Interreg
Italia-Österreich
European Regional Development Fund

EUROPEAN UNION

Interreg V-A Italia-Austria
2014-2020
Interreg V-A Italien-Österreich
2014-2020

EXOTHERA

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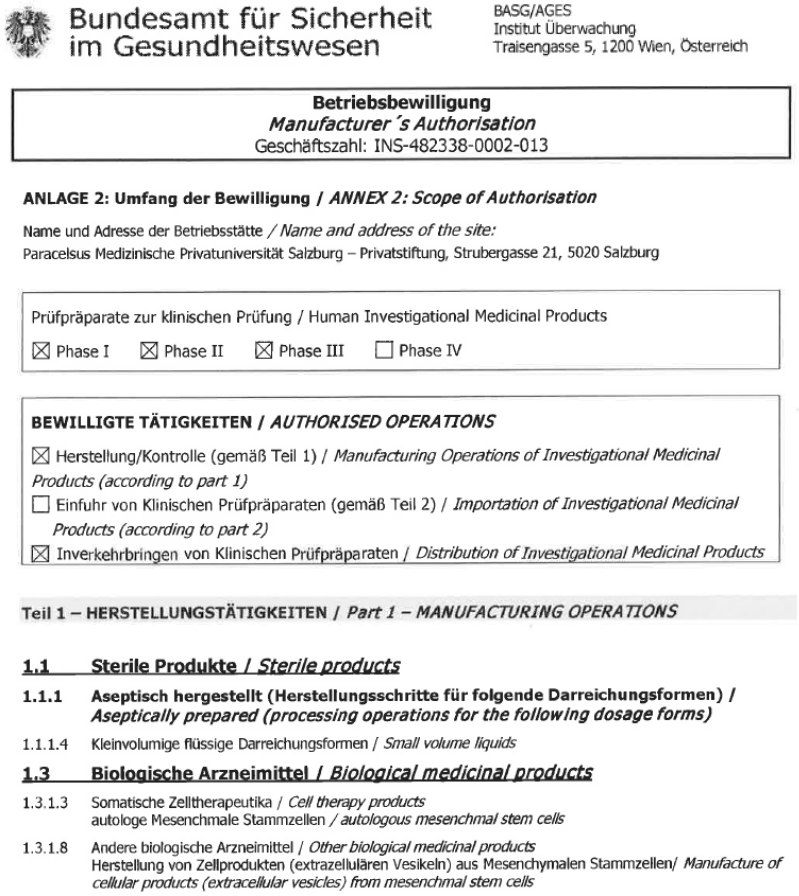
Exosomes for regenerative, immunosuppressive, neuroprotective and oncosuppressive therapies

Elettra Sincrotrone Trieste
PARACELSUS MEDIZINISCHE PRIVATUNIVERSITÄT
UNIVERSITÀ DEGLI STUDI DI UDINE
hic sunt futura
ASUTs
UNIKLINIKUM SALZBURG
REGIONE AUTONOMA FRIULI VENEZIA GIULIA
Azienda Sanitaria Universitaria Integrata di Udine

www.interreg.net

The GMP unit @ PMU: who we are

The Laboratory is accredited for the production of mesenchymal stem cell therapeutics for clinical testing and holds a GMP license according to § 63 AMG.
Primary obligation of the unit is the maintenance of a certified manufacturing site with an attached quality control area for the production, treatment and storage of human stem cells and stem cell products under GMP compliant conditions for clinical evaluation (stem cell therapy) in human patients.



Bundesamt für Sicherheit im Gesundheitswesen

BASG/AGES
Institut Überwachung
Traisengasse 5, 1200 Wien, Österreich

Betriebsbewilligung
Manufacturer´s Authorisation
Geschäftszahl: INS-482338-0002-013

ANLAGE 2: Umfang der Bewilligung / *ANNEX 2: Scope of Authorisation*

Name und Adresse der Betriebsstätte */ Name and address of the site:*
Paracelsus Medizinische Privatuniversität Salzburg – Privatstiftung, Strubergasse 21, 5020 Salzburg

Prüfpräparate zur klinischen Prüfung / Human Investigational Medicinal Products
☒ Phase I ☒ Phase II ☒ Phase III ☐ Phase IV

BEWILLIGTE TÄTIGKEITEN / *AUTHORISED OPERATIONS*
☒ Herstellung/Kontrolle (gemäß Teil 1) / *Manufacturing Operations of Investigational Medicinal Products (according to part 1)*
☐ Einfuhr von Klinischen Prüfpräparaten (gemäß Teil 2) / *Importation of Investigational Medicinal Products (according to part 2)*
☒ Inverkehrbringen von Klinischen Prüfpräparaten / *Distribution of Investigational Medicinal Products*

Teil 1 – HERSTELLUNGSTÄTIGKEITEN / *Part 1 – MANUFACTURING OPERATIONS*

1.1 Sterile Produkte / *Sterile products*

1.1.1 Aseptisch hergestellt (Herstellungsschritte für folgende Darreichungsformen) / *Aseptically prepared (processing operations for the following dosage forms)*

1.1.1.4 Kleinvolumige flüssige Darreichungsformen / *Small volume liquids*

1.3 Biologische Arzneimittel / *Biological medicinal products*

1.3.1.3 Somatische Zelltherapeutika / *Cell therapy products*
autologe Mesenchmale Stammzellen */ autologous mesenchmal stem cells*

1.3.1.8 Andere biologische Arzneimittel / *Other biological medicinal products*
Herstellung von Zellprodukten (extrazellulären Vesikeln) aus Mesenchymalen Stammzellen/ *Manufacture of cellular products (extracellular vesicles) from mesenchmal stem cells*

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Layout of the GMP Lab: class B environment

Open Communication Design




Hygienic Design

Hygienic Design





Issues to solve before

EVs turn into a therapeutic product

TERMINOLOLOGY

EVs

or

vesicular paracrine factors

or

the particulate secretome

or

vesicular secretome fraction (VSF)

Issues for future EV therapy

Safety	**- Shelf life** **- Overall product stability** **- Toxicity**
Identity	**- Which EVs are therapeutically active in the heterogeneous preparation** (secretome)
Potency	**- Dose** **- Mode-of-action** **- Bioavailability**
Purity	**- Co-purifying components** **- Excipients in the final product**
Quality	**- Quality control (producer cells and EVs)** **- Product release criteria**

Issues for future EV therapy

Availability	**- Considerable benefit and advantage of EVs over cells** **- Prototype allogeneic therapeutic substance**
Route & mode of administration	**- Dependent on disease model** **Many possibilities - more than live cells**
Production & Upscaling	**- Growth conditions** **- Bioreactors** **- Stable cell lines** **- Scalable enrichment / purification** **- Aseptic filling** **- Container closure** **- Overall GMP compliance**

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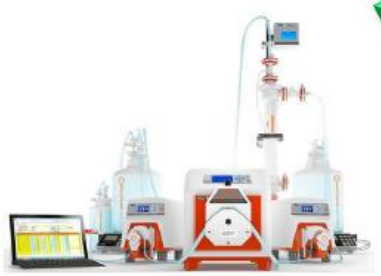
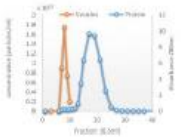
GMP grade enrichment / purification strategies for MSC-derived exosomes

EV-free culture & harvest conditions for MSCs

Ultracentrifugation under class B



cross flow & diafiltration (TFF / DF)



SE Chromatography (optional)

Sterile filtration

Aseptic filling & storage

Product testing

PRODUCT

Determining identity, quality and quantity of EVs for release criteria

- **NTA *(number & size)***
  - tunable resistance pulse sensing, image flow
  - microfluidics

- **EM *(shape)***

- **miRNA analysis and profiling *(characterization of the cargo)***
  - Proteomics, Lipidomics, Metabolomics & Mitomics
  - Domainome analysis

Determining purity and quality of EVs for release criteria

- **Identity markers**
  - Westen blotting, ELISA or AFM
- **Non-EV particles present in the final product**
  - Lipids, soluble proteins
- **In vivo efficacy**
  - Preclinical animal studies
  - Large animal models & First -in-man studies
  - Controlled phase II clinical trials

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Eva Rohde
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(Transfusion Medicine Salzburg, SALK)

Grazie!

UNIVERSITY HOSPITAL
UNIKLINIKUM
SALZBURG

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MEDIZINISCHE PRIVATUNIVERSITÄT

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Ludwig Aigner Lab
Sebastien Couillard-Despres Lab
Dirk Strunk Lab
(PMU)

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