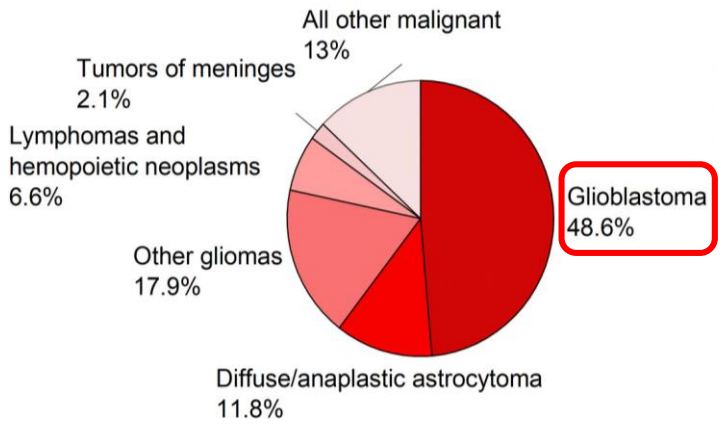
Targeting Medium-Chain Acyl-CoA Dehydrogenase (MCAD) for Glioblastoma (GBM)

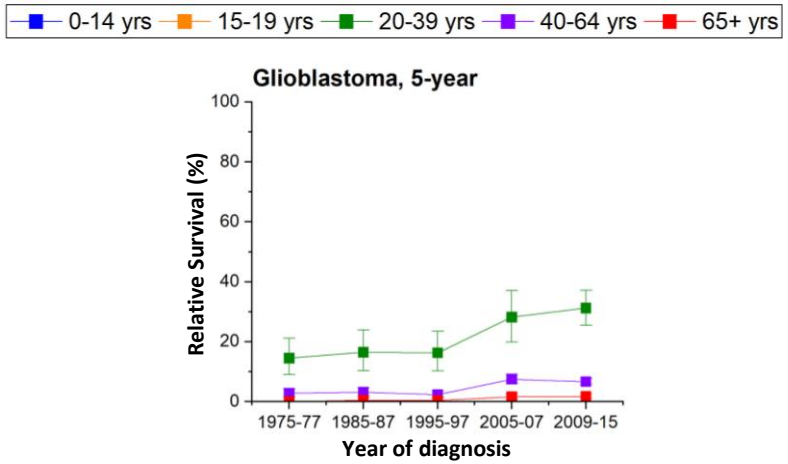
MCAD as a key vulnerability unique to GBM identified by an *in vivo* functional genomic screen

GBM is the most common and aggressive primary brain cancer, with about 12,000 new diagnoses each year.

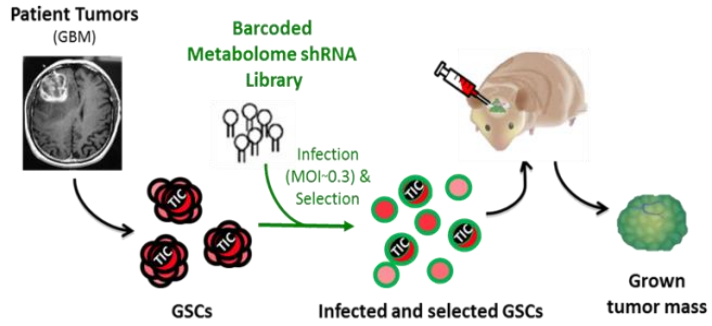
Malignant Brain Tumor Statistics, 2021

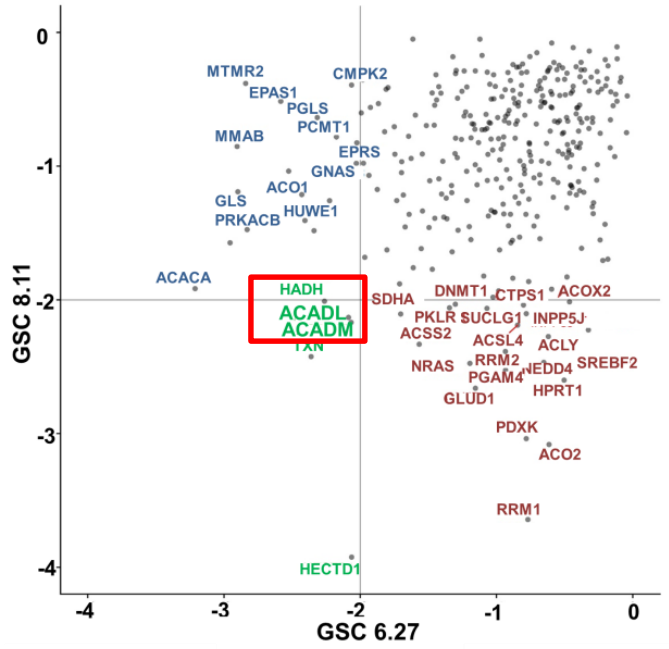


Not much improvement in survival since 1975 for elders



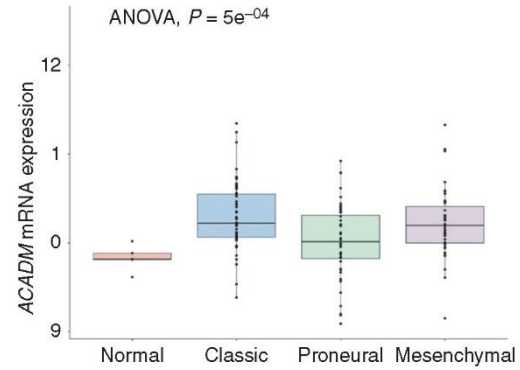
A functional genomic screen of metabolism genes in an *in vivo* model using patient-derived GBM cells (GSCs) uncovered importance of enzymes involved in fatty acid oxidation.



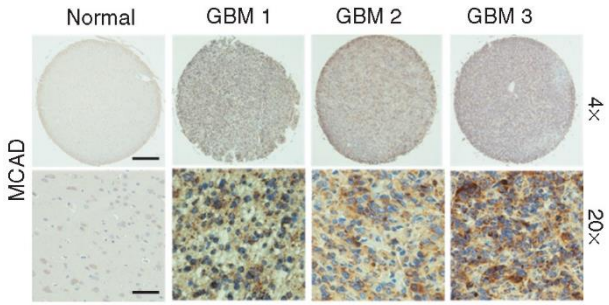


Elevated expression of MCAD in patient GBM samples vs. normal brain.

***ACADM* mRNA levels in glioma subtypes vs. normal brain (TCGA data set).**



Immunohistochemistry for MCAD on tissue microarray derived from normal brain and GBM tissue



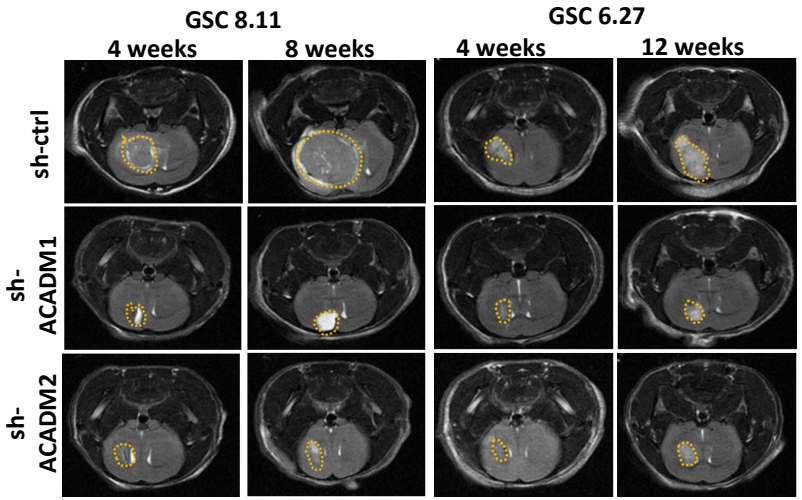
Scale bars, 100 μm for ×4 and 25 μm for ×20.

CA: A Cancer J Clinicians, 71(5): 381-406. DOI: 10.3322/caac.21693.
Cancer Discov, 11(11): 2904-2923. DOI: 10.1158/2159-8290.CD-20-1137.

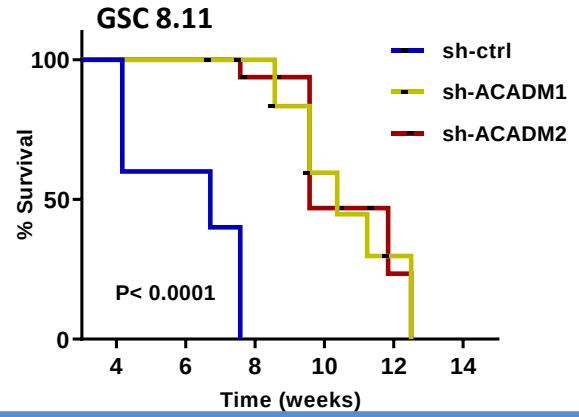
Targeting Medium-Chain Acyl-CoA Dehydrogenase (MCAD) for Glioblastoma (GBM)

Downregulation of MCAD resulted in severe mitochondrial failure in GBM and longer animal survival

MCAD-knockdown dramatically attenuated tumor growth using GSC8.11 and GSC6.27.

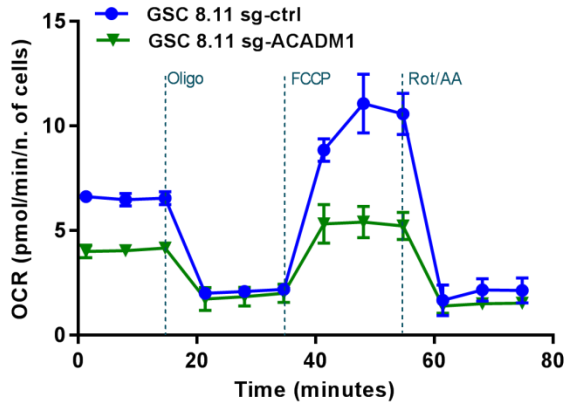


MCAD-knockdown significantly extended survival time.

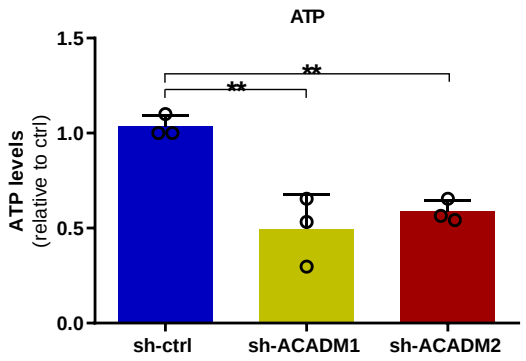


Downregulation of MCAD impaired mitochondrial function

oxygen consumption rate significantly decreased in basal respiration and reserve respiratory capacity in *ACADM*-deleted GSCs

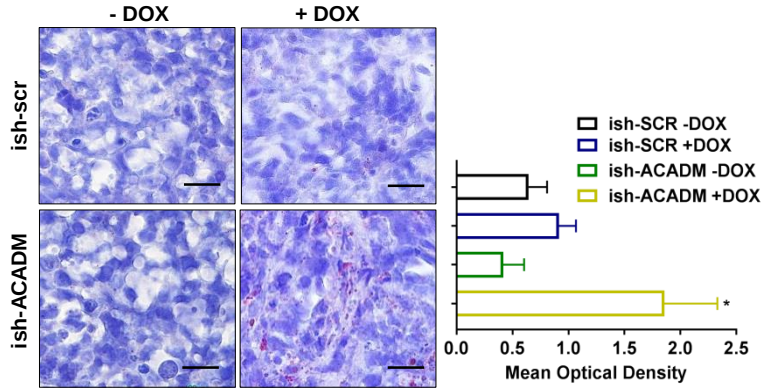


decrease in ATP content in MCAD-depleted GSCs

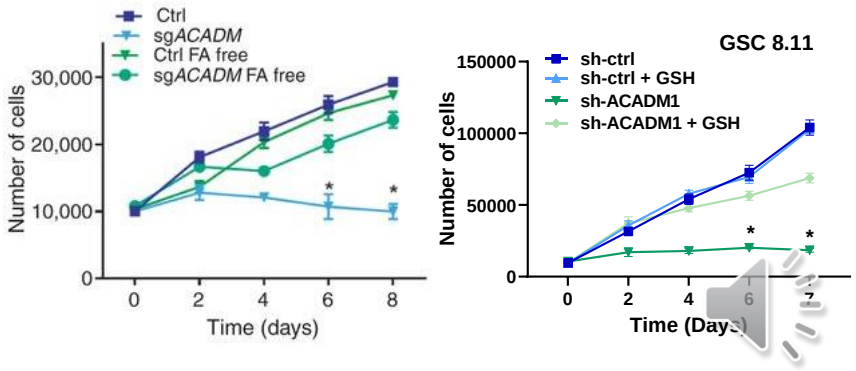


Lipid accumulation and reactive oxygen species (ROS)-related damage in MCAD-knockdown GSCs

GSC 8.11 xenograft tumor tissues showed lipid accumulation upon *ACADM* silencing



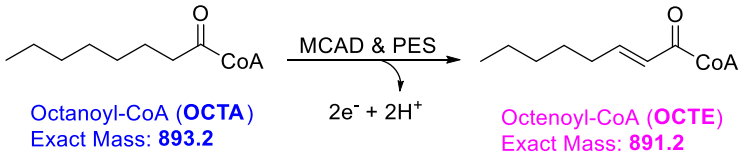
MCAD-knockdown GSC 8.11 partially rescued in fatty acid free medium (left) and by GSH (right)



Targeting Medium-Chain Acyl-CoA Dehydrogenase (MCAD) for Glioblastoma (GBM)

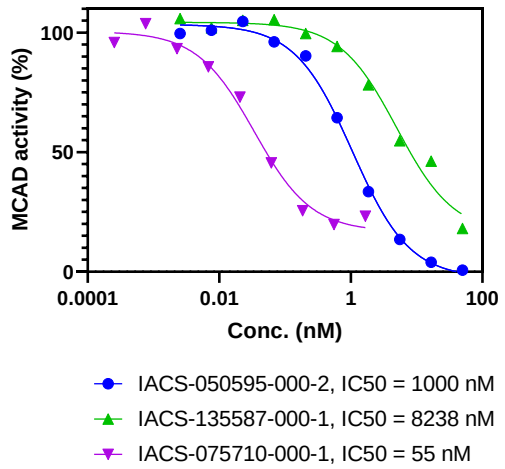
Developing potent, selective MCAD inhibitors

Hits identified by high-throughput screen of 278k compounds based on RF-MS.



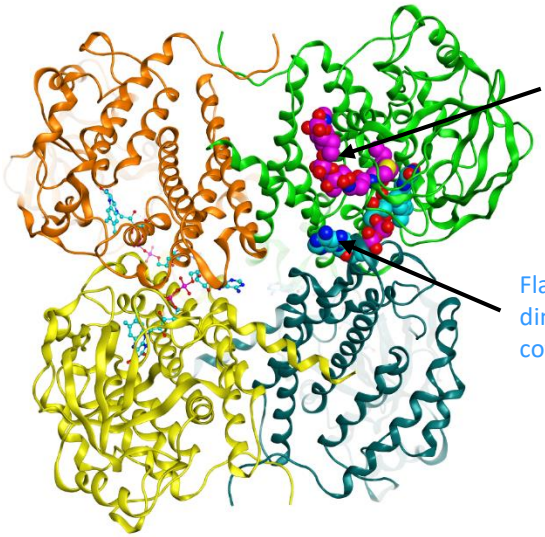
Octanoyl-CoA (**OCTA**)
Exact Mass: **893.2**

Octenoyl-CoA (**OCTE**)
Exact Mass: **891.2**

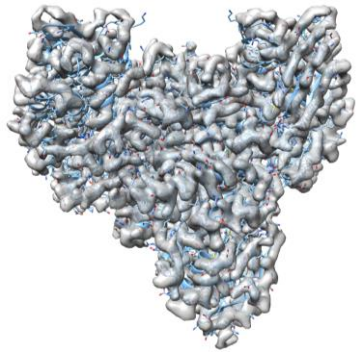


MCAD structures with screening hits guides small molecule optimization.

Crystal structure of MCAD:Octanoyl-CoA



Cryo-EM structure of MCAD



Refined map at 3.3 Å
Using 88k particles

Example of a partially optimized screening hit with cellular potency < 1 µM.

Properties	Cmpd ID: 75915
MCAD IC_{50} (nM)	37
SCAD IC_{50} (nM)	>5,600
LCAD IC_{50} (nM)	>5,600
VLCAD IC_{50} (nM)	>5,600
MCAD CETSA IC_{50} (nM)	~200
MCAD OCCT (nM)	540
Pampa Pe (x10^{-6}cm/s (% rec))	11(60%)
Plasma St. (m/r/d/h $t_{1/2}$ min)	330/100/360/99
MW/cLogP/TPSA	459/2.28/116
MPO/BBB	3.83/3.16

F Yu[1], P Leonard[1], M Hamilton[1], F Puca[2], N Pham[2], N Rogers[1], F Alvarez[1], C Rodriguez[1], V Nair[1], N Akkaladevi[1], R Thapar[1], S Vaccaro[1], A Mendiola[1], Q Xu[1], M Geck Do[1], J Cross[1], M Soth[1], Y Jiang[1], G Draetta[2], and P Jones[1]

[1] Institute for Applied Cancer Science
[2] Department of Genomic Medicine