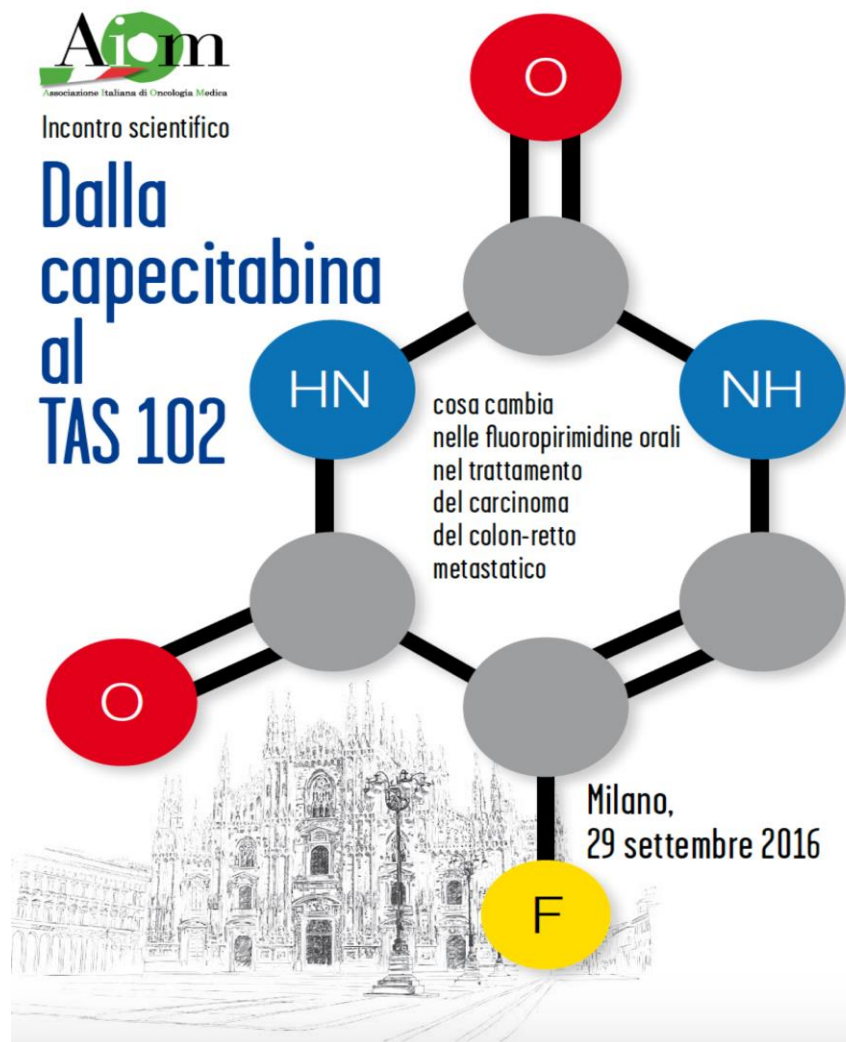




Incontro scientifico

Dalla
capecitabina
al
TAS 102



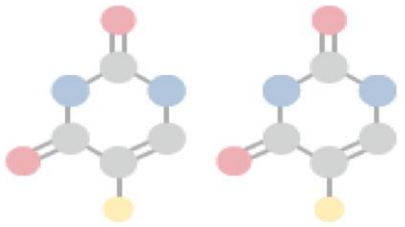
Milano,
29 settembre 2016

La farmacologia

Romano Danesi

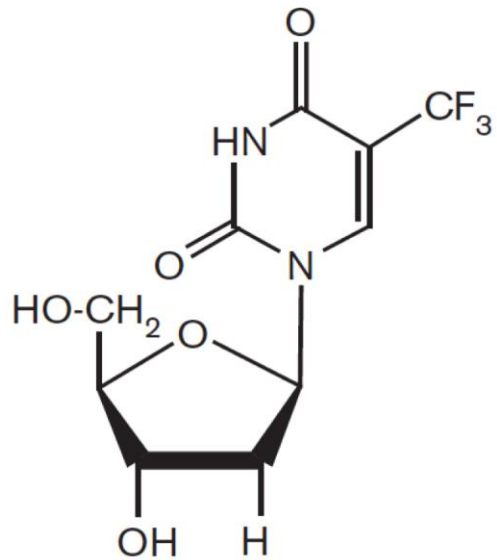
UOC Farmacologia clinica e Farmacogenetica

Università di Pisa

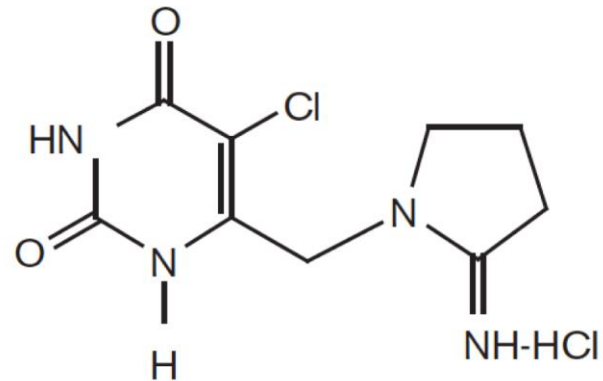


Chemical structures of trifluorothymidine (TFT) and thymidine phosphorylase inhibitor (TPI)

TFT



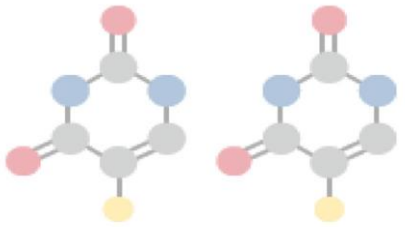
TPI



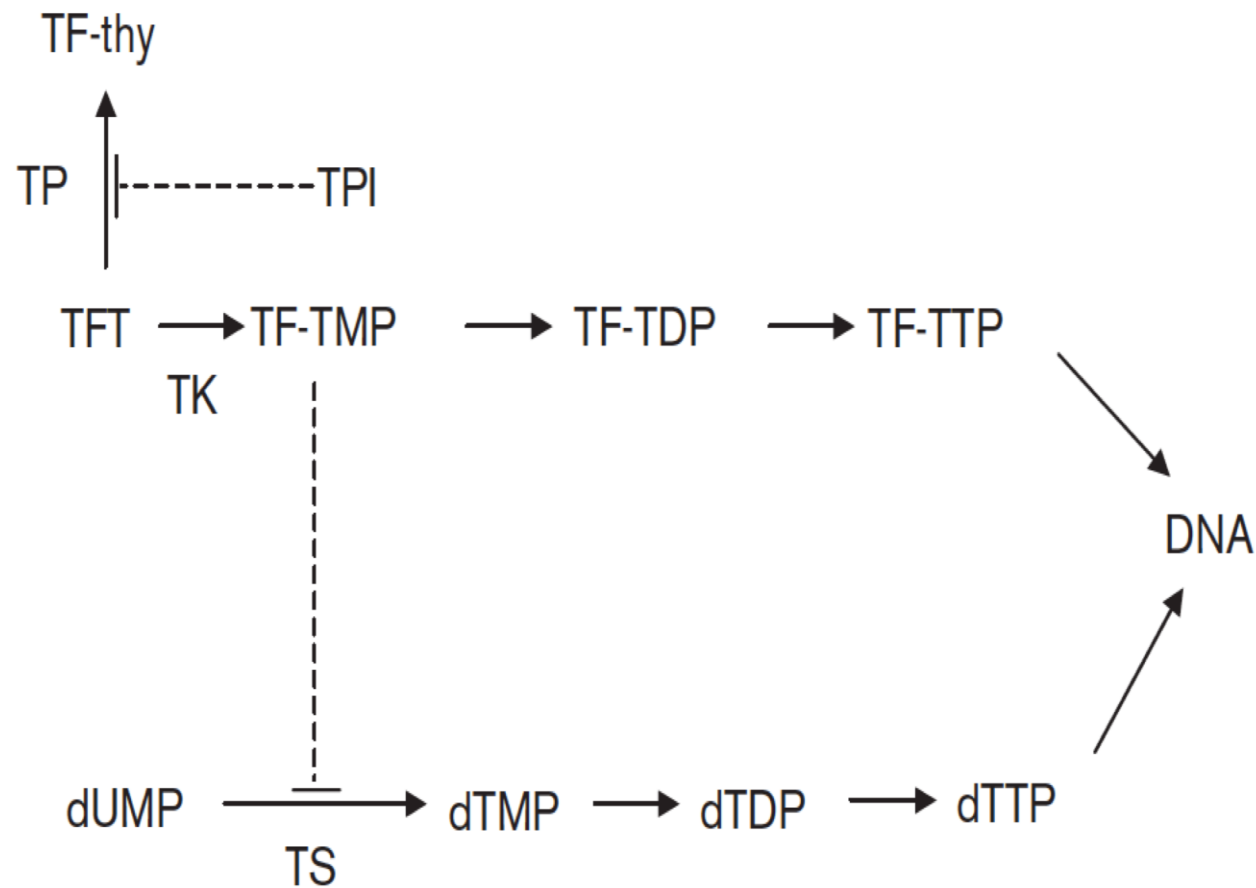
Determinants of trifluorothymidine sensitivity and metabolism in colon and lung cancer cells

Olaf H. Temmink^a, Michiel de Bruin^a, Elizabeth M. Comijn^a, Masakazu Fukushima^b and Godefridus J. Peters^a

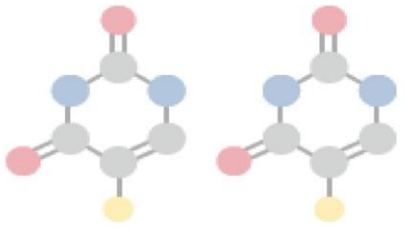
Anti-Cancer Drugs 2005, Vol 16 No 3



Mechanism of action of TFT and TPI

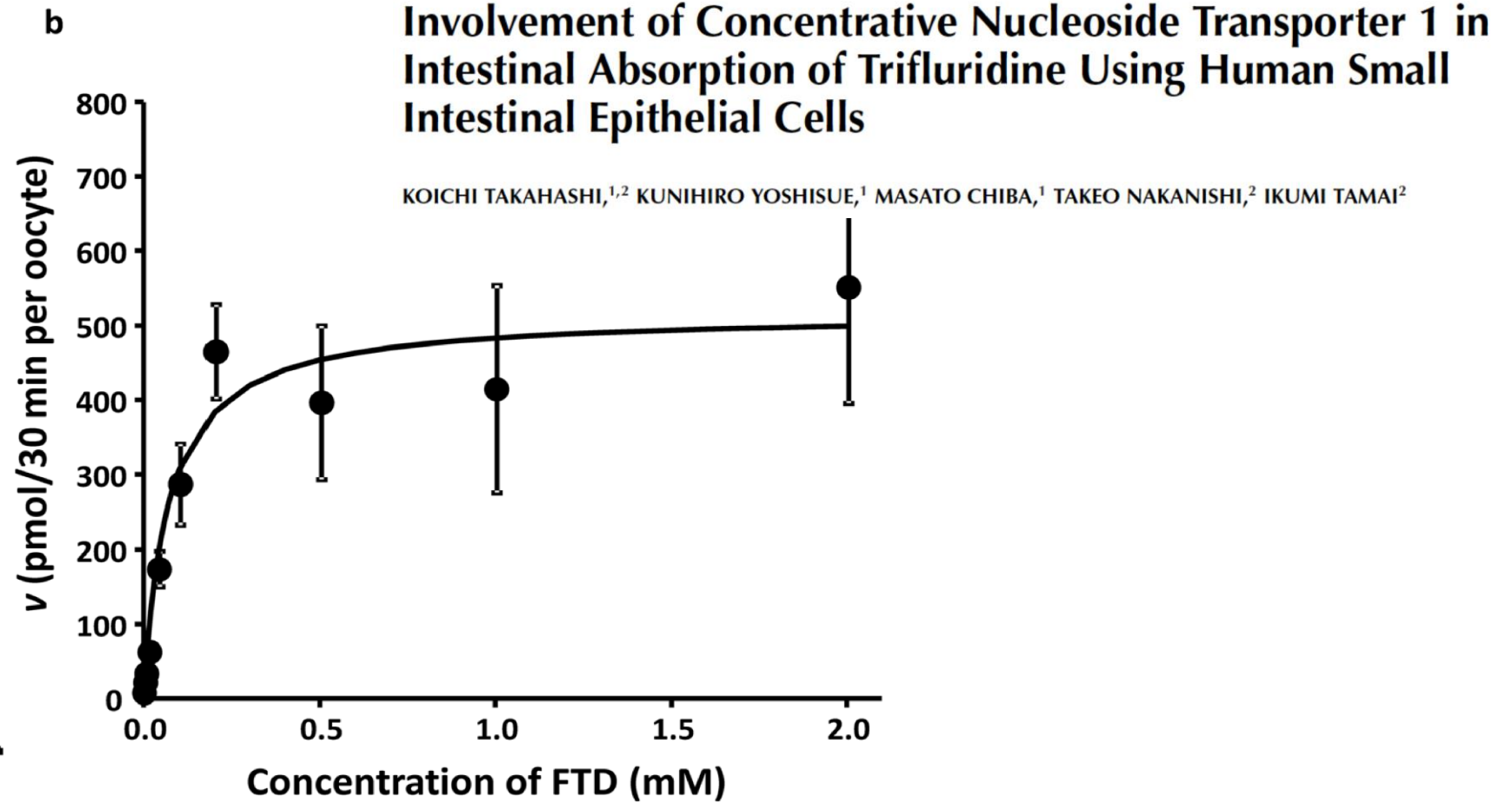
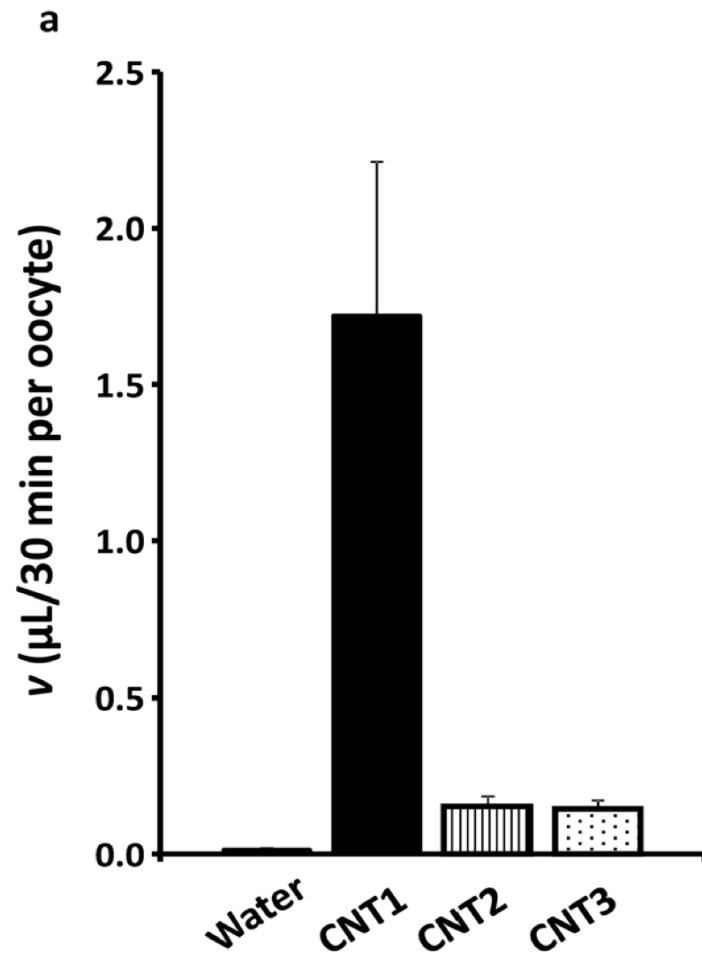


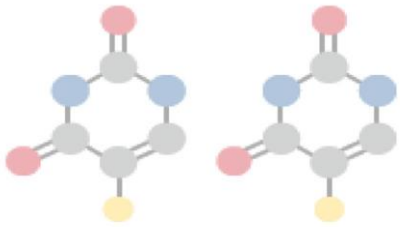
Our in vitro data also show that the mode of cytotoxicity exerted by TFT is dependent on exposure time and that a longer exposure can bypass resistance due to increased TS expression. Therefore, this time dependent pharmacologic effect of TFT should be translated in repeated administration of TAS-102 which will be the most optimal schedule, because it will lead to a prolonged exposure to TFT similar to in cell lines.



Uptake of FTD by cells expressing human CNT1, CNT2, or CNT3

RESEARCH ARTICLE – *Pharmacokinetics, Pharmacodynamics and Drug Transport and Metabolism*





British Journal of Cancer (2007) 96, 231–240

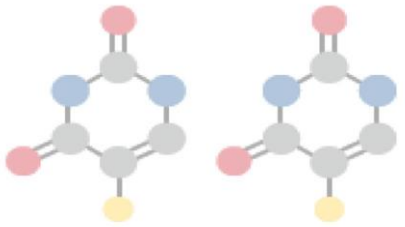
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www.bjcancer.com

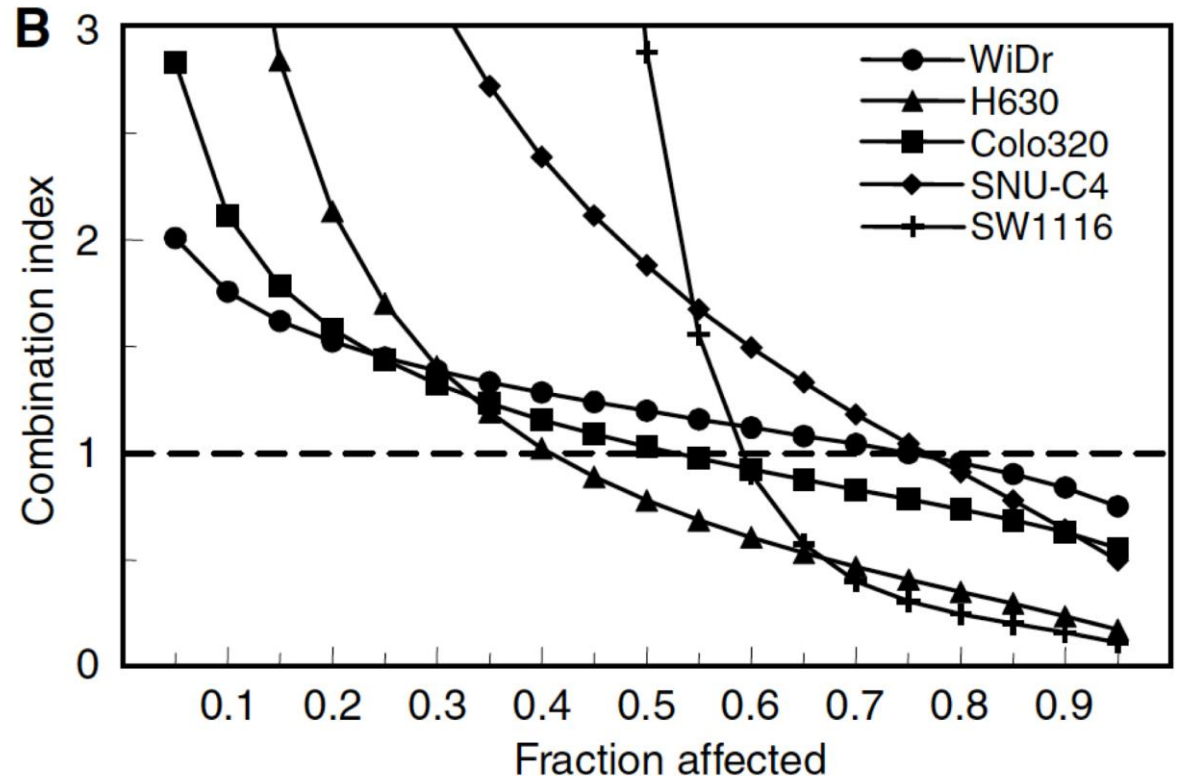
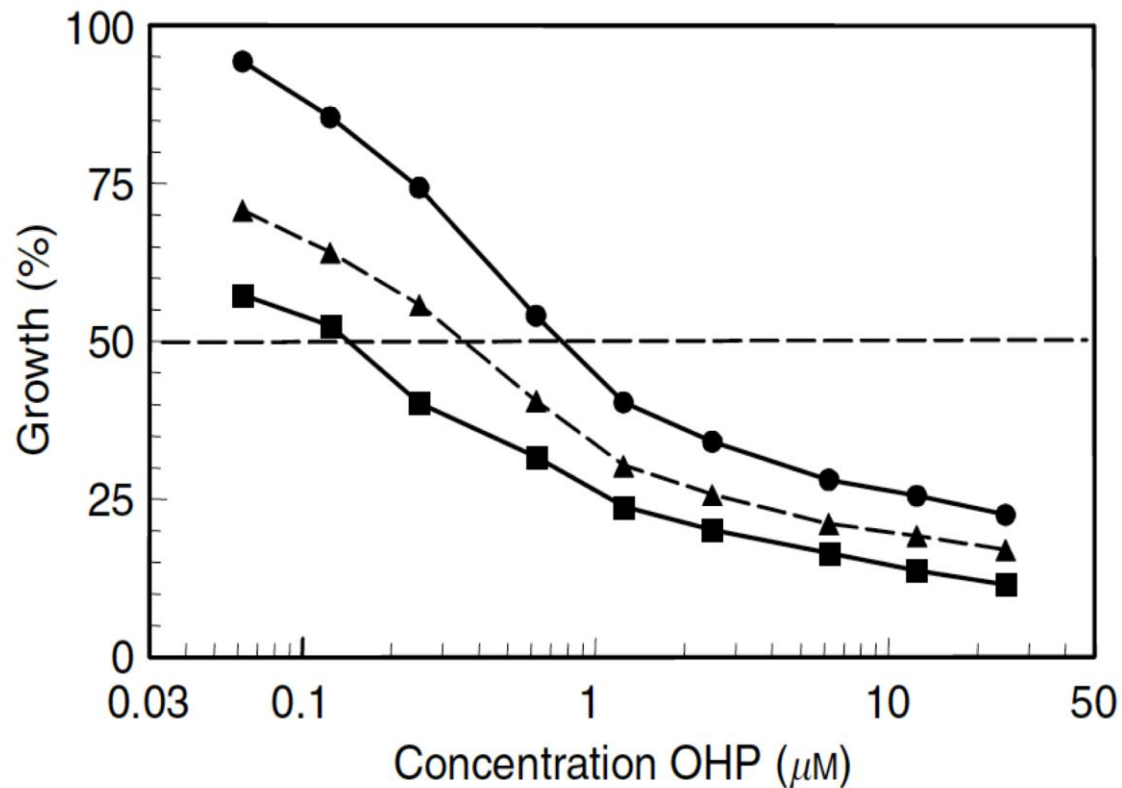
Mechanism of trifluorothymidine potentiation of oxaliplatin-induced cytotoxicity to colorectal cancer cells

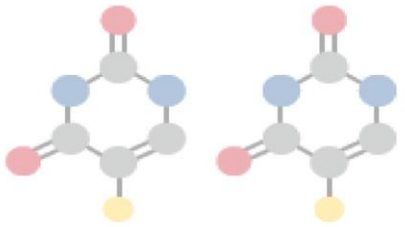
OH Temmink¹, EK Hoebe¹, K van der Born¹, SP Ackland², M Fukushima³ and GJ Peters^{*,1}

¹Department of Medical Oncology, VU University Medical Center, Amsterdam, The Netherlands; ²Department of Medical Oncology, Newcastle Mater Misericordiae Hospital, Waratah, NSW, Australia; ³Tokushima Research Center, Taiho Pharmaceutical Co., Tokushima, Japan

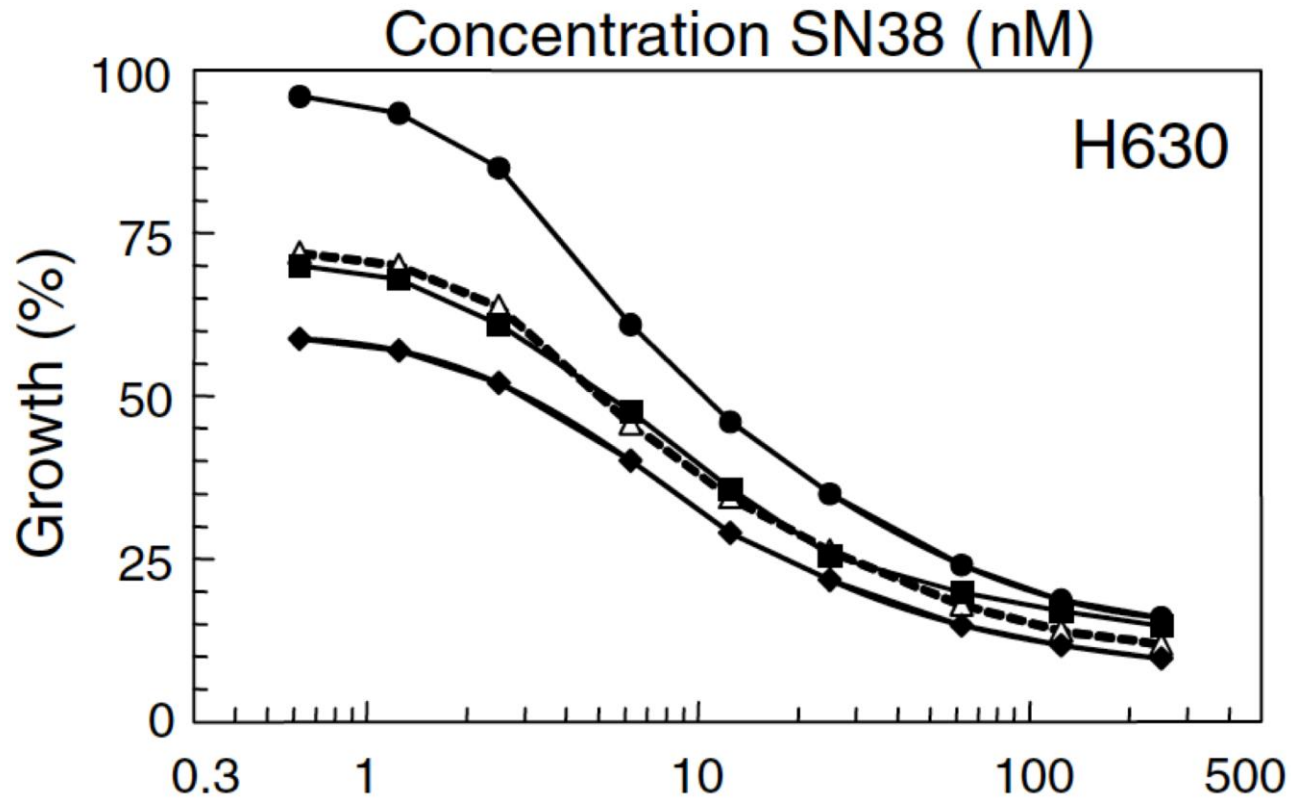


Representative growth inhibition curves for the combination OHP-TFT





Representative growth inhibition curves for the combinations using a variable drug ratios



EUROPEAN JOURNAL OF CANCER 43 (2007) 175–183



available at www.sciencedirect.com

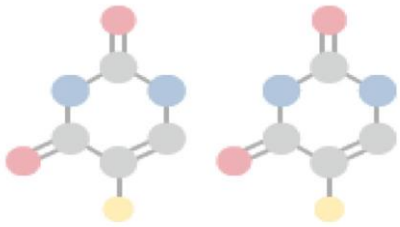


journal homepage: www.ejconline.com



Irinotecan-induced cytotoxicity to colon cancer cells *in vitro* is stimulated by pre-incubation with trifluorothymidine

Olaf H. Temmink^a, Eveline K. Hoebe^a, Masakazu Fukushima^b, Godefridus J. Peters^{a,*}



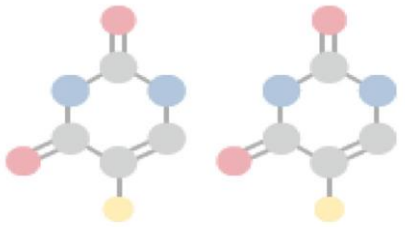
Cancer Chemother Pharmacol (2015) 76:325–333

DOI 10.1007/s00280-015-2805-9

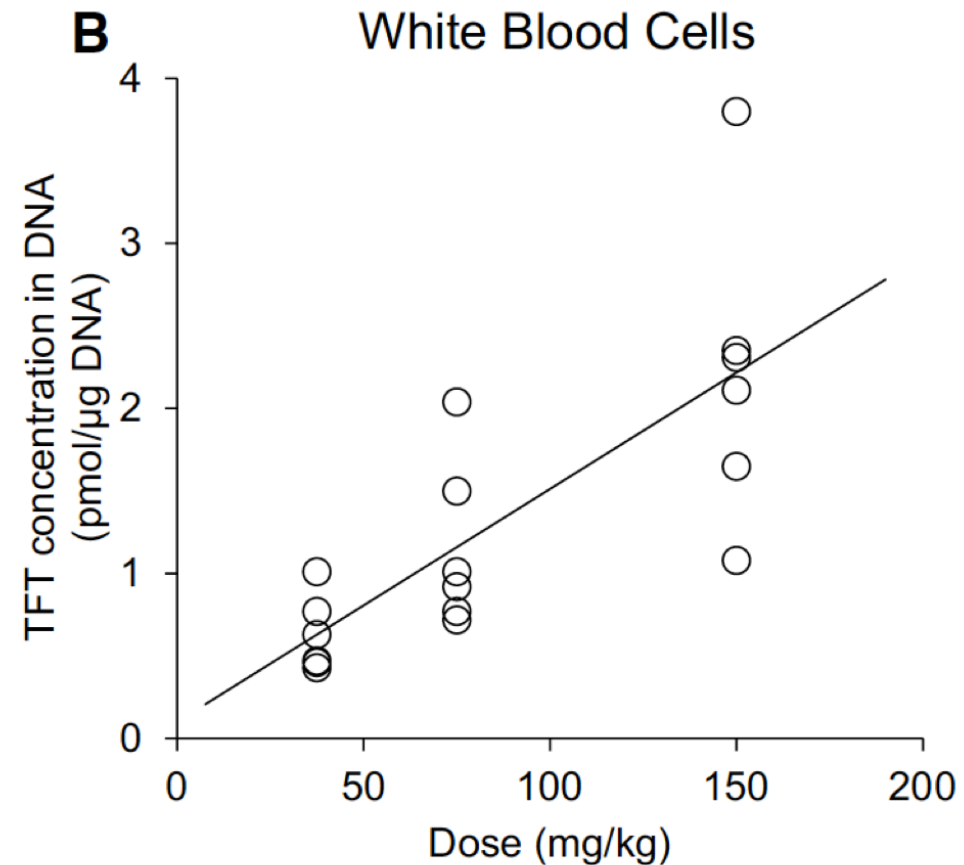
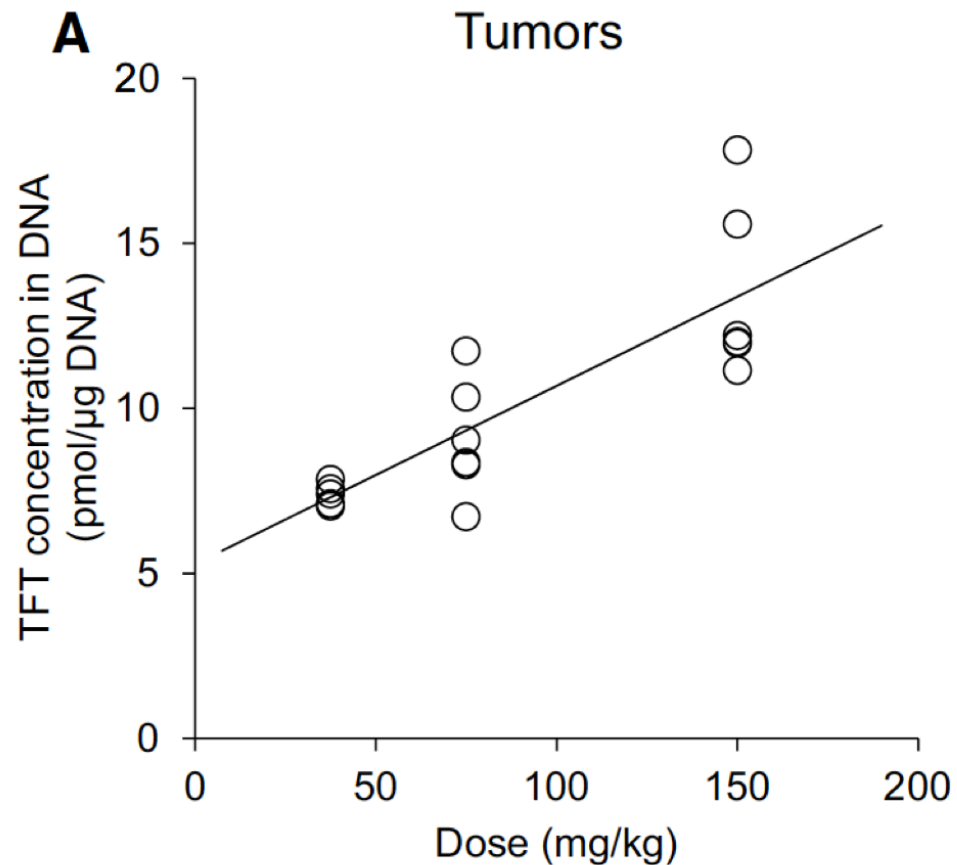
ORIGINAL ARTICLE

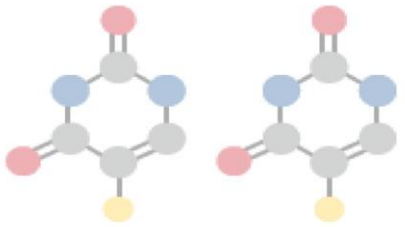
Exposure-dependent incorporation of trifluridine into DNA of tumors and white blood cells in tumor-bearing mouse

**Fumiaki Yamashita¹ · Ikumi Komoto¹ · Hiroaki Oka² · Keizo Kuwata¹ ·
Mayuko Takeuchi¹ · Fumio Nakagawa³ · Kunihiro Yoshisue¹ · Masato Chiba¹**

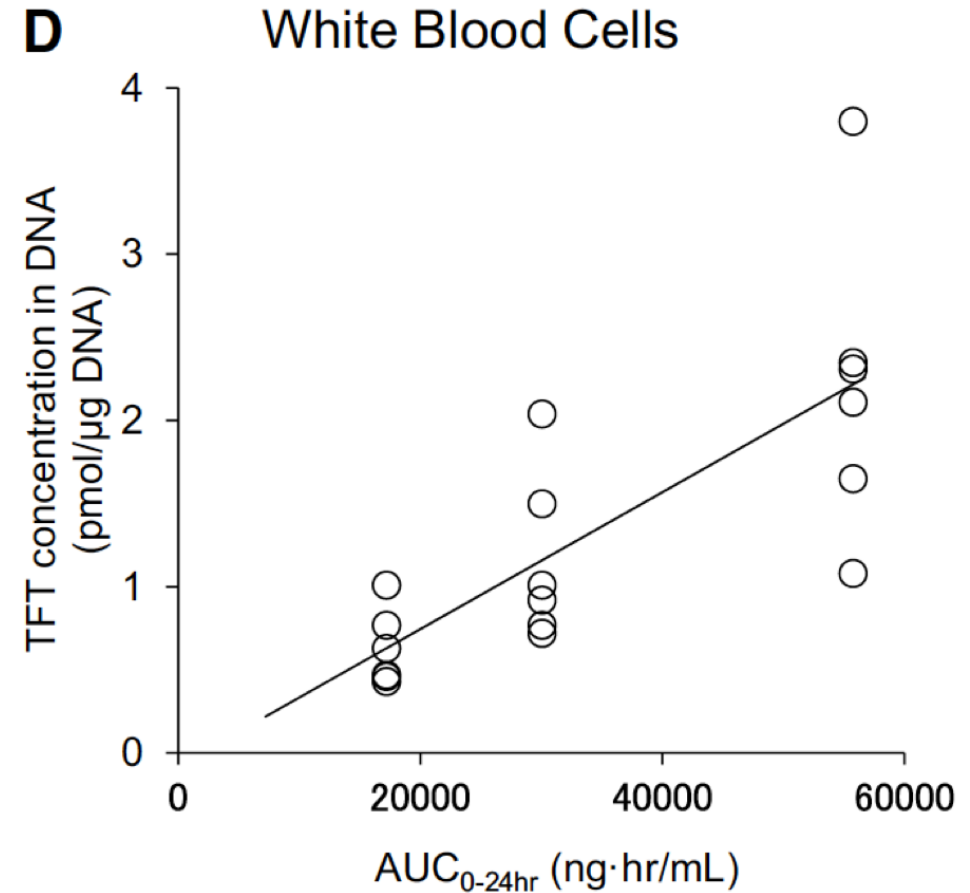
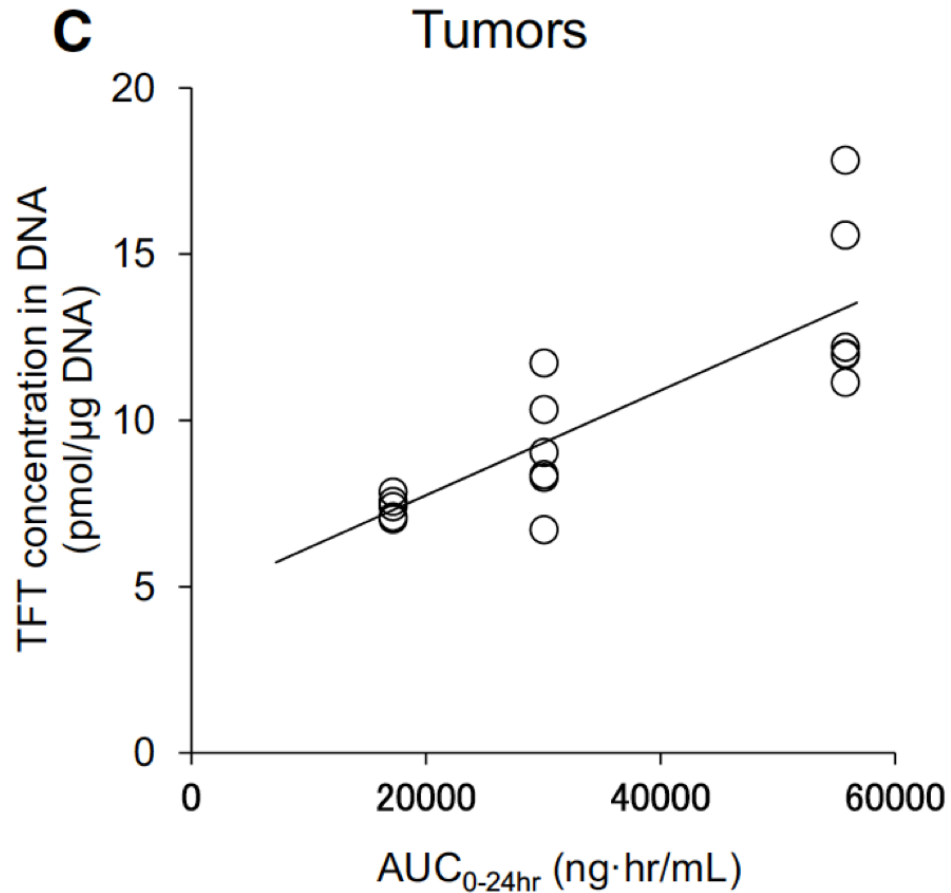


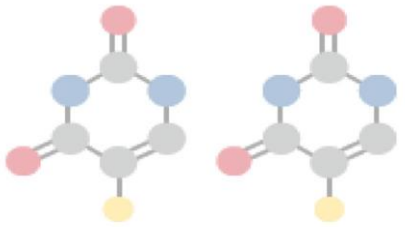
Relationship between TFT doses and its incorporation into the DNA of tumors or white blood cells





Relationship between TFT AUC and its incorporation into the DNA of tumors or white blood cells



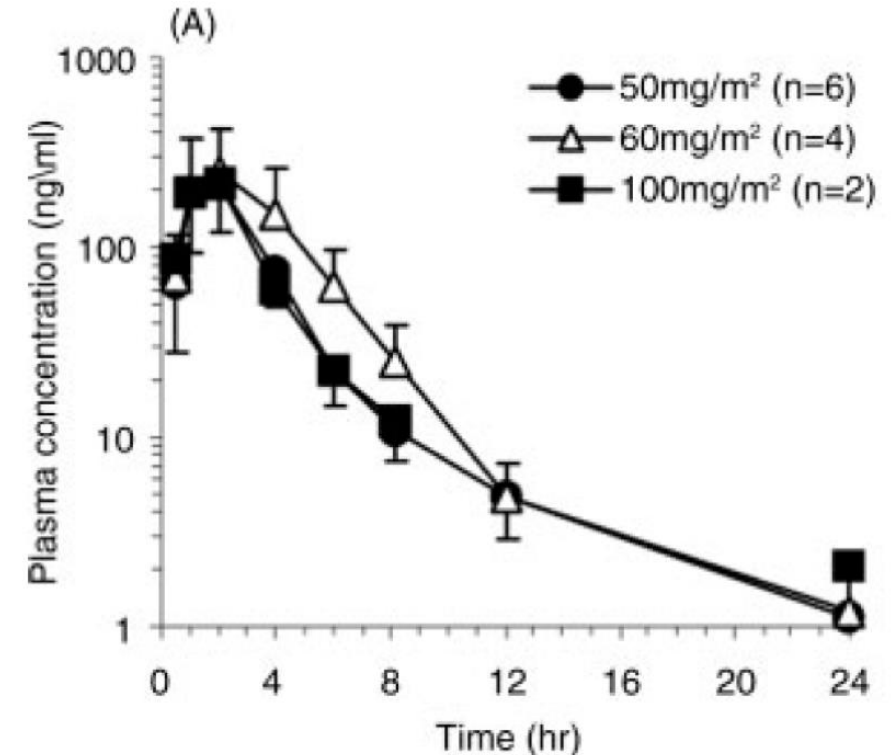
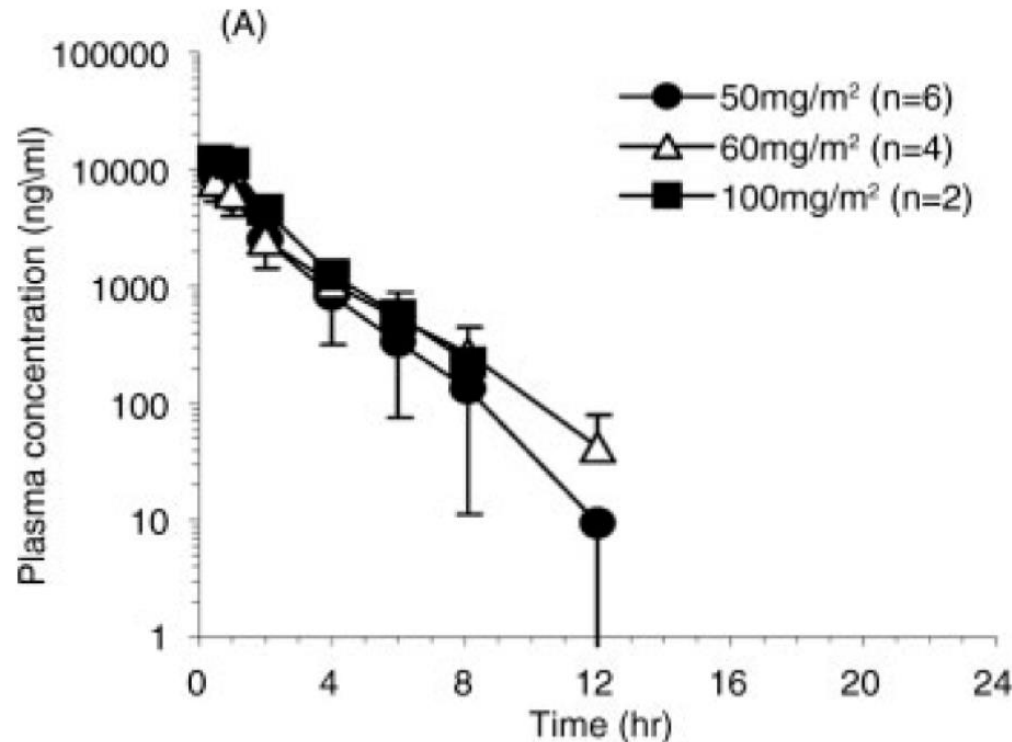


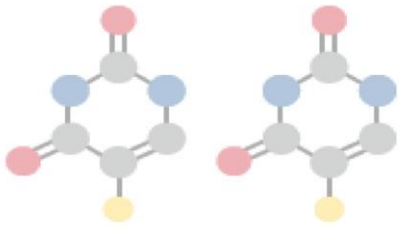
Mean plasma concentration (ng/mL) of trifluorothymidine (left) and tipiracil (right)

CANCER September 15, 2006 / Volume 107 / Number 6

David S. Hong, MD¹
James L. Abbruzzese, MD¹
Karla Bogaard¹
Yvonne Lassere¹
Masakazu Fukushima²
Akira Mita²
Keizo Kuwata²
Paulo M. Hoff, MD¹

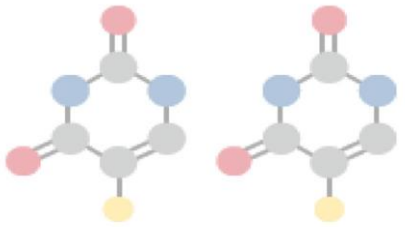
Phase I Study to Determine the Safety and Pharmacokinetics of Oral Administration of TAS-102 in Patients With Solid Tumors



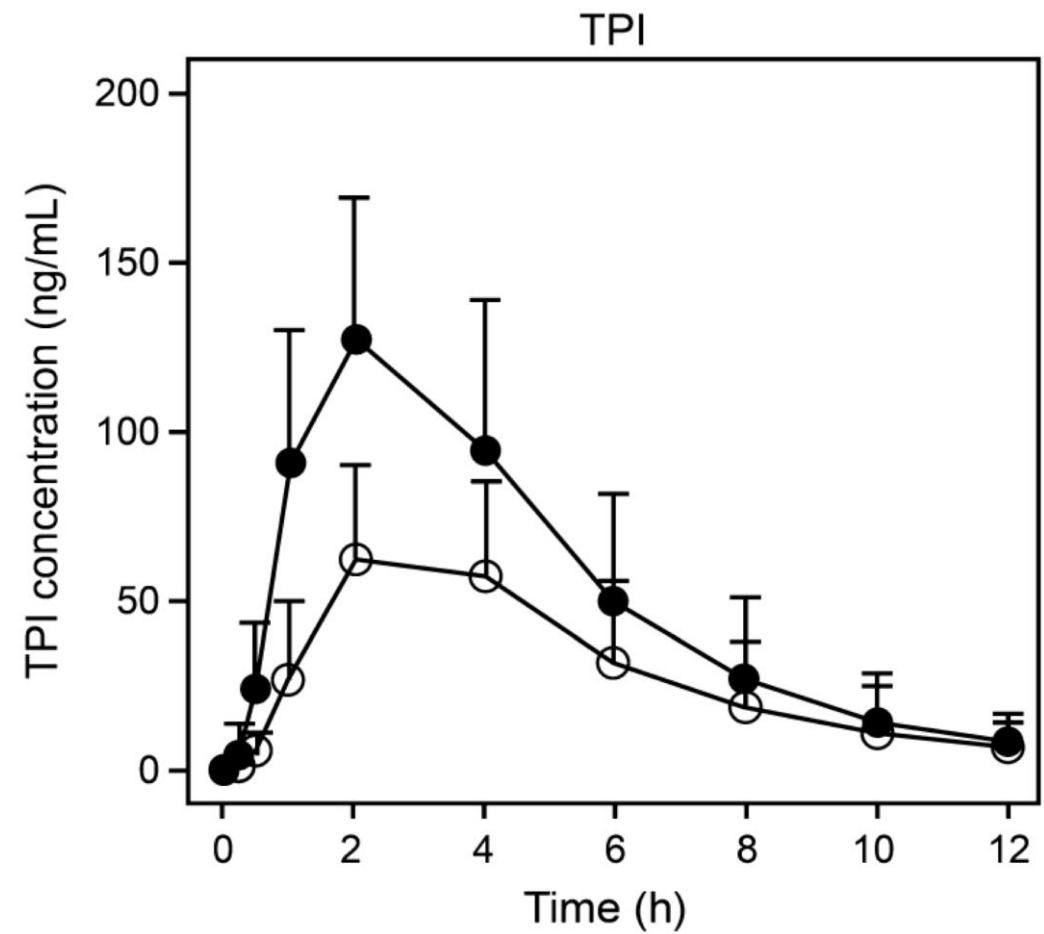
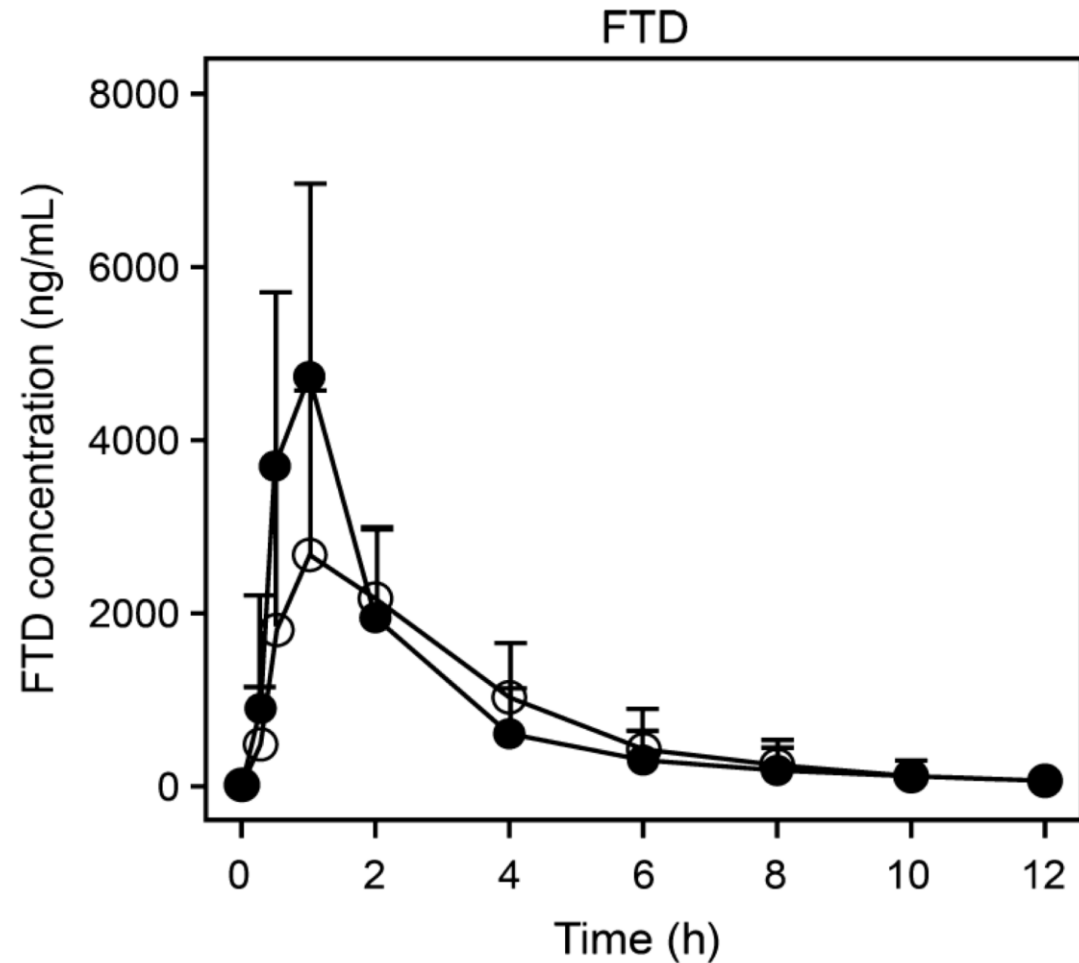


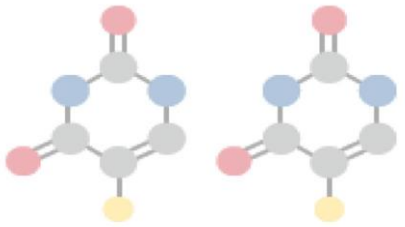
Effect of food on the pharmacokinetics of TAS-102 and its efficacy and safety in patients with advanced solid tumors

Takayuki Yoshino,¹ Takashi Kojima,¹ Hideaki Bando,¹ Tomoko Yamazaki,² Yoichi Naito,³ Hirofumi Mukai,³ Nozomu Fuse,¹ Koichi Goto,⁴ Yuko Ito,⁵ Toshihiko Doi¹ and Atsushi Ohtsu¹

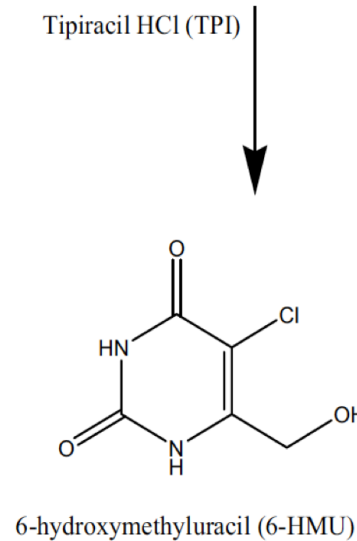
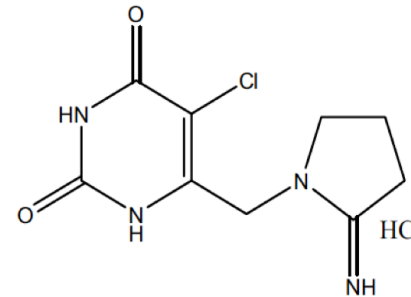
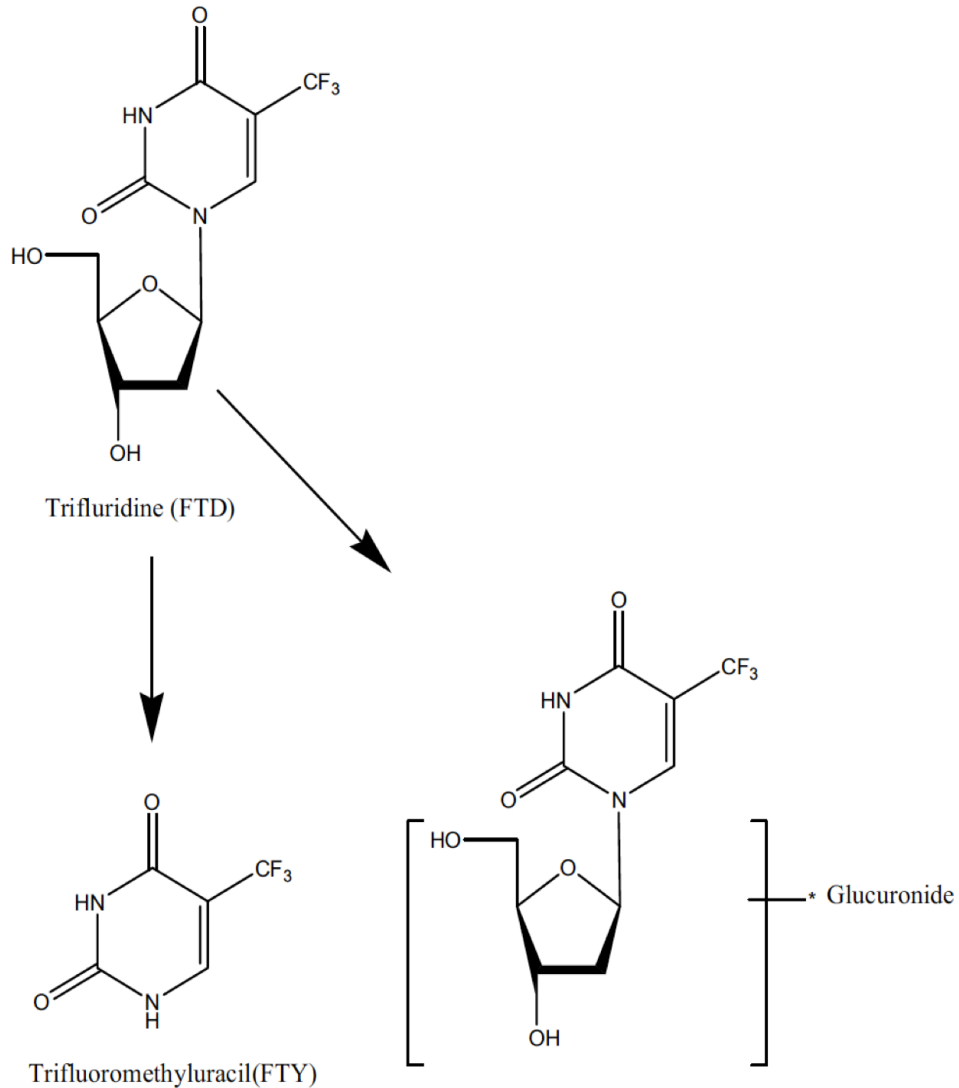


Plasma PK of FTD and tipiracil in patients with solid tumors following treatment with TAS-102 at 35 mg/m² under fasting (closed circles) and fed (open circles) conditions





Proposed metabolism of FTD and TPI in humans

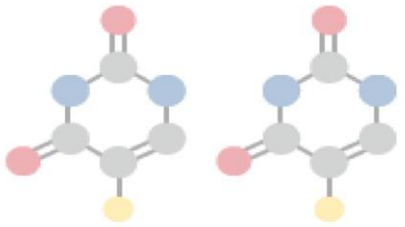


Cancer Chemother Pharmacol (2016) 77:515–526
DOI 10.1007/s00280-016-2965-2

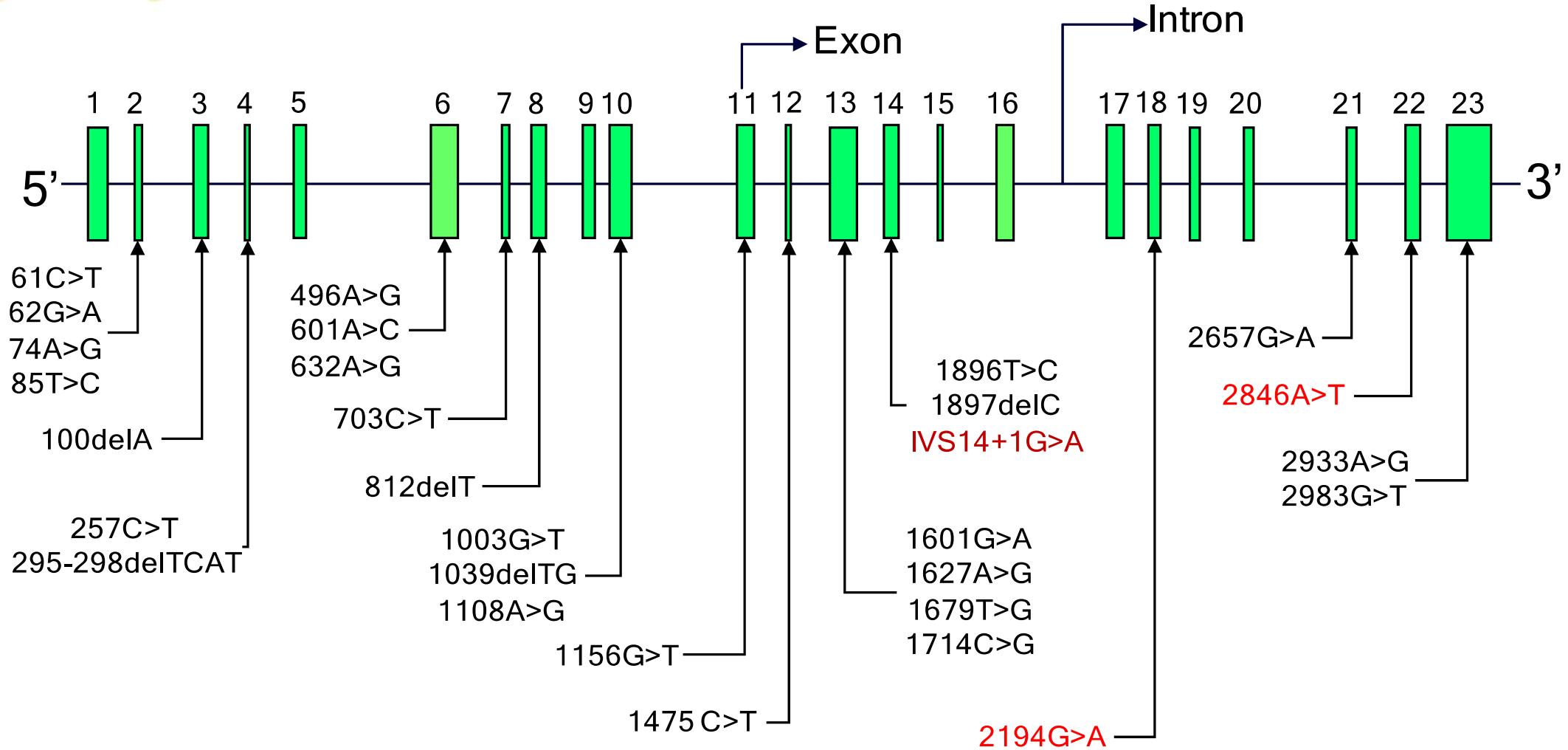
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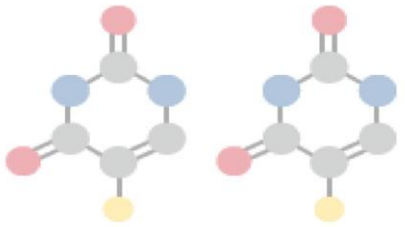
Human mass balance study of TAS-102 using ^{14}C analyzed by accelerator mass spectrometry

James J. Lee^{1,2} · Javed Seraj³ · Kenichiro Yoshida³ · Hirokazu Mizuguchi³ · Sandra Strychor¹ · Jillian Fiejdaz⁴ · Tyler Faulkner⁴ · Robert A. Parise¹ · Patrick Fawcett⁴ · Laura Pollice⁴ · Scott Mason⁵ · Jeremy Hague⁶ · Marie Croft⁶ · James Nugteren⁶ · Charles Tedder⁷ · Weijing Sun^{1,2} · Edward Chu^{1,2} · Jan Hendrik Beumer^{1,2,8}



Genetic variants of DPD





Conclusions

- Novel mechanism of action
- Predictable efficacy of combinations with other cytotoxic drugs
- Predictable pharmacokinetics
- Still to be investigated human metabolism – prevention of bone marrow toxicity?