



Ein Unternehmen der  
Johann Wolfgang Goethe-Universität Frankfurt am Main



## Clinically approved mesenchymal stromal cell preparation for treatment of inflammatory diseases

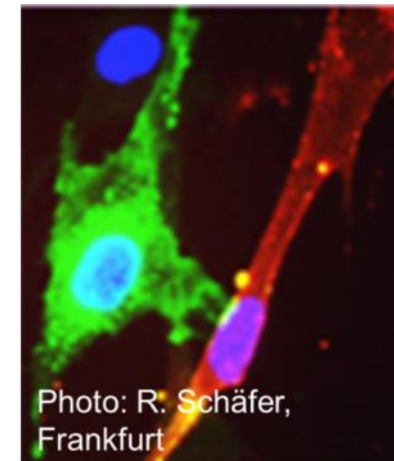
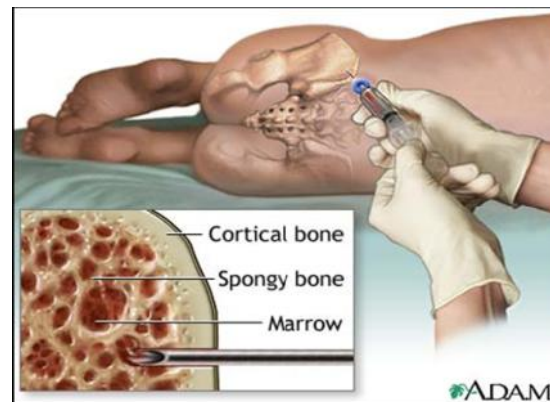


Prof. Dr. Peter Bader, Dr. Selim Kuci, Dr. Zyrafete Kuci; University Hospital Frankfurt/Main;  
Prof. Dr. Halvard Böniig, German Red Cross Blood Center Frankfurt/Main;  
Dr. Kirstin Schilling, Innovectis GmbH



## Mesenchymal Stroma Cells (MSC) - Characteristics

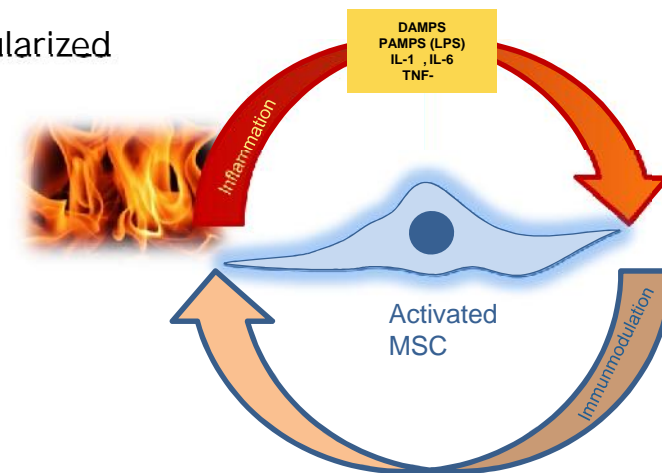
- MSCs are self-renewing, multipotent precursor cells.
- They can be isolated from bone marrow and other vascularized tissues.





## Mesenchymal Stroma Cells (MSC) - Characteristics

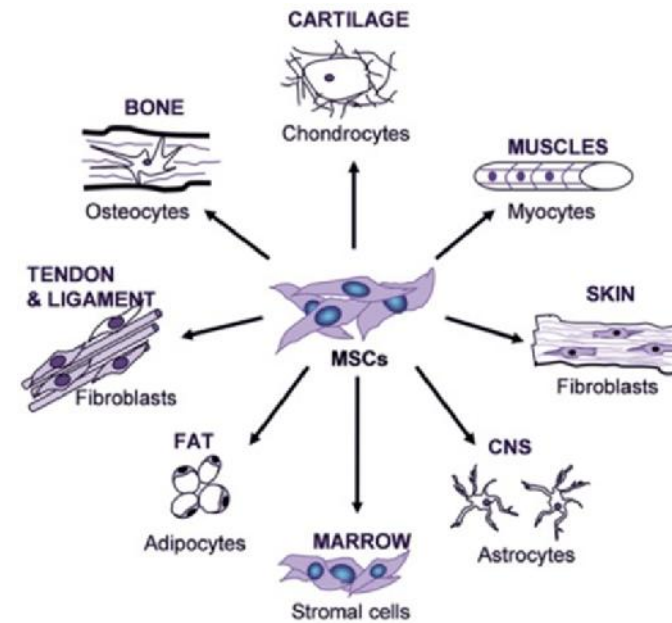
- MSCs are self-renewing, multipotent precursor cells.
- They can be isolated from bone marrow and other vascularized tissues.
- MSCs modulate the immune response and provide anti-inflammatory properties.





## MSC – Differentiation Potential

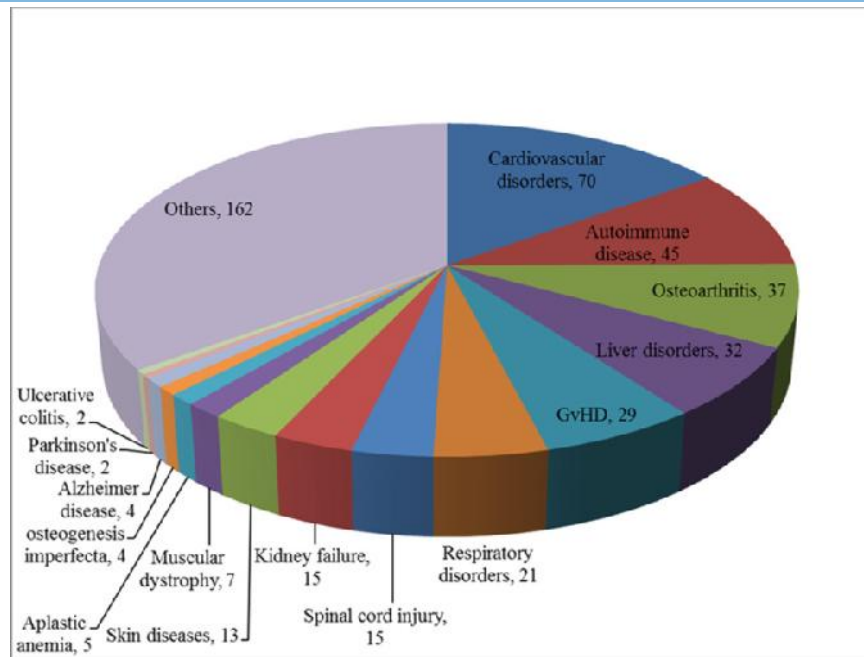
- MSCs have the ability to differentiate into mesodermal lineages, such as chondrocytes, osteoblasts and adipocytes.



[www.sci-therapies.info](http://www.sci-therapies.info)



## Mesenchymal Stroma Cells (MSC) – Therapeutic Potential



Ullah, I. et al. Biosci. Rep. (2015) / 35 / art:e00191 / doi 10.1042/BSR20150025

### Cell therapy:

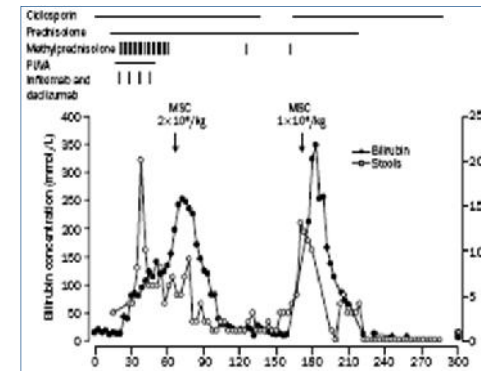
- Immunomodulation
- Bone repair and tissue regeneration
- Neovascularization & Angiogenesis



## MSCs and Graft-versus-Host Disease

### Treatment option for patients with Graft-versus-Host Disease (GvHD)

- Most frequent immunological complication after transplantation
- Donor T cells → recipient Ag, 35-80 % tx recipients
- If first line treatment with steroid fails → 20 % OS at 5 years.
  
- MSCs are modulating the immune response.
- As they do not express MHC class 2 molecules, they do not elicit a rejection response.



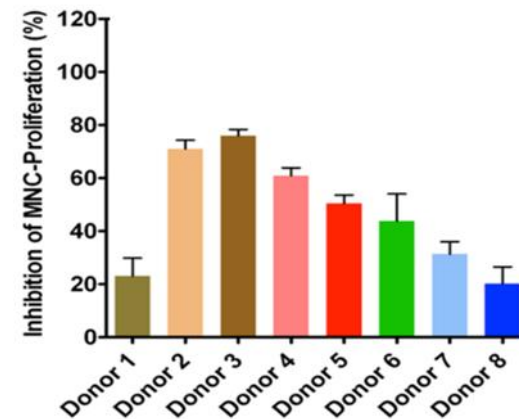
Le Blanc, et al. The Lancet 2004



## Obstacles for MSC Therapy

Considerable variation from donor to donor:

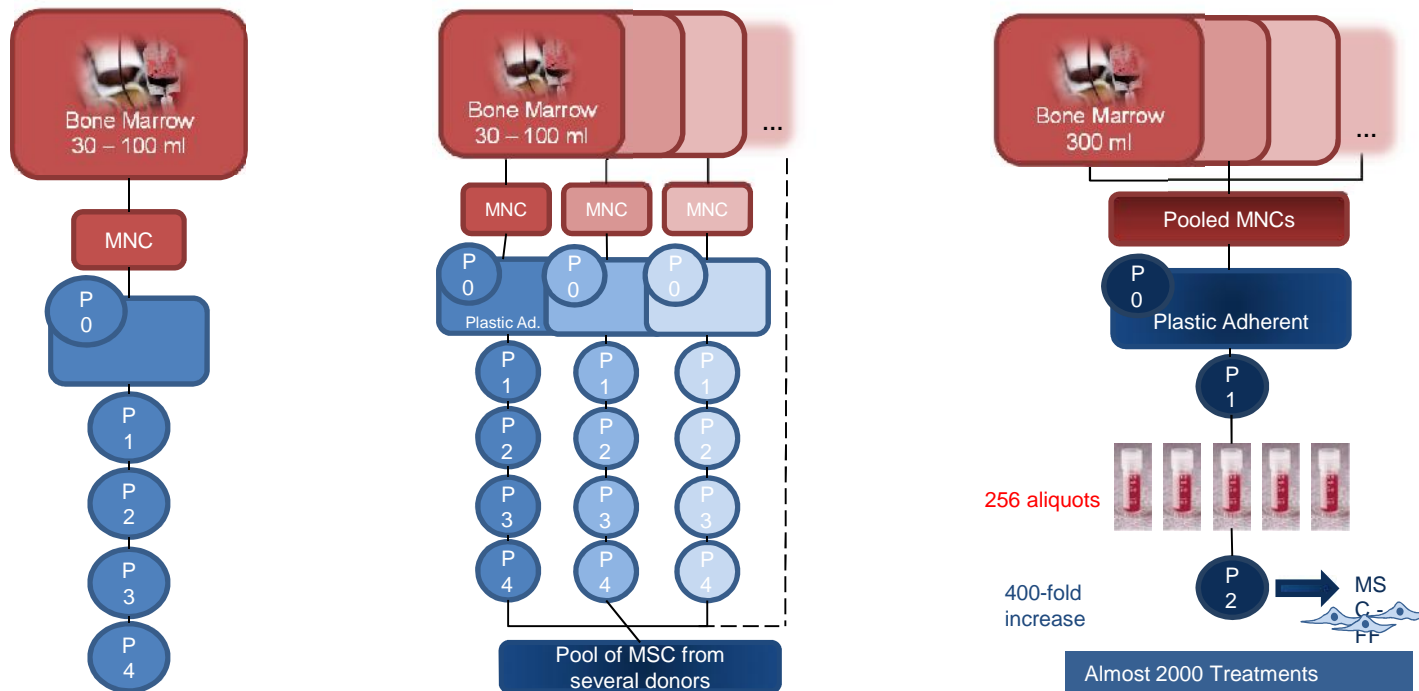
- Efficacy to generate MSC
- Proliferation of MSC
- Differentiation capacity
  
- Possibility for standardization?



Kuçi, et al.: Haematologica 2016



## Generation of a GMP-grade MSC Cell Bank

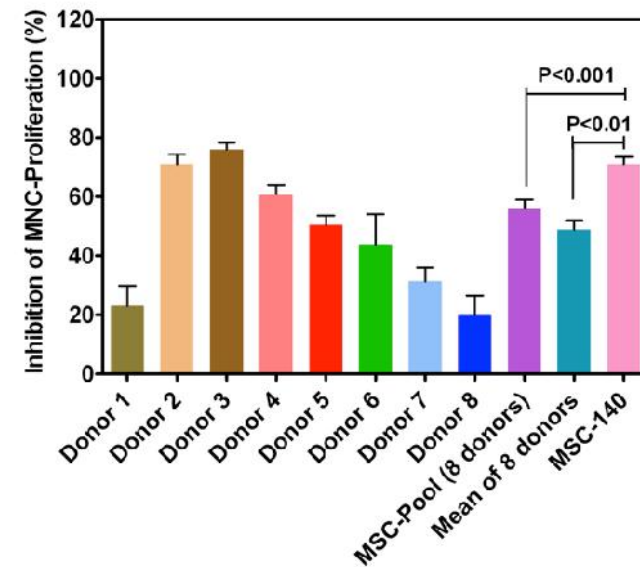






## MSC-FFM – A Standardized Product with Predictable Effectiveness

- *In vitro* higher allosuppressive potential than conventional MSC
- Standardized product, hence predictable effectiveness

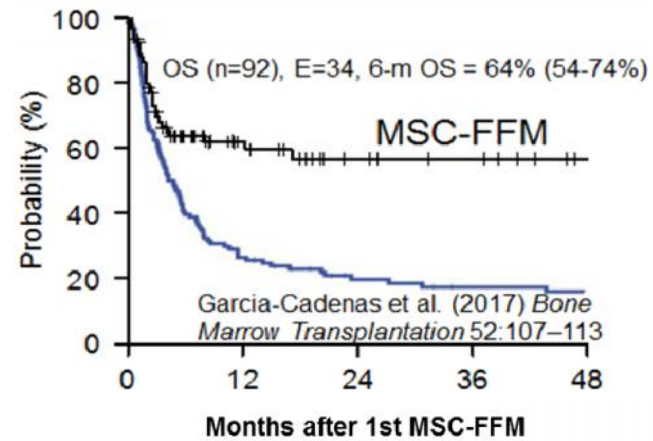
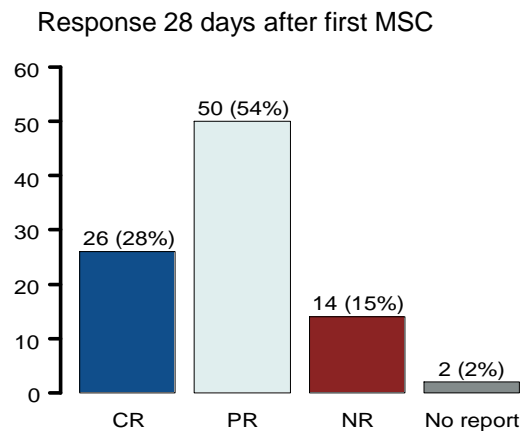


Kuçi, et al.: Haematologica 2016



## MSC-FFM as a Rescue Therapy in Patients with severe GvHD

- Highly effective for aGvHD treatment



32 days after 4th MSC-discharge



## A clinically approved “Off-the-shelf” MSC Product

- Analysis of outcomes after routine post-approval treatment  
69 patients  
19 centers, 6 countries

Study	Patient numbers	aGVHD Grade N(%)	Response Day 28 N (%)	OS N (%)
Bader et al.; 2018	n = 69 ≤18 : n = 51 >18 : n = 18	aGvHD II: n = 3 (4%) III: n = 25 (36%) IV: n = 41 (59%)	CR = 31.9% PR = 50.7% OR = 82.6%	6-month OS = 71 ± 6%

- Licensed in Germany acc. to Hospital Exemption for treatment of steroid-refractory aGvHD
- Randomized trial for the treatment of steroid ref. aGvHD to start in 2019



## Patent Protection of MSC-FFM

- EP Priority Patent Application filed on July 16<sup>th</sup>, 2014
- European Patent granted EP no. EP Nr. 14 177 312.7 (validated in DE)
- Patent proceedings pending in AU, BR, CA, CN, EA, EP, IN, JP, IR, KR, MX, NZ, SA, SG, UA, US

(16) (17)

(11) EP 2 975 118 B1

(12) EUROPEAN PATENT SPECIFICATION

(43) Date of publication and mention of the grant of the patent:  
24.08.2016 Bulletin 2016/34

(51) Int. Cl.:  
C12N 03/09 (2014)

(21) Application number: 14177312.7

(22) Date of filing: 18.07.2014

(54) Generation of a mesenchymal stromal cell bank from the pooled mononuclear cells of multiple bone marrow donors  
Erzeugung einer mesenchymalen Stromazellenbank von mononucleären Zellen mehrerer Knochenmarkspender  
Génération d'une banque de cellules stromales mésenchymales provenant des cellules mononucléaires en pool de donneurs de moelle osseuse multiples

(57) Abstract: [Text partially obscured]

(84) Designated Contracting States:  
DE

(86) Reference to: WO-A-2011064732

(13) Date of publication of application:  
20.08.2016 Bulletin 2016/33

(71) Applicant:  
• Johann Wolfgang Goethe-Universität, Frankfurt am Main  
80333 Frankfurt am Main (DE)  
• ORK Biotechnologies  
Ruden-Wilhelmstr. 6, Rosen 95044  
95048 Rosenheim am Main (DE)

(72) Inventors:  
• Stefan Peter  
03133 Dusseldorf (DE)  
• Axel Sehm  
60599 Frankfurt am Main (DE)  
• Karl Zyslein  
60598 Frankfurt am Main (DE)  
• Birgit Malsch  
60427 Frankfurt (DE)

(74) Representative: Krause, Jan  
Börschmann & Partner  
Anwaltskanzlei mbH mbH  
Rudow-Strasse 15-17  
10335 München (DE)

(88) References cited:  
• O'RINGDEN ET AL. "Pooled MSCs for treatment of severe hemophilia," *STEM CELL TRANSPLANTATION*, vol. 6, no. 8, 1 August 2011 (2011-08-01), pages 1161-1169, XP05542474, ISSN: 1525-2875, DOI: 10.1038/sc.2010.202

• KHUSHNUMA COOPER ET AL. "Establishment of a Mesenchymal Stem Cell Bank," *STEM CELL INTERNATIONAL*, vol. 16, no. 1, 1 January 2011 (2011-01-01), pages 123-129, XP05918844, ISSN: 1547-3288, DOI: 10.1186/1547-3288-16-1-123

• THIRUMALA SRIBESHVAR ET AL. "Manufacturing and banking of mesenchymal stem cells," *EXPERT OPINION ON BIOLOGICAL THERAPY: SUPPLEMENTAL THERAPY*, vol. 13, no. 5, 1 May 2013 (2013-05-01), pages 673-699, XP059190164, ISSN: 1744-7625, DOI: 10.1177/1744762513505920

• SIMONE DAL POZZO ET AL. "High recovery of mesenchymal progenitor cells with non-density gradient separation of human bone marrow," *CYTOTHERAPY*, vol. 12, no. 5, 1 September 2010 (2010-09-01), pages 179-186, XP059191636, ISSN: 1473-3099, DOI: 10.1089/cyt.2010.0150

How to cite this document: EP 2 975 118 B1

EP 2 975 118 B1

Printed on: 25/01/2016 14:56:29



## MSC-FFM Commercialization

- Exclusive License of MSC-FFM Patent Rights to medac, Wedel, Germany
- Marketing of MSC-FFM for Treatment of SR-aGvHD
- Production at German Red Cross Blood Center, Frankfurt am Main



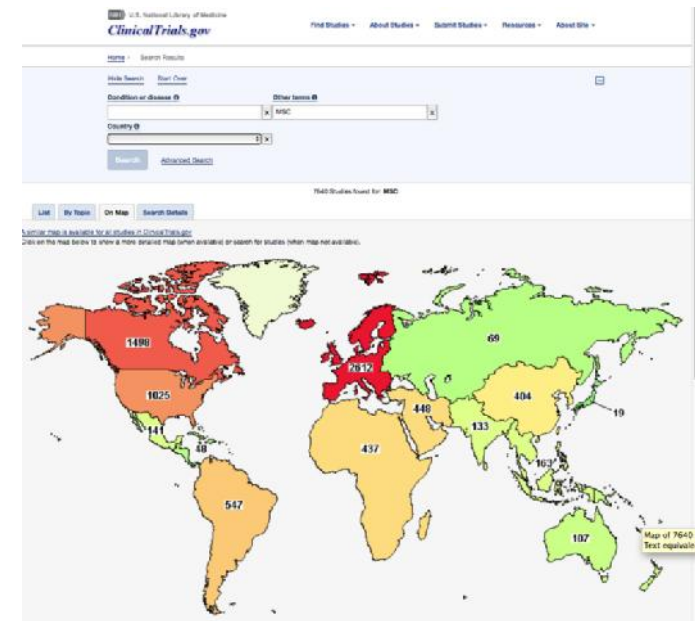


## MSC-FFM Therapy – Future Indications

### Studies Using MSC 2019 Clin. Gov. – 7,640 Studies

#### Medical Indications of Interest:

- Avascular Osteonecrosis
- Acute Respiratory Distress Syndrome (ARDS)
- Distress Syndrome in Premature Neonates
- Prediabetes (Honeymoon Period)





## MSC-FFM for Treatment of Osteonecrosis

### **Risk factors:**

ALL, high dose steroids, radiation therapy,  
young age

### **Incidence:**

ALL patients: 29 % children, 8 % adults  
within 10 years after radiation therapy

### **Therapy:**

Corrective Osteotomy, Joint replacement



[https://images.radiopaedia.org/images/4140964/f9534d67db53e92896907762042afb\\_big\\_gallery.jpg](https://images.radiopaedia.org/images/4140964/f9534d67db53e92896907762042afb_big_gallery.jpg)



Ein Unternehmen der  
Johann Wolfgang Goethe-Universität Frankfurt am Main



Prof. Dr. Peter Bader, Dr. Selim Kuci, Dr. Zyrafete Kuci  
Pediatric Stem Cell Transplantation & Immunology, University Hospital Frankfurt/Main

Prof. Dr. Halvard Bönig, Frankfurt am Main  
German Red Cross Blood Center, Institute for Transfusion Medicine and Immunohematology, Frankfurt/Main

Dr. Kirstin Schilling, Innovectis GmbH, Frankfurt/Main