Peer-Review

Foo, Hayley. 2026. “Recent Advances in Hepatic Tissue Engineering for the Treatment of Liver Disease.” *Journal of High School Science* 10 (2): 329–54. https://doi.org/10.64336/001c.162801.

This is a very well written and researched narrative review. However, it does not the Journal’s specifications for a review manuscript (see here: https://jhss.scholasticahq.com/for-authors , types of manuscripts, review papers.

Here’s what I suggest:

You have completely left out injecting heptatocytes into lymph nodes. This is actually a very viable strategy and is in phase 2 clinical trials (lygenesis.com). Please thoroughly research this strategy and discuss extensively in the manuscript with relevant references. Convince yourself that it provides hepatocyte survival and engraftment but not full functionality (biliary limitation); whereas the approches you have described (for the most part) support functionality but not early survival (vascularity).

Then propose that a merging of these two attributes is necessary for significant translational advancement.

You would fabricate and expand an autologous lymph node-stromal niche within a ‘conventional’ fabricated scaffold.

Insert a subsection such as “Lymph Node–Based Hepatocyte Engraftment: A Permissive Expansion Niche and Its Translational Implications”

A central limitation in hepatic tissue engineering is early graft failure due to insufficient vascularization, which results in ischemia and rapid loss of transplanted hepatocytes. While scaffold-based approaches aim to reconstruct liver architecture, they frequently fail at this initial survival stage. An alternative strategy that has emerged in preclinical and early clinical studies is the use of lymph nodes as ectopic sites for hepatocyte engraftment. Unlike engineered scaffolds, lymph nodes provide a pre-existing, highly vascularized stromal microenvironment that supports rapid cell survival and expansion.

Lymph nodes have been established as a biologically validated “permissive niche” for hepatocyte survival and expansion across multiple biological scales.

Mechanistically, the success of lymph node engraftment arises from several convergent properties. First, the fibroblastic reticular cell (FRC) network provides a pre-formed extracellular matrix scaffold that supports immediate cell adhesion and prevents anoikis. Second, the dense vascular architecture, including high endothelial venules, enables rapid perfusion and minimizes the ischemic window that typically limits graft survival. Third, lymph nodes are intrinsically capable of dynamic remodeling and expansion, allowing transplanted hepatocytes to proliferate without the spatial and competitive constraints present in native liver tissue. Finally, the local immune environment exhibits a degree of tolerance that permits engraftment without triggering severe inflammatory or fibrotic responses.

Despite these advantages, lymph node–based hepatic tissue formation remains fundamentally limited in its capacity to recapitulate full liver function. Ectopic hepatocyte clusters lack key architectural features of the native liver, including sinusoidal organization, metabolic zonation, and, critically, a functional biliary drainage system. As a result, while lymph node grafts can provide partial metabolic support, they are unlikely to achieve complete physiological replacement of liver function. This distinction highlights an important conceptual separation between “expansion niches,” which enable cell survival and proliferation, and “functional niches,” which support full organ-level activity.

Lymph nodes effectively solve the problem of early vascularization and cell survival but fail to reproduce organ-specific architecture, whereas engineered scaffolds aim to reconstruct hepatic structure but are limited by poor initial engraftment. This dichotomy suggests that successful liver regeneration may require a staged or hybrid approach that integrates both paradigms.

One potential extension of this concept is the engineering of an autologous lymph node–derived stromal niche to enhance hepatocyte engraftment within the liver itself. In this framework, stromal cells or extracellular matrix components derived from patient-specific lymph nodes could be used to construct a permissive microenvironment that is implanted into the diseased liver alongside hepatocytes or induced pluripotent stem cell–derived hepatic cells. Such a niche would be expected to improve early survival by recapitulating the adhesion, vascularization, and immune-modulatory properties of lymph nodes. However, this strategy would remain constrained by the same limitations observed in ectopic lymph node grafts, particularly the absence of biliary integration and liver-specific architectural cues, unless combined with additional scaffold-based or biofabrication approaches.

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Revision Tracker (per Reviewer Feedback)

1. Abstract Addition: *"In parallel, emerging... by insufficient perfusion."* This portion covers the inclusion and exploration of lymph node / hepatocyte injection as an avenue of hepatic tissue engineering.

2. Added Section on Lymph Node Engraftment, titled *"***5.3. Lymph Node-Based Hepatocyte Engraftment: A Permissive Expansion Niche and Its Translational Implications."** This whole section thoroughly identifies and explores how injecting hepatocytes into lymph nodes helps increase survival of said hepatocytes and thus can be a potential source of hepatic re-engineering. I establish clearly that there is a central limitation in functionality, whereas other approaches satisfy this but do not guarantee the survival aspects that lymph node integrations fulfill. Thus, I indicate that those implementations would serve best when complementary to existing scaffolding and stem-cell-based biofabrication techniques.

3. As necessary, I added references **(73)** to **(77)** which proved crucial for my exploration of lymph nodes and their role in hepatic tissue engineering.

4. I tightened the expository language and tones I used, careful to avoid speaking in first-person point of view and adjusting the tenses when grammatically necessary, when speaking about central findings and existing studies to use the past perfect in reference.

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Thank you for addressing my comments. I recommend accept with the addition of the following content to the conclusion :

"Future regenerative strategies may additionally depend on integrating permissive vascularized engraftment niches with scaffold-based architectural reconstruction approaches. In particular, lymph node–derived microenvironments and related stromal niche engineering strategies may help address one of the central limitations in hepatic tissue engineering: the mismatch between early hepatocyte survival and long-term organ-level functional integration. "