Name	DIMITRIOS ANASTASIOU
Position	Group Leader (2nd 6)
Year joined *(Crick or founder institute)*	2012

Career History

2001-2006: University of Basel, Switzerland - PhD in Biochemistry
2007-2012: Beth Israel Deaconess Medical Center & Department of Systems Biology, Harvard Medical School, Boston, USA - Postdoctoral fellow
2012: Harvard Medical School, Boston, USA - Instructor in Medicine

Major Awards, Honours and Prizes

2012: MRC Centenary Award
2012: DKFZ Harald zur Hausen Inaugural Fellowship (declined)

Membership of external committees, editorial boards, review panels, SABs etc.

Peer Review Board Member, Molecular and Cellular Oncology

Lab Name	***Cancer Metabolism Laboratory***

Research programme and achievements

Changes in glucose metabolism have been linked to the pathogenesis of many cancers and are widely used for tumour diagnosis. However, current attempts to target glycolysis for cancer therapy have shown limited success, at least in part due to an incomplete understanding of how glucose metabolism is regulated at the cellular and the subcellular levels. It is also not clear how perturbation of these regulatory mechanisms in tumours affects whole-body glucose homeostasis. The overarching goal of our research is to identify the fundamental principles that underlie the spatiotemporal regulation of glucose metabolism at multiple scales, and then use them to guide improved cancer diagnosis, therapy and prevention.

Since its establishment in 2012, our lab has focused on elucidating cell-autonomous mechanisms that control glycolysis. We generated computational and optogenetics tools that are necessary for our future work to understand how allosteric enzyme control regulates glycolysis. Our work has also revealed new synergies between proteins that provide NAD^+ to increase glycolysis, a process that is essential for cancer cell survival during the early stages of hypoxia. Moreover, we have discovered a new mode of action for dimethyloxalylglycine (DMOG), a compound that is widely used to increase glycolysis

by stabilising the transcription factor HIF1α. We found that MOG, a major product of DMOG degradation, is selectively cytotoxic to cells that express the pyruvate transporter MCT2, through simultaneous inhibition of multiple key metabolic enzymes. We have synthesised MOG analogues that we are now testing in mice as diagnostic imaging tools.

To study the physiological relevance of our findings in cultured cells and to understand their impact upon whole-body glucose homeostasis, we have established mouse models of hepatocellular carcinoma (HCC) and liver regeneration. To facilitate our research in this area, we have developed new methods, such as ^{13}C-magnetic resonance spectroscopy (MRS), which allow us to measure mouse liver metabolism dynamically *in vivo* and *ex vivo*. Using these methods, we discovered a significant increase in the contribution of glycerol to the elevated glucose production in the liver of mice with HCC.

Together, our past work has revealed novel insights into the cell-autonomous mechanisms that regulate glycolysis and has highlighted new molecular mechanisms and target combinations that will help perturb glycolysis specifically in cancer cells, despite its ubiquity throughout the human body. We have also generated mouse models and methods that have highlighted the influence of HCC on host metabolism.

In ongoing and future work, we have been building upon these discoveries about how glucose metabolism is regulated at the molecular and cellular levels, with an increased emphasis on *in vivo* interactions between tumour and host metabolism. We have set out to identify the molecular factors from HCC that reprogramme host glucose metabolism and we will genetically and pharmacologically perturb host gluconeogenesis, in part using the tools and insights from our past discoveries. The proposed research programme will allow us to define new ways to target host metabolism, alone or simultaneously with HCC metabolism, in order to prevent and to treat liver cancer.

Research outputs

Macpherson, J.A., Theisen, A., Masino, L., Fets, L., Driscoll, P.C., Encheva, V., Snijders, A.P., Martin, S.R., Kleinjung, J., Barran, P.E., Fraternali, F.*, and Anastasiou, D.* (2018). *Functional cross-talk between allosteric effects of activating and inhibiting ligands underlies PKM2 regulation*. eLife 8:e45068 (2019) (* co-corresponding). DOI: 10.7554/eLife.45068
This work reveals that amino acids, rather than FBP, are the relevant cellular regulators of PKM2, a critical node in cancer metabolism. It further elucidates the molecular mechanism of PKM2 regulation by amino acids with a new algorithm that predicts allosteric pathways in proteins, a major and difficult problem in structural biology.

Fets, L., Driscoll, P.C., Grimm, F.*, Jain, A. *, Nunes, P.M. *, Gounis, M., Doglioni, G., Papageorgiou, G., Ragan, T.J., Campos, S., Silva dos Santos, M., MacRae, J.I., O'Reilly, N., Wright, A.J., Benes, C.H., Courtley, K.D., House, D., and Anastasiou, D (* equal contribution). (2018) *MCT2 mediates concentration-dependent inhibition of glutamine metabolism by MOG*. Nat Chem Biol. 14(11):1032-1042. DOI: 10.1038/s41589-018-0136-y
DMOG is a compound that has been widely used to support the involvement of prolyl hydroxylases (PHDs) in disease, thereby leading to multiple, currently active, drug discovery programmes for PHD inhibitors. This paper reveals a new, PHD-independent,

mechanism of action for DMOG through targeting of multiple enzymes in glutamine metabolism, thereby leading to cytotoxicity only against some cells.

Gehrig, S., Macpherson, J.A., Driscoll, P.C., Symon, A., Martin, S.R., MacRae, J.I., Kleinjung, J., Fraternali, F., and Anastasiou, D. (2017). ***An engineered photoswitchable mammalian pyruvate kinase*****. FEBS J 284, 2955-2980. DOI: 10.1111/febs.14175**
This paper describes the first light-controllable mammalian metabolic enzyme and demonstrates that glycolysis can be modulated reversibly with light. Optogenetic control of glycolysis opens the door to elucidating the elusive function of glycolytic oscillations in mammalian cells.

Grimm, F., Jain, A., Silva dos Santos, M., Kleinjung, J., Nunes, P.M., Gehrig, S., Fets, L., MacRae, J.I., and Anastasiou, D. ***GOT1 primes the cellular response to hypoxia by supporting glycolysis and HIF1α stabilisation*****. Cell Reports, under revision**
Tumour hypoxia is associated with poor prognosis and resistance to therapy. This manuscript demonstrates that GOT1 and LDHA synergise to support cell survival in early hypoxia; their combined inhibition is cytotoxic only in hypoxia and could therefore be used to selectively kill cancer cells before they adapt to chronic hypoxia.