At the foundation of cellular and tissue growth stands the transfer of chemical energy from nutrients into macromolecules. Tumours are no exception to this principle, and unavoidably seek metabolic states that support anabolism and growth. Our vision is that the tissue of origin influences the biochemical pathways utilised by tumours to grow in two ways. On the one hand by imposing environmental constraints, the tissue of origin exposes metabolic vulnerabilities of the tumour. On the other hand, enzymes normally restricted to a defined population of differentiated cells, and required for tissue physiological functions, can be hijacked by cancer cells to enhance their metabolic fitness.

Glutamine and glutamate metabolism in brain and liver cancer

Glutamine and glutamate are instrumental to physiological processes, such as neurotransmission in the brain and ammonia homeostasis in the liver. At the same time, they are obligate substrates for anabolism of tumours required for nucleotide biosynthesis in glutamine-restricted glioblastoma, the most aggressive type of glioma. Currently, we are assessing the effects of GS interference on the metabolism and growth of human primary glioblastoma cells and xenografts.

The liver is an ammonia-detoxifying organ and maintains homeostatic levels of circulating ammonia and glutamine. The functional unit of the liver constitutes an elegant example of metabolic zonation. In fact, the periporal zone, where hepatocytes express the urea cycle enzymes, converts the majority of ammonia into urea. The ammonia escaping this metabolic zone is captured by the hepatocytes surrounding the central vein, which express GS. This enzyme has a high affinity for ammonia, and incorporates it into the non-toxic glutamine, that can be returned to blood circulation. In liver tumours this metabolic zonation is disrupted. Liver tumours with an overactive WNT/β-catenin signalling pathway show a widespread GS expression.

By means of HPLC–mass-spectrometry-based metabolomics and cell biology approaches, we are studying the carbon and nitrogen metabolism of liver tumours with high GS expression.

Identification of metabolic vulnerabilities elicited by glutocorticoids in glioma

Glucocorticoids (e.g. dexamethasone) are part of the mainstay of treatment for glioma patients and are administered to reduce the peritumoural oedema, and to mitigate the adverse side effects of radio- and chemotherapy. As indicated by the name (glucocor + cortex + steroid) glucocorticoids exert regulatory effects on glucose metabolism. However, the metabolic effects of glucocorticoids are not limited to systemic homeostasis of glucose and may modulate the fitness of glioma cells in the brain environment. While the anti-inflammatory action of glucocorticoids is a mainstay for the clinical management of glioma patients, the metabolic effects of these drugs on the cancer cells could be exploited to improve the prognosis of brain tumour patients. On this basis, we developed Plasmax™ (Figure 2) a cell culture medium with nutrients and metabolites at the concentration normally found in human blood. The newly formulated medium allows the culture of mammalian cells with reduced supplementation of foetal bovine serum (Figure 3). We are currently testing Plasmax™ in a variety of cell culture systems, including murine normal, stem and cancer cells, as well as in primary human bone marrow derived mesenchymal stromal cells.

In 2020, Plasmax™ became the first physiological cell culture medium to obtain results more relevant to human tumour biology. Despite it seeming obvious that the nutrient composition of culture medium affects the phenotypic behaviour of the cells, very little attention has been devoted in perfecting the formulation of historic media.

Indeed, the vast majority of biomedical research employs commercially available growth media, based on the pioneering work done 60 years ago by Harry Eagle. However, these formulations were not designed to reproduce the physiological cellular environment, but rather to enable the continued culture of cells with minimal amount of serum (i.e. Minimal Essential Medium, MEM). Consequently, a standard culture medium known as DMEM is distant from the nutrient levels found in normal human blood and it profoundly skewes the metabolism of cancer cells in culture (Vande Voorde et al., 2019, Sci Adv.; Ackermann et al., 2019 Trends Cancer). For example, glucose in DMEM is at five-fold the normal glycaemia. A similar ratio applies to glutamine, the most abundant amino acid in circulation. Conversely, non-essential proteins and amino acids normally circulating in blood are missing from DMEM.

On this basis, we developed Plasmax™ (Figure 2), a cell culture medium with nutrients and metabolites at the concentration normally found in human blood. The newly formulated medium allows the culture of mammalian cells with reduced supplementation of foetal bovine serum (Figure 3). We are currently testing Plasmax™ in a variety of cell culture systems, including murine normal, stem and cancer cells, as well as in primary human bone marrow derived mesenchymal stromal cells.

In 2020, Plasmax™ became the first physiological medium to be commercially available (Xmibo, corr). In 2021, we tested the stability of Plasmax demonstrating that the medium stored at 4°C for up to 12 months, supported cell growth and colony formation comparably to freshly produced medium and better than DMEM. (Figure 3).

The availability of a physiologically relevant cell culture medium will further reduce the inconsistencies between in vitro and in vivo results, thus favouring more translational biomedical research.