To understand the negative impact of chronic nutrient overload in systemic metabolism, and because the liver has a key role in metabolic homeostasis, we generated mice that have chronically high nutrient signalling only in hepatocytes (by liver-specific expression of an active RagA allele: RagA\textsuperscript{L119F}). RagA\textsuperscript{L119F} livers exhibited high phosphorylation of mTOR targets (S6K1 and 4E-BPs, FIGURE A) and, importantly, the sole activation of RagA in the liver, without altering nutrient intake, impaired glucose homeostasis, as revealed by loss of glucose tolerance (FIGURE B). This result highlights the relevance of a chronic nutrient surplus – liver Rag GTPase signalling axis in metabolic complications of the obesity state.

Studying the connections of nutrients and cancer, we previously found that activating mutations in the gene called Ragc (key player, together with RagA, in the signal transduction of cellular nutrient levels) result in a subtype of B cell lymphoma, follicular lymphoma. Thus, a lot of interest to develop pharmacological inhibitors of this nutrient signalling pathway has recently spurred, but these drugs are still to be developed. Thus, to determine both the efficacy and safety of inhibition of nutrient signalling against follicular lymphomas, we undertook a genetic approach: we now generated mice expressing a hypomorphic allele of Ragc, and asked whether 1) decreased nutrient signalling could suppress the development of follicular lymphoma; and 2) unanticipated side effects could preclude the use of such inhibitors. Hypomorphic Ragc\textsuperscript{L119F} mutant mice (Ragc\textsuperscript{L119F/-}) showed a significant extension of survival when follicular lymphomas were induced (FIGURE C), and an exhaustive analysis of potential side effects revealed that B cells were selectively affected (FIGURE D), importantly, without detectable undesirable trade-offs in other organs (not shown). These results support both the efficacy and safety of nutrient signalling inhibitors in the treatment of B cell neoplasms.

Our studies support the targeting of nutrient signalling as a novel, efficacious and safe approach against the aberrant metabolism of cancer cells and to combat the process of ageing.