Macrophage-mediated delivery of protein drug depots for immunotherapy of solid cancers

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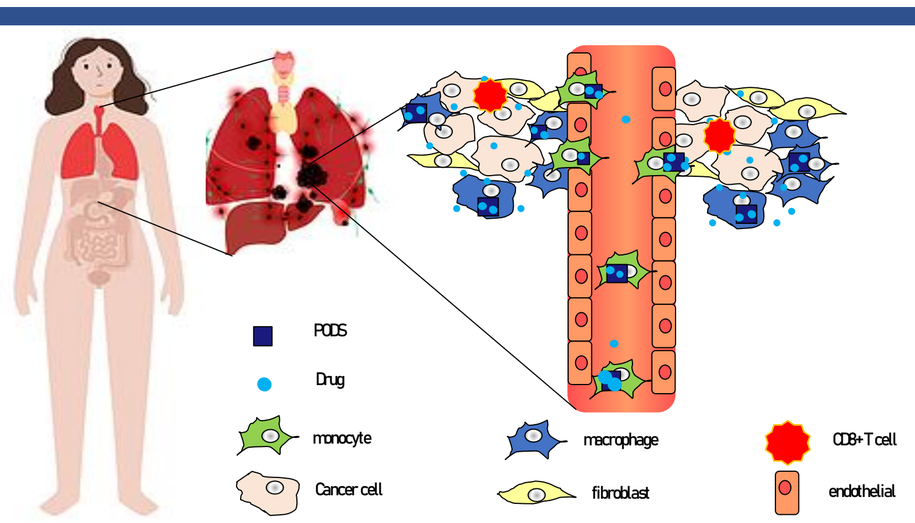
GRAPHICAL ABTRACT

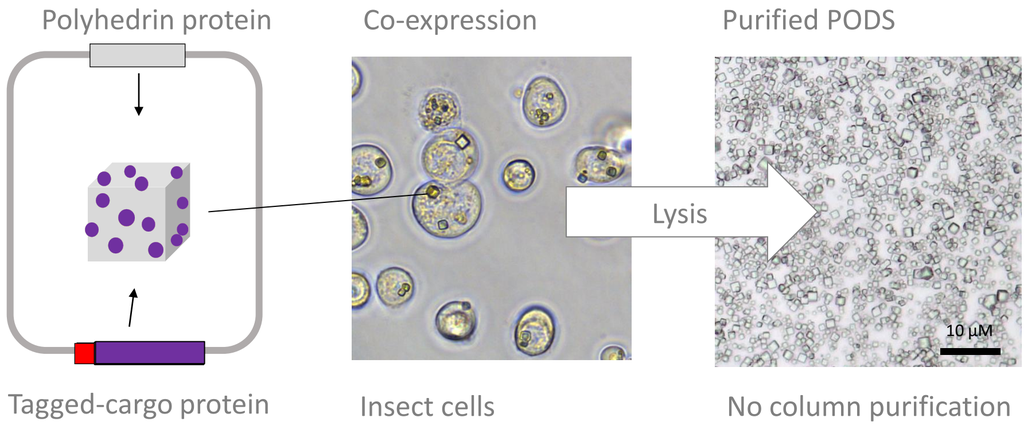


The problem Systemically delivered protein drugs used in the management of cancer suffer from dose- limiting side effects and low target availability.

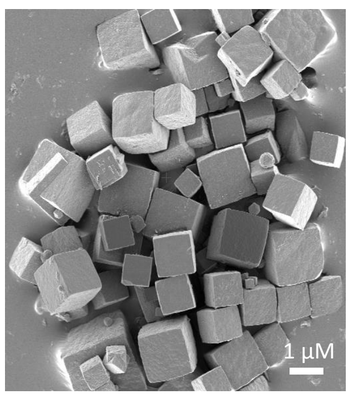
Drug delivery technologies that improve a therapeutic protein's access to the tumour microenvironment and limit access to off-target tissues can improve clinical outcomes for cancer. Nanocarrier and microcarrier drug delivery technologies can improve delivery but are complex, expensive and difficult to scale.

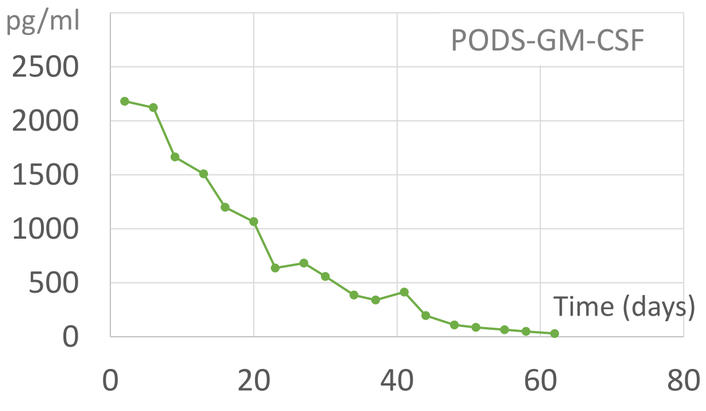
Our solution We have developed a simple microparticle technology that generates protein co-crystals composed of polyhedrin and cargo proteins. These PODS® crystals (PODS) are readily phagocytosed following intravenous injection and are then able to exploit the behaviour of phagocytic immune cells to actively deliver protein cargos to cancer. We have tested PODS containing immuno-modulatory cytokines against melanoma and renal cell carcinoma (RCC).

PODS baculovirus-based manufacturing process

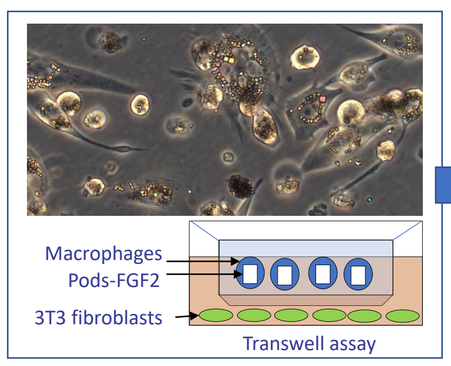


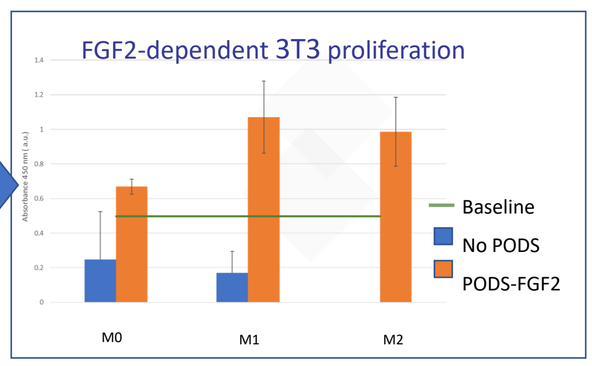
Protease-responsive cargo release in-vitro



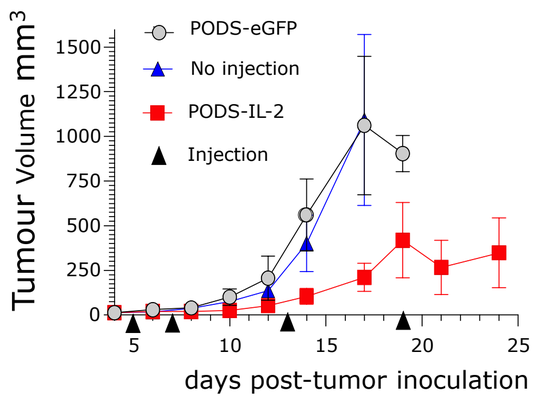


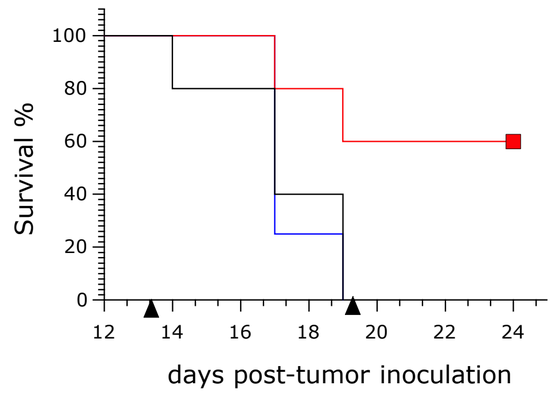
Cargo protein bioactivity following phagocytosis



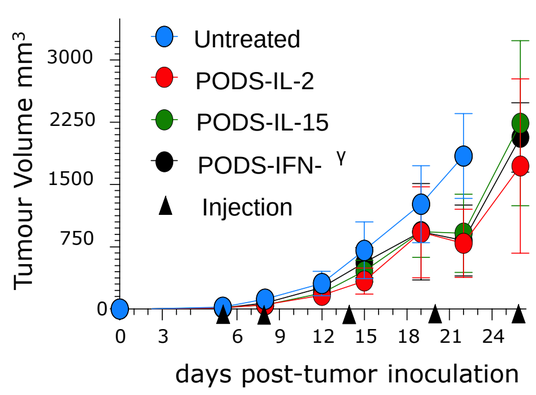


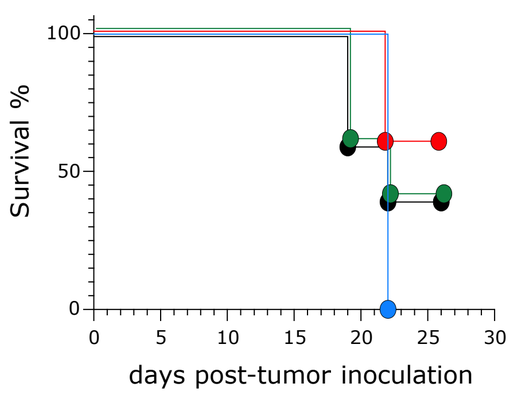
Melanoma 40 Mn PODS/injection (IL-2)





RCC 10 Mn PODS/injection (IL-2, IL-15, IFNγ)





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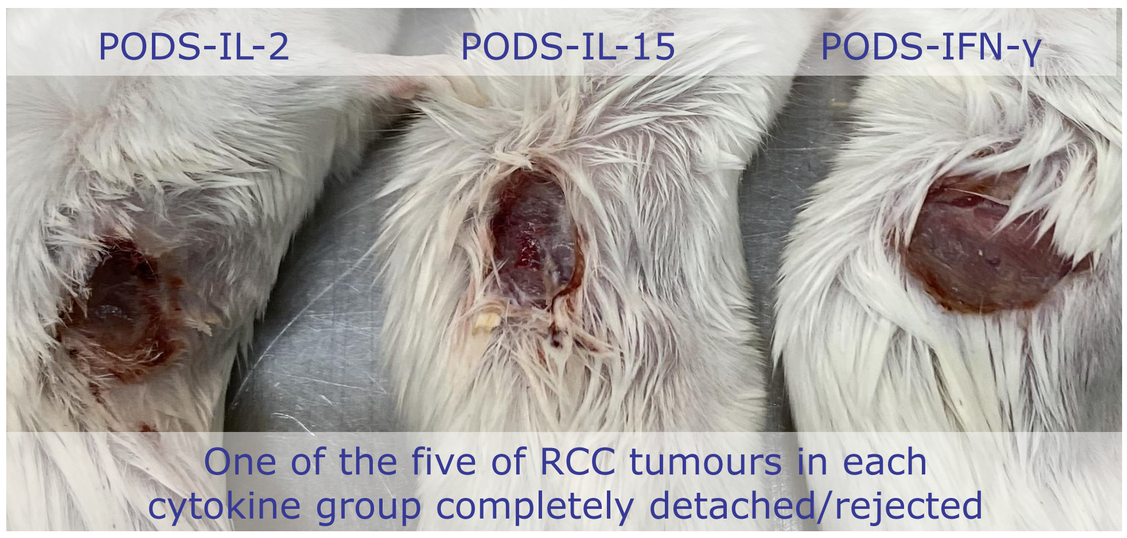
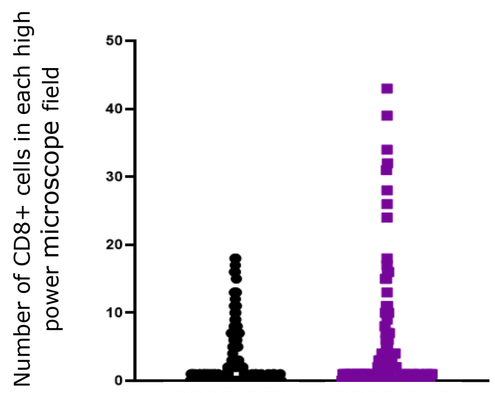
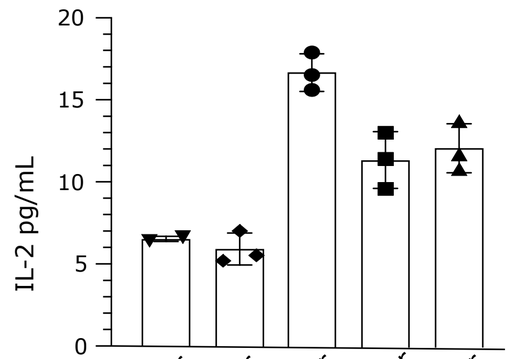


CD8+ T cells in PODS-IL-2 treated melanoma



IL-2 serum levels remain at background



Conclusions

- ❑ PODS sustainably release bioactive proteins via protease-dependent matrix degradation
- ❑ Bioactive proteins are secreted by mononuclear phagocytes following phagocytosis
- ❑ Melanoma growth is supressed by PODS-IL2
- ❑ CD8+ T cell numbers increase in melanoma/IL-2 and serum IL-2 levels are supressed
- ❑ RCC growth is suppressed by PODS-IL-2, PODS-IL-15 and PODS-IFNγ. Complete rejection was achieved in some cases.
- ❑ PODS offers a robust platform for highly effective systemic delivery of protein drugs to cancer