An assessment of the mutational load caused by various reactions used in DNA encoded libraries

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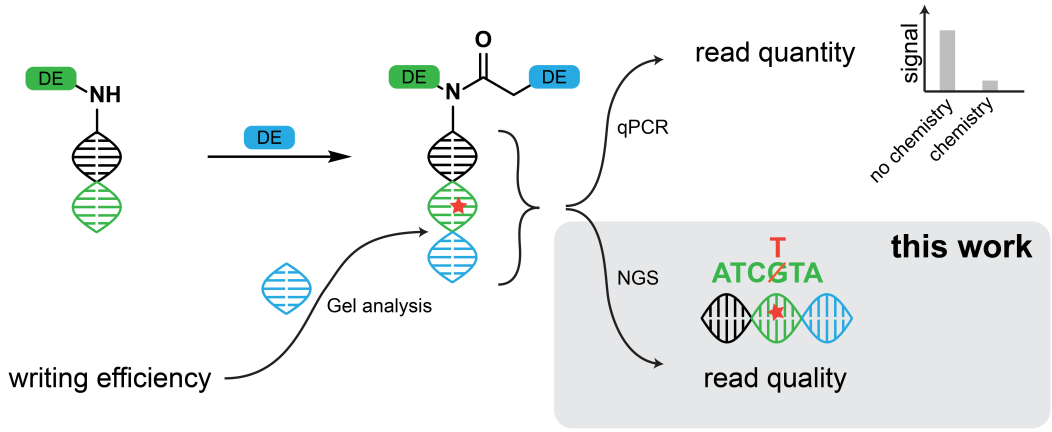
DNA encoded libraries have become an essential hit-finding tool in early drug discovery[1]. Recent advances in synthetic methods for DNA encoded libraries have expanded the accessible chemical space, and several techniques to measure library quality have been established. Quantitative PCR has been used to measure the amplifiability of the DNA and thus the quantity of intact DNA after a chemical reaction[2]. Moreover, the interference of DNA damage with writing efficiency has been studied by quantifying the DNA ligation yield[3]. However, both of these methods quantify only overall integrity, but do not report on specific damages in the encoded information. Sanger sequencing does[4], but is limited to strong answers and does not allow for precise quantification of the damage.



Herein, we use next generation sequencing (NGS) to measure the quality of the read signal in order to quantify the truthfulness of the retrieved information[5]. We identify CuAAC to be the worst offender in terms of DNA damage amongst commonly used reactions in DELs, causing an increase of G→T transversions. Furthermore, we show how this analysis can be used after library synthesis to reveal the full mutational load accumulated during library construction.

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