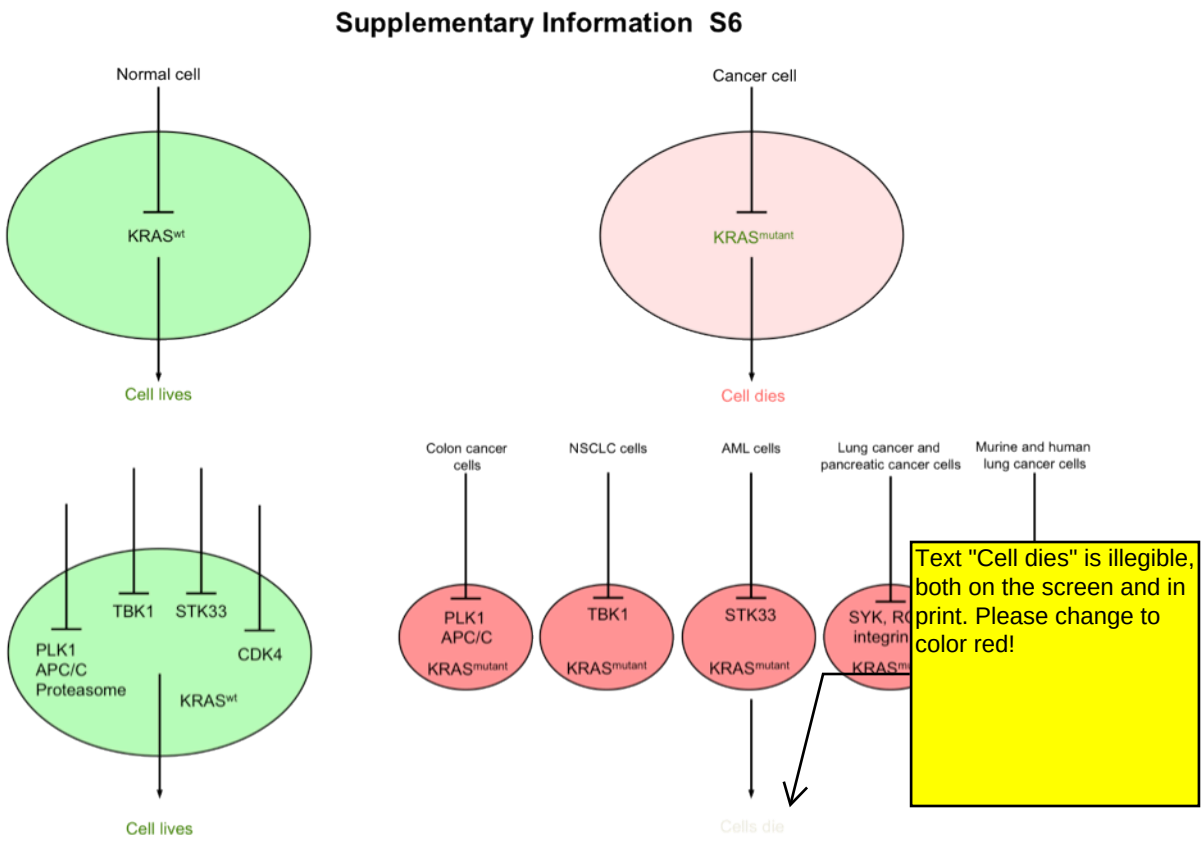

Supplementary Information S6 (Figure) | **Targeting KRAS-dependent tumours by exploiting synthetic lethality**. Many tumours are dependent on KRAS for survival. Eliminating KRAS function would, therefore, be predicted to specifically kill such cancer cells, but, given the lack of specific KRAS inhibitors, this is not a viable option at present. However, as several recent studies have shown, cancer cells harbouring mutant KRAS show other vulnerabilities that might be targeted with single agent therapies [1-6]. The question is why six studies identified at least five major and distinct targets whose knockdown specifically kills KRAS-dependent cancer cells. For instance, in DLD1 colon cancer cells expressing mutant KRAS, survivin or PLK1 was identified in screens using RNAi libraries targeting 4,000 [1] or 13,000 genes [4], respectively. However, in the genome-wide screen reported by the Elledge laboratory, the survivin gene had not been included [4]. Another simple but plausible explanation may be context dependence: Thus, TBK1 was found in human NSCLC cells [2], STK33 in human AML cells [3], Syk, RON and integrin β6 were found in lung and pancreatic cancer cells [5], and CDK4 was identified in lung cells from transgenic mice with KRAS-induced NSCLC [6]. It may also be possible that the RNAi screens failed to detect loss of CDK4 as a synthetic lethal event because

the CDK4 siRNAs were suboptimal. It should also be noted that a recent study could not confirm that STK33 is required for the survival of several KRAS-dependent cancer cell lines, suggesting that the earlier result described by Scholl *et. al.* [3] may have been due to different assay conditions or off-target effects of the STK33 shRNAs employed [7].

AML: acute myeloid leukaemia, APC/C: anaphase-promoting complex/cyclosome, CDK4: cyclin-dependent kinase 4, NSCLC: non-small cell lung cancer, PLK1: polo-like kinase 1, TBK1: TANK-binding kinase 1, STK33: Serine/threonine protein kinase 33.

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