
Proceedings Paper:
Walter, M. orcid.org/0000-0003-3241-522X, Homan, E., Koolmeister, T. et al. (3 more authors) (2021) Development of small molecule NUDT22 inhibitors for uses in cancer. In: Medical Sciences Forum. IECC 2021: 1st International Electronic Conference on Cancers, 01-14 Feb 2021, Online. MDPI .

https://doi.org/10.3390/iecc2021-09197

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medical sciences forum

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Extended Abstract

Development of Small Molecule NUDT22 Inhibitors for Uses in Cancer †

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† Presented at the 1st International Electronic Conference on Cancers: Exploiting Cancer Vulnerability by Targeting the DNA Damage Response, 1–14 February 2021; Available online: https://iecc2021.sciforum.net/.

Keywords: NUDIX protein family; pyrimidine salvage pathway; DNA replication stress; first-in-class inhibitors

Here, we present the characterisation of the so-far-unstudied NUDIX hydrolase family member NUDT22. We previously identified the unique hydrolase activity of NUDT22 towards UDP-glucose from a family-wide biochemical substrate screen. UDP-glucose hydrolysis was found to result in the production of uridine monophosphate (UMP) and glucose 1-phosphate (G-1-P). We furthermore solved the first crystal structure of NUDT22 in complex with its substrate UDP-glucose [1]. Our mechanistic studies revealed increased replication stress in *NUDT22*-deficient cells that could be rescued by nucleoside supplementation. We therefore propose the discovery of a novel NUDT22-mediated pyrimidine salvage pathway. Increased replication rates resulting in replication stress is a hallmark of cancer cells, and *NUDT22* gene expression alterations are present in several cancer tissues, which makes NUDT22 an interesting new target for the development of small molecule inhibitors for uses in cancer. We employed our NUDT22 crystal structure to perform an *in silico* docking screen on available small molecule libraries to identify starting points for the development of first-in-class NUDT22 inhibitors. Chemically optimised NUDT22 inhibitors are currently being validated in biochemical assays and cellular target engagement assays, and their cellular activity is being assessed in vitro.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/IECC2021-09197/s1.

Reference

1. Carter, M.; Jemth, A.S.; Carreras-Puigvert, J.; Herr, P.; Carranza, M.M.; Vallin, K.S.; Throup, A.; Helleday, T.; Stenmark, P. Human NUDT22 Is a UDP-Glucose/Galactose Hydrolase Exhibiting a Unique Structural Fold. *Structure* **2018**, *26*, 295–303. [CrossRef] [PubMed]

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Citation: Walter, M.; Homan, E.; Koolmeister, T.; Almlöf, I.; Mortusewicz, O.; Helleday, T.; Herr, P. Development of Small Molecule NUDT22 Inhibitors for Uses in Cancer. *Med. Sci. Forum* **2021**, *3*, 1. https://doi.org/10.3390/IECC2021-09197

Academic Editors: Nicola Curtin and Helen E. Bryant

Published: 29 January 2021

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