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Project Title	Humanizing the Rat Immune System: A Transformative Tool for Preclinical Cancer Research	
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(Form 2)

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Joint Research Report (Annual/Project Completion)

Annual Report

Humanizing the Rat Immune System: A Transformative Tool for Preclinical Cancer Research

Background and Rationale

The immune system plays a critical role in cancer development, progression, and therapeutic response. Preclinical models that accurately recapitulate human immune-tumour interactions are essential for advancing cancer biology and immunotherapy development. However, current mouse models do not fully capture the complexity of the human immune system or its interaction with human tumours and their microenvironment. Rats offer advantages including larger body size and closer physiological similarity to humans, but remain underdeveloped in the context of immune system humanization.

This project aims to establish a humanized immune system in immunocompromised F344 *Il2rg* and *Rag2* double knockout (FRG) rats developed by Prof Tomoji Mashimo [1]. This is achieved through depletion of the native rat immune system followed by transplantation of human $CD34^+$ haematopoietic stem cells (HSCs). The model is intended to provide a more physiologically relevant platform for future studies of immune-tumour interactions and immunotherapy.

Research Progress to Date and Future Plans

Initial studies demonstrated that while human $CD34^+$ HSCs could engraft in the original FRG rat model, this engraftment was not sustained long term. Based on this limitation, and the known importance of SIRPα-CD47 signalling in preventing macrophage-mediated clearance of human cells [2], a modified rat strain incorporating a human *SIRPα* knock-in (FRGS rat) has been developed by the team of Prof. Mashimo.

Preliminary comparative studies indicate that the FRGS rat supports improved and sustained human HSC engraftment relative to the FRG strain. Current work is focused on optimization and characterization of this model.

The research plan for the continuation period will focus on:

- Optimization of myeloablative conditioning (radiation dose and timing)
- Determination of optimal $CD34^+$ HSC transplantation dose
- Evaluation of recipient age at transplantation
- Comparison of delivery routes (intravenous and alternative approaches)
- Longitudinal monitoring of peripheral blood chimerism using human-specific markers (e.g. huCD45, huCD34, huCD19, huCD3)
- Endpoint analysis of bone marrow, spleen, and thymus via flow cytometry and histology to assess multilineage differentiation

Dr McGovern will visit IMSUT in 2026 to undertake collaborative analysis of bone and bone marrow tissues and further characterise immune system reconstitution in the FRGS rat model.

References

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