Molecular Enzymology and Drug Targets

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Asia Pharma 2016 : Development of inhalable Paclitaxel and Curcumin formulation for lung cancer therapys - Wing Hin Lee - Woolcock Institute of Medical Research

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Cancer is a leading cause of disease worldwide. Lung, female breast, colorectal and stomach cancers accounted for more than 40% of cancer cases diagnosed worldwide; with the World Health Organization reporting an estimated 14.1 million new cancer cases worldwide in 2012 .Among them, lung cancer is one of the most common, with 16.7% of all new cases diagnosed in men .In Australia alone, lung cancer has accounted for over 11,000 new cancer cases in 2012. Additionally, lung cancer is the most common cause of cancer-related death for men and women and the financial burden to the healthcare system is estimated at >100 million dollars annually in Australia . Importantly, lung cancer has the highest mortality rate of all common cancers and a miserable dismal rate of less than 5 years. Out of the 8.2 million deaths caused by cancer in 2011 globally, mortality from lung cancers contributed the highest, with 1.3 million deaths alone. Historically lung cancer has been linked to smoking and consequently classified as a social disease with a stigma attached . Contrary to popular belief, lung cancer not only affects smokers but also non-smokers. For example, in women, only 65% of cancer deaths can be attributed to smoking, with lung cancer killing more women than breast, uterine, and ovarian cancers combined in women. Irrespective of cause, mortality from lung cancer is high; with only 15% of lung cancer patients surviving for more than 5 years after diagnosis. Surgery, chemotherapy and radiation are standard treatment options for lung cancer depending on the stage of malignancy, resectability and overall performance. Chemotherapy is a first-line treatment for advanced stage of lung cancer in which chemotherapeutic drugs are usually administered intravenously for systemic circulation. Challenges and advantages involved in the delivery of inhalation therapeutic drug includes upgraded utilizing pneumonic conveyance since lung has restricted intracellular and extracellular medication using chemical exercises dissimilar to gastrointestinal tract and liver . What's more, this choice likewise diminishes non-reversible tissue harm brought about by medications' cytotoxicity. Also, higher retention rate, diminished medication dosages and fast beginning of activity are among the upsides of aspiratory organization. The bio-hindrances existing in the respiratory aviation route frameworks, for example, bodily fluid, ciliated cells and inhabitant macrophages are powerful to constrain the confinement, entrance and adsorption of medications in the lung . The leeway components of breathed in drugs are enacted relying upon the area of kept medication. Medication restricted at the upper aviation routes are expelled by ciliated cells in the epithelia locale while those in lower aviation routes were secured by inhabitant alveolar macrophages. Occupant alveolar macrophages identify the nearness of outside particles, trailed by engulfment by means of phagocytosis lastly absorption in lysosomal of macrophages. The bioavailability of against malignant growth medications to disease cells gives a backhanded impression of accomplishment pace of treatment. To accomplish this, we ought to decide the key factors that influence the bioavailability of medication in lungs, for example, watery solvency, disintegration rate, efflux of medications and medication leeway by alveolar macrophages. Table 1 layouts the variables associated with deciding the bioavailability of medications into tumor cells. Lung offers numerous advantages as a delivery route for non-invasive drugs especially for localized therapy, i.e. lung cancer and treatment of airway diseases such as asthma, cystic fibrosis and chronic obstructive pulmonary disease (COPD). Compared to other delivery methods such as oral or intravenous injection, it is envisaged that the bioavailability of drugs in lung could be The physiochemical properties of drugs play an important role in therapy index. For that, most anti-cancer drugs are poorly soluble in aqueous physiological condition at pH7.4. These include taxane-based drugs (paclitaxel and docetaxel) and camptothecin derivatives (9-nitrocamptothecin). The fundamental properties of anticancer drug such as log P and pKa values are important for designing the delivery methods as well as clearance from the lungs. According to Lipinski's rule, the solubility of anti-cancer drug would affect their permeability and potency of the cancer treatment.

The ability to design nanoparticles as personalized medicine is seductive and ideal for lung cancer therapies. Combinational approaches with intricate balance between targeting moieties and anti-cancer agents have been widely documented in recent years. In a nutshell, multicomponent nanoparticle systems are usually designed to encapsulate and stabilize poorly soluble anti-cancer agents while simultaneously anchored with specific targeting moiety on the surface to impart selective targeting at desired sites. However, the translation of nanoparticle-based drug delivery in lung cancer therapy specifically as inhalation medication to clinic is extremely challenging. Firstly, synthesizing nanoparticles designed with specific size distribution and ability to evade clearance as well as residing for sufficient time at targeted site has always been tricky and complicated. Poly(lactic-co-glycolic acid) (PLGA), a biocompatible and non-cytotoxic polymer, is the most commonly used either as carrier or excipient in drug delivery to achieve sustained release of drug. In a study by Tomoda and co-workers, nanoparticles-in-microparticles dry powder was prepared to ensure effective drug deposition into deep lung. For this PLGA nanoparticles loaded with anti-cancer drug (TAS-103) with average size diameter of approximately 200 nm were first synthesized as primary particle and subsequently spray-dried in the presence of trehalose as excipient . Higher aerosol performance coupled with sustained release profile was achieved for PLGA nanoparticles loaded with 5% of TAS-103. In comparison, the FPF value for spray-dried formulation was 14.35% while only 0.79% was found for primary TAS-103 loaded PLGA nanoparticles. Liposome is

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one the most successful nano-based drug delivery systems to date with several FDA-approved liposomal formulations in the market.

Biography :

Wing Hin Lee is an early career fellowship Researcher funded by Cancer Institute New South Wales and is based in Woolcock Institute of Medical Research. He has obtained his PhD in 2013 on the modulation of protein adsorption on calcium phosphate-based biomaterials. During his PhD, he collaborated with Ultraceuticals Ltd., in developing sunscreen for skin cancer prevention. He is highly interested in the treatment of cancer using nanotechnology approaches. Currently, he is actively devoting his efforts to develop potential lung cancer treatments via inhalation. He has published almost 40 peer reviewed articles and 1 book chapter. In addition, he serves as a Reviewer for several well-known international scientific journals in the field of cancer therapeutics and pharmaceutical sciences.

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