Tell us about your experiences as a New American – whether as an immigrant yourself or as a child of immigrants – and how those experiences have informed and shaped what you have accomplished so far in your life. The program is especially interested in accomplishments – in any aspect of your life - that help us understand your originality, initiative and creativity. Feel free to discuss how parents, teachers, mentors and or institutions have supported – or impeded – your progress. If you believe that distinctive features of American governance and society have been important to an understanding of your story, feel free to discuss that as well.

To convince my parents to give me an allowance in fifth grade, I surveyed my peers' allowances, which ranged from a flat amount per week to a rate per chore or "A" grade. I tabulated the data, made charts, took averages, and presented the results to my parents. They were impressed that I collected this data, but they never received an allowance and weren't planning on giving me one. They were appalled that some parents were paying their children for what they should be doing -- keeping the house clean and doing well in school. Since they didn't like the chore idea, I asked for $5 a week. They gave me $1.

My parents expect me to seize opportunities, as I did in a small way with allowances, and as they did when they emigrated from the Soviet Union (USSR). Sensing rising political tensions in 1991, my father took a short teaching opening in the United States (US). The USSR collapsed later that year. In the USSR, post-secondary education is not as meritocratic, and if we had stayed, I could not have attended the Massachusetts Institute of Technology (MIT).

I was excited to attend MIT because it played a pivotal role in the Human Genome Project, which I was fortunately exposed to in eighth grade. To me, the genome represents a future of personalized medicine, so I seized every opportunity to learn more about genomics, exploring four different labs in college. In my first research experience at Prof. Martha Bulyk's lab, I performed molecular biology experiments and ran Perl scripts. I was amazed at how microarrays polka-dotted with tens of thousands protein-DNA binding pairs could be transformed into eight-letter binding affinities. This experience hooked me on computation; I saw how much power there was in using mathematics and computer science to solve biological problems. During my first computational lab experience with Dr. Sean Eddy at Howard Hughes Medical Institute Janelia Farm, I developed a null model for protein sequence comparison using Hidden Markov Models. Thirsty for more research experiences, I explored two more laboratories: in Prof. David Gifford's lab I worked on network differences between two yeast strains, and on modeling infection in the immune system; in Prof. Sebastian Seung's lab I studied neuron orientation in rabbit retina. After college, I worked at the Broad Institute with Dr. Jill Mesirov and helped develop REVEALER, an algorithm that finds novel associations between genetic mutations and gene expression. We discovered several exciting alternative oncogenes that explain high cancer pathway expression.

After working at the Broad, I wanted more formal training in bioinformatics, so I began a Master's degree at the University of California, Santa Cruz (UCSC). There, I noticed I already took one of the classes, Computational Systems Biology, so to waive the requirement I TA'd the course, the first 1st-year student to TA a graduate-level course. Additionally, I took an extra course each quarter and completed the 2-year MS program in 9 months. Under the supervision of Prof. Nader Pourmand, I studied chemotherapy resistance in breast cancer at the single cell level, and will continue single-cell analysis during my PhD at UC-San Diego (UCSD).

At UCSC, I took advantage of every opportunity to teach. As part of a team of students and a professor, I pioneered bioinformatics teaching modules in high school biology. My curriculum was the best-received and was titled "Genes and Disease," in which students chose a gene related to a familiar disease or condition and explored its properties - protein size, biological function, chromosomal location, and so on. One creative group explored "maple syrup urine syndrome," and found that the gene associated with this condition plays a role in sugar metabolism. This bridge from genetic defect to disease causation was an anomaly, as most students found tangled links between disease and genes, as in true research. Pleased with the success of the pilot project, we released the curriculum on the web, where it has hundreds of international views. I am continuing to refine this unit and develop others through UCSD's ScienceBridge, which targets underserved high schools in San Diego. Any computer on the web can do bioinformatics, and I hope that in teaching underprivileged students these skills, I can empower them to pursue science.

This summer, I built on my earlier experiences and developed a stem cell biology curriculum for minority undergraduates embarking on a summer research project. I believe it is important to target minorities because while the US is more meritocratic than the USSR, these students may have faced subtle discrimination and hopefully in the future we won't need these targeted programs. My favorite aspect of the course, though it was also the most difficult, was planning the "inquiry" part of the curriculum, where learners developed their own unique method of investigation, as in authentic research. Our process goal was for learners to realize that cell identity is a continuous spectrum and to become more comfortable with conflicting information – important realities of research. As one of three facilitators, I taught bioinformatics as a method of exploring biology. I debated whether to clean up the data, but decided it would diminish the experience of mirroring authentic research, as real data is not clear-cut whatsoever. The students' dedication to science in face of overwhelming amounts of data was inspiring.

In addition to teaching, I also enjoy organizing conferences as it is critical to effectively communicate scientific research. This summer I was the youngest co-chair of the Student Council Symposium (SCS) at Intelligent Systems for Molecular Biology (ISMB), the largest international computational biology conference, held in Long Beach, CA. We had 60 attendees from six continents, and I savored meeting the travel fellowship recipients and experiencing their unyielding commitment to research. The SCS is a great venue for students to present to a broad audience, and some for the first time in English. I was honored to be able to facilitate such a life-changing event for my peers.

As a New American, I have seized opportunities in education, bioinformatics research, teaching, and conferences that would have been inaccessible had my family stayed in the USSR. I hope to continue to give back, be inspired by the people around me, and deepen my appreciation for opportunities in the US through the Paul and Daisy Soros Fellowship for New Americans.

Tell us about your current and near-term career-related activities and goals, indicating how you see your current work and study informing your forthcoming academic work and early career goals. If you are already enrolled in - or have been accepted into - the program for which you seek support under this fellowship, tell us why you chose that program. If you are still applying for one or more programs for which you will seek support under this fellowship, tell us about the primary considerations that are shaping your aspirations and priorities.

As I progress through my bioinformatics career, I realized that we in biomedical research are still far from widespread personalized medicine, and we need to better understand the basic biology of complex diseases such as cancer before we can provide disease cures for all. Through my research experiences, I have been exposed to a variety of methods of studying biology through mathematics and computer science, and I have been constantly drawn to the differences between cells of the same genetic code; those that have the same programming in their DNA, but how they look and act are completely different. Why are our skin cells constantly dividing and dying, and yet our retinal cells and neurons can never be replaced? How do these mechanisms differ in cancer, and specifically what are the subpopulations that contribute to cancer resistance?

My early career goals are to understand differences between cell types within a complex tissue such as a tumor. Currently, we treat a tumor like a ball of dough, as a mass of identical cells. But it is much more complex, like an orange, with an exterior rind containing a system of seeds, pith, and segments. If we introduce a drug that kills all the juice droplets in an orange but not the seeds or the rind, we haven't fully destroyed the tumor, and these remaining seeds may create additional cells and cause relapse. Tumors are a chaotic mix of different, interacting cell types, and we need to study these subpopulations to understand how the mosaic of individual cells help the larger cancer survive. During my Master's, I developed an RNA-Sequencing analysis package to study resistance to the chemotherapy paclitaxel in a breast cancer cell line at the single-cell level, and one of the major challenges was determining whether a mutation occurred solely in the RNA transcript via RNA editing or whether this mutation occurred in the genome as well.

In my dissertation work, I want to deepen our understanding of the relationship between DNA and RNA, and tease out sub-populations within a primary tumor, by developing simultaneous RNA and DNA sequencing methods from a single cell, which would authoritatively determine RNA editing and alternative splicing events. Merging the fields of alternative splicing and single-cell analysis would uncover differences in individual cells' RNA regulation and how it affects disease. The crossroads of alternative splicing and single-cell analysis are only available here at University of California, San Diego (UCSD) with Prof. Gene Yeo, who has a prototype of a single-cell sorting device that I will use for my graduate work.

[Another reason] I chose to come to UCSD was while some schools are strong in pure biological, engineering, mathematical, or computational sciences alone, UCSD has experts in all of these fields actively collaborating on interdisciplinary projects. Additionally, San Diego is home to many top-notch biological research facilities, such as the Sanford Institute for Regenerative Medicine, where Yeo's lab is, the J. Craig Venter Institute where Dr. Roger Lasken, the world's expert in single-cell analysis is, and the Moores Cancer Center, where I will collaborate with world-renowned cancer researchers such as Dr. Thomas Kipps to obtain patient samples. San Diego is also a major biotechnology hub, which adds to the infectious excitement for biological innovation present in the air.

UCSD also has numerous teaching opportunities, which is important to me because training the next generation of scientists is critical for global future success. As a teacher, a key component of my style is mirroring authentic research. I want learners to relish the struggle of a problem because it leads to marvelous moments of insight. Building on my previous experience of teaching a "Genes and Disease" bioinformatics module in high school biology, I will participate in the ScienceBridge program at UCSD, which teaches scientific labs to high school students.

Additionally, I will continue to teach at the university level. As bioinformatics is inherently an interdisciplinary science, the students entering our PhD program often have wholly biological or computational experiences, and to get everyone on the same page, the senior graduate students hold a "bootcamp." I want to teach our program's bootcamp next year, using a strategy from the stem cell curriculum I helped develop at UCSC, where learners became experts by exploring biology with a particular technique, then collaborate with with experts from other disciplines. To this end, we the bootcamp teachers would develop a three-dimensional mini-research module, with key findings in each component track: a computational endeavor for life science majors, a biology project for computer science folks, and a third venture for those who have experience in both. Then, representatives from these three groups would meet and piece together their discoveries to realize a larger concept of biology that would not be possible with one technique alone.

Collaboration is integral to bioinformatics, where the quote, "None of us is as smart as all of us," rings increasingly true. We cannot do bioinformatics as hermits; we need experimentalists, clinicians, and biotechnologists to drive forward our understanding of biology. I want to become a professor at a top research institution, where I will be surrounded by incredibly intelligent people who will question, support, and challenge my research. I hope to be constantly humbled by my colleagues and forge connections with experts in other disciplines to create new fields of research. With my colleagues, I want to create a collaborative research institute that integrates genomics, proteomics, and future technologies to solve biological problems. We would partner with biotechnology companies to transform research advancements into realized pharmaceuticals as quickly as possible. This way, the discoveries aren't locked away in an ivory tower, but used to improve public health.

As a professor, I want to continue to push the boundary of what we can accomplish with bioinformatics as a collaborator, help train the future generation as a teacher, and help create opportunities as a volunteer. With the Paul and Daisy Soros Fellowship for New Americans, I will have the freedom to pursue my own research ideas, develop research-intensive collaborative curricula, and focus my teaching on underserved groups.

Optional Exhibit

Website
olgabotvinnik.com

Blog
blog.olgabotvinnik.com

On my blog, I discuss productivity in the academic world and write R tutorials.

AP Biology curriculum materials
http://compbio.soe.ucsc.edu/binf-in-AP/

RNA-Sequencing Differential Expression package
https://github.com/olgabot/rna-seq-diff-exprn

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My most popular post on Eric Lander: bit.ly/PMMkWz

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blog post on usage: bit.ly/PMMiOc

BROAD INSTITUTE

Olga Botvinnik

ASSOCIATE COMPUTATIONAL BIOLOGIST

KEYWORDS: WHO IS BROAD? (/KEYWORDS/WHO-BROAD-0)

Olga Botvinnik

Olga Botvinnik loves algorithms and biology.

"What's incredible about the Broad is that there are lots of other people who love algorithms and biology," she says. "What I love about the Broad is that the algorithm design process is not just an iterative process, but a convergent symbiotic evolution of biologists and mathematicians."

As an undergrad at MIT earning degrees in both mathematics and biological engineering, Olga worked in several computational biology labs. She got her first taste of the Broad's collaborative atmosphere during a freshman pre-orientation program.

"I was completely enthralled. 'I *have* to work here,' " she recalled thinking to herself.

Later she worked with MIT Professor and Broad Associate Member Martha Bulyk. That got her hooked on computational biology.

Olga also tutors math and science, volunteering with sixth- through eigth-grade students at Mission Hill School in Boston. Through the Science Club for Girls, a Boston-area after-school club whose mission is to boost young girls' interest in science, she taught an anatomy curriculum called "Body Maps to second-graders. "That was tiring but very fun."

Olga, who grew up in Eugene, Oregon, joined the MIT DanceTroupe and continues to dance with them as an alumna. She now enjoys doing heated vinyasa flow yoga near her home in Cambridge.

She plays the cello and loves to have friends over for a great meal. She'd love to visit Japan, having been an "anime nerd" and learned Japanese in high school. So far her favorite destination is Vienna, where she presented her work from the Broad at the largest computational biologist conference in the world, the Intelligent Systems for Molecular Biology. "Vienna was beautiful, and I had a great time hanging out with fellow lab members."

Olga says her role models are all the female postdocs and principal investigators she has worked with, including Jill Mesirov, director of computational biology and bioinformatics, and Martha Bulyk.

Her motto? "глаза боятся, а руки делают," a saying in Russian whose literal translation is "The eyes are afraid, but the hands do." Her interpretation is "You may be afraid of what you can accomplish, but just go for it."

Locals complete training

Olga Botvinnik and **Leonid Chindelevitch** of Cambridge have completed Foundations in Medical Interpreting offered by Culture InSight, an operating program of the Harvard Pilgrim Health Care Foundation.

"Culture InSight is so pleased to have added these professionals to the medical interpreter ranks," said Shani Dowd, director of Culture InSight. "The growing diversity of our region's population makes these medical interpreters critical members of the health care profession."

This 48-hour program enables students who are fluent in English and at least one other language to become competent medical interpreters. Training includes basic interpreter skills and roles, interpreter ethics and fundamental medical terminology in English and the target language. An experienced clinician, who is also an interpreter, offers basic anatomy.

Once participants pass written and oral exams, they are able to become medical interpreters. The program meets or exceeds the requirements of the Massachusetts Emergency Room Interpreter Law and adheres to federal mandates and guidelines on culturally and linguistically appropriate health care.

Culture InSight, an operating program of the Harvard Pilgrim Foundation, provides cultural competency and medical interpreter training to health and human service professionals and organizations throughout Massachusetts, New Hampshire and Maine.

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Cell

Variation in Homeodomain DNA Binding Revealed by High-Resolution Analysis of Sequence Preferences

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SUMMARY

Most homeodomains are unique within a genome, yet many are highly conserved across vast evolutionary distances, implying strong selection on their precise DNA-binding specificities. We determined the binding preferences of the majority (168) of mouse homeodomains to all possible 8-base sequences, revealing rich and complex patterns of sequence specificity and showing that there are at least 65 distinct homeodomain DNA-binding activities. We developed a computational system that successfully predicts binding sites for homeodomain proteins as distant from mouse as *Drosophila* and *C. elegans*, and we infer full 8-mer binding profiles for the majority of known animal homeodomains. Our results provide an unprecedented level of resolution in the analysis of this simple domain structure and suggest that variation in sequence recognition may be a factor in its functional diversity and evolutionary success.

INTRODUCTION

The approximately 60 amino acid homeobox domain or "homeodomain" is a conserved DNA-binding protein domain best known for its role in transcription regulation during vertebrate development. The homeodomain can both bind DNA and mediate protein-protein interactions (Wolberger, 1996); however, the precise mechanisms that dictate the physiological function and target range of individual homeodomain proteins are in general either unknown or incompletely delineated (Banerjee-Basu et al., 2003; Svingen and Tonissen, 2006). In several cases, functional specificity can be traced to the homeodomain itself (Chan and Mann, 1993; Furukubo-Tokunaga et al., 1993; Lin and McGinnis, 1992), indicating that individual homeodomains have distinct protein- and/or DNA-binding activities. Since many homeodomains have similar DNA sequence preferences, much attention has been paid to the role of protein-protein interactions in target definition (Svingen and Tonissen, 2006), despite evidence that the sequence specificity of monomers contributes to targeting specificity (Ekker et al., 1992) and that binding sequences do vary, particularly among different subtypes (Banerjee-Basu et al., 2003; Ekker et al., 1994; Sandelin et al., 2004). Indeed, it has been proposed that the DNA-binding specificity of homeodomains is determined by a combinatorial molecular code among the DNA-contacting residues (Damante et al., 1996).

Efforts to understand the physiological and biochemical functions of homeodomains have been hindered by the fact that most have only a few known binding sequences, if any. Position weight matrices (PWMs) have been compiled for 63 distinct homeodomain-containing proteins from human, mouse, *D. melanogaster*, and *S. cerevisiae* in the JASPAR (Bryne et al., 2008) and TRANSFAC (Matys et al., 2003) databases. These matrices are based on 5 to 138 individual sequences (median 18), presumably capturing only a subset of the permissible range of binding sites for these factors. Further, the accuracy of PWM models has been questioned (Benos et al., 2002), and there are many examples in which transcription factors bind sets of sequences that cannot be described in a conventional PWM representation (Blackwell et al., 1993; Chen and Schwartz, 1995; Overdier et al., 1994).

Moreover, the sequence preferences of the individual proteins can, in some cases, be altered by the binding context: For instance, the binding specificity of the complex of *Drosophila* Hox-Exd homeodomain proteins is remarkably different from

CANCER

MicroSCALE Screening Reveals Genetic Modifiers of Therapeutic Response in Melanoma

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Cell microarrays are a promising tool for performing large-scale functional genomic screening in mammalian cells at reasonable cost, but owing to technical limitations they have been restricted for use with a narrow range of cell lines and short-term assays. Here, we describe MicroSCALE (Microarrays of Spatially Confined Adhesive Lentiviral Features), a cell microarray–based platform that enables application of this technology to a wide range of cell types and longer-term assays. We used MicroSCALE to uncover kinases that when overexpressed partially desensitized *B-RAF*^{V600E}–mutant melanoma cells to inhibitors of the mitogen-activated protein kinase kinase kinase (MAPKKK) RAF, the MAPKKs MEK1 and 2 (MEK1/2, mitogen-activated protein kinase kinase 1 and 2), mTOR (mammalian target of rapamycin), or PI3K (phosphatidylinositol 3-kinase). These screens indicated that cells treated with inhibitors acting through common mechanisms were affected by a similar profile of overexpressed proteins. In contrast, screens involving inhibitors acting through distinct mechanisms yielded unique profiles, a finding that has potential relevance for small-molecule target identification and combination drugging studies. Further, by integrating large-scale functional screening results with cancer cell line gene expression and pharmacological sensitivity data, we validated the nuclear factor κB pathway as a potential mediator of resistance to MAPK pathway inhibitors. The MicroSCALE platform described here may enable new classes of large-scale, resource-efficient screens that were not previously feasible, including those involving combinations of cell lines, perturbations, and assay outputs or those involving limited numbers of cells and limited or expensive reagents.

INTRODUCTION

Gain- and loss-of-function screens are powerful experimental approaches that can be leveraged to reveal the mechanistic underpinnings of a wide range of mammalian cellular biological processes (*1*–*5*). However, the costs and logistical challenges of current screening techniques restrict the range and extent of their application. These restrictions are particularly evident in large-scale screens involving multiple cell lines, genetic and pharmacological perturbations, or assay outputs, or alternatively in cases where cells, detection reagents, or other material resources are limited. Arrayed screens in multiwell plates can provide discrete, multiplexed measurements in proliferation- and image-based assays, but cost, labor requirements, and the need for specialized screening facilities equipped with appropriate biosafety and fluid-handling equipment limit their deployment (*3*, *5*, *6*). Pooled screening approaches address a number of these limitations and enable the screening of larger numbers of genetic constructs at lower cost (*5*, *7*–*10*). However, pooled screening is incompatible with image-based assays and typically requires large quantities of cells and reagents and libraries of genetic overexpression or knockdown reagents that are barcoded. Further, the scale of tissue culture required for pooled screens may present logistical challenges when large numbers of screens, for example, of many different cell lines or environmental perturbations, are required.

Cell microarrays have the potential to combine the best features of existing screening technologies, such as the assay versatility of multiwell plate–based screening and the high efficiency of pooled screening (*11*–*14*). Cell microarrays consist of hundreds to thousands of distinct genetic reagents printed as individual, microscopic "features" on glass slides, which are then seeded with adherent cells that attach and become treated with the reagent present on each feature (*13*, *15*). In principle, these systems make it possible to perform and analyze many parallel genetic perturbations on a single slide with high screening throughput and low cell and reagent consumption. In practice, although they have been featured in a number of interesting proof-of-concept studies describing variations on the basic cell microarray design with potential applications in several areas of cell biology (*13*, *14*, *16*–*21*), these systems have only rarely been adopted in large-scale screening applications because of several technical limitations (*22*, *23*). Namely, microarrays based on chemically delivered DNA expression plasmids or small interfering RNAs can only be used with cell types that are easily transfectable (for example, human embryonic kidney 293T cells) and with screening assays that are short in duration (typically 1 to 3 days) because of the inefficient and transient nature of nonviral transgene expression (*13*–*15*). Conversely, microarrays based on virally delivered open reading frames (ORFs) or short hairpin RNAs (shRNAs) can stably and efficiently infect a wide range of cell types but require large libraries of concentrated, purified viruses that cannot be prepared in a labor- or time-efficient way with existing methods (*24*). Both formats are further limited because cells tend to migrate away from the features on which they originally land and intermix with cells on neighboring features, an effect that considerably decreases the achievable spatial density of printed features

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JOURNAL OF HEMATOLOGY & ONCOLOGY

RESEARCH Open Access

Prediction of response to therapy with ezatiostat in lower risk myelodysplastic syndrome

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Abstract

Background: Approximately 70% of all patients with myelodysplastic syndrome (MDS) present with lower-risk disease. Some of these patients will initially respond to treatment with growth factors to improve anemia but will eventually cease to respond, while others will be resistant to growth factor therapy. Eventually, all lower-risk MDS patients require multiple transfusions and long-term therapy. While some patients may respond briefly to hypomethylating agents or lenalidomide, the majority will not, and new therapeutic options are needed for these lower-risk patients. Our previous clinical trials with ezatiostat (ezatiostat hydrochloride, Telentra®, TLK199), a glutathione S-transferase P1-1 inhibitor in clinical development for the treatment of low- to intermediate-risk MDS, have shown significant clinical activity, including multilineage responses as well as durable red-blood-cell transfusion independence. It would be of significant clinical benefit to be able to identify patients most likely to respond to ezatiostat before therapy is initiated. We have previously shown that by using gene expression profiling and grouping by response, it is possible to construct a predictive score that indicates the likelihood that patients without deletion 5q will respond to lenalidomide. The success of that study was based in part on the fact that the profile for response was linked to the biology of the disease.

Methods: RNA was available on 30 patients enrolled in the trial and analyzed for gene expression on the Illumina HT12v4 whole genome array according to the manufacturer's protocol. Gene marker analysis was performed. The selection of genes associated with the responders (R) vs. non-responders (NR) phenotype was obtained using a normalized and rescaled mutual information score (NMI).

Conclusions: We have shown that an ezatiostat response profile contains two miRNAs that regulate expression of genes known to be implicated in MDS disease pathology. Remarkably, pathway analysis of the response profile revealed that the genes comprising the jun-N-terminal kinase/c-Jun molecular pathway, which is known to be activated by ezatiostat, are under-expressed in patients who respond and over-expressed in patients who were non-responders to the drug, suggesting that both the biology of the disease and the molecular mechanism of action of the drug are positively correlated.

Background

Myelodysplastic syndrome (MDS) is a clonal stem cell disorder resulting in bone marrow failure and variable cytopenias. Development of new treatment strategies has greatly improved the outlook for patients with MDS. There are three FDA-approved drugs for therapy of patients who have become transfusion-dependent, including two hypomethylating drugs (HMAs), azacitidine and decitabine, and the thalidomide derivative lenalidomide. Patients with higher-risk disease have been shown to benefit from HMA therapy [1,2], while patients with lower-risk disease with a karyotype of clonally restricted deletion of the long arm of chromosome 5 (deletion 5q or del[5q]) are highly responsive to lenalidomide [3,4]. Only 26% of transfusion-dependent lower-risk patients without del(5q) will also become transfusion-independent while on treatment [5], but the FDA has not approved lenalidomide for these patients. There are few treatment options for the majority of transfusion-dependent MDS patients with lower-risk disease. This situation represents a significant unmet medical need. Once disease-modifying therapy is

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