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REVIEWS

Spotlight

Nanoinformatics Revolutionizes Personalized Cancer Therapy

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Designing personalized cancer nanomedicines is a challenging process. The emerging field of nanoinformatics can facilitate this process by enabling computational design of nanocarrier-encapsulated drugs. Recent data show that quantitative structure–nanoparticle assembly calculations predict particle formation and size, and can lead to safer and more effective personalized cancer therapeutics.

Personalized cancer therapy stands at the forefront of science and technology, providing therapeutics customized to the unique genetic composition of a patient's tumor. Of these therapeutics, dozens of kinase inhibitors have received US Food and Drug Administration (FDA) approval and many more are in clinical phase trials, showing clinical success and improved outcome [1]. Yet, many factors impede the clinical efficacy of such drugs. Major obstacles are high hydrophobicity, severe adverse effects due to accumulation in off-target tissues, and the frequent need for high-dose, multiple daily treatments [1]. These challenges have prompted the development of improved drug delivery systems that not only target proteins and pathways implicated in cancer, but can also specifically reach tumor sites. Innovative and 'smart' nanotechnologies for therapeutic and diagnostic (theranostic) applications have the potential to greatly advance personalized cancer treatment [2]. Various types of nanoparticles are able to overcome biological barriers, specifically target tumors, and achieve enhanced uptake in tumor cells. Cancer nanomedicines passively accumulate in solid tumors through the enhanced permeability and retention (EPR) effect, caused by leaky tumor vasculature and impaired lymphatic drainage; nanomedicines can also be actively targeted to tumors by coating with targeting molecules [2]. These important features improve the drug therapeutic index by reducing off-target tissue exposure and increasing drug efficacy [3].

However, clinical translation of nanomedicines is frequently hindered due to the challenging processes involved in their development. The assembly of drug–nanoparticle carriers currently entails manual trial-and-error-based design and formulation. These procedures are further encumbered by many different parameters that affect efficient drug encapsulation within the particle. New methods are required to overcome the complexities of designing targeted nanocarriers, solubilizing cancer therapeutics at a sufficient dose, and predicting, controlling, and implementing these processes [4].

Powerful machine-learning algorithms and predictive analytics are now emerging as useful tools that can considerably facilitate the design of more efficient nanocarriers. Such algorithms, which can identify patterns in complex data and, thus, provide predictive knowledge on future data, have been mainly applied for predicting cellular uptake, activity, and cytotoxicity of nanoparticles (e.g., [5,6]). Such studies are gradually shaping the novel field of nanoinformatics. Now, Shamay *et al.* [7] show that machine learning and nanoinformatics can be used for the *de novo* design of personalized drug nanocarriers.

First, the authors screened for stabilizers that would expedite the self-assembly of hydrophobic anticancer drugs into colloidally stable nanoparticles. Out of a range of excipient types, they found that a sulfated indocyanine dye allowed rapid and efficient self-assembly of a subset of drugs into sub-100-nm nanoparticles, coated by the dye molecules. Remarkably, and unlike typical nanocarriers, the indocyanine nanoparticles showed high drug loadings of up to 90%.

Next, the authors used computational models to examine whether this self-assembly process could be accurately and quantitatively predicted based on structural patterns of drug molecules [7]. They used retrospective quantitative structure–nanoparticle assembly prediction (QSNAP) calculations to identify and validate which molecular descriptors of the drugs enabled nanoparticle formation (Figure 1A). Molecular descriptors transform the chemical characteristics of a molecule (e.g., atomic charge, polarizability, geometrical complexity, bond order, heteroatoms, and many more) into numbers. This enables quantitative characterization and classification of structure–activity and structure–property patterns [8]. Using a training data set of particle-forming and nonforming drugs, the retrospective analysis identified four molecular descriptors (out of 4886 descriptors) that highly correlated with the nanoparticle self-assembly data. Of these, QSNAP distinguished a topochemical descriptor as the most prominent predictor of drug nanoassembly with indocyanine; in addition, an electronegativity descriptor was identified as a highly predictive indicator of nanoparticle size. The predictive ability of the model was experimentally validated in additional drug sets. Among these was a library of 5653 small-molecule drugs, categorized in a decision tree according to their anticipated ability to self-assemble, based chiefly on the molecular descriptors. The analysis predicted that approximately 300 drugs would be

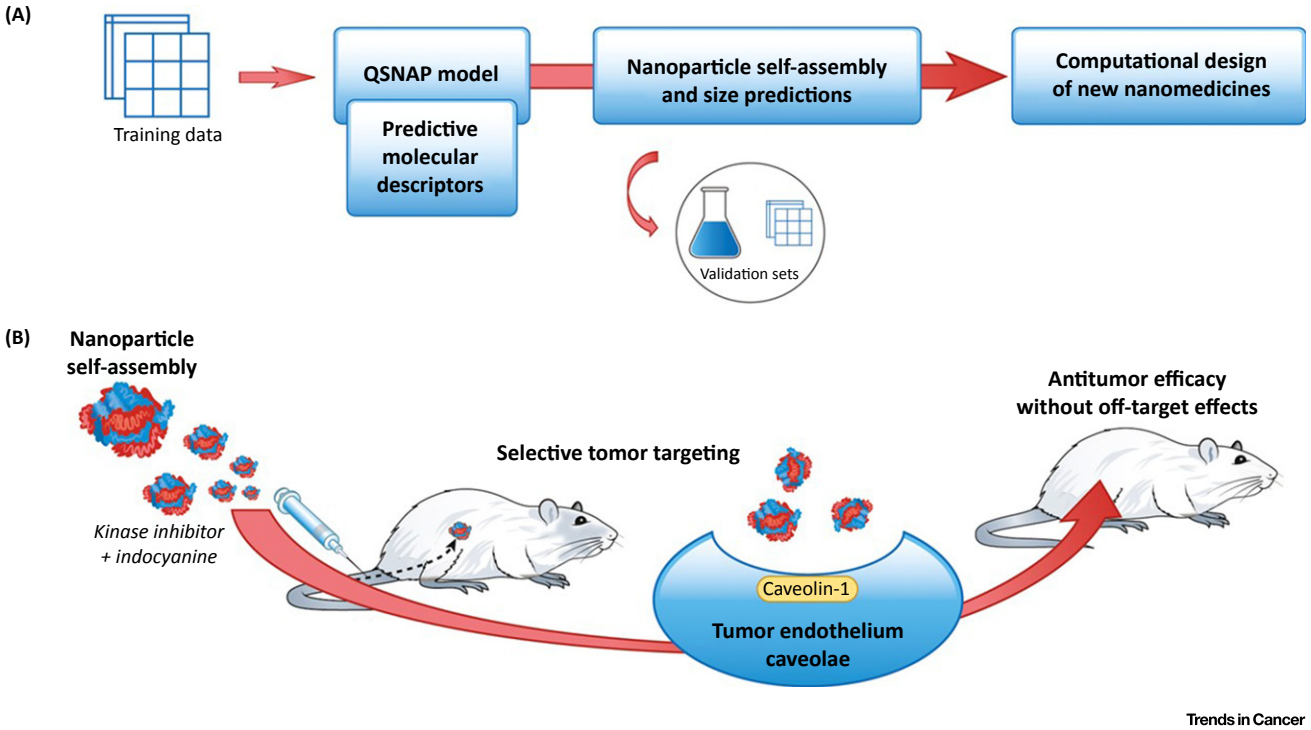

Figure 1. Nanoinformatics Facilitates the Design of Safe and Effective Personalized Nanomedicines. (A) Flowchart depicting the process of quantitative self-assembly prediction of targeted nanomedicine. The model was trained on a known data set of nanoparticle-forming and non-particle-forming hydrophobic drugs. The QSNAP model identified electrotopological molecular descriptors as highly predictive indicators of nanoparticle assembly and nanoparticle size. Based on the molecular descriptors, the model predicted both nanoparticle size and self-assembly of a new set of drugs. The drugs were experimentally examined (validation sets) and were found to behave as predicted by the model. These findings indicate that novel nanomedicines can be designed via computational models of drug payload selection. (B) A computationally predicted, stable nanoparticle self-assembled, comprising a hydrophobic kinase inhibitor (blue) and indocyanine coating (red). The nanoparticles were intravenously injected into mouse models of liver or colon cancer, and were selectively taken up into caveolin-1-expressing tumors. The nanoparticles showed high tumor accumulation and antitumor efficacy, and prevented skin rash, a prominent dose-limiting adverse effect of kinase inhibitors [7]. Abbreviation: QSNAP, quantitative structure–nanoparticle assembly prediction.

capable of forming stable indocyanine nanoparticles and, indeed, over 60 experimentally examined compounds were found to perform in accordance with the prediction.

The authors then focused on the biological activity of two of the computationally predicted indocyanine particles, encapsulating the tyrosine kinase inhibitors sorafenib or trametinib [7]. Uptake of kinase-inhibitor indocyanine nanoparticles was observed in a range of cell types, and was found to occur mainly by caveolae-mediated endocytosis, denoted by expression of caveolin-1, the main integral protein of caveolae lipid rafts, and which is often overexpressed in tumors [9]. In murine autochthonous liver carcinoma and xenograft colon cancer models, sorafenib and trametinib nanoparticles were selectively taken up by tumors via caveolae-mediated endocytosis in tumor endothelium (Figure 1B). Nanoparticle uptake is likely due to targeting of caveolae by indocyanine sulfate groups [10]. Importantly, both types of kinase inhibitor nanoparticles, in addition to having no *in vivo* toxicity, exhibited superior tumor accumulation and antitumor efficacy compared with free drug. Nanoparticle encapsulation also increased the therapeutic index of trametinib. Encapsulation lowered the effective dose of the drug (2 mg/kg/week intravenous trametinib particle injection, versus 1 mg/kg/day oral free drug), and prevented inhibition of downstream ERK phosphorylation in healthy skin [7], which is a dose-limiting adverse effect of kinase inhibitors that leads to severe skin rash.

Thus, machine-learning approaches provide a new set of parameters for designing personalized drugs that can be readily incorporated into therapeutic nanoparticles, and offer an efficient alternative to the tedious and costly process of experimentally based drug encapsulation. Computational prediction can not only transform our ability to predict drug carrier design and nanoformulations, but also deliver safer and more effective cancer nanomedicines. The challenge for these

computational tools is to expand the suite of excipients or carrier systems for which drug loading can be predicted. Furthermore, it would be valuable to broaden the range of parameters that can be predicted, such as drug release kinetics or tumor accumulation profiles of nanoparticles. Although this would be challenging due to the multiple, interlinked biological events that affect nanoparticle uptake in tumors (including interactions between nanoparticles and circulating proteins or the perivascular tumor microenvironment; as well as tumor tissue penetration and tumor cell internalization of nanoparticles), computational approaches have nevertheless successfully modeled various complex biological endpoints [5]. Thus, the new field of nanoinformatics holds promise to revolutionize personalized medicine, and bring tailor-made cancer treatments within reach.

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https://doi.org/10.1016/j.trecan.2018.04.002

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Spotlight

Mutant *Kras* Dosage and Chromothripsis: The Right Ingredients for a Pancreatic Cancer Catastrophe

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Pancreatic ductal adenocarcinoma is a deadly disease requiring early identification but this is a challenging task in humans. Therefore, disease modeling in mice could provide important insights into early genetic events. In an article in *Nature*, Mueller *et al.* show that changes in mutant *Kras* allele dosage and chromothripsis are important events, both for tumor progression and to establish genetic contingencies that highlight how the tumor progresses and acquires major biological features.

Pancreatic ductal adenocarcinoma (PDAC) is not only the tumor with the worst prognosis but also the one for which a greatest mortality increase is predicted in the Western world over the next decade [1]. Characterized by a rapid progression and high propensity to metastasize, the classical PDAC progression model has proposed the occurrence of sequential genetic alterations: activation of oncogenic *KRAS*, followed by inactivation of *CDKN2A*, then *TP53* and *SMAD4* ('the usual suspects') [2]. Over the past decade, genetic mouse models (GEMMs) have been extensively used to address questions related to the molecular pathophysiology of PDAC and to gain insight into novel therapeutic avenues [3].

Through a formidable genomic effort, Mueller *et al.* have recently reported how $Kras^{G12D}$ gene dosage evolves during murine tumor development/progression and the associated genetic contingencies [4]. The authors analyzed the exome and copy number changes of 38 cultures from tumors arising in mice in which the expression of $Kras^{G12D}$ had been activated in the embryonic pancreas. A comparison of mouse and human PDAC showed a higher mutational burden in the latter (1.5- and 3.3-fold higher for single nucleotide variants and indels, respectively). In this setting, mutant *Kras*-initiated tumors were 'allowed' to evolve without additional experimentally imposed genetic constraints: recurrently altered genes were infrequent, an aspect that also highlights the genetics of human PDAC where, beyond the four 'usual suspects', few genes are recurrently mutated [5].

One of the main findings was that 34% of the tumors displayed complex genomic rearrangements with ±1 copy number oscillations associated with accelerated tumor development, consistent with chromothripsis. Recently, Notta *et al.* have reported a high frequency of chromothripsis events in human PDAC, suggesting that PDAC progression often occurs in a catastrophic fashion both in mice and patients [6,7].

Perhaps not surprisingly, among the loci showing common gene copy number alterations were *Kras* and *Cdkn2a,* coding for p16. Four *Kras* gene dosage states were found: (i) focal gains, (ii) arm-level gains, (iii) copy-neutral loss of the wild type allele, and (iv) no alterations. Overall,