A precision medicine approach for nonsense mutations: study of novel small molecules for the rescue of p53 protein expression.

Emanuele Vitale[1], M. Menditto[1], D. Ricci[1], P. S. Carollo[1], I. Fiduccia[1], R. Varrica[1], I. Cruciata[1], R. Melfi[1], A. Pace[1], I. Pibiri[1], B. S. Cooperman[2], L. Lentini[1]

[1]Department of Biological, Chemical and Pharmaceutical Sciences and Technologies, University of Palermo, Palermo, Italy.
[2]Department of Chemistry, University of Pennsylvania, Philadelphia, USA.

Precision medicine represents a new insight in genetic medicine to treat the mutation profile of a patient. Currently, suppression therapy is focused on addressing nonsense mutation diseases for which no treatments are approved that stimulate readthrough. This approach uses translational readthrough-inducing drugs (TRIDs) against premature termination codons (PTCs) occurring in mRNA. Our studies center on understanding the mechanism of action (MoA) of the newly synthetized TRIDs NV848, NV914 and NV930, congeners of the TRID ataluren, which has conditional approval in Europe for treatment of Duchenne muscular dystrophy. For this purpose we determined NV TRID effects on readthrough in a human cancer cell line harboring the PTC mutant H1299-p53^{R213X}, and used the reconstituted *in vitro* model system PURE-LITE, which allows separate determination of TRID effects on both readthrough and termination activities. We find that all three NVs induce readthrough both in cancer cells and in PURE-LITE, but do so with MoAs different from that of ataluren. This work is part of our continuing effort to develop targeted cancer therapies to address nonsense mutations within tumor suppressor genes.