expressed in a cervical tissue derived from transgenic mouse, when compared with a cervix derived from normal mouse. From these results, we conclude that the E7 transgene expression inactivates the transactivation function of IRF-1 *in vivo*, which might be important for the elucidation of the E7-mediated immune evading mechanism that is frequently found in cervical cancer.

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Tumor necrosis alpha (TNFa) blockade as an adjunct to dose intense chemotherapy

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TNFa can be responsible for the fatigue/cachexia associated with malignancies. Docetaxel(D)when given weekly produces asthenia/fatigue in most patients(pts). We evaluated the ability of etanercept(soluble TNF receptor that neutralizes bioactive TNFa)to maintain the intensity of weekly D chemotherapy. 12 pts with refractory solid malignancies were randomized to receive D 43mg/m^2/wk $\times$ 6, every 8 wks)or D(same dose-schedule)plus etanercept(E)25mg SQ twice weekly. Escalations in the weekly doses of D in additional pts receiving E were planned in the event that dose intensity was maintained at the 43mg/m^2 dose. Plasma/serum samples for pharmacokinetics (PK) and unbound-TNF,and peripheral blood cells lysates for evaluation of the TNF-downstream transcription factor NF-kB and the relative expression of cytokines IL-1B,TNFa,IFNg and IL-6(TaqMan real time RT-PCR)were obtained. 12 pts received 111 doses of D(alone,32 doses;D/E,79 doses). Three pts, all in the D/E arm, achieved partial antitumor responses and received at least 3 cycles (6 months). During the 1st cycle, 9 doses (38%)of D were missed due to toxicity on the D arm,whereas none were missed on the D/E group. D PK parameters(AUC0-6,ng*hr/mL) were similar between days 1 and 29(717$\pm$372 and 817$\pm$470, respectively(n=12)and between single agent D(648$\pm$297,d1; 985$\pm$121,d29) and D/E (787$\pm$453,d1; 678$\pm$268,d29). Serum concentrations of unbound TNF were undetectable by bioassay in both arms. However, NF-kB relative activity (to HeLa+ cells)(9 pts) decreased on day 29(23.9$\pm$7) compared to baseline (36.9$\pm$6)in patients receiving D/E(mean % decrease, 30), and not in pts receiving D(d29, 35.2$\pm$12; baseline 32.1$\pm$12)(mean % increase, 17). Mean relative expression of IL-1B,TNFa,IFNg and IL-6 decreased on day 29 compared to baseline by 81,59,83 and 82%, respectively in pts receiving D/E (n=4) but increased with D alone (n=1). Three additional pts received D/E at 52mg/m^2/wk D. At this dose, myelosuppression (grade 3 WBC) but not fatigue was the major factor limiting dose intensity (4/18 doses missed). In summary, the current study indicates that D PKs are similar after 4 wks of administration with or without E and that the D/E combination is well tolerated. The improved compliance in this preliminary study with this dose-intense chemotherapy regimen would suggest a role for TNFa in the associated asthenia/fatigue and offers a rationale for randomized studies focused in quality of life at conventional doses of weekly D. The cytokine and NF-kB regulated-gene expression patterns observed provide rationale for hypothesis driven explorations of this combination in man.

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A phase II trial of etanercept, a tumour necrosis factor-a inhibitor in recurrent ovarian cancer

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Purpose: There is preclinical data to support the role of TNF-a in the pathogenesis of ovarian cancer. We have initiated a phase II trial with etanercept (ENBRL) in patients with recurrent ovarian cancer.
Methods: 17 patients received etanercept at a dose of 25 mg SC twice weekly. All patients were planned to receive a minimum of 3 months of treatment up to a maximum of 1 year, with disease evaluation at 3 monthly intervals. Surrogate end points for biological effect of etanercept included sE- Selectin, TNF- a, TNF-R1, MCP-1 and MMP-3 which were measured in the plasma (13 patients). A whole blood cytokine release inhibition assay was performed for IL-6 and MCP-1. The time points were pre treatment, 24hours, 7 days, 28 days and 4 weekly there after.
Results: Median age was 54 years (range 34-75). 15/17 patients had optimal surgery, and 2/17 had suboptimal surgery. The histological subtypes were serous (13), clear cell (1), endometroid (2) and mixed tumour (1). Previous chemotherapy included carboplatin and/or Taxol (12 platinum sensitive and 5 resistant), 11/17 patients had second line and 7/17 had third line chemotherapy. 11/17 patients completed 3 months or more of treatment. There was no significant toxicity. Two patients achieved stabilisation of disease for 6.3 and 10 months respectively with improvements in quality of life. Median overall survival was 9.6 months. There was a significant reduction in IL-6 levels in 9/13 patients (24 hours) which was maintained until 12 weeks (6/8 patients). MCP-1 levels declined in 8/12 patients on day 1 and by 3 months was inhibited by 50% (6 patients). All other surrogate markers did not change significantly with treatment.
Conclusions: Definite biological effect is seen at 3 months of etanercept therapy. A new cohort of patients are being treated with a dose of etanercept at 25mgs thrice weekly.

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Modulation of cytokine production by SRIK-NKL, a Rare CD8+ NK cell line, by hormones: implications for carcinogenesis and treatment

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Natural killer (NK) lymphocytes are non-MHC restricted T cells involved in host defense against infection and malignancy, and can contribute to chronic inflammation via cytokine and defensin 6 production. Tight regulation of NK function is critical, but mechanisms not fully defined. Modulation of NK activity is a potential strategy for cancer prevention and treatment. We established a unique CD8+ NK cell line (SRIK-NKL) from a patient with ALL and previously reported its constitutive cytokine profile (MIP-1alpha, MIP-1beta, RANTES, GRO-alpha, IL-10, IL-4, TNF-alpha, TNF-beta, IFN-gamma, LIF, GM-CSF positive; IL-8, IL-6, IL-7, SCF negative). SRIK-NKL allowed us to further investigate the behavior of this unusual CD8+ subset of NK cells, specifically hormone responsiveness. Cells were incubated at 0.5x106 cells/ml in RPMI 1640 5%FCS/no antibiotics in CO2 incubator at 37 degrees C for up to 24 hours with and without hormone (tamoxifen or mifepristone 0.05-0.5 mcM; progesterone, estradiol, or testosterone 0.5-5 mcM; retinoic acid 1-10 mcM; epinephrine 1 mcg/ml; substance P, VIP, somatostatin, or gastrin 1-10 mcM) and supernatants quantitated for cytokines by ELISA (R&D). RANTES was significnatly inhibited to 35-59% control by mifepristone and tamoxifen; MIP-1 alpha was decreased by retinoic acid to 52% control; but substance P and VIP greatly increased TNF-alpha to 166-226% control. Thus, cytokine production by CD8+ NK cells is altered by the hormonal milieu. This may be an important regulatory mechanism to consider when designing NK-dependent biologic treatments for cancer, or during the use of hormonal agents such as tamoxifen for established disease.

Gene therapy and antisense approaches

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Phase II study of ONYX-015 in patients with hepatobiliary tumors with p53 correlative studies

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ONYX-015 is a genetically modified adenovirus, which was designed to replicate preferentially in p53 mutated cells.To test the efficacy of ONYX-015, a phase II trial of intralesional ONYX-015 was conducted in patients with hepatobiliary tumors.All patients had biopsy-proven, measurable tumors of the liver, gall bladder or bile ducts which were beyond the scope of surgical resection. Patients received intralesional injections of ONYX-015 at either 6 $\times$ 109 or 1 $\times$ 1010 pfu/lesion up to a total dose of 3 $\times$ 1010 pfu. The status of p53 was assessed by immunohistochemistry (IHC) or Affymetrix GeneChip microarray analysis. Studies were conducted for viral shedding and for the presence of anti-adenoviral antibodies prior to and