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Presentation Abstract

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Presentation Title:	Inhaled buformin for lymphangioleiomyomatosis and early (airway confined) lung cancer
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Abstract Body:	Pulmonary lymphangioleiomyomatosis (LAM) is a low grade neoplasm related to tuberous sclerosis (TSC) occurring in a sporadic form affecting only females, usually of childbearing age, with an incidence of less than one case per 100,000 population per year. LAM is associated with over-proliferation of bronchial smooth muscle, infiltration and cystic destruction of the lung. Clinically, LAM is characterized by progressive dyspnea on exertion, recurrent pneumothorax, abdominal and thoracic lymphadenopathy, and abdominal tumors. Oral sirolimus (rapamycin) has recently been reported to be an effective therapy that halts progression of LAM. Rapamycin works by inhibiting mTOR, the mammalian target of rapamycin, a serine/threonine protein kinase that regulates cell growth. mTOR integrates the input from upstream pathways, including insulin, growth factors (such as IGF-1 and IGF-2), and amino acids. mTOR also senses cellular nutrient and energy levels. The mTOR pathway is dysregulated in human diseases, especially cancers. Because LAM is predominantly a pulmonary neoplasm, an inhaled therapy, targeting only the lung, could be highly desirable. Rapamycin (sirolimus) cannot be safely inhaled because of its well-documented lung toxicity, interstitial pneumonitis. We propose to test an inhaled version of the biguanide anti-diabetic buformin for LAM. Biguanides also inhibit mTOR, but have no known lung toxicity after decades of use in millions of patients. Buformin would be used rather than metformin because buformin requires one eighth the inhaled dose of powder, and can be given in inhaled doses that may be one tenth or less of the toxic dose of buformin required to produce lactic acidosis, its principal side-effect. Buformin has an octanol/water partition coefficient (log P) of -1.2 and is hydrophilic. Hydrophilic small molecules with a log P less than 0 have a mean lung half life (t½) of about one hour. Long lung residence time of buformin could be increased even further with an appropriate formulation. Pulmonary buformin would likely be useful only for sporadic LAM, because TSC-LAM has been shown to represent clones of the smooth muscle in those patients' renal angiomyolipomas, believed to represent metastases of this "benign" tumor. Buformin has a known systemic safety profile, well established chemistry, manufacturing and control profile, an inexpensive supply with Drug Master Files on file, is non-toxic compared to the vast majority of anti-cancer agents, and readily administered by inhalation aerosol. Inhaled buformin, which is a radiation sensitizer, could also be used to treat early lung cancer detected on spiral CT lung cancer screening. Lung cancer screening will be covered by Medicare. There will be huge numbers of airway-confined lung cancers to treat. In addition, inhaled buformin could prevent lung cancer in heavy smokers.

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