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Cascade PRODRUG™ Tumor Targeting Chemotherapy

CPD l00Li

Targeting the Tumor Microenvironment

CPD 100Li is a liposome-formulated prodrug of the chemotherapeutic compound Vinblastine Sulfate. Under normal oxygen (O_2) levels, this N-oxide derivative significantly reduces the cytotoxic effect of vinblastine on normal cells, but switches to cytotoxic vinblastine by the action of a reductase enzyme activated at the low O_2 levels common to the microenvironment of many solid tumors.

The tumor microenvironment (TME) denotes the milieu of non-cancerous cells and additional cellular components present in the tumor (including molecules produced and released) that are in the immediate vicinity of a solid tumor. The constant interactions between tumor cells and the TME play decisive roles in tumor initiation, progression, metastasis, and response to therapies.[1]

The TME, which is strongly influenced by hypoxia, is an influential fixture of numerous tumors. Better understanding of the multiple effects of hypoxia on the TME and potential therapeutic interventions is a very active area in oncology research, and is thought to be a key element in breaking through the existing barriers of conventional tumor treatment. A variety of biological behaviors of tumor cells are affected by factors within the TME, many of which are closely related to hypoxia.[2] Therefore, targeting hypoxia as an activating mechanism of a potent cytotoxin holds great promise in providing a tangible advancement for anti-tumor therapy -- capable of killing simultaneously both the cancerous cells and their associated support systems within the TME.

In multiple studies of mouse xenograft tumor models, CPD 100Li has demonstrated excellent cancer killing activity, a dramatically improved safety profile, and evidence of a targeted effect influencing the TME.

Pancreatic Cancer: In a human Panc-1 orthotopic pancreatic cancer model, both as a single agent and in combination therapy with gemcitabine, CPD 100Li led to remarkable tumor destruction. The CPD 100Li/gemcitabine combo led to ***complete tumor regression***. Mechanistically, CPD 100Li reduces epithelial-to-mesenchymal transitions (EMTs) in the Panc-1 model, lessening tumor growth and progression -- an effect not seen with gemcitabine alone. These promising results resulted in the FDA's (Food and Drug Administration) recent decision to grant Orphan Drug Designation (ODD) to CPD 100Li for the treatment of pancreatic cancer. This is a clear affirmation of the drug's potential in treating this universally fatal disease. This designation not only grants the company ***market exclusivity for seven (7) years after approval***, but also provides tax benefits and reduces some of the costly burdens within the drug approval process.

Colon Cancer: In the syngeneic CT29 mouse colon cancer model, the impact of CPD 100Li on lymphocytic and myeloid cellular components in the tumor microenvironment reveal a profound reduction in resident and

infiltrating immunosuppressive lymphocytes, with demonstrable preservation of anti-tumor macrophages and marked reduction in tumor-friendly macrophages – effectively reducing tumor-supportive cells while preserving host-supportive cell populations.

Also, in the CT29 model, CPD100Li in combination with an anti-CTLA-4 agent provided extended survival that was markedly longer than either agent alone. This represents another potential development pathway, i.e. exploring combination therapy with immune-modifying chemotherapeutic agents -- which in this colon cancer model was ***not only additive, but synergistic.***

In summary, solid tumors develop a ***unique hypoxic tumor microenvironment*** which enhances aggressive tumor growth behavior, supports resident and infiltrating immunosuppressive cells, leads to exclusion and dysfunction of cytotoxic T cells, and induces epithelial-to-mesenchymal transitions (EMTs) -- all examples of activities that increase the chances of tumor survival, promote the growth of the parent tumor, and thus lead to poor clinical outcomes for cancer patients.

The Cascade Prodrug CPD 100Li ***specifically targets these elements of the tumor microenvironment*** resulting in enhanced tumor penetration, potency, and lethality toward tumor cells. This occurs in conjunction with the associated potential to eliminate resident and infiltrating immunosuppressive cells and reducing EMTs. This performance is extremely valuable as it demonstrates potent and improved efficacy with a markedly enhanced safety profile. The prodrug is NOT activated in the normal oxygen levels present in the hosts 'circulation, but only in the presence of low oxygen levels, i.e. hypoxic environments. The result?

A targeted chemotherapy intervention that leads to more effective treatment with a substantial decrease in toxic side effects.

References:

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