NEWS RELEASE

Identification of Dasatinib as a potential combination therapy for AZD6738 in ovarian cancer

- *Potential of ABL1 kinase inhibitor to address ATR inhibitor (AZD6738) resistance*
- *Rapid identification in silico using proprietary ALaSCA approach*

London, November 06, 2023 - Incubate Bio has applied its proprietary approach to identify dasatinib as a potential combination therapy with AstraZeneca's AZD6738 ATR inhibitor [1]. ATR inhibitors show variable efficacy in ovarian cancer due to genetic differences observed in the cell lines, limiting their use to so-called ATRi-sensitive ovarian cancer.

Applying ALaSCA in silico, the team at Incubate Bio investigated AstraZeneca's AZD6738 ATR inhibitor [2] to identify potential combination therapies from DNA Damage Repair (DDR) pathways that will allow their use in both ATR inhibitor sensitive and non-sensitive ovarian cancers. AZD6738's IC50 values were used as a measure of sensitivity across ovarian cancer cell lines and transcriptomic data were used to represent the DDR pathways in the cell lines.

ABL1 pathways were identified that contribute to innate ATRi resistance across ovarian cancer cell lines - specifically through affecting ATRs IC50 through the E2F3 downstream pathway. Bristol-Myers Squibb's ABL1 inhibitor - dasatinib [3] – was identified as a potential combination therapy to allow ATRi use in all ovarian cancer. Dasatinib has the potential to be used either as a sensitizing agent in the case of ATRi sensitive ovarian cancer or to overcome innate resistance in non-sensitive ovarian cancer.

The ABL1 gene was identified as having the strongest effect on AZD6738 sensitivity in Ovarian cancer. The top causal paths through which ABL1 exerts its effect on drug sensitivity is shown in the table below:

Gene	Pathway	Total Causal effect	Approved drug	Clinical trial	# Patent
ABL1	G1S, HR, G2M	52.46	4	5	19
TFDP1	G1S	16.09	0	0	0
ATM	G1S, HR, G2M	12.06	0	3	0

Table 1: ABL1 is predicted to have the strongest effect on AZD6738 sensitivity in Ovarian cancer through its E2F3 downstream pathway.

Further research identified that a decrease in ABL1 expression improves the sensitivity to AZD6738 in a sensitive (Hey) and less sensitive (OV7) ovarian cancer cell line by decreasing their IC50 values in a simulated intervention [4].

Golovine *et al*., (2023) corroborate ABL1 as a potential combination therapy target for ATR inhibitors [5]. They show that ABL1 kinase inhibitors enhance sensitivity to ATR inhibitors in leukemia models, possibly by inhibiting the phosphorylation of the downstream targets of ATR, CHK1 and CHK2, reducing the expression of certain DNA repair proteins, and inducing apoptosis in cells which are already stressed by ATR inhibition.

A link between the ABL1 gene and drug sensitivity is indicated by dasatinib's primary targeting of the kinase activity of ABL1 and inhibition of its function. By targeting ABL1, dasatinib has the potential to disrupt the signaling pathways involved in cancer cell growth and survival.

In the context of DNA damage repair (DDR), the sensitivity of ABL1-deficient cells to DNA-damaging agents, such as ionizing radiation and chemotherapeutic drugs, has been observed in both in vitro and in vivo studies. However, the specific sensitivity of ABL1-deficient cells to drugs targeting ABL1 itself (e.g., dasatinib) in the context of the DDR is not well-documented. Further research is needed to explore the potential synergistic effects of ABL1 inhibition and DNA-damaging agents such as ATRi in the treatment of cancer.

"*Biology is complex and any approach that enhances the understanding of disease pathways and crucial targets is incredibly valuable in identifying potential new combination therapies to address issues like treatment resistance in certain sub-populations,*" **commented Dr Raminderpal Singh, CEO of Incubate Bio**.

We are excited by the potential of our novel methodology for not only deepening our understanding of the biological landscape around a target of interest or disease pathway, but also its ability to identify biological data cost-effectively and rapidly for promising therapeutic assets."

To access ALaSCA and to find out more detailed information, please see https://www.incubate.bio/

[1] https://openinnovation.astrazeneca.com/preclinical-research/preclinical-molecules/azd6738.html

[2] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9367423/

[3] https://en.wikipedia.org/wiki/Dasatinib

[4] http://incubate.bio/ovarianddr

[5] Golovine *et al.*, Blood Cancer Journal, 2023: https://www.nature.com/articles/s41408-023-00810-0

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