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Comparing cancer drug effectiveness from cells to mice to man

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Science is very good at determining how drugs work in experimental models. New research out of Dartmouth's Norris Cotton Cancer Center led by Alan Eastman, PhD, helps to bridge the gap when it comes to ensuring that drugs work by the same mechanism in human patients.

The study focused on the cancer drug gemcitabine in cell culture, animal models, and humans. With the right preclinical analysis, coupled with appropriate proof-of-concept experiments in human patients, the Eastman team was able to more precisely establish the mechanism by which gemcitabine works in cancer patients than was previously known. Such information can also be used to develop more effective gemcitabine drug combination therapies to treat cancer, and to more rationally approach clinical trial design going forward.

Eastman's research has been able to equate drug doses from laboratory models, through animal models into human patients, and in turn define preclinical conditions that are representative of what happens in the human. "Specifically, we have defined how the drug, gemcitabine, works in cells, mice and man, have described conditions that cause cell cycle perturbation in each model, and defined the time at which most cells are arrested in the DNA synthetic phase (S phase), and therefore most susceptible to treatment with another drug that will only work in S phase," said Eastman. "Under these conditions gemcitabine can be said to sensitize cells to our other drug, a Chk1 inhibitor, and vice versa."

Their paper "Cell cycle perturbation induced by gemcitabine in human

tumor cells in cell culture, xenografts and bladder cancer patients: implications for clinical trial designs combining gemcitabine with a Chk1 inhibitor," which represents a vast amount of unique research across multiple cancer models— cell culture, mice, and human—has recently been published in *Oncotarget*.

"Few studies have ever tried to extrapolate across multiple models in this manner. Too many studies focus on preclinical models with no consideration as to whether they are relevant to the patient," said Eastman. Such information can then be used for more rational approaches to clinical trial designs that have proof-of-concept aspects to them. "The most complex part of this study was probably accruing bladder cancer patients to the proof-of-concept clinical trial. We are extremely grateful for patients who are willing to contribute tumor tissue at defined times while on therapy so that we can evaluate biological events occurring in their tumor over time and facilitate improvements in cancer therapy."

Ongoing clinical trials are already basing their schedule of drugs on the results of this study. Next steps include dissecting additional drug combinations based on the team's early results that suggest that lower doses of gemcitabine than usually prescribed might work as well in patients, and low dose with more frequent administration may be a better schedule of drug administration. "Scientists need to have a much better idea of how a drug works in a patient, and to not work in a lab in isolation of the clinical relevance," said Eastman. "Proof-of-concept studies are so important for drug development and effective therapy."

More information: Ryan Montano et al, Cell cycle perturbation induced by gemcitabine in human tumor cells in cell culture, xenografts and bladder cancer patients: implications for clinical trial designs combining gemcitabine with a Chk1 inhibitor, *Oncotarget* (2017). DOI: 10.18632/oncotarget.18834