Background Intra-tumour heterogeneity (ITH) presents a significant obstacle in formulating effective treatment strategies in clinical practice. Single-cell RNA sequencing (scRNA-seq) has evolved as a powerful instrument for probing ITH at the transcriptional level, offering an unparalleled opportunity for therapeutic intervention. Results Drug response prediction at the single-cell level is an emerging field of research that aims to improve the efficacy and precision of cancer treatments. Here, we introduce DREEP (Drug Response Estimation from single-cell Expression Profiles), a computational method that leverages publicly available pharmacogenomic screens from GDSC2, CTRP2, and PRISM and functional enrichment analysis to predict single-cell drug sensitivity from transcriptomic data. We validated DREEP extensively in vitro using several independent single-cell datasets with over 200 cancer cell lines and showed its accuracy and robustness. Additionally, we also applied DREEP to molecularly barcoded breast cancer cells and identified drugs that can selectively target specific cell populations. Conclusions DREEP provides an in silico framework to prioritize drugs from single-cell transcriptional profiles of tumours and thus helps in designing personalized treatment strategies and accelerating drug repurposing studies. DREEP is available at https://github.com/gambalab/DREEP. Keywords Drug prediction, Single-cell transcriptomics, Precision oncology, Cancer