ReNeuron

Exosome Nanomedicine Platform

Hosted by: Olav Hellebø, CEO

Thursday, 17th May 2018

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ReNeuron Snapshot

Multi-asset, allogeneic cell therapy company with lead programmes in clinical development in the US

- CTX stem cell therapy candidate for stroke disability:
  - Positive long term data from Phase IIa clinical trial
  - IND approval for Phase IIb, placebo-controlled clinical trial. To commence in 40 US centers in mid-2018
- hRPC stem cell therapy candidate for retinal diseases:
  - Retinitis Pigmentosa program - Phase IIa study underway at Mass Eye and Ear Infirmary, Boston
  - Phase IIb studies planned to commence in 2019 in Retinitis Pigmentosa and Cone Rod Dystrophy
- Exosome nanomedicine platform:
  - Positive pre-clinical data with ExoPr0 exosome therapy candidate demonstrates potential of ExoPr0 to target multiple diseases
- Solid foundations:
  - Cash position - £45.3m ($63m)
  - Strong management team and solid institutional investor support
  - Clinical operations managed from newly established US office in Boston, MA

R&D day agenda

Welcome/Introduction	**Olav Hellebø** Chief Executive Officer
CTX cell line	**John Sinden, PhD** Founder and Chief Scientific Officer
Exosomes: Biology & Applications	**Stephen J Gould, PhD** Professor of Biological Chemistry The Johns Hopkins University School of Medicine
ExoPr0 – a new class of anti-cancer therapy	**Randolph Corteling, PhD** Head of Research
Q&A Session	**Richard Beckman, MD** Chief Medical Officer
Closing/Adjournment	**Olav Hellebø** Chief Executive Officer

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CTX cell line

John Sinden, PhD

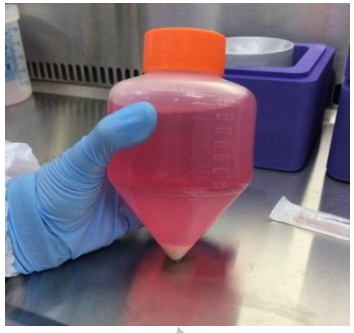
Founder and Chief Scientific Officer

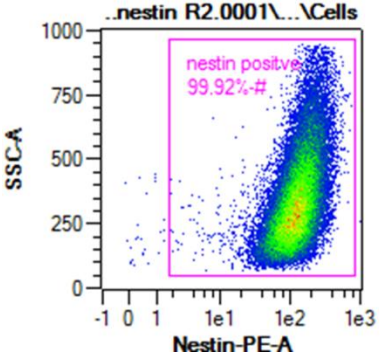
CTX cell product

Manufacturing and Delivery

1. Isolate Human Neural Stem Cells

4. Process and analytical development

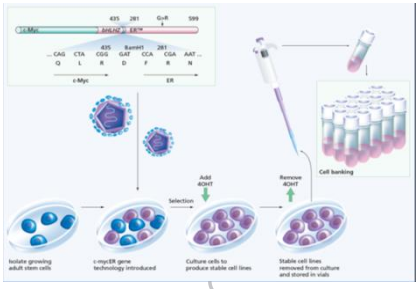




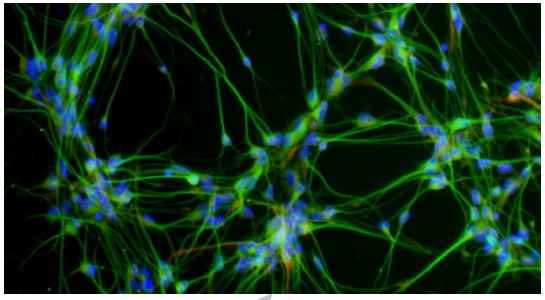
5. Manufacture to GMP at scale

6. Formulate Drug Product

2. Genetically modify & isolate clones



3. Demonstrate phenotype and functionality



8. Patient treatment

7. Quality Control

- Safe ✓
- Pure ✓
- Active ✓

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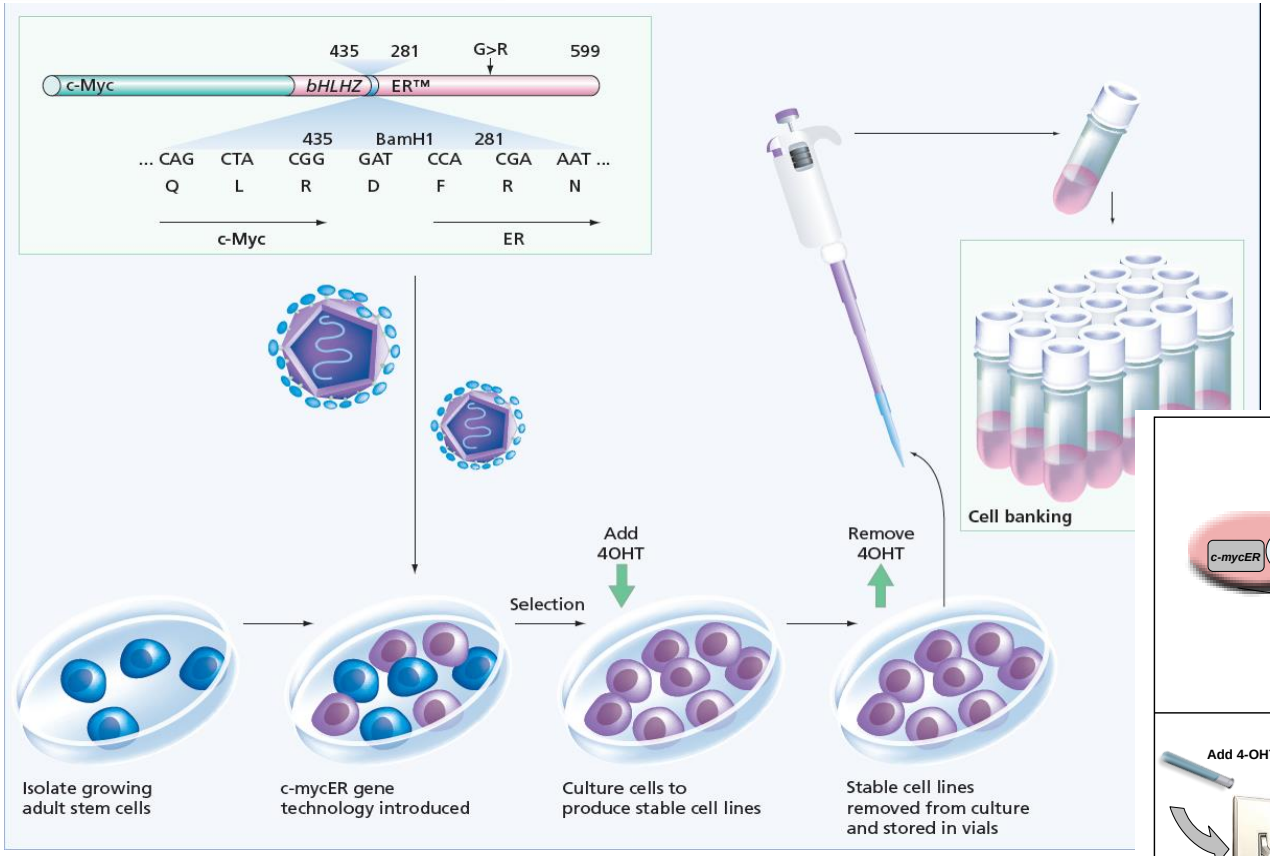
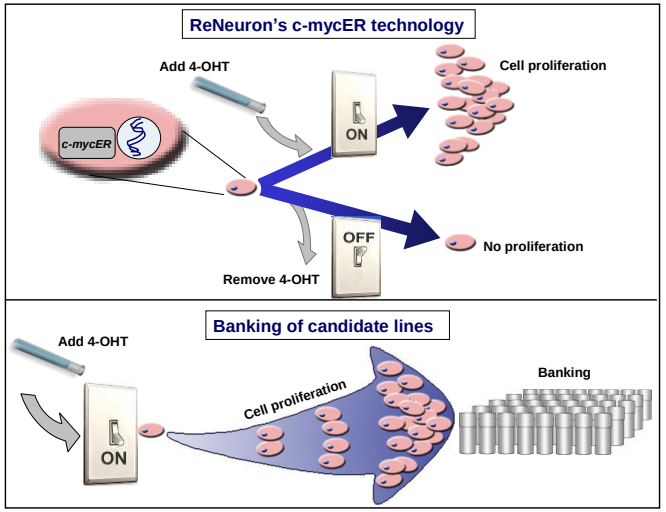
Genetically modify & isolate clones

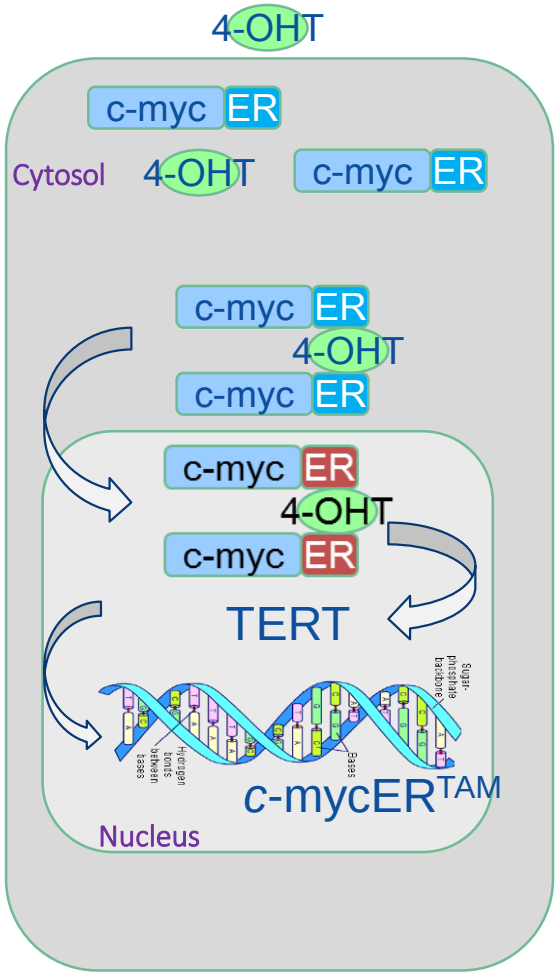


Isolate Human Neural Stem Cells



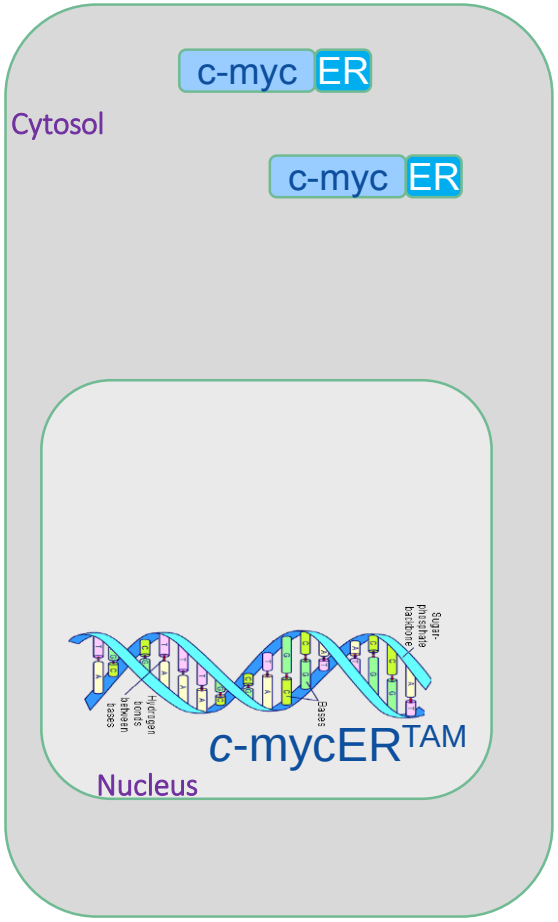
** 4OHT = 4-hydroxy tamoxifen, a metabolite of tamoxifen*

A) In proliferation culture



Proliferation / Self-renewal

B) Removal of 4-OHT



Differentiation

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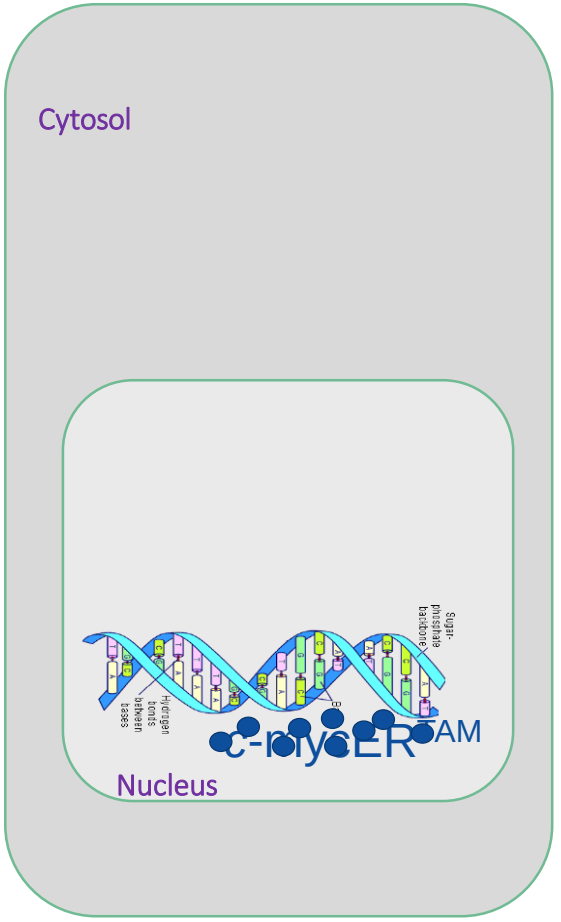
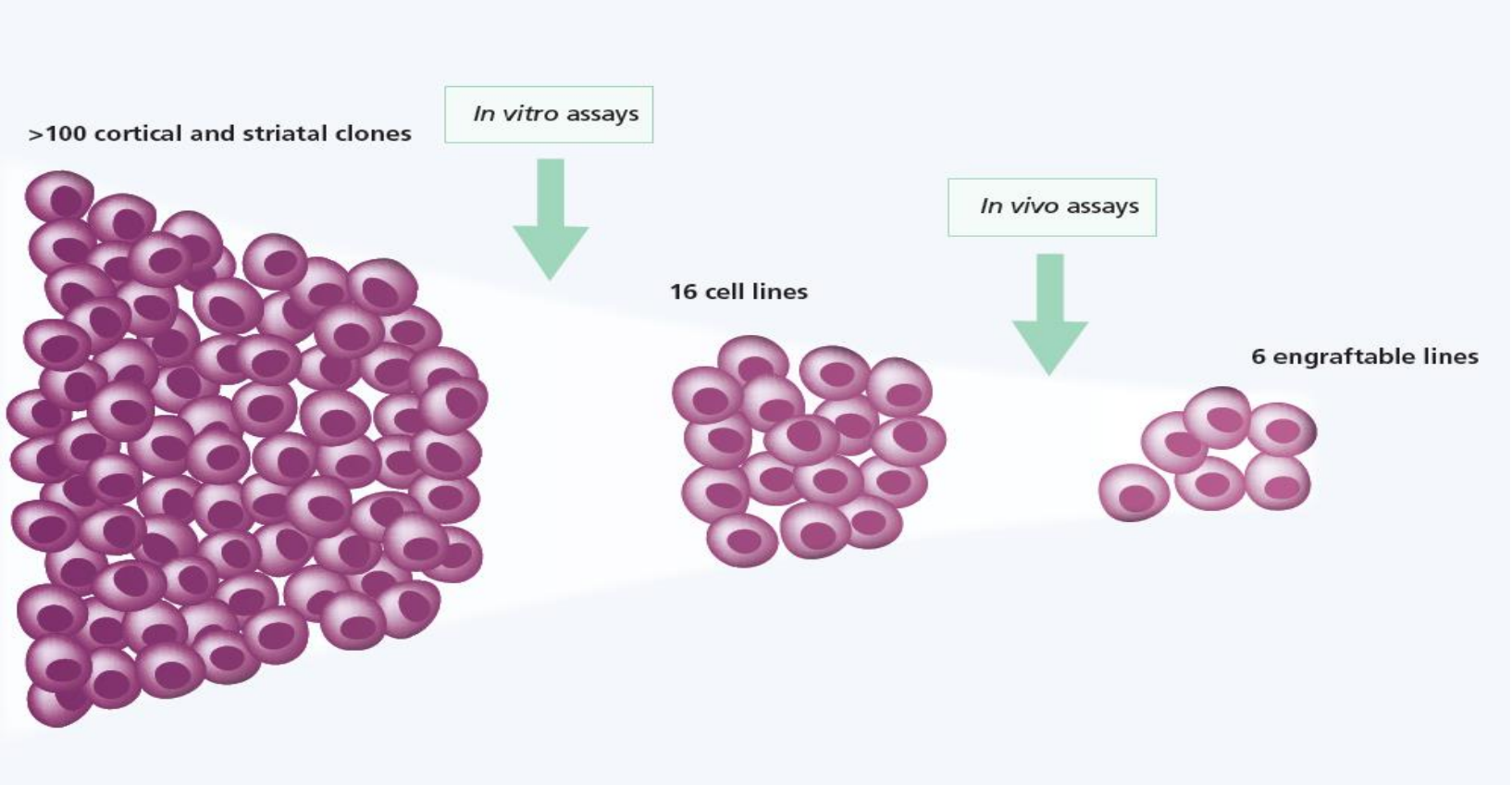
C) *In Vivo* environment



DNA Methylation
Gene Silencing

CTX cell line derivation and selection



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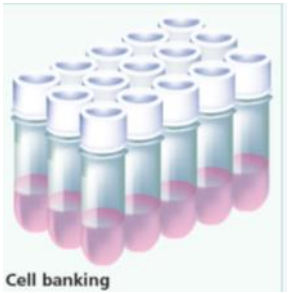
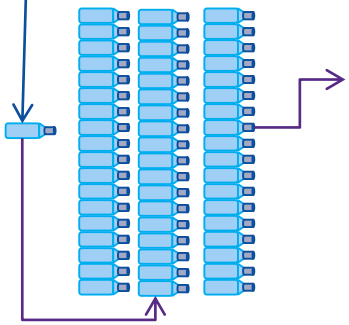
GMP Manufacturing strategy

Master Cell Bank



Hundreds of vials

1 Vial

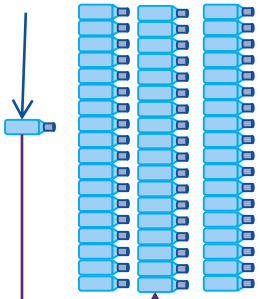


Multiple passages

Working Cell Bank

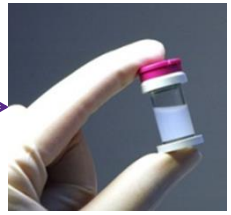
Hundreds of vials

1 Vial



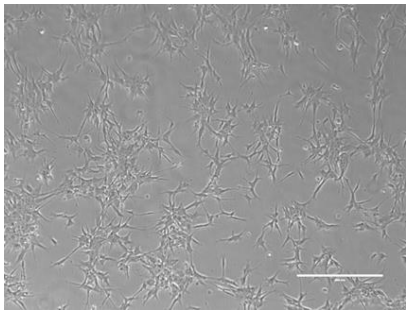
Multiple passages

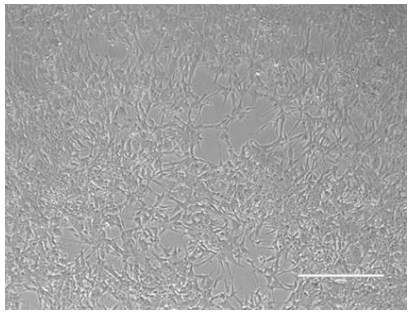
Formulated Drug Product

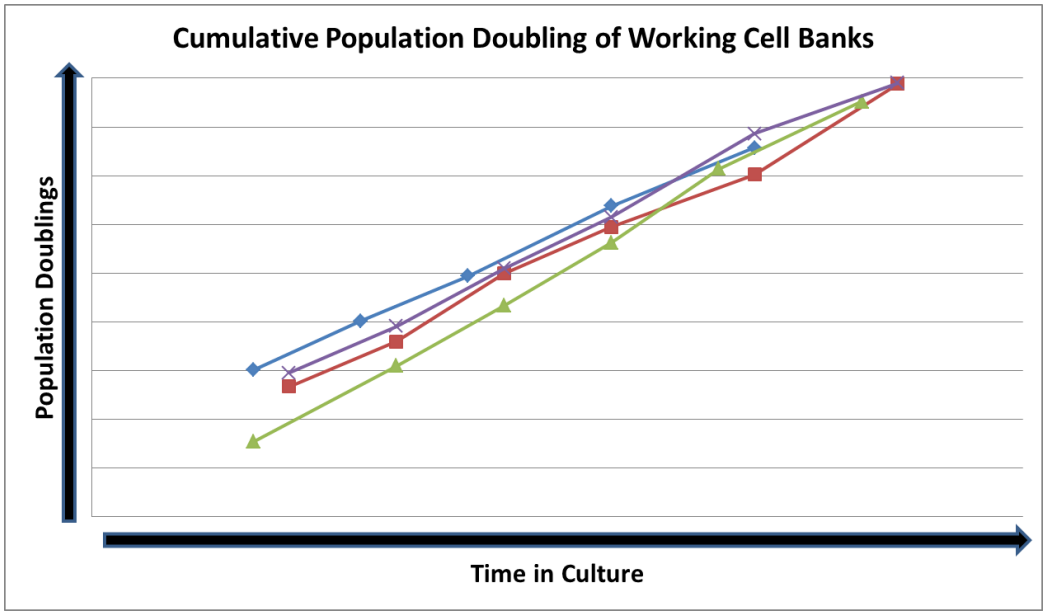


Hundreds of vials

GMP Working Cell Bank Manufacture



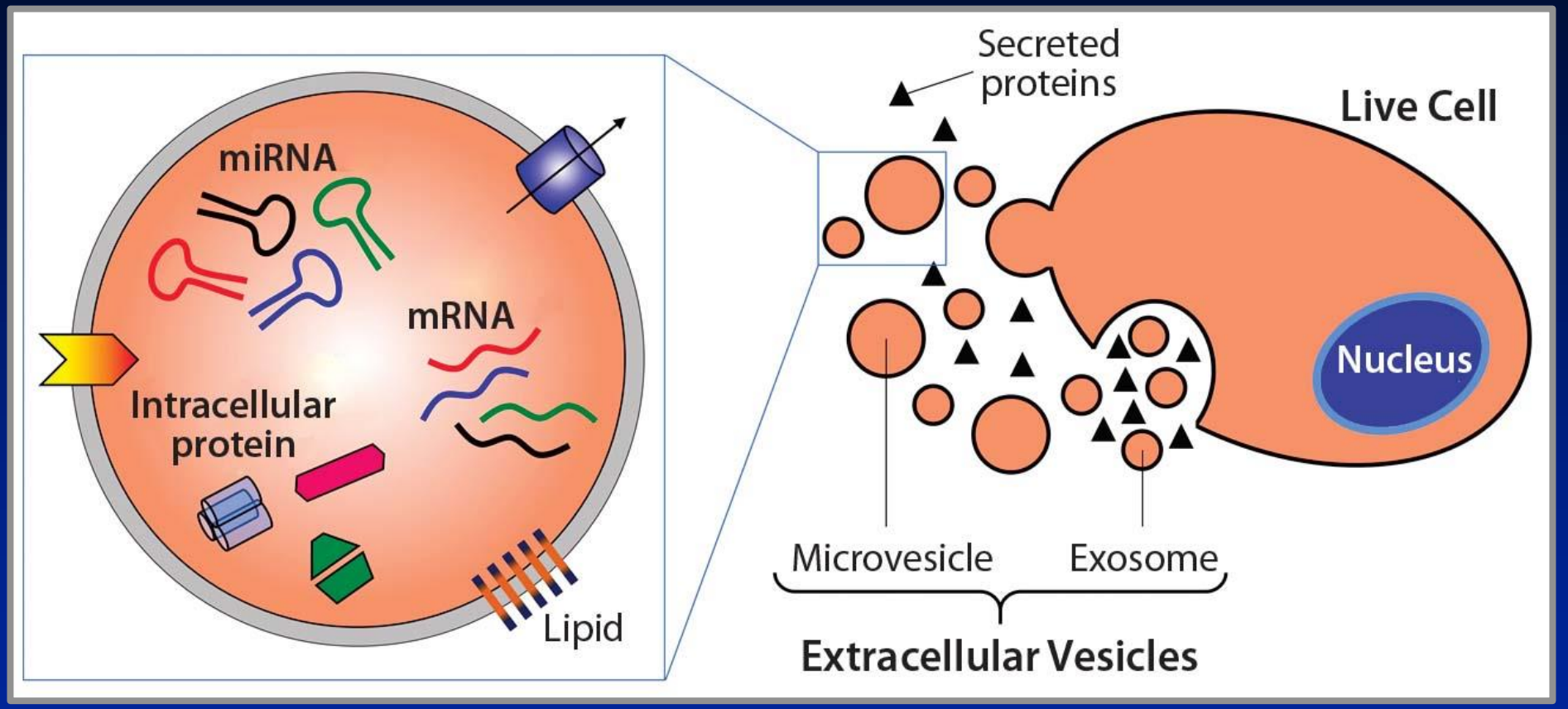




Cell Therapies & Exosomes

- ***Multiple cell therapies show little to no engraftment***
- ***Cell-induced, repaired tissue is often dominated by host cells***
- ***Cell-derived conditioned media often induces similar repair as the cell therapy***
- ***Most of the 'regenerative activity' resides in the exosomes***

Exosomes: Biology & Applications



Stephen J. Gould
Professor of Biological Chemistry, Johns Hopkins University, Baltimore, MD, USA
President, American Society for Exosomes & Microvesicles

S.J. Gould Conflicts (2018)

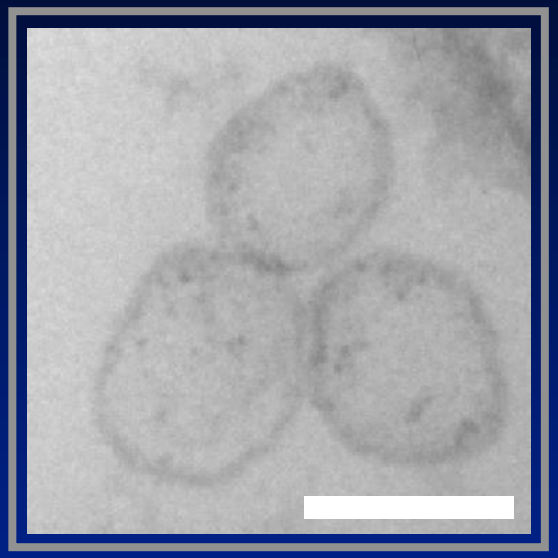
Support:

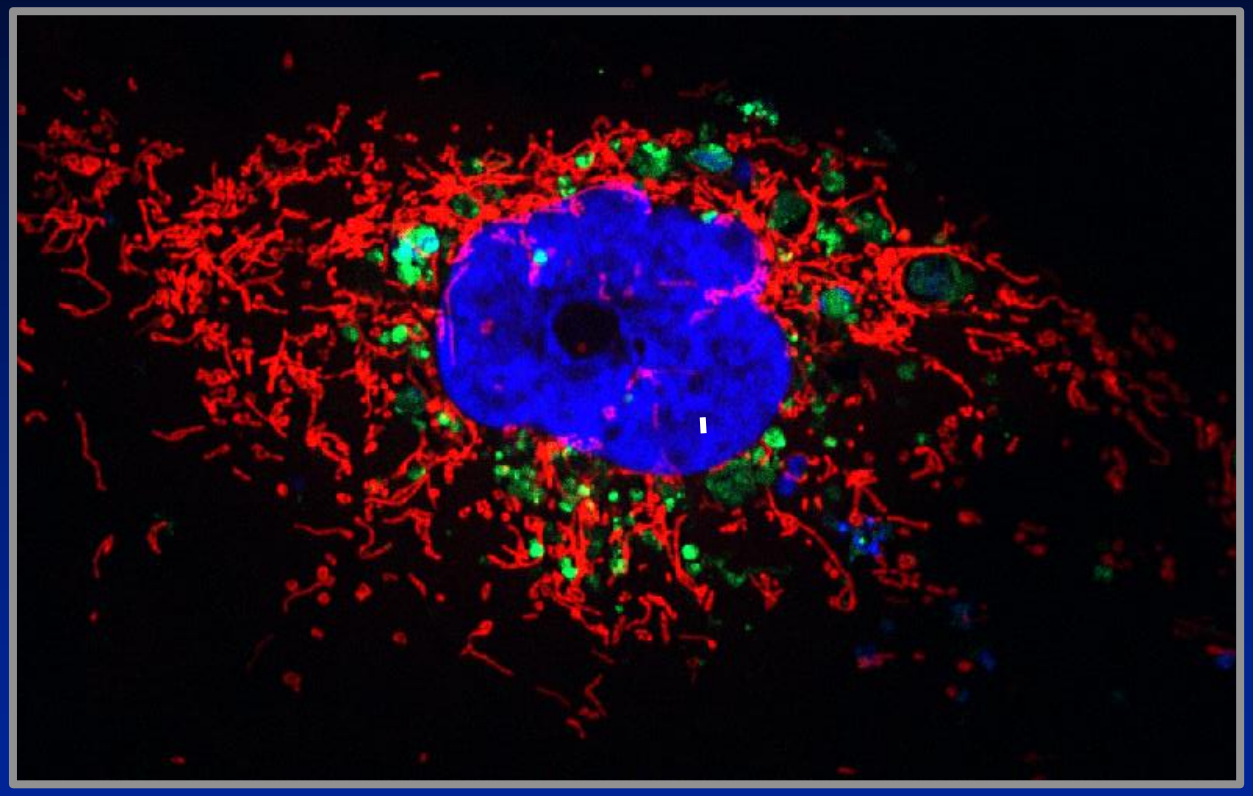
National Institutes of Health USA
TAVEC
Abbvie
Patrick Walsh Foundation
Johns Hopkins University

Consult/licensing/equity:

AbbVie
ReNeuron
PureTechHealth
Beckman-Coulter
SystemBiosciences
Cellex
NanoView
Exocyte
Cascent
TAVEC
GSC Services
ASEMV
Exosoma

Exosomes: The Basics

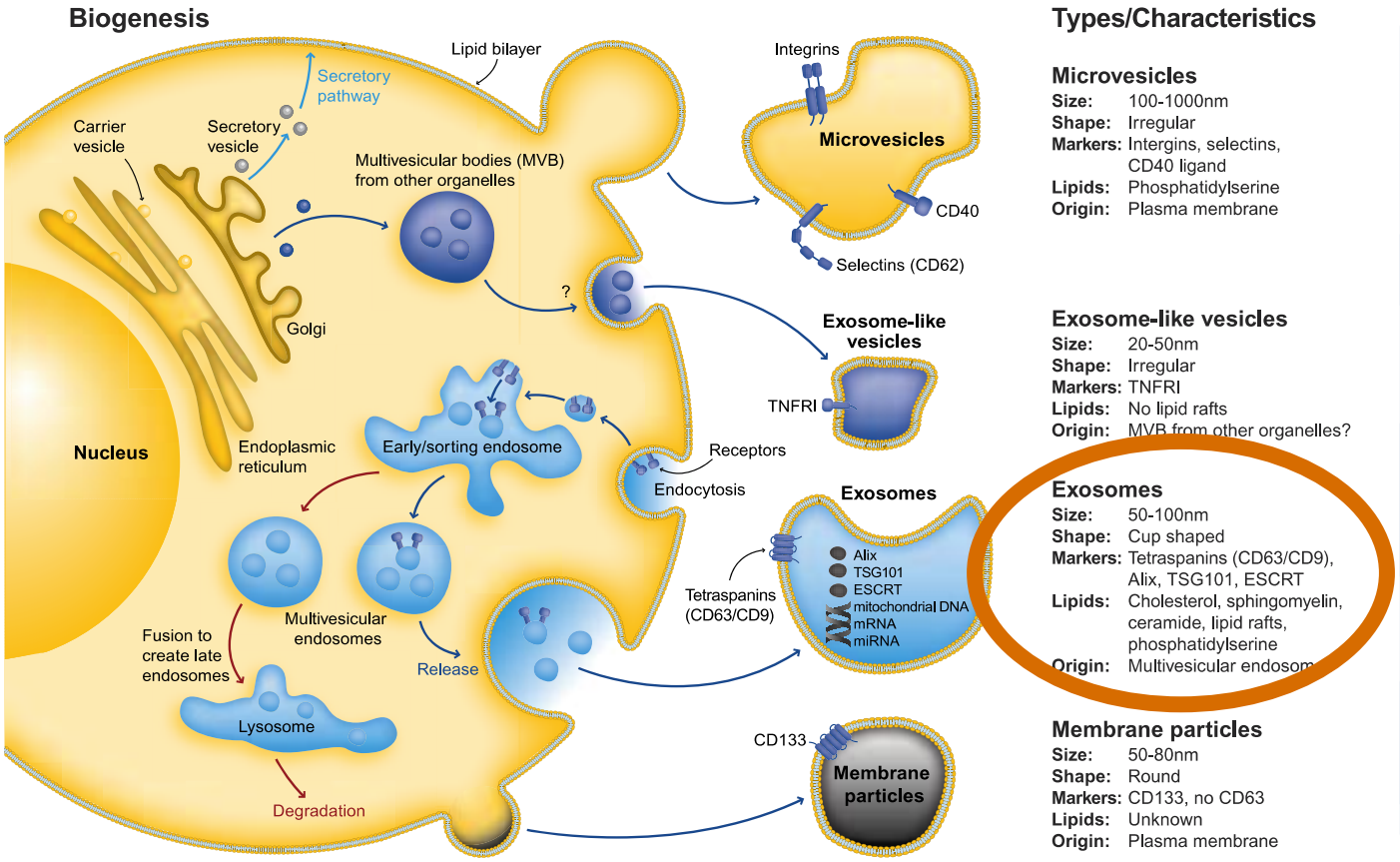




exosome vs cell:

radius = ~1/200 ***area = ~1/40,000*** ***volume = ~1/8,000,000***

Extracellular Vesicle 'Zoo'



Types/Characteristics

Microvesicles
- **Size:** 100-1000nm
- **Shape:** Irregular
- **Markers:** Intergins, selectins, CD40 ligand
- **Lipids:** Phosphatidylserine
- **Origin:** Plasma membrane

Exosome-like vesicles
- **Size:** 20-50nm
- **Shape:** Irregular
- **Markers:** TNFRI
- **Lipids:** No lipid rafts
- **Origin:** MVB from other organelles?

Exosomes
- **Size:** 50-100nm
- **Shape:** Cup shaped
- **Markers:** Tetraspanins (CD63/CD9), Alix, TSG101, ESCRT
- **Lipids:** Cholesterol, sphingomyelin, ceramide, lipid rafts, phosphatidylserine
- **Origin:** Multivesicular endosom

Membrane particles
- **Size:** 50-80nm
- **Shape:** Round
- **Markers:** CD133, no CD63
- **Lipids:** Unknown
- **Origin:** Plasma membrane

Functions

Various secreted extracellular vesicles are present in urine, amniotic fluid, bronchoalveolar lavage fluid, breast milk, saliva and blood.

Cellular uptake mechanisms

- Ligand/receptor interactions
- Attachment and fusion via integrins and cell adhesion molecules
- Transcytosis

Physiological functions

- Inter-cellular communication
- Disposal of defective or effete proteins
- Formation of morphogen gradients for tissue patterning during development
- Antigen presentation to T cells

Pathological functions

- Transmission of viruses, prions and β-amyloid in Alzheimer's disease
- Tumor pathogenesis

Also…..endogenous retroviruses, virus-like particles (VLPs), viruses, & defective interfering particles

How Is This Heterogeneity Interpreted?

- ***Splitters' point of view:***

  exosomes, microvesicles, ectosomes, oncosomes, exosome-like vesicles, and other smallish EVs (~30-300 nm dia.) are:

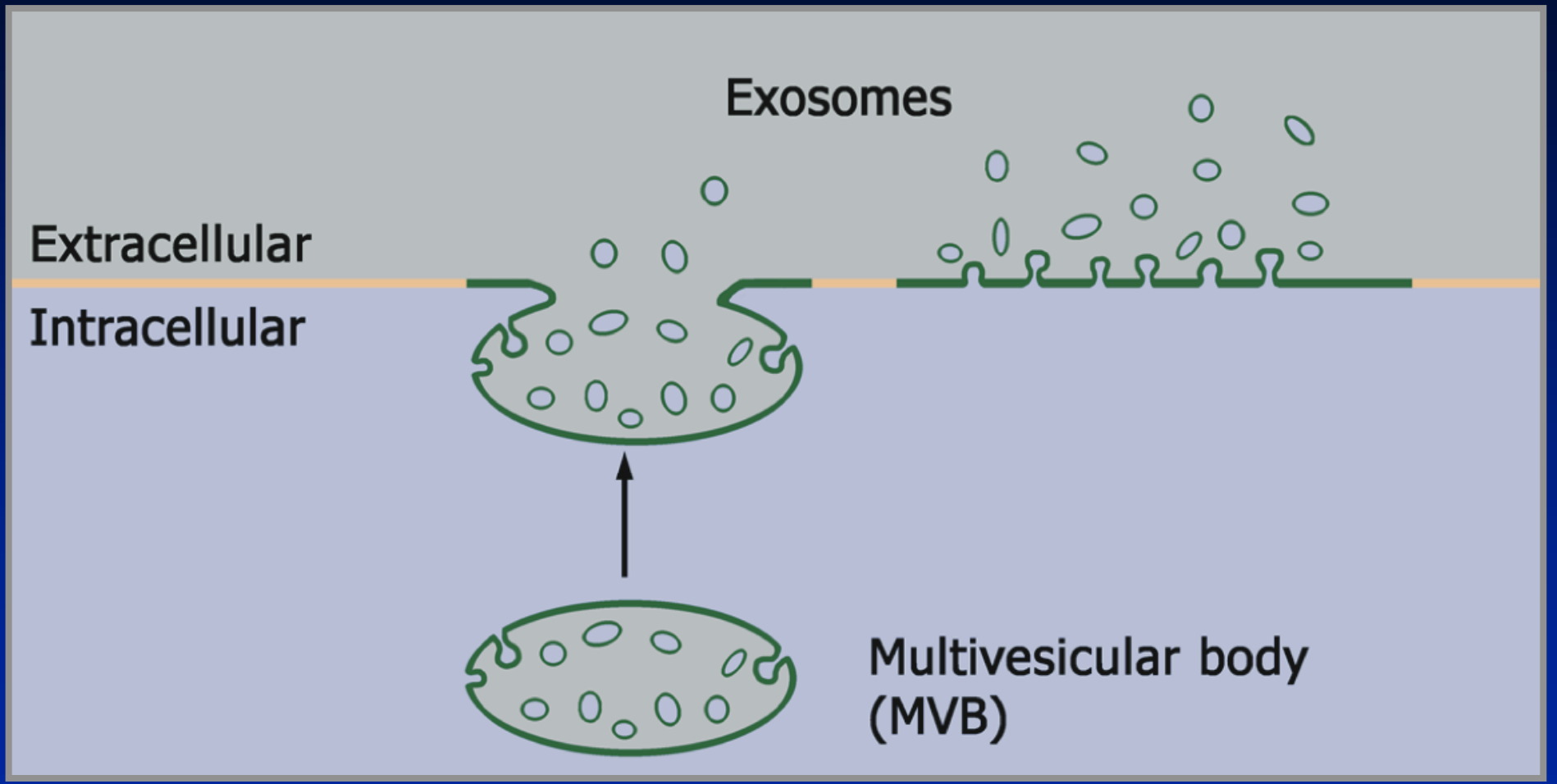
  - ***made by different mechanisms, &***
  - ***carry distinct, non-overlapping sets of cargo molecules***

- ***Lumpers' point of view:***

  All small secreted vesicles are exosomes (Trams et al., 1981 BBA 645:63-70), with vesicle heterogeneity generated by:

  - ***the stochastic nature of organelle biogenesis, &***
  - ***the small size of the vesicles***

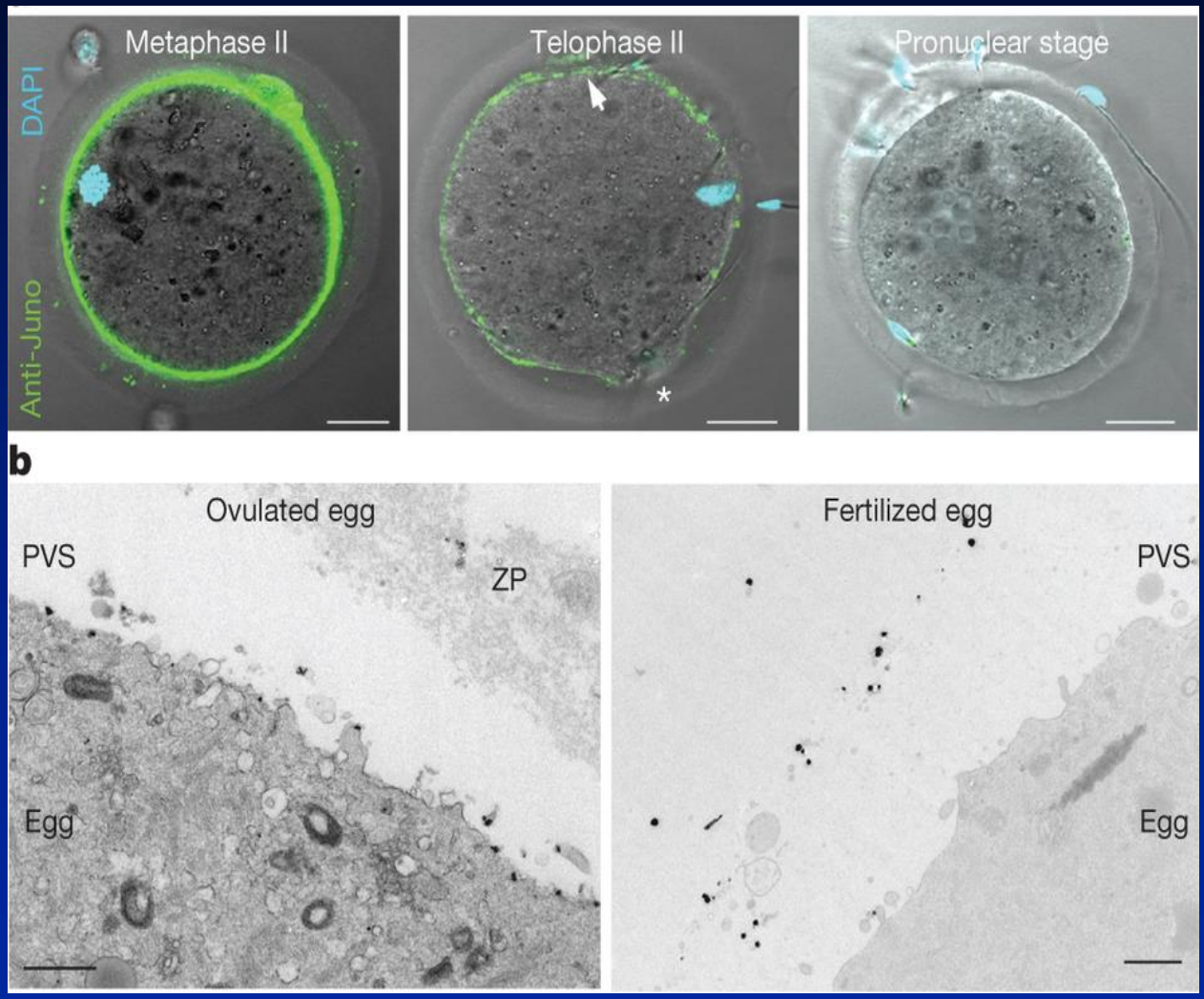
Exosomes: Delayed & Immediate Modes of Biogenesis



Biological Roles of Exosomes

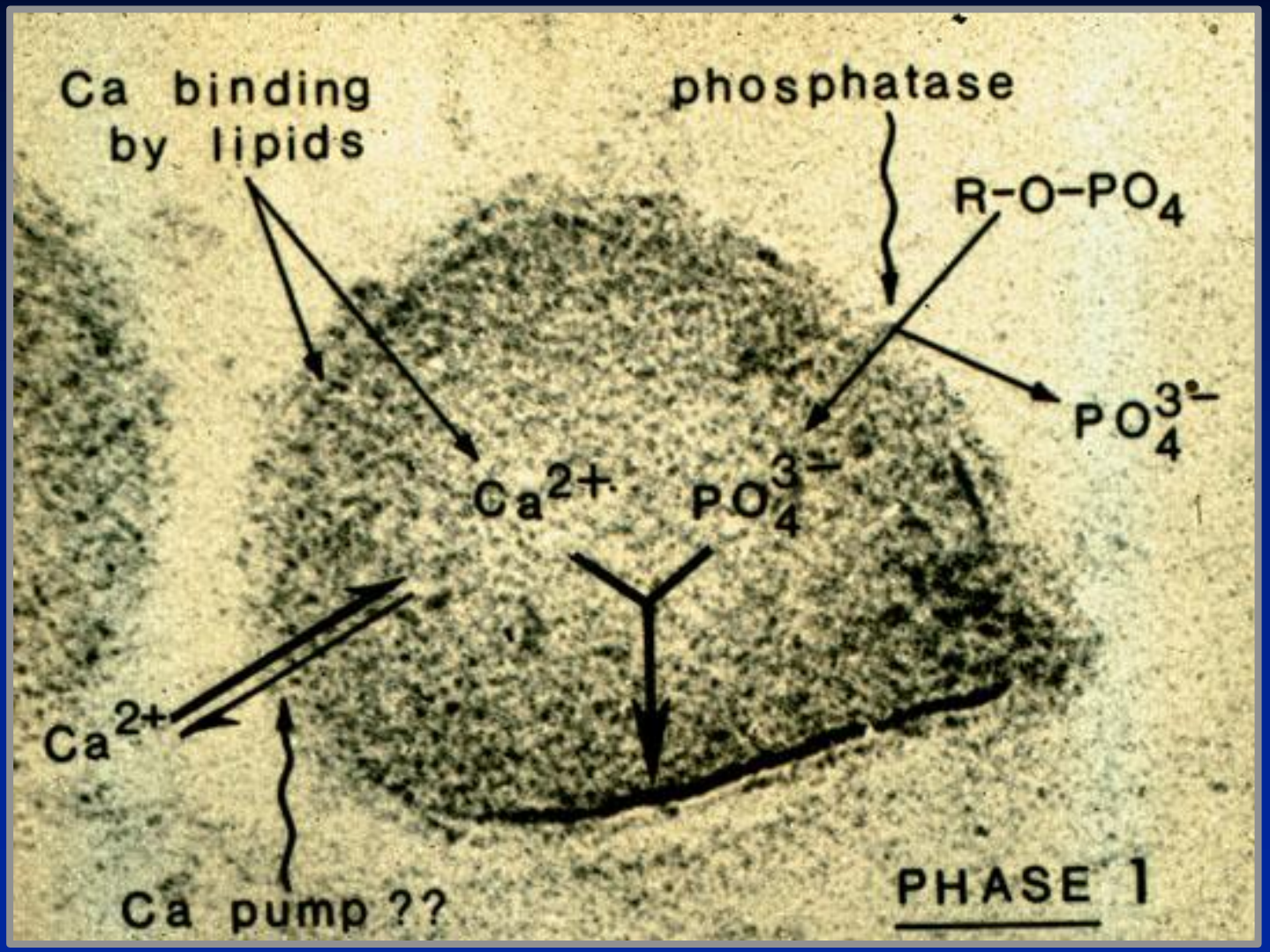
- ***Cell-autonomous effects:***
  - ***Protein Quality Control***
  - ***Cell Polarity***
  - ***Differentiation***
  - ***Extracellular Matrix***
- ***Non cell-autonomous effects***
  - ***Intercellular transfer of***
    - ***signals***
    - ***molecules &***
    - ***genetic information***

Exosome Biogenesis As A Mechanism of Protein Quality Control



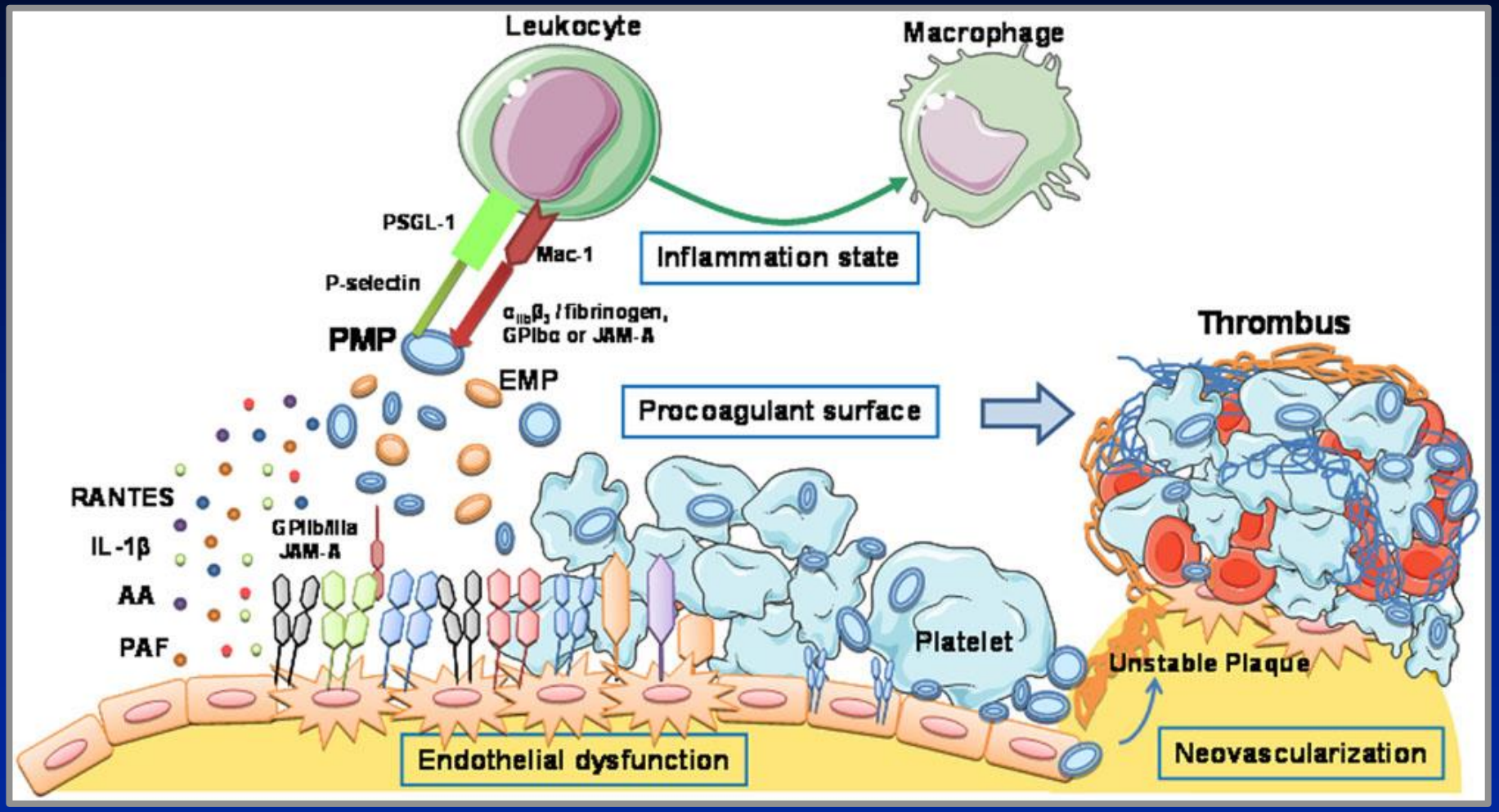
Juno is the egg Izumo receptor and is essential for mammalian fertilization
Bianchi E., Doe B, Goulding D., Wright GJ. Nature 2014 508:483-487

Exosomes Mediate Bone Formation



Hydroxyapatite crystallization initiates in the exosome lumen (Anderson, 1969)

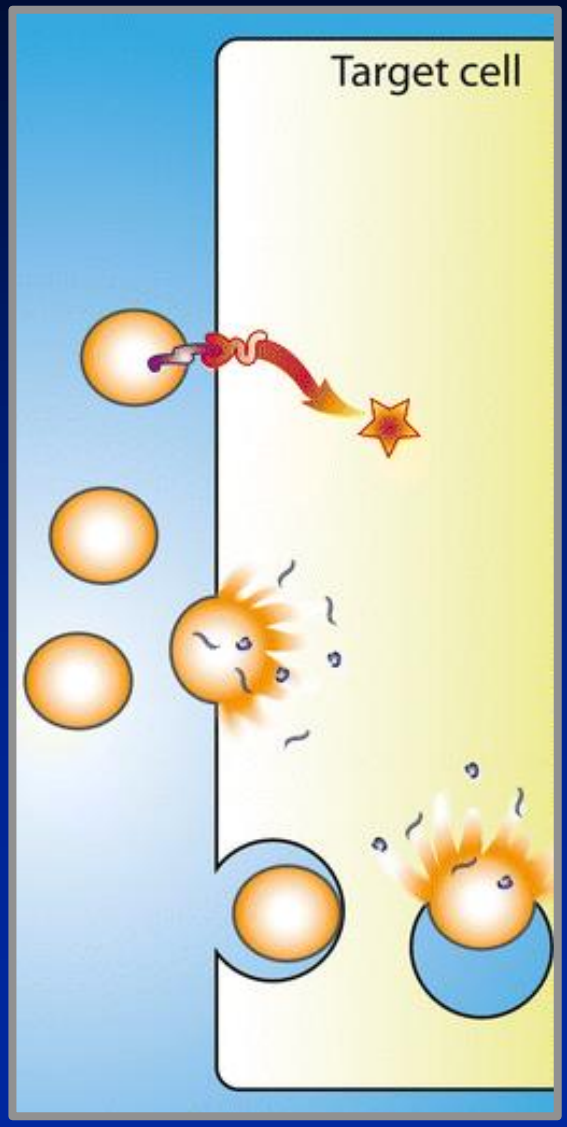
Exosomes Mediate Blood Clotting



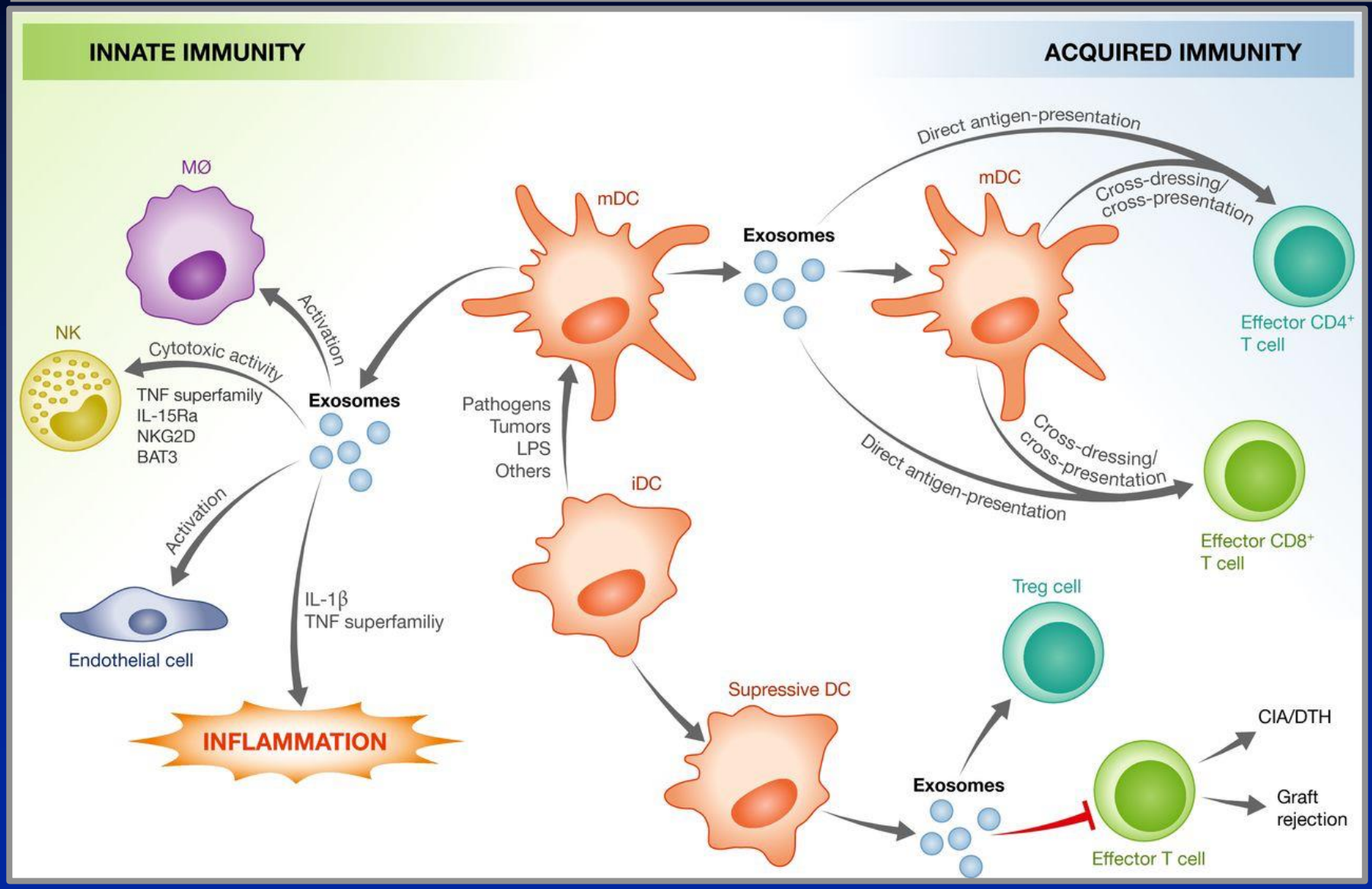
Platelet & endothelial exosomes & MVs promote normal and pathological clotting (Barone et al., 2016)

Exosomes Are Signaling Platforms

- *Cell-autonomous effects:*
  - *Protein Quality Control*
  - *Cell Polarity*
  - *Differentiation*
  - *Extracellular Matrix*
- ***Non cell-autonomous effects***
  - ***Intercellular transfer of***
    - ***signals***
    - ***molecules &***
    - ***genetic information***



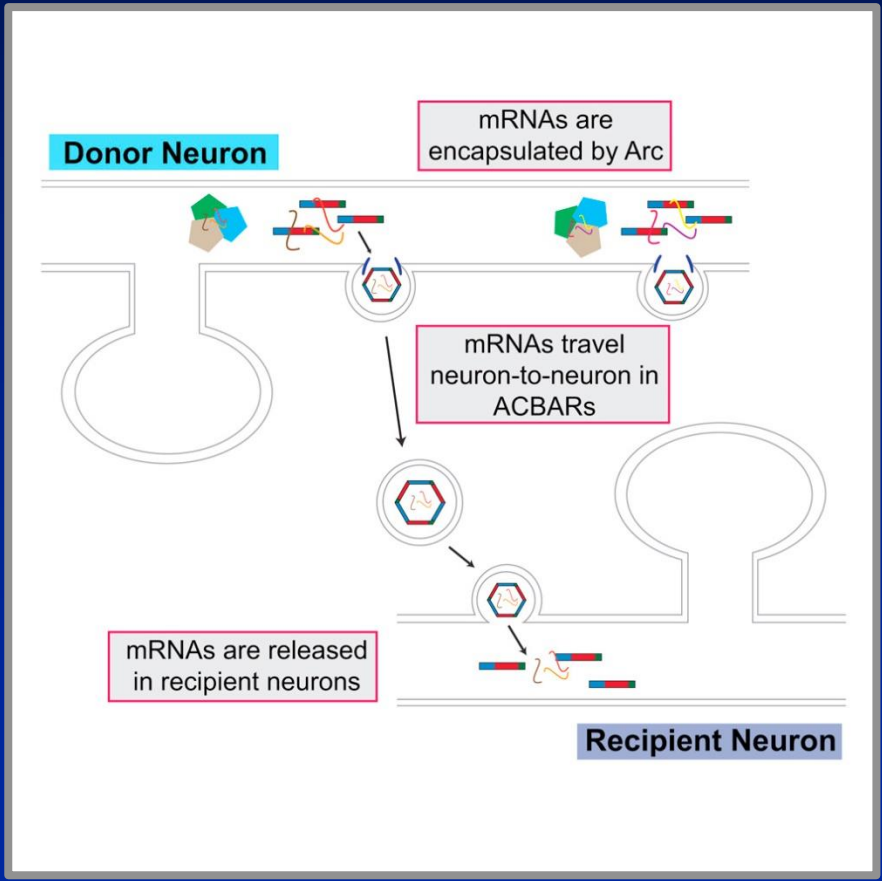
Exosomes In Immune Signaling



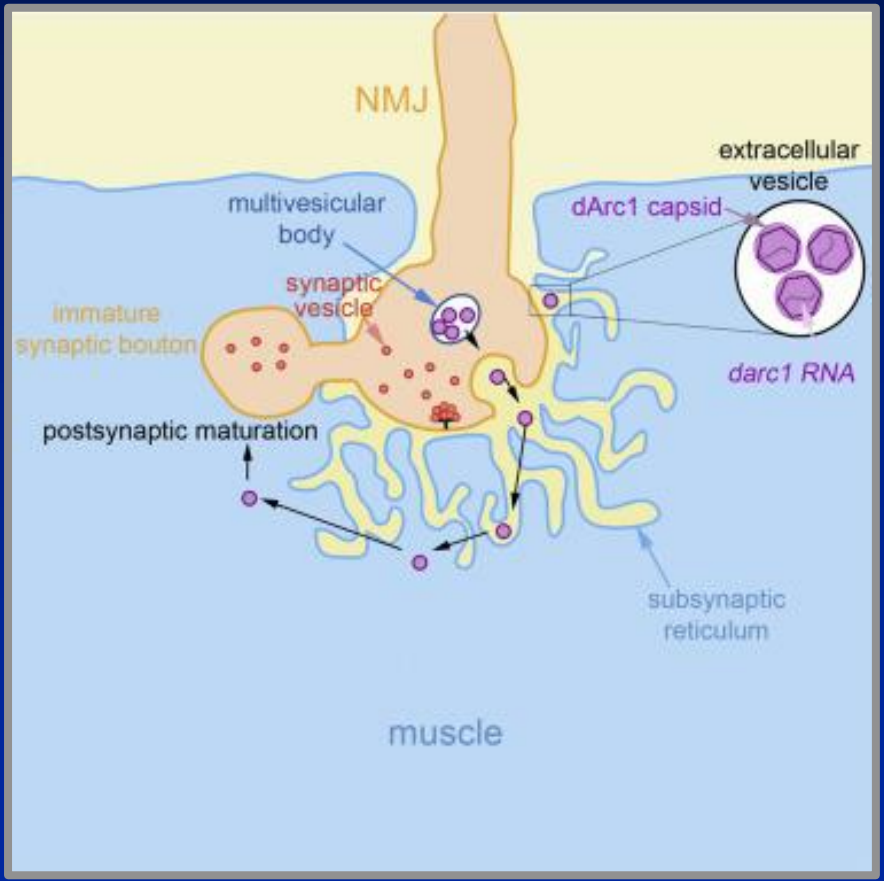
Exosomes In Neuronal Signaling

ARC: ***mediates learning & memory & is perturbed in multiple forms of cognitive deficiency (autism, Angelman syndrome, etc.)***

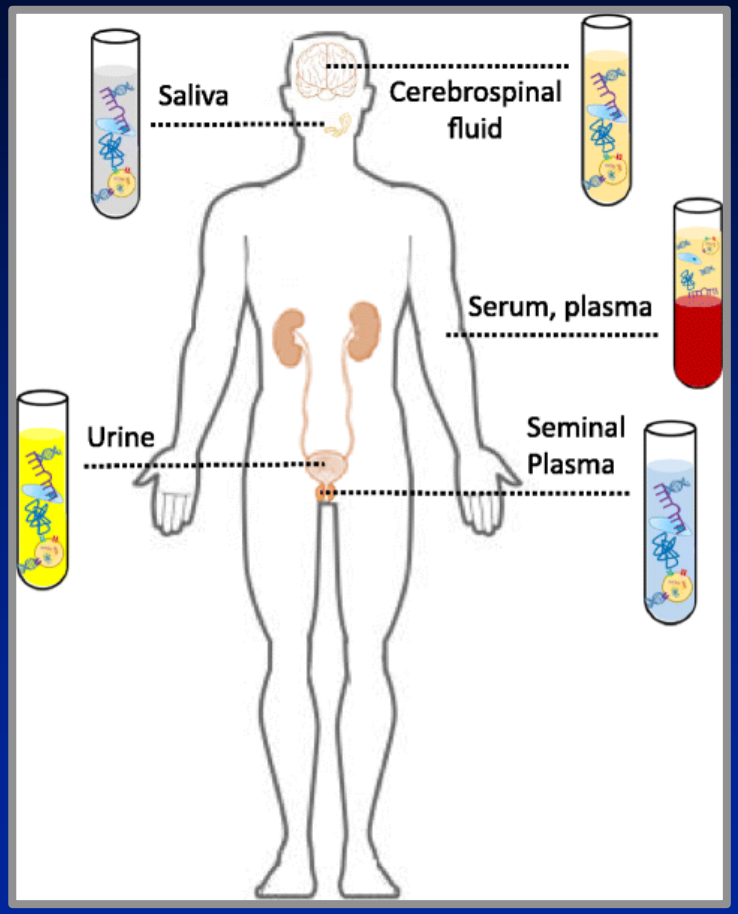
neuron-to-neuron ARC Xfer



neuron-to-muscle ARC Xfer

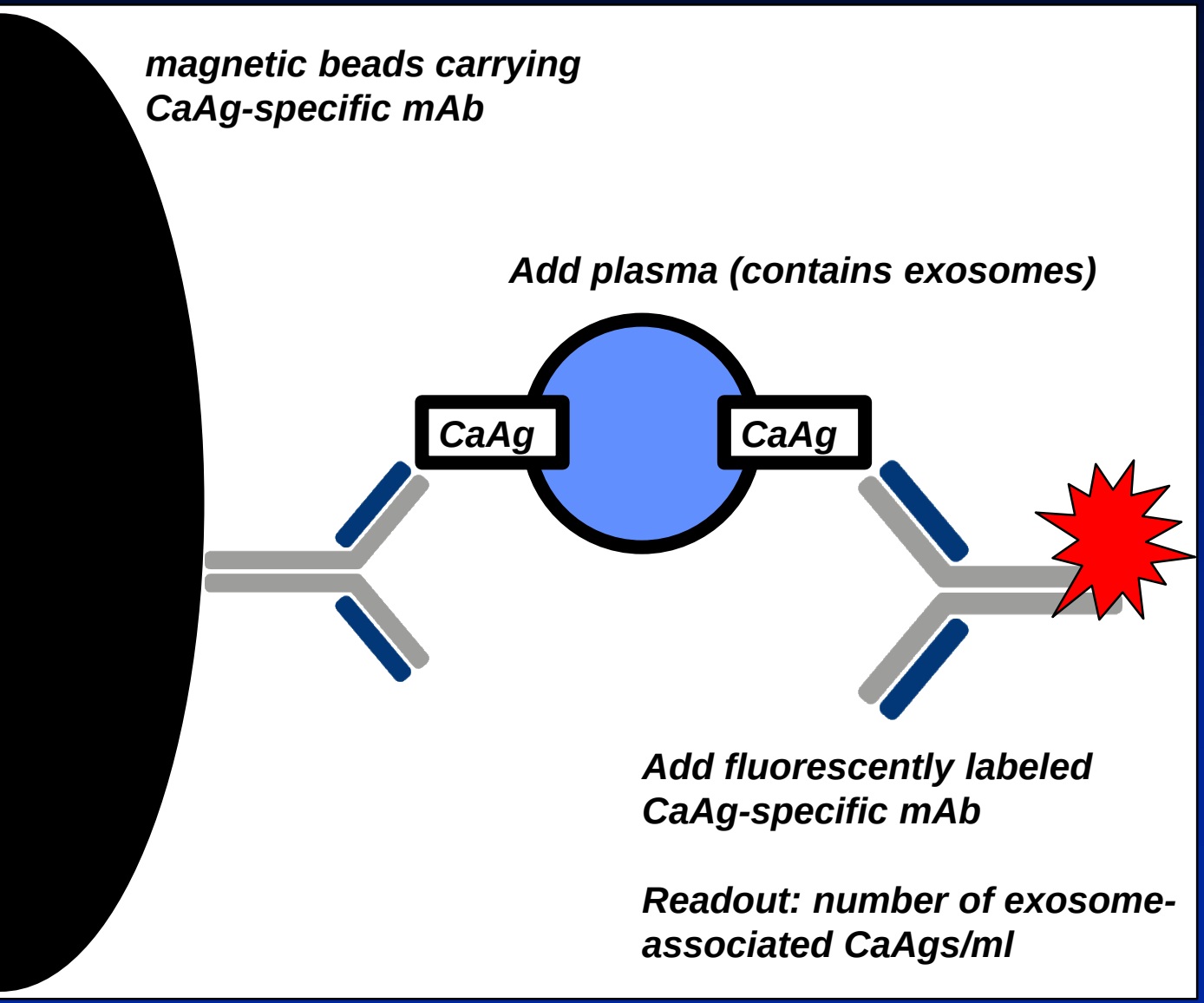


Applications in Liquid Biopsy



- *collect biofluid*
- *purify/isolate vesicles*
- *assay for RNA, DNA, or antigens*
- *requires 10-20 ml blood & expert handling*

Low Volume, Automated Alternative For Cancer Diagnostics



- mix bead-mAb w/ plasma sample
- add Fl-Ab
- dilute
- assay by flow cytometry
- Quantifies vesicle-associated CaAg in sample
- 3 min/sample, automated, robotic

Exosome-Based Therapeutics

- *Cell-autonomous effects:*
  - *Protein Quality Control*
  - *Cell Polarity*
  - *Differentiation*
  - *Extracellular Matrix*
- ***Non cell-autonomous effects***
  - ***Intercellular transfer of***
    - ***signals***
    - ***molecules &***
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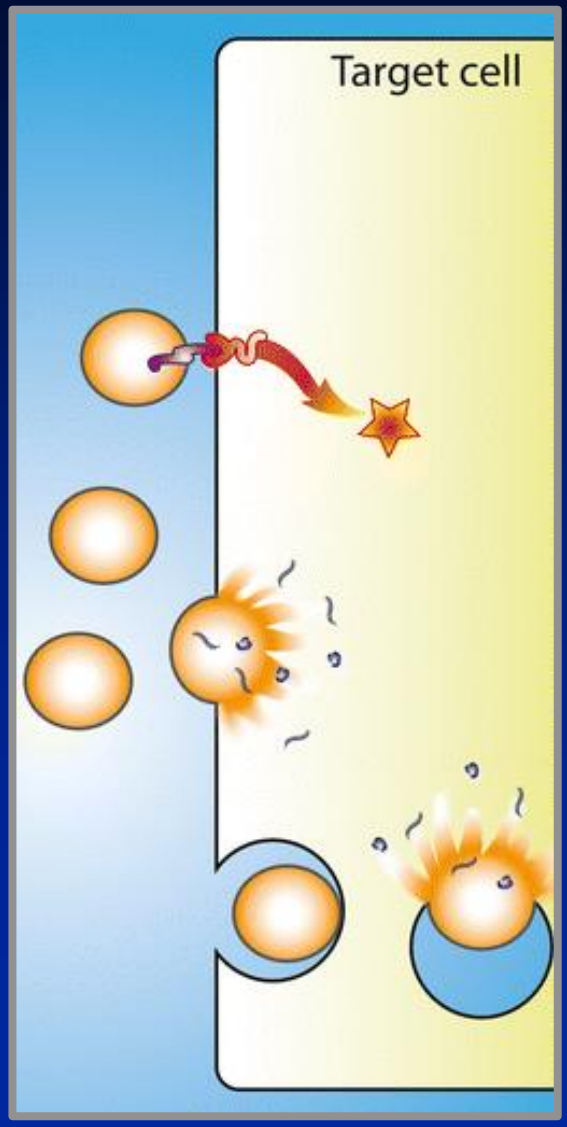
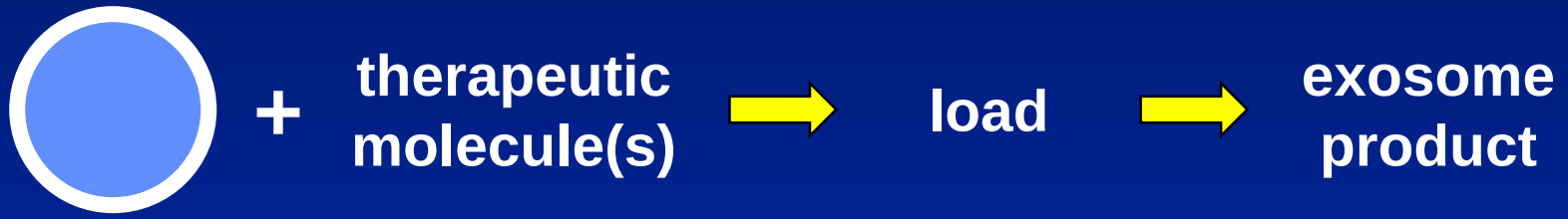


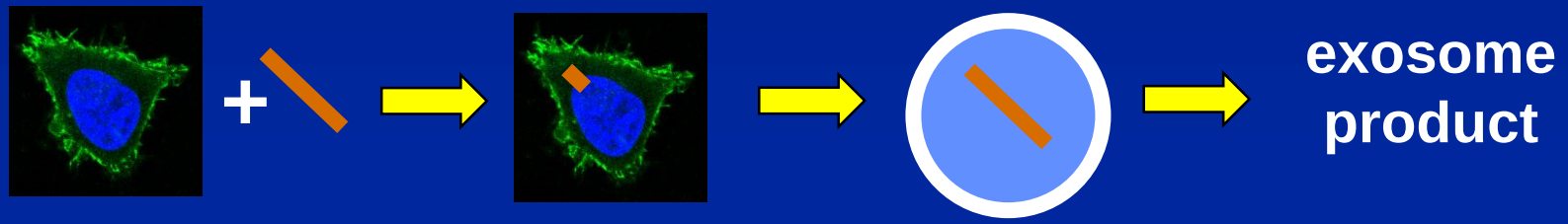
Modes of Exosome Therapy

- ***Intrinsic Exosome Therapies***

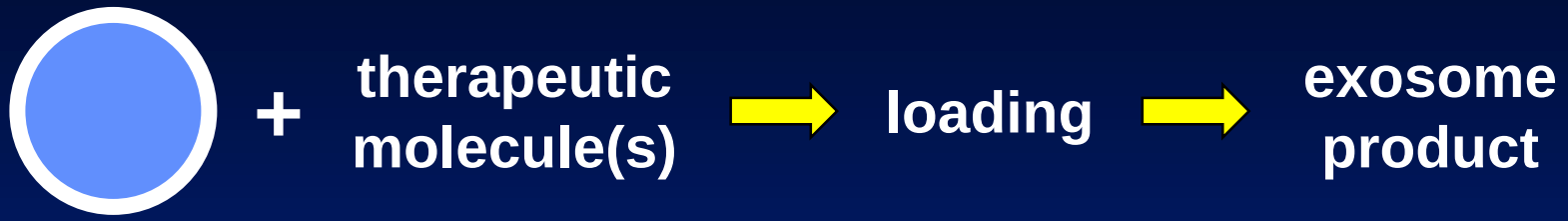
- ***Engineered Exosome Therapies***



- ***Cell-Engineered Exosome Therapies***

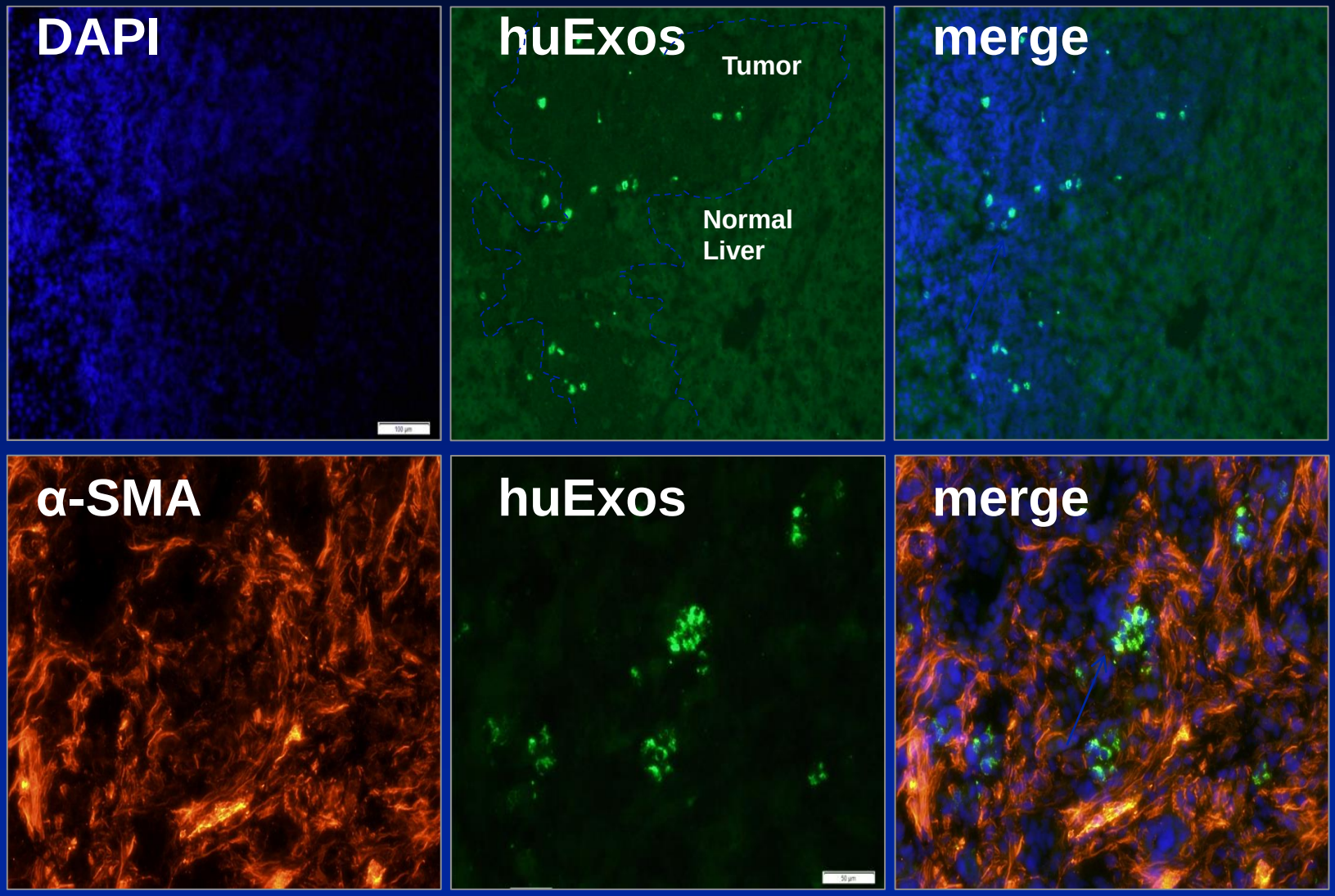


Engineered Exosome Formulation

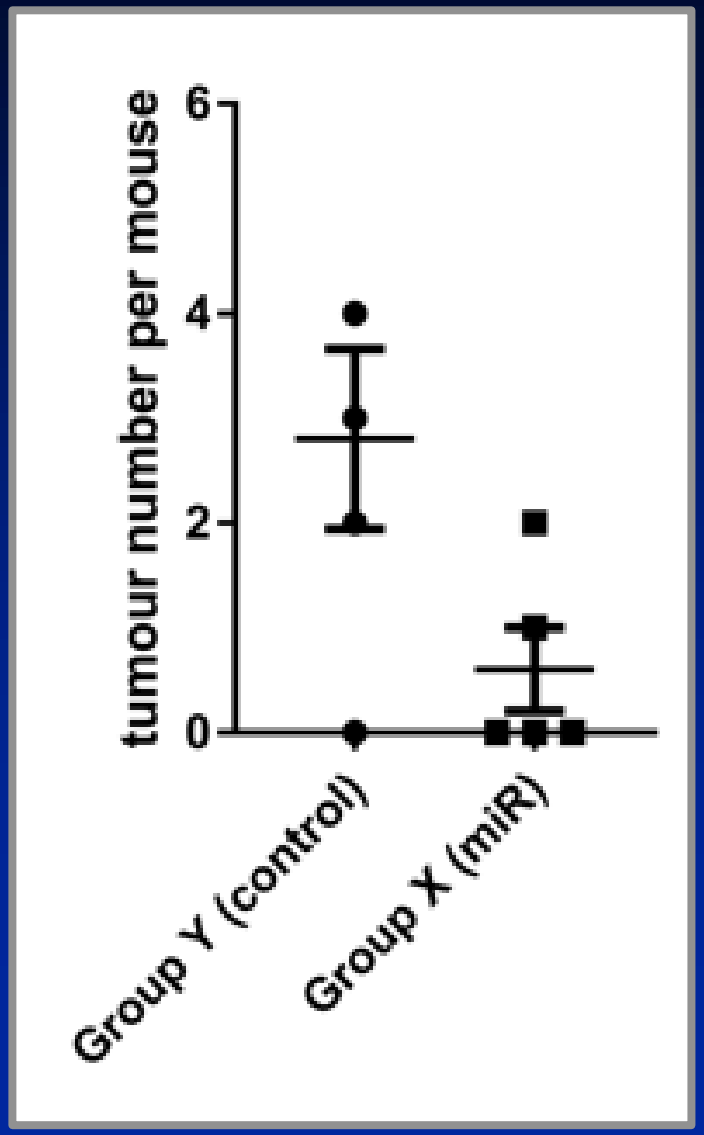


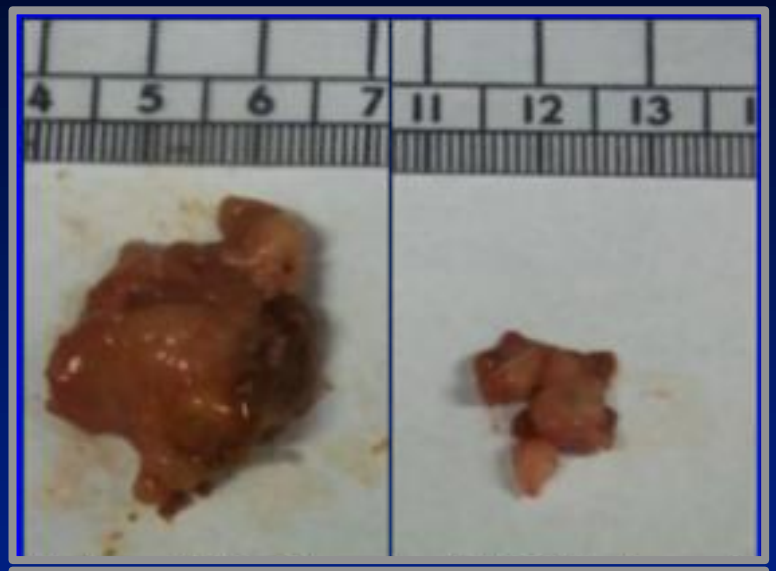
- ***Consistent cell factory***
- ***Consistent production process***
- ***Defined mechanism, via cargo***
- ***Easily multiplexed***
- ***Regulatory simplicity***

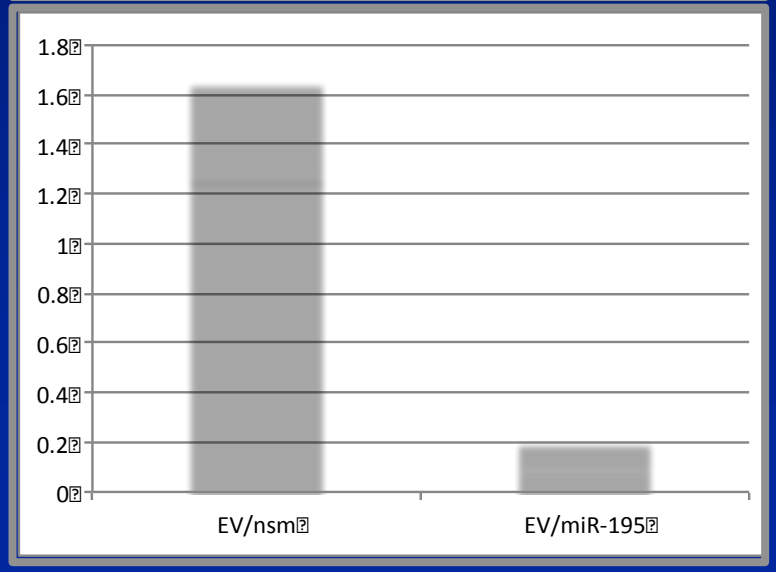
Injected Exosome Formulations Selectively Accumulate In Tumor Cells



Injected Exosome Formulations Can Treat & Prevent Cancers







Exosome Therapeutics Overview

- ***Intrinsic, engineered, & cell-engineered***
- ***Each has distinct pros & cons***
- ***Selective accumulation at sites of damage***
- ***Broad platform for targeted drug delivery***
- ***Modest competition***
- ***Favors those with cell therapy experience***

ReNeuron & Exosome Therapies

- ***Consistent cell factory & validated cell banks***
- ***Established GLP/GMP cell culture***
- ***Already generating GMP conditioned media***
- ***Exosome QC metrics same as for cells***
- ***Established CRO relationships***
- ***Regulatory approval & expertise***

ReNeuron

ExoPr0 - a new class of anti-cancer therapy

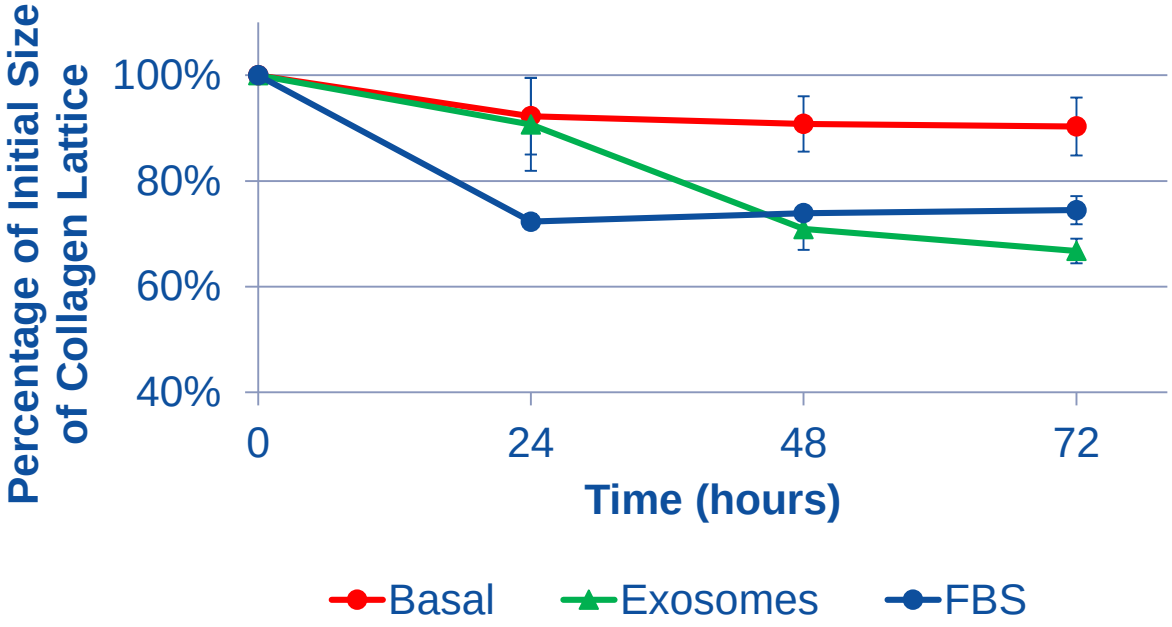
Randolph Corteling, PhD

Head of Research

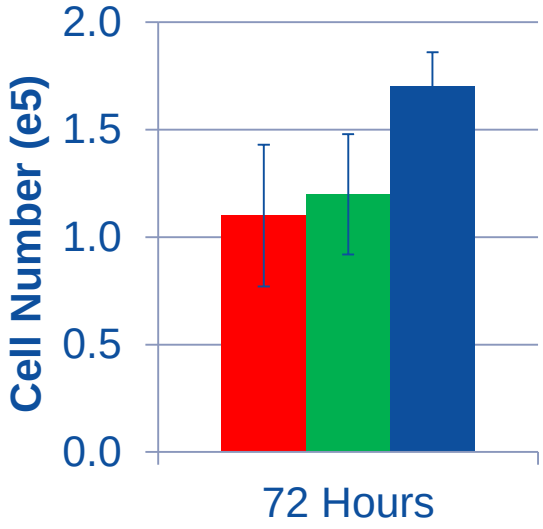
A global leader in stem cell-derived exosome therapeutics

- Exosome platform established at ReNeuron in 2011
- Significant IP portfolio established
- Qualified, scalable GMP process
- Proprietary clinical-grade producer cell line (CTX), giving high yields
- Stable and consistent product
- Established analytics
- Broad anti-cancer properties (ExoPr0)

ExoPr0 induces fibroblast differentiation



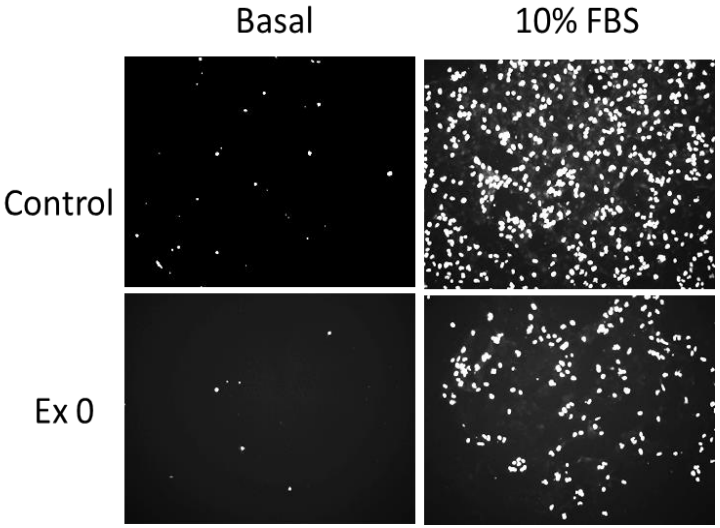
- **Basal** = Negative Control
- **FBS** = Positive Control
- **Exosomes** = ExoPro

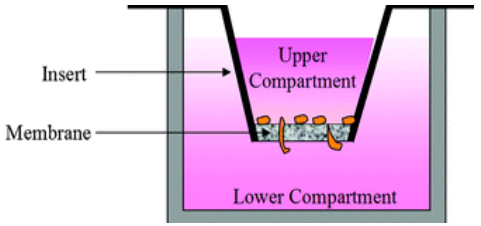


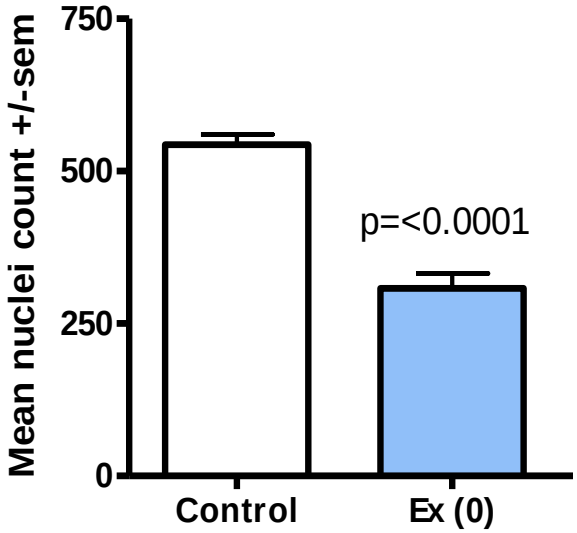
ExoPr0 induces contraction through differentiation, independently of proliferation

ExoPr0 inhibits the migration of cancer cells

- U373 MG $1x10^5$ + exosome 20µg/ml
- 24hr migration towards 10% FBS
- Nuclei counts







Overcoming barriers to commercialisation

The limited scalability of stem cell producers severely curtails the clinical utility of exosomes at a commercially relevant scale.

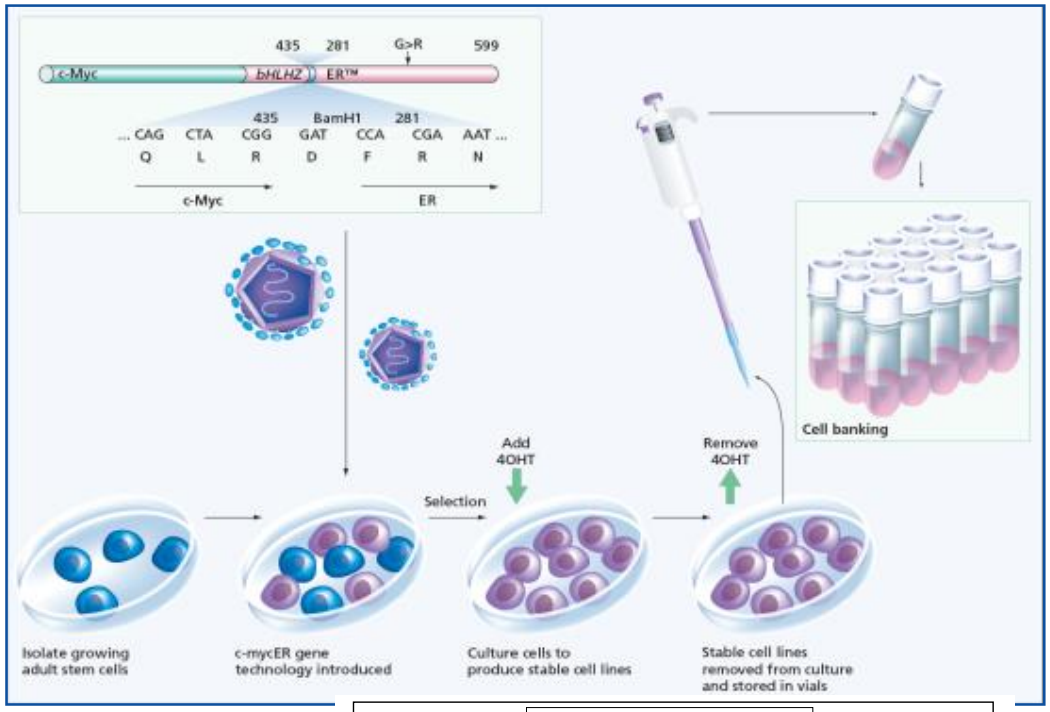
At a quality and consistency that doesn't affect their therapeutic function

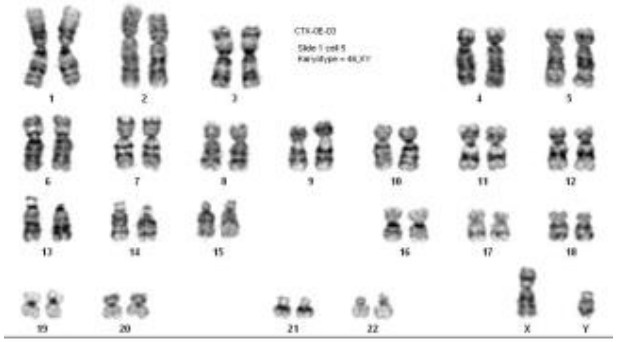
Our approach

Conditionally immortalised human neural stem cell line that is a highly efficient producer of EVs.

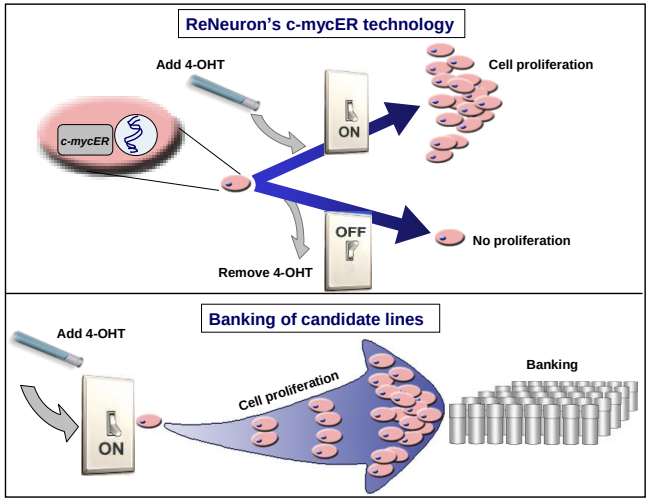
- Clonal standardisation – batch to batch consistency
- Scalability
- Demonstrated therapeutic relevance

Stable producer cell line – conditional immortalisation





** 4OHT = 4-hydroxy tamoxifen, a metabolite of tamoxifen*



Stable producer cell line

- Consistent phenotype maintained over multiple passages.

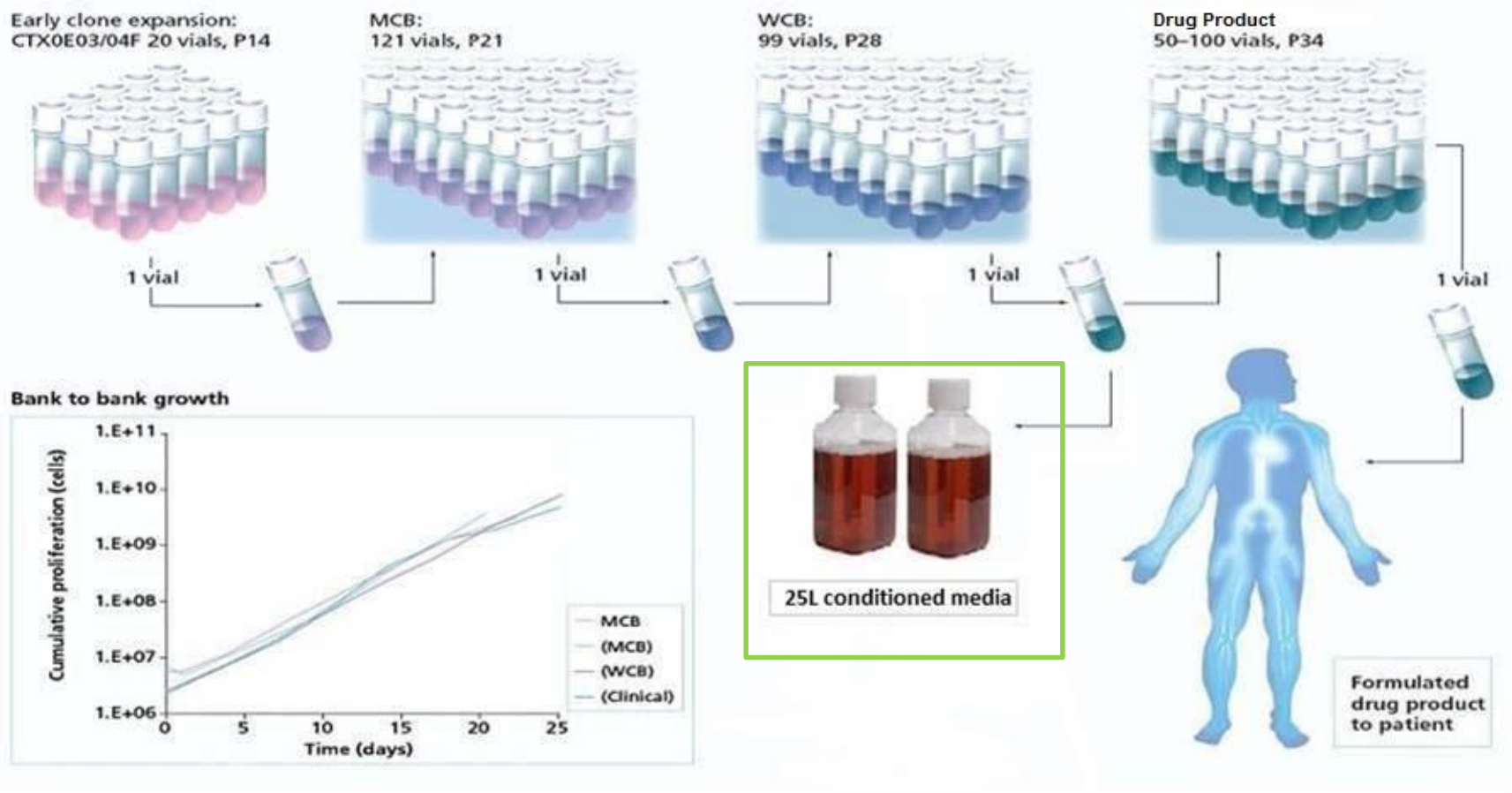
Fully qualified Xeno-free GMP process with strict release criteria

- Serum free process
- Raw materials and process accepted by both MHRA and FDA

Scalability

- Produced to a commercially relevant scale in multi tier tissue culture flasks or bioreactors.

Production of starting material to cGMP



Product by Process

Upstream Process:

Conditioned media from current GMP cell DP manufacture (25-50L).

Downstream Process:

2-part purification process: Hollow-fibre tangential flow filtration (TFF) and size exclusion chromatography

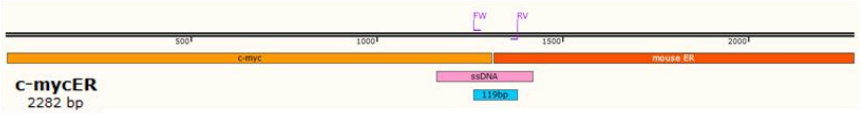
- 100% scalable – we currently operate at a fraction of the scale possible
- Reduced shear stresses
- Concentration, elimination of contaminants and buffer exchange
- Process delivers approximately 50-100ml purified exosomes at approx. 10^{11}-10^{12} particles/ml
- Secondary concentration is possible to deliver higher dose range for e.g. toxicity studies

Formulation:

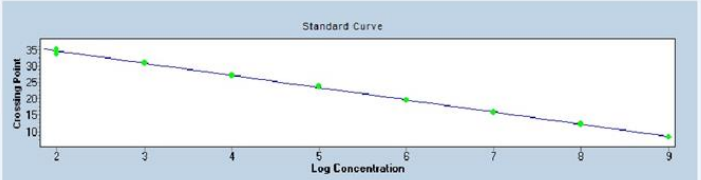
- Very simple: PBS at 2-8°C
- Estimated stability 6-12 months
- Possibility for enhanced formulation: frozen (-20°C), lyophilisation for long-term stability.

Absence of c-mycER transfer to ExoPr0

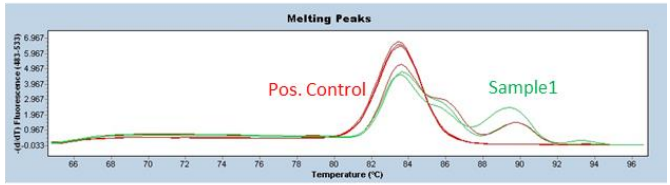
qPCR assay: Absolute quantification of c-mycER



- Specific primers for qPCR spanning both c-*myc* and mouse ER sequence (119bp).
- Primers concentrations and PCR efficiency have been validated using a ssDNA oligo (ssDNA)
  - ✓ PCR Efficiency = 90%.
  - ✓ Detection up to 100 molecules
  - ✓ No specific products detected in samples after qPCR
  - ✓ Will using hRPC Exosomes as negative control for QC assays

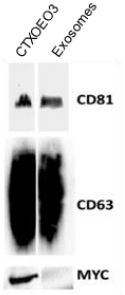


St. Curve. Efficiency= 1.868 (90.72%). Slope= -3.684. Error=0.0633



Tm. Curve. Sample=ExoPro UC purified.

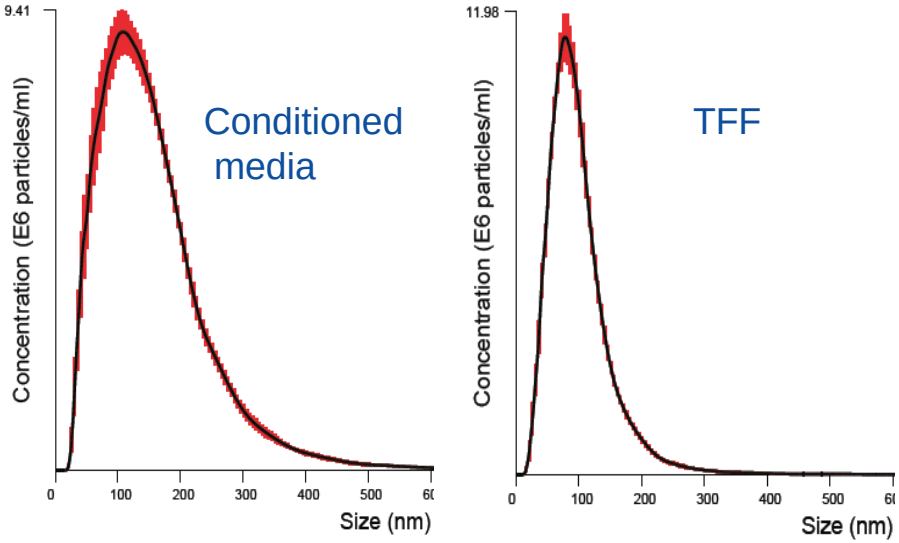
WB assay: Exosomes enriched markers and c-myc



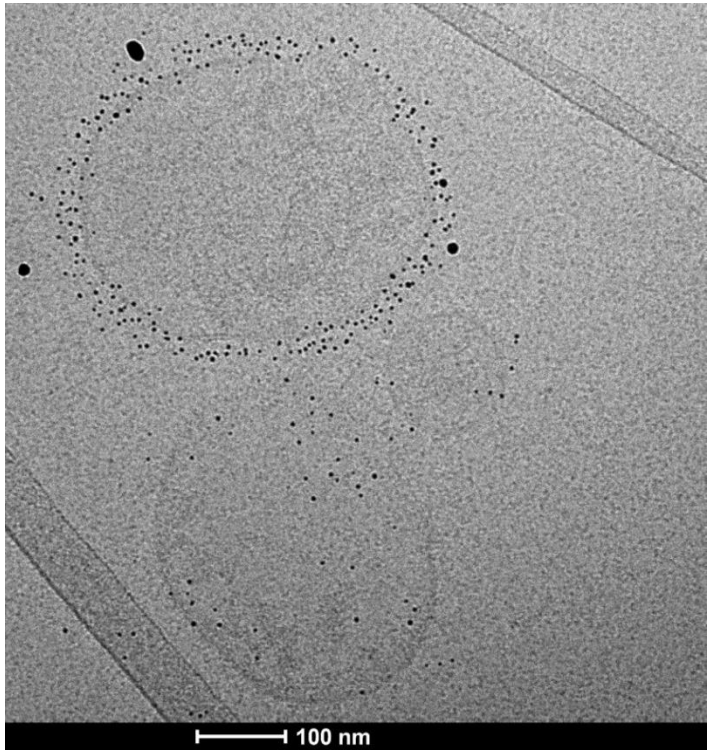
- ✓ Exosome fraction identified by CD81 and CD63
- ✓ No c-myc present in the Exosome fraction

Stevanato et al. 2016

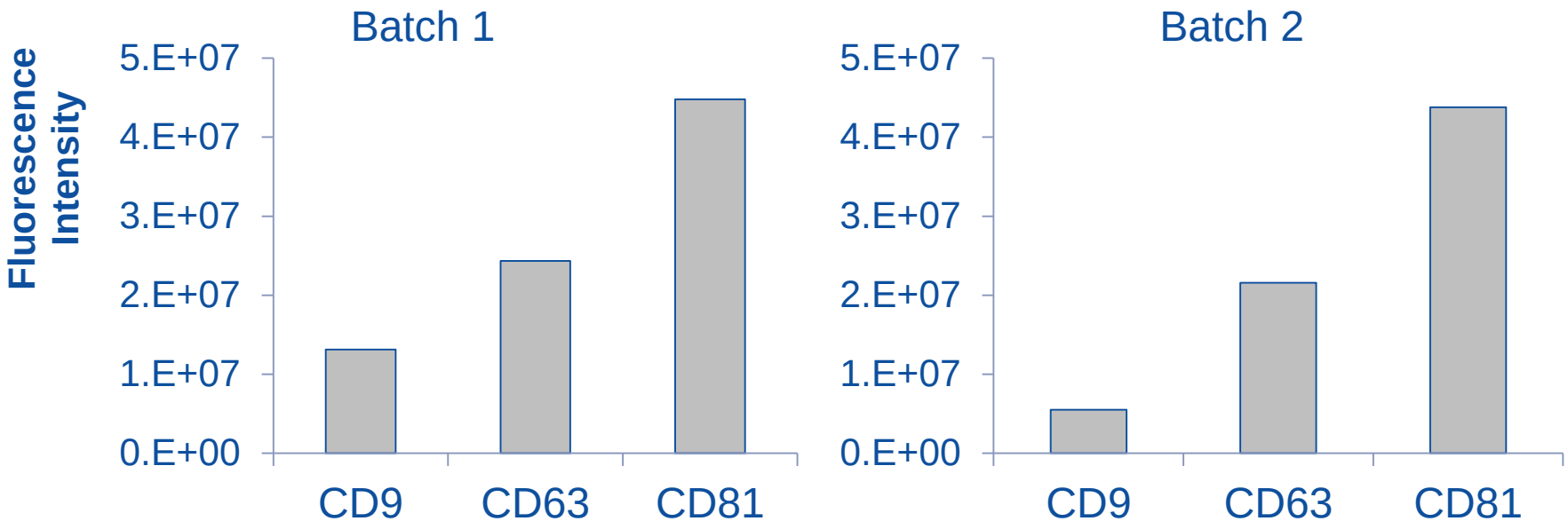
ExoPr0 Isolation from Conditioned Medium



	Mean particle size (nm)	No. of particles /mL	Total protein (mg/mL)	Purity (Particles /µg protein)
Engineering run 1	131	$1.58x10^{12}$	0.695	$2.3x10^{9}$
Engineering run 2	131	$1.29x10^{12}$	0.672	$1.9x10^{9}$
Engineering run 3	128	$9.7x10^{11}$	0.556	$1.7x10^{9}$



Consistent expression of characteristic exosome markers



Batch-to-batch consistency

Exosome Batch		Particle Concentration (p/mL)	Mean Size (nm)	Mode Size (nm)	Protein (µg/mL)	Purity (particles/ µg protein)	CD Marker (Relative Abundance)
ReN 9	Process run A	4.48E+11	121.3	98.9	444	1.01E+09	CD81>CD63>CD9
ReN 8	Process run A	9.50E+11	138	116	403	2.36E+09	CD81>CD63>CD9
	Process run B	1.21E+12	142	121	495	2.45E+09	CD81>CD63>CD9
ReN 6a	Process run A	9.67E+11	140.6	126.5	537	1.80E+09	CD81>CD63>CD9
	Process run B	2.74E+11	140.9	114.2	167	1.64E+09	CD81>CD63>CD9
ReN 5	Process run A	9.77E+11	119 ±1.8	100 ±3.6	568	1.70E+09	CD81>CD63>CD9
	Process run B	1.58E+12	131 ±1.2	101 ±3.8	695	2.30E+09	CD81>CD63>CD9
ReN 4	Process run A	9.70E+11	128 ±1.5	105 ±4.9	556	1.70E+09	CD81>CD63>CD9
	Process run B	1.29E+12	131 ±6.7	104 ±3.9	672	1.90E+09	CD81>CD63>CD9
	Process run A + B	9.24E+11	129 ±2.3	104 ±7.9	657	1.40E+09	CD81>CD63>CD9

Established analytics – defined exosome 'Fingerprint'

Aim

- Monitor **consistency** of the products for **quality control**
- Assess the impact of process changes for **process development**

RT-qPCR – miRNA fingerprint

- Quantitative analysis
- Highly sensitive

Capillary Gel Electrophoresis - Proteomic fingerprint

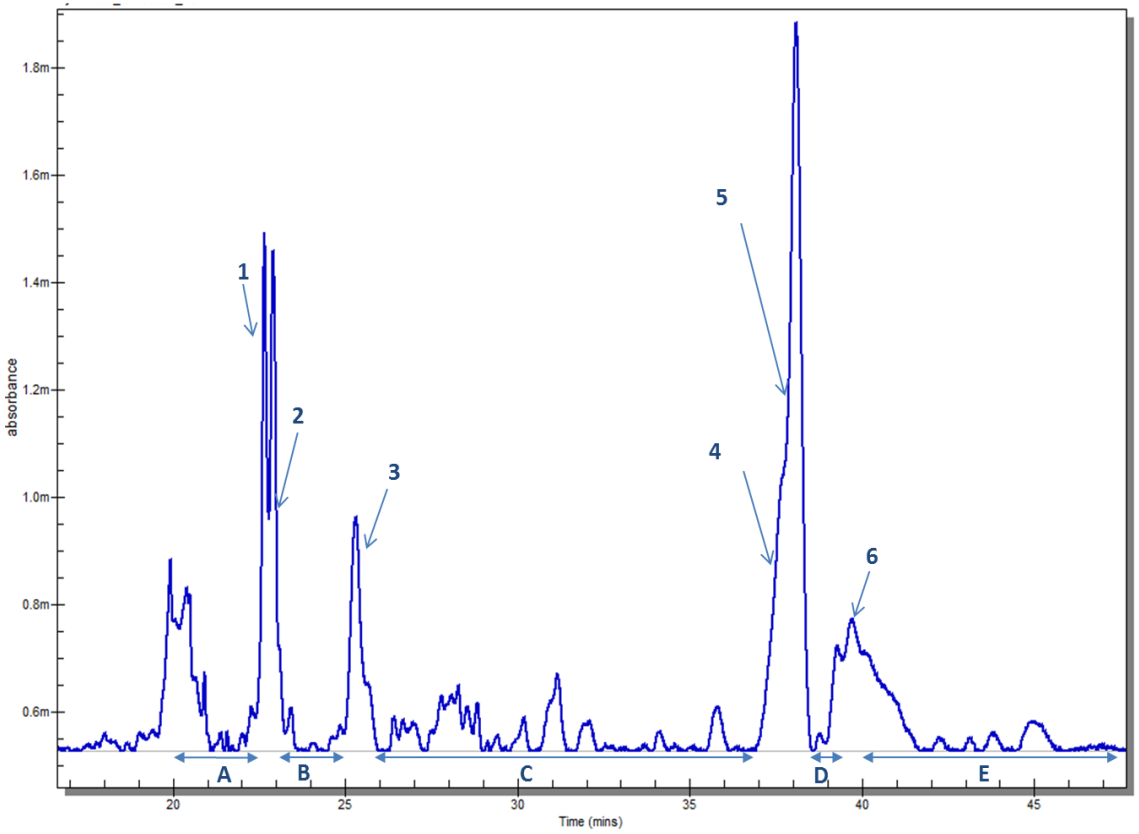
- Fast – approximately 30 minutes
- Requires approximately 20ng/ run
- Identify and quantify exogenous **contaminating** proteins in the product through purity / impurity analysis

Consistent miRNA profile

- Multiple rounds of NGS reveals consistency in the most common and abundant miRNAs detected within ExoPr0
- Batch-to-batch variability in terms of miRNA content is minimal.
- Targets in the process of validation by qPCR

	Manufacturing site 1		Site 2	Site 3
	Batch 1	Batch 2	Batch 3	Batch 4
hsa-miR-A	1	2	1	1
hsa-miR-B	2	1	3	3
hsa-miR-C	3	3	4	4
hsa-miR-D	4	5	2	2
hsa-miR-E	5	7	6	7
hsa-miR-F	6	6	5	5
hsa-miR-G	7	12	9	10
hsa-miR-H	8	8	8	8
hsa-miR-I	9	11	12	15
hsa-miR-J	10	4	13	14

Consistent proteomic profile



	% peak area
Peak 1	10.0
Peak 2	10.1
Peak 3	9.35
Peak 4	7.12
Peak 5	19.0
Peak 6	3.98
Region A	14.62
Region B	3.12
Region C	13.0
Region D	2.23
Region E	7.47

Quantitative batch to batch analysis

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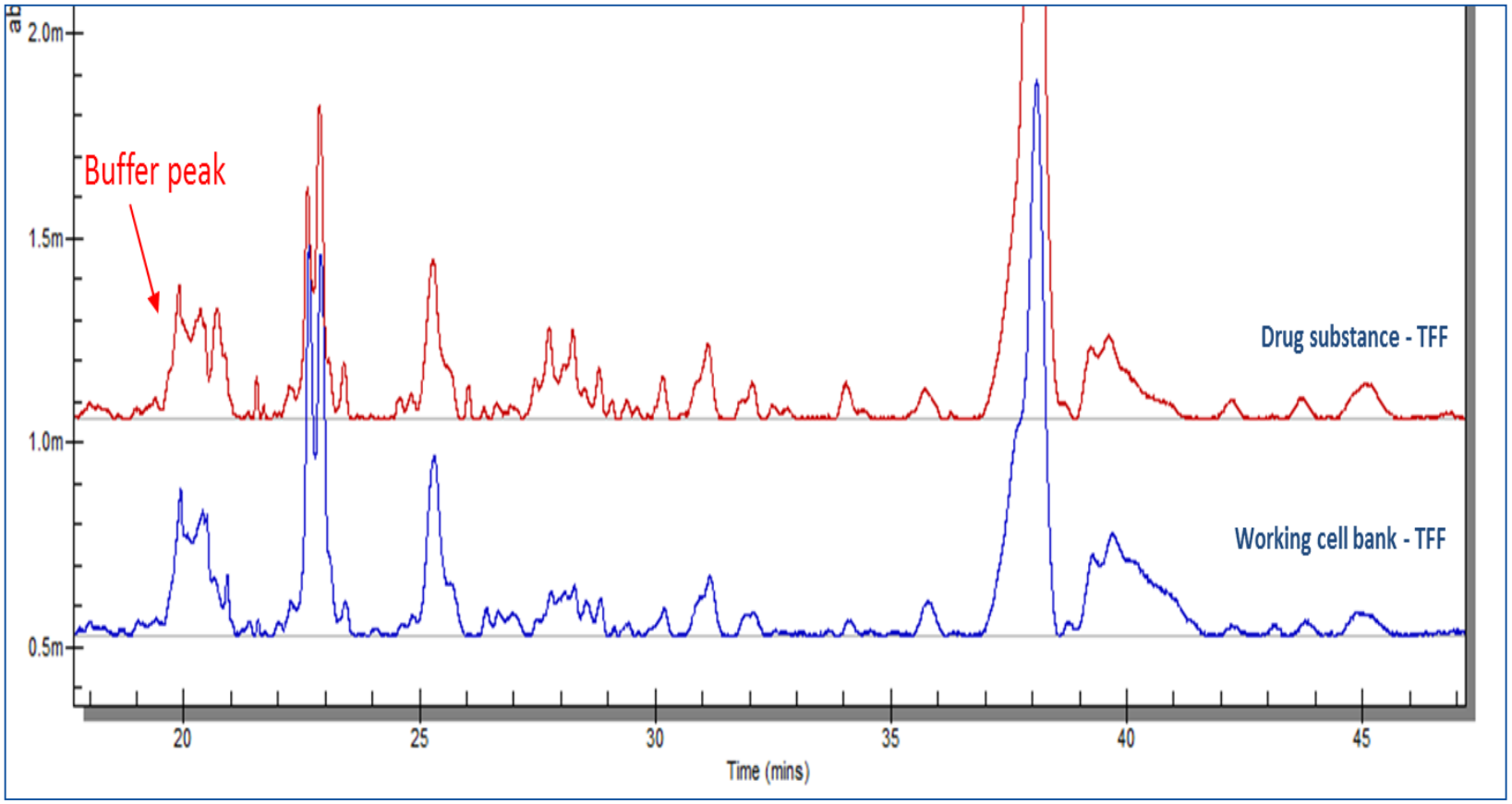
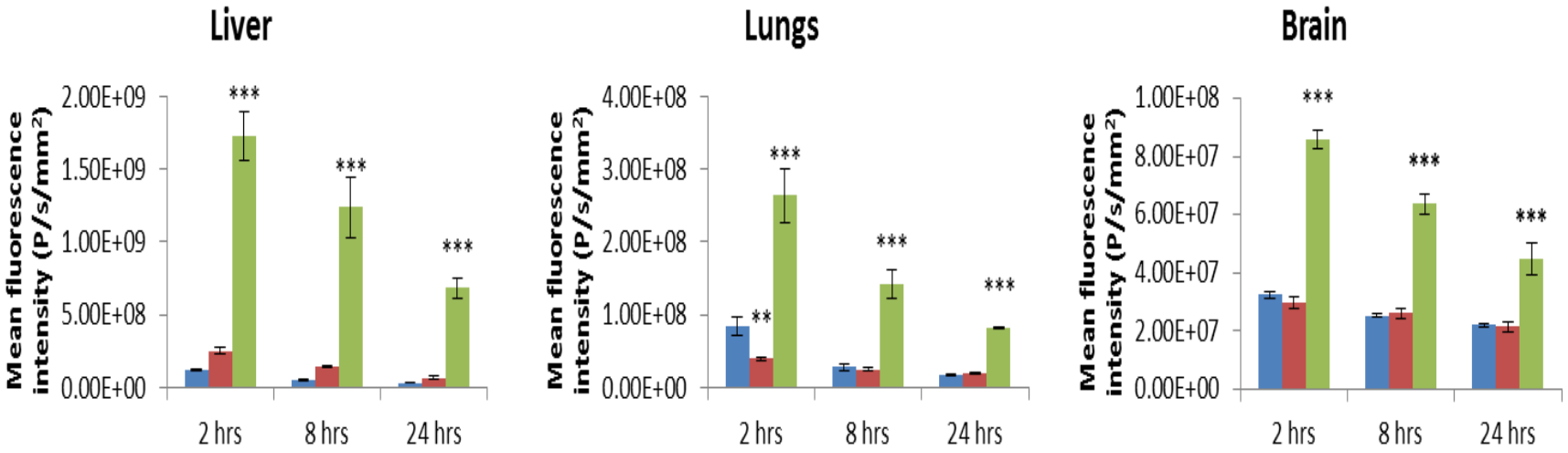
Consistent proteomic profile throughout the manufacturing process



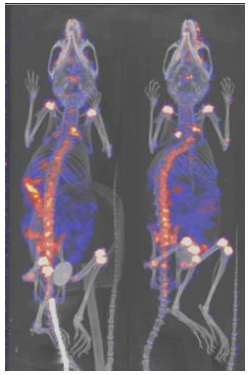
Established analytics

Characteristic	Assay	Test	Specification – ExoPr0
Purity			
Vesicle no. and Size distribution	**Established**	NTA (30-200nm)	Mode particle size 100±25nm
Protein content	**Established**	A280	10^8 vesicles/µg protein
Identity			
Surface markers	**Established**	ELISA (CD63, 81, 9)	CD81>CD63>CD9
miRNA profile	NGS (**Established**) QPCR modification (in development)	PCR	Presence of specific miRNA
Proteomic fingerprint	**Established**	Capillary Electrophoresis (relative abundance)	Peak 1 – TBD Peak 2 – TBD Peak 5 - TBD
Potency			
Potency	**Established**	U373 cell migration	>50% reduction in cell migration @24hrs
FIO			
Visualisation	**Established**	Cryo-TEM	Particle size 20-250nm

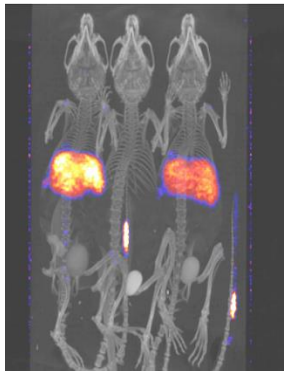
Specific tissue tropism



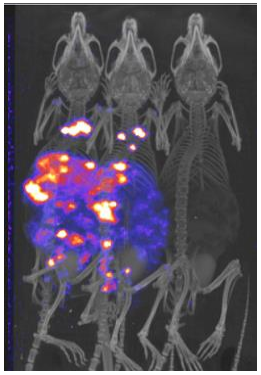
ExoPr0 crosses the blood-brain barrier



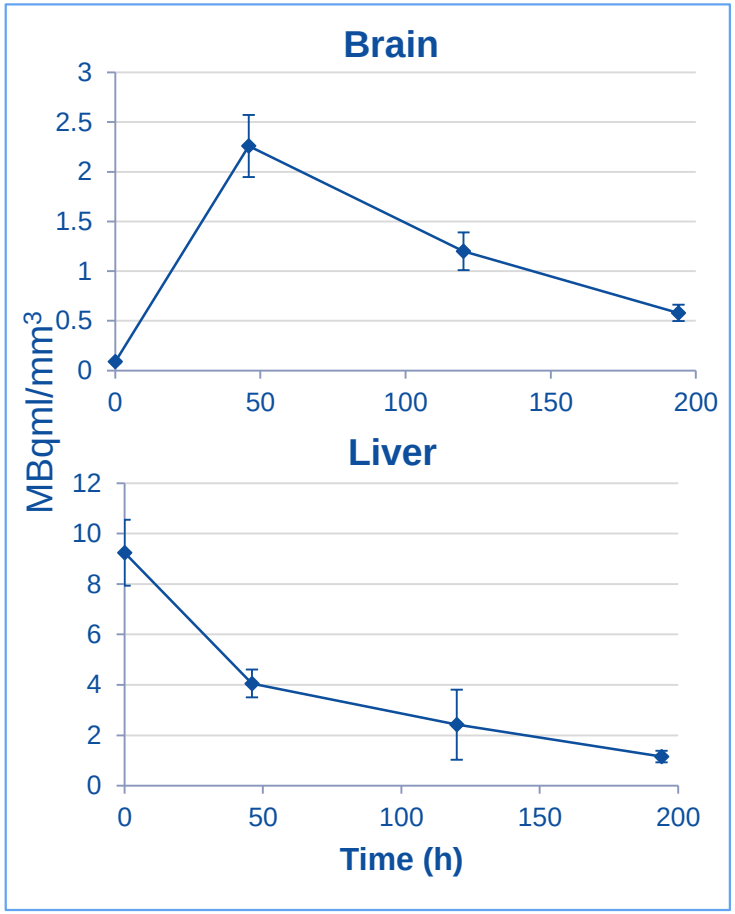
Free ^{89}Zr Control
i.p.
50 hours
post-dose



^{89}Zr-labelled ExoPr0
i.v.
48 hours
post-dose



^{89}Zr-labelled ExoPr0
i.p.
48 hours
post-dose

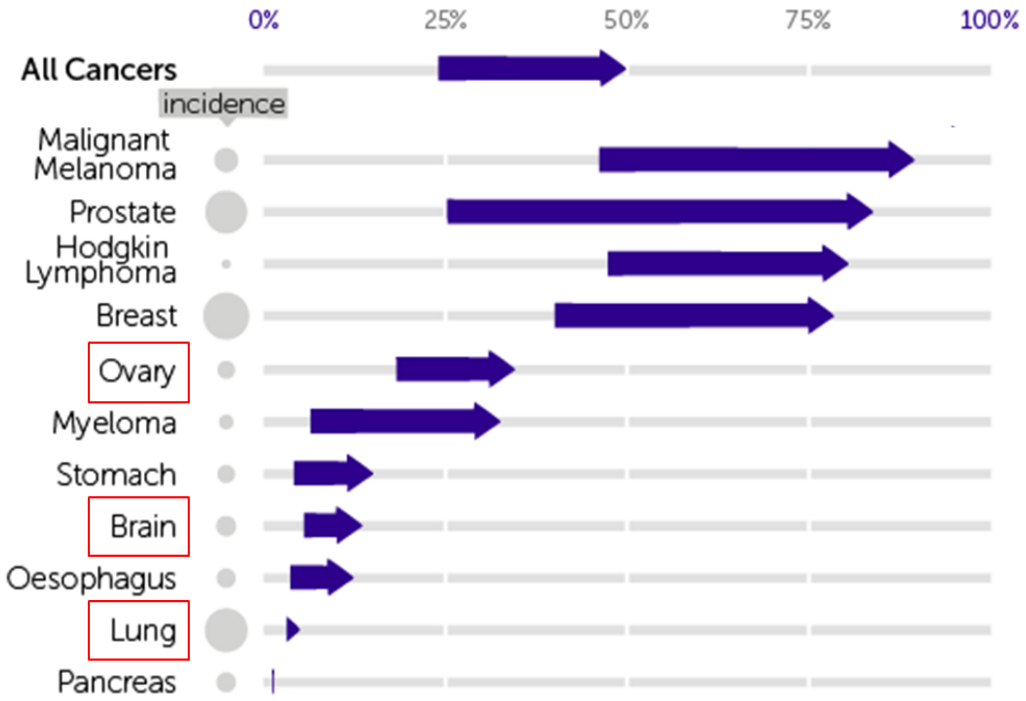


^{89}Zr conjugation to ExoPr0 exosomes using Zr-Oxine internalisation method

Unmet medical need in cancer

World-wide:

14.1 million new cases per year
8.2 million deaths per year
Projected to increase 68% by 2030



Changes in 10 year survival, 1971-72 to 2010-11

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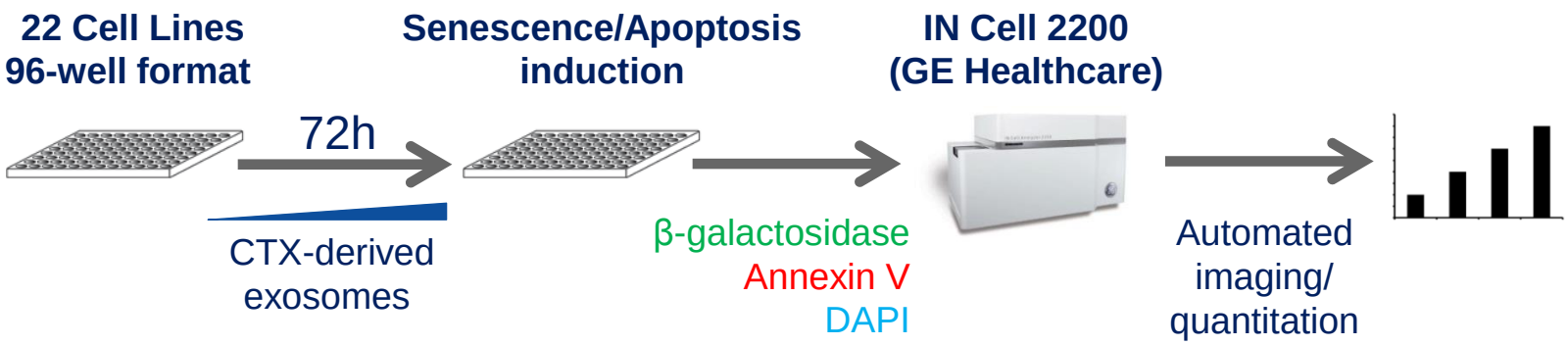
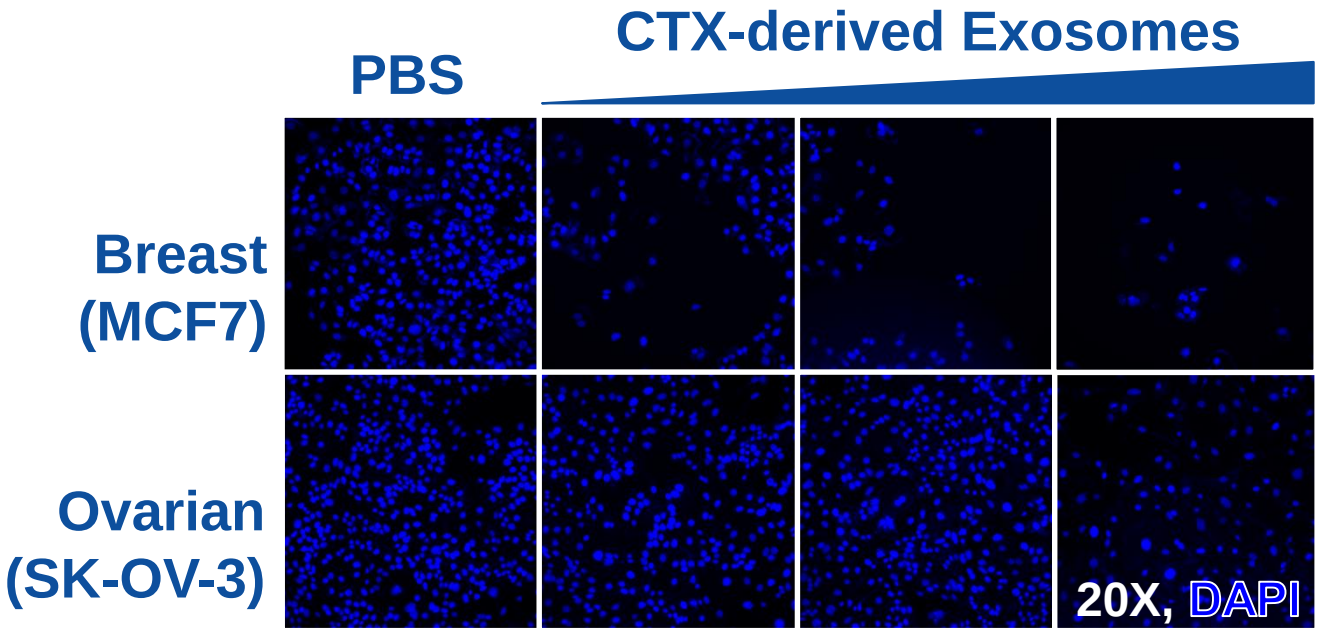
Source/Credit: Cancer Research UK CancerStats

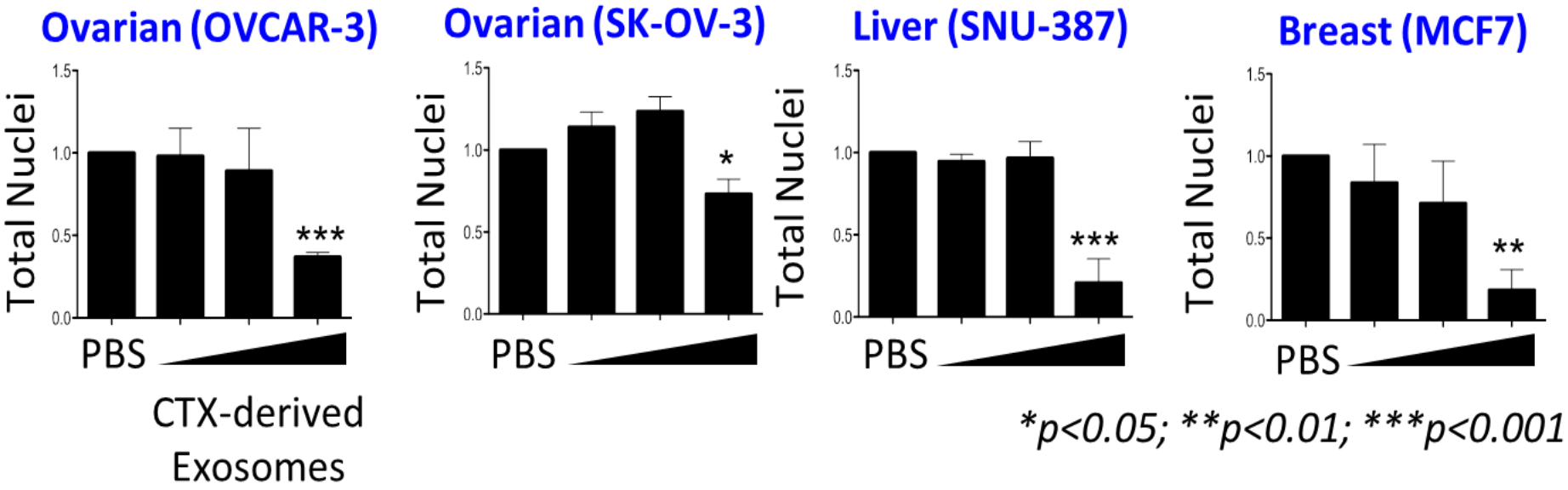
Cancer Cell Line Screen



ExoPr0 inhibits proliferation of diverse cancer cell lines



ExoPr0 inhibits proliferation of diverse cancer cell lines



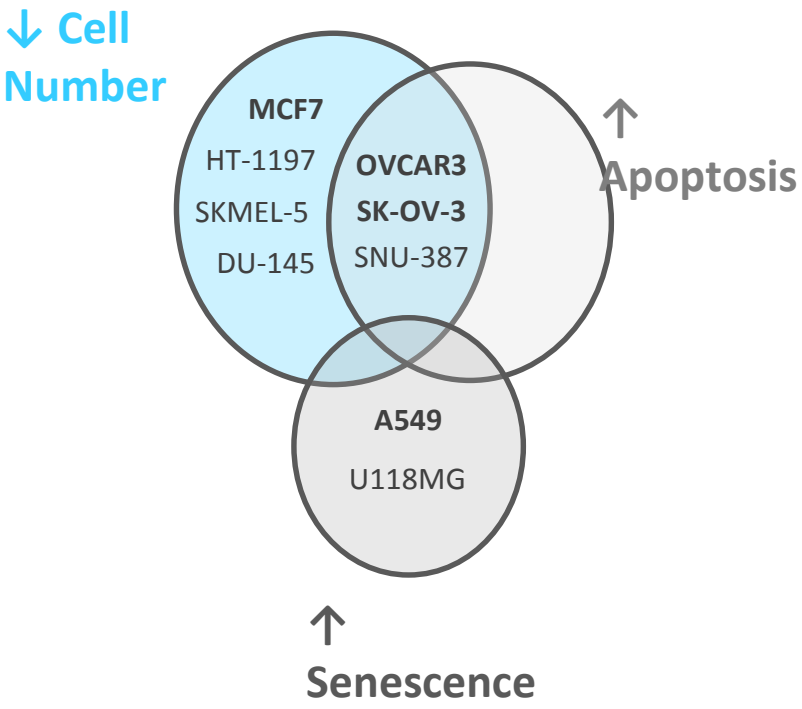
*p<0.05; **p<0.01; ***p<0.001

Anti-cancer activity through apoptosis and/or senescence

In total, 9 of 22 cancer cell lines screened showed a response to treatment with ExoPr0

- Induction of senescence and apoptosis was observed in discrete cell lines

Responder cell lines are derived from diverse tumour types with varied mutational spectra



ExoPr0 Pivotal Preclinical Study

6-arm study in 5 xenograft models, cohorts of n=15

A549 – Lung

U87 - Glioma

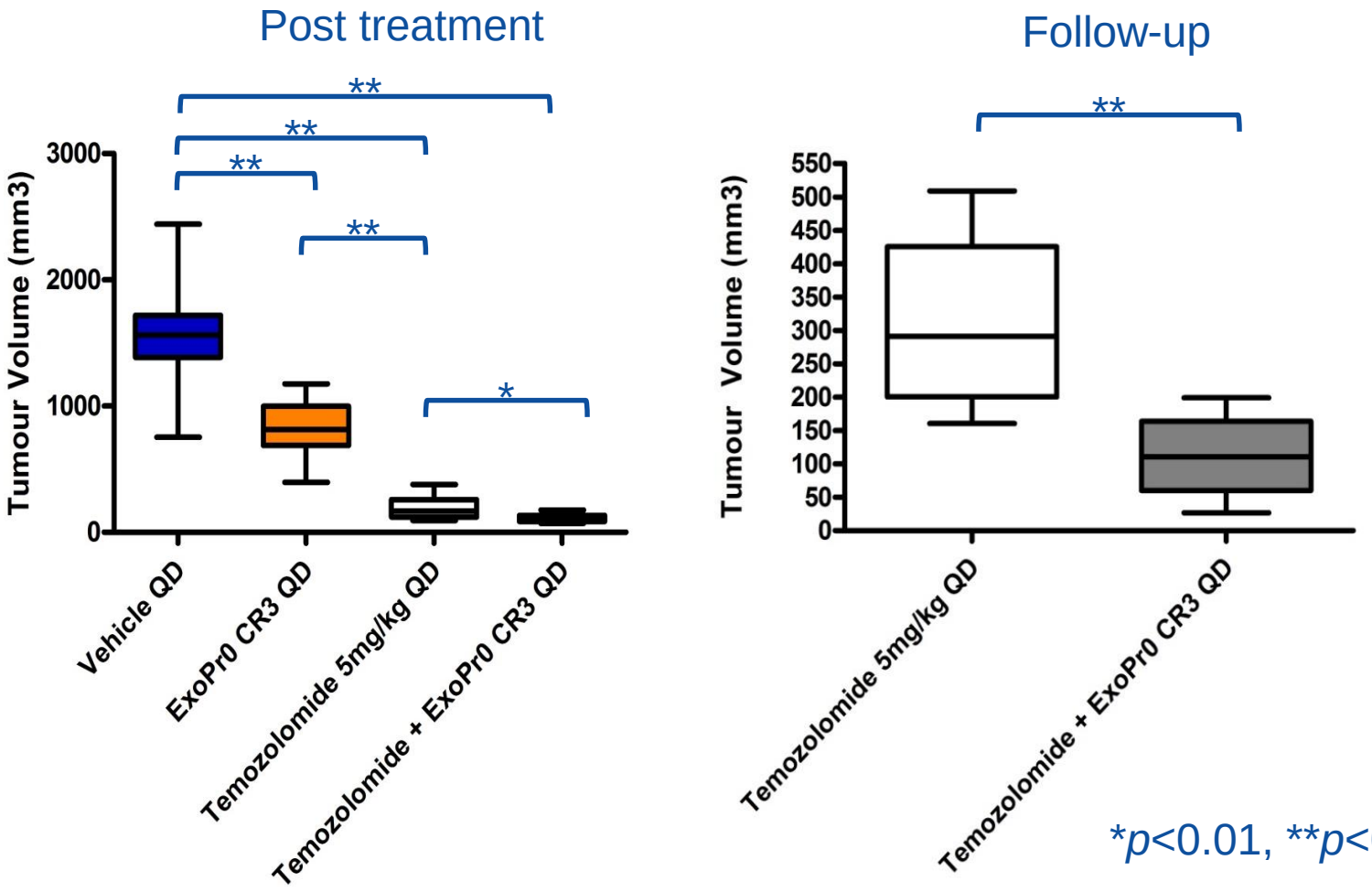
OVCAR3 - Ovarian

MCF7 - Breast

SKOV-3 - Ovarian

- Intra-tumoural injection
- Daily and weekly dosing schedules
- Single-agent ExoPr0 and in combination with standard-of-care (Temozolomide or Paclitaxel)

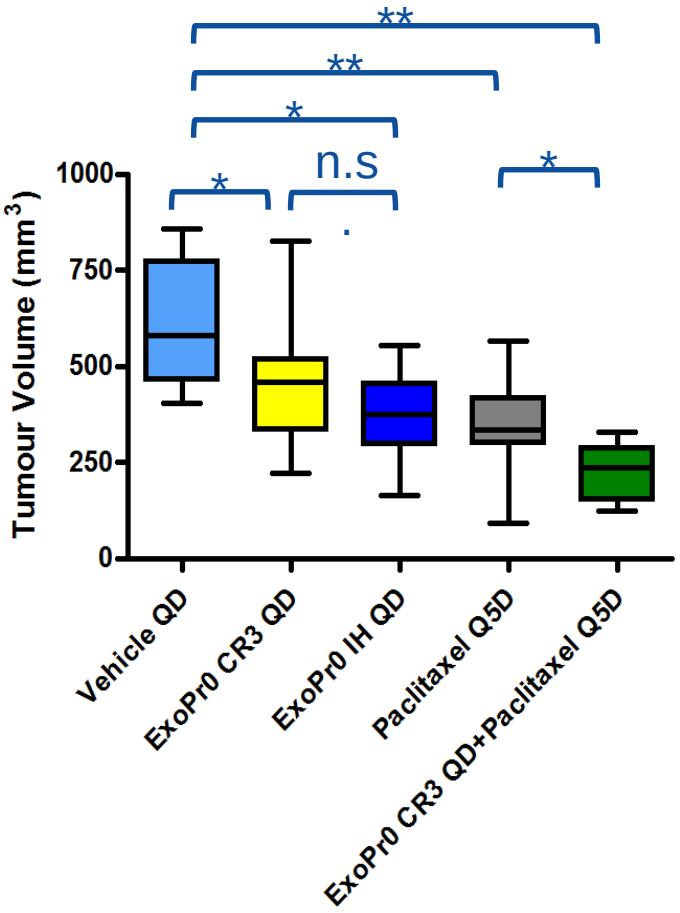
ExoPr0 inhibits tumour growth in a xenograft mouse model of GBM



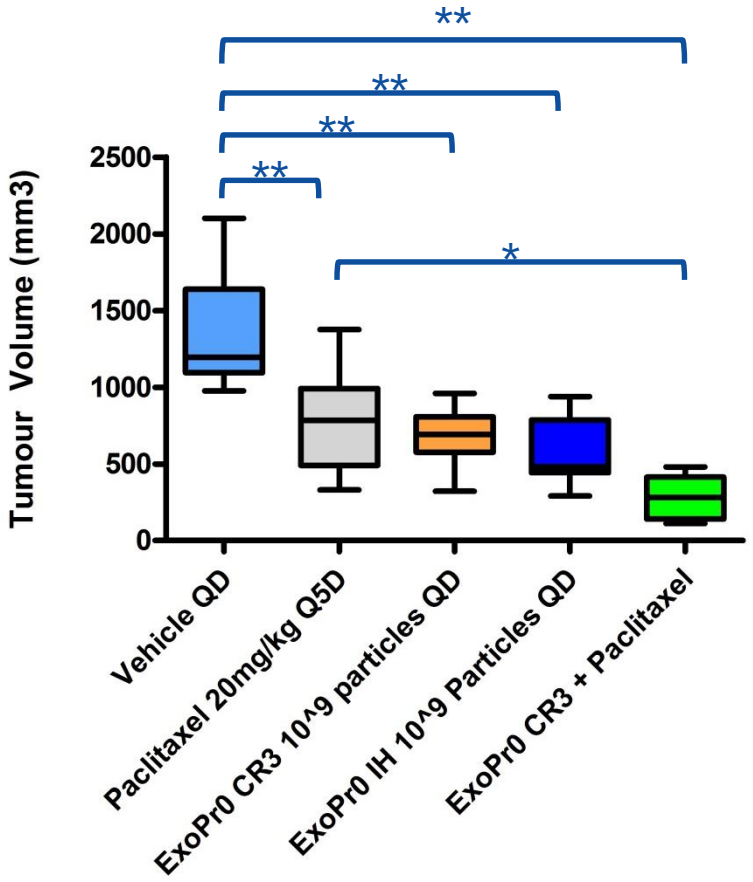
*p<0.01, **p<0.001

ExoPr0 inhibits tumour growth in a xenograft mouse model of lung cancer

Post treatment



Follow-up



In vivo summary

- **Anti-proliferative** effects observed with the administration of ExoPr0 in diverse cancer models
- Effects of ExoPr0 is **consistent** throughout the treatment groups
- 2 separate batches of ExoPr0 induced the same significant anti-proliferative effect and supports **batch to batch consistency**
- **Additive effect** of ExoPr0 when administered in combination with standard of care
- ExoPr0 induces a **sustained anti-proliferative effect** after treatment has stopped

Platform expansion

- Growing body of evidence suggests that exosomes could be a valuable delivery vehicle for therapeutic DNA, RNA and protein
  - LNPs (lipid nanoparticles) are currently the most advanced delivery system, but:
  - Precise mechanism underlying LNP delivery not yet understood
  - Low efficiency (>90% degraded in lysosomes)
  - Significant inflammatory response

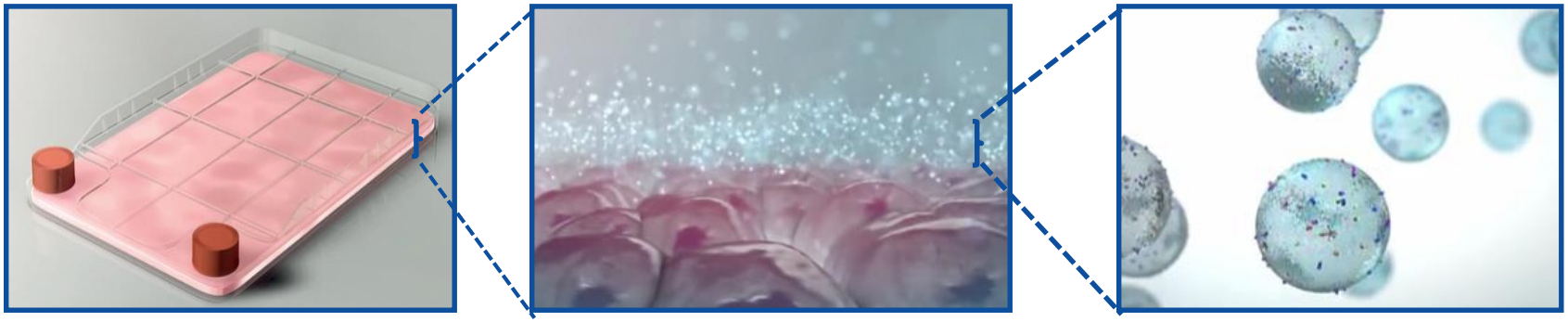
- Opportunity to exploit the ExoPr0 platform to deliver a variety of therapeutics
  - mRNA
  - miRNA/siRNA
  - Antibodies
  - Small molecules

Next-Generation Exosome Products

Endogenous CTX Exosomes

Bespoke CTX Exosomes

CTX Exosomes delivery platform



Culture Conditions

- Modification of e.g.
  - growth medium
  - formulation,
  - environmental culture conditions

Producer Cells

- Directed expression and trafficking of desirable exosome cargoes

Extracted exosomes

- Surface modification e.g.
  - targeting ligands
- Post-production loading of exogenous cargoes e.g.
  - siRNAs
  - proteins,
  - small-molecule inhibitors
  - chemotherapeutics

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Conclusion

- Consistent and scalable exosome producer cell line using conditional Immortalisation
- Product based on defined manufacturing process (USP and DSP)
- Established analytical package for in-process controls and batch to batch consistency
- Rapid POC due to established GMP process
- ExoPr0 demonstrates broad anti-cancer properties
- Favourable distribution across the BBB and distinct distribution profile based on route-of-administration
- Scope to tailor ExoPr0 to specific targets via loading of exogenous nucleic acids

ReNeuron

Q&A session

Richard Beckman, MD

Chief Medical Officer