The probability of DNA breakage and consequently illegitimate ligation of these breaks, varies along the genome. This nonuniformity of genome vulnerability is tightly linked to chromatin structure and cellular processes, and hence differs among cell-types, pathologies and treatments, giving rise to a typical translocation landscape for a given cancer. Topoisomerase II (TOP2) has been implicated in translocations associated with childhood leukemia, etoposide (ETO)-induced secondary leukemias and androgen-induced prostate cancer. Through studying the repertoire of TOP2-mediated breakage and translocations, I will draw the path that starts from DNA lesions and ends in cancer transformation.