

# CRT Licensing Opportunity



## Small Molecule Inhibitors of Telomerase Expression

- Potent and selective lead compounds targeting telomerase expression identified
- Drug-like molecules with excellent *in vitro* ADME properties
- Compounds inhibit emerging novel targets modulating telomerase activity

SMALL MOLECULES | Lead Optimisation

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## Commercial Opportunity

A cellular screen has identified potent (< 100 nM) inhibitors of telomerase expression, which bind to novel targets in this pathway. CRT is seeking a commercial collaboration to progress the compounds with the view to offer an option for the exclusive licensing of these telomerase inhibitors.

## Therapeutic Rationale

The end of linear chromosomes is formed by a special heterochromatic structure, known as the telomere. During cell cycle division telomeres shorten as a result of incomplete replication of DNA molecules by conventional DNA polymerases, a process known as telomere shortening which ultimately leads to senescence or apoptosis. Excessive telomere shortening can also trigger a DNA damage response at the chromosome ends, which are recognized as double strand breaks. Telomerase compensates for telomere shortening by synthesising telomeric DNA at chromosome ends. In human cells, the enzyme complex functions by the *de novo* addition of TTAGGG repeats by the reverse transcriptase catalytic subunit (hTERT) using an integral RNA component (hTR) as a template for synthesis.

Dysfunctional telomeres can be a source of genomic instability in highly proliferating pre-cancerous cells and can lead to cancer depending on the integrity of the cell's DNA damage response (1).

Telomerase is encoded by a non-redundant gene and its expression is found in germline cells, but not in normal human somatic tissues. In cancer, one of the important tumour escape mechanisms is reactivation of telomerase expression

via signal transduction pathways to circumvent cell mortality. Telomerase is expressed in > 85% of tumours from all types of cancer and its reactivation is thought to stabilise telomere length, compensating for telomere erosion and hence preventing senescence and apoptosis whilst providing unlimited proliferative capacity to malignant cells (2, 3).

Inhibition of telomerase in tumour cells is an attractive anticancer therapy which should disrupt telomere maintenance in malignant cells leading them to proliferative crisis followed by senescence or cell death. Hanahan and Weinberg have recently identified inhibition of telomerase as one of the key therapeutic points to address one of the so called "hallmarks of cancer" (Figure 1) (4).

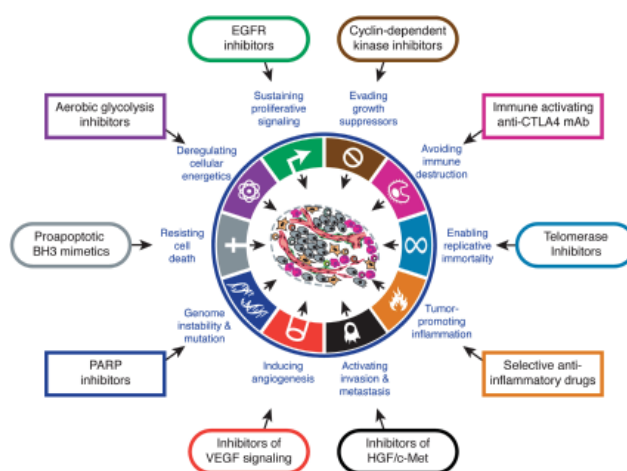


Figure 1: Therapeutic targeting of the hallmarks of cancer. Reproduced from reference (4)

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## Cellular Screen for Inhibitors of hTR and hTERT Promoter Activity

Understanding telomerase gene regulation has formed the focus of this therapeutic development program. Reporter gene assays for the hTR and hTERT promoters have been established in multiple cancer cell lines. Proof of concept studies have validated the applicability of these cell based assays to identify novel small molecule inhibitors of endogenous telomerase expression and activity (5).

A cell based high throughput screen of a diverse library of drug-like small molecules using transfected luciferase as a reporter of hTR promoter activity in an ovarian carcinoma cell line was used to identify a novel series of compounds with potent and specific cellular activity. These hits have been validated in a range of further cancer cell lines transfected with the hTR and hTERT reporter constructs indicating that the targeted pathway is conserved in cells of diverse origin including bladder, colorectal, cervical and lung.

## Potent Inhibitors of Telomerase Expression

Representative lead compounds have cell based  $IC_{50}$ s below 100nM in both promoter assays and have been shown to inhibit the expression of endogenous hTERT in a colorectal carcinoma cell line (Figure 2). Limited structure based drug design has been applied in the identification of new analogues with increased potency in cell assays. Use of surface plasmon resonance indicates that the lead series demonstrates reversible binding with fast  $K_{on}$  and  $K_{off}$  rates.

Preliminary analysis demonstrates that the compounds show good physicochemical properties, with no major liabilities identified.

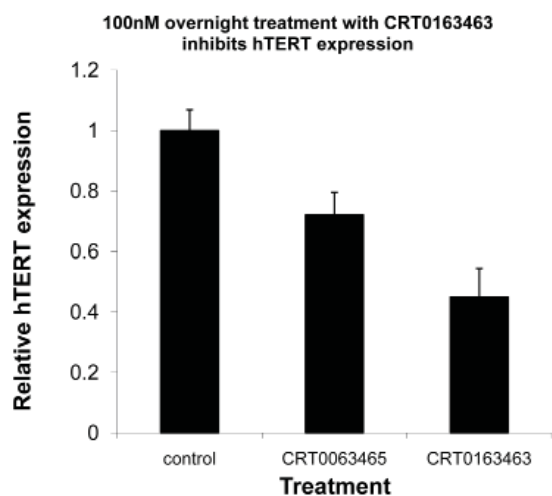


Figure 2: Inhibition of endogenous hTERT expression by overnight treatment with 100nM of compound.

## Molecular Target Deconvolution

Using over expression and siRNA screens, putative targets were independently identified as modulators of hTR and/or hTERT promoter activity, with the molecular targets of the lead compounds being identified via a photoaffinity approach and confirmed through co-crystallography. The directional SAR apparent in the cell based reporter assay can be rationalised by the bound ligand conformation and modelling studies have identified a potential mode of action for the compound.

## Originating Institute and Academic Collaborators

The programme originates from research in the laboratory of Professor Nicol Keith based at the Institute of Cancer Sciences, University of Glasgow and is a collaborative discovery programme with Cancer Research Technology's Discovery Laboratories (CRTDL). Both partners bring extensive experience and expertise in the biology and drug discovery.

## Cancer Research Technology Ltd

CRT is an oncology-focussed development and commercialisation company. Identification of small molecule inhibitors of telomerase expression is one of a robust pipeline of projects currently underway in CRTDL. CRTDL bridges the gap between academia and industry by working in collaboration with the originating academic laboratories and enabling their discoveries to be turned into projects that are readily recognisable and valued by the pharmaceutical industry.

## References

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