lung. Its relative high sensitivity allows confident evaluation of changes as small as 25% in a single-patient. The small estimated sample sizes needed to determine therapeutic responses of as small as 25% change make DCE-MRI a promising tool to assess tumor perfusion and permeability, particularly in the antiangiogenic/antivascular arena.

Table. Confidence levels that a clinical determination of a change in K^{trans} or $IAUC_{BN}$ values for a single patient is not due to chance.

Percentage decrease	Confidence	
	Liver	Lung
10%	70%	60%
20%	87%	71%
30%	96%	82%
40%	99%	90%
50%	100%	96%
60%	100%	99%
90%	100%	100%

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An adaptive phase I design for identifying a dose-outcome region for two drug combinations

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Purpose: Historically, designs for dose seeking trials using drug combinations have been geared towards finding the maximum tolerated dose of the combination, with safety as the primary outcome. With target based agents whose dose-efficacy curves are unknown and whose dose-toxicity relationships are expected to be minimal, alternative designs to identify a biologically optimal drug doses for combination regimens have become necessary.
Methods: The present approach is a natural extension of an adaptive single agent dose-finding design previously presented (Zhang, Sargent, Mandrekar, Statistics in Medicine, 2005). A generalization of the continuation ratio model to characterize the true toxicity and efficacy curves of the drug combination, allowing separate toxicity and efficacy curves for each agent to generate a dose outcome surface is used. A continual reassessment method with straightforward dose selection criterion is employed using data from all patients treated up until that time point.
Results: Our simulation studies based on 500 trials with 3 and 5 dose levels for the two agents under nine different dose-toxicity (e.g. monotonically increasing, flat) and dose-efficacy (e.g. monotonically increasing, quadratic or unimodal, monotonically decreasing) scenarios demonstrated that the proposed design has favorable operating characteristics in terms of experimentation and recommendation rates for the combination dose levels, and the average sample size. Specifically, the average sample size ranged from 19 to 43 for the different scenarios considered, with recommendation rates for the optimal dose-outcome region greater than 70% for certain combinations.
Conclusions: We believe that our present approach incorporating both toxicity and efficacy of a drug combination into the identification of a biologically optimal region in a phase I setting is novel and warrants further consideration.

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Development of a high-sensitive antibody-based protein array system that quantitatively detects serum Fatty Acid Synthase (sFASN) in breast cancer: correlation with Her-2/neu (erbB-2) expression and trastuzumab efficacy

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Background: A bi-directional association between the Her-2/*neu* oncogene and the lipogenic enzyme Fatty Acid Synthase (FASN) has recently been described in human breast carcinomas. While FASN is overexpressed in Her-2/*neu*-positive tissues and cell lines, FASN inhibition transcriptionally suppresses Her-2/*neu* and synergistically enhances the efficacy of the anti-Her-2/*neu* antibody (Ab) trastuzumab (Herceptin®). Here, we sought to develop a new antibody-based protein array system for the quantitative determination of serum FASN (sFASN) and to determine the clinical utility of sFASN in monitoring breast cancer patients undergoing trastuzumab-based therapies.
Materials and Methods: ECL membranes were soaked with an anti-FASN monoclonal ("capture") Ab, air-dried, and then placed on the top of a template of micro-spots generated from a computer. Through the white light, the dark spots in the template were clearly visualized and used as guide to spot solution onto the membranes. Quantities of 0.25 L of standards (affinity-purified FASN), conditioned media from cell cultures or patient's sera were manually loaded onto membranes in duplicate. Membranes were then incubated with an anti-FASN polyclonal ("detector") Ab binding to the sFASN captured on the membrane. After a short incubation, the excess Ab was washed out and goat anti-rabbit immunoglobulin G conjugated to HRP, which binds to the "detector Ab", was added. Signals were developed by an ECL system and their intensities were scanned by Scion densitometry and plotted against different concentrations of FASN standards.
Results: (a.) "sFASN" was highly detected in supernatants from cancer cells naturally overexpressing Her-2/*neu* but not in those from Her-2/*neu*-negative cancer cells. (b) Cancer cells engineered to stably overexpress Her-2/*neu* dramatically up-regulated the expression and secretion of "sFASN". (c) Trastuzumab treatment significantly impaired the appearance of "sFASN" in the supernatant of Her-2/*neu*-overexpressors. (d) Preliminary analyses of sera obtained retrospectively from 114 subjects with advanced or metastatic breast cancer revealed the existence of high levels of sFASN in patients with elevated serum Her-2/*neu* concentrations.
Conclusions: This is the first practical protein array system developed to profile sFASN expression from patient's sera with high sensitivity. The utility of sFASN as a complementary tool in predicting responses to trastuzumab-based therapies warrants further studies.

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Discovery of DNAa hypermethylation targets associated with bladder cancer progression using CpG island microarrays

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Purpose: CpG islands arrays represent a high-throughput epigenomics discovery platform to identify global promoter hypermethylation events associated with bladder cancer progression. We investigated the role of CpG island hypermethylation in silencing targets identified using CpG arrays and their clinical/prognostic relevance.
Patients and Methods: Hypermethylation patterns of DNA obtained from ten pairs of bladder tumors were profiled versus their respective normal urothelium using differential methylation hybridization on custom-made arrays, containing 12,288 CpG island clones. Promoter CpG island methylation status of identified genes was analyzed by bisulfite genomic sequencing and methylation-specific polymerase chain reaction (MS-PCR) in bladder cancer cells (n = 12), and primary bladder tumors (n = 100). SOX9, PMF1 and CMKOR1 expression was assessed by oligonucleotide arrays, RT-PCR, and Western blot.
Results: Among the identified epigenetic signatures associated with bladder cancer progression, 84 clones showed up as hypermethylated in at least 70% of the samples. Bisulfite sequencing and MS-PCR confirmed Promoter CpG island methylation in bladder cancer cells for identified targets such as SOX9 (J82); PMF1 (TCCSUP); and CMKOR1 (RT4). The presence of hypermethylation was associated with gene expression loss, being restored *in vitro* by a demethylating agent. In primary tumors, hypermethylation and transcript levels of SOX9, PMF1 or CMKOR1 was associated with tumor stage and overall survival ($P < 0.05$).
Conclusion: Epigenetic silencing of the SOX9, PMF1 and CMKOR1 genes was identified by CpG island promoter hypermethylation using CpG arrays. The association of hypermethylation to low transcript levels also supported the role of methylation at silencing these critical genes in bladder cancer progression. Their association with poor survival in bladder tumors, suggested their important clinical implications at stratifying clinical outcome of bladder cancer patients and as therapeutic targets.

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Use of semilog plots and nonlinear regression analysis of survival curves to identify prognostically distinct patient subgroups

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Background: Kaplan-Meier survival curves are often multiphasic. Biological processes often follow first-order kinetics, in which semilog plots yield straight lines. In other biological processes (eg, pharmacokinetics [PK]), inflection points on semilog plots arise from distinct factors that