A New Small-Volume MR-Compatible Hollow-Fiber Bioreactor Cell Culture System

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Introduction: Hollow fiber bioreactors (HFBRs) allow three dimensional cell cultures to be grown to high cell densities and maintained for long periods of time under controlled conditions. Currently, however, there is no commercially available bioreactor system that is compatible with conventional MRS/MRI hardware. Moreover, commercial bioreactors are large and expensive to operate which severely limits their use in MRS/MRI research utilizing cell cultures. To overcome these drawbacks we have exploited the capabilities of new high-resolution 3D polymer printing to manufacture small-volume MR-compatible HFBRs (SVMR-HFBRs). The SVMR-HFBR device is compatible with conventional vertical-bore MR magnets (top loading) and do not require any modification of conventional 5 mm RF probes.

Methods: The SVMR-HFBR was designed using the Solidworks CAD program (Dassault Systemes Solidworks, Santa Monica, CA). The Solidworks design was then saved as an STL file, and transferred to an Objet Connex350^{TM} multi-material 3D printer (Objet Geometries Ltd.,, Billerica, MA). The Connex 350 printer can create polymer structures up to 350 mm x 350 mm x 200 mm in size at very high spatial resolutions (42 µm x 42 µm x 16 µm in the x, y and z dimensions). Following printing, the SVMR-HFBR was populated with polysulfone hollow fibers with an OD of 360 µm (Minntech, Minneapolis, MN) that are used to supply nutrients to the cells within the SVMR-HFBR. Demonstration MRI and MRS data were collected on a Bruker Avance 9.4 T spectrometer.

Results: The HFBR design is shown schematically in Fig. 1. The polymers used in the HFBR need to be MR compatible i.e. the materials used cannot distort the magnetic field, nor generate signal in spectroscopic or imaging experiments. Figure 2 and 3 demonstrate the suitability of Objet polymer for MR studies. The SVMR-HBFR design showed a much narrower linewidth (7Hz FWHM) than the 27mm HBFR (30Hz FMHW) while losing only a factor 2 in signal to noise ratio. The smaller volume (60 times less volume compared to the commercial 27 mm OD HFBR used for comparison) is compensated by the higher sensitivity of 5 mm RF probes.

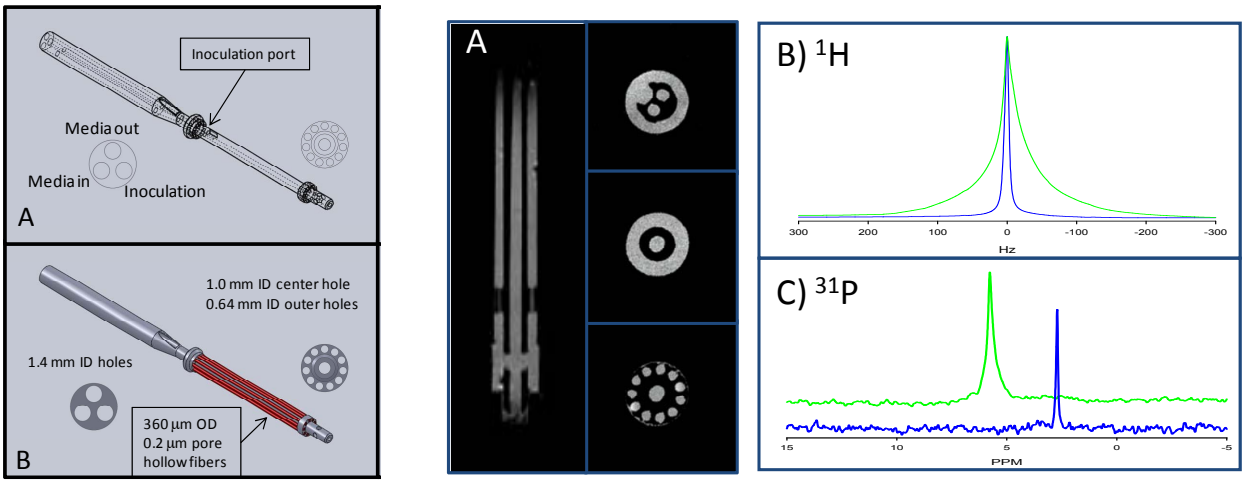

Fig. 1 (Left panel: Schematic Solidworks^{TM} drawings of a prototype small-volume HFBR. A line drawing of the central structure of the HFBR is shown in A. A surface rendering of this structure is shown in Panel B. This structure is printed as a single piece by the Connex 350 printer. Cells can be introduced into the assembled HFBR through the inoculation port that opens to the extrafiber space.; Right panel: A) Longitudinal and cross sectional spin-echo images of the 5 mm bioreactor filled with culture media (in plane pixel resolution = 100 µm). B) Proton spectra of 27 mm (green) and 5 mm (blue) HFBRs filled with culture media. C) ^{31}P spectra collected from 27 mm HFBR and 5 mm HFBRs filled with culture media (5 mM inorganic phosphate, P_i).

Conclusion: A small-volume MR compatible HBFR is presented which is readily built with novel 3D high-resolution printing. This new research tool will allow MR studies of cell cultures to be carried out with better (narrow) spectral lineshapes and only a modest reduction in SNR. Furthermore, the small volume of the HFBR will allow studies to be carried out at a much lower cost, which in turn will allow more specialized cell cultures or contrast agents to be studied.