DDAH says NO to ADMA
Let the beads go on

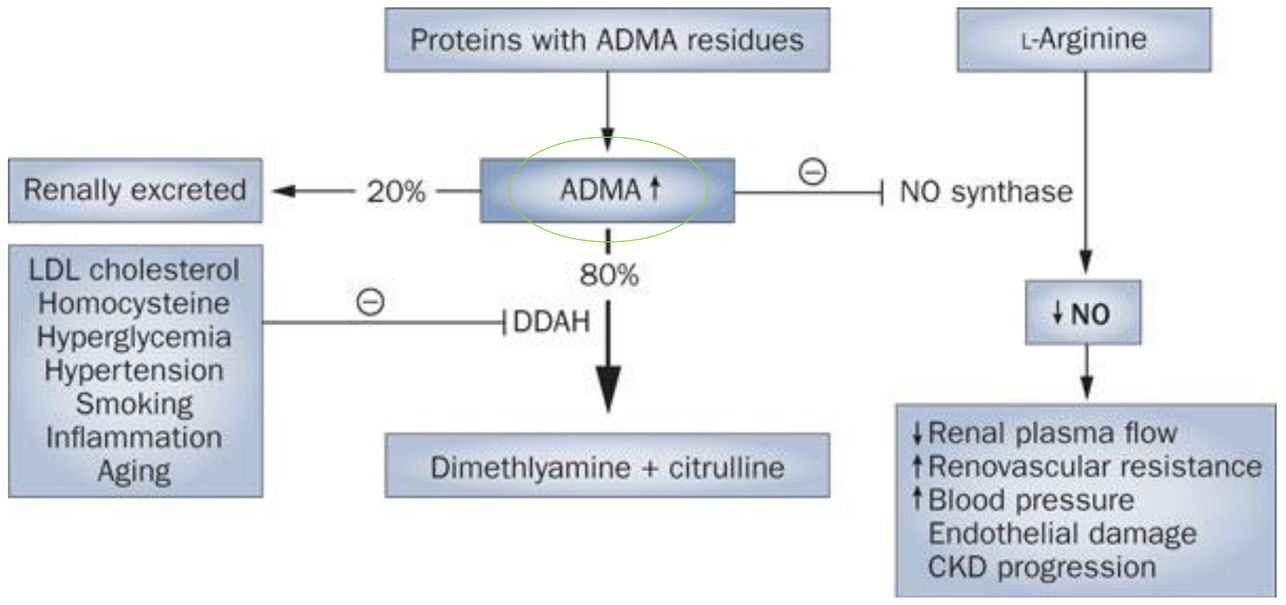
Olivier C. Manintveld, E.K. van den Akker, M. van de Heuvel, H.J. Houtgraaf, H. Kirisli

Molecular Cardiology Laboratory, Thoraxcenter, Erasmus University Medical Center Rotterdam, The Netherlands;
Department of Experimental surgery, Erasmus University Medical Center Rotterdam, The Netherlands;
Department of Cardiology, Thoraxcenter,Erasmus University Medical Center Rotterdam, The Netherlands
Department of Medical informatics, Erasmus University Medical Center Rotterdam The Netherlands

Introduction

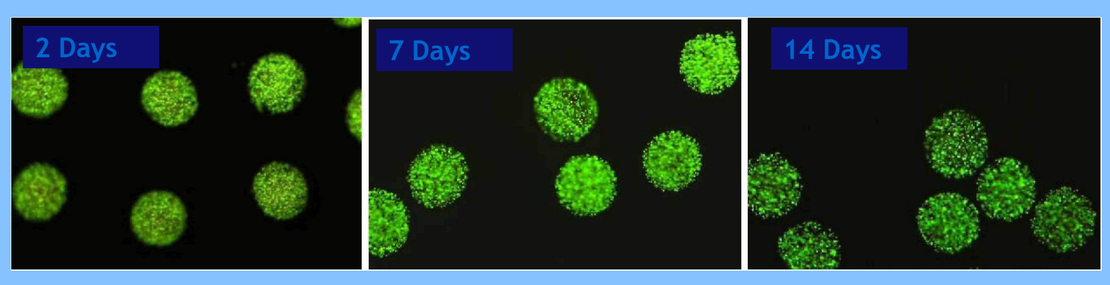
With aging populations and rise in diseases like diabetes and hypertension, incidence of chronic renal failure is rising. Renal disease results in increase of Asymmetric Dimethylarginine (ADMA) in the blood. ADMA is a byproduct of cell metabolism and acts as a NO-inhibitor. ADMA has been shown to be a strong predictor of cardiovascular mortality in patients with renal disease. Also, high ADMA-levels (and thus NO-inhibition) contribute to hypertension, immune dysfunction and cardiovascular disease. More specifically, comorbidities like polyneuropathy, atherosclerosis and progression of kidney disease.
DDAH is the endogenous enzyme that accounts for over 80% of ADMA clearance, whereas 20% is excreted by the kidney. In chronic renal disease, DDAH levels are declined. Increasing DDAH expression will result in ADMA degradation and therefore in a decrease in concominant morbidity and mortality. In this aspect, cell therapy will be a novel approach.

Cell beads were recently developed as potential devices for continuous delivery of high concentrations of endogenous proteins that would otherwise be rapidly degraded. Cell beads are 170 µm alginate microspheres that contain mesenchymal stem cells (MSC) genetically modified to express high levels of DDAH-1. Transplanting cell beads in patients suffering from chronic renal failure might reduce ADMA and ultimately abrogate morbidity, and attenuate progression of renal disease.
Also MSC secrete several immunomodulatory cytokines that have been shown to attenuate inflammation and might have an additional beneficial effect on renal disease.
Lastly, inherent angiogenic factors (i.e. VEGF) produced by MSC might enhance angiogenesis and improve endothelial function (NO and EDHF), thereby reducing cardiovascular disease.

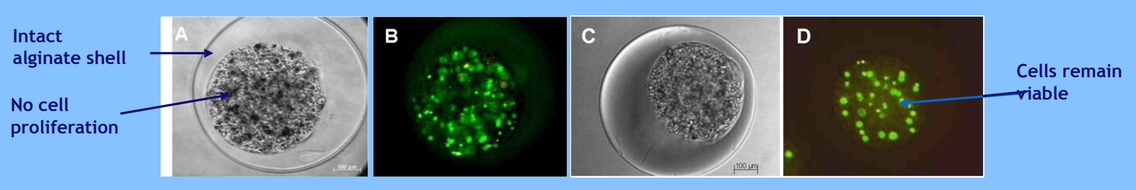


Viability was tested by implantation of CellBeads containing hMSC into rats

- **>90% viability** established for the encapsulated hMSC cells post explantation after **14 days**
- Mesenchymal **s**tem **c**ells remain **viable**, even after **6 months implantation**

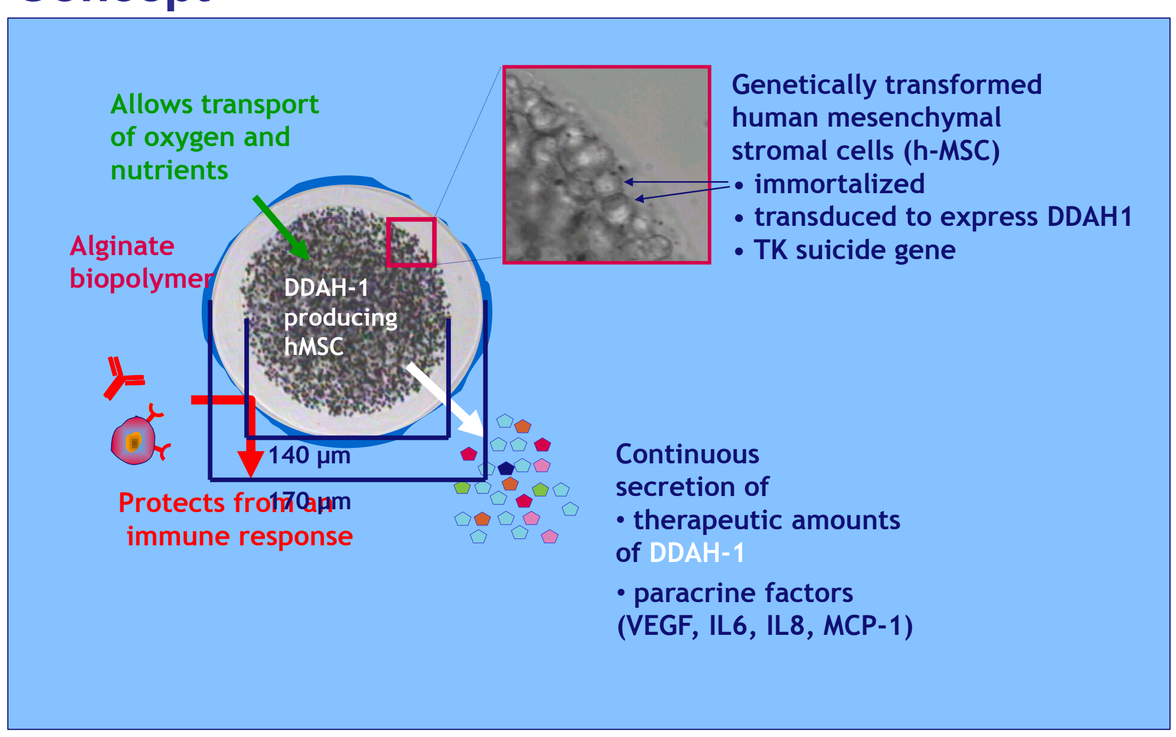


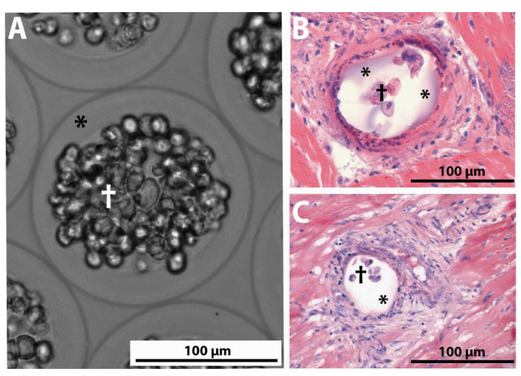
Example fluorescence microphotographs of cell beads explanted from rats.



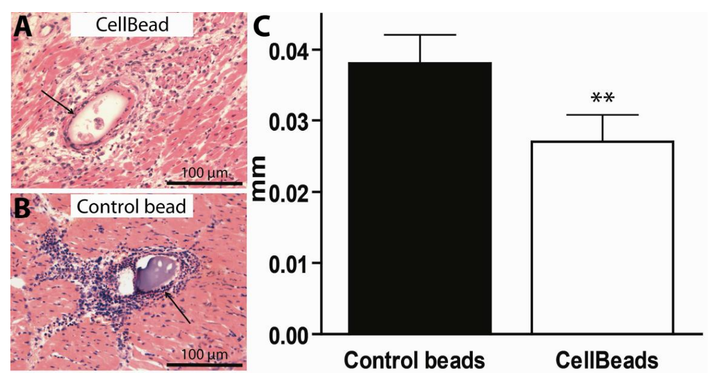
Microphotographs of cell beads explanted after a 3 month (A, B) or 6 month (C, D) implantation period in the brain of rats

Concept



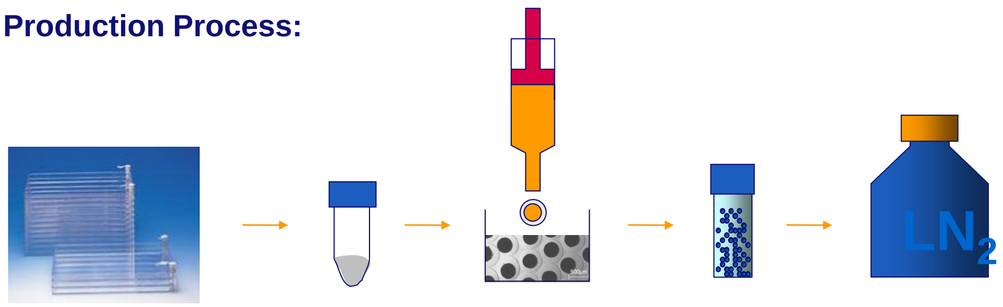


A. Light photomicrograph of a cell bead prior to infusion. B. H&E stained section of a coronary arteriole containing one cell bead, two days after infusion. C. H&E stained section of a coronary arteriole containing one cell bead, seven days after infusion. The intact alginate (*) can be seen containing MSC(†).



Peri-bead inflammatory infiltration after two days. A. A thin rim of neutrophilic granulocytes is evident surrounding a single cell bead (arrow). B. A more pronounced inflammatory reaction around a control alginate bead (arrow). C. Comparison of inflammatory reaction reveals significant decrease in inflammatory response to the cell beads as compared to the control alginate beads (** P= 0.001)

Production Process:



A well characterized human MSC
A GMP Master Cell Bank exists for these h-MSCs
Manufactured to GMP standards
Are stored frozen, with simple thaw process prior to use

Conclusion

DDAH-1 eluting cell bead transplantation may provide a new therapeutical approach to the treatment of chronic renal failure and prevent progression, concominant morbidity and mortality.
This will reduce need for kidney transplantation, and costs associated with the treatment of chronic renal failure as dialysis and expensive immunosuppressive therapy.