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Therapeutic and diagnostic formulations for the treatment of skin and endoscopic accessible cancers

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Abstract

The hedgehog pathway has been shown to be a causative factor in basal cell carcinomas (BCCs). During mammalian development, the hedgehog pathway is responsible for embryonic patterning and hair follicle development, as well as cellular proliferation, growth, and invasion. Binding of the hedgehog ligand to PTCH1 disrupts its function, alleviating repression of SMO and allowing the production of GLI transcription factors, eventually resulting in the development of carcinomas. Two drugs that have been shown to successfully disrupt the hedgehog pathway and could be used in the treatment and prevention ofBCCs are itraconazole and arsenic trioxide. Itraconazole is a fungicide that has been shown to inhibit the hedgehog pathway at the level of SMO, whereas arsenic trioxide does so by specifically targeting GLI transcription factors. Kim et al. 2013 has shown that these drugs can be used in combination to inhibit the growth of BCCsand medulloblastomas in vivo. However, when used systemically these drugs can pose many health concerns. Itraconazole has been shown to interact adversely with bortezomib and terfenadine, leading to an increased risk of peripheral neuropathy and arrhythmia, respectively. Arsenic is a known carcinogen, and intravenous administration has been shown to lead to leukocytosis, nausea, vomiting, diarrhea, dyspnea, and other ill-effects. An effective treatment for BCCs would involve disruption of the hedgehog pathway while simultaneously avoiding these negative consequences. We have successfully formulated a delivery cream that is able to cross the stratum corneum of the skin and penetrate into cancerous tumors. Our results suggest the effectiveness ofitraconazole and arsenic trioxide creams at inhibiting the hedgehog pathway, thereby obstructing the growth of BCCs, while concurrently avoiding systemic toxicity.We have also developed novel fluorescence imaging agents that are formulated to targetcyclooxygenase-2 (COX-2), the enzyme highly expressed in premalignant and malignant tumors. Thus, a combination of these creams allows us to detect and disrupt cancerous growths in many parts of the body, whether it is on the skin or internally via the use of an endoscope.

Biography

Jayakumar Rajadas's research interests are in the development and application of biophysical techniques for drug formulation and delivery systems. He has been involved in synthesizing innovative therapeutic molecules and materials for regenerative medicine for over two decades. Dr. Rajadas is the founding director of the Biomaterials and Advanced Drug Delivery Laboratory at Stanford University. Before moving to Stanford, he served as the founding chair of the Bio-organic and Neurochemistry Division at one of India's national laboratories, Chennai, India.He is currently working with his research team to develop drug delivery devices and formulation for stem cell homing,tissue regeneration and anticancer therapeutics. He has authored over 144 peer-reviewed journal articles and has thirty patent disclosures filed. Five of the disclosures have resulted in commercial ventures. He has spent over twenty years developing small molecule pharmaceuticals and biomaterials, and is committed to designing novel technologies for clinical applications.