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4-hydroxy-2-oxoglutarate metabolism in a mouse model of Primary Hyperoxaluria Type 3

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ABSTRACT

Primary Hyperoxaluria Type 3 (PH3) results from 4-hydroxy-2-oxoglutarate (HOG) aldolase (HOGA) deficiency, which causes an increase in endogenous oxalate synthesis leading to calcium oxalate kidney stone disease. The mechanisms underlying HOG metabolism and increased oxalate synthesis in PH3 are not well understood. We used a *Hoga1* knock-out mouse model of PH3 to investigate two aspects of HOG metabolism: reduction to dihydroxyglutarate (DHG), a pathway that may limit oxalate synthesis in PH3, and metabolism to glyoxylate, which is a direct precursor to oxalate. The metabolism of HOG to DHG was highest in liver and kidney cortical tissue, enhanced in the cytosolic compartment of the liver, and preferred NADPH as a cofactor. In the absence of HOGA, HOG to glyoxylate aldolase activity was highest in liver mitoplasts, with no activity present in brain tissue lysates. These findings will assist in the identification of enzymes responsible for the metabolism of HOG to DHG and glyoxylate, which may lead to novel therapeutic approaches to limit oxalate synthesis in those afflicted with PH3.

1. Introduction

Primary Hyperoxaluria (PH) Type 3 (PH3) is a poorly understood form of PH for which no effective targeted therapies have yet been developed. This autosomal recessive genetic disease results from a deficiency in the hepatic and renal mitochondrial enzyme 4-hydroxy-2-oxoglutarate aldolase (HOGA) [1]. HOGA is involved in the metabolic pathway that breaks down hydroxyproline (Hyp), an imino acid abundant in collagen, and thus sourced both from the diet and collagen turnover (Fig. 1). Characteristic features of the disease include increased urinary excretion of 4-hydroxy-2-oxoglutaric acid (HOG), the substrate for HOGA, and other Hyp metabolites, including 4-hydroxy-glutamate, dihydroxyglutarate (DHG) and oxalate [2]. The increase in urinary oxalate excretion in PH3 can result in calcium oxalate kidney stone formation and chronic kidney disease [3]. A buildup of glyoxylate and its oxidation to oxalate by lactate dehydrogenase (LDH) is thought to be the major mechanism by which oxalate synthesis increases in PH3, as with other types of Primary Hyperoxaluria. However, the processes by which glyoxylate levels buildup in PH3 are not entirely clear. One proposed mechanism is that the buildup of HOG results in inhibition of the enzyme glyoxylate reductase [4], resulting in an increase in glyoxylate (Fig. 1). It has also been demonstrated that in the absence of HOGA, HOG can be metabolized to glyoxylate by an alternative aldolase or aldolases [5–7]. A more recent hypothesis is a deficiency in HOGA may alter cellular redox balance resulting in increased metabolic flux of glyoxylate to oxalate by LDH [8]. It is possible all 3 proposed mechanisms contribute to increased glyoxylate and oxalate levels in PH3, but the relative contributions of each pathway are still unknown. The glyoxylate fluxes and relative enzyme compartmentalization are likely to play an important role in the extent of oxalate synthesized in PH3, but haven't been investigated and would require novel approaches and models.

Potential therapeutic approaches for reducing endogenous oxalate synthesis in PH3 include inhibiting hepatic lactate dehydrogenase (LDH) activity and reducing the buildup of HOG (Fig. 1). An RNAi approach to knockdown of hepatic LDHA was recently FDA approved for treatment of PH1 [9], although its efficacy in reducing urinary oxalate excretion in PH3 is unclear [10]. Possible approaches to decrease the buildup of HOG include, either the inhibition of Hyp metabolism by reducing the expression and/or activity of hydroxyproline dehydrogenase (HYPDH),

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the first enzyme in the hydroxyproline breakdown pathway [11], or enhancing metabolic pathways that degrade HOG. The phenotype of a mouse model of PH3 [*Hoga1* gene knockout (KO)] has previously been described by our group [7], and surprisingly does not have increased endogenous oxalate synthesis as observed in humans. However, consistent with humans with PH3, the *Hoga1* KO mouse excretes elevated levels of DHG. This observation suggests that conversion of HOG to DHG can be protective. The primary objective of this study was to perform preliminary studies in the *Hoga1* KO mouse to further investigate HOG metabolism, as this knowledge may assist in the identification of proteins responsible for HOG to DHG and HOG to glyoxylate metabolism, which may lead to novel approaches to limit oxalate synthesis in those afflicted with PH3.

2. Materials and methods

Wild-type and *Hoga1* knock-out male and female, adult mice (12–16 weeks of age) on a C57BL/6J background were used. The phenotype of these mice has been previously described [7]. Mice were maintained in a barrier facility with a 12 h light/dark cycle, ambient temperature of 23 ± 1 °C and free access to standard rodent chow (NIH-31 Open formula mouse/rat irradiated diet) and water. For necropsy and tissue harvest, mice were fasted for 4 h prior to necropsy in clean cages with free access to water but no food. Necropsy was performed at the same time of day and mice anesthetized with isoflurane. Tissue was harvested immediately, flash frozen and stored in liquid nitrogen.

For enzyme assays, tissue lysates were prepared by sonication of 1 wt tissue with 9 vol of lysis buffer [25 mM HEPES, pH 7.3, 0.1 % Triton, Protease inhibitors (Thermo Fisher Halt™ Protease Inhibitor Cocktail)]. HOG to DHG assay conditions: 25 mM HEPES buffer, pH 7.3, 100 mM KCl, 1 mM $MgCl_2$, 0.2 mM NADPH or 0.2 mM NADH, 1 mM HOG, 2 min, 37 °C. HOG to glyoxylate assay conditions: 100 mM TRIS buffer, pH 8.5, 0.5 mM HOG, 10 min, 37 °C. Protein concentration was determined by the Bicinchoninic acid method (Thermo Fisher). DHG was measured by ion chromatography mass spectrometry (IC/MS), as previously described [6]. Glyoxylate and pyruvate were quantified by HPLC after derivatization with phenylhydrazine, as previously described [12]. Liver mitochondria and mitoplasts were purified as previously described [13].

For liver organic acids analysis, wild-type and *Hoga1* knock-out animals (12–16 weeks of age) were fed 1 % *trans*-4-hydroxy-L-proline (Sigma-Aldrich, Missouri, USA) for 7 days ad libitum and euthanized humanely at the same time of the day (n = 3 per group). Livers were harvested after a 4 h fast and snap frozen in liquid nitrogen within 10 s of cardiac arrest. Organic acids were extracted from liver tissue and measured by IC/MS, as previously described [7].

All studies were approved by the Institutional Animal Care and Use Committee at University of Alabama at Birmingham (UAB), AL. All protocols used were consistent with the applicable local, state and federal regulations, and with adherence to the NIH Guide for the Care and Use of Laboratory Animals.

3. Results and discussion

In vitro experiments conducted in this study suggest that HOG to DHG metabolism is: (i) similar in both *Hoga1* KO and wild-type liver tissue (Fig. 2A), (ii) utilizes NADH and NADPH as a cofactor, but with a preference for NADPH (Fig. 2B), (iii) occurs in liver, brain and kidney cortical tissue, with highest activity in the kidney cortex (Fig. 2C), and (iv) occurs in both the cytosol and mitochondria of hepatocytes, but is enhanced in the cytosolic compartment (Fig. 2D). These data suggest that there are enzymes capable of reducing HOG to DHG. Aldo-keto reductases are a superfamily of structurally-related proteins of common ancestry that catalyze simple oxidation-reduction reactions, have a broad substrate specificity and wide tissue expression, prefer NADPH as a cofactor, and play an important role in detoxification of reactive aldehydes [14]. Examples of proteins in this family include the aldose and aldehyde reductases, which may be capable of reducing HOG to DHG and warrant further investigation [15]. Future studies should focus on fractionating cytosolic extracts to identify the enzymes responsible for the reduction of HOG to DHG. We hypothesize that the efficient metabolism of HOG to DHG may be a protective pathway by which the mouse limits the buildup of HOG within cells in the absence of HOGA. Future comparative studies are needed to quantify tissue levels of HOG and DHG in human and mouse tissue, including the kidney, to support the hypothesis that the HOG to DHG pathway is a more efficient mechanism in limiting HOG buildup in the mouse versus the human. Identification of the enzymes that reduce HOG to DHG may lead to the development of strategies for reducing HOG levels in those afflicted with PH3.

Previous human and mouse studies have also demonstrated that HOG can be metabolized to glyoxylate in the absence of the HOGA enzyme [6,7], which may contribute to increased oxalate synthesis in PH3. In this study, we harvested tissues from both wild-type and *Hoga1* KO animals to measure HOG aldolase activity. Whole liver lysate aldolase activity was not significantly different between male and female wild-type and *Hoga1* KO animals (data not shown), and further experiments were only performed in male animals. The concentration dependence of HOGA activity in wild-type males and *Hoga1* KO mice, as measured by the formation of glyoxylate and pyruvate in purified liver mitochondria, is shown in Fig. 2E. This experiment confirmed that HOGA activity predominates in wild-type animals, and that cleavage of HOG, via an alternative aldolase, can still occur in the *Hoga1* KO mice but at much lower levels (~20-fold lower with maximum activity at

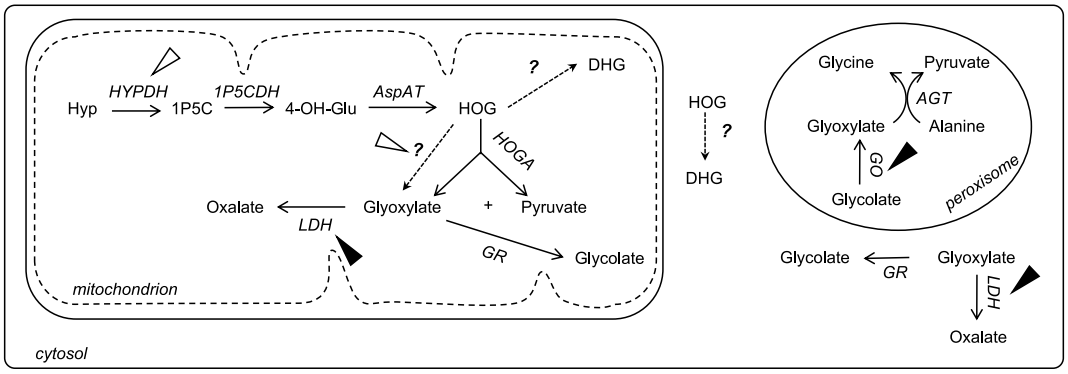

Fig. 1. Current understanding of hepatic metabolism of 4-hydroxy-2-oxoglutaric acid and oxalate synthesis in Primary Hyperoxaluria Type 3. HYPDH: hydroxyproline dehydrogenase; 1P5C: Δ^1-pyrroline-5-carboxylate; 1P5CDH: Δ^1-pyrroline-5-carboxylate dehydrogenase; AspAT: aspartate amino transferase; HOG: 4-hydroxy-2-oxoglutaric acid; HOGA: 4-hydroxy-2-oxoglutarate aldolase (enzyme deficient in PH type 3; GR: glyoxylate reductase (enzyme deficient in PH type 2); LDH: lactate dehydrogenase; GO: glycolate oxidase; AGT: alanine:glyoxylate aminotransferase (enzyme deficient in PH type 1). Both GO and AGT are peroxisomal and liver specific. Therapeutic targets are indicated by triangles: black, targets that have FDA-approved drugs; white, potential treatment targets.

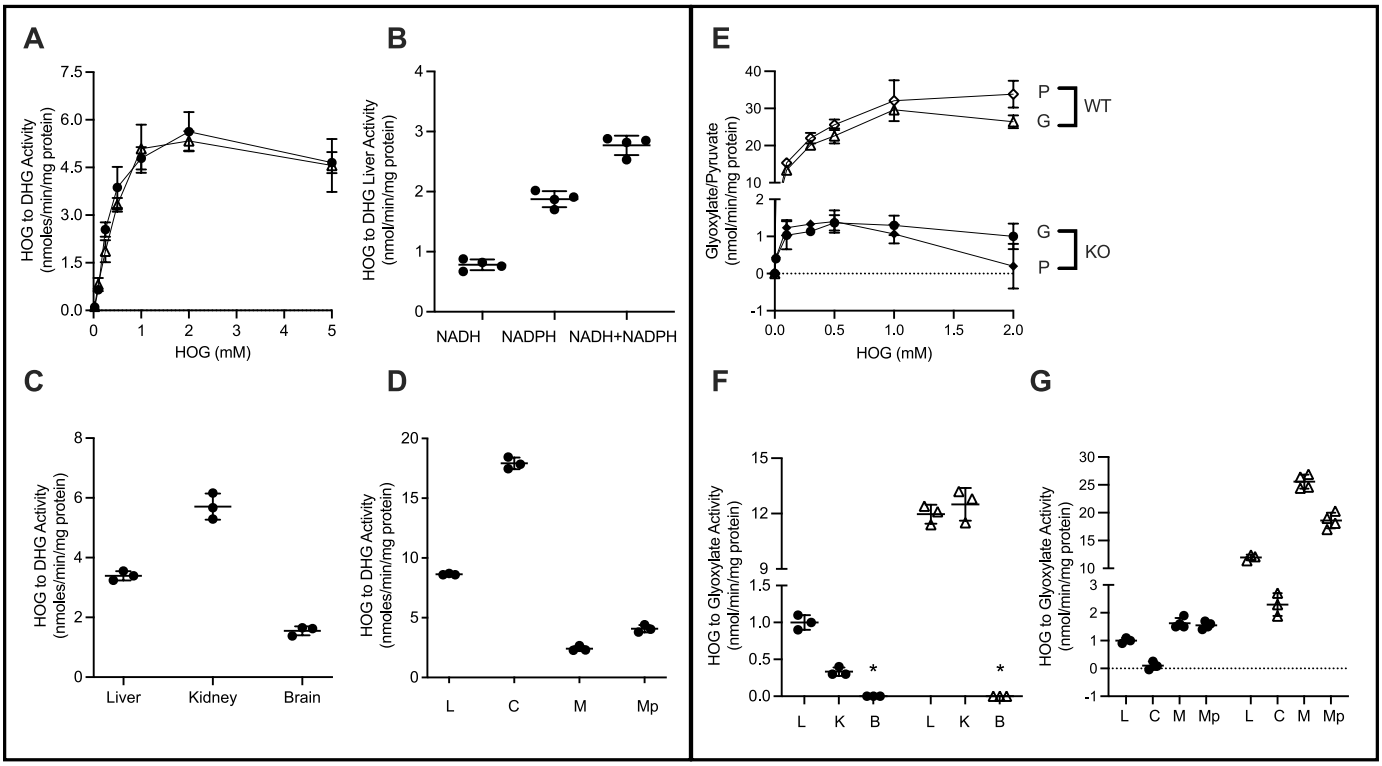

Fig. 2. Metabolism of 4-hydroxy-2-oxoglutaric acid in Primary Hyperoxaluria Type 3.
Panel A. HOG to DHG specific activity in whole liver lysates. Black circles (●): *Hoga1* knock-out; open triangles (Δ): wild-type, adult male mice.
Panel B. **Cofactor dependence of HOG to DHG activity** in whole liver lysates of *Hoga1* knock-out, adult male mice.
Panel C. HOG to DHG activity in different tissues in whole tissue lysates of *Hoga1* knock-out, adult male mice.
Panel D. **HOG to DHG activity in different liver cell fractions** of *Hoga1* knock-out, adult male mice. L: total cell lysate; C: cytosol; M: mitochondria; Mp: mitoplast.
Panel E. HOG aldolase activity in purified liver mitochondria in adult, male mice. The production of glyoxylate and pyruvate were determined to verify that equimolar amounts were produced. Black circles (●): *Hoga1* knock-out glyoxylate; black diamond (◆): *Hoga1* knock-out pyruvate; open triangles (Δ): wild-type glyoxylate; open diamond (◇): wild-type pyruvate.
Panel F. HOG aldolase activity in different tissues (whole tissue lysates). Black circles (●): *Hoga1* knock-out; open triangles (Δ): wild-type, adult male mice. L: liver; K; kidney; B: brain. Stars (*): values below detection levels.
Panel G. HOG aldolase activity in different liver cell fractions. Black circles (●): *Hoga1* knock-out; open triangles (Δ): wild-type, adult male mice. L: total cell lysate; C: cytosol; M: mitochondria; Mp: mitoplast.

approximately 1 mM HOG). Regarding tissue distribution, HOGA activity was highest in liver and kidney whole tissue lysates in wild-type mice (Fig. 2F), as previous reported [7]. In *Hoga1* KO mice, an alternative HOG aldolase activity (cleavage of HOG to glyoxylate and pyruvate) was highest in whole lysates of liver, with lower activity in kidney cortical lysates, and no activity detected in whole brain lysates (Fig. 2F). Fractionation of liver lysates from *Hoga1* KO and wild-type animals revealed alternative aldolase activity in purified mitochondria, specifically within mitoplasts, and insignificant activity in the cytosolic fraction (Fig. 2G). N-acetylneuraminate lyase (NAL), also a Class 1 aldolase, has been suggested as a candidate enzyme for the cleavage of HOG to glyoxylate and pyruvate, but recombinant NAL from Escherichia coli K12 was found to have minimal activity with HOG as a substrate [4]. Future studies could focus on fractionating proteins from hepatic mitoplasts of *Hoga 1* KO mice to identify other HOGA-like enzymes. Alternatively, given the lack of increased oxalate synthesis and the low levels of alternative aldolase activities in the *Hoga1* KO mouse model, performing such investigations in human HOGA1 KO hepatic and/or renal cell lines is warranted.

HOGA is thought to have a wider role in metabolism [8]. We performed a pilot *in vivo* study to investigate if a deficiency in HOGA results in abnormal liver organic acid metabolism. To test this hypothesis, *Hoga-1* KO and wild-type animals were fed a diet rich in hydroxyproline (1 g Hyp per 100 g diet for 1 wk) to accentuate any potential impact of a deficiency in HOGA on organic acid metabolism. Organic acids in whole liver extracts were measured by ion chromatography coupled with mass spectrometry (IC/MS) (Table 1). Under both zero and high hydroxyproline conditions, no differences in liver levels of HOG, glycolate, lactate, pyruvate, and the mitochondria-associated metabolites fumarate, succinate, citrate and malate were observed between wild-type and *Hoga1* KO male and female animals. The only significant change detected by IC/MS was a higher DHG level in *Hoga1* KO animals compared with wild-type control animals (~16-fold and ~26-fold, respectively, for male and female mice), highlighting the very efficient reduction of HOG to DHG in *Hoga1* KO mice. Thus, the identification and overexpression of the enzyme(s) responsible for the conversion of HOG to DHG could be a useful strategy to remove HOG in PH3 patients. The change in HOG tissue levels to Hyp feeding in this study were not consistent with our previous report, which did show a significantly higher liver HOG level in female *Hoga1* KO animals compared to wild type controls [7]. The reason for this discrepancy between the studies is not clear but may be due to a difference in approach (this study measured metabolites in liver after one week 1 % Hyp feeding vs. 2 weeks in the previous study). Another possibility could be a shift in phenotype of the model; since the previous report in 2015, we have backcrossed our *Hoga1* heterozygote mice several times with wild-type C57Blk6j mice to maintain colony rigor. This process may have altered the HOG metabolic phenotype. The current study also did not determine HOG and DHG levels in kidney tissue with and without hydroxyproline feeding. Future examination of the contribution of the

Table 1
Liver organic acids after 1 % dietary hydroxyproline feeding.

	Female				Male				ANOVA P value			
	1 % Hyp		0 % Hyp		1 % Hyp		0 % Hyp					
	KO	WT	KO	WT	KO	WT	KO	WT	Sex	Diet	Genotype	Interaction
HOG	4.2 ± 0.8	3.6 ± 0.3	2.8 ± 0.7	3.2 ± 0.5	3.8 ± 0.6	3.3 ± 0.4	3.3 ± 0.2	3.3 ± 0.5		0.017		
DHG	195 ± 21	9.4 ± 3.3	7.4 ± 0.9	1.4 ± 0.4	153 ± 23	11 ± 2.1	9.6 ± 1.2	1.3 ± 0.1	0.048	<0.001	<0.001	0.021
Glycolate	75.7 ± 6.7	64.3 ± 18.4	46.3 ± 1.1	46.1 ± 1.9	47.6 ± 16.9	49 ± 6.1	38.1 ± 5.3	39.6 ± 4	0.002	0.001		
Fumarate	202 ± 24	165 ± 21	189 ± 40	154 ± 24	172 ± 69	125 ± 28	114 ± 19	137 ± 30	0.013			
Succinate	799 ± 334	679 ± 290	831 ± 528	736 ± 121	972 ± 374	775 ± 29	656 ± 173	866 ± 565				
Malate	921 ± 133	774 ± 93	853 ± 165	731 ± 68	784 ± 257	640 ± 118	594 ± 72	681 ± 136	0.012			
Citrate	234 ± 103	184 ± 57	180 ± 62	184 ± 17	136 ± 64	127 ± 46	127 ± 36	169 ± 76	0.045			
Pyruvate	30.2 ± 8.2	32.7 ± 10.5	27.4 ± 10.9	29.2 ± 6.4	19.8 ± 2.7	24.3 ± 1.4	19.5 ± 1.7	26.4 ± 17.2				
Lactate	4510 ± 788	3929 ± 1275	4246 ± 760	3951 ± 698	7075 ± 1452	6090 ± 160	5404 ± 627	6367 ± 1381	<0.001			

Data expressed as mean ± SD. All metabolites expressed in nmoles/mg wet weight tissue. HOGA has been shown to exhibit oxaloacetate decarboxylase activity [8]; however, oxaloacetate was not measurable by this IC/MS method (limit of detection <1 nmol/g tissue). Three-way ANOVA was used to analyze the effect of sex, diet, genotype, and the interaction. Significant changes ($P < 0.05$) are indicated in table. HOG, 4-hydroxy-2-oxoglutarate; DHG, dihydroxyglutarate.

kidneys to HOG and DHG synthesis is warranted. Studies are also needed to measure HOG and DHG levels in both human liver and kidney tissue.

In conclusion, these preliminary *in vitro* experiments using tissues from the *Hoga1* KO mouse suggest that the metabolism of HOG to glyoxylate is primarily confined to the mitoplasts of hepatocytes, and the conversion of HOG to DHG occurs in kidney, liver and brain, is enhanced in the cytosolic fraction of the liver and primarily utilizes NADPH as a cofactor. Identification of the enzymes responsible for these reactions may lead to novel approaches to limit oxalate synthesis in PH3, for which no effective targeted treatment currently exists.

Data availability

Data will be made available on request.

CRediT authorship contribution statement

Xingsheng Li: Writing – review & editing, Methodology, Investigation. **Owen P. Cunneely:** Writing – review & editing, Investigation. **Sonia Fargue:** Writing – review & editing. **Kyle D. Wood:** Writing – review & editing. **Dean G. Assimos:** Writing – review & editing. **John Knight:** Writing – review & editing, Writing – original draft, Supervision, Resources, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: John Knight reports a relationship with Chinook Therapeutics Inc that includes: consulting or advisory, equity or stocks, and funding grants. John Knight reports a relationship with Arbor Pharmaceuticals LLC that includes: consulting or advisory and funding grants. John Knight reports a relationship with Novo Nordisk that includes: consulting or advisory. John Knight reports a relationship with Prolacta biological sciences that includes: consulting or advisory and funding grants. John Knight reports a relationship with BioMarin Pharmaceutical Inc that includes: consulting or advisory. John Knight reports a relationship with Synlogic that includes: funding grants. John Knight reports a relationship with Novome Biotechnologies, Inc. that includes: consulting or advisory. Kyle Wood reports a relationship with Chinook Therapeutics Inc that includes: consulting or advisory. Kyle Wood reports a relationship with Arbor Pharmaceuticals that includes: consulting or advisory and funding grants. Kyle Wood reports a relationship with BioMarin Pharmaceutical Inc that includes: consulting or advisory. Kyle Wood reports a relationship with Synlogic that includes: consulting or advisory. Kyle Wood reports a relationship with Novome Biological Sciences that includes: consulting or advisory. Kyle Wood reports a relationship with Novo Nordisk that includes: consulting or advisory and funding grants. Kyle Wood reports a relationship with Alnylam Pharmaceuticals Inc that includes: consulting or advisory. Kyle Wood reports a relationship with Bridge Biotherapeutics Inc. that includes: consulting or advisory and funding grants. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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