

natural science

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Data Collection

The microsatellite genetic data were collected from 100 individuals in a herd that had previously been collected and archived at Texas A&M University. Previously established protocols were used for the collection and genotyping of microsatellite markers. The markers used were: *BM1313*, *BM1314*, *BM1315*, *BM1316*, *BM1317*, *BM1318*, *BM1319*, *BM1320*, *BM1321*, *BM1322*, *BM1323*, *BM1324*, *BM1325*, *BM1326*, *BM1327*, *BM1328*, *BM1329*, *BM1330*, *BM1331*, *BM1332*, *BM1333*, *BM1334*, *BM1335*, *BM1336*, *BM1337*, *BM1338*, *BM1339*, *BM1340*, *BM1341*, *BM1342*, *BM1343*, *BM1344*, *BM1345*, *BM1346*, *BM1347*, *BM1348*, *BM1349*, *BM1350*, *BM1351*, *BM1352*, *BM1353*, *BM1354*, *BM1355*, *BM1356*, *BM1357*, *BM1358*, *BM1359*, *BM1360*, *BM1361*, *BM1362*, *BM1363*, *BM1364*, *BM1365*, *BM1366*, *BM1367*, *BM1368*, *BM1369*, *BM1370*, *BM1371*, *BM1372*, *BM1373*, *BM1374*, *BM1375*, *BM1376*, *BM1377*, *BM1378*, *BM1379*, *BM1380*, *BM1381*, *BM1382*, *BM1383*, *BM1384*, *BM1385*, *BM1386*, *BM1387*, *BM1388*, *BM1389*, *BM1390*, *BM1391*, *BM1392*, *BM1393*, *BM1394*, *BM1395*, *BM1396*, *BM1397*, *BM1398*, *BM1399*, *BM1400*.

Genetic Analysis

To analyze the structure of the population, I used the software program STRUCTURE (Pritchard et al., 2000). I used the admixture model and ran seven repetitions for each number of assumed genetic clusters and calculated the mean of logarithmic likelihood scores. The number of genetic clusters was determined by the change in the mean of logarithmic likelihood scores as the number of genetic clusters increased. The mean of logarithmic likelihood scores was calculated for each number of genetic clusters (K) and the value of K was determined by the value of K that resulted in the highest mean of logarithmic likelihood scores.

The K genetic cluster values based on methods published in the literature were used to determine the genetic structure of the population.

The two indices of genetic diversity, heterozygosity (H_E) and the number 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

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μ values and shows the most probable
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 different populations interbreed and gene frequencies are averaged.

the genetic variation within the loci. natural log probabilities between $K = 2$ and $K = 3$ are similar, suggesting that perhaps two clusters are forming in the population. Future studies could potentially identify more genetic loci.

[...]

The mean expected heterozygosity was relatively low for the markers used in this study and heterozygosity for the other markers was also low. Heterozygosity is commonly used as a measure of genetic variation and the values are expressed as the frequency of heterozygotes. The low heterozygosity in this population is a consequence of the small population size and the fact that levels are expected to decline due to a random loss of alleles (Allendorf & Luikart 2007). Population reduction can also result in inbreeding, or the mating between closely related individuals. Inbreeding increases the proportion of homozygotes (thereby reducing heterozygosity).

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ALK-EML₄-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.

[...]

diseases currently being researched, lung cancer is one of

initial slope of the curve and a larger EC_{50} for crizotinib, indicating higher biological activity. Paragazole exhibited the least potency, by far, with an EC_{50} of $1.4 \mu M$. Perhaps the most striking characteristic of paragazole treatment compared to that of treatment with either ALK inhibitor was the relatively miniscule slope and maximal effect. Based on the data produced from single-drug treatments, it is evident that each drug can achieve powerful maximal effects at reasonable concentrations, in terms of short-term *in vitro* treatment. Paragazole, on the other hand, exhibits

low activity, even at concentrations much larger than that of either ALK inhibitor. Clearly, it is the kinase activity 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 Treatments

The focus of this 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 CI index, which is indicative of antagonism, additivity, and synergism, respectively.

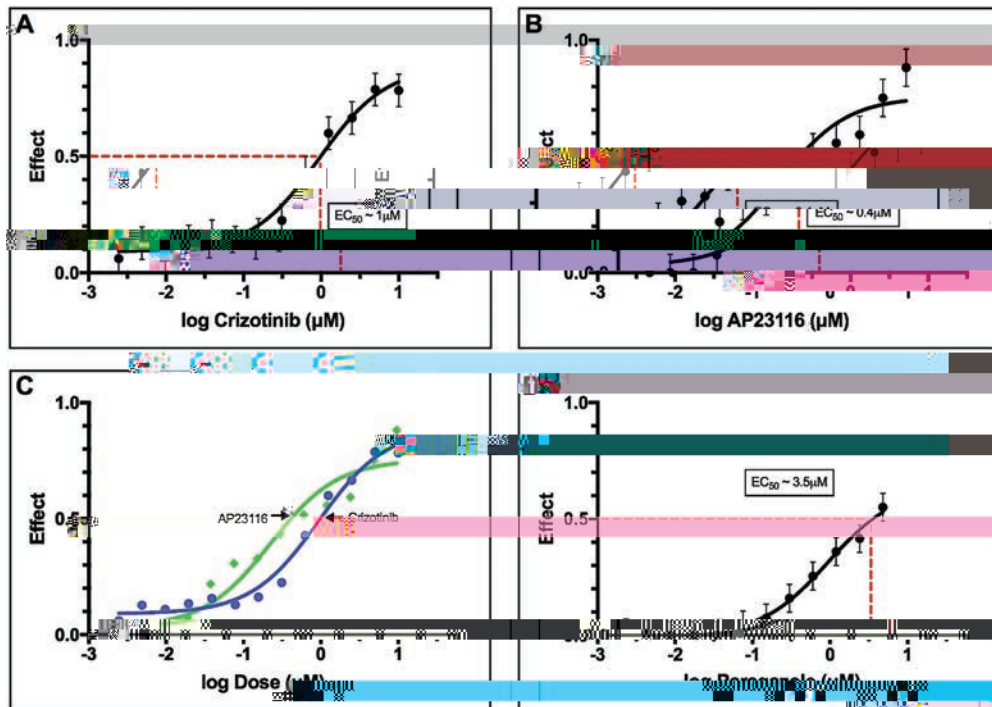


Figure 1. Dose-response curves for crizotinib, AP23116, and paragazole. Panel A shows crizotinib with $EC_{50} \sim 1 \mu M$. Panel B shows AP23116 with $EC_{50} \sim 0.4 \mu M$. Panel C shows a combination of AP23116 and crizotinib with $EC_{50} \sim 3.5 \mu M$. Each graph plots Effect (0.0 to 1.0) against log concentration (μM) (-3 to 1).

A crucial element of the experiment is establishing the baseline activity of each individual drug. This is done by testing each drug "in combination" with themselves in order to achieve purely additive responses. These self-self combinations are used to determine the baseline activity of each drug. 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 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 HDAC. Each drug pair is tested on two microplates, with the two drugs added in two different combinations, crizotinib/paragazole and crizotinib/HDAC. All results yielded positive k values, yet with varying magnitudes due to the synergistic relationship between each ALK inhibitor and paragazole. All results yielded p values less than 0.05, indicating strong synergistic activity for each

ALKi/HDACi pair. 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 and crizotinib/HDAC response surfaces. This rounding indicates that as the concentration of one drug increases, less and less of the other drug is required to produce a synergistic relationship between each ALK inhibitor and paragazole. All results yielded positive k values, yet with varying magnitudes due to the synergistic relationship between each ALK inhibitor and paragazole. All results yielded p values less than 0.05, indicating strong synergistic activity for each

° compared to when crizotinib was the initial treatment (1-^a . Also, as expected, a higher potency was observed with secondary 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 fact that both ALK inhibitors and paragazole. In the case of paragazole single-drug treatment, it would not be expected that HDAC inhibition would lend itself to great results. Simultaneous 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 have to be conducted.

Since synergistic activity was observed with each ALKi/HDACi combination, staggered combination experiments were conducted in order to determine if the responses were dependent on ALKi or HDACi. These experiments were done by initiating treatment with one drug followed by the addition of the other. The results showed that combinations yielded stronger responses when ALKi was the initial treatment. As expected, due to the fact that both ALK inhibitors, the initial administration of either drug yielded higher potency and biological activity (Fig.

Combination therapy is becoming a widely used strategy to treat lung cancer each year (Sasaki et al.). Lung cancer harboring genetic mutations that confer drug resistance. Approximately 30% of lung cancer cases are resistant to ALK inhibitors. The combination of ALK inhibitors and HDAC inhibitors 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

been shown to induce intrinsic apoptosis. Inactivating nuclear histone deacetylase preventing its inactivation via ubiquitination of many downstream pro-apoptotic factors. Finally, HDAC inhibition activity, an essential transcriptional regulator of factors that promote cell survival, growth, proliferation, and 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.

tainly a threshold is reached where 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 of combining ALKi with HDACi cancers. In addition to establishing the precise mechanisms that confer synergy between these two drugs, employing this combination therapy 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 cancers.

The fact that both ALKi and HDACi produce overlapping and stimulating pro-apoptotic pathways could very well explain the synergistic relationship between the two inhibitors when administered to ALK-tyrosine kinase inhibitors, concurrent activation of the TNF pathway, along with the inhibition of histone hyperacetylation, HDACi may overcome pro-survival mechanisms

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apy, schizophrenia patients showed

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1 «...» 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 «...» music and speech were used as stimuli. It was found that music and speech produced almost the same results, with distribution of activity as shown «...»

[...]

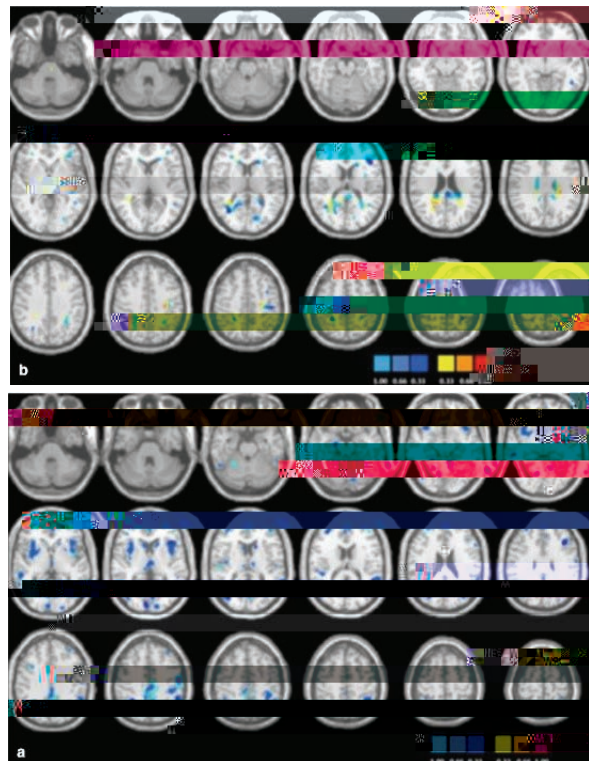
While fMRI proves to be a consistent and reliable tool for studying the brain, electroencephalogram «...» the exact locations of the brain that processes music (Nizamie and Tik-«...» acoustic circuit involves the auditory nerve, brainstem, medial geniculate, body of the thalamus, and auditory «...» Not only do these areas of the brain strongly correlate to the limbic system, but after undergoing music ther-

there is a fair amount of documented functional imaging of disorders and In order to ensure that music would affect the brain during an fMRI, Stewart et al. Musical listening disorders did in fact Variation with music stimuli. Stewart et al. 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 agnoses remaining constant upon a second evaluation by a psychiatrist (Merten et al.,) of personality disorders, but the most common are bipolar disorder, antisocial personality disorder, and narcissistic personality disorder. Bipolar disorder (.) be the most common of the three, and upon using manual tracing methods with fMRI, behavioral dysregulation, impairments of prosody and interpersonal connections, and disturbed relatedness, as well amygdala and hippocampus (Schulze)

. 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 would react to music. Antisocial personality disorder (.) narcissistic personality disorder (.) both showed lower activation of the amygdala with orbitofrontal and ventromedial implications (Shulze) differences between is key in looking for potential diagnostic abilities, as focuses on a smaller focuses on lower activation, as

[...]



1 patients with bipolar disorder and healthy in-

Major depression disorder

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and change the means, accuracy, and costs of mental health issue diagnosis and treatment.

In summary, all psychiatric disorders discussed present with orbitofrontal regions, lingual gyrus, or cingulate gyrus, which are all regions connected to the processing of music in healthy individuals as well as 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 has been done studying music and the brain in healthy individuals and functional imaging of some psychiatric disorders, the field of music psychophysiology is hardly complete. There is enough information to build a foundation for future research, but more research is needed on 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 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 able to identify unique stimuli while listening to music that is both unique to the disorder and reliable, the treatment of psychiatric disorders may be brought to the community

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