Calithera Biosciences, Inc. (CALA)

Initiating Coverage at Market Outperform; Unplugging the Cancer Cell's Power Source

MARKET DATA

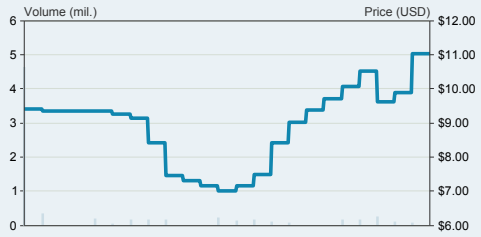
Price	$11.04
52-Week Range:	$6.51 - $11.24
Shares Out. (M):	17.6
Market Cap ($M):	$194.3
Average Daily Vol. (000):	68.0
Cash (M):	$108

Source: Thomson Reuters and JMP Securities LLC

FY DEC		2013A	2014E	2015E
Revenue ($M)	1Q	--	$0.0A	$0.0
	2Q	--	$0.0	$0.0
	3Q	--	$0.0	$0.0
	4Q	--	$0.0	$0.0
	FY	**--**	**$0.0**	**$0.0**
EPS	1Q	--	--	($0.32)
	2Q	--	($1.22)A	($0.32)
	3Q	--	($0.29)	($0.32)
	4Q	--	($0.31)	($0.32)
	FY	**($3.03)**	**($1.39)**	**($1.27)**
	P/E	NM	NM	NM

Source: Company reports and JMP Securities LLC

STOCK PRICE PERFORMANCE



MARKET OUTPERFORM | Price: $11.04 | Target Price: $20.00

INVESTMENT HIGHLIGHTS

Initiating coverage on Calithera Biosciences at Market Outperform with a $20 price target; unplugging the cancer cell's power source. Calithera recently completed its IPO transaction on October 2, 2014. The company is an early stage, oncology-focused, drug discovery and development company attempting to exploit the increasing knowledge of the cancer cell's ability to hijack the energy production mechanisms required for the utilization of energy from a variety of sources. The company's first product candidate, CB-839, is a novel inhibitor of glutaminase, an enzyme that converts glutamine to glutamate, the latter of which is a critical feedstock for the cell's energy production system. The company was founded by Susan and Chris Molineaux, two of the founders of Proteolix, the company that developed Kyprolis (carfilzomib), which was eventually sold to Onyx for $700MM. Onyx, in turn, was sold to Amgen (AMGN, NC) in 2013 for $10 billion. Our $20 price target is based on the synthesis of our DCF, SOTP, and comparable companies valuation methodologies.

Inhibition of tumor metabolism is an orthogonal approach to cancer therapy, and opportunity favors the nimble. The exploitation of tumor metabolism is an area that is quite new to cancer research, and consequently, the field has been left open to a select number of leading players. The best known of these is Agios Pharmaceuticals (AGIO, NC), which boasts a market cap of ~$2.7 billion. Agios' most advanced programs target two isoforms of the enzyme isocitrate dehydrogenase (IDH1 and 2) for a variety of tumor types. In our view, the data that have been presented for the lead compound, AG-221, strongly validate the concept that interdiction of an essential cellular metabolic pathway can exert a meaningful therapeutic effect, and do it in a way that is well-tolerated. Calithera's CB-839 is an inhibitor of glutaminase, an enzyme that converts glutamine to glutamate, which, in turn, becomes a critical component of the cell's energy cycle. In cancer cells, the dependence upon glutamate is significantly elevated compared to that of a normal cell. Therefore, cutting off the cell's supply of this key source of energy should result in a profound effect on tumor growth inhibition.

CB-839 looks like a winner; Calithera has the right team to succeed, in our view. CB-839 is an wholly owned oral drug that has demonstrated encouraging preclinical activity in a variety of tumor types, including triple negative breast cancer (TNBC), multiple myeloma, and certain subsets of non-small cell lung cancer and lymphoma. Calithera is currently running studies in TNBC, myeloma, and certain rare cancer types that possess mutations driving the TCA (tricarboxylic acid, also referred to as Krebs) cycle. While the company has abstracts accepted for both the American Society of Hematology and the San Antonio Breast Cancer conferences, major data inflection points for CB-839 will likely come at meetings in 2015 once the company has achieved a recommended Phase II dose (RP2D) based on safety and efficacy in Phase I.

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CALA shares trading marginally above the IPO price, clinical validation during 2015 could bring significant appreciation. By the end of 2014, Calithera should reach the RP2D of CB-839 that provides the best activity against the three different cancer subgroups under study: solid tumors (mainly TNBC), myeloma/non-Hodgkin lymphoma, and acute leukemias. This dose could be viewed as the "biologically optimal dose" as it may not be a maximum-tolerated dose in the traditional sense. Once this dose has been reached, investors should expect CALA to enroll additional patients at this dose, and to begin combination studies with therapies that are traditionally used in the respective clinical settings. We anticipate that the dose escalation and biologically optimal dose data will be presented at a scientific conference during 2015, with the likelihood being AACR or ASCO (or potentially both). Should the data be compelling, we could envision a replication of the stock price activity of Agios that occurred in November 2013 through April 2014 (Figure 2). We believe a second leg of appreciation could take place during in late 2015 when data are presented from the combination studies of CB-839 and standard therapies for the aforementioned tumors.

INVESTMENT THESIS

The observation that cancer cells exhibit markedly different metabolic processes compared to normal cells goes back nearly 100 years to the postulate of Otto Heinrich Warburg, who observed that cancer cells ferment sugar (glucose) even when appropriate amounts of oxygen are present to enable normal respiration (oxidative phosphorylation, or OXPHOS). The use of glycolysis over OXPHOS is far less efficient with one molecule of glucose giving rise to one or two molecules of ATP (energy) production, compared to 35-38 molecules of ATP through OXPHOS, and drives a large requirement for glucose.

This observation, commonly referred to as the Warburg effect, was thought by Warburg to be the cause of cancer. While it was later shown that the Warburg effect was a consequence of the aberrant expression of genes and not a cause, recent understanding of the role of cellular metabolic processes on the initiation and perpetuation of cancer has had a significant impact on the way we think about cancer, and the development of novel agents directed at the interdiction of these aberrant processes. Aberrant metabolic signaling has been shown to occur in multiple, interconnected pathways regulating glucose, amino acids, nucleic acids and fatty acid metabolism, with each area drawing considerable scientific interest as potential targets of therapeutic intervention.

While much has yet to be learned about the target space within cancer metabolism, the discovery of the first "oncometabolite" was made by Agios Pharmaceuticals. This oncometabolite, 2-hydroxyglutarate (2HG), is over-produced by mutations in two forms of the isocitrate dehydrogenase (IDH) gene-IDH1 and IDH2. Normal versions of the IDH gene make alpha-ketoglutarate (α-KG) from isocitrate; when mutations are present in IDH1 and IDH2, their metabolic process is essentially thrown into reverse, and the cells begin siphoning off alpha-ketoglutarate, resulting in abnormal levels of 2HG. The 2HG, in turn, results in abnormal cell signaling through epigenetic modifications, some of which is thought to run through EZH2.

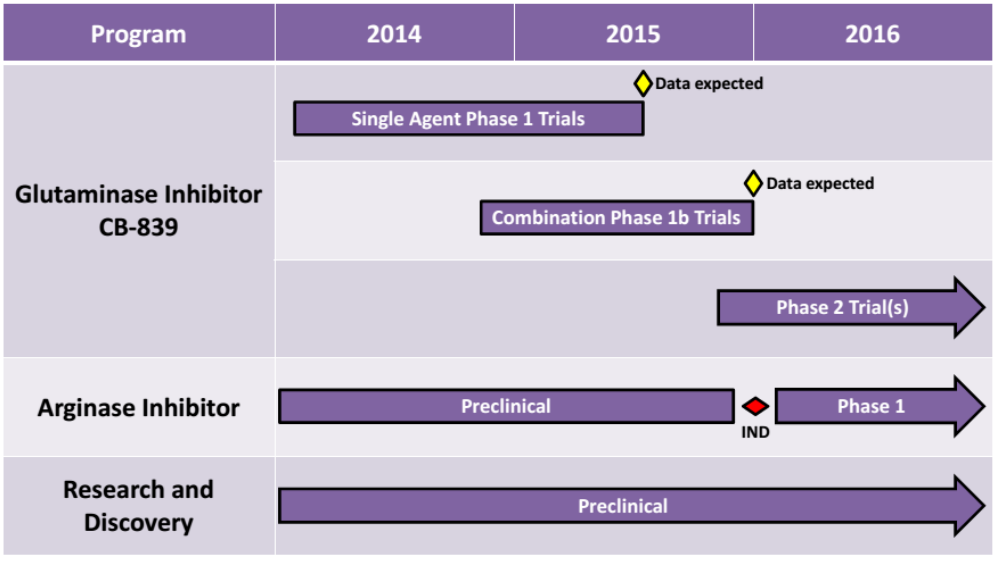
Agios is developing AG-221, an inhibitor of IDH2, in conjunction with Celgene (CELG, MO, $117 PT). In our view, the first proof-of-concept that a compound that alters the cancer cell's abnormal metabolism was presented at the AACR meeting in 2014, at which Agios presented data showing six of 10 enrolled

patients (and six of seven evaluable) with AML harboring IDH2 mutations responded robustly to treatment with AG-221. Perhaps more impressive, three patients experienced a complete response (CR), while three additional patients experienced a complete response with incomplete platelet recovery (CRp). These data were updated at the European Hematology Association (EHA) meeting in June 2014, and while the overall response rate diminished somewhat (14 of 25 patients exhibited an objective response, with six CRs and two CRps), there was no longer any doubt that this approach was viable and could provide meaningful benefit in patients with severe illness.

Into this complex mix of target white space stepped Calithera, with two seasoned biopharmaceutical executives at the helm: Susan and Chris Molineaux. The risk-reduction afforded to the investor committing capital to this space by investing with experienced management teams cannot be understated, in our view. Examples abound here: Agios, David Schenkein, Genentech and Millennium; Alnylam (ALNY, MO, $102 PT), John Maraganore and Barry Greene, Millennium; Clovis Oncology (CLVS, NR), Patrick Mahaffy, Pharmion; Karyopharm (KPTI, MO, $44 PT), Michael Kauffman, Millennium and Proteolix/Onyx; Puma, (PBYI, NR), Alan Auerbach, Cougar; Tesaro (TSRO, NR), Lonnie Moulder, MGI Pharma and Abraxis.

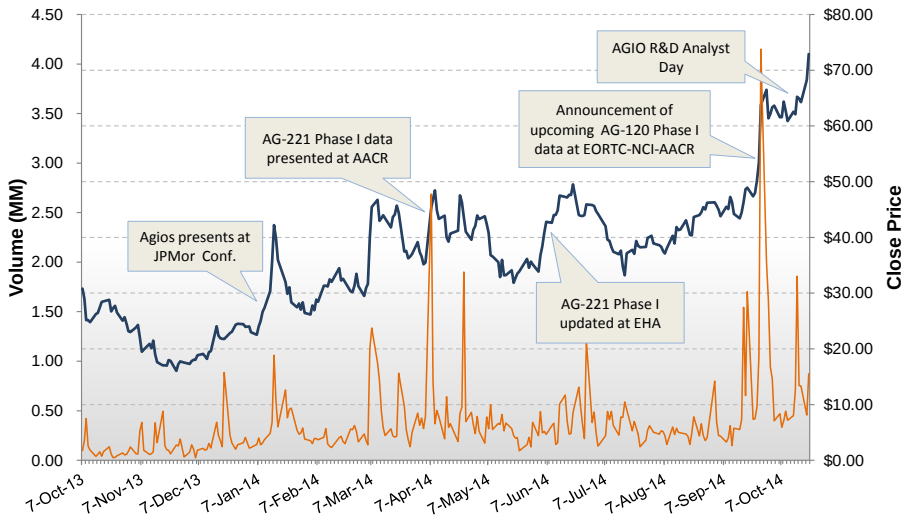
For a variety of reasons discussed throughout this report, glutaminase makes an attractive target for intervention in cancer. Preclinical experiments have shown that glutamine addiction “rewires” a cell to the point where glutamine becomes essential for the cell’s survival. Tumors with certain well-documented tumor drivers, such as KRAS mutations and mTOR activation, appear to lead to an increase of flux throughout the Krebs cycle. In these cells, targeting both glucose and glutamine metabolism induces death in the cancer cell. In our view, the success generated by the Molineaux duo in the area of proteasome inhibition (when the world was convinced there was no need for another proteasome inhibitor) is an ideal template for success in glutaminase inhibition, in particular, and cancer metabolism, in general.

FIGURE 1. CALA Development Program and Timeline



Source: Company Reports

FIGURE 2. AGIO Price Chart



Source: Thomson Reuters

FIGURE 3. Upcoming Catalysts

Timing	Catalyst
4Q14	Preclinical presentations at ASH (Dec. 6-9) and San Antonio Breast Cancer Symposium (Dec. 9-13)
4Q14	Initiation of Phase Ib combo expansion trials (TNBC + paclitaxel, R/R MM + pomalidomide)
1H15	Anticipated presentation of CB-839 Phase I safety and efficacy in solid and heme tumors
2H15	IND filing for arginase inhibitor

Source: Company Reports

VALUATION

We derive our twelve-month price target of $20 based on a synthesis of methodologies, including a discounted cash flow analysis (DCF), a valuation by the sum-of-the-parts that looks at CB-839 revenue forecasts by indication, and a relative valuation against a group of comparable-stage, oncology-focused biotechnology companies (Figure 4).

FIGURE 4. Price Target Synthesis

Synthesis of Valuation Approaches		
Approach	Weight	Valuation
DCF Analysis	70%	$17.19
SOTP NPV	20%	$19.78
Comparables	10%	$36.88
Price Target		**$20.00**

Source: JMP Securities LLC

Our DCF valuation projects CB-839 sales in the U.S. and royalties related to sales ex-U.S. out to 2025 (although CB-839 patent life extends to 2032), while subtracting COGS, projected operating expense, and tax. Net cash flows to the company are discounted back to 2015 year end, by an integrated, risk-adjusted, discount rate of 35% that takes into account CB-839's early stage of development. A terminal value for the company, calculated by applying a -5% long-term growth rate was similarly discounted to present day. Present value of free cash flows, together with the terminal value, were added to arrive at a residual value for the company, to which estimated cash and long-term debt were added and subtracted, respectively, to arrive at an equity valuation of $320MM. Dividing this by our estimated 2015 year-end outstanding share count, we derive a per share valuation of ~$17.19. Our DCF assumptions are detailed further in Figure 5.

FIGURE 5. Discounted Cash Flow Analysis

Discounted Cash Flow Model	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E
CB-839 Sales, US	$ -	$ -	$ -	$ 55	$ 310	$ 625	$ 965	$ 1,269	$ 1,460	$ 1,552	$ 1,617
Ex-US Royalties	-	-	-	-	6	41	87	133	183	211	226
Total Revenues	**$ -**	**$ -**	**$ -**	**$ 55**	**$ 317**	**$ 666**	**$ 1,052**	**$ 1,401**	**$ 1,642**	**$ 1,763**	**$ 1,843**
Cost of product sales			-	6.5	37.3	75.0	115.8	152.2	175.2	186.2	194.0
Gross Profit	-	-	-	48.0	279.5	591.1	935.9	1,249.2	1,467.3	1,576.7	1,649.1
R&D expense	21.5	43.0	86.0	133.3	173.3	207.9	228.7	251.6	276.8	304.5	334.9
SG&A expense	6.0	13.1	39.3	70.7	102.5	128.1	140.9	153.6	165.9	174.2	182.9
Total operating expenses	27.5	56.1	125.3	204.0	275.8	336.1	369.7	405.2	442.7	478.7	517.8
Operating income (EBIT)	**(27.5)**	**(56.1)**	**(125.3)**	**(156.0)**	**3.8**	**255.0**	**566.2**	**844.0**	**1,024.6**	**1,098.0**	**1,131.3**
Operating margin (%)				*-285.8%*	*1.2%*	*38.3%*	*53.8%*	*60.2%*	*62.4%*	*62.3%*	*61.4%*
Taxes	-	-	-	-	0.2	25.5	113.2	253.2	358.6	384.3	396.0
Tax rate					*5%*	*10%*	*20%*	*30%*	*35%*	*35%*	*35%*
After tax operating income	(27.5)	(56.1)	(125.3)	(156.0)	3.6	229.5	453.0	590.8	666.0	713.7	735.3
PV	(25.5)	(38.5)	(63.8)	(58.8)	1.0	47.5	69.4	67.1	56.0	44.5	33.9
Residual value of cash flow	$218								**Terminal Value**		84.8
+ Cash and Cash equivalents	103										
Company value	320										
- Long-term debt on 12/31/14	0										
Value of equity	$320										
Fully diluted shares outstanding on 12/31/14	18.6										
Price/share	**$17.19**										
Discount Rate	35.0%										
Terminal growth rate	-5%										

Source: JMP Securities LLC

To further test our assessment of Calithera's valuation, we completed a sum-of-the-parts analysis, incorporating U.S. sales and ex-U.S. royalty income from each of the four primary indications where we anticipate CB-839 approval. NPV contributions from CB-839 used in the treatment of MM, DLBCL, TNBC, and acute leukemia are detailed in Figure 6.

FIGURE 6. Sum-of-the-Parts NPV Analysis

Sum-of-the-Parts Analysis		
CB-839 Indication	**Value ($MM)**	**Per Share**
Myeloma	**$78.5**	**$4.21**
US	66.1	3.55
Ex-US Royalty	12.3	0.66
DLBCL	**$102.4**	**$5.50**
US	84.6	4.54
Ex-US Royalty	17.8	0.95
Triple Negative Breast	**$55.5**	**$2.98**
US	48.7	2.62
Ex-US Royalty	6.8	0.36
Acute Leukemia	**$14.1**	**$0.75**
US	11.4	0.61
Ex-US Royalty	2.7	0.14
Pipeline Valuation	**$15.0**	**$0.81**
YE Cash and Equivalents	**$102.9**	**$5.52**
Total NPV	**$368.3**	**$19.78**

Source: JMP Securities LLC

Finally, by taking the mean market cap valuation from a peer group of platform and/or early stage, oncology-focused biotechnology companies, we derive a comparable valuation for CALA of $36.88 (Figure 7).

FIGURE 7. Comparable Company Valuation

Comparable Stage Biotech Companies						
Comparable	**Ticker**	**Price**	**Market Cap**	**Cash**	**Debt**	**EV**
Agios Pharmaceuticals Inc	AGIO	$68.25	$2,352	$72	$0	$2,280
Array Biopharma Inc	ARRY	$3.47	$458	$69	$104	$493
Epizyme Inc	EPZM	$27.59	$927	$124	$0	$804
Exelixis	EXEL	$1.65	$322	$104	$335	$553
Five Prime Therapeutics Inc	FPRX	$12.08	$260	$8	$0	$252
Ignyta Inc	RXDX	$6.96	$136	$0	$0	$136
Infinity Pharmaceuticals Inc	INFI	$12.95	$629	$68	$0	$561
Karyopharm Therapeutics Inc	KPTI	$35.01	$1,144	$156	$0	$988
Loxo Oncology Inc	LOXO	$11.17	$186	$15	$0	$171
NewLink Genetics Corp	NLNK	$31.44	$877	$61	$7	$823
TG Therapeutics Inc	TGTX	$10.10	$385	$45	$0	$340
Verastem Inc	VSTM	$9.20	$238	$19	$0	$219
Average			**$660**			**$635**
Calithera Biosciences Inc	CALA	$10.07	$180	$34	$0	$146

Comparable Valuation	**$36.88**

Source: Thomson Reuters

COMPANY OVERVIEW

Calithera Biosciences, based in San Francisco, CA, is a clinical-stage biotechnology company focused on the discovery and development of novel small molecules directed against cancer and immune cell metabolism in order to treat both solid tumor and hematologic malignancies. The company's lead product candidate, CB-839, is an internally discovered and wholly owned potent, oral selective inhibitor of glutaminase. Inhibition of glutaminase by CB-839, in effect, starves cancer cells of glutamate - a critical substrate for cancer cell metabolism, growth and survival. CB-839 is currently in Phase I development in both solid and hematologic tumors. Planned Phase Ib cohorts in combination with standard of care agents in triple negative breast cancer and multiple myeloma are expected to initiate by YE14.

A second wholly owned pre-clinical candidate is Calithera's first-in-class arginase inhibitor, directed at immune checkpoint modulation and engaging the activation of cytotoxic T-cells. Calithera intends to submit an IND with the FDA for the arginase program in late 2015.

INVESTMENT RISKS

Scientific and clinical. Drug development is an inherently risky business. Cancer metabolism, and specifically the role of glutaminase in cancer pathogenesis, remains largely unproven, creating significant risk associated with Calithera's scientific platform. Like all clinical trials, CB-839 clinical development carries some risk of failure. CB-839 may fail to maintain the requisite safety or to demonstrate meaningful efficacy to warrant further development through to regulatory approval.

Regulatory and commercial. The ability of Calithera or its potential partners to market its drugs depends on those drugs obtaining approval from the FDA and foreign regulatory agencies. Failure to achieve approval or delays in the timelines to approval could negatively impact the company's share price.

Competitive. Oncology drug development is an increasingly competitive field. Calithera faces competition from companies developing small molecule therapies also directed at cancer cell metabolism in ways that may resemble those of Calithera's pipeline. Small molecule oncology therapies employing other mechanisms of action are also in development by several biopharma companies to treat similar patient populations to that of CB-839 and may yield superior risk/benefit outcomes. Some of these companies may have access to greater resources, development, and commercial expertise compared to Calithera.

Financial. Taking into account the ~$86MM net proceeds raised in its IPO, we estimate that Calithera will finish FY14 with cash and cash equivalents of ~$103MM – adequate resources, in our view, to fund company operations into 2017. We anticipate that Calithera may seek additional equity financing in the form of a secondary offering in order to complete development of CB-838 and advance its future pipeline candidates, exposing existing shareholders to some degree of dilution risk.

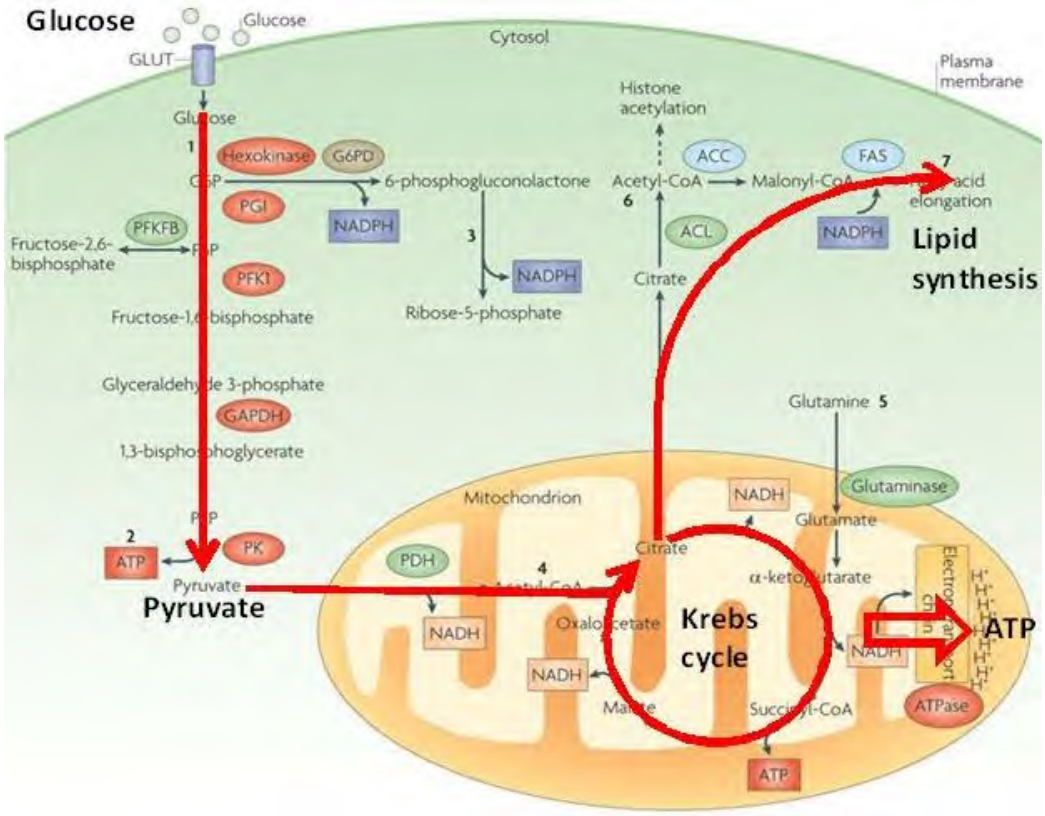
CB-839 - EXPLOITING GLUTAMINE ADDICTION IN TUMORS

To most biotech investors, normal eukaryotic cell metabolism is the stuff of middle school biology class: cellular fuel in the form of glucose is processed by enzyme cascades in the cytosol and mitochondria, respectively, called glycolysis and TCA/Krebs cycle, to produce energy in the form of ATP. Meanwhile, byproducts from these processes are redirected to function as building blocks in the assembly of macromolecules, such as fatty acids, or signaling molecules in form of steroids (Figure 8, also refer to Appendix C for an in-depth review).

It has long been observed, however, that malignant cells exhibit aberrant metabolic processes compared to normal counterpart tissue, beginning famously with the work by Otto Warburg in the 1920s showing that cancer cells favor aerobic glycolysis over the Krebs cycle. Whether this shift in metabolism and overconsumption of glucose (the 'Warburg effect') takes place to satisfy the energy and biosynthetic demands of a rapidly dividing cell population or is rather the phenotypic consequence of oncogene activation (driving non-essential glucose uptake) remains an ongoing debate. Nevertheless, in the time since Warburg's discovery, scientific consensus has coalesced around the idea that cellular metabolism is dramatically altered during tumorigenesis. Over the last decade, this has spurned a robust effort to identify and exploit metabolic targets on the basis of altered metabolic balance in cancer cells.

More recently, the deregulation of certain metabolic pathway intermediates, either through mutation or post-translational modification, have been shown to either drive or facilitate tumorigenesis. Dysregulation of PKM2 (the M2 form of pyruvate kinase) via aberrant phosphorylation and destabilizing mutation has been shown to result in a declining conversion of phosphoenolpyruvate (PEP) to pyruvate during glycolysis, and accumulation of glycolytic intermediates that support the biosynthetic demands of hyperproliferation. Gain of function mutations to isocitrate dehydrogenase 1 (IDH1) and IDH2, both operating within the Krebs cycle, have been shown to drive production of an oncometabolite, 2-hydroxyglutarate (2HG), in favor of the normal metabolite α-ketoglutarate (α-KG), initiating a dedifferentiation phenotype via epigenetic modification. In part, through similar epigenetic regulation, loss of function mutations to Krebs cycle intermediate enzymes fumarate hydrogenase (fumarase, FH) and succinate dehydrogenase (SDH) have also been linked to the tumorigenesis of cancers, including renal cell carcinomas (RCC), hereditary leiomyoma, hereditary paraganglioma, thyroid cancers, and GIST tumors.

FIGURE 8. Overview of Cellular Metabolism via Glycolysis and the Krebs Cycle



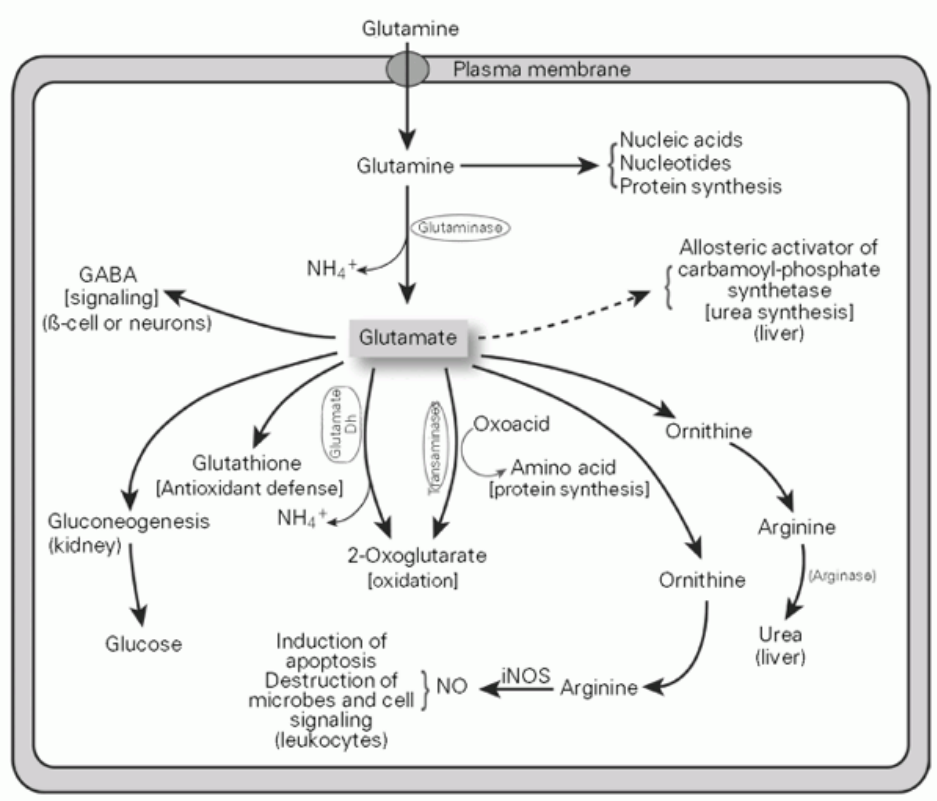
Source: Adapted from Buchakjian and Kornbluth, Nature Reviews Molecular Cell Biology, 2010.

CB-839 and Cancer Cell Glutamine Dependence

Another widely observed metabolic trait of malignant cells is an exquisite dependence on the amino acid glutamine for growth and survival. Enzymatic conversion of cytoplasmic glutamine to glutamate by glutaminase feeds into several metabolic and biosynthetic processes, including the Krebs cycle, nucleic acid synthesis, amino acid synthesis, and gluconeogenesis. Glutamine metabolism is also used to replenish stores of the neurotransmitter GABA (Figure 9). As the most abundant amino acid, and capable of being produced biosynthetically from the other amino acid substrate, glutamine is generally not considered an essential amino acid. Given the energetic and biosynthetic demands of rapidly dividing cells and the diversity of biosynthetic routes that utilized glutamate; however, it is thought that glutamine uptake readily becomes a choke point in cancer cell metabolism.

More specifically, it is thought that as cancer cells shift their metabolism away from one in which glycolysis end-products (pyruvate namely) feed into the Krebs cycle to satisfy anabolic and energetic requirements, the Krebs cycle sources alternative substrates for pathway intermediates. Glutamate, converted from glutamine, is subsequently converted in the mitochondrial inner matrix into Krebs cycle intermediate α-ketoglutarate (α-KG). Accordingly, suppression of glutaminase expression (encoded by the gene *GLS*) by genetic knockdown has been shown to demonstrate tumor suppressive activity across a broad array of tumor types in a manner correlating with decreased glutamine consumption and detection of glutamate dependent metabolites.

FIGURE 9. Effector Processes Dependent on Glutamine Metabolism

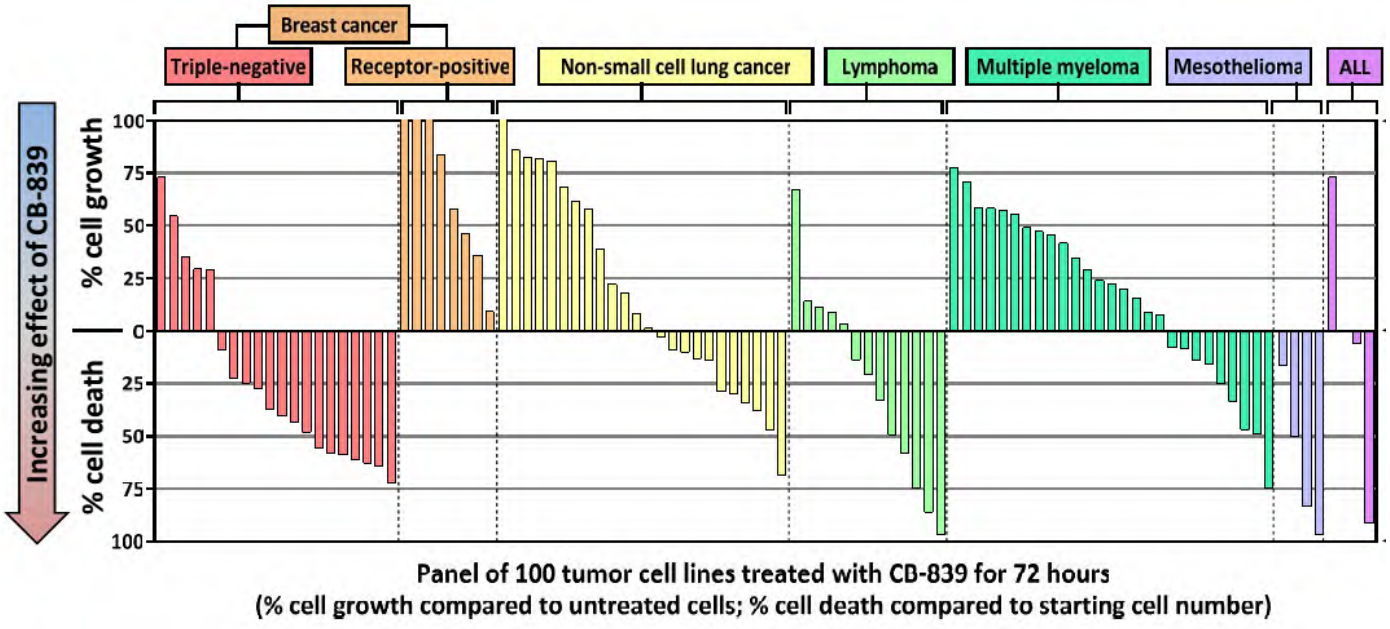


Source: Newsholme P, et al. BJMBR, 2003

CB-839 was discovered by scientists at Calithera, and is an orally bioavailable, potent and selective inhibitor of glutaminase. As an allosteric inhibitor, CB-839 binds glutaminase at a region distinct from the enzyme active site; however, in contrast to previously described allosteric glutaminase inhibitors, CB-839 does so in a non-competitive fashion. In biochemical assays, CB-839 exhibits slow-on/slow-off reversible enzyme kinetics, with drug potency increasing with lengthening exposure, independently of glutamine concentration. In cell proliferation assays, treatment with CB-839 has been shown to slow growth or induce cell death in a significant proportion of tumor cell lines of differing origin (Figure 10), including receptor positive and negative breast cancer, lung cancer, mesothelioma, lymphoma, and myeloma.

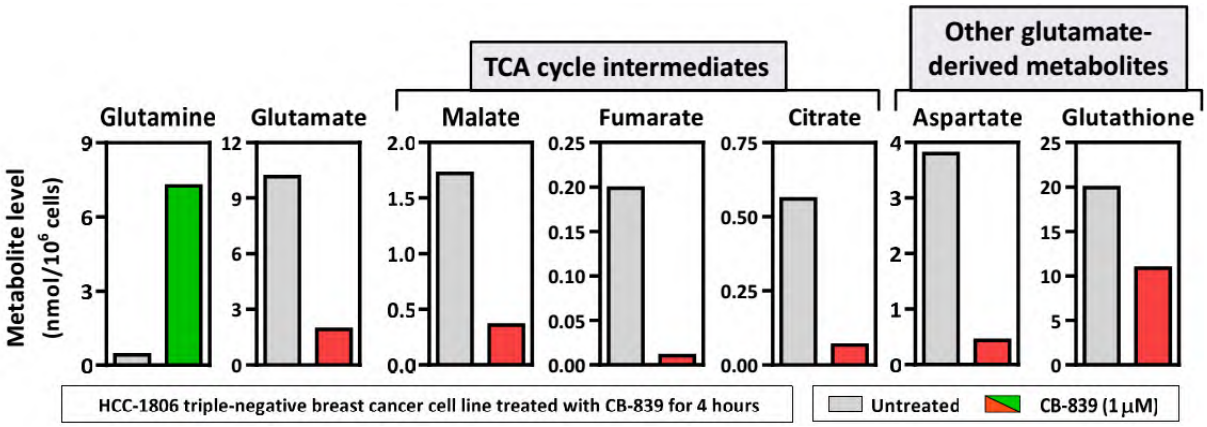
This tumor growth inhibition corresponds with decreasing production of glutamate-derived metabolites (Figure 11). In stark contrast to the effects seen in drug sensitive tumor cell lines, minimal impact to normal metabolite flux has been observed in normal counterpart tissues, despite ready drug uptake and wide tissue distribution, implying a favorable therapeutic index. Further preclinical data show CB-839 treatment as being able to slow the growth of murine xenograft tumors generated from both cell lines and patient derived samples of triple negative breast cancer and multiple myeloma (Figure 12). Combined CB-839 treatment with standard-of-care agents, paclitaxel and the immunomodulatory therapy (pomalidomide), respectively, have been shown to be more effective than SOC therapy alone, in some cases yielding tumor regression.

FIGURE 10. CB-839 Anti-Proliferative Activity Across Tumor Cell Types



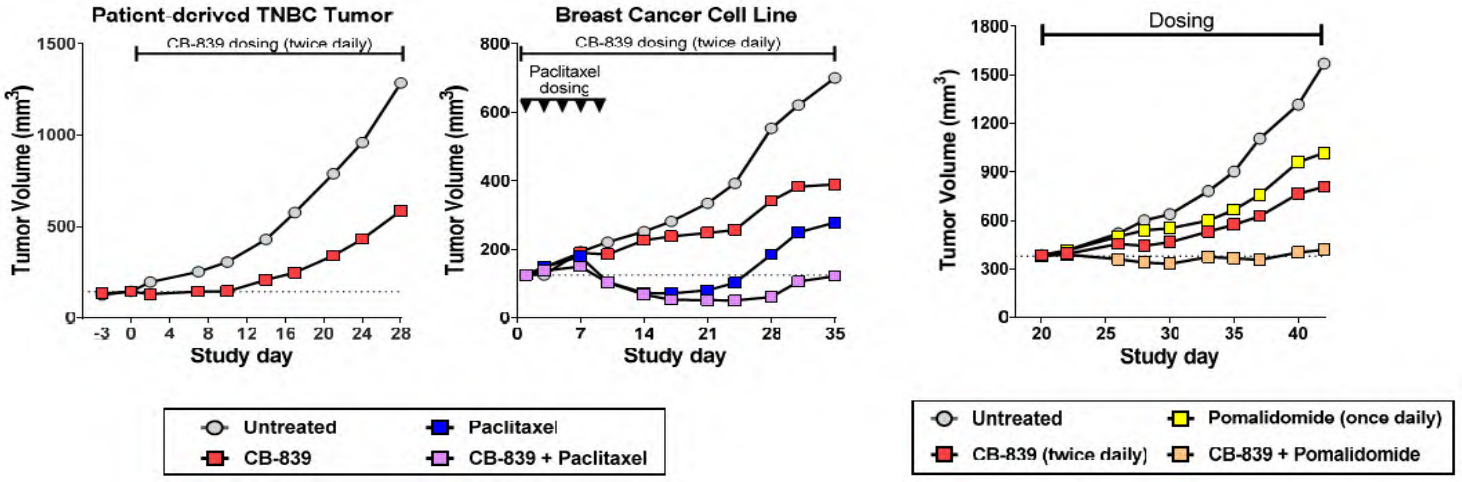
Source: Company presentation

FIGURE 11. Declining Glutamine Metabolite Production in CB-839 Treated TNBC Cell Lines



Source: Company presentation

FIGURE 12. CB-839 Activity in TNBC and Multiple Myeloma Xenograft Models



Source: Company presentation

CB-839 Clinical Development

Phase I clinical testing with CB-839 was initiated in February 2014 in patients with solid tumors, hematologic malignancies, and acute leukemias. Each of the three distinct Phase I trials currently underway adopts a two-stage trial design, beginning with a dose-escalation study in unselected, advanced and/or refractory patient populations in order to establish safety, tolerability, and recommended Phase II dosing (RP2D), before further evaluating antitumor activity through expansion enrollment cohorts. CB-839 is administered as an oral capsule at a starting dose of 100mg, three times daily (TID). Initial pharmacokinetic analysis reportedly shows dose-dependent increases in plasma drug concentration and a six- to eight-hour drug half-life. Initial clinical data reported to date also show corresponding declines in glutaminase activity in collected blood platelet samples. Calithera investigators estimate that doses between 400mg to 800mg TID will be sufficient to achieve a target of 90% continuous glutaminase inhibition in order to maximally effect the suppression of tumor growth as informed by preclinical data.

Planned Phase I expansion cohorts in the solid tumor study (CX-839-001; target enrollment of ~165 patients) include patients with triple negative breast cancer, adenocarcinoma NSCLC, RCC, and mesothelioma. Additional planned cohorts will be comprised of patients with tumors with genetic defects to Krebs cycle intermediate enzymes, including succinate dehydrogenase (SHD)-deficient GIST and non-GIST tumors, and tumors, such as subsets of RCC, that are deficient for fumarate hydratase (FH). As of last report (July 25, 2014 per S-1 filing), 15 patients (five TNBC, five colorectal cancer, two RCC, and one patient each with cholangiosarcoma, sarcoma, and mesothelioma) had been enrolled into the study, and treated up to a maximum dose of 250mg TID. A best response of stable disease was observed in two patients (TNBC and mesothelioma) lasting at least three to five cycles.

We would anticipate that, as the trial continues to dose-escalate, the frequency, depth and durability of antitumor response of CB-839 as a single agent will improve. Nevertheless, based on potentially synergistic activity from combined treatment in preclinical analysis, the trial plans to enroll a Phase Ib cohort (initiating near term) consisting of TNBC patients treated with CB-839 in combination with paclitaxel. Calithera also sees potentially beneficial combinations of CB-839 with EGFR-targeted therapy in EGFR mutation positive lung cancer, VEGFR TKI therapy in patients with RCC, and with KIT-targeted agents in GIST tumors.

FIGURE 13. Solid Tumor Phase I (CX-839-001), Reported Efficacy

Solid Tumor Phase I Trial Efficacy				
		Best Response		
Indication	Enrolled	ORR	SD	PD
All patients	**15**		**2**	
Colorectal cancer	5			
Triple negative breast cancer	5		1	
Renal cell carcinoma	2			
Cholangiocarcinoma	1			
Sarcoma	1			
Mesothelioma	1		1	

Source: Company Reports

In the non-acute heme malignancy study (CX-839-002; target enrollment of ~65 patients), planned Phase I expansion cohorts comprise multiple subtypes, including multiple myeloma, DLBCL, Waldenstrom's macroglobulinemia (WM), T-cell lymphoma and other B-cell lymphomas. At last report, three patients with multiple myeloma had been enrolled into the study, two of which achieved a best response of stable disease lasting at least five cycles (we presume at a dose of 100mg TID, given that these patients were likely enrolled in the first cohort). Here again, we would expect that with an increasing dose, CB-839 will evoke greater responses in patients with multiple myeloma and other malignancies. Furthermore, building on preclinical data suggesting synergistic activity, in combination with immunomodulatory agents, a planned Phase Ib trial exploring CB-839 in combination with pomalidomide (Pomalyst) and dexamethasone is set to initiate near term.

FIGURE 14. Heme Malignancy Phase I (CX-839-002), Reported Efficacy

Hematologic Malignancy Phase I Trial Efficacy				
		Best Response		
Indication	Enrolled	ORR	SD	PD
All patients	**3**		**2**	
Mulitple myeloma	3		2	
DLBCL				
Waldenstroms Macroglobulinemia				
Other B-cell Lymphoma				
T-cell Lyphoma				

Source: Company Reports

Finally, a Phase I trial of ~50 patients is being conducted with both acute myeloid (AML) and acute lymphocytic leukemias (ALL), adhering to a single-patient, dose-escalation schema. As of last reporting, five AML patients and one ALL patient had been enrolled into the study, receiving dose levels of up to 600mg TID. However, no clinical responses have been reported to date. Expansion enrollment at an RP2D of 600mg is currently underway which, in addition to all-comer relapse/refractor AML and ALL patients, seeks to enroll patients positive for IDH1 and IDH2 mutations as well a patient with myelodysplastic syndrome (MDS).

FIGURE 15. Acute Leukemia Phase I (CX-839-003), Reported Efficacy

Acute Leukemia Phase I Trial Efficacy				
		Best Response		
Indication	Enrolled	ORR	SD	PD
All patients	**6**			
Acute myeloid leukemia	5			
Acute lymphomcytic leukemia	1			

Source: Company reports

Reported safety data to date from a total 24 patients across the three Phase I studies show CB-839 to be generally well-tolerated. Reported adverse events (AEs) deemed likely related to drug were mostly low Grade (21 Grade 1, two Grade 2 and two Grade 3 AEs reported) comprised mostly of GI toxicity (Grade 1 fatigue, nausea, and diarrhea). Worsening Grade 2 anemia and Grade 2 fatigue were observed in two patients with multiple myeloma. Transient Grade 3 neutropenia was observed in one patient with RCC. Transient Grade 3 creatinine elevation was observed in one patient with CRC treated at 250mg TID, which was subsequently determined as the dose-limiting toxicity (DLT). Dose escalation continues as of last report; however, with a maximum tolerated dose not having yet been determined.

Cancer Metabolism Competitive Landscape

There are several early to mid-stage oncology directed development programs that seek to exploit unique aspects of cancer cell metabolism. Chief among these, in our view, are the IDH1/2 programs in development by Agios Pharmaceuticals (AGIO, NC). Other competitor programs include a dual PDH/KDH inhibitor program CPI-613 in development by Cornerstone Pharmaceuticals (private).

Regarding Agios, the company's IDH2 inhibitor AG-221 is currently in Phase I development in patients with IDH2 mutant AML and other hematological malignancies. Both of AGIO's IDH1 and 2 programs are rooted in the observation that, for a subset of malignancies, isocitrate dehydrogenase (IDH), an intermediate enzyme in the Krebs cycle, diverts α-KG substrate to produce 2-hydroxyglutarate (2-HG) upon gain of function mutation. 2-HG has been observed to drive oncogenesis through epigenetic modifications. Overall, IDH1 and IDH2 mutations have been shown to arise with 5-20% frequency across myeloid leukemic subtypes including MDS, AML, and CMML, and with higher frequency (up 80%) in low- and high-grade gliomas. Initial clinical data with AG-221, most recently presented at EHA in June, showed compelling clinical activity in patients with IDH2 mutant relapse/refractory AML (56% objective response (14/25) and 32% (8/25) CR/CRp). AG-221 has also shown to be well-tolerated, the most notable side effects being Grade 1/2 nausea and pyrexia (both 22%), Grade 3 thrombocytopenia (17%) and Grade 3 febrile neutropenia (17%).

AGIO's IDH1 inhibitor AG-120 is currently in Phase I analysis in both patients with IDH1 mutation hematologic and solid tumor malignancies, with initial data from the heme study to be presented near term at the EORTC-NCI-AACR meeting in November (late breaker abstracts go up on Thursday, October 30). Early successes with AG-221 and the IDH2 paradigm in AML are expected to carry over to AG-120. While both agents ostensibly compete with CB-839, given the common focus on acute leukemia and the somewhat overlapping mechanism of action dependent upon α-KG metabolism, we believe CB-839 is capable of demonstrating activity across a broader set of patients, not limited to the presence of IDH1/2 mutation.

Cornerstone's CPI-613 is a first-in-class lopate derivative inhibitor of mitochondrial metabolism, targeting the activity of Krebs cycle intermediate enzymes α-ketoglutarate dehydrogenase (KDH) and pyruvate dehydrogenase (PDH). The dual inhibition of PDH and KDH interrupts the supply of Krebs cycle substrate material derived from glucose, in the form of acetyl-CoA, and glutamate, in the form of α-KG, respectively, causing a depletion of ATP and cell death. Phase I analysis of CP-613 in patients with advanced hematologic malignancies CPI-613 was recently published in Clinical Cancer Research, showing a 19% response rate (4/21) and 10% prolonged stable disease. Dose-limiting toxicity of Grade ≥3 acute renal failure was observed in 15% (4/26) patients, and in our view, could hamper continued development.

Other identified programs in the cancer metabolism space are either very early stage or had limited success to date. Both Tolero Pharmaceuticals (private) and Astex Pharmaceuticals (now Otsuka) have had PKM2 activator programs in pre-clinical development; however, the current status of these programs is unknown. Recently announcing its entry to the space with a focus on 'one-carbon metabolism' (specific targets not described), Raze Therapeutics (private) recently secured $24MM in a Series A round led by Atlas Ventures and joined by MPM Capital, Partners Innovation, and pharma venture funds at Astellas, Novartis, and Merck.

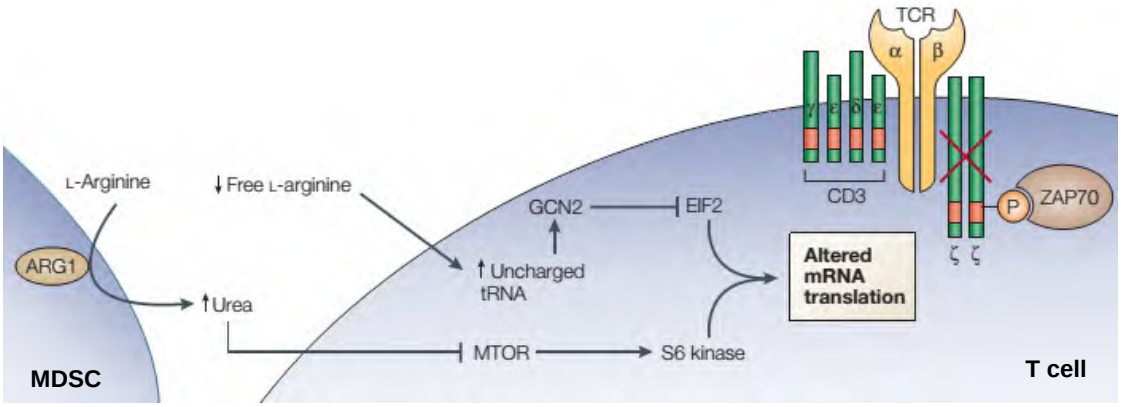
Arginase Tumor Immunology Program

Calithera's second proprietary pipeline program is focused on developing a small molecule arginase inhibitor. Arginase is commonly known for its function in carrying out the final step of the urea cycle during protein metabolism, catalyzing the conversion of arginine and water to ornithine and urea. Arginine metabolism has recently garnered renewed appreciation for its role in the regulation and accumulation of myeloid derived suppressor cells (MDSC) and their ability to impair the response of T-cells during tumorigenesis. Elevated arginine depletion in the tumor microenvironment, resulting from arginase overexpression and secretion by MDSCs, has been shown to inhibit the re-expression CD3 ζ-chain in neighboring T-cells. Suppressed CD3 expression impairs the assembly of the functional T-cell receptor (TCR) and, in turn, the activation of cytotoxic T-cells. As such, inhibitors of arginase are thought to be capable of restoring tumor initiated T-cell activation, potentiating an anti-tumor immune response.

A similar tumor immunology paradigm is being followed in the metabolism of the amino acid tryptophan. Depletion of tryptophan in the tumor microenvironment by the enzyme idoleamine 2, 3-dioxygenase (IDO) has been shown to suppress T-cell activation. Inhibitors of IDO are currently in clinical development by companies such as Incyte Corp. (INCB24360; INCY, MO, $76 PT, Bayko) and NewLink Genetics (indoximod and NLG919; NLNK, NC). Compelling Phase I/II combination data INCB24360 plus the anti-CTLA4 antibody Yervoy (ipilimumab, BMY, NC) were presented at ASCO in June, showing an objective rate of 42% in patients with metastatic melanoma, and 75% stable disease. Clinical data with NewLink's IDO pipeline, while early, have also been encouraging. Results from a Phase I trial published in August 2014 showed 18% objective response in mixed metastatic solid tumors in combination with docetaxel. Perhaps as a greater point of validation, NLG919, NLNK's second IDO/TDO inhibitor candidate, was recently announced the subject of ~$1billion collaboration agreement with Roche (RHHBY, NC), including a $150 million upfront payment.

We would speculate that similar opportunities lie ahead with Calithera's arginase inhibitor program (Figure 16) as it matures from the drug discovery optimization phase and into the clinical stage. Submission of arginase inhibitor IND is planned for the 2H15. Given the early stage of the program, however, arginase inhibitor projections remain upside to our present valuation.

FIGURE 16. Arginase Function During T-cell Activation



Source: Bronte and Zanovello, Nature Reviews Immunology, 2005.

Commercial Opportunity and Revenue Model

We model CB-839 sales in the U.S., Europe and Japan related to the treatment of several solid tumor and hematologic cancers either presently undergoing Phase I testing or that are the subject of planned clinical trials in the near term. Specifically, these include relapsed/refractory multiple myeloma (MM), relapsed/refractory diffuse large B-cell lymphoma (DLBCL), acute myeloid and lymphocytic leukemias (AML and ALL), and triple negative breast cancer. Together, we believe these markets represent nearly $3 billion in peak sales potential within 7-8 years of product launch as detailed below (Figures 17 -21).

Multiple myeloma. Beginning in the U.S., our multiple myeloma models assume a current multiple myeloma prevalence population of approximately 78,000 patients (according to SEER estimates) and continued growth with the introduction of new therapies capable of extending survival. Segmentation by line of therapy is difficult to pinpoint, however, our research suggests a roughly even distribution across the newly diagnosed, first relapsed/refractory (second-line), and multiple relapsed/refractory (third-line and greater) patient populations. We assume initial use of a later-line therapy (3L+) beginning in 2018 with moderately increasing market penetration to 20% by 2025.

Subsequent migration to the second-line setting, potentially in combination with current standard of care agents (proteasome inhibitors and immunomodulatory therapy) is modeled beginning in 2020. Combined, we forecast MM sales of ~$530 million in the U.S. by 2025. We assume a similar demographic breakdown and market uptake dynamics for Europe and Japan, starting with prevalence populations of 78,000 and 12,400, respectively. We forecast peak $435 sales in Europe and ~$80 in Japan in 2025, delivering ~$80MM in royalty revenue to Calithera, assuming ex-U.S. sales being led by a global commercial partner and a straight-line royalty at 15%.

DLBCL. Non-Hodgkin lymphoma (NHL) is the fifth most common lymphatic disease, diagnosed in nearly 70,000 in the United States in 2013, resulting in over 19,000 deaths according to SEER estimates. Diffuse large B-cell lymphomas (DLBCL) comprise a substantial fraction of the aggressive

NHL, accounting for approximately 30% of those diagnosed with NHL annually. While outcomes data vary, a majority (55-80%) of patients enter remission following treatment with standard front-line anthracycline and Rituxan-based immunotherapy (R-CHOP) within one or two years. With the remainder progressing from first-line therapy, we model a second-line prevalence population of ~22,000 patients. Similarly, a minority of these patients are anticipated to progress from various second-line options, contributing to a third-line prevalence population of ~5,500 patients.

Our model projects CB-839 use beginning in third-line DLBCL in 2018 in the U.S., before migrating to the second-line setting in subsequent years (with correspondingly longer-treatment periods). In both lines of therapy, we model moderately increasing market penetration, plateauing at 25%, to arrive at a revenue estimate of ~$623MM in 2025. We assume a similar demographic breakdown for Europe and Japan, beginning with baseline NHL incidence rates of nearly 94,000 and 13,000 patients, respectively. We also assume a similar market uptake dynamic to the U.S., beginning in 2019 for Europe and in 2020 in Japan. Our ex-U.S. sales forecasts reach ~$570MM in Europe and ~$100MM in Japan in 2025, culminating in $100MM royalty revenue to Calithera.

Acute leukemias. Approximately 15,000 new cases of acute myeloid leukemia (AML) are diagnosed in the U.S. per year, according to SEER estimates, culminating in over 10,000 deaths. Whereas younger and fitter patients might be treated with 7+3 induction chemotherapy (seven consecutive days of cytarabine IV infusion followed by three consecutive days of anthracycline by IV push per 28-day cycle), patients over the age of 70 with greater comorbidity may typically receive low-intensity treatment with low-dose cytarabine or hypomethylating agents (HMA) such as Dacogen (Eisai/JNJ) and Vidaza (CELG). This latter population of elderly front-line AML is where we believe CB-839 may find use within the broader treatment paradigm. Given a median age of onset of 67, it is estimated that ~45% of new diagnoses are patients 70 years of age and older (~6,700 patients in the U.S. in 2014).

Meanwhile, the incidence rate of acute lymphocytic leukemia (ALL) approximates ~6,000 cases per year, 25% among patients at least 40 years of age and who are far less likely than children and younger adults to respond to chemotherapeutic intervention. Among adult ALL patients, we assume 75% with disease negative for the Philadelphia chromosome (Bcr-Abl) and, thus, are in eligible for TKI agents such Gleevec, Sprycel, Tasigna, or Iclusig (ARIA, MO, $7 PT). Our market model assumes product launch with CB-839 in acute leukemia beginning in 2018. Absent clinical data to date with which to assess the potential depth and durability of response in either indication, we assume modest penetration for the time being, plateauing to ~20% in both indications. In the U.S., our model forecasts ~$125MM in sales by 2025. We assume similar demographic and market uptake dynamics for Europe and Japan beginning in 2019 and 2020, respectively, arriving at ~$80MM in ex-U.S. sales, delivering nominal royalty revenue to Calithera.

Triple Negative Breast Cancer. Our TNBC model assumes 15% of the overall breast cancer incidence population (~230,000 U.S. diagnoses in 2014 by SEER estimates) being characterized as a triple negative disease, and CB-839 development being directed toward patients with both metastatic and lymphoid regional disease (~37% of the overall incidence population). We assume product launch in the indication beginning in 2019 in the U.S., mean duration of therapy of 3.5 to 4 months, a market share accretion to 55%, to arrive at peak U.S. sales of ~$335MM. We assume similar demographics and market dynamics for the EU and Japan; however, with product launches in 2020 and 2021, respectively, arriving at peak ex-U.S. sales of ~$250MM and ~$40 royalty revenue to Calithera.

FIGURE 17. CB-839 Revenue Breakdown by Geography and Indication

CB-839 Revenue Summary	2016E	2017E	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E
WW Sales		$ -	$ 55	$ 353	$ 899	$ 1,542	$ 2,155	$ 2,678	$ 2,959	$ 3,125
US		-	55	310	625	965	1,269	1,460	1,552	1,617
Ex-US Sales		-	-	42	274	577	886	1,219	1,407	1,508
Effective royalty rate			*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*
Royalty Revenue to CALA			$ -	$ 6	$ 41	$ 87	$ 133	$ 183	$ 211	$ 226
Breakdown by Geography and Indication										
US		$ -	$ 55	$ 310	$ 625	$ 965	$ 1,269	$ 1,460	$ 1,552	$ 1,617
Myeloma		-	23	96	183	283	379	462	510	533
DLBCL		-	11	108	225	366	517	573	599	623
TNBC		-	-	63	148	228	270	309	321	334
Acute Leukemia		-	21	44	70	88	102	117	122	127
EU				$ 42	$ 266	$ 523	$ 780	$ 1,063	$ 1,198	$ 1,266
Myeloma				19	77	142	216	319	401	435
DLBCL				13	118	240	379	521	555	568
TNBC				-	48	103	131	160	176	196
Acute Leukemia				11	23	39	54	63	65	68
JPN					$ 8	$ 54	$ 106	$ 156	$ 209	$ 242
Myeloma					4	15	29	44	64	81
DLBCL					2	21	42	66	91	98
TNBC					-	12	27	34	42	50
Acute Leukemia					2	5	9	12	12	12

Source: JMP Securities LLC

FIGURE 18. CB-839 Market Model in Multiple Myeloma, U.S.

CB-839 for Multiple Myeloma ($MM)	2017E	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E
MM Prevalence, US	82,380	83,616	84,870	86,143	87,435	88,746	90,078	91,429	92,800
% Growth	*1.5%*	*1.5%*	*1.5%*	*1.5%*	*1.5%*	*1.5%*	*1.5%*	*1.5%*	*1.5%*
Second-Line (2L) MM									
Number of 2L MM Patients	27,185	27,593	28,007	28,427	28,854	29,286	29,726	30,172	30,624
% of total	*33%*	*33%*	*33%*	*33%*	*33%*	*33%*	*33%*	*33%*	*33%*
Proportion treated with Chemotherapy	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*
Addressable 2L MM population	19,030	19,315	19,605	19,899	20,197	20,500	20,808	21,120	21,437
Market Penetration				***2%***	***4%***	***7%***	***9%***	***10%***	***10%***
2L patients on CB-839	-	-	-	398	808	1,435	1,873	2,112	2,144
Duration of Therapy (cycles)				6.7	9.0	10.2	11.0	11.0	11.0
2L cycles on therapy				2,666	7,271	14,637	20,600	23,232	23,581
Cost per cycle therapy			$ 10,079	$ 10,381	$ 10,692	$ 11,013	$ 11,343	$ 11,684	$ 12,034
Price increase			*3%*	*3%*	*3%*	*3%*	*3%*	*3%*	*3%*
2L CB-839 Sales, US ($MM)			$ -	$ 27.7	$ 77.7	$ 161.2	$ 233.7	$ 271.4	$ 283.8
Third-Line and Beyond (3L+) MM									
Number of 3L+ MM Patients	24,302	24,667	25,037	25,412	25,793	26,180	26,573	26,972	27,376
% of total	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*
Proportion treated with Chemotherapy	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*
Addressable 3L+ MM population	17,011	17,267	17,526	17,788	18,055	18,326	18,601	18,880	19,163
Market Penetration		***2%***	***8%***	***12%***	***15%***	***15%***	***15%***	***15%***	***15%***
3L+ patients on CB-839		345	1,402	2,135	2,708	2,749	2,790	2,832	2,874
Duration of Therapy (cycles)		6.7	6.8	7.0	7.1	7.2	7.2	7.2	7.2
3L+ cycles on therapy		2,314	9,534	14,942	19,229	19,792	20,089	20,390	20,696
Cost per cycle therapy		$ 9,785	$ 10,079	$ 10,381	$ 10,692	$ 11,013	$ 11,343	$ 11,684	$ 12,034
Price increase			*3%*	*3%*	*3%*	*3%*	*3%*	*3%*	*3%*
3L+ CB-839 Sales, US ($MM)		$ 22.6	$ 96.1	$ 155.1	$ 205.6	$ 218.0	$ 227.9	$ 238.2	$ 249.1

Source: JMP Securities LLC

FIGURE 19. CB-839 Market Model in DLBCL, U.S.

CB-839 for DLBCL ($MM)	2017E	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E
DLBCL									
NHL Incidence, US	70,443	71,147	71,859	72,577	73,303	74,036	74,776	75,524	76,279
% Growth	*1.0%*	*1.0%*	*1.0%*	*1.0%*	*1.0%*	*1.0%*	*1.0%*	*1.0%*	*1.0%*
% DLBCL	*29%*	*29%*	*29%*	*29%*	*29%*	*29%*	*29%*	*29%*	*29%*
Number of 1L DLBCL Patients	20,428	20,633	20,839	21,047	21,258	21,470	21,685	21,902	22,121
% treated with chemotherapy	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*
1L Treated DLBCL Patients	15,321	15,474	15,629	15,786	15,943	16,103	16,264	16,426	16,591
Second-Line (2L) DLBCL									
Five-Year Prevalence of DLBCL	76,606	77,372	78,146	78,928	79,717	80,514	81,319	82,132	82,954
% Second-Line	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*
Addresable 2L DLBCL Patients	22,982	23,212	23,444	23,678	23,915	24,154	24,396	24,640	24,886
Market Penetration			**5%**	**10%**	**15%**	**20%**	**20%**	**20%**	**20%**
2L patients on Selinexor			1,172	2,368	3,587	4,831	4,879	4,928	4,977
Duration of Therapy (cycles)			7.0	7.5	8.0	8.5	9.0	9.0	9.0
2L cycles on therapy			8,205	17,759	28,698	41,062	43,912	44,352	44,795
Cost of therapy			$ 10,079	$ 10,381	$ 10,692	$ 11,013	$ 11,343	$ 11,684	$ 12,034
Price incresae				*3%*	*3%*	*3%*	*3%*	*3%*	*3%*
2L Selinexor Sales, US ($MM)			**$ 82.7**	**$ 184.4**	**$ 306.8**	**$ 452.2**	**$ 498.1**	**$ 518.2**	**$ 539.1**
Third-Line (3L) DLBCL									
% progressing from 2L	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*
Addresable 3L DLBCL Patients	5,745	5,803	5,861	5,920	5,979	6,039	6,099	6,160	6,222
Market Penetration		**5%**	**10%**	**15%**	**20%**	**20%**	**20%**	**20%**	**20%**
3L patients on Selinexor		290	586	888	1,196	1,208	1,220	1,232	1,244
Duration of Therapy (cycles)		4.0	4.2	4.4	4.6	4.9	5.4	5.6	5.6
3L cycles on therapy		1,161	2,462	3,907	5,500	5,918	6,587	6,899	6,968
Cost of therapy		$ 9,785	$ 10,079	$ 10,381	$ 10,692	$ 11,013	$ 11,343	$ 11,684	$ 12,034
Price incresae			*3%*	*3%*	*3%*	*3%*	*3%*	*3%*	*3%*
3L Selinexor Sales, US ($MM)		**$ 11.4**	**$ 24.8**	**$ 40.6**	**$ 58.8**	**$ 65.2**	**$ 74.7**	**$ 80.6**	**$ 83.9**

Source: JMP Securities LLC

FIGURE 20. CB-839 Market Model in Triple Negative Breast Cancer, U.S.

CB-839 in mTNBC ($MM)	2017E	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E
Breast Cancer Incidence, US	242,237	244,659	247,106	249,577	252,073	254,593	257,139	259,711	262,308
% Growth	*1.0%*	*1.0%*	*1.0%*	*1.0%*	*1.0%*	*1.0%*	*1.0%*	*1.0%*	*1.0%*
% triple negative breast cancer	*13%*	*13%*	*13%*	*13%*	*13%*	*13%*	*13%*	*13%*	*13%*
% regional disease	*32%*	*32%*	*32%*	*32%*	*32%*	*32%*	*32%*	*32%*	*32%*
% metastatic disease	*5%*	*5%*	*5%*	*5%*	*5%*	*5%*	*5%*	*5%*	*5%*
# pts with Triple Negative Breast Cancer	11,652	11,768	11,886	12,005	12,125	12,246	12,368	12,492	12,617
Market Penetration			*15%*	*32%*	*44%*	*50%*	*55%*	*55%*	*55%*
Patients on CB-839			**1,783**	**3,841**	**5,335**	**6,123**	**6,803**	**6,871**	**6,939**
Duration of therapy (cycles)			3.5	3.7	4.0	4.0	4.0	4.0	4.0
Total Patients cycles on therapy			6,240	14,213	21,339	24,492	27,210	27,483	27,757
Cost per Month of Therapy			$ 10,079	$ 10,381	$ 10,692	$ 11,013	$ 11,343	$ 11,684	$ 12,034
% increase				*3%*	*3%*	*3%*	*3%*	*3%*	*3%*
CB-839 TNBC Sales, US			**$ 62.9**	**$ 147.5**	**$ 228.2**	**$ 269.7**	**$ 308.7**	**$ 321.1**	**$ 334.0**

Source: JMP Securities LLC

FIGURE 21. CB-839 Market Model in Acute Leukemias (AML and ALL), U.S.

CB-839 Acute Leukemia ($MM)	2017E	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E
Elderly AML									
AML indicence, US	15,577	15,810	16,047	16,288	16,532	16,780	17,032	17,288	17,547
%Growth	*1.5%*	*1.5%*	*1.5%*	*1.5%*	*1.5%*	*1.5%*	*1.5%*	*1.5%*	*1.5%*
% pts > 70 yrs of age	*44.3%*	*44.0%*	*43.8%*	*43.5%*	*43.3%*	*43.0%*	*42.8%*	*42.5%*	*42.3%*
Addressable ederly AML patients	6,893	6,956	7,021	7,085	7,150	7,216	7,281	7,347	7,414
Market penetration		***5%***	***10%***	***15%***	***18%***	***20%***	***22%***	***22%***	***22%***
Elderly AML patients on CB-839		348	702	1,063	1,287	1,443	1,602	1,616	1,631
Duration of Tx (cycles)		5.7	5.8	5.9	5.9	5.9	5.9	5.9	5.9
Total AML patient cycles on Tx		1,983	4,072	6,271	7,594	8,514	9,451	9,537	9,623
Cost of Tx (per cycle)		$ 9,785	$ 10,079	$ 10,381	$ 10,692	$ 11,013	$ 11,343	$ 11,684	$ 12,034
% price increase			*3%*	*3%*	*3%*	*3%*	*3%*	*3%*	*3%*
CB-839 AML Sales, US		**$ 19.4**	**$ 41.0**	**$ 65.1**	**$ 81.2**	**$ 93.8**	**$ 107.2**	**$ 111.4**	**$ 115.8**
T-ALL									
ALL Incidence, US	6,347	6,442	6,539	6,637	6,737	6,838	6,940	7,044	7,150
% Growth	*1.5%*	*1.5%*	*1.5%*	*1.5%*	*1.5%*	*1.5%*	*1.5%*	*1.5%*	*1.5%*
% ≥ 40 yrs	*25.0%*	*25.0%*	*25.0%*	*25.0%*	*25.0%*	*25.0%*	*25.0%*	*25.0%*	*25.0%*
% Ph-negative pts	*75.0%*	*75.0%*	*75.0%*	*75.0%*	*75.0%*	*75.0%*	*75.0%*	*75.0%*	*75.0%*
Addressable adult ALL patients	1,190	1,208	1,226	1,244	1,263	1,282	1,301	1,321	1,341
Market Penetration		***5%***	***12%***	***18%***	***25%***	***30%***	***32%***	***35%***	***35%***
ALL patients on CB-839		60	147	224	316	385	416	462	469
Duration of Tx (cycles)		2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Total ALL patient cycles on Tx		121	294	448	632	769	833	925	938
Cost of Tx (per cycle)		$ 9,785	$ 10,079	$ 10,381	$ 10,692	$ 11,013	$ 11,343	$ 11,684	$ 12,034
% price increase			*3%*	*3%*	*3%*	*3%*	*3%*	*3%*	*3%*
CB-839 ALL Sales, US		**$ 1.2**	**$ 3.0**	**$ 4.7**	**$ 6.8**	**$ 8.5**	**$ 9.4**	**$ 10.8**	**$ 11.3**

Source: JMP Securities LLC

SUMMARY AND CONCLUSION

As a fast-follower in the cancer metabolism space, we find an exceptional risk/reward profile in Calithera shares. Cancer metabolism is a space that is rapidly gaining scientific credibility but is lacking in the availability of high-quality, credentialed chemical compounds. We believe CB-839 could be the next attractive asset in the space, and look forward to the company's progress throughout the remainder of 2014 and 2015. The critical year for Calithera will be 2015, when data becomes available for the single-agent studies at the RP2D, and in the combination studies of CB-839 and standard-of-care agents. We have a high degree of confidence in the discovery and development capabilities of the company's management team, and believe they will parlay their success at Proteolix/Onyx into another successful endeavor in Calithera. Finally, our financial analysis of the prospects for CB-839 suggests a fair value significantly higher than the current valuation. We are, therefore, initiating coverage on Calithera with a Market Outperform rating and $20 price target.

APPENDIX A – MANAGEMENT TEAM

Susan M. Molineaux, Ph.D., Founder, President and Chief Executive Officer

Dr. Molineaux has served as Calithera Biosciences' President, Chief Executive Officer, and a member of its board of directors since she co-founded Calithera in March 2010. Prior to Calithera, Dr. Molineaux co-founded Proteolix, Inc. in 2003 and served as Chief Scientific Officer and later as Chief Executive Officer in the company, prior to its acquisition by Onyx Pharmaceuticals, Inc. in 2009. Dr. Molineaux led the team that discovered the proteasome inhibitor carfilzomib (marketed as Kyprolis) and conducted the Phase 2 clinical trials that led to the accelerated approval of Kyprolis for the treatment of refractory multiple myeloma in 2012. Prior to founding Proteolix, Dr. Molineaux held various senior scientific and management positions at Rigel Pharmaceuticals, Inc., Praecis Pharmaceuticals Inc., and Merck & Co. She currently serves as a member of the board of directors of Geron Corporation, a biopharmaceutical company. She also serves as the Chairman of BayBio, Northern California's Life Science Association. Dr. Molineaux received a B.S. degree in Biology from Smith College, a Ph.D. degree in Molecular Biology from Johns Hopkins University, and completed a postdoctoral fellowship at Columbia University.

William D. Waddill, Senior Vice President and Chief Financial Officer

Mr. Waddill has served as Calithera Biosciences' Senior Vice President, Chief Financial Officer and Secretary since April 2014. From 2007 to 2014, Mr. Waddill served as Senior Vice President and Chief Financial Officer at OncoMed Pharmaceuticals, Inc., a biopharmaceutical company, where he was the finance lead for the successful completion of a $94 million initial public offering in July 2013, a $126 million private equity financing in December 2008 and three major collaborations with pharmaceutical companies. Prior to OncoMed, Mr. Waddill was Senior Vice President and Chief Financial Officer at Ilypsa, Inc., where he was the finance lead for the company's $420 million acquisition by Amgen Inc. in 2007. Mr. Waddill received a B.S. degree in accounting from the University of Illinois, Chicago, and certification as a public accountant (inactive) after working at PricewaterhouseCoopers and Deloitte in Boston.

Eric B. Sjogren, Ph.D., Senior Vice President of Drug Discovery

Dr. Sjogren has served as Calithera Biosciences' Senior Vice President of Drug Discovery since June 2010. Dr. Sjogren has over 25 years of experience in small molecule drug discovery in the pharmaceutical industry. Prior to joining Calithera, Dr. Sjogren was Vice President and Head of Medicinal Chemistry at Roche Palo Alto, LLC from 2003 through 2009, where he directed a small molecule drug discovery team in the areas of inflammation, virology, and central nervous systems disorders. Dr. Sjogren received a B.A. degree in Chemistry from the University of California, San Diego and a Ph.D. degree in Chemistry from Harvard University.

Mark K. Bennett, Ph.D., Senior Vice President of Research

Dr. Bennett has served as Calithera Biosciences' Senior Vice President of Research since June 2010. From 2003 through 2009, Dr. Bennett was at Proteolix, Inc., most recently as Vice President of Research, where he led the research efforts in the discovery of carfilzomib, oprozomib, and PR-957. Dr. Bennett previously was Director of Cell Biology at Rigel Pharmaceuticals, Inc. and an Assistant Professor of Molecular and Cell Biology at the University of California, Berkeley. Dr. Bennett received a B.S. degree in Biochemistry and Biophysics from Oregon State University, a Ph.D. degree in Neuroscience from the California Institute of Technology, and completed postdoctoral fellowships at the European Molecular Biology Laboratory and Stanford University.

Christopher J. Molineaux, Ph.D., Senior Vice President of Development

Dr. Molineaux has served as Calithera Biosciences' Senior Vice President of Development since April 2013. From 2010 to 2013, Dr. Molineaux served as President of INDStrat LLC, a consulting firm. From 2004 to 2009, Dr. Molineaux was Vice President of Development at Proteolix, where he led the team that developed carfilzomib (marketed as Kyprolis) through the completion of Phase 2 clinical trials for accelerated approval in the United States for the treatment of refractory multiple myeloma. Previously, Dr. Molineaux led the oral anemia project team at FibroGen, Inc. and prior to that, led the team at Praecis that discovered and developed abarelix (marketed as Plenaxis), which was approved for the treatment of prostate cancer. Dr. Molineaux received a B.S. in Zoology from University of Maryland, College Park, a Ph.D. in Immunology and Infectious Diseases from Johns Hopkins University, and completed his postdoctoral fellowship at the Uniformed Services University of the Health Sciences.

Curtis C. Hecht, Vice President of Business and Corporate Development

Mr. Hecht has served as Calithera Biosciences' Vice President of Business and Corporate Development since April 2014. From 2013 to 2014, Mr. Hecht served as Vice President of Business Development at inVentiv Health, a global healthcare commercialization and consulting services company. Since 2011, he has also served as a Partner at DNA Ink, a life sciences business development and licensing firm. Prior to that, Mr. Hecht served in a number of roles at Hoffman La-Roche Inc., most recently as Global Alliance Director and Director of Global Business Development. While at Roche, he managed the Roche-Genentech Joint Development and Operations Committee that oversaw the global development for Avastin, Herceptin, Rituxan, Tarceva, Perjeta, Erivedge, and TDM1. He currently sits on the advisory board to Biocision, LLC. Mr. Hecht received a B.S. in Chemistry from California State University, Sacramento and an M.B.A. from Carnegie Mellon University.

Stephanie Wong, Vice President of Finance

Ms. Wong joined Calithera as Vice President, Finance in April 2014. From 2009 to 2013, Ms. Wong was at SciClone Pharmaceuticals, a publicly traded, commercial-stage pharmaceutical company, most recently as Vice President, Finance and Controller. From 2008 to 2009, Ms. Wong was Senior Director, Finance at AcelRx Pharmaceuticals. From 2001 to 2008, Ms. Wong held various positions at Kosan Biosciences, a publicly traded biotechnology company until its acquisition by Bristol-Myers Squibb, most recently as Senior Director and Controller. Prior to that, Ms. Wong worked as an audit manager at PricewaterhouseCoopers. Ms. Wong received a B.S. degree in Business Administration from the University of California, Berkeley and is a Certified Public Accountant in the State of California.

Hagit Glickman, Ph.D., Head of People and Culture

Dr. Hagit Glickman has been with Calithera Biosciences since the company's founding in June 2010. She has 20 years of experience in business and has served as an advisor to numerous biotech and pharmaceutical companies including Proteolix, NovaBay, Takeda, and Novartis. She has founded and been CEO of startup companies in the healthcare industry. Dr. Glickman has a B.A. degree in Psychology from the University of California, Irvine and a Ph.D. in Clinical Psychology from the Pacific Graduate School of Psychology in Palo Alto.

Source: Company website

APPENDIX B – ABERRANT REGULATION AND POTENTIAL DRUG TARGETS IN CANCER METABOLISM

It has long been held that cancer cells possess an altered metabolism relative to normal cells in order to accommodate/satisfy the energy demands of rapid cell proliferation. This concept was most famously pioneered through the work of Otto Warburg, who observed that most cancer cells, even when in oxygen rich environments capable of supporting oxidative phosphorylation (OXPHOS), relied on glycolysis and lactate fermentation to drive energy production (the so-called "Warburg Effect")[1,2]. The use of glycolysis over OXPHOS is far less efficient, with one molecule of glucose giving rise to two molecules of ATP production (compared to 35-38 molecules of ATP through OXPHOS), and drives a large requirement for glucose. This dependence has been exploited through the use of radiolabeled F-2-deoxyglucose, allowing visualization of tumors due to the dramatic increase of glucose in the tumor.

As deregulated cellular metabolism has grown to become one of the critical hallmarks of cancer over the past decade, so too has this phenomenon become of increasing interest to both the academic research and biopharma development communities. Aberrant metabolic signaling has been shown to occur in multiple, interconnected pathways regulating glucose, amino acid, nucleic acid and fatty acid metabolism, each drawing considerable interest as potential targets of therapeutic intervention. Herein, we provide a broad look at what we observe to be some of the key areas of discovery in tumor metabolism today, while highlighting burgeoning targets, drug candidates and biotechnology companies within the space. Overall, we believe that while the space remains by and large less mature than the epigenetics space (also of increasing promise in oncology in recent years), cancer metabolism is a compelling area of cancer research and drug development, presenting several attractive investment opportunities.

Oncogenic Signaling Pathways Deregulate Cancer Cell Metabolism

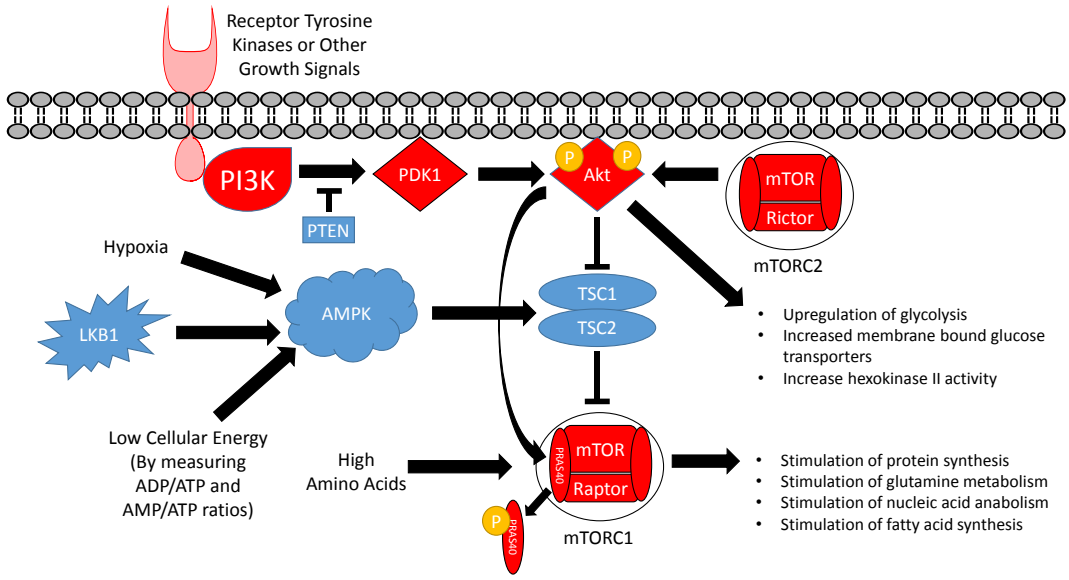
The ability of a normal cell to shift from anabolism (building macromolecules from smaller units) to catabolism (breaking down macromolecules in order to utilize their components) and the large overlap between various metabolic processes allows the cell to maintain homeostasis depending on the available nutrients. For example, a normal cell in the presence of oxygen relies predominantly on OXPHOS for energy and can upregulate glycolysis under oxygen limiting situations. Once oxygen is plentiful again, the cell can switch back to OXPHOS. However, in most cancers, basal energy requirements are drawn primarily from glycolysis even in the presence of oxygen[1,2], suggesting a loss of flexibility by the cancer cell.

Since Warburg's initial observations, numerous additional metabolic alterations in cancer have been elucidated. In addition to shifting energy production toward glycolysis, cancer cells also become dependent on several other biosynthetic pathways including: 1) glutamine metabolism (glutaminolysis) for energy and building blocks; 2) increased flux through the pentose phosphate pathway (PPP); 3) increased utilization of serine for biosynthetic reactions; 4) fatty acid synthesis; and 5) the metabolic scavenging pathways, specifically autophagy (we refer readers to Appendix A for a more in-depth review of normal cellular metabolic pathways). Recent advances in the field would suggest that dramatic departures from normal cellular metabolism in a fully transformed cell could be necessary to accommodate tumorigenesis, tumor progression, and/or tumor maintenance, the corollary being that each of these mechanisms provide opportunities for therapeutic intervention.

PI3K and mTORC1 pathway deregulation in cancer metabolism. The phosphoinositide 3-kinase (PI3K) pathway is one the most heavily characterized signaling pathways in oncology to date and enjoys a high profile in academia and drug development alike, stemming from a high frequency of activating mutation to subunit isoform within the enzyme PI3KCa (encoded by the *PIK3CA* gene) in breast cancer. In its native form, however, PI3K functions a central regulator of normal cell metabolism, stimulating glucose uptake downstream of growth factor receptor stimulation. PI3K activation, through a succession of effector molecules including Akt and mTOR, leads to increased glycolysis[4], the trafficking of glucose transporters to the cell membrane[5] and the activation of hexokinase II[6], an enzyme that catalyzes the first step of glycolysis (Figure 22). The mammalian target of rapamycin (mTOR) functions as the catalytic subunit of two molecular complexes, mTORC1, containing the protein Raptor, and mTORC2, containing the protein Rictor. The mTORC1 complex is responsible for mTOR's function as a regulator of nutrient sensing[7,8], oxygen redox status[9], energy levels[8], and biomass synthesis[8,10-12] (Figure 22). Interestingly, mTOR can signal as either an upstream (when in the mTORC2 complex) or downstream (when in the mTORC1 complex) node in the PI3K pathway, through the regulation of Akt. Another method of mTORC1 regulation by Akt occurs through the phosphorylation and subsequent inactivation of the tumor suppressor TSC1/2 complex containing the tuberous sclerosis proteins, TSC1 and TSC2[14].

The mTORC1 complex is also regulated by nutrient signals. The role of the main regulator of nutrient sensing is carried out by a serine/threonine kinase complex called the AMP-activated protein kinase (AMPK). AMPK measures intracellular energetics due to the ratios of AMP:ATP and, to a lesser extent, the ratio of ADP:ATP[15]. AMPK activation leads to the cell switching from an anabolic state to producing more energy in the form of ATP, with one mechanism of this being the activation of the TSC1/2 tumor suppressors to repress mTORC1. AMPK can be activated by the serine/threonine kinase, liver kinase B1 (LKB1), when it is in a complex with other proteins. A simplified diagram of nutrient sensing is depicted in Figure 22.

FIGURE 22. PI3 Kinase/mTOR Signaling is a Key Regulator of Cellular Biosynthesis

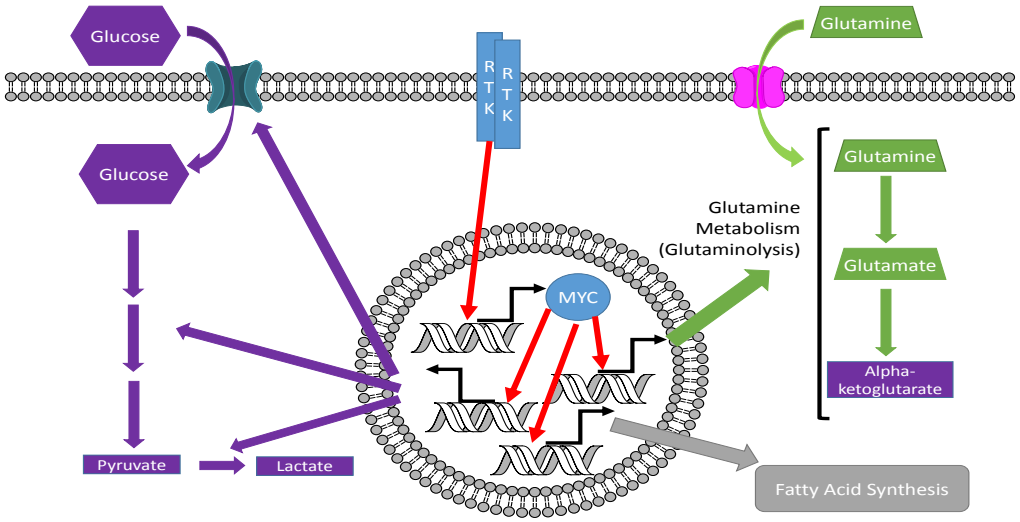


Source: JMP Securities LLC

In cancer, PI3K/Akt can be activated by mutated and/or amplified upstream receptor tyrosine kinases such as EGFR, Her2, Her3, c-MET, PDGFRa and KIT, and can be activated mutations in Ras[16]. As we highlight above, aberrant activation of the PI3K pathway can also occur in response to mutation of the catalytic subunit *PIK3CA* (p110a), but also through inactivation of the negative regulator of the PI3K pathway, PTEN, and by activating mutations in Akt, all of which confer constitutive PI3K pathway signaling[16]. While activation of the PI3K pathway leads to an activation of mTORC1 and subsequent increase in protein synthesis, glutamine metabolism, nucleic acid synthesis, and fatty acid synthesis, alterations to the direct regulators of mTORC1 have also been found. Mutations that inactivate LKB1 or deletions of the LKB1 gene have been found in multiple cancers, predominantly colorectal cancer, breast cancer, and lung cancer[17]. The negative regulators TSC1 and TSC2 have been found to be either mutated, amplified, or deleted in numerous cancer types[18,19]. The multiple alterations that lead to constitutive signaling of PI3K and mTORC1 in cancer illustrate the important role it plays in pathogenesis.

MYC deregulation in cancer metabolism. Activation of PI3K and mTOR are not the only critical regulators of cancer metabolism, and numerous studies have demonstrated that MYC activation may also lead to metabolic changes[20-22] in connection with tumorigenesis. MYC is a transcription factor that is considered to be one of the main regulators of cellular growth downstream of RTK, and has been found to be altered in many cancers. MYC expression is induced by upstream signaling of RTKs and the PI3K pathway, but also has been shown to undergo mutation in manners that stabilize its expression, amplify its gene locus, and promote constitutive expression[23]. MYC binds to other transcription factors, triggering transcription of many genes required for proliferation, stem cell self-renewal, cell growth, and protection from apoptosis. The genetic targets of MYC include nutrient uptake, glucose transport, glycolysis, glutaminolysis, pyruvate conversion into lactate, and fatty acid synthesis[21] (Figure 23). The aberrant activation of MYC dramatically alters the needs of the cell for certain metabolites to the point of dependence. It has been shown that cells expressing activated MYC and depleted of an external source of glutamine undergo apoptosis, despite MYC-driven upregulation of glucose metabolism[24,25]. This latter aspect highlights the potent ability of MYC to alter normal cellular metabolism. Finally, MYC has also been shown to alter cellular metabolism through a post-transcriptional stabilization transcription factor, HIF-1α, which itself is an oncogene and modulator of cell metabolism as discussed below[26].

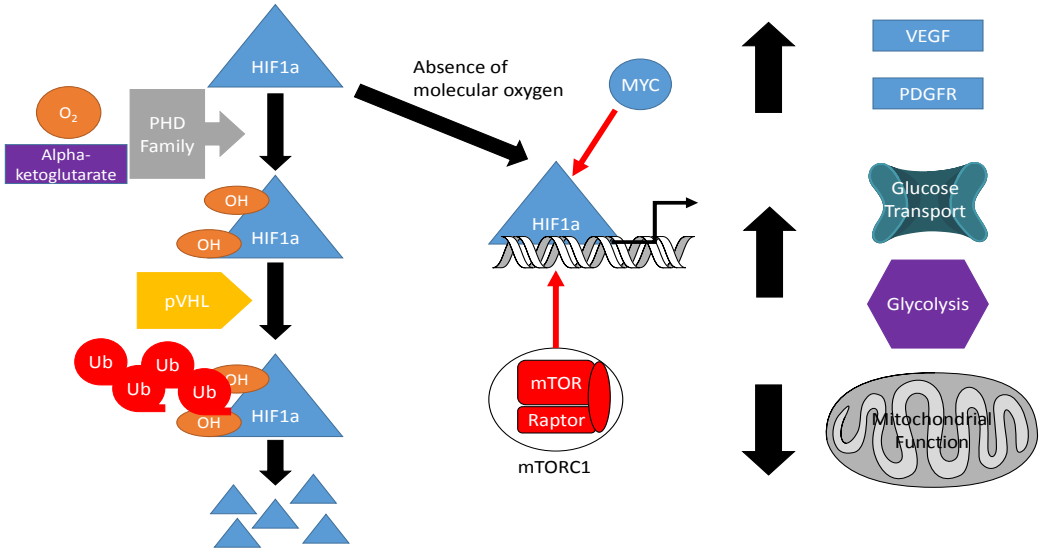
FIGURE 23. MYC Activation Drives Aberrant Signaling of Multiple Biosynthetic Routes



Source: JMP Securities LLC

HIF-1α activation and cancer metabolism. The ability for a normal cell to produce adequate energy under conditions of low oxygen is due to the oxygen-dependent transcription factor, HIF-1α. In the presence of oxygen, HIF-1α is targeted for degradation by the prolyl hydroxylase domain-containing protein (PHD) family which are alpha-ketoglutarate (α-KG) dependent oxygenases (refer to Appendix for context)[27]. When HIF-1α is hydroxylated by PHD enzymes, VHL (Von Hippel-Lindau tumor suppressor) binds to HIF-1α and targets it for polyubiquitination and degradation[28]. In the absence of oxygen, the PHDs are no longer able to hydroxylate HIF-1α, leading to stabilization and HIF-1α-initiated transcription of HIF-1α target genes that upregulate glycolysis enzymes, glucose transporters, angiogenic growth factors, VEGF and PDGF, and other key factors which aim to increase oxygen transport through angiogenesis[29,30] (Figure 24). In short, when HIF-1α is constitutively stabilized, cells cease being oxygen sensitive and subsist on a dramatically altered metabolism. As further examples of HIF-1α-modified metabolism, mTORC1 activation has been shown to induce HIF-1α target gene expression in the presence of oxygen, and hypoxia activated AMPK suppressing mTORC1 function[31] (Figures 22 and 24). Aberrant activation of HIF-1α, in cancer, can also occur through loss of the tumor suppressor VHL, accumulation of ROS, hypoxia induced by the tumor due to lack of adequate blood flow, and by the presence of high levels of succinate or fumarate.

FIGURE 24. Cancer Cell Accumulation of HIF1a Promotes RTK Expression and Anaerobic Respiration



Source: JMP Securities LLC

TP53 altering cellular metabolism. The tumor suppressor TP53 has an integral role in protecting a normal cell from transformation through DNA damage repair and the ability to induce apoptosis, but the role that TP53 plays in metabolism has become abundantly clear with TP53 being able to promote OXPHOS and PPP while suppressing glycolysis[32,33]. TP53 is subject to both activating and inactivating mutations, gene deletion, suppression of gene expression, and aberrant degradation of the protein[34]. One of the major pathways that TP53 uses to alter cellular metabolism is via the control of the expression of the TP53-inducible glycolysis and apoptosis regulator (TIGAR), which leads to the suppression of glycolysis[35]. TIGAR decreases the rate of glycolysis, increases gluconeogenesis, shunts glucose-6-phosphate into the PPP, and inhibits autophagy.

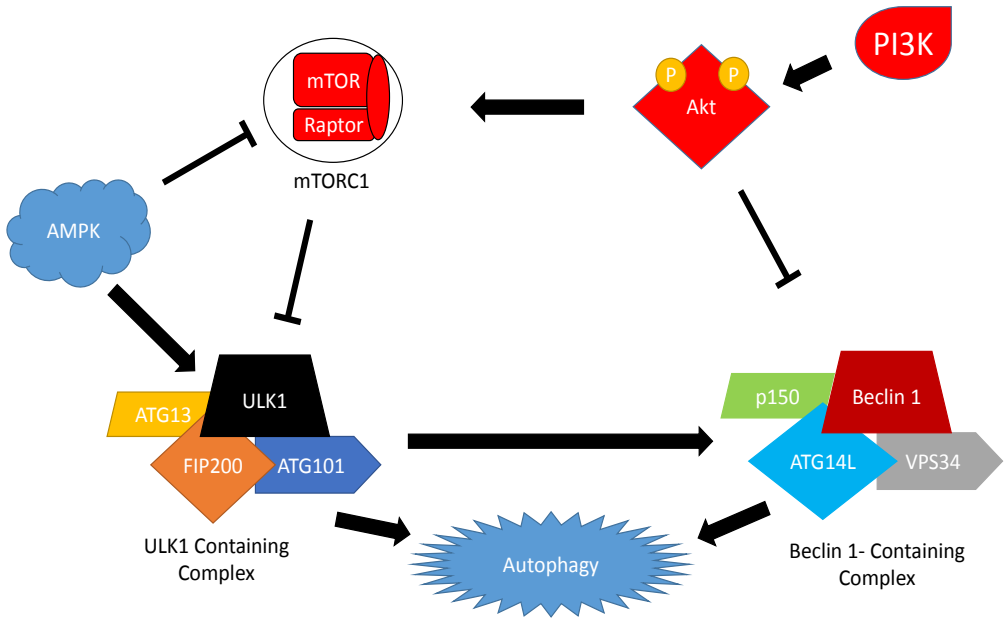
While loss of TP53 and suppression of TIGAR would lead to an upregulation of glycolysis, it has been found that in certain contexts, TIGAR function is important for tumorigenesis through the shuttling of metabolites into the PPP and maintaining proper redox status through NADPH generation[36]. TP53 regulates NADPH production, lipogenesis, and glutamine metabolism through an inverse relationship with the enzymes responsible for converting malate to pyruvate: malic enzyme 1 (located in the cytosol) and malic enzyme 2 (located in the mitochondria)[37]. Thus, the effects of TP53, and by extension TIGAR, on metabolic flux in both directions depend on the particular requirements of a cancer cell. While TP53 has direct effects on cellular metabolism, it also interacts with AMPK directly and indirectly and increases TSC2 expression leading to the regulation of cellular metabolism (as outlined above) and autophagy[32].

Autophagy and the scavenging for nutrients. Aberrant signaling by PI3K/mTORC1, MYC, and HIF-1α pathways alter the ability of the cell to take up nutrients and means in which nutrients are processed. Upregulation of these pathways also creates a large demand for nutrients that the cancer cell can either acquire exogenously or in instances of starvation (limited supply of exogenous nutrients) through the alternative mechanism of autophagy. Autophagy describes the process by which a cell scavenges for nutrients by breaking down and recycling its cellular components. This process allows a cell to respond to conditions of stress/starvation that can promote survival benefit or induce cell

death[38]. Under conditions of stress, the cell sequesters cytoplasmic components in autophagosomes that fuse to lysosomes, where the cytoplasmic components can be metabolized to counteract the stress. The ability of the cell to induce autophagy and respond to various environmental stimuli is regulated by mTORC1 and PI3K-Akt (Figure 25). Under energy low conditions, AMPK phosphorylates[39] the UNC-51 like kinase 1 (ULK1) in complex with ATG13, ATG101, and FIP200 to activate autophagy, while simultaneously inhibiting mTORC1 (a negative regulator of the ULK1 complex).

Under energy high conditions or PI3K pathway activation, mTORC1 phosphorylates ULK1 inhibiting its function, and Akt phosphorylates Beclin 1 (a BCL-2 family protein) in a complex with VPS34 (a class III phosphatidylinositol 3-kinase), ATG14L, and p150[39,40]. The Beclin 1 complex is important for producing phosphatidylinositol-3-phosphate (PIP3) that is used for autophagosomal membrane nucleation, while the ULK1 initiates autophagy and phosphorylates Beclin 1 to stimulate PIP3 production[41]. Altered expression of autophagic proteins has been reported in multiple cancers leading to poor prognosis, aggressive tumor phenotypes, and resistance to multiple cancer therapies[38]. The alterations to the autophagic process can lead to suppression of autophagy or activation of autophagy, and depending on the context, can be have either tumor promoting or tumor suppressing functions.

FIGURE 25. Autophagy Inducing Signaling Pathways



Source: JMP Securities LLC

Alterations to Metabolic Enzymes during Tumorigenesis

Changes in PI3K/Akt signaling, mTORC1 signaling, MYC directed transcriptional activation, HIF-1α directed transcriptional activation, or alterations in the autophagy machinery all alter cellular metabolism. More recently, however, alterations to metabolic enzymes themselves, either through mutation or aberrant expression, have been observed in cancer cells with dysregulated metabolism. These metabolic enzymes have been shown to be either oncogenes or tumor suppressors highlighting the importance of metabolism in the development of cancer[42].

Succinate dehydrogenase and fumarate hydratase. In the TCA cycle, the enzyme succinate dehydrogenase converts succinate to fumarate, which is subsequently converted into malate by fumarate hydratase. Inactivating mutations of succinate dehydrogenase (SDH) genes have been shown to increase intracellular concentrations of succinate, while inactivating mutations of fumarate hydratase (FH) have been found in association with increased concentrations of fumarate. SDH mutations have been found in gastrointestinal stromal tumors, pheochromocytomas, and paragliomas, while FH mutations have been found in leiomyomas, renal cell cancer, Leydig cell tumors, ovarian cystadenomas, cerebral cavernomas, uterine leiomyosarcomas, and breast cancer[43].

The increased concentrations of succinate and fumarate are thought to act as suppressors of alpha-ketoglutarate dependent oxygenases, one of which is the PHD enzymes that degrade HIF-1α along with suppressing mitochondrial function and increasing reactive oxygen species (ROS). Activation of HIF-1α and suppression of mitochondrial function would dramatically alter the metabolism of the cell. The function of these enzymes is that of a tumor suppressor since loss of function leads to tumorigenesis. These mutations are germline[43].

IDH1 and IDH2. The isocitrate dehydrogenase enzymes, IDH1 and IDH2, are also found mutated in a range of cancers, most frequently in lower grade gliomas, acute myeloid leukemia, and chondrosarcomas[44]. These two proteins share a high degree of homology; however, IDH1 is located in the cytosol and the peroxisome, while IDH2 is located in the mitochondria. IDH1 functions to maintain levels of cellular NADPH and redox status of the cell along with the pentose phosphate pathway, and malic enzyme 1 (ME1) outside the mitochondria. IDH2 helps maintain NADPH levels and redox status in the mitochondria, and contributes to the reverse flux of α-KG to isocitrate in the TCA cycle. Originally thought to be loss of function mutations similar to the mutations found in SDH and FH, it was subsequently found that mutated IDH aberrantly produces 2-hydroxyglutarate (2HG) from alpha-ketoglutarate (α-KG) and NADPH[45].

While the mechanism by which mutated IDH contributes to cancer is not confirmed, it is believed that 2HG competes with α-KG for use by α-KG dependent oxygenases either as an agonist or an antagonist. The simplest extrapolation would be that 2HG could interfere with the PHD family and alter HIF-1α function leading to altered metabolism. The role that both play in maintaining NADPH levels and redox status could also dramatically affect cellular metabolism.

PKM2. Pyruvate kinase, the enzyme that catalyzes the final irreversible step in glycolysis of phosphoenolpyruvate (PEP) to pyruvate, is found in four isoforms: PKL (liver/kidneys), PKR (red blood cells), PKM1, and PKM2. While the L and R isoforms are restricted in expression, the M1 and M2 isoforms are not tissue specific, but the M2 isoform is expressed in predominantly all proliferating cells including cancer cells[46]. PKM2 is found as both an active tetramer and an inactive dimer. It is the inactive dimer complex of PKM2 that is more often found in tumor cells, and PKM2 activity can be regulated by metabolic intermediates, tyrosine phosphorylation, and other post-transcriptional modifications[47].

While the normal flux of glucose to pyruvate to acetyl-CoA leads to the production of energy in the TCA cycle, the presence of the inactive dimer of PKM2 dramatically decreases that flux. This leads to an increase in the concentration of the metabolites upstream of PK including PEP and 3-phosphoglycerate which can then be shuttled into serine synthesis helping the cancer cell meet its biomass requirements. In order to recoup the loss of energy produced, many cancer cells turn to glutaminolysis for the production of pyruvate and lactate fermentation[48]. PKM2 and PKM1 are isoforms of the gene PKM and

differ by one alternatively spliced exon. The determinants of which of the two isoforms are expressed can be directly controlled by downstream effectors of MYC activation[49], while both HIF-1α[50] and PI3K/Akt/mTORC1 activation have been shown to regulate PKM2 transcription and expression, respectively[51]. The multiple ways that PKM2 can be regulated and expressed, and its universal expression pattern, demonstrate its importance for proper cancer cell metabolism.

Clinical Successes and Failures of Metabolic Therapies

The understanding that cancers can harbor a dramatically altered metabolome from that of normal tissue suggests that this metabolome can potentially be exploited for therapeutic intervention, and in a way that could be universal across cancer types. The dependence of cancer on higher glucose levels allows for in vivo positron emission tomography (PET) imaging with radiolabeled fluoro-deoxyglucose, and would suggest that blocking the ability of the cancer cell to take up and use glucose could starve the cell. Unfortunately, clinical trials evaluating the glucose analogue, 2-deoxyglucose, produced less than encouraging results, and were halted for reason of high toxicity[52]. As such, some have suggested that targeting metabolism may only allow for a small therapeutic window.

Targeting metabolism through nucleoside pathways with agents such as 5-fluorouracil, hydroxyurea, and gemcitabine has seen greater success, although these agents have not proved curative. One specific example is methotrexate, a competitive inhibitor of dihydrofolate reductase (DHFR), which blocks the ability of the cell to synthesize the nucleotide thymidine and is a commonly used chemotherapeutic in multiple cancers including breast, head and neck, leukemia, lymphoma, lung, bone, and bladder cancers. While this anti-metabolic therapy works in multiple tumor types, it is not curative in most cases, and causes a broad array of adverse side effects, with high doses resulting in acute kidney failure and life-threating central nervous system toxicity. Here again, the clinical experience of methotrexate would suggest there is a relatively narrow therapeutic window permitted through the use of anti-metabolites.

There are some successful examples, however, where therapeutic benefit has been achieved through targeting cancer metabolism, including the observation that metformin decreases the risk of multiple cancers[53], though these data are admittedly mixed and mainly retrospective in general. Metformin is thought to work by inhibiting gluconeogenesis (glucose creation) through activation of AMPK (the master nutrient sensing protein in the cell) and/or by inhibiting mitochondrial complex I[52]. Activation of AMPK leads to alterations in cellular metabolism, which appear to block a cancer cell's ability to survive. AMPK is able to detect the ratio of AMP to ATP in the cell, allowing it to regulate its energy status. AMPK is activated by LKB1 and, in turn, activates the TSC1/2 proteins leading to suppression of mTORC1 function.

While these retroactive studies suggest a potential action of metformin, no trials have been completed to demonstrate efficacy once tumors have become established. Interestingly, targeting mTORC1 through the use of targeted agents (e.g., rapamycin and rapamycin analogues such as everolimus (Afinitor; NVS) and temsirolimus (Torisel; PFE)) have proven efficacious in a relatively small number of cancers, even though most tumors have upregulated mTORC1 function[52]. Metformin is commonly used in the management of Type II diabetes, particularly for those who are overweight or obese. As obesity rates continue to rise and the relationship to increased risk of cancer is reinforced, metformin has the potential to become increasingly important tool in the oncologist's tool kit.

When looked at in a broad fashion, metabolic agents may not be able to treat a huge range of cancers irrespective of their underlying genetic abnormalities even though the same metabolic pathways are upregulated, and instead need to be more focused on which metabolic requirements/dependencies exist. This hypothesis is reinforced based on what we know for the rapamycin analogue mTOR inhibitor Afinitor, which works only in certain cancers (e.g., advanced kidney cancer, subependymal giant cell astrocytoma, and certain pancreatic neuroendocrine tumors). The most dramatic result was found where patients who harbor a mutation in TSC1 are sensitive to treatment with Afinitor, and can go into full remission[54]. This might be the key to proper metabolic therapy, where mutations confer loss of flexibility to the metabolic pathway, creating a synthetic lethal relationship.

Understanding which tumors have specific metabolic dependences is further exemplified by treatment of pediatric acute lymphoblastic leukemia (ALL) with L-asparaginase in combination with chemotherapy. L-asparaginase depletes the blood of asparagine, which in turn prevents the tumor from taking up asparagine from the blood[48,52]. The mechanism of action for why L-asparaginase works remains to be fully understood, but the success of this therapy together with that of Afinitor suggests hope for targeted metabolic therapy.

Potential of Targeted Metabolic Intervention

Success in targeted therapy development in cancer is dictated in large by the ability to first identify the specific oncogenic drivers for a given tumor, the paragon example being the Bcr-Abl fusion gene and development of Gleevec for CML. Given the flexibility and redundancy held within the various metabolic pathways outlined thus far, the greatest opportunities for targeted metabolic intervention lie wherever there is a loss of such flexibility. This hypothesis is supported by Afinitor's efficacy in patients with mutated TSC1 protein and, presumably, aberrant TSC1/2 complex function. When TSC1/2 was no longer functional, neither AMPK nor Akt are able to regulate mTORC1 activity. Using this paradigm as an example, understanding which tumors have an addiction to metabolic pathways and how these pathways help the cancer grow and/or survive will be key to selecting the proper therapeutic intervention.

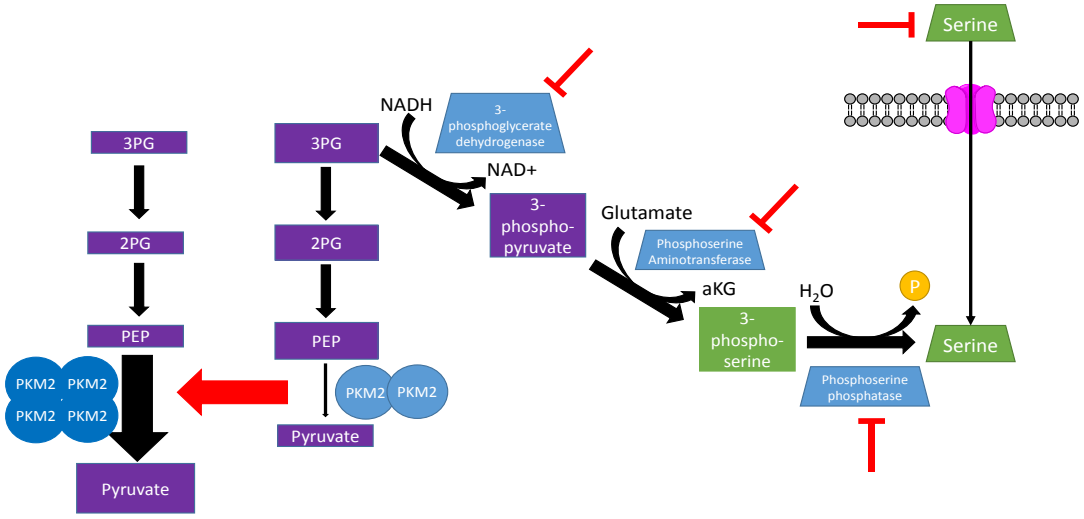
Serine metabolism. One method of identifying dependences can be done through looking at how different metabolic enzymes are expressed and utilized. For example, PKM2 is overexpressed as an inactive dimer in tumors. Serine can be generated in the cell either through transport from outside the cell, metabolism of glucose to form 3-phosphoglycerate, or by salvage pathways. Serine metabolism has come to the forefront of cancer research due to the near universal expression of PKM2 in cancer cells[46]. In the proposed mechanism, PKM2 as a dimer is inefficient at converting PEP into pyruvate and, as a consequence, backup metabolite intermediates produced during glycolysis are used for biomass production[55]. Overexpression of PKM2 induces tetramer formation, and permits efficient conversion of glucose into pyruvate, blocking the cell's ability to create biomass de novo (Figure 26 left side, activator is red arrow). Recent work has shown that small molecule activators of PKM2 can be developed[56,57] that are capable of decreasing tumor cell proliferation. Specifically, modulation PKM2 complex formation through the addition of targeted small molecules, from an inactive dimer to an active tetramer, has been shown to upregulate serine transporter activity in order to meet the high level serine requirements for continual growth[56]. However, it is only when both axes of serine metabolism (e.g., glycolytic intermediates feeding into serine biosynthesis and serine import) are blocked that cancer cells die.

This model suggests that the multiple arms of serine metabolism are not lost during tumorigenesis and that the way in which nutrients are shuttled determines the predominant pathway. In contrast, serine deprivation alone is able to induce stress and cell death in the context of TP53 loss[58]. If cancer cells contain functional TP53, serine deprivation and subsequent cell death are staved off by upregulation of serine synthesis, suppressed glycolysis, and increased flux through the TCA cycle. Just as PKM2 and TP53 alterations support serine biosynthesis as an attractive target, amplification of 3-phosphoglycerate dehydrogenase (3PGDH) in breast cancers suggest tumor reliance on this enzyme for sustained growth[59,60]. Knockdown of 3PGDH in the cancer cell lines where it is amplified or overexpressed has been shown to decrease viability, underscoring the importance of this pathway to breast cancer growth.

Therapies targeting the serine synthesis, either through activation of PKM2 or inhibition of serine biosynthesis (3-phosphglycerate dehydrogenase, phosphoserine-aminotransferase 1, or phosphoserine phosphatase), or serine deprivation enzymes (see Figure 6 red arrows and red inhibitor bars), can have different effects depending on the background genetics of the cell; in the right context, targeted serine modulation may be a relevant therapy. However, the clinical experience using this line of therapy is rather limited. Agios Pharmaceuticals recently published preclinical results with its PKM2 activator molecule, showing that combined serine depletion and PKM2 activation is required to induce toxicity[56], and that PKM2 activators can decrease tumor cell proliferation[57].

Preclinical work using PKM2-activating molecule by Astex Pharmaceuticals (now Otsuka; 4578-TO) also shows a decrease in lung adenocarcinoma xenograft growth upon treatment[61]. Similarly, Pfizer has published work describing 2-((1H-benzo[d]imidazol-1-yl)methyl)-4H-pyrido[1,2-a]pyrimidin-4-ones as potential PKM2 activators, although results have suggested that activation of PKM2 by itself is not sufficient to deleteriously alter cellular metabolism[62]. Dynamix Pharmaceuticals (private[63]) and Tolero Pharmaceuticals (private) both have a small molecule activator of PKM2, further to underscoring the perception that PKM2 holds significant potential either through selective target inhibition or through combination approaches. While PKM2 activators have been a hot area of drug development, the recent contributions of amplified 3PGDH in breast cancer highlight the appeal of other members of the serine biosynthetic pathway for pharmacologic intervention.

FIGURE 26. Mediators of Serine Biosynthesis Are Attractive Drug Targets

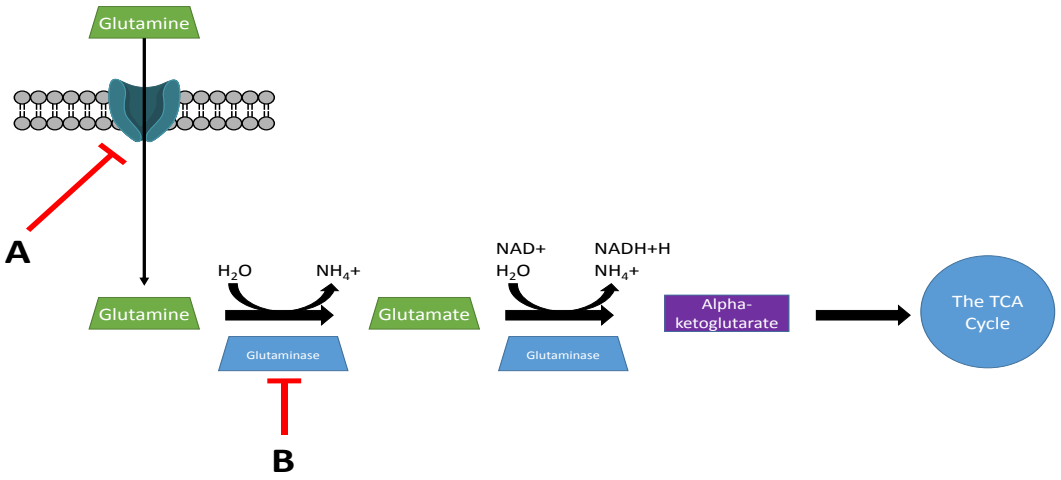


Source: JMP Securities LLC

Glutamine synthesis. Like serine deprivation, glutamine deprivation, caused by removal of glutamine from media, in the presence of MYC activation has been shown to lead to the induction of cell death[24,25,64,65]. While the cell death can be rescued with the addition of pyruvate or oxaloacetate, cell cycle arrest cannot. Glutamine addiction remains present even in the absence of MYC signaling, suggesting a permanent rewiring of the cancer with glutamine metabolism a critical node for survival. While MYC activation clearly alters the cancer cell's need for glutamine, glutamine also supports mutant KRAS mediated pancreatic cancer growth[66]. In pancreatic ductal adenocarcinoma, glutamine is converted to oxaloacetate, and then into malate, thereby increasing NADPH levels and maintaining the proper cellular redox state. Suppression of any enzyme or transporter in the glutamine pathway leads to suppression of growth in the presence of oncogenic KRAS. This could be due to the activity of oncogenic KRAS, where it has been shown that oncogenic KRAS uncouples glycolysis from the TCA cycle and forces cells to instead rely more heavily on glutamine flux through the TCA cycle[67]. A second oncogenic context that could lead to glutamine dependence is mTORC1 hyperactivation. It has been shown that hyperactivity of mTORC1 results in dramatically stimulated glutamine metabolism, and targeting both glucose and glutamine metabolism induces in cancer cell death[68].

Exogenous glutamine is transported into cells by active transporters such as ASCT2 and SLC38A1, both of which can be targeted by small molecules (Figure 27). Once glutamine has been transported into the cell, it is hydrolyzed by glutaminase into glutamate, which is then metabolized into aKG (Figure 27). Glutaminase can be expressed by either the GSL1 or GSL2 gene, and MYC potentiates the expression of GSL1[24,25]. Changes in glutaminase expression make it an interesting target for pharmacological inhibition, and pre-clinical data suggest that inhibiting glutaminase could lead to a clinical response[69-71].

FIGURE 27. Targets Mediating Glutamine Metabolism Blunt Tumor Growth



Source: JMP Securities LLC

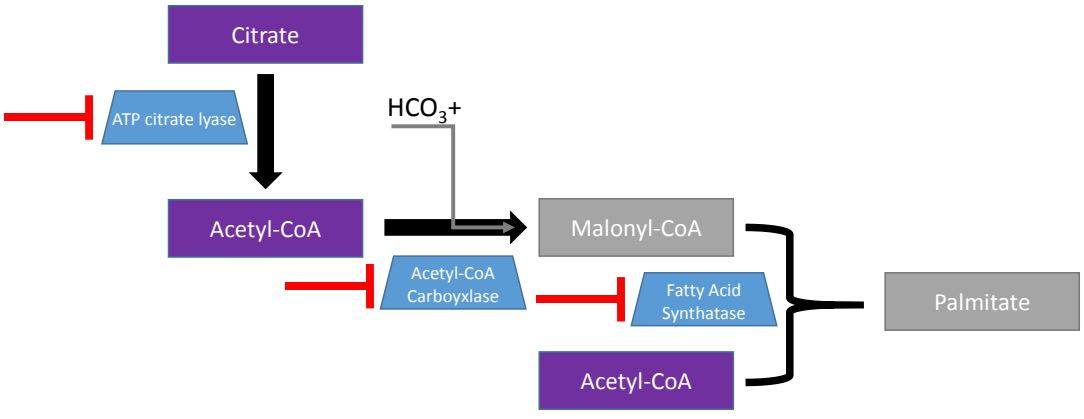
Lipid synthesis. Nutrient dependence in cancer cells is not limited to amino acids like serine, glutamine, and asparagine (pediatric ALL), but rather extends to lipids. When PI3K/Akt, mTORC1, MYC, or HIF-1α are deregulated in cancer, each activates sterol regulatory element binding proteins (SREBPs) that induce fatty acid synthesis and cholesterol biosynthesis. De novo fatty acid synthesis is carried out by three enzymes: ATP-citrate lyase (ACL), acetyl-CoA carboxylase (ACC), and fatty acid synthase (FASN) (Figure 28), which convert acetyl-CoA into long carbon chains via the use of NADPH.

All three enzymes are aberrantly altered in cancer, which should not be surprising given the important role fatty acids play in membrane structure, organization, signaling, and energy production[74,75]. The importance of fatty acid synthesis to cancer cell survival was initially made clear through pre-clinical studies showing that downregulation of ACL (by knockdown or small molecule inhibition) caused a decrease in tumor cell survival[76,77]. While these results could connote a general lipid dependence across all cancer cells, it appears that cells with low basal levels of reactive oxygen species and phosphorylated AMPK are more likely to respond to ACL inhibition[78].

Interestingly, ACC and FASN inhibition can also negatively impact the growth of tumor cells when either enzyme is inhibited in pre-clinical models[79,80]. When the tumor suppressors TSC2 and TP53 are deleted, cells die in response to lipid depletion while TSC2 intact cells do not[81]. This finding was attributed to mTORC1 dysregulation in the context of TSC2. Importantly, mTORC1 activation by itself is not enough to confer desaturated lipid dependence. Whether or not TSC1 loss or LKB1 mutation (proteins that are epistatic with TSC2) confer lipid dependence remains to be seen. The uptake and metabolism of certain lipids might be required under specific genetic situations, and de novo synthesis might also be required for cancer growth. In addition, while it seems that multiple cancers depend on these enzymes for survival, understanding the right context for dependence should maximize their success in the clinic, in our view.

Cancer drug development efforts that have attempted to exploit fatty acid synthesis machinery have centered on three enzymes in particular (Figure 28, red bars), including ATP citrate lyase (ACL; (targeted by the small molecule inhibitor SB-204990 from GSK), acetyl-CoA carboxylase (ACC), and fatty acid synthetase (FASN; targeted by the GSK837149A, also from GSK)[82]. It should be noted, however, that while pre-clinical studies have suggested inhibitors of these enzymes can suppress tumor growth, they have yet to be tested in the clinical setting. Other inhibitors include cerulenin, an antifungal antibiotic, and orlistat, the bile acid sequestrant developed by Roche. As of yet, there has been no fatty acid synthesis inhibitors that have made it to the clinic, even though multiple academic labs and companies have developed small molecules targeting this pathway. In animal studies, a major side effect was rapid weight loss due to these inhibitors, so it remains to be seen if these drugs will have the global toxicity that was seen with 2DG or they are better tolerated.

FIGURE 28. Potential Drug Targets Directed at Fatty Acid Synthesis Inhibition



Source: JMP Securities LLC

Lactate metabolism. Glucose metabolism that shuttles mainly through glycolysis and lactate fermentation ("The Warburg Effect") can lead to a buildup of lactate due to the conversion of pyruvate to lactate to recycle NADH. The conversion of pyruvate to lactate is reversibly driven by lactate dehydrogenase A (LDHA) or lactate dehydrogenase B (LDHB). Recent work has shown that cancer cells that are more dependent on glycolysis undergo cell death due to oxidative stress and altered cellular energy metabolism when LDHA is inhibited[83,84]. LDHA's expression is regulated by MYC activation and/or HIF-1α activation.

While a cancer cell produces lactate, it can also take it up for conversion back into pyruvate. This phenomenon highlights the heterogeneity of metabolism in a cancer cell. Cells under conditions of low oxygen (hypoxia) depend highly on glycolysis, while those under conditions of high oxygen (normoxia) depend more on the TCA cycle. Oxygen concentration can vary significantly within a tumor, leading to diverse metabolic functions within the same tumor. Hypoxic tumor cells take up large amounts of glucose and secrete large amounts of lactate, while normoxic cells take up lactate by monocarboxylate transporter 1 (MCT1) and convert it into pyruvate via LDHB, which then preferentially converts lactate to pyruvate. Inhibiting MCT1 induces tumor cells, in normoxia, to switch to glycolysis from the TCA cycle, and the tumor cells, in hypoxia, to undergo apoptosis, due to glucose deprivation that is caused by the glycolytic normoxic tumor cells. Inhibiting MCT1 has been shown to cause tumor shrinkage, allowing for the rest of the glycolytic normoxic cells to be targeted by radiation[85]. This type of therapy would require an intact hypoxia sensing mechanism, because if the cells are hypoxic to begin with (e.g., due to mutation of VHL causing stabilization of HIF-1α irrespective of oxygen status), inhibiting MCT1 might not be efficacious. Targeting MCT1 in endothelial cells decreased the ability of these cells to upregulate HIF-1α activation induced by lactate[86], and therefore decrease angiogenesis. This could highlight the importance of using MCT1 inhibition in combination with other therapies. AstraZeneca has a promising MCT1 inhibitor in preclinical development.

Targeting autophagy. The role of autophagy in cancer is contradictory. Autophagy has been found to promote tumorigenesis in some instances and prevent tumorigenesis in others[87]. Yet, autophagy plays a large role in protecting a cancer cell from itself by recycling proteins, lipids, and organelles to protect the cell from the deregulated metabolism found in the many cancer cells[88]. Proteins that are instrumental in the autophagic process are highly altered both by loss of expression and gain of expression in tumors and, by extension, it has been found to play a role in both pro-survival signals and pro-death signals in the tumor cell[89]. What this means is that the right context would need to be uncovered where inhibitors or inducers of autophagy would be therapeutically relevant.

One way of modulating autophagy is by targeting the signals upstream including AMPK, PI3K/Akt, and mTORC1. Clinical trials using inhibitors of the PI3K pathway, of Akt, and/or mTOR are already being conducted. While this is in the context of inhibiting the signals, these inhibitors would also activate the autophagic machinery due to the loss of suppression by mTORC1. AMPK activators, like metformin, would also induce the autophagic machinery. On the other hand, inhibiting autophagy has studied in the clinic using chloroquine and its analog hydroxychloroquine, which seems to be well tolerated, and is being used in combination with other therapies[90,91].

Combination Approaches with Metabolic Therapies

The clinical successes of metabolic therapy for the most part come in the form of combination therapy. L-asparaginase is used to treat pediatric ALL in combination with prednisolone/dexamethasone, and vincristine and methotrexate can be used alone and in combination with other agents. The promise of metabolic therapy might not be fully realized until it is used in combination with other therapies. In the case of MCT1 targeting (see above), the most dramatic tumor regression response is seen with radiation therapy, as pharmacologic inhibition of MCT1 itself is not sufficient to clear the tumor. This may be due to several factors, including switching the slow growing OXPHOS cells to faster growing glycolytic cells, and multi-drug resistance. When a therapy debulks a tumor, the tumor eventually regrows, and this has been postulated to be caused by slow growing cells that depend more on OXPHOS than glycolysis. This resistance can be attributed to both targeted kinase therapy and chemotherapy agents. When the OXPHOS population is targeted with agents that broadly disrupt mitochondria function, the response to targeted kinase and chemotherapy is dramatically enhanced[92].

While broad targeting of the mitochondria leads to sensitization to multi-modality therapies, understanding the interplay between oncogenes and the specific axis allows for more selective inhibition. For example, the mitochondrial gatekeeper pyruvate dehydrogenase is phosphorylated by the inhibitor enzyme pyruvate dehydrogenase kinase 1 (PDK1), and in the absence of this kinase, BRAF V600E mutations lead to oncogene induced senescence, forcing the cell to undergo cell cycle arrest and apoptosis[93]. This enzyme also seems to be responsible for maintaining a small population of cells that are resistant to targeted BRAF inhibition. This population can be completely depleted with inhibition of PDK1, showing the potential of a targeted metabolic therapy combined with a targeted kinase therapy.

Conclusion

While metabolic targeting as a viable clinical therapy has seen failures and successes, it still remains an active area of research with high promise to make a significant impact on cancer therapy. Understanding the exact genetic context that leads to dependencies in specific metabolic pathways will allow for better targeted treatment either alone, in combination with established chemotherapeutics, or in combination with targeted kinase agents. The attractiveness of the metabolic space should be viewed in the same way that targeted kinase therapy has evolved.

In our view, to date, there does not appear to be a magic bullet that allows for a large population of a specific cancer histology to be treated with a metabolic therapy, but instead a small subset of patients with the right genetic lesions that might be histology agnostic who would benefit from metabolic therapies. What we believe needs to be determined before long-term success with metabolically targeted therapies, is what lesions lead to loss of metabolic flexibility and/or metabolic addition. If glutamine metabolism is targeted, but the cancer cell still retains the ability to shunt TCA intermediates to salvage the loss of glutamine, the targeted therapy will most likely fail. If, instead, a cell has lost the ability to regenerate glutamine due to metabolic demands/dependencies on that pathway, then the targeted therapy has a higher chance of success. Targeting metabolic addiction should mirror the lessons learned from targeting kinase addiction for maximum success, in our view.

APPENDIX C – OVERVIEW OF NORMAL CELL METABOLIC MECHANISMS

In order to fully understand why a cancer alters its metabolic program, it is first important to understand how a normal cell carries out energy and biomass production. Metabolism for the cell compromises both anabolic (building) processes and catabolic (breaking down) processes (Figure 29). The biomass required for normal cell homeostasis, in the form of sugars (mainly glucose), nucleic acids, amino acids, lipids, and their respective derivatives, can either be absorbed outside the cell, specifically for those molecules that cannot be synthesized by the cell, scavenged from pathway intermediates or even from the cell itself (autophagy), or via de novo synthesis of the necessary biomass. As more research becomes available, it is becoming abundantly clear how interconnected these pathways become.

Normal energy production. Generally, a normal cell takes up glucose where it is irreversibly phosphorylated into glucose-6-phosphate by hexokinase, and further metabolized to produce pyruvate. The flux of one molecule of glucose through glycolysis produces the energy molecule, adenosine triphosphate (ATP), the electron transporter, nicotinamide adenine dinucleotide (NADH,H+), and pyruvate. To increase the amount of energy produced, pyruvate is converted to acetyl-CoA, by pyruvate dehydrogenase – generating NADH, and shuttled into the citric acid cycle (the TCA cycle). The acetyl group from acetyl-CoA is combined with oxaloacetate to generate citrate, and citrate then proceeds into the TCA cycle. Here, electrons are continually stripped off of the intermediates produced by the metabolism of citrate back into oxaloacetate and transferred to NAD+ and another electron acceptor, flavin adenine dinucleotide (FAD+). The reduced forms of NAD+, NADH, and FAD+, FADH2, which are generated by the TCA cycle are used to produce ATP by the electron transport chain (ETC), where the electrons are transferred to a series of electronegative acceptor proteins with oxygen being the final acceptor of the electrons, and this transfer drives the production of ATP. The TCA cycle and the ECT are collectively known as OXPHOS. For a schematic representation of OXPHOS, see Figure 29 with the OXPHOS and its intermediates colored in purple.

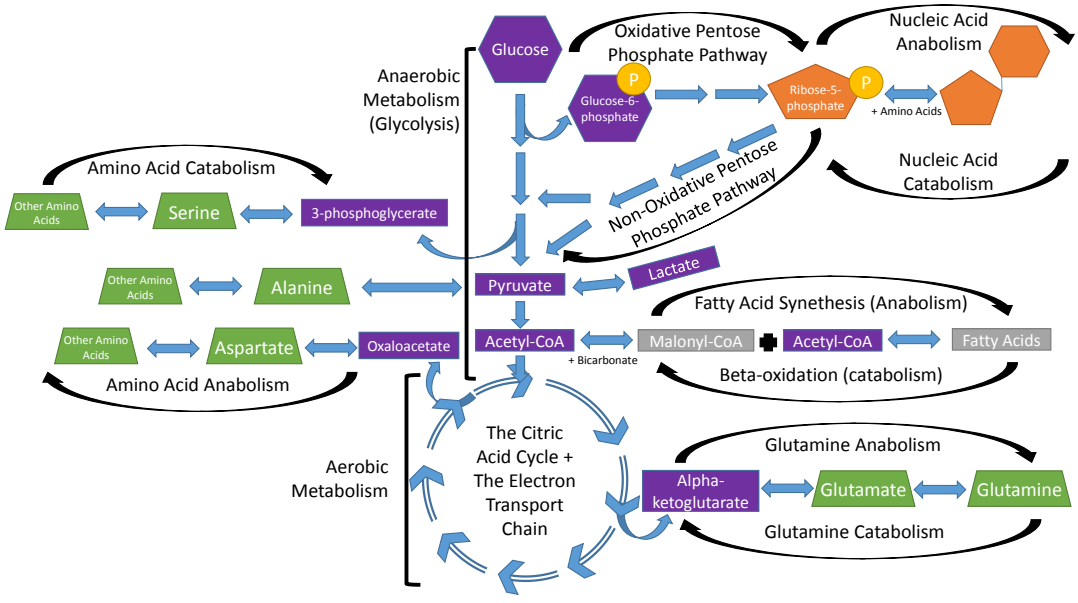
Nucleic acid metabolism. The synthesis of nucleic acids requires a pentose sugar that serves as the backbone for the molecule, and can be generated through the pentose phosphate pathway (PPP) by metabolizing glucose-6-phosphate from glycolysis into ribose-5-phosphate. The pathway can be broken into two phases, an oxidative phase where ribose-5-phosphate is produced and a non-oxidative phase where ribose-5-phosphate is metabolized to produce intermediates that can be subsequently used in glycolysis: fructose-6-phosphate and glyceraldehyde-3-phosphate (see Figure 29, upper right side, orange metabolites). Ribose-5-phosphate along with glycine, aspartate, and glutamate are used in the de novo synthesis of the purine nucleotides, and ribose-5-phosphate, aspartate, and glutamate are used in the de novo synthesis of the pyrimidine nucleotides. Besides synthesizing nucleic acids, the normal cell can either take up nucleic acids from the surrounding milieu, or can scavenge them from the breakdown of DNA and RNA in the cell.

Besides sharing metabolite products that can be transferred from the PPP to glycolysis and vice versa, both pathways generate reducing agents; glycolysis produces NADH from NAD+ (nicotinamide adenine dinucleotide) while the PPP produces NADPH from NADP+ (nicotinamide adenine dinucleotide phosphate). The main role of these two reducing agents are to act as electron shuttles and are used as cofactors in reducing-oxidation (redox) reactions with NADH functioning primarily in OXPHOS, NADPH in anabolism, and both working to maintain the proper redox status of the cell.

Amino acid metabolism. The synthesis of amino acids and their derivatives begins with the carbon backbone coming from glycolysis and the TCA cycle (see Figure 29, left side and bottom right side, with metabolites colored in green). Serine is synthesized from 3-phosphoglycerate (glycolysis) and alanine and aspartate can be synthesized by transanimation of pyruvate (glycolysis and the TCA cycle) and oxaloacetate (the TCA cycle), respectively. Glutamate acts as the nitrogen donor and glutamine can act as another nitrogen donor to convert aspartate to asparagine. Glutamate can be synthesized from alpha-ketoglutarate (α-KG) (the TCA cycle) and further conversion by glutaminase gives rise to glutamine (see Figure 29, green metabolites, bottom right). Glutamine is the major nitrogen donor in the cell, and therefore the central molecule for nitrogen metabolism and is tightly regulated by glutaminase. The energy producing pathways can feed into amino acid anabolism, and amino acid catabolism can feed back into the energy pathways. Glutamine that is transported into the cell can be converted to glutamate which is further converted to α-KG, feeding into the TCA cycle. Many of the synthesis reactions can be reversed to produce the necessary intermediates for glycolysis and the TCA cycle, which are then used to synthesize the amino acids, allowing for energy production under conditions of low glucose.

Lipid Metabolism. NADPH is a key factor in fatty acid synthesis (FAS) where acetyl-CoA, derived from glycolysis, the TCA cycle, fatty acid degradation, or amino acid degradation, is added to elongating chains of carbon to form the necessary fatty acids required by the cell. The elongating chains of carbon are initiated when one molecule of acetyl-CoA along with one molecule of bicarbonate are combined to form malonyl-CoA using ATP (see Figure 29, gray metabolites, middle right). Acetyl-CoA is further added to malonyl-CoA by an enzyme called fatty acid synthetase (FASN) that uses NADPH. The NADPH that is required can be produced from the PPP, the conversion of isocitrate into alpha-ketoglutarate by the cytosolic isocitrate dehydrogenase enzyme (IDH1), or by the conversion of malate into pyruvate by cytosolic NADP dependent malic enzyme (ME1). The metabolism of the fatty acids by beta-oxidation produces acetyl-CoA, FADH2, and NADH, all of which can feed back into OXPHOS to produce energy.

FIGURE 29. Overview and Intersection of Cellular Biosynthetic Pathways



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