Platelet-rich plasma improves the therapeutic efficacy of mesenchymal stem cells by enhancing their secretion of angiogenic factors in a combined radiation and wound injury model.

Myung H et al.

Exp Dermatol. 2019 Sep 27. doi: 10.1111/exd.14042.

Radiation Therapy vs. skin

- 60% radiotherapy patients experience radiation-induced skin injury
  - Damage to the skin barrier
  - Prolonged cell cycle
  - Disturbed proliferation of endothelial cells and fibroblasts
  - Decreased neovascularization (endothelial dysfunction) and collagen synthesis
  - Delayed wound repair and remodelling
    - VEGF, TGF-ß , fibroblast growth factors

MSCs – Cells of hope and glory

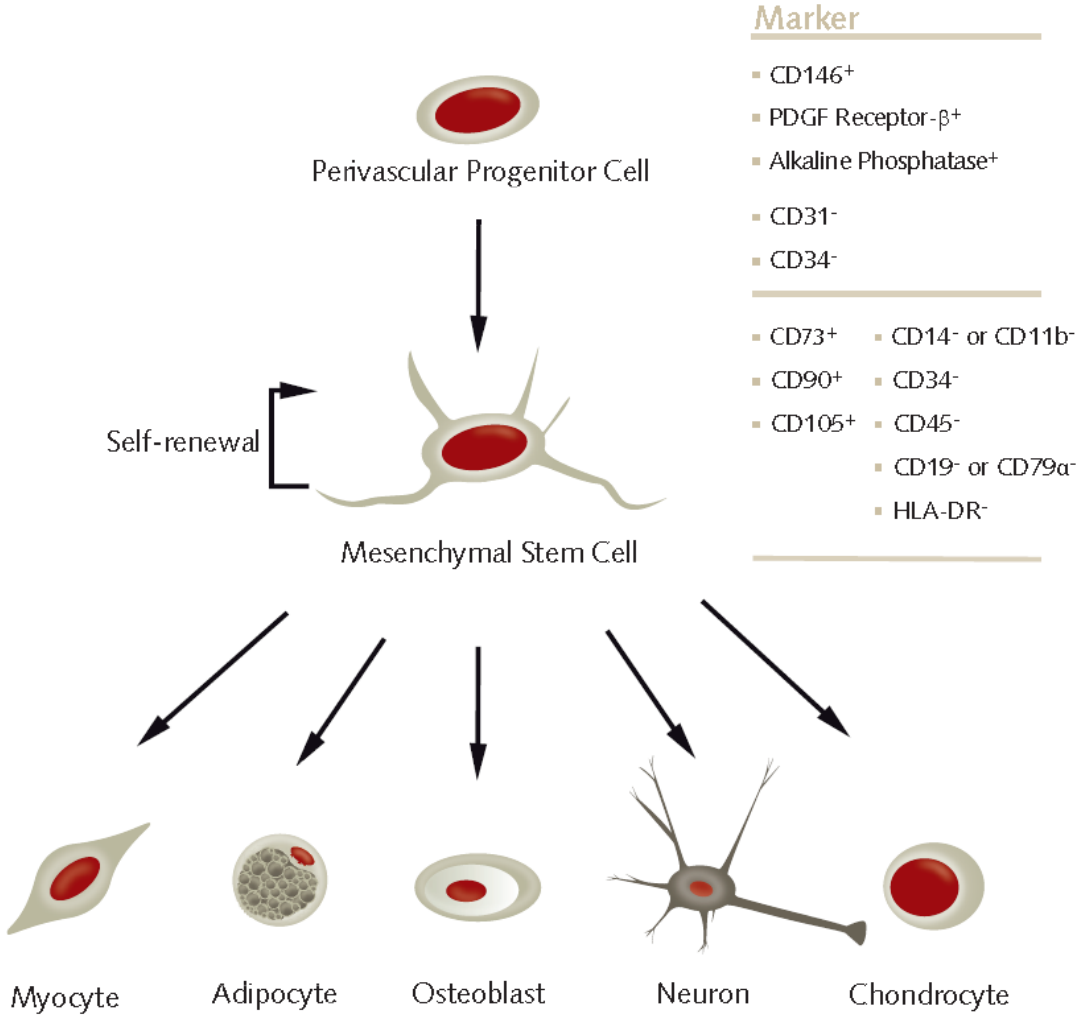
- Mesenchymal stem cells – novel therapeutic agent
- Promising in regeneration and tissue repair
- Wound healing potential (critical limb ischemia, diabetic wound)
- Self renewal capacity and differntiation potential (multipotent)

- Easily isolated
- BM MSCs, UCB MSCs, AT MSCs – plentiful supply, no ethical issues

- Results remain somewhat uncertain

- MSC engraftment improved via neovascularization potential boosting?

MSCs – Cells of hope and glory



PRP – Platelets Resolve Problems

- Platelets and wound healing:
  - release especially growth factors (haemostasis, angiogenesis)
- Easy and safe application (in human autolog)

- Platelet-rich plasma = blood-derived fraction enriched with platelets
- Work well to treat: mild arthritis, small tendon/ligament tears or degeneration, torn spinal discs

PRP – Platelets Resolve Problems

„PRP“ Activation:

- Freeze-thaw process (85%)
  - Problem: platelet cryopreservation effect
- Calcium + Thrombin (receptor activation ->platelet aggregation, intracellular alpha-granule lysis)
  - Risks: allergic reactions, xenogen
- Bead mill homogenizer

Material and Methods

- Platelet-rich plasma from UCB

- UC-MSCs (Passage 4)
  - Medium: minimal essential medium-alpha, 10% FBS, 1% AB
- ELISA-Kits (R&D)
- PCR
- Tube-like structure formation assay
- Histologic examination

Material and Methods

- Combined radiation and wound injury

  SKH-1 hairless mice (male)

  Irradiation: 20-Gy x-ray 27, 28

  5 groups a 8 mice:

  - non irradiated
  - irradiated
  - irradiated + PRP
  - irradiated + UCB-MSCs
  - irradiated + UCB-MSCs + PRP

  Implantation at the beginning and after one week , euthanize after 3 weeks

Results

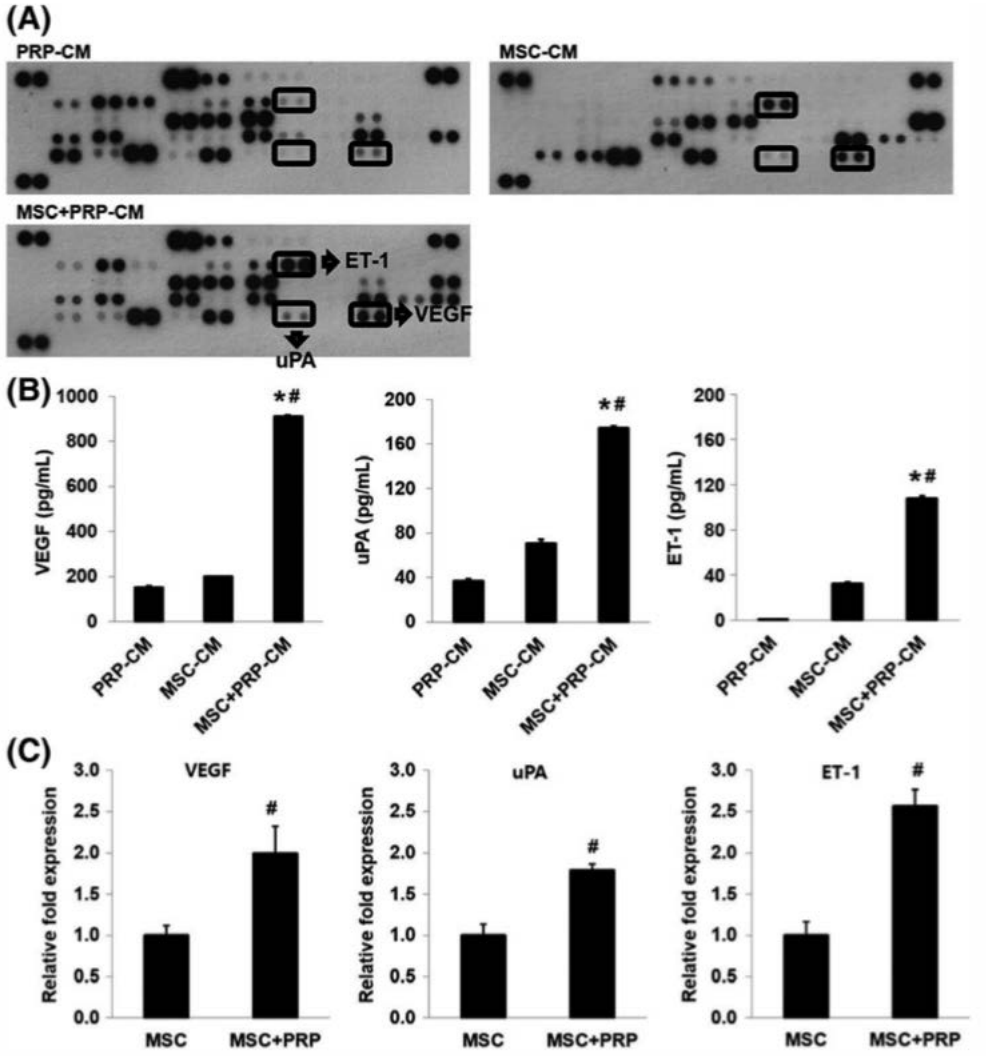


Figure 1) Analysis of angiogenic factors synthesized and secreted by UCB-MSCs in 3 Conditions

A: Cytokine Array

B: CM-ELISA

C: PCR

Results

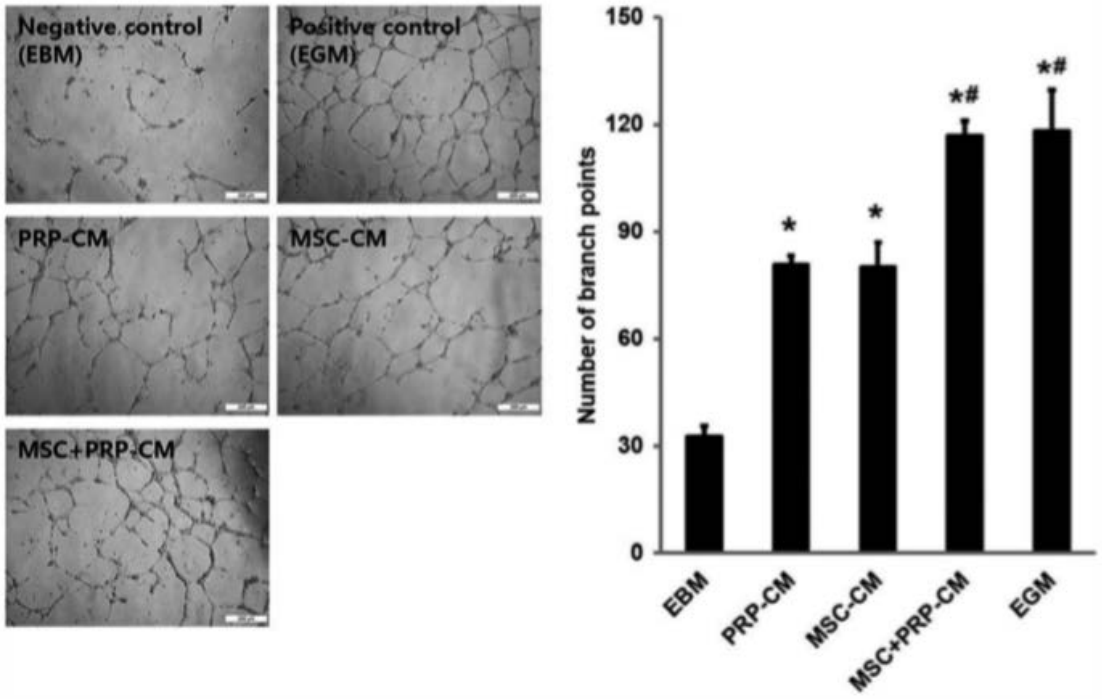
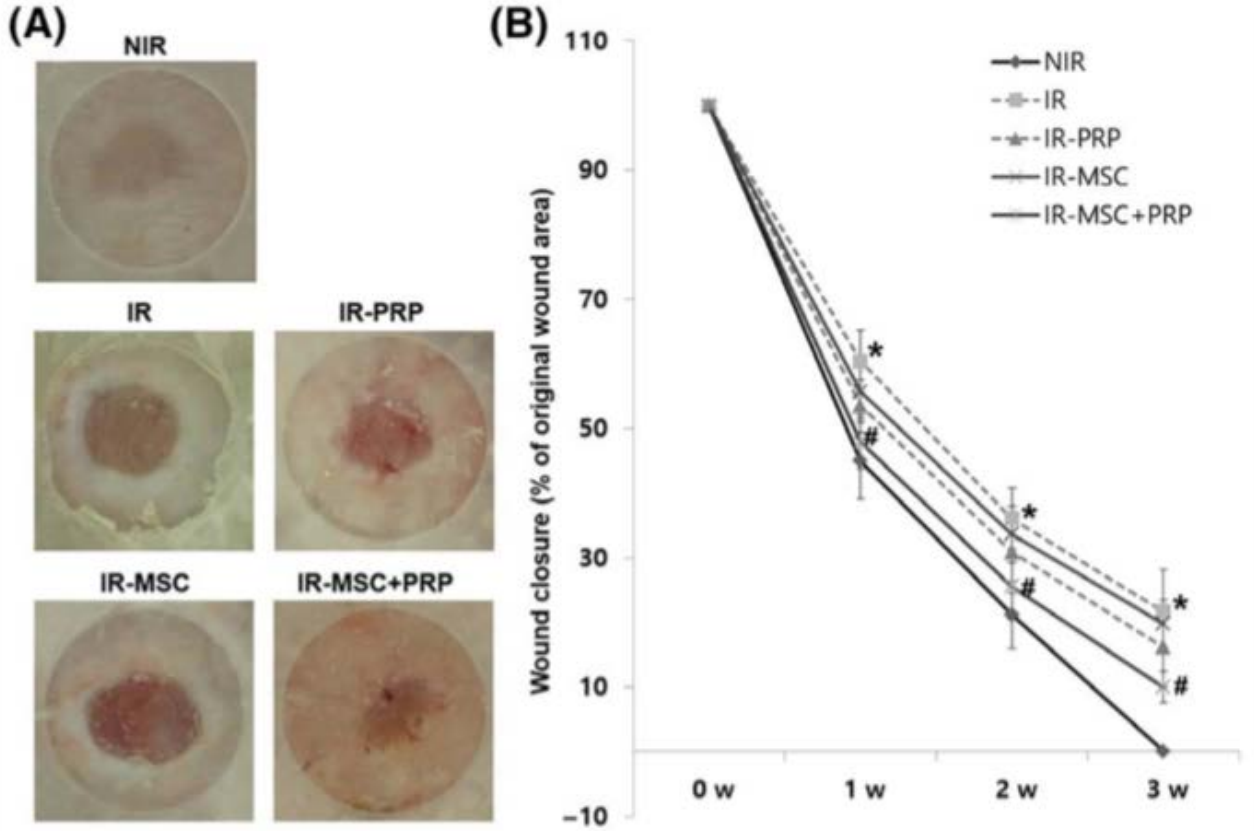


Figure 2)

Tube-like structure formation assay in HUVECs

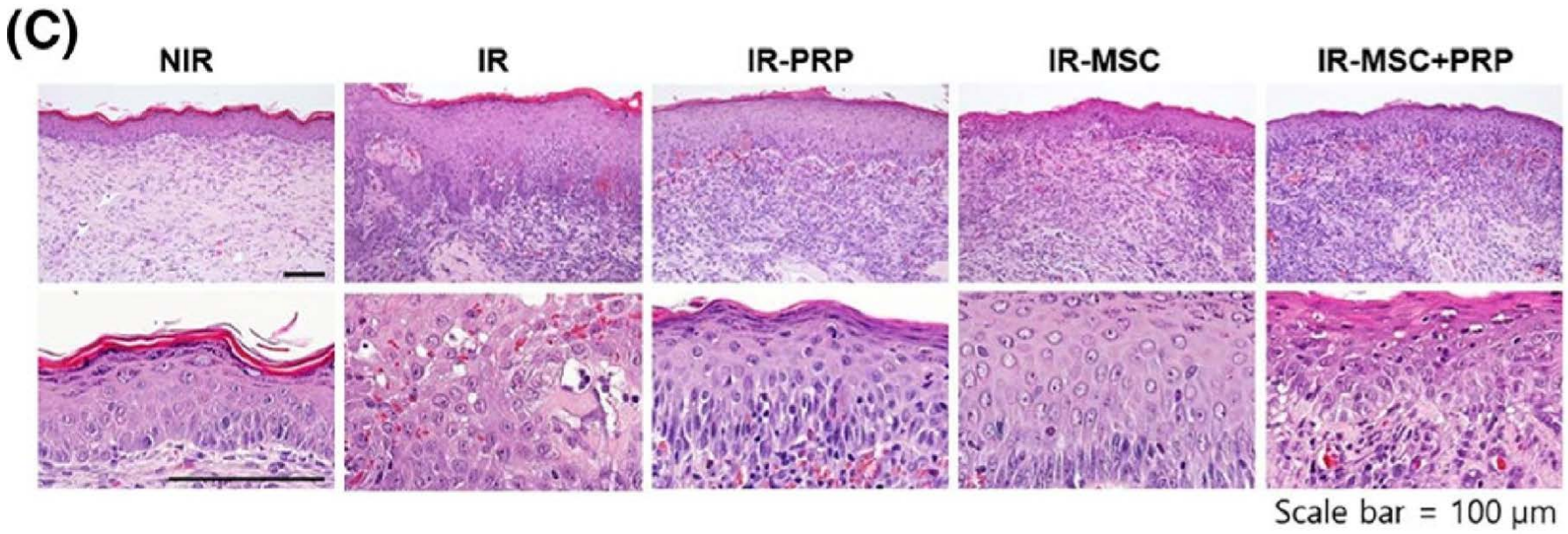
Results

Figure 3) CRWI –model



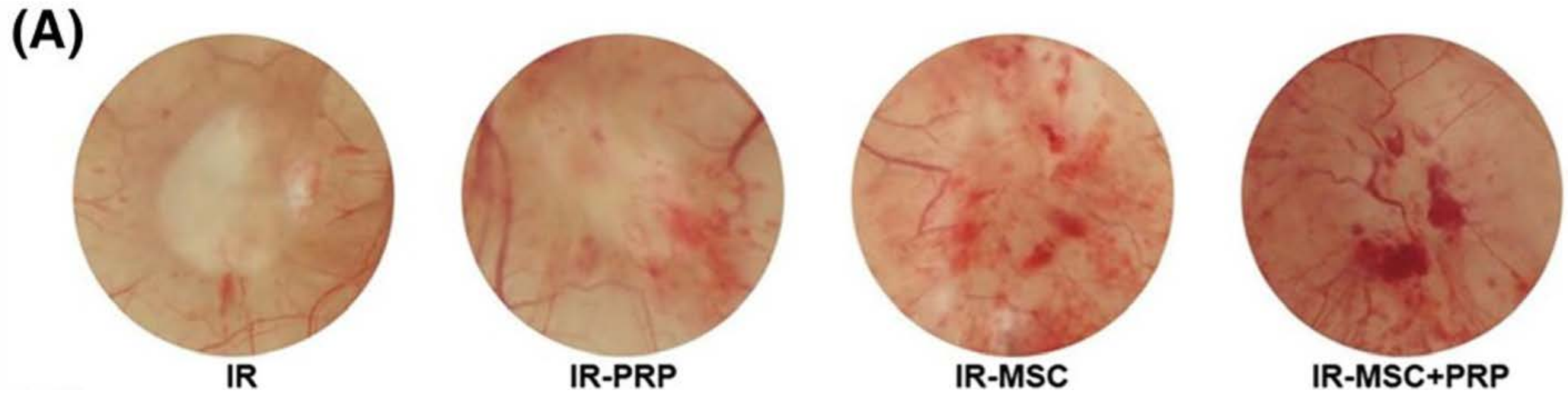
Results

Figure 3) CRWI –model



Results

Figure 4) Angiogenic effect of UCB-MSCs and PRP in a CRWI-model



Results

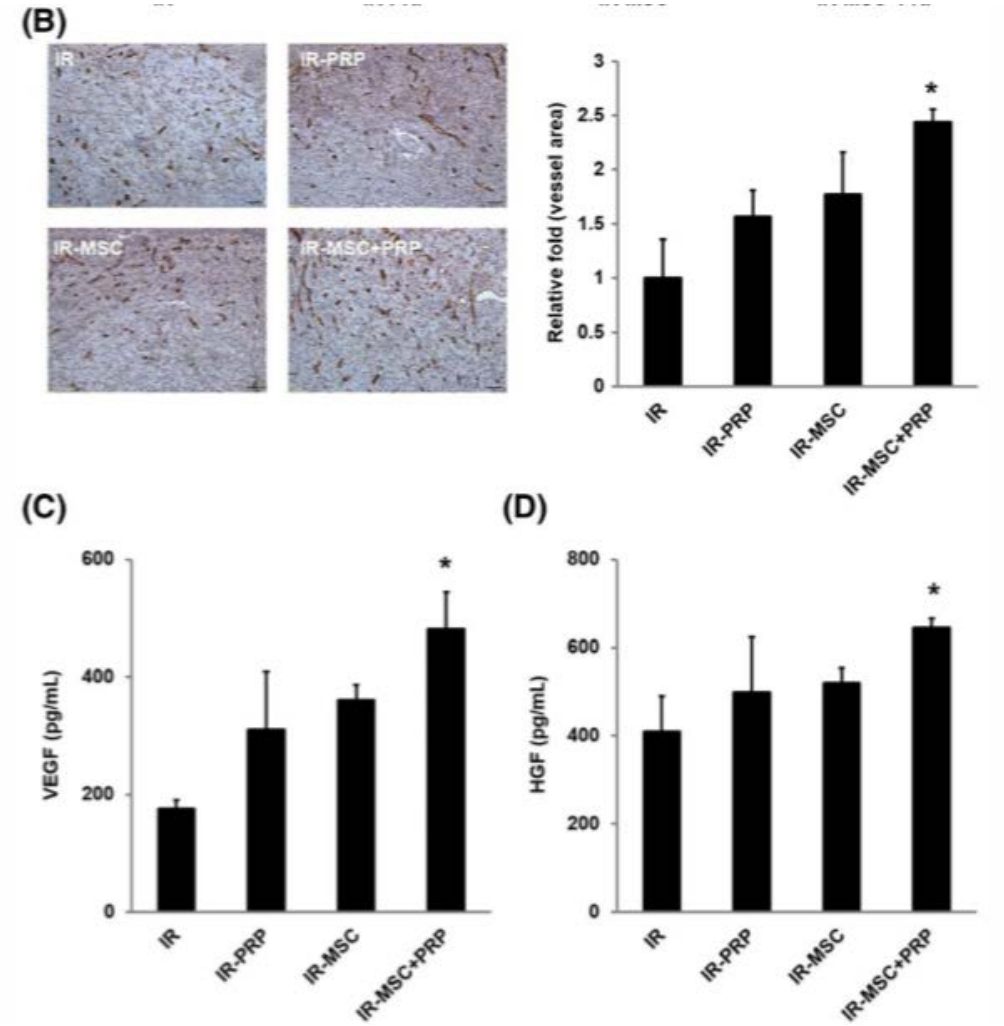


Figure 4) Angiogenic effect of UCB-MSCs and PRP in a CRWI-model

B: Morphometric Analysis (CD31-stained)

C/D: VEGF / HGF measured in the wound bed

Discussion

- PRP promotes cell growth and chemotaxis … promising vehicle for MSCs in cell therapy
- PRP enhances skin repair efficacy of UCB-MSCs (activates paracrine effects)
- Increased synthesis and secretion of angiogenic factors (VEGF, ET-1, uPA) by UCB-MSCs cultured in PRP may enhance angiogenesis in vitro
- Previous Study: UCB-MSCs alone don´t accelerate wound healing in CRWI model
- Combination accelerates epidermal and dermal regeneration in CRWI model
- VEGF and HGF increase in vivo model -> enhance angiogenesis and wound healing

Conclusion

- Effect of PRP on paracrine secretion by UCB-MSCs
  - Release of angiogenic factors improved (in vitro)
  - Angiogenesis and wound healing promoted (in vivo CRWI –model)

  - PRP can improve the therapeutic efficacy of UCB-MSCs

Limitations of the study

- Xenogen (human in mouse)
- UCB for PRP
- PRP and platelet lysate?!?!?!
- Long term effect on the skin complete recovery? (histology)