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INVITED COMMENTARY

Advancing gastric cancer precision medicine with novel genomic screens†

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†Invited Commentary for Liu *et al*. Functional genomics screening identifies aspartyl-tRNA synthetase as a novel prognostic marker and a therapeutic target for gastric cancers. *J Pathol* 2022; **258**: 106–120.

Abstract

A recent study published in *The Journal of Pathology* used an shRNA library targeting all known human genes involved in metabolism to identify genes important for gastric cancer. The screen identified aspartyl-tRNA synthetase (DARS) as a potential drug target, and patients whose tumors had high DARS levels had a worse prognosis, particularly among diffuse-type gastric cancer. These findings identify a potential therapeutic target for precision medicine of gastric cancer patients, and may be useful for further investigations to discover additional interacting targets.

Keywords: gastric cancer; metabolism; aspartyl-tRNA synthetase; synthetic lethality

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Worldwide, gastric cancer (GC) is the fifth most common cancer type and the fourth leading cause of cancer-related deaths. GC risk is higher among countries across Eastern Asia, Eastern Europe, and South America [1]. There are several well-known GC risk factors, such as chronic infections (*Helicobacter pylori*, Epstein–Barr virus), diet (high salt, processed meat), and lifestyle choices (alcohol consumption, smoking), as well as genetic predisposition [1,2]. Large-scale patient cohort sequencing studies have further increased our knowledge of GC at the molecular level, providing molecular subtype classifications for use in precision medicine [3].

Despite its high burden and our increased understanding of GC risk and development, few targeted therapeutics have been approved for its treatment. Among these are the monoclonal antibodies trastuzumab for $HER2^+$ GC, ramucirumab (an anti-VEGFR2), pembrolizumab, and nivolumab (PD-L1-expressing, microsatellite instability-high, high tumor mutational burden GC) [4]. Together, these therapeutics target a relatively small subset of GCs, leaving many patients without molecularly guided therapy as an option. Moreover, high levels of GC intratumoral heterogeneity (ITH), both within the primary tumor and between primary and metastatic sites, have limited biomarker-driven clinical trial success with variable biomarker expression and an increased likelihood of genomic alterations that confer therapeutic resistance [5]. Thus, the discovery of new GC drug targets, especially those with a broad molecular subtype application, is a critical and immediate goal for cancer precision medicine.

In a recent issue of this journal, Liu and collaborators provide a timely contribution that addresses the current issue of limited GC treatment options [6]. Their study utilized a short hairpin RNA (shRNA) library targeting all known human metabolism genes ($n = 2{,}096$) in two GC cell lines, one derived from a histologically well-differentiated GC tumor and the other from a poorly differentiated tumor. Liu *et al* focused on metabolism genes that are fundamental in gastric biology. Their screen identified the product of the aspartyl-tRNA synthetase (*DARS*) gene as a novel GC drug target candidate. They also showed that patients whose tumors had high DARS expression had a worse prognosis, particularly among diffuse-type malignancies. *In vitro* experiments further confirmed DARS's role in carcinogenesis via activation of the MAPK–ERK pathway. Their results highlighted *DARS* as a novel prognostic marker and a potential GC druggable candidate.

This study provided a critical discovery for novel molecular targets for GC therapeutic development. These results highlighted druggable pathways applicable

for the diffuse histological GC subtype, which is associated with a poorer prognosis, a lack of molecular targets, and worse survival than intestinal-type tumors [5]. While long defining distinct GC clinical presentations, the Laurén histological classification of intestinal and diffuse subtypes has previously failed to demonstrate therapeutically relevant stratification [7]. This study provides a crucial bridge for this gap. Furthermore, the combination of genome-wide screening technology with *in vivo* models of cancer, such as mouse xenograft models by Liu *et al*, increases the clinical translational power of their preclinical discoveries. With more cost-effective and more accessible next-generation sequencing technologies, genome-wide screens have become a powerful new tool for unbiased drug target discovery. Liu and co-authors virally introduced a metabolism gene-wide shRNA screen into GC cell lines and injected infected cells into immune-comprised mice, allowing assessment of GC essential genes within an *in vivo* system, more representative of actual tumor development compared with cells growing in a 2D monolayer. Liu *et al* demonstrate the value of genome-wide screens and translational cancer models for preclinical drug target discovery studies.

Despite these advances, more work is still required to translate these discoveries into clinical use – namely, greater use of more translational preclinical cancer models and candidate drug target refinement for toxicity considerations. As previously mentioned, a major obstacle in targeted therapy clinical trial success is high ITH among GC tumors [5,7]. As the authors pointed out, the use of established GC cell lines, which are monoclonal in nature, precludes the ability to investigate the effect of ITH on therapeutic response. However, more recently developed *in vitro* models, such as patient-derived organoids (PDOs), which grow three-dimensionally and can maintain the genomic landscape of the original patient tumor, including ITH, may alleviate this issue [8]. Moreover, using PDOs may also help to diversify the patient population represented in these preclinical studies. The role of genetic variation associated with ancestry as a modifier of cancer risk and treatment response is gaining traction in the field of cancer precision medicine. While most established cell lines are derived from patients of European/White ancestry, PDOs provide a platform for the inclusion of known high-risk populations based on global data, such as Latinos, East Asians, and indigenous American communities, which may improve clinical translation of these discoveries [8]. However, performing genome-wide screens in PDOs remains extremely labor- and cost-intensive compared with using established cancer cell lines. Further advances in model and screening technologies and downstream analysis software will be required to make this more broadly feasible for the cancer research field.

While genome-wide screens are a powerful tool for drug target discovery, it is important to consider the cancer-specific expression of candidate targets for drug development. Many genes identified through these screens are essential not only for tumor growth and survival but also for normal tissue homeostasis. *DARS* is a critical regulatory component of aspartyl-tRNA synthesis and, ultimately, translation of the amino acid aspartate. Though its upregulation in GC patients with a worse prognosis deems it a viable drug candidate, targeted inhibition of such an essential protein is bound to elicit significant toxic effects on normal cell function if administered. The authors identify that the proteins most likely affected by DARS inhibition include calmodulin and other calcium-binding proteins, which are critical for a wide range of normal physiological functions [9]. Genome-wide screening can and has been adapted to address this issue in the form of synthetic lethality. Synthetic lethality refers to a relationship between two genes in which individual inactivation of either confers negligible effect on cellular viability but induces cell death when both are simultaneously inactivated [10]. Synthetic lethal interactions have led to the approval of PARP inhibitors for *BRCA*-mutant ovarian and breast tumors. Where *BRCA1/2*-mutant cancer cells would be sensitive to PARP inhibition, normal cells with at least one functional copy of *BRCA1/2* would survive with a relatively limited toxicity [10]. Synthetic lethal interactions provide a mechanism for identifying cancer cell-specific drug targets that possess the advantage of reduced toxicity and patient side-effects. Future studies utilizing screens for DARS' synthetic lethal interaction discovery may provide compelling alternative drug targets for diffuse-type GC.

Identification of novel gene targets for cancer therapeutic development is a persisting issue. The discovery of new drug targets is crucial in reducing cancer mortality, particularly for GC, which has a significantly shorter survival time for advanced stages compared with other common solid tumors but benefits from relatively few approved targeted therapeutic options. Liu *et al* provide a significant discovery in precision GC medicine, identifying DARS as a candidate target for diffuse-type GC, a subtype with particularly poor patient prognosis. This study demonstrates the effective use of genome-wide screening technology and translational *in vivo* cancer models for preclinical drug discovery, providing a path for future applications. Increasing use of more advanced translational models, such as PDOs, and a greater focus on cancer-specific drug target identification with synthetic lethal interaction discovery will bolster the clinical application of preclinical studies such as this to address the critical lack of targeted therapeutics for this debilitating disease.

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Author contributions statement

NBH and LGC both contributed to the conceptualization, writing and editing of the manuscript.

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