

New targets for pyrimidine antimetabolites in the treatment of solid tumours

1. Thymidylate synthase

• C.L. van der Wilt and G.J. Peters

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Figures

The worst mistake in this article was the printing of the wrong Figures 1 and 4. The correct Figures appear here.

Tables

In Table 3, the heading 'Colorectal cancer' should have been *Human colorectal cancer*, and the heading 'Liver' should have been *Liver cancer*. The same applies to Table 4.

The investigations in reference 62, as reported in Table 5, apply to *Balb/c mice*; the schedule is *c.i.* 5FU₁₀ + *i.p.* LV_{100/10/5}, fluorouracil was administered as a continuous infusion during 3 weeks, and the dosage of folinic acid is *q7dx3*, *q3dx6* and *q1dx5*, respectively. The Lewis lung system (Table 5, ref. 64) was studied in *C57Bl/6 mice*. The meaning of the abbreviations in the *Schedule* column of Table 5 is as follows: *i.p.*: intraperitoneal; *c.i.*: continuous infusion; *s.c.*: subcutaneous; *i.v.*: intravenous. Doses (subscripts) are in mg/kg, but where the sign ‡ appears, LV doses are in mg/m². Footnote § should have read: 'Three courses were administered with one week interval between the courses.'

In Table 6, the heading 'Cervix' should have read *Cervix cancer*.

In the footnotes to Table 8, '5-fluoro-2'-deoxy-uridine' must be replaced by *5-fluoro-2'-deoxyuridine*.

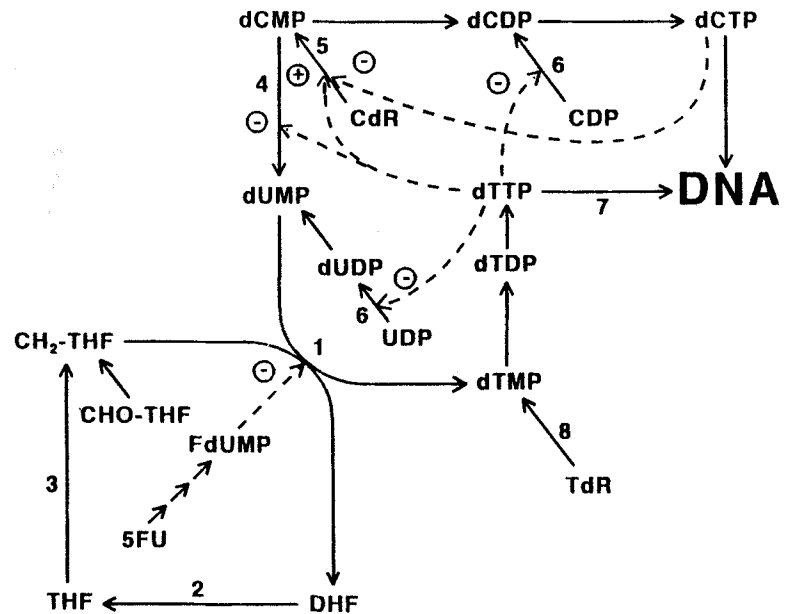
In Table 13, only Colon 26 is a Murine colon cancer; Colo201 and WiDr are *Human colon cancers*.

In Table 14, footnote †, the dosage is just in U.

Text

In the text on page 86, line 18-20 should have read "... that do not have an antitumour effect and which can enhance the binding of FdUMP to TS *only to a minor extent, ...*".

In the right-hand column of page 89, line 6 from the bottom should have mentioned "Colon 26

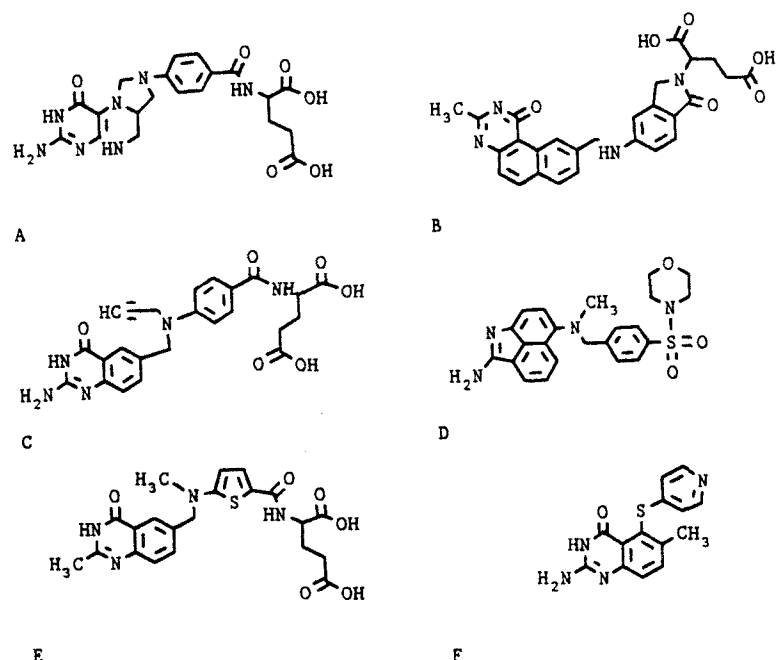


▲ **Figure 1**

Diagram showing the interaction of thymidylate synthase with different enzymes of folate and pyrimidine metabolism. Activating and inhibitory effects of the various metabolites are indicated by + and - signs, respectively. 1: thymidylate synthase; 2: dihydrofolate reductase; 3: serine hydroxymethyltransferase; 4: deoxycytidylate deaminase; 5: deoxycytidine kinase; 6: ribonucleotide reductase; 7: DNA-polymerase; 8: thymidine kinase; THF: tetrahydrofolate; DHF: dihydrofolate; CH₂-THF: 5,10-methylenetetrahydrofolate; CHO-THF: folinic acid (leucovorin); TdR: thymidine

► Figure 4

Structural formulas of 5,10-methylenetetrahydrofolate (5,10-CH₂-H₄-folate; A), N-[[4-[[[(3-amino-1,2-dihydro-1-oxobenzof[quinazolin-9-yl)methyl]-N-methylamino]-2-isoindolyl]-L-glutamic acid (1843U89; B), N¹⁰-propargyl-5,8-dideazafolic acid (CB3717; C), N-[4-(N-morphinosulphonyl)benzyl]-N-methyl-2,6-diaminobenz[cd]indole glucuronate (AG331; D), N-[5-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-methylamino]-2-thenoyl]-L-glutamic acid (D1694; E) and 3,4-dihydro-2-amino-6-methyl-4-oxo-5-(4-pyridylthio)quinazoline dihydrochloride (AG337; F)



tumour line" and line 7 from the bottom "CD8F₇ breast tumour lines". The same applies to page 90, left-hand column, line 3. The dosages of LV in this paragraph are in mg/m².

The last sentence on page 92 should be: "A dose-dependent increase of pyrimidine nucleoside phosphorylase activity was caused by interferon- α [79]; uridine phosphorylase activity also increased after interferon- α [90]."

On page 94, left-hand column, line 12-13 should have read "... could not be modulated by interferon- α [43]." The last sentence of the left-hand column should read "The number of cell lines for which interferon- β acts...".

On page 98, line 13-14 from the bottom should read "... allow the cell to grow and divide [110]."

On page 100 the last sentence of the first paragraph should be changed to: "ICI D1694 (Tomudex)

has been evaluated in several phase I trials [131]. A preliminary evaluation of phase II trials (in 44 patients) revealed a response rate of 27% in patients with colorectal cancer [133]." Also on page 100, left-hand column, lines 2-3 from the bottom should have stated that "Both compounds are currently being tested in a clinical trial [136]."

References

The correct page numbers of references 70 are 35-44.

Reference 133 should be changed to: "Zalberg J, Cunningham D, van Cutsem E, et al. Good antitumour activity of the new thymidylate synthase inhibitor tomudex (ZD1694) in colorectal cancer [abstract]. *Ann Oncol* 1994;5 Suppl 5:133."

New targets for pyrimidine antimetabolites in the treatment of solid tumours

2. Deoxycytidine kinase

- Veronique W.T. Ruiz van Haperen and Godefridus J. Peters

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Tables 1 and 2 contain some wrong figures and references. The relevant parts of these Tables are corrected below. In the caption to Figure 1, 'xTP' should have read NTP. The correct form of reference 57 is: "Xu YZ, Plunkett W. Modulation of deoxycytidylate deaminase in intact human leukaemia cells. *Action of 2',2'-difluorodeoxycytidine*. *Biochem Pharmacol* 1992;44:1819-27."

Table 1 Kinetic properties of deoxycytidine kinase (purified) from different sources

Source	K_m ($\mu\text{mol/l}$)			Relative activity			Phosphate donors	Reference
	dC	dA	dG	dC	dA	dG		
A2780 cells	0.4	nd	nd	1	nd	nd	ATP	16
	23.2	nd	nd	3.3	nd	nd		
WiDr cells	0.9	nd	nd	1	nd	nd	ATP	16
	27.2	nd	nd	3.2	nd	nd		

Table 2 Phosphorylation kinetics of deoxycytidine and deoxyadenosine analogues

Source	K_m ($\mu\text{mol/l}$)				Relative activity				Reference
	dC	Ara-C	dFdC	Analogue	dC	Ara-C	dFdC	Analogue	
A2780 cells	23.2				1		1.4		16, 27
WiDr cells	27.2				1		1.6		16, 27