Optimising P(MMA-NVP) hydrogels for orthotropic, self-inflating tissue expanders

Ms Jessica R Smith[1], Dr Zamri Radzi[2], Dr Jan T Czernuszka[1]
[1]Department of Materials, Parks Road, Oxford, OX1 3PH
Jessica.smith@materials.ox.ac.uk
[2]Faculty of Dentistry, University of Malaya, 50603 Kuala Lumpur, Malaysia

Introduction and Aims

Tissue expanders are used to grow excess skin prior to reconstructive surgery[1]. A device is implanted below the skin and is subsequently inflated. As it expands it stretches the overlying tissue and causes it to grow. At the time of surgery the device is removed and this new, healthy skin can be used in the reconstruction. It is an alternative to skin grafting.

Current tissue expansion devices consist of a silicone balloon, a filling tube and a metal port. It is inflated with weekly saline injections. However these devices are bulky, require regular hospital visits for injections, and expand equally in every direction[2]. This makes them unsuitable for a number of anatomical sites, such as the palate, eye lid and digits. There is evidence that tissue expansion could improve the success of surgeries in these locations (particularly in the restoration of a cleft palate, cross-bite and anophthalmia) and so a new device must be developed to meet this need.

Work has been done on hydrogel tissue expanders, which self-inflate when implanted under the skin by absorbing tissue fluid[3]. This device has a smaller starting size, and does not require injections in order for expansion to occur, but is still inappropriate for use in the previously mentioned locations as it expands isotropically. In order to overcome this final hurdle, orthotropic hydrogels have been developed. These consist of poly(methylmethacrylate-co-N-vinylpyrrolidinone) [P(MMA-NVP)] hydrogel, which has been compressed at the glass transition temperature[4]. When hydrated the compressed hydrogels expand in one direction only (parallel to compression). These new devices have significant potential, and further work has been undertaken to optimise their performance.

In collaboration with the University of Malaya, and with support from Oxtex Ltd, this project aims to optimise P(MMA-NVP) hydrogels, for use as self-inflating, orthotropic tissue expanders. The variation in behaviour with changing compression ratio is observed, as well as the effect of silicone membranes. Finally, the results of animal models are presented.

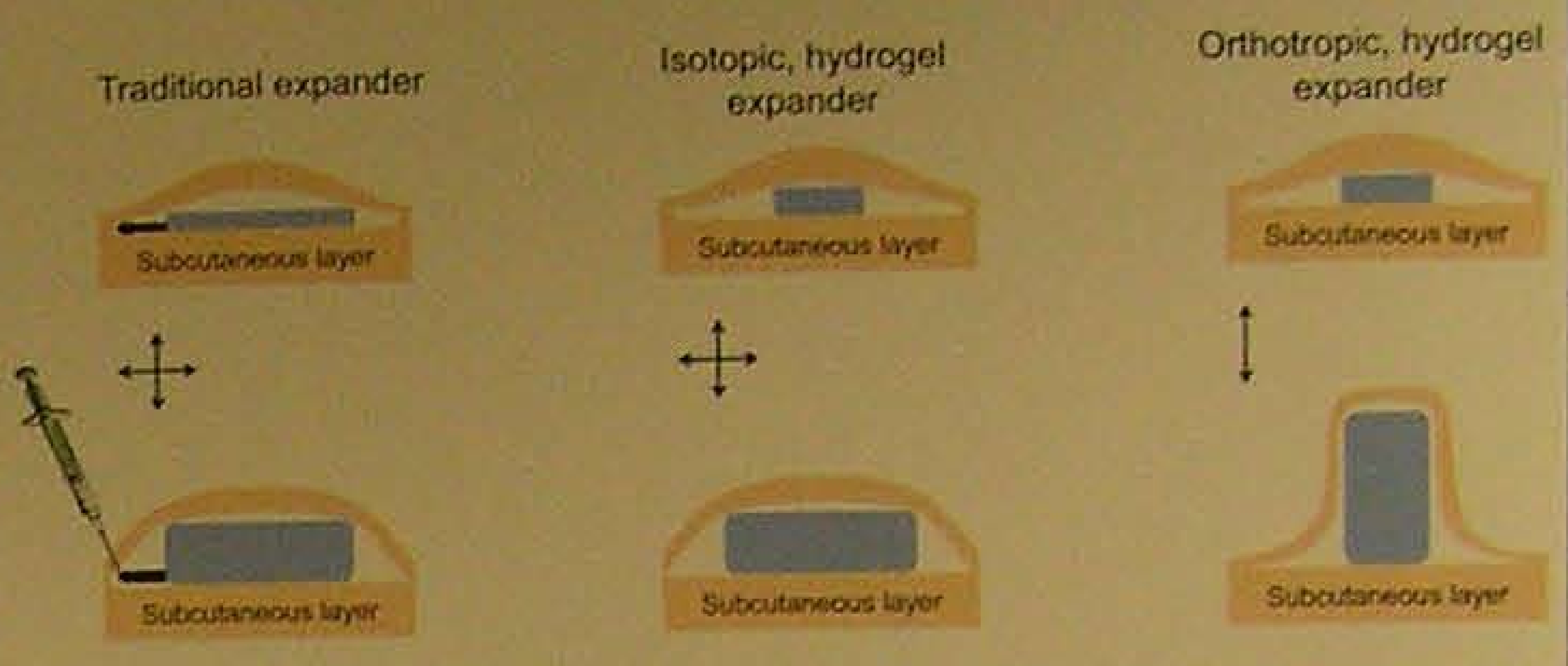
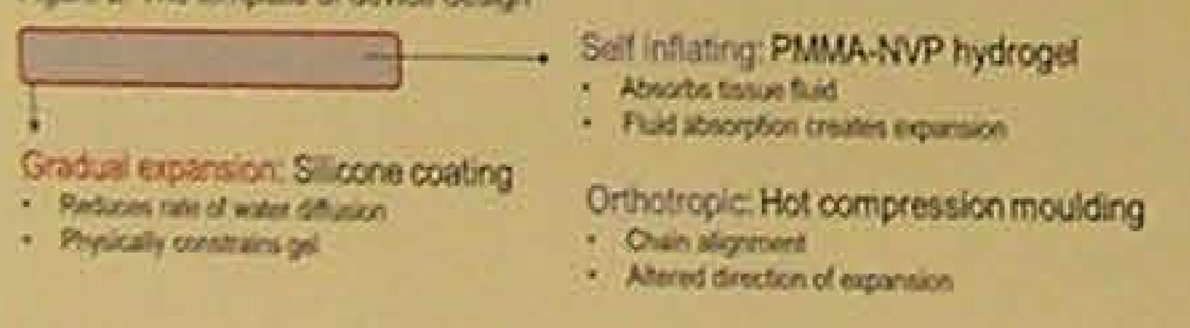


Figure 1. A 2D representation of three types of tissue expander before (above) and after (below) expansion. From left to right: traditional balloon expander, isotropic hydrogel expander, and orthotropic expander. The directions of expansion are indicated by the arrows.

Methods and Materials

P(MMA-NVP) hydrogels were synthesised by Polymeric Sciences Ltd in a ratio of 10:90 respectively. Gels were pressed at the glass-transition temperature and left to cool under a load. Silicone membranes were applied and samples were sterilized using gamma radiation. The compression ratios and silicone thicknesses were varied between samples. The samples were expanded in a water bath at 37°C, with mass and dimension changes measured at regular intervals. The optimum design was then inserted in a both a Wistar rat model and a Dorper sheep model. Figure 2 shows the structure of the device, and Figure 3 and Figure 4 show a comparison between isotropic (not pressed) and orthotropic (compressed) hydrogels on expansion.

Figure 2. The template of device design



Self inflating: PMMA-NVP hydrogel
- Absorbs tissue fluid
- Fluid absorption creates expansion

Gradual expansion: Silicone coating
- Reduces rate of water diffusion
- Physically constrains gel

Orthotropic: Hot compression moulding
- Chain alignment
- Altered direction of expansion

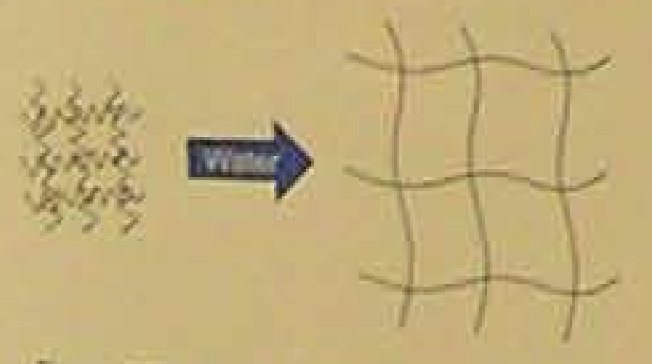


Figure 3. The isotropic expansion of a hydrogel network

Figure 4. The orthotropic expansion of a compressed hydrogel network

Laboratory results

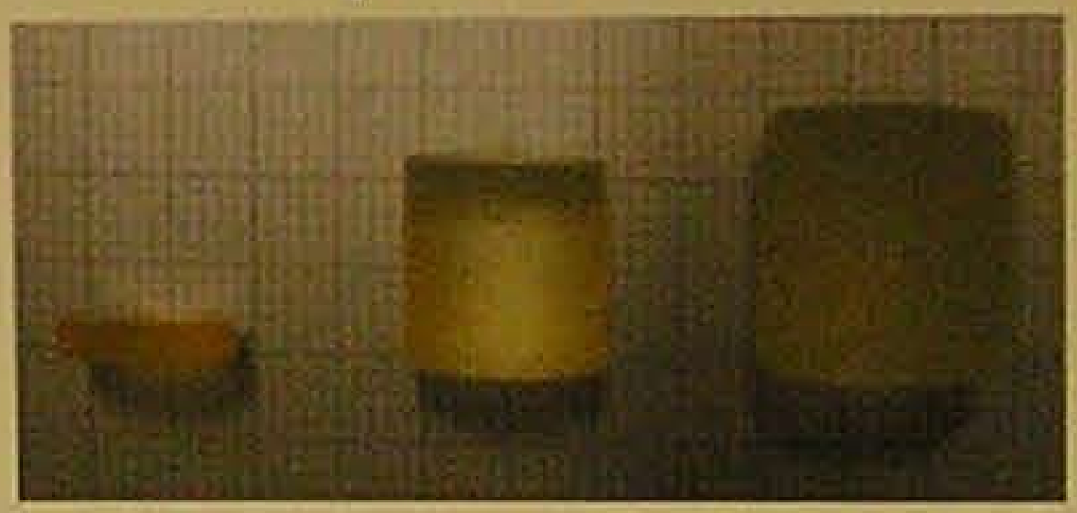


Figure 5. Expansion of a compressed hydrogel (compression ratio 3), before, during, and after expansion.

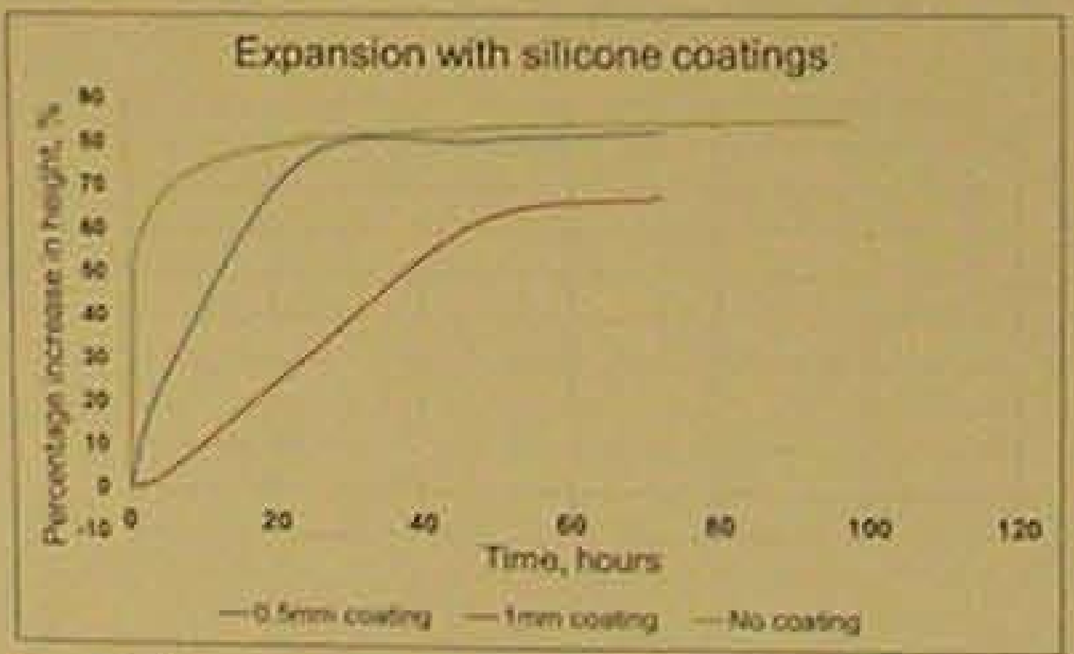


Figure 7. Expansion of hydrogels with compression ratio C=3, with different thickness of coating.

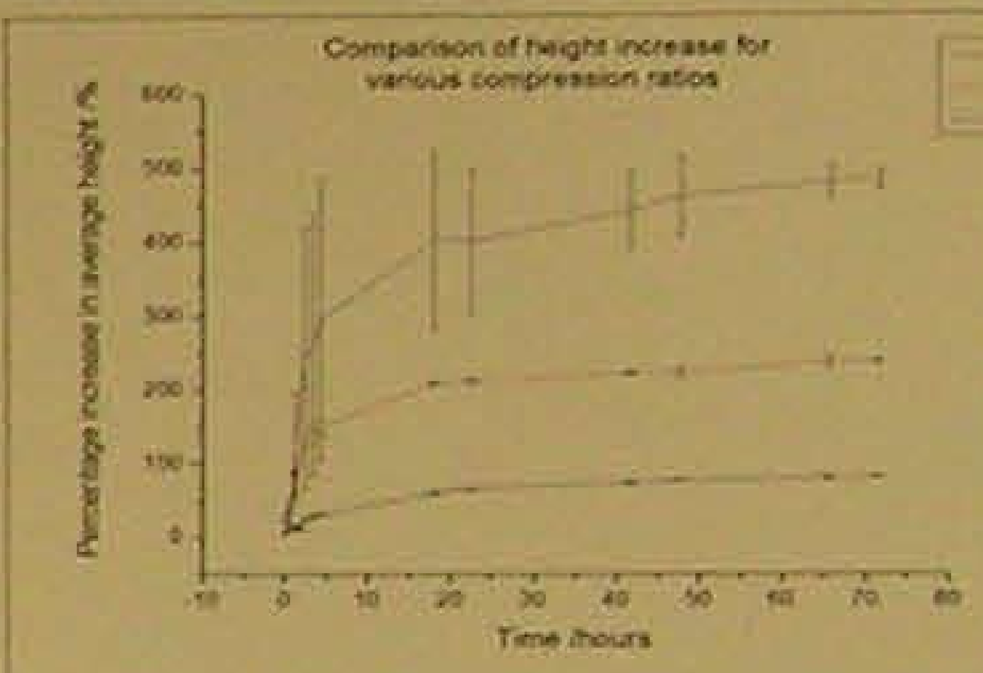


Figure 6. A comparison between three different compression ratios (C=1, C=2, C=3).

Swelling mass uptake results indicate that as the compression ratio is increased, so does the percentage increase in height. For the same samples the percentage increase in mass was found to be constant. Compression ratios of above four were found to be unstable during expansion. A compression ratio of between three and four was found to be both reliable and give a sufficient percentage increase in height. This was tested for a number of initial starting heights and diameters. The minimum successful height was found to be 4mm and the minimum successful diameter was found to be 6mm.

The addition of a silicone coating reduced both the rate of expansion, and the expansion equilibrium. A coating of approximately 1mm was most effective at controlling the initial stages of expansion.

Animal models

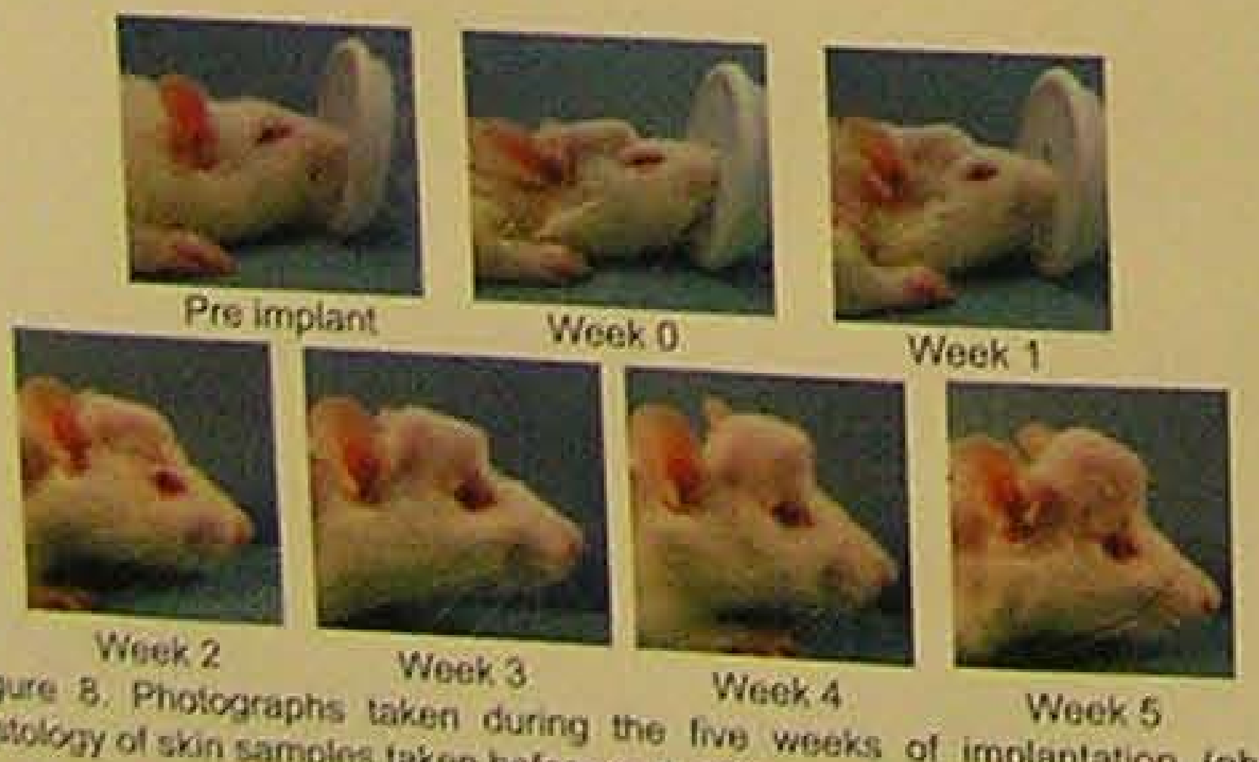
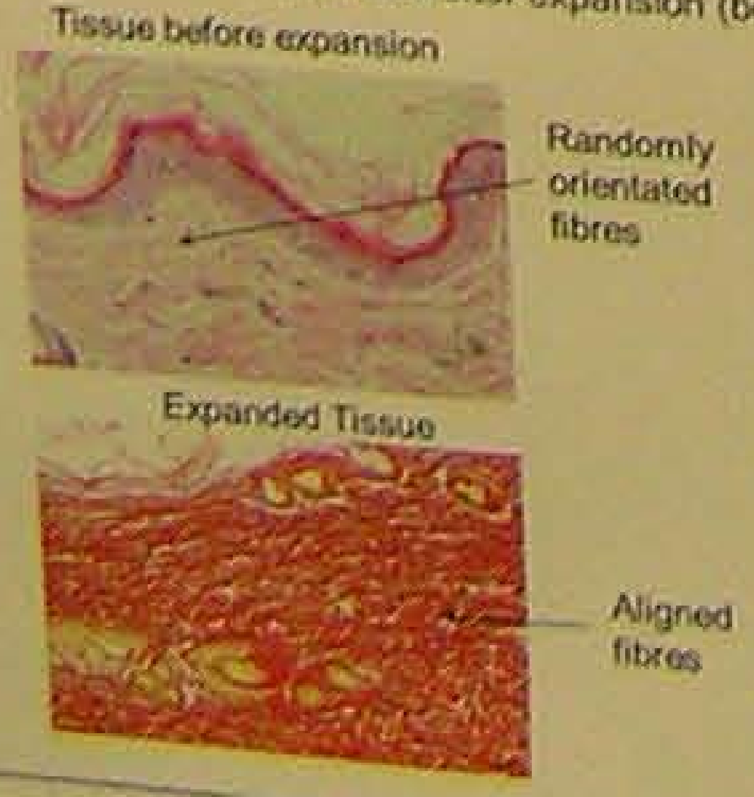


Figure 8. Photographs taken during the five weeks of implantation (above). Histology of skin samples taken before and after expansion (below).



Initial studies in Wistar rats proved very promising. The devices expanded gradually, and orthotropically over the five weeks, creating new tissue. During this time the rats displayed no evidence of pain or discomfort, and there was no disruption to their feeding. Throughout the expansion, there was no distortion to the eye ball, eye socket, or ear. This is a very promising result for those hoping to use this device in delicate areas, such as the palate. Histology of expanded tissue showed a greater degree of alignment in collagen fibres.

Subsequent studies in Dorper sheep have begun, and initial results are very promising. Figure 9 shows photographs taken six weeks after implantation, and new fur is visible on the tissue overlying the device. This suggests that new, healthy skin is being produced. Regular CT scans, Doppler ultra sounds, X-rays and 3D images are being taken, with results expected for publication later this year.

Figure 9. Photographs taken six weeks after implantation in Dorper sheep.

Summary and conclusions

- There is a significant clinical demand for a self-inflating, orthotropic, tissue expander
- This can be achieved by using compressed P(MMA-NVP) hydrogels, with a silicone coating
- A rat model proved successful
- Initial trials in a distal sheep model are promising

Future work in this area will include further analysis of the distal sheep model, followed by a palate model conducted in sheep. The latter will be of great importance as one of the key uses of the device would be in palate reconstructions. If these trials are successful, adult clinical trials will begin in Kuala Lumpur in 2015.

Acknowledgments

The authors would like to thank the Department of Materials at the University of Oxford and the Faculty of Dentistry at the University of Malaya for the use of facilities. We would also like to thank Oxtex Ltd for support and project funding, and the University of Malaya High Impact grant for funding (number: UM.C/625/1/HIR/MoE/Dent 21). Finally we would like to thank Polymeric Sciences Ltd for supplying the hydrogel.

References

1. "Risk Factors for Complications of Tissue Expansion: A 20-Year Systematic Review and Meta-Analysis" Plast.Reconstr Surg. H.Xiaoxu; Q.Xinhua; L.Qingfeng 2011, 128, 3, 787-797
2. "Advances in tissue expansion" Clinics in Plastic Surgery. Argenta, LC; Marks, MW; Pasyk, KA. 1985, 12, 2, 159-171
3. "Osmotically induced tissue expansion with hydrogels: a new dimension in tissue expansion? A preliminary report" Journal of Cranio-Maxillofacial Surgery. Wiese, K.G. 1993, 21, 7, 309-313
4. "Synthesis and properties of a novel anisotropic self-inflating hydrogel tissue expander" Acta Biomaterialia. Swan, M.C, Bucknall, D.G, Goodacre, T.E.E, Czernuszka, J.T, 2011, 7, 3, 1126-1132