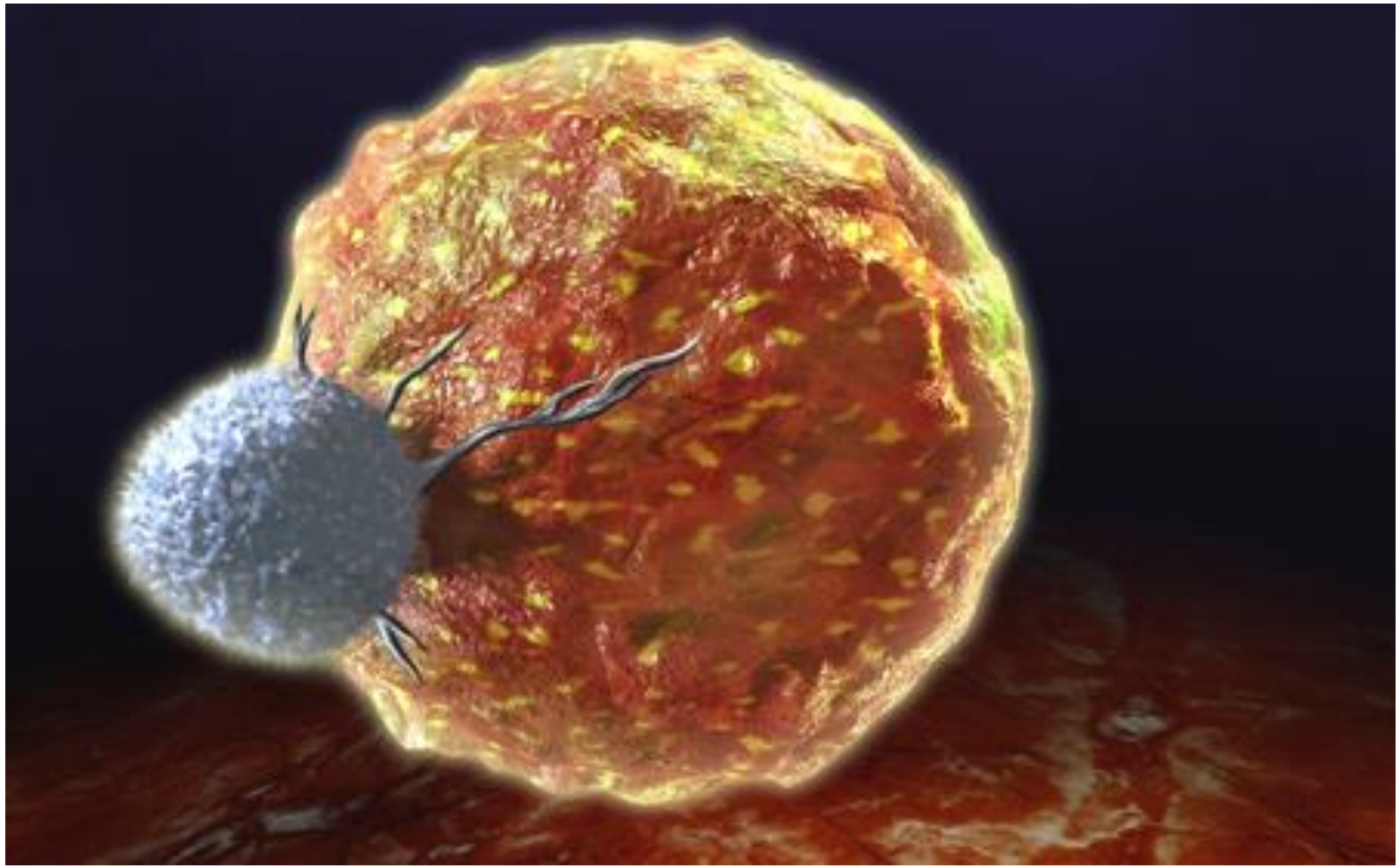
KU LEUVEN

Immuno oncology *in vitro* assays

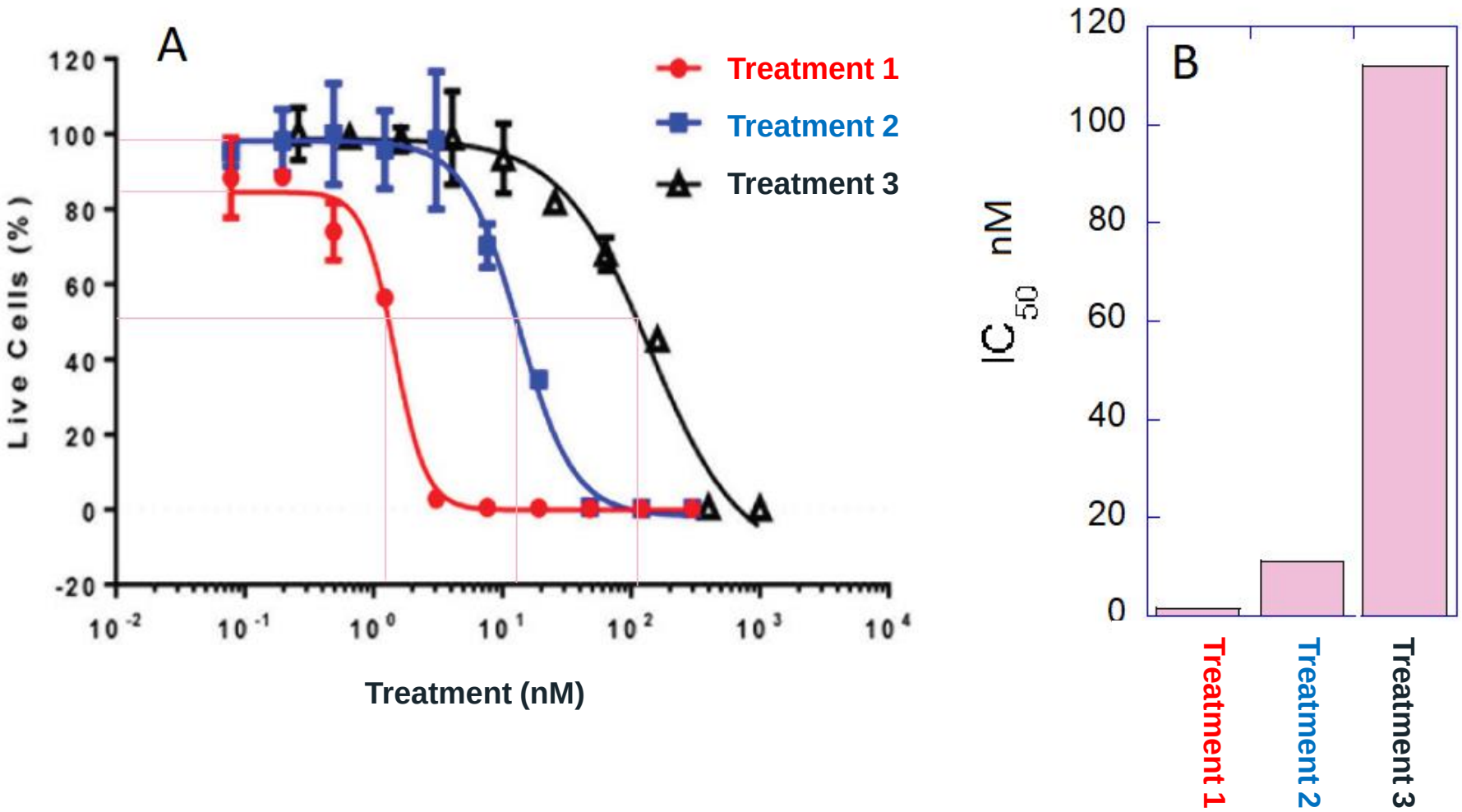
Dr. Bart Landuyt

Functional Genomics & Proteomics

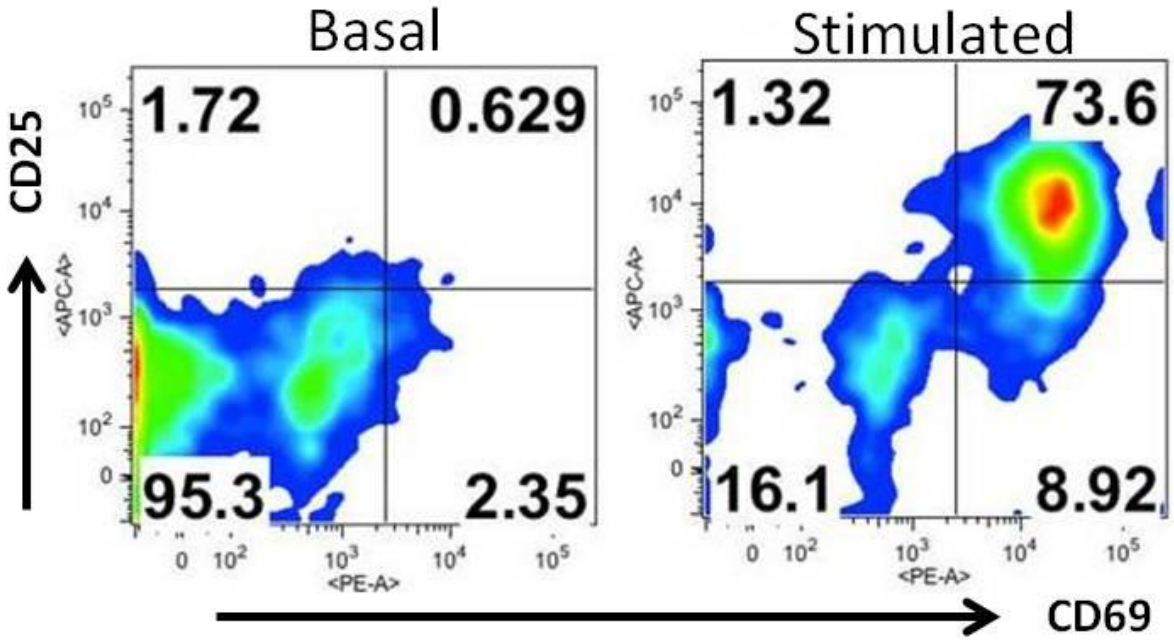
Immuno oncology

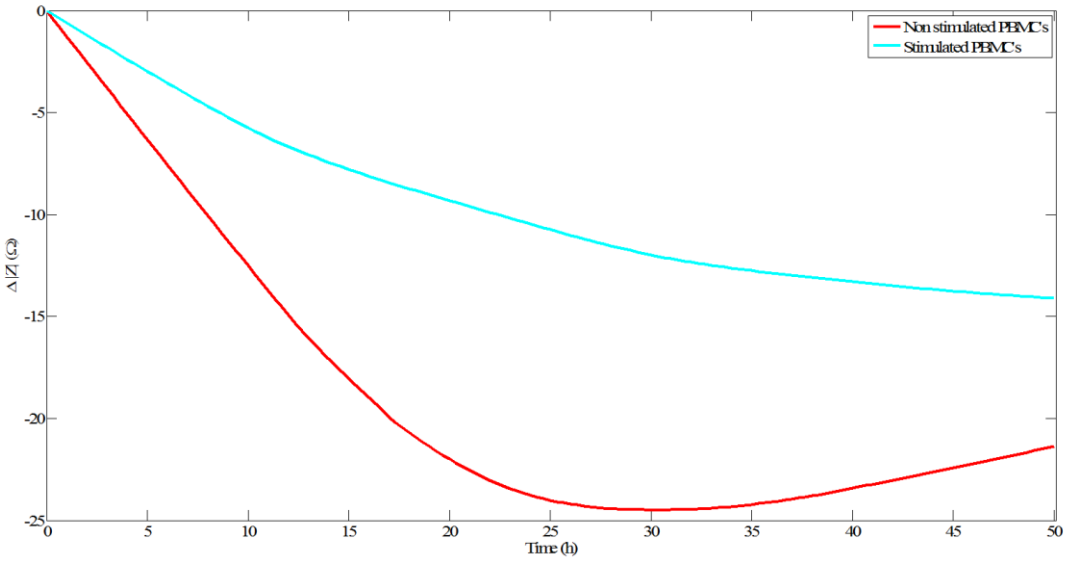


Tumor cell killing by CTLs



CTL activation





Contact

bart.landuyt@kuleuven.be

Functional Genomics & Proteomics

Naamsestraat 59

3000 Leuven

KU LEUVEN

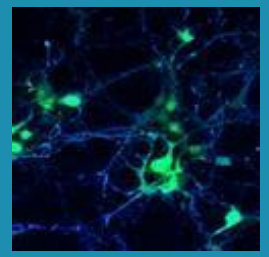
KU LEUVEN

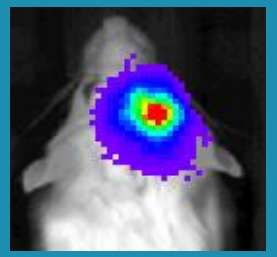
Pre-clinical models for Parkinson's disease drug discovery

The Baekelandt Lab – KU Leuven

Veronique Daniëls, PhD

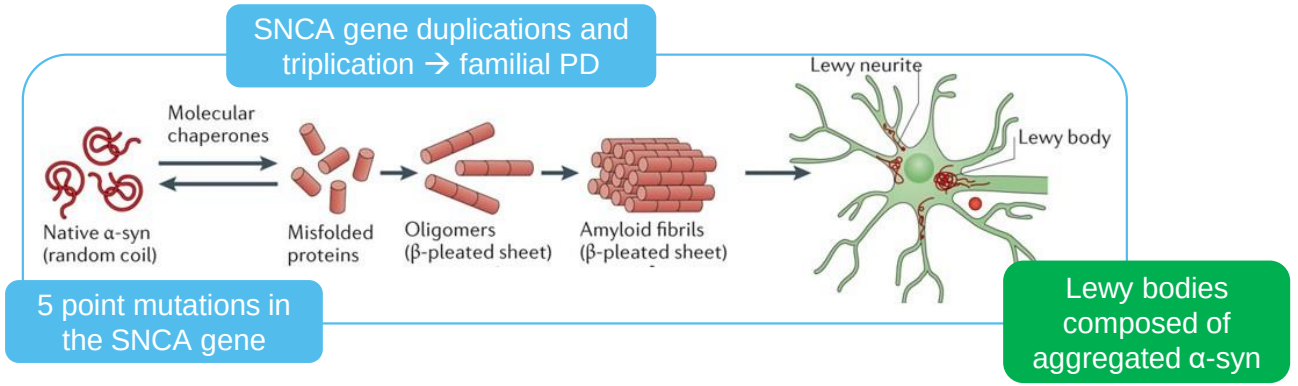
Laboratory for neurobiology and gene therapy





α-synuclein based models for Parkinson's disease (PD)

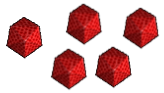
α-synuclein, a gentically validated target for PD



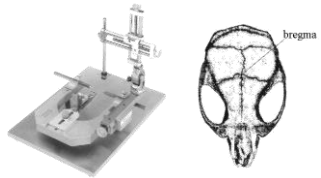
Rodent α-synuclein based PD models: robust & validated

α-synuclein overexpression using **rAAV vectors**

LVVC
Leuven Viral Vector Core



rAAV2/7 CMVie-Synapsin1-α-syn
(wt or A53T)



Stereotactic injection
(rat or mouse brain)

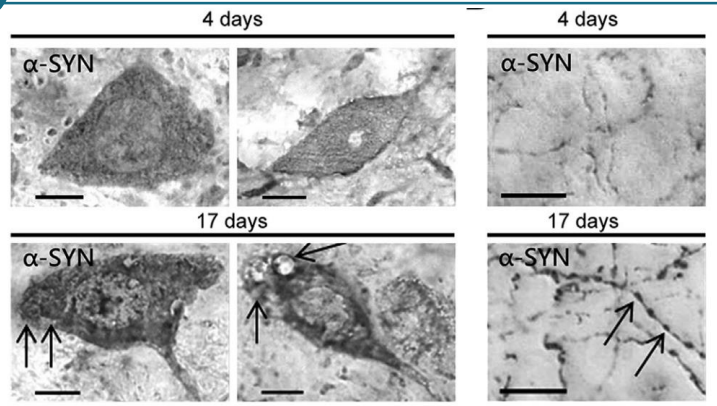
1. α-synuclein aggregation
2. Neurotoxicity
3. Behavioural deficits

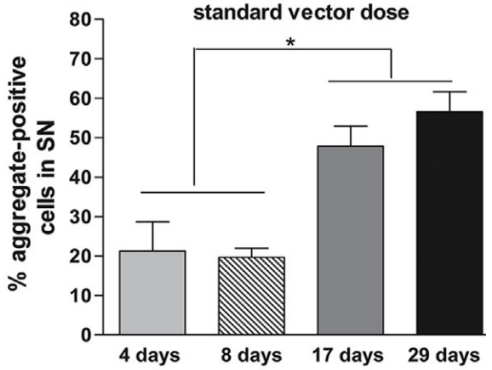
KU LEUVEN

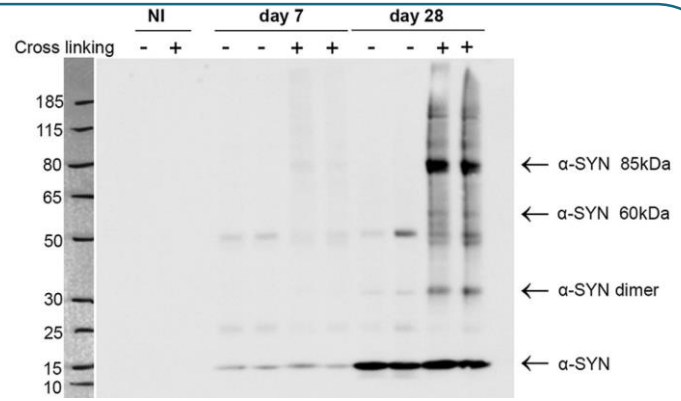
Rodent models for Parkinson's disease

1 α-synuclein aggregation

Van der Perren A., *et al.* NBA 2015

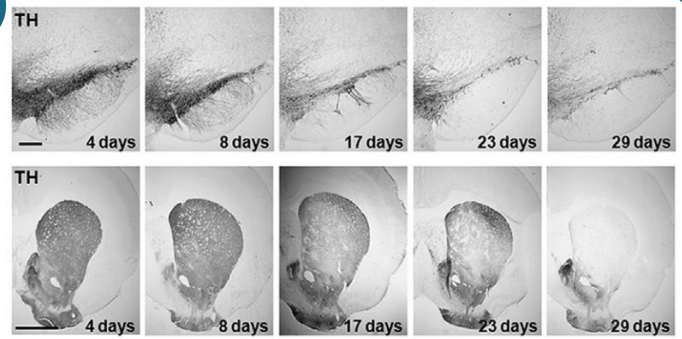


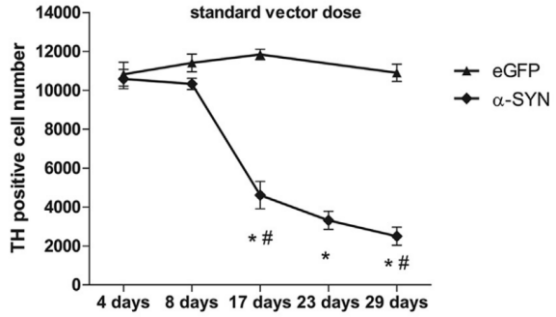




Neurotoxicity – dopamingergic cell death

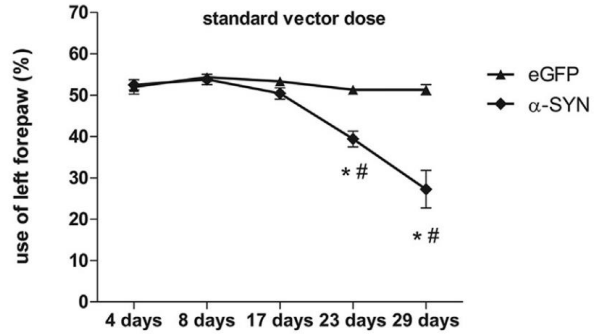
2





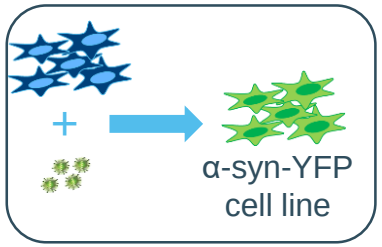
Behavioural deficits

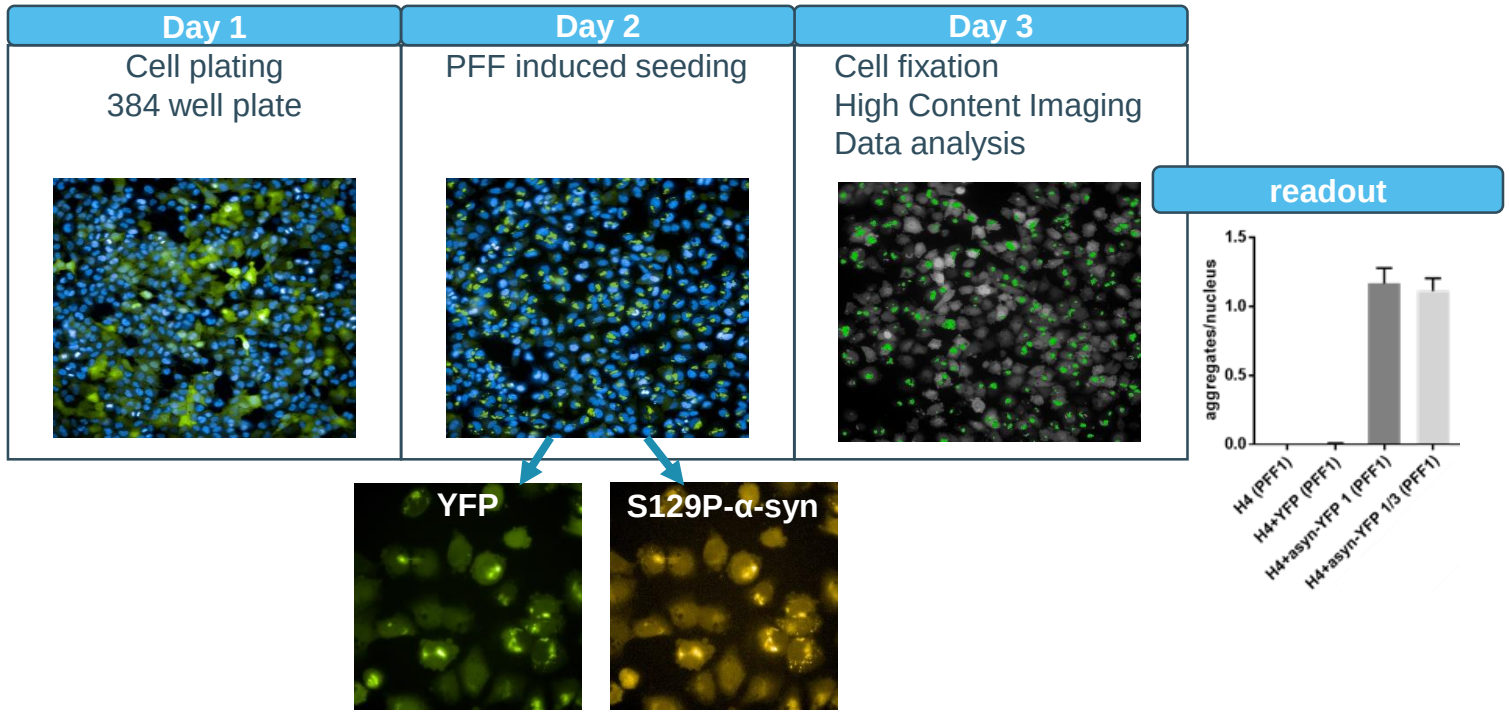
3



Cellular model for Parkinson's disease

Induction of α-synuclein aggregates in neuroglioma cells





Access our PD models:

1. Fee-4-Service or Research collaboration (Baekelandt lab)
2. Obtain our AAV2/7-α-synuclein vectors through the LVVC

www.lvvc.be www.parkinsonresearch.be

veronique.daniels@kuleuven.be.be

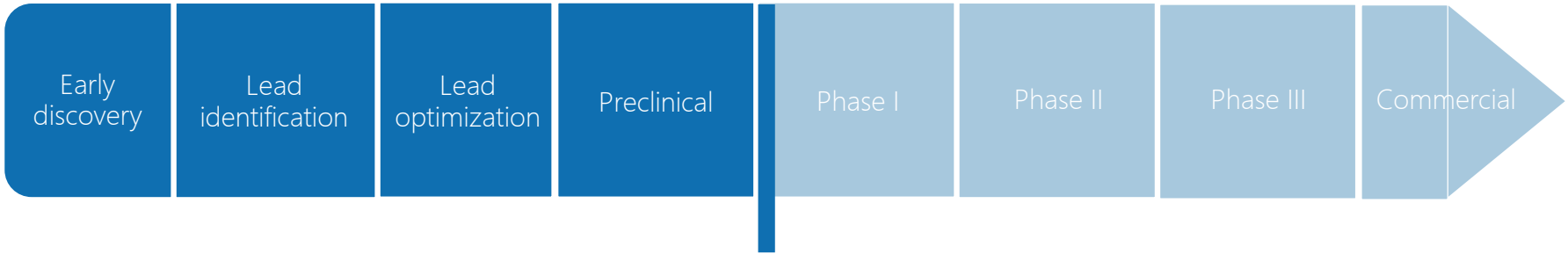
KU LEUVEN

Zebrafish platform for toxicity assessment and neuroactive drug discovery

Annelii Ny
Laboratory for Molecular Biodiscovery

KU LEUVEN

Problem



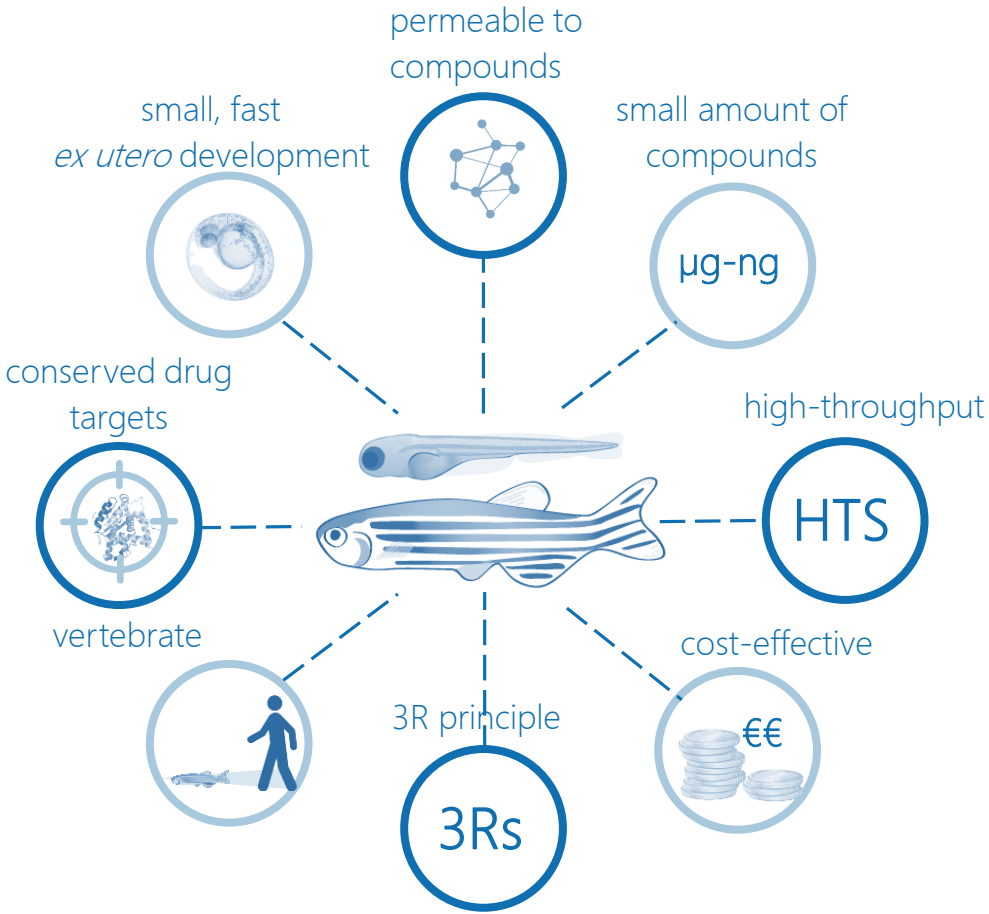
90% of drug candidates that enter clinical trials

fail

Toxicity

Lack of **efficacy**

Solution


permeable to compounds
small, fast *ex utero* development
small amount of compounds
µg-ng
conserved drug targets
high-throughput
HTS
vertebrate
cost-effective
€€
3R principle
3Rs

Toxicity

General morphology

- normal morphology

- abnormal morphology

heart edema

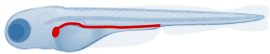
curved tail

Organ specific assays

- hepatotoxicity

- neurotoxicity

- nephrotoxicity



International Journal of Molecular Sciences

MDPI

Article

Cell Imaging Counting as a Novel Ex Vivo Approach for Investigating Drug-Induced Hepatotoxicity in Zebrafish Larvae

Xuan-Bac Nguyen [1,†], Stanislav Kislyuk [2,†], Duc-Hung Pham [1], Angela Kecskés [1], Jan Maes [1], Deirdre Cabooter [2], Pieter Annaert [3], Peter De Witte [1,*] and Annelii Ny [1]

janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Functional assays

- cardiac function
- kidney filtration rate
- whole brain activity

improve safety of drug leads, decreased risk of late phase attrition

Neuroactive drug discovery

Drug discovery

Epilepsy models

- 4 chemical
- 1 mechanical
- 5 genetic

- PCT/EP2018/073147
- PCT/EP2018/073149
- PCT/EP2018/073159

Target validation

- CRISPR/Cas9
- morpholino

ucb Zogenix

Functional assays

- locomotor assay
- epileptic activity (EEG)
- whole brain activity (neuroluminescence)
- social behavior

epilepsy drug candidates with improved efficacy and *in vivo* translatability

annelii.ny@kuleuven.be

Low-cost pose estimation for rehabilitation

March 19, 2019

BiR&D Industry Meets University

Fons De Mey (fons.demey@uantwerpen.be)

Jan Steckel (jan.steckel@uantwerpen.be)

Pose estimation = Motion Capturing

Available solutions

- ☺ High accuracy
- ☺ High precision

- ☹ Very expensive (Installation & Maintenance)
- ☹ Fixed Installation
- ☹ Normal gait assumptions
- ☹ Limited Availability

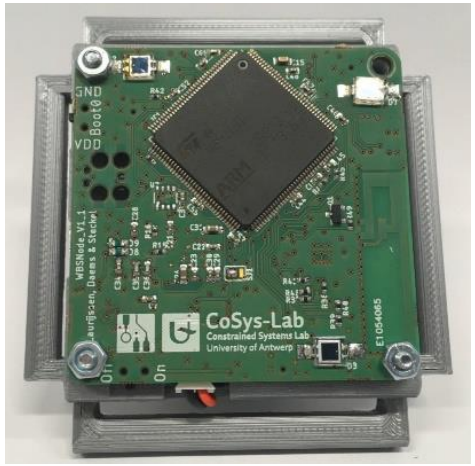
- ☺ Low cost
- ☺ Widely available
- ☺ Plug-and-play

- ☹ Low accuracy
- ☹ Low precision

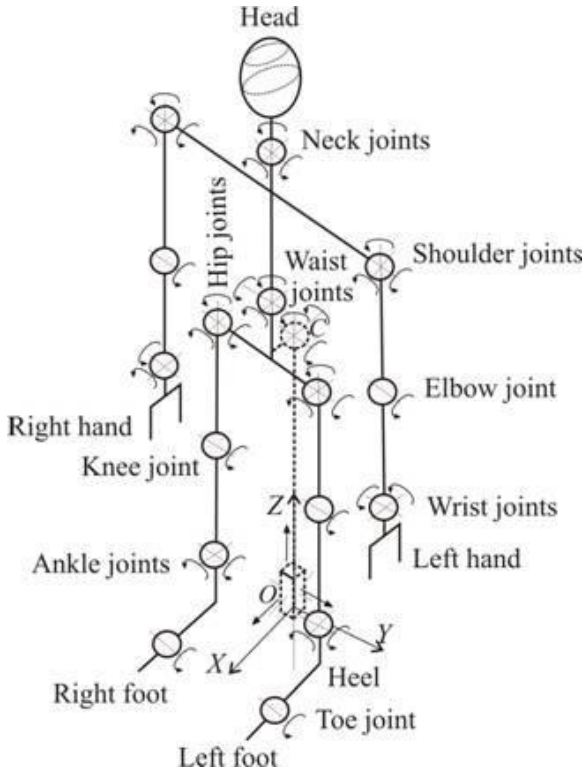
Our solution

Probabilistic Sensor Fusion

WBSN



Kinematic Chain



Advantages

- ☺ Low cost
- ☺ High accuracy
- ☺ High precision
- ☺ Widely available

Available for kinesitherapists for whom installation of a high-end motion lab is not viable

The ELIDOT Platform

The alliance between Immunodot and ELISA technologies

ELISA	*IMMUNODOT*
+ Automatisable	*Multiplexin*
+ Well adapted to high-throughput laboratories	*Flexible design*
- Only one biomarker per plate	*Not fully automated*
- Poor flexibility	*Adapted for small and medium-sized laboratories*

ELIDOT

+ Automatisable
+ Well adapted to high-throughput laboratories
+ Multiplexing
+ Flexible design

We Apply Science

Wallonie

Solution

Antigens are first coated onto the nitrocellulose membrane (Fig. n°1). The membrane can even be printed for alphanumerical recognition. Then, the strips are fixed into the 96-well plate (Fig. n°2).

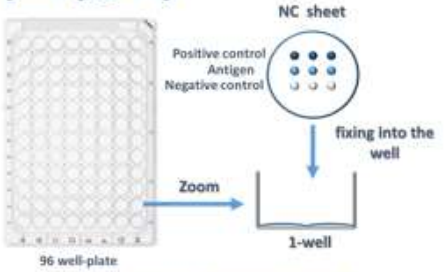
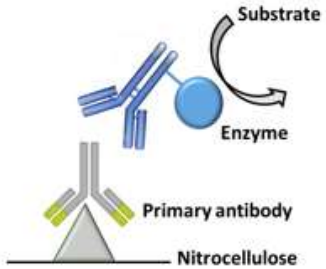


Fig. n°1: step representation of the ELIDOT platform

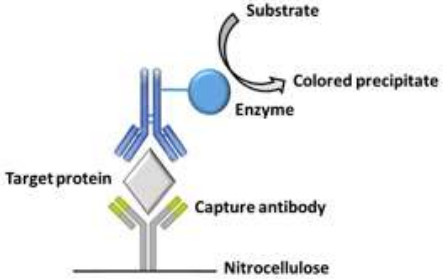
Fig. n°2: ELIDOT plate

EIA test

Indirect assay



Capture assay « Sandwich »



Interpretation system

Reading system

Fig. n°3: CL-reader

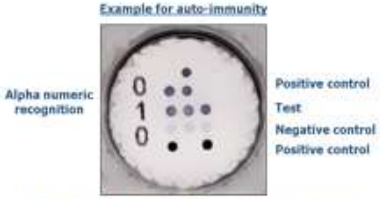


Fig. n°4: Detection of autoantibodies

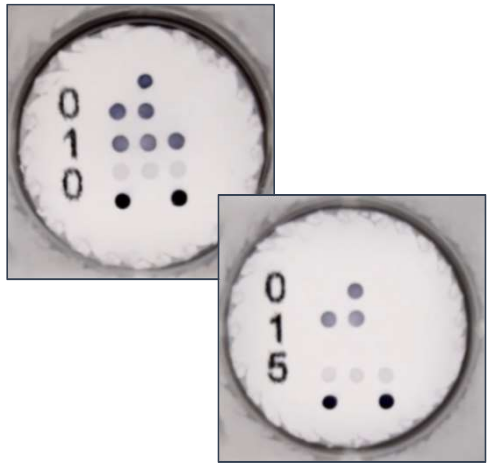
Software

- Flexible
- Customized
- Full traceability
- Quantitative or Semi-quantitative

The ELIDOT Platform

Key characteristics

- Multiplexing on nitrocellulose
- Up 25 parameters in duplicate
- Up to 96 patients tested per run
- Fully automated test procedure
- Sample volume needed: 10µl
- Processing time: min. 1h30
- Innovative and rapid drying plate process in less than 10 minutes
- Flexible interpretation software incorporated into the reader



Unique features and benefits

- Flexible
- Rapid
- Compatible with ELISA automates
- Full traceability
- Multiplexing
- Quantitative (standard curve)
- Breakable wells (12x8)

Wallonie

We are currently looking for collaborations and new partners

- Extension to new applications
- Transferability studies

Contact :

QUINTING Birgit	b.quinting@helmo.be
BIEMAR Sandrine	s.biemar@helmo.be
	+32 4 220 16 39
	+32 4 349 03 45
AUTEM Benoit	bautem@d-tek.be
BODART Nicolas	nbodart@d-tek.be
	+32 65 84 18 88

The ELIDOT Platform

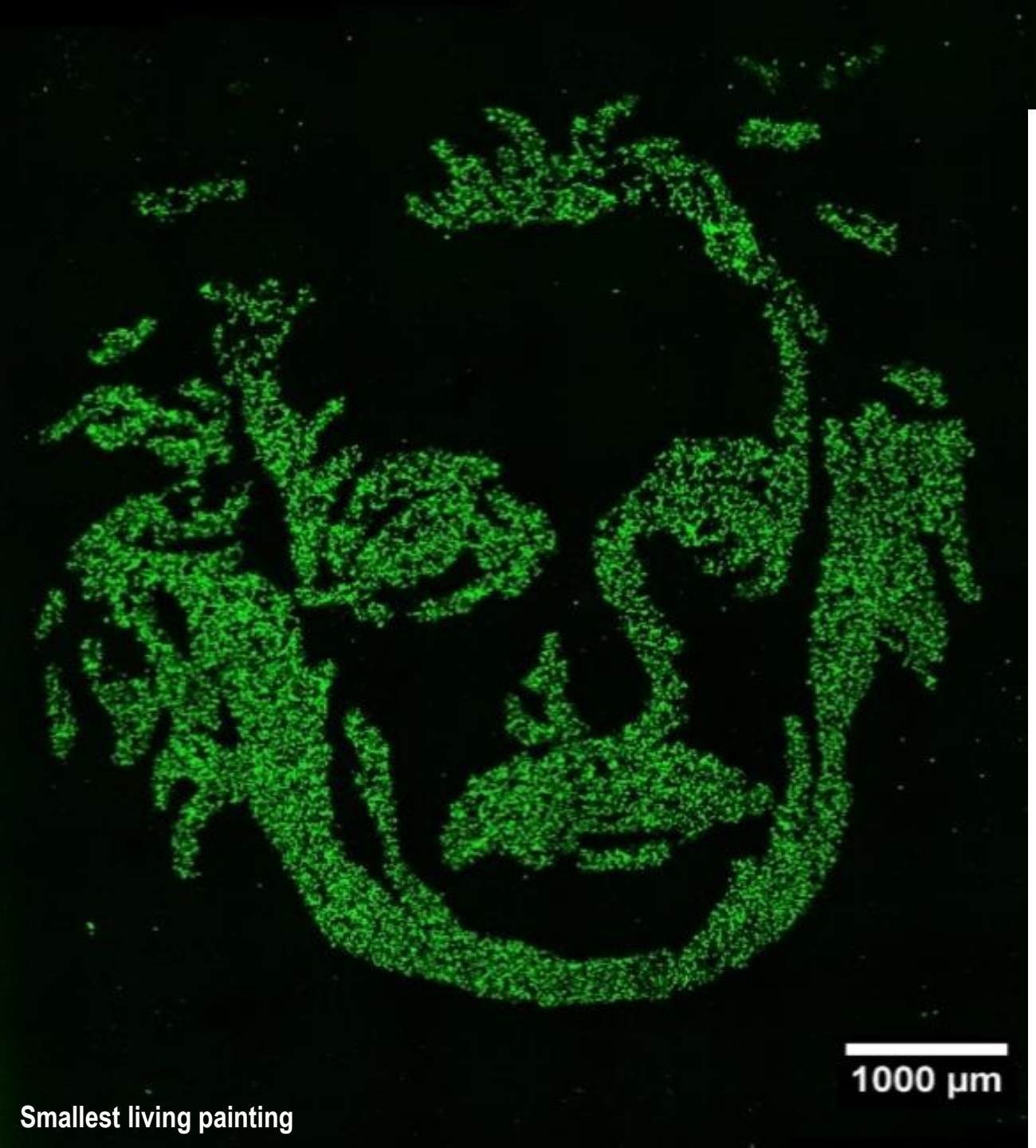
HELMO CRIG RECHERCHE - FORMATION CONTINUE

HELMO Haute Ecole Libre Mosane PARAMEDICAL

D-tek We Apply Science

SYNHERA

DGO 6 Wallonie



Smallest living painting

A Ghent University Spin-off project

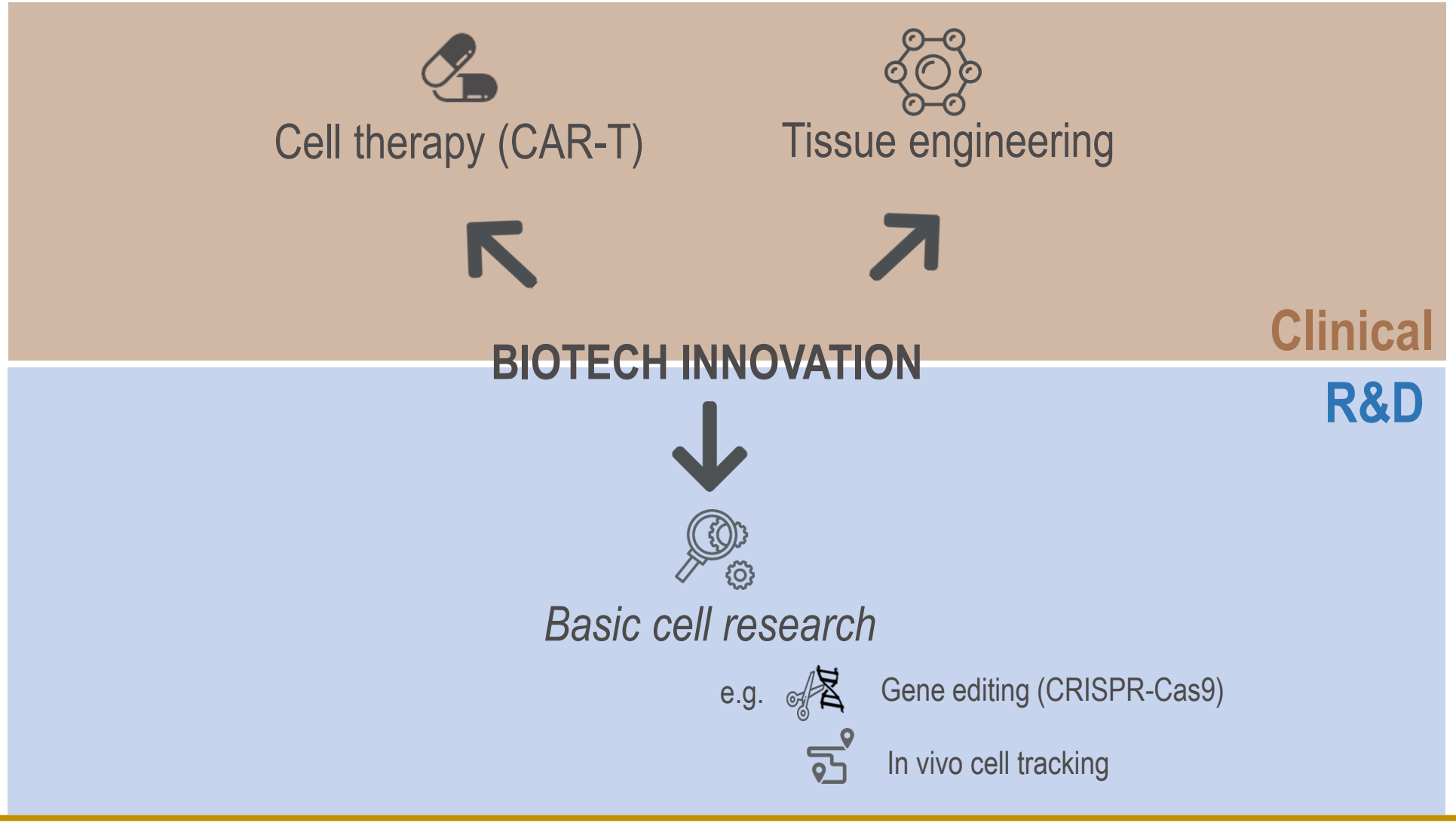
UNIVERSITEIT GENT

TRinCE

precision transfections

Allowing delivery of macromolecules into any cell with enhanced efficiency and unpreceded accuracy.

Biotech innovations result in new (clinical) markets



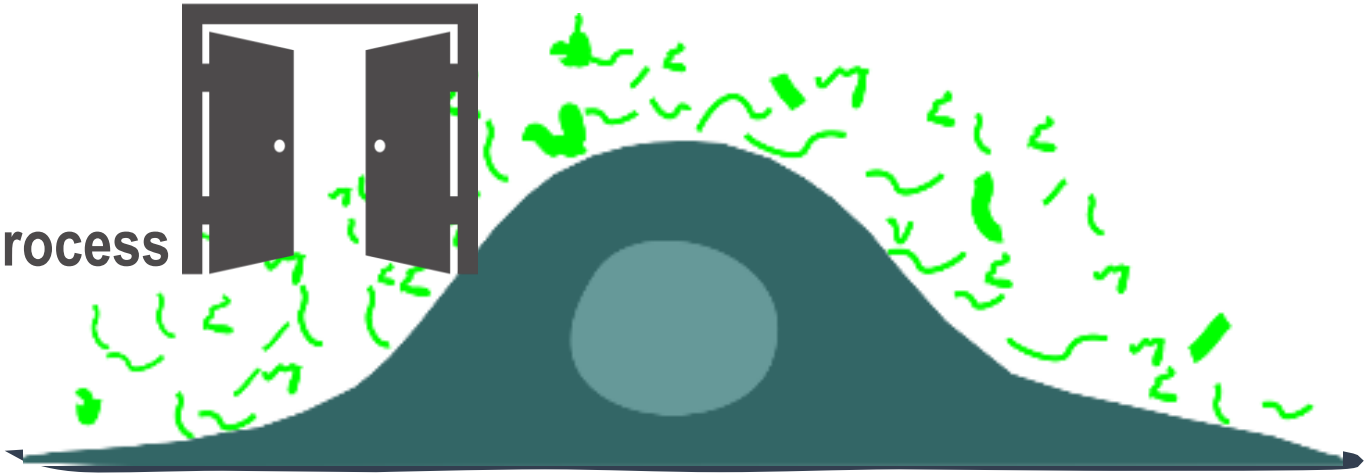
Biotech driven markets depend on adequate tools to deliver macromolecules into cells

Market need: overcome the cell membrane barrier

Basis = Modifying cells by introducing foreign materials

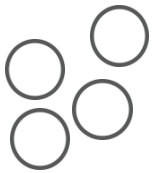
- Genetic content
- Peptides
- (labelled) Antibodies
- (targeted) Quatum Dots
- (labelled) Polymers

TRinCE™ facilitates this process



Current delivery technologies do not meet the requirements

Liposomes/Polysomes



Low efficiency

Limited cargo flexibility

Electroporation/Nucleofection

High toxicity

Extensive cell manipulation

Trends*

- Importance ↗ primary cells
- Versatility of cargo
- Miniaturisation (single cell)

Viral vectors

High cost, long development time

Safety concerns

Limited cargo flexibility

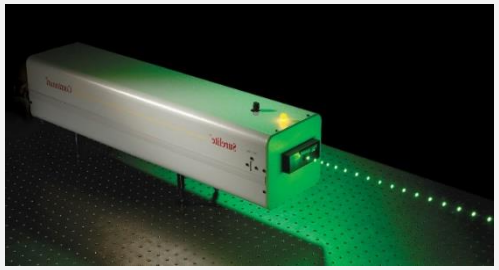
*Source: www.marketsandmarkets.com: Transfection reagents and equipment market – Analysis & Global forecast to 2021

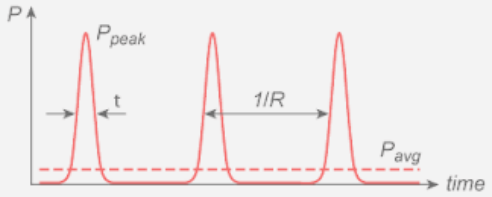
TRinCE™ provides an improved transfection platform

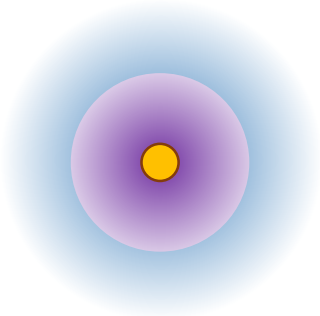
LumiPore™ platform

New technology to overcome the cell membrane based on a combination of photonics and nanoparticles

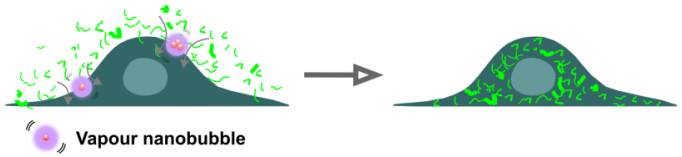
PULSED LASER LIGHT → MECHANICAL ENERGY (@ nano-scale) → MACROMOLECULE DELIVERY VIA PORES IN CELL MEMBRANE

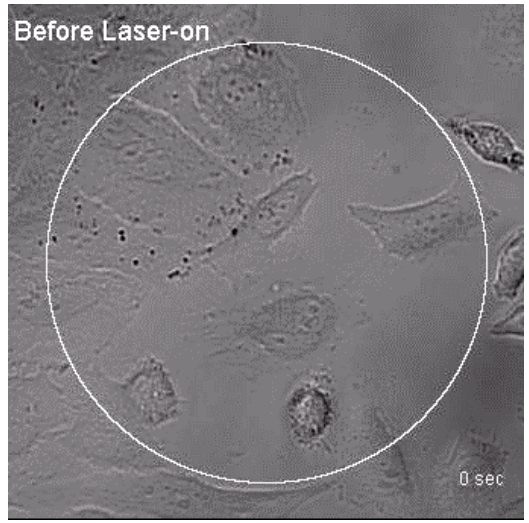




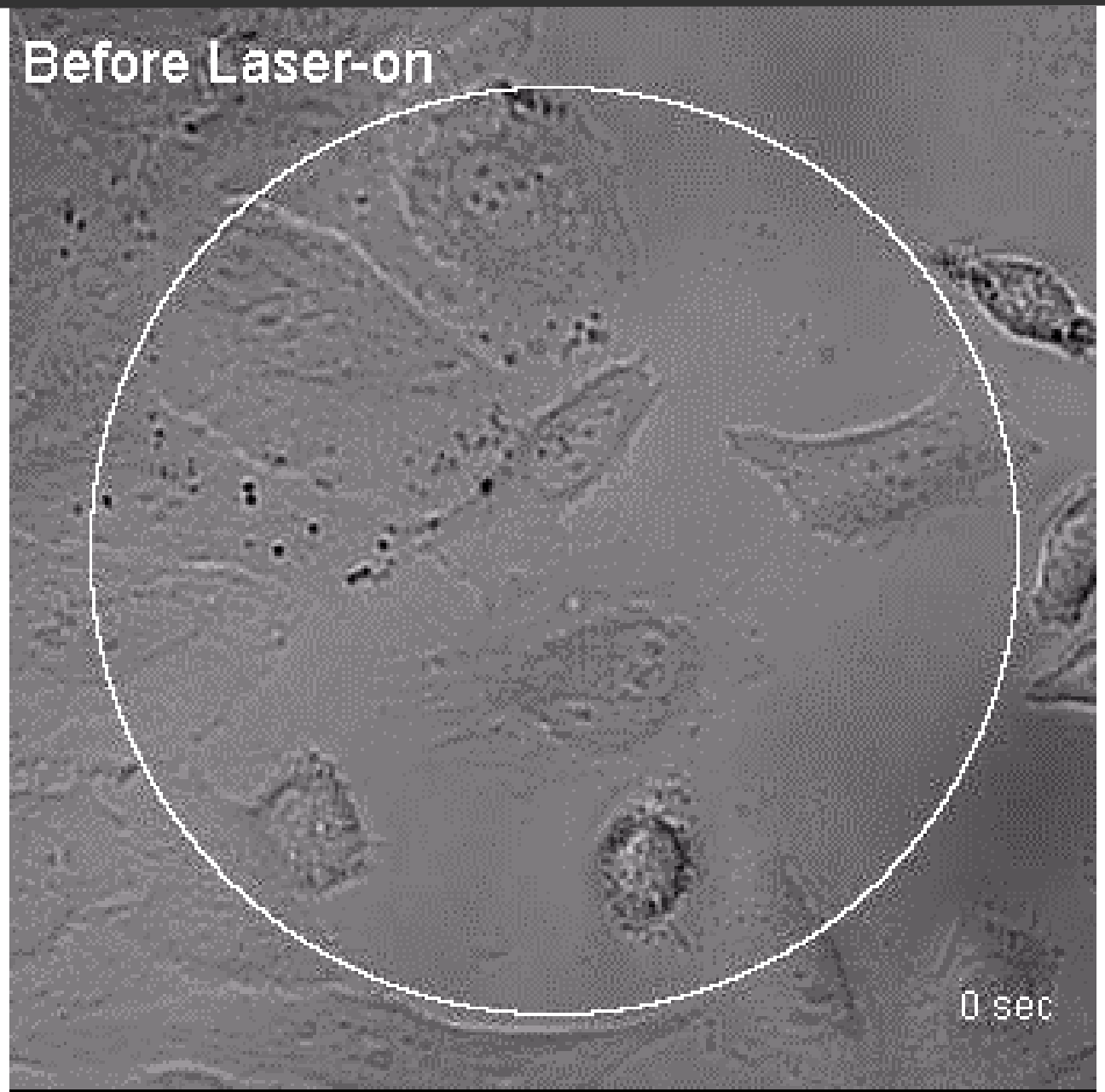


Vapour nanobubble (VNB)





TRinCE™ provides an improved transfection platform

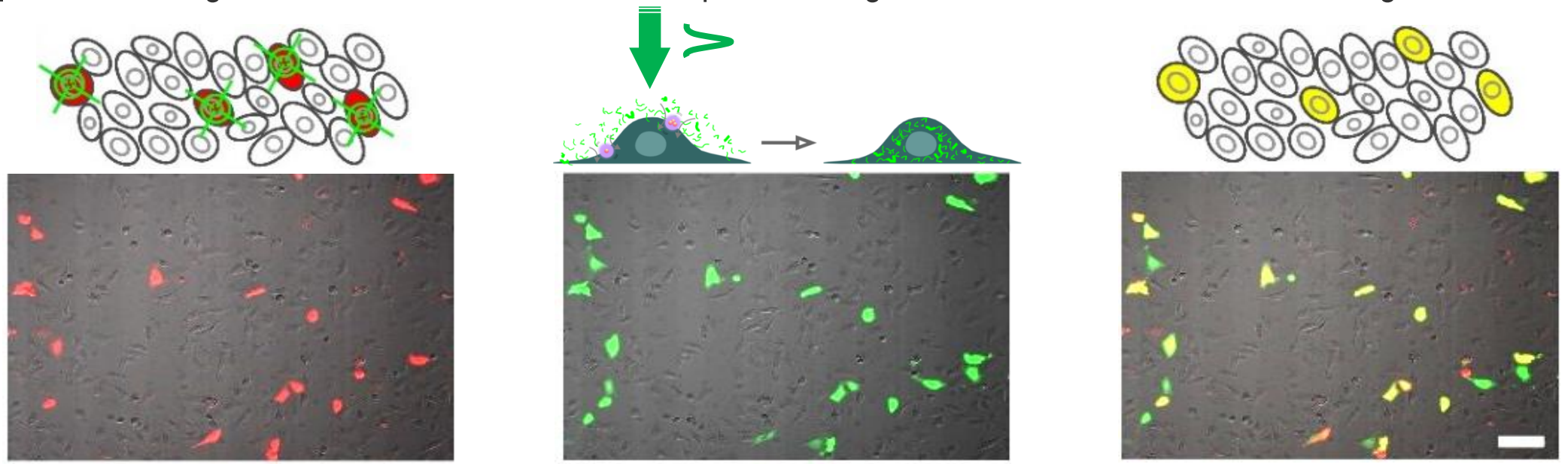


TRinCE™ technology is best suited for a changing market

USP 1 Unique ability to transfect specific cell subpopulations

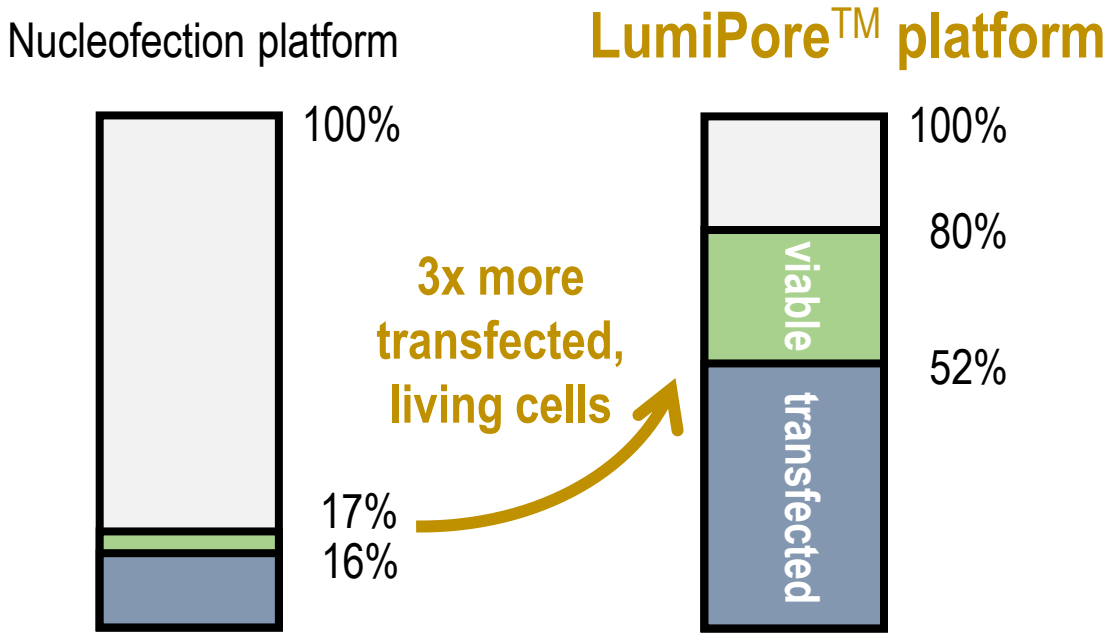
LumiPore™ CELLect platform

Platform workflow: Find target cells → Deliver pulse to target cells → Transfected target cells



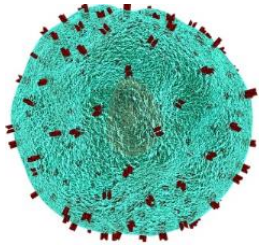
TRinCE™ technology is best suited for a changing market

USP 2 Improved performance for DTC (vs market leader)



Published as: Wayteck et al. *J. Control. Release* 2017

CD8+ **T-cell** **siRNA**



KYMRIAH™ (tisagenlecleucel) Suspension for IV infusion

FDA APPROVED YESCARTA™ (axicabtagene ciloleucel) Kite Pharma

TRinCE™ technology is best suited for a changing market

USP 3 Minimal cell manipulation required

- Hands-on time ↘
- Automation potential ↗
- Risk of contamination ↘
- Regulatory compliance ↗

TRinCE™ development track

Research initiation

PoC

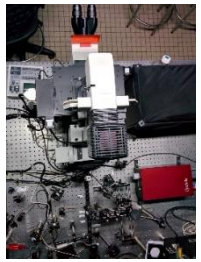
Research funding
~ €4 600 000

Seed funding
~ €620 000

Anticipated market entry

2012 | 2014 | 2016 | 2018 | 2020

Platform development



Prototype dev.

Beta-customer testing

Application development

Internal innovation → Strong track record of top **scientific publications/awards** + **IP portfolio**

Light Science & Applications

nature COMMUNICATIONS

ACS NANO

First market traction→
Academic facilities : VIB, CRIG, VUB
Pharma/biotech companies

Non-dilutive funding

Target the R&D market with device + reagents

Devices

- LumiPore™
- LumiPore™ CELLect

+

Reagents

- Oligo-Sensitizer
- Macro-Sensitizer
- Efficiency indicator (oligo)
- Efficiency indicator (macro)

+

Services

knowhow

Patent portfolio

TRinCE™ future pipeline

Cell therapy production

Device

Patent pending

Reagents

Patent pending

Kit 2

Patent pending

Substrate 1

What are we looking for?

R&D Applications
Academic and
Biotech/Pharma

Contact: **Daisy Flamez**, PhD Daisy.Flamez@ugent.be +32 9 264 99 12

TRinCE™ Core Team

A Ghent University Spin-off project

UNIVERSITEIT GENT

Prof. Kevin Braeckmans

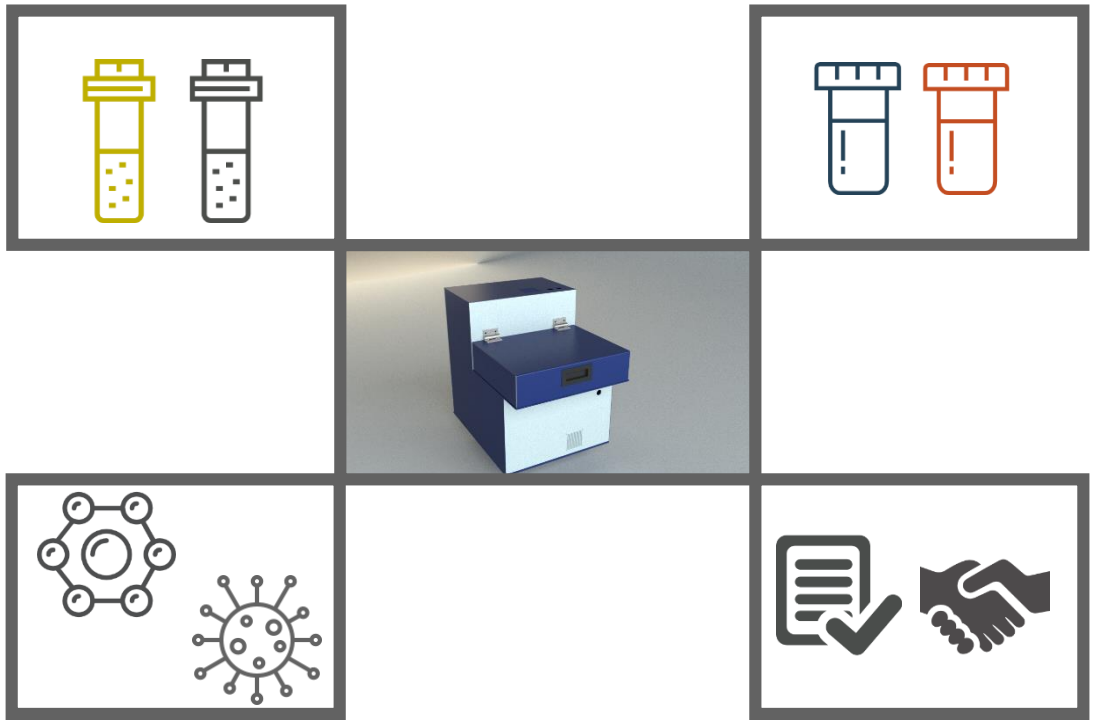
Stephan Stremersch, PhD

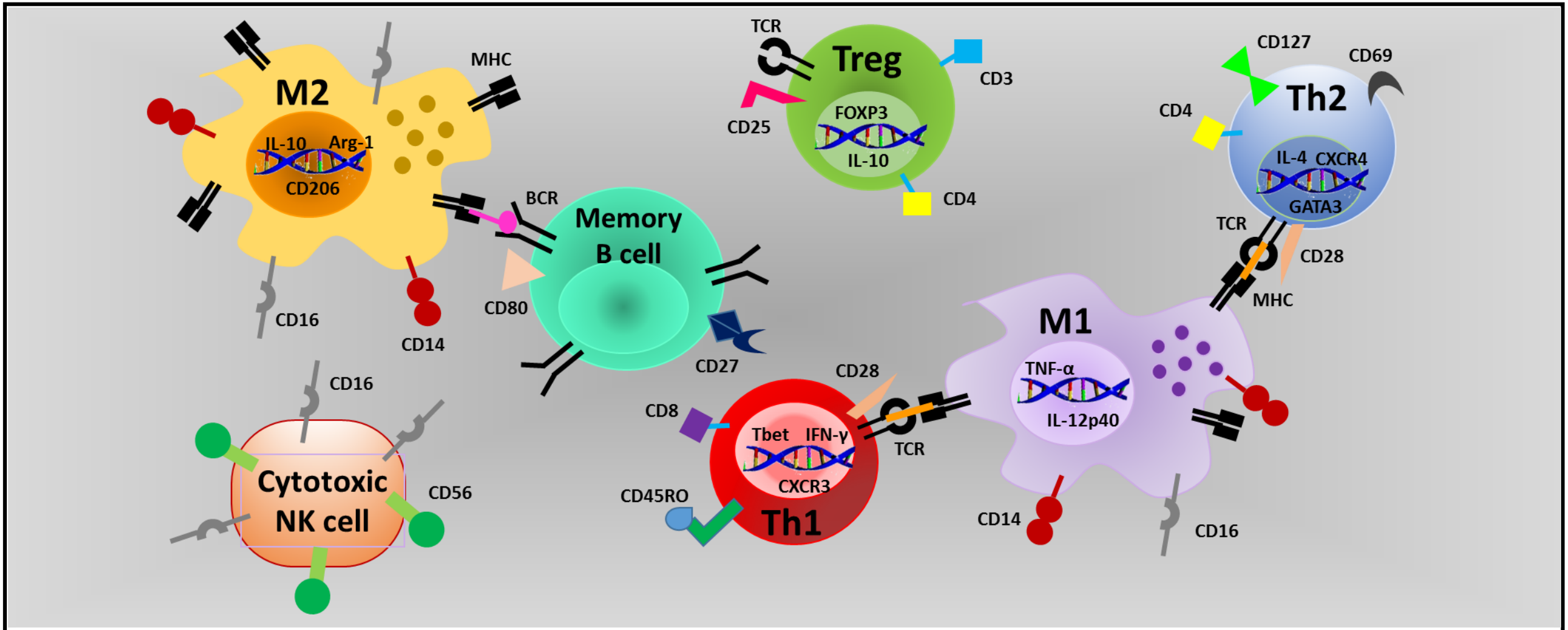
Daisy Flamez, PhD

Toon Brans, PhD

TRinCE

precision transfections





Monitor immune status (changes) in function of therapy response and disease development

An Voets, PhD – business developer Uhasselt - BIOMED

BIOMED
BIOMEDISCH
ONDERZOEKSINSTITUUT
UHASSELT

YOUR NEEDS

CONTENT WISE

- **Monitoring of the immunological status of patients** in respect to the development of diseases and the effect of therapy
- **Cell sorting** of different populations for further analysis or culturing
- Measurement of **extracellular vesicles and nanoparticles** (uptake)
- Scientific (immunology) **advice on experimental set-up**

OTHER REQUIREMENTS

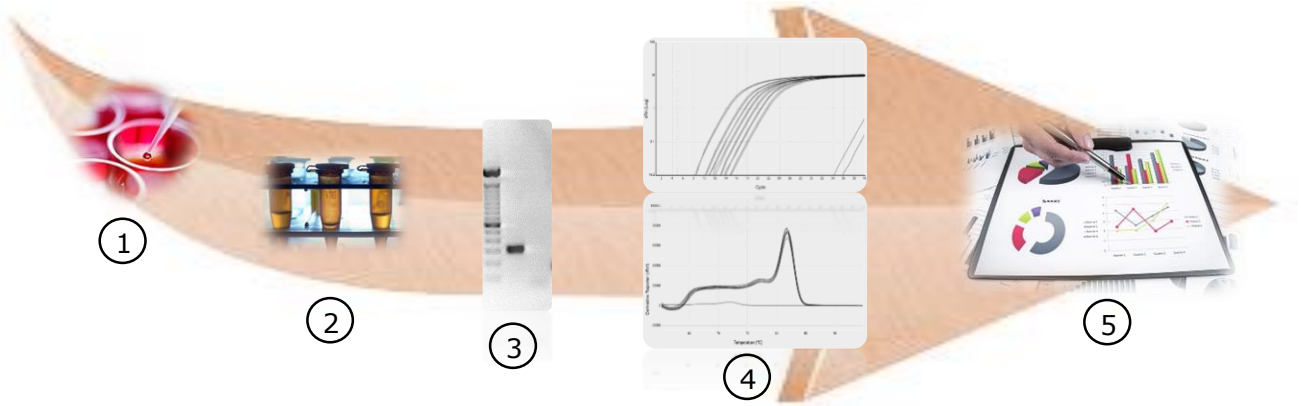
- Speed
- Quality
- Flexibility

BIOMED
BIOMEDISCH
ONDERZOEKSINSTITUUT
UHASSELT

OUR SOLUTION

Off-the-shelve validated and standardized qPCR and flow cytometry analyses building on our vast experience in (neuro)immunology!

qPCR service options



1) cell culture, 2) RNA isolation and cDNA synthesis, 3) cDNA quality control, 4) quantitative PCR analyses, 5) report

Human and murine cell subsets:

T cells
Macrophages
Pro- and anti-inflammatory cytokines
Neurotrophic factors

Flow cytometry panels

Starting material: serum, plasma, supernatant, other complex biological matrices

Available panels:

- Immune cell surface markers
- T cell surface markers
- B cell surface markers
- B cell survival surface markers
- Immune cell apoptosis
- T cell cytokines
- Murine immune cells from spleen, lymph nodes and brain/spinal cord tissues

BIOMED
BIOMEDISCH ONDERZOEKSINSTITUUT
UHASSELT

KEY FEATURES

ADVANTAGES

- **Team**

dedicated qualified technicians + professors

- **Fast**

off-the-shelf, optimized analyses

- **Quality**

SOPs with necessary controls, reproducible

- **Flexibility**

pick and combine

COLLABORATION OPTIONS

- Fee-for-service
- Consultancy and training
- Research collaboration (joint project proposals)

TRACK RECORD

- Bogie et al. Mult Scler 2018; 24:290-300
- Ravanidis et al. Stem Cells International, vol. 2017, Article ID 2353240
- Claes et al. J Immunol 2016; 197:4576-4583
- Thewissen et al. Cell Transplant 2016; 25:1207-1218
- Dhaeze et al. J Immunol 2015; 195:832-840
- …

BIOMED
BIOMEDISCH ONDERZOEKSINSTITUUT
UHASSELT

Contact: An Voets, an.voets@uhasselt.be - +32 11 269323

Technology Offers

Rapid diagnostic for bacterial infections

Bacterial infection, rapid diagnostic, RNA, patient blood, antibiotic resistance

Laboratory

- **Molecular Bacteriology Laboratory**
  (Faculty of Medicine)

Dr Pierre Smeesters is a paediatrician and microbiology researcher with a strong clinical background in paediatric infectious diseases. Dr Smeesters was awarded the triennial GlaxoSmithKline Biologicals Award from the Belgian Royal Academy of Medicine in June 2013.

Team expertise

- Long-standing know-how in bacterial genetics and mobile genetic elements
- Translational research line in the field of bacterial infections to provide clinically relevant outcomes based on basic science expertise
- Modern molecular techniques offer the potential to develop new rapid diagnostic test for infectious diseases as they provide extensive information about the infecting bacteria more rapidly than conventional microbiology testing and yield thereby better decision for the clinician

Rapid diagnostic for bacterial infections

State of the art

- Current microbiological diagnosis of bacterial infections is mainly based on growth of clinical specimens on specific media.
  Time to receive the first results: 24 to 48 hours.
- An alternative consists in detecting the presence of its DNA in the clinical specimen. This diagnostic technique is faster than culture, but often lacks sensitivity and/or specificity.
- Another option: **detect the presence of bacterial specific RNA** in the clinical sample.
  - Technically difficult but has the advantages to detect genes that are expressed by the living bacteria (such as antibiotic resistance genes).
  - **All these results can be obtained in less than two hours**. The clinical potential of such RNA diagnostic test will improve the management of patients with infectious diseases and decrease antibiotic missuse.

Technology description

- New technique for extraction and detection of bacterial RNA in patient blood by quantitative PCR (qPCR)
- The value of this promising technique evaluated on 117 patients with pneumonia
- The new diagnostic test detected the presence of bacterial RNA in 52% of patients (against 16% with the classical diagnostic, blood culture)
- Further improvements of the test are being made to allow for the detection of a broader array of bacterial pathogens and their antibiotic resistance profiles.

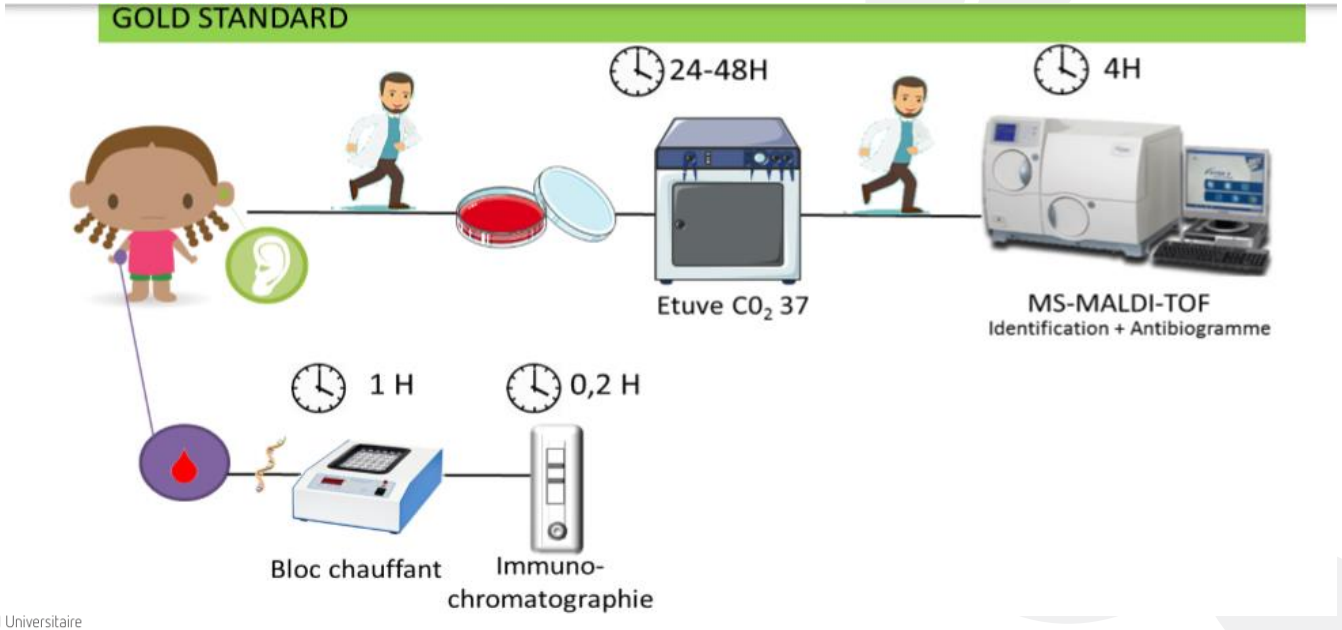
Rapid diagnostic for bacterial infections

Key advantages

- Rapid diagnostic (2 hours versus 48 hours with the classical diagnostic)
- Detect more cases (better sensitivity)
- Simultaneous detection of antibiotic resistance profile

Commercial Interest

- Collaborative research & development (preclinical, early-phase clinical)
- Licensing



IP Status & Contact

Intellectual Property:

- **STREPTOCOCCUS PNEUMONIAE DETECTION IN BLOOD**
- Priority Filing: PCT/EP2011/070127 (15.11.2011) WO 2013/071954
- Granted Patents: JP 6181660 (16.08.2017); US 9,890,431 (13.02.2018); EP 2780466 (27.02.2019)
- Patent Application Pending: US 2018/0208973 (Continuation 26.07.2018)

Contact Labo :
Prof. Pierre Smeesters
pierre.smeesters@huderf.be

Contact KTO :
Arnaud Quintens, Business Developer
arnaud.quintens@ulb.ac.be
+32 479/912-265

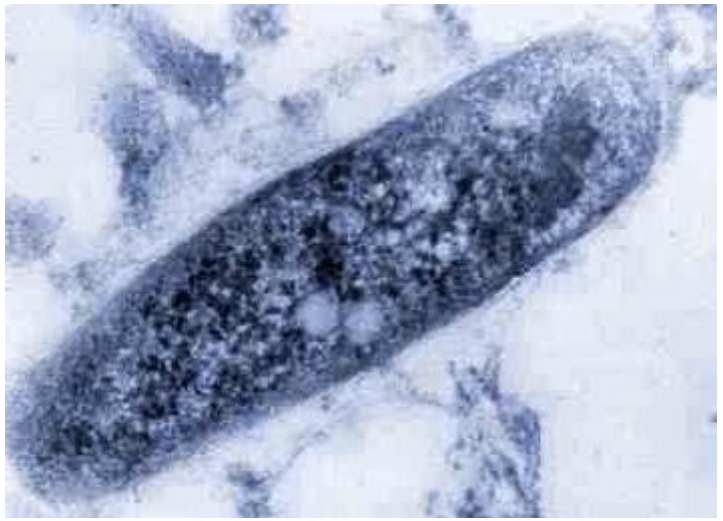
Technology Offers

New drug combinaison acting on M.Tuberculosis

Mycobacterial infections treatment; MDR and XDRTuberculosis treatment; MDR-TB; XDR-TB

Laboratory

- Unit of Pharmaceutical Microbiology and Hygiene (**ULB-micropharma**)



Team expertise

- **Research activities:** study of microorganisms and antimicrobial defenses, among others the study of microbial invasion and the development of new therapeutics against bacteria, viruses or cancers induced by microorganisms.
- **Two main axes:**
  - **Mycobacteriology:** better characterization of proteins involved in the synthesis of the waxy cell wall and identification of compounds able to inhibit the synthesis of this wall in order to target multidrug resistant Mycobacterium tuberculosis
  - **Virology:** regulation of the HPV-16 early gene expression

New drug combinaison acting on M.Tuberculosis

State of the art

- More than 2 billion people worldwide infected with Mycobacterium tuberculosis (World Health Organization). In 2014, 9.6 million people fell ill with TB and 1.5 million died from the disease.
- High intrinsic resistance to the majority of clinically applied antibiotics, which severely limits treatment options.
- Urgent and unmet need to develop new treatments for TB (no susceptibility to most antibiotics & evolution of drug resistance)

Technology description

- New specific pharmaceutical compositions based on the **combination of a glycopeptide antibiotic and a lipase inhibitor**
- **-> significant mycobacteriostatic** properties towards multidrug-resistant or extensively drug-resistant mycobacterial strains and a **new array of combination treatments**
- **Screening of new compounds** useful for the treatment of MDR or XDR mycobacterial infections

New drug combinaison acting on M.Tuberculosis

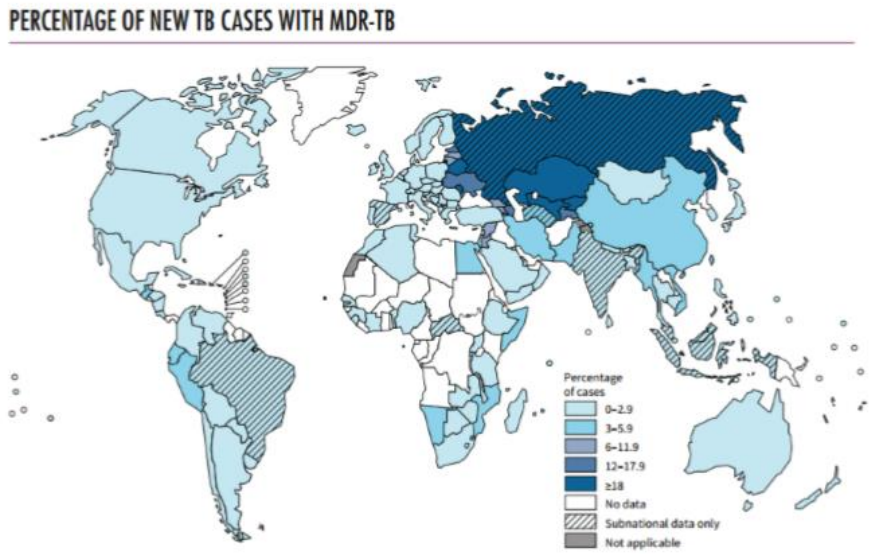
Key advantages

- New strategies against all mycobacteria including MDR and XDR-TB
- Successful in vitro antimycobacterial activity

Commercial Interest

- Collaborative research & development (preclinical, early-phase clinical)
- Licensing

WHO 2014 Drug-resistant TB: Surveillance & Response. Supplement of Global TB Report 2014



MDR-TB

480 000 cases
5 % of TB cases
4,6 % of new TB cases
20.5 % of previously treated for TB

>50% of global MDR-TB cases are found in 3 countries:
India, China and the Russian Federation

IP Status & Contact

Intellectual Property

- **COMPOSITION COMPRISING VANCOMYCIN AND ORLISTAT**
- Priority Filing: EP 14199908.6 (22.12.2014)
- Patent Applications Pending : EP, EA (Eurasian Patent)
- Publication: EP3237011 (01.11.2017); EA201791218 (29.12.2017)

Contact Lab :
Prof. Véronique Fontaine
Veronique.Fontaine@ulb.ac.be

Contact KTO :
Arnaud Quintens, Business Developer
arnaud.quintens@ulb.ac.be
+32 479/912-265

A reference standard (rEV) bringing extracellular vesicle analysis to the next level.

Expertise Ghent University: **Prof An Hendrix, Prof Olivier De Wever**

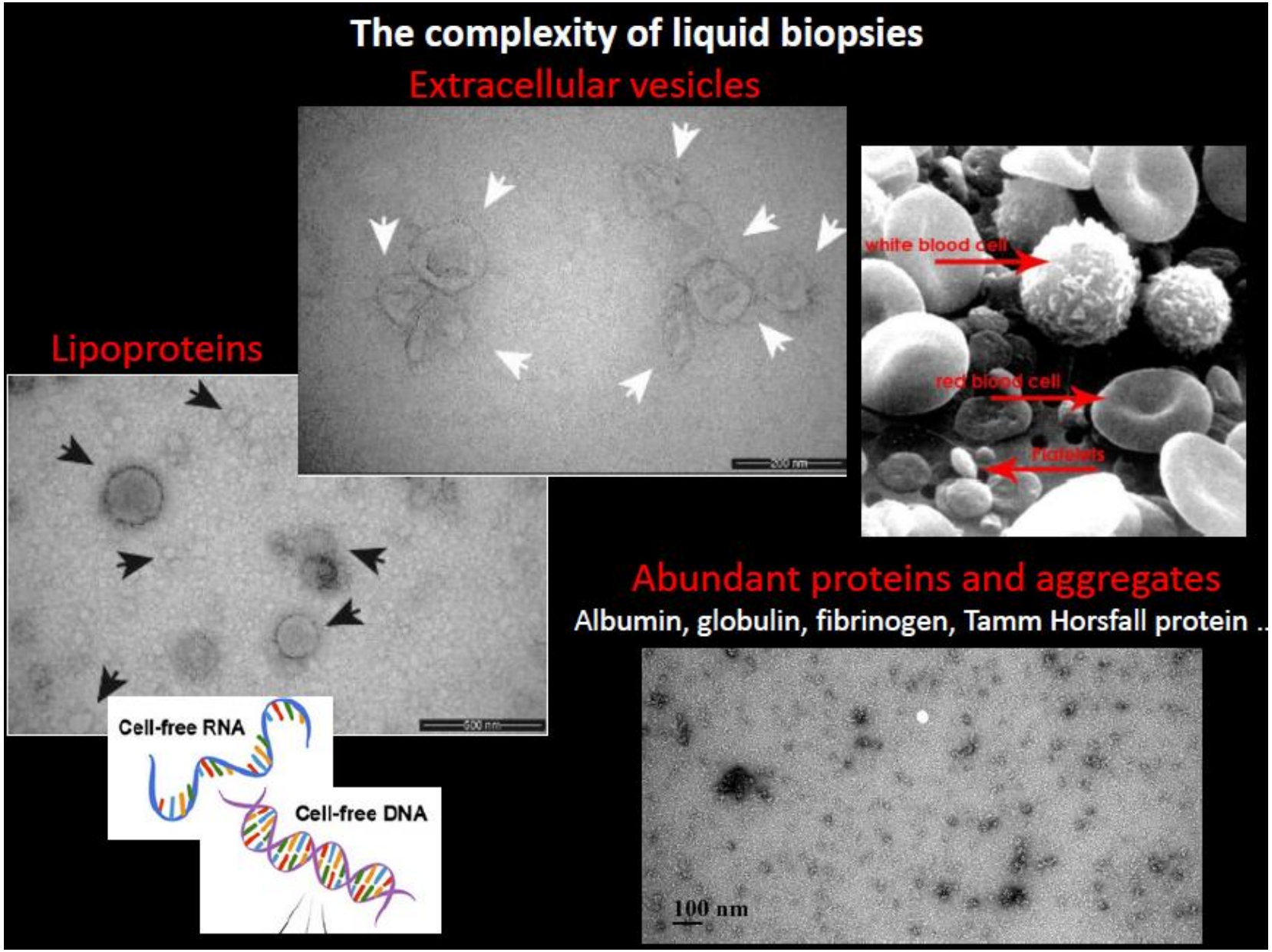
Daisy Flamez, IOF Business developer

GHENT UNIVERSITY

FACULTY OF MEDICINE AND HEALTH SCIENCES

CRIG LECR

Introduction: Non-invasive diagnostics



GHENT UNIVERSITY

Introduction: Extracellular vesicles (EV)

Extracellular vesicles (EV) are membrane nanometer-sized vesicles produced via endosomal compartments, they are secreted by all cell types.

EVs

- contain cell-type-specific combinations of proteins, nucleic acids and metabolites.
- transmit information between different cell types, organs and even between organisms,
- have been detected in multiple body fluids,
- orchestrate physiological and pathophysiological processes

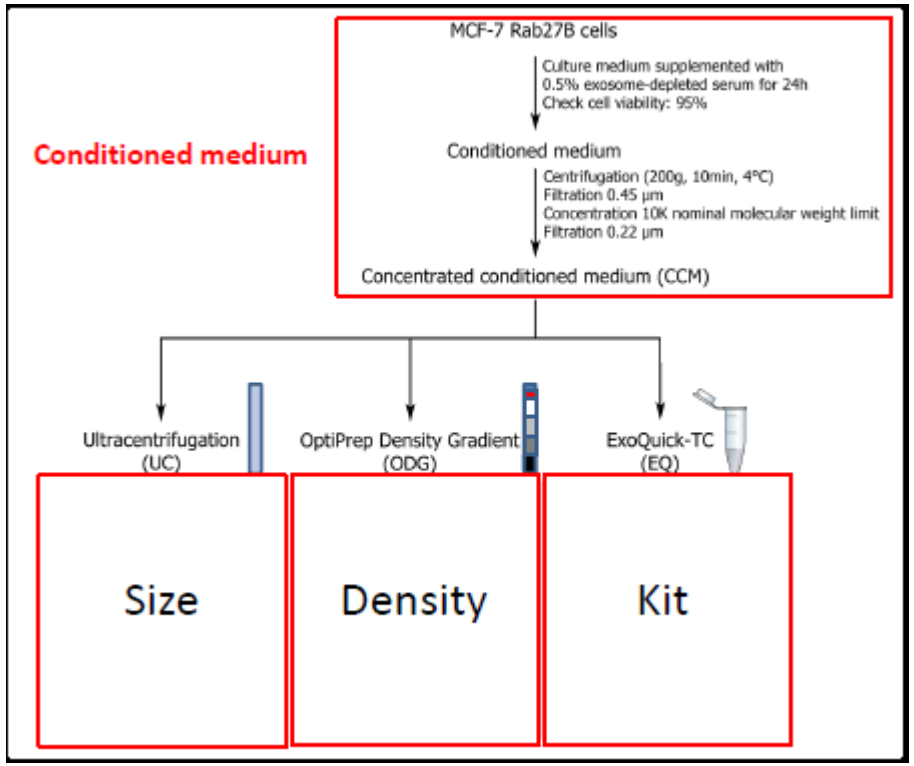
Tumor-derived EVs enter the circulation to assist organ metastasis, a process responsible for more than 90% of cancer-associated mortality. The content of EVs reflects the origin and state of the cell.

Quantification and characterization of tumor-derived EVs obtained by liquid biopsy may enable the prognosis of patients or predict therapy response.

Market Need: standardized and reproducible EV isolation

Because of the EV involvement in disease progression and their presence in different easy accessible **biofluids** these EV have gained interest for the use as **diagnostic** biomarker

but currently with poor clinical relevance !!!



Different isolation methods enrich for single or multiple EV subtypes with divers composition and variable purity, thus identifying method-dependent EV content and function

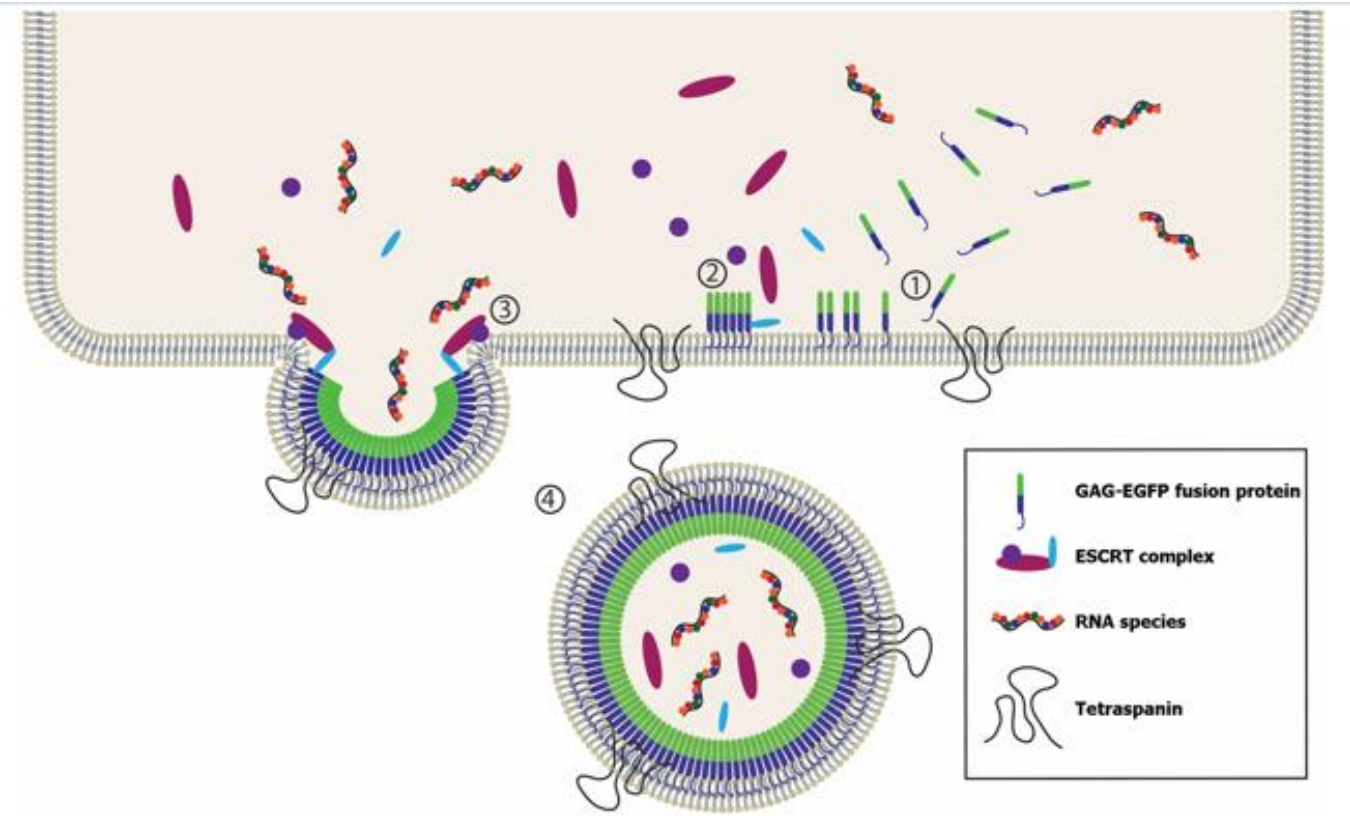
The current lack of standardized isolation methods is due to the **complete lack of a standard reference material that mimics the physical and biochemical properties of natural occurring EVs.**

GHENT UNIVERSITY

Solution: R-EV a biological reference material for EV-analysis

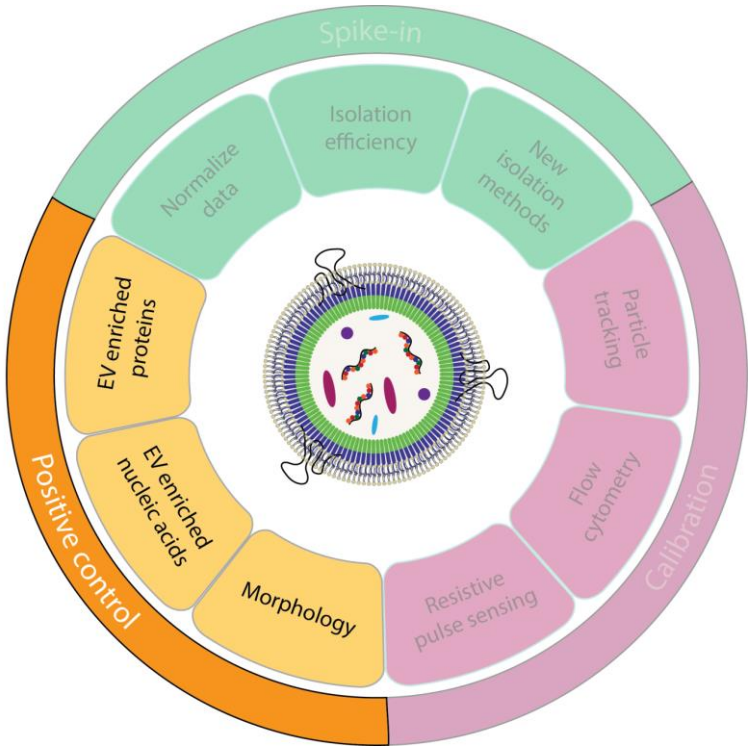
Development of a biological reference material (R-EV) that comprises :
a) a self-assembling protein (retroviral group specific antigen (GAG)
that directs its own release through EV as a luminal membrane bound protein
b) a heterologous marker such as the light-emitting enhanced green fluorescent protein (EGFP).

Patent PCT

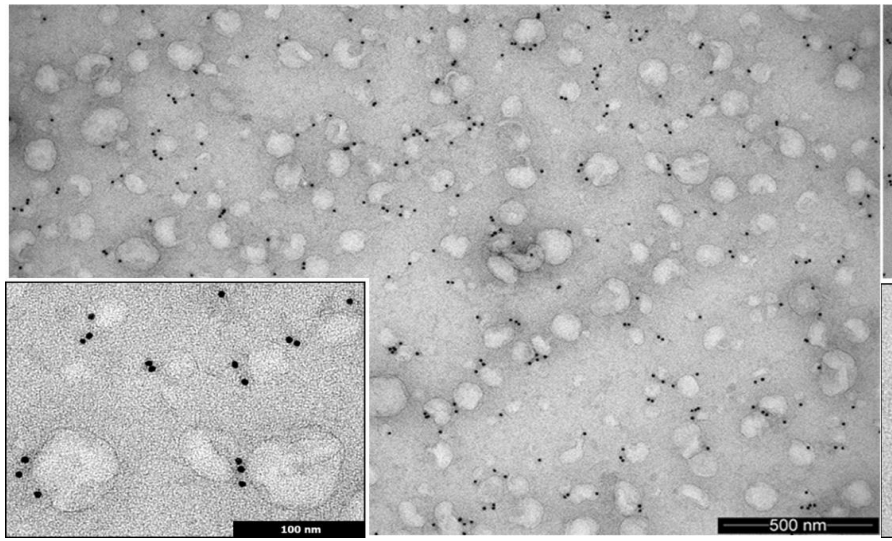


GHENT UNIVERSITY

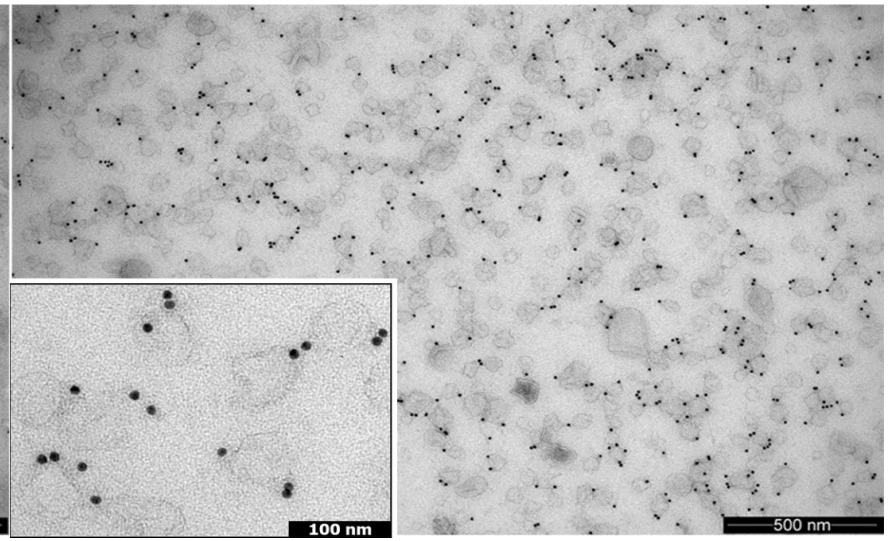
R-EV positive control: EV like physical and biochemical characteristics



rEV – CD63 IEM



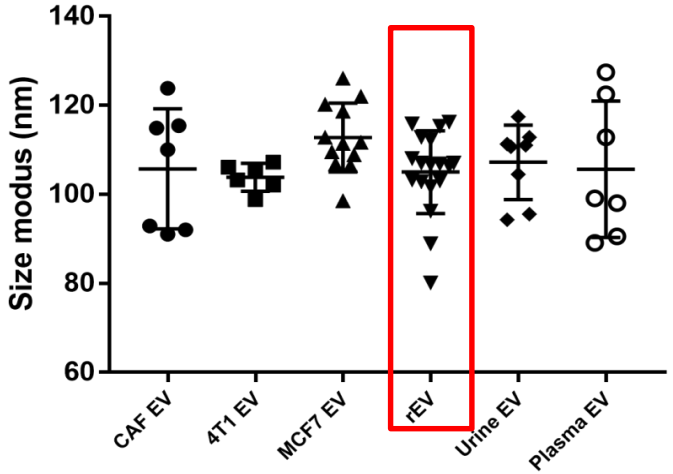
EV – CD63 IEM



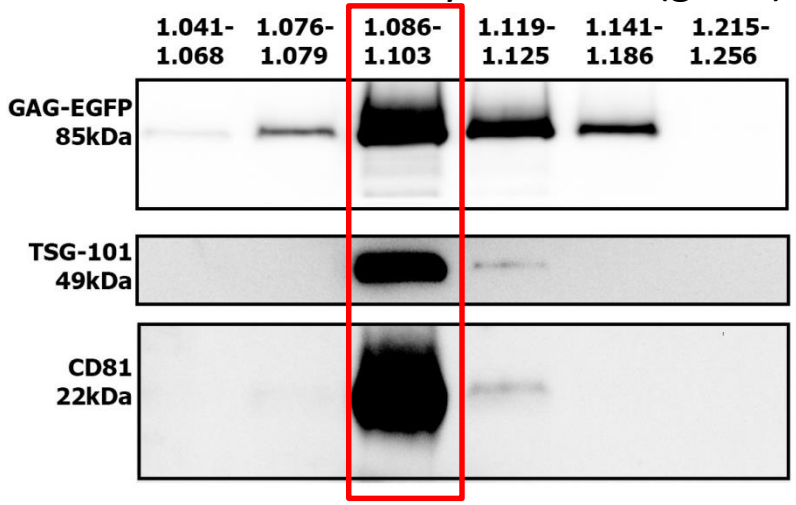
GHENT UNIVERSITY

R-EV positive control: EV like physical and biochemical characteristics

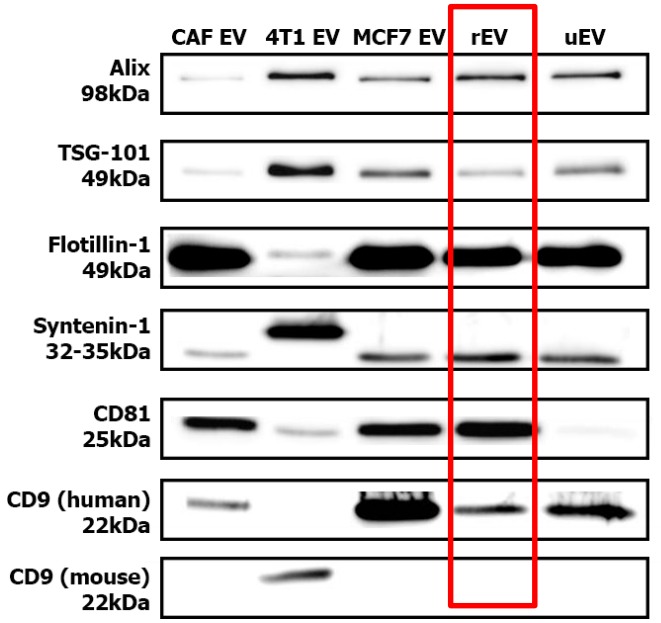
Size



Iodixanol density fractions (g/mL)

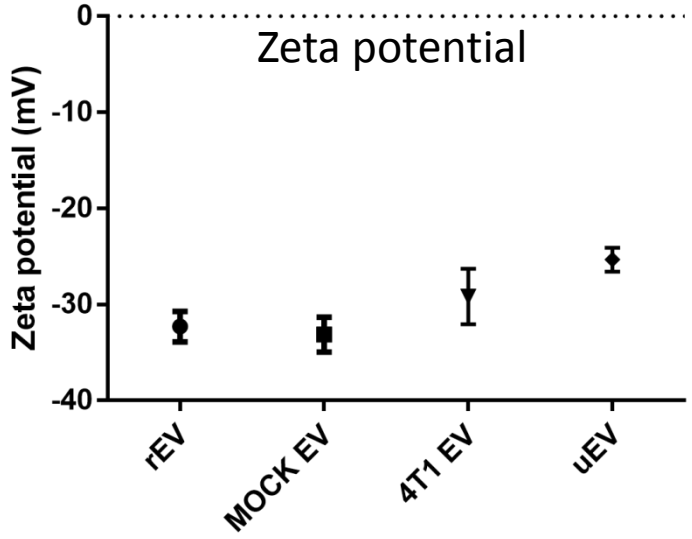


EV marker proteins

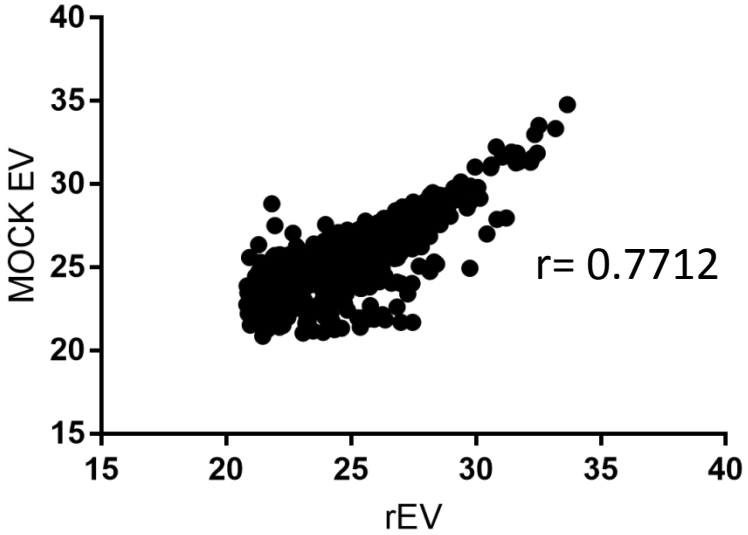


GHENT UNIVERSITY

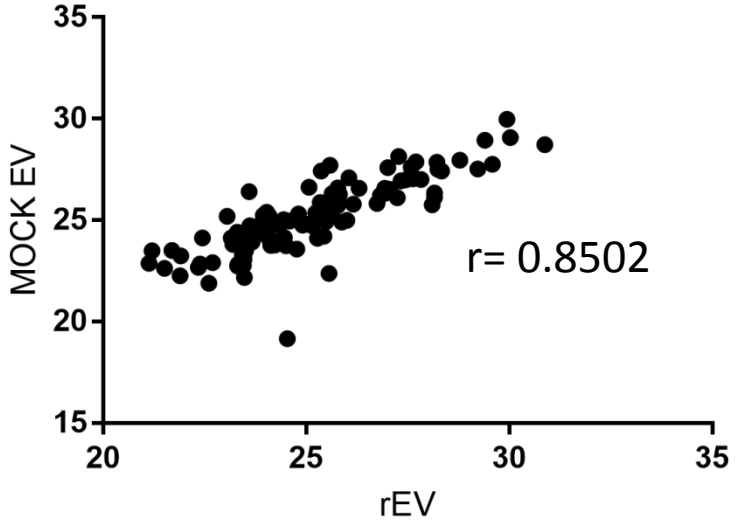
R-EV positive control: EV like physical and biochemical characteristics



rEV vs MOCK EV proteomics

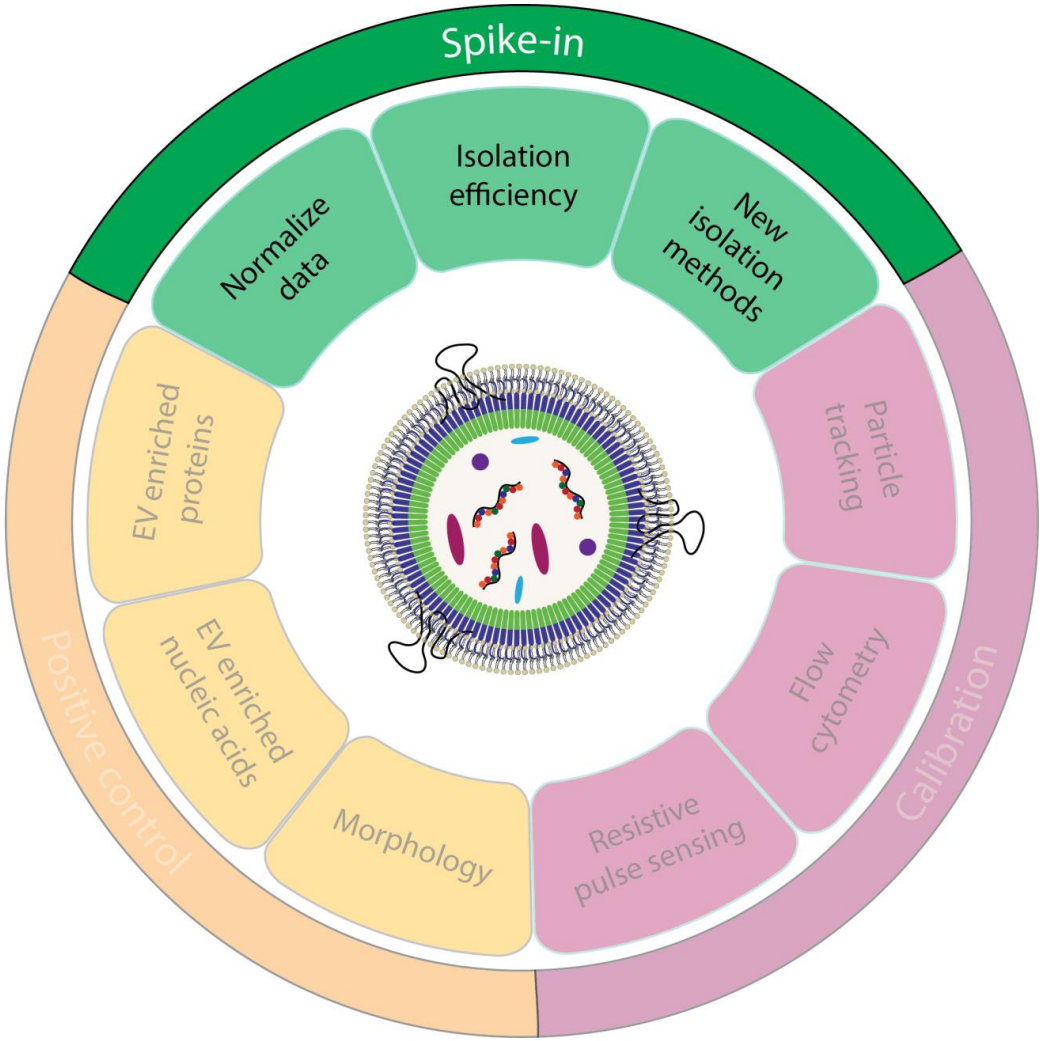


rEV vs MOCK EV lipidomics



GHENT UNIVERSITY

R-EV as a spike-in material: read out methods



- Fluorescent NTA
- Fluorescent threshold flow cytometry

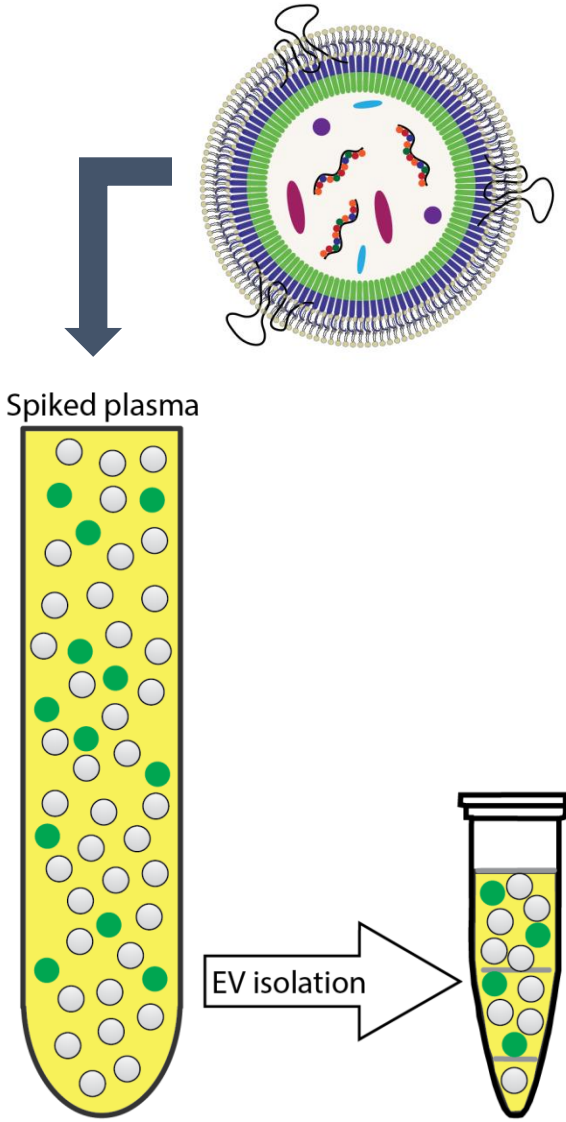
Direct

- Fluorescent plate reader
- Anti-GAG ELISA
- RT-qPCR for EGFP mRNA

Indirect

GHENT UNIVERSITY

R-EV as a spike-in material: calculate isolation efficiency



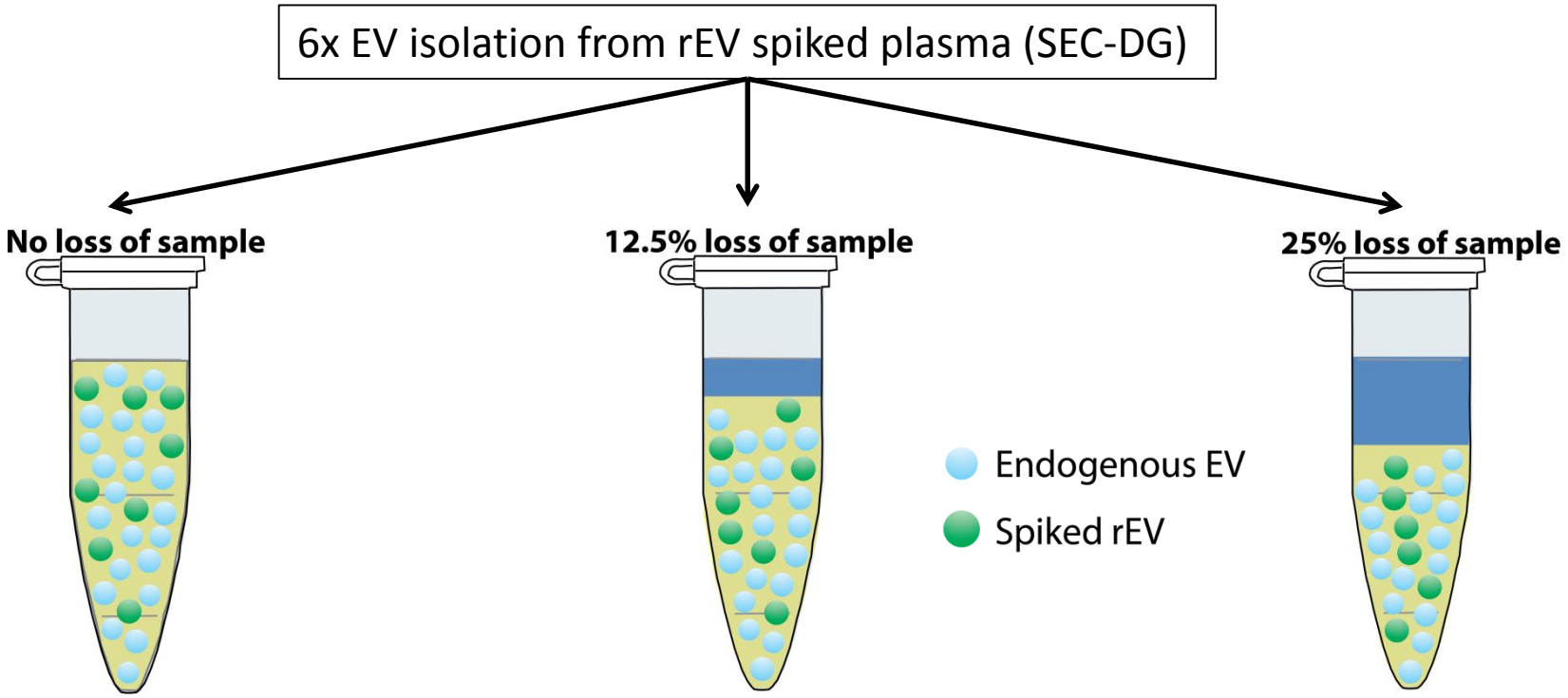
Frequently used EV isolation methods

- Differential ultracentrifugation (dUC)
- Density gradient centrifugation (DG)
- Size exclusion chromatography (SEC)

➔ Calculated recovery rate

GHENT UNIVERSITY

R-EV as a spike-in material: normalize data



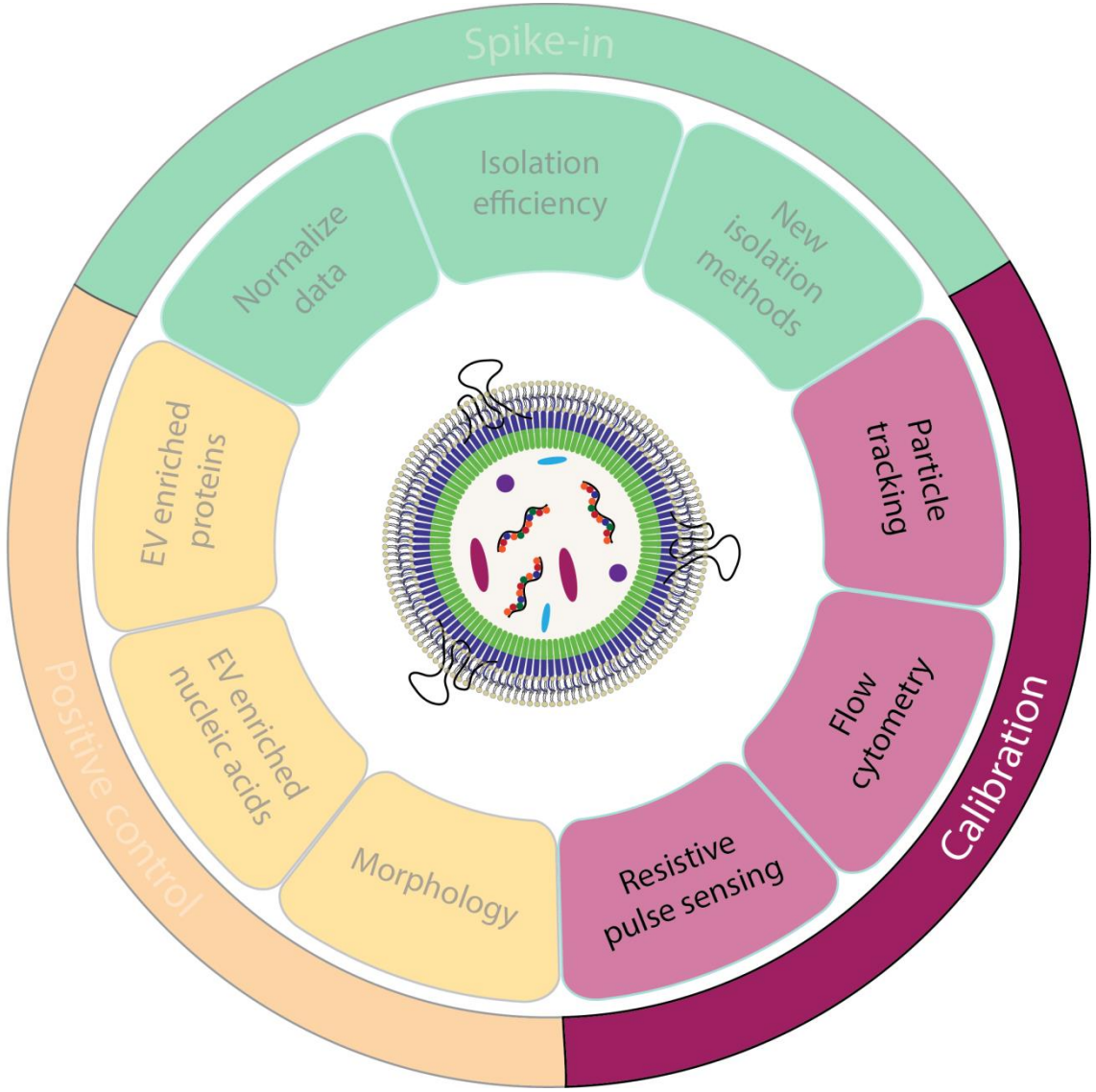
1) **NTA** ➔ Absolute EV concentration

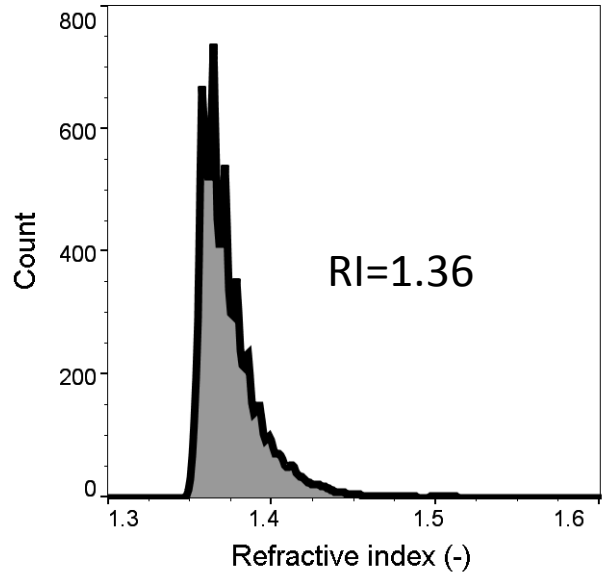
2) **fNTA** ➔ Isolation efficiency

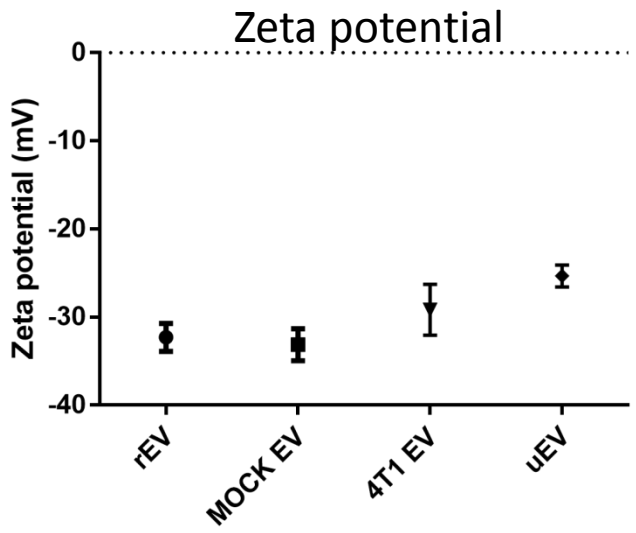
➔ **Normalized EV concentration**

GHENT UNIVERSITY

R-EV for calibration



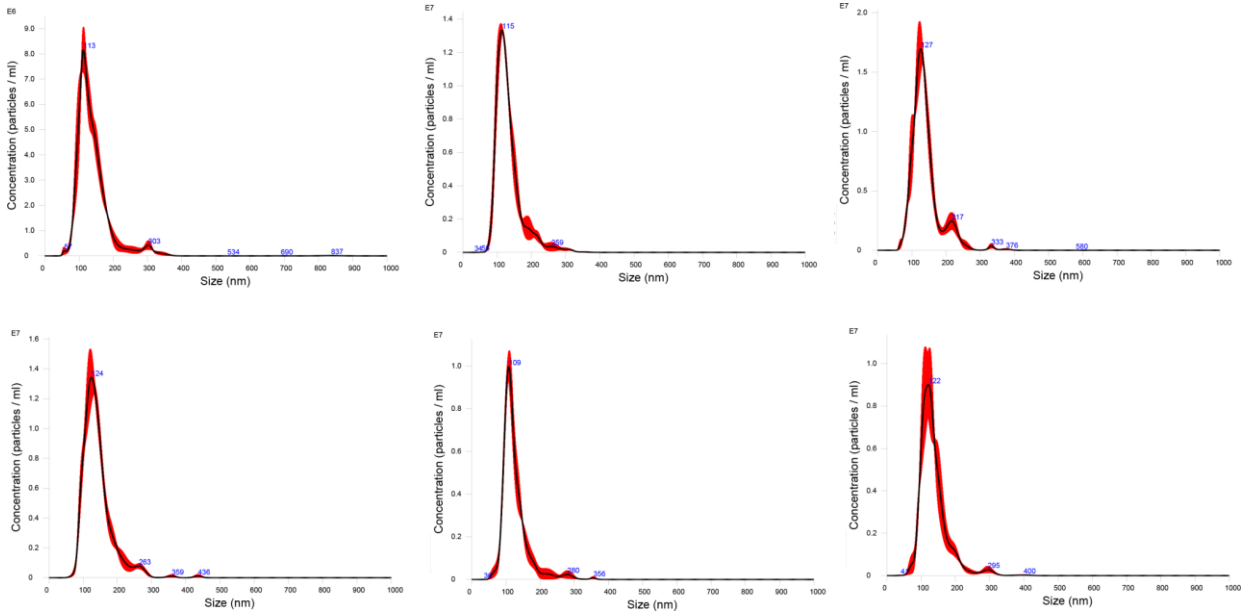




GHENT UNIVERSITY

R-EV Advantages

+ R-EV is highly fluorescent and traceable.
+ R-EV is stable.
+ R-EV can be produced in high quantities and can be detected in a very sensitive manner.
+ R-EV reflects physical, biochemical characteristics of endogenous sample EV.
    1) R-EV has common traits with sample EV
    2) unique properties distinguish R-EV from sample EV



Batch to batch variability of rEV

GHENT UNIVERSITY

Stage of development and what are we looking for?

Patent PCT

Validated via beta users
(Batches produced in house)

EV-TRACE
EV Tracking using surface proteins and
Resonance Assays to detect breast Cancer in Early stage

Searching for a licensing partner to bring R-EV to the market worldwide

R&D Applications Academic and Biotech/Pharma

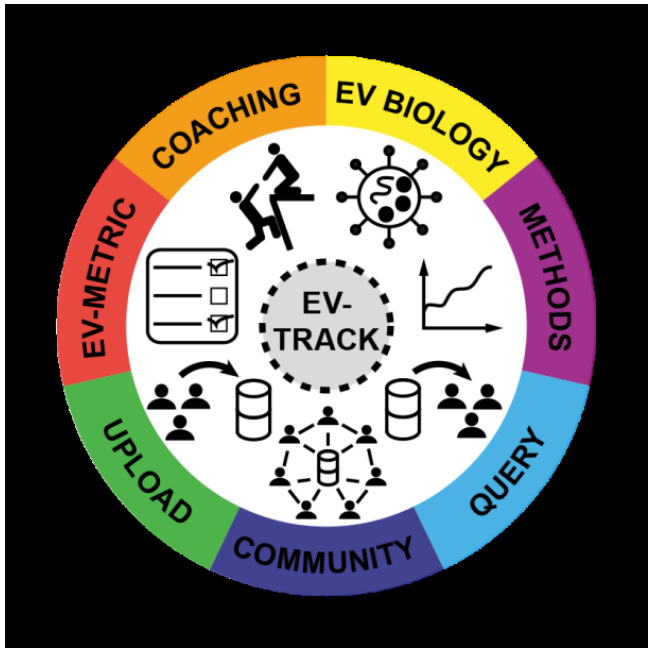
Contact: **Daisy Flamez**, PhD Daisy.Flamez@ugent.be +32 9 264 99 12

GHENT UNIVERSITY

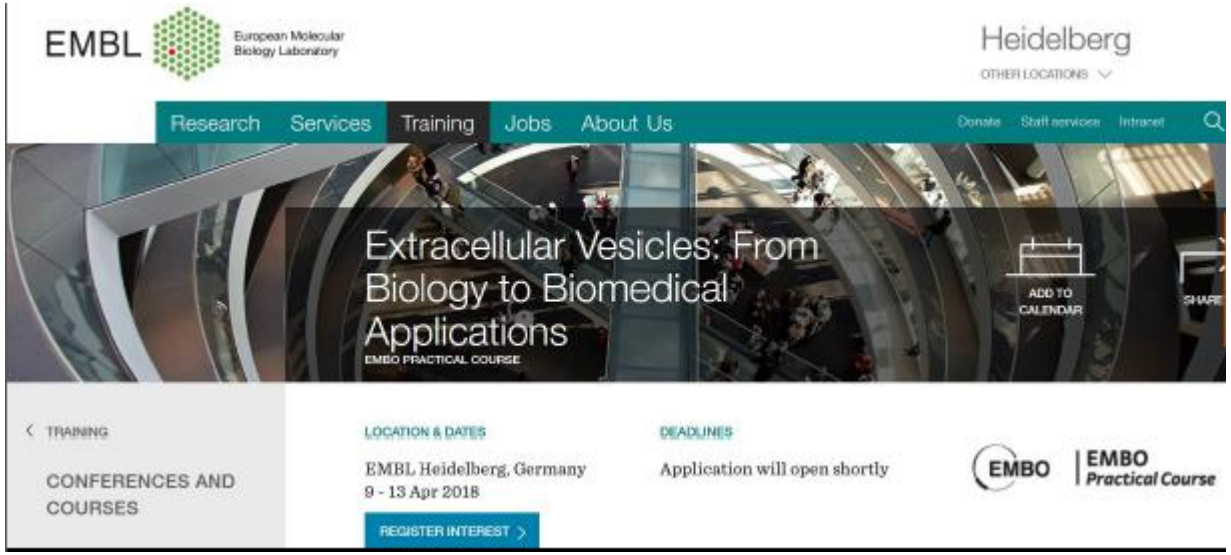
Team Laboratory of Experimental Cancer Research

Prof An Hendrix
Ghent University

Gut. 2018 Dec 5. (IP 17)
Increased levels of systemic LPS-positive bacterial extracellular vesicles in patients with intestinal barrier dysfunction.



Van Deun et al. Nature Methods 2017



GHENT UNIVERSITY