Project Details	
Project Code	MRC23IIARBa Gurevich
Title	Integrating biology and population health science to investigate obesity and deficient wound healing
Research Theme	Infection, Immunity, Antimicrobial Resistance and Repair
Summary	Obesity is a systemic disease that disrupts many cell and tissue functions, with impaired healing a key complication. This project will investigate the impact of obesity on deficient wound healing by integrating approaches from the biological and population health sciences. Key tools include epidemiological multi-omics data, zebrafish transgenesis and imaging, and human tissue culture assays, to reveal potential therapeutic targets for improving patient outcomes.
Description	Rationale: Obesity affects over 1 billion people globally and is causally implicated in numerous diseases and complications. Recent biological evidence indicates that obesity triggers chronic inflammation, decreased capillary density and poor oxygenation throughout the body in general, and aberrant inflammation, impaired angiogenesis, reepithelialisation and fibrosis as well as hypoxia at wound sites in particular. A poor blood supply and excessive inflammation are well accepted clinically as key in establishing chronic wounds. It is therefore plausible that obesity causes impaired wound healing at a population level, but this remains to be established. Tissue repair is incredibly complex, involving many cell lineages and signalling pathways that are under-investigated, particularly in the context of obesity. Therefore, the precise mechanisms driving deficient wound healing in individual obese patients remain poorly understood. This lack of understanding is driven partly by the inherent heterogeneity of obesity: furthermore, issues of bias in population data make it challenging to infer group-level causality. This project will integrate biology and population health science including genetic epidemiology to unravel the underlying mechanisms of tissue repair that are dysregulated as a result of obesity and examine how these might be ameliorated to rescue wound healing among patients. Aims & objectives: Our overall objective is to understand whether and how obesity causes impaired tissue repair and compromised wounds. This project has 3 main aims: 1) To establish whether adiposity influences wound repair at a population level. . 2) To define which obesity-related genes are related to deficient wound healing at an individual level and how these genes affect wound healing by dissecting these targets in vivo using zebrafish. 3) To identify potential therapeutic drug targets that might rescue wound healing in obese patients. Methods: We will use large-scale human data on adiposity/body scanning and proteomics with techniques of genetic epidemiology, particularly genome-wide association studies (GWAS) and Mendelian Randomisation (MR) analyses, to generate population-level causality estimates (Aim 1). These analyses will also allow us to prioritise adiposity-associated genes and pathways related to inflammation and other specific outcomes related to deficient wound healing, using ICD codes from hospital records. (Aim 2). To dissect how these obesity related genes mechanistically affect wound healing, we will use recent advances in zebrafish CRISPR mutagenesis, in combination with established zebrafish obesity models, wound assays and high resolution

	fluorescence imaging, to define what effect manipulating these genes has on key aspects of tissue repair such as re-epithelialisation, inflammation, angiogenesis and fibrosis (Aim 2). We will also use proteomic data and MR approaches to identify factors that modulate these key repair processes, which might rescue these obesity-related wound healing defects in patients and represent future therapeutic targets (Aim 3). This will facilitate us performing a small molecule screen on wounded, obese zebrafish, and we will validate the most promising targets using established tissue culture and co-culture assays performed on tissue samples (e.g. immune cells) obtained from overweight/obese patients (Aim 3). Within this broad framework, we will encourage the student to actively steer the project in terms of genetic epidemiology analyses used, repair processes to be focused on, and therapeutic targets to be pursued. References: Pierpont Y. et al. ISRN Obesity. 2014. doi:10.1155/2014/638936. Sen C. Adv. Wound Care, 2019;8(2):39-48. doi: 10.1089/wound.2019.0946. Sobczyk M. et al. Bioinformatics, 2021;37(1):1-8. doi: 10.1093/bioinformatics/btaa1096 Gurevich D. et al. EMBO J, 2018; 37(13):e97786. doi: 10.15252/embj.201797786
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