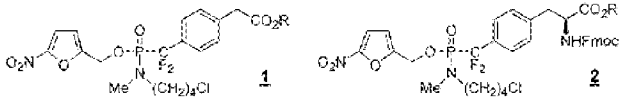
respectively. As anticipated, the PSA variants were activated to a greater extent by the PSA positive LNCaP cell line (LNCaP>DU145>COS-1). Data demonstrating the maximum tolerated dose and efficacy in mouse prostate cell xenograft models is presented.

579 POSTER

Design and synthesis of difluoromethylphosphonamidates for prodrugs of non-hydrolyzable phosphotyrosine peptidomimetics

R. Borch, I. Boutselis, R. Huang. *Purdue University, Cancer Center, West Lafayette, USA*

Our laboratory has reported previously a prodrug strategy to achieve intracellular delivery of nucleotides and phosphotyrosine peptidomimetics. However, the potential therapeutic benefit of such prodrugs is likely to be diminished by intracellular nucleotidases/phosphatases that can cleave the phosphate group from the drug species released in the cell. This difficulty can be circumvented for the phosphotyrosine peptidomimetics by incorporating the non-hydrolyzable difluoromethylphosphonate moiety in place of the phosphate group. We have now extended our prodrug strategy to the synthesis of aryl(difluoromethyl)phosphonate prodrug compounds **1** and **2** (R = H) that are suitable for incorporation into non-hydrolyzable phosphotyrosine peptidomimetics. The synthetic approach is based upon assembly of the analogous diethyl phosphonates and subsequent conversion of these intermediates to the nitrofuryl N-methyl-N-chlorobutyl phosphoramidates. The prodrug activation chemistry was verified for these difluoromethyl phosphonate analogs by hydrogenolysis of a model compound (**1** where the nitrofuryl group is replaced by benzyl) to the corresponding phosphonamidic acid. This intermediate was then dissolved in buffer and its conversion to the phosphonic acid monitored by ^{31}P nmr; a half life of 44 minutes (37ºC, pH = 7.4) was observed for this conversion, confirming the feasibility of this prodrug approach for the delivery of difluoromethyl phosphonates. The application of this chemistry to the synthesis of non-hydrolyzable phosphotyrosine peptidomimetics will be described, and approaches to the synthesis of analogous non-hydrolyzable phosphoserine peptidomimetics will also be presented.



580 POSTER

In vitro release of 17-demethoxy-17-allylaminogeldannamycin from its prodrugs

E. Tabibi[1], L. Zhao[2,4], B.R. Vishnuvajjala[3], S.H. Yalkowsky[4]. [1]*National Cancer Institute, Pharmaceutical Resources Branch, Bethesda, USA;* [2]*Aventis Pharmaceuticals, Bridgewater, USA;* [3]*National Cancer Institute, Pharmaceutical Resources Branch, Bethesda, USA;* [4]*The University of Arizona, College of Pharmacy, Tucson, USA*

Methods: In vitro stability procedure was established for both standard curves and actual plasma samples. A small amount of acetonitrile was used to help solublize prodrugs. The plasma samples were incubated at 37ºC over 24-hour period. Excess acetonitrile was used to stop possible enzymatic reactions in plasma at preset time points. Each prodrug was studied individually by HPLC to monitor the concentrations of both the remaining prodrug and the accruing 17-AAG at each time points. The conversion of each prodrug was investigated in mouse plasma, recovered, and fresh human plasma.

R	Name	NSC
-H	17-AAG	330507
-CO-(CH2)3NH2,HCL	11-(4'-amino)-butanoate HCl	683201
-CO-CH2NH2,HCL	11-(2'-amino)-acetate HCl	683661
-CO-CH2N(CH3)2,HCL	11-(2'-N,N-dimethylamino)-acetate HCl	683662
-CO-(CH2)2NH2,HCL	11-(3'-amino)-propionate HCl	683663
-CO-(CH2)2N(CH3)2,HCL	11-(3'-N,N-dimethylamino)-propionate HCl	683664
-CO-(CH2)4NH2,HCL	11-(4'-N,N-dimethylamino)-butanoate HCl	697886
-CO-(CH2)3N(CH3)2,HCL	11-(5'-amino)-pentanoate HCl	697866

Results: It was found that each individual prodrug has a comparable degradation pattern in three different plasmas. The 17-AAG is the major degrading compound that was observed for all seven prodrugs. In all plasma samples, NSC-683662 and NSC-683664 were the least stable: about 50% of these prodrugs released 17-AAG in the first five hours. Note that both of these prodrugs have a tertiary amine on the end of acyl chain. Though the NSC-697886 is similarly structured, its release rate is far slower: the release of 17-AAG was only about 10% after 24 hours. It appears that the number of $-CH_2-$ group affects the degradation rate: there are three $-CH_2-$ groups on the acyl chain in the NSC-697886 while only one in the NSC-683662 and two in the NSC-683664. It also appears that the prodrugs that have side chains with terminal primary amino group degrade to a lesser extent: the NSC-683201 almost has no degradation over 24 hours. In the first 6 hours NSC-683661, NSC-683663, and NSC-683666 only degrade marginally.

Conclusions: Stability profiles indicate that for each individual prodrug the degradation pattern is comparable in three different plasmas with 17-AAG as the major product. The NSC-683662 and NSC-683664 are least stable, thus are good candidates for further development.

Chemoprevention

581 POSTER

Lycopene, alone or combined with vitamin E, reduces orthotopic growth and plasma PSA release of PC-346C prostate tumors

J. Limpens[1], F.H. Schröder[1], C.M.A. de Ridder[1], C.A. Bolder[1], M.F. Wildhagen[1], U.C. Obermüller-Jevic[2], B. Nowakowsky[2], K. Krämer[2], W.M. van Weerden[1]. [1]*Erasmus MC, Urology, Rotterdam, The Netherlands;* [2]*BASF Aktiengesellschaft, Ludwigshafen, Germany*

Background: Epidemiologic and clinical studies have indicated that high intake of lycopene or vitamin E is associated with a reduced prostate cancer risk, but no firm conclusions about protective effects can be drawn from these studies. The current study was undertaken to investigate whether lycopene or vitamin E, alone or in combination, may suppress orthotopic prostate tumor growth and whether blood PSA levels may serve as a surrogate marker for antitumor-efficacy.

Materials and Methods: The androgen responsive, PSA-releasing, human prostate cancer cell line PC-346C was injected into the dorsolateral lobe of the prostate of athymic nude mice. Three days after tumor inoculation, mice were supplemented on a once daily oral basis with synthetic lycopene (5 and 50 mg/kg BW), synthetic vitamin E (5 and 50 mg/kg BW), a mixture of lycopene and vitamin E (5 mg/kg BW each), or placebo. Tumor growth was followed weekly by transrectal ultrasonography of the mouse prostate and plasma was sampled for PSA analysis at 2-weekly intervals. Mice were sacrificed when tumor load exceeded 1000 mm^3 or at day 95, when the study was terminated. The prostate (including tumor) and liver were analyzed for the presence of lycopene isomers and α-tocopherol by HPLC-methodology.

Results: The low dose of 5 mg/kg BW lycopene significantly suppressed the growth of the prostate xenograft by 53% at day 42 and extended the tumor doubling time accordingly. All other single treatments, either with the high lycopene dose or with both vitamin E doses, had no significant tumor-inhibiting effect. Combined treatment with the low lycopene-vitamin E mixture gave by far the greatest tumor inhibition (73% at day 42). PSA values and PSA doubling times matched the tumor responses in all experimental groups. Vitamin E and lycopene were effectively taken up at nanogram levels in the prostate and liver. Although lycopene was mainly present in the *all-trans* conformation in the dietary supplement (90%), the lycopene in the tissues existed primarily as cis-isomers (70%), a pattern similar to that observed for humans and other species.

Conclusions: Synthetic lycopene in low doses may inhibit prostate cancer, but combining it with vitamin E may enhance its effects. The absence of a selective effect on PSA supports the usefulness of PSA as a surrogate marker for these supplements in clinical prostate cancer trials.

582 POSTER

Chemoprevention of ovarian cancer in primate model

M. Brewer[1], J. Ranger-Moore[1], Z. Hao[1], J. Wang[1], J. Wharton[2], D. Gershenson[2], C. Zou[1]. [1]*University of Arizona, Obstetrics and Gynecology, Tucson, USA;* [2]*UT M.D. Anderson Cancer Center, Gynecologic Oncology, Houston, TX*

Ovarian cancer is the most lethal tumor among the gynecologic cancers and is associated with an extremely high mortality rate, partially due to the late stage of diagnosis and partially due to the lack of a durable response to cytotoxic chemotherapy. Primate models are ideal for developing strategies for both treatment and prevention because of the genetic similarity between primates and humans, such as hormonal regulation and menstrual cycle. 4-(N-hydroxyphenyl) retinamide (4HPR), a retinoid derivative, and the oral contraceptive (OCP) is currently being studied as chemopreventive agents for ovarian cancer but the mechanisms of their prevention activity are unclear.

We studied the effect of 4-HPR and OCP alone and in combination on the ovaries of 16 monkeys. The expression of retinoid receptors, hormone receptors, as well as apoptosis induction were tested in vivo. ERα was not detected in the primate ovaries, but ERβ, RARα and β, RXRα, and