analysis. Kruskal-Wallis one-way nonparametric AOV was used to estimate whether the LRP expression was related to: tumor differentiation (well, moderately, poorly); TNM classification and histology. IH of the tumor sections showed different expression of LRP in the different histological subtypes of lung cancer (squamous cell carcinoma 83%; adenocarcinoma 59%; large cell/undifferentiated carcinoma 36% and SCLC 5%). LRP expression was significantly higher in squamous cell carcinoma than in the other subtypes ($P < 0.05$). Furthermore adenocarcinomas showed a significant ($P < 0.05$) higher LRP expression than the SCLC. No significant difference in expression levels was found between patients with different TNM-classification or tumor differentiation. In this relatively small group of patients, there was no relation between LRP expression and survival. Prospective research is being performed in patients undergoing chemotherapy.

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IDOXIFENE DELAYS ACQUIRED ANTI-OESTROGEN RESISTANCE IN MCF-7 HUMAN BREAST CANCER XENOGRAFTS

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Idoxifene (IDOX) is a new anti-oestrogen with less agonist activity than tamoxifen (TAM). We (i) compared the inhibition by IDOX and TAM of the growth of MCF-7 breast cancer xonografts, (ii) determined whether IDOX delayed acquired resistance, and (iii) assessed whether IDOX inhibited the growth of TAM resistant tumours. Forty tumours were established with oestradiol (E2) support in ovariectomised athymic mice and continued with E2, no support, TAM or IDOX (mean serum TAM 35 ng/ml, IDOX 28 ng/ml). The reductions in tumour volume (mean percentage baseline ± SEM) after 2 and 6 m were as follows: TAM 71.8% (± 10.5) and 81.1% (± 14.8); IDOX 47.2% (± 9.3) and 51.0% (± 14.3); E2 withdrawal 30.7% (± 5.2) and 13.1% (± 4.3), respectively. IDOX appeared to give greater tumour regression compared with TAM. Furthermore, after 6 months 3/10 TAM-treated but 0/10 IDOX-treated tumours developed acquired resistance and started to re-grow. In separate studies significantly fewer TAM-resistant tumours were supported by IDOX than by TAM (3/12 vs 8/12; $P = 0.04$ Chi-Squared). These data indicate that IDOX shows reduced growth support of MCF-7 xenografts compared with TAM and appears to delay the development of acquired resistance. Furthermore IDOX may share only partial cross-resistance with TAM. The reduced agonist activity of IDOX may, in part, explain these observations.

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MARINE (MA) DEPSIPEPTIDES (DEP) WITH ACTIVITY (A) AGAINST SOLID TUMOURS (ST) MODELS

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Two MADEP from our R + D program are presented. KahalalideF (KF) is a MADEP isolated from a Hawaiian mollusc; it displays selective A *in vitro* (IVT) in Prostatic cancer cell lines (PROca) (TG1 at 4.22E−07 MOLAR), COMPARE analysts (COa) fails to match KF with any standard anticancer drug and initial data indicates KF promotes an extensive vaculorization in cultures COS1 and HELA cells and might interact with specific component(s) of the cell surface. *In vivo*, KF lacks A in P388 but has A in A549 lung ca xenograft (X) (37% T/C at KF dose = 2 mg/kg/Q4D × 3). Thiocoraline (THIO), MADEP isolated from a MA micro-organism from Mozambique; THIO has IVT A in melanoma, colon and lung ca cell lines (TGIs = 4.09E-09, 2.50E-09 and 2.50E-09 respectively). THIO binds to DNA (> luM); kinetic studies suggests THIO inhibits cell cycle progression at G1, S, G2 and M phases (reversible after washing) and COs matches THIO with doxo and daunorubicin. THIO lacks *in vivo* A in P388 but has A in A549 X (31%T/C; 6 mg/Kg/Q4Dx3). THIO assessment in NSCLC and colon Xs is ongoing. Large scale supply is feasible by fermentation.

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ACTIVITY OF N4-OCTADECYL-ARA-C IN HUMAN SOLID TUMOR XENOGRAFTS AND LEUKEMIAS

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A series of new Ara-C derivatives with alkyl chains at N4 has been tested in-vivo in subcutaneously growing human xenografts. The liposomal preparation of N4-Octadecyl-Ara-C (NOAC) was studied in 2 human leukemias and in 6 solid cancers. At the MTD of 150 mg/kg/day injected ip on day 1, 4, 7 and 10 NOAC showed a higher antitumor activity than the equitoxic dose of Ara-C in the promyelocytic leukemia HL-60, tumor volumes being 3% and 52% of the controls, respectively. In the acute T lymphoblastic leukemia CCRF-CEM both compounds were highly active. An impressive *in vivo* activity could be demonstrated in solid tumors. In the mammary cancer MAXF 401 NOAC effected a T/C of 18% versus 42% obtained with Ara-C, in the small cell lung cancer LXFS 605 T/C values were 27% versus 56%. The new derivative showed activity in a large cell cancer of the lung and in the prostate cancer PC3M with a T/C of 17%. The activity in PC3M was higher than obtained with 7 standard agents. In conclusion the new Ara-C derivative NOAC is a promising new compound which should be developed in solid tumors (mammary and prostate cancers) as well as in leukemias.

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ADDITION OF OXALIPLATIN (L-OHP®) TO CHRONOMODULATED (CM) 5-FLUOROURACIL (5-FU) AND FOLINIC ACID (FA) FOR REVERSAL OF ACQUIRED CHEMORESISTANCE IN PATIENTS WITH ADVANCED COLORECTAL CANCER (ACC)

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L-OHP®/5-FU/FA CM combination partially circumvented 5-FU resistance in patients (pts) with ACC (*Cancer* 1992, **69**, 893). L-OHP® delivered as q 3 wks CM or bolus showed a 10% (14/138) overall response rate (ORR) in ACC pts with proven progressive disease (PD) while getting 5-FU/FA treatment. The non-cross resistance and/or synergy of L-OHP® with 5FU/FA was assessed in 25 pts with acquired resistance (20 with CT scan-proven [PD]—and 5 with median 5 months [2.5–12] disease stabilisation [ST]) while on 5-day (d) CM 5-FU (700–1000 mg/sqm/d)/FA (300 mg/sqm/d) (peak delivery at 4.00 h) (FF). L-OHP® (20 to 25 mg/sqm/d, peak at 16.00 h) was added to this schedule in 2nd (12 pts) or 3rd line (13 pts) (FFL) according to 2 different schedules: 5d q 3 wks (14 pts) or 4 d q 2 wks (11 pts). *Selection criteria:* Pretreated ACC, no other intercurrent chemotherapy between the 2 schedules, measurable lesion. *PT Characteristics:* M/F = 10/15, median age = 59, colon/rectum = 14/11, PS 0–1 vs 2–3 = 22/3, nb of sites <2 vs ⩾ 2 = 8/17, liver involvement = 21 (94%). Previous 5-FU time exposition = median 7.2 months (1.5–25.2), FF (CM) median dose intensity (DI) = 1050 mg/sqm/wk. *FFL (CM) Treatment:* 171 cycles, median = 7 (1–15), time to exposition = 5 mo (1–9), 5-FU DI = median 1072 mg (831–1580), L-OHP® DI = median 35.7 mg (24–43). *Toxicity (per pt):* grade 3–4: nausea-vomiting = 25%, diarrhea = 16%, mucositis = 8%. No gr 3–4 hematotoxicity. No renal or auditive toxicity was observed. No toxic death. *Efficacy:* 7 PR (29.2%), 5 minor reponses (21%), 4 SD (17%) and 8 PD (33%). One pt too early. Duration of response was 8.5 mo, disease-free progression 5.8 mo and median survival 12 mo. *Conclusion:* Addition of L-OHP® can reversed FF resistance to CM 5-FU/FA in one third of pts. This further suggests a synergistic and/or modulatory effect between 5-FU and L-OHP®.

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DRUG RESISTANCE MECHANISMS TO CISPLATIN IN H-HAS AND V-MYC TRANSFECTED FIBROBLASTS

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Cisplatin is a widely used antitumor agent. To investigate the role of oncogenes in drug resistance to cisplatin we determined the sensitivity