Cancer Breakthrough

Hon A/Prof Tracey Brown has been in the news this week as the scientist behind a cancer breakthrough. Dr Brown has developed a new drug delivery platform known as the Hyaluronan ChemoTransport (HyACT) Technology. The treatment makes chemotherapy up to 40 times more effective without an equivalent increase in chemotherapy side effects. It is currently being tested, with remarkable results, and overseas trials are planned to make it more widely available.

Those who are interested in the trial and have small cell lung cancer can contact: Peter Midolo, Research Manager, Monash Medical Centre on 03 9928 8195.

Synopsis

The basis of Dr Brown’s translational research at Monash University is using the naturally occurring polysaccharide, hyaluronan (HA) as a drug delivery vehicle that transports currently approved anti-cancer drugs to solid tumours which over-express activated CD44. The HA-drug extravasates into the tumour followed by active internalization of the HA/drug complex by tumour cells. The therapeutic end result of the increased drug uptake is increased efficacy and a reduction in the side-effects commonly observed when using currently approved cytotoxic drugs.

General Background on the Technology

In an attempt to increase the benefit associated with irinotecan-based treatment, and/or to reduce the dose-limiting toxicity often associated with this therapy, irinotecan has been formulated with the naturally ubiquitous polysaccharide, hyaluronan (HA), resulting in a proprietary product (HA-Irinotecan). This product utilizes the unique physicochemical and biologic properties of HA as a macromolecular carrier of drugs to solid tumors. Several intrinsic characteristics of HA highlighted its potential as a drug delivery vehicle: i) the amphiphilic nature of HA enables it to form a large coiled meshwork at low concentrations making it an ideal vehicle for the solvation and entrainment of smaller molecules; (ii) up-regulation of the HA receptor CD44 on malignant tissue where activation of the CD44 within the tumoral environment mediates HA internalization; and iii) HA is non-immunogenic and considered by regulatory bodies as a biologically-inert compound. After intravenous administration, the HA-derivitzed drug rapidly enters the tumor and aggregates thereby forming a vascular microembolism within the tumor. Of smaller molecules; (ii) up-regulation of the HA receptor CD44 on malignant tissue where activation of the CD44 within the tumoral environment mediates HA internalization; and iii) HA is non-immunogenic and considered by regulatory bodies as a biologically-inert compound. After intravenous administration, the HA-derivitzed drug rapidly enters the tumor and aggregates thereby forming a vascular microembolism within the tumor. Of smaller molecules; (ii) up-regulation of the HA receptor CD44 on malignant tissue where activation of the CD44 within the tumoral environment mediates HA internalization; and iii) HA is non-immunogenic and considered by regulatory bodies as a biologically-inert compound.
HyACT and Cancer Stem Cells

The target protein for the HyACT drugs is CD44. CD44 is a protein that is over-expressed on hyper-proliferative cancer cells and is also considered a reliable contributor to the CSC phenotype in breast, pancreatic, small cell and non-small cell lung cancer, colorectal and prostate cancer. In preclinical studies the Hyaluronan Laboratory demonstrated that HyACT drugs were capable of targeting chemotherapeutic drugs to cancer stems thereby overcoming treatment resistance and increasing tumour responses up to 40-fold. These data were presented at the American Academy of Clinical Research (AACR) in 2010 which prompted oncologists to consider using the lead HyACT drug, HA-Irinotecan as a cancer stem cell targeting therapy. Since 2010 Dr Brown’s team has completed the preclinical assessment of HA-Irinotecan in small cell lung cancer where it was substantiated that the HA-drugs could target and kill cancer stem cells.

Dr Vinod Ganju at Monash Medical Center has worked with the Hyaluronan Laboratory team and designed and initiated a randomized, Investigator-sponsored Phase II study in first-line, extensive stage small cell lung cancer patients where the primary end-point will be to quantitate the cancer stem cells (CD44+/CD133+/ALDH+/ABCG2+) before, during and after therapy. The secondary end-points will be to investigate the effect of the therapy on progression free survival and overall survival.

The Phase II trial was commenced 3 weeks ago and within 7 days after commencing therapy the initial two patients have demonstrated complete responses of metastatic lesions and 80-100% remission of the primary lung tumour. These data have obtained media attention because responses within such a short period is highly encouraging but also unexpected as normally such responses, if obtained would take >40 days in this patient demographic.

Determining the effect of hyaluronan on the internalization and intracellular localization of doxorubicin in Hs578T breast cancer cells

The Hs578T breast cancer cell line was seeded at 60% confluence on sterile glass coverslips. After 8h the cells were exposed to 800nM doxorubicin or 800nM HA-Doxorubicin. Coverslips were harvested at 2 hours after application of the test compound. At each time point the media was removed, cells washed with PBS and the coverslip removed from the well and placed in phenol-red free growth media. The internalisation of doxorubicin or HA-Doxorubicin was monitored using an Olympus FV1000 spectral confocal microscope (absorbance and emission wavelength of 600-650nm) where cells were incubated at 37°C in a temperature controlled observation chamber. White arrows indicate the nuclear envelope and vesicle-associated localization of the HA-doxorubicin or doxorubicin. The accumulation of doxorubicin was evidently increased in CD44+ cell subpopulations when formulated with the CD44-targeted HA drug delivery vehicle.