**The host bone marrow stem cell repopulation is crucial to the permanent tolerance in 50% liver transplantation**

For operational tolerance induction, we made three shifts: ①the immunology problem of tolerance is shifted to liver regeneration, ②and the interventional target is shifted from the host (immune system ) to the graft. ③the dynamic conformational change of MHC molecules leads to the failure of MHC–peptide binding or recognition. For my study, optimized liver transplant (LT) procedures are not our main point. 50% LT is performed to trigger liver regeneration, on ischemia-reperfusion, hepatocytes enlarge(normal→hypertrophy→normal) and hyperplasia discontinues (7-10 days), consequently, their spatial conformations of MHC molecules is changed, as a result the MHC molecule-peptide binding fails, so immune response does not occur; on the other hand, host bone marrow stem cells are mobilized, they repopulate and differentiate into hepatocytes to change the allograft microenvironment, so acute or chronic rejection does not happen, this is a widespread and early operational tolerance after LT.

I summarized and compared my study protocol with current strategies as follows:

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| --- | --- | --- |
|  | **Classic protocols** | **mine** |
| **target or subject** | The host (its immune system) | The donor (graft) |
| **design rationale** | immune response (MHC-Peptide recognition, T cell proliferation, effect) | liver regeneration |
| **strategies** | clearance of T cell, blockade of co-stimulatory signals, transferring regulatory T cells, complete donor chimerism etc | 50% liver allograft,  bone marrow stem cells |
| **mechanism** | Stable conformation of MHC | Changed conformation of MHC |
| **avenue** | Chemical (drugs, antibodies etc) | Mechanic (portal shear pressure) |
| **Site** | downstream | Start (MHC-binding failure) |
| **hallmarks** | complicated, transiently and low efficient (<20%), poor operability, low reproducibility | long and stably efficient, readily operable, 100% reproducible |
| **adverse effects** | severe (fatal infections, graft versus host disease etc) | none or mild |
| **donor specific hypo-response** | yes | no |
| **third party immune** | yes | yes |
| **other** | 1 donor to 1 recipient | 1 donor to 2 recipients |
| **clinical application** | None | Highly promising |

In addition, The index of liver regeneration can be used as a biomarker to monitor immunology activity. From the efficiency, novelty, operability, reproducibility and applicable value, my study is a great innovation to benefit thousands of patients each year.

There text-book will be-written for tolerance induction, which is particular relevance of clinic and to be a therapeutic paradigm.

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