OGG1 Inhibition as a Novel Anti-Cancer Strategy

Bishoy M. F. Hanna[1], Torkild Visnes[1,2], Carlos Benítez-Buelga[1], Armando Cázares-Körner[1], Kumar Sanjiv[1], Oliver Mortusewicz[1], Geoffrey Masuyer[3,4], Olov Wallner[1], Maurice Michel[1], Olga Loseva[1], Ann-Sofie Jemth[1], Christina Kalderén[1], Pål Stenmark[3,5], Ulrika Warpman Berglund[1], Thomas Helleday[1,6]

[1] Science for Life Laboratory, Department of Oncology-Pathology, Karolinska Institutet, S-171 21 Stockholm, Sweden, [2] Department of Biotechnology and Nanomedicine, SINTEF Industry, N-7465 Trondheim, Norway, [3] Department of Biochemistry and Biophysics, Stockholm University, S-106 91 Stockholm, Sweden, [4] Centre for Therapeutic Innovation, Department of Pharmacy and Pharmacology, University of Bath, Bath BA2 7AY, UK, [5] Department of Experimental Medical Science, Lund University, SE-221 00 Lund, Sweden, [6] Weston Park Cancer Centre, Department of Oncology and Metabolism, University of Sheffield, Sheffield S10 2RX, UK

Background

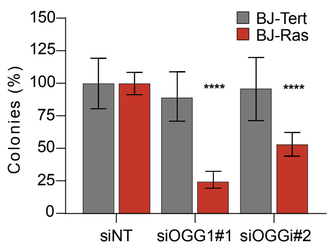
Due to oncogene expression and altered metabolism, reactive oxygen species (ROS) production is augmented in cancer cells resulting in oxidative DNA damage. 8 oxoguanine (8-oxoG) is one of the most abundant oxidative DNA lesions. This premutagenic lesion is eliminated from duplex DNA by 8-Oxoguanine DNA Glycosylase (OGG1), a key player in the base excision repair (BER) pathway. Here, we validate OGG1 as a potential anti-cancer target. OGG1 depletion impairs the growth of A3 T-cell lymphoblastic acute leukemia both *in vitro* and *in vivo*, but is well tolerated in non-transformed immortalized cells[1]. To further validate our findings, we developed TH5487, a potent small-molecule inhibitor that targets OGG1's active site[1,2]. We show that TH5487 suppresses the growth of a wide range of tumor cells, with a favorable therapeutic index compared to non-transformed cells[1]. Mechanistically, TH5487 treatment inhibits the repair of potassium bromate-induced 8-oxo(d)G lesions, affects OGG1-chromatin dynamics, and hinders OGG1 recruitment to DNA damage regions[3]. Importantly, TH5487 induces replication stress and proliferation arrest[1]. This study presents a novel mechanistic strategy to exploit ROS elevation in cancer by inhibiting OGG1.

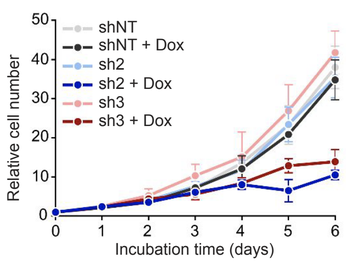
Aims

1. Evaluating OGG1 as a potential anti-cancer target
2. Studying target engagement of TH5487, an in-house developed OGG1 inhibitor
3. Characterization of TH5487 in terms of its effect on OGG1 glycosylase activity, OGG1-chromatin binding and OGG1 recruitment kinetics
4. Examining the consequences of targeting OGG1 on replication fork dynamics and cell proiferation

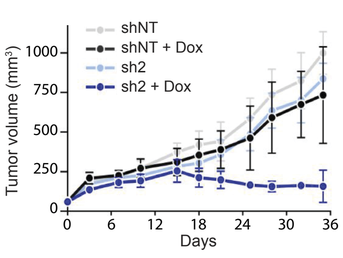
A OGG1 knockdown (KD) suppresses clonogenic ability and reduces tumor growth *in vivo*[1]

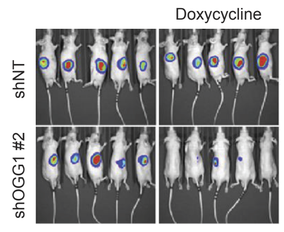
in vitro KD





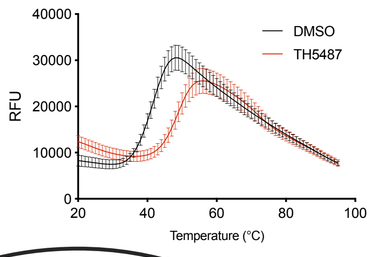
in vivo KD



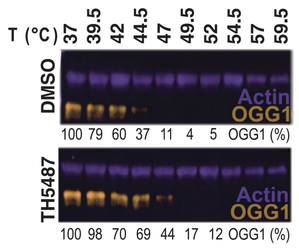


B TH5487 engages with OGG1 targeting its active site[1,2]

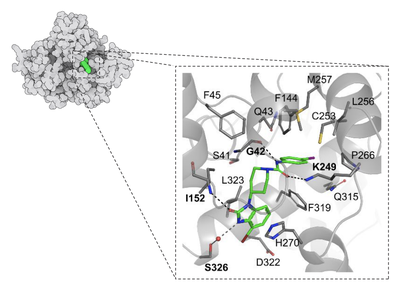
Differential Scanning Fluorimetry

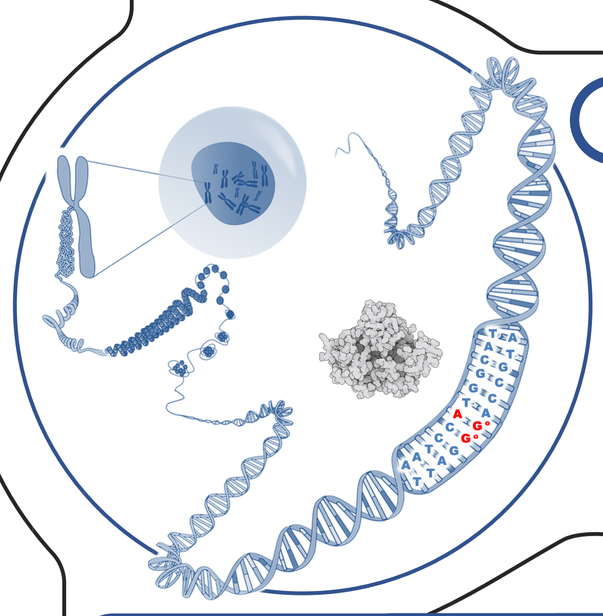


Cellular Thermal Shift Assay

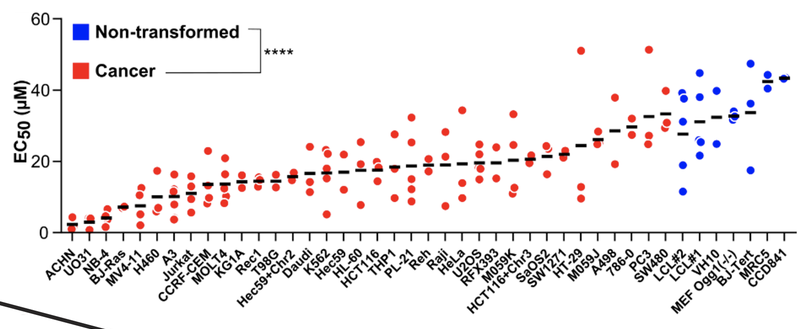


X-ray Crystallography



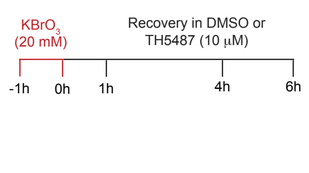


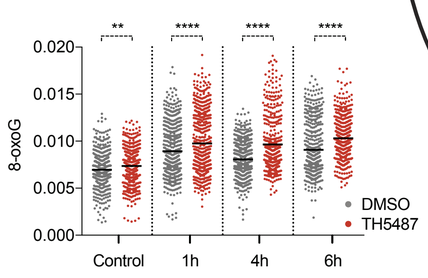
C TH5487 is selectively toxic to cancer cells[1]



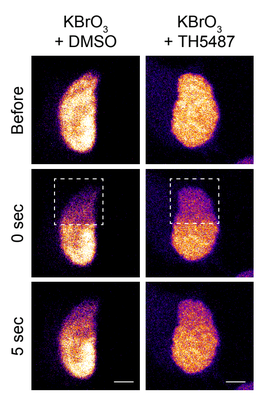
D TH5487 inhibits the repair of 8-oxo(d)G, alters OGG1 chromatin dynamics and OGG1 recruitment kinetics[3]

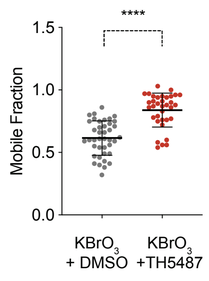
Immuno-staining of 8-oxoG

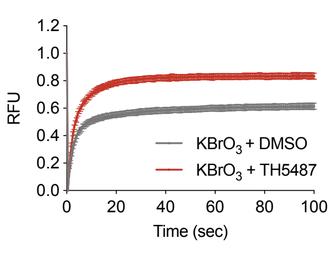




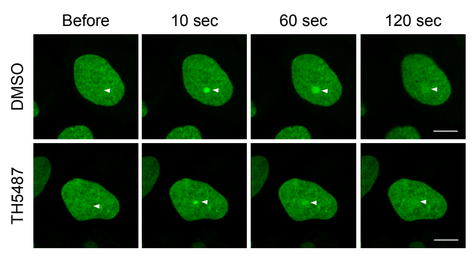
FRAP assay to study OGG1-chromatin binding

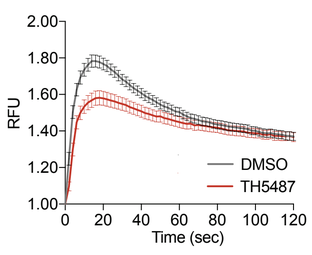






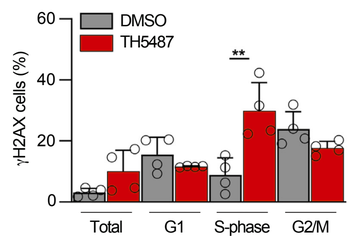
OGG1 recruitment to laser-induced DNA damage regions



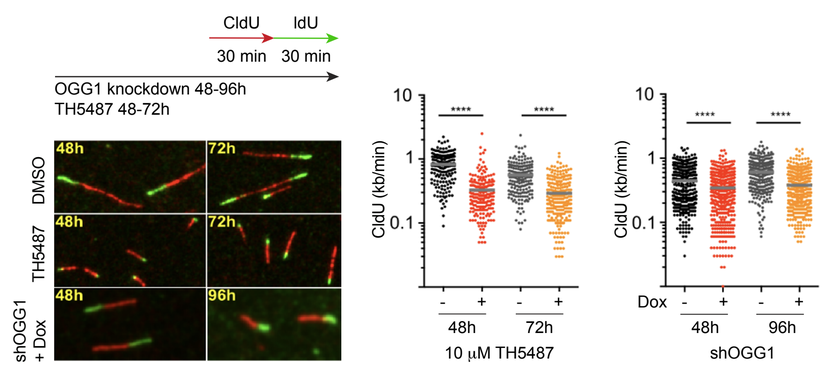


E TH5487 induces DNA damage during the S-phase of cell cycle and reduces replication fork speed[1]

Relative γH2AX distribution after TH5487 treatment for 72 h



DNA fiber assay following OGG1 inhibition or depletion



Conclusions

- **A** OGG1 depletion obstructs A3 T-cell lymphoblastic acute leukemia growth *in vitro* and *in vivo*, validating OGG1 as a potential anti-cancer target[1].
- **B** TH5487 is an active site inhibitor of OGG1[1,2].
- **C** TH5487 is well-tolerated by non-transformed cells, but induces proliferation arrest in oncogene-expressing cells[1].
- **D** TH5487 impairs the recruitment and binding of OGG1 to damaged chromatin inhibiting the repair of 8-oxoG[3].
- **E** OGG1 inhibition induces γH2AX accummulation in S-phase cells and reduces replication fork speed[1].

References

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Bishoy M. F. Hanna
bishoy.hanna@ki.se
Department of Oncology-Pathology
Karolinska Institute
Stockholm, Sweden

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