Tissue-engineered prostate tumours shed light on cancer spread

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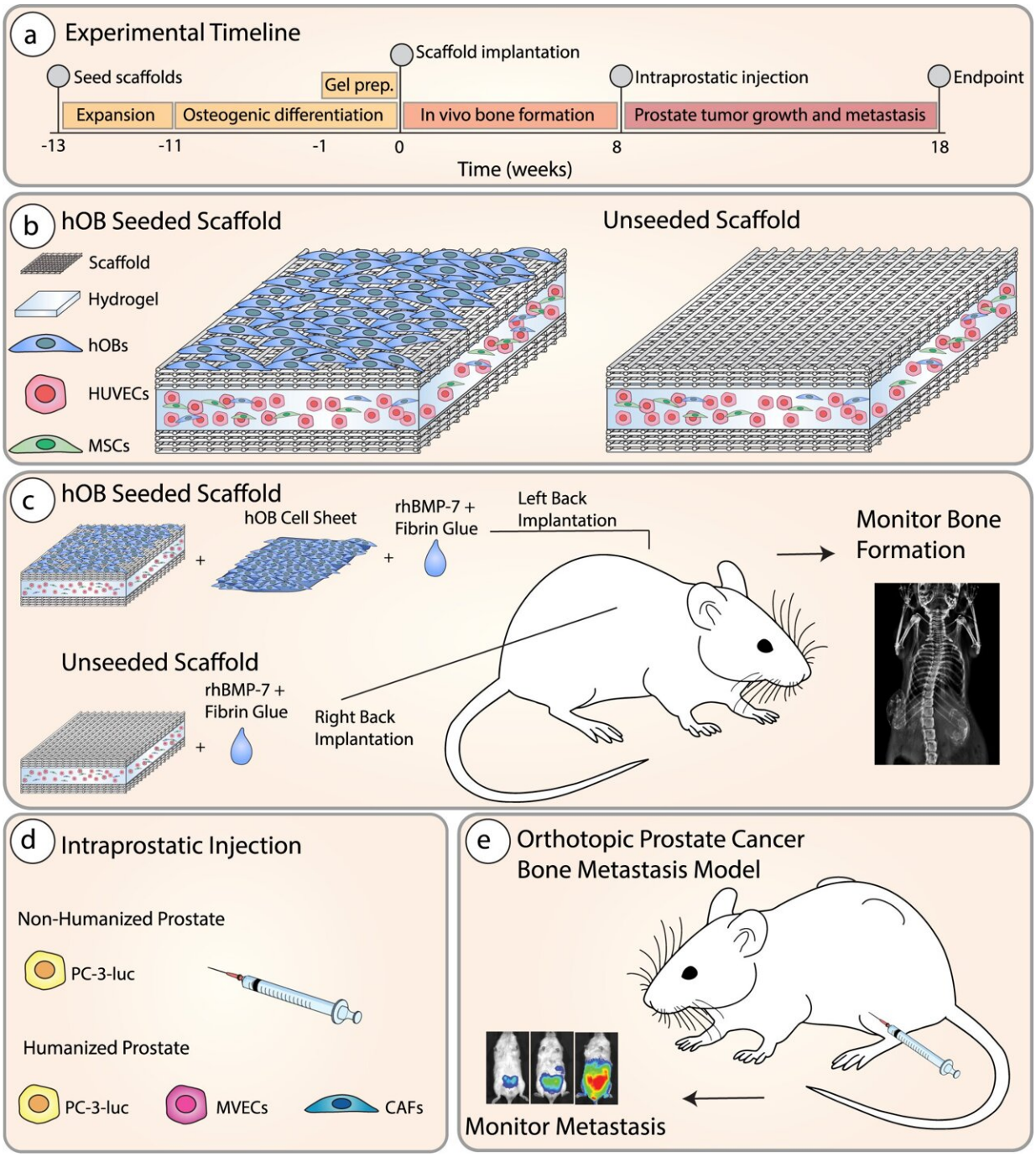

Fig. 1: Schematic of experimental design. a Overview of the experimental timeline for the study. The human tissue-engineered bone construct (hTEBC) was created by seeding human osteoblasts (hOBs) onto quadratic calcium phosphate-coated melt electrowritten medical-grade polycaprolactone (mPCL) scaffold sheets with 95% porosity. The hOBs formed a dense cell/extracellular matrix (ECM) network throughout the scaffold architecture over 2 weeks before

culture conditions were switched to osteogenic media for 11 weeks. b One week before implantation, star-shaped polyethylene glycol (sPEG) heparin gels were prepared containing hOBs, human mesenchymal stromal cells (MSCs), and human umbilical vein endothelial cells (HUVECs) and cultured to form capillary-like networks. A total of n = 10 mice were used for this study. Prior to subcutaneous implantation the sPEG-heparin gels were sandwiched together between two quadratic in vitro-engineered constructs. c The left-back of the male NSG mice received in vitro engineered constructs seeded with hOBs and combined with hOB cell sheets within the fibrin glue (in n-10 mice), whereas the right-back received unseeded scaffolds with the cell-loaded sPEG-heparin gel (in n = 10 mice). Both the cell-laden and cell-free in vitro engineered constructs were combined with recombinant human bone morphogenetic protein-7 (rhBMP-7) and fibrin glue immediately prior to implantation. The bone was allowed to develop for 8 weeks before intraprostatic injection and monitored using X-ray. d Humanization of the mouse prostate was performed via injection of PC-3-luc cells together with prostate lymphatic and blood vessel endothelial cells (BVECs) and PCa-derived fibroblasts (CAFs) performed in n = 5 mice, whereas the non-humanized group received an intraprostatic injection of PC-3-luc cells alone performed in n = 5 mice. e Growth of the primary prostate tumor and metastasis to distant organs were monitored weekly using in vivo bioluminescent imaging for 10 weeks. The mouse schematic image was sourced from Wikimedia Commons52. Credit: DOI: 10.1038/s42003-021-02527-x

The international team led by Dr. Jacqui McGovern, from the Centre for Biomedical Technologies, used tissue engineering and regenerative medicine principles to create primary tumors with their microenvironment and humanized bone as a metastatic site for prostate cancer cells to spread to.

They used two types of prostate cancer cell lines—one that is sensitive to male hormones (androgens) (LNCaP) and the other, a more aggressive type (PC-3), which is non-sensitive to androgens.

"We found that the tumor microenvironment influences the spread of cancer to bone and visceral organs in a manner specific to the cells with low (LNCaP) and high (PC-3) metastatic potential," said Dr. McGovern, a member of the QUT School of Biomedical Sciences.

"Our aim was to study the interaction of cancer cells and the bone metastatic microenvironment to better understand the complex interactions between them," Dr. McGovern said.

"We know the primary tumor's microenvironment is an agent for prostate cancer development, growth, progress and metastasis but because the tumor microenvironment is complex and multifaceted it is difficult to delineate the roles of its specific components."

Dr. McGovern said the team engineered primary prostate tumors in a mouse model using two critical prostate cancer tumor microenvironment cell types—fibroblasts and microvascular endothelial cells—which have been implicated in directly contributing to prostate cancer metastasis.

"Both the LNCaP and PC-3-derived primary prostate tumors containing these critical cells type developed and metastasized over a 10–11-week period," she said.

"Interestingly, the humanized tumor microenvironment showed a trend to decrease metastasis of the more aggressive PC-3 cells to humanized bone but did not influence metastasis to the mouse bones or visceral organs.

"In contrast, the LNCaP primary tumor microenvironment actually enhanced tumor growth and bone metastasis.

"These results uncover a potential new role of the tumor microenvironment in prostate cancer's tendency to metastasise to bone

which warrants further investigation.

"However, we are only at the beginning of exploring how the signaling processes between cancer cells and the microenvironment can structure tumor cell communities."

"A humanized orthotopic tumor microenvironment alters the bone metastatic tropism of prostate cancer cells" is published *Nature Communications Biology*.

More information: Jacqui A. McGovern et al, A humanized orthotopic tumor microenvironment alters the bone metastatic tropism of prostate cancer cells, *Communications Biology* (2021). DOI: 10.1038/s42003-021-02527-x

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