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TITLE

CNOB/ChrR A New Non-invasively Visualizable Therapeutic Regimen

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6-chloro-9-nitro-5-oxo-5H-benzo[a]phenoxazine (CNOB) is a fluorescent compound that is harmless both in vitro and in vivo. Upon reduction by the Escherichia coli enzyme, ChrR, it is converted to 9-Amino-6-chloro-5H-benzo(a)phenoxazine-5-one (MCHB). MCHB is highly cytotoxic. It binds mitochondrial DNA, causes an increase in cell surface Annexin V, caspase-3 and caspase-9 activities, and mitochondrial depolization, and kills by apoptosis initiated through the intrinsic mitochondrial pathway and cytochrome c release. This mechanism is effective against growing and non-growing cells, an advantage, since tumors contain a significant number of quiescent cells. MCHB has an efficient bystander effect and the regimen effectively treated implanted 4T1 breast tumors in immunocompetent BALB/c mice whose tumors expressed the chrR gene. While control mice injected with PBS were all dead within 25 days, 40% of the treated mice showed complete remission. IV-administered CNOB mainly accumulated in lung, liver, kidney and spleen, but MCHB accumulated mainly in tumors expressing the chrR gene. It shows a 3-compartment pharmacokinetic model and was retained in tumors at 10 ng/ml for over 10 h; no MCHB was detected in tumors not expressing the gene. The IV- administered CNOB is excreted via both feces and urine in the forms of CNOB, MCHB and as yet unidentified metabolites. A big advantage of the CNOB/ChrR regimen is that the prodrug and especially the cytotoxic moiety (MCHB) are fluorescent at a wavelength that can be visualized in living mice, permitting real time imaging. Indeed, the data referred to above were obtained by both imaging and LC/MS/MS and showed close correlation. This greatly facilitates development of methods of gene delivery and effective tumor penetration. We have recently crystallized the activating enzyme ChrR. It is a tetramer and possesses a typical a flavodoxin fold. Tyr128/Asn substitution greatly increases enzyme activity. Crystal structure suggests that this is due to a closer interaction between enzyme dimers and a widening of the cavity harboring FMN. The resulting improved enzyme will further enhance the effectiveness of this therapy.

Biography

A. C. Matin did his Ph.D. with distinction at UCLA. Following 4 years of senior lecturership at the State University of Groningen, The Netherlands, he joined Stanford University, where he is a full professor. He has contributed extensively to many areas of microbiology, including cancer chemotherapy and imaging. He is recipient of several awards, editor of several journals, and an elected fellow of American Academy of Microbiology and and Associate Fellow of Aerospace Medical Association.