



OPEN ACCESS

EDITED AND REVIEWED BY

José A. G. Agúndez,
University of Extremadura, Spain

*CORRESPONDENCE

Karunakaran Kalesh,
✉ k.karunakaran@tees.ac.uk
Liang Xue,
✉ liang.xue@pfizer.com

RECEIVED 07 February 2026

REVISED 09 February 2026

ACCEPTED 10 February 2026

PUBLISHED 16 February 2026

CITATION

Kalesh K and Xue L (2026) Editorial:
Integrating genetics and proteomics for
drug discovery.

Front. Genet. 17:1806492.

doi: 10.3389/fgene.2026.1806492

COPYRIGHT

© 2026 Kalesh and Xue. This is an open-access article distributed under the terms of the [Creative Commons Attribution License \(CC BY\)](#). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Editorial: Integrating genetics and proteomics for drug discovery

Karunakaran Kalesh^{1*} and Liang Xue^{2*}

¹School of Health and Life Sciences, Teesside University, Middlesbrough, United Kingdom, ²Research and Development, Pfizer Inc., Cambridge, MA, United States

KEYWORDS

biomarker, co-localization, drug discovery, genetics, mendelian randomisation, protein quantitative trait loci (pQTL), proteogenomics, proteomics

Editorial on the Research Topic

Integrating genetics and proteomics for drug discovery

Why this Research Topic matters

Genetics has mapped thousands of robust, human-anchored associations with disease, yet many programmes still stall when attempting to move from “variant” to “valid target.” Integrating genetics with proteomics helps close this gap by testing whether genetic signals manifest as protein-level changes in the relevant tissues, pathways, and cell states. This integration strengthens causal inference (via pQTLs, colocalization, and Mendelian randomization), reveals drug-amenable biology such as isoforms, complexes, post-translational regulation, and yields biomarkers that reflect underlying mechanism rather than superficial correlation (Sun et al., 2018; Giambartolomei et al., 2014). In short, it advances discovery from statistical association to experimentally tractable hypotheses.

Equally, it makes development more predictable. Protein-aware, genetics-informed strategies help anticipate on-target safety liabilities using human data. They also support the design of pharmacodynamic readouts that align with mechanism and enable patient stratification based on the biology a medicine truly modulates. As platforms expand—from bulk tissue-based and affinity-based assays to single-cell and spatial modalities—rigorous harmonization and transparent analytic pipelines become essential. These practices ensure that multi-omic findings generalize across cohorts and remain reliable for use in clinical trials.

Together, the five papers in this Research Topic demonstrate how integrating multi-omic data can (i) elevate genetically supported causal targets, (ii) reveal biomarker candidates for patient stratification and pharmacodynamic (PD) monitoring, and (iii) sharpen clinical trial design by embedding findings within a systems-level biological context.

From associations to actionable biology

A central theme is the move beyond single-omic signals to convergent evidence across layers. Gong et al. conduct a systematic, tiered integration of genome-wide association studies (GWAS) with expression (eQTL), protein (pQTL), and metabolite (mQTL) quantitative trait loci to prioritize mitochondrial genes across prostatic diseases. They then test whether the observed effects are mediated through metabolites and immune traits. Their framework highlights DCXR

(Tier 1) as a candidate for benign prostatic hyperplasia and nominates additional gene–disease links—such as **ELAC2** and **ACAT1**—that become tractable hypotheses for experimental perturbation and pharmacodynamic (PD) readouts in early development.

Jin et al. take a complementary, disease-centred route in hepatocellular carcinoma, aligning transcriptomics with proteomics from the Clinical Proteomic Tumour Analysis Consortium (CPTAC), copy-number variation (CNV) data, and tumour-microenvironment (TME) analyses. They show that several pseudouridine synthases - RNA-modifying enzymes such as **DKC1**, **PUS1**, and **PUS7** - are upregulated and have diagnostic and prognostic value. By linking these RNA-modification enzymes to pathway activity and immune context, they outline a mechanistic space where genetic or pharmacological modulation could intersect with biomarker-driven trials.

Jiang et al. explore lipid metabolism at the interface of tumour immunity, nominating **CPT2** (carnitine palmitoyltransferase 2) as a pan-cancer biomarker candidate linked to immune-cell infiltration and survival in patients receiving immunotherapy. Although primarily a computational analysis, their work argues for incorporating metabolic-immune axes such as fatty-acid oxidation (FAO) into proteomic panels used for patient stratification or pharmacodynamic (PD) monitoring in mechanism-anchored studies.

Proteogenomics, platforms and practicality

Philips et al. review opportunities for predictive proteogenomics biomarkers of drug sensitivity in epithelial ovarian cancer, a setting where **BRCA1/BRCA2** status and homologous recombination deficiency (HRD) are necessary but not sufficient for treatment decisions. They highlight use cases in which proteome-level pathway activity—such as DNA-repair programs or immune signatures—and target-adjacent proteins help explain why patients vary in their responses to poly(ADP-ribose) polymerase (PARP) inhibitors, anti-angiogenic agents, and antibody–drug conjugates (ADCs). For drug discovery, these insights support trial designs that include proteogenomics baselines (paired genomic and proteomic profiling before therapy) and on-treatment proteomics to confirm mechanism engagement and detect early resistance biology.

As single-cell technologies scale, the bibliometric analysis by Chen et al. highlights how rapidly increasing resolution and throughput are accompanied by mounting integration challenges. Their mapping of methodological hotspots underscores the need for rigorous cross-platform harmonization. This includes careful batch handling, the use of bridge samples to link datasets, and attention to epitope-altering variants that can distort affinity-based assays. It also highlights the importance of transparent analysis pipelines that explicitly connect cell-type-resolved expression to protein changes and clinical phenotypes. Together, these practices form the foundation for achieving reproducible causal inference in multi-omic studies.

An emerging playbook for genetically-informed proteomics

Taken together, the Research Topic points to a pragmatic playbook:

1. Elevate causal targets with convergent instruments. Use cis-pQTLs and co-localization to raise the prior on true target-disease links; where feasible, triangulate with eQTLs, mQTLs and metabolite instruments. Gong et al.'s tiering provides a template for rank-ordering genes before expensive wet-lab validation.
2. Design biomarkers on the causal path. Prioritise proteins that either *mediate* genetic risk or report on target-pathway modulation. Jin et al. and Jiang et al. illustrate how pathway-anchored proteins (RNA-modification enzymes; fatty-acid oxidation components) can serve as diagnostic and prognostic markers and candidate PD readouts.
3. Exploit proteogenomics where DNA alone is silent. Isoform-specific or post-transcriptional effects often determine druggability and resistance. Philips et al. make the case for proteogenomics baselines and on-treatment sampling to capture pathway rewiring that genomics alone misses.
4. Plan for scale and heterogeneity. As Chen et al. show, single-cell and spatial methods are exploding; combining these with bulk and affinity proteomics will demand rigorous QC, common data models, and pre-registered analysis plans so findings generalise across cohorts and platforms.

Outlook: from genetic clues to actionable studies

Begin with targets grounded in human genetics. Then verify—using the relevant tissues and cell types—that the intervention modulates the protein and perturbs the pathway as intended. Define the purpose of each biomarker upfront: prognostic (risk), predictive (who benefits), or pharmacodynamic (evidence of target engagement). Establish decision-enabling thresholds early in development to ensure biomarkers can guide actionable choices. (Nelson et al., 2015). By pairing causal genetics with proteomic readouts and practical measurement plans, we can move more quickly from association to action. This approach supports the selection of safer targets, the design of smarter trials, and the earlier reduction of development risk.

Author contributions

KK: Conceptualization, Visualization, Data curation, Validation, Methodology, Investigation, Supervision, Writing – review and editing, Resources, Funding acquisition, Writing – original draft, Software, Formal Analysis, Project administration. LX: Formal Analysis, Visualization, Project administration, Validation, Data curation, Resources, Supervision, Investigation, Software, Methodology, Writing – review and editing, Conceptualization, Funding acquisition, Writing – original draft.

Funding

The author(s) declared that financial support was not received for this work and/or its publication.

Acknowledgements

We thank all contributing authors, reviewers and editors for their rigorous work and the Frontiers editorial office for their support throughout the process. We gratefully acknowledge Amina Bedrat, Topic Coordinator, for her valuable support throughout the editorial process.

Conflict of interest

Author LX was employed by Pfizer Inc.

The remaining author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author KK declared that they were an editorial board member of Frontiers at the time of submission. This had no impact on the peer review process and the final decision.

References

Giambartolomei, C., Vukcevic, D., Schadt, E. E., Franke, L., Hingorani, A. D., Wallace, C., et al. (2014). Bayesian test for colocalisation between pairs of genetic association studies using summary statistics. *PLoS Genet.* 10, e1004383. doi:10.1371/journal.pgen.1004383

Nelson, M. R., Tipney, H., Painter, J. L., Shen, J., Nicoletti, P., Shen, Y., et al. (2015). The support of human genetic evidence for approved drug indications. *Nat. Genet.* 47, 856–860. doi:10.1038/ng.3314

Generative AI statement

The author(s) declared that generative AI was not used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Sun, B. B., Maranville, J. C., Peters, J. E., Stacey, D., Staley, J. R., Blackshaw, J., et al. (2018). Genomic atlas of the human plasma proteome. *Nature* 558, 73–79. doi:10.1038/s41586-018-0175-2