

The Research Group

Cellular and Molecular Immunology

has the honor to invite you to the public defense of the PhD thesis of

Sweta Parik

to obtain the degree of Doctor of Bioengineering Sciences

Joint PhD with KU Leuven

Title of the PhD thesis:
Investigating the role of fatty acid desaturation in cancer

Promotors:

Prof. dr. Sarah-Maria Fendt (KU Leuven)

Prof. dr. ir. Jo Van Ginderachter (VUB)

The defense will take place on
**Thursday, December 15, 2022 at 9.30h at
UZ Leuven, Gasthuisberg, auditorium GA2,
ON1.**

Link for live stream:

[streaming-video-live \(kuleuven.be\)](https://streaming-video-live.kuleuven.be)

Code:53311

Members of the jury

Prof. dr. Baki Topal (KU Leuven, chair)

Prof. dr. Joris Messens (VUB, secretary)

Prof. dr. ir. Kiavash Movahedi (VUB)

Prof. dr. Patrizia Agostinis (KU Leuven)

Prof. dr. Massimiliano Mazzone (KU Leuven)

Prof. dr. Nils Halberg (University of Bergen)

Prof. dr. Olivier Feron (UCLouvain)

Curriculum vitae

Sweta Parik obtained her Master's degree in Biology at Tata Institute of fundamental research, India in 2017. She was then awarded VIB international PhD fellowship and stated her doctorate studies as a joint PhD student in the Myeloid Cellular Immunology group, Prof. Jo Van Ginderachter, VUB and Laboratory of cellular metabolism and metabolic regulation, Prof. Sarah-Maria Fendt, KUL. During this period she presented her work in multiple international conferences and was listed as an author in 5 research articles and 1 review article.

Abstract of the PhD research

Cancer is a global health concern, therefore, studies over several years have intensively investigated the specific characteristics of cancer cells, outlining several hallmarks of cancer. Metabolic reprogramming, a cellular response that aids cancer cell growth has emerged as one of these hallmarks. One aspect of metabolic reprogramming is rewiring of the fatty acid (FA) metabolic pathway in cancer cells so as to fulfill the biological requirements of the rapidly proliferating cancer cells. FAs are biological molecules composed of a carboxy terminal and a hydrocarbon chain, and aid cancer cell growth by impacting various aspects of cell physiology. Cancer cells often display elevated FA levels facilitated by an increase in *de novo* synthesis from glucose or glutamine by FA synthase (FASN) and/or uptake by FA transport proteins. Indeed, abrogation of FASN or specific FA uptake proteins limits growth of certain tumors. Intracellular saturated FAs may subsequently be elongated to longer chain FAs or desaturated by stearoyl coA desaturase (SCD), the canonical monodesaturase that converts the 16-carbon saturated FA, palmitate (16:0) to palmitoleate (16:1 n-7). Indeed, pre-clinical studies have demonstrated benefits of SCD inhibition in cancer. However, a major hindrance to their clinical translation has been that not all cancers respond to SCD targeting. In this thesis, we uncovered that this can be attributed to an alternative palmitate monodesaturation pathway catalyzed by fatty acid desaturase 2 (FADS2) and leading to the production of the unusual FA, sapienate (16:1 n-10). We then showed that FADS2 silencing sensitized previously insensitive cells to an SCD inhibitor and markedly curbed the growth of liver tumours. Next, we extended these findings in glioblastoma (GBM), a particularly hard to treat cancer displaying high sapienate production. Current standard of care for GBM is radiation with temozolomide (TMZ) chemotherapy, despite which tumours always recur and median survival is ~17 months. We investigated the metabolic heterogeneity in GBMs and found that FASN, SCD and FADS2 expression shows intra-tumoral heterogeneity, reflecting this characteristic feature of GBM. Further, we found that intracellular palmitate accumulation synergizes with TMZ and markedly induces lipotoxic cell death in newly diagnosed and recurrent GBM cells cultured *in vitro* under physiological conditions.