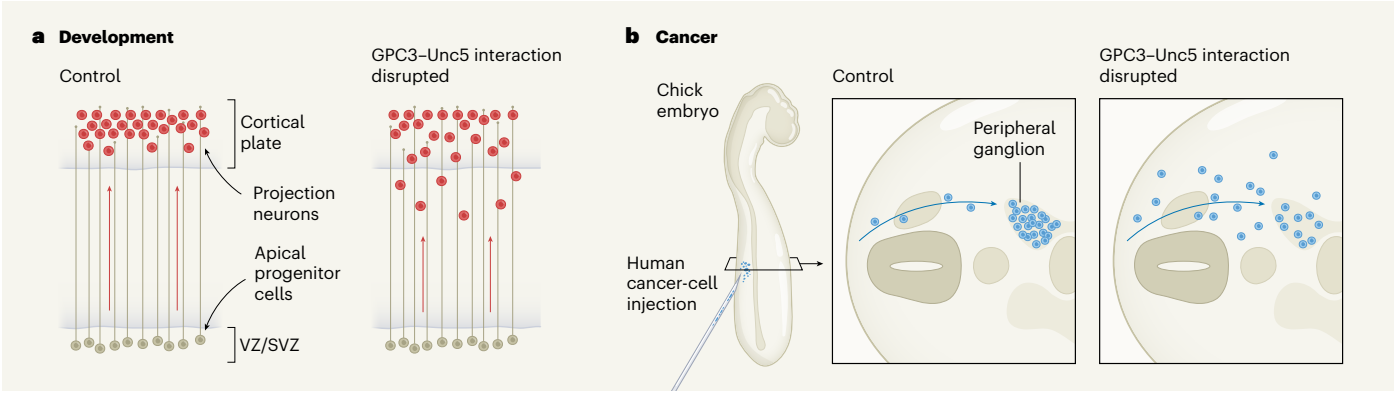


**Figure 2 | GPC3–Unc5 controls neuronal and cancer-cell migration.** **a**, In the cerebral cortex of the developing mouse brain, cells called projection neurons that express Unc5 migrate from a region called the ventricular/subventricular zone (VZ/SVZ) to the cortical plate, moving along processes from apical progenitor cells that express GPC3. Akkermans *et al.* demonstrated that disrupting GPC3–Unc5 interactions prevents normal migration. **b**, Similarly, when human cancer cells that express both Unc5 and GPC3 are injected into the back of chick embryos, they migrate along nerves to colonize structures called peripheral ganglia — but interfering with GPC3–Unc5 interactions prevents this directed migration, with tumour cells instead dispersing and invading other organs.

tumour-cell migration, cohesion and homing to peripheral ganglia (Fig. 2b).

In sum, these results define the GPC3–Unc5 complex as a key regulator of both normal neuron migration and aberrant tumour-cell migration. Although Akkermans and colleagues' study focused on cell migration, Unc5 receptors are also involved in cancer-cell survival, triggering cell death in the absence of Netrin-1 (ref. 9). It is tempting to speculate, then, that enhancing GPC3–Unc5 interactions might prevent Unc5 from binding to Netrin-1, killing tumour cells.

Akkermans *et al.* have added to the already impressive diversity of Unc5 binding partners. Going forward, much remains to be learnt about the potential influence of other Unc5 partners on the stability and function of the GPC3–Unc5 complex. For instance, Unc5-binding proteins called fibronectin leucine-rich transmembrane proteins (FLRTs) can also modulate cortical-cell migration in an Unc5-dependent manner[11]. Is there a hierarchy involving Unc5, GPC3 and FLRTs or other partners? Moreover, because Akkermans and colleagues' structures each contained only one type of Unc5 receptor, owing to difficulties in controlling the stoichiometry of multiple receptors, an open question is whether GPC3 can bind to different combinations of Unc5. It will also be interesting to analyse how Unc5 receptors integrate the choir of upstream signals, and whether the downstream pathways elicited by them are shared or different. Discerning how Unc5 interprets these converging signals is key to understanding how neurons or cancer cells choose to stop or go.

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1. Yamada, K. M. & Sixt, M. *Nature Rev. Mol. Cell Biol.* **20**, 738–752 (2019).
2. Seiradake, E., Jones, E. Y. & Klein, R. *Annu. Rev. Cell Dev. Biol.* **32**, 577–608 (2016).
3. Akkermans, O. *et al. Cell* **185**, 3931–3949 (2022).
4. Brenner, S. *Genetics* **77**, 71–94 (1974).
5. Leung-Hagesteijn, C. *et al. Cell* **71**, 289–299 (1992).
6. Leonardo, E. D. *et al. Nature* **386**, 833–838 (1997).
7. Ackerman, S. L. *et al. Nature* **386**, 838–842 (1997).
8. Jackson, V. A. *et al. Nature Commun.* **7**, 11184 (2016).
9. Brisset, M., Grandin, M., Bernet, A., Mehlen, P. & Hollande, F. *EMBO Mol. Med.* **13**, e14495 (2021).
10. Verschueren, E. *et al. Cell* **182**, 329–344 (2020).
11. Seiradake, E. *et al. Neuron* **84**, 370–385 (2014).

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Structural biology

# Folate transporter offers clues for anticancer drugs

**Larry H. Matherly & Zhanjun Hou**

Structural insights into a long-studied folate-transport protein provide evidence that might lead to entirely new targeted anticancer treatments, or boost the success of immunotherapy approaches to tackling tumours. **See p.170**

The transport protein SLC19A1, better known as the reduced folate carrier, resides in the cell membrane. It has been studied for decades because it is the main tissue transporter of the B9 vitamins (called folates), which are required for reactions needed to make certain types of nucleotide and to make the amino-acid residues serine and methionine[1]. SLC19A1 also happens to be the main transporter of the drugs methotrexate and pemetrexed — which are called antifolates, because they block the action of folates. These drugs are used in the treatment of cancer, rheumatoid arthritis and psoriasis[1]. In 2019, a new role for SLC19A1 was identified, as a transporter of signalling molecules called cyclic dinucleotides (CDNs), which stimulate a wide range of immune-system cellular responses[2,3].

Although extensive biochemical and molecular studies have implicated structural and functional determinants of folate transport by SLC19A1, the detailed molecular basis for the binding of various SLC19A1 substrates and their movement through the transporter, from outside the cell into the cytoplasm, is largely unexplored. Zhang *et al.*[4] (page 170) and Wright *et al.*[5] (in a study published in September) shed some light on this.

These studies used cryo-electron microscopy (cryo-EM) to determine the molecular structures of human SLC19A1 without a binding partner (in what is known as the protein's apo form) and with bound folates, antifolates or CDNs (Fig. 1). In both reports, SLC19A1 assumed a structure with 12 membrane-spanning segments in an 'inward'-facing orientation opening onto the cytoplasm — with membrane-spanning segments surrounding a positively charged substrate-binding pocket that is lined



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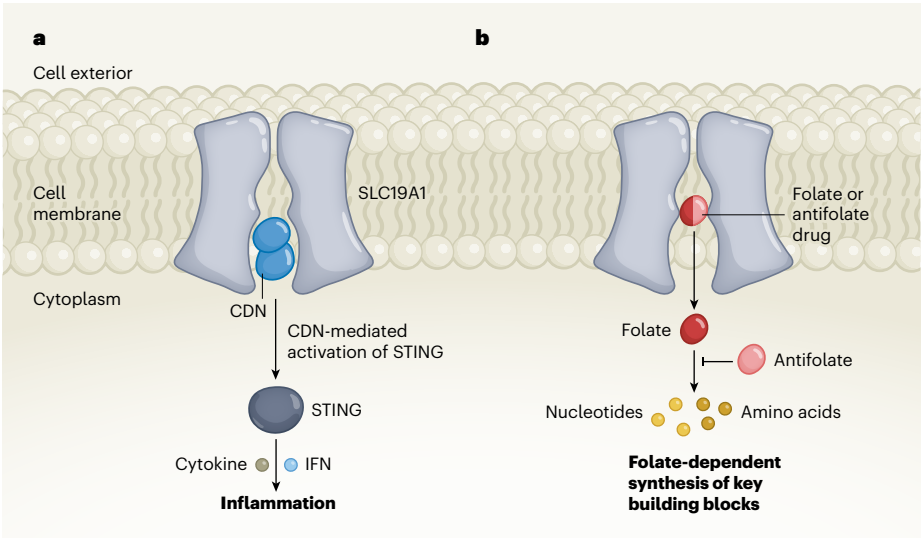


**Figure 1 | Structural insights into the SLC19A1 protein.** Zhang *et al.*[4] and a study this year by Wright *et al.*[5] report cryo-electron microscopy data that reveal details of how this transporter binds to its substrates. **a**, SLC19A1 transports molecules called cyclic dinucleotides (CDNs) that drive inflammatory defence responses. These responses are mediated by the protein STING, and by molecules called cytokines and the protein interferon (IFN). Zhang *et al.* report that CDNs are found in pairs in the transporter near to the cytoplasmic side of the membrane. **b**, Molecules called folates, which are required to make certain cellular building blocks of nucleotides and amino acids, enter cells through SLC19A1 — as do anticancer drugs, termed antifolates, that block folate action. Zhang and Wright and their respective colleagues report that folates and antifolates bind to a central part of SLC19A1 (this binding site differs from the one for CDNs). This structural information might pave the way for the design of improved anticancer or immunotherapy treatments.

by evolutionarily conserved amino-acid residues.

In mammalian cells, CDNs serve as prominent signals of danger that are recognized by an immune-system sensor protein called STING, which is located in cells in an organelle called the endoplasmic reticulum[6]. STING activation generates a signalling cascade that results in a rise in the concentration of proteins called type I interferons, and in assorted signalling molecules called cytokines. Mammalian cells (including tumour cells) produce the CDN molecule 2′,3′-cGAMP as a response to the abnormal presence of double-stranded DNA, and the production of this CDN is catalysed by the enzyme cGAS. Other CDNs, such as 3′,3′-cGAMP, can be generated by bacteria.

Given the role of cGAS and STING signalling in anticancer defence responses, there has been a surge of interest in STING-activating drugs (STING agonists) as cancer therapeutics; among these drugs are those that mimic 2′,3′-cGAMP. Drug-induced activation of STING in animal studies drives enhanced immune responses mediated by the activation of immune cells called T cells; this inhibits tumour growth[7]. Natural and synthetic STING agonists have been tested clinically and are safe. However, they have shown only modest therapeutic activity. Thus, there is a need for more potent and selective CDNs with improved delivery into tumours. This could enhance responses to current immunotherapies, including STING agonists.

For CDNs to function as immune modulators, they must cross the cell membrane to activate STING. This is a challenge, because CDNs are negatively charged, which prevents them from crossing the membrane by diffusion. The recognition that CDNs are transported by SLC19A1 provided at least a partial solution to the conundrum of how they enter cells (other transporters are probably also involved in CDN uptake)[2,3]. However, transport of CDNs by SLC19A1 is poor compared with the protein's ability to transport folate substrates[2,3] — which is unsurprising, given the dissimilar chemical structures of CDNs and folates.

Zhang and colleagues' study initially determined structures of SLC19A1 with CDNs that included 2′,3′-cGAMP, the bacterial CDN 3′,3′-cyclic di-AMP and synthetic 2′,3′-bisphosphothioate-cyclic di-AMP. Surprisingly, given that one might expect the typical scenario of a single molecule binding to its transporter, Zhang *et al.* report that all of these CDNs bind to SLC19A1 as a well-organized, tightly packed pair (dimer) of CDNs. This binding was in a common binding site and occurred through processes that included stacking, hydrogen bonding and charge interactions, albeit with different conformations for the respective CDNs. The conical substrate-binding cavity was found to extend from the intracellular face of SLC19A1 nearly to the extracellular side of the transporter. CDNs bound in the wider intracellular entrance of the transporter, extending to the middle of the transmembrane region.

For comparison, Zhang *et al.* present structures of SLC19A1 bound to 5-methyl tetrahydrofolate, the main form of folate found in the body, and pemetrexed — both of which bound to SLC19A1 as single molecules (monomers), attaching to a distinct region of the binding pocket that overlapped only slightly with that for the CDNs. To extend their studies, Zhang and colleagues performed molecular-dynamics simulations and functional tests exploring different versions of SLC19A1 protein that had targeted mutations affecting certain amino acids. The authors thereby identified key determinants of SLC19A1's transport selectivity for CDN and folate substrates, and pinpointed key features for substrate recognition by SLC19A1.

As might be expected, the effect of individual mutations on CDN binding compared with folate binding were not entirely the same. The main determinants of antifolate binding identified by Zhang *et al.* largely agree with those of Wright and colleagues. The latter group had previously described cryo-EM structures of SLC19A1 in the apo form and treated with a version of methotrexate that had been designed to bind covalently to a particular amino acid (lysine-411) of SLC19A1.

Both reports are extraordinary because of the abundant structural, functional and computational data presented, and the rich insights they provide into substrate recognition and transport by SLC19A1. That said, establishing the detailed mechanism of substrate transport will require interrogation of alternative SLC19A1 conformations bound to substrate(s). Indeed, given the distinct binding poses of pemetrexed and 5-methyl tetrahydrofolate compared with CDNs, it is possible that — should SLC19A1 transport dimeric CDNs — the mechanism might be distinct from that used for folate substrates.

For folate and antifolate substrates, these two reports provide mechanistic insights into the consequences of loss-of-activity and disease-related mutations of SLC19A1. The work also provides mechanistic interpretations of SLC19A1 mutations associated with treatment failure identified in human tumours after treatment with methotrexate, and in antifolate-resistant tumour cell lines grown in the laboratory. In addition, the studies offer insights into amino-acid residues that had been previously implicated as structurally and functionally important. This conclusion was drawn partly from SLC19A1 studies that explored similarities between the protein in various species (homology studies), and partly from evidence gathered from mutant versions of the protein.

Together, the two reports point to SLC19A1 having a key role both in immune-system function and in anticancer immunology — in addition to its established role in transporting folates and antifolates. Potential applications of the findings include using the new SLC19A1 structures to design next-generation CDNs,



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with greater specificities and potencies, and newer antifolates to treat an assortment of cancers and autoimmune disorders. In connection with the latter, SLC19A1 is one of the two main folate transporters in tissues; the other is SLC46A1, which is known as the proton-coupled folate transporter[8]. SLC46A1 is needed for gut absorption of dietary folates and is a key transporter of folates in human tumours at the acid pH of the tumour microenvironment[8,9]. Particular interest has focused on the discovery of new SLC46A1-specific antifolates that have limited transport by SLC19A1 and greater tumour selectivity than is the case for antifolates such as methotrexate[9]. When combined with the cryo-EM structure of SLC46A1 in its apo- and pemetrexed-bound forms[10], the SLC19A1 structures provide the foundation for designing a new generation of more-selective therapeutics for cancer[9], on the basis of their preferential transport by SLC46A1 rather than SLC19A1.

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1. Matherly, L. H., Hou, Z. & Deng, Y. *Cancer Metast. Rev.* **26**, 111–128 (2007).
2. Luteijn, R. D. *et al. Nature* **573**, 434–438 (2019).
3. Ritchie, C., Cordova, A. F., Hess, G. T., Bassik, M. C. & Li, L. *Mol. Cell* **75**, 372–381 (2019).
4. Zhang, Q. *et al. Nature* **612**, 170–176 (2022).
5. Wright, N. J. *et al. Nature* **609**, 1056–1062 (2022).
6. Hopfner, K.-P. & Hornung, V. *Nature Rev. Mol. Cell Biol.* **21**, 501–521 (2020).
7. Demaria, O. *et al. Proc. Natl Acad. Sci. USA* **112**, 15408–15413 (2015).
8. Qiu, A. *et al. Cell* **127**, 917–928 (2006).
9. Matherly, L. H., Schneider, M., Gangjee, A. & Hou, Z. *Expert Opin. Drug Metab. Toxicol.* **18**, 695–706 (2022).
10. Parker, J. L. *et al. Nature* **595**, 130–134 (2021).

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Quantum physics

# A holographic wormhole in a quantum computer

**Adam R. Brown & Leonard Susskind**

A system of nine quantum bits has been used to simulate a state known as a holographic wormhole, a concept that features in attempts to reconcile quantum mechanics with the general theory of relativity. **See p.51**

The holographic principle is a guide in our quest to understand how to combine the two most celebrated theories of modern physics — quantum mechanics and general relativity. According to this principle, theories that include both quantum mechanics and gravity can be exactly equivalent to other theories that involve quantum mechanics but not gravity. Such an alternative description is known as a dual, and has fewer dimensions than its gravitational counterpart — much like how a hologram projected on a 2D surface displays a 3D image. On page 51, Jafferis *et al.*[1] report using a quantum computer to generate a state that mimics a hologram whose dual is an entity known as a wormhole, and then evolving this state to simulate a message traversing the wormhole.

The idea of a wormhole dates back to 1935, when Albert Einstein and his collaborator, Nathan Rosen, studied black holes in the context of Einstein's general theory of relativity[2]. Every black hole has both an interior region, from which nothing can escape, and an exterior region, from where escape is still possible. The two regions are demarcated by a surface called the event horizon. What Einstein and Rosen noticed is that, in a mathematical idealization of a black hole, there is actually not one exterior region, but two, and they are connected through a kind of wormhole now known as an Einstein–Rosen bridge.

But this is no ordinary bridge. On the one hand, in the version studied by Einstein and Rosen (and unlike that considered by Jafferis and colleagues), it is impossible to travel through the wormhole from one exterior region to the other — the wormhole cannot be traversed. On the other hand, if someone jumps into the interior region of the black hole from one exterior region, it is possible for them to meet someone jumping in from the other exterior region, but their time together would be brief, because by jumping in they'd be doomed to certain death. The bridge cannot be crossed, but people from opposite ends can briefly meet in the middle.

In the same year, Einstein and Rosen wrote another paper, this time in collaboration with Boris Podolsky[3]. The trio's paper examined quantum mechanics (without gravity), and identified the phenomenon

## From the archive

**A book captures a snapshot of scientists around the globe, and the pages of an encyclopedia contain an indexing mirage.**

### 50 years ago

*Passion to Know: The Scientists of Today's World — Who They Are, What They Are Doing and Why!* By Mitchell Wilson — Mitchell Wilson was an American physicist who assisted Fermi in cosmic ray research. He is now a writer. ... Sir George Weidenfeld, the publisher, proposed that he should travel around the world, visiting the most interesting centres of science, meet the most interesting people, and write a book on what he had heard and seen. The result is a readable mixture of fact, reporting, and opinion ... The feature he found common to all scientists was the passion to know.

**From *Nature* 1 December 1972**

### 150 years ago

Can any of your readers inform me if there is such a thing as a good and honestly constructed cyclopaedia — one that does not ... refer you ... to articles that do not exist? I have been repeatedly annoyed by this kind of will-o'-the-wisp, but have to-day met with such an outrageous example of it, that, although it involves some trouble, I feel it to be a duty to make a public exposure of it in your columns. Requiring some facts on unusual atmospheric refraction, I turned to "Refraction" in the "English Encyclopaedia". This article referred me to "Mirage, Fata Morgana," &c., for information on this branch of the subject. Turning to "Mirage," I found not a word but another reference to "Reflection and Refraction, Atmospheric, Extraordinary." Next I tried "Fata Morgana," again the same reference. Coming back to letter R, I found the article "Reflection and Refraction," but was here referred to "Light, Optics, Refraction, Refrangibility;" then to letter A, "Atmosphere, Atmospheric" — nothing on the subject. Letter E, "Extraordinary Refraction" — nothing but a reference back again to "Mirage!" ... I was thus sent on a search through five volumes of the work, and made to hunt out nine distinct headings for what does not exist.

**From *Nature* 28 November 1872**




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