Chloroquine Nanoparticles Improve Biodistribution and Sensitize Pancreatic Cancer to Oxaliplatin and Radiation Therapy

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Despite our continued efforts, pancreatic cancer (PC) has the shortest average survival of all cancers, 5-7 months, and death rates continue to rise. In fact, PC has overtaken breast cancer as the third leading cause of cancer-related mortalities, and by 2030, PC will overtake colon cancer for second. Our inability to treat PC is largely a consequence of PC readily developing resistance to chemotherapy.

Chloroquine (CQ), a safe and well-tolerated antimalarial drug that has been used for over 70 years, can sensitize cancer cells to the anticancer effects of oxaliplatin (OX) and radiation therapy (RT). However, CQ has poor tumor uptake and is rapidly metabolized. The significance of this research is that we have created a nanoparticle formulation of CQ, chloroquine-nanoparticles (CQ-NPs), to enhance blood circulation levels and reduced hepatic metabolism leading to improved tumor accumulation and sensitization to OX or RT.

We hypothesize that CQ-NPs can improve tumor accumulation of CQ and sensitize PC cells to the deleterious effects of OX/RT leading to improved anticancer effects.

CQ-NPs were formulated and physically characterized via GPC, NMR, and elemental analysis. DLS and AFM assessed the size of CQ-NPs, ~15 nm diameter. Live cell imaging and LC3 levels confirmed that the biological activity of CQ was not altered after nanoformulation. *In vitro* studies showed CQ-NPs synergistically improve the cytotoxic effects of OX and RT. In *in vivo* mouse models, CQ-NPs extended blood circulation half-life from 11.7 to 19.4 hours, slowed the metabolism of CQ, reduced tumor volumes by nearly two-thirds ($P<0.001$), and decreased liver metastasis ($P = 0.04$).

In conclusion, CQ-NPs retain the biological activity of CQ, sensitize PC to OX *in vitro*, improve blood half-life of CQ, and reduce PC growth and metastasis *in vivo*. Future studies will investigate the ability of CQ-NP to improve RT and OX efficacy *in vivo*.