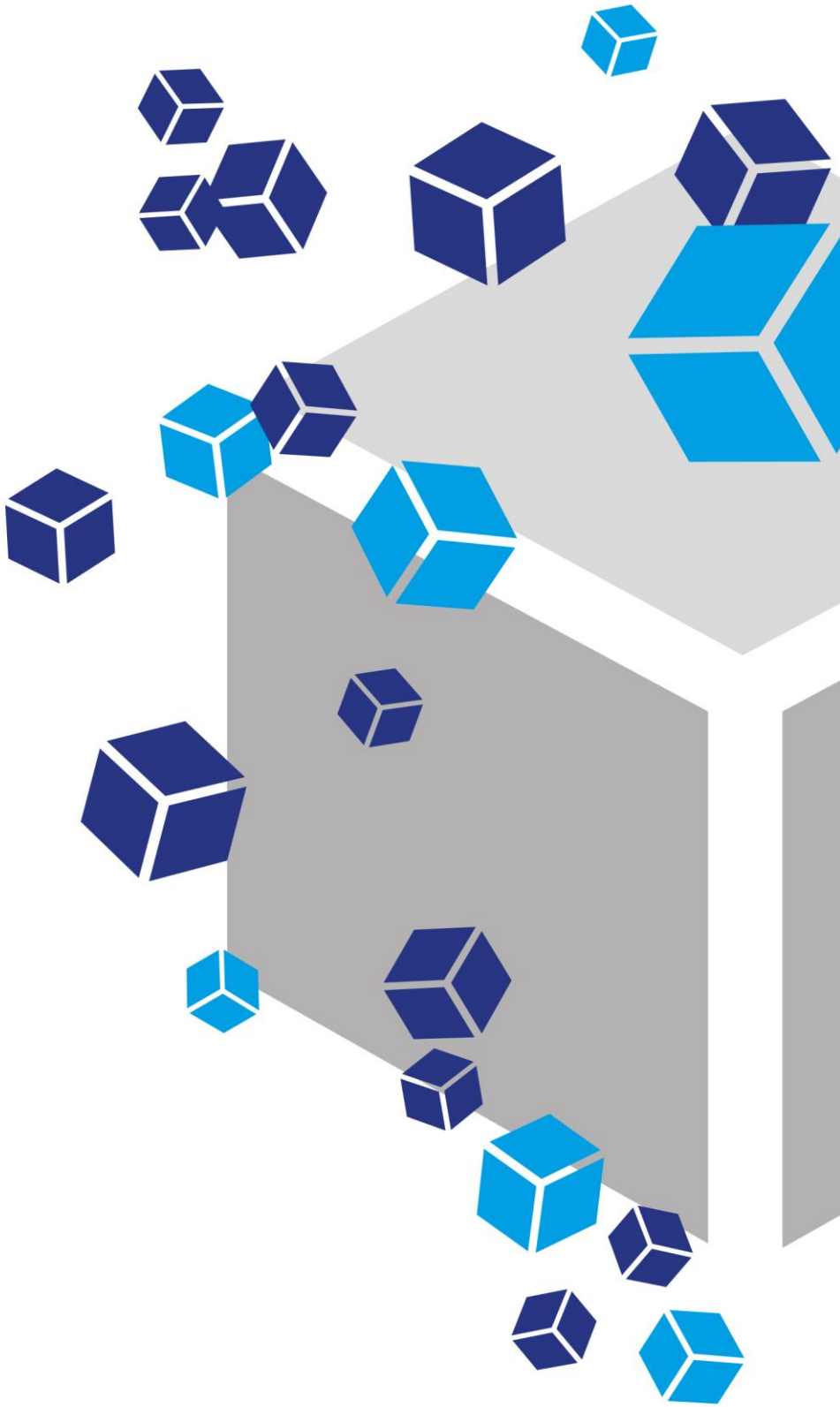
CELL guidance systems

Application Note

PODS® Immune Cell Reprogramming



PODS® for the reprogramming of monocytes, macrophages and other phagocytic immune cells

Introduction to PODS®

The challenge for conventional growth factors

Many proteins, especially growth factors and cytokines, when used as a reagent, degrade quickly, rapidly losing their bioactivity. Additionally, they can also suffer from lot-to-lot product variation. This fragility and variability hampers research and significantly limits the therapeutic potential of proteins.

Protein Micro-depots

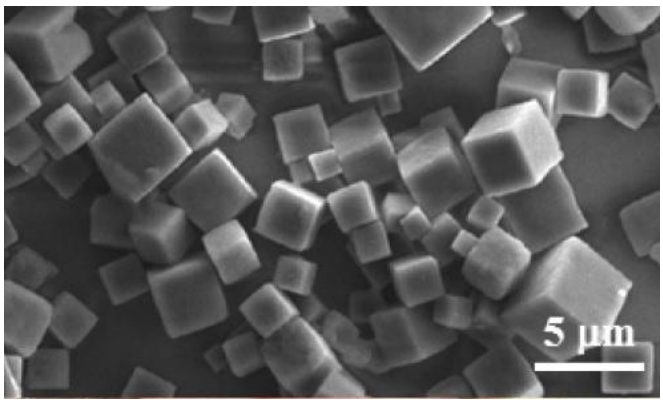
Development of a technology that can continuously replenish active protein from a local, microscopic store, has been a significant challenge, but one that could transform the fields of cell culture and medicine by allowing greater control and reproducibility of cell culture.

Introducing PODS®

PODS® is a sustained release system which continuously replenishes proteins from millions of local microscopic stores which can be placed next to (or at a distance from) cells, either randomly or in precise locations. Just like cells, these micro-depots release a steady stream of bioactive protein. This protein can be limited to local surroundings or dispersed more widely, or made to form a gradient.

How does it work?

At the heart of PODS® is an extraordinary polyhedrin protein. This specific polyhedrin protein has the unique ability to encase cargo proteins within perfect, transparent, cubic, micro-sized crystals, much smaller than the cells. These protein crystals form admixtures of the polyhedrin and cargo proteins which slowly degrade, releasing the biologically active cargo protein.



How can PODS® help my research?

PODS® are tough and will withstand physical and chemical stress, so you can handle them with ease. PODS® typically release intact cargo protein over several weeks and months. Using PODS® you can readily create a steady-state protein environment in microscopic detail wherever you want, tailored exactly to your requirements. This is the power of PODS®. PODS® proteins are now available for many growth factors and cytokines and are already being used in many leading world-class research labs. PODS® protein applications include:

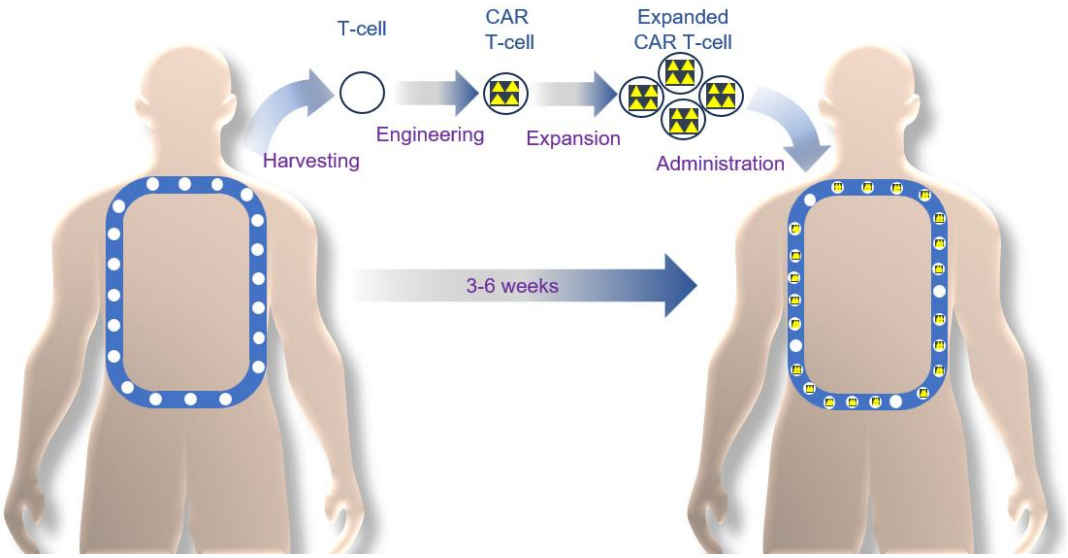
- Micropatterning
- Physiological, stable gradient formation
- Bioinks for 3D printing
- Microcarriers
- Functionalizing scaffolds
- Microfluidics (lab on a chip)
- Improved and simplified stem cell culture
- Therapeutic protein delivery
- Cell Engineering

Immune Cell Reprogramming

Immune cell reprogramming is widely used to enhance immune cell function for disease treatment. This approach is successful for some types of immune cell, such as T-cells, but reprogramming of monocytes, macrophages and other phagocytic cells has historically been difficult. At Cell Guidance Systems, we have simplified the engineering of monocytes and other mononuclear phagocytes by using sub-micron scale sustained-release protein crystals that durably alter the cell's proteome. This simple technique opens the possibility of new research avenues and cost-effective, reiterative autologous immune cell therapies to treat a range of diseases.

Autologous Immune Cell Enhancement

Treatments that enhance the function of a patient's immune cells are effective in treating diseases including cancer. This therapeutic approach is known as autologous immune enhancement therapy, or (for cancer therapy) adoptive cell therapy (ACT).



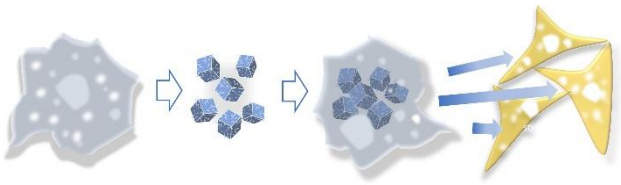
CAR-T therapy *with DNA and RNA modification. T cells are harvested from the patient, engineered to improve their function, expanded and returned to the patient. The process is expensive and slow and only works with leukaemia and lymphoma*

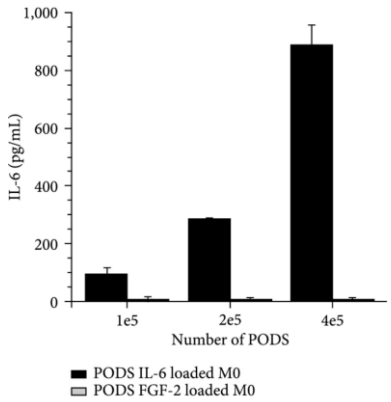
Chimeric Antigen Receptor T cells (CAR-T cells), are an example of ACT. They are made using recombinant DNA and RNA to engineer a patient's T cells. CAR-T cell therapy is effective for treating leukaemia and lymphoma, but is expensive, time-consuming and doesn't work well with solid tumours.

PODS® Engineering of Monocyte Cells

Engineering monocytes (or macrophages) for autologous immune cell therapy is an attractive strategy but, unlike CAR-T cells, can't be achieved efficiently with DNA and RNA-based technologies

To address this, a simple process has been developed that uses PODS protein crystals that are ingested by phagocytic cells including monocytes and macrophages. This phagocytic process quickly (within 24 hours) and efficiently (70% of harvested cells are engineered) reprograms monocytes to create a novel class of modified immune cell for therapy. These enhanced cells durably express the protein contained in the PODS crystal for several days or weeks..





PODS modified monocytes and macrophages secrete protein cargos in a dose dependent manner.

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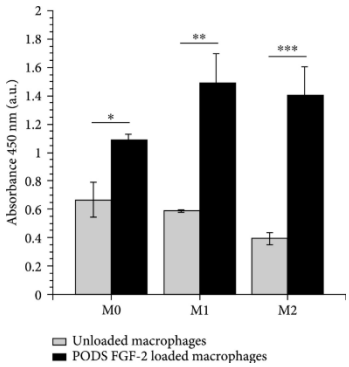
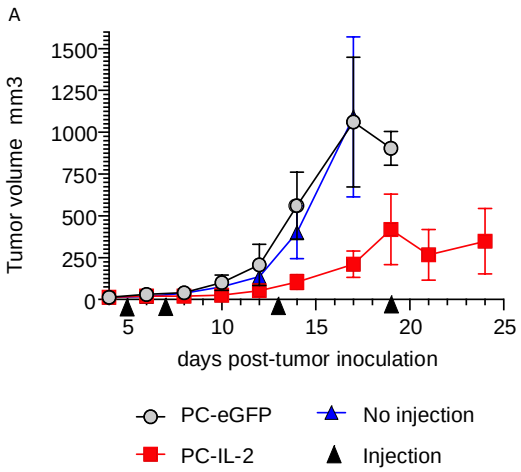
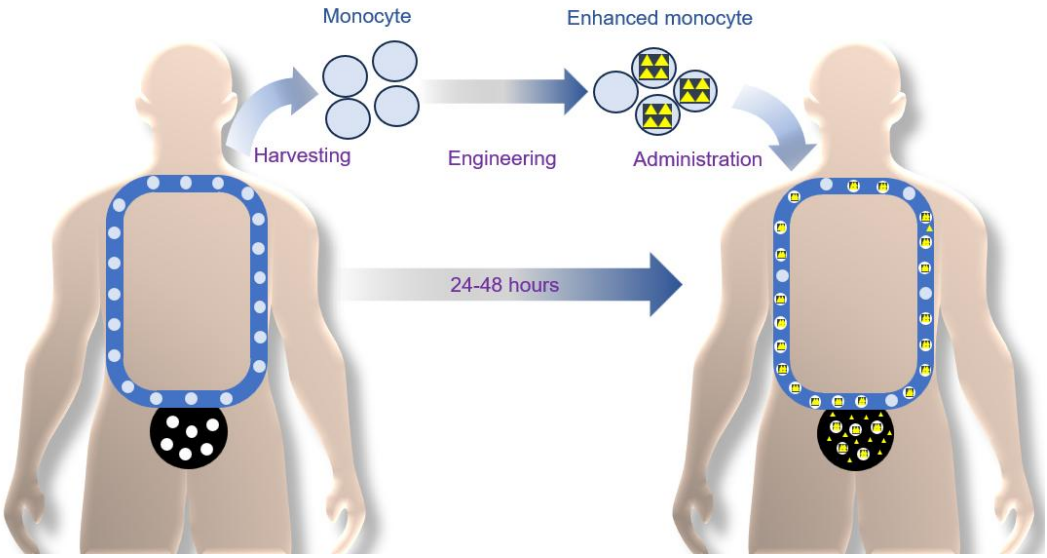


The secreted protein has been shown to modulate the behaviour of other, adjacent cells and to reduce the growth of tumours in a mouse model of cancer. FGF-2 secreted from M0, M1 and M2 macrophages engineered with PODS enhance proliferation of fibroblasts.



Cancers in mice grow significantly slower after tail vein injection of PODS containing IL-2



Monocyte therapy with sustained release protein PODS. Monocytes are harvested from a patient, engineered by phagocytosis of PODS protein crystals and returned to the patient within 48 hours. Rapid, responsive therapy is possible. The engineered monocytes actively infiltrate the cancer. Note Concept only. Currently not in the clnic.

Can other Phagocytic cells be reprogrammed?

Yes, PODS are ingested by all professional phagocytes and are even phagocytosed efficiently by cartilage cells.

References

- Wendler A, James N, Jones MH, Pernstich C (2021) Phagocytosed Polyhedrin-Cytokine Cocrystal Nanoparticles Provide Sustained Secretion of Bioactive Cytokines from Macrophages **BioDesign Research**, vol. 2021, Article ID 9816485, 12 pages, 2021. https://doi.org/10.34133/2021/9816485
- Michael H. Jones, N. E. Quispe Calla, Robert Smith, C. Talbot-Cooper, Simon Rudge, Hiroyuki Kusano, T. Shiomi, Yuichi Ishikawa, Hong Zeng, Jonathan Best (2023) Low-dose cytokine immunotherapy of solid cancers enabled by phagocytic-competent protein co-crystals. **bioRxiv DOI:**10.1101/2023.04.06.534711

For more information and a full list of our current PODS® growth factors, please visit our website www.cellgs.com.

Cell Guidance Systems' reagents and services enable control, manipulation and monitoring of the cell, both *in vitro* and *in vivo*

Growth Factors
- Recombinant
- Sustained Release

Exosomes
- Purification
- Detection
- Services

LipoQ lipid assay

Small Molecules

Cell Counting Reagent

Matrix proteins
- PeptiGel
- Softwell
- RGD& Collagen

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