Research Strategy: Fiona Jackson

Targeting one-carbon metabolism in cancer

Despite its well-established role in cancer biology, one-carbon metabolism has long been regarded as a challenging therapeutic target. In 2017, Raze Therapeutics Inc, one of the most prominent companies pursuing this approach at the time, ceased operations after investors concluded that the underlying biology remained too difficult to translate into effective therapies[1]. In 2024, Ribon Therapeutics Inc was shuttered after pursuing enzyme-targeted therapies aimed at stress-response and metabolic vulnerabilities in cancer cells[2].

These setbacks form a small chapter of a longer story: past efforts to drug the one-carbon pathway in cancer were repeatedly limited by toxicity because they could not adequately distinguish cancer-rewired metabolism from the metabolism of healthy tissue. Daiichi Sankyo Co Ltd has developed a small molecule inhibitor targeting this pathway in cancer, though that programme remains at the preclinical stage[3]. Interest in the enzyme, methylenetetrahydrofolate dehydrogenase 2 (MTHFD2), now extends beyond oncology: Oxford-based Sitryx Therapeutics Ltd advanced an oral MTHFD2 inhibitor, SIT-047, toward first clinical entry in psoriatic arthritis in 2026, with a broader autoimmune footprint under consideration. That growing activity reflects the enzyme's fundamental role across proliferative disease. In cancer specifically, however, no company has yet translated MTHFD1/MTHFD2 inhibition into a clinical programme – the gap One-carbon Therapeutics AB hopes to close.

One-carbon enzymes are responsible for transferring single-carbon units that are essential for fundamental cellular processes, including nucleotide biosynthesis, amino acid metabolism and DNA repair. Among the most important of these enzymes are MTHFD1 and MTHFD2.

MTHFD2 (mitochondrial/nuclear) is an oncofetal protein expressed during embryonic development to support rapid cell growth, silenced in most differentiated adult tissues, and re-expressed in tumours. MTHFD1 (cytoplasmic) plays a central role in normal cellular metabolism throughout adult life and is also up regulated in malignancy. MTHFD2 is one of the most consistently up regulated proteins in cancer and is associated with significantly worse overall survival[4]. Together, the two enzymes represent one of the most compelling and well-validated metabolic dependencies in oncology – and one that has, until now, resisted successful drug development.

One-carbon Therapeutics, a clinical-stage precision oncology company and Karolinska Institutet spin-out headquartered in Solna, Sweden, was founded in 2020 to exploit this cancer-specific dependency. The company's premise is that the differentiator lies not only in *what* is targeted but also in *how* it is targeted – a granular understanding of the pathway that previous programmes lacked. Its lead programme, TH9619, is a first-in-class, potent, small-molecule inhibitor of MTHFD1 and MTHFD2. Structure-guided drug design, enabled by the identification of the target crystal structure by scientific founder Professor Thomas Helleday, delivered a breakthrough: TH9619 binds selectively in the folate pocket of both enzymes with nanomolar potency, according to the company.

The compound selectively kills cancer cells through toxic folate trapping[5]. In cancer cells, high levels of MTHFD2 drive initial release of formate from mitochondria into the cytosol, which is then coupled to tetrahydrofolate by MTHFD1 to generate 10-CHO-THF (formyl-tetrahydrofolate), an essential one-carbon donor for nucleotide biosynthesis. Inhibition of MTHFD1 by TH9619 prevents further use of 10-CHO-THF for downstream thymidylate synthesis, creating a folate trap that depletes the tetrahydrofolate required for nucleotide production. The resulting nucleotide shortage triggers replication stress and DNA damage, starving cancer cells of DNA building blocks and leading to cancer cell death[6]. Because normal cells express MTHFD2 to a lesser extent, they lack the formate overflow required to generate this trap and are therefore spared. This is the distinction that eluded earlier programmes in the space: an approach differentiated from conventional chemotherapy,

Background and Rationale

Cancer cells depend on one-carbon metabolism to sustain rapid DNA synthesis and survival. Two key enzymes in this pathway, MTHFD1 (cytoplasmic) and MTHFD2 (mitochondrial/nuclear), are highly and consistently overexpressed in solid tumours compared with normal tissues. This creates a cancer-specific dependency that TH9619 is designed to exploit with high selectivity.

MTHFD2 is one of the most overexpressed genes in cancer and consistently associated with significantly worse overall survival across multiple cancers.

TH9619 Mechanism of Action

TH9619 is a small molecule MTHFD 1/2 inhibitor (intravenous administration) that selectively kills cancer through folate trapping.

- In cancer cells, high MTHFD2 expression drives the release of formate from mitochondria into the cytosol, to generate 10-CHO-THF (formylfolate);
- Inhibition of MTHFD1 by TH9619 prevents further use of 10-CHO-THF for downstream thymidylate synthesis;
- This creates a folate trap, depleting the folate (THF) necessary for thymidylate production, resulting in nucleotide shortage, DNA damage, and cancer cell death;
- Normal cells lack MTHFD2 expression and the formate overflow needed to create this trap.

Source: Moreno, V, et al, A Phase 1/2 First-in Human Study of TH9619 in Patients With Advanced Refractory Solid Tumours, *ASCO Publications*, 27 May 2026.

which targets rapidly dividing cells indiscriminately, and from classical synthetic lethality strategies, which depend on specific genetic mutations.

In September 2025, One-carbon initiated the ODIN first-in-human Phase 1/2 study (NCT07151040) to evaluate TH9619 as a monotherapy in patients with advanced refractory solid tumours[7]. The study is designed to drive decisions on dose, indication selection and expansion. Phase 1a establishes safety and tolerability and identifies the recommended dose, with escalating intravenous doses of TH9619 starting at 500 mg/m² in 28-day cycles until disease progression or unacceptable toxicity. This flexible architecture – with expansion only where early signals justify it – is intended to reduce risk for what remains, for now, a single-asset company. Clinical results are expected to be available in 2027.

In parallel, the company has a strategic collaboration with Tempus AI Inc, a technology company leading the adoption of AI to advance precision medicine. This collaboration will utilise Tempus' analytical services to characterise the expression landscape across prioritised solid tumor indications[8]. By integrating RNA sequencing data with clinical variables, the teams aim to uncover deep molecular insights that will inform the development of TH9619.

The trial-in-progress poster (TPS3165) presented by Moreno et al. at ASCO 2026 confirmed that recruitment is underway across four academic and clinical research centres in the United Kingdom, France and Spain – the Northern Centre for Cancer Care in Newcastle; Institut Gustave Roussy in Villejuif; and, in Spain, START Madrid–FJD at Hospital Fundación Jiménez Díaz, and the Hospital Universitari Vall d'Hebron in Barcelona – with expansion to additional European sites planned in the coming months[9].

Development of the ODIN study has been supported by a group of family offices and private Swedish investors, several of whom bring backgrounds from leading European venture funds – a deliberately non-traditional early cap table that One-carbon says was chosen to build value ahead of a larger institutional round. Most recently, the company secured SEK 153 million ($16.1 million) in a funding round completed at the end of 2025.

Management is candid about the road ahead. Despite the common challenges with clinical development, particularly with first-in class compounds, the scientific opportunity is significant.

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