microASSIST: drug loaded microspheres for tissue engineering produced by microfluidics

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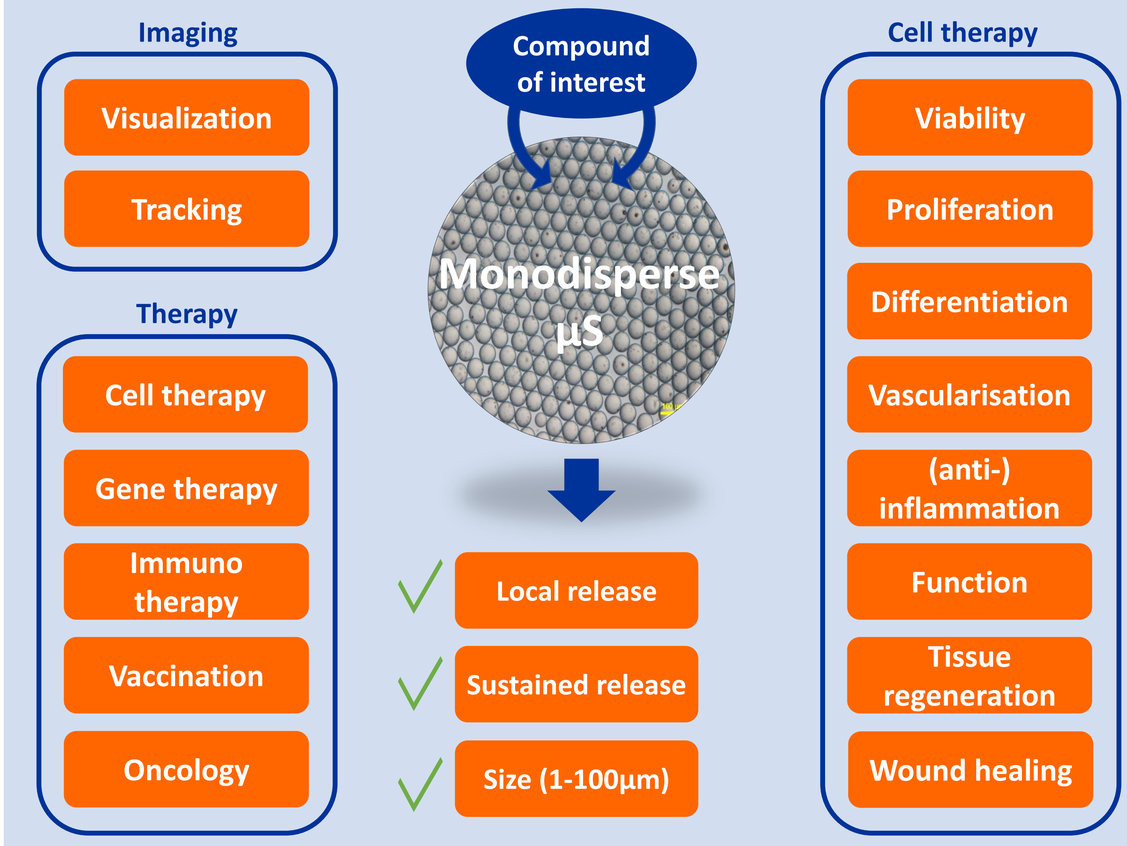
MICROASSIST for targetted cell therapies

Drug-loaded microspheres (**µS**) have many attractive features for clinical appliance. They can be used for topical applications where sustained release of the active agent is required and when high systemic drug concentrations must be avoided, or just injected to reach a specific site with high precision. In addition, in the context of stem cell therapies, they can also be used to assist therapeutic implants, by providing factors that support survival or functional differentiation of the cells, or by adjusting their microenvironment accordingly.

MicroASSIST currently works with poly lactic-co-glycolic acid polymers (**PLGA**) that are biocompatible, biodegradable and FDA/EMA approved for medical use. **PLGA-µS** can be loaded with a wide variety of compounds specific to the users needs. Some examples of therapeutically interesting compounds that can be encapsulated in our µS, are small molecules, proteins, enzymes, nanobodies, DNA/RNA fragments, etc.

Fig.1: Particle toolbox



µFlow - MICROFLUIDICS

The **µFLOW** and **microASSIST** teams are working closely together to create microfluidic devices that will allow industrial scale production of monodisperse drug-loaded µS, with improved characteristics as compared to conventional methods. With the upscaling of the production, the team is also working on miniaturization of the device with an on-chip approach (1). This should allow for easy integration into the industry.

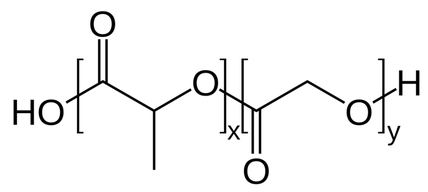
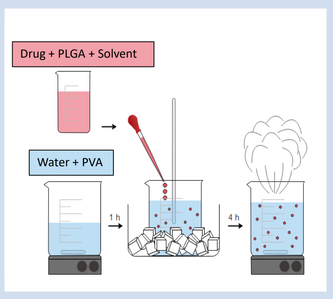
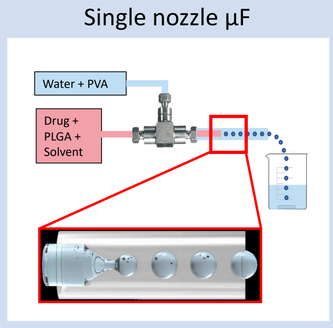
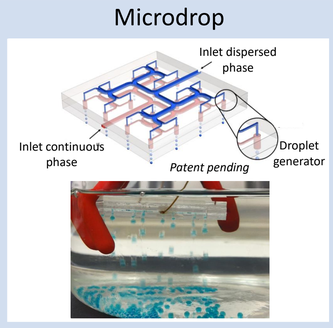
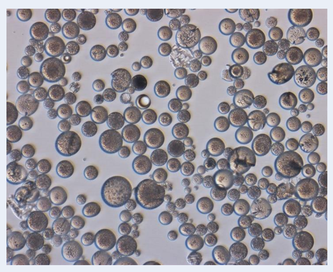
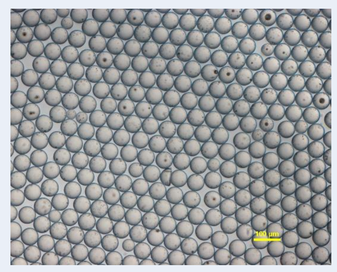


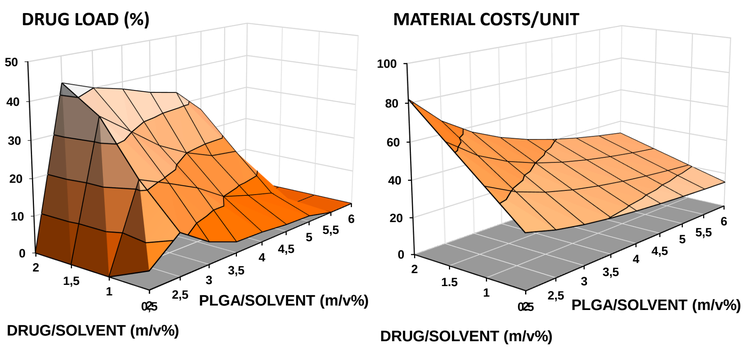
Fig. 2: Structure of PLGA
X = number of lactic acid units
Y = number of glycolic acid units
The ratio of lactic and glycolic acid determines the physiochemical properties of the polymer. Side groups can be added to modify the properties.

Table 1: Comparison between different production methods for dug-loaded µS

Solvent extraction	Single nozzle µF	Microdrop
		
		
• Polydisperse µS • CV > 50% • Small scale production • Low reproducibility • Fast (4h)	• Monodisperse µS • 10-100µm with CV < 10% • Scalable & reproducible production • Slower (8-10h)	• Monodisperse µS • 10-100µm, with CV < 5% • Industrial scale production • Increased drug load • High throughput

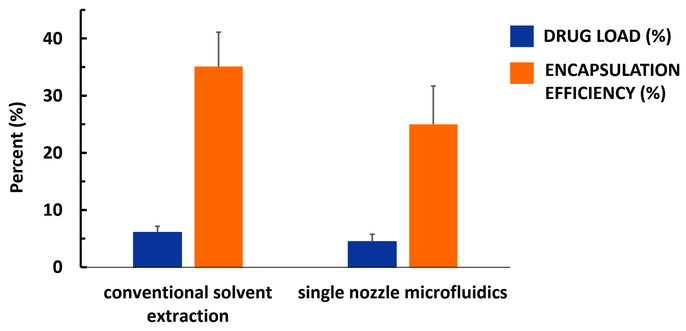
MULTI FACTORIAL µS DESIGN

Fig.3



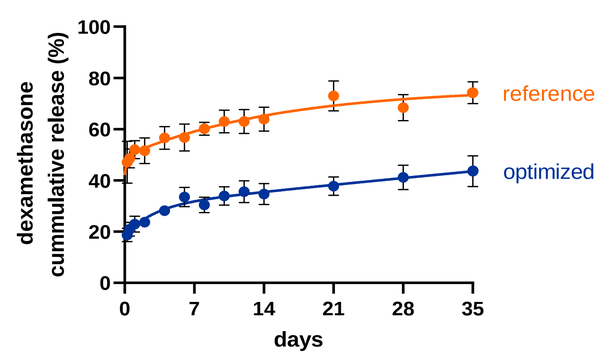
The **drug load** (**DL**) and **encapsulation efficiency** (**EE**) are important features that determine the quality of the µS. We use a multifactorial experimental design to optimize these characteristics, while also keeping the economic aspects under control. **Fig.3** shows the effect of different ratios of PLGA/solvent and drug/solvent on the DL and on the material costs per unit. **Fig.4** Single nozzle microfluidics and solvent extraction have comparable outcome.

Fig.4



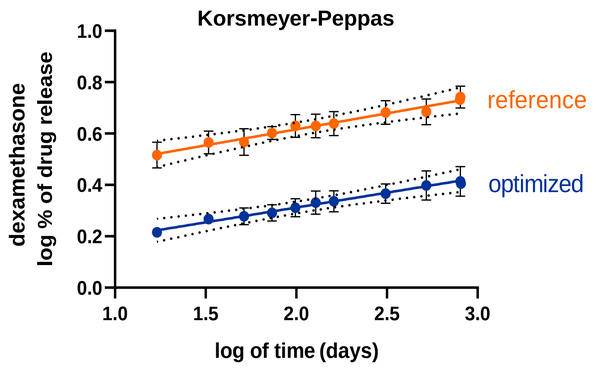
SUSTAINED DRUG RELEASE

Fig.5



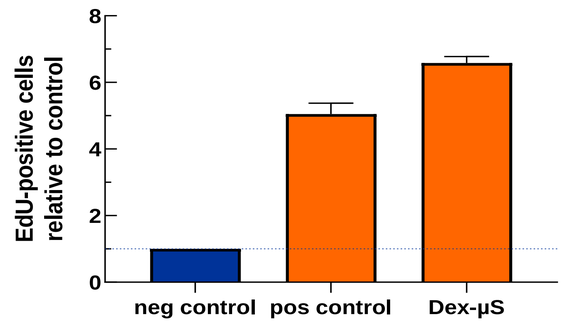
An additional defining feature of drug-loaded µS is their drug release potential. **Fig.5** shows how, thanks to our multifactorial approach, we could reduce the burst release of dexamethasone-loaded µS, resulting in a **sustained release** over a period of more than 5 weeks, even up to 10 weeks. **Fig.6**, this follows dissolution kinetics that can be fitted in the Korsmeyer-Peppas model, which indicates that the drug is primarily **released by diffusion**.

Fig.6



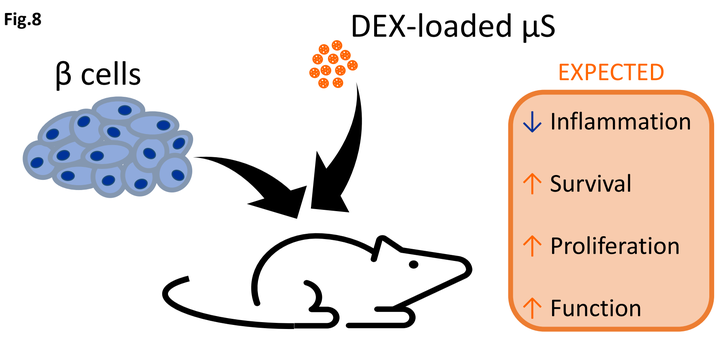
BETA CELL THERAPY IN DIABETES

Fig.7



Dexamethasone (DEX) is used in clinics for its anti-inflammatory and immunosuppressant effects. A **localized delivery** could reduce the inflammatory stress experienced by transplanted pancreatic β-cells. Moreover, we have shown that DEX stimulates β-cell proliferation, which may support engraftment of the cells (2,3). **Fig.7** DEX-µS induce a 6-fold increase in the number of proliferating β-cells. We are now evaluating DEX-µS in islet transplant models.

Fig.8



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3. Akbib, S., et al., PLoS One, 2019. Glucocorticoids and checkpoint tyrosine kinase inhibitors stimulate rat pancreatic beta cell proliferation differentially.

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