DRUG DISCOVERY

Computational Repositioning of the Anticonvulsant Topiramate for Inflammatory Bowel Disease

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Inflammatory bowel disease (IBD) is a chronic inflammatory disorder of the gastrointestinal tract for which there are few safe and effective therapeutic options for long-term treatment and disease maintenance. Here, we applied a computational approach to discover new drug therapies for IBD in silico, using publicly available molecular data reporting gene expression in IBD samples and 164 small-molecule drug compounds. Among the top compounds predicted to be therapeutic for IBD by our approach were prednisolone, a corticosteroid used to treat IBD, and topiramate, an anticonvulsant drug not previously described to have efficacy for IBD or any related disorders of inflammation or the gastrointestinal tract. Using a trinitrobenzenesulfonic acid (TNBS)–induced rodent model of IBD, we experimentally validated our topiramate prediction in vivo. Oral administration of topiramate significantly reduced gross pathological signs and microscopic damage in primary affected colon tissue in the TNBS-induced rodent model of IBD. These findings suggest that topiramate might serve as a therapeutic option for IBD in humans and support the use of public molecular data and computational approaches to discover new therapeutic options for disease.

INTRODUCTION

Inflammatory bowel disease (IBD), of which Crohn's disease (CD) and ulcerative colitis (UC) are the most common clinically defined manifestations, represents a group of chronic, progressive inflammatory disorders of the intestinal tract that affects more than 1 million individuals in North America alone (*1*). There is currently no known cure for IBD, and available treatment options are aimed toward controlling symptoms, promoting remission, and preventing relapse. Current treatment protocols for IBD incorporate chronic administration of corticosteroids and systemic anti-inflammatory drugs to reduce or inhibit primary inflammation, along with antibiotics to treat secondary infection (*2*). Chronic use of corticosteroids or systemic anti-inflammatory drugs (for example, 6-mercaptopurine) typically used to treat IBD is associated with severe side effects, and more targeted therapies such as anti-TNFα (tumor necrosis factor–α) drugs incur high costs and elicit a therapeutic response in only a subset of affected patients (*3*). Surgical removal of affected regions of the small or large intestine is also used as a treatment strategy. This option is expensive and highly invasive, and the disease can often remanifest in previously unaffected locations along the intestinal tract (*2*).

Here, we aimed to discover and validate new therapeutic options for IBD, using a systematic computational approach for drug repositioning that is based on integration of public gene expression signatures of drugs and diseases (*4*). We systematically evaluated gene expression signatures of IBD derived from public microarray data against a compendium of gene expression signatures comprising 164 drug compounds to infer previously undescribed therapeutic relationships between drug-disease pairs represented in the data sets. Among the highest-scoring therapies predicted from our approach was the corticosteroid prednisolone, a known treatment for IBD. The approved antiepileptic drug topiramate, which has not previously been described to have a therapeutic association with IBD or any other intestinal disorders, was unexpectedly ranked higher by our method (that is, higher predicted therapeutic score for IBD) than prednisolone. We therefore evaluated the efficacy of topiramate for IBD in three independent experiments using a trinitrobenzenesulfonic acid (TNBS)–induced rodent model of colitis.

RESULTS

Prediction of known and previously undescribed drugs for IBD

To discover new therapeutic agents for IBD, we compared the gene expression profiles from a compendium of 164 drug compounds (*5*) to a gene expression signature of IBD derived from publicly available experiments obtained from National Center for Biotechnology Information (NCBI) Gene Expression Omnibus (GEO) (*6*). We derived therapeutic predictions for drug-disease pairs based on the hypothesis that if a drug has a gene expression signature that is opposite of a disease signature, that drug could potentially be used as a treatment for that disease. Our method produces a negative score when the drug signature is oppositional to the disease signature and a positive score when they are concordant (see Materials and Methods). Among the strongest therapeutic predictions for CD is the corticosteroid prednisolone (score = −0.216), a well-known treatment for these conditions (*7*) (Fig. 1). We observed that topiramate, an anticonvulsant drug currently used to treat epilepsy, had a stronger therapeutic score for Crohn's (−0.220) (Fig. 1, red arrow) than the established therapeutic

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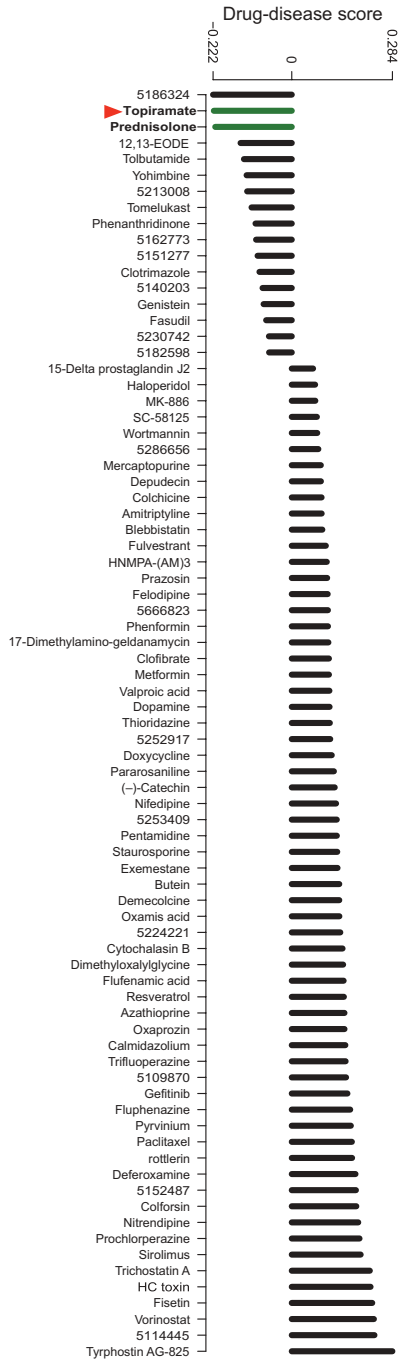

Fig. 1. Significant drug-disease scores for Crohn's disease (CD). The names of the drugs are placed along the bottom axis, and the vertical bars above the drug name indicate the computationally predicted therapeutic score for the drug based on comparison of the gene expression signature of the drug with the gene expression signature of CD. A positive score indicates that the drug exhibits an expression pattern that is synergistic with the disease, whereas a negative score indicates that the drug exhibits an expression pattern that is oppositional to the disease. Drugs are sorted from left to right starting with those predicted to be most efficacious for the disease. Green bars indicate drugs that are discussed in the text. The red triangle points toward the anticonvulsant drug topiramate, which was selected for experimental validation.

prednisolone. Based on our analysis, topiramate is also one of the strongest predicted therapies for UC, with a score of −0.219. Although another compound, an isoindoline carboxamide (ChemBridge 5186324), scored higher than topiramate by our method, we focused on topiramate for experimental validation because it is a Food and Drug Administration (FDA)–approved compound known to be generally safe in humans and is readily available for clinical use.

Experimental validation of topiramate as an indication for IBD

To determine whether our in silico drug indication predictions would translate into therapeutic efficacy in vivo, we tested whether topiramate would show efficacy for IBD by means of a TNBS-induced rat model of IBD. We performed an initial pilot validation experiment followed by two independent replication experiments in male Sprague-Dawley rats given TNBS [5% (w/v) total of 100 mg/kg] intrarectally to induce colitis. One group was not induced with TNBS and was treated with vehicle only, another group was induced with TNBS and treated with vehicle (TNBS + vehicle), and the third group was induced with TNBS and treated with topiramate (80 mg/kg per day) by oral gavage (TNBS + topiramate). A fourth group that was induced with TNBS and treated with prednisolone (3 mg/kg per day) served as a positive control (TNBS + prednisolone). After the initial TNBS induction, animals were treated for 7 consecutive days, and the induced IBD phenotype was assessed in vivo by video endoscopy at days 3 and 7.

Disease severity was assessed over the course of treatment by observation of clinical signs and by gross inspection of affected colon tissues after treatment termination. Animals treated with both prednisolone (TNBS + prednisolone) and topiramate (TNBS + topiramate) exhibited reduced incidence of diarrhea over the course of treatment compared to affected animals administered vehicle alone (TNBS + vehicle) (Fig. 2).

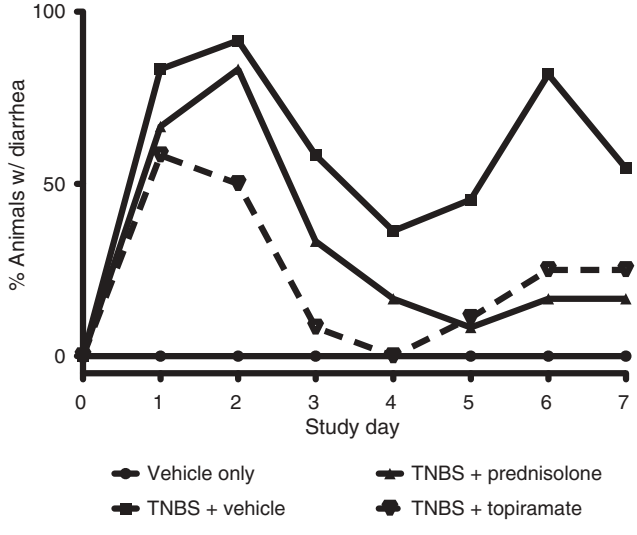

Fig. 2. Effect of topiramate on clinical evaluation of IBD severity. For each study day, treatment groups were scored by percent of animals with diarrhea within each group (n = 12 animals per group). The preponderance of diarrhea was found to be significantly different among treatment groups (one-way ANOVA, $P < 0.005$). IBD-induced animals treated with topiramate (TNBS + topiramate) exhibited significantly reduced diarrhea over the course of the study compared to the respective control (TNBS + vehicle; Tukey-Kramer test, $P < 0.05$).

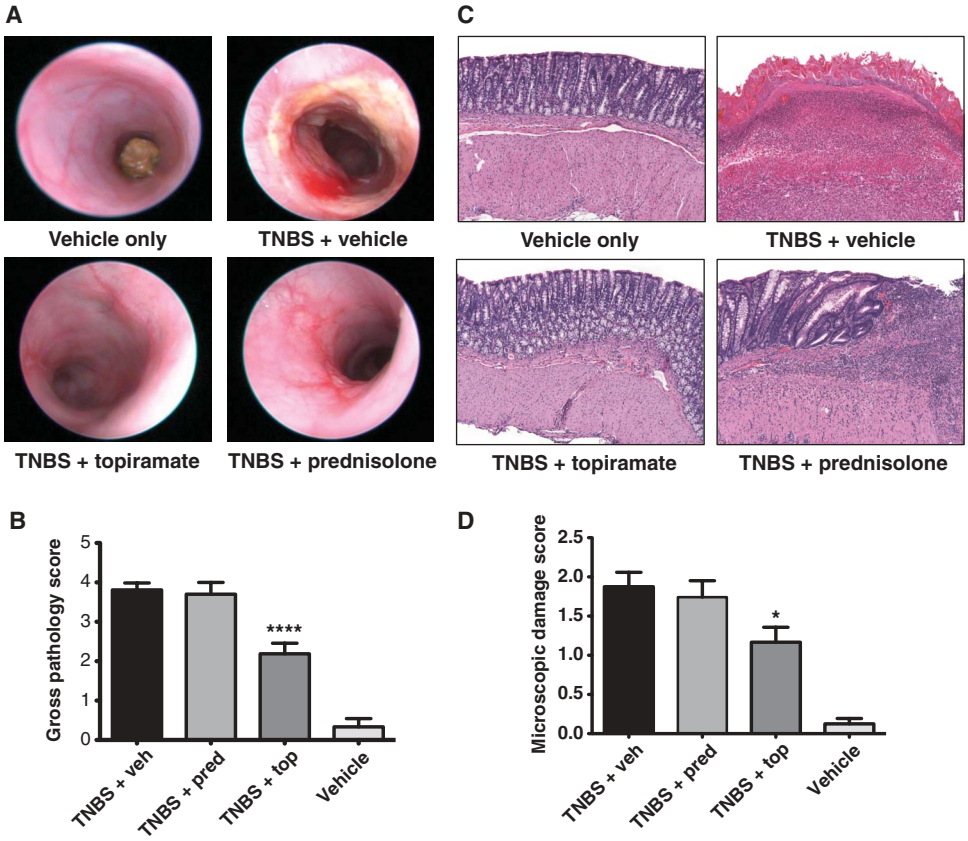

Fig. 3. Effect of topiramate on pathological assessment of IBD severity. (**A**) Clinical endoscopy captured from live animals on day 7 of the study. (**B**) Gross pathology score. (**C**) Micrographs of H&E-stained colon tissues showing microscopic damage to the mucosal and epithelial layers of the colon wall between treatment groups. (**D**) Macroscopic damage score assessed from light microscopy of fixed colon tissues. Data graphs represent the mean and SEM estimated from three independent experiments (n = 12 rats per group). *P < 0.05; ****P < 0.00005, two-sided Mann-Whitney U test.

Assessment of colitis by visual inspection of endoscopy video captured on day 7 of treatment and scoring of disease severity demonstrated reduced gross pathological inflammation and ulceration in the topiramate- and prednisolone-treated groups relative to the untreated (TNBS + vehicle) group (Fig. 3A and videos S1 to S4). Quantitative assessment of the gross pathological characteristics revealed that animals in the topiramate-treated group (TNBS + topiramate) exhibited significantly reduced swelling, ulceration, and other gross pathological characteristics compared to animals in the untreated (TNBS + vehicle) group (P < 0.0001, Mann-Whitney U test; n = 12 per group) (Fig. 3B).

Microscopic damage was assessed by histopathology analysis of fixed colon tissue sections harvested at the conclusion of the dosing schedule. Visual inspection of fixed colon tissues revealed extensive destruction of the colon mucosal layer in the untreated colitis-induced group (TNBS + vehicle), which was substantially ameliorated in colitis-induced animals receiving topiramate (TNBS + topiramate) (Fig. 3C). Quantitative evaluation demonstrated significantly reduced microscopic damage in animals treated with topiramate compared to animals in the untreated (TNBS + vehicle) group (P < 0.05, Mann-Whitney U test; n = 12 per group) (Fig. 3D). Together, these data provide evidence that topiramate exhibits efficacy against IBD in the TNBS model, as predicted by our computational method.

Expression signature evaluation

The predicted efficacious relationship between IBD and topiramate was inferred from public data, suggesting that particular sets of genes would exhibit oppositional expression between drug and disease. Comparative visual inspection of the Crohn's and topiramate expression signatures revealed the expected antithetical expression patterns between the drug and the disease, and functional enrichment analysis indicated that genes involved with gastrointestinal disease, inflammatory response, and other immune-related functions were reciprocally expressed between the drug-affected and the disease-affected conditions (Fig. 4A).

We performed quantitative polymerase chain reaction (qPCR) analysis spot checks of postmortem colon tissues to evaluate whether the expected expression patterns of genes reflected in the public gene expression data driving our prediction were observed in the animal validation study. We randomly selected eight genes for qPCR analysis from those genes exhibiting opposing expression patterns between drug and disease expression signatures and for which commercial primers were available (see Materials and Methods). qPCR analysis revealed that two of these genes, *TRPV1* and *IFI30*, were differentially expressed between treatment groups in the direction expected from comparison of the public molecular data (Fig. 4B). *TRPV1* was significantly up-regulated in the topiramate-treated group (TNBS + topiramate) relative to the untreated disease-induced group (TNBS + vehicle) (P < 0.05, Mann-Whitney U test; n = 12 per group), and *IFI30* was significantly down-regulated in the topiramate-treated group relative to the untreated disease-affected group (TNBS + vehicle) (P < 0.005, Mann-Whitney U test; n = 12 per group). These findings corroborate the expected oppositional relationships between these genes reflected in the expression signatures that were used to computationally predict an efficacious relationship between topiramate and IBD.

DISCUSSION

Using an in silico approach based on the integration of publicly available gene expression data, we inferred that the anticonvulsant topiramate was a potential new therapeutic agent for IBD and performed an experimental validation that confirmed topiramate's efficacy in ameliorating a TNBS-induced rodent model of IBD. The precise mechanism of action for topiramate is unknown, but it is known to enhance the activity of γ-aminobutyric acid (GABA)–activated chloride channels, activate kainate and AMPA receptors, and inhibit the activity of some carbonic anhydrase enzymes (*8*). Topiramate is administrated orally

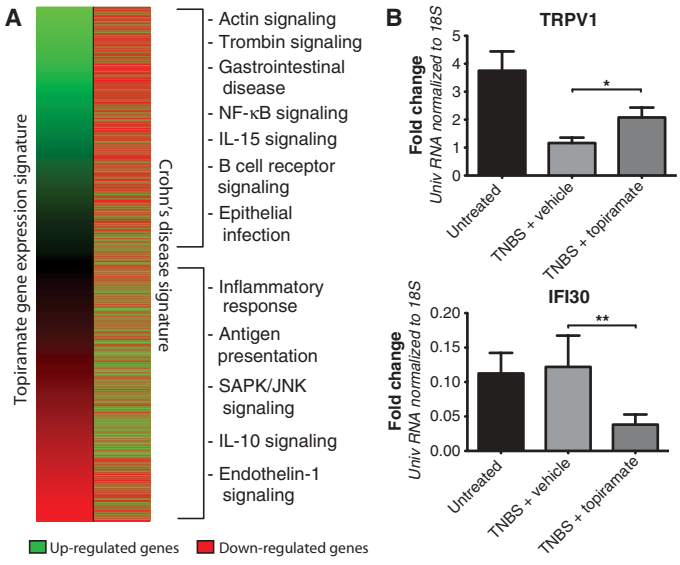

Fig. 4. Evaluation and comparison of gene expression signatures for the drug compound topiramate and CD. (**A**) Comparison of the CD signature (right) to the topiramate gene expression profile (left) showing a generally anticorrelated pattern, with genes at the top- and bottommost ends of the expression pattern showing generally oppositional expression patterns. Genes that are up-regulated are shown in green. Genes that are down-regulated are shown in red. The pathways and functional groups significantly enriched (enrichment $P < 0.05$) in the top and bottom 25% of genes are shown on the right-hand side. (**B**) qPCR results showing that gene transcripts for *TRPV1* and *IFI30* have oppositional gene expression levels in the disease condition (TNBS + vehicle) relative to the drug-treated condition (TNBS + topiramate) in colon tissues collected from the animal validation study, which corroborates their expected oppositional relationship from initial comparison of the topiramate and Crohn's expression signatures. *MAPK3*, *ALOX5*, and *CHRM3* also showed transcript abundance trends in the expected direction but did not reach statistical significance ($n = 12$ rats per group). $^*P < 0.05$; $^{**}P < 0.005$, two-sided Mann-Whitney *U* test. Error bars, SEM. Univ RNA, Universal Rat Reference RNA.

and is often used to treat seizures and migraines as well as depression. Although topiramate has not previously been suggested as a therapy for IBD, it has been investigated for off-label use in treating obesity and type 2 diabetes (*9*, *10*) and was recently shown to be effective against multiple sclerosis (*11*). Although elucidation of the precise mechanism of action by which topiramate acts to ameliorate the induced IBD phenotype in our study requires follow-up investigations, functional enrichment analysis reveals that sets of genes related to nuclear factor κB (NF-κB) signaling, the inflammatory response, and antigen presentation—all of which are relevant to the pathophysiology of IBD—are antithetically expressed in the disease and drug expression profiles (Fig. 4). Previous work has demonstrated that inhibition of carbonic anhydrase IV, a known target of topiramate, enhanced recovery from colitis in a dextran sulfate sodium–induced murine model of colitis (*12*). Here, topiramate may therefore be acting at least in part through this mechanism to ameliorate the TNBS-induced IBD phenotype.

Using a TNBS-induced rodent model of IBD, we demonstrated that induced animals treated with topiramate (TNBS + topiramate) showed improvements in both gross and microscopic measures of disease pathology relative to the relevant vehicle-treated group (TNBS + vehicle), with endpoints exceeding even the prednisolone-treated positive control group. Both topiramate and prednisolone reduced the severity of diarrhea over the course of treatment relative to the vehicle-treated group (TNBS + vehicle); however, only the topiramate-treated group exhibited significantly reduced gross pathology and microscopic damage scores (Fig. 3, B and D). Although prednisolone is an established treatment for IBD in humans and was correctly identified as therapeutic by our computational method, previous studies have reported limited efficacy of prednisolone in chemically induced rodent models of IBD (*13*). Prednisolone does prevent the complete loss of the mucosal layer observed in the induced vehicle-treated animals (TNBS + vehicle); however, the potent immunosuppressive effects of prednisolone likely slow healing from the initial chemical insult and may render damaged tissues more susceptible to secondary bacterial infections.

Although the experimental results from the rodent model of IBD corroborate our computational predictions derived from gene expression measurements of human disease, there are several caveats that could potentially limit the interpretation of the results. Foremost, we have only demonstrated the efficacy of topiramate for IBD in one animal model, which may not be representative of IBD pathology in humans. The TNBS model used in this study is the most widely used rodent model for human IBD, and previous molecular studies have established that it shares many molecular characteristics of human IBD, such as overproduction of interferon-γ (IFN-γ) mediated by T helper 1 (T_H1) T cells (*14*, *15*). However, rat-based TNBS models tend to develop colitis with fibrosis in the distal colon, whereas the ileum is the primary site of CD in human subjects (*16*). Furthermore, the TNBS-induced rodent model is more representative of an acute IBD flare-up than the chronic condition; therefore, additional studies are needed to determine whether topiramate could serve as an effective long-term therapy for chronic IBD in humans. Next, we noted that only two of the eight genes from the human IBD gene signature chosen for PCR validation in the rodent model showed a statistically significant difference between the induced untreated (TNBS + vehicle) and the topiramate-treated groups (TNBS + topiramate). This may be explained by species differences in gene expression between human intestinal tissue, which was used to select the genes, and rat intestinal tissue. In addition, several of these genes may reach distinguishing expression levels only after a longer period of treatment. Finally, our study evaluated only a single, albeit relatively conservative, dose level of topiramate; therefore, additional studies are needed to evaluate the optimal dose ranges for use of topiramate.

Here, we demonstrated that computational approaches leveraging public gene expression microarray data can be used to infer potential drug therapies for IBD and offer experimental evidence that the anticonvulsant topiramate is capable of ameliorating disease pathophysiology in a TNBS-induced rodent model of IBD. Because topiramate is already established as a safe and effective drug for treating neurological diseases in humans, and the side effect profile is generally more favorable than that of most drugs typically used to treat IBD (*2*, *17*), these results suggest that additional clinical investigation into the use of topiramate for treating IBD in human subjects could be beneficial. Additionally, these findings support the need for future studies in which computational approaches for leveraging publicly available molecular data for drug repurposing are further developed and applied toward additional diseases.

MATERIALS AND METHODS

Computational prediction and assessment of novel IBD therapies

Computational prediction and assessment of novel IBD therapies was performed as described in a paper appearing in this issue (*4*). In brief, publicly available gene expression measurements were obtained from NCBI GEO (*6*), with data from a previously published experiment measuring CD and UC in human intestinal tissue obtained by biopsy (GDS2642). Array probes were mapped to NCBI Entrez gene identifiers with the AILUN system (*18*). In cases where multiple microarray probes mapped to the same NCBI gene identifier, we averaged across individual probe expression values and assigned the averaged value to the gene. Using the significance analysis of microarrays (SAM) software, we created a disease gene expression signature (that is, disease signature) by deriving the set of differentially expressed genes between the disease-affected and healthy control samples (*19*).

We systematically compared gene expression profiles of drugs obtained from the Connectivity Map (*5*) to derive a therapeutic score. A randomization approach was used to determine statistical significance, and drugs with predicted therapeutic scores below the significance threshold were ranked in reverse order according to their score. Drugs with significant negative scores have gene expression patterns that are anticorrelated, or in opposition to the disease gene expression pattern, and therefore represent putative new therapeutic indications. Specific details regarding the genes and expression levels contributing to the predicted therapeutic match between IBD and topiramate are listed in table S1.

Functional analysis of IBD and topiramate expression signatures

Functional analysis of the up- and down-regulated genes in the Crohn's and topiramate signatures (Fig. 4) was performed through the use of IPA (Ingenuity Systems). This functional analysis identified the biological functions and/or diseases that were most significant to the data set. Genes in the top and bottom 25% of rank change versus normal in both drug-affected and disease-affected conditions and that were associated with biological functions and/or diseases in the Ingenuity Knowledge Base were considered for the analysis. Right-tailed Fisher's exact test was used to calculate a *P* value determining the probability that each biological function and/or disease assigned to that data set is due to chance alone.

Experimental evaluation of topiramate in a rodent TNBS model of IBD

Experimental validation of treatment efficacy was performed with a TNBS (also known as picryl sulfonic acid)–induced rodent model of IBD (*20*, *21*). Male Sprague-Dawley rats weighing ~300 to 350 g were used in the study. Rats were fasted overnight before initialization of the study. TNBS (100 mg/kg) diluted in 50% ethyl alcohol was administered via a polyethylene catheter (PE-90) 4 to 5 cm from the anus as a rectal enema to rats under 2% isoflurane inhalation anesthesia. The control group of rats got equal volume of the vehicle (50% ethyl alcohol in water). Topiramate (80 mg/kg) dissolved in 1 M sodium hydroxide [2.5% (v/v)] or vehicle used for topiramate was administered through a stainless steel feeding needle as oral gavage daily for 7 days starting a day after TNBS administration. Rats were monitored daily for signs of colitis (diarrhea). On day 8, all the rats were killed and tissues (distal segment of the colon) were harvested for macroscopic damage scores (MDSs) and histology. The initial pilot study used eight animals per treatment group. Two independent replication studies used 12 animals per treatment group. The initial animal study was performed at Stanford University School of Medicine. The independent replicate studies were performed by Biomodels LLC and MD Biosciences Inc.

Quantitative reverse transcription–PCR analysis

Extraction of RNA. RNA was extracted from tissue with a standard protocol for Trizol (Invitrogen, Life Technologies)/chloroform. In brief, frozen colon tissues were transferred into 1 ml of Trizol and homogenized in a rotor stator homogenizer (Polytron PT 1200 E, Kinematica AG). After homogenization and addition of chloroform, tissue suspensions were centrifuged at 4°C for 15 min, resulting in the formation of three phases. Total RNA, located in the upper aqueous phase, was subsequently precipitated with isopropanol (100%). After two wash steps in 75% ethanol, RNA was pelleted and diluted in tris-EDTA buffer (Ambion, Life Technologies). Concentration of RNA was assessed by NanoDrop (Thermo Fisher Scientific Inc.).

Reverse transcription. For complementary DNA (cDNA) synthesis, 2 μg of total RNA was reverse-transcribed with SuperScript III (Invitrogen) according to the manufacturer's protocol.

Gene expression analyses. Transcriptional levels for nine genes, including *18S* as an endogenous control gene, were assessed in 36 samples (12 controls, 12 vehicle-treated, and 12 drug-treated rats) in duplicates with quantitative reverse transcription–PCR (qRT-PCR). All reagents were purchased from Applied Biosystems, and reactions were run on a TaqMan HT7900 machine (Applied Biosystems, Life Technologies) for a total of 40 cycles. Gene expression assays had the following accession numbers: *18S* (Hs99999901_s1), *ALOX5* (Rn00563172_m1), *ALOX5AP* (Rn00568506_m1), *TRPV1* (Rn00583117_m1), *CHRM3* (Rn00560986_s1), *IFI30* (Rn01420317_m1), *MAPK3* (Rn00820922_g1), *IL-6* (Rn01410330_m1), and *IL-10* (Rn00563409_m1). Gene expression levels were calculated with the $\Delta\Delta C_t$ method.

Macroscopic damage assessment

MDS was assessed in a blinded fashion by examination of excised colons harvested at study termination. After removal of the distal colon segment (~5 to 7 cm), tissue specimens were cut longitudinally, flushed gently with normal saline to clear the fecal matter, and photographed. They were scored by a blinded observer for tissue damage with the following criteria: 0, no inflammation; 1, swelling or redness; 2, swelling and redness; 3, one or two ulcers; 4, more than two ulcers or one large ulcer; 5, necrosis.

Histopathology and microscopic damage assessment

A piece of the colon tissue was placed in 10% buffered formalin and fixed overnight. The next day, they were paraffin-embedded and cut into 5-μm sections. The sections were stained with hematoxylin and eosin (H&E) and examined under light microscopy. The slides were scored according to a grading system established previously (*22*).

Endoscopy

Endoscopy was performed in a blinded fashion with a small animal endoscope (Karl Storz Endoskope). To evaluate colitis severity, we anesthetized animals with isoflurane and subjected them to video endoscopy of the lower colon.

SUPPLEMENTARY MATERIAL

www.sciencetranslationalmedicine.org/cgi/content/full/3/96/96ra76/DC1
Table S1 caption.
Video descriptions.
Table S1. Details of drug and gene signatures (Excel file).
Video S1. Endoscopy of healthy controls.
Video S2. Endoscopy of TNBS-induced untreated.
Video S3. Endoscopy of TNBS-induced treated with prednisolone.
Video S4. Endoscopy of TNBS-induced treated with topiramate.

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Computational Repositioning of the Anticonvulsant Topiramate for Inflammatory Bowel Disease

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Editor's Summary

Greening Drug Discovery

Recycling is good for the environment—and for drug development too. Repurposing existing, approved drugs can speed their adoption in the clinic because they can often take advantage of the existing rigorous safety testing required by the Food and Drug Administration and other regulatory agencies. In a pair of papers, Sirota *et al*. and Dudley *et al*. examined publicly available gene expression data and determined the genes affected in 100 diseases and 164 drugs. By pairing drugs that correct abnormal gene expression in diseases, they confirm known effective drug-disease pairs and predict new indications for already approved agents. Experimental validation that an antiulcer drug and an antiepileptic can be reused for lung cancer and inflammatory bowel disease reinforces the promise of this approach.

The authors scrutinized the data in Gene Expression Omnibus and identified a disease signature for 100 diseases, which they defined as the set of mRNAs that reliably increase or decrease in patients with that disease compared to normal individuals. They compared each of these disease signatures to each of the gene expression signatures for 164 drugs from the Connectivity Map, a collection of mRNA expression data from cultured human cells treated with bioactive small molecules that is maintained a t the Broad Institute at Massachusetts Institute of Technology. A similarity score calculated by the authors for every possible pair of drug and disease ranged from +1 (a perfect correlation of signatures) to −1 (exactly opposite signatures). The investigators suggested that a similarity score of −1 would predict that the drug would ameliorate the abnormalities in the disease and thus be an effective therapy.

This proved to be true for a number of drugs already on the market. The corticosteroid prednisolone, a common treatment for Crohn's disease and ulcerative colitis, showed a strong similarity score for these two diseases. The histone deacetylase inhibitors trichostatin A, valproic acid, and v orinostat were predicted to work against brain tumors and other cancers (esophagus, lung, and colon), and there is experimental evidence that this is indeed the case. But in the ultimate test of method, the authors confirmed two new predictions in animal experiments: Cimetidine, an antiulcer drug, predicted by the authors to be effective against lung cancer, inhibited tumor cells in vitro and in vivo in mice. In addition, the antiepileptic topiramate, predicted to improve inflammatory bowel disease by similarity score, improved damage in colon tissue of rats treated with trinitrobenzenesulfonic acid, a model of the disease. These two drugs are therefore good candidates for recycling to treat two diseases in need of better therapies—lung cancer and inflammatory bowel disease—and we now have a way to mine available data for fast routes to new disease therapies.

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