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Employing the concept of ectopic tissue organogenesis within the lymph nodes could provide an application to the shortage of viable and complimentary transplant organs, a cure for Type 1 Diabetes and cancer.

Introduction;

Approximately 1600 Australians are currently awaiting an organ transplant[i] with another 1200 on last resort treatments such as dialysis as a result of severe medical conditions[i]. Despite this demand, the availability of organ donors is far less, with only 1500 of these 2800 receiving these lifesaving transplants each year[i]. Thus, the necessity for alternate methods of long-term treatments is rapidly increasing. Furthermore, for years, scientists have endeavoured to find better cures for diseases such as cancer and type 1 diabetes that effect 1 in 2[ii] and 1 in 8,000[iii] people in Australia respectively. Organogenesis, the natural process of tissue regeneration, could provide a basis for effective and minimally invasive methods of regeneration to organs[iv] such as the liver, thymus and pancreas. This technology could aid in the transplant organ shortage and provide cures for other diseases.

Scientific Background;

The complex process of organogenesis is done by injecting healthy donor cells into the lymph node. Here, they differentiate to form extra nodules that take on the role of the desired organ[v]. For example, in the endeavour to grow an ectopic liver, donor hepatocytes (liver cells) are injected into a lymph node[v]. After approximately 10 days, in the efforts to protect homeostasis, the lymph nodes enable the original donor hepatocytes to start multiplying through organogenesis[v], much like an embryo within the womb[iv]. This ultimately forms small cyst like structures that can serve the purpose of a conventional liver[vi]. 10 weeks after the initial injection of the donor hepatocytes, the now extra hepatic nodules (previously smaller cysts) migrate through the body through the lymphatic system to distribute closer to the organism's original liver[v] (figure 1).

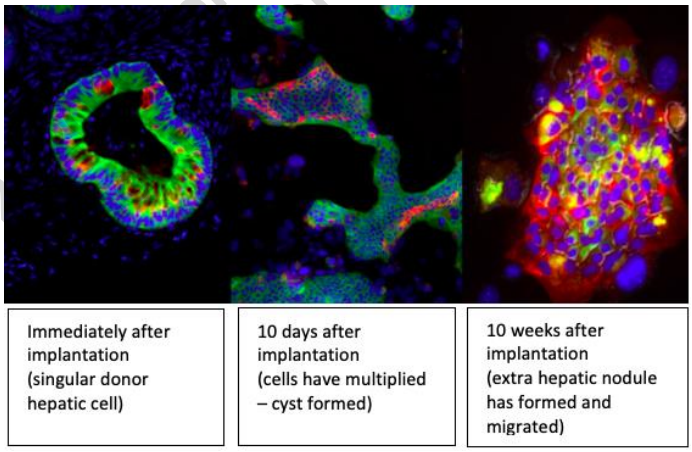


Figure 1: The multiplication of donor hepatic cells within the lymph node[vii]

The lymph nodes are ideal vivo (within the body)[viii] bioreactors for this process for many reasons[iv]. Firstly, their position within the lymphatic system (a system of veins near the blood stream that contain the cells of the immune system) means that they have access to adequate nutrients and hormones that assist in hepatic nodule growth[iv]. Secondly, they have the unique ability to expand, and can sacrifice their traditional role within the body based on their abundance making up for the specific deficits[iv]. Most research has shown that the most effective lymph node for completing the process has been the jejunal lymph

node. This is due to its functions closely mimicking that of the nearby appendix or small intestinal lymph nodes so they can easily serve the same purposes[ix]. This is shown by figure 2 in which the jejunal lymph nodes has created the largest ectopic liver in comparison to the lymph node that has received no treatment (circled and characterised by a dark red-brown colour).

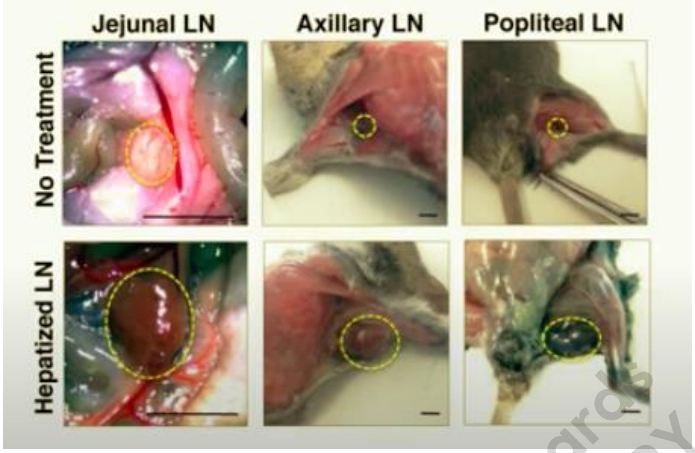


Figure 2; Evidence of research showing effectiveness of different lymph nodes in producing ectopic tissue in rats.[v]

This process can be applied to many different medical needs such as cancer treatments through the production of an ectopic thymus, type 1 diabetes cures through the production of ectopic islet cells and liver and kidney transplants as described above.

SHE Concepts;

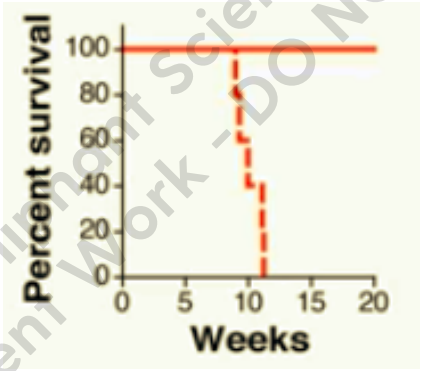
Application and Limitation

As discussed above, there is a major disparity between the demand of viable and matched transplant organs and their available supply. As a result, the average Australian will wait four years to receive the lifesaving organ[x] despite 90% of the adult population being registered as organ donors[i]. Using the technologies found in the organogenesis of ectopic tissue could be used as an **application** to this problem as a fully functioning donor transplant organ is not required. Rather, a single transplant organ could provide donor cells to dozens of patients, minimising the number of whole donor organs that are needed for the entire recipient population. Therefore, rather than the majority of organ donors being those who have died, samples of donor cells can be taken at minimal detriment from healthy donors. Also, the parameters of donors that can give their organs is widened and the disparity between the demand and availability of organs is lessened. Furthermore, as only a small sample of donor cells are transplanted and the organogenesis is occurring within the recipient's bodies, the rate of rejection of the cells is expected to be a lot lower than that of conventional transplantation where 18% of organs are rejected[x].

Many terminal conditions are a direct result of organ deficits therefore, replacing the organs has often proven to be beneficial in curing or minimising the symptoms of the condition[xi]. Type 1 diabetes, in which the pancreas has an absence of islet cells that create and regulate insulin production, could be cured by applying the same technology[v]. Rather than injecting hepatic cells, donor islet cells (pancreatic cells) could be injected into the lymph nodes to produce an ectopic pancreas that could resume insulin production and regulation[xii].

Using the same technology to provide a more effective cure for cancer is also a possibility. The thymus is responsible for differentiating T cells, which play a role in the cell-mediated immune response that is specifically used in fighting cancers. As a result, growing a thymus using organogenesis may halt multiple processes that allow cancers to thrive, ultimately providing a plausible treatment.

Despite this technology proving helpful in providing alternate therapies for those needing organ transplants, there are a number of **limitations** to the phenomenon. Specifically, the treatment takes 10 weeks to be completed[v] so would not be useful to patients in dire situations that are in need of immediate transplants (a large percent of cases)[xiii]. Another limitation results from the limited organs that this technology can produce. Namely, the simpler structure of organs such as the liver, kidney, pancreas and thymus allow the technology to be used as the accuracy of the function of the cells is more vital to their success than their arrangment[vi]. Conversely, organs such as the heart and intestines that have their structure play a larger role in their function could not be created using ectopic tissue and the process merely replicates cells rather than arranging them into specific patterns. Finally, even within the small rodent trials the mortality rate of the subject is very high with 100% dying after 11 weeks (see graph 1)[v]. Despite this, with each trial that is conducted, the mortality rate is decreasing suggesting that with further research and testing, the technology could provide a treatment would be beneficial to humans[v].



Graph 1: mortality of rats in early hepatic cell reception studies[v]

Influence:

Health care is one of the country's leading costs, with the average transplant costing an average of $139,900[xiv], cancer treatments costing $7,500[xiii] and type 1 diabetes treatments costing an average of $16,698 per year[xv]. These essential, life-sustaining treatments are often economically unavailable or place families in serious financial debt. In addition, major surgeries that result from transplants and cancer treatments often require extended hospital stays requiring time off work which place an increased economic cost to both the societal economy and the patient and family. Consequently, using the new technology of organogenesis to grow ectopic tissue within the lymph node may be more widely accepted within the community as it eliminates much of this economic **influence**. As it only requires a simple, minimally invasive procedure and the entire process occurs in vivo[v], hospitalisation is often a lot shorter and the consumables and personnel needed are minimalised. Similarly, with diabetes, after the treatment the disease can possibly be considered cured and

therefore further treatment is not required. As a direct result, the costs associated with medical needs and time absent from work are also minimised.

Current Applications

Whilst the technology has proven very effective in early studies and trials, further testing is required to warrant acceptance and certification as a possible treatment in a clinical setting. To aid in this, large animal studies for liver regeneration have been successfully completed and phase 2 human trials started in the first quarter of 2020[xi], ultimately being promising in paving the way to full endorsement and ultimate applications in the medical field.

Conclusion

In conclusion, the organogenesis of ectopic tissue could be used to eradicate the need for some organ transplants and thus, eliminate the disparity between organ donors and recipients. Furthermore, the technology could also provide highly sought-after cures for type 1 diabetes and cancer by replacing the effected organs and increasing the abilities of the immune system. This technology could prove to be more widely accepted due to its ability to eliminate the economic detriment that results from prolonged hospitalisations and subsequent time off work. Despite these applications, there are some limitations to the new treatments such as its extended time that takes to be completed, its limited parameters in terms of organs can be produced and its high mortality rates in early small mammal trials (being rectified in current large mammal and early human testing).

Word Count; 1,507 words

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