Received: 3 December 2024 | Revised: 2 January 2025 | Accepted: 4 January 2025

DOI: 10.1111/bph.17469

THEMED ISSUE REVIEW

System level network data and models attack cancer drug resistance

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Funding information
Ministry for Innovation and Technology in Hungary, Grant/Award Number: TKP2021-EGA-24; Semmelweis University; National Research, Development and Innovation Fund, Grant/Award Number: 2024-2.1.1-EKÖP-2024-00004

Drug resistance is responsible for >90% of cancer related deaths. Cancer drug resistance is a system level network phenomenon covering the entire cell. Small-scale interactomes and signalling network models of drug resistance guide directed drug development. Recently, proteome-wide human interactome and signalling network data have become available, which have been extended by drug–target interactions, drug resistance-inducing mutations, as well as by several cancer and drug resistance-related multi-omics datasets. System level signalling network models have become available examining therapy resistance, performing in silico clinical trials, and conducting large, in silico drug combination screens. Drug resistance network data and models have become interoperable and reliable. These advances paved the road for building proteome-wide drug resistance models.

KEYWORDS
artificial intelligence, epithelial-mesenchymal transition, network pharmacology, personalized medicine, resistome

1 | ANALYSIS OF CANCER DRUG RESISTANCE MECHANISMS REQUIRES NETWORK MODELS

Four new cases and one death from cancer occurred every minute of 2024 in the United States alone (https://cancerstatisticscenter.cancer.org/module/BmVYeqHT/). More than 90% of cancer-related deaths are associated with cancer drug resistance (Huang et al., 2023). Drug-resistant cancer cells develop dozens of evasion mechanisms including (1) changes in drug uptake/efflux (Marin et al., 2024); (2) mutations in drug targets (Hu et al., 2021; Milacic et al., 2024; Nussinov et al., 2021); (3) alternative signalling pathways (Cao et al., 2024; Guo et al., 2025; Hu et al., 2021; Li et al., 2020; Nussinov et al., 2020; Nussinov et al., 2021); (4) alternative metabolic pathways (Hashimoto et al., 2022; Robinson et al., 2020); (5) genomic instability (Fessler et al., 2024; Hu et al., 2021); (6) changed chromatin structure (Cao et al., 2024; Guo et al., 2025; Zhao et al., 2020) and (7) increased cellular plasticity leading to cancer stem cell formation and tumour heterogeneity (Firdous et al., 2022; Golkowski et al., 2023; Hashimoto et al., 2022). Numerous scientific efforts analyse these escape routes as independent entities. However, cellular signalling and changes in chromatin structure regulate all other processes; genomic instability causes drug-resistant mutations; mutations affect cellular signalling and metabolism, etc. (Bueschbell et al., 2022; Fessler et al., 2024; Golkowski et al., 2023; Hashimoto et al., 2022; Nussinov et al., 2024; Reviejo et al., 2021; Robinson et al., 2020). Thus, cancer drug resistance mechanisms form a proteome-wide molecular network covering the entire cancer cell and need network models to understand their complexity (Figure 1).

Abbreviations: CBM, Cellworks Computational Omics Biology Model; PARP, poly-(ADP-ribose)-polymerase; PPI, protein–protein interaction.

Dávid Keresztes and Márk Kerestély contributed equally to this paper.

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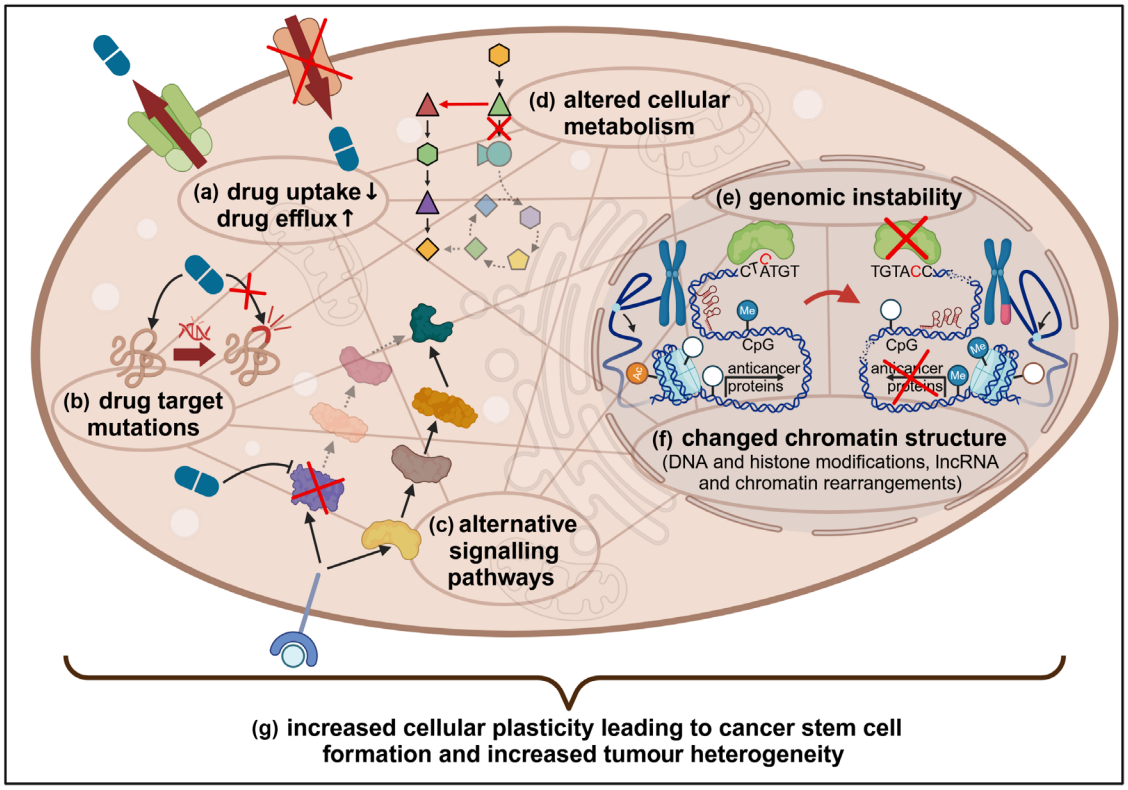

FIGURE 1 Cancer drug resistance: a network phenomenon. The figure illustrates how evasion mechanisms of drug-resistant cancer cells mobilize the entire cellular machinery. (a) Decreased drug uptake and increased drug efflux. (b) Mutations in drug targets making them drug-resistant. (c) Alternative signalling pathways (e.g., redundant, parallel and compensatory pathways). (d) Altered cellular metabolism (e.g., increased glucose consumption, glycolysis, lipogenesis, cholesterol biosynthesis/mevalonate pathway, glutamine addiction, increased autophagy and pinocytosis). (e) Increased genomic instability (e.g., increased mutation rate, chromosomal rearrangements and decreased DNA-repair). (f) Changed chromatin structure (e.g., decreased DNA-methylation at CpG dinucleotides, increased DNA methylation of promoter regions of anticancer —e.g., apoptotic— proteins, dominantly histone hypermethylation and deacetylation, lnc-RNA rearrangements and altered long-range chromatin contacts). (g) Increased cellular plasticity leading to cancer stem cell formation and increased tumour heterogeneity. All these mechanisms are interlinked, and form a network covering the entire cancer cell. Created with Biorender.com.

Small-scale protein–protein interaction (PPI) and signalling network models give a first approximation of cancer drug resistance mechanisms. In agreement with prevailing studies, small-scale models focus on specific areas (such as DNA repair, the epithelial-mesenchymal transition or effects of drug-resistance-inducing mutations) and suggest successful drug combinations and personalized therapies (Ayala-Zambrano et al., 2023; Gómez Tejeda Zañudo et al., 2021; Gupta, Silveira, Lorenzoni, et al., 2024; Gupta, Silveira, Piedade, et al., 2024; Jiang et al., 2024; Latini et al., 2024; Mendik et al., 2022; Montagud et al., 2022; Wooten et al., 2021). However, a thorough analysis requires much larger network models. Recently, important preconditions of large-scale (system level) network models were fulfilled. First, both PPI networks (interactomes) and signalling networks grew to cover the entire human proteome (Csabai et al., 2022; Oughtred et al., 2021; Szklarczyk et al., 2025). Second, these networks were extended by drug–target interactions, drug resistance-inducing mutations, as well as by several cancer and drug resistance-related multi-omics datasets (Hu et al., 2021; Li et al., 2020; Oughtred et al., 2021; Du et al., 2021; Knox et al., 2024; Panneerselvam et al., 2024; Jiang et al., 2025). Third, network analysis methods were established to identify central network nodes that can control a desired set of proteins involved in drug resistance development, to determine network groups (network modules) enriched in proteins involved in drug resistance development, as well as to compare drug-sensitive and drug-resistant networks (Bueschbell et al., 2022; Siminea et al., 2024). These advances paved the way for building drug resistance models of whole cancer cells. System level signalling network models including several thousands of participating proteins and RNAs have examined the sensitivity of 776 KRAS-mutated tumours for **PD-(L)1** immunotherapy (Padda et al., 2021), performed in silico clinical trials (Castro et al., 2021; Castro et al., 2022), and conducted large in silico drug combination screens (Papp et al., 2024). Even larger, proteome-wide drug resistance network models require standardized data organization and model structure. Proper benchmarks ensuring model reliability are also needed. We summarize the results of the intensive community effort to establish these requirements (Dai et al., 2021; De Jonghe et al., 2024; Diamant et al., 2025; Eckhart et al., 2024;

Feng et al., 2024; Jia et al., 2023; Niarakis et al., 2022; Panneerselvam et al., 2024; Piochi et al., 2023; Puniya et al., 2024; Szalai et al., 2023; Tatka et al., 2023; Touré et al., 2020; Wang et al., 2024). This rapid progress and the recent applications of artificial intelligence (AI) methods in building system level molecular models (Bunne et al., 2025; Rood et al., 2024; Valous et al., 2024) make it a sensible expectation that in the very near future proteome-wide network models of cancer drug resistance will be available.

2 | SMALL-SCALE CANCER NETWORK MODELS GUIDE DIRECTED DRUG DEVELOPMENT

Small-scale network models provide the first approximation of the networking events of cancer drug resistance. Protein–protein interaction (PPI) network models identify cancer network modules and offer clues to drug targeting and drug combinations (Cheng et al., 2021; Gysi & Barabási, 2023; Huang et al., 2023; Nogales et al., 2022). Small-scale signalling networks bring us one step closer to efficient drug resistance models. Signalling networks centred around DNA repair, epithelial-mesenchymal transition or genetic changes inducing cancer drug resistance (Table 1), give insight into drug-resistant metastasis formation and the design of personalized therapies.

2.1 | Interactomes reveal proteins and RNAs participating in drug resistance development

PPI networks contain disease-modules, that is, network modules associated with a certain disease, such as cancer (Gysi & Barabási, 2023; Nogales et al., 2022). The recent work of Gysi and Barabási (2023) extended the human interactome by noncoding RNAs. Their work showed that the extended PPI network contains a high number of cancer modules associated with various types of cancer including melanoma, glioma, neuroblastoma and endometrioid carcinoma. Complex tumours may contain more than 10 such cancer modules (Nogales et al., 2022). Proteins of cancer modules may reveal novel drug targets and drug combinations (Gysi & Barabási, 2023; Nogales et al., 2022). Not only network modules (i.e., groups of neighbouring network nodes), but already connected network node-pairs (PPIs) may be highly informative on cancer progression mechanisms. Analysis of 10,861 tumour exomes established 470 putative onco-PPIs changed by oncogenic mutations. The study validated 13 among them including the interactions between **ALOX5** and MAD1L1, HOMEZ and EBF1, as well as **RHOA** and ARHGDIA. The 470 oncoPPIs were highly correlated with patient survival and drug resistance (Cheng et al., 2021). Recently, 11 cancer-specific small-scale PPI networks were developed (where each contained ~150 proteins) and were used to assess 61,754 potential anti-cancer drug combinations by the proximity of drug targets and clustering (Table 1; Jiang et al., 2024). While larger interactomes increase the chances of unexpected discoveries,

TABLE 1 Small-scale network models of cancer drug resistance.

Name or type	Network (number of nodes)	Cancer type	Brief description	References
PPI	11 cancer-specific small-scale interactomes (e.g., 136, 147)	Various	Assessment of 61,754 potential drug combinations by the proximity of drug targets and clustering	Jiang et al. (2024)
Boolean	**Small-scale signalling networks**: DNA double strand break repair (22)	Various	Assessment of drug resistance-inducing non-canonical repair	Ayala-Zambrano et al. (2023)
Boolean	Epithelial-mesenchymal transition (31 and 43)	Various	Assessment of BM1, MALAT1, miR-145-5p and PTEN1/miR-21/PTEN in drug-resistant cells	Gupta, Silveira, Lorenzoni, et al. (2024); Gupta, Silveira, Piedade, et al. (2024)
Boolean + protein translocation	Epithelial-mesenchymal transition (70 reduced to 19)	Various	Shows different functions before and after protein translocation	Mendik et al. (2022)
Boolean	FLT3 tyrosine kinase internal tandem duplication network (76)	Acute myeloid leukaemia	Personalized predictive models of the signalling landscape of drug-resistant patients	Latini et al. (2024)
Boolean	(ER^+) PI3KCA mutant drug-resistant cells (101)	Breast cancer	Modelling combinations of the PI3Kα inhibitor, alpelisib with BH3 mimetics	Gómez Tejeda Zañudo et al. (2021)
Boolean	Prostate cancer personalized to 488 patients (133)	Prostate cancer	Personalized modelling of drug combinations	Montagud et al. (2022)
Boolean	FLT3-mutant drug-resistant cells (186)	Acute myeloid leukaemia	Probabilistic Bayesian model of acquired resistance of six drug treatments including quizartinib and dexamethasone	Wooten et al. (2021)

PPI, protein–protein interaction.

cancer modules, onco-PPIs and specifically designed small-scale PPI networks may accelerate concept-directed drug development.

A potentially very important PPI network model is the resistome, which contains interactions of several hundred proteins involved in drug resistance (Marin et al., 2024; Reviejo et al., 2021). Key segments of the human resistome are centered around the transportome of the solute carrier superfamily (SLC) proteins and around multidrug-resistance (MDR) proteins mediating drug uptake and efflux, respectively (Marin et al., 2024; Reviejo et al., 2021). Time dependent single-cell RNA-sequencing (sncRNA-seq) data of cancer cells developing drug resistance (e.g., against tamoxifen-treatment; Iida & Okada 2024) revealed several hundred genes exhibiting multistable expression states in drug-sensitive and -resistant cell subpopulations. The PPI network of these genes was associated with cell survival and metastasis-related pathways (Iida & Okada 2024). We also have extensive data on the changes of the antibiotic resistance related PPI network of the gut microbiome of non-small cell lung cancer patients treated with the immune checkpoint inhibitors **nivolumab**, **pembrolizumab** or **atezolizumab** (Iwan et al., 2024) or that of pancreatic cancer patients (Liu et al., 2024). Despite of these efforts, dedicated network data of the human cancer resistome have not been assembled yet.

2.2 | Small-scale signalling network models of cancer drug resistance

Signalling networks contain directed connections, which encode an even higher level of information than the undirected interactions of interactomes. Directionality can be obtained from literature evidence or by experiments using targeted perturbations and measuring time-series data (Peidli et al., 2024). Time series analysis of protein kinases helped to elucidate the drug resistance mechanisms of colorectal cancer cells (Rosenberger et al., 2024) and suggested the adapter-associated kinase (**AAK1**) complex as responsible for the epithelial-mesenchymal plasticity and drug resistance (Golkowski et al., 2023; Katebi et al., 2021). However, directed interactions make the analysis of signalling networks longer and more difficult. Therefore, signalling networks are often optimized to be large enough to capture regulatory details (e.g., more than ~30 nodes total), but not too large for easy simulation (e.g., fewer than ~200 nodes). In Boolean networks, a regulatory function with N inputs has 2^N possible input conditions which restricts the number of input nodes to around seven (Wooten et al., 2021). Such considerations set the number of nodes of currently available cancer drug resistance-related Boolean networks between 22 and 186 (Table 1). Small-scale signalling network analysis recovered the drug-resistant behaviour of the **BRCA1**/FANCS mutant (Ayala-Zambrano et al., 2023), **PTEN** (Gupta, Silveira, Piedade, et al., 2024) and **GSK3B** (Wooten et al., 2021), as well as identifying the **TIP60** complex (Ayala-Zambrano et al., 2023), miR-145 (Gupta, Silveira, Lorenzoni, et al., 2024), the JNK kinase pathway (Latini et al., 2024), FOXO3 (Gómez Tejeda Zañudo et al., 2021) and a compartment-specific role of GSK3B/GLI (Mendik et al., 2022)—as all potentially playing roles in cancer drug resistance. Small-scale signalling networks also helped the design of combination therapies (Gómez Tejeda Zañudo et al., 2021; Montagud et al., 2022) and personalized therapies (Latini et al., 2024; Montagud et al., 2022) in cancer drug resistance.

3 | SYSTEM LEVEL NETWORK DATA ORGANIZE OUR KNOWLEDGE OF CANCER AND DRUG RESISTANCE

Small-scale network models are not able to cover the richness of drug resistance evasion mechanisms mobilizing the entire cancer cell. For the construction of system level network models proteome-wide network data are required. Table 2 shows a comprehensive summary of the system level network databases developed in the last few years.

The first two large human protein–protein interaction (PPI) networks (interactomes) already contained 53 (Luck et al., 2020) and 118 thousand interactions (Huttlin et al., 2021), respectively. These were followed by updates of the extensive PPI databases BioGRID (Oughtred et al., 2021), STRING (Szklarczyk et al., 2025) and that of the IMEx consortium, containing four previous databases (Panneerselvam et al., 2024). Already, the BioPlex dataset included 88% of cancer-related genes (Huttlin et al., 2021). All these databases contain a broad description of the function of each protein included including their role in cancer and drug resistance. BioGRID has a special glioblastoma-specific subnetwork of 53,689 interactions (https://thebiogrid.org/project/5/glioblastoma.html; Oughtred et al., 2021). The number of interactions of the human PPI network was doubled by the addition of noncoding RNAs (Gysi & Barabási, 2023). More specific interactomes of human tissues (Ziv et al., 2022), cancer drivers (Du et al., 2021) and cancer stem cells (Firdous et al., 2022) were also developed.

System level signalling networks are exemplified by OmniPath, SignaLink, SIGNOR and Reactome network databases (Csabai et al., 2022; Lo Surdo et al., 2023; Milacic et al., 2024; Türei et al., 2024). The 2025 version of the STRING interactome (Szklarczyk et al., 2025) contains a 'regulatory network', which is, in fact, a signalling network. Already the first high-confidence interactomes (Huttlin et al., 2021; Luck et al., 2020) covered more than one third of the human proteome, which grew close to two thirds (Milacic et al., 2024; Türei et al., 2024), have reached full coverage in recent PPI and signalling datasets (Oughtred et al., 2021; Csabai et al., 2022; Szklarczyk et al., 2025; https://string-db.org/overview/overview.9606.html). The coverage of drug resistance-related processes of signalling networks is extended further by the addition of noncoding RNA–RNA and RNA–target interactions (Cui et al., 2025; Guo et al., 2025; Zhao et al., 2020) and by the addition of drug resistance-related noncoding RNAs (Cao et al., 2024). The inclusion of drug—target interactions (Knox et al., 2024; Li et al., 2020) gave another crucially important link of signalling networks to anti-cancer drug design. Drug resistance rewires human signalling (Nussinov et al., 2020; Nussinov et al., 2024). In KinaseMD, 252,000 such signalling pathway rewiring

TABLE 2 Large-scale network databases helping cancer drug resistance therapy.

Database name	Type and system level of network data	Relation to cancer drug resistance	Latest update	References
IMEx	**Protein–protein interaction (PPI) network** database consortium containing IntAct, MINT, MatrixDB and DIP databases (D; 1.5)[a]	Over a thousand IntAct interactions related to human drug resistance; cancer- and mutation-related specific IntAct datasets	2024	Panneerselvam et al. (2024)
STRING	PPI including only physical or complex functional associations (D; >20,000)	Human experimental data, gene ontology (GO) terms and regulation pathways are available	2025	Szklarczyk et al. (2025)
BioGRID	PPI built on biomedical literature (D; 1.9)	Integrated chemical target, biomolecular interaction and resistant phenotype data for drug discovery	2024	Oughtred et al. (2021)
NCI	PPI including noncoding RNA interactions (H; D; 1.1)	Disease modules, including various types of cancer	2023	Gysi and Barabási (2023)
TissueNet	PPI specific for 125 adult and 7 embryonic tissues (H; D; 0.5)	GO terms are available	2022	Ziv et al. (2022)
BioPlex	High-confidence proteome-wide human PPI (H; D; 0.118)	88% of cancer-related genes and expression data of 378 cancer cell lines	2021	Huttlin et al. (2021)
HuRI	High-confidence proteome-wide human PPI (H; D; 0.053)	Cancer-related subnet is available	2020	Luck et al. (2020)
PINA	PPI of 33 cancer types (H; D; 0.4)	Cancer drivers, therapeutic targets, biomarkers are available	2021	Du et al. (2021)
BCSCdb	PPI of 171 cancer stem cell biomarkers of 10 cancer types (H; D)	Cancer stem cells are primary causes of drug resistance	2022	Firdous et al. (2022)
Reactome	**Signalling network** (SigNet) of intracellular pathways (H; D; 0.015)	1544 disease-specific reactions, effects of 1119 drugs, mutation-effects	2024	Milacic et al. (2024)
SIGNOR	SigNet including chemicals, stimuli, phenotypes besides proteins (H; D; 0.033)	Cancer-related proteins are over-represented	2024	Lo Surdo et al. (2023)
SignaLink	SigNet including microRNAs (D; 0.752)	Was used for cancer research and drug discovery	2022	Csabai et al. (2022)
OmniPath	SigNet from >100 datasets including intercellular communication (D; 0.015)	Cancer drivers, cancer pathway associations	2021	Türei et al. (2024)
KinaseMD	SigNet rewiring by protein kinase mutations (H; D; 0.252)	Level of potential cancer drug resistance is calculated	2021	Hu et al. (2021)
LncCancer	lncRNA-circularRNA interactions (H; D; 0.001)	9254 lncRNA/cancer associations, drug resistance data included	2022	Guo et al. (2025)
miRTArBase	microRNA-target interactions (H; D; 2.2)	microRNA-s a frequently involved in drug resistance	2025	Cui et al. (2025)
LncTarD	lncRNA-target interactions (H; D; 0.006)	Drug resistance-related lncRNA-target interactions	2020	Zhao et al. (2020)
NoncoRNA	Noncoding RNA-drug target interactions (H; D; 0.008)	Drug resistance-related microRNA- and lncRNA-target interactions	2020	Li et al. (2020)
ncRNADrug	Drug resistance associated noncoding RNAs (H; D; 0.009)	Drug resistance-related noncoding RNAs	2024	Cao et al. (2024)
Human1	**Metabolic network** genome-scale model of human metabolism (H; D; 0.013)	33 cancer metabolic models showing changes of drug-resistant phenotypes	2023	Robinson et al. (2020)

[a](H; D; number) H; D and the number in parentheses refer to databases dedicated only to human data (H) download options (D) and the number of interactions covered in millions, respectively. PPI, protein–protein interaction.

protein kinase mutations were catalogued, and the level of their potential drug resistance was calculated (Hu et al., 2021).

The great potential of signalling networks to describe cancer drug resistance can be further expanded by the integration of multi-omics data. Recent advances doubled omics datasets every 6 months for the past several years (Bunne et al., 2025) and provided close to a hundred cancer-related omics datasets (including DepMap and LINCS among many others) (Bueschbell et al., 2022; Huang et al., 2023; Jiang et al., 2025; Siminea et al., 2024; Yue & Dutta, 2022). Proteome-wide PPI and signalling networks together with their extensions of noncoding RNAs, drug targets and drug resistance-related multi-omics data organize our current knowledge on cancer and drug resistance and

offer a framework for the ongoing efforts to develop system level models of cancer drug resistance.

4 | STRUCTURAL ANALYSIS OF LARGE NETWORKS UNCOVERS DRUG RESISTANCE MECHANISMS

Small-scale networks have the advantage that their visualization already gives an insight to identify central, potentially actionable proteins. However, visualization of system level interactomes and signalling networks often results in a hedgehog image, where central network nodes cannot be readily identified (Siminea et al., 2024). However, the mathematical analysis of the proteome-wide network connection structure is able to distinguish central network nodes encoding potential drug targets or biomarkers (Bueschbell et al., 2022; Siminea et al., 2024). The review of Siminea et al. (2024) gives a state-of-the-art list of freely accessible softwares for network structure analysis. NetControl4BioMed is a recently developed web-tool to discover an important type of central network node, that is, source nodes of signalling networks that can control a desired set of targets including proteins involved in drug resistance development. Such controlling source nodes are candidates of potential drug targets. The pre-built dataset of the tool already includes 52 sets of cancer-specific survival genes from COLT, 1526 sets of cancer-mutated genes from DepMap and drug–target interactions from DrugBank. However, users may also upload their own drug-resistance-specific networks for analysis (Popescu et al., 2021).

Besides finding central network nodes, another important task of network structure analysis is to compare networks (e.g., those of drug-sensitive and -resistant cells). To help this, a network correlation analysis methodology was developed to show the similarities and differences in network structures between cancer types, stages of the epithelial-mesenchymal transition and drug resistance development (Bueschbell et al., 2022). Extraction of common network structures identified **gefitinib**- and **erlotinib**-resistance mechanisms of EGFR-independent cells (Park et al., 2022). PANDA is an integrative tool for network comparison, which incorporates a PPI network, transcription factor binding motifs and single-cell RNA-seq data. PANDA can be used to compare drug-sensitive and drug-resistant cell lines. The method identifies drug resistance pathways and evaluates alternative drugs that could potentially overcome drug resistance (The et al., 2023).

Recent studies extended the structural analysis of PPI and signalling networks to networks containing noncoding RNAs. The mRNA-microRNA-lncRNA network analysis method, ncDRMarker, identified noncoding RNA network signatures of drug resistance (Yang et al., 2020). The comprehensive characterization of a drug resistance-related mRNA-microRNA-lncRNA network of 15 anti-cancer drug categories distinguished clinically actionable genes associated with patient survival and cancer stage (Liu et al., 2021). These examples show that structural analysis of large networks is able to point out key aspects of drug resistance mechanisms.

5 | SYSTEM LEVEL MODELS OF CANCER DRUG RESISTANCE

The richness of network databases and tools for the analysis of large network structures enable the construction of system level drug resistance models. System level modelling (often mentioned also as system level simulation) is a well-known methodology to model complex cyber-physical systems as distant as space flights or self-driving cars. Recently, cancer drug resistance dynamic signalling network models reached the system level.

5.1 | System level modelling

System level modelling (also called system level simulation) is a widely applied methodology of industrial automation modelling the global behaviour of large cyber-physical systems, for example, space-flights or self-driving cars (Deubert et al., 2024). Main goals ("readouts") of (1) space-flights; (2) self-driving car development and (3) drug-resistant cancer patient therapy are surprisingly similar: (1) completed mission, survival and safe landing of astronauts; (2) completed journey, survival and safe arrival of passengers and (3) completed treatment, survival and safe recovery of patients (Deubert et al., 2024; Tatka et al., 2023). Not surprisingly, NASA, NIH, the FDA and European Medicines Agency (EMA) developed similar standards to assess the credibility of computational models and simulations (Tatka et al., 2023).

System level modelling often has the *curse of dimensionality* leading to unacceptable computation times (Eckhart et al., 2024). Order reduction (dimension reduction) of models by (1) modularization, (2) developing domain-independent system architecture (which is specified by domain-specific elements), (3) building hierarchical structures helps both the overview of the system level model and the discovery of design-flaws. Order reduction significantly shortens simulation run-time. Partitioning to subsystems also allows parallel computing. However, subsystems need careful design of their coupling and synchronization at the system level (Deubert et al., 2024; Tatka et al., 2023). From 2021 foundation models were introduced, where AI is trained on extensive datasets, and fine-tuned to specific applications by transfer learning (Bommassani et al., 2024). From 2022 exascale supercomputers (computing 10^{18} floating point operations per second) became available, which will significantly accelerate the discovery process in cancer drug resistance. However, exascale computers require a re-design of today's simulation algorithms (Chang et al., 2023).

5.2 | System level models of cancer drug resistance

In the last few years, several methodologies have been developed to provide a dynamic system level network model of healthy and cancer cells (Table 3). The Computational Biological Modelling

TABLE 3 System level network models of cancer drug resistance.

Name or type	Network (number of nodes)	Cancer type	Brief description	References
Computational biological modelling	System level signalling network + metabolic, epigenetic and transcriptional pathways (3300)	Applied to non-small-cell lung cancer	PD-(L)1 immunotherapy sensitivity of KRAS-mutated molecular subgroups in 776 patients	Padda et al. (2021)
Cellworks computational omics biological model (CBM)	System level cancer signalling network (3765)	Applied to glioblastoma	Assessment of temozolomide, lomustine combination therapy in patients with methylated-MGMT; successful personalized therapy for a relapsed glioblastoma patient	Castro et al. (2021); Castro et al. (2022)
Turbine simulated cell	System level cancer signalling network (1997 growing to 8000)	Various	Difference equation-based simulation of signal propagation in a system level human signalling network to reveal bests of 66,348 drug combination–cell line pairs	Szalay and Csermely (2020); Papp et al. (2024)

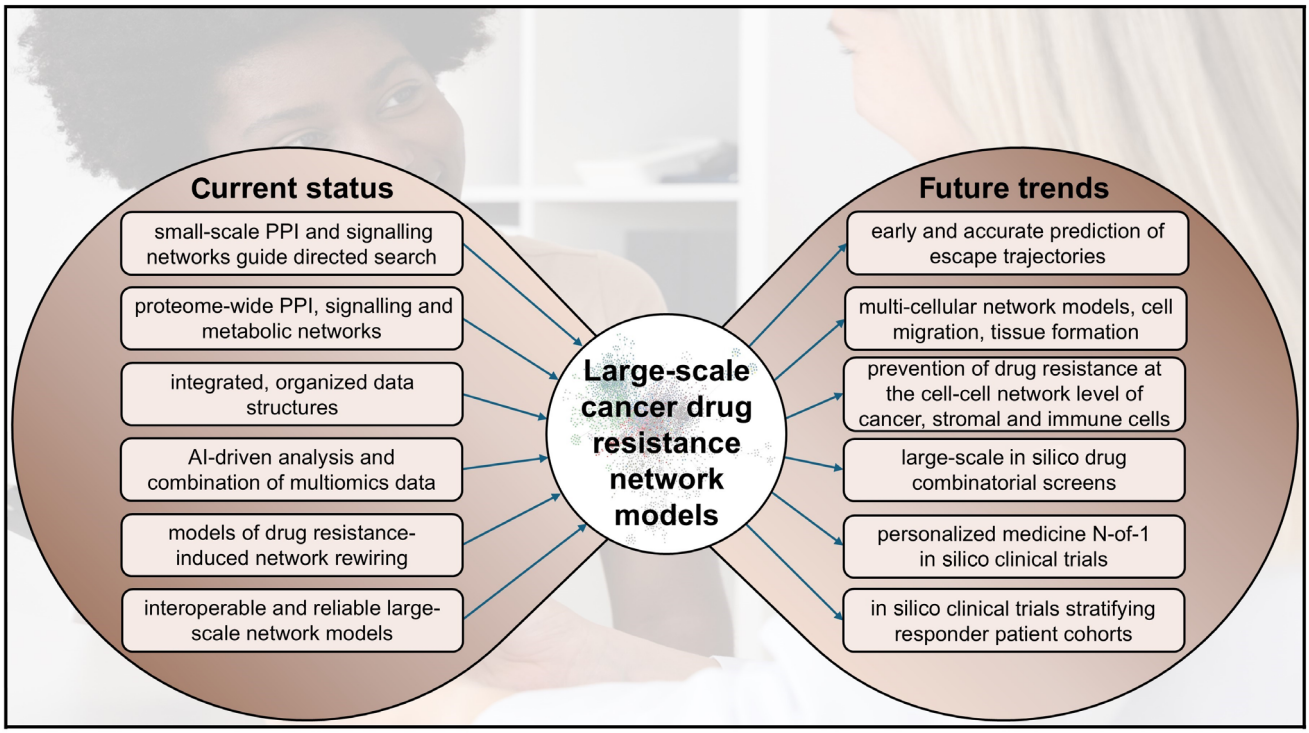

FIGURE 2 Current status and future trends of cancer drug resistance system level models. The spectacular development of network data and models has enabled the formation of system level cancer drug resistance models—where "system level" already means several thousand proteins, and expected to mean proteome-wide soon—in several ways: (a) small-scale PPI and signalling networks guide directed search in system level models; (b) system level human PPI, signalling and metabolic networks became available; (c) integrated and organized data structures were developed; (d) Artificial Intelligence (AI)-driven network analysis and combination of multi-omics data has become possible; (e) models of drug resistance-induced network rewiring have been established; (f) interoperable and reliable dynamic system level network models have been developed. All of these recent advances make a rapid expansion of the field possible in the near future in the following areas: (a) multi-cellular molecular network models are expected incorporating tissue structure, cell migration and tissue formation; (b) early and accurate prediction of escape trajectories of drug resistant cells will be available; (c) system level in silico drug combinatorial screens will accelerate drug discovery and clinical translation; (d) personalized N-of-1 in silico clinical trials will guide the therapy of drug resistant patients; (e) in silico clinical trials will stratify best-responder patients to single drug or combinatorial treatments; (f) rapid advance in the system level models of cancer drug resistance will help the discovery of new antibiotics and fungicides. Background image is designed by Freepik.

approach includes 3300 genes and >85,000 functional interactions (i.e., signalling, metabolic, epigenetic and transcriptional regulatory pathways) of cancer, and uses ordinary differential equations as a kinetic model. Computational Biological Modelling was used to model KRAS-mutated non-small cell lung cancer sensitivity to PD-(L)1 immunotherapy (Padda et al., 2021).

The Cellworks Computational Omics Biology Model (CBM) contains 3765 genes and 29,181 functional interactions of cancer signalling, and uses Michaelis–Menten equation-based simulations until the system reaches homeostasis. Somatic gene mutations and gene copy number variations (CNVs) of individual patients are also built in to this model. An important output of CBM is a composite score representing cell numbers with cancer hallmark behaviours. CBM was used to assess the response of 274 newly diagnosed patients with methylated-MGMT glioblastoma for **temozolomide** or **lomustine** treatments, or their combination showing strong, modest/intermediate, negligible or harmful effects for patient subgroups (Castro et al., 2021). The model was also used to design a successful personalized therapy for a patient with relapsed glioblastoma (Castro et al., 2022).

The Turbine Simulated Cell model has a difference equation-based simulation of signal propagation (i.e., perturbation propagation) (Szalay & Csermely, 2020) in a system level human signalling network containing 1997 nodes and 5004 interactions (version #4; Papp et al., 2024). Version #8 of Simulated Cell is already graph neural network-based, and the size of its network grew to 8000 nodes and 35,000 interactions (Daniel V. Veres, personal communication). Simulated Cell was used to predict 66,348 drug combination–cell line pairs of a combinatorial screen of 684 drug combinations across 97 cancer cell lines. The network structure made the predictions interpretable, and—as prior knowledge—extrapolated monotherapy-trained data to combination therapy predictions. The study highlighted drug combination pairs that interact with DNA-damage response pathways, and identified biomarkers driving the combination strategy and guiding clinical translatability. Among others, this study highlighted the use of poly-(ADP-ribose)-polymerase (PARP) inhibitors to overcome resistance against ataxia-telangiectasia mutated kinase (**ATM**) inhibition, and WNT inhibition against **PARP** inhibitor resistance (Papp et al., 2024).

6 | CHALLENGES TO BUILDING PROTEOME-WIDE DRUG RESISTANCE MODELS

We already have proteome-wide network data, hundreds of cancer-related and drug resistance-related databases, network analysis methods giving us priorities for network node integration into system level models, as well as both small-scale and system level models of cancer drug resistance. What are the challenges and next steps to building proteome-wide drug resistance models? The growth in model size raises several new questions, since the manual curation of data and models becomes increasingly difficult. Current datasets often use different identifiers, which hinders their combination. Data have different quality: many of them are experimentally verified. However, a significant segment of data is only predicted. Therefore, confidence scores of data are also needed. Moreover, both the network data and models need to be comprehensive, findable, accessible, interoperable, reusable and reproducible (Niarakis et al., 2022; Panneerselvam et al., 2024; Touré et al., 2020). Due to the extraordinarily large model size, special care must be taken in the validation of models, which requires verifiable predictions and tests against reliable benchmarks (Chang et al., 2023; Eckhart et al., 2024; Feng et al., 2024; Jia et al., 2023; Piochi et al., 2023; Szalai et al., 2023; Wang et al., 2024). The buildup, runs and analysis of proteome-wide models is greatly helped by artificial intelligence (AI) technology. However, the rapid development of AI has not yet specified its exact role in system level models of drug resistance.

6.1 | Integration and confidence scores of network and cancer multi-omics data

Network and cancer multi-omics databases (Bueschbell et al., 2022; Huang et al., 2023; Panneerselvam et al., 2024; Siminea et al., 2024; Touré et al., 2020; Yue & Dutta, 2022) often use different identifiers for network constituent proteins and RNAs, as well as for mutated proteins inducing cancer drug resistance, cancer drivers, drug targets, cancer biomarkers, etc. For proteome-wide models an extensive cross-reference of resource-specific identifiers is required. In recent years, standards for both network and multi-omics data description were described, and harmonized databases have been provided (Dai et al., 2021; Diamant et al., 2025; Panneerselvam et al., 2024; Touré et al., 2020). Integration of network and cancer multi-omics data must also consider the different levels of data-reliability, since only a part of the data is experimentally verified. MI2CAST (Touré et al., 2020) and PSI MI (Panneerselvam et al., 2024) include comprehensive confidence scores, as well as discriminating between required core information and other details. However, an integrated, comprehensive list, annotation and confidence scores of cancer drug resistance proteins (and noncoding RNAs) is missing. Such a dataset would greatly help the construction of proteome-wide models of drug resistance.

6.2 | Standardization of cancer network models

Standardization of input data is only a first step towards building of cell-size network models. To build efficient, widely useable drug resistance models, the interoperability and reusability of computational models themselves must also be increased. In the last few years, an intensified effort was taken to fulfil this initiative by the BioModels, CoLoMoTo, COMBINE, SysMod and scTrends consortia (De Jonghe et al., 2024;Niarakis et al., 2022; Puniya et al., 2024). In these efforts, the community standards of the Systems Biology Graphical Notation (SBGN) project, the Systems Biology Markup Language (SBML) and the simulation experiment markup language (SED-ML) were developed (Tatka et al., 2023). Giving the minimum information about a simulation experiment by the MIASE and MIRIAM checklists, and keeping the FAIR principles for data stewardship are also recommended to maximize reusability and ensure reproducibility (Niarakis et al., 2022). These standardization methods have been already used in building models of the epithelial-mesenchymal transition (Niarakis et al., 2022; Puniya et al., 2024) and abnormal cancer metabolism

(Puniya et al., 2024). The standardized models identified pathways of cancer progression (Puniya et al., 2024).

6.3 | Proper benchmarks of cancer and drug resistance models

Standardized data and models are only the initial steps for building proteome-wide drug resistance models. Whole cell models require proper benchmarks. Recently, the comprehensive benchmarking of synthetic lethality prediction models in seven models of cancer tested on four cancer cell lines (Feng et al., 2024), the identification of perturbed cancer pathway in 12 types of cancer (Wang et al., 2024), as well as the prediction of personalized anticancer drug response (Jia et al., 2023) and anticancer drug sensitivity (drug resistance) (Eckhart et al., 2024; Piochi et al., 2023; Szalai et al., 2023) were published. These studies showed that a statistical bias detector framework correcting cell line- and perturbation-specific biases (Szalai et al., 2023), screening of negative samples (Feng et al., 2024), removing results calculated during the training process (Feng et al., 2024) and feature selection by the minimum-redundancy-maximum-relevance principle (Eckhart et al., 2024) may significantly improve model predictions. Standard metrics, like Pearson correlation, often cannot differentiate between models, as simple models with uninformative features have similar performance to ones using biologically informative features (Szalai et al., 2023). Benchmark studies identified cancer-specific synthetic lethality pairs (Feng et al., 2024), prognostic pathways across 12 cancer types (Wang et al., 2024), drug repurposing options for potential anticancer therapies (Wang et al., 2024), as well as **BCL2L1** and **SLC27A5** as potential drug resistance biomarkers (Eckhart et al., 2024).

6.4 | The help of AI in building proteome-wide drug resistance models

Standardized input data, model structures and benchmarks give a stable framework for building proteome-wide cancer drug resistance models. However, models larger than a few hundreds of nodes and a thousand connections cannot be manually curated. Thus, proteome-wide models need to use artificial intelligence (AI) for their assembly, training and predictions. The recent boom of AI technologies led to the development of foundation models (also known as AI-models), which are machine learning models trained on a vast dataset often including network data (Bunne et al., 2025; Rood et al., 2024). Importantly, network-based datasets not only give a highly organized, machine-readable summary of prior knowledge, but also offer the verifiable interpretability of the results (Diamant et al., 2025; Valous et al., 2024). AI-driven models have already been used for the integration of cancer multi-omics data to network data, cancer type classification, cancer subtype analysis, cancer gene prediction, pathway identification, stratification of cancer patients and the analysis of resistance development (Bunne et al., 2025; Rood et al., 2024; Valous et al., 2024).

7 | CONCLUDING REMARKS AND FUTURE PERSPECTIVES

In this review, we show that cancer drug resistance is a network phenomenon mobilizing the entire cancer cell to evade drug action. Small-scale PPI and signalling network models of cancer and drug resistance focus on a specific segment of the interlinked molecular mechanisms suggesting potential drug targets, and helping the design of personalized drug combinations. Novel network analysis tools highlight key network segments in large networks, which may initiate novel small-scale models in the future. The availability of proteome-wide PPI and signalling network data resolved an important obstacle to build system level cancer drug resistance networks. We reviewed the available system level models, which assess sensitivity of KRAS-mutated molecular subgroups for PD-(L)1 immunotherapy in 776 patients (Padda et al., 2021), conduct in silico clinical trials (patient stratification, selection of the potentially best-responder patient cohort and N-of-1 clinical trials) (Castro et al., 2021; Castro et al., 2022) and provide system level drug combination screens in a short time (Papp et al., 2024). We listed the novel questions brought by the growing model size and variability. We also summarized the intensive community efforts to make cancer and drug resistance network data and models interoperable and reliable (Figure 2).

Our review was restricted to cancer drug resistance. However, recent studies highlighted several similarities of drug survival of cancer cells, fungi and bacteria, for example, increased DNA damage and general stress responses (El Meouche et al., 2024). These similarities make several considerations of cancer drug resistance studies useful in the design of new antibiotics and fungicides. In the last 4 years reviewed here there has been a rapid increase in publications in the fast-growing field of cancer drug resistance network models. We apologize to those colleagues whose work we were unable to cite.

The remarkable progress of recent studies revealed several areas where further advances can be made in system level cancer drug resistance network models. There is a pressing need to integrate the time component of drug resistance development to proteome-wide models leading to early and accurate prediction of escape trajectories. This will help to set the balance of drug combination, dosing and sequence strategies to kill enough cancer cells, but still limit the pressure for drug resistance development. Current network models focus on a single, drug-resistant cancer cell. There are ongoing efforts to connect the PPI and signalling networks of neighbouring cells enriching the current models with the communication of cancer cells with each other, tumour-associated macrophages, the vasculature and stromal cells. We expect that growing network data and models will accelerate the attack on cancer drug resistance.

7.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and

are permanently archived in the Concise Guide to PHARMACOLOGY 2021/22 (Alexander, Fabbro, Kelly, Mathie, Peters, Veale, Armstrong, Faccenda, Harding, Davies, Amarosi, et al., 2023; Alexander, Fabbro, Kelly, Mathie, Peters, Veale, Armstrong, Faccenda, Harding, Davies, Annett, et al., 2023; Alexander, Kelly, Mathie, Peters, Veale, Armstrong, Buneman, Faccenda, Harding, Spedding, Cidlowski, et al., 2023).

AUTHOR CONTRIBUTIONS

M. Kerestély: Visualization; writing—review and editing; funding acquisition. **D. Keresztes, L. Szarka**, **K. Schulc**: Writing—review and editing. **D. V. Veres**: Conceptualization; writing—review and editing. **P. Csermely**: Conceptualization; funding acquisition; project administration; writing—original draft.

ACKNOWLEDGEMENTS

We apologize to those whose work was not cited, as we covered only the most related papers between 2020 and December 2024. Authors thank Kristóf Z. Szalay (founder and Chief Technology Officer of Turbine Simulated Cell Technologies, Budapest, Hungary) for his advice writing the manuscript. This work was supported by the Thematic Excellence Program (Tématerületi Kiválósági Program TKP2021-EGA-24) of the Ministry for Innovation and Technology in Hungary, within the framework of the Molecular Biology Thematic Program of the Semmelweis University (P.C.) and by the 2024-2.1.1-EKÖP-2024-00004 University Research Scholarship Program of the Ministry for Culture and Innovation from the source of the National Research, Development and Innovation Fund (M.K.).

CONFLICT OF INTEREST STATEMENT

M.K., D.K., L.S., B.M.K., K.S. and P.C. declare no competing interests. D.V.V. is a co-founder and Chief Scientific Officer of Turbine Simulated Cell Technologies (Budapest, Hungary), a commercial company developing network-based simulated cell models to identify optimal preclinical experiments for cancer drug target validation and best responder patients leading to drug candidates tested in its own wet-lab and consecutive clinical trials.

DATA AVAILABILITY STATEMENT

Data availability is not applicable to this article, because it is a review article. No new data were created or analysed.

DECLARATION OF TRANSPARENCY AND SCIENTIFIC RIGOUR

This Declaration acknowledges that this paper adheres to the principles for transparent reporting and scientific rigour of preclinical research as stated in the *BJP* guidelines for Design and Analysis (10.1111/bph.15867) and as recommended by funding agencies, publisher, and other organizations engaged with supporting research.

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How to cite this article: Kerestély, M., Keresztes, D., Szarka, L., Kovács, B. M., Schulc, K., Veres, D. V., & Csermely, P. (2025). System level network data and models attack cancer drug resistance. *British Journal of Pharmacology*, 1–13. https://doi.org/10.1111/bph.17469