natural science

increase meat quality and quantity,

ɷ ĸ¥Ħ ç Ƙγ

Data Collection

The microsatellite genetic ËÈÛÈ ÍÖÙ Û Ï Ì , ÌËÈÕÖı9È×ÈÛÈ 1ÈÕÊ Ï herd had previously been collected and archived at Texas A&M University. Previously established protocols φ ' ÈóÉ ÌÙÛ Ì Û ÈóƾƖƨƨƒA Þ ÌÙÌ ÜÚÌË ÛÖ ÈÚ-ÚÌÚÚóÌÝÌóÚ ÖÍ ÊÈŲóÌ Î ÌÕÌ ÐÕÛÙÖ Î ÙÌÚÚÐÖÕ ÈÛ ΣΤ ËÐÈ ÎÕÖÚÛÐÊ ÈÕË ×ÖóàÔÖÙ×ÏÐÊ φÊÖÕÛÈÐÕÐÕÎ ÔÖÙÌ ÛÏÈÕ ÖÕÌ ÈóóÌóÌA microsatellite markers. The markers ÈÕÈóàáÌË Þ ÌÙÌó &+ ΣƯ &+ ƖƱƫ !, ΣƫΣΤ !, ΤƫƨƯ !, ΤƒΣƫ !, ƯΣΤƒ !, 2ƖƖƯƨ !, 2ΤƨΤƨ "22, ƫƮ "22, ΤƖ 1, ΣưƒƗ 1, ƒƨƨ 2/2ΣΣƫ ÈÕË 3&+ ƖƖƯƾ3 Ï Ì ÔÈÙÒÌÙÚ ×ÈÕÕÌË Σƨ ÊÏÙÖÔÖÚÖÔÌÚ φÖÍ ƫƨ ÛÖÛÈó ÊÏÙÖ-ÔÖÚÖÔÌÚ ÐÕ ÉÐÚÖÕA ÈÕË Þ ÌÙÌ ÜÚÌË ÛÖ ÌÐÛ Ï ÌÙ ËÐÈ ÎÕÖÚÌ ÖÙ ÊÖÕƭÙÔ Þ Ï ÌÛ Ï-ÌÙ ÊÈŲóÌ Î ÌÕÌ ÐÕÛÙÖ Î ÙÌÚÚÐÖÕ Ï ÈË ÖÊ-ÊÜÙÙÌË φ ' ÈóÉ ÌÙÛ Ì Û Èóƾ ƖƨƨƒAƾ

#ÈÛÈ ÕÈóàÚÐÚ

To analyze the structure of the population, I used γ¥Υɏƙ¥ɏΥĸ v. ƖƾƫƾΤ φ/ÙÐÛÊ Ï ÈÙË Ì Û Èóƾ ƖƨƨƨA Þ ÐÛ Ï Û Ï Ì ΣΤ ÔÐÊÙÖÚÈÛ ÌóóÐÛ Ì óÖÊÐ ÍÖÙ ÈóóΣƠƯƨƨ ÐÕ-dividuals. I used the admixture model and ran seven repetitions for each *ÝÈóÜÌ φΣıΤAó Þ ÐÛ Ï *ÉÌÐÕÎ Û Ï Ì ÕÜÔ-ber of assumed genetic clusters and calculated the mean of logarithmic ×ÙÖÉÈÉÐóÐÛà φ"ÈÖ Ì Û ÈóƾƖƨΣƯAƾ (ÜÚÌË ÈÕ ÉÜÙÕıÐÕ ×ÌÙÐÖË ÖÍ ƒƨƨƨƨƨ ÚÛÌ×Ú ÈÕË , ÖÕÛÌ "ÈÙóÖ , ÈÙÒÖÝ "ÏÈÐÕ φ , " , "A ÙÌ×óÌÕÎÛ Ï ÖÍ ƒƨƨƨƨƨƨ ÚÛÌ×Ú ÈÕË ÊÏÖÚÌ the K genetic cluster values based on methods published in the literature φ/ÐÕáÖÕÌ ÈÕË #àÌÙ ƖƨΣƫAƾ

The two indices of genetic diÝÌÙÚÐÛà Û Ï ÈÛ (ÜÚÌË Þ ÌÙÌ φΣA Ìß×ÌÊÛÌË heterozygosity (H_EA ÈÕË φƖA ÕÜÔÉÌÙ of alleles and their associated frequencies. Expected heterozygosity is an indicator of genetic variation and provides information on the fre-

es the results from the analysis, and

values and shows the most probable

likelihood value

Torrey Davis

ed my hypothesis that there would be multiple clusters. This indicates that the individuals are part of one interbreeding, or admixing, population and that genes are randomly distributed among individuals. Admixture occurs when individuals from ÛÞÖ ÖÙ ÔÖÙÌ ÎÌÕÌÛÐÊÈÓÓà ËÐř ÌÙÌÕÛÐÈÛ-ed populations interbreed and gene ŘÖÞ ÖÊÊÜÙÚ φ1ÐÜÚ ÈÕË #ÈÙÓÐÕÎ ʅƨΣΤȀō (ÕÈËËÐÛÐÖÕÓ Û Ï Ì Ì ř ÌÊÛÚ ÖÍ Û Ï Ì ÏÐÚÛÖÙÐÊ ÉÖŲÓÌÕÌÊÒ ÈÙÌ ÓÐÒÌÓà ÛÖ ÏÈÝÌ ÙÌËÜÊÌË the genetic variation within the loci. 3ÏÌ ËÐřÌÙÌÕÊÌ ÐÕ ÔÌÈÕ ÌÚÛÐÔÈÛÌË natural log probabilities between K = ΣÈÕË *ấʅÓ ÏÖÞ ÌÝÌÙÓ ÐÚ ÊÓÖÚÌÙ ÛÏÈÕ the other clusters, hinting that perhaps two clusters are forming in the population. Future studies could poÛÌÕÛÐÈÓÓà ÐÕÝÌÚÛÐÎÈÛÌ ÛÏÐÚ ÌřÌÊÛ ÜÚÐÕÎ more genetic loci.

[…]

(ÕËÐÊÌÚ ÖÍ &ÌÕÌÛÐÊ #ÐÝÌÙÚÐÛà

The mean expected heterozygosity was relatively low for the markers used in this study and ÛÏÌ ÛÖÛÈÓ ÕÜÔÉÌÙ ÖÍ ÈÓÓÌÓÌÚ ÈÛ ÛÏÌ ΣΤ markers was also low. Heterozygosity is commonly used as a measure of genetic variation and the values are expressed as the frequency of heteroáàÎÖÛÌÚ φÐōÌō ÛÏÌ ÈÓÓÌÓÌÚ ÈÙÌ ËÐřÌÙÌÕÛ ÈÛ ÌÈÊÏ ÓÖÊÜÚȀō(ÛÐÚ ÓÐÒÌÓà ÛÏÈÛ ÛÏÌ ÓÖÞ ÝÈÓÜÌ ÐÕ ÛÏÌ ,ÌËÈÕÖı9È×ÈÛÈ ÉÐÚÖÕ population is a consequence of the ÏÐÚÛÖÙÐÊÈÓ ÉÖŲÓÌÕÌÊÒō 3à×ÐÊÈÓÓàÓ ÈÍÛÌÙ È ÉÖŲÓÌÕÌÊÒ ÌÝÌÕÛÓ ÏÌÛÌÙÖáàÎÖÚÐÛà levels are expected to decline due to a random loss of alleles (Allendorf ÈÕË +ÌÈÙà ΣƟư'ƮÓ -ÌÐ ÌÛ ÈÓō ΣƟƯƒȀō population reduction can also result in inbreeding, or the mating between closely related individuals. Inbreeding increases the proportion of homozygotes (thereby reducing ÏÌÛÌÙÖáàÎÖÚÐÛàȀ ÈÕË ÊÈÕ ÈÓÚÖ ÐÕÊÙÌÈÚÌ sult in inbreeding, mono treiscicu 09D01F00239D08E009B02CID 423909D00A21.4 009D009100008E008

ÉÜřÈÓÖшĐÕшÛÏÌш4ÕĐÛÌËш2ÛÈÛÌÚшÈÕËш
"ÈÕÈËÈшÉÌÛÞÌÌÕшΣưưƨшÈÕËшΣƱʅƨǒш
PhD Thesis, Ohio State University.
#ÈÙàш#шφΣƱưƱАш*3ÏÌш!ÜřÈÓÖш!ÖÖÒǿшÛÏÌш%ÜÓÓш2ÈÎÈшÖÍшÛÏÌшÔÌÙÊÈÕш ÕĐÔÈÓ.*
Swallow Press, Chicago.
Derr JM, Hedrick PW, Halbert ND ÌÛшÈÓǒшφʅƨΣʅАш/ÏÌÕÖÛà×ĐÊшÌřÌÊÛÚш ÖÍшÊÈŲÓÌшÔĐÛÖÊÏÖÕËÙÐÈÓш#-шĐÕш American bison. *2ÖÊĐÌÛàшÍÖÙш"ÖÕservation Biology*, **26**φʈАÓшΣΣʈƨıΣΣʈʈǒ
Freese CH, Aune KE, Boyd DP et ÈÓǒшφʅƨƨƱАш2ÌÊÖÕËшÊÏÈÕÊÌшÍÖÙшÛÏÌш plains bison. *Biological Conservation*, **136**, ΣƱfłΣưTǒ
Gates CC, Freese CH, Gogan PJP, *ÖųÔÈÕш,шφʅƨΣƨАшÔÌÙÊÈÕш bison: status survey and conservation guidelines. IUCN, Gland, 2ÞĐųÌÙÓÈÕËǒ
&ÖÖËÕĐÎÏÛш"шφΣƱΣTАш,àÌß×ÌÙÌÕÊÌш with bison hybrids. *Journal of Heredity*, **5**ÓшΣƱƱłΣƱƱǒ
'ÈÓÉÌÙÛш-#Óш#ÌÙÙш)-шφʅƨΣƨАш!ĐÚÖÕш Genetics of the Great Sand Dunes National Park. Final Project Report, Texas A&M University.
Halbert ND, Ward TJ, Schnabel RD et al. φʅƨƨfАш"ÖÕÚÌÙÝÈÛĐÖÕшÎÌnomics: disequilibrium mapping ÖÍшËÖÔÌÚÛĐÊшÊÈŲÓÌшÊÏÙÖÔÖÚÖÔÈÓш segments in North American bison populations. *Molecular $ÊÖÓÖÎà*Ó**14** 'шφʅƨΣ Õш!ĐÚÖÕш

[illegible] animals: synthesis. *[illegible]* *Biology*, **20**[illegible]

[illegible]-ic admixture to the success of colonizing populations? *Trends* *[illegible]* **29(4)**, [illegible]

Sanderson EW, Redford KH, Weber B et al. [illegible] future of the North American bison: conceiving long-term, large-scale conservation of wildlife. *Conservation Biology*, **22**[illegible]

Schnabel RD, Ward TJ, Derr JN [illegible]-satellites for parentage testing in North American bison, *Bison bison* [illegible] *Genetics*, **31**[illegible]

Ward TJ, Bielawski JP, Davis SK et al. [illegible]-tle and bison species: a general approach using mtDNA markers and the parametric bootstrap. *[illegible]* **2**, [illegible]

[illegible]-netic variation within and relatedness among wood and plains bison populations. *Genome,* **42**, [illegible]

ALK-EML$_4$-Positive Cancers and Combination Therapy

Probing the Apoptotic Threshold

Teagan H. Glass

The following is an excerpt from a longer piece. For full text, please visit www.honorsjournal.com.

[…]

ĸĶɣ¥Yĸķ¥

çĦ▯ĸ🄀🄀▯¥Ħĸ diseases currently being researched, lung cancer is one of

initial slope of the curve and a larger Ì ř ÌÊÛ ÈÛ Û Ï Ì ÚÈÔ Ì ÊÖÕÊÌÕÜÈÛÐÕÕÚ ÈÚ crizotinib, indicating higher biolog-ÐÊÈÓ ÈÊÛÐÝÐÛà ÈÕË ÔÈßÐÔÈÓ Ì Ś ÊÈÊà Paragazole exhibited the least potency, by far, with an EC_{50} ÖÍ ţ ſ µM (%ÐÎ Σ#Ⱥ. Perhaps the most striking characteristics of paragazole treatment compared to that of treatment with either ALK inhibitor was the relatively miniscule slope and maximal Ì Ś ÊÈÊà ÖÍ Û Ï Ì ËÖÚÌıÙÌÚ×ÖÕÚÌ 6 ÏÐÓÌ higher concentrations of paragazole would be necessary to achieve a complete sigmoidal dose-response, the data collected represents the relative ÐÕÌ ř ÌÊÛÐÝÌÕÌÚÚ ÖÍ ' # "ÐÖÕÐÛÚ ÖÞÕ Based on the data produced from single-drug treatments, it is evident ÛÏÈÛ ÉÖÛÏ ÊÙÐáÖÛÐÕÐÉ ÈÕË /ţΣΣŢ ÖÕ their own achieve powerful maximal Ì Ś ÊÈÊÐÌÚÓÈÚ Þ ÌÓÓ ÈÚ ×ÖÛÌÕÊÐÌÚ ÈÛ ÙÌÈ-sonable concentrations, in terms of short-term *in vitro* treatment. Paragazole, on the other hand, exhibits ÔÐÕÐÔÈÓ ×ÖÛÌÕÊà ÈÕË ÔÈßÐÔÈÓ Ì Ś-cacy, even at concentrations much larger than that of either ALK inhibitor. Clearly, it is the kinase activity ÖÍ Û Ï Ì +*ı$, +T ÍÜÚÐÖÕ ×ÙÖÛÌÐÕ Û ÏÈÛ predominantly confers survival. Due ÛÖ Û Ï Ì ËÐÚ×ÈÙÐÛà ÉÌÛ Þ ÌÌÕ Û Ï Ì Ì ř ÌÊÛÚ of individual HDAC and ALK inhibition, it is not obvious that much stronger activity would be achieved in response to treatment with paragazole in combination of each of the two ALK inhibitors.

Combination ҚΥĸӈҞ Treatments

The focus of ҚΥĸӈҞ analysis is being able to quantify synergistic activity between two drugs in combination by creating a response surface model. Drug relationships are represented and evaluated by the Ғ ÝÈÓÜÌ Þ ÏÌÙÌ ҒØƔ ҒåƔ ÈÕË ҒøƔ ÈÙÌ indicative of antagonism, additivity, and synergism, respectively.

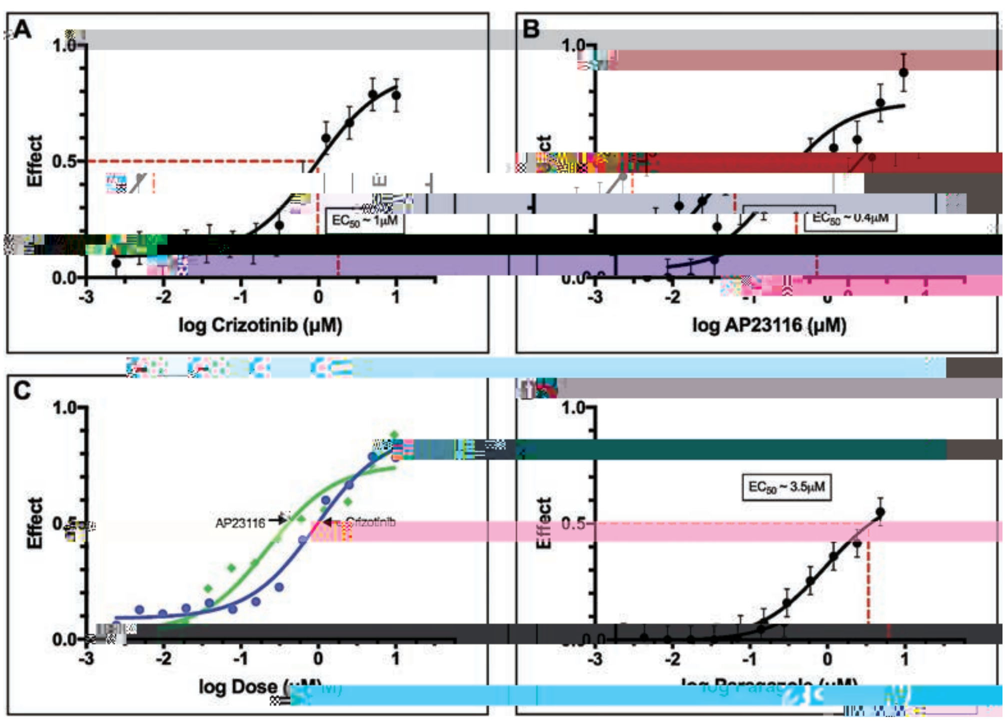


Figure 1. 2ÐÕÎÓÌıËÙÜÎ ËÖÚÌıÙÌÚ×ÖÕÚÌ φ Ⱥ #ÖÚÌıÙÌÚ×ÖÕÚÌ ÖÍ ' ţΣʅʅ ÛÖ ÊÙÐáÖÛÐÕÐÉ φ ! Ⱥ #ÖÚÌıÙÌÚ×ÖÕÚÌ ÖÍ ' ţΣʅʅ ÛÖ /ʅţΣΣţŢ φ " Ⱥ . ÝÌÙÓÈà ÖÍ ËÖÚÌıÙÌÚ×ÖÕÚÌ ÖÍ ' ţΣʅʅ ÛÖ ÊÙÐáÖÛÐÕÐÉ φ ÉÓÜÌ Ⱥ & /ʅţΣΣŢ φ ÎÙÌÌÕ Ⱥ ÈÕË Þ ÚÐÕÎÓÌ ÊÖÔÉÐÕÈÛÐÖÕ ÖÍ $" $_{50}$ φ # Ⱥ #ÖÚÌıÙÌÚ×ÖÕÚÌ ÖÍ ' ţΣʅʅ ÛÖ ×ÈÙÈÎÈáÖÓÌ

A crucial element of the experiment is establishing the baseline activity of each individual drug. This ÞÈÚ Ë ÖÕÌ É à ÛÙÌÈÛÐÕÎ ' ţΣ ļ ÞÐÛÏ ÊÙÐáÖÛÐÕÐÉÓ /ļţΣΣΤÙ ÈÕË ×ÈÙÈÎÈáÖÓÌ "in combination" with themselves in order to achieve purely additive responses. These self-self combinations àÐÌÓËÌË ƑÝÈÓÜÌÚÝÌÙà ÊÓÖÚÌ ÛÖ áÌÙÖ (%ÐÎõ ļÃõ3ÏÌ ÚÓÐÎÏÛËÌÝÐÈÛÐÖÕ ÖÍ ÛÏÌÚÌ ÝÈÓÜÌÚ ÍÙÖÔ ƑåƨÐÚ ÕÖÛÐÕËÐÊÈÛÐÝÌ ÖÍ antagonism, in the case of ALK self-self trial, or synergism, in the case of the HDAC self-self trial, but rather demonstrates that the set-up for the experiment was less than perfect; the numerous intensive and tedious steps of the drug addition process for ƘYĸĦƘ analysis yield many opportunities for small errors to be made. The presented data were produced from two biological replicated of each combination.

Establishing an additive baseline with the self-self trials is necessary to accurately determine the relationship between ALK and ' # "ÐÕÏÐÉÐÛÖÙÚ Þ Ï ÌÕ ' ţΣ ļ Ú Þ ÌÙÌ treated with the two combinations: ÊÙÐáÖÛÐÕÐÉƴ×ÈÙÈÎÈáÖÓÌ ÈÕË /ļţΣΣΤƴ paragazole. In order to verify the combination response, each drug pair is tested on two microplates, with the two drugs added in two ËÐř ÌÙÌÕÛÖÙÐÌÕÛÈÛÐÖÕÚõ%ÖÙ ÌÈÊÏ ÊÖÔ-bination, crizotinib/paragazole and /ļţΣΣΤƴ×ÈÙÈÎÈáÖÓÌÔƑÝÈÓÜÌÚÖÍ Þ ÌÓ over zero were produced, indicating strong synergistic activity for each ALKi/HDACi pair (%ÐÎõ ţÃõ - ÖÛÖÕÓà ËÖÛÎ Ì ƑÝÈÓÜÌÚÊÖÕÍÌÙ ÚàÕÌÙÎ àÛ ÉÜÛ so do the response surfaces produced by the ƘYĸĦƘ analysis (%ÐÎõ *TÃ*. The key feature of a synergistic surface response is the rounding of the response as the concentrations of each drug increase. This is clearly seen in both the crizotinib/paragazole (*Fig. T* È ÕË /ļţΣΣΤƴ×ÈÙÈÎÈáÖÓÌ ¶*Fig. T!Ã* response surfaces. This rounding indicates that as the concentration of one drug increases, less and less of the other drug is required to proËÜÊÌ ÛÏ Ì ÚÈÔ Ì Ì ř ÌÊÛÛ ÌßÌ Ô×ÓÐÍàÐÕÎ a synergistic relationship between each ALK inhibitor and paragazole. All results yielded positive k values, yet with varying magnitudes due All results yielded p9s the conce13 k SMC /Span a

2ÛÈÎÎÌÙÌË "ÖÔÉÐÕÈÛÐÖÕ 3ÙÌÈÛÔÌÕÛÚ

Since synergistic activity was observed with each ALKi/HDACi combination, staggered combination experiments were conducted in or- ËÌÙ ÛÖ ÌÚÛÈÉÓÐÚÏ ÐÍ ÛÏÌ ÖÉÚÌÙÝÌË Ìř ÌÊÛÚ were dependent on ALKi or HDACi. These experiments were done by ini- ÛÐÈÓÓà ÛÙÌÈÛÐÕÎ ' ţΣʅʅÚ ÞÐÛÏ ÖÕÌ ËÙÜÎ followed by the addition of the other ËÙÜÎ ÖÍ ÛÏÌ ×ÈÐÙ ÈÍÛÌÙ ʅƮ ÏÖÜÙÚ. ! ÖÛÏ combinations yielded stronger responses when ALKi was the initial treatment. As expected, due to the ËÐř ÌÙÌÕÊÌ ÐÕ ×ÖÛÌÕÊà ÉÌÛÞÌÌÕ ÛÏÌ two ALK inhibitors, the initial ad- ËÐÛÐÖÕ ÖÍ /ʅţΣΣƮ ÌßÏÐÉÐÛÌË ÏÐÎÏÌÙ potency and biological activity (*Fig. ƮA*) compared to when crizotinib was the initial treatment (*%ÐÎ ƮA*). Also, as expected, a higher potency was ÈÊÏÐÌÝÌË ÞÏÌÕ /ʅţΣΣƮ ÞÈÚ ÛÏÌ ÚÌÊondary treatment compared to crizotinib. Due to the fact that survival of ALK+ cancers is highly dependent on constitutive ALK activation, it is not surprising that ALK inhibition appears to be the dominating factor. However, the discrepancy between responses of ALKi as initial vs. secondary treatment could be due to the ÓÈÙÎÌ ËÐřÌÙÌÕÊÌ ÐÕ ×ÖÛÌÕÊà ÉÌÛÞÌÌÕ both ALK inhibitors and paragazole.)ÜËÎÐÕÎ Éà ÛÏÌ ÙÌÓÈÛÐÝÌÓà ÓÖÞ ÌŚÊÈÊà of paragazole single-drug treatment, it would not be expected that HDAC inhibition would lend itself to greatÌÙ +*Ð ÌřÌÊÛÐÝÌÕÌÚÚ ÌÛÚ ÚÐÔÜÓÛÈneous combination treatment yields dramatic results. In order to truly determine whether or not the observed synergistic activity is HDAC- or ALK-dependent, comprehensive mechanistic studies would be have to be conducted.

ƘĦɣƙҰɣɣĦçÇ

Combination therapy is becoming a widely used strategy to ÔÖÙÌ ŚÊÈÊÐÖÜÚÓà ÛÙÌÈÛ ×ÈÛÐÌÕÛÚ ËÐÈÎnosed with cancers harboring genetic ÈÉÌÙÙÈÛÐÖÕÚ ×ÌÊÐŗÊÈÓÓà ÛÏÖÚÌ ÞÏÐÊÏ confer drug resistance. Approximateóà ƱƨóƨƨƨƨƨƧƧ ×ÌÖ×ÓÌ ÈÙÌ ËÐÈÎÕÖÚÌË ÞÐÛÏ +*ı$, +Tı×ÖÚÐÛÐÝÌ ÕÖÕıÚÔÈÓÓ ÊÌÓÓ lung cancer each year (Sasaki et al. ʅƨΣƨA). 3ÏÌ ×ÙÌÝÈÓÌÕÊÌ ÖÍ ÛÏÌÚÌ ËÐÈÎnoses necessitates the formulation of ÌřÌÊÛÐÝÌ Ú×ÌÊÐŗá ÌË ÛÙÌÈÛÔÌÕÛÚ ÛÏÈÛ can overcome the resistance mech-

product, acquired drug resistance to ALK inhibition therapy is nearly inevitable. Therapeutic combinations are a promising method to overcome resistance mechanisms such as ALK Î ÌÕÌ ÈÔ×ÓÐ ÊÈÛÐÖÕ ÈÕËÍ ×ÖÐÕÛ ÔÜÚÈ

φ9ÏÈÕÎÌÛÈÓ5ls2ΣTA5' # "ÐÏÈÚÈÓÚÖ been shown to induce intrinsic apopÛÖÛÐÊ×ÈÙÏ ÞÈàÚÝÐÈ×ƒţÈÊÛÐÝÈÛÐÖÕ5!à inactivating nuclear histone deaceteÓÈÚÌÚ×ƒţÉÌÊÖÔÌÚÏà×ÌÙÈÊÌÛàÓÈÛÌËÓ preventing its inactivation via ubiqÜÐÛÐÕÈÛÐÖÕÉà, #, lφ9ÏÜÈÕÎls2ΣţA5 ×ƒţ ÈÊÛÐÝÈÛÐÖÕ ÐÕËÜÊÌÚ ÌßׯÙÌÚÚÐÖÕ of many downstream pro-apoptotic ÍÈÊÛÖÙÚ ÖÍ ÛÏÌ !ÊÓılÍÈÊÛÖÙÚÐÚÈÓÚÖÔÌÈËÐÈÛÌËÉà ÏàׯÙÈÊÌÛàÓÈÛÐÖÕ ÖÍ ÛÏÌ 'ţÈÕË 'T histone subunits, a result of class-I HDAC inhibition. Bao et al. also obÚÌÙÝÌË ÛÏÐÚ ÏàׯÙÈÊÌÛàÓÈÛÐÖÕ ÖÍ 'ţ ÈÕË 'T ÈÚ È ÙÌÚÜÓÛ ÖÍ ØÜÐÚÐÕÖÚÛÈÙ treatment. Finally, HDAC inhibition ÏÈÚÉÌÌÕ ÚÏÖÞÕ ÛÖ ÈÉÙÖÎÈÛÌ 23 3ţ activity, an essential transcriptional regulator of factors that promote cell survival, growth, proliferation, and ËÐřÌÙÌÕÛÐÈÛÐÖÕφ3ÈÒÌáÈÞÈ ÌÛÈÓ5ls2ΣΣA5 'àׯÙÈÊÌÛàÓÈÛÐÖÕ ÖÍ 23 3ţ ËÜÌ ÛÖ HDACi has been shown to inhibit its phosphorylation and catalyze its translocation from the nucleus to the cytoplasm, therefore diminishing its capability to induce transcription of its downstream factors (Gupta et al. ls2s0Ù9ÏÜÈÕÎls2ΣţA5

The fact that both ALKi and HDACi produce overlapping and ÕÖÕıÖÝÌÙÓÈ××ÐÕÎ ÌřÌÊÛÚ ÐÕ ÛÌÙÔÚ ÖÍ stimulating pro-apoptotic pathways could very well explain the synergistic relationship between the two inhibitors when administered to ALK$,+TÊÈÕÊÌÙÚ5 6 ÏÌÕÊÖÔÉÐÕÌËÞÐÛÏ ËÌ×ÓÌÛÐÖÕ ÖÍ +*ÈÕËÈ23 3ţÈÊÛÐÝÐty via ALKi, concurrent activation of the TNF pathway, along with the Ü×ıÙÌÎÜÓÈÛÐÖÕ ÖÍ ×ÙÖıÈ×Ö×ÛÖÛÐÊ!ÊÓılׯÙÖÛÌÐÕÚ ÝÐÈ×ƒţÐÕËÜÊÛÐÖÕ ÈÕËÏÐÚtone hyperacetylation, HDACi may overcome pro-survival mechanisms ÜÛÐÓáÌËÉà +*ı$,+T-2"+"Ú5"ÌÙtainly a threshold is reached whereÐÕÛÏÌ×ÙÖıÈ×Ö×ÛÖÛÐÊÌřÌÊÛÚ ÖÍ +* and HDAC inhibition overcome all pro-survival pathways and induce cell death. While much mechanistic-focused work must be done to validate this hypothesis, recent research, as well as the data presented ÐÕÛÏÐÚ×È×ÌÙÛÊÖÕ¸ÙÔÚÛÏÌÛÓÌÎÐÛÐÔÈcy of combining ALKi with HDACi ÈÚÈ ÔÌÈÕÚ ÖÍ ÛÙÌÈÛÐÕÎ +*ı$,+T cancers. In addition to establishing the precise mechanisms that confer synergy between these two drugs, employing this combination thera×àÖÕ +*ı$,+TÊÌÓÚÛÏÈÛ ÌßÏÐÉÐÛ ALKi-resistance would further the validity and value of this particular approach. Only by formulating a specialized treatment that is capable of overcoming acquired drug resistance to ALKi therapy can we improve the quality and longevity of life of those ËÐÈÎÕÖÚÌËÞÛÏ +*ı$,+Tı×ÖÚÛÐÝÌ cancers.

Bao, Lianmin, Hua Diao, Nian #ÖÕÎ◊7ÐÈÖØÐÖÕÎ◊2Ü◊!ÐÕÎÉÐÕ◊ Wang, Qiongya Mo, Heguo Yu, 7ÐÈÕÎËÖÕÎ◊6ÈÕÎ◊ÈÕË◊" ÏÌÕÎ-shui Chen. “Histone Deacetylase Inhibitor Induces Cell Apoptosis and Cycle Arrest in Lung Cancer Cells via Mitochondrial Injury ÈÕË◊/ƒţ◊4×ı ÊÌÛàÓÈÛÐÖÕ◊ɔ◊*Cell Biology and Toxicology*◊ţ◊ÕÖ◊Ţ◊ φ#ÌÊÌÔÉÌÙ◊Σ◊ɻɔΣŢÁò◊TŢƱłưɻ◊

Bayliss, Richard, Jene Choi, Dean A. Fennell, Andrew M. Fry, and Mark W. Richards. “Molecular

%ÈÕÎ ÌÛ ÈÓõ φ¶ƨΣƒÁ ÈÓÚÖ ÊÖÙ-related music to language and found that both music and speech involve perception, action, learning, memory, and emotion. They led a data-driven analysis in which participants underwent a natural stimulus ÍÜÕÊÛÐÖÕÈÓ , 1(φ - ıÍ , 1(Á Þ ÏÐÓÌ ÔÜ-sic and speech were used as stimuli. It was found that music and speech produced almost the same results, with distribution of activity as shown ÐÕ3ÈÉÓÌΣφ%ÈÕÎ ÌÛÈÓõÛ¶ƨΣƒÁõ

[…]

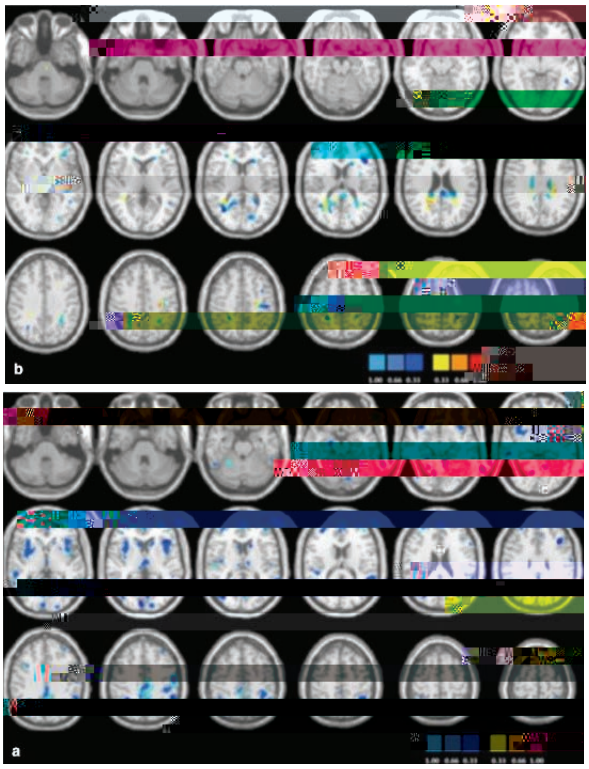
While fMRI proves to be a consistent and reliable tool for studying the brain, electroencephalogram φ$$&Á ÐÚ ÈÕÖÛÏ ÌÙ ÞÈà ÛÖ ËÌÛÌÙÔÐÕÌ the exact locations of the brain that processes music (Nizamie and TikÒÈÓ ¶ƨΣTÁõ(Û ÞÈÚ ËÐÚÊÖÝÌÙÌË Û Ï ÈÛ Û Ï Ì acoustic circuit involves the auditory nerve, brainstem, medial geniculate, body of the thalamus, and auditory ÊÖÙÙÌß φ - ÐáÈÔÐÌ ÈÕË 3ÐÒÒÈÓ ¶ƨΣTÁõ Not only do these areas of the brain strongly correlate to the limbic system, but after undergoing music therapy, schizophrenia patients showed ÚÐÎÕÐ¸ÊÈÕÛ ÊÏÈÕÎÌÚ ÐÕ ÛÏÌ ÍÙÖ

œ ’ • — ’ V • Ü aRsA L->Ìš¢ A ˜ — «êÔ „ÊÓì`ƒ`

there is a fair amount of documented functional imaging of disorders and ÛÏÌ ÈÙÌÈÚ ÖÍ ÛÏÌ ÉÙÈÐÕ ÛÏÌà ÌřÌÊÛõ (Õ order to ensure that music would affect the brain during an fMRI, StewÈÙÛ ÌÚ ÈÓõ ɻƨƨƬÆ ÍÖÜÕËÆÛÏÈÛ ÊÌÙÛÈÐÕ ÔÜsical listening disorders did in fact ÚÏÖÞ ÚÐÎÕÐ ÊÈÕÛ ËÐřÌÙÌÕÊÌÚ ÐÕ ÈÊÛÐvation with music stimuli. Stewart et ÈÓõ ɻƨƬÆ ÈÓÚÖ ÍÖÜÕËÛÏÈÙ óáÏÌÐÔÌÙÚ produced increased perfusion in the left temporal lobe and angular gyrus, and that musical hallucinations often occurred in patients with depression, schizophrenia, obsessive-compulsive disorder, and alcoholism. This review will not focus on Alzheimer's or alcoholism, but the research done by Stewart is worth mentioning as it is one of the only studies connecting music and psychiatric disorders during functional imaging.

Personality disorders are a common issue in today's society but is frequently misdiagnosed, with only È××ÙÖßÐÔÈÚÌóà ƯΣõƯŭ ÖÍ ËÐagnoses remaining constant upon a second evaluation by a psychiatrist (Merten et al., ɻƨΣƯÆõ 3ÏÌÙÌ ÈÙÌ ÔÈÕà Ûà×ÌÚ of personality disorders, but the most common are bipolar disorder, antisocial personality disorder, and narcissistic personality disorder. Bipolar disorder (ǨǨÆ ÏÈ××ÌÕÚ ÛÖ be the most common of the three, and upon using manual tracing methods with fMRI, ǨǨ ÚÏÖÞ ÚÈřÌÊÛÐÝÌ ÈÕË behavioral dysregulation, impairments of prosody and interpersonal connections, and disturbed relatedness, as well ÈÚ ÚÔÈÓÓÌÙ ÎÙÌà ÔÈỤÌÙ ÝÖÓÜÔÌ ÐÕ ÛÏÌ amygdala and hippocampus (Schulá Ì ÈÕË 1ÖÌ×ÒÌÚ ɻƨΣTÕ %ÙÈÕÎÖÜ ÌÛ ÈÓõ ɻƨΣTÆõ 3ÏÌÙÌ ŗÕËÐÕÎÚ ÈÙÌ ÚÐÎÕÐŗÊÈÕ in relation to this review because the amygdala and hippocampus are both involved in processing music, and the impairments in prosody shown could relate to how a person with ǨǨ would react to music. Antisocial personality disorder (ǩƬǨÆ ÈÕËÕÈÙcissistic personality disorder (ÇƬǨÆ both showed lower activation of the amygdala with orbitofrontal and ventromedial implications (Shulze ÈÕË 1ÖÌ×ÒÌÚ ɻƨΣTÆõ 3ÏÌ ÚÜÉÛÌ ËÐÍferences between ǨǨ and ÇƬǨ is key in looking for potential diagnostic abilities, as ǨǨ focuses on a smaller ÎÙÌà ÔÈỤÌÙ ÖÍ ÛÏÌ ÈÔà ÎËÈÓÈÚ ÞÏÐÓÌ ÇƬǨ focuses on lower activation, as ÚÏÖÞÕ ÉÆ %ÐÎÜÙÌ ɻõ

[…]



%ÐÎÜÙÌ ɻõ # ÐÚÊÙÐÔÐÕÈÛÐÖÕ ÔÈ×ÚÍÖÙ ÎÙÌà ÔÈỤÌÙ ÈÆÈÕËÆ ÞÏÐÛÌ ÔÈỤÌÙ ÉÆÈÓÈÚÐŗÊÈÛÐÖÕÉÌÛÞÌÌÕ patients with bipolar disorder and healthy inËÐÝÐËÜËÈÓÚõ %ÙÈÕÎÖÜ ÌÛ ÈÓõ ɻƨΣTÆ

ķçÇķ₢¥ɣɨçÇ

In summary, all psychiatric disorders discussed present with ËÐřÌÙÌÕÊÌÚ₪ÐÕ₪Û˙Ì₪ÈÔàÎËÈÓÈÓ₪ÐÕÚÜÓÈÓ₪ orbitofrontal regions, lingual gyrus, or cingulate gyrus, which are all regions connected to the processing of music in healthy individuals as ÞÌÓÓß₪ 3˙ÌÙÌ₪ ÈÙÌ₪ ÜÕÐØÜÌ₪ ËÐřÌÙÌÕÊÌÚ₪ for each disorder which lends to the hypothesis that music may be a reliable stimulus that produces unique results when studying functional imaging of the brain. While there is È₪ÚÐÎÕÐ˛ÊÈÕÛ₪ÈÔÖÜÕÛ₪ÖÍ₪ÙÌÚÌÈÙÊÏ₪ÛÏÈÛ₪ has been done studying music and the brain in healthy individuals and functional imaging of some psychiÈÛÙÐÊ₪ËÐÚÖÙËÌÙÚÛ₪ÙÌÚÌÈÙÊÏ₪ÐÕ₪Û˙Ì₪˛ÌÓË₪ of music psychophysiology is hardly complete. There is enough information to build a foundation for future research, but more research is needÌË₪ ÛÖ₪ ÊÙÌÈÛÌ₪ ÊÖÕÚÐÚÛÌÕÛ₪ ˛ÕËÐÕÎÚ₪ ÐÕ₪ the functional imaging of some disorders, such as in schizophrenia, depression, and others not mentioned in this review.

[…]

Based on the information given by the current research, it can be concluded that psychiatric disorders ÞÖÜÓË₪ÚÏÖÞ₪ËÐřÌÙÌÕÊÌÚ₪ÐÕ₪Û˙Ì₪ÉÙÈÐÕ₪ when stimulated with music and it may be hypothesized that one could use music in conjunction with fMRI to diagnose the aforementioned psychiatric disorders. If researchers are ÈÉÓÌ₪ ÛÖ₪ ˛ÕË₪ È₪ ÊÖÙÙÌÓÈÛÐÖÕ₪ ÉÌÛÞÌÌÕ₪ ÝÐÛÈÓÚ₪ ÔÜÚÐÊÔ₪ÈÕË₪Ú×ÌÊÐ˛Ê₪ËÐÚÖÙËÌÙÚ₪ while listening to music that is both unique to the disorder and reliable, È řÖÙËÈÉÓÌ₪Ï˙ÌÈÓÛÏÊÈÙÌÓ₪ËÐÈÎÕÖÚÐÚÓ₪ÈÕË₪ treatment of psychiatric disorders may be brought to the community and change the means, accuracy, and costs of mental health issue diagnosis and treatment.

Almeida, J. R. C. de, Versace, A., Mechelli, A., Hassel, S., Quevedo, K., Kupfer, D. J., & Phillips,

ΣʅưƗΣTƨǒ

Rogalsky, C., Rong, F., Saberi, K., &' ÐÊÒÖÒ&ǒφʅƨΣΣȺǒ%ÜÕÊÛÐÖÕ-al Anatomy of Language and Music Perception: Temporal and Structural Factors Investigated Using fMRI. *3ÏÌ)ÖÜÙÕÈÓÖÍ - ÌÜÙÖ-ÚÊÐÌÕÊÌ3ÏÌ . ŚÊÐÈÓ)ÖÜÙÕÈÓÖÍÛÏÌ 2ÖÊÐÌÛàÍÖÙ - ÌÜÙÖÚÊÐÌÕÊÌ, ƫΣφΣƨȺ*
ƫưTƫƗƫưƒʅǒ

Schulze, L., &1ÖÌ×ÒÌ2ǒφʅƨΣTȺǒ Structural and Functional Brain Imaging in Borderline, Antisocial, and Narcissistic Personality Disorder. In , *1(ÐÕ /ÚàÊÏÐÈÛÙà* φ××ǒƫΣƫƗƫTƨȺǒ2×ÙÐÕÎÌÙ! ÌÙÓÐÕ Heidelberg.

Smith, R., Fadok, R. A., Purcell, M., Liu, S., Stonnington, C., Spetzler, R. F., &! ÈßÛÌÙ+ǒ" ǒφʅƨΣΣȺǒ Localizing Sadness Activation Within the Subgenual Cingulate in Individuals: a Novel Functional MRI Paradigm for Detecting (ÕËÐÝÐËÜÈÓ# Ðř ÌÙÌÕÊÌÚÐÕÛ ÏÌ Neural Circuitry Underlying Depression. *! ÙÈÐÕ(ÔÈÎÐÕÎÈÕË! Ì-ÏÈÝÐÖÙ(ÕËÐÈÕÈ×ÖÓÐÚ, ƒφƫȺʅʅƱƗƫƱǒ*

2×ÖÖÙÔÈÒÌÙ5ǒ(ǒ5ÌÙÔÌŲÌÕ$ǒ Czisch, M., & Wilhelm, F. H. φʅƨΣTȺǒ%ÜÕÊÛÐÖÕÈÓ - ÌÜÙÖÐÔÈÎÐÕÎ of Anxiety Disorders. In , *1(ÐÕ /ÚàÊÏÐÈÛÙà*φ××ǒʅưƱƗƫƨΣȺǒ2×ÙÐÕÎ-er, Berlin, Heidelberg.

2ÛÈÕÈÙËÓ1ǒ/ǒφʅƨƨƨȺǒ ÚÚÌÚÚÔÌÕÛ