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Editorial

Development of small molecule fluorescent dye drug conjugates in targeted cancer therapy

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Since the beginning of the 20th-century use of chemical dyes opened the doors for cancer treatment with the development of Paul Ehrlich's ground-braking concepts of chemotherapy and the magic bullet (*Zauberkugel*); an ideal therapeutic agent that would selectively kill only targeted pathological organisms without damaging the patient [1]. Now at the beginning of the 21st century, Dr. Leland W K Chung's vision of developing a cancer magic bullet chemical dye has become a reality entering clinical trials.

Conventional cytotoxic agents used in cancer treatment are effective in slowing progression in some tumors. They do not, however, fully discriminate between normal and cancer cells and cannot produce effective therapeutic effects without doing extensive harm to healthy tissues. Treatment with cytotoxic drugs also inevitably leads to tumor resistance. Striving for new agents prolonging survival and curing cancer patients much effort was invested in targeted therapy.

Much effort in current cancer drug development is invested in strategies employing targeted cancer therapy. These efforts have been driven by promising results with increased progression-free survival (PFS), allowing many patients to be eligible for more treatment options and clinical trials. Sadly, most agents considered as targeted therapies are not specific enough nor are they active enough against cancer cells. As such they fail in their attempts to limit toxicity and increase overall survival (OS). Combining targeted delivery mechanisms with conventional effective cytotoxic agents has been showing promising results in clincial trials.

How to further proceed in finding more effective cancer agents? What we can see from the current *status quo* in cancer drug treatment is that most targeted agents do not possess strong enough antitumor properties, are not selective enough, and are not thorough enough to eliminate all cancer cells regardless of their resistance, clonal heterogeneity, or *stemness* properties. There is a clear need to further enhance drug delivery to reduce toxicity to normal cells and increase cancer cell killing capabilities by finding ways to effectively remove the complete tumor population, inducing complete remissions, and preventing relapses. An emerging idea to achieve this is by repurposing the already effective conventional cytotoxic and potent cell-killing agents with a wide variety of specific cancer cell targeting moieties like antibodies, aptamers, small protein scaffolds, peptides, and low-molecular-weight non-peptidic ligands [2].

Multifunctional cell targeting constructs can briefly be divided into antibody-drug conjugates (ADC) and small molecule or peptide-protein ligands which are conjugated with small molecule cytotoxic drugs for cancer therapy, radioligands for imaging or therapy, proteolysis targeting chimeras for protein degradation and immunotherapy and tumor fluorescent dyes for imaging and therapy [3].

While antibody drug conjugates are dominating the field of cell targeting constructs, development of small molecule drug conjugates has been modest so far and the field is still in its infancy. This sounds illogical since the development, production, and effectiveness of these agents should be in favor of small molecule drug conjugates [3]. Agents using delivery strategies like σ2-opioid receptor [4], folate receptor [5], carbonic anhydrase IX inhibitor [6], PSMA [7] or HSP90 [8] ligands and cytotoxic drugs have shown early promising results. A σ2-opioid receptor ligand-SMAC mimetic conjugate SW IV-134 has shown increased survival in mouse pancreatic cancer xenograft models increasing median overall survival (OS) by 36 days compared to vehicle (88 vs. 52 days) [4]. A combination of this drug yielded an increased median OS when compared to gemcitabine alone (60 vs. 46 days) [9]. STA-8666, an HSP90 inhibitor/SN-38 drug conjugate has showed increased OS in mouse Ewing sarcoma and osteosarcoma xenograft models, with median OS not reached with STA-8666 compared to irinotecan and ganetespib and increased OS in Ewing sarcoma mouse PDX model with median OS not reached with STA-8666 compared to irinotecan and irinotecan + ganetespib [8]. A small molecule drug conjugate, VIP236, composed of a peptidomimetic $\alpha_v\beta_3$ integrin antagonist linked to a cytotoxic camptothecin derivative has shown preclinical activity in multiple cancer types [10]. Furthest evidence was provided with vinca alkaloid DAVLBH-folic acid derivative conjugate vintafolide in folate receptor-expressing tumors. In preclinical studies, human nasopharyngeal carcinoma and murine B-cell lymphoma mouse models were tested with complete curative results in both models [5]. The drug was subsequently evaluated in two clinical trials. In a PROCEED phase III trial for the treatment of platinum-resistant ovarian cancer, there was no difference in PFS and OS in combination with vintafolide with pegylated liposomal doxorubicin (PLD) or PLD alone. In the phase IIb TARGET trial comparing vintafolide as second-line treatment with vintafolide plus docetaxel and docetaxel alone in patients with non-small cell lung cancer (NSCLC) who have FR+ tumors, there is evidence for increased OS in the vintafolide + docetaxel arm (11.5 vs. 8.8 months) [11].

The use of small molecule fluorescent dye conjugates in imaging started more than a decade ago with Dr. Chung's pivotal work on the use of heptamethine cyanine NIR fluorophores (HMCDs) in cancer imaging. Immediately he proposed their use for cancer therapy by means of conjugation with cytotoxic agents [12]. Advances with small molecule fluorophores introduced a plead of non-cleavable and cleavable conjugates of different NIR agents like Rhodamine Green, BODIPY, SiR-COOH, tetraphenylethane, Oregon Green, and naphtalamide conjugated with agents like ibrutinib, suldinac, tamoxifen, GABA, camptothecin, coumarin, gemcitabine, and doxorubicin for cancer imaging and treatment [13].

On the other hand, much effort was put into the research of certain heptamethine carbocyanine dyes (HMCDs) due to their potential for preferential targeting and accumulation in tumors mitochondria and lysosomes but not normal cells making them perfect candidates for drug conjugation [14]. This was confirmed in a variety of cell culture models, mouse and dog tumor models, patient-derived xenografts, and perfused kidney cancers in patients [12, 15-18]. Suggested tumor uptake of HMCDs is mediated in part by organic anion-transporting polypeptides (OATPs) but endocytosis and albumin-mediated transport could also play a role [16, 19]. So far HMCDs IR-780, IR-783, IR-786, MHI-148 and DZ-1 have been conjugated with a variety of agents like docetaxel, gemcitabine, clorgiline, methotrexate, erlotinib, genistein, isoniazid, crizotinib, dasatinib, rucaparib, cisplatin, and simvastatin for a variety of cancer types [14, 19]. Some of these agents are in a process of entering clinical trials. Remarkably conjugation of many of these agents with HMCDs not only increased potency and properties of the involved cytotoxic agents by many times but also changed them in a way that the HMCD-drug conjugate could be considered as a completely new drug. For example, the DZ-1-cisplatin conjugate was found to be a potent c-myc inhibitor and altered expression of epigenetic regulatory protein in Burkitt lymphoma cell line models [14].

Our story regarding the use of small molecule dye drug conjugates is just at the beginning as we consider that our possibilities are almost endless. It is certainly possible to find better and more selective dyes that target and accumulate specifically within tumor cells. Moreover, it is certain that it will be possible to modulate

the drug conjugates with a multitude of anticancer agents linked to one dye molecule with different mechanisms of action. This could allow the creation of compounds able to inhibit the mitochondrial respiratory chain proteins and lead to certain tumor cell death leaving cancer cells incapable of developing resistance. The vision and challenge passed onto us by Dr. Chung seems bright and shiny!

Disclosure of conflict of interest

None.

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