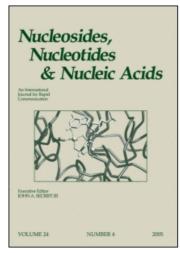
This article was downloaded by:

On: 27 January 2011

Access details: Access Details: Free Access

Publisher *Taylor & Francis*

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information: http://www.informaworld.com/smpp/title~content=t713597286

Thymidylate Synthetase-Positive and -Negative Mouse Mammary Carcinoma Cell Lines: Useful Model for Monitoring the Incorporation of Pyrimidine Nucleoside Analogues into Host Cell DNA and for Detecting Thymidylate Synthetase Inhibitors

J. Balzarini^a; E. De Clercq^b; D. Ayusawa^b; T. Seno^b

^a Department of Immunology and Virology, Saitama Cancer Center Research Institute, Japan ^b Rega Institute, Katholieke Universiteit Leuven, Leuven, Belgium

To cite this Article Balzarini, J. , De Clercq, E. , Ayusawa, D. and Seno, T.(1985) 'Thymidylate Synthetase-Positive and - Negative Mouse Mammary Carcinoma Cell Lines: Useful Model for Monitoring the Incorporation of Pyrimidine Nucleoside Analogues into Host Cell DNA and for Detecting Thymidylate Synthetase Inhibitors', Nucleosides, Nucleotides and Nucleic Acids, 4: 1, 283

To link to this Article: DOI: 10.1080/07328318508077890 URL: http://dx.doi.org/10.1080/07328318508077890

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.informaworld.com/terms-and-conditions-of-access.pdf

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

THYMIDYLATE SYNTHETASE-POSITIVE AND -NEGATIVE MOUSE MAMMARY CARCINOMA CELL LINES: USEFUL MODEL FOR MONITORING THE INCORPORATION OF PYRIMIDINE NUCLEOSIDE ANALOGUES INTO HOST CELL DNA AND FOR DETECTING THYMIDYLATE SYNTHETASE INHIBITORS

J. Balzarini^{*}, E. De Clercq, D. Ayusawa and T. Seno Rega Institute, Katholieke Universiteit Leuven, B-3000 Leuven, Belgium and Department of Immunology and Virology, Saitama Cancer Center Research Institute, Ina-machi, Saitama-ken 362, Japan.

<u>Summary</u> - The dTMP synthetase-positive and -negative murine mammary FM3A carcinoma cell lines can be proposed as a useful system for identifying specific dTMP synthetase inhibitors, and for measuring the incorporation of pyrimidine nucleoside analogues into host cell DNA.

The combined use of the thymidylate (dTMP) synthetase-negative mutant cell line (FM3A/TS $^-$) and its dTMP synthetase-positive parental cell line (FM3A/0) permits the detection of dTMP synthetase inhibitors. This approach is based upon the reasoning that compounds which exert their cytotoxic effects by inhibiting the activity of dTMP synthetase, are significantly less inhibitory for the mutant than for the parental cell line. This has been demonstrated for a series of established dTMP synthetase inhibitors, i.e. 5-fluoro-dUrd, 5-trifluoromethyl-dUrd, 5-ethynyl-dUrd, 5-nitro-dUrd, 5-formyl-dUrd as well as for methotrexate and 5-fluoro-uracil. Other dUrd analogues, which do not act as specific inhibitors of dTMP synthetase, i.e. (\underline{E}) -5-(2-bromovinyl)-dUrd, 5-ethyl-dUrd, 5-hydroxymethyl-dUrd, are equally inhibitory to the growth of both cell lines.

The FM3A/TS cell line, which is auxotrophic for dThd, has also proven useful for investigating the incorporation of various 5-substituted dUrd, dCyd, $1-\beta-D$ -arabinofuranosyluracil (araU) and $1-\beta-D$ -arabinofuranosylcytosine (araC) analogues into host cell DNA. We have demonstrated that several dUrd analogues, substituted at C-5 with an halogen, alkyl, alkenyl or alkynyl group, and several dCyd analogues, substituted at C-5 with an halogen or alkyl group, are able, like dThd itself, to sustain the growth of FM3A/TS cells, and are, therefore, assumed to be incorporated into host cell DNA.