The replacement joint of the future, naturally grown

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A pioneering study published Online First in the *Lancet* has shown that failing joints can be replaced with a joint grown naturally using the host's own stem cells. The work paves the way for a future of naturally grown joints that would last longer than currently used artificial joints. The work was carried out by Professor Jeremy J Mao, and his team at Columbia University Medical Center, New York, USA, and colleagues from University of Missouri and Clemson University.

Patients having joints replaced almost always want to know how long their artificial joint will last. But with ageing populations, and an increasing number of patients under 65 requiring replacement joints, there is a real danger many patients will outlive their replacement joint. These patients would then need another gruelling operation, at an advanced age, and yet without much bone left to support another metallic joint.

In this proof-of-concept study, Professor Mao and colleagues removed the forelimb thigh joint of 10 rabbits, and then implanted three dimensional biomaterial scaffolds infused with growth factor. The rabbits' own stem cells were 'homed' by the growth factor to go to the location of the missing joint, and regenerated cartilage and bone in two separate layers. Just four weeks later, the rabbits were able to resume normal movements, similar to rabbits with normal functional joints. These rabbits had grown their own joint using their own stem cells, instead of stem cells harvested apart or outside of the host.

Prior to the work reported in this Lancet paper, no one has been able to regenerate a limb joint with either stem cells harvested or the host's endogenous stem cells. Thus there are two new aspects to this work: 1) a limb joint regenerated for the first time with the animals involved resuming functions on the new joint; and 2) the regenerated limb joint being created from host's own endogenous stem cells, not stem cells that are harvested and manipulated outside the host's body.

Professor Mao says: "This is the first time an entire joint surface was regenerated with return of functions including weight bearing and locomotion. Regeneration of cartilage and bone both from the host's own stem cells, rather than taking stem cells out of the body, may ultimately lead to clinical applications. In patients who need the knee, shoulder, hip or finger joints regenerated, the rabbit model provides a proof of principle. Several scientific and regulatory issues must be dealt with prior to patient applications."

He adds that the load bearing recovery in human patients will be more challenging than in animal models, due to humans being two-legged. He says: "Also, patients may have pre-existing conditions and medication that could affect joint regeneration, and this is clearly difficult to replicate in a study using animal models. However, human patients would benefit from post-operative rehabilitation."

In an accompanying Comment, Dr Patrick H Warnke, Bond University, Gold Coast, Australia, describes the work as "a renaissance of use of the host as a bioreactor and recruitment of the host's endogenous cells, including stem or progenitor cells, for tissue regeneration". But he adds that not all patients would have the same capacity for natural regeneration, for example elderly people with diabetes. He adds that the period of immobility while a person's joint regenerates also presents its own risks, and a standard metal joint would reduce these risks.

Discussing ways to reduce regeneration time, Dr Warnke says: "Another promising approach would be to commence the entire cultivation of the joint replacement inside the patient, but to change the site of tissue growth. Tissue at the size of a joint could be grown inside a muscle first and subsequently transplanted to replace the original joint."

He concludes: "The optimum way to grow a biological joint remains a controversy…Although we are yet to see a biological joint replacement in man, Lee and colleagues have offered a promising insight into what might be on the horizon."

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