Targeting target cancer metabolism
what is fuelling the resurgence?

Targeting the metabolic pathways of cancer is a hot topic for drug discovery. The central dogma is that cancers have a higher demand for metabolic inputs to aid proliferation and survival and that this could be an Achilles heel which could be exploited therapeutically. This central metabolic facet of cancer has been known for more than 50 years so what are the recent discoveries that have fuelled the renewed investment in metabolic targets in cancer?

In recent years there has been resurgence in interest in metabolism as a possible area for development of novel anti-cancer agents. This has been fuelled by advances in technology and understanding of cellular metabolism and how targeting this area could be of therapeutic benefit. The drivers behind these advances have come from academic-led research pushing our understanding of cancer cell metabolism and the interplay between these pathways and other cancer related signalling events linked to changes in oncogene or tumour suppressor gene status/function. In the past few years this spiralling interest has lead to a rapid increase in the number of publications on metabolism, multiple focused cancer metabolism conferences and the renewed interest from the pharmaceutical industry in this area of anti-cancer research.

This interest has lead to the establishment of several new companies focused on this area and to the generation of partnerships between the Pharma industry and research organisations to understand this complicated field and hunt for new targets. For example, Agios Pharmaceuticals was founded by key academic experts in cancer, oncogenic signalling and metabolism research (Lewis Cantley, Craig Thompson and Tak Mak) to focus on cancer metabolism as a new approach to cancer treatment and has an active pipeline of metabolism targets including isocitrate dehydrogenase (IDH1/2)\(^1\) and Pyruvate kinase-M2 (PK-M2)\(^2\), targets which will be discussed in more detail later. Agios has also recently entered into a $130 million strategic alliance with Celgene to explore novel drug targets in Cancer metabolism.

Cornerstone Pharmaceutical was also founded through academic researchers (Paul Bingham and Zuzana Zachar) with a focus on targeting cancer metabolism and has a candidate drug, CPI-613, which targets pyruvate dehydrogenase\(^3\) currently in multiple Phase I/II clinical trials. Another biotech, Advanced Cancer Therapeutics, has invested in research at the James Graham Brown Cancer Centre and the University of Louisville Research Foundation to pursue cancer metabolism targets for example; PFKFB3, a glycolytic regulator\(^4\) and choline kinase \(\alpha\) component of lipid metabolism pathways\(^5\). Likewise AstraZeneca is midway through a multi-project three-year alliance with Cancer Research Technology, Cancer Research UK’s commercialisation and development arm to work on a portfolio of targets selected from Cancer Research UK’s biological research in the emerging field of cancer metabolism.

By Dr Neil P Jones
Many potential drug targets within the metabolic field are currently being evaluated as potential therapeutics in all stages of the drug development progress from early development, through pre-clinical development and into clinical trials although as yet no agent targeting a core metabolic pathway has been approved for cancer\(^6\). Figure 1 summarizes some of the core metabolic pathways and some of the agents in development looking to target different areas of cancer metabolism. In order to fully understand why there are so many agents and pathways under consideration in cancer metabolism it is important to investigate the main drivers for targeting cancer metabolism. The rest of this review will therefore consider why cancer metabolism could make an attractive area for therapeutic intervention and how our understanding of these pathways and advances in technology/knowledge is driving the hunt for new therapeutics.

**Cancer metabolism and the Warburg Effect**

Dividing cells require ATP to maintain energy status, increased biosynthetic intermediates and maintenance of cellular redox status. In order to meet these needs carbohydrates, proteins, nucleotide and lipid alterations are required. Both cancer cells and rapidly proliferating normal cells require some of these adaptations for proliferation, however cancer cells must implement these processes in very different and often harsh or stressful environments where nutrients supplies may be low and where redox balance, pH and oxygen levels may not be maintained. Cancer cells have found ways to adapt to these dynamic situations and regulate their metabolic status in order to survive, grow and even prosper.

The links between cancer and altered metabolism is not a new phenomenon. Otto Warburg, a Nobel prize-winning scientist (for the discovery of cytochrome oxidase) noted more than 80 years ago that in tumour tissue slices ATP is generated from glucose via aerobic glycolysis which is an oxygen independent process rather than by oxygen dependent oxidative phosphorylation even when oxygen is present\(^7,8\). This switch in ATP generation which has been termed the Warburg Effect is initially paradoxical as while ATP generation is more rapid via glycolytic pathways, far less ATP is generated (2 molecules ATP/molecule glucose) than via oxidative phosphorylation (up to 36 molecules ATP/molecule glucose).

In more recent times this switch has been attributed to the ability of glycolytic pathways to supply...
essential intermediate components and co-factors via branches off of the core glycolysis pathway including via the pentose phosphate pathway which supplies NADPH for redox balance and lipid metabolism and ribose-5-phosphate for nucleotide synthesis and via the serine biosynthesis pathway (Figure 1)\(^9,10\). Alongside this it has been postulated that glycolytic adaption could be the result of adaptations to hypoxic conditions during early tumour development and in order to generate ATP and metabolites at a higher rate when glucose is not limiting\(^11\). What is clear is the Warburg shift demands that tumour cells implement an abnormally high rate of glucose uptake to meeting their increased demands for biosynthesis, energy and reducing equivalents.

The advent of Fluorodeoxyglucose-positron emission topography (18F-FDG-PET) imaging\(^12\), in which a radioactive glucose analogue is used to assess glucose uptake, has confirmed that many tumour types have high glucose uptake and is now used as part of clinical diagnostic packages for tumours. \(^{18}F\)-FDG (2-deoxy-2-(\(^{18}F\))fluoro-D-glucose), first synthesised in the 1970s is a glucose analogue which enters the cell in normal ways and is phosphorylated like normal glucose to prevent it being released again but cannot then be further processed by glycolytic pathways before radioactive decay and so is a good reflection of glucose uptake in the body\(^13,14\). This ability to monitor glucose within tumours and surrounding tissues and the clear increases in glucose uptake and utilisation in tumours confirms aspects of Warburg’s hypothesis and underlies the important of glucose metabolism in many cancers\(^15,16\).

It has also been know for more than 50 years that many tumours have increased rates of glutamine uptake and consumption. In fact many cancer cells cannot survive without exogenous glutamine and display a glutamine addiction\(^17\). As was seen with glucose, the initial assumption was that the metabolism of glutamine by tumours is inefficient. However, recent studies have shown that glutamine is a key initial substrate in many processes essential for cancer cell maintenance and growth. Products of glutamine metabolism have been found to be essential for the generation of acetyl CoA (the starting block of lipid synthesis), for NADH generation (for lipid synthesis and redox balance), for glutathione synthesis (for redox balance) and for serine synthesis (for nucleotide and protein synthesis)\(^18,19\). A large proportion of glutamine is also converted to lactate in a process which generates NADPH an essential reducing equivalent in lipid and nucleotide synthesis and in redox balance. The multi-step conversion of glutamine to lactate helps to explain high lactate levels in tumours even when glycolytic flux has been slowed to generate key intermediates via branched pathways\(^20,21\) (Figure 1).

For both glucose and glutamine metabolism improved imaging techniques coupled with enhanced methods to monitor metabolic flux and identify metabolites (nmr and mass spectroscopy) has really enabled researchers to elucidate what is happening to the key metabolic start points in cancer cells compared with other tissues and help to understand how cancer cells adapt to use these effectively to maintain growth and survival\(^22,23\). The advent of technologies such as RNAi, alongside advances in genomic and proteomic profiling, metabolic modelling and improved access to tumour samples, has proved invaluable in allowing researches to really probe metabolic functionality in cancer. Coupled with the enhanced understanding into the fates of glucose and glutamine this has driven advances in understanding the complex nature of metabolic pathways in cells and how these are deregulated in cancers\(^24,25\).

**Cancer metabolism pathways: drivers and their potential metabolic targets**

In recent years what has really catapulted cancer metabolism right back into the spotlight is the understanding of the mechanism by which metabolic adaptations are controlled and regulated in tumours by known oncogenic signalling mechanism\(^25\). Alongside this has been the discovery that within several metabolic components there are cancer-related mutations (ie IDH1/2)\(^26,27\) or cancer-specific isoforms (ie PK-M2)\(^28\) that are critically linked to progression of certain tumour types. The ability to sequence large sample banks of tumours and understand the data has unlocked many of the secrets of different cancers and helped us begin to understand what drives tumour formation and progression with deregulation of cellular energetic now recognised as one of the hallmarks of cancer\(^29\).

It is now clear that many oncogenic (Myc\(^18,30,31\), PI3k/AKT\(^32,34\), Ras\(^10,35\)) and tumour suppressor proteins (p53\(^36,38\), PTEN\(^39,40\), LKB1\(^41,42\)) directly affect the expression, regulation and activity of key components of metabolic pathways and it is now believed that these tumourgenic alterations act in part to drive cancer progression via promoting metabolic adaptation towards enhanced glucose and glutamine dependence (see Table 1). For example, Myc has been shown to upregulate glutaminolysis via...
increasing the expression key components of the glutamine metabolic pathway\(^43\) and to enhance oxidative metabolism of glucose via increased pyruvate dehydrogenase\(^44\) and lactate dehydrogenase expression/activity\(^45\), HIF1α\(^43,46-48\), a transcription factor which can be upregulated in hypoxic conditions or by enhanced oncogenic (ie Myc\(^49,50\)) or decreased tumour suppressor (ie Von Hippel-Lindau\(^51\)) function is also known to upregulate the expression of many metabolic enzymes including glucose transporters (GLUT\(^44\), metabolic regulators (PFKFB\(^3,52,53\), PFKFB\(^4,52\), pyruvate dehydrogenase kinase (PDK\(^1\)), hexokinase-2 (HK\(^2\)), PK-M\(^2\), lactate dehydrogenase (LDH\(^a\)), monocarboxylate transporter 4 (MCT\(^4\)). This suggests that metabolic adaptations also play a role in maintaining tumour growth and survival in hypoxic conditions. Akt also increases glycolysis by increasing glucose transporter expression\(^32\) and facilitating hexokinase translocation to the mitochondria where it functions to initiate glycolytic flux\(^34,35\). The tumour suppressor protein p53\(^59,60\) has also been shown to regulate expression of various glycolytic proteins including upregulation of hexokinase and of a protein called TIGAR which acts as a negative regulator of glycolysis\(^34,35\). p53 also promotes oxidative phosphorylation via upregulation of SCO\(^2\) and suppresses glycolysis via expression of PTEN, a negative regulator of the PI3K pathway\(^64\). Therefore, while loss of p53 may drive acquisition of the glycolytic phenotype it will be important to understand metabolic regulation in p53 wild type and mutant tumours.

Understanding the interplay between oncogenes and tumour suppressors and metabolic pathways will be key to deciphering how metabolism integrates into tumour initiation and progression and in looking for potential therapeutic targets with clear clinical stratification. The rest of this review will take a stripped-down look at metabolism and introduce a couple of potential metabolism targets which are currently being extensively investigated both by academia and industry.

### The basic stages of glucose and glutamine metabolism in cancer

At its simplest level the complex process of glucose and glutamine metabolism can be split into four key phases (Figure 2). The first phase is the uptake of these essential metabolic substrates into the cell via transporter proteins. The process actively imports high concentrations of glucose or glutamine into the cell ready for utilisation and in cancer GLUT1 and GLUT4 for glucose\(^65\) and ASCT2(SLC1A5) for glutamine\(^65\). GLUT1 and GLUT4 have been found to be overexpressed in many cancers and to be upregulated by ras and myc signalling\(^65,67\). Currently there are no clear inhibitors of GLUT1/4 published although the natural dihydrochalcone, Phloretin is reported to have GLUT inhibitory activity and be effective in inducing apoptosis in vivo cancer models\(^68\). ASCT2 is also overexpressed in some tumours\(^69\) and reported to be directly upregulated by myc\(^18,70\) although as yet no clear inhibitors of this transporter have been reported. The oncogenic upregulation of glucose and/or glutamine transporters in cancer helps to explain how tumours adapt to facilitate their increased reliance on glucose and/or glutamine and how tumours can accumulate high levels of these metabolites.

The next step is the initial processing of these imported metabolites by conversion into the first metabolic product which can act as an entry substrate into the main metabolic processing pathways. This conversion acts to trap the imported metabolite within the cell and to commit it to further processing into downstream intermediates as well as shift equilibrium balances to allow the influx of more glucose or glutamine to meet the
cell’s high demand for these metabolites. For glucose, this initial step is conversion to glucose-6-phosphate by the hexokinase’s of which hexokinase 2 appears to predominant in many cancers and has shown to be regulated by both AKT and mutant p53. siRNA studies or use of non-hydrolysable glucose mimics which have been shown to inhibit Hexokinase-2 activity, suggest that modulating Hexokinase-2 activity could be of therapeutic benefit in cancer. Two of these potential hexokinase inhibitors; 2-doexyglucose and 3-bromopyruvate have shown promising anti-cancer activity in multiple pre-clinical models but as yet data from clinical trials has not supported their use as clinical anti-cancer agents. For glutamine the first step is conversion of glutamine to glutamate by glutaminase proteins (GLS1/2). GLS1 expression has been shown to be increased in several tumour types and to be under indirect control from Myc via myc-dependent regulation of miR23a/b levels. Studies using siRNA technology or potential inhibitors of GLS1 (DON, 96883) have suggested that inhibition of this target could be of benefit in glutamine dependent tumour cells.

The next phase of metabolite processing involves the conversion of these metabolites into a series of intermediates through metabolic cascades. This process is not a linear and intermediates can be further processed through branched pathways (i.e. tri-carboxylic acid cycle, pentose phosphate pathway or serine biosynthesis pathway) to yield additional products. The net result of all of the processing pathways of core metabolism is; the generation of biosynthetic intermediates for the manufacture of lipids, proteins, nucleotides and complexes sugars, the generation of energy in the form of ATP and the generation of key co-factors, i.e. glutathione, NADH and NADPH, which are essential for the functionality of many protein and have key roles in protecting the cell from oxidative stress. Multiple proteins on these pathways have been shown to be over expressed in cancer, dependent on oncogenic control or in inhibition studies (RNAi or tool compounds) been shown to be involved in cell proliferation and/or survival mechanisms. Proteins which are of potential interest as possible therapeutic targets include the glycolytic enzymes (e.g. Hexokinase-2, Phosphoglycerate kinase-1, Phosphoglycerate mutase, and Pyruvate kinase); the pentose phosphate proteins (e.g. Glucose-6-phosphate dehydrogenase, transaldolase and transketolase) and lipid synthesis/fatty acid metabolism targets (e.g. ATP citrate dehydrase).
lyase\textsuperscript{99,100}, fatty acid synthase\textsuperscript{101,102}, monoglyceride lipase\textsuperscript{103,104} and carnitine palmitoyltransferase\textsuperscript{1}\textsuperscript{105}). See\textsuperscript{6,84,106} for more detailed reviews of some of these.

The final process within centralised metabolism is the export of end-point products/waste from the cell in order to protect the cell from build up of potentially toxic components and also to modify the extracellular vicinity around the cell which may act to assist the cell’s establishment in this environment. In cancer cells the main exported substance from glucose metabolism is lactate which is effluxed via the transporter proteins MCT1 and MCT4\textsuperscript{57,66}. Studies have found MCT transporters to be overexpressed in multiple tumour types\textsuperscript{107-110} and that chemical or genetic inhibition of MCT function can reduce tumour growth suggesting that molecular targeted therapy against MCT transporters could be a possible mechanism for targeting cancer metabolism\textsuperscript{57,111}. Inhibitors targeting MCT1 have been successfully shown to affect in vitro and in vivo tumour growth and a MCT1 inhibitor designed by AstraZeneca (AZD-3965) is about to enter clinical trials as part of the CR:UK clinical development partnership.

Therefore even in this stripped-down version of metabolism it is clear that tumours are adapting to maximise the usage of glucose and glutamine to promote survival and even growth in potential hostile environments and targeting these adaptions could be a therapeutic mechanism. As understanding of cancer metabolism develops, potential therapeutic targets are identified based on their roles in cancer metabolism coupled with cancer specific expression/isoforms, potential mutations and oncogenic control mechanisms. Targets which fit these profiles have been at the forefront of the new push for cancer metabolism drugs and examples include Pyruvate kinase M2 and Isocitrate dehydrogenase.

**Pyruvate kinase M2 (PKM2)**

Pyruvate kinase (PK) catalyses the conversion of phosphoenolpyruvate (PEP) into pyruvate in a rate limiting and ATP generating step within glycolysis (Figure 3\textsuperscript{2}). There are many isoforms of PK of which the muscle form is of key interest in cancer cells\textsuperscript{89}. PKM1 is found in muscle and brain and is
reported to be constitutively active whereas PKM2 is present in embryonic and adult stem cells and controlled by various regulator mechanisms. It has been widely reported that PKM2 is also overexpressed in many tumour cells and a switch from PKM1 to PKM2 expression in cancer has been proposed\(^2,28,89\). The PKM2 isoform is generated by alternative splicing of exon 10 on the PK gene, an event shown to be under myc regulation suggesting a potential oncogenic driver for PKM2 expression in cancers\(^30,112\). However, the PKM2 expression hypothesis has been recently questioned in a study which used mass-spectroscopy to identify PK isoforms and reported that PKM2 is expressed in normal tissues as well as cancers and that PKM1 had low expression in cancers as well as in normal tissue\(^113\). Although the ratio of PKM2 to PKM1 expression was similar between cancers and matched normal tissues, the actual amounts of each protein were much higher in the tumours suggesting that both PKM2 and PKM1 were overexpressed in tumour samples\(^113\).

Studies in which PKM2 is knockdown or replaced by PKM1 have shown that PKM2 is involved in tumour progression and that PKM2 expression confers a tumourigenic advantage over PKM1 expression\(^89\). However, it has also been shown that while PKM1 can efficiently promote glycolysis, PKM2 is characteristically found in an inactive state and is inefficient in promoting glycolysis\(^2,28,89,114\). PKM2 exists in two possible conformations, an inactive dimer and more active tetramer (Figure 3). Oncogenic tyrosine kinases (eg fibroblast growth factor receptor kinase) have been found to promote the formation of the inactive dimer via the phosphorylation of tyrosine 705 on PKM2\(^90,114\). PKM2 activity has also been shown to be negatively regulated by acetylation induced by high levels of glucose\(^115\). This data collectively suggests that expression of PKM2 in cancer could actually decrease glycolytic flux. While this was initially thought to be counterintuitive, when considered in terms of the cancer cell’s metabolic needs, a mechanism which slows glycolysis is actually potential advantageous. By slowing glycolytic flux the cancer is able to obtain building block, co-factors and precursors by

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allowing glucose metabolites to enter subsidiary pathways including pentose phosphate, serine biosynthesis, hexosamine and glycerol synthesis pathway which support cancer proliferation and survival. Another metabolic role for PKM2 is a proposed direct interaction and stabilisation of Hif1α which in turn acts to promote glycolytic metabolism, angiogenesis and cancer progression. An alternative glycolytic route which bypasses PK in the conversion of PEP into Pyruvate has recently been identified. This route uncouples ATP and Pyruvate generation and could provide biosynthetic intermediates without potential feedback inhibition of glycolysis from ATP accumulation.

The key question around PKM2 is whether activators or inhibitors or PKM2 kinase activity would be the best strategy and if PK-M2 would really be a cancer specific target. Recent publications have shown that progress is being made in designing tool compounds to test out the PKM2 hypothesis and it will be interesting to monitor the outcome of studies with these and other PKM2 modulation agents to see if a clear rationale and patient selection strategy can be defined for this complex metabolic target.

Isocitrate dehydrogenase (IDH1/2)

Advances in large scale sequencing technologies has enabled more in-depth profiling of the genetics of multiple metabolism and oncogenic components in far larger sample sets (often more than 200 samples) and in multiple tumour types. Using these techniques it has been found that 60-90% of secondary gliomas (around 5% of primary gliomas) and 12-18% of acute myeloid leukaemias have mutations in the oxidative phosphorylation/TCA cycle components IDH1 or IDH2. For gliomas the common mutations are IDH Arg132 and IDH2 Arg140 and Arg172 whereas for glioma most mutations are in the IDH2 protein. It is also worth noting that the vast majority of these mutations are heterozygous.

Mutations affecting the catalytic sites of IDH1 or 2 are thought to be functionally equivalent and were initially reported to negatively affect IDH catalytic activity by reducing isocitrate binding and the ability to convert isocitrate into alpha-ketoglutarate (α-KG). However, recent mass-spectroscopy data has discovered IDH mutations exhibit an altered catalytic activity and convert α-KG into 2-hydroxyglutarate (2-HG). 2-HG is believed to inhibit α-KG dependent processes including TET1/2 methyltransferase and the histone demethylase KDM2a leading to epigenetic disregulation. 2HG may also act to stabilise HIF1α.

Abbreviations: CS – citrate synthase; ACO1/2 – Aconitase 1/2; IDH – isocitrate dehydrogenase; mIDH – mutant isocitrate dehydrogenase; OGDH – α-ketoglutarate (α-KG) dehydrogenase; SCS – succinyl-CoA synthetase; SDH – succinate dehydrogenase; FH – Fumarate hydratase; MDH2 – malate dehydrogenase 2; PDH – pyruvate dehydrogenase; GLS1 – glutaminase 1

Figure 4: Isocitrate dehydrogenase mutations and the TCA cycle. In the normal mitochondrial TCA cycle IDH2/3 enzymes convert isocitrate to α-ketoglutarate (α-KG) and IDH1 converts cytoplasmic isocitrate to α-KG. However, mutant IDH1/2 enzymes (shown in red boxes) have a neomorphic enzyme capacity and convert α-KG into 2-hydroxyglutarate (2-HG). 2-HG is believed to inhibit α-KG dependent processes including TET1/2 methyltransferase and the histone demethylase KDM2a leading to epigenetic disregulation. 2HG may also act to stabilise HIF1α.
profile corresponding to the oligodendrocyte subtype of glioma. Similar changes in DNA methylation profiling were also seen in human AML samples. A decrease in α-KG levels (probably due to heterodimerisation between α-KG producing WT IDH and α-KG metabolising mutant IDH [Figure 3]) coupled with an increase in 2-HG levels is reported to block epigenetic events including histone demethylase and TET1/2 (hydroxylases which usually produce 5-hydroxymethylcytosine) activity and are believed to be the major mechanism by which IDH mutants function in tumours. 2HG has also been reported to stabilise HIF1α which can regulate many metabolic components and also promote VEGF signalling, a driver of tumour angiogenesis.

Therefore, IDH mutants represent an attractive target for targeted therapy as they show a unique cancer specific function and generate a potential cancer biomarker in 2HG for disease stratification. However, one intriguing recent piece of evidence is that in IDH mutant appear to have slightly prolonged survival which adds more complexity to this intriguing target.

**Future challenges in targeting cancer metabolism**

The challenges around targeting metabolism will involve a clear understanding of how a cancer cell differs in its metabolism to that of a rapidly proliferating normal cell. It has long been known the neurological cells also have high glucose demands and also a reliance on other metabolites linked to some of the canonical metabolism pathways and linked to cancer, for example glutamine and serine. For example, it has been shown in normal T-lymphocytes and astrocytes that siRNA depletion of metabolic enzymes such as PFKFB3 decreases the proliferation rates of these ‘normal’ cell lines. Therefore it will be important to fully understand the metabolic drivers by which a cancer cells may differ from normal cells and also the potential toxicity risk associated with targeting metabolism.

Another challenge will be around patient stratification/selection. While many tumours may display high glucose or glutamine uptake/utilisation, this alone is likely to be insufficient as a predictive marker for therapeutic potential of an anti-metabolism agent. It will be important to fully understand how known oncogenic drivers of cancer (ie myc, ras, PI3K) or loss of tumour suppressor genes (ie p53, PTEN, LKB1) impact on metabolic flux and/or regulation of key metabolic points in different tumour types. While a few mutations in metabolism enzymes in cancer have been identified, it is likely that in many tumours the impact of metabolism targets will be a complex interplay between expression, regulation, flux and oncogenic changes. It will also be important to consider that within metabolism pathway there are plenty of opportunities for tumour cells to evade metabolic blocks through bypass pathways and redundancy, so understanding key nodal points and possible combination strategies or synthetic lethality approaches will be essential. Likewise the interplay between metabolism targets and current chemotherapies (many of which create increased demand for biosynthetic intermediates as the tumour attempts to survive these agents) could be an important therapeutic strategy to consider as more metabolism targeting agents reach clinical trials in the future.

Pharma is rapidly adapting to these needs by the way it is approaching this area with ties to leading academic experts in cancer metabolism and utilisation of existing expertise against metabolic disorders for which many companies already have a platform. It is hoped that with this approach and the renewed interest in cancer metabolism the way is paved for a new generation of cancer metabolism therapeutics.
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