
  - MRD Panel mix >600 variants
  - Custom solutions

THE EUROPEAN LIQUID BIOPSY SOCIETY

3rd ctDNA technology working group meeting (3 of 3)

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July 5th 2022

Reference materials

Highlights:

- Sens-ID
  - Randomly sheared
  - Patient-like materials
  - Methylation options available

Conclusions:

- Copy number alteration are underrepresented
- New tools leveraging methylomics and fragmentomics are evolving > > need for more complex refmats

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4th ctDNA technology working group meeting (1 of 2)

September 27th 2022

16:00 – 17:30	**Presentations on the topic of IVDR** **Moderation by Ed Schuuring**
16:00 – 16:30	**Dr. Els Dequeker**, University of Leuven, Belgium *What does the IVDR mean for diagnostic laboratories and what are the associated challenges?* - 5-10min discussion
16:30 – 17:00	**Dr. Uwe Oelmüller,** Vice President Head of MDx Development Sample Technologies; QIAGEN *Standardized Pre-analytics: The Key for Reliable Liquid Biopsy Diagnostics & Research* - 5-10min discussion
17:00 – 17:30	**Dr. Claudia Ruivenkamp,** University of Leiden, Netherlands *A national initiative: the Dutch IVDR taskforce* - 5-10min discussion
17:30 – 17:45	**Dr. Marc Van den Bulcke**; Sciensano, Bruxelles, Belgium *IVDR: the perspective of EU pre-commercial procurement actions and the OncNGS Consortium.* - 5min discussion
17:45 – 18:00	**General Discussion** **Moderation by WG Leads**

TOPIC:
IVDR

Highlights:

- CE-IVD vs IH-IVD (in house)
- Medical devices for ctDNA testing and IVDR
- IVDR implementation timeline
- ISO 15189 is not sufficient

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4th ctDNA technology working group meeting (2 of 2)

September 5th 2022

16:00 – 17:30	**Presentations on the topic of IVDR** **Moderation by Ed Schuuring**
16:00 – 16:30	**Dr. Els Dequeker**, University of Leuven, Belgium *What does the IVDR mean for diagnostic laboratories and what are the associated challenges?* - 5-10min discussion
16:30 – 17:00	**Dr. Uwe Oelmüller,** Vice President Head of MDx Development Sample Technologies; QIAGEN *Standardized Pre-analytics: The Key for Reliable Liquid Biopsy Diagnostics & Research* - 5-10min discussion
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17:45 – 18:00	**General Discussion** **Moderation by WG Leads**

TOPIC:
IVDR

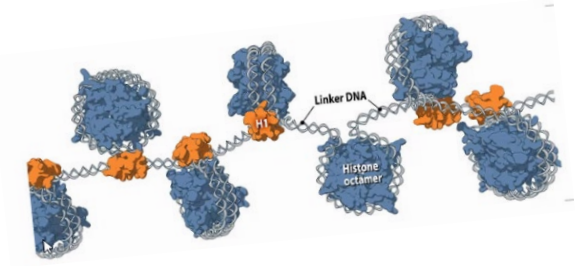
Highlights:

- Marketing strategies and IVDR
- Networking and national initiatives to deal with regulatory bodies
- Specific examples from Pre-Commercial Procurement (PCP)

Outlook for 2023

- European survey of LB-applications (ctDNA, CTCs) that have entered clinical practice
- Get in touch with various societies beyond ELBS (EFLM, ESP, ESHG)
- **Financial/biostatistic support would be needed !!**

- ELBS-curated (online) catalogue of reference materials available from different providers
- Guidance for ref materials provider
- **Position paper from ELBS: Summary of refmats, guidelines on how to use reference materials, identification of needs**



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Outlook for 2023

- What are important challenges for EQA providers and where can ELBS be helpful ?
  - e.g. harmonization of certain parts/steps of EQA logistics
  - e.g. costs of prep, of transport ?
  - e.g. assessment procedures ?
  - e.g. supporting possible collaborations between providers
  - e.g. providing an overview of available EQA schemes
  - e.g. selection of targets

- Can ELBS provide guidance for standardization of best practice reporting LB data for clinicians
  - “Harmonization” of reporting
  - Publish European guideline(s) on ctDNA testing (various separate steps ?) representing vision of all involved EQA providers

1) **Organisation of a workshop in collaboration with Simon Patton (EMQN) and Sandi Deans (GenQA)**

2) **Hosted by Rodrigo Toledo (Barcelona)**

3) **Details will follow soon…**

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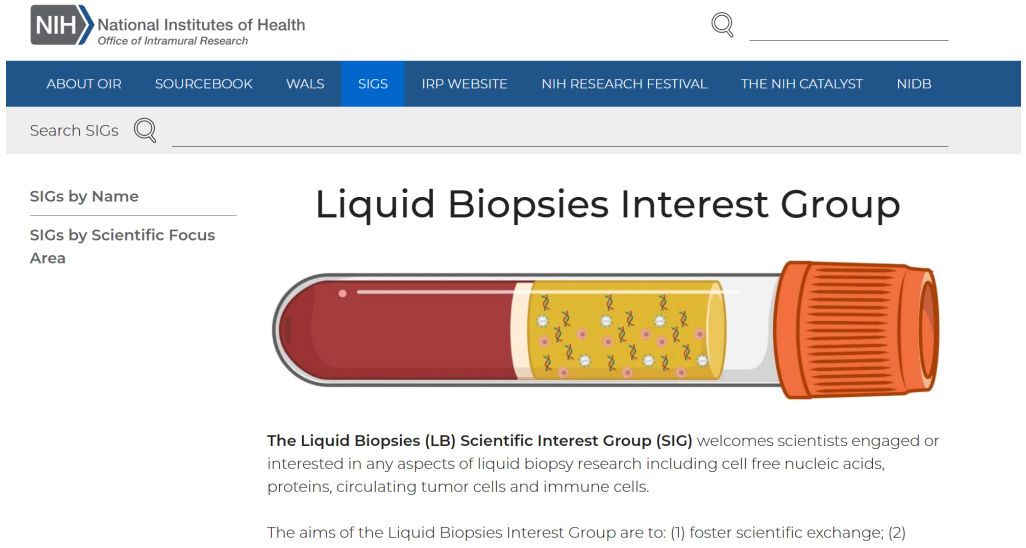
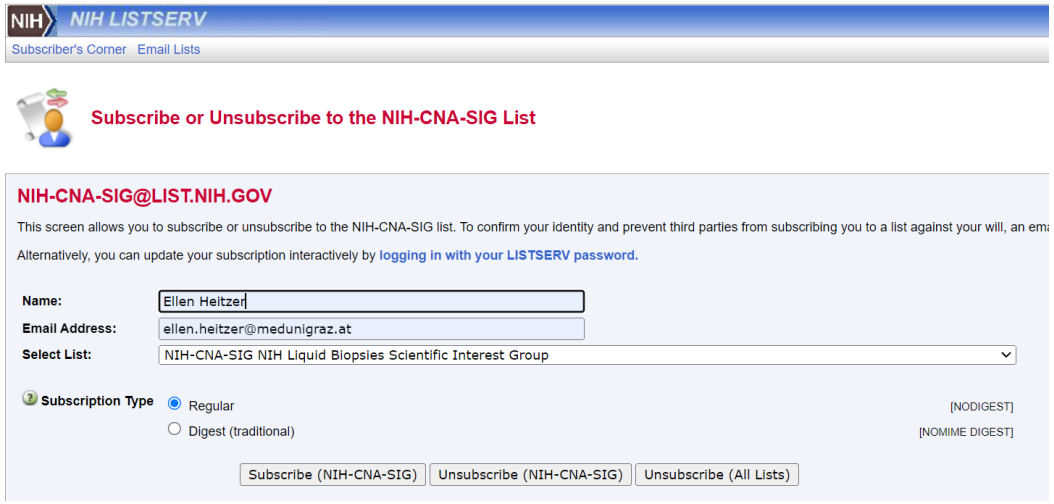
Outlook for 2023

- Suggestions of topics to be covered in 2023 from ELBS members
- Touch base with other concortia to join forces (BloodPAC, FNIH25, etc.)





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General Assembly of the European Liquid Biopsy Society (ELBS)

28th of October 2022

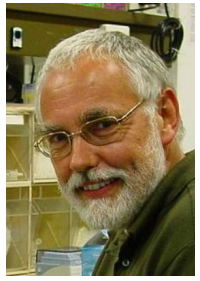
Montpellier, France

General Assembly of the European Liquid Biopsy Society (ELBS)

28th of October 2022

Montpellier, France

An Hendrix
Ghent University
Belgium



Rienk Nieuwland
Amsterdam UMC
The Netherlands

Franz Ricklefs
University Medical Center Hamburg
Germany

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Extracellular vesicles: society

INTERNATIONAL SOCIETY *for* EXTRACELLULAR VESICLES

Explore the World of ISEV

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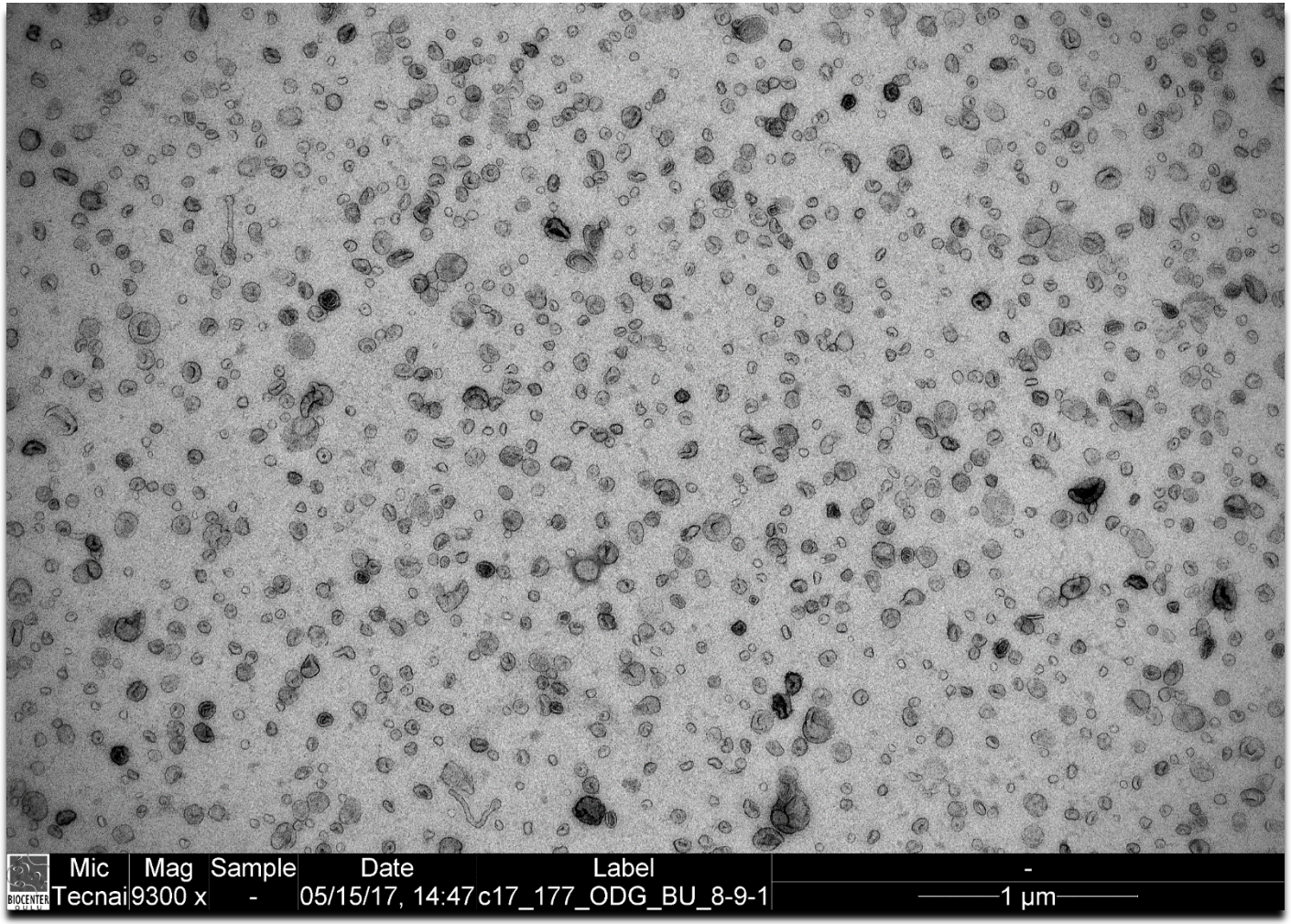
Extracellular vesicles

MISEV2018 guidelines

Generic term for particles naturally released from the cell that are delimited by a lipid bilayer and cannot replicate, i.e. do not contain a functional nucleus.

electron microscopy



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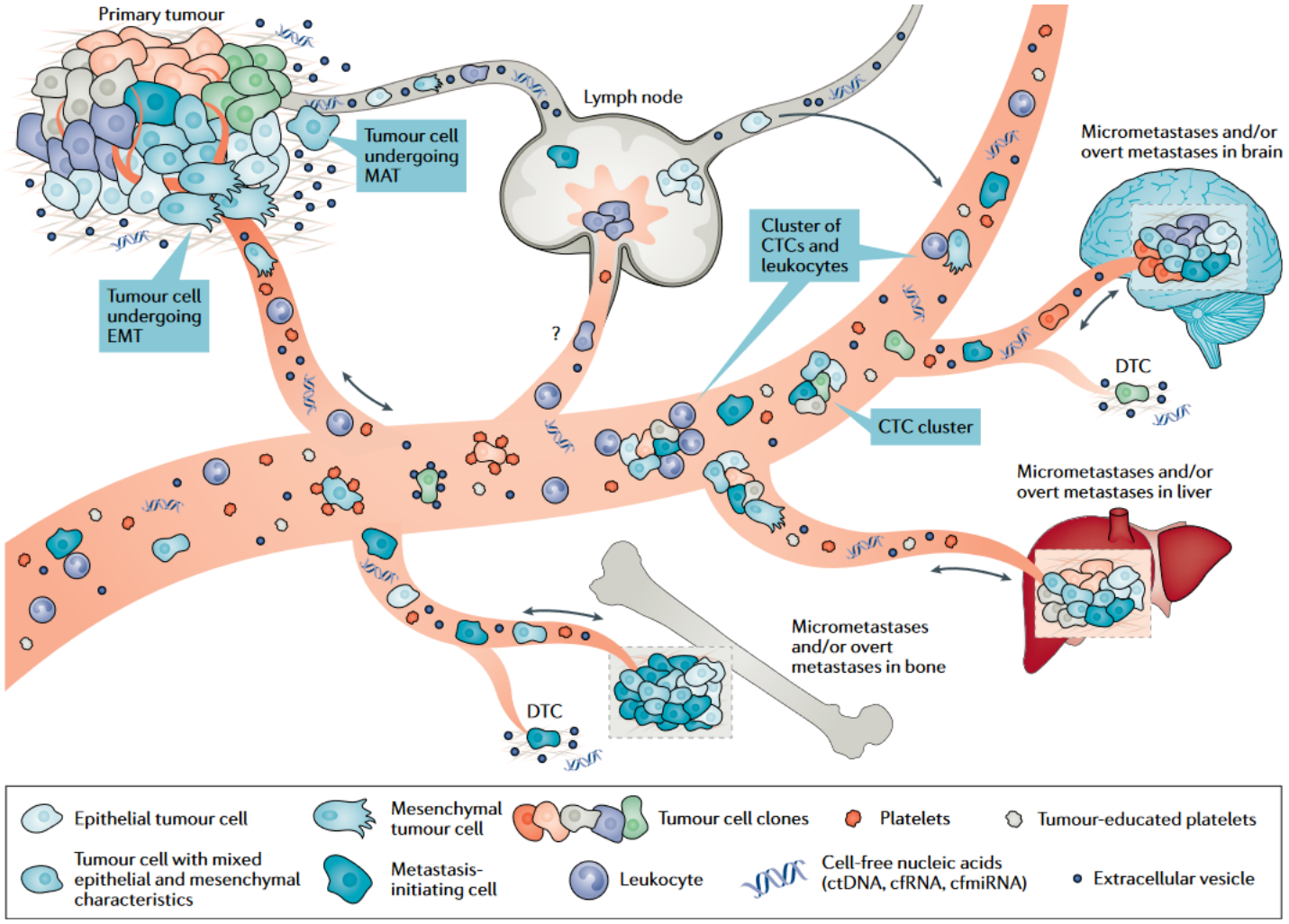
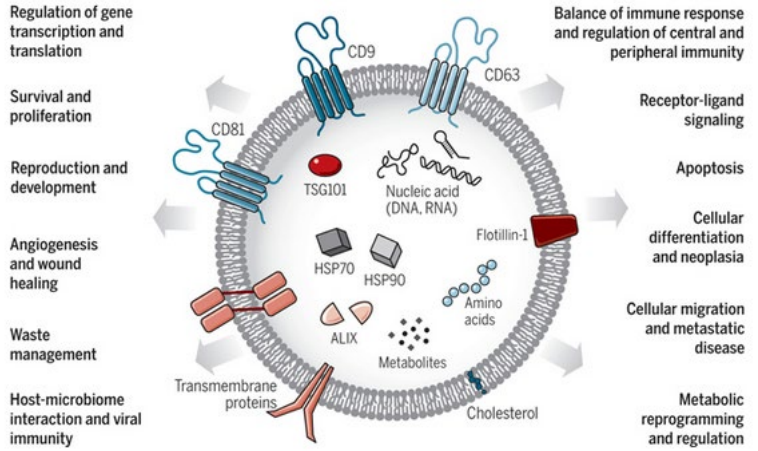
Extracellular vesicles: liquid biopsy



Keller and Pantel, Nat Rev Cancer, 2019

Hallmarks of extracellular vesicles



Kalluri and LeBleu, Science, 2020

Multicomponent biomarker platform

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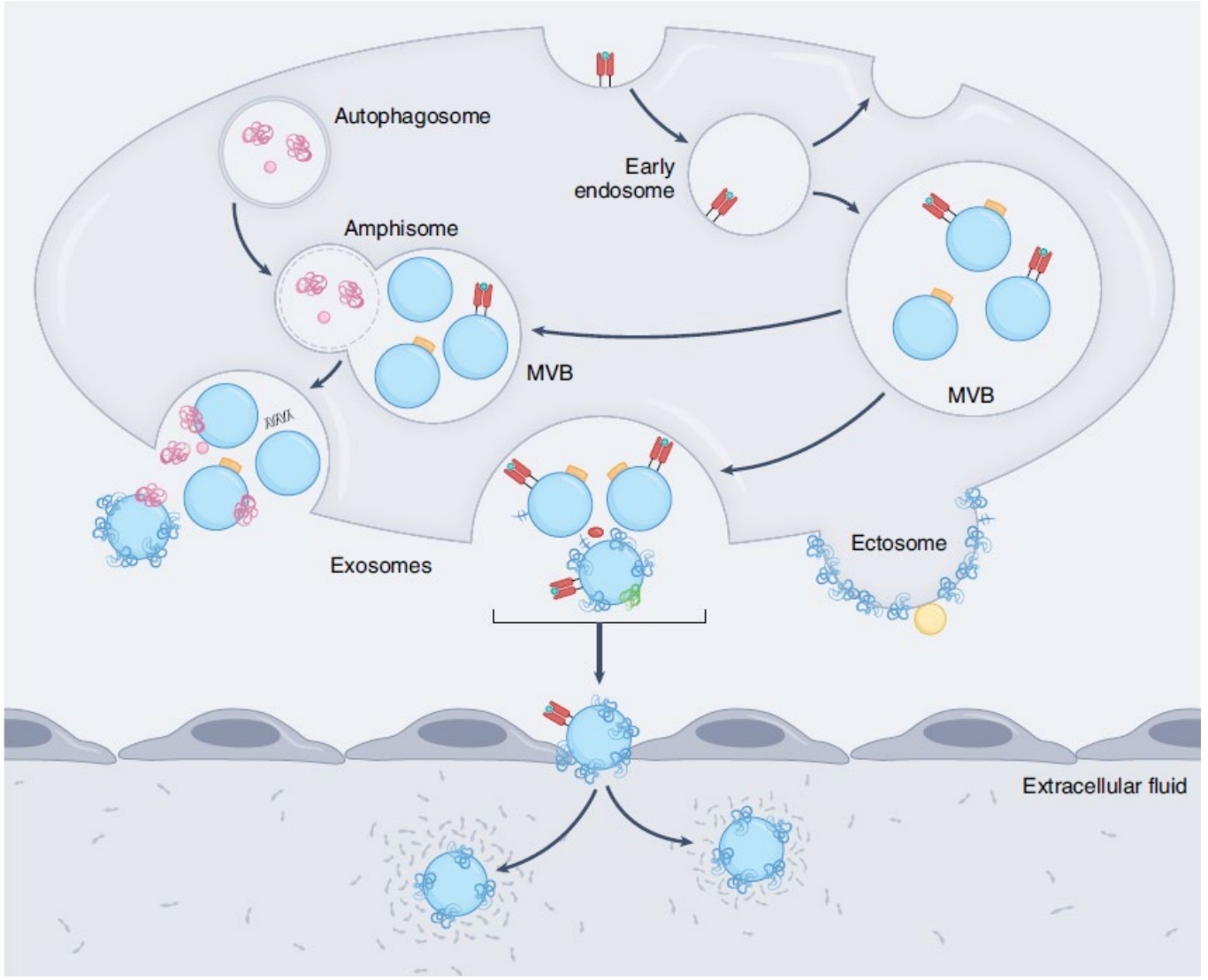
Extracellular vesicles: nomenclature

biogenesis

biomolecular corona



Buzas, Nat Cell Biol, 2022

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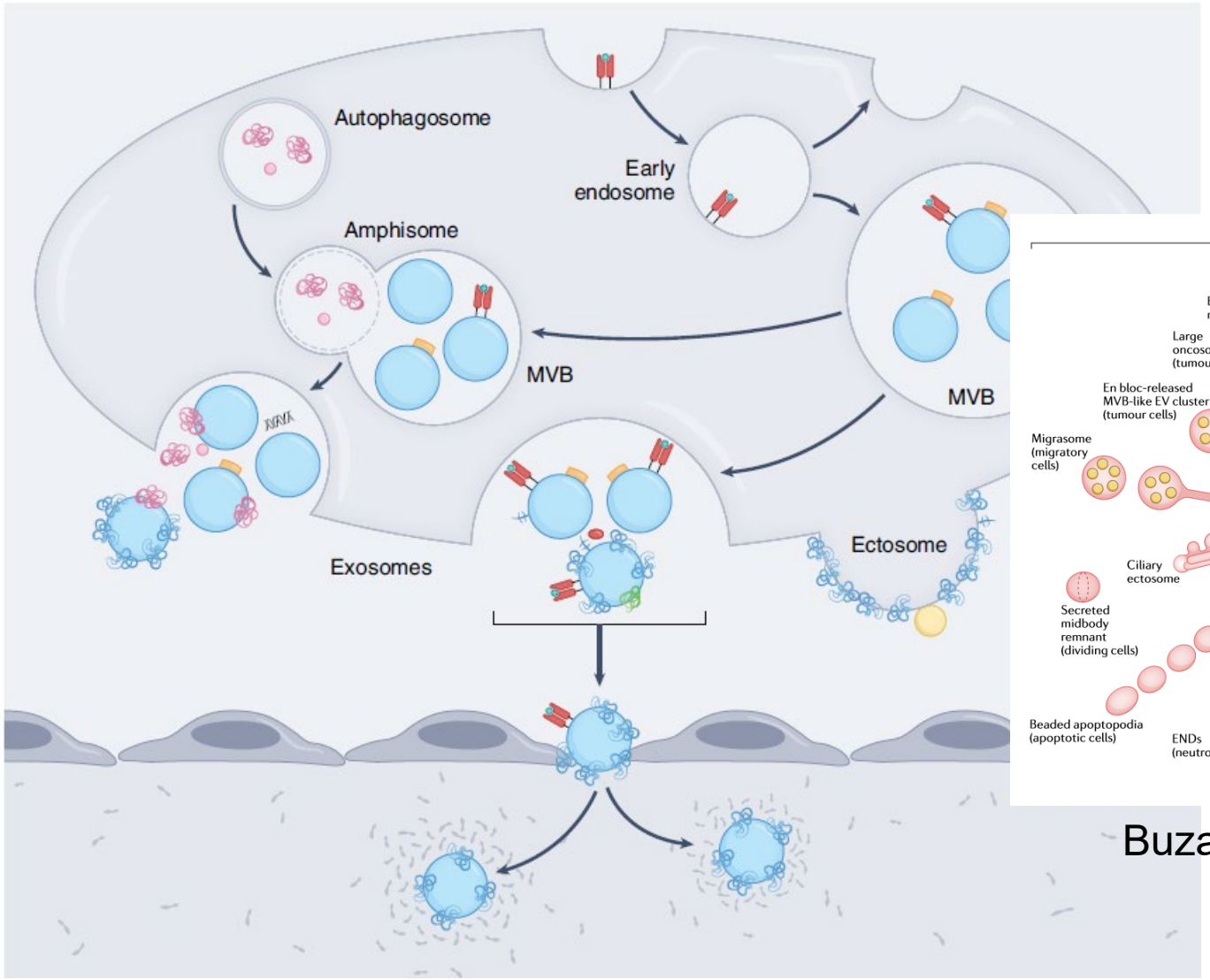
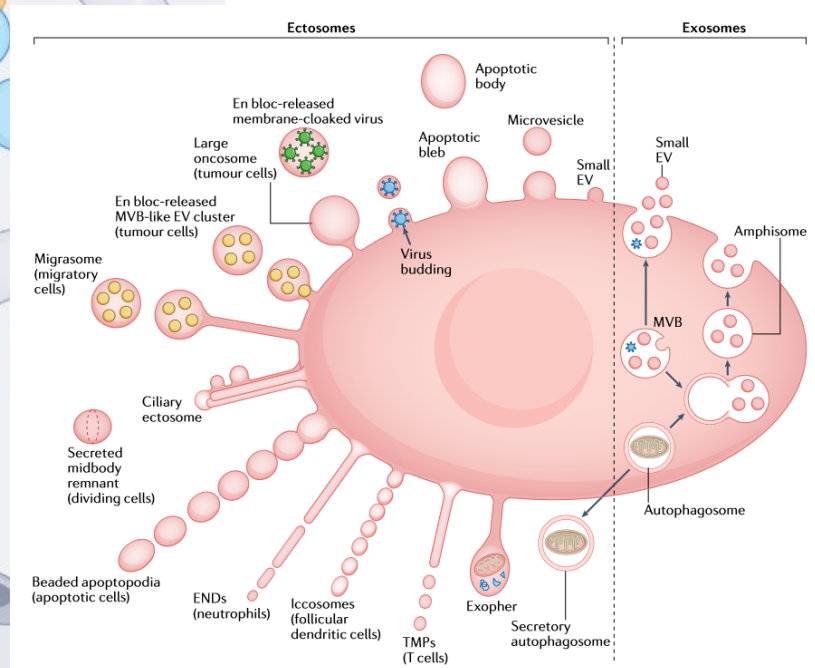
Extracellular vesicles: nomenclature

biogenesis





Buzas, Nat Rev Immunol, 2022

biomolecular corona

Buzas, Nat Cell Biol, 2022

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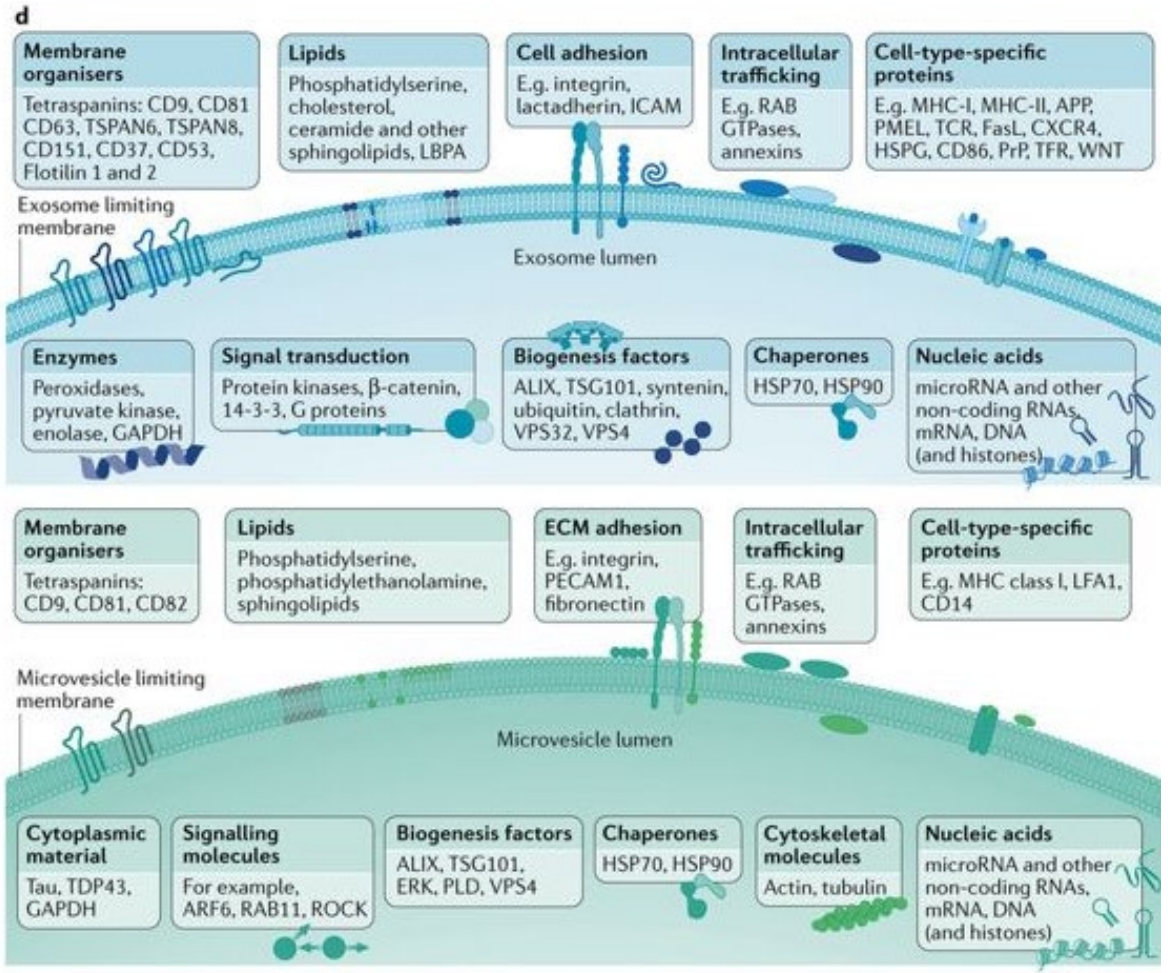
Extracellular vesicles: nomenclature

MISEV2018 guidelines

Assigning an EV to a particular biogenesis pathway remains extraordinarily difficult unless, e.g. the EV is caught in the act of release by live imaging techniques.

exosomes

ectosomes



Van Niel et al., Nat Rev Mol Cell Biol, 2018

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Extracellular vesicles: nomenclature

Extracellular vesicles or exosomes? On primacy, precision, and popularity influencing a choice of nomenclature

Kenneth W. Witwer & Clotilde Théry

The ISEV consensus recommendation on nomenclature is to use “extracellular vesicle” as the “generic term for particles naturally released from the cell that are delimited by a lipid bilayer and cannot replicate” and to modify “EV” based on clear, measurable characteristics such as cell of origin, molecular markers, size, density, function, etc.

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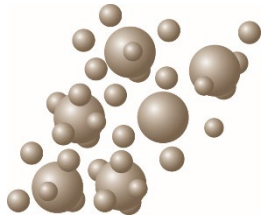
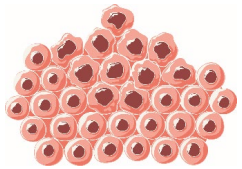
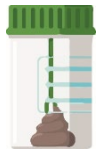
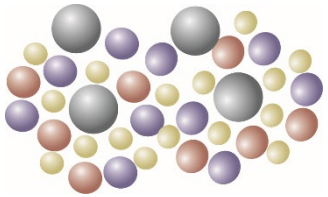
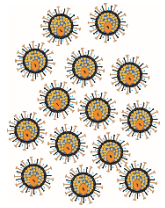
Extracellular vesicles: methodology

		biofluid specific particles	universival particles	EV subpopulations
urine		 Tamm-Horsfall protein	 proteins	
tissue		cell debris		 extracellular vesicles
feces		pilli, fibers, ...	 nucleic acids	 bacterial extracellular vesicles
blood		 lipoprotein particles	 virions	

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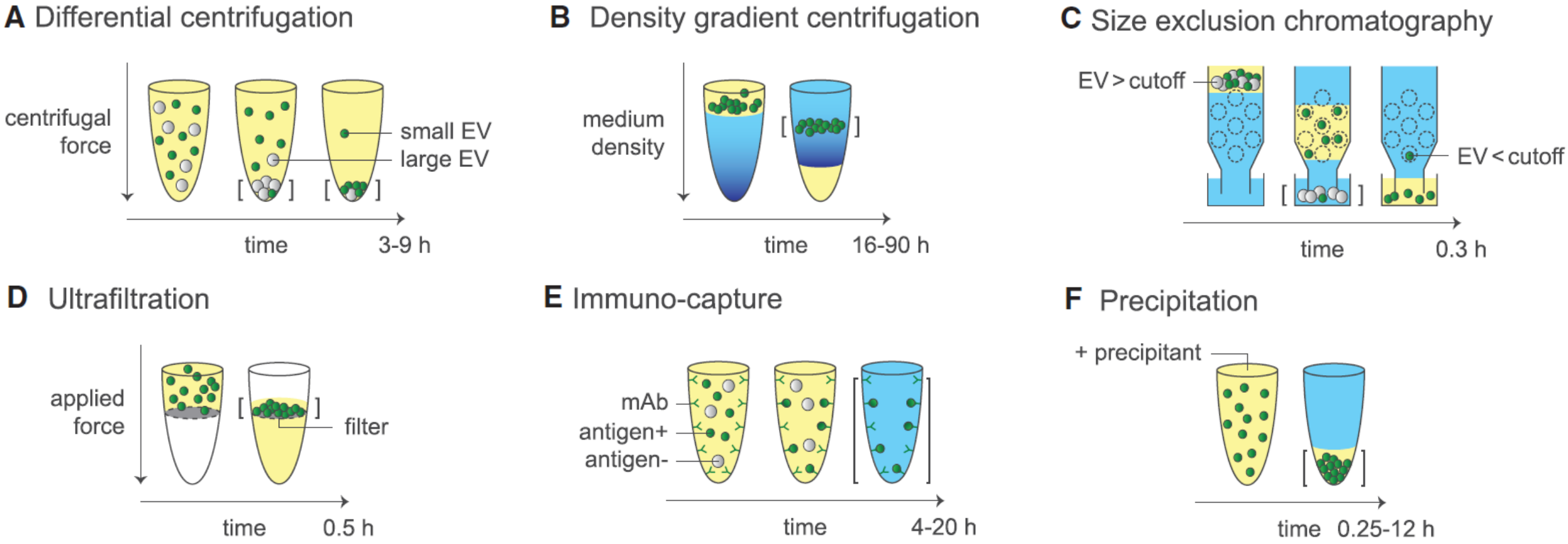
Extracellular vesicles: methodology



Trade-off between specificity (purity) and efficiency (recovery)

Coumans et al., Circ Res, 2017

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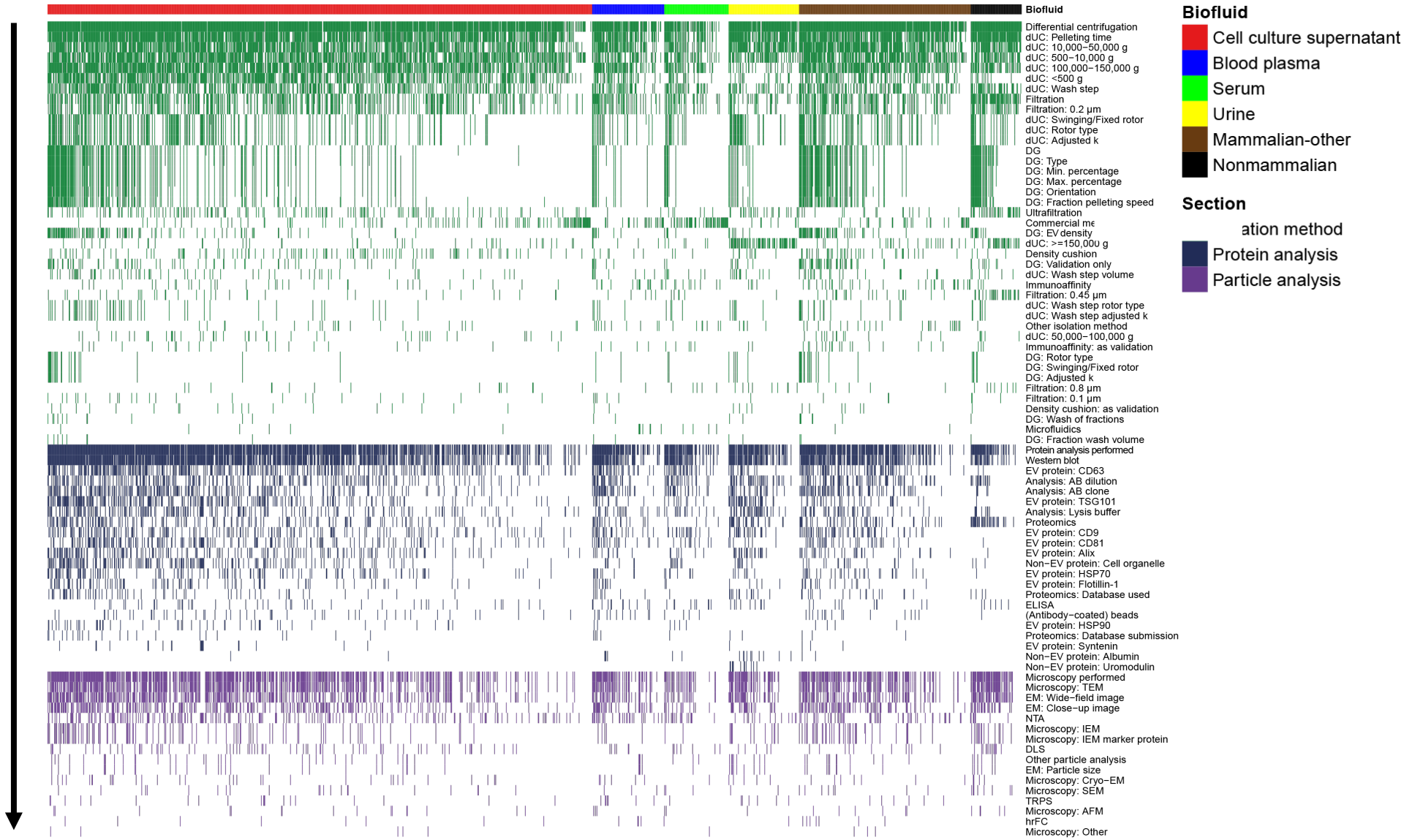
Extracellular vesicles: methodology

1226 publications

115 experimental parameters



Van Deun et al., Nature Methods, 2017

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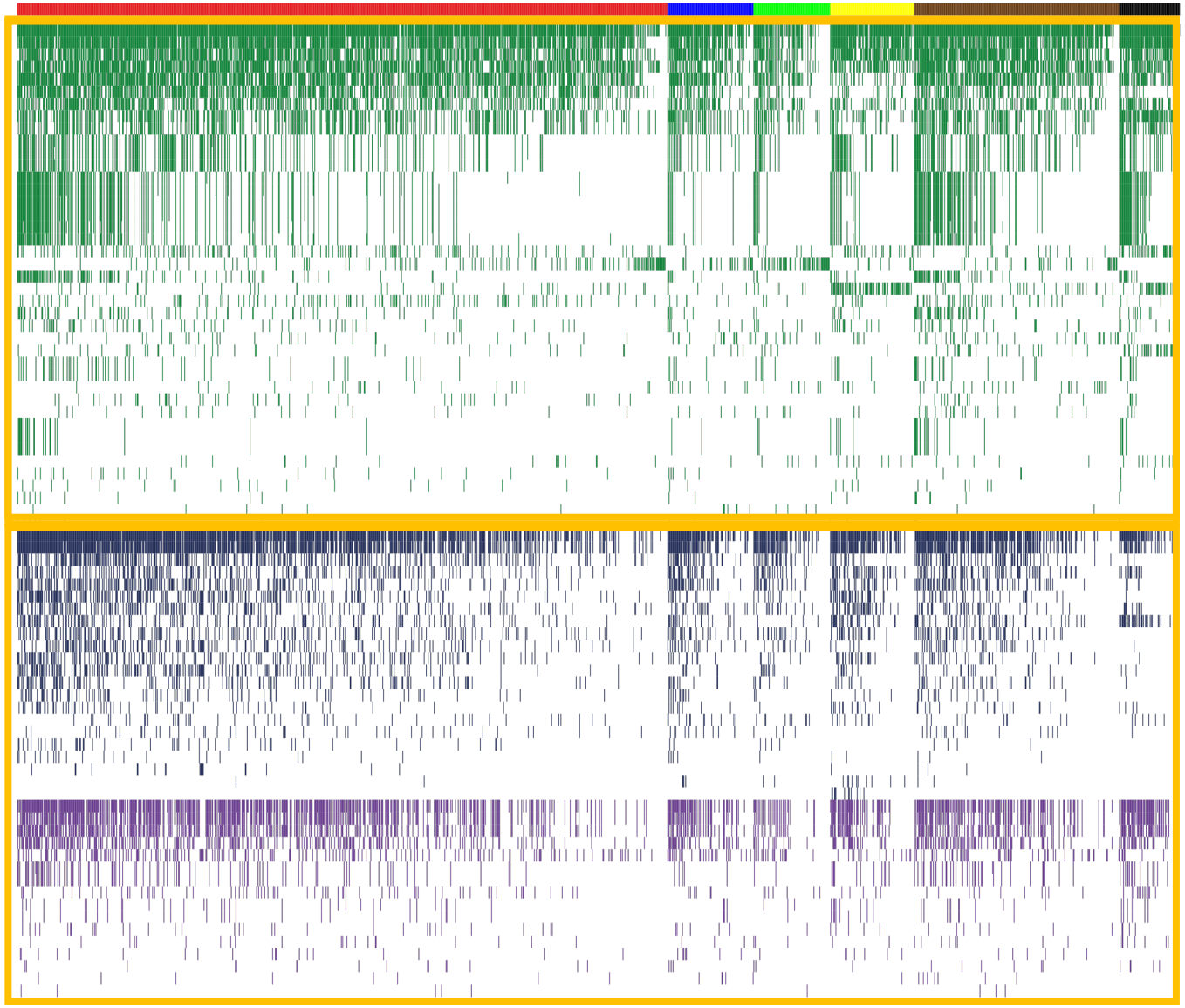

1. Heterogeneity:

1226 publications

1038 unique separation protocols

2. Inconsistent reporting:

17% provide no characterization of EV preparations

Van Deun et al., Nature Methods, 2017

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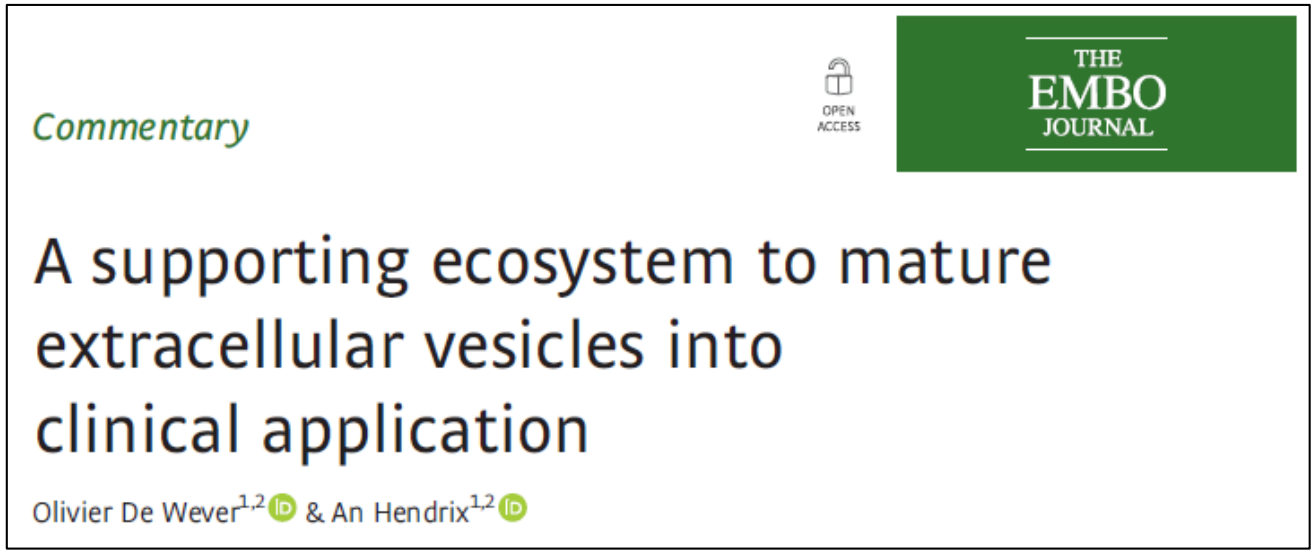
Extracellular vesicles: rigor and standardization

- Different separation methods enrich for single or multiple EV subpopulations with diverse composition and variable purity, thus identifying method-dependent EV content and function.

- The implementation of different methods requires validated controls and transparency. Failure to follow these principles can result in data that are difficult to interpret and reproduce.



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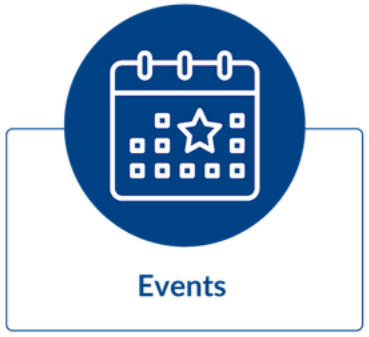
Extracellular vesicles: rigor and standardization

INTERNATIONAL SOCIETY *for* EXTRACELLULAR VESICLES

Explore the World of ISEV



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Example 1

JOURNAL OF EXTRACELLULAR VESICLES
2018, VOL. 7, 1535750
https://doi.org/10.1080/20013078.2018.1535750

2023 update!

Taylor & Francis
Taylor & Francis Group

OPEN ACCESS Check for updates

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

Clotilde Théry [103*£], Kenneth W Witwer [217,218*&£], +380 co-authors

Characterization of EV preparations by multiple complementary methods allows to adequately interpret results of EV experiments

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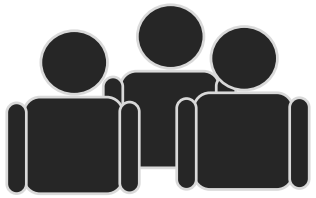
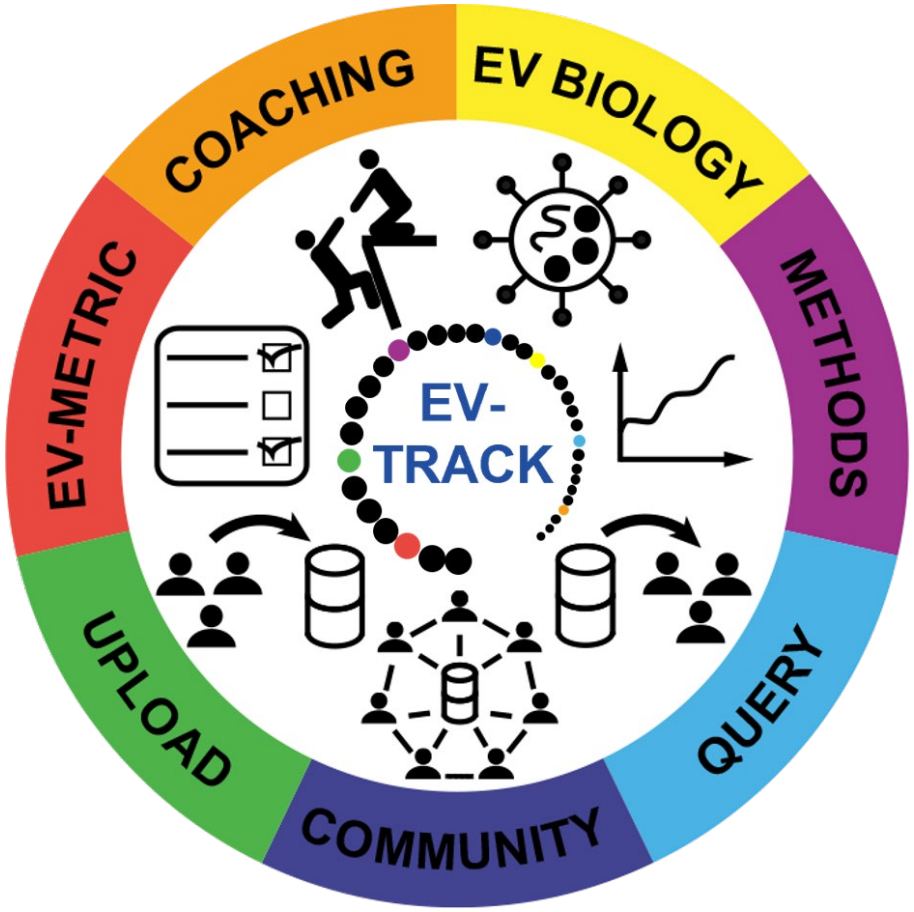
Example 2

EV-TRACK



1202 accounts
> 900 institutions



Van Deun et al., Nature Methods,

2023 update!
Endorsed by ISEV!

https://evtrack.org/
@EVTRACKplatform

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Example 3: Rigor and Standardization subcommittee

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

- Improve reliability and reproducibility of EV research
- Ensure dissemination and incorporation of MISEV guidelines
- Platform for collaboration and outreach to other societies
  ISEV – ISAC – ISTH
  ISEV – ISCGT
- Working group => example MIFlowCyt-EV

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Example 3: Rigor and Standardization subcommittee

JOURNAL OF EXTRACELLULAR VESICLES
2020, VOL. 9, 1713526
https://doi.org/10.1080/20013078.2020.1713526

Taylor & Francis
Taylor & Francis Group

OPEN ACCESS Check for updates

MIFlowCyt-EV: a framework for standardized reporting of extracellular vesicle flow cytometry experiments

Joshua A. Welsh[a], Edwin Van Der Pol[b,c,d], Ger J.A. Arkesteijn[e], Michel Bremer[f], Alain Brisson[g], Frank Coumans[b,c,d], Françoise Dignat-George[h,i], Erika Duggan[j], Ionita Ghiran[k], Bernd Giebel[f], André Görgens[f,l,m], An Hendrix[n], Romaric Lacroix[h,i], Joanne Lannigan[o], Sten F.W.M. Libregts[e,p], Estefanía Lozano-Andrés[e], Aizea Morales-Kastresana[a], Stephane Robert[m], Leonie De Rond[b,c,d], Tobias Tertel[f], John Tigges[k,q], Olivier De Wever[n], Xiaomei Yan[r], Rienk Nieuwland[c,d], Marca H.M. Wauben[e], John P. Nolan[j] and Jennifer C. Jones[a]

ISEV ISAC ISTH

EV Flow Cytometry Working Group

Welcome

There have been several efforts worldwide to develop and refine methods for EV flow cytometry, but until 2015, there was no rigorous, consistent framework established for validating these methods or for conducting EV flow cytometry experiments with appropriate controls. In collaboration with flow cytometry experts from the International Society for Extracellular Vesicles (ISEV), International Society for the Advancement of Science (ISAC), and International Society on Thrombosis and Hemostasis (ISTH), we have established an EV Flow Cytometry Working Group that is working to establish guidelines for best practices for this area of research. The working group webpage contains links to the societies and standardization initiatives, webinars, and resources.

YouTube LinkedIn Twitter

jth

RECOMMENDATIONS AND GUIDELINES

Minimum information to report about a flow cytometry experiment on extracellular vesicles: Communication from the ISTH SSC subcommittee on vascular biology

Edwin van der Pol[1,2,3] | Joshua A. Welsh[4] | Rienk Nieuwland[1,2]

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- Working group => example MIFlowCyt-EV
- Task forces => example blood EV task force

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Example 3: Rigor and Standardization subcommittee

JOURNAL OF EXTRACELLULAR VESICLES
2019, VOL. 8, 1647027
https://doi.org/10.1080/20013078.2019.1647027

Taylor & Francis
Taylor & Francis Group

OPEN ACCESS Check for updates

Considerations towards a roadmap for collection, handling and storage of blood extracellular vesicles

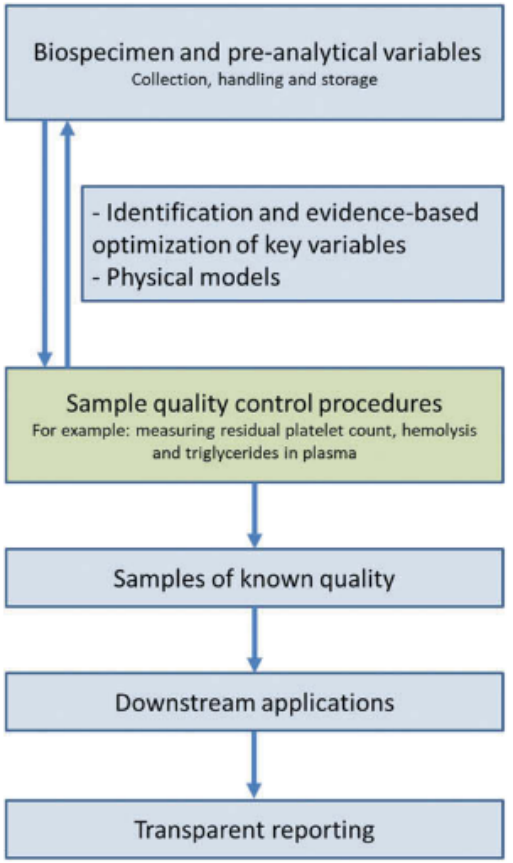
Aled Clayton[a], Eric Boilard[b], Edit I Buzas[c,d], Lesley Cheng[e], Juan Manual Falcón-Perez[f,g], Chris Gardiner[h], Dakota Gustafson[i], Alice Gualerzi[j], An Hendrix[k,l], Andrew Hoffman[m], Jennifer Jones[n], Cecilia Lässer[o], Charlotte Lawson[p], Metka Lenassi[q], Irina Nazarenko[r,s], Lorraine O'Driscoll[t], Ryan Pink[u], Pia R-M Siljander[v], Carolina Soekmadji[w,x], Marca Wauben[y], Joshua A Welsh[n], Ken Witwer[z], Lei Zheng[aa] and Rienk Nieuwland[bb]

jth

ORIGINAL ARTICLE

Removal of platelets from blood plasma to improve the quality of extracellular vesicle research

Britta Bettin[1,2,3] | Aleksandra Gasecka[1,2,4] | Bo Li[1,2,5] | Bert Dhondt[6,7,8] | An Hendrix[6,7,8] | Rienk Nieuwland[1,2] | Edwin van der Pol[1,2,3]



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Example 3: Rigor and Standardization subcommittee

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- Working group => example MIFlowCyt-EV
- Task force => example blood EV task force
- Task force => example reference materials

Rienk Nieuwland
Amsterdam UMC
The Netherlands

Juan Falcon-Perez
CIG bioGUNE
Spain

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Example 3: Rigor and Standardization subcommittee

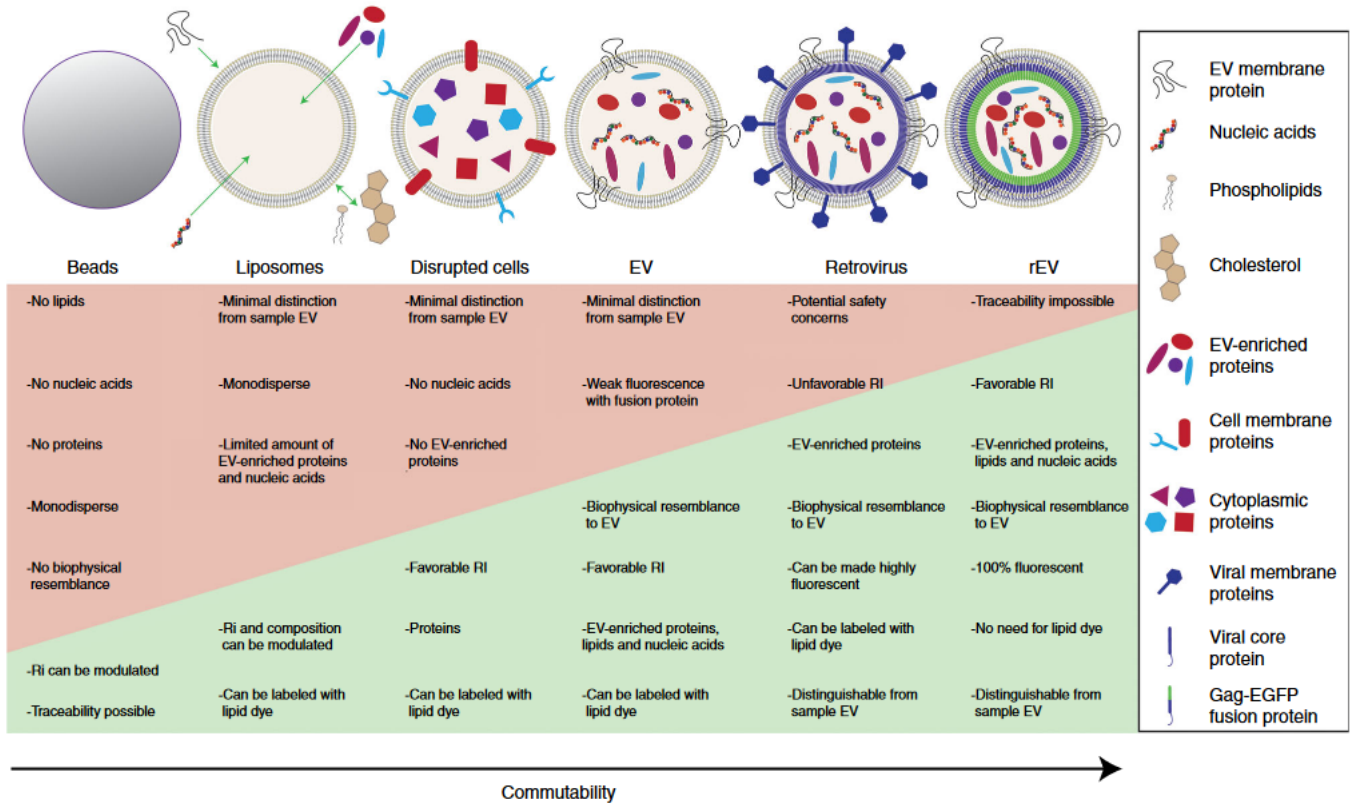

Fig. 1 | Comparison of rEV with other reported reference materials. A schematic overview of reported reference materials for EV research with their advantages (green) and limitations (red).

Geeurickx et al., Nat Protoc, 2021

EV Work group: Envisioned activities

- Biobanking and pre-analyticals:

⇒ How to collect the biofluid?
⇒ What is the minimal quality control of the biofluid?
⇒ How to process and store the biofluid?
⇒ Learning from other working groups? Evolving towards defined biofluids applicable for multiple liquid biopsy targets …

- Biomarker potential:

⇒ Learn from other working groups? Evolving towards multicomponent biomarkers …

- Stimulate interactions between ISEV and ELBS

⇒ Joined meetings and discussions to steer interactions

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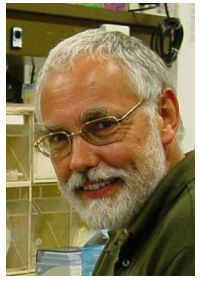
Extracellular vesicles

Thank you for your attention!

An Hendrix
Ghent University
Belgium



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