Project title: Developing transcription inhibitors as a new class of cancer therapeutics.

Project Summary: Deregulation of gene expression programs is now known to be a common feature of most cancers. Indeed, transcription factors (TF) that control high level expression of the genes that drive tumour growth and metastasis are frequently mutated. For example, the most commonly amplified gene across cancer types, the MYC oncogene, is a TF. Other TFs are critical drivers in specific tumour types, best exemplified by high-level expression and transcriptional importance of the etrogen receptor (ER) in the majority of BC. ER action only infrequently involves ER gene mutations/rearrangements in primary BC, but activating mutations, amplification and rearrangements are common in acquired ET resistance. Another example is the androgen receptor (AR), which drives prostate cancer development and progression; and again AR gene rearrangements/mutations are common in prostate cancer. This dependency has been termed cancer transcriptional addiction.

Transcriptional addiction in so many cancer types, including the most common cancers in women and men, on transcriptional signalling led us to hypothesise some years ago that inhibiting cancer gene expression by targeting transcriptional processes could provide a new class of cancer drugs. We focussed on targeting RNA polymerase II (PolII), the enzyme required for expression of all protein coding genes. Progression through different stages, transcription initiation, elongation, termination and PolII recycling to initiation are controlled by modification of PolII sequentially by a series of cyclin-dependent kinases, CDK7, CDK9, CDK12/13 and CDK8/19. This transcription cycle is remarkably reminiscent of the sequential role of other CDKs in cell cycle progression through G1, S, G2/M, back to G1.

We are investigating the potential for specific drug-like inhibitors of CDK7, CDK9 and CDK12/13 as cancer therapeutics focussing on hormone-dependent cancers (breast, prostate). As proof-of-concept, we designed and published the first-in-class selective CDK7 inhibitors. These showed strong activity in vitro and in vivo and we have just published the results including demonstration of efficacy in a Phase 1 expansion cohort for ER+ and triple-negative breast cancer (PMID: 37488191). Phase 2 clinical trials for ER+ BC, TNBC have been initiated, following granting of FDA fast-track designation for these two diseases.

Our current efforts are in improving understanding of the mechanisms of action of our CDK7 inhibitor, towards improving patient selection and identifying appropriate combination strategies for breast, prostate and ovarian cancer. We have also obtained selective CDK9 and CDK12 inhibitors and are investigating their models of action and clinical utility. We are especially interested in CDK12 because it is frequently amplified/mutated in breast and other cancer types. Our studies are being conducted through collaboration with Carrick Therapeutics who licensed our CDK

inhibitor program and have been able to progress the CDK7 inhibitor through to phase 2, with the CDK12 inhibitor (CT7439) recently receiving FDA clearance for phase 1.

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Clinical Specialities: N/A