Periodic Report I publishable summary

MgSafe **MSCA-ITN-ETN** Project Reference No. 811226

Project Title: *MgSafe* - Promoting patient safety by a novel combination of imaging technologies for biodegradable magnesium implants

Summary of the context and overall objectives of the project

Biomedical imaging has gained a significant technological push and is the mainstay for diagnosis and therapy monitoring. Still, imaging is yet not optimized for the new class of biodegradable Mg-based implants. This class of implant materials serves a demand which rises from ageing populations, an ever-increasing incidence of obesity and a rapid rise in osteoporosis-related fractures, along with increasing high-risk sports activities. So far, these indications are typically treated with non-degradable metal implants, which commonly require surgical removal after complete bone healing. From the health care and patients' point of view, degradable implants provide a viable, cost-effective, and patient-friendly alternative. From 2013 on, the first degradable metal implant made from a Mg-alloy (compression screw of partner SYN) was CE certified and has been implanted into tens of thousands of patients so far.

During the follow-up of Mg-based implants, it became evident that monitoring implant performance and degradation with the existing imaging techniques can be challenging: the contrast is low for X-ray imaging. MR artifacts are induced by the use of conducting metal. PET, IR or ultra-sound imaging are so far not used to study this new class of materials, and the proof of principle has to be given that the modalities can be used at all for these implants. Solving these scientific and technical issues may support a broad clinical acceptance of implantable products made of Mg.

The key research objective of MgSafe is to develop and optimise imaging technologies for recently established Mg implants by quantifying their physical impact and suitability for this class of materials in future human applications. Highly sophisticated imaging techniques (nano and micro-computed tomography (nano, µCT), Magnetic Resonance Tomography (MRT), Positron Emission Tomography (PET), Ultrasound and Photoacoustic (USPA), Near Infra-red (NIR) imaging) will be developed beyond the forefront of medical device production *in vivo* and with *in situ* labelling options to obtain as much information as possible over time. The aim is to deliver non-invasively data on different time and length scales of the body reaction and material behaviour during Mg degradation with a precision and plethora of details which is currently not available.

Work performed from the beginning of the project to the end of the period covered by the report and main results achieved so far

Mg alloys and pure Mg as control (as test specimen and orthopaedic implants) were manufactured, characterized and partially implanted. These implants were studied in parallel in rats and sheep, and the consortium took care that comparable animal models were chosen. Multimodal imaging techniques (nano and µCT, MRT, PET, USPA, IR) were used, further developed, and combined. Data obtained from non-invasive *in vivo* and *in situ* labelling studies is currently analysed to understand the correlation between Mg degradation and the body reaction on different time and length scales. An additional dimension was added by the

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analysis of explants to obtain the highest resolution chemical and material science data. In addition, for the larger implants, dummy studies - as required for biomedical approval - were performed (following ASTM rules). First concepts were developed to merge all relevant biological and chemical *in vivo* and *ex vivo* data by computational 3D methods, simulations and machine learning approaches. The combination of these results will not only allow for an upscaling of the processes towards humans but will also deliver valuable data in terms of patient safety.

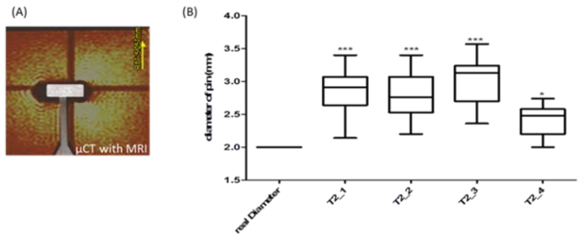

Fig. 1 (A) combination of µCT and MRI of the Mg pin showing the artefacts in MRI around the edges of the pin. (B) Plot of the Mg pin size in after different changes in sequences to reduce the artefacts. (ESR 5, MHH)

Applications are one essential driver for innovations. As mentioned above, the presence of Mg biodegradable implants inside an MRI scanner may reduce image quality and cause radio frequency heating induced safety hazards for patients. To study and address these constraints RF transmitter arrays were simulated and designed with the goal to provide a strong and uniform transmission field for MRI and to reduce local RF power deposition. For optimization a multi objective genetic algorithm (GA) was used. This approach provided substantial enhancements in transmission field efficiency and uniformity while reducing RF power deposition in the target region around the implant by about 46%. By using optimized multi-channel RF transmitter array configurations in conjunction with GA optimization facilitates mitigation of the undesired effects of Mg implants *en route* to the clinics. In parallel, the impact of Mg materials on artefact production in MRI has been quantified and reduced by novel MRI protocols which also minimize imaging artefacts for Mg implants (Fig. 1).

The combination of USPA and NIR was further developed to study implants deep in the tissues, especially around the bone-implant interface. By a newly developed AI algorithm, it was possible to extract functional, anatomical, and molecular information from tissues surrounding Mg implant by USPA imaging technology. The approach is based on Non-negative Matrix Factorization (NNMF) to detect and quantify the molecular tissue components from a spectral

INPUT	UNSUPERVISED UNMIXING	OUTPUT
Spectral PA Images	Non-Negative Matrix Factorization	Source Spectra & Abundance Maps

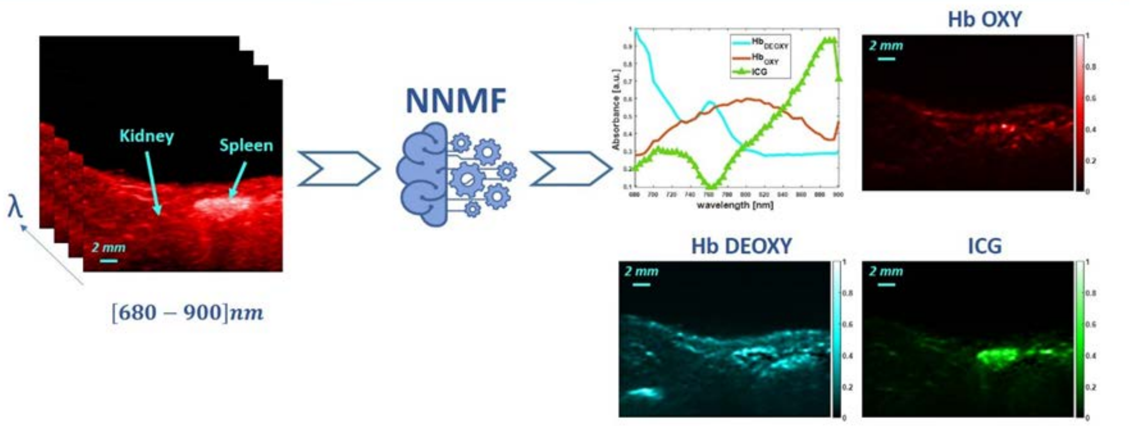

Fig. 2: Schematic chart of the NNMF-based unmixing approach to detect endogenous chromophores such as Oxygenated (Hb Oxy) / Deoxygenated (Hb Deoxy) Haemoglobin and exogenous contrast agents such as ICG, after intravenous injection in a CD1 healthy mouse model. ESR 15 (VSI) published in V. Grasso et al.: An Automatic Unmixing Approach to Detect Tissue Chromophores from Multispectral Photoacoustic Imaging. Sensors 2020, 20(11), 3235; https://doi.org/10.3390/s20113235

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Photoacoustic data set. The algorithm has been optimized to extract the tissue chromophores in the wavelength range of 680–900 nm. As a result, the proposed approach can automatically detect oxy/deoxy-haemoglobin and exogenous dyes with higher sensitivity without any user interactions. Figure 2 summarizes the proposed unsupervised approach. The Photoacoustic spectral images were used to input the algorithm and source spectra (absorption curves of the prominent absorbers) and abundance maps (spatial distribution of the source components) were obtained as output.

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