

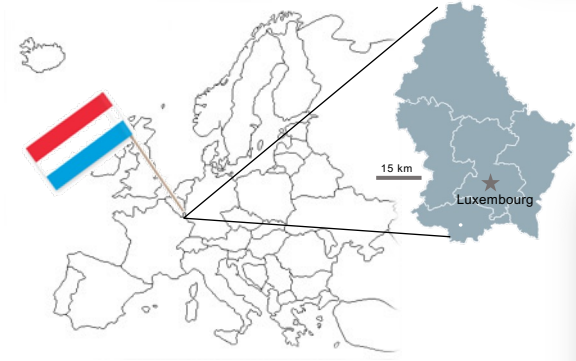
Plasticity of one-carbon metabolism and its exploitation for toxic folate trapping in cancer cells



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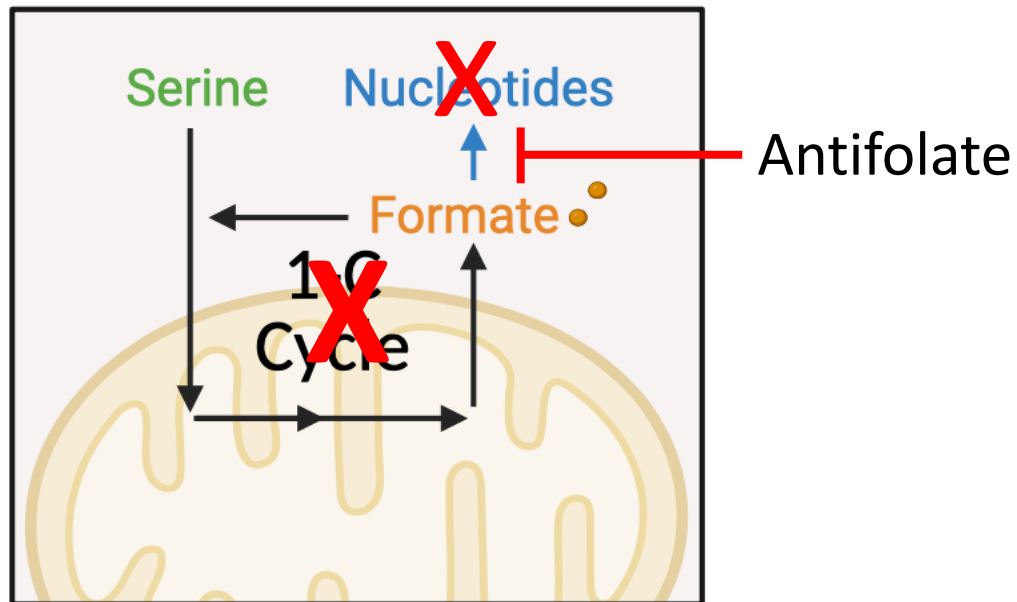


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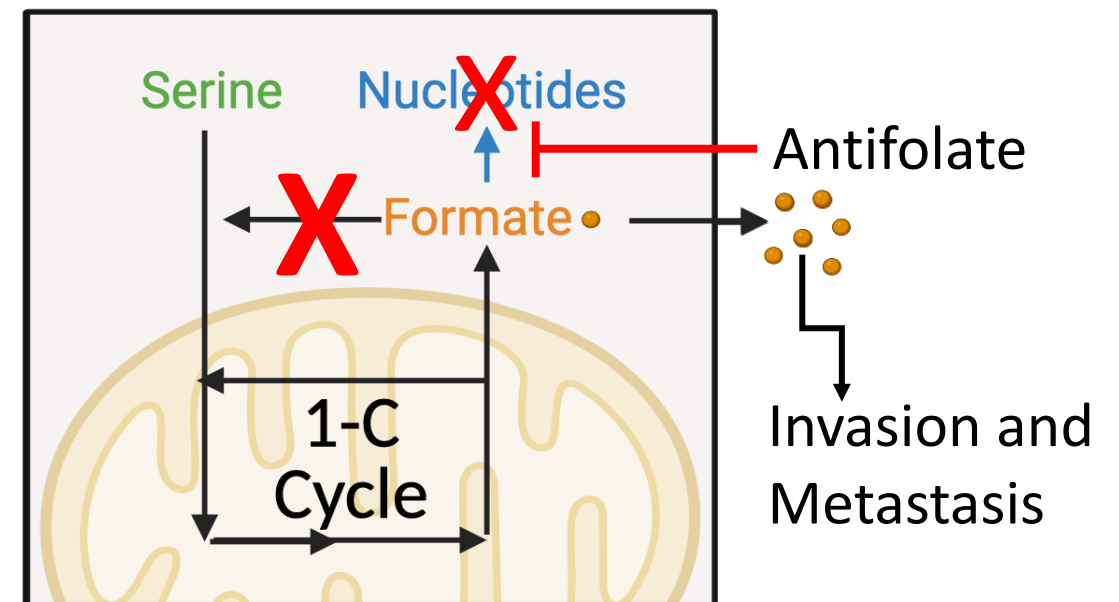


Formate is essential for nucleotide synthesis (anabolism) and has non-anabolic functions

Anabolic function of formate

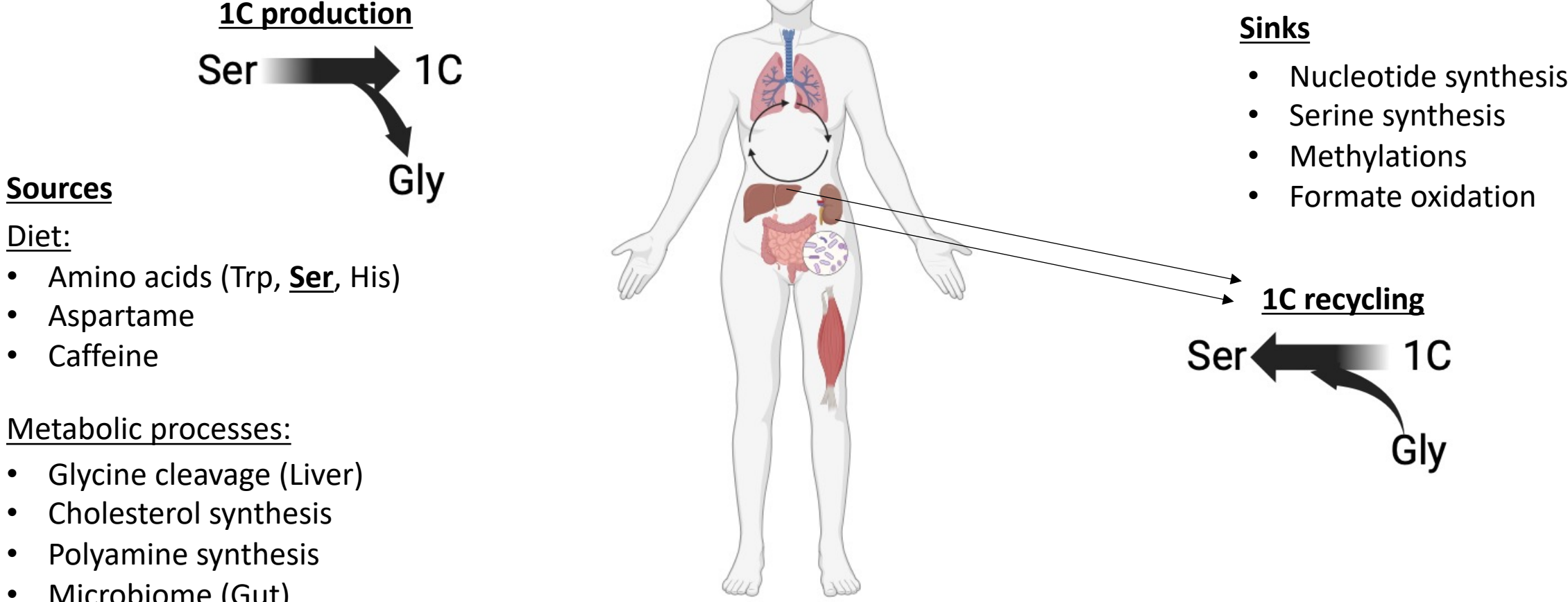


Formate overflow



Meiser et al., *Science Adv.*, 2016
Meiser et al., *Nature Com.* 2018
Ternes et al., *Nature Metab.* 2022
Kiweler et al., *Nature Com.* 2022
Delbrouck et al., *Cell Reports* 2023

Systemic formate concentrations are balanced by inter-organ metabolism



Sources

Diet:

- Amino acids (Trp, Ser, His)
- Aspartame
- Caffeine

Metabolic processes:

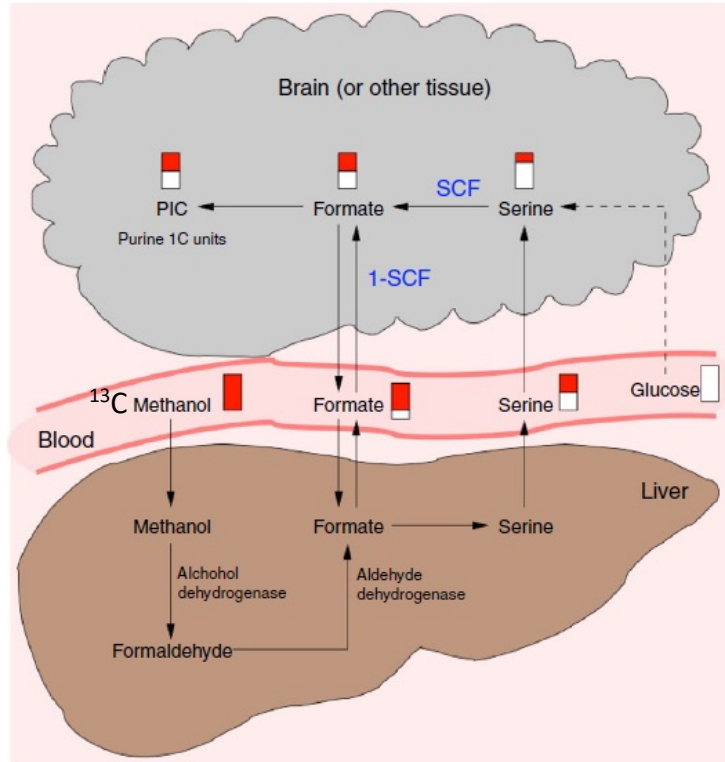
- Glycine cleavage (Liver)
- Cholesterol synthesis
- Polyamine synthesis
- Microbiome (Gut)

Physiological formate concentration:

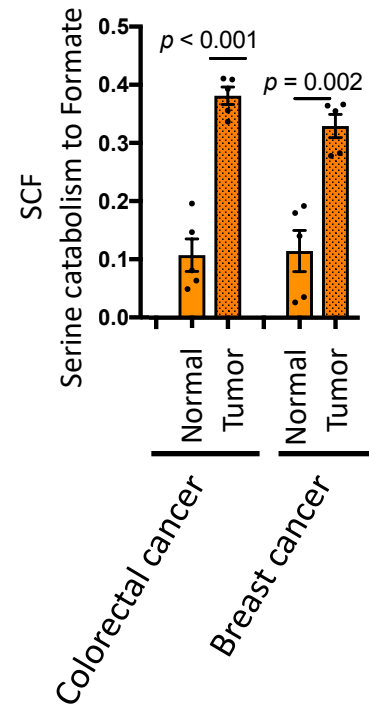
Plasma: ~ 20 – 100 μM
Gut: low mM range

Serine catabolism is increased in oxidative tumors *in vivo*

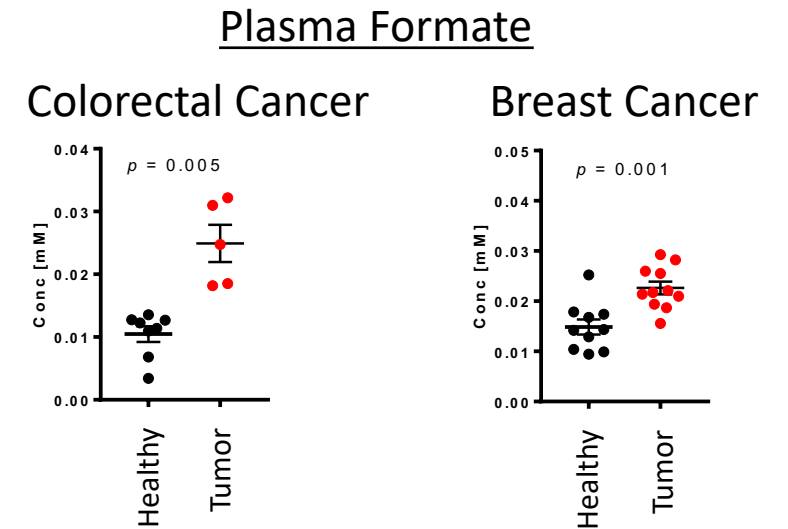
in vivo Metabolic Flux Analysis



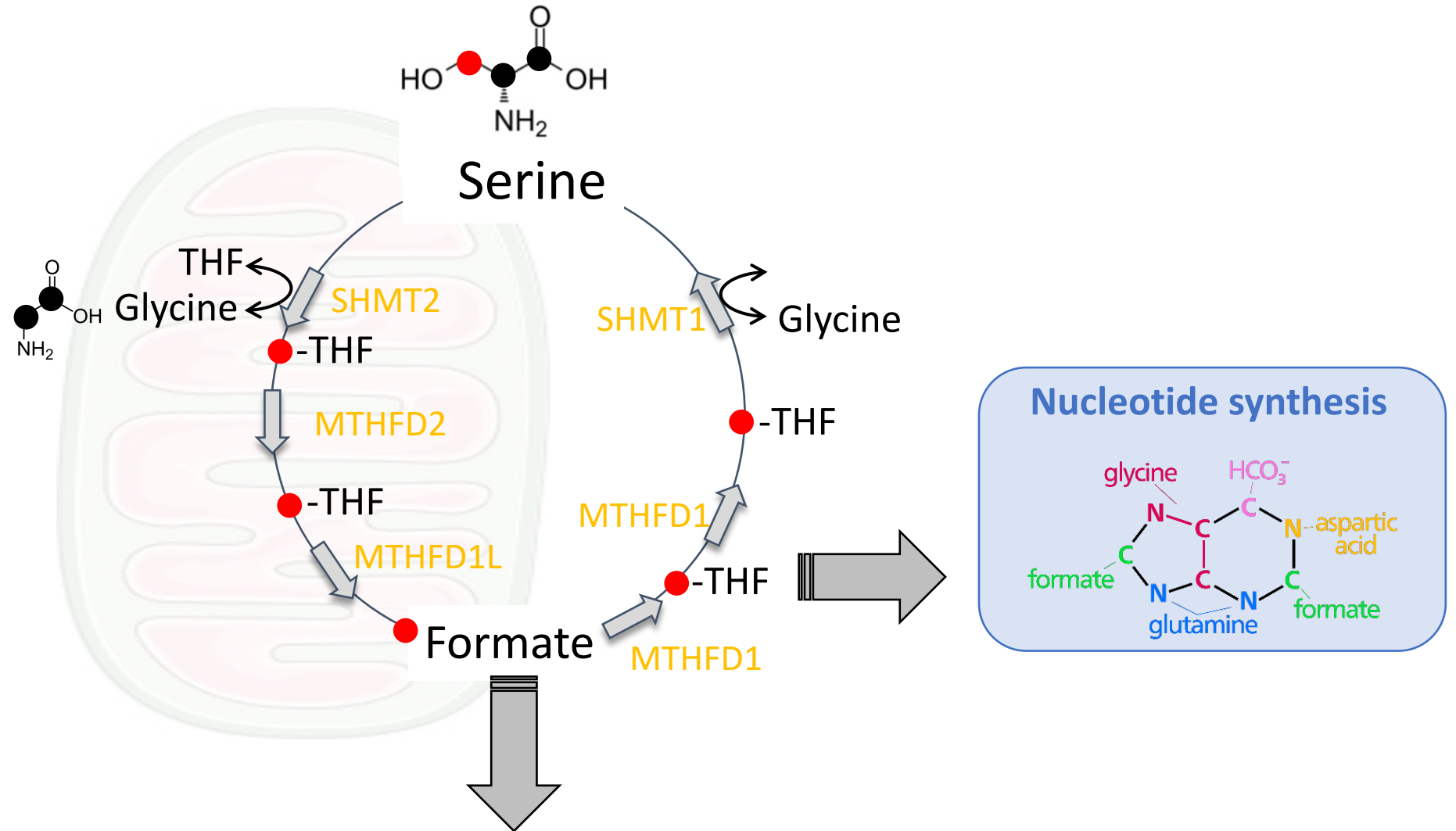
Rate of formate production in tumors *in vivo*



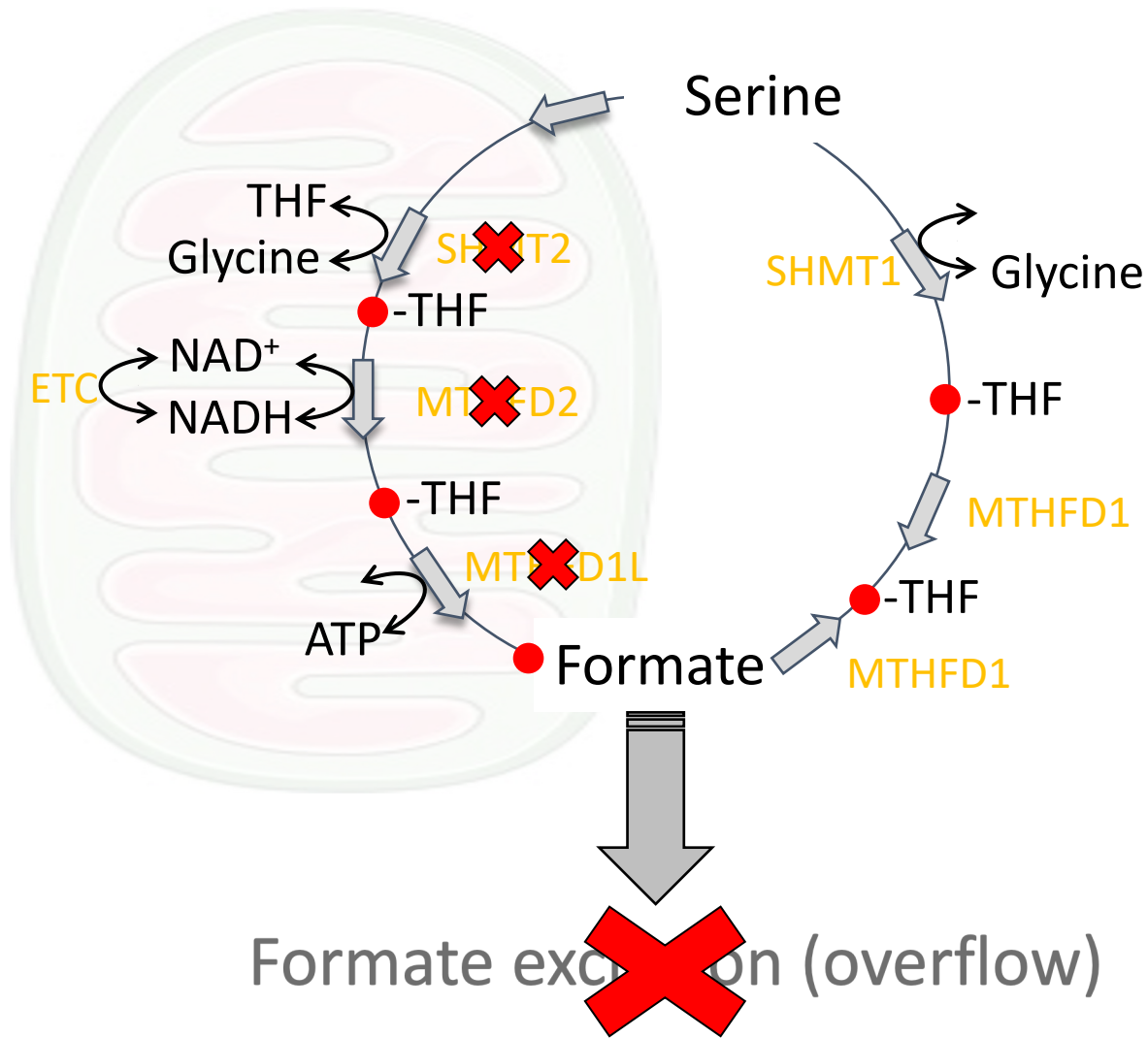
Plasma analysis



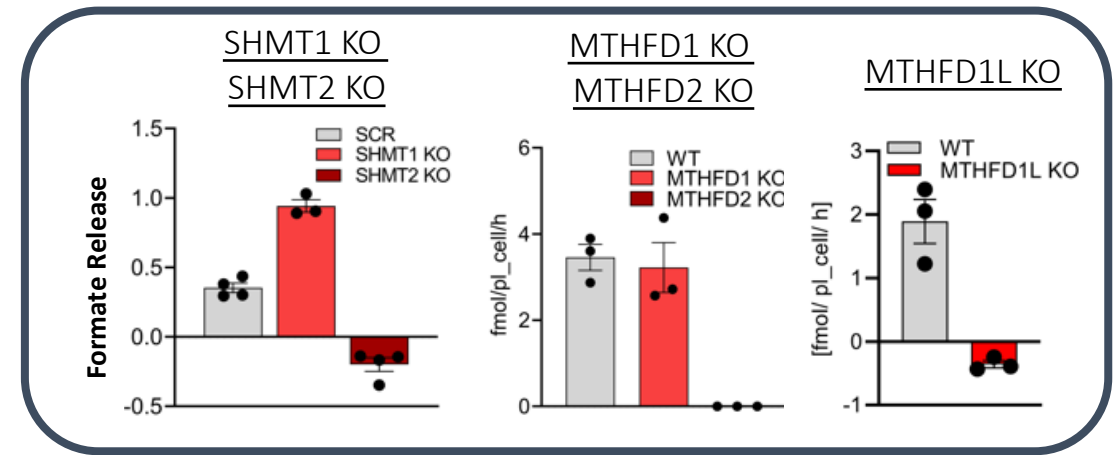
1C metabolism is compartmentalised



Formate overflow depends on mitochondrial one-carbon metabolism and can not be compensated by cytosolic 1C flux



Loss of mitochondrial 1C flux prevents formate overflow but does not affect proliferation



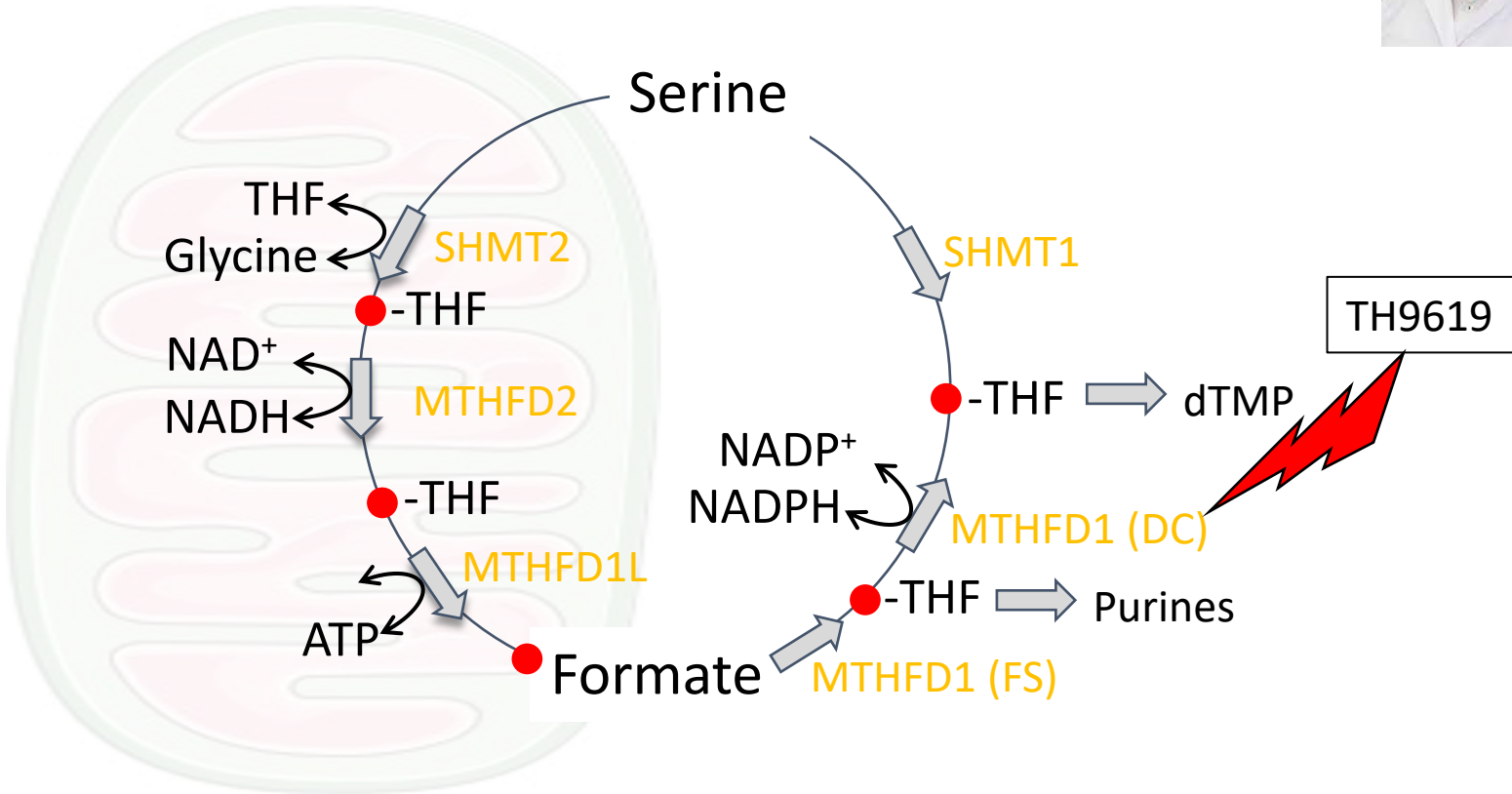
Meiser et al., *Science Adv.* 2016
 Meiser et al., *Nature Com* 2018
 Kiweler et al., *Nature Com.* 2022

Can we exploit or target formate overflow?

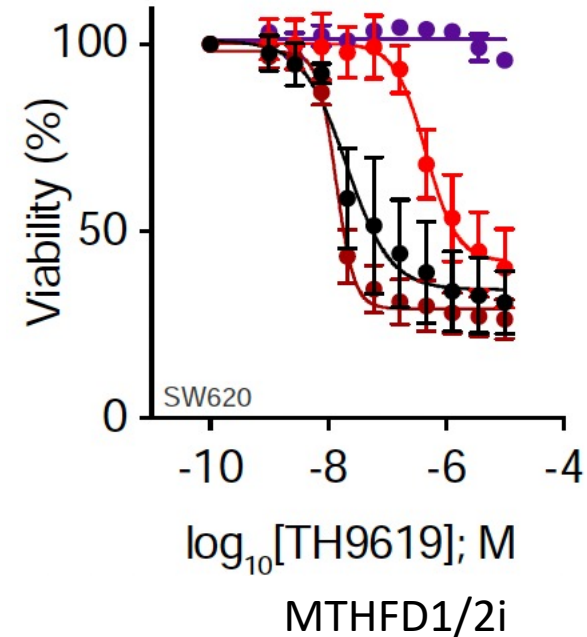
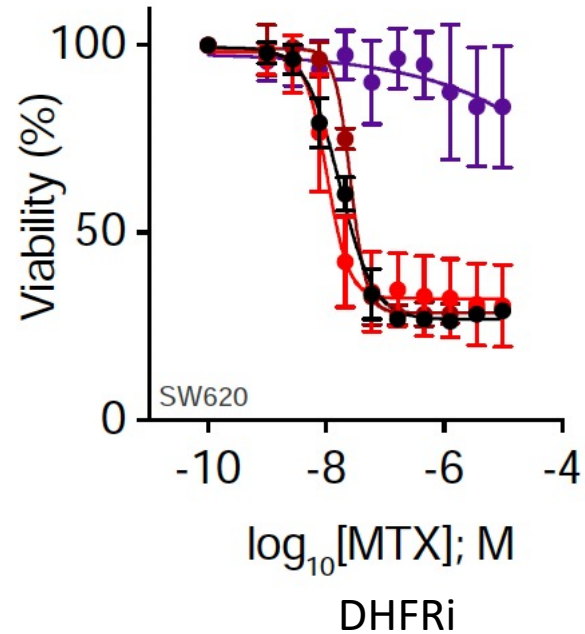
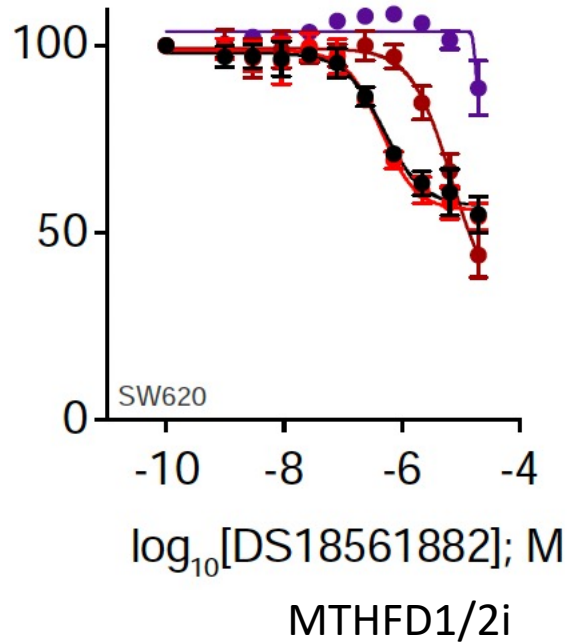
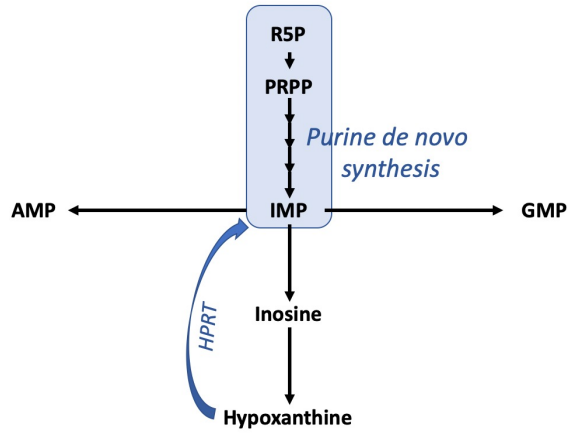
TH9619 targets cytosolic MTHFD1 and nuclear MTHFD2



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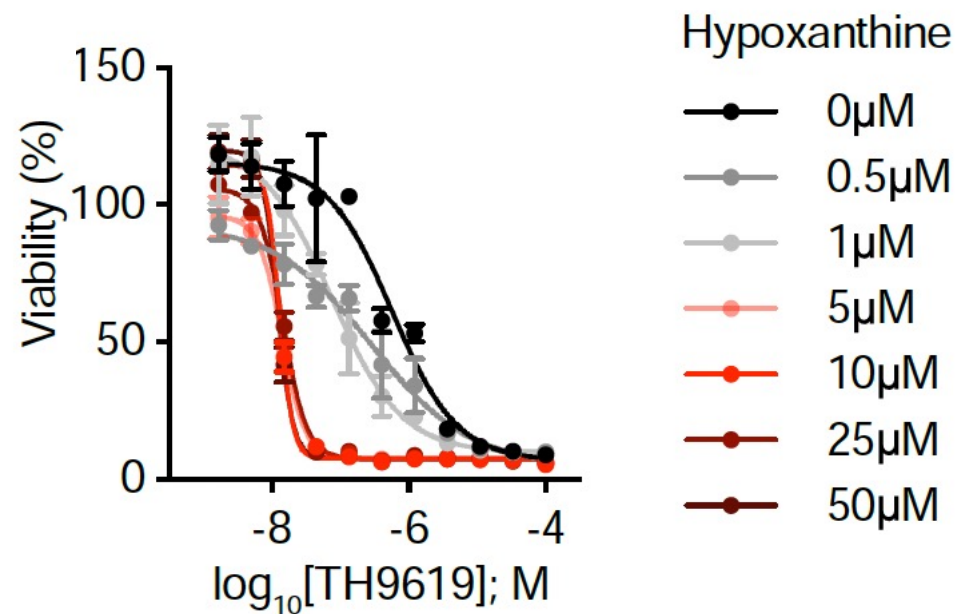


TH9619 has a unique mode of action

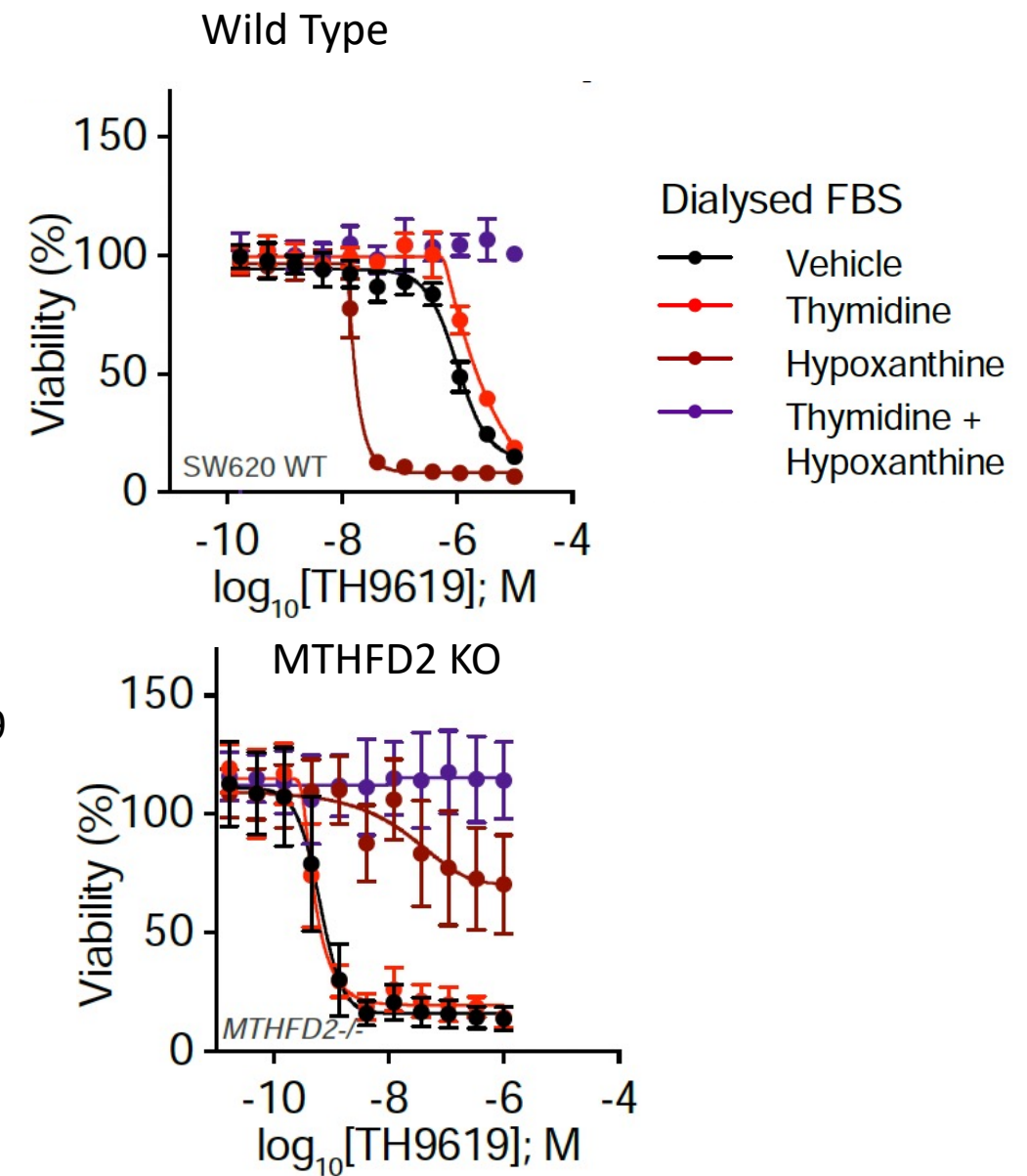
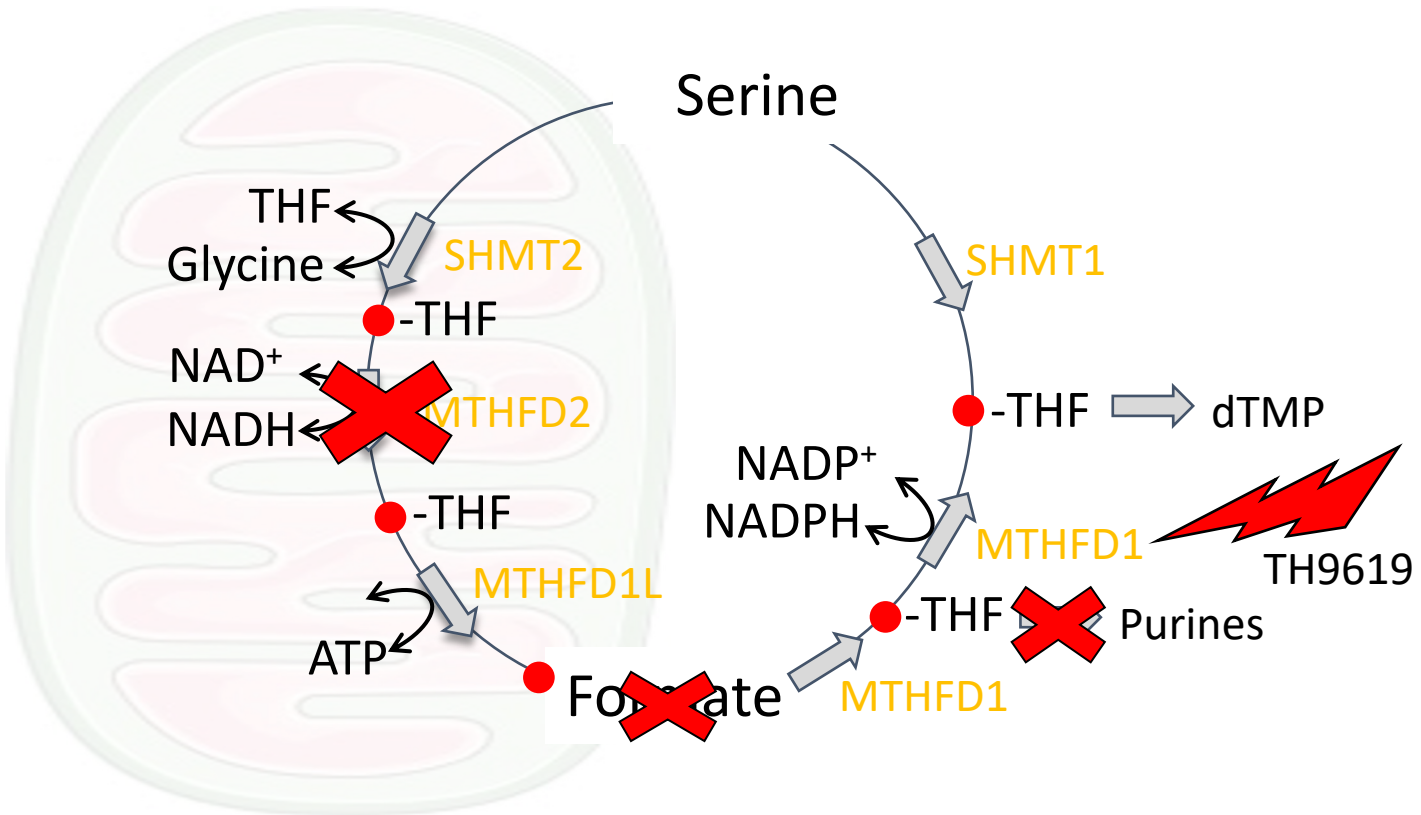


- Vehicle
- Thymidine
- Hypoxanthine
- Thymidine + Hypoxanthine

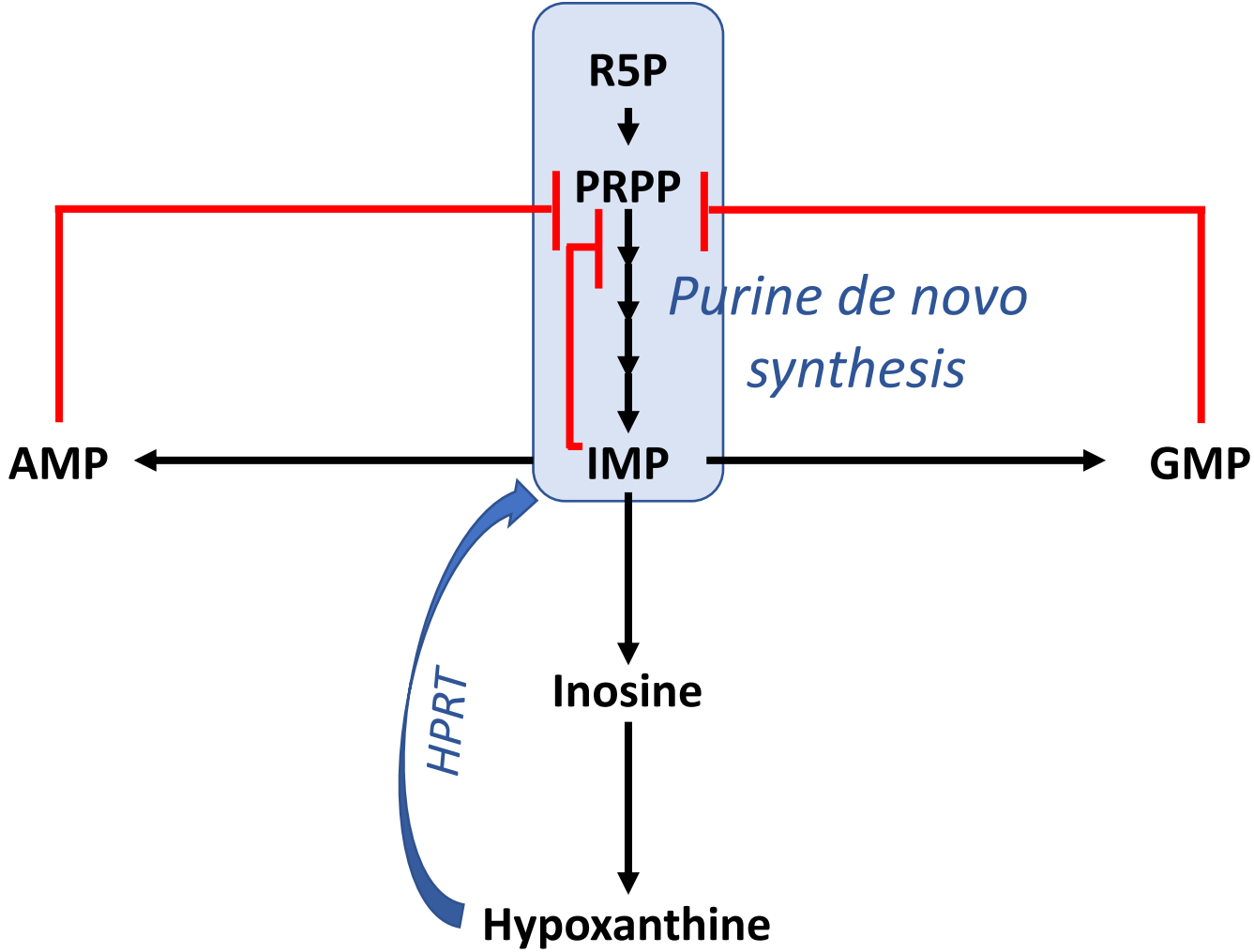
Hypoxanthine exacerbates TH9619 efficacy



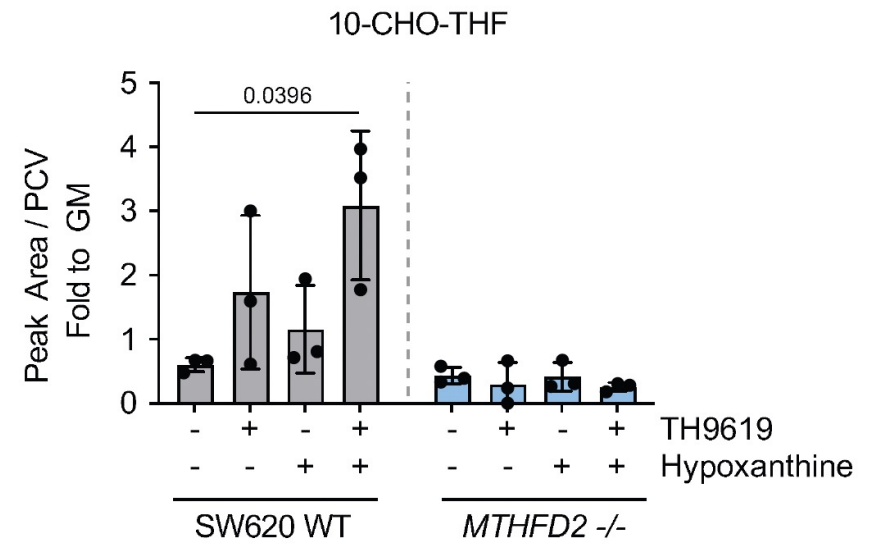
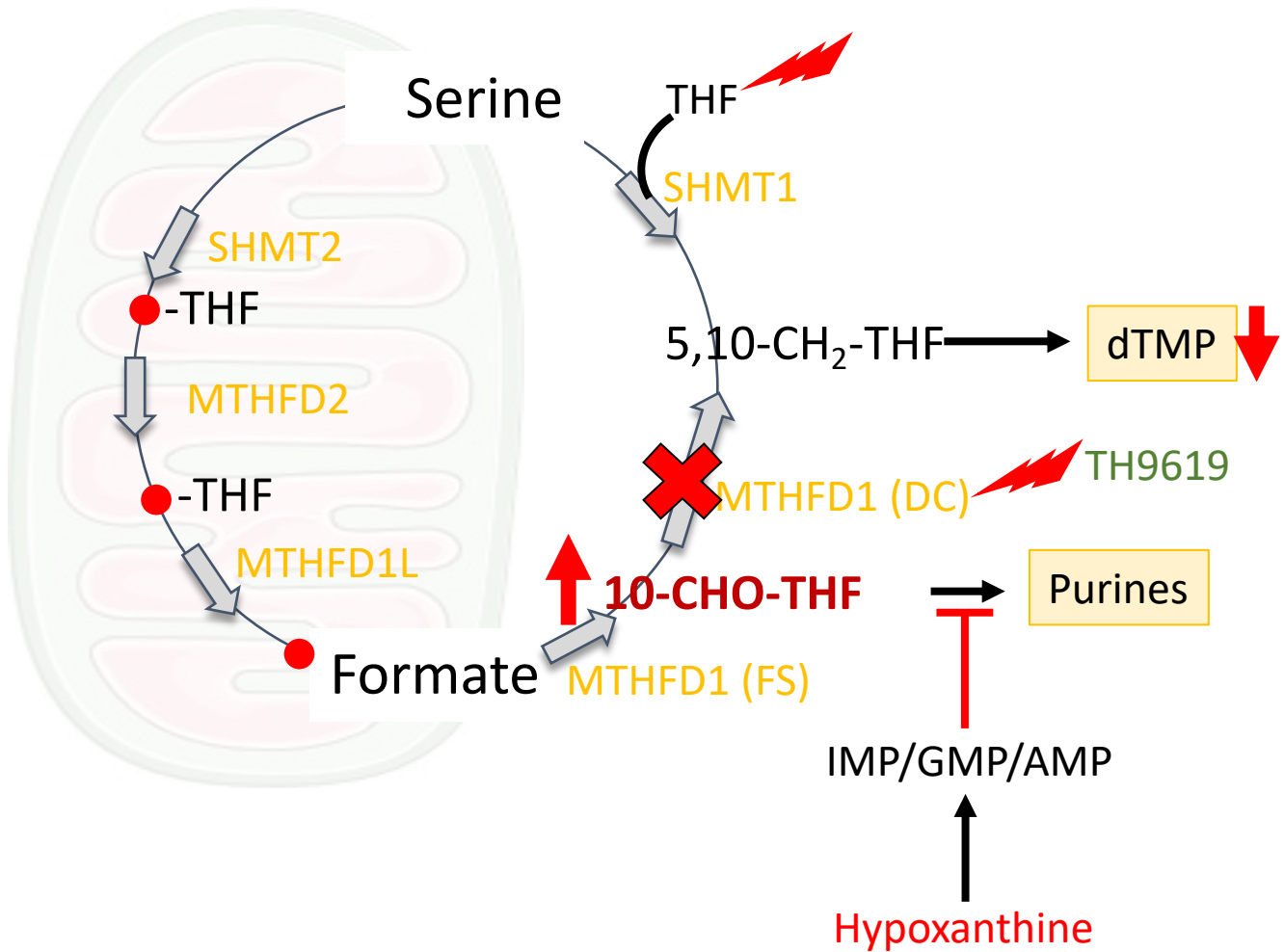
Hypoxanthine exacerbates TH9619 efficacy in WT cells but not MTHFD2^{-/-} cells



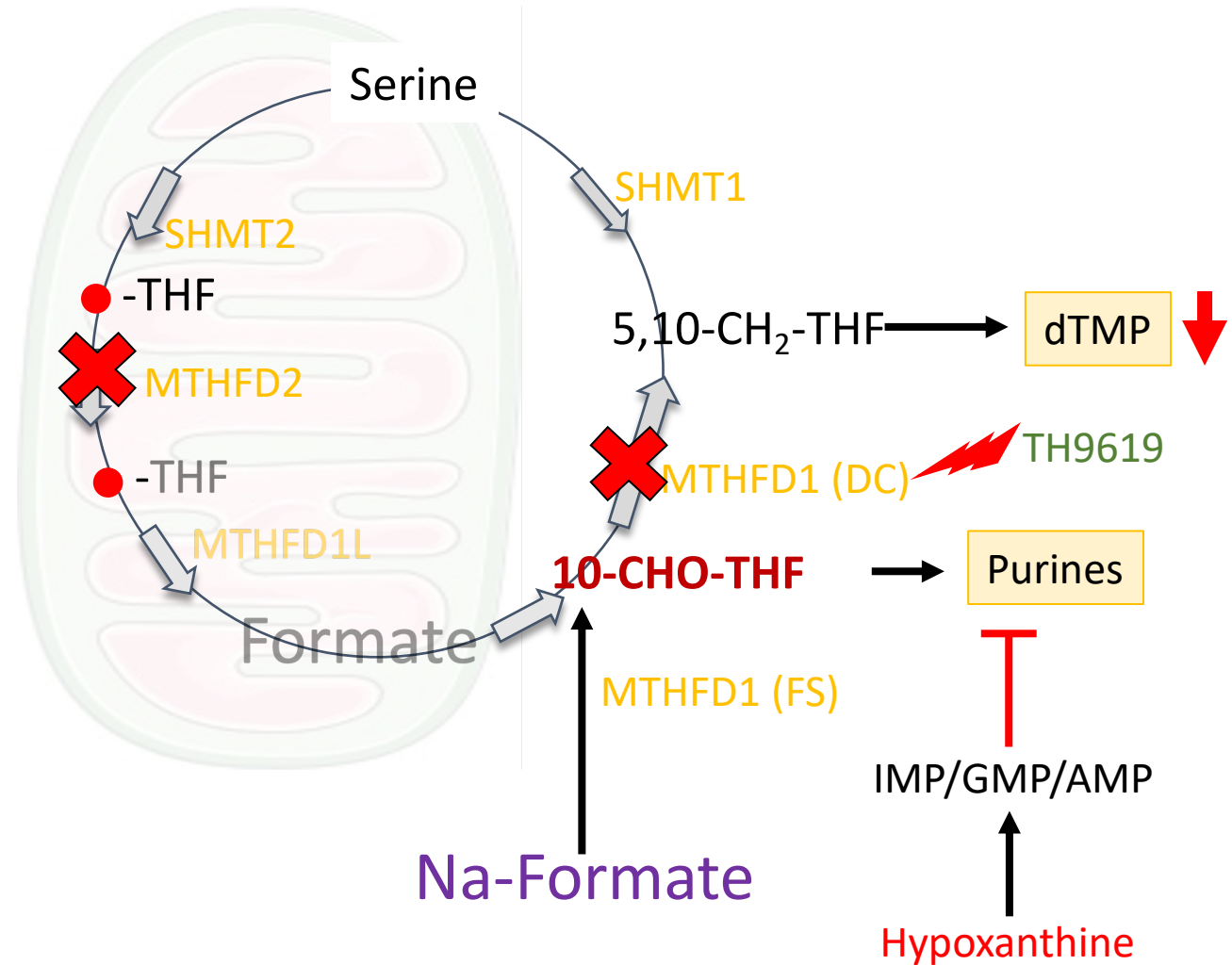
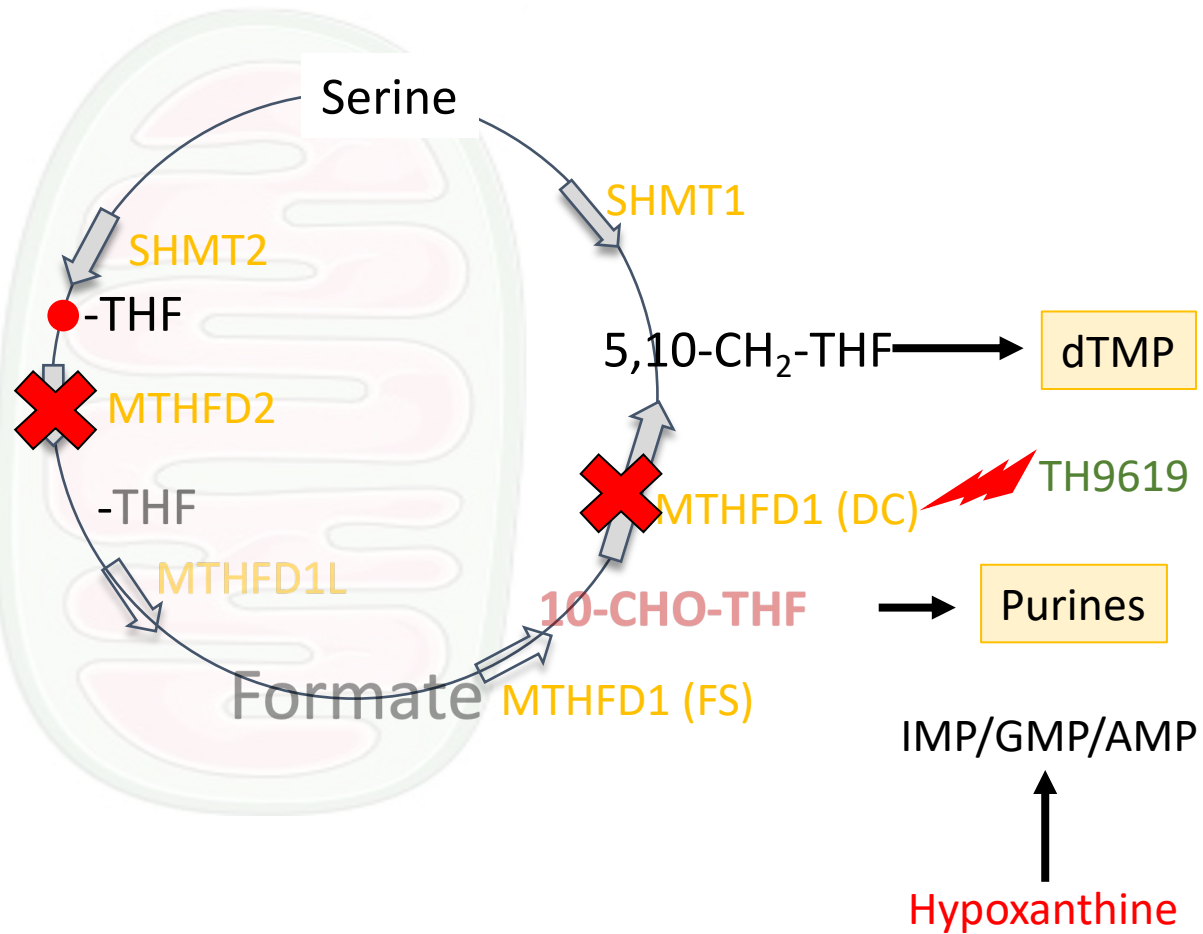
High Hypoxanthine flux inhibits *de novo* purine synthesis



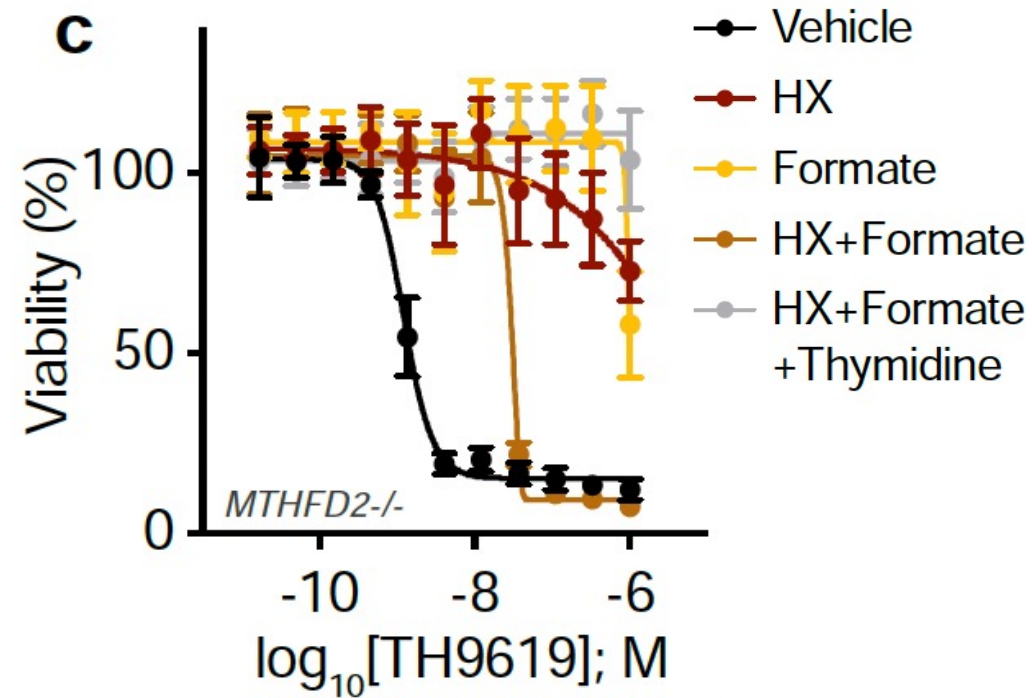
Hypoxanthine promotes 10-CHO-THF accumulation



Does TH9619 mode of action depend on formate overflow?

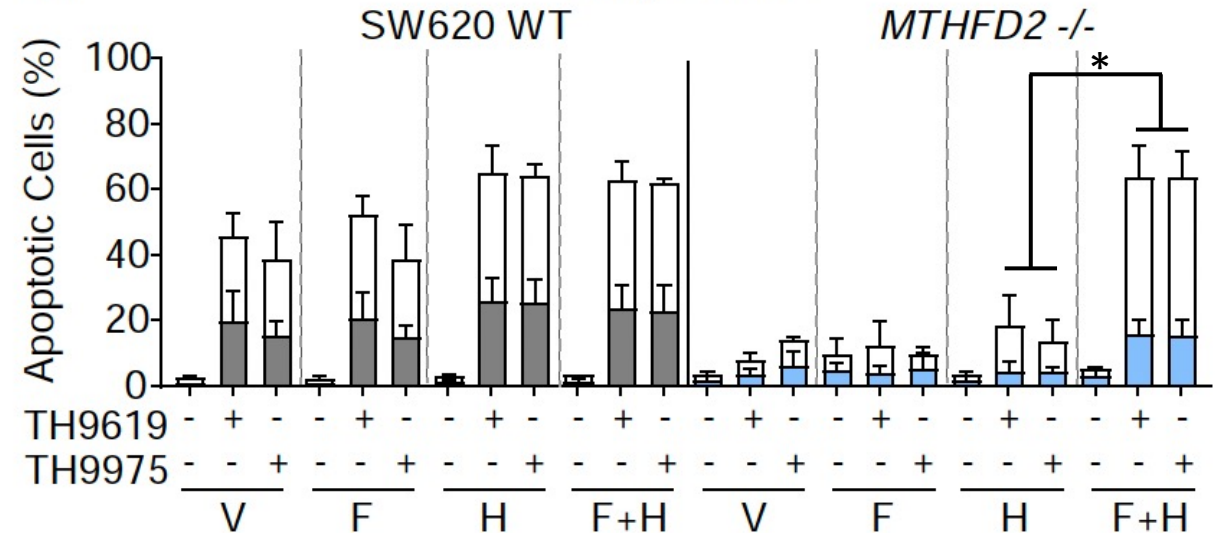
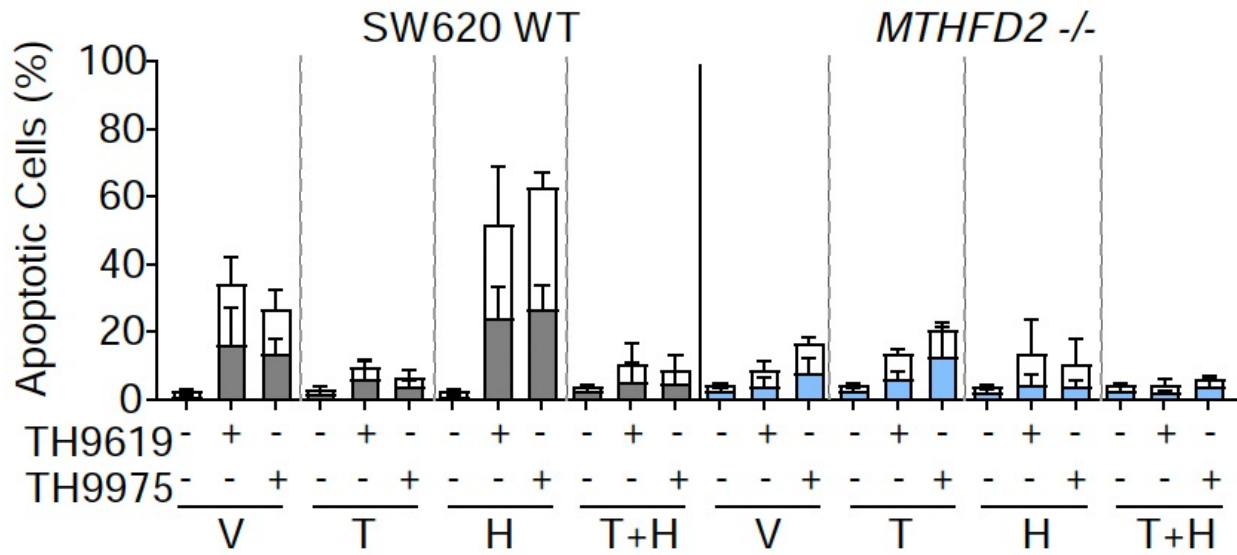


High mitochondrial formate flux is required to induce cytosolic folate trapping

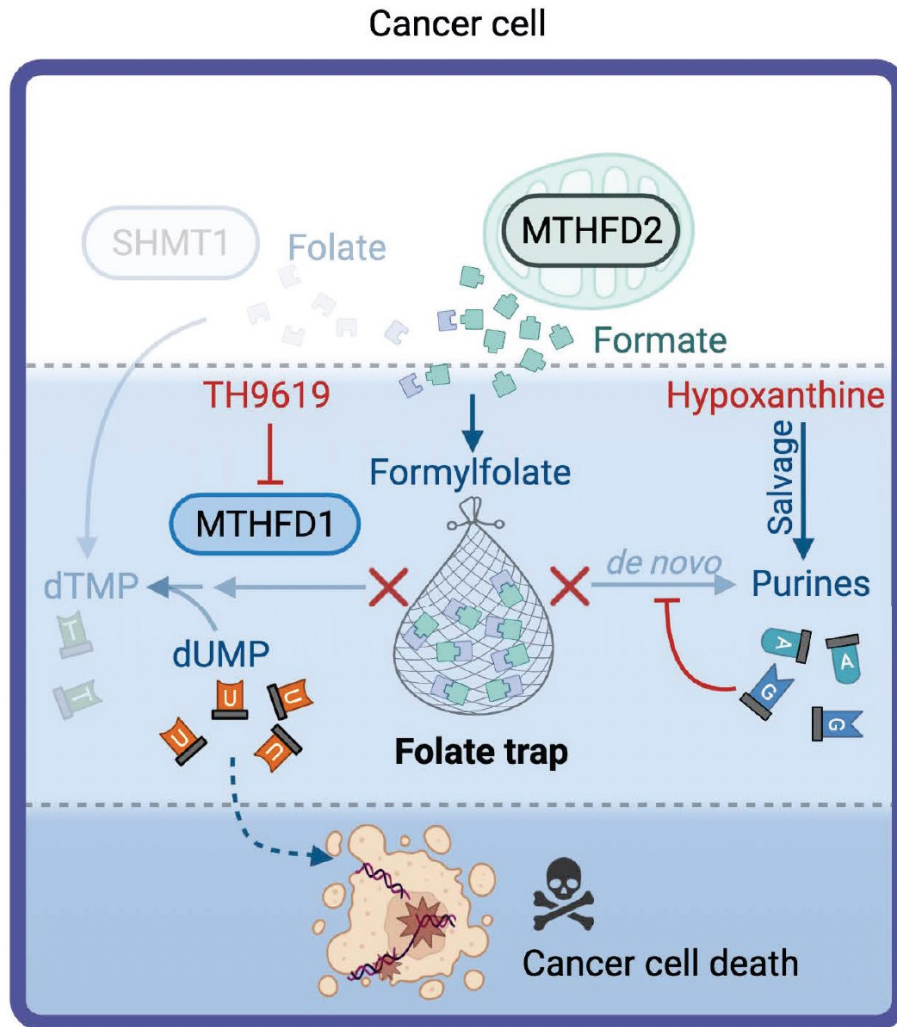



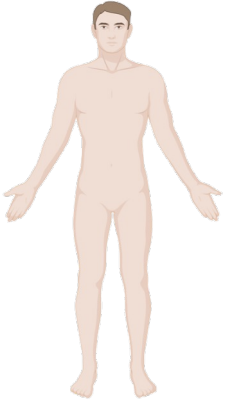
High mitochondrial formate flux is required to induce cytosolic folate trapping

Annexin V⁺/PI⁻
 Annexin V⁺/PI⁺
 Annexin V⁻/PI⁺



Formate overflow drives toxic folate trapping in MTHFD1 inhibited cancer cells



	 Mouse	 Human
Folate	High (~ 250 nM)	Low (~ 20 nM)
Thymidine	High (> 1 μM)	Low (< 1 μM)
Hypoxanthine	Low (~ 23 nM)	High (~ 3-10 μM)

Cancer Metabolism Group @LIH



External Funding Sources

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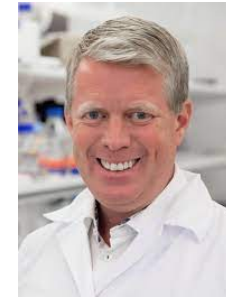


Postdoc positions available!

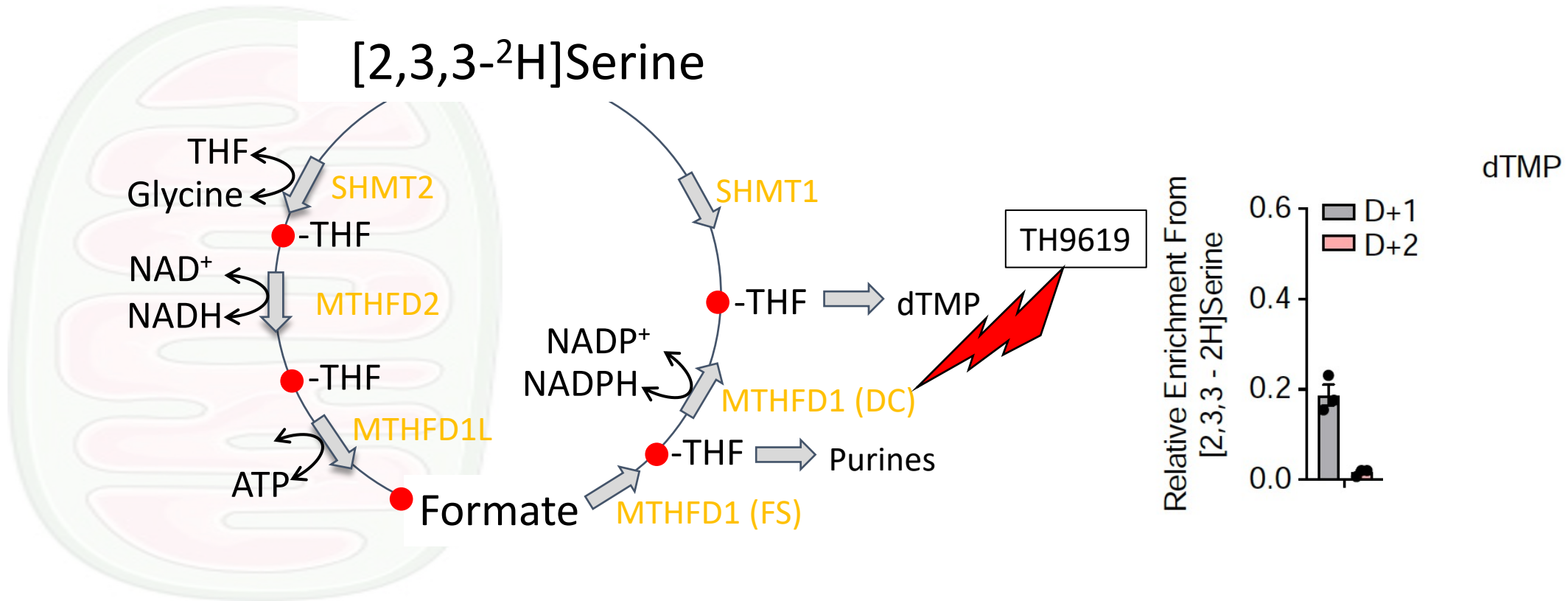


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TH9619 targets cytosolic MTHFD1



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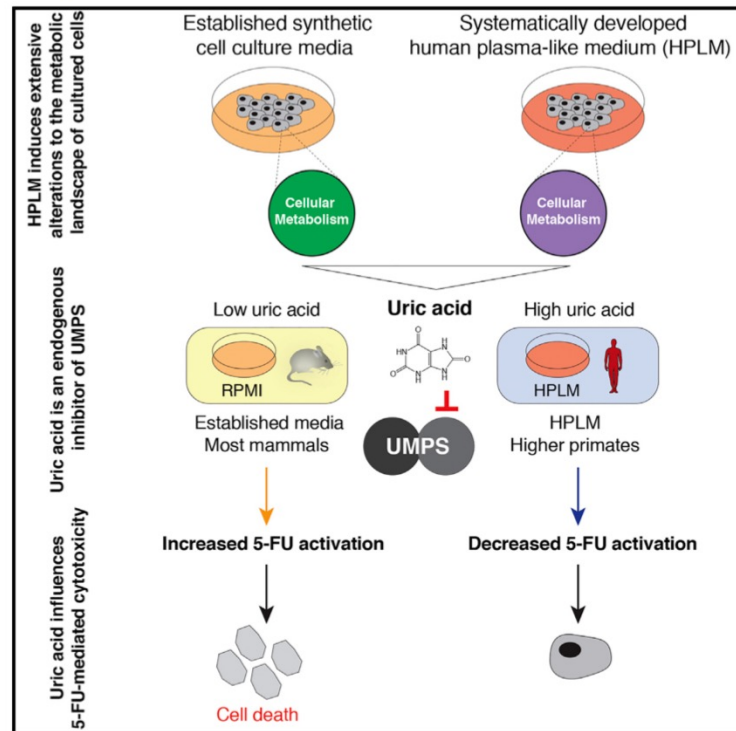


Hypoxanthine does *not* induce toxicity by inhibiting UMPS

Cell

Physiologic Medium Rewires Cellular Metabolism and Reveals Uric Acid as an Endogenous Inhibitor of UMP Synthase

Graphical Abstract



ARTICLE

Authors

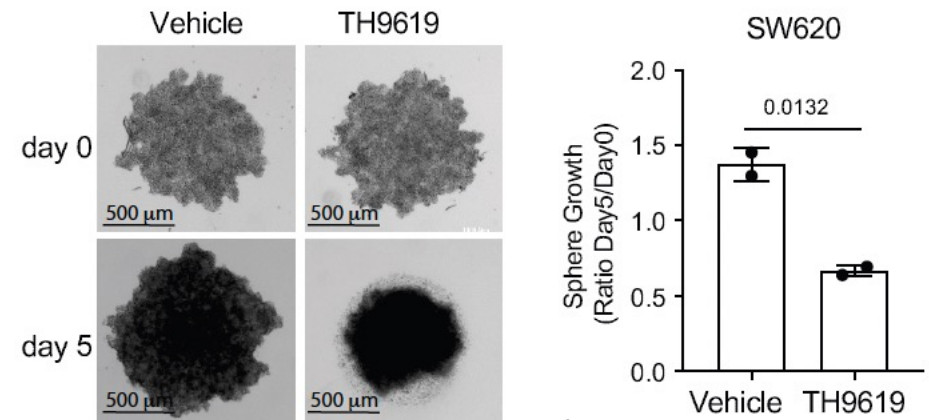
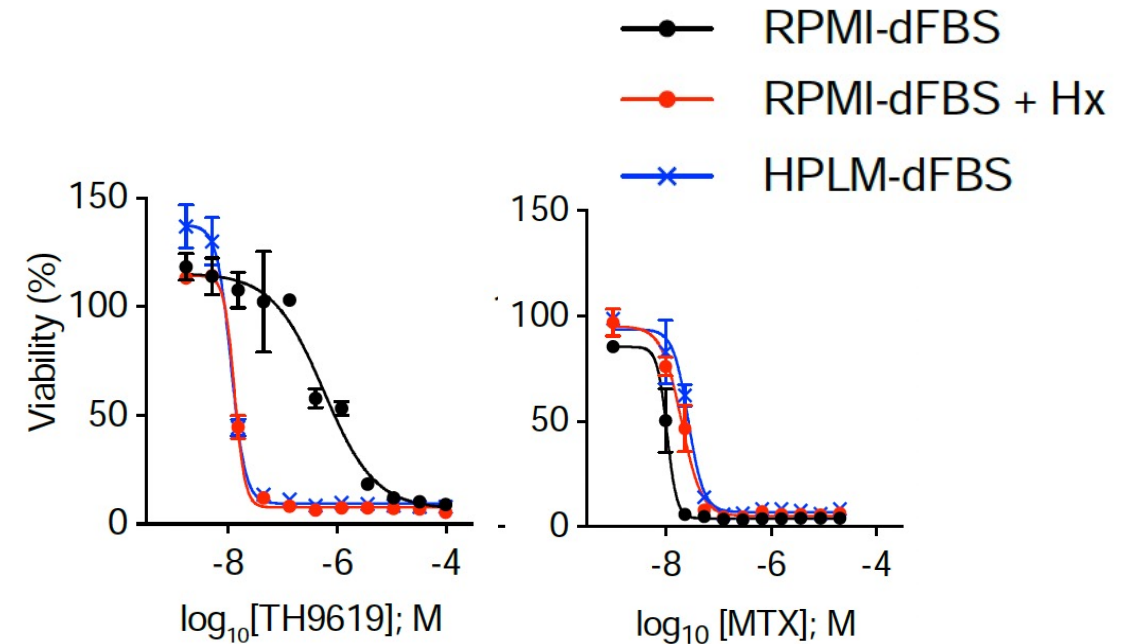
Jason R. Cantor, Monther Abu-Remaileh, Naama Kanarek, ..., Abner Louissaint, Jr., Caroline A. Lewis, David M. Sabatini

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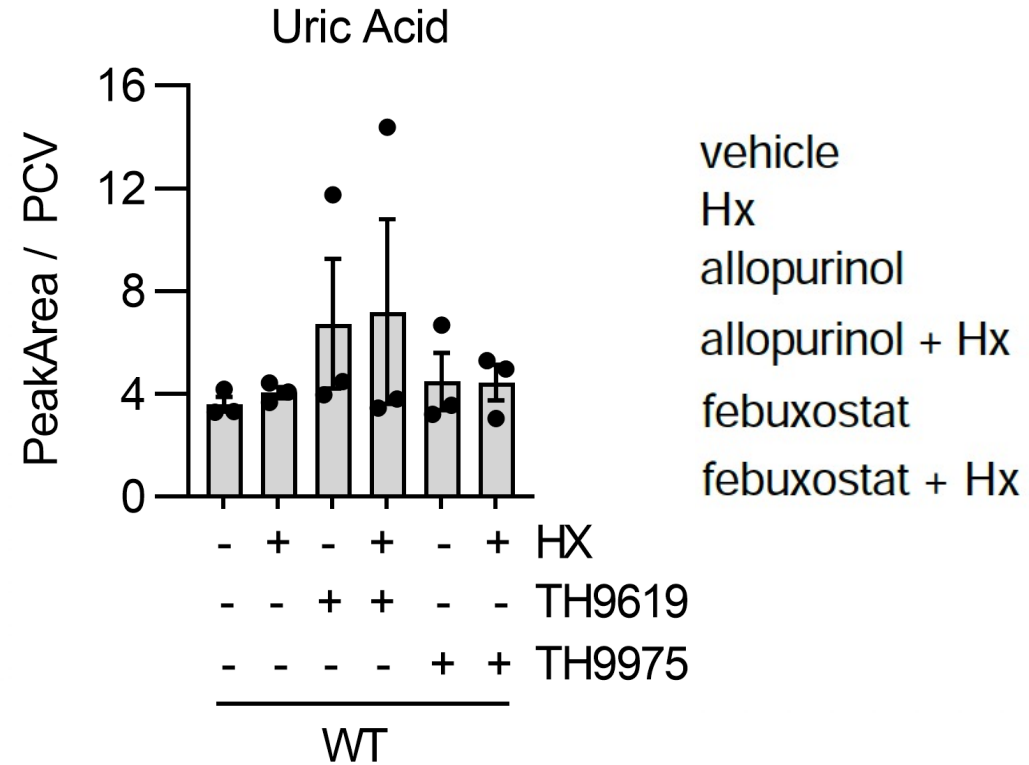
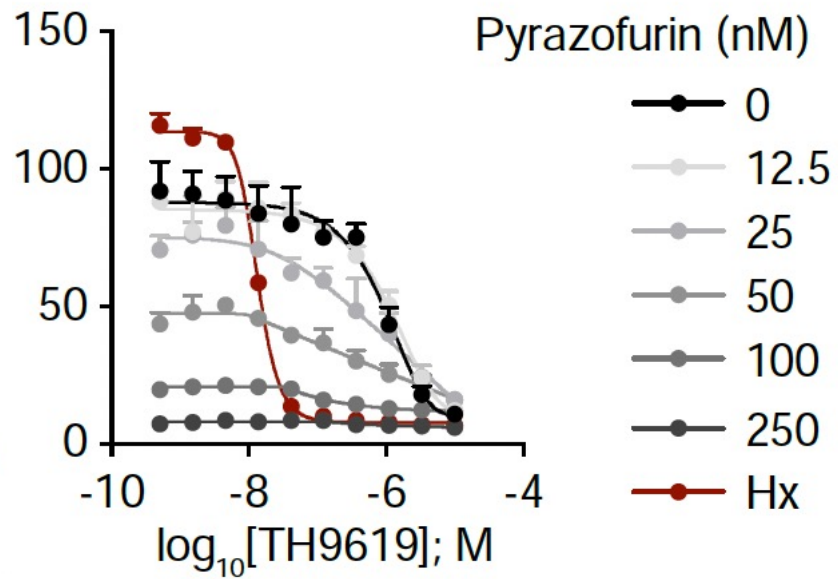
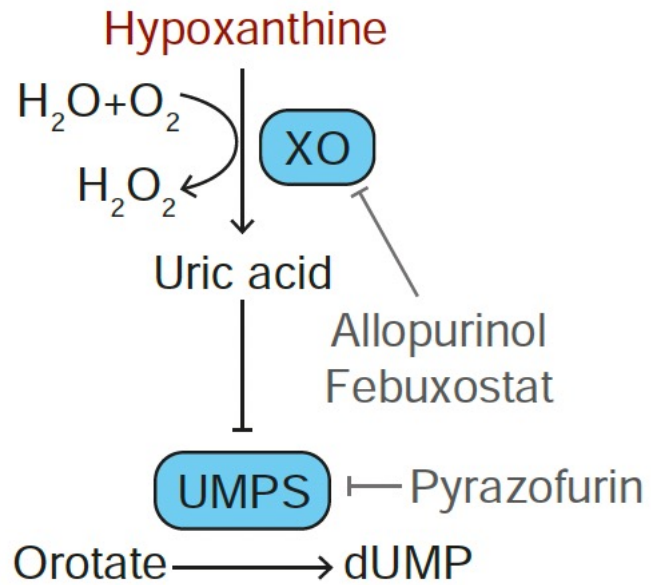
In Brief

Mimicking the metabolite composition of human plasma in culture extensively alters the metabolic landscape of cells and highlights the potential to uncover new metabolite-drug interactions.

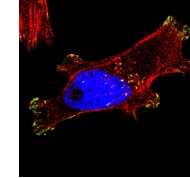
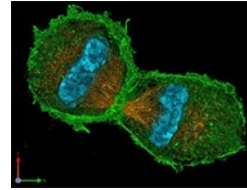
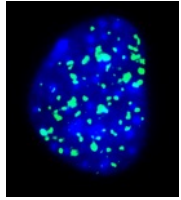


Plasmax

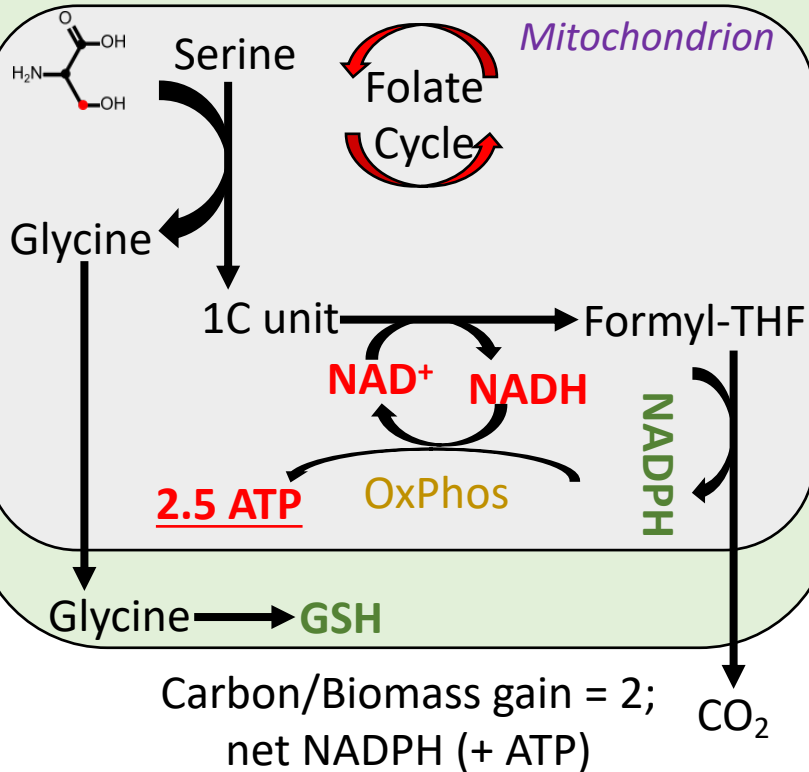
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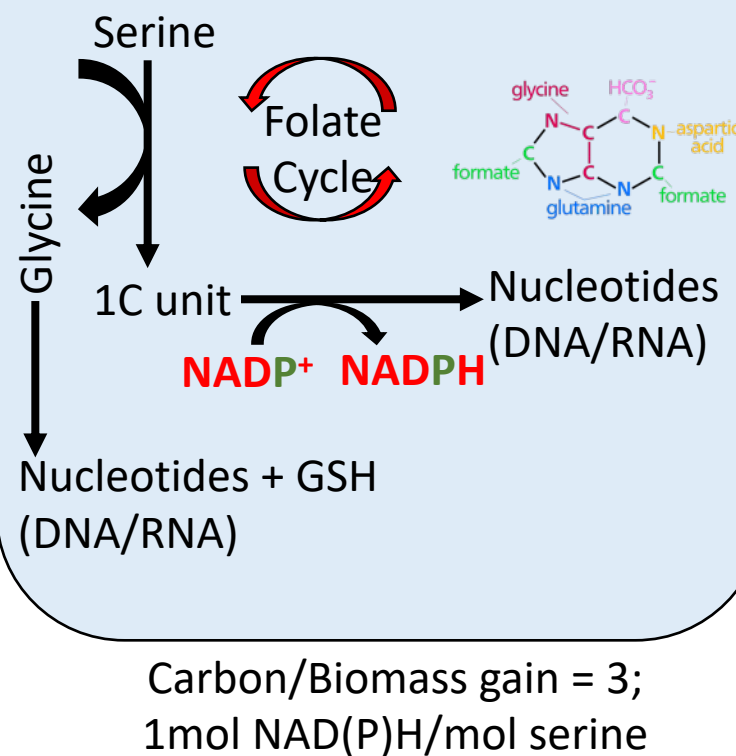
Serine provides metabolic flexibility to sustain challenging microenvironments



RedOx driven serine catabolism



Anabolic role of serine



Alternative route for serine catabolism

