ONCOTREAT Report Summary

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Mid-Term Report Summary - ONCOTREAT (Identification of Novel Targeted Therapies for Renal Cancer)

The two key aims of the project and related findings are:

1. to identify novel inherited RCC genes.

We have identified germline CDKN2B mutations in a subset of patients with features of inherited RCC and undertaken functional investigations of candidate somatic and germline CDKN2B mutations. These investigations have revealed that the results of in silico structural prediction tools correlate with the results of functional analysis such that the former might be used to determine the likely pathogenicity of germline and somatic CDKN2B variants.

Analysis of 94 inherited cancer predisposition genes in ~100 patients with features of inherited RCC without mutations in known RCC-predisposition genes has revealed rare candidate mutations in double strand break repair gene(s) in a subset of patients. Work is ongoing to validate this novel finding.

To identify additional novel causes of inherited RCC we have undertaken whole exome (n=77) and whole genome sequencing (n=41) in individuals with features of inherited RCC that is unexplained. Analysis is currently ongoing.

2. to generate and characterise human cell line models for inherited RCC genes and identify candidate therapeutic agents from human cell line models of inherited RCC genes

A panel of RCC cell lines (n=18) have been characterised to identify those containing mutations in 94 inherited cancer predisposition genes (to date mutations have been identified in VHL, TP53, BAP1, NF2, FANCM, PTEN). Four pairs of VHL defective and pVHL wild type resored RCC cell lines have been established and one paired CDKN2B deficient/expressing RCC cell line.

Two human proximal tubule-derived cell lines (HK-2 and HKC-8) have been characterized in various culture conditions and HKC-8 was found to be the more suitable for transfection and in vitro proliferation assays. Three human haploid knockout cell lines (HAP1 a leukaemia derived cell line) have been generated and knock-out of VHL, BAP1 and CDKN2B validated (knockouts for SDHB and FH were non-viable).

Investigations of targeted approaches to the treatment of VHL-deficient RCC cell lines are in progress. A short interfering RNA (siRNA) library was used to interrogate 710 human kinase genes (with 2130 unique siRNAs) in paired pVHL deficient/expressing isogenic RCC cell lines and, from the initial screen, 16 candidate synthetic lethality targets were then further evaluated. After further analysis five targets were then selected for ongoing analysis in four paired VHL-null/restored isogenic RCC cell lines. In parallel, studies of selective siRNA targeting of WAVE regulatory complex components are in progress in paired VHL-null/restored isogenic RCC cell lines.

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