Induction of specific chromosomal rearrangements by targeting sensitive genomic loci using I-125-labeled Triplex-forming oligonucleotides

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Introduction:
DNA-Triplex-forming oligonucleotides (TFO) bind to the DNA double helix in a sequence specific manner (Fig. 1). The Auger electron emitter (AEE) I-125 ejects during decay on average 21 low energetic electrons leading to the deposition of large amounts of energy in a rather small volume. When located close to the DNA high-LET-type damage were observed (Fig. 2). I-125-labeled TFO were shown to induce sequence specific DNA double-strand breaks (DSB) in vitro and were chemically stable in a cellular environment (Fig. 3; Dahmen & Kriehuber, 2012).

In this study we investigated the effects of I-125-TFO-BCL2 targeting a sequence located within intron 2 at 5422 bp downstream of the BCL2 promoter on gene expression, translocation frequency and protein expression of the human BCL2 gene.

Results:
• The relative gene expression of BCL2 in I-125-TFO-BCL2 transfected cells showed a ~ 2-fold up-regulation when compared to the negative control and almost 7-fold in comparison to I-125-TFO-QRT transfected cells (Fig. 5).
• BCL2 t(14;18) translocation frequency was 1.8- to 2-fold increased (Fig. 7).
• No increase above control level could be detected on the protein level (Fig. 8).

Conclusions:
• I-125 decays within the BCL2 gene promote the occurrence of the t(14;18) chromosomal translocation in SCL-II cells.
• The increased translocation frequency of t(14;18) contributes to the observed overall enhanced BCL2 expression.