Therapies targeting mutated proteins hold much promise in the treatment of cancer, but the emergence of resistance to these therapies presents a major barrier to cures. Recent work, including some recent work from our lab in melanoma, shows that non-genetic cellular plasticity may provide a mechanism of resistance to these therapies. Furthermore, the addition of the drug itself converts this transient plasticity into a new, stably resistant cell state via cellular reprogramming. We further describe a genome-wide method of identifying high-memory rare-cell expression programs.