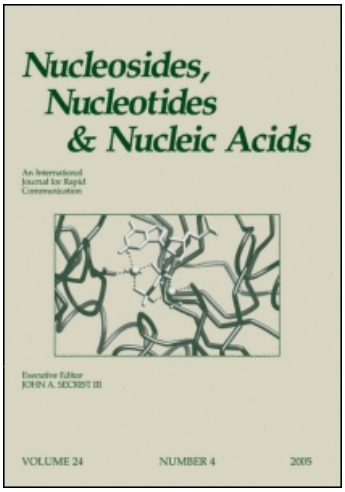

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Thymidylate Synthetase-Positive and -Negative Mouse Mammary Carcinoma Cell Lines: Useful Model for Monitoring the Incorporation of Pyrimidine Nucleoside Analogues into Host Cell DNA and for Detecting Thymidylate Synthetase Inhibitors

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

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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.

Summary - 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. (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-β-D-arabinofuranosyluracil (araU) and 1-β-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.

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