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A 'switch' model for de-repression of translation of transfected RNA heteroduplexes in breast cancer cells

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The aim of this work was to construct a proof of principle model system to test a mechanism for inducing production of protein from externally introduced RNA as a novel means of inducing selective cell death dependent upon over-expression of endogenous genes. mWasabipIVT2.0 plasmid was modified to include 2 short tandem repeats of human estrogen receptor (ER) coding sequence followed by a Kozak initiation sequence, coding sequence of eGFP and 3' untranslated rabbit β globin polyadenylation signal sequences. An upstream 5' T7 promoter was utilised for *in vitro* transcription and capped, polyadenylated transcripts were translated in rabbit reticulocytes before and after hybridisation to short oligos complementary to the ER sequence to ensure that only un-hybridised RNA produced eGFP, detectable by western blotting. Anticipated production of the eGFP with un-hybridised but not with the hybridised duplex RNA (that should prevent ribosomal processing of the transcript) when transfected into ER negative MDA231 cells, was determined by eGFP fluorescence. Transfection of the pre-hybridized RNA into ER expressing MCF7 cells was expected to result in a competitive transfer of the ER oligos from the construct onto cellular ER mRNA permitting translation of the eGFP; preliminary experiments indeed showed partial switch on off expression from the RNA/ER duplex. Substitution of the eGFP with pertussis toxin sequence resulted in significant cell death 72h post-transfection in both MCF7 and MDA231 with un hybridised transcripts. Further experiments are needed to optimize dosing of hybridized transcripts to obtain a differential killing effect between ER expressing and non-expressing cells.

Biography

Yunus A Luqmani graduated from Chelsea College, University of London and obtained his PhD in Neurochemistry from Imperial College, followed by Postdoctoral research at Max Planck Institut fur Biophysikalische Chemie, Gottingen. After further appointments at various London institutes, including Queen Elizabeth College, Ludwig Institute for Cancer Research at Royal Marsden Hospital, St George's and Charing Cross Hospitals, he was appointed Associate Professor at Kuwait University in 1994 where he is currently Professor and Chairman, Dept. of Pharmaceutical Chemistry in the Faculty of Pharmacy. His research work focuses on identifying cellular processes that are implicated in resistance to endocrine therapy of breast cancer.

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