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Promising strategies for overcoming cancer drug resistance: from nanomedicine to artificial intelligence

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Abstract

Cancer is one of the most diffused and deadly diseases worldwide. Unfortunately, due to the very heterogeneous nature of tumors, it has been very challenging finding efficient treatments. Standard clinical procedures present many adverse side effects and may often cause drug resistance with consequent therapy failure, onset of metastases and relapse. Combination therapy has demonstrated limited success due to the difficulties in matching different molecules pharmacokinetic properties and in tuning the best dosage in order to achieve the desired effects. Recently, innovations in the nanotechnology field have allowed to design *ad hoc* nanocarriers able to selectively deliver drugs to target cells and release them upon specific triggers. Artificial intelligence approaches have been also developed and advances in the computational modeling field have greatly impacted human healthcare. The possibility to exploit algorithms for predicting drug responsiveness based on data retrieved from databases is greatly improving clinical strategies and supporting therapeutic decisions. In this review, we report recent advances in the nanomedical and artificial intelligence fields and describe novel strategies adopted for counteracting cancer drug resistance. Limits and promises of these approaches are discussed, together with some examples of preclinical and clinical applications.

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Introduction.

Cancer is one of the leading causes of death worldwide and one of the costliest diseases. Standard therapeutic treatments are mainly based on surgery, chemotherapy, radiation therapy and, recently, on targeted immunotherapy. Unfortunately, these approaches present many undesirable side effects, they are invasive and very often do not display enough selectivity for cancer cells. One phenomenon that commonly arises in patients during and upon chemotherapy is drug resistance, namely the capacity of tumor cells to become tolerant to the administered chemical agents and sometimes also to unrelated drugs, leading to multidrug resistance (MDR) [1,2]. This situation is correlated to therapy failure and is responsible for the diffusion of metastatic cancer and tumor relapse [3,4]. In the last years, researchers have focused on unraveling the mechanisms involved in cancer drug resistance, such as apoptosis inhibition, DNA damage repair, drug inactivation, altered drug efflux and target modifications [1,5,6]. Many strategies have been adopted for circumventing drug resistance, for instance by administering drug combinations

and small molecule inhibitors or by performing gene therapy [7]. Nevertheless, complications with tuning the right doses for achieving an appreciable effect and the difficulty to match the pharmacokinetic profiles of the proposed drugs has led to many unpredictable outcomes [8,9]. Indeed, each patient presents unique responses to a specific drug and this is especially true in very heterogeneous disorders such as cancer, thus making diagnosis and treatment very challenging [10,11]. Recently, the concept of precision medicine has gained fundamental importance in the clinical context, for establishing specific treatments for each patient, based on their peculiar genetic and epigenetic features [12]. Currently, efforts are centered on two innovative approaches, nanomedicine and artificial intelligence (AI), which are developing as intertwined tools for counteracting cancer drug resistance through personalized medicine. Nanotechnology has provided the means for designing and engineering nanomaterials formulated for delivering multiple drugs, ameliorating their physicochemical properties, enhancing their effectiveness and reducing possible adverse side effects [13–15]. Both inorganic and organic nanocarriers have been developed and modified, making them not merely subjected to passive delivery but also able to actively reaching specific tumor cells by means of functionalization with targeting ligands [16–20]. Thanks to this feature, nanocarriers can circumvent cell membrane transporters and enter the cells by endocytosis [18]. Interestingly, nanomedicines responsive to external stimuli display the great advantage of releasing the drug on site and upon specific triggers [20]. The importance of predicting drug responsiveness in oncology is fundamental and many efforts have been focused on developing appropriate techniques, from cell culture based chemosensitivity tests [21] to computational models [22]. However, standard methods present limitations, partially overcome by the advent of DNA, RNA, and protein-based assays [23,24], which rely on predictions coming from a defined number of genes [22,25]. Despite the many successes in reducing mortality, however it remains relatively difficult to find the correct genes to be analyzed as prognostic markers of drug resistance [25]. Examples in this direction are the publicly available Gene Expression Omnibus (GEO) database and The Cancer Genome Atlas (TCGA) that have provided huge amounts of data [26]. This review reports innovative nanomedical and AI approaches for counteracting drug resistance in cancer. A special focus on the developments at the preclinical and clinical stages is made, discussing the advantages and limits of this vibrant field of research.

1. Nanomaterials for overcoming cancer drug resistance.

Nanomaterials are contributing to personalized medicine from diagnosis to therapy: improvements in many technologies have allowed to perform single molecule DNA sequencing [27] and to exploit nanosensors to detect biomarkers with femtomolar concentration sensitivities [28]. In particular, advances in the design of theranostic agents combining drug delivery and imaging agents have revolutionized the field of nanomedicine [29]. Multiple kinds of carriers have been developed, thanks to their intrinsic properties such as i) high surface to volume ratio, and ii) several possibilities of modification by specific ligand functionalization for responding to external stimuli (Figure 1).

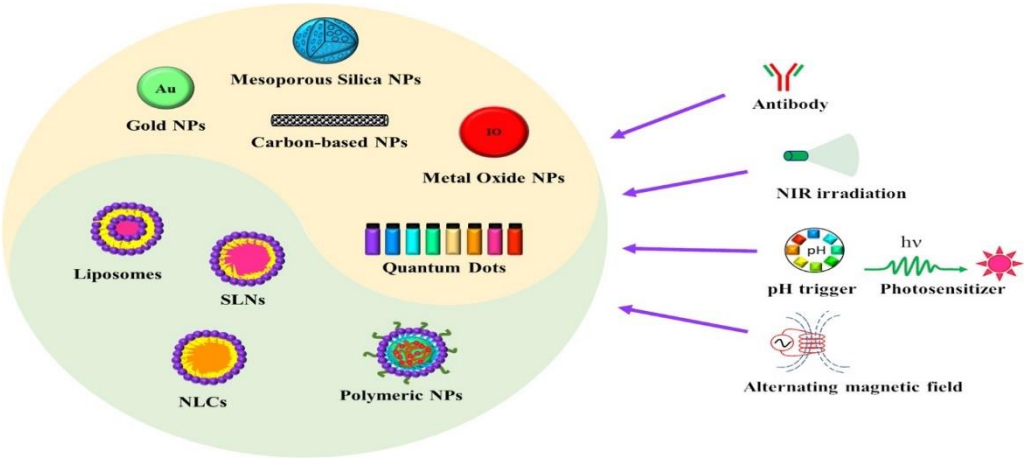

Figure 1. Scheme of the main inorganic and organic nanoparticles developed for counteracting cancer drug resistance. Possible functionalization with targeting ligand and external stimuli exploited for triggered drug release are reported. NPs: nanoparticles, IO: iron oxide, SLNs: solid lipid nanoparticles, NLCs: nanostructured lipid carriers, NIR: near-infrared.

Interestingly, nanoparticles (NPs) can easily penetrate cells by endocytic mechanisms, avoiding pump transporters involved in multidrug resistance. Considering inorganic nanomaterials, iron oxide NPs have been used for carrying chemotherapeutic molecules to drug resistant HeLa cells [30], and have displayed a more efficient behavior respect to the free molecule itself *in vivo* [31]. As mentioned before, the possibility to load NPs with multiple drugs for simultaneous delivery is of prominent importance for improving the potential of combination therapy, overcoming the limits due to pharmacokinetics and tumor microenvironment heterogeneity [32,33]. One further advantage of using metallic NPs is that they are responsive to alternating magnetic fields, generating localized hyperthermia, gaining drug release and efficient resistance reversal [34,35]. Similarly, to iron oxide, gold NPs have been synthetized and conjugated to specific drugs, achieving significant cytotoxic effects in drug resistant cancer cells [36,37]. Interestingly, a therapeutic approach, called photothermal therapy (PTT) has been adopted, based on the conversion of absorbed near-infrared (NIR) light to heat, specifically destroying cancer cells [38]. A recent study showed its efficacy upon administration of NPs to MDR tumor xenografts [39]. An interesting material used in nanomedicine is constituted by mesoporous silica nanoparticles (MSNs), excellent carriers of molecules inside drug resistant cancer cells [40]. When exploited for delivering siRNAs targeting P-glycoprotein (P-gp, also known as multidrug resistance protein 1) and doxorubicin, they showed accumulation due to enhanced permeability and retention effect, with resulting downregulation of specific protein expression [41]. Carbon based nanocarriers have been widely employed in nanomedicine for their high surface-to-volume ratio, thermal conductivity and ease of functionalization. For instance, i) carbon nanotubes, used in many applications such as imaging agents responsive to NIR irradiation [42] and as carriers for chemotherapeutics and P-gp inhibitors *in vitro* and *in vivo* [43–45], and ii) graphene oxide loaded with siRNAs and chemotherapeutic agents, that have revealed successful in targeting drug resistant tumor cells [46,47]. Concerning organic materials, they have raised increasing interest thanks to i) biocompatibility, due to the presence of natural components in their formulations, and ii) high biodegradability. In this section, some researches concerning the use of lipidic and polymeric NPs will be reported. Liposomes, thanks to their nature, can encapsulate hydrophilic and hydrophobic molecules [48], they easily accumulate into tumors and, when appropriately modified (i.e., by PEGylation), they can be made enough stable to enhance their circulation times [49] eluding transporters involved in MDR [50]. Liposomes loaded with multiple drugs revealed to be effective both *in vitro* and *in vivo*, efficiently overcoming MDR [51,52]. Modifications that made them responsive to external stimuli, further enhanced their efficacy [53]. Another kind of lipid NPs, constituted by lipids solid at body temperature and a stabilizing surfactant, are called solid lipid nanoparticles (SLNs) [54]. They present higher stability and a more sustained release respect to liposomes. MDR was successfully overcome in breast cancer cells upon SLNs administration [55] and in *in vitro* and *in vivo* models of hepatocellular carcinoma [56]. Nanostructured lipid carriers (NLCs) constituted by one or more liquid lipid allowing to encapsulate high amounts of drugs [57] have demonstrated efficient in combination therapy, delivering paclitaxel and indocyanine green, targeting tumor cells and releasing chemicals upon laser irradiation *in vitro* and *in vivo* [58]. NLCs mediated targeted delivery of doxorubicin and vincristine revealed effective *in vitro* and *in vivo* [59]. Highly biocompatible polymeric NPs have been successfully used for circumventing MDR in cancer [50]. Multifunctional NPs loaded with chemotherapeutic agents and responsive to external triggers have displayed effectiveness in MDR tumors [60,61]. Interestingly, modifications have been performed allowing to specifically downregulate the expression of proteins correlated to multidrug resistance [62]. The biopolymer poly lactide-co-glycolide (PLGA) has been widely explored for fabricating NPs carrying paclitaxel and siRNAs directed against focal adhesion kinase and for treating ovarian cancer *in vitro* and *in vivo* [63]. Interestingly, poloxamers, copolymers able to interfere with P-gp efflux pumps, have been combined to PLGA for obtaining docetaxel-loaded PLGA d-α-tocopheryl polyethylene glycol 1000 succinate (TPGS)/Poloxamer 235 NPs for breast cancer treatment [64]. In spite of the advantages of nanoparticle-based treatments, it is important to know that very few trials have been registered involving their clinical translation. Formulations of camptothecin conjugated to cyclodextrin-based polymers, have been reported for treating recurrent platinum-resistant ovarian, tubal and peritoneal cancer [65], castration resistant prostate cancer patients already treated with enzalutamide [66] and, combined with Olaparib, recurrent ovarian cancer [67]. Studies involving the administration of paclitaxel albumin-stabilized NPs, alone or in combination with other molecules, have been reported in platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer [68–70], in taxol resistant patients with metastatic breast cancer [71] and in advanced gastric tumors [72]. Two clinical trials have been registered for studying the effects of the administration of docetaxel NPs in metastatic castration resistant prostate cancer [73] and in platinum-

resistant ovarian cancer patients [74]. Concerning liposomes as therapeutic agents, one study is expected to administer irinotecan liposomes and bevacizumab to patients with platinum resistant ovarian, fallopian tube, or primary peritoneal cancer and to subjects with recurrent and refractory cancer [75]. Another trial performing a treatment with anti-EGFR immunoliposomes carrying cytotoxic molecules, and specifically targeting solid tumors overexpressing EGFR, has been described [76].

2. Artificial intelligence for overcoming cancer drug resistance

In the last decades, AI has revolutionized many fields of human life [77] impacting with ground-breaking healthcare strategies and supporting problem solving and decision making in oncology [78]. Similarly to traditional medical approaches, where multidisciplinary teams integrating the most different competences are involved in finding the correct diagnosis, analyzing data and finally developing a treatment strategy, computational models are capable to learn and predict patterns, by mining and linking data, often walking along roads that researchers and physicians can't walk [79] (Figure 2). Computational strategies can drastically improve basic research and precision oncology [78], cancer medical imaging (i.e., radiographic imaging [80,81] and digital pathology [82,83]) and translational oncology (i.e., cancer therapy [84–86] and drug discovery [87,88]), allowing to plan personalized treatments. From a generic point of view, computational technologies allow to i) collect huge amounts of digital data, acquired from heterogeneous sources, such as different types of images, next generation sequencing, large scale clinical trials and patients health records, and ii), improve drug discovery, correct diagnosis and therapy by early detection, modeling-based predictions, pattern recognition and data correlations, based on "automatically improve through experience" algorithms[78].

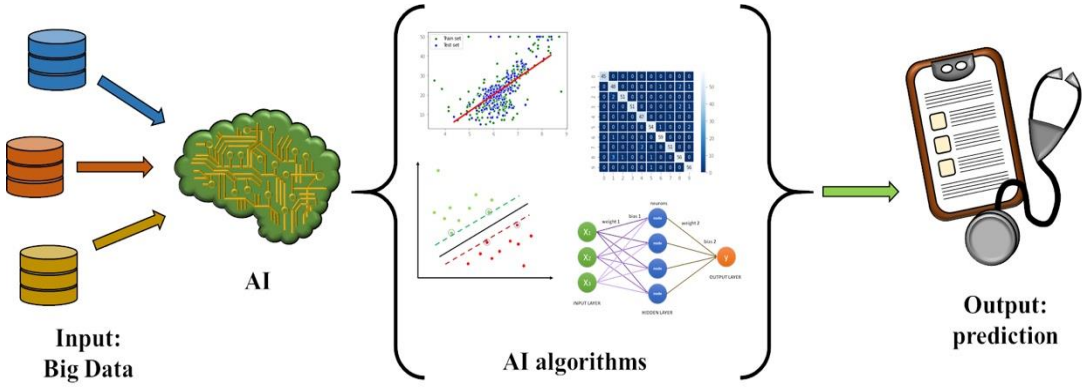

Figure 2. Scheme of an artificial intelligence algorithm. In input, Big Data are retrieved from different databases. The dataset collected is subsequently analyzed by artificial intelligence (AI) algorithms with specific architectures. In order to improve the result, several solutions can be combined in a single algorithm. The obtained output is a prediction able to improve medical strategies and therapeutic decisions.

Because the complexity and quantity of databases developed in the last decades are experimentally and economically not affordable by *in vitro* and *in vivo* researches, computational methods have revealed to be the most promising tools for supporting drug discovery and for screening drug combinations [89]. Machine learning (ML) algorithms are a subclass of AI, typically divided into different categories, depending on the signal or feedback provided to the learning system and on the statistical and probabilistic approach adopted [90,91]. Support-vector machines (SVMs) are a ML supervised approach, able to analyze data for classification and regression processes, very useful to recognize patterns in complex data [90]. Hazai et al., exploited a model of SVM to predict substrates of human breast cancer resistance protein (BCRP), involved in multidrug resistance onset, and demonstrated this method as an affordable system for the analysis of pharmacokinetics, efficacy and safety of specific drugs [92]. In a recent study, a SVM algorithm was implemented, presenting a high accurate solution in predicting drug responsiveness in many cancer cell lines. To train and test the model, datasets of gene expression and drug response collected in the National Cancer Institute panel of 60 human cancer cell lines (NCI-60) were used [93]. Another architecture exploited in the ML field is the Bayesian algorithm, a statistical model based on Bayes' theorem [90]. Costello et al., demonstrated its impact in predicting drug response by analyzing 44 drug sensitivity prediction algorithms trained on datasets collected from

genomic, epigenomic and proteomic analyses performed in human breast cancer cell lines [94]. In order to unravel the highly heterogeneous nature of a pathology such as cancer, Gönen et al., proposed computational algorithms able to mining genomic information for obtaining robust predictors of drug responses. They focused on a Bayesian algorithm with two main properties: i) developing a simultaneous predictive model for all the drugs considered, stressing their common parameters, and ii) handling missing data concerning drug susceptibility measurements, in order not to discard data with missing outputs [95]. It is well known that patients affected by the same tumor display heterogeneous behaviors towards the same kind of therapy. Therefore, computational models have developed the so-called ensemble methods, that use multiple learning algorithms to obtain a better predictive performance than using their learning algorithm alone. A typical example of an ensemble method is the "random forest" model, a ML strategy for classification using determined numbers of predictive sub-models called "decision trees". A recent work demonstrated that adopting a random forest it could be feasible mapping pharmacogenomics alterations in 1,001 human cancer cell lines and correlating the analysis with possible sensitivity to 265 drugs. The study showed the importance of different kinds of data in predicting drug response of specific tumor populations [96]. Cortés-Ciriano et al., applied the random forest integrating chemical and biological information for modelling 50% growth inhibition bioassay endpoint of thousands of compounds screened against 59 cancer cell lines. The algorithm was able to elaborate compound bioactivities in input and output, with the possibility to be extended to different cell lines, tissues and compounds, predicting drug-pathway associations and growth inhibition patterns [97]. Naulaerts et al., created a ML model for comparing commonly considered single-gene markers with multi-gene markers, exploiting genomic data for distinguishing sensitive *vs.* resistant cancer cell lines. The study demonstrated that sensitivity to specific drugs can be better predicted by these kinds of models [98]. Interestingly, it has been shown that is possible to overcome the "trial and error method" while looking for the identification of the best drug mixtures for circumventing drug resistance, by using a computational ensemble predictive model greatly reducing the complexity of combination therapy [99]. Very recently, Sharma et al., applied a modified rotation forest from a specific ensemble learning framework to Genomics of Drug Sensitivity in Cancer (GDSC) and Cancer Cell Line Encyclopedia (CCLE) drug screens, and obtained very robust drug-response predictions [100]. An artificial neural network is a ML network composed by nodes interconnected and controlled by a linear combination of weights and its name originates from the computational attempts to mimic a biological brain. Artificial neural networks can learn by training through datasets, allowing to obtain probabilistic responses moving through complex and apparently unrelated information. Menden et al., exploited an artificial neural network for designing *ad hoc* drug-cell screenings, suggesting an *in silico* massive test both for drug discovery and sensitivity evaluation [101]. As studies progress, new computational solutions have been gradually introduced to improve the efficiency of the process. Deep learning (DL) is a particular subclass of ML [90], specifically based on artificial neural networks [102,103], where the adjective "deep" refers to the multiple layers used in the construction of the network architecture. In many studies, DL algorithms have shown robust prediction of drug response when applied to pharmacological and cell line -omics data [104]. As for ML technology, DL can investigate huge amounts of multi factor and noisy data while defining nonlinear relations in datasets and bypassing the complexity of biological data [105]. Like for ML, different strategies can be used for elaborating a DL algorithm. The more intuitive is an artificial neural network with a large number of fully connected hidden layers, where the information flows through the nodes in one direction [106]. Regardless of its simplicity, this model has been already successfully used in drug response analysis [107]. Another type of DL model is the convolutional neural network where, in specific points of the network, the algorithm applies convolutions and the final layers result to be fully connected for a supervised classification or regression. Importantly, convolutional neural networks are used for drug response prediction based on input data like 2D compound structures, named "compound images" [108]. Finally, the network can present cycles connecting adjacent edges. In this case, the DL model is named recurrent neural network, whose main application is modeling sequential data. For instance, Oskooei et al., developed a prediction algorithm for anticancer compound sensitivity (PaccMann), integrating molecular structure of drugs, transcriptomic profiles of cancer cells and data related to protein-cell interactions [109]. DL methods with unsupervised architecture have been also described, analyzing both chemical structures and -omics data for elaborating a predictive model of drug interaction [110–112].

Conclusions.

Considering the reported researches on nanomaterials, it is possible to infer that further studies will be required before a broad diffusion of nanoparticles in the medical context. Although the application of nanotechnology for targeted drug delivery is clearly a very promising strategy for counteracting cancer drug resistance, however more knowledge is required concerning the behavior of the delivered drugs and the metabolism of nanomaterials inside human body, especially in the long-term [113]. Assessment of nanotoxicity and nanosafety is a fundamental prerequisite for clinical applications and it is at this point that innovative multidisciplinary approaches such as computational technologies, could help predicting and finely tuning the best treatment for achieving the best therapeutic result in very much intricate pathologies like tumors [114,115]. Although the vast majority of the artificial intelligence studies are performed at a preclinical stage, importantly the possibility to perform clinical trials aimed at collecting radiomics, metabolic, genetic, pathological data for establishing multi-omics AI systems for predicting the effect of neoadjuvant therapy and better explore drug resistance is now becoming reality [116]. Obviously, the success of the computational approaches in the clinical field will be determined in large part by the efforts to translate mathematical abstract models into healthcare strategies. Some issues have been already raised, such as i) standardization of databases and predictions, ii) difficulties in translating diagnostic tasks into Boolean values, and iii) necessity to overcome the gap between medical professionals and computer scientists [117,118]. Furthermore, data collection raises some ethical issues, because it determines a potential exposure to hacking attacks or illegal access to very sensitive data and personalized medicine exposes to the risk of profiling patients into their privacy [119]. In conclusion, even though surveillance by human specialists (i.e., ethical commissions, cyber security experts, bioinformatics and physicians) is still indispensable, however researches in the artificial intelligence field are exponentially growing, laying foundations for future integrations with medicine.

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