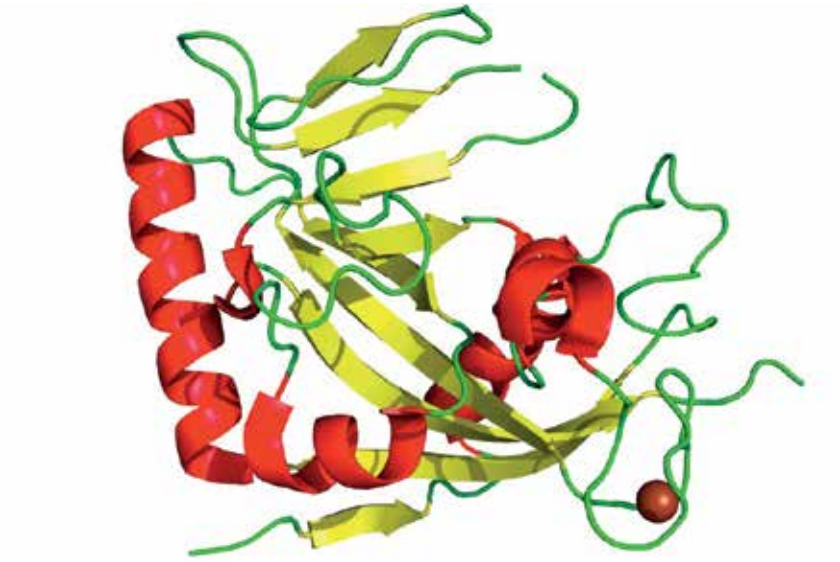
Novel tankyrase inhibitors for cancer therapy



Opportunity

One of the most promising advances in drug development in recent years has been the development of small-molecule inhibitors of the poly (ADP-ribose) polymerase (PARP) enzyme superfamily. Already PARP1/2 inhibitors have entered oncology clinical trials and are showing promise in the treatment of *BRCA1/2* mutant cancers. More recently, the potential for targeting an additional PARP enzyme, tankyrase 1 (TNKS1), has been proposed, not only in the oncology setting but also for the treatment of pathologies as diverse as neurodegenerative diseases and lung fibrosis.

Building upon their work identifying PARP1/2 inhibitors as a synthetic lethal treatment for cancer, Ashworth and colleagues at the Institute of Cancer Research (ICR), London, have now designed nanomolar IC_{50}, drug-like small molecule tankyrase (TNKS) inhibitors. These inhibitors offer the opportunity to target two of the most common characteristics of tumour cells – the dependency upon telomere maintenance and Wnt dependency. The recent demonstration that TNKS inhibitors can modulate cellular phenotypes associated with cardiac repair, pulmonary fibrosis and neurodegenerative disease suggests that TNKS inhibitors could also have a much wider application outside of the oncology setting.

Unmet need

Approximately 1.5 million new cases of colorectal cancer (CRC) are diagnosed each year. Survival rates in CRC are relatively poor (five-year survival < 56%), despite the identification of many of the genetic factors that drive this disease. For example, over 90% of colorectal tumours are predicted to carry DNA mutations that drive tumour-specific constitutive Wnt signalling (such as those in the *APC* gene). Although constitutive Wnt signalling is one of the more predominant characteristics of CRC, efforts to identify viable targets that inhibit this pathway have, until recently, proved difficult. The demonstration in 2009 that small-molecule tankyrase inhibitors can restrict Wnt signalling and inhibit colorectal tumour cells has proved to be one of the more promising findings in this area and demonstrates that drug-like tankyrase inhibitors could have significant potential in this area of unmet need.

Project information is provided overleaf.

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Image: Catalytic domain of tankyrase 1. See Lehtiö et al. J Mol Biol 2008;379:136–45.

Profile of preclinical candidates

Preclinical candidates developed by the ICR team are potent (nanomolar) inhibitors of tankyrase with the following characteristics:

Potency and selectivity
- Low nM activity against tankyrase in cell-free and cell-based assays.
- Low nM IC50 suppression of Wnt signalling (Figure 1).
- Significant selectivity versus the homologous enzymes PARP1 and PARP2.

DMPK
- Good solubility (≈ 1.4mM).
- Optimal lipophilicity (logD ≈ 1.6).
- Good oral bioavailability (%F ≈ 66) with long plasma half-lives (> 1 hr) *in vivo*.
- Low mouse and human *in vitro* metabolism.

Safety and toxicity
- Do not inhibit hERG.
- No cytotoxicity to normal cells.

In vivo efficacy
The preclinical candidates exhibit good oral bioavailability and inhibit tumour growth in APC mutant colorectal xenograft models (figure 2).

Intellectual property

There is a robust patent portfolio protecting the lead series and surrounding chemical space, with both composition of matter and medical use claims to the key compounds.

Originating laboratory

The research programme originates from the laboratory of Professor Alan Ashworth FRS and Dr Chris Lord at the ICR. This laboratory has a proven track record in moving candidate targets from the bench into the clinic. Most notably, Ashworth and Lord identified the synthetic lethality between PARP inhibitors and BRCA dysfunction, moving PARPi outside from their intended role as chemo/radio sensitisers into a role as a single agent targeted therapy. Ashworth and Lord have developed the preclinical candidates in collaboration with Professor Caroline Springer (ICR) and Professor Laurence Pearl FRS (University of Sussex).

The ICR together with its partner organisation Royal Marsden Hospital NHS Foundation Trust form the largest comprehensive cancer centre in Europe and one of the largest in the world. As Ashworth and colleagues have shown, the team is well placed to work with the ICR Clinical Trials Unit to write the first clinical trial protocol and conduct the first-in-man trial of a tankyrase 1 inhibitor.

Figure 1
Suppression of Wnt signalling in a colorectal tumour cell line system. Performance of an ICR tankyrase inhibitor ('test compound') is compared to the PARP1/2 inhibitor olaparib.

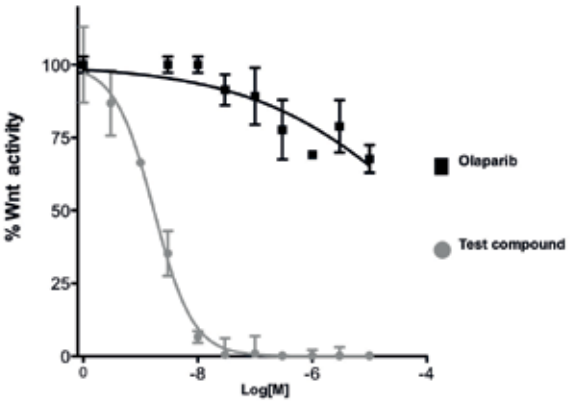
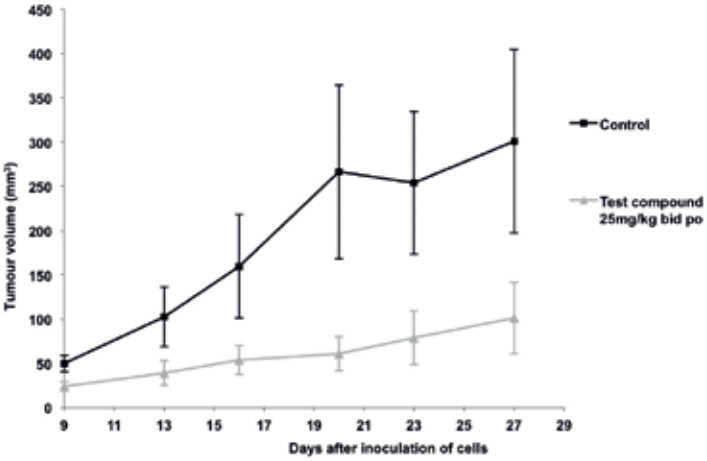


Figure 2
Oral therapeutic efficacy of an ICR tankyrase inhibitor candidate compound ('test compound') on an APC mutant human CRC tumour xenograft.



Commercial partnership

The Wellcome Trust is seeking a commercial partner on this exciting programme to undertake commercial development and bring a product to the clinic.

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