August 19, 2013

OUTPERFORM

Reason for report:

INITIATION

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AGIOS PHARMACEUTICALS, INC.

Transforming Cutting-edge Science Into a Clinical Pipeline, Initiate at OP

• **Bottom Line:** We are initiating coverage of AGIO with an OP rating and $38 valuation. AGIO's strong platform in cellular metabolism has resulted in seminal discoveries which the company has been able to capitalize and translate into a full array of early clinical or late-preclinical pipeline agents targeting cancer and ultra-orphan indications of inborn errors of metabolism (IEMs).

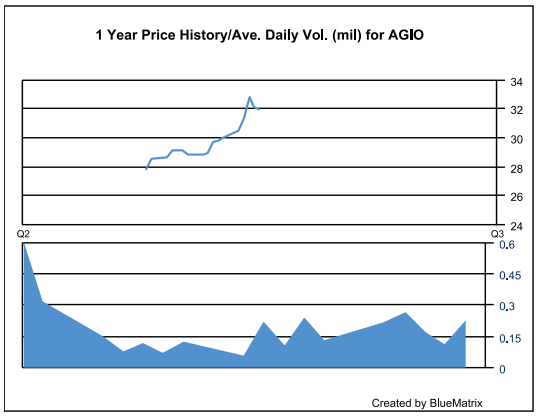
• **Transformative potential -- cancer metabolism may be a fruitful area of exploration for new cancer therapeutics.** Elevated or altered metabolic needs to support rapid growth may be an Achilles' heel for cancer cells. AGIO is a clear leader in the discipline of cancer metabolism.

• **Although we are clearly mindful that AGIO's pipeline is very early, there is very strong genetic validation as well as underlying science for the lead candidates.** The observations of single mutations in IDH1 and IDH2 (isocitrate dehydrogenase) on a single allele being associated with cancer point to gain-of-function alterations that are well suited for drug therapeutics. As AGIO pioneered the field, there does not appear to be visible competition. MEDACorp key opinion leaders expressed high interest in these compounds.

• **Strong partnership with CELG not only funds the programs but also leaves good upside including full US rights for 1 in 3 compounds.** These terms, based purely on the cancer metabolism platform with compounds still on the drawing board, are impressive and in our view provides clear validation for AGIO. Strong balance sheet of $225M pro-forma cash together with CELG partnership are expected to support AGIO beyond the end of 2016.

• **Full upside retained for ultra-orphan programs.** AGIO is leveraging its metabolism platform to target rare IEMs that we believe could provide a rapid path to market. Its lead IEM compound AG-348, appears to be able to accomplish the difficult task of activating multiple defective forms of pyruvate kinase-R and potentially provides a therapy for pyruvate kinase deficiency (PKD), a rare blood disorder.

Key Stats:	**(NASDAQ:AGIO)**
S&P 600 Health Care Index:	**1,311.61**
Price:	**$31.91**
Price Target:	$38.00
52 Week High:	$33.45
52 Week Low:	$18.00
Shares Outstanding (mil):	30.3
Market Capitalization (mil):	$966.9
Book Value/Share:	$0.16
Cash Per Share:	$7.42
Dividend (ann):	$0.00
Dividend Yield:	0.0%



Dec Yr	1Q	2Q	3Q	4Q	FY Rev	1Q	2Q	3Q	4Q	FY EPS	P/E
2012A	--	--	--	--	$25.1	--	--	--	--	($1.18)	NM
2013E	$6.3A	$6.3	$6.3	$6.3	$25.1	($0.39)A	($0.30)	($0.24)	($0.24)	($1.14)	NM
2014E	--	--	--	--	$7.3	--	--	--	--	($1.77)	NM

Source: Company Information and Leerink Partners LLC Research
Revenues in millions.

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The Healthcare Investment Bank™

Agios Pharmaceuticals

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AGIO Overview

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- Strong scientific platform on cellular metabolism for the treatment of cancer and inborn errors of metabolism (IEMs). The company has been closely involved in the cutting-edge science of cancer metabolism and made some of the key discoveries in the field.
- An early pipeline of internally discovered compounds is under development. Four compounds could potentially enter Phase I by 2014.
- CELG partnership independently validate the platform and provide cost-effective development path.
- Most advanced candidates AG-221 and AG-120 targeting mutations in the enzymes isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2). Both targets are genetically validated and mutations have been identified in acute myeloid leukemia. brain cancer, sarcoma, and biliary tract cancers.
- Third candidate AG-348 targets the ultra-orphan blood disorder of pyruvate kinase deficiency which is an IEM manifested by severe hemolysis.
- Key financials: 30.3M shares, ~$225M cash ($7.42/share).

Investment Thesis

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- **World-class scientific engine.** AGIO's strong platform in cellular metabolism has resulted in seminal discoveries which the company has been able to capitalize and translate into a full array of early clinical or late-preclinical pipeline agents targeting cancer and ultra-orphan indications of inborn errors of metabolism (IEMs).
- **Cancer metabolism may be a fruitful area of exploration for new cancer therapeutics.** Elevated or altered metabolic needs to support rapid growth may be an Achilles' heel for cancer cells. AGIO is a clear leader in the discipline of cancer metabolism.
- **Although we are clearly mindful that AGIO's pipeline is very early, there is very strong genetic validation for the lead candidates.** The observations of single mutations in IDH1 and IDH2 (isocitrate dehydrogenase) on a single allele being associated with cancer point to gain of function alterations that are well suited for drug therapeutics. As AGIO pioneered the field, there does not appear to be visible competition. MEDACorp key opinion leaders expressed high interest in these compounds.

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- **Full upside retained for ultra-orphan programs.** AGIO is leveraging its metabolism platform to target rare IEMs that we believe could provide a rapid path to market. Its lead IEM compound AG-348, appears to be able to accomplish the difficult task of activating multiple defective forms of pyruvate kinase-R and potentially provides a therapy for pyruvate kinase deficiency (PKD), a rare blood disorder.

Valuation

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- We value AGIO at $38 per share based on NPV and sum of the parts methodology.
- We assume AGIO's IDH2 inhibitors launch starting in 2018 and reach 45% peak penetration of total IDH2 market in 2022. We assume IDH1 inhibitors launch starting in 2019 in the US and 2020 in EU, and reach 45% peak penetration of total IDH1 market in 2023 and 2024, respectively. We also assume AGIO's PKR activator launches in 2019 in the US and 2020 in EU reaching 50% peaking penetration in 2023 and 2024, respectively. Our royalty assumption is 10-13% for IDH2 w/w sales and IDH1 OUS sales.
- We discount our estimates projections by assumed probability of success of 20% for IDH1, 25% for IDH2 and 15% for PKR. Our projection for probability weighted sales reach $395M and royalties reach $61M by 2034.
- We include $500M valuation for the platform and other pipeline, and estimated $146M cash at YE:14.

Risks to Valuation

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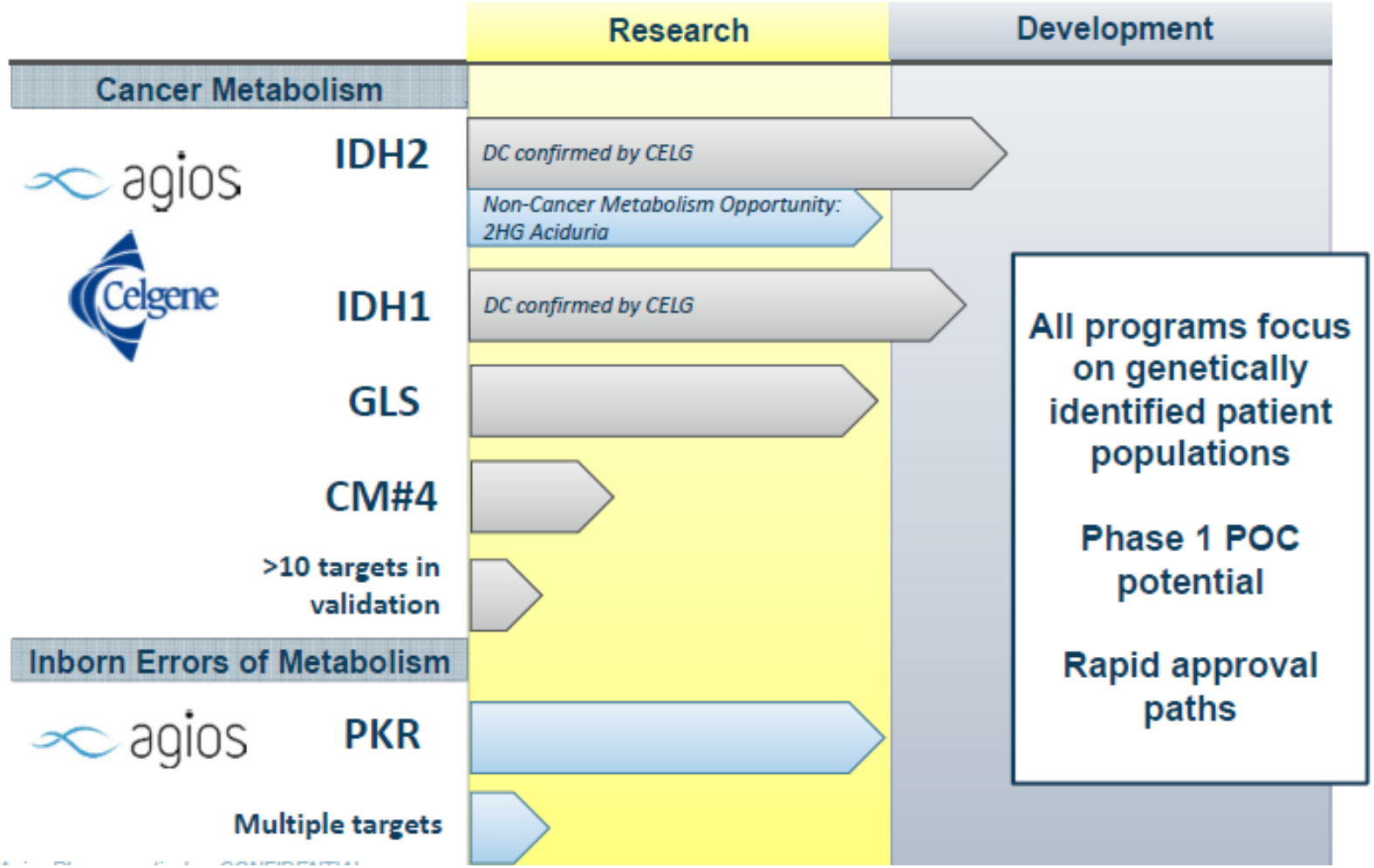
- All pipeline assets are still in early-stage clinical or preclinical development and many hurdles remain.
- AGIO's agents have been all first-in-class. Clinical toxicity and efficacy of Agios compounds as well as proof of principle remain to be established.
- AGIO had an estimated pro forma cash of ~$225M (including IPO proceeds) at the end of 1Q:13. We believe this could be sufficient to fund operations beyond the end of 2016 without assuming the renewal of CELG collaboration, although it is likely that additional funding will be required before turning profitable.

AGIO – Internally Discovered Pipeline



IDH – isocitrate dehydrogenase; GLS – glutaminase; PKR – pyruvate kinase R; POC – proof of concept

Source: Company Reports and Leerink Swann

Product Candidates

Drug	Status	Note
AG-221 (IDH2 inhibitor)	Phase I	IND filed in June, 2013. Phase I dose escalation study in advanced hematologic malignancies with an IDH2 mutation open for enrollment in Aug, 2013.
AG-120 (IDH1 inhibitor)	Preclinical	IND filing in 1Q:14
AG-348 (PKR activator)	Preclinical	IND filing in 2014
GLS (Glutaminase inhibitor)	Preclinical	IND filing in 2014

IDH – isocitrate dehydrogenase; GLS – glutaminase; PKR – pyruvate kinase R

Source: Company reports and Leerink Swann

Key Expected Events – Data News Flow
Clinical Data Starting in 2H:14

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Compound	Timing	Event
AG-221 (IDH2)	2H:13	Pre-IND discussion with FDA in D2HG aciduria (D2HGA)
	2H:13	Ongoing Phase I dose escalation trial in advanced hematologic malignancies with an IDH2 mutation
	4Q:13	Phase I initiation in solid tumors
AG-120 (IDH1)	1Q:14	IND filing
AG-348 (PKR activator)	2014	IND filing
GLS (Glutaminase inhibitor)	2014	IND filing

IDH – isocitrate dehydrogenase; GLS – glutaminase; PKR – pyruvate kinase R; D2HGA – D-2 hydroxyglutaric aciduria

Source: Company reports and Leerink Swann

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KEY INVESTMENT CONSIDERATIONS

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TARGETING ELEVATED AND ABNORMAL METABOLISM IN CANCER IS AN IMPORTANT AVENUE FOR DEVELOPING NEW CANCER THERAPEUTICS

Cancer cells are markedly different from normal cells in their metabolism

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- **Growth needs lead to elevated metabolic requirement.** Cancer cells have greater needs for energy and synthesis of building blocks.
- **Warburg effect establishes one of the earliest examples of altered metabolism in cancer.** Studies from carcinoma slices from rats and humans suggested an increased uptake of glucose in cancer cells vs. normal tissues and metabolize through oxygen-independent aerobic glycolysis vs. more efficient oxygen-dependent oxidative phosphorylation. This phenomenon is known as Warburg effect, which suggests a fundamental change in glucose metabolism in cancer cells. The observation that tumors can outcompete surrounding tissues for glucose is the basis for FDG-PET imaging of tumors.
- **Targeting metabolism as cancer's Achilles heel.** There has been a dramatic increase in interest in therapeutically targeting metabolic pathways.
- **Agios is a pioneer and a leader in the field of cancer metabolism.**

Source: DeBerardinis et al, Cell (2012) 148:1132-1144.; Jones et al, Drug Discov Today (2012) 17:232-241; Butler et al, Cancer Res (2013) 73:2709-2717.

Metabolism in Tumors Outcompete Normal Tissue, Genetically Defined At Cellular Level

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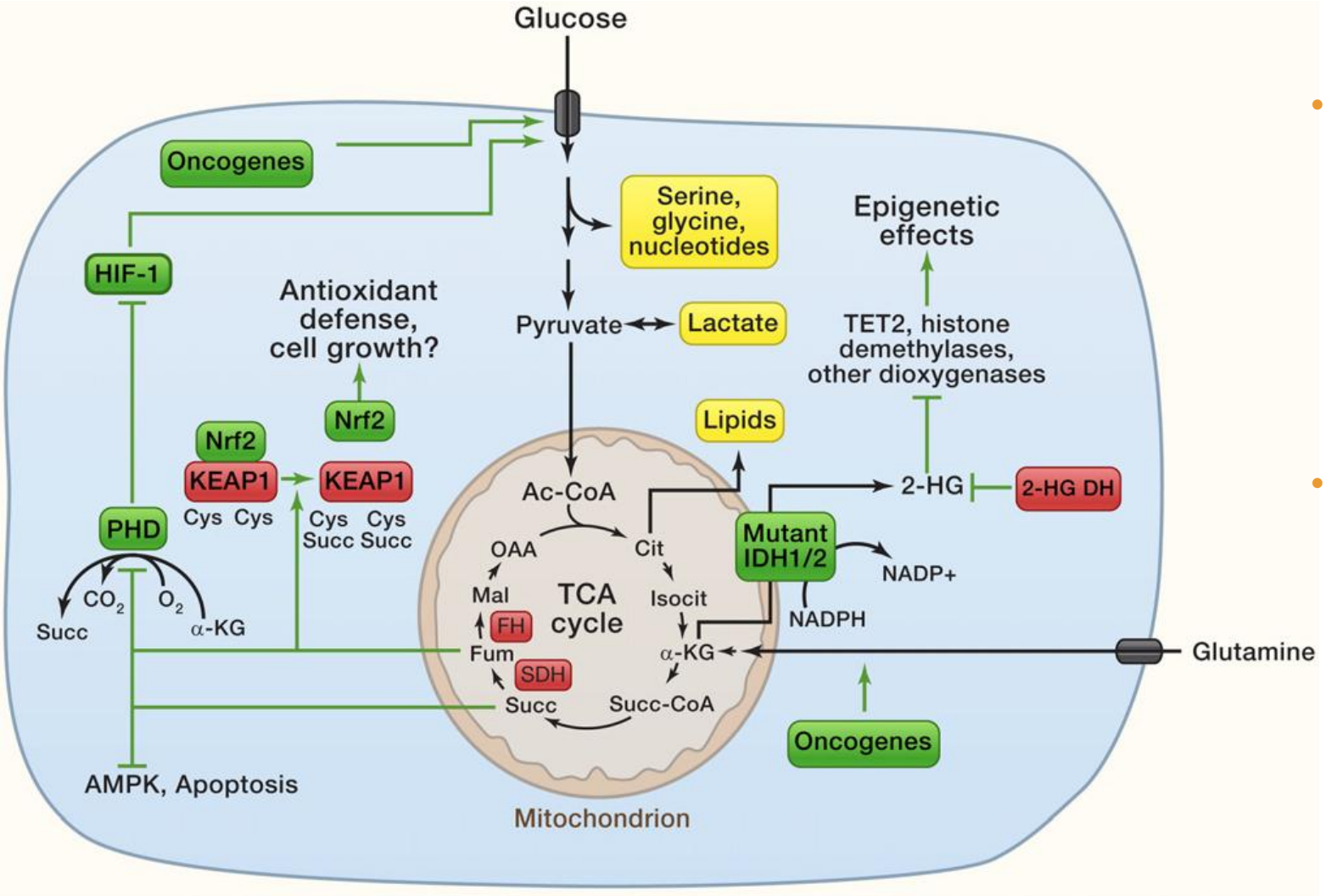
- **Metabolism reprogram in cancer.** Hypothesis that metabolism is reprogrammed in cancer cells is supported by many studies where tumors can outcompete surrounding tissues for glutamine metabolizing and fatty acid synthesis.
- **Genetically defined.** Similar to IEMs, abnormal metabolism in tumors is genetically defined. However, different from IEMs where mutations occur in germ line cells and affect whole body, mutations in cancers are generally somatically acquired and have an impact only at the cellular level.

Source: DeBerardinis et al, Cell (2012) 148:1132-1144.; Jones et al, Drug Discov Today (2012) 17:232-241; Butler et al, Cancer Res (2013) 73:2709-2717.

Cancer Cells Rely Largely On Glucose and Glutamine to Supply Metabolism



- Metabolic pools highlighted in yellow are essential for tumor cell growth.
- Potential tumor suppressors (red) and oncogenes (green) control the level of a handful of key metabolites.

Source: DeBerardinis et al, Cell (2012) 148:1132-1144.

Two Different Classes of Mutations Lead to Abnormal Metabolism in Tumor

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- Many **oncogenes and tumor suppressors** regulate glucose metabolism and mutations in these genes normally lead to enhanced energy production that support self growth.
  - For example, activation of the PI3K/Akt/mTOR pathway promotes proliferation and protein synthesis. Inhibition of mTOR leads dephosphorylation of Lipin-1, a phosphatidic acid phosphatase, leading to inhibition of lipid synthesis.
- Mutations occur directly on the **metabolic enzymes**.
  - Initial indirect evidence was observed in a subset of IEMs patients who showed an increased risk of hepatocellular carcinoma.
  - Some mutations in metabolic enzymes mimics an oncogenic state such as Glucose-6-phophatase (G6Pase) where its deficiency leads to fasting intolerance and hypoglycemia and subsequence large flux of G6Pase may provide energy source for tumor, although tumorigenesis is still unclear.
  - A handful of tumor specific metabolic mutations have been identified.

Source: DeBerardinis et al, Cell (2012) 148:1132-1144.; Jones et al, Drug Discov Today (2012) 17:232-241; Butler et al, Cancer Res (2013) 73:2709-2717.

Tumor Specific Metabolic Mutations Behave Similar to Oncogenes/Tumor Suppressors

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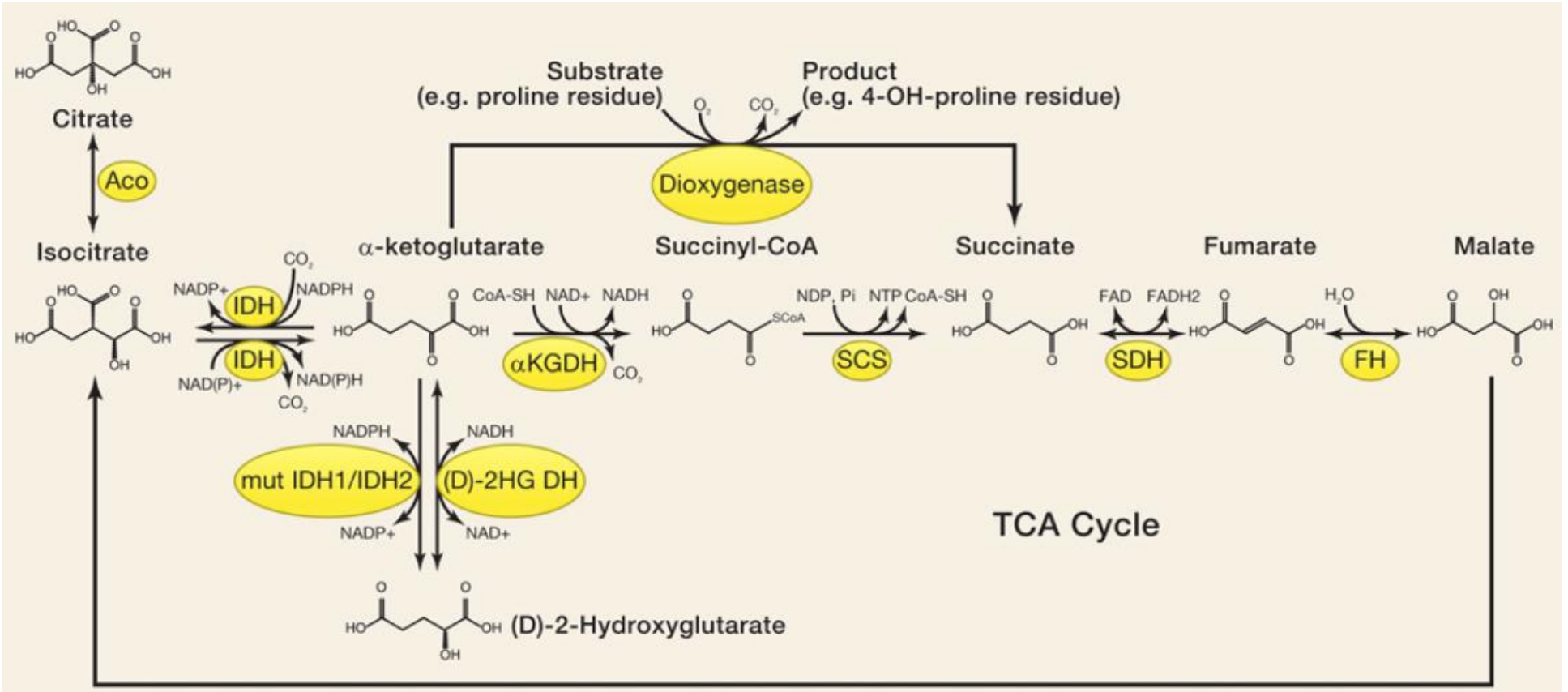
- Cancer specific metabolic mutations have been identified in TCA cycle enzymes including succinate dehydrogenase (SDH), fumarate hydratase (FH), isocitrate dehydrogenase (IDH1 and IDH2).



Source: DeBerardinis et al, Cell (2012) 148:1132-1144.

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AGIOS SCIENTISTS DISCOVERED THE ALTERED METABOLISM ASSOCIATED WITH IDH MUTATIONS AND HAS CONVERTED THIS DISCOVERY INTO IDH1/2 MUTANT INHIBITORS

Gain of Function Mutations in IDH1 and IDH2

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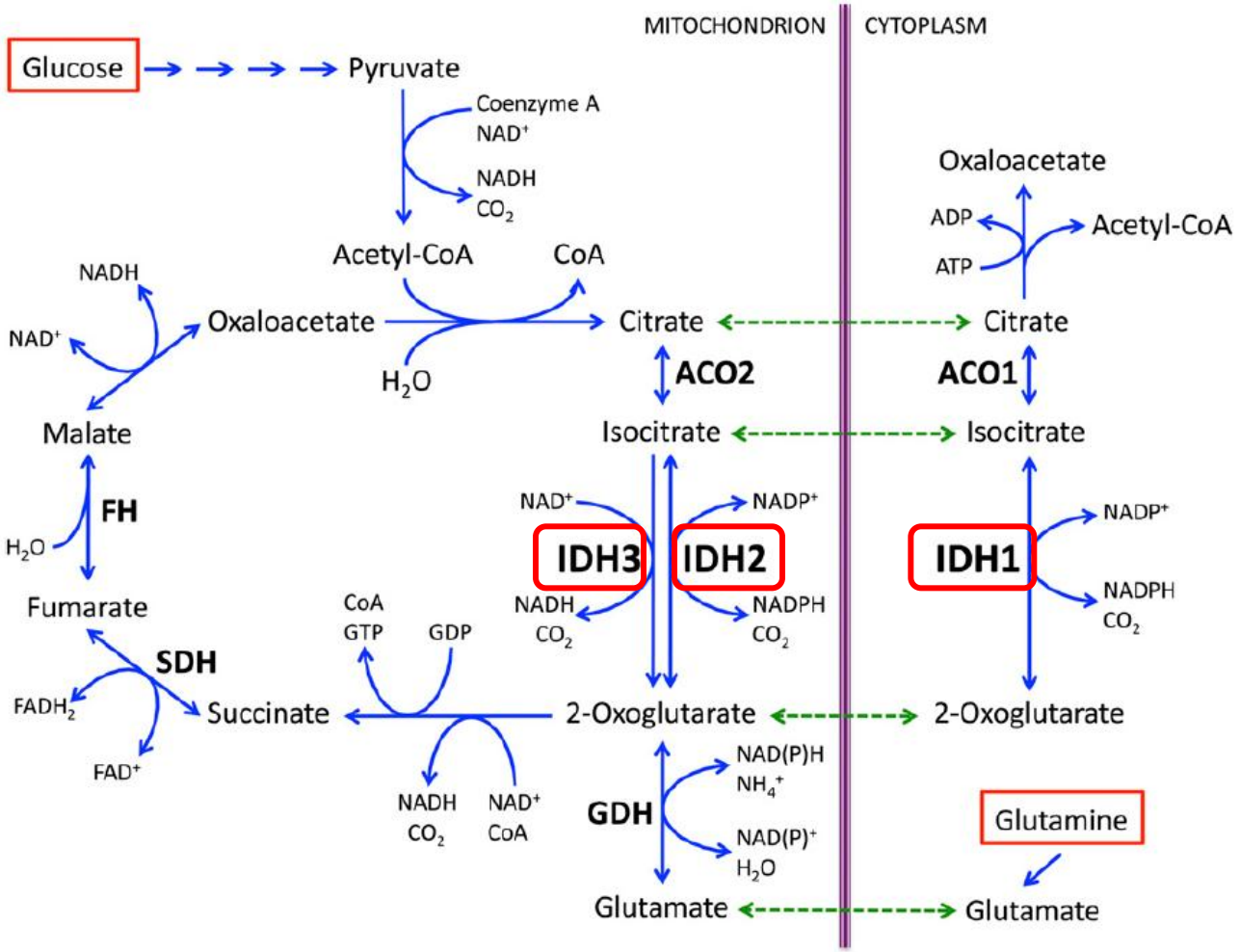
- Mutations in two isoforms of NADP+ dependent isocitrate dehydrogenase (IDH1 and IDH2) have been identified in acute myelogenous leukemia (AML) and glioma.
- In AML and glioma, normal process of isocitrate oxidation to α-ketoglutarate was blocked and large quantity of a metabolite (D)-2-hydrozyglutarate (R-2HG) was produced.
- These mutations are somatically acquired and presented in only one allele, suggesting that they are gain-of-function mutations.

Source: DeBerardinis et al, Cell (2012) 148:1132-1144.

IDH Isoforms Play Essential Role in Cellular Metabolism

- Isocitrate dehydrogenase (IDH) is an enzyme which catalyzes decarboxylation of isocitrate to produce α-ketoglutarate (also known as 2-oxoglutarate, 2-OG).



Source: Losman et al, Gene Dev (2013) 27:836-852.

IDH Isoforms Have Overlapping but Distinct Functions in Cellular Metabolism

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- IDH has three isoforms (IDH1, IDH2, and IDH3) and each one has overlapping but non-redundant role in cellular metabolism.
- **IDH1** is localized in the cytoplasm and catalyzes reversible $NADP^+$-dependent reaction. IDH1 generates non-mitochondrial NADPH, an essential antioxidant for cell proliferation and protecting cells from hypoxia. Reversibly, IDH1 catalyzes 2-OG to isocitrate, which can be further metabolized to support lipid biosynthesis.
- Both IDH2/IDH3 are localized in the mitochondria. Similar to IDH1, **IDH2** regulates energy metabolism in mitochondria by modulating the relative amount of isocitrate and 2-OG through reversible reaction. It is unclear if IDH2 contributes to flux, like IDH3, through the TCA cycle.
- **IDH3** plays a critical role in mitochondrial respiration by regulating a rate-limiting step in the TCA cycle. IDH3 catalyzes the NAD^+-dependent, irreversible reaction of isocitrate to 2-OG, which is further metabolized to succinate while NADH is used by electron transport chain to generate ATP.

Source: Losman et al, Gene Dev (2013) 27:836-852.

Somatic Acquired IDH1/IDH2 Mutations in Gliomas

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- Glioblastoma Multiforme (GBM, brain cancer) is a highly invasive tumor that is refractory to chemo and radiation therapy and currently has limited therapeutic choices.
- In an initial effort of genome screening in 22 GBM tumors, IDH1 R132 mutations have been identified in 5/6 secondary GBM but none of 16 primary GBMs. Multiple follow-up sequencing suggested R132 mutations are common in low grade malignant glioma, occurring in >70%of adult Grade 2/3 glioma and >80% of secondary GBMs.
- Majority of the Grade 2/3 glioma and secondary GBM patients (85-90%) have mutations at either R132 of IDH1 or R172 of IDH2, where R132H mutation is the most prominent form.
- Less than 10% of primary GBMs and pediatric GBMs have IDH mutations, and no IDH mutations have been identified in non-glial subtype brain tumors.

Source: Losman et al, Gene Dev (2013) 27:836-852.

Somatically Acquired IDH1/IDH2 Mutations in Acute Myeloid Leukemia (AML) and Other Myeloid Disorders

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- A mutation at R132 of IDH1 was initially identified through whole genome sequencing of one case of normal karyotype AML (NK-AML). Additional sequencing confirmed that IDH mutations are highly recurrent in clonal myeloid disorders, representing 5-20% of de novo NK-AML and 10-20% of secondary AML.
- IDH1 mutations occur mostly at R132, while IDH2 mutations are at either R140 or R172. Among all mutations, the most common mutation in NK-AML is R140Q of IDH2 (30-50%).
- IDH mutations present at lower frequency (5-10%) in chronic-phase myelodysplastic syndrome (MDS) and myeloproliferative neoplasm (MPN). IDH2 mutations (but not IDH1 mutations) are also presented in 10-40% angioimmunoblastic T-cell lymphoma (AITL); however, uncommon in other T-/B-cell lymphomas.

Source: Losman et al, Gene Dev (2013) 27:836-852.

IDH1/IDH2 Mutations in Other Solid Tumors

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- IDH mutations have been found in over 50% of **chondrosarcoma**, a cancer derived from transformed cells that produce cartilage. The most common mutation is R132C of IDH1, occurred in 40-50% patients.
- IDH mutations (mostly R132C) was found in 37/40 patients with **Ollier disease and Maffucci syndrome**, a rare pediatric non-hereditary disease characterized by multiple central cartilaginous tumors that are accompanied by soft tissue hemangiomas in Maffucci syndrome*.
- IDH mutations have been found in 10-20% of **cholangiocarcinoma**, a cancer composed of mutated epithelial cells that originated in the bile ducts, and less commonly, in **paraganglioma**, **colon cancer**, **prostate cancer** and **lung cancer**.

*Source: Losman et al, Gene Dev (2013) 27:836-852.; * Amary et al, Nat Genet (2011) 43:1262-1265.*

Mutant IDH1/IDH2 Produces R-2HG, Resulting in Gain of New Enzymatic Function

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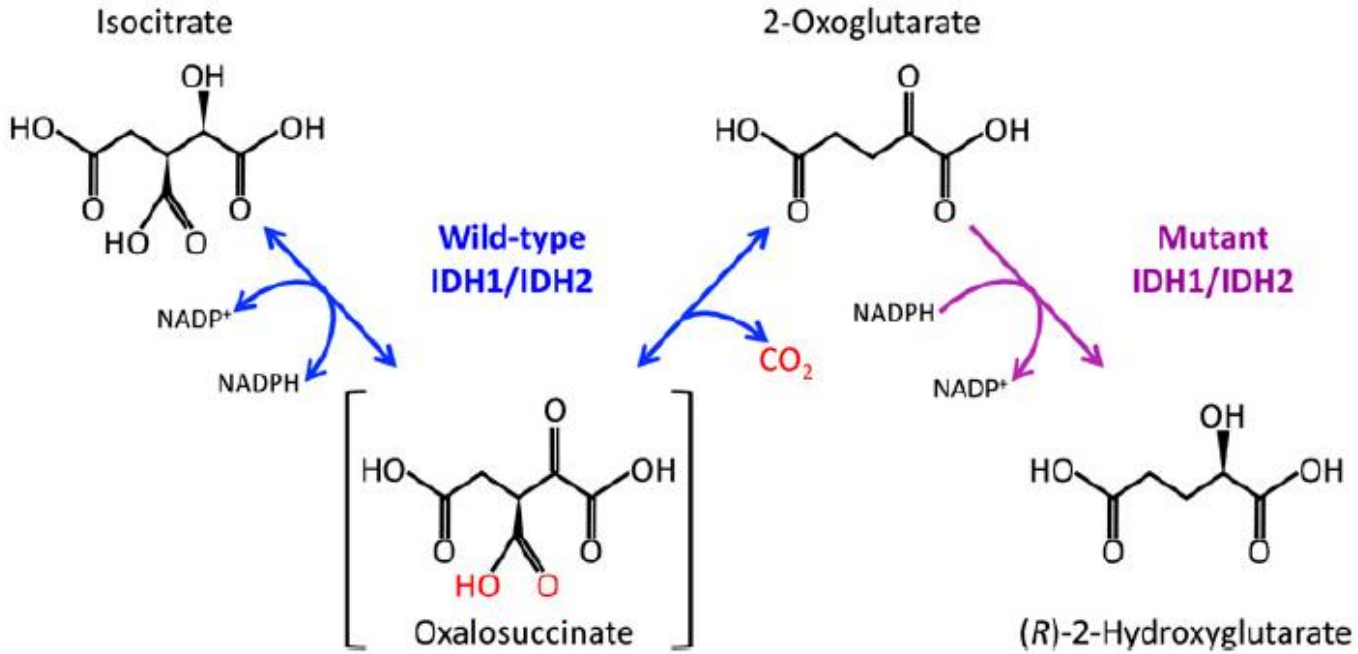
- **Wild type IDH1/IDH2** reversibly catalyzes isocitrate to the unstable intermediate oxalosuccinate where $NADP^+$ acts as the hydrogen acceptor and is reduced to NADPH. In the second step, β-carboxyl group was released as CO2, producing 2-oxoglutartate (2-OG).
- **AGIO scientists made the discovery that mutant IDH1/IDH2 produce (R)-2-hydroxyglurate (R-2HG).** It is a one-step, irreversible reaction where NADPH is oxidized to $NADP^+$, and 2-oxoglutarate is reduced to R-2HG. Elevated R-2HG leads to an elevated risk of malignant tumor. Since mutation only occurs in a single copy of IDH gene, it suggests a gain-of-function mutation and is consistent with genetic findings.



Source: Losman et al, Gene Dev (2013) 27:836-852; Dang et al, Nature (2009) 462:739; Ward et al, Cancer Cell (2010) 17:225-234.

R-2HG is Produced in Normal Tissue But in Very Limited Amount

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- There are two enantiomers of 2HG, (R)-2HG and (S)-2HG in normal cells. (R)-2HG is generated through concomitant reduction of 2-OG during conversion of γ-hydroxybutyrate to succinic semialdehyde by hydroxyacid-oxoacid transhydrogenase (HOS). (S)-2HG is generated during conversion of oxaloacetate to (L)-malate by (L)-malate dehydrogenase of the TCA cycle. R-2HG is converted back to 2-OG through two enzymes (D)-2HG and (L)-2HG dehydrogenase (2HGDH).
- Although both (R)-2HG and (S)-2HG are byproducts of normal mitochondrial metabolism, there are no known physiologic functions for either enantiomer and they are believed to be unwanted with each intracellular level maintained at <0.1mM in normal cells.
- IDH mutants produce the (R) enantiomer of 2HG, where concentration was elevated ranging from 1-30mM. This is likely the result of over-capacity for D2HGDH to oxidize the excess (R)-2HG back to 2-OG.

Source: Losman et al, Gene Dev (2013) 27:836-852.

Cells Expressing Mutated IDH1 Contain High Level of 2HG

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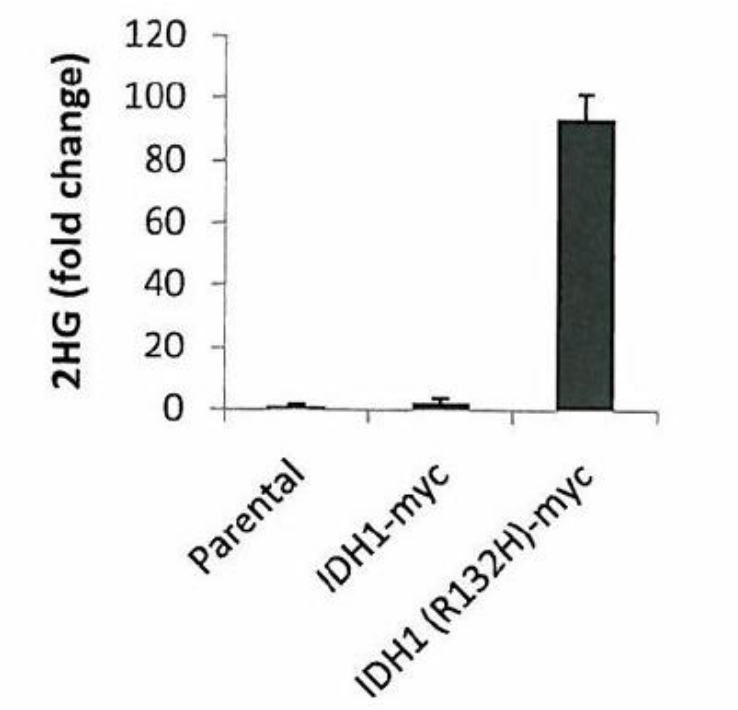
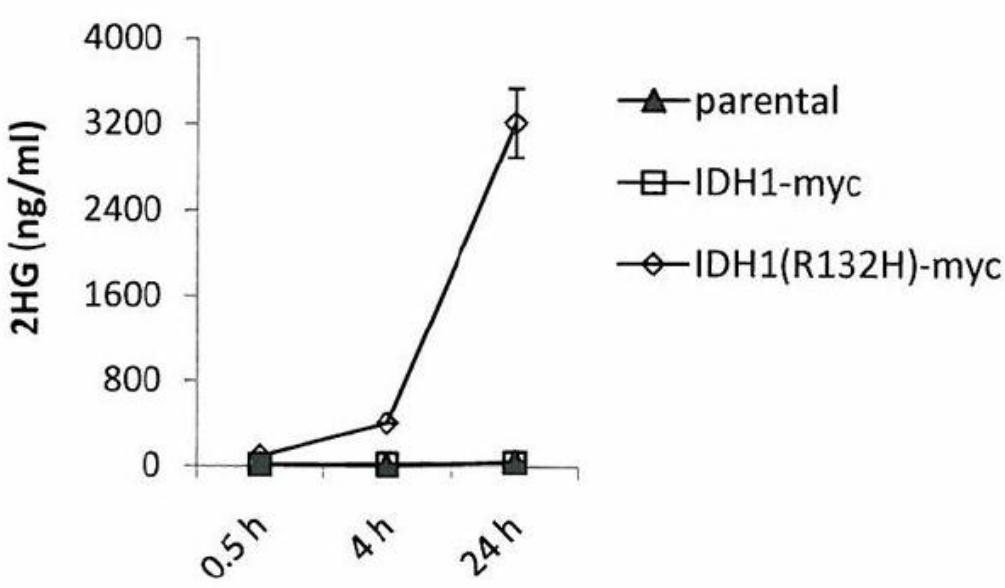
- Cells expressing R132H IDH1 show time-dependent 2HG accumulation in cell culture media.





Source: Dang et al, Nature 2009, 462(7274): 739

Human Gliomas with IDH1m Contain High Level of 2HG

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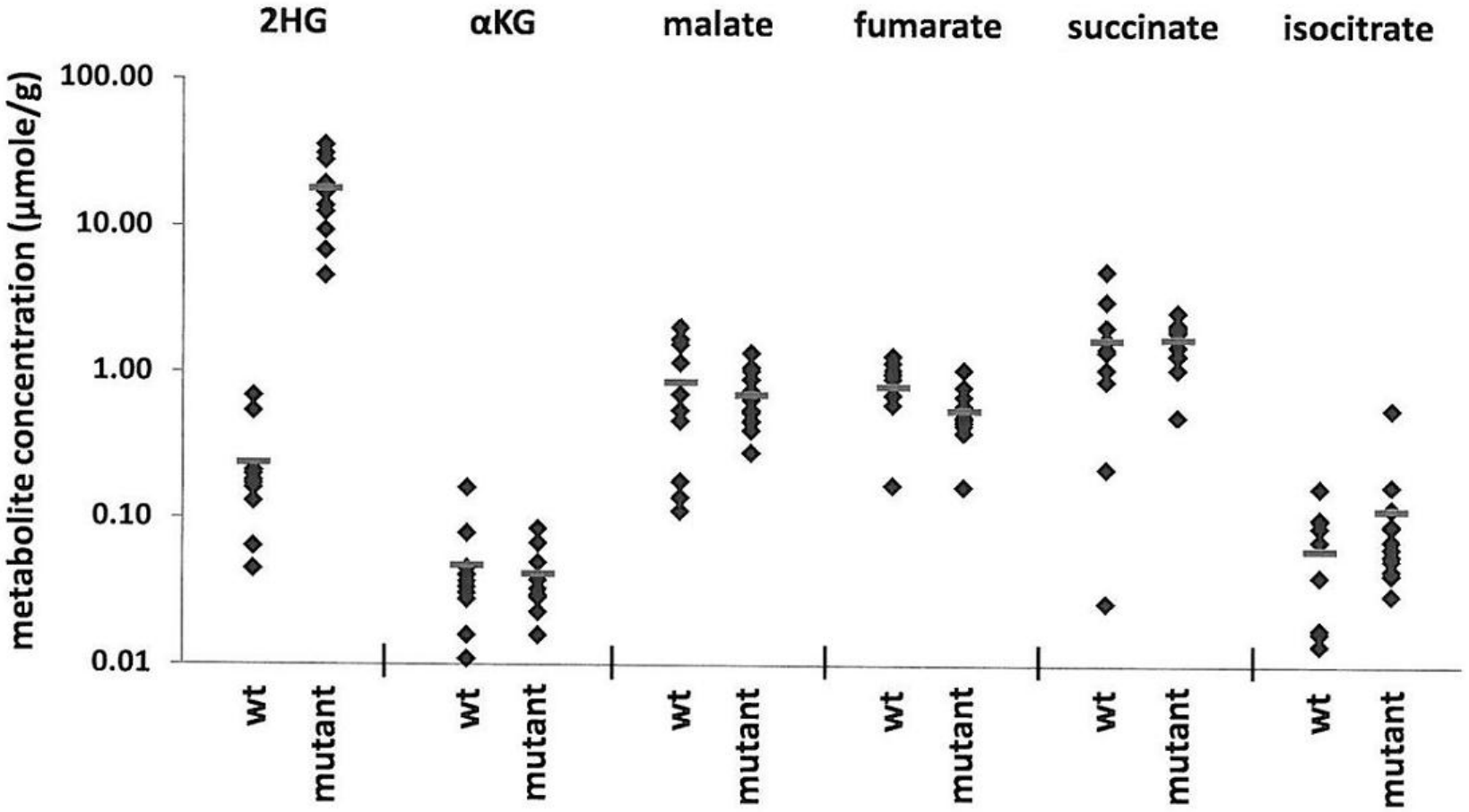
- LC-MS data was collected from surgical resection from 10 wild-type (WT) and 12 IDHm patients with human gliomas.



Source: Dang et al, Nature (2009) 462: 739-744.

Mutant IDH-Derived R-2HG is An Oncometabolite

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- **Elevated R-2HG leads to in vitro tumorigenesis of IDH mutant cells.** Treatment of TF-1 leukemia cells with R-2HG results in inhibition of cell differentiation of fibroblasts and myeloid progenitor cells, and withdrawal of R-2HG reverses and restores differentiation ability*.
- **Inhibition of IDH mutation result in reverse of cell transformation and induced cell differentiation.** Treatment with inhibitors targeting IDH specific mutations (R132H of IDH1 and R140Q of IDH2) induced differentiation of TF-1 leukemia cells in vitro*,***, and impaired colony formation and tumor engraftment in vivo with glioma cells**.
- Since IDH mutations are somatically acquired and confined to the active site of the enzyme, and there is only one copy of mutation in the IDH gene, these are evidence of gain of function mutations leading to altered enzymatic active site, suggesting that R-2HG is an oncometabolite.

*Source: Losman et al, Gene Dev (2013) 27:836-852; * Losman et al, Science (2013) 339:1621-1625; **Rohle et al, Science (2013) 340:626; ***Wang et al, Science (2013) 340:622-666.*

Observations in L2HGA and D2HGA Patients Provide Somewhat Conflicting But Overall Supportive Data in Our View on the Link of 2HG to Cancer

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- **Elevated levels of 2HG are also seen in L2HGA and D2HGA patients.** (L)-2-hydroxyglutaric aciduria (L2DGA) is an autosomal-recessive condition caused by deficiency of (L)-2-HG dehydrogenase, which converts 2-HG to a-ketoglutarate. This results in the accumulation of 2-HG in all body fluids. (D)-2-hydroxyglutaric aciduria (D2HGA) is an inborn neurometabolic disorder. Type I D2HGA is caused by germline mutations in D2HGDH, an enzyme converts 2-HG to 2-OG. In these patients, R-2HG levels are elevated but to a much lesser extent than is observed in IDH mutant tumors. Type II D2HGA is caused by germline IDH2R140Q and R140G mutations and is associated with higher levels of R-2HG and a more severe clinical course.

- **A large portion of children with L2HGA develop brain tumors or other types of tumors.** This supports the role of R-2HG in tumor transformation.On the other hand, D2HGA is not known to be associated with an increased incidence of cancer. The explanation for this is that these patients tend to a severe course of disease and die in infancy and early childhood.

Source: Losman et al, Gene Dev (2013) 27:836-852; DeBerardinis et al, Cell (2012) 148:1132-1144; Moroni et al, Neurology (2004) 62:1882-1884.

Proposed Mechanisms of Tumorigenesis Mediated by Mutant IDH

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- **2-OG antagonism due to competitive inhibition, resulting in epigenic changes.** R-2HG competitively inhibits 2-OG dependent ~70 enzymes, including enzymes methylate DNA and histone and function as tumor suppressors (see expanded discussion later in this report). Therefore elevated 2-HG mediates epigenetic changes. This proposed mechanism for transformation by 2-HG has gained the most traction.
- **Mitochondrial dysfunction**. R-2HG directly interferes with normal mitochondrial function and inhibits complex IV (cytochrome c) and V (ATP synthase), two critical enzyme complexes in electron transport chain.
- **Dysregulation of cellular redox.** IDH mutants have impaired ability to neutralize reactive oxygen species (ROS). Conversion of 2-OG to R-2HG by mutant IDH consumes NADPH, resulting reduction of reduced glutathione, a principal antioxidant that regulates cellular redox.
- **Deficiency of wild-type IDH activity.** Rare IDH mutations that do not produce R-2HG have been recently identified in lymphoid and thyroid tumors*. These IDH1 SNPs V71I, V178I and a number of non-synonymous mutations are monoallelic and lead to either decreased enzymatic activity or loss of expression of the mutant enzyme.

*Source: Losman et al, Gene Dev (2013) 27:836-85; * Ward et al, Oncogene (2012) 31:2491-2498. .*

AGIO Has Developed Mutant-Specific IDH1 and IDH2 Inhibitors

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- IDH1 inhibitors
  - AGIO's first IDH1m inhibitor 35 showed potent inhibition against R132H with IC_{50}=70nM.
  - AG-5198 selectively inhibits IDH1m with IC_{50}=70nM against R132H mutation, but not IDH2m or wild type.
  - AG-120 is a reversible and selective IDH1m inhibitor with nM potency (IC_{50}=8nM) against R132C, but also highly selective against wild type.
- IDH2 inhibitors
  - Treatment of AG-6780, an IDH2m inhibitor, restored the expression in R140Q mutant.
  - AG-221 showed nM potency (IC_{50}=12nM) against IDH2 R140Q mutation.

Source: Company Reports

Recent In Vivo Data Provide Encouraging Preclinical Proof of Principle

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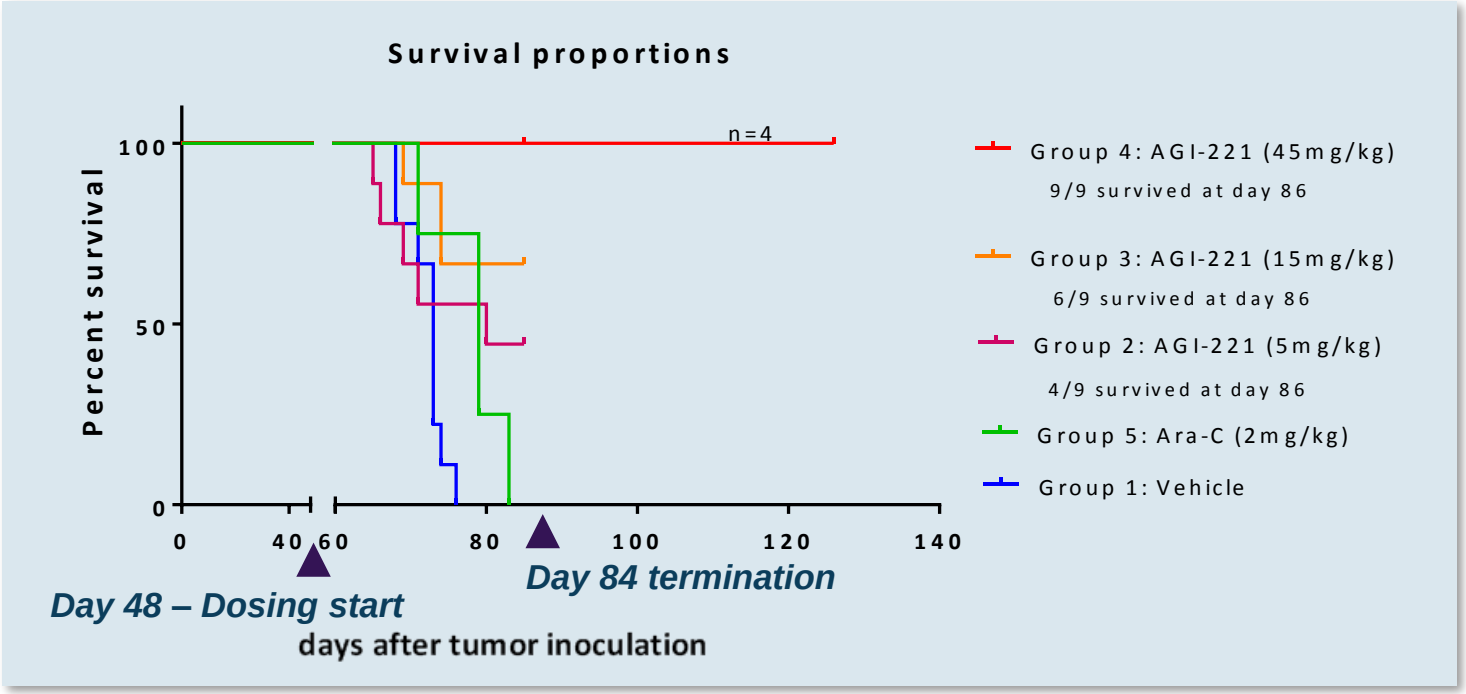
- AG-221 (IDH2 inhibitor) induces dose-dependent survival benefit vs. chemo in an aggressive IDH2m AML mouse model.
- The group of animal received 45mg/kg AGI-221 all survived at day 86 until the study was completed.
- A dose dependent decrease in leukemia and 2-HG, as well as evidence of normal differentiation were observed in all doses.



Source: Company Reports

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MARKET OPPORTUNITIES AND THERAPEUTIC CONSIDERATIONS FOR IDH1/2 INHIBITORS

Targeted Population with IDH1/IDH2 Mutations is ~43,000 Patients, Translating to a Potential Opportunity of ~$4.3B

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Tumor Type		Incidence (US/EU27/JP)	Pricing Assumption (cost per course)	IDH1m (%)	IDH1m (n)	Market Potential ($MM)	IDH2m (%)	IDH2m (n)	Market Potential ($MM)
Brain tumors		**28,337**			**11,260**	**1,126**		**753**	**75**
High Grade (3/4)	Primary glioblastoma	14,962	$100,000	8.5%	1,272	127	2.0%	299	30
	Secondary glioblastoma	1,662	$100,000	80.5%	1,338	134	0.0%	0	0
	Anaplastic astrocytoma	2,911	$100,000	64.0%	1,863	186	2.5%	73	7
	Anaplastic oligodendrogliomas	1,956	$100,000	62.0%	1,213	121	6.5%	127	13
	Anaplastic oligoastrocytomas	978	$100,000	83.0%	812	81	6.0%	59	6
Low Grade (1/2)	Diffuse astrocytoma	1,956	$100,000	78.0%	1,526	153	4.0%	78	8
	Oligodendrogliomas	1,956	$100,000	76.5%	1,496	150	5.0%	98	10
	Oligoastrocytomas	1,956	$100,000	89.0%	1,741	174	1.0%	20	2
Acute Myelogenous Leukemia (AML)		48,000	$100,000	7.5%	3,600	360	15.0%	7,200	720
MDS/MPN		40,000	$100,000	5.0%	2,000	200	5.0%	2,000	200
Chondrosarcoma		9,200	$100,000	50.0%	4,600	460			
Intrahepatic cholangiocarcinoma		8,000	$100,000	20.0%	1,600	160			
Others (colon, melanoma, lung)		~500,000	$100,000	1-2%	8,000	800			
Angio-immunoblastic NHL		1,600	$100,000				25.0%	400	40
Type II D-2HG aciduria		50	$300,000				50.0%	50	15
Others (melanoma, glioma, chondro)			$100,000				3-5%	1,500	150
Total					31,060	**$3,106**		11,903	**$1,200**

Source: Agios estimates, Leerink Swann

Therapeutic Issue to Consider: Can AGIO's IDH1/2 Inhibitors Cover All or Major Mutations?

LEERINK SWANN

- Different IDH1/IDH2 mutations have been identified in various human cancers including glioma, acute myeloid leukemia (AML), chondrosarcoma and cholangiocarcinoma.

Tumor type	IDH mutated	$IDH1^{mut}$:$IDH2^{mut}$	Mutant alleles	Allele frequency	Reference
Grade II/III glioma 2° GBM	80%–90%	20:1	***IDH1* R132H**	**85%–90%**	
			IDH1 R132C/S/L/G/V	5%–8%	Chang et al. 2011
			IDH1 R100Q	<1%	Pusch et al. 2011
			IDH2 R172K/M/W/S/G	3%–5%	
NK-AML secondary AML	10%–30%	1:1 - 1:2	*IDH1* R132H	10%–20%	
			IDH1 R132C/S/L/G/P	15%–30%	Abbas et al. 2010
			***IDH2* R140Q**	**30%–50%**	Marcucci et al. 2010
			IDH2 R140W/L	3%–5%	Paschka et al. 2010
			IDH2 R172K/G/M/Q	10%–15%	Koszarska et al. 2012
AITL	10%–40%	IDH2 only	***IDH2* R172K**	**60%**	Cairns et al. 2012
			IDH2 R172G/T/S	35%	
			IDH2 R140G	< 5%	
Chondrosarcoma	50%–70%	20:1	***IDH1* R132C**	**40%–50%**	Amary et al. 2011a
			IDH1 R132G/H/L/S	30%–50%	Pansuriya et al. 2011
			IDH2 R172S/T	5%–10%	Arai et al. 2012
Cholangiocarcinama	10%–20%	10:1	***IDH1* R132C**	**50%–60%**	Borger et al. 2012
			IDH1 R132L/G	30%–40%	
			IDH2 R172W	10%	

Source: Losman et al, Gene Dev (2013) 27:836-852.

AGIO's IDH1 Inhibitors Have Potent Activity Against Major Mutations

LEERINK SWANN

- AG-120 showed nM potency (IC_{50}=8nM) against R132C, but also have high selectivity against IDH wild type.
- AG-5198 has been selected as an inhibitor against R132H-IDH1 (IC_{50}=70nM); however, AG-5198 is also potent against R1322C (IC_{50}=160nM)*.

AG-5198	IDH1	
R132H	R132C	wildtype
IC_{50} (μM)	IC_{50} (μM)	IC_{50} (μM)
0.07	0.16	> 100
AG-5198	**IDH2**	
R140Q	R172K	wildtype
IC_{50} (μM)	IC_{50} (μM)	IC_{50} (μM)
> 100	> 100	> 100

AGI	HT1080 R132C Cell IC_{50} (nM)
12910	8

*Source: *Rohle et al, Science 2013, 340(6132): 626-630*

AGIO's IDH2 Inhibitor Has Potent Activity Against 80% of AML Patients with IDHm

LEERINK SWANN

- AG-221 showed a reversible and selective nM potency (IC_{50}=12nM) against R140Q, representing ~80% of AML patients with IDH mutations.
- However, activity against R172K, a mutation representing ~20% of IDHm AML patients, was less potent. Despite less potent activity, management believes AG-221 could still has some level of activity.
- Phase I trial is open for enrollment in advanced hematologic malignancies with all IHD2 mutations.

AGI-6780 Biochemical Properties, IC_{50} for α-KG Reduction		
Enzymes Assayed	*Incubation Time (h)*	*IC_{50} (nM)*
IDH2-R140Q	1	170 ± 47
IDH2-R140Q	16	23 ± 1.7
IDH2-R140Q/WT	1	120 ± 42
IDH2-R140Q/WT	16	4.0 ± 1.2
IDH1-R132H	16	11000 ± 84
AGI-6780 Biochemical Properties, IC_{50} for Isocitrate to α-KG		
Enzymes Assayed	*Incubation Time (h)*	*IC_{50} (nM)*
IDH2-WT	1	2700 ± 31
IDH2-WT	16	190 ± 8.1
IDH1-WT	16	>100000

AGI	R140Q Cell IC_{50} (uM)
221	0.012

Source: Company Reports

Therapeutic Implications of Selectivity Findings of Agios IDH1/2 Inhibitors

LEERINK SWANN

- Agios IDH1 inhibitors are active against all major IDH1 mutations (R132). Agios IDH2 inhibitors are active against the major IDH2 mutations at R140 (~80% of patients) but less so against IDH2 R172 mutations (~20% of patients).
- Agios IDH inhibitors are specific to IDH1 or IDH2 mutants respectively. However, IDH1 and IDH2 mutations are generally mutually exclusive. Therefore Agios IDH1 and IDH2 inhibitors are not expected to be combined with each other.
- Agios IDH1 inhibitors appear to be more selective against the mutants relative to the wildtype. The IDH2 inhibitors, based on available published data, may have some inhibition of IDH wildtype depending on the dose used. It is not fully clear what the consequence of inhibiting IDH wildtype is but knockout mice data show that even full inhibition is not lethal.

Therapeutic Issue to Consider: At Least in Some Cancers, IDH1/IDH2 Mutations Are Associated with Better Prognosis

LEERINK SWANN

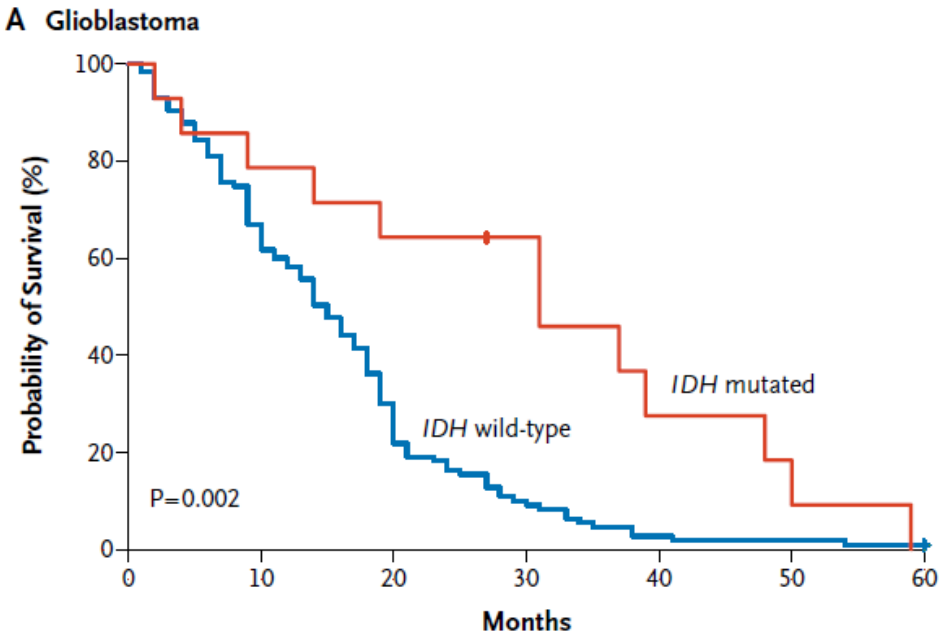
- In **glioma**, IDH mutations are associated with favorable prognosis, where a median survival reached 31 months for patients with IDH mutations vs. 15 months for wild type.
- In **AML**, several studies reported non-prognostic characteristics of the IDH mutations, whereas other studies suggested that IDH mutations are associated with an increased or decreased risk of disease relapse vs. wild-type patients, depending on the specific patient population.
- In **MDS and MPN**, IDH mutations have been consistently associated with poor prognosis.
- Based on the observation that IDH mutation occurs more frequently in later stage of MDS and MPN, as well as secondary AML, IDH mutations are speculated to be involved in progression of chronic phase to full blown leukemia.

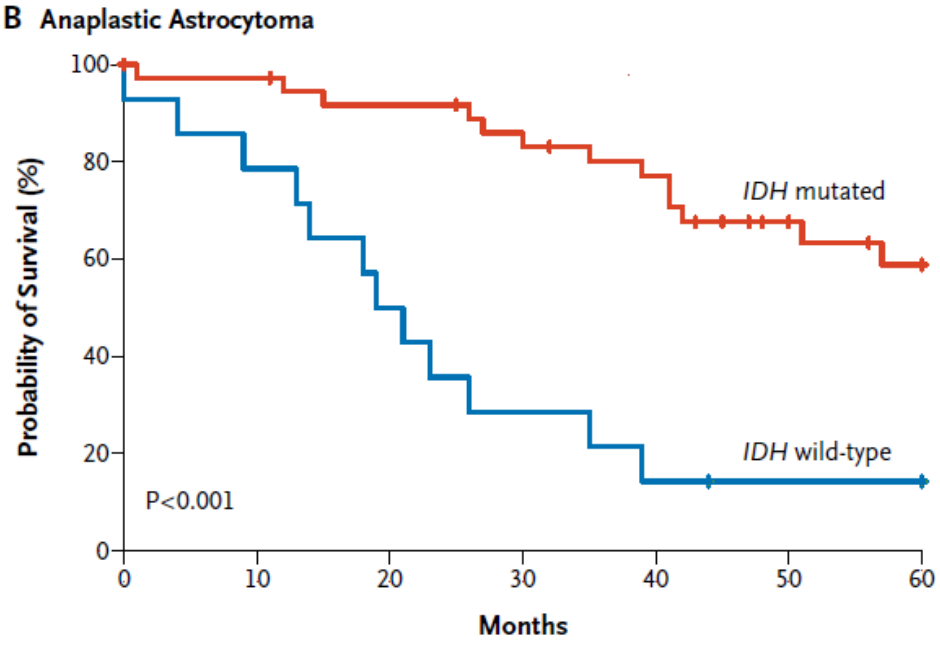
Source: Losman et al, Gene Dev (2013) 27:836-852.

IDH Mutations in Gliomas Showed Better Survival

LEERINK SWANN

- For patients with glioblastomas, median survival was 31 months for 14 patients with IDH mutations vs. 15 months for the 115 wild-type patients.
- For patients with anaplastic astrocytoma, median survival was 65 months for 38 patients with IDH mutations vs. 20 months for 14 wild type patients.





Source: Yan et al, N Engl J Med (2009) 360:765-773.

Data on Prognostic Impacts of IDH Mutations in AML Are Not Consistent

LEERINK SWANN

Reference	Number of Patients	Mutational Frequency	Clinical Implications Investigated	Patient Population/ Comments
IDH1-R132, IDH2-R140, and *IDH2-R172* codons sequenced				
Abbas et al[29]	893	17% (*IDH1* 6% and *IDH2* 11%)	No effect on overall cohort or CN-AML overall Adverse effect of *IDH1* mutations on OS and EFS in subset of patients with *FLT3*–wild-type/*NPM1*–wild-type genotype	Patients were culled from multiple different HOVON AML protocols (HO04, HO04A, HO029, HO029, HO42, HO42A, HO43).
Paschka et al[34]	805	16% (*IDH1* 7.6%, *IDH2* 8.7%)	No effect on overall cohort or patients with CN-AML overall Adverse effect of *IDH1* or *IDH2* mutants on patients with CN-AML with *NPM1*-mutant/*FLT3*–wild-type genotype	All patients were on AMLSG HD98A or HD95 studies and younger than 60 years
Marcucci et al[53]	358	33% (14% *IDH1*, 19% *IDH2*)	*IDH1* mutations associated with worsened DFS and *IDH2-R172* mutation associated with lower CR	All patients with de novo CN-AML from multiple CALGB trials (9621, 19808, 8525, 8923, 9420, 9720, or 10201)
Rockova et al[54]	439	15.4% (7.2% *IDH1*, 8.2% *IDH2*)	No effect of *IDH* mutations on overall cohort but combined with gene expression analysis, *IDH2* associated with a distinctive improved survival	De novo AML and MDS RAEBt patients, all younger than 60 years, treated on HOVON protocols between 1987 and 2006
Only *IDH1-R132* and *IDH2-R172* codons sequenced				
Boissel et al[19]	520	12.6% (*IDH1* 9.6%, *IDH2-R172* 3.0%)	*IDH1* mutations found to be associated with higher RR and shorter OS in patients with CN-AML with *NPM1* or *CEBPA* mutations but no *FLT3* mutations *IDH2-R172* mutations were associated with higher RR and shorter OS in patients with CN-AML overall	Adult patients with AML of all ages and assigned to French Acute Leukemia French Association -9801 and -9802 trials

Source: Abdel-Wahab et al, Hematolo Oncol Clin North AM (2011) 25:1119-1133.

Data on Prognostic Impacts of IDH Mutations in AML Are Not Consistent

LEERINK SWANN

Only *IDH1* or *IDH2* sequenced				
Schnittger et al[55]	1414	6.6% *IDH1*	*IDH1-R132* mutations associated with decreased EFS	Adult patients with AML of all ages and assigned to AMLSG to receive induction either with a standard-dose (cytarabine, daunorubicin, and 6-thioguanine) and a high-dose (cytarabine and mitoxantrone) combination, or with two courses of the high-dose combination
Green et al[32]	1333	8% *IDH1*	No effect on overall cohort or CN-AML overall Adverse effect on relapse in patients with *FLT3*–wild-type genotype but favorable effect in *FLT3ITD* mutant patients.	All patients were on UK MRC AML10 or AML12 trials
Green et al[31]	1473	10% *IDH2*	*IDH2-R140Q* mutation found to be have favorable effect for RFS and OS in overall cohort and *FLT3*–wild-type/*NPM1*-mutant subset	All patients were on UK MRC AML10 or AML12 trials
Chou et al[30]	493	5.5% *IDH1*	No effect of *IDH1-R132H* on clinical outcome	Patients with *IDH1*-mutant genotype followed serially, and 61.1% of patients who experienced relapse had reemergence of the *IDH1* mutation at relapse
Thol et al[56]	272	12.1% *IDH2*	No impact of *IDH2* mutations on response to therapy, OS, and RFS in patients with CN-AML	All patients with CN-AML, younger than 60 years
Wagner et al[57]	275	10.9% *IDH1*	No effect of *IDH1R132H* on clinical outcome	All patients with CN-AML, younger than 60 years, and treated on AML Suddeutsche Hamoblastose Gruppe trials 0295 or 0199

Source: Abdel-Wahab et al, Hematolo Oncol Clin North AM (2011) 25:1119-1133.

If an IDH1 Mutation Confers Better Prognostics, Why Inhibit It?

LEERINK SWANN

- Even with improved prognostics, glioma patients still invariably die of the cancer.
- In patients with IDH1/2 mutations, these mutant enzymes are believed to be the driver. Therefore even though these patients have better prognostic compared to other glioma patients whose cancer is presumably driven by other mutations, it would still be therapeutic to inhibit IDH1/2 mutants and block the production of 2-HG.
- Two clear examples of this are EGFR activating mutations and ALK translocations which are both associated with better prognostic in non-small cell lung cancer patients. EGFR and ALK inhibitors have both been shown to have dramatic therapeutic effects with response rates in the 50-70% range and longer survival vs. conventional chemo.

Source: Butler et al, Cancer Research, 2013; Lee et al, Cancer (2012) 118:3579-3586.

Survival Analysis Suggests EGFR Mutation Is Associated with Longer OS

LEERINK SWANN

Survival Variable	*ALK* Positive, *N* = 23	*EGFR* Mutation Positive, *N* = 46	WT/WT, *N* = 46
OS			
No. of patients	23	46	46
Median OS (95% CI), mo	12.23 (6.60-17.87)	29.63 (24.73-34.53)	19.33 (9.11-29.55)
P vs ALK-positive[a]		.001	.127
PFS after first-line chemotherapy			
No. of patients	21	34	37
Median (95% CI), mo	3.87 (0.43-7.31)	4.93 (4.40-5.46)	3.73 (2.32-5.14)
P vs ALK-positive[a]		.825	.474
PFS after EGFR TKI therapy			
No. of patients	10[b]	42	27
Median (95% CI), mo	1.37 (1.07-1.67)	9.80 (4.94-14.66)	2.07 (0.15-3.99)
P vs ALK-positive[a]		<.001	.037

Abbreviations: ALK, anaplastic lymphoma kinase; CI, confidence interval; EGFR, epidermal growth factor receptor; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; WT, wild type.

[a] Log-rank P values were derived from a comparison of Kaplan-Meier estimates between patients who had ALK-positive tumors versus patients who had other tumor types.

[b] Excludes patients who were enrolled because of a previous nonresponse to EGFR TKIs.

Source: Lee et al, Cancer (2012) 118:3579-3586.

IDH1 mutations occur most frequently in lower-grade gliomas or secondary GBM

LEERINK SWANN

	Tumor	Annual Incidence[1]	IDH1m (%)	IDH1m (n)	IDH2m (%)	IDH2m (n)
Higher-grade 3-4	Primary GBM	14,962	8.5%	1272	2%	299
	Secondary GBM	1,662	80.5%	1338	0	0
	Anaplastic Astrocytoma	2911	64%	1863	2.5%	73
	Anaplastic Oligodendrogliomas	1956	62%	1213	6.5%	127
	Anaplastic Oligoastrocytomas	978	83%	812	6%	59
Low-grade 1-2	Diffuse Astrocytoma	1956	78%	1526	4%	78
	Oligodendrogliomas	1956	76.5%	1496	5%	98
	Oligoastrocytomas	1956	89%	1741	1%	20

1. US, EU27, Japan. GBM: glioblastoma multiforme; IDH1/2m: IDH1/2 mutation

Source: Company reports

Therapeutic Implications of Prognostic Findings

LEERINK SWANN

- For brain cancer, as IDH mutations occur primarily in low-grade gliomas and IDH mutations confer improved prognostics, it could require a long (and possibly large) trial to demonstrate survival benefit. One possible initial path to registration could be in the recurrent setting. Both Temodar and more recently Avastin received accelerated approval based on durable response rate, in anaplastic astrocytoma (grade III glioma) and glioblastoma multiforme (grade IV glioma) respectively. Once approved, low-grade gliomas may represent a more attractive commercial market.
- Chondrosarcoma and cholangiocarcinoma may represent initial registration settings for Agios' IDH1 inhibitor.
- Inconsistent prognosis of specific IDH mutations in AML may require patient stratification based on each mutation in order to ensure a balanced population or possibly allele-specific trials. But we do not view this to be a big hurdle.

MEDACorp KOL feedback on outlooks of IDH1/2 inhibitors

LEERINK SWANN

- MEDACorp brain cancer and leukemia key opinion leaders (KOLs) are highly interested in IDH inhibitors
- Brain cancer KOLs noted that even though IDH1 mutations occur primarily in lower grade gliomas who have better prognosis, there remains a high unmet need as gliomas are still deadly. In particular, low-grade gliomas occur in younger patients in their 20s – 30s with the most productive period still ahead, there is a high interest in maximizing therapeutic benefit. We note that there is also likely a stronger pharmacoeconomic argument when it comes to pricing. KOLs stated that IDH1/2 mutation testing is already common in academic centers. One KOL commented that he can't think of a more interesting targeted agent in development for gliomas and another KOL stated that if the drug is shown safe and effective, majority of the low grade glioma patients will receive the drug.

MEDACorp KOL feedback on outlooks of IDH1/2 inhibitors, continued

LEERINK SWANN

- Leukemia KOL also stated that IDH1/2 mutation testing is already done at major academic centers and the doctors know who the patients with mutations are. He would have high enthusiasm in testing Agios's IDH1/2 inhibitors. However, due to the aggressive nature of AML, he was pessimistic about seeing dramatic single agent activity in the relapsed and refractory setting. He expects the IDH1/2 inhibitors to be combined with chemotherapy and he believes the treatment paradigm will likely to be to continue IDH1/2 inhibitors after chemo for an extended duration.

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BEYOND IDH1/2, CAN AGIO'S CANCER METABOLISM PLATFORM GENERATE A SUSTAINABLE PIPELINE?

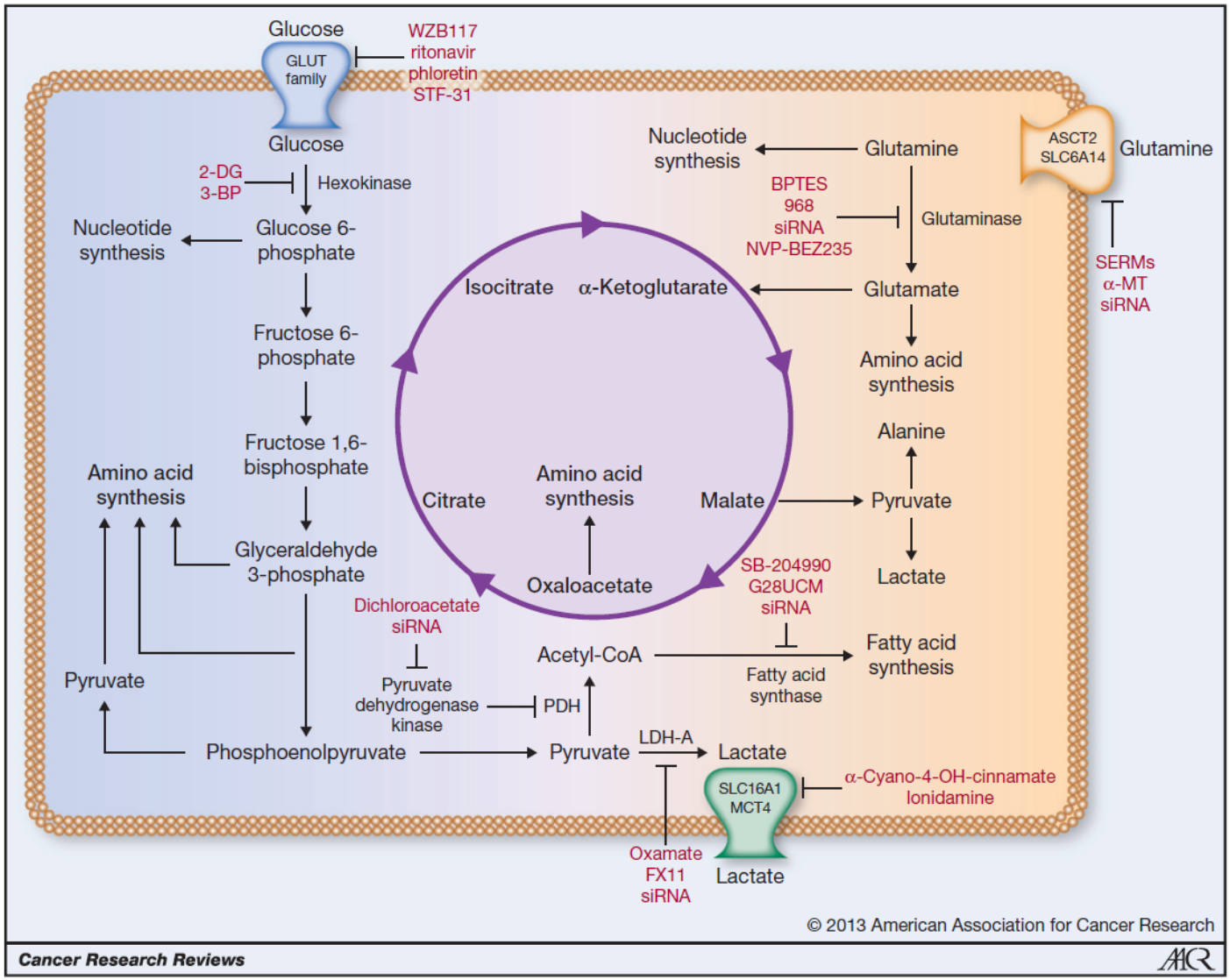
A Wide Range of Opportunities Exist for Targeting Cancer Metabolism

LEERINK SWANN

- Cancer cells has distinctive metabolic pathways to fuel cellular growth and survival.
- **Targeting the resource absorption.** The uptake of glucose and glutamine, the most common metabolites, is often increased in tumor cells to supply fuel for tumor growth. This is mostly a result of up-regulation of glucose and glutamine transport.
- **Targeting metabolic machinery.** This includes a wide range of biosynthetic pathways that are critical for metabolism, including glycolysis, glutamine catabolism, lactate production and export, citric acid cycle, and fatty acid synthesis.

Source: Butler et al, Cancer Research, 2013

A Wide Range of Opportunities Exist for Targeting Cancer Metabolism



- Glucose and glutamine are metabolized into intermediates for cell growth such as amino acid, nucleotide, and fatty acid.
- Disruption of these metabolic networks can reduce drug resistance and make tumors more susceptible to drugs.

Source: Butler et al, Cancer Research, 2013

A Wide Range of Opportunities Exist for Targeting Cancer Metabolism

LEERINK SWANN

Summary table of potential drugs/compounds targeting cancer metabolism. Examples listed are of published compounds or pipeline candidates that are designed to target cancer metabolism pathways and, where possible, details of molecular target, biological rationale/validation and status are given

Drug/compound (Source/reference)	Molecular or pathway target	Biological validation	Current status (if known)
Phloretin	GLUT1/4	Blocks glucose uptake	Early development
2-Deoxyglucose	Hexokinase (glycolysis)	Blocks glycolytic flux	Reported in clinical trials
3-Bromopyruvate	Hexokinase (+ other glycolytic targets?)	Blocks glycolytic flux	Preclinical development
Lonidamine	Hexokinase	Blocks glycolytic flux	Clinical trials ongoing
3PO [+ derivatives] (Advanced Cancer Therapeutics)	Phosphofructose kinase 2 [PFKFB3]	Blocks positive regulation of PFK1 and glycolysis	Preclinical development
Cap-232/TLN-232 (Thallion Pharmaceuticals)	Pyruvate kinase-M2	Blocks pyruvate formation via PK route	Trial suspended owing to licensing dispute
(Agios Pharmaceuticals)	Pyruvate kinase-M2	Blocks pyruvate formation via PK route	Preclinical
(Agios Pharmaceuticals)	Pyruvate kinase-M2 activators	Promotes glycolytic flux reducing synthesis of biosynthetic intermediates	Preclinical
Dichloroacetate	Pyruvate dehydrogenase kinase (+ metabolic targets?)	Activates PDH and promotes oxidative phosphorylation	Basic Phase I trial completed, Phase II studies proposed
FX11 (University of New Mexico/ The John Hopkins University)	Lactate dehydrogenase	Blocks metabolic flux pathways	Early development
Oxamate	Lactate dehydrogenase and aspartate aminotransferase	Blocks metabolic flux pathways	Early development
Amino oxyacetate	Aspartate aminotransferase	Blocks metabolic flux pathways	Early development
AZD-3965 (AstraZeneca)	MCT1	Blocks lactate secretion	Phase I/II trials planned with CR:UK
5-Dehydroepiandrosterone [DHEA]	Glucose-6-phosphate dehydrogenase + multiple non-metabolism targets	Blocks oxidative pentose phosphate pathway (PPP)	Early development
Oxythiamine	Transketolase	Blocks non-oxidative PPP	Early development
(Tarvagenix)	Transketolase-like 1 (TKTL1)	Could block non-oxidative PPP in cancer	Early development (no published data)
6-Diazo-5-oxo-L-norleucine	Glutaminase (glutaminolysis)	Blocks glutamine conversion to glutamate	Toxicity issue Early development
968 (Cornell University)	Glutaminase	Blocks glutamine conversion to glutamate	Early development
BPTES	Glutaminase	Blocks glutamine conversion to glutamate	Early development
GSK837149A (GSK)	Fatty acid synthase	Blocks fatty acid synthesis	Preclinical
Orlistat (Roche)	Fatty acid synthase	Blocks fatty acid synthesis	Preclinical
C75	Fatty acid synthase	Blocks fatty acid synthesis	Early development
SB-204990 (GSK)	ATP citrate ligase	Blocks fatty acid synthesis	Preclinical
(Agios Pharmaceuticals)	Mutant IDH1/2	Blocks alternative catalytic function of mIDH	Preclinical
CPI-613 (Cornerstone Pharmaceutical)	Pyruvate dehydrogenase complex/ Pyruvate dehydrogenase kinase	Mitochondrial energy metabolism	Phase I/II trials ongoing
Metformin	Energy sensing pathways (AMPK) and other targets	Blocks lipid and protein synthesis and glycolytic regulation	Used in diabetes, clinical trials in cancer ongoing
MPC-9528 (Myrexis)	Nicotinamide phosphoribosyltransferase	Blocks NAD production and reduces glycolysis	Preclinical

Source: Jones and Schulze, Drug Discovery Today 2012

Mutations in SDH and FH Function as Tumor Suppressors in Cancer

LEERINK SWANN

- Cancer specific metabolic mutations have been initially identified in TCA cycle enzymes in familial cancer syndromes.
- Loss of function mutations in succinate dehydrogenase (SDH), an oxidoreductase complex involved in both ETC and TCA cycle, were identified in dominantly inherited familial paraganglioma.
- Mutations in the TCA cycle enzyme fumarate hydratase (FH) have been identified in familial syndromes susceptible to renal cell cancer and leiomyomatosis.
- Both SDH and FH functions as tumor suppressors since loss of one allele result in tumorigenesis.

Source: DeBerardinis et al, Cell (2012) 148:1132-1144.

PHGDH Over-expression May Lead to tumorigenesis

LEERINK SWANN

- High levels of phosphoglycerate dehydrogenase (PHGDH), an enzyme producing amino acid serine and glycine from glucose, have been identified in breast cancer patients.
- Although it remains to be established whether PHGDH is a bona fide oncogene, over expression of PHGDH promotes anchorage independence and disturbs cell polarity.

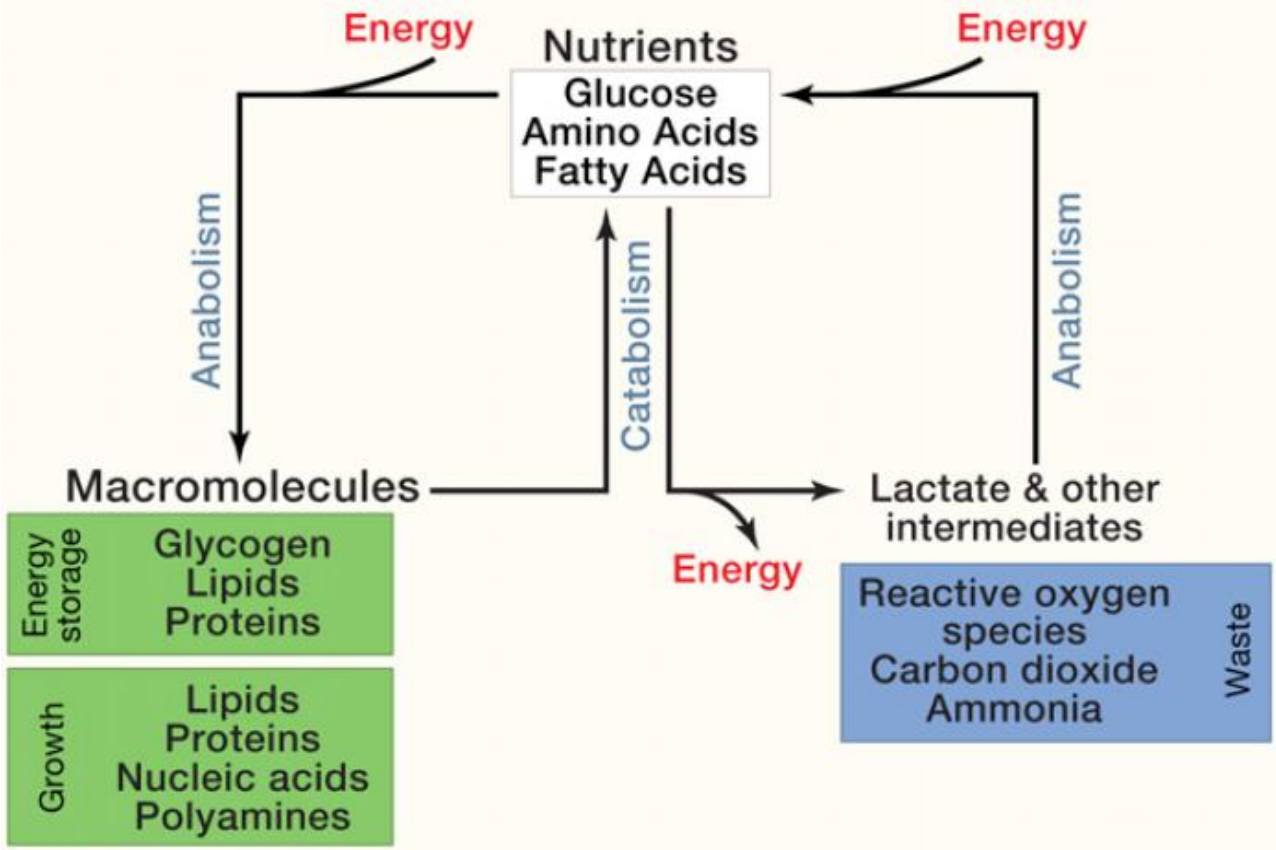
Source: DeBerardinis et al, Cell (2012) 148:1132-1144.

LEERINK SWANN

APPLICATIONS IN INBORN ERRORS OF METABOLISM (IEM) REPRESENT ANOTHER ATTRACTIVE OPPORTUNITY

Cellular Metabolism

- Metabolism is defined as the sum of biochemical processes of consuming and producing energy. Core metabolism includes three classes 1) anabolism or synthesis of small molecules into more complex macromolecules, 2) catabolism which is degradation of molecules to release energy, and 3) waste disposal that eliminate the toxic waste.



Source: DeBerardinis et al, Cell (2012) 148:1132-1144.

Metabolic Variation is Genetically Defined, IEMs Are the Largest Category of Inheritable Human Diseases

LEERINK SWANN

- Metabolic variation among individuals are genetically defined and mutations resulting in metabolic abnormalities are collectively termed inborn errors of metabolism (IEMs). Currently there are ~500 recognized IEMs, the largest category of heritable human diseases.
- The vast majority of IEMs result from recessive loss-of-function mutations in enzymes and transporters. Individuals with IEMs usually have near complete loss of normal pathway function, making them nearly equivalent to human knockouts.
- However, many severe IEMs are not lethal and some are asymptomatic for newborns where diseases could be controlled by the early initiation of therapies.

Source: DeBerardinis et al, Cell (2012) 148:1132-1144.

Newborn Screening and Early Treatment Minimize Symptoms of IEMs; However, Many Remain as Unmet Medical Needs

LEERINK SWANN

- The first successful case was the screening of newborns with phenylketonuria (PKU), where genetic mutations in phenylalanine (Phe) oxidation cause accumulation of toxic Phe-related metabolites that impair cognitive development. Early initiation of low-Phe diets successfully minimized the symptoms.
- Starting in 1960's when a simple assay was developed to detect PKU, full-scale screening program were underway within 10 years in the US and EU.
- Following initial full-scale screening in the US and EU for PKU, more than 20 IEMs have been routinely tested from a single blood sample. As a result, once highly severe IEMs now appear to be clinically silent in some patients where early therapy becomes available.
- However, supportive care remains as the mainstay for some other IEMs, such as pyruvate kinase deficiency (PKD), where no approved drugs are available, leaving large unmet medical needs.

Source: DeBerardinis et al, Cell (2012) 148:1132-1144.

Inborn Errors of Metabolism (IEM) and Pyruvate Kinase Deficiency (PKD)

LEERINK SWANN

- Inborn errors of metabolism (IEM) are genetic disorders in which defects in enzymes causes a metabolic block with pathologic consequences
- Pyruvate kinase is the key glycolytic enzyme that catalyzes the synthesis of ATP, which is the final step in glycolytic pathway
- Pyruvate kinase deficiency (PKD) is inherited in autosomal recessive manner, and is the most common abnormality among glycolytic defects and cause of hereditary non-spherocytic hemolytic anemia, with prevalence of 1:20.000 in white population
- PK deficiency leads to ATP depletion, and accumulation of 2,3-diphosphoglycerate (2,3-DPG), which impairs the glycolytic flux through the inhibition of hexokinase
- PKR enzyme is an isoform of PK present in red blood cells (RBC)
- No specific therapy for PKD is available; the standard of care is generally supportive, to improve in vivo activity, while red cell transfusion is used for severely anemic patients
- AG-348, an activator of PK, is the lead molecule of AGIO's IEM program

Source: Zanella et al, British J of Haematology 2005, 130; 11-25

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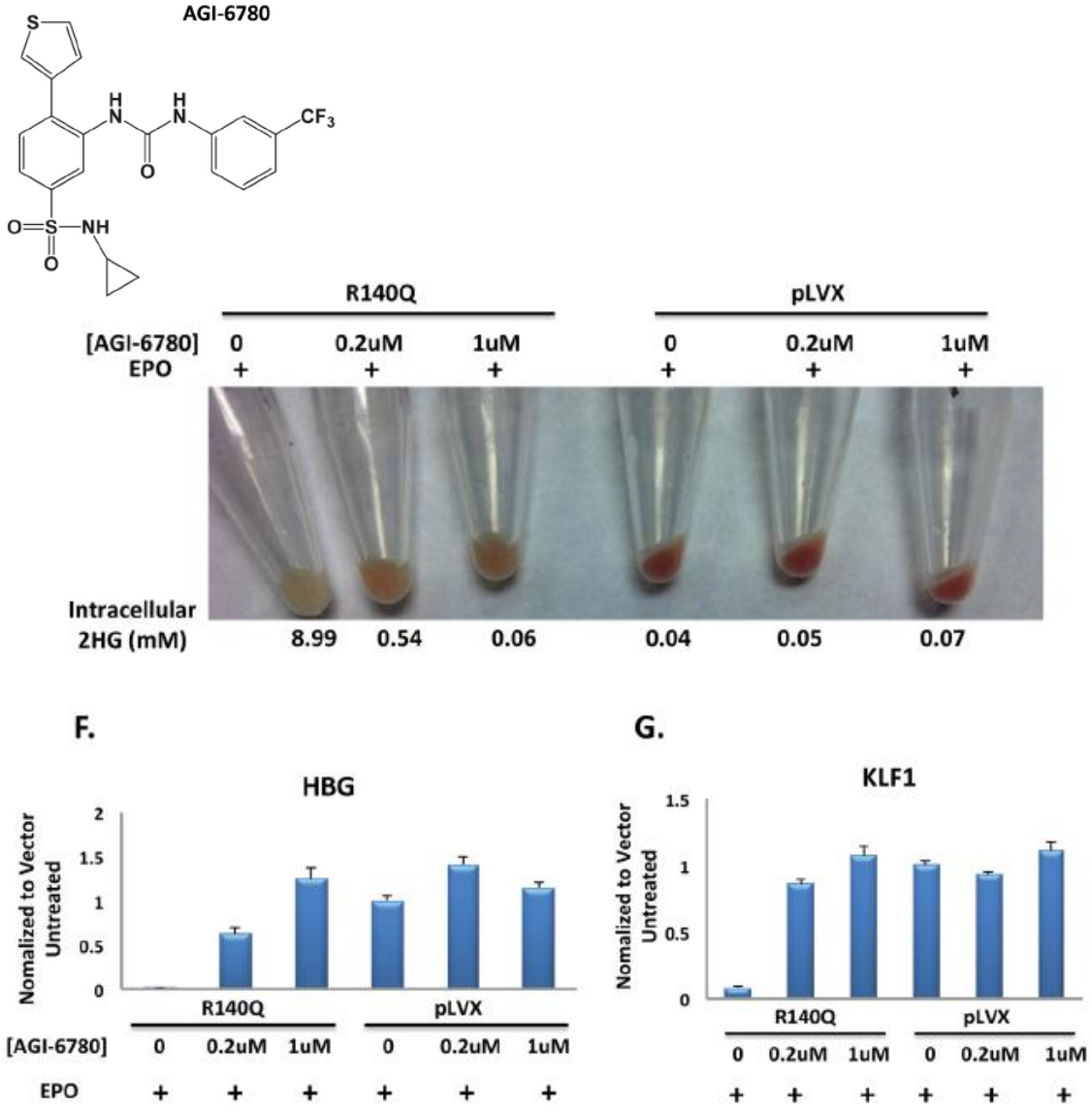
PRECLINICAL DATA FOR IDH2 INHIBITORS – AG-221, AG-6780

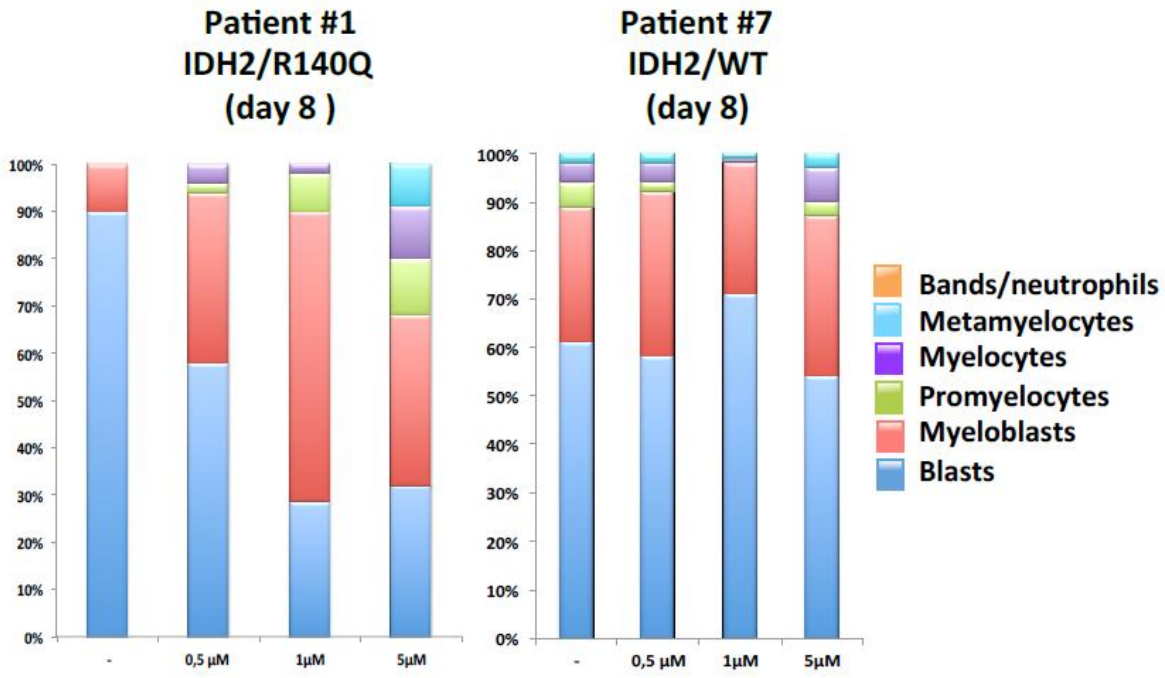
AG-6780 Treatment of Mutant TF-1 Cells Resulted in Restoring the Ability of Cell Differentiation



- AG-6780 is a IDH2 mutant inhibitor developed for the treatment of AML.
- Both HGB and KLF1 are induced by erythropoietin (EPO), and expressed in wild type but not in mutant IDH2 TF-1 cells.
- Mutant TF-1 cells did not differentiate as the wild type did after EPO stimulation.
- With AG-6780 treatment, mutant cells restored the expression in R140Q mutant. Treatment also restored the color change associated with differentiation.

Source: Wang et al, Science, 2013, 340(6132): 622-626

AG-6780 Inhibits IDH2m and Restored Cell Differentiation in Patient-Derived Tumor Samples



[AGI-6780]	% Blasts Patient #1 (R140Q) day 8	% Blasts Patient #3 (R140Q) day 9	% Blasts Patient #6 (WT) day 8	% Blasts Patient #7 (WT) day 8
-	90	29	100	54
DMSO	90	26	90	61
0.5 uM	58	17	90	58
1 uM	28	13	92	71
5 uM	32	9	95	54

- It was shown for the first time the effects of inhibiting IDH2m in patient-derived tumor samples.
- Blasts were decreased significantly only in IDH2 mutant samples.
- Mutant with treatment showed a dose-dependent reduction in blasts for over 70%.

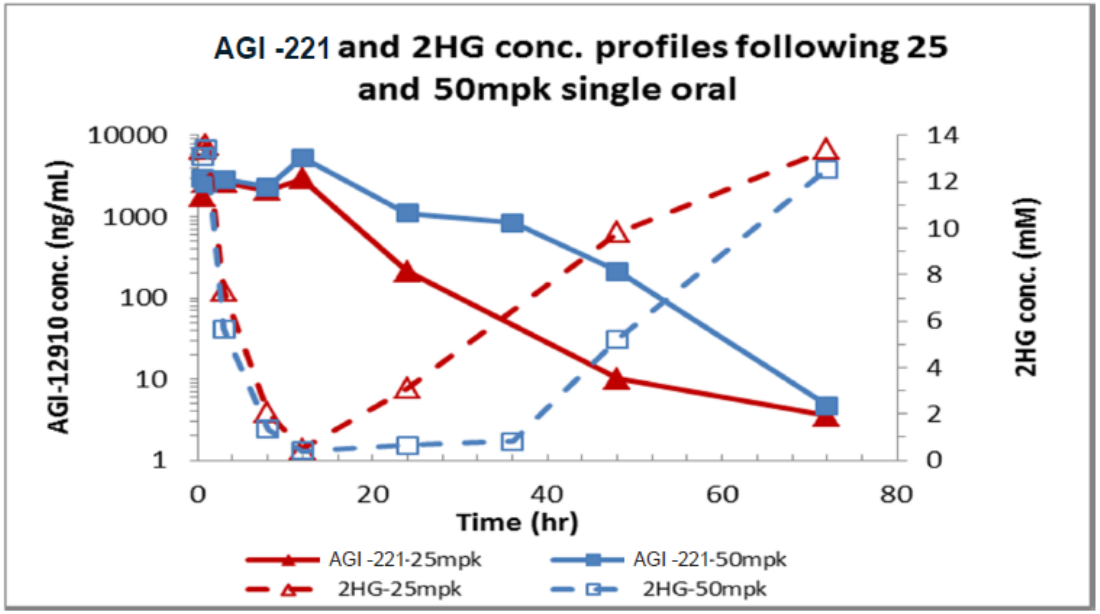
Source: Wang et al, Science, 2013, 340(6132): 622-626

AG-221 is the Lead Candidate for AGIO's IDH2 Program Targeting R140Q IDH2 with nM Potency

LEERINK SWANN

- AG-221 is a reversible IDH2m inhibitor targeting mostly R140Q mutation.
- In vitro studies showed nM potency (IC50 - 12nM) and toxicology study displayed wide therapeutic window (>AUC97).
- It is administrated twice daily oral dosing.

AGI	R140Q Cell IC_{50} (uM)	Solubility pH 2 / H_2O (µM)	Microsome stability Eh Human/dog/rat	PPB hu / mu (% F_u)	Mouse PKPD EAUC97 12 h (ng*hr/mL)	Rat / Monkey Oral F %	Human Oral F% projected	Human dose projection BID (g/dose)	Brain:Plasma
221	0.012	41 / 10	0.06 / 0.26 / 0.04	2.3 / 6.5	15200	41% / 37%	50	0.4 - 1.1	0.14



Source: Company Reports

AG-221 Phase I Trial in Patients with Advanced Hematologic Malignancies Opened in Aug 2013

LEERINK SWANN

- It is a dose escalation study (NCT01915498) evaluating safety and tolerability of AG-221 in advanced hematologic malignancies that harbor an IDH2 mutation.
- AG-221 is administered orally, twice daily on days 1-28 (1 cycle=28 days) until disease progression or unacceptable toxicities, to assess safety and determine maximum tolerated dose (MTD).
- Estimated enrollment is 57 patients with anticipated primary completion date in January, 2016.

Source: ClinicalTrial.gov

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PRECLINICAL DATA FOR IDH1 INHIBITORS – AG-120, AG-5198

AGIO's First IDH1m Inhibitor Shows Robust In Vivo Potency in Xenograft Mouse Model

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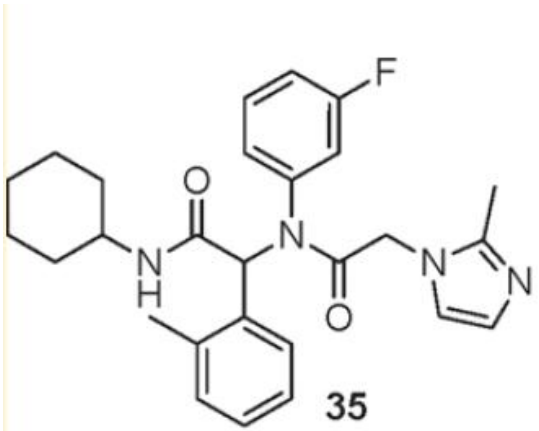
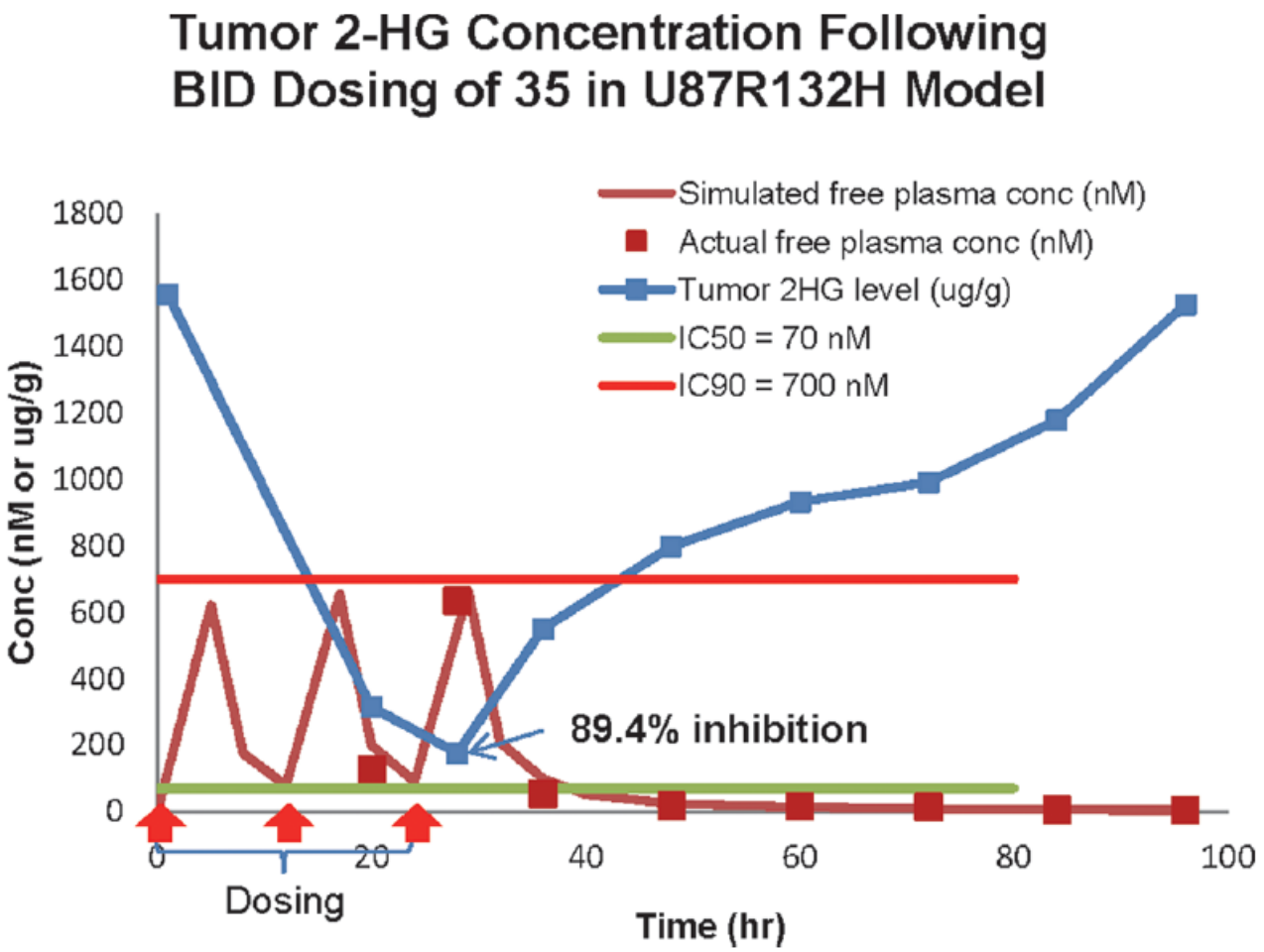
- Compound 35 was selected by high-throughput screening (HTS)



R132H IC_{50} = 0.07 μM
U87 IC_{50} = 0.07 μM

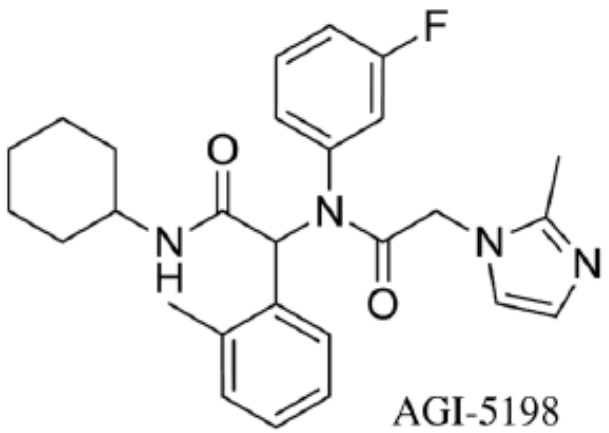


Source: Popovici-Muller et al, ACS Med Chem Lett, 2012, 3: 850-855

AG-5198 Inhibits R-2HG production

LEERINK SWANN

- AG-5198 is an R132H-IDH1 inhibitor that blocks the production of *R*-2-hydroxyglutarate (*R*-2HG)
- AG-5198 induced demethylation of histone H3K9me3 and expression of genes associated with gliogenic differentiation.
- Blockade of IDH1m impaired the growth of IDH1-mutant glioma cells without appreciable changes in genome-wide DNA methylation.



AGI-5198

IDH1		
R132H	**R132C**	**wildtype**
IC_{50} (μM)	IC_{50} (μM)	IC_{50} (μM)
0.07	0.16	> 100
IDH2		
R140Q	**R172K**	**wildtype**
IC_{50} (μM)	IC_{50} (μM)	IC_{50} (μM)
> 100	> 100	> 100

Source: Rohle et al, Science 2013, 340(6132): 626-630

AG-5198 Selectively Inhibits IDH1m, not IDH1 WT or IDH2 Isoforms

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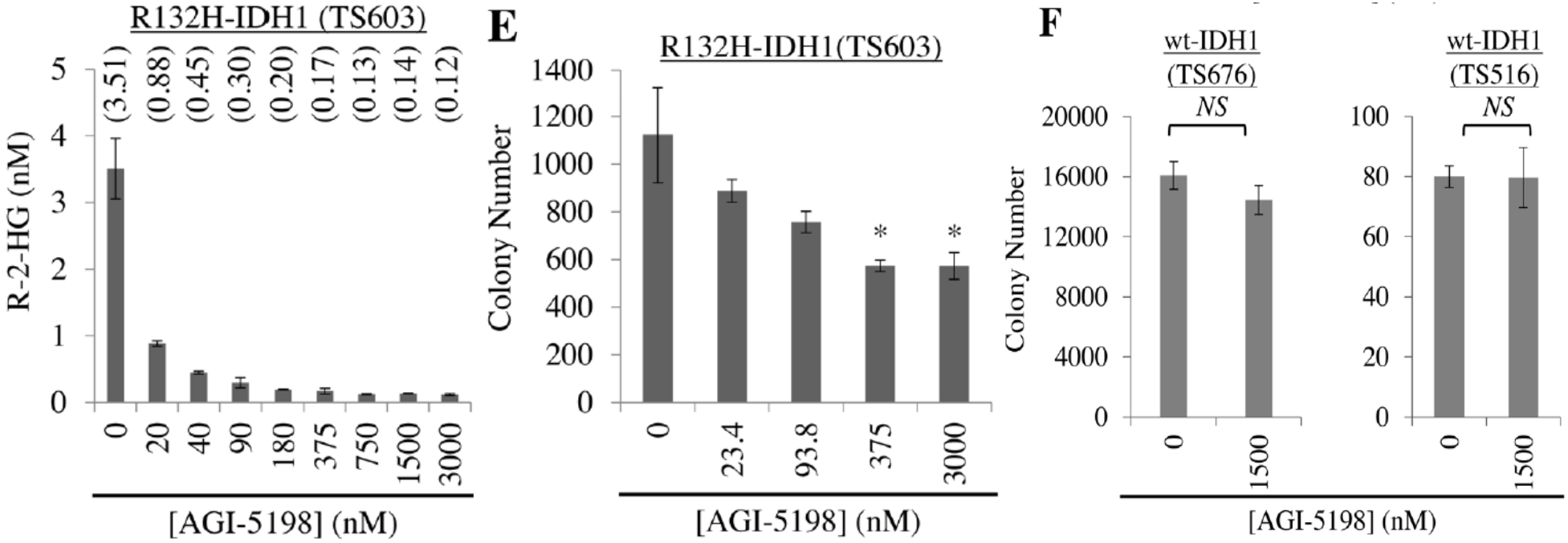
- R-2HG concentration in TS603 glioma cell pellets decreases significantly as AG-5198 inhibition increases.
- AG-5198 selectively inhibited colony formation in TS603 glioma cells in agar, while did not impair patient-derived glioma lines that expressed WT-IDH1.



Source: Rohle et al, Science 2013, 340(6132): 626-630

Treatment with AG-5198 Reduces R-2HG Level and Inhibits Tumor Growth

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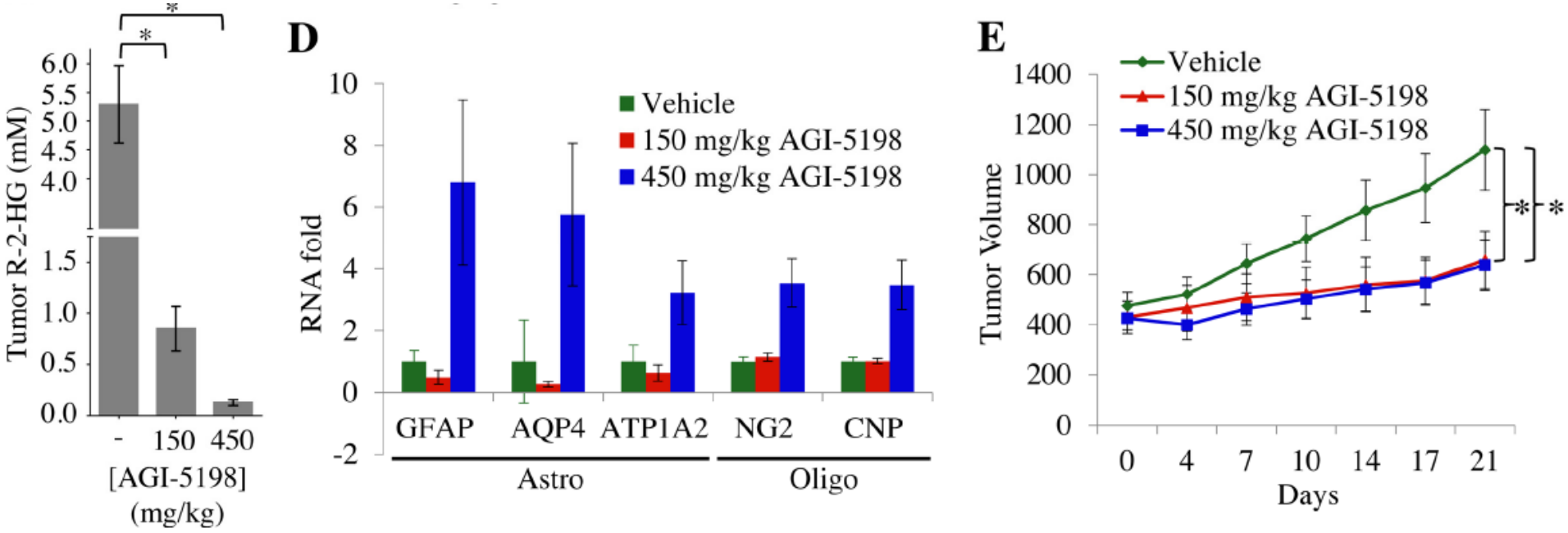
- AG-5198 treatment reduced intratumoral R-2HG concentration to nearly zero at 450 mg/kg dose in a mouse model.
- Tumor inhibition was similar at both 150 mg/kg and 450 mg/kg dosing while expression of astroglial differentiation genes only occurred at 450 mg/kg.



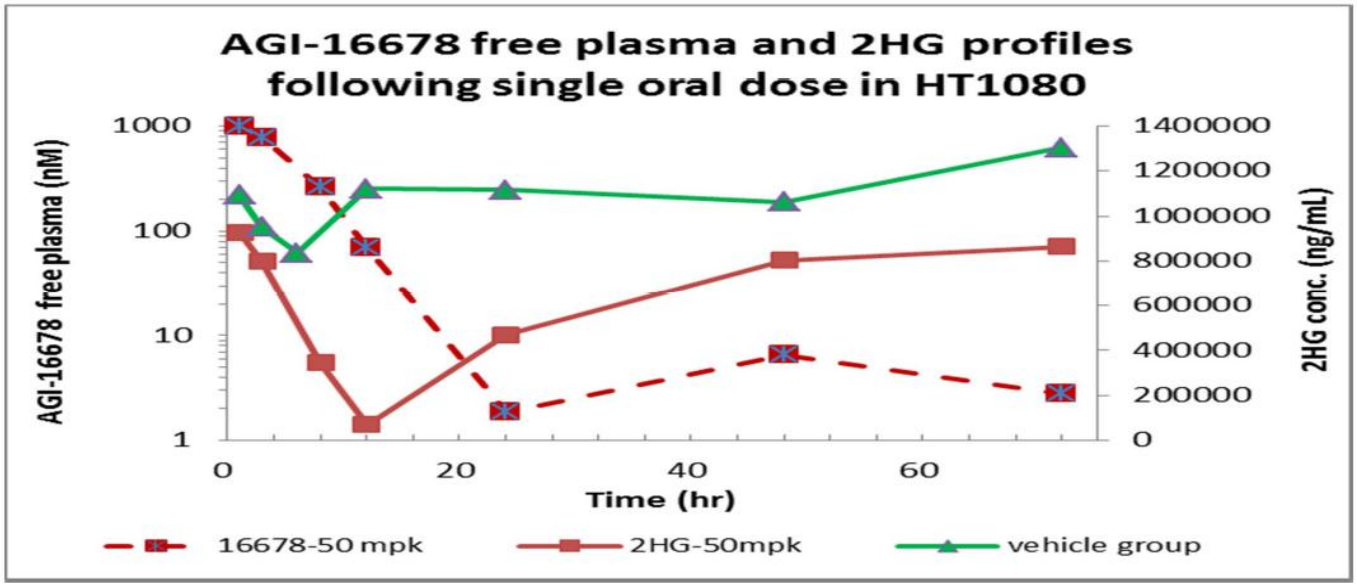
Source: Rohle et al, Science 2013, 340(6132): 626-630

AG-120 (AG-16678) is the Lead Candidate for Agio's IDH1 Program

LEERINK SWANN

- AG-120 is a reversible and selective IDH1 mutation inhibitor. It has nM potency (IC50 – 8nM) against R132C mutation and has highly selectivity against IDH wild type.
- Animal toxicology showed no MTD in rats and 20X margin in monkeys.
- Development is accepted by CELG in Mar, 2013; IND filing is expected in early 2014.

AGI	HT1080 R132C Cell IC_{50} (nM)	Solubility pH 7.4 / 2 (µM)	Microsome stability Eh Human / Cyno / Rat	PPB hu / mu (% F_u)	Mouse PKPD EAUC97 12 h (ng*hr/mL)	Rat / Monkey Oral F %	Human Oral F% projected	Human dose projection BID (g/dose)	Brain:Plasma
12910	8	24 / 21	0.23/0.09/0.25	4.4 / 9.3	12900	41% / 37%	50	0.6 (~ 0.3 – 0.9)	0.01



Source: Company Reports

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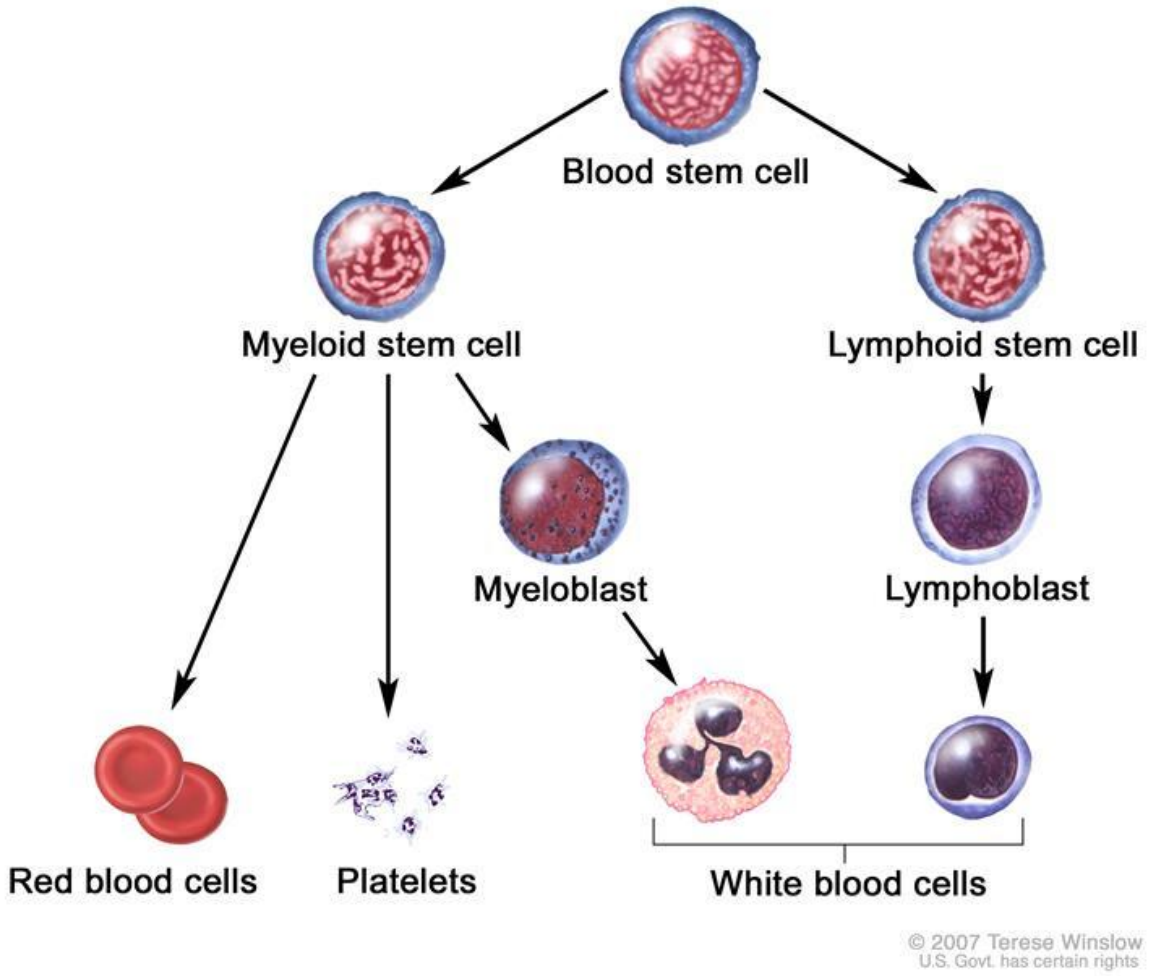
ACUTE MYELOID LEUKEMIA (AML)

Acute Myelogenous Leukemia (AML) is the Most Common Acute Leukemia in Adults



- In normal blood cell development, myeloid stem cell becomes red blood cells, white blood cells, or platelets.
- Acute Myelogenous Leukemia (AML) is a cancer of blood and bone marrow, in which the bone marrow produces myeloblasts (or myeloid blasts), a type of abnormal white blood cell

Source: National Caner Institute

AML Statistics

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- AML incidence 2006-2010
  - Incidence rate: 3.7 per 100,000
  - Median age at diagnosis: 67
  - IDH2 mutation ~15%
  - IDH1 mutation ~7.5%
- AML mortality
  - Death rate: 2.8 in 100,000
  - Median age at death: 72
- 5 year relative survival rate: 25%
- Current Standard Treatment
  - Chemotherapy, Radiation therapy, Stem cell transplant

Region	AML Incidence	Annual Deaths
United States	13,780	10,200
Europe	15,150	
Japan	5,230	

Source: National Caner Institute

AML Standard of Care

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- AML is the uncontrolled growth of abnormal white blood cells (blasts) accumulated in the bone marrow
- Standard therapy for AML is a combination of cytarabine and an anthracycline, with a CR rate of 60-70% and a cure rate of 15-25% in front line
- Patients with t(8;21), inversion 16 or t(15;17) have CR rate of 90% and cure rates of 50-80%; for patients (<65 years old) without these chromosome markers, CR rate is 70-80% and cure rate is 30-35% in front line
- Patients (>65 years old) with adverse karyotypes have CR rate of 35-50% and cure rate of <10% in front line
- Median PFS is ~7months and most patients will still relapse and require salvage therapy

Source: MD Anderson Cancer Center

AML Salvage Therapy

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- Treatment options are categorized based on cytogenetic and molecular markers at relapse
- Further stratification is based on duration of initial remission and whether therapy is for first or subsequent relapses
- Acute promyelocytic leukemia is treated as a separate entity due to its varied clinical course and treatment regimens

Source: MD Anderson Cancer Center

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GLIOMAS

Low-Grade (Grades I and II) and High-Grade (Grades III and IV) Gliomas

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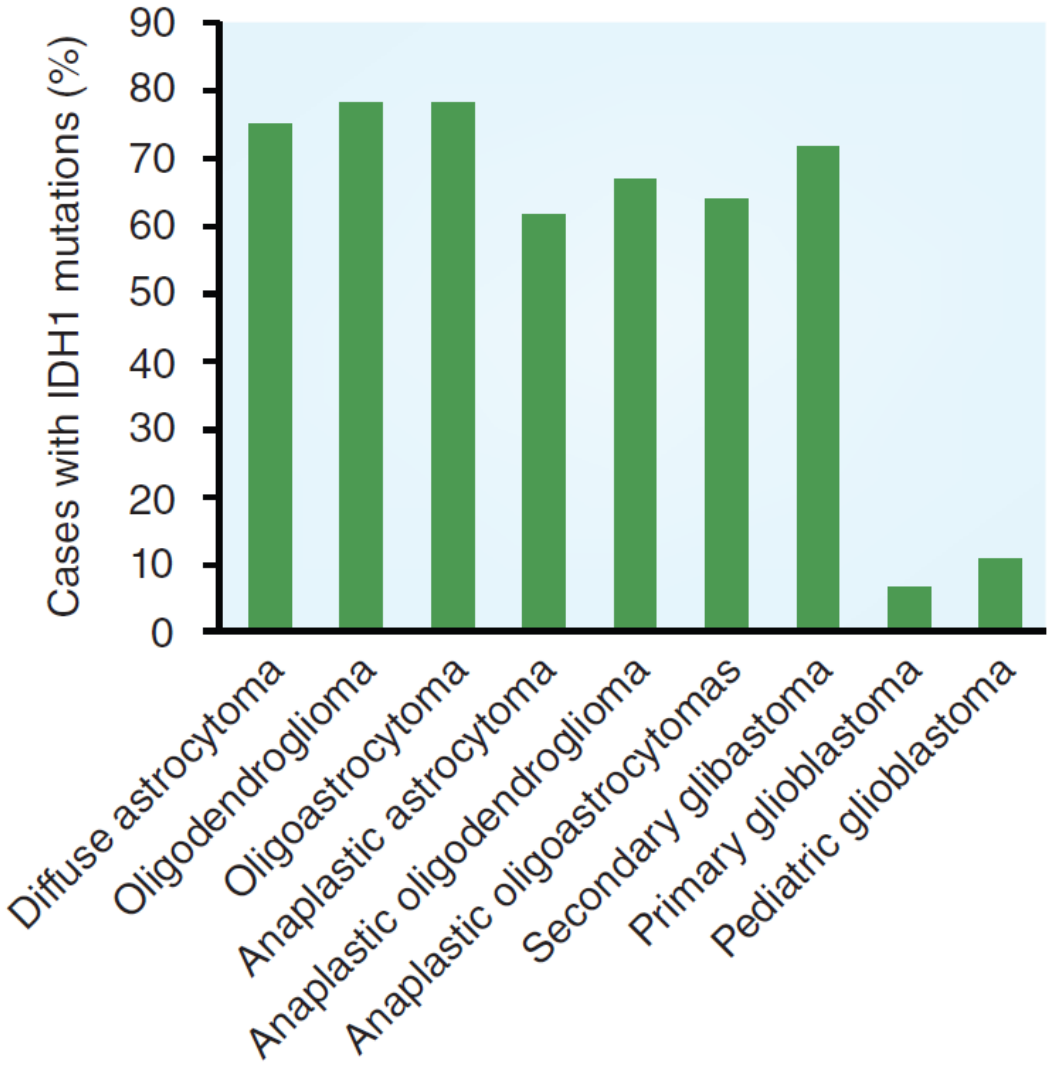
- Grade II constitutes 10–20% of primary brain tumors
- IDHm is identified in most grade II&III gliomas
- Standard of care for grade II gliomas: surgical resection and radiotherapy
- No biomarker has been validated for grade II glioma to determine the treatment of chemo vs radiotherapy
- IDH1 mutations' presence in early stage of brain tumors, provides potential use of IDH1 for prognostics of clinical therapies as a biomarker, especially for young patients with few symptoms

Frequency of IDH1 Mutations in Glial tumors



Source: Neurosurg. Clin. N. Am. (2012) 23: 471-480

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CHONDROSARCOMA

IDH1 and IDH2 Mutations are Detected in Central and Dedifferentiated Chondrosarcoma

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- Chondrosarcoma is a skeletal system cancer in which cells produce cartilage as they invade the bone
- Enchondroma can transform into chondrosarcoma grade I (low-grade cartilaginous tumors) and into chondrosarcoma grades II and III (high-grade)
- IDH1/2 mutations were detected in conventional central and dedifferentiated chondrosarcomas, but not in peripheral chondrosarcomas
- Research shows that among tumor samples that harbored IDH1/2 mutations, 54.3% were detected in enchondroma/chondrosacoma grade I, and 45.7% in grade II, grade III and dedifferentiated chondrosarcomas

Source: Amary et al, J of Pathology (2012) 224: 334-343

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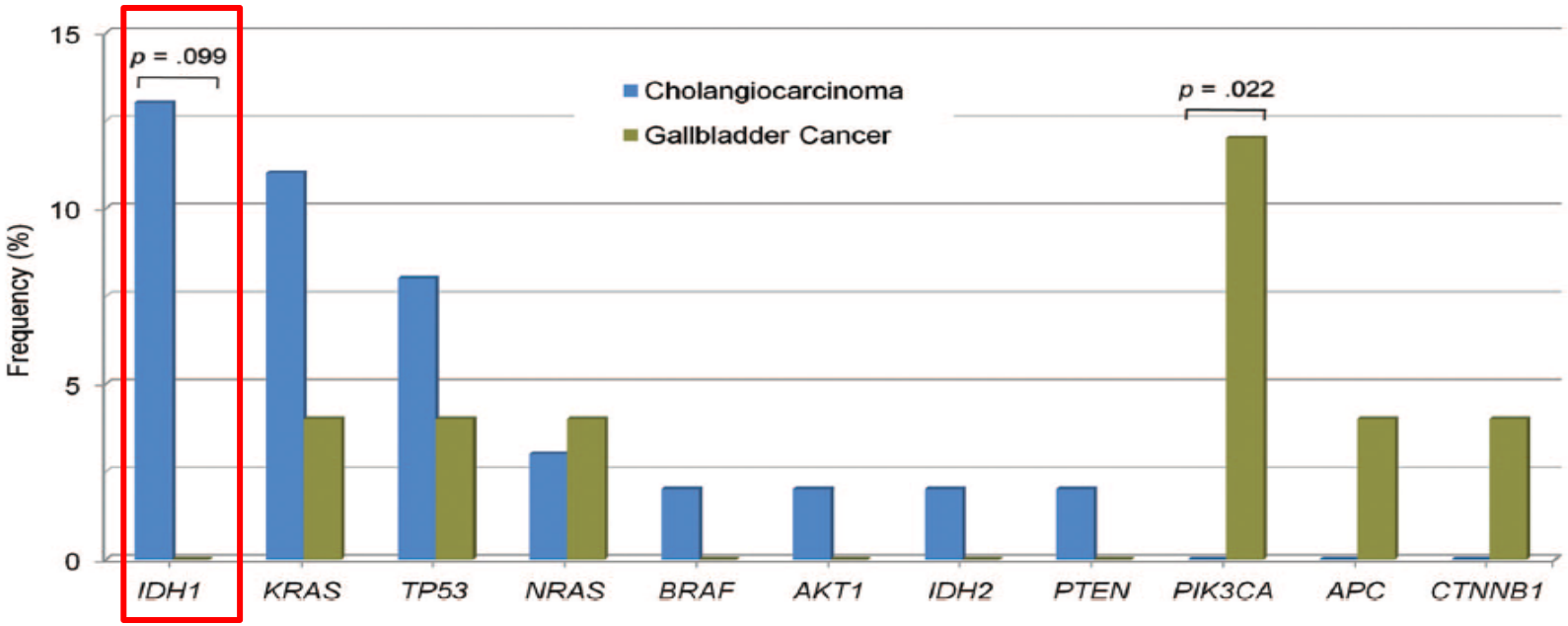
CHOLANGIOCARCINOMA

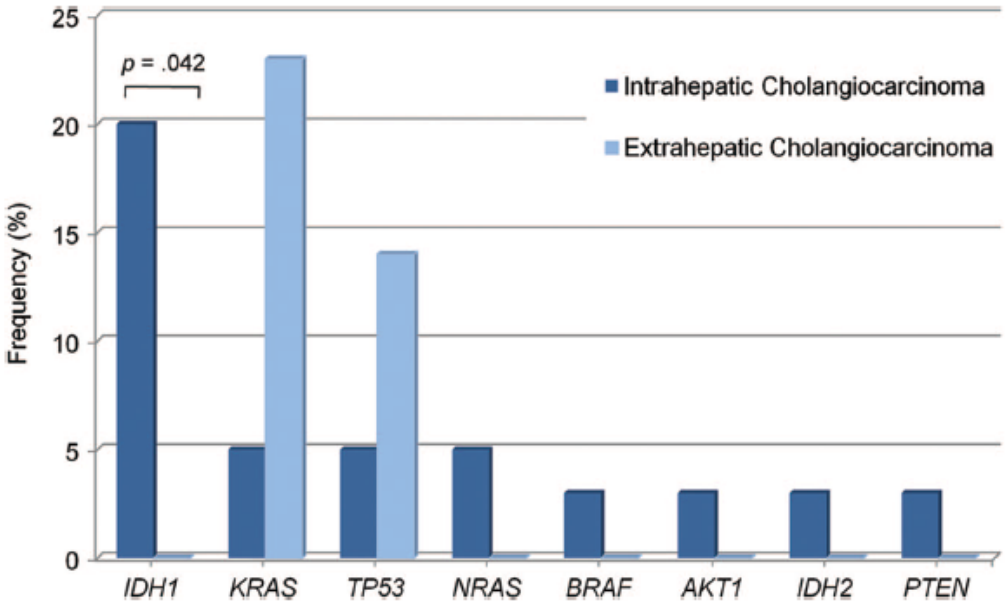
Clinical Tumor Genotyping Across Patients Shows Frequent IDH1 Mutations in Cholangiocarcinoma

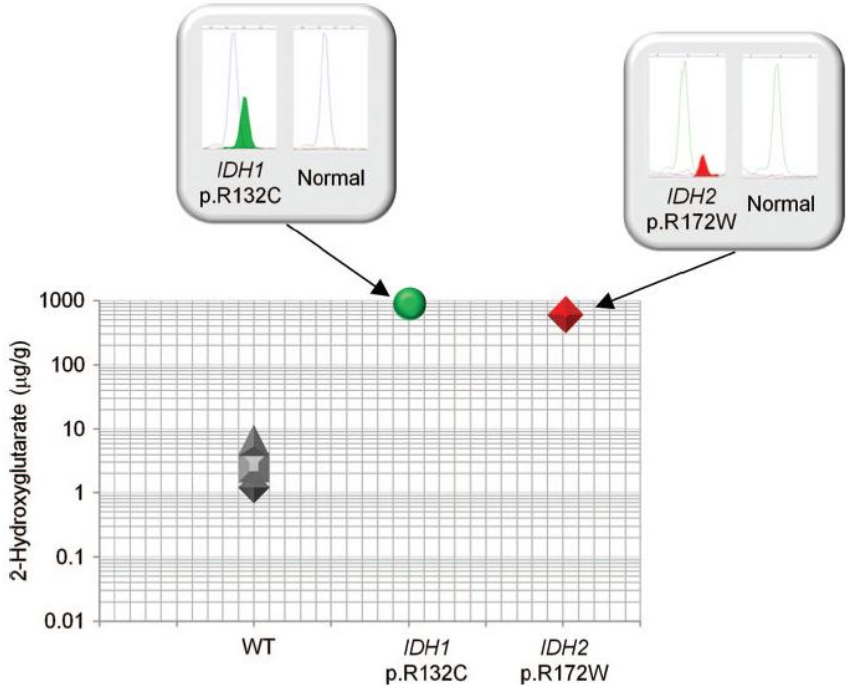


- Cholangiocarcinoma is a cancer that arises from the cells within the bile and is composed of cells of epithelial differentiation
- *IDH1* was the most frequently mutated gene in cholangiocarcinomas (eight of 62 clinical screened patient samples)

Source: Borger et al, Oncologist 2012, 17: 72-79

IDH Abnormalities in Cholangiocarcinoma Provide Potential Therapeutic Target





- IDH1 and IDH2 mutations were both exclusive and predominant in intrahepatic cholangiocarcinoma samples (23% of total samples)
- 2-HG accumulation is a consequence of mutant IDH1 and IDH2 in cholangiocarcinoma patients

Source: Borger et al, Oncologist 2012, 17: 72-79

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D2HGA – AN IEM RELATED IN PART TO IDH2 MUTATIONS

D2HGA Type I and II Patients

LEERINK SWANN

- D-2-Hydroxyglutaric Aciduria (D2HGA) is an inherited neurometabolic disorder; some patients are asymptomatic while others exhibit developmental delay, epilespsy, hypotonia and cardiomyopathy.
- High levels of 2-HG in urine, plasma and cerebrospinal fluid are detected in most D2HGA patients
- 50% of patients are D2HGA type I, with mutations in the gene D2HGDH encoding D2-hydroxyglutarate dehydrogenase
- D2HGA type II patients possess IDH2 mutations R140Q and R140G
- Hyperproduction of D2HG causes the higher urinary excretion of D2HG in type II patients

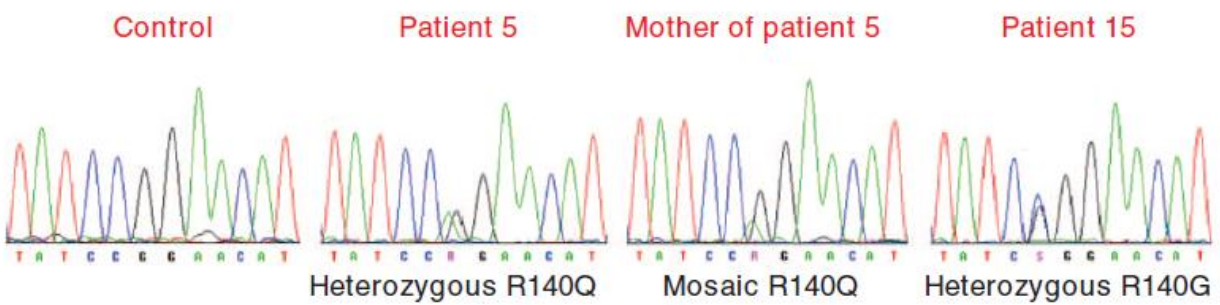
Source: Kranendijk et al, Science 2010, 330(6002); 336

IDH Mutations are De Novo in D2HGA Patients

LEERINK SWANN

- Open reading frame (ORF) of IDH1 and IDH2 of 17 unrelated patients are sequenced. Most sets of parents do not have R140Q mutation, suggesting that the mutation arose de novo. IDH2 R140Q mutation was detected in DNA of patient 5's mother only.
- None of the patients in the study has been diagnosed with cancer.

	D-2-HGA type I	D-2-HGA type II
Number of participants	24	15
Urinary D-2-HG (mmol mol creat.$^{-1}$) [normal amount in controls < 17.0]	Mean = 969 (n = 20)	Mean = 2153 (n = 14)
Gene and accession no.	*D2HGDH* NM_152783.3	*IDH2* NM_002168.2
Type of mutations	Heterogeneous (*5*, *6*)	c.419G>A, R140Q (n = 14) c.418C>G, R140G (n = 1)
Trait	Autosomal recessive	Autosomal dominant
Probability of affected fetus	25%	>0%–50%



Source: Kranendijk et al, Science 2010, 330(6002); 336

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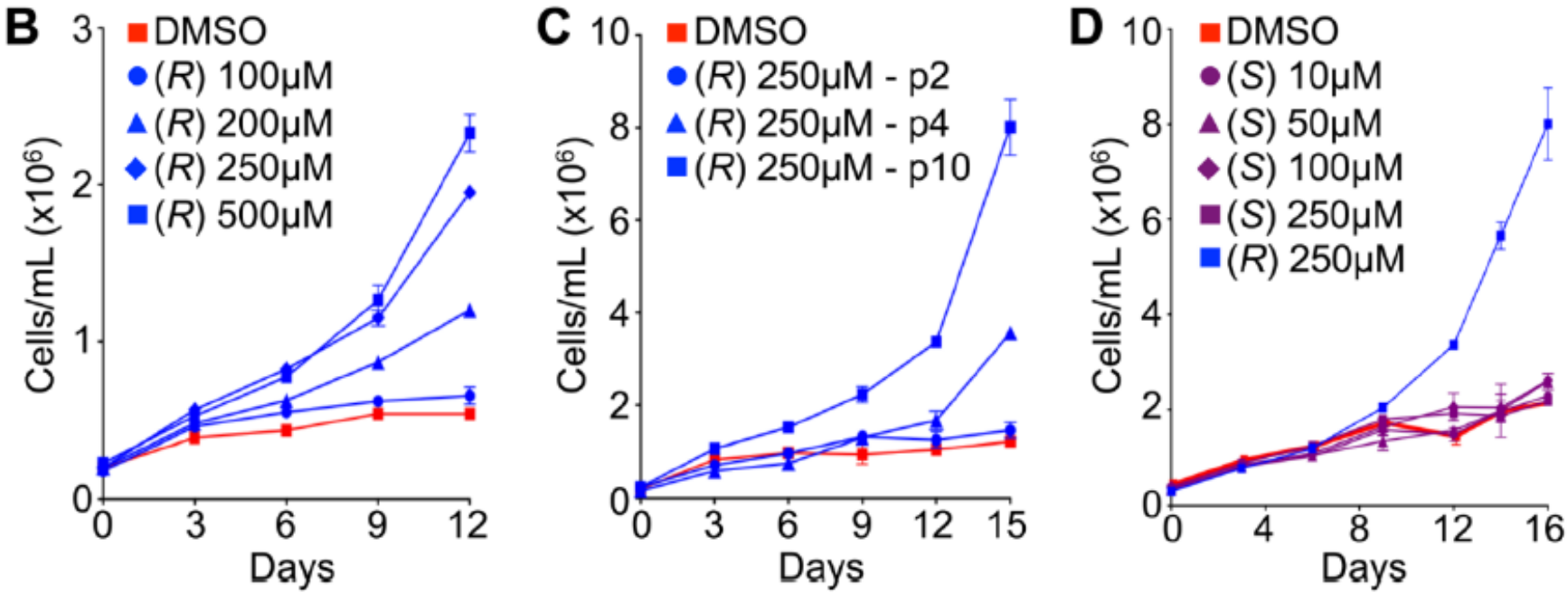
MECHANISTIC LINK BETWEEN 2-HG AND CANCER

R-2HG Promotes Leukemogenesis

- TF-1 cells passaged in TFMB-(*R*)-2-HG became growth factor-independent, and leukemogenesis promotion was dose-dependent and passage-dependent
- TFMB-(*S*)-2-HG did not promote cytokine-independence at any concentration or time point



Source: Losman et al, Science, 2013, 339(6127); 1621-1625

Removal of R-2HG Restored Cell Differentiation

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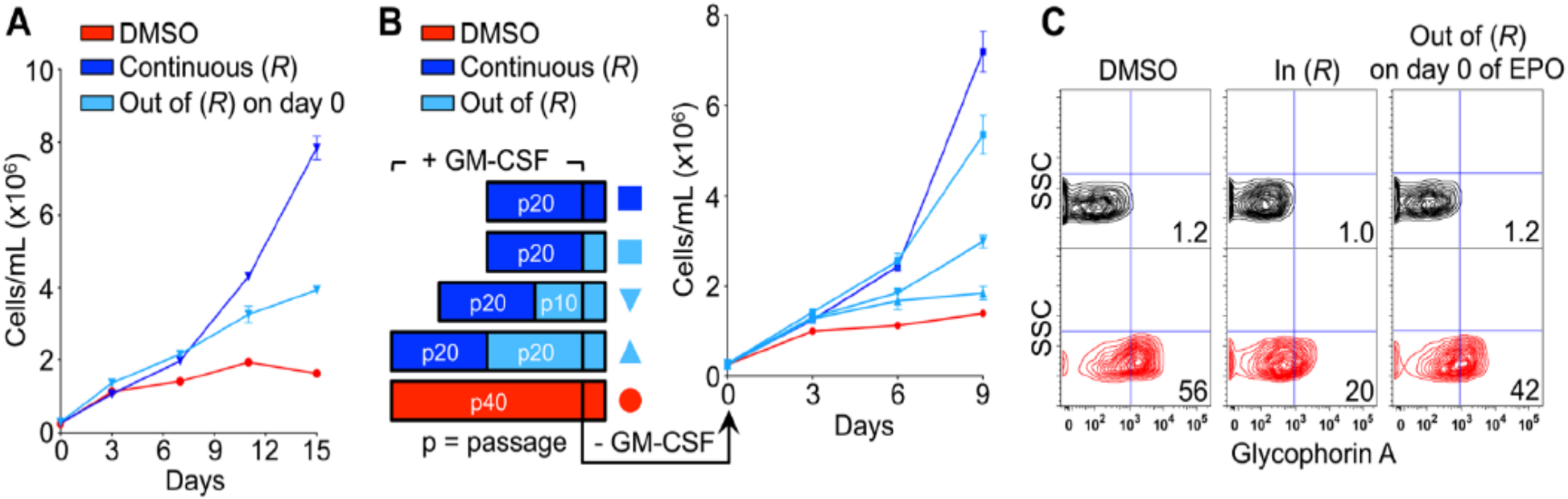
- Reversion time of growth factor independence was influenced by the number of passages of TFMB-(*R*)-2-HG exposure
- Removal of TFMB-(*R*)-2-HG restored TF-1 cells differentiation in response to EPO



Source: Losman et al, Science, 2013, 339(6127); 1621-1625

R-2HG Leads to Competitive Inhibition of 2-OG Dependent Enzymes

LEERINK SWANN

- The hypothesis that has gained the most traction about how R-2HG leads to transformation is that R-2HG competitively inhibits 2-OG dependent enzymes that function as tumor suppressors. Approximately 70 known and putative 2-OG dependent dioxygenases could be potential targets for R-2HG in mutant IDH patients, among which, key candidates include TET2 (DNA/RNA modifying enzymes), JmjC histone demethylases, EglN prolyl-4hydrozylase.

Table 2. *List of known and putative 2OG-dependent dioxygenases in the in the GenBank DNA database*

DNA/RNA-modifying enzymes	JmjC domain-containing enzymes		Proline/lysine hydroxylases	Other hydroxylases
TET1	KDM2A	KDM7A	EGLN1	ASPH
TET2	KDM2B	KDM8	EGLN2	ASPHD1
TET3	KDM3A	HR	EGLN3	ASPHD2
ABH1	KDM3B	JARID2	P4HA1	BBOX1
ABH2	KDM4A	JHDM1C	P4HA2	FIH1
ABH3	KDM4B	JMJD1C	P4HA3	HSPBAP1
ABH4	KDM4C	JMJD4	P4HB	OGFOD1
ABH5	KDM4D	JMJD6	P4HTM	OGFOD2
ABH6	KDM5A	JMJD7	PLOD1	PAHX-AP1
FTO	KDM5B	JMJD8	PLOD2	PHYH
	KDM5C	MINA	PLOD3	PHYHD1
	KDM5D	NO66	LEPRE1	
	KDM6A	PHF2	LEPREL1	
	KDM6B	PHF8	LEPREL2	
		UTY	BBOX2	

Source: Losman et al, Gene Dev (2013) 27:836-852.

TET is 2-OG Dependent DNA-Modifying Enzyme

LEERINK SWANN

- TET1, 2 and 3 are members of 2-OG dependent DNA-modifying enzymes which hydroxylate 5-methylcytosine (5mC) to 5-hydroxymethycytosine (5hmC) and oxidize 5hmC to 5-formylcytosine (5fC) and 5-carboxylcytosine (5caC). Somatic mutations in TET2 are common in clonal myeloid disorders with 10-40% in AML, MDS, MPN and CMML (chronic myelomonocytic leukemia). Majority of the mutations are heterozygous.
- TET enzymes are believed to play an important role in the epigenetic regulation by demethylating DNA. Oxidation of 5mC by TET enzymes followed by TDG (thymine-DNA glycosylase) mediated base excision or 5caC decarboxylation would result in DNA demethylation.
- However, studies showed inconsistent results between TET2 mutation status and DNA methylation status in myeloid diseases. It is possible that TET2 mutations alter DNA methylation at specific loci while regulating global DNA methylation at various level.

Source: Losman et al, Gene Dev (2013) 27:836-852.

TET2 is An Important Target of R-2HG in Mutant IDH-Mediated Transformation

LEERINK SWANN

- Several lines of evidence suggest that TET2 is an important target of R-2HG in mutant IDH-mediate transformation.
  - Catalytic activity of TET2 is potently inhibited by R-2HG in in vitro studies.
  - IDH mutant brain tumors and leukemias usually have global DNA hypermethylation.
  - IDH mutations and TET2 mutations are mutually exclusive in AML, suggesting two mutations acting on the same pathway.
  - R-2HG enhances transforming effects of partial inhibition of TET2.

Source: Losman et al, Gene Dev (2013) 27:836-852.

IDH Mutations Directly Cause DNA Hypermethylation

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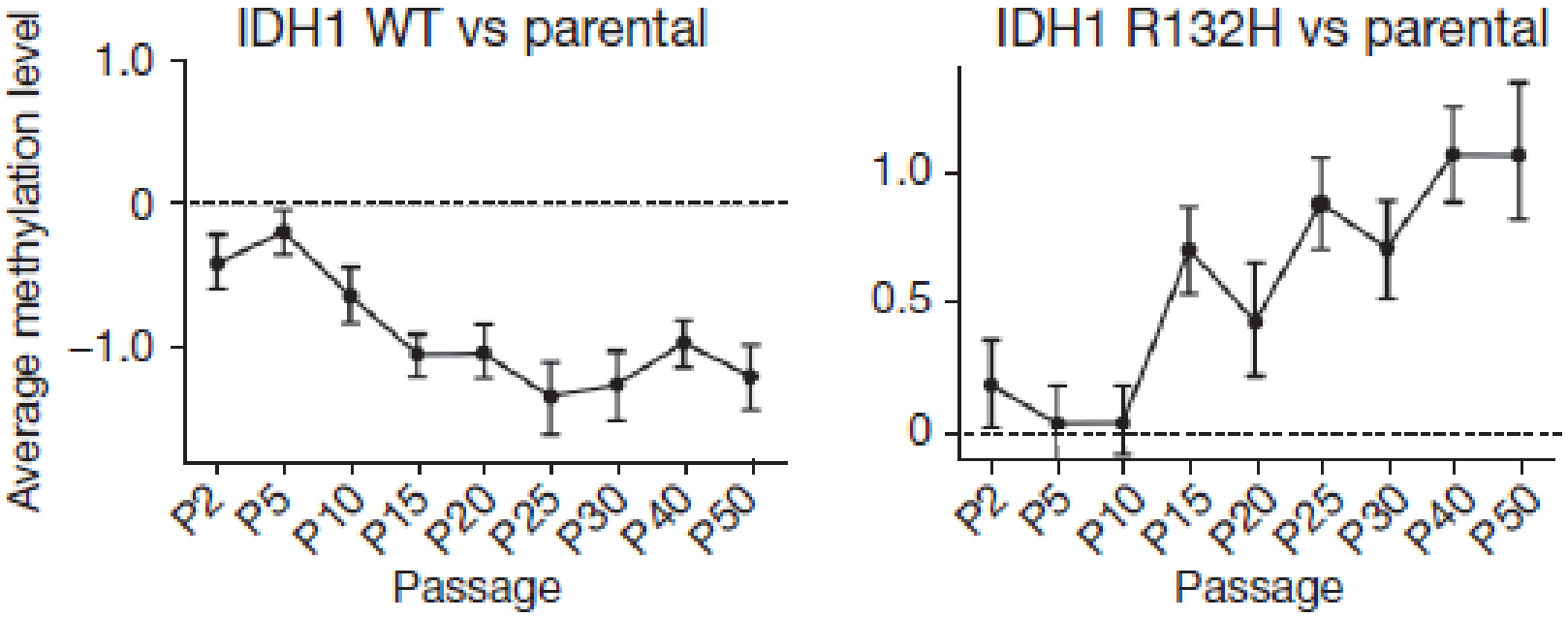
- Expression of IDH1m enhances the methylation level, while IDH1 WT shows methylation decrease.
- IDH1 caused hypomethylation from P10, indicating that 2HG and 2-OG affect methylome simultaneously.



Source: Turcan et al, Nature 2012, 438; 479-483

JmjC Histone Demethylases are 2-OG Dependent Enzymes Functioning as Tumor Suppressors

LEERINK SWANN

- JmjC histone demethylases are tumor suppressors
  - H3K36 JmjC demethylase KDM2B is a transcription repressor and its expression level is significantly lower in brain tumors.
  - H3K9 JmjC demethylase KDM3B is frequently deleted in 5q- MDS and AML.
  - H3K4 JmjC demethylase KDM5C is occasionally mutated and inactivated in clear cell renal carcinoma.
  - H3K27 JmjC demethylase KDM6A negatively regulate Notch and block cell cycles and KDM6B involves in P53 regulation and promote the terminal differentiation of glioblastoma cells.

Source: Losman et al, Gene Dev (2013) 27:836-852.

IDH Mutants Increase Histone Methylation and 2HG Level in Transfected Cells and Tumor Tissue

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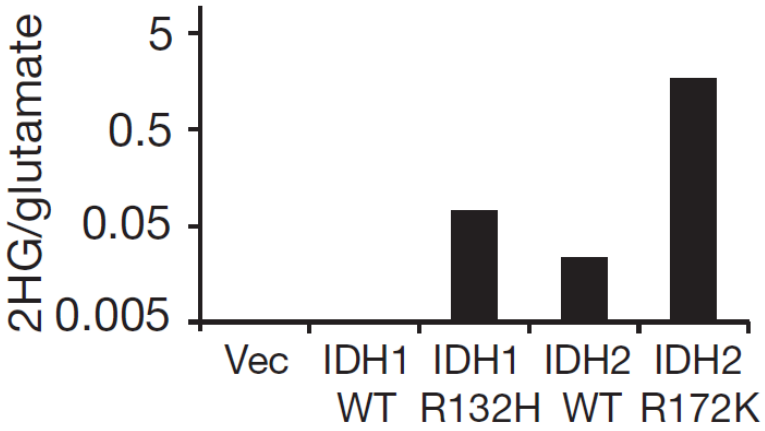
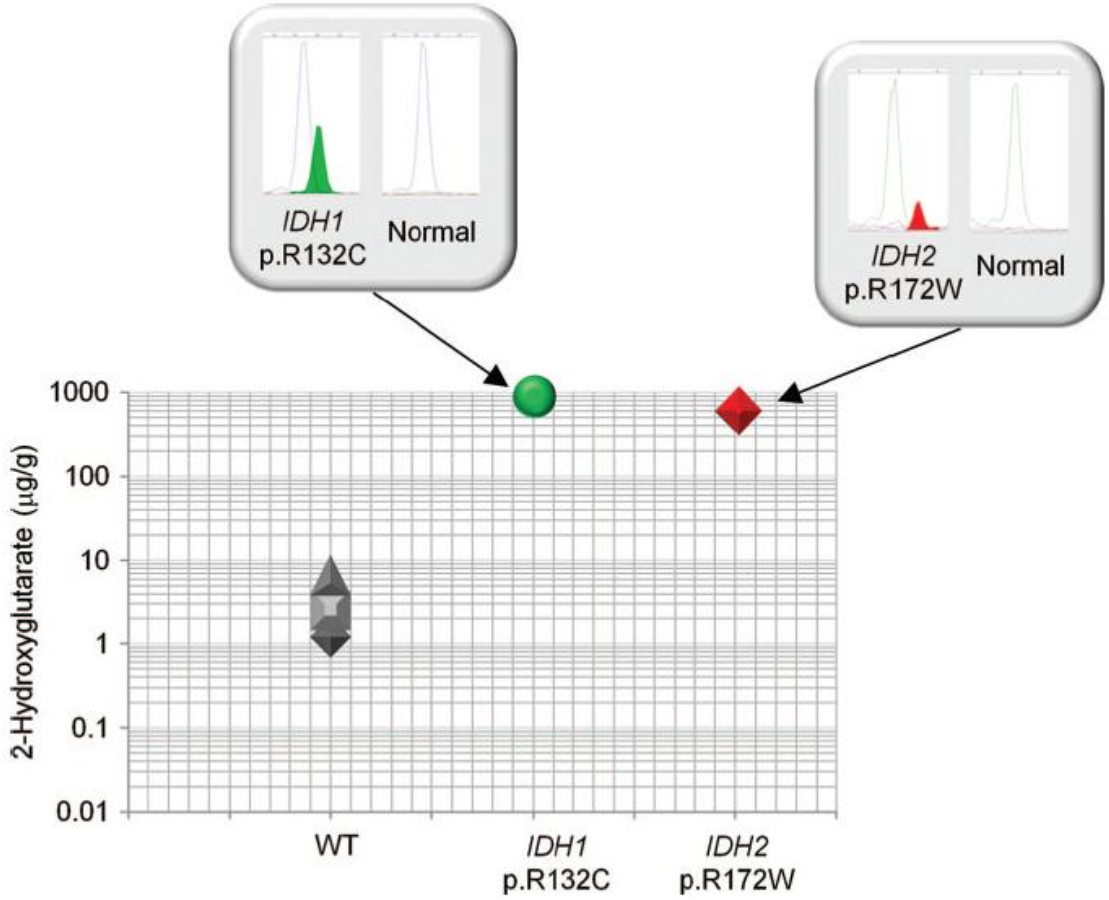
- Quantification of Intracellular 2HG/Glutamate in Transfected 293T Cells





Source: Lu et al, Nature 2012, 483(7390):474-478; Borger et al, Oncologist 2012, 17: 72-79

However, Direct Link Between JmjC Histone Demethylases and R-2HG Is Still Missing

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- It is not known whether R-2HG affects histone methylation in primary human IDH mutant tumors. It is possible that R-2HG induces histone methylation at specific loci.
  - Aberrant histone methylation in brain tumors is common regardless of IDH mutation status.
  - IDH1 R132H knock-in mice only showed modest increase in methylated H3K4 levels but no change in other histone methylation marks.

Source: Losman et al, Gene Dev (2013) 27:836-852.

Inhibition of EglN Prolyl-4-hydroxylase by R-2HG May Lead to Reversal of Tumorigenesis

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- EglN1, 2, 3 are members of family of 2-OG dependent dioxygenases that regulate the activity of HIF, a transcription factor that regulates gene expression in response to hypoxia.
- Studies suggest that R-2HG potentiates EglN activity and reduces HIFα induction in response to hypoxia. Consistent with in vitro studies, IDH mutant brain tumors showed decreased HIF activation.
- Although IDH1 R132H knock-in mice showed elevated HIFα in the brains, early death due to hemorrhage suggesting brain perfusion during development was abnormal and tissue hypoxia rather than a direct effect of R-2HG on EglN activity is the underlying cause.
- Depletion of EglN1 in mutant IDH-transformed astrocytes inhibits colony formation. Inhibition of EglN1 by (S)-2HG reverse the leukemia transformation that would otherwise occur due to its inhibition of TET2 activity.

Source: Losman et al, Gene Dev (2013) 27:836-852.

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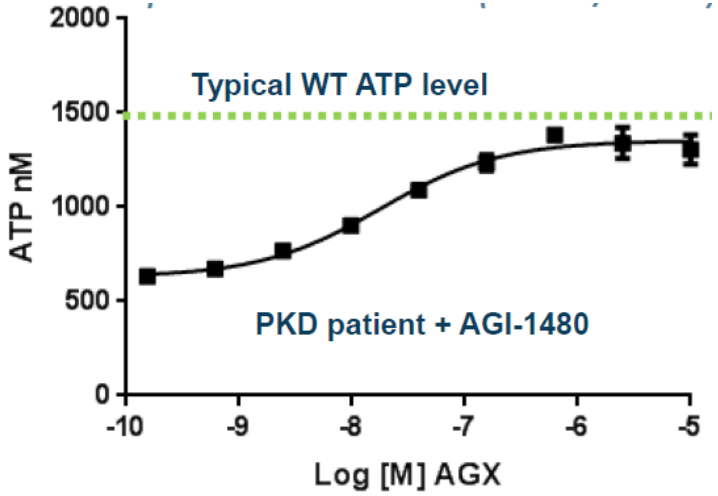
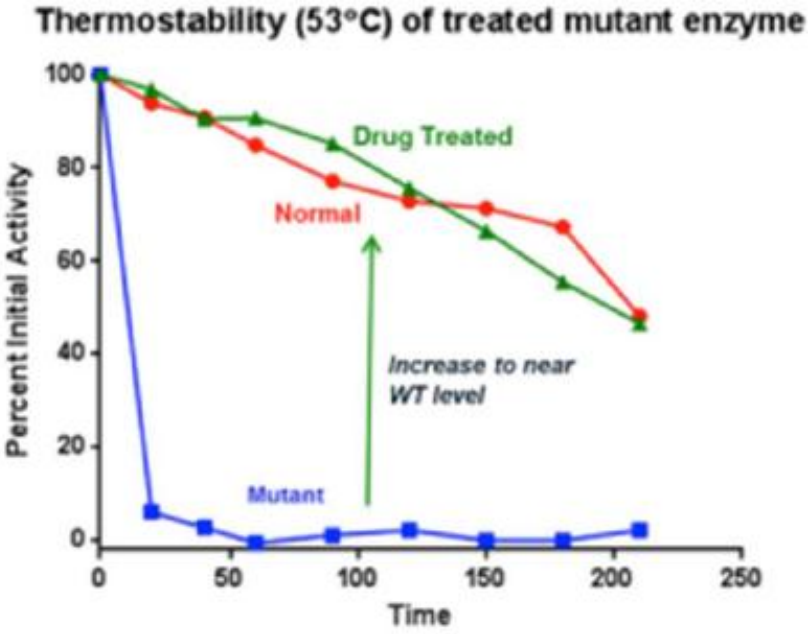
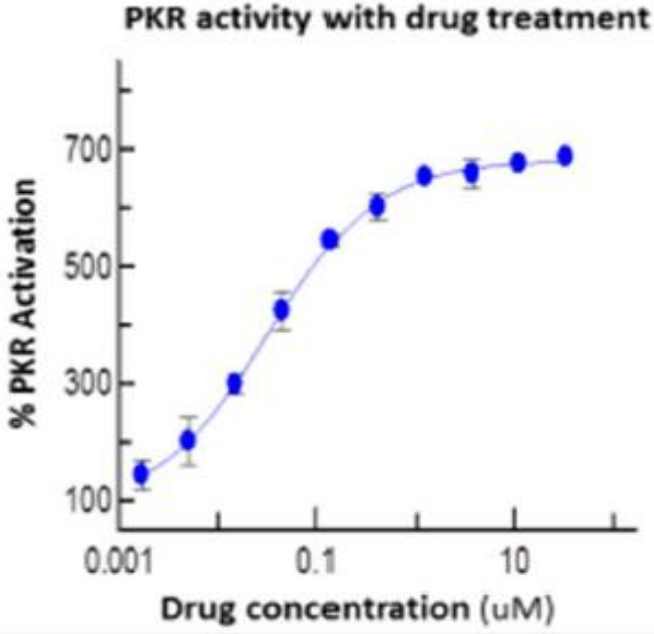
PRECLINICAL DATA FOR PKR ACTIVATOR – AG-348, AG-1480

AG-1480 Restores Kinetics and Functions of Mutant Enzymes



- AG-1480 is a PKR activator that corrects metabolic defect in red blood cells (R486W/G341A)
- AG-1480 restored thermo stability in vitro and ATP level in ex vivo samples from patients





Source: Company Reports

AGIO's PKR Activators Showed Potent Activity in Animal Studies

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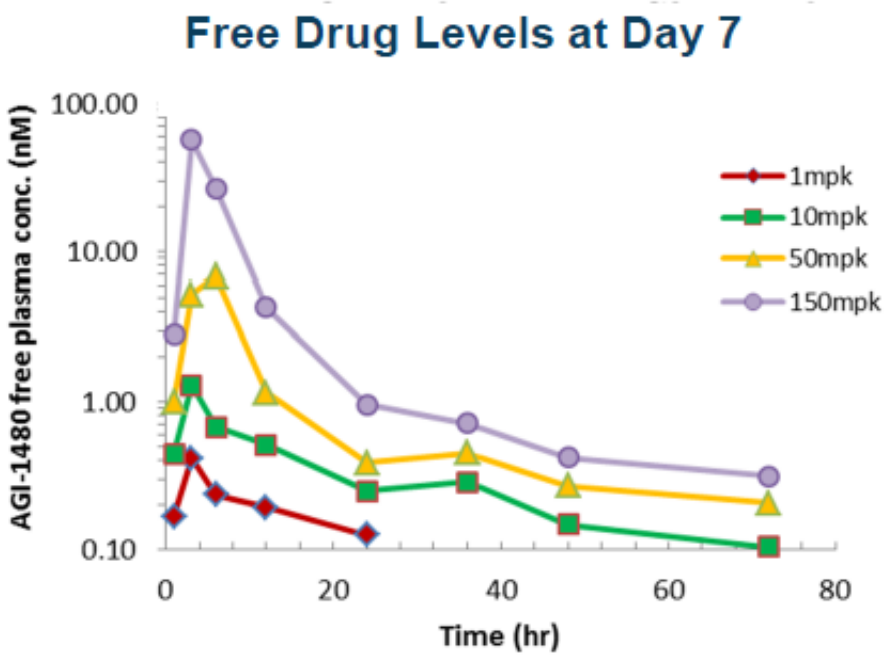
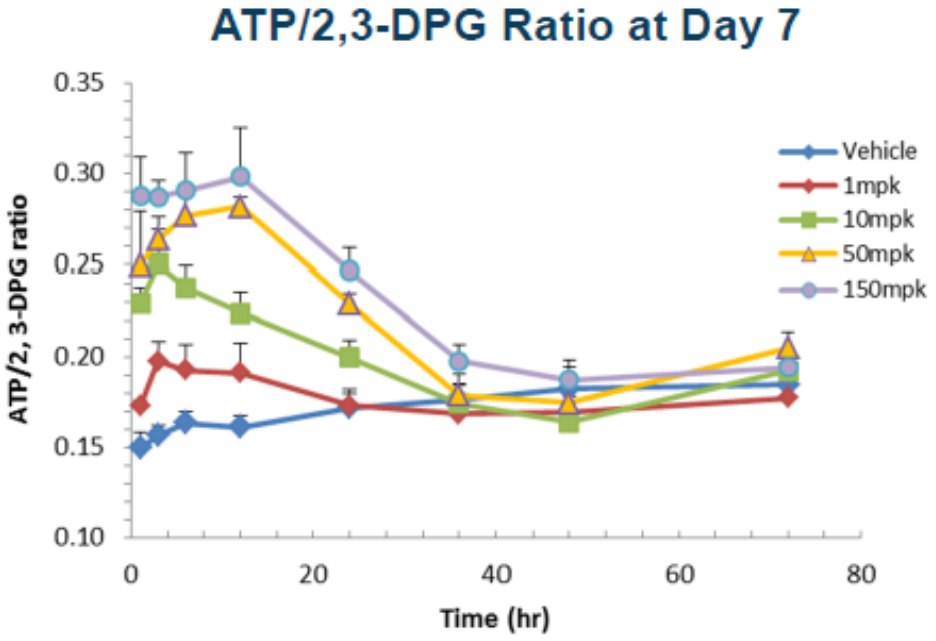
- WT mice administrated orally with PKR activators showed an increase in ATP/2,3-DPG ratios.
- In vivo potency: ~20 nM.





Source: Company Reports

Agios PK activators can activate the most common mutations

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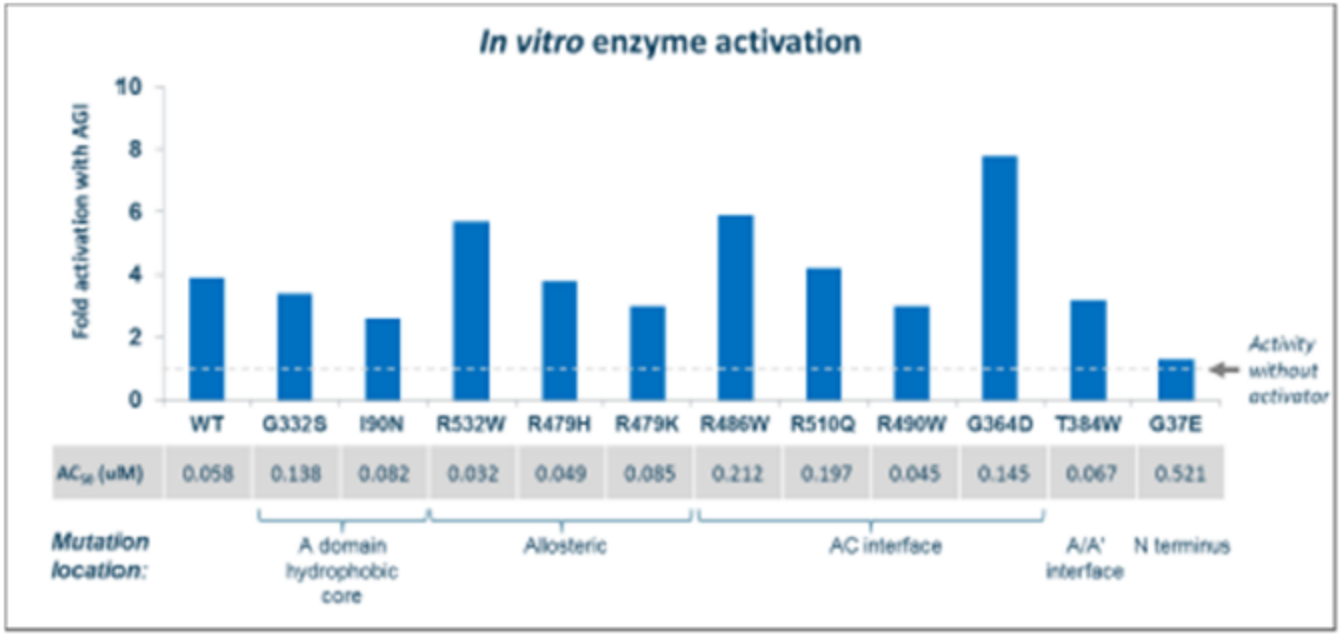
- There are over 120 PK mutations reported. Agios lead compounds can active 11 of 12 most common mutations. The frequency of the remaining mutation (G37E, see below) is not clear.
- Since people with a single wildtype allele are normal, the PK activators do not need to restore activity to more than 50% of the wildtype. Management states that in vitro experiments show that its PK activators can restore ATP production to nearly 100% of the wildtype.



Source: Company reports

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GLUTAMINASE (GLS)

Glutaminase (GLS) is Essential for Cancer Cell Growth

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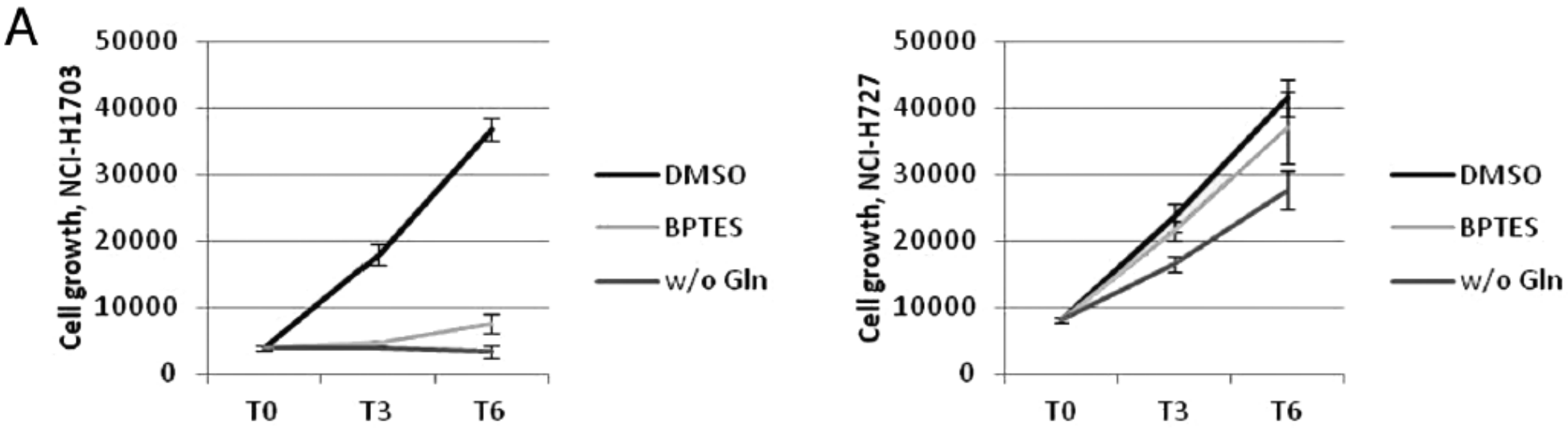
- Glutaminase (GLS), is an enzyme that converts glutamine (Gln) into glutamate, and subsequently a-KG before entering TCA cycle.
- GLS can be expressed as isoforms GLS1 (kidney glutaminase) and GLS2 (liver glutaminase); GLS1 can be expressed as variants GAC and KGA
- GAC is the predominant GLS1 variant in Non-small cell lung cancer (NSCLC)
- Agios has identified a method of identifying the patients whose tumors are addicted to GLS enzyme, and drug discovery is currently in the late lead optimization stage

Source: Company reports and Leerink Swann

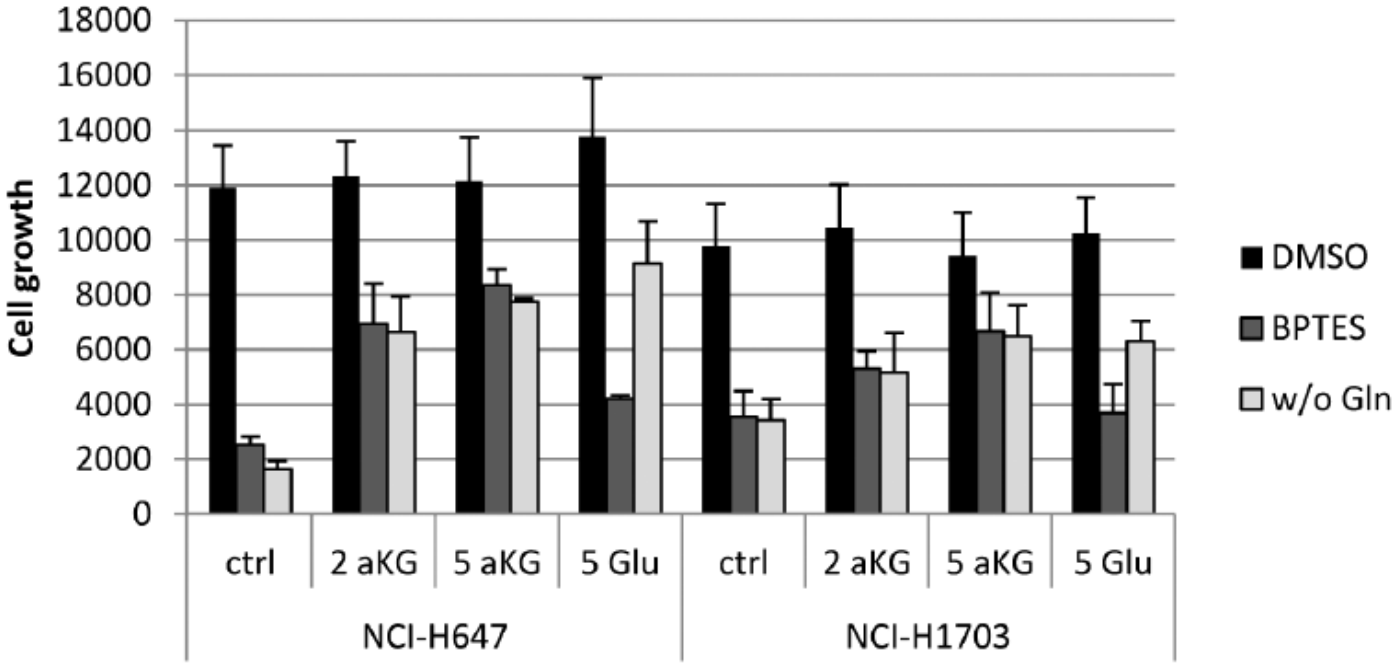
Glutamine Depletion and GLS1 Inhibition Have Similar Effects on Glutaminolysis



- Research shows that GLS is an essential enzyme in NCI-H1703 cells for glutaminolysis, while knockdown of other enzymes had no effect on cell growth
- GLS1 inhibitor bis-2[5-phenylacetamido-1,2,4-thiadiazol-2-yl]ethylsulfide (BPTES) has similar effects as Gln depletion in Gln-dependent cell line (NCI-H1703), and Gln-independent cell line (NCI-H727)

Source: Pieter et al, Cancer Bio & Therapy (2012) 13:1185-1194.

Both a-KG and Glutamate Can Rescue Cell Growth



- In Gln withdrawal, both are able to rescue cell growth; in BPTES treatment, only a-KG can rescue growth
- Gln depletion affected cell growth by decreased glutaminolysis
- GLS1 inhibition has similar effects and downstream metabolites a-KG can partially rescue growth

Source: Pieter et al, Cancer Bio & Therapy (2012) 13:1185-1194.

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PARTNERSHIPS

CELG Partnership

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- In April 2010 Agios entered into a Collaboration and License Agreement with CELG on cancer metabolism programs
  - Received $121M upfront and $9M from the sales of $9M in series B convertible preferred stock
  - Rec'd additional $20M as CELG extends the discovery phase until April 2014
  - CELG has option to obtain exclusive rights for further development and commercialization of certain programs. CELG can extend such period through April 2016 by making up to $40M extension payments
  - AGIO can convert 1 of every 3 programs following IND filing into a split licensed program, where AGIO retains US rights and WW development cost will be split 50:50. AGIO retains the option for exclusive US rights on AG-120
  - For programs that CELG licenses WW rights, CELG pays for all development costs and pays royalties at tiered rate of 10-15%
  - Eligible to receive up to $120M in milestone payments for all programs

Source: Company Reports

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INTELLECTUAL PROPERTY

Intellectual Property

- Claims of biochemistry and diagnosis for therapeutics directed to cancer metabolism, including IDH2, IDH1 and GLS; and to IEM, including PKR
- ~30 pending U.S. patent applications
- ~120 pending foreign patent applications
- Expected expiry between 2027 and 2034

Source: Company Reports

Cancer Metabolism Patent Estate

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- *IDH2:* 2 US pending patent applications for composition of matter, methods of making and use AG-221
  - Related international and 1 PCT applications pending
- *IDH1:* 5 US pending patent applications for compositions of matter, methods of making and use for AG-120
  - Related international and 4 pending PCT applications
- *GLS:* 2 US pending patent applications for compositions of matter, methods of making and use for the lead series
  - Related 1 pending PCT application
- Pending applications for compositions of matter and methods of use on biomarkers related to IDH1, IDH2 and GLS

Source: Company Reports

IEM Patent Estate

- *PKR:* 2 US pending patent applications for directed to compositions of matter, methods of making and use for AG-348
  - Related international and 7 pending PCT applications

Source: Company Reports

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MANAGEMENT

Management Team

Management	Title	Prior Experience
David Schenkein, MD	CEO	Sr VP of clinical hematology/ oncology at Genentech, Sr VP of clinical research at Millennium
Duncan Higgons	COO	President and COO of Archemix, COO of TransForm Pharma.
Scott Biller, Ph.D.	CSO	VP and head of global discovery chemistry at the NIBR, VP of pharmaceutical candidate optimization at BMS
Glenn Goddard	VP, Finance	VP of Finance at Archemix, Corporate controller at ImmunoGen

Source: Company Reports

AGIO Income Statement	2011A	2012A	Mar-13A	Jun-13E	Sep-13E	Dec-13E	2013E	2014E	2015E	2016E	2017E	2018E
Collaboration agreements												
Royalties												1,595
Sales												0
Total revenue	21,837	25,106	6,268	6,268	6,268	6,268	25,072	7,268	0	0	0	1,595
COGS										0	0	0
% of revenue										*5%*	*5%*	*5%*
R&D	31,253	41,037	11,462	11,577	11,692	11,809	46,540	53,445	55,048	56,699	58,400	60,152
G&A	7,215	7,064	1,852	1,871	1,889	1,908	7,520	8,635	9,499	10,449	15,000	25,000
% of revenue												
Total operating expenses	38,468	48,101	13,314	13,447	13,582	13,717	54,060	62,080	64,547	67,148	73,400	85,152
Net income (loss) from operations	(16,631)	(22,995)	(7,046)	(7,179)	(7,314)	(7,449)	(28,988)	(54,812)	(64,547)	(67,148)	(73,400)	(83,557)
Investment income	132	69	8	0	0	0	8	0	0	0	0	0
Net income (loss) before income taxes	(16,499)	(22,926)	(7,038)	(7,179)	(7,314)	(7,449)	(28,980)	(54,812)	(64,547)	(67,148)	(73,400)	(83,557)
Provision (benefit) for income taxes	7,207	(2,824)	190	0	0	0	190	0	0			
Tax rate												
Net income (loss)	(23,706)	(20,102)	(7,228)	(7,179)	(7,314)	(7,449)	(29,170)	(54,812)	(64,547)	(67,148)	(73,400)	(83,557)
Cumulative preferred stock dividends	(3,100)	(7,190)	(1,798)	(1,797)	0	0	(3,595)	0	0			
Net income (loss) to common stockholders	(26,806)	(27,292)	(9,026)	(8,976)	(7,314)	(7,449)	(32,765)	(54,812)	(64,547)	(67,148)	(73,400)	(83,557)
Net loss per share	**(8.90)**	**(1.18)**	**(0.39)**	**(0.30)**	**(0.24)**	**(0.24)**	**(1.14)**	**(1.77)**	**(1.98)**	**(1.97)**	**(2.05)**	**(2.22)**
Basic shares	3,013	23,133	23,390	30,303	30,454	30,606	28,688	30,991	32,540	34,167	35,876	37,670
Dilutive shares			23,390	33,998	34,032	34,066	31,371	34,100	35,805	37,595	39,475	41,448

Source: Company Reports and Leerink Swann

7.42

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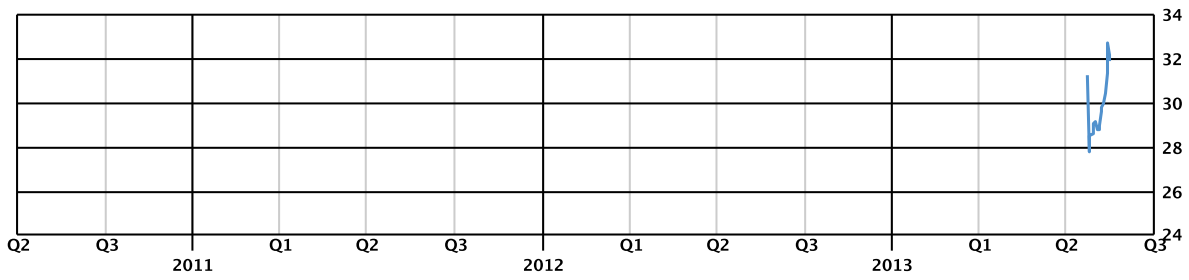
Disclosures Appendix

Analyst Certification

I, Howard Liang, Ph.D., certify that the views expressed in this report accurately reflect my views and that no part of my compensation was, is, or will be directly related to the specific recommendation or views contained in this report.

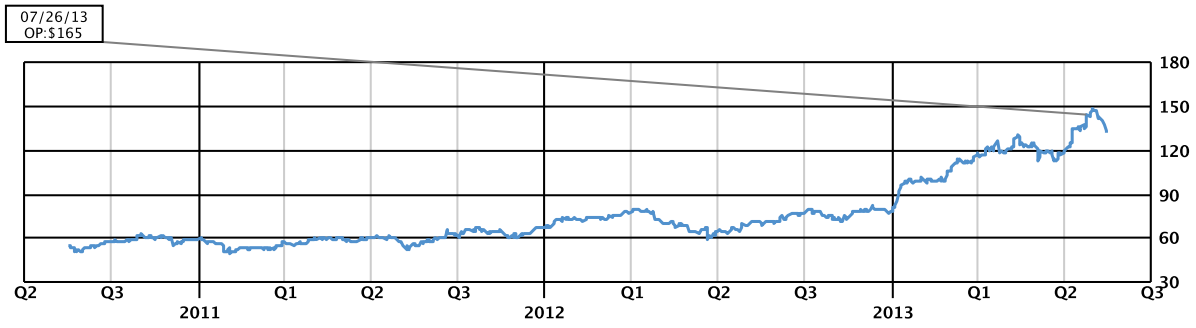
Rating and Price Target History for: Agios Pharmaceuticals, Inc. (AGIO) as of 08-16-2013



OP=Outperform MP=Market Perform UP=Underperform D=Drop Coverage I=Initiate SC=Suspend Coverage

Created by BlueMatrix

Rating and Price Target History for: Celgene, Inc. (CELG) as of 08-16-2013



Leerink Swann initiated coverage of CELG with an Outperform rating on February 7, 2003. On June 11, 2013, Leerink Swann began a transition to specific price targets for the stocks under its coverage, replacing valuation ranges.

OP=Outperform MP=Market Perform UP=Underperform D=Drop Coverage I=Initiate SC=Suspend Coverage

Created by BlueMatrix

Distribution of Ratings/Investment Banking Services (IB) as of 12/31/13				
			IB Serv./Past 12 Mos.	
Rating	Count	Percent	Count	Percent
BUY [OP]	118	64.50	30	25.00
HOLD [MP]	65	35.50	2	3.00
SELL [UP]	0	0.00	0	0.00

Explanation of Ratings

Outperform (Buy): We expect this stock to outperform its benchmark over the next 12 months.

Market Perform (Hold/Neutral): We expect this stock to perform in line with its benchmark over the next 12 months.

Underperform (Sell): We expect this stock to underperform its benchmark over the next 12 months.The degree of outperformance or underperformance required to warrant an Outperform or an Underperform rating should be commensurate with the risk profile of the company.

For the purposes of these definitions the relevant benchmark will be the S&P 600® Health Care Index for issuers with a market capitalization of less than $2 billion and the S&P 500® Health Care Index for issuers with a market capitalization over $2 billion.

Important Disclosures

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Leerink Partners LLC makes a market in Agios Pharmaceuticals, Inc. and Celgene, Inc.

In the past 12 months, an affiliate of the Firm, Leerink Swann Consulting LLC, has received compensation for providing non-securities services to: Celgene, Inc.

Leerink Partners LLC has acted as a co-manager for a public offering of Agios Pharmaceuticals, Inc. in the past 12 months.

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