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Clinically Irrelevant Concentrations of Kinase Inhibitors Contribute to Failure of Drug Repurposing Efforts in Clinical Trials: a Meta-Analysis

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ABSTRACT

Given drug development's rising costs and the need to combat cancer's devasting consequences, drug repurposing – positioning approved drugs to treat diseases beyond their original context – is an efficient approach to develop new cancer treatments. The repurposing of targeted kinase inhibitors has especially been encouraged. However, the overall high failure rates of cancer clinical trials indicate a negative outlook for repurposing and call for explanations. A major consideration is ineffective preclinical development, starting from *in vitro* studies where faulty claims of a drug's activity can be based on clinically irrelevant concentrations. This misleading *in vitro* rationale can support clinical lines of research. To further explore these issues, we used the clinicaltrials.gov and MEDLINE databases to conduct a meta-analysis on clinical trials involving established kinase inhibitors, imatinib and erlotinib, and the concentrations used by supporting *in vitro* studies. Our objective was to understand if there is a relationship between clinical outcomes of the drugs in the tested diseases and the clinical relevance of the supporting *in vitro* concentrations. We found that the imatinib and erlotinib repurposing efforts were more likely to fail and were correlated with exceedingly high concentrations used in supporting *in vitro* studies. Our findings highlight and expand existing *in vitro* and clinical trial trends involving other cancer drugs and non-cancer drugs. Future meta-analyses can extend into other kinase inhibitors and other preclinical development considerations. The work reported here adds support to the concept that improving translational cancer research will lead to successful drug repurposing and positive clinical trials.

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- Figure 1: Kady Dennis
- Figure 2: Kady Dennis, Scott Leighow
- Figure 3: Kady Dennis, Scott Leighow
- Figure 4: Kady Dennis
- Figure 5: Kady Dennis

Chapter 1

Introduction

Given the rapid and dramatic expansion of our understanding of cancer biology in the last few decades, it is concerning to see high rates of negative clinical trials involving cancer drugs. The clinical success rate for the approval of cancer drugs has remained at 20% from 1993-2004, even as the investment into drug development has steadily increased (DiMasi et al. 2010; Rubin & Gilliland 2012). While this continued low clinical success rate was similar for many therapeutic areas, the probability of cancer drugs gaining licensing or exhibiting efficacy in Phase III trials was lower at 55% compared to the overall 64% probability in other areas (DiMasi et al. 2010). Repurposing approved drugs for diseases they were not initially positioned for has been pitched as a way to develop new, effective cancer treatments at the fraction of the cost of typical drug development processes. However, these overall low clinical success rates suggest that these repurposing efforts are not viable yet and reflect a larger need to examine factors that undermine the successful translation of research to clinical trial design. One significant factor is the quality of preclinical rationale which initiates the clinical testing of drugs because the larger outstanding demand for cancer treatments may lend itself to substandard preclinical rationale even from the level of *in vitro* research (Begley & Ellis 2012).

In *in vitro* research, it is crucial to use appropriate cancer cell lines, assays, concentrations, and conditions to understand the effects of a drug on cell proliferation, viability, and apoptosis and define potential molecular markers for diseases (Ferreira et al. 2013). *In vitro* results then guide *in vivo* research involving animal models and together, these results make up a

preclinical rationale to encourage or discourage clinical lines of research for the drug in diseases. While both *in vivo* and *in vitro* models have their limitations, *in vivo* models have been under growing scrutiny for their high potential costs and unreliability in predicting cancer drugs' efficacies in clinical trials. In an analysis of compounds from the National Cancer Institute (NCI)'s Developmental Therapeutics Program, there was a correlation for activity in some Phase II trials for those NCI compounds active in at least 33% of *in vivo* xenograft models (Johnson et al. 2001). However, there was no close correlation between *in vivo* activity in animal tumor models and activity in the same human cancer histology. A more recent study suggested that patient-derived *in vivo* xenograft models (PDXs) better predict clinical drug response through an *in vivo* high-throughput screen of 1000 PDXs (Gao et al. 2015). However, high-throughput drug screening with PDXs is expensive and impractical for most laboratories. Gao et al.'s study itself was limited to only 62 treatments and to single doses/schedules which led to the majority of treatments failing to produce significant responses (2015; Eastman 2017).

Examining the *in vitro* front underlying these aforementioned studies shows the inherent importance and affordability of *in vitro* work in preclinical development. Johnson et al. found a significant positive relationship between potency in a 60-cell line *in vitro* screen and hollow fiber assay activity, an effective predictor of *in vivo* response, and Gao et al. tested cancer treatments that were already developed through *in vitro* assays in a more expensive manner (2001; 2015). Furthermore, due to the genetic instability of PDX models, a single PDX doesn't always represent the genomic landscape of primary tumors more effectively than multiple cell line derived from a primary tumor which can retain more original and heterogeneous genetic characteristics, as emphasized by another study (Ben-David et al. 2017). Collectively, these

studies overall illustrate that *in vivo* and *in vitro* results must be paired to facilitate effective preclinical development for a drug.

Considering that *in vitro* research is technically the foundation to even initiate testing a novel or repurposed cancer drug on animal models and patients, it is crucial to improve the quality of a drug's preclinical rationale here to induce greater chances of clinical success in cancer clinical trials. An aspect to consider is whether *in vitro* experiments are testing cancer drugs at concentrations that are both achievable in the human body and show targeted effects before concluding the potential of the drug clinically. Previous work from the Pritchard lab has looked to understand human serum protein binding effects in determining clinically relevant concentrations of kinase inhibitors *in vitro*. Serum protein binding effects can describe how the efficacy of a drug decreases, as more of its molecules reversibly bind proteins in the blood and then are unable to target cancer cells (McIlroy 2020). In comparing dose-response experiments with and without serum proteins involving several kinase inhibitors, an increase in IC_{50} values, the concentration at which cell viability is 50% inhibited, was found for experiments in serum conditions – this effect was labeled as a rightward "serum shift" (McIlroy 2020; Leighow et al. 2021). These serum-shifted IC_{50} values match known *in vivo* pharmaceutical exposures and help to calculate each drug's effective C_{ave}, the average serum concentration a certain dose of a drug reaches in the body before another dose is administered. Hence, the C_{ave} represents an effective measure of clinically relevant concentrations (McIlroy 2020; Leighow et al. 2021).

Kinase inhibitors are a particularly important class of targeted cancer drugs to focus on for the case of improving *in vitro* drug development because they have thousands of overlapping interactions for human protein kinases which make them especially attractive to be repurposed for many new diseases (Karaman et al. 2008). Therefore, it is critical that the clinical testing and

repurposing of kinase inhibitors is supported by a body of *in vitro* research using clinically relevant concentrations. With this in mind, it is then concerning to learn that the clinical activity of sorafenib, a well-established kinase inhibitor, has been inaccurately reported based on clinically irrelevant concentrations *in vitro*, exhibited in a survey of preclinical studies and publications (Smith & Houghton 2013). Specifically, according to Smith & Houghton, sorafenib shows targeted effects at low nanomolar concentrations but was more commonly seen to be used at micromolar concentrations which trigger nonspecific effects (2013). The reason that such high *in vitro* concentrations are chosen is that they are physiologically achievable. However, these micromolar concentrations are not adjusted for "serum shift" effects – sorafenib is highly protein-bound – which in reality makes them clinically irrelevant for successful translation (Smith & Houghton 2013). In a further survey of the results database clinicaltrials.gov, Smith & Houghton found sorafenib to have hundreds of clinical trials across a wide range of diseases, including those it was not federally approved for, and many of trial rationales were partly based on sorafenib's micromolar *in vitro* activity (2013). These unsettling trends found in sorafenib's clinical testing and *in vitro* studies encourage the examination of other established kinase inhibitors like imatinib and erlotinib to see if they are being successfully repurposed to show efficacy in new diseases and if the initiation of these repurposing efforts is also rationalized by *in vitro* studies using clinically irrelevant concentrations.

Imatinib, the first developed kinase inhibitor initially federally approved in 2001 for chronic myeloid leukemia (CML), is currently approved for a total of 7 diseases including gastrointestinal stromal tumors (GIST) and acute lymphocytic leukemia (ALL) (Gleevec; Novartis Pharmaceuticals Crop, East Hanover, NJ). Because it is specific for the tyrosine kinase domain in *bcr-abl*, c-kit, and PDGF-R, imatinib has been and continues to be tested in diseases

that involve the same or downstream pathways in its repurposing efforts. Erlotinib, initially federally approved in 2004 for non-small cell lung cancer (NSCLC), is currently and specifically approved for NSCLC with epidermal growth receptor (EGFR) mutations which make up about 30% of all NSCLC cases (Zhang et al. 2016). It is also approved for pancreatic cancer and is commonly tested to be repurposed in diseases that involve the EGFR or downstream pathways (Tarceva; Genentech Inc, South San Francisco, CA).

We examine imatinib and erlotinib clinical trials to understand: 1. The success rate of repurposing efforts in new diseases for both drugs 2. And if there is a relationship between the clinical outcomes of the drug in diseases and the clinical relevance of *in vitro* drug concentrations in disease models that form the supporting rationale for the trial(s). Our approach involves a tailored meta-analysis, in which we developed a methodology to comprehensively review and categorize each imatinib and erlotinib clinical trial found on the clinicaltrials.gov database and to identify and collect drug concentrations used in supporting *in vitro* studies through citations from trials' published papers or available on the MEDLINE database if there is no published paper. We test the hypothesis that more diseases, in which erlotinib and imatinib fail to show efficacy through clinical trials, will be supported by *in vitro* studies using clinically irrelevant concentrations of the drug as rationale, as compared to diseases in which the drug show clinical efficacy.

Chapter 2

Results

In all, 50 imatinib and 76 erlotinib clinical trials were analyzed for the meta-analysis. First, the success of repurposing each drug in diseases was examined through the classification of a disease's clinical outcome. Of the 35 unique diseases that imatinib was clinically investigated in, 82.9% were unapproved, while 17.1% reached approval status and therefore were marked as having a successful clinical outcome due to their overwhelmingly positive clinical trial results (Figure 1A). Of the 29 unapproved diseases, imatinib had a successful clinical outcome in only one disease, but it had a failed clinical outcome in 86.2% of diseases due to their overwhelmingly negative clinical trial results (Fig. 1A). Of the 30 unique diseases that erlotinib was clinically investigated in, 93.3% were unapproved and 6.7% reached approval and therefore, had successful clinical outcomes (Figure 1B). Of the 28 unapproved diseases, erlotinib had a failed clinical outcome in 82.1% of diseases and did not have any successful outcomes. These results overall suggest that the repurposing efforts of erlotinib and imatinib in new diseases are more likely to fail than succeed (Fig. 1B).

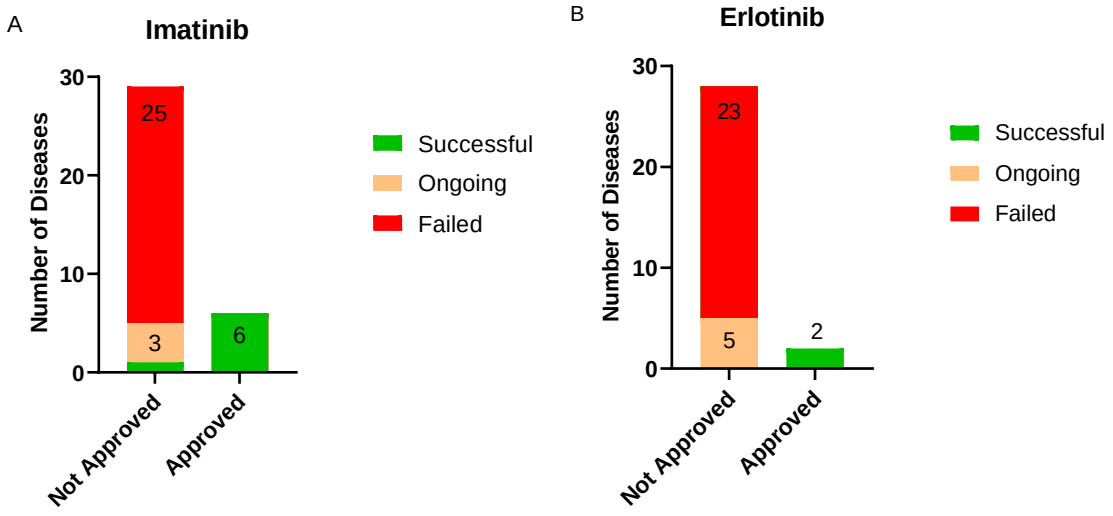

Figure 1. Imatinib and erlotinib repurposing efforts
Summary of A) imatinib meta-analysis and B) erlotinib meta-analysis through clinical outcomes of the drug in each of the unique diseases. The diseases are divided by their approval status; diseases with successful clinical outcomes (green) had clinical trials meet their primary endpoints, diseases with ongoing clinical outcomes (light orange) had an ambiguous mix of clinical trials meeting and not meeting their primary endpoints, diseases with failed clinical outcomes (red) had a majority of clinical trials not meet their primary endpoints.

Clinical trials for 32 unique diseases targeted by imatinib and 27 unique diseases targeted by erlotinib were then examined to identify and group *in vitro* studies supporting the investigation of the drugs in each of the diseases. For each of these collected *in vitro* studies, the drug concentrations that were used and/or noted as effective were recorded, but specifically, the lowest efficacious concentration used in an appropriate disease model was considered against each drug's effective C_{ave} at an average or commonly used dose (Leighow et al. 2021). The few diseases that were excluded in this representation of the data and analysis did not have any *in vitro* rationale in appropriate disease models cited by the trial/its publication of results nor found on the MEDLINE database or did not have a lowest efficacious concentration. Of the unique diseases that imatinib was successful in, 5 out of 6 diseases were supported by *in vitro* work whose efficacious concentrations were below imatinib's effective C_{ave} and therefore had

clinically relevant concentrations (Figure 2). All of the diseases that imatinib failed in, except for one, were supported by *in vitro* work whose efficacious concentrations were higher than the effective C_{ave} and therefore had clinically irrelevant concentrations (Fig. 2). Similarly, for erlotinib, 1 out of 2 diseases it was successful in was supported by *in vitro* studies whose efficacious concentrations were below erlotinib's effective C_{ave} (Figure 3).

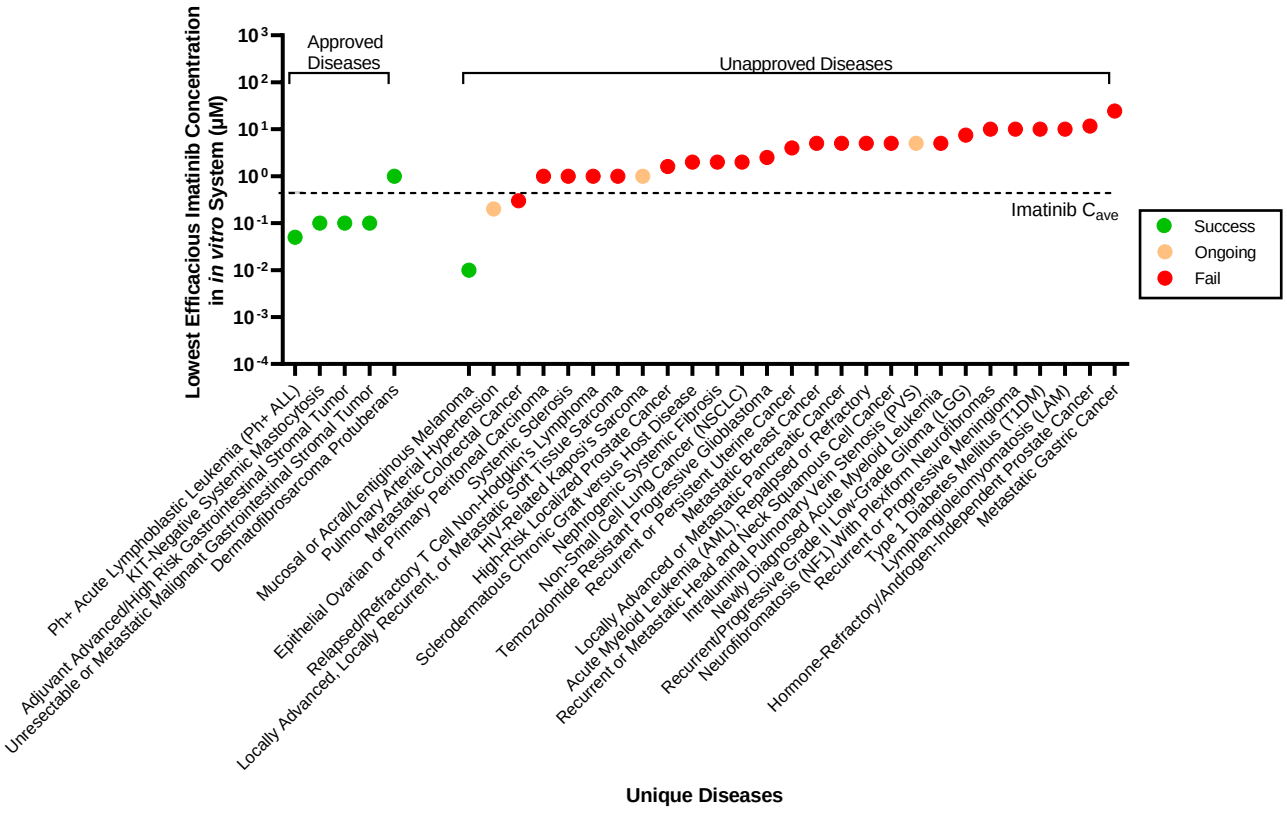

Figure 2. Imatinib repurposing efforts through *in vitro* efficacy
Summary of imatinib meta-analysis through *in vitro* efficacy and clinical outcome for each unique disease. The y-axis shows the lowest concentration in which an inhibitory effect was observed in an *in vitro* disease model supporting imatinib's clinical investigation in a disease. The dotted black line indicates the effective C_{ave} at 0.444 uM for a standard, prescribed dose of imatinib 400 mg, once a day (Leighow et al. 2021). The color of the dot shows the level of success for imatinib repurposing in a disease, as described in Figure 1.

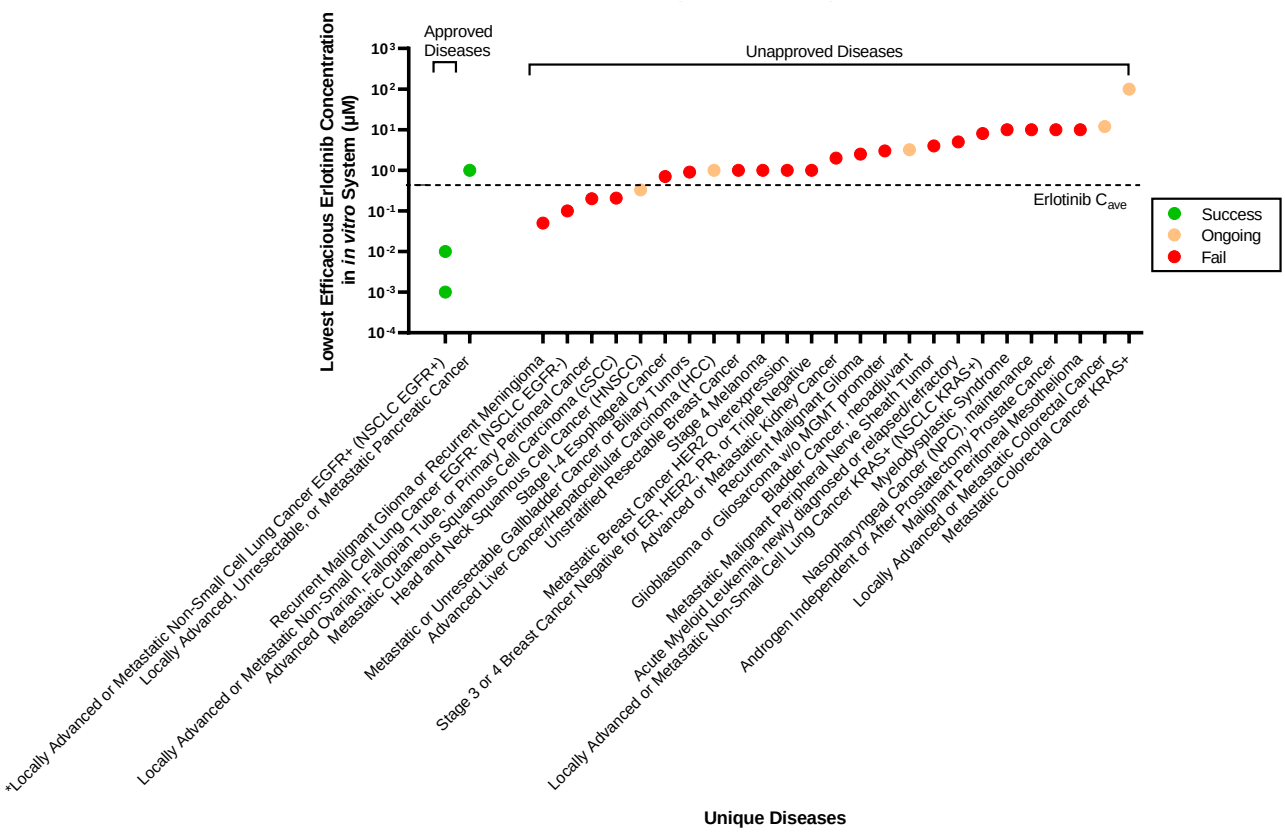

Figure 3. Erlotinib repurposing efforts through *in vitro* efficacy
Summary of erlotinib meta-analysis through *in vitro* efficacy and clinical outcome for each unique disease. The y-axis shows the lowest concentration in which an inhibitory effect was observed in an *in vitro* disease model supporting erlotinib's clinical investigation in a disease. The dotted black line indicates the effective C_{ave} at 0.4247 uM for a standard, prescribed dose of erlotinib 150 mg, once a day (Leighow et al. 2021). The color of the dot shows the level of success for imatinib repurposing in a disease, as described in Figure 1. (* = NSCLC EGFR+ is plotted with two points that represent the two approved EGFR mutations: 10^{-3} uM for exon 21 L858R mutation and 10^{-2} uM for exon 10 deletion)

To determine the statistical significance of the meta-analysis's results by *in vitro* efficacy and clinical outcome, a Fisher's exact test was conducted on imatinib and erlotinib results together. It revealed that the probability of imatinib and erlotinib failing to treat diseases while being supported by *in vitro* concentrations above the effective C_{ave} is nearly 23 times more than

that of these kinase inhibitors failing to treat diseases while being supported by *in vitro* concentrations under the effective C_{ave} (OR = 22.8, p-value = 0.00058; Table 1). The imatinib results alone were also significant through the Fisher's exact test (OR = 110, p-value = 0.00029) (Supplementary Table 1). While the erlotinib results alone were not significant through this test, this statistical insignificance is due to the lack of data points for successful clinical outcomes for erlotinib in diseases (OR = 4, p-value = 0.41125; Supp. Table 1).

Table 1. Fisher's exact test contingency table for combined imatinib and erlotinib results

	Successful clinical outcome in disease	Failed clinical outcome in disease
In vitro concentration **above** effective C_{ave}	2	38
In vitro concentration **below** effective C_{ave}	6*	5

* = NSCLC EGFR+ is counted as one data point because it is one disease supported by 2 *in vitro* concentrations both under the C_{ave}

Collectively, these results show that most clinical trials repurposing erlotinib and imatinib in new diseases fail, as only small percentages of the unique diseases for both drugs had successful clinical outcomes. Furthermore, these results also suggest that clinically irrelevant concentrations used by *in vitro* studies significantly correlate with and even underlie these failed repurposing efforts by potentially providing false notions of imatinib's or erlotinib's potential efficacy in diseases.

Chapter 3

Discussion

The inherent potential of kinase inhibitors in drug repurposing coupled with the high failure rates in cancer clinical trials reflects a need to consider the faults of preclinical development from its basis in *in vitro* research. In this meta-analysis, clinical trials, and corresponding *in vitro* studies involving kinase inhibitors imatinib and erlotinib were examined to identify the clinical outcome of and supporting efficacious *in vitro* concentrations for each tested disease. Through the careful characterization of clinical trial data and the systematic comparisons of the efficacious *in vitro* concentrations to effective C_{ave} values, we found that repurposing efforts in new diseases for both imatinib and erlotinib were more susceptible to failure. Furthermore, clinically irrelevant concentrations used by supporting *in vitro* studies seem to contribute to this failure, as they were significantly correlated with a higher amount of failed clinical outcomes for the kinase inhibitors in diseases.

Our findings not only fall in line with the tested hypothesis, but also directly support, expand, and quantify the aforementioned trends in *in vitro* studies and clinical trials for sorafenib to other established kinase inhibitors (Smith & Houghton 2013). Not only do we show a body of erlotinib and imatinib *in vitro* studies that exceed C_{ave} values – sometimes as great as 100-fold – but also, we show that this body of research supports the initiation of clinical trials in new diseases and that these repurposing efforts more commonly fail. While no other publications were found focusing on the trends of clinically irrelevant concentrations and the clinical testing of kinase inhibitors to our knowledge, there is work that illustrates how these trends extend to other cancer agents, as well as agents from other therapeutic areas. Smith & Houghton primarily explored sorafenib in their perspective article, but they also looked into the cancer agent

vorinostat and metformin, an antidiabetic agent with the repurposing potential in cancer (2013). A review of both agents' *in vitro* studies revealed that the majority of concentrations used were above even the approximate maximum achievable concentration in humans (Smith & Houghton 2013). Additionally, a literature review of *in vitro* studies involving statins that propose repurposing for anti-inflammatory and immune-modulatory functions showed that the average concentration of statins in human serum at therapeutic doses was significantly lower than the concentrations stated to have pleiotropic effects from a majority of *in vitro* studies (Björkhem-Bergman et al. 2011).

While our meta-analysis found supporting *in vitro* studies using clinically relevant concentrations and overall, literature is available with consideration to concentrations at which a drug has targeted effects in human serum conditions, this is not the primary trend. Furthermore, to our knowledge, there is widespread support for better translational research at all levels and so, we found no publications supporting otherwise. In terms of our finding of failed repurposing efforts in imatinib and erlotinib, a recent analysis revealed that drug repurposing overall has not been successful in the last few decades (Neuberger et al. 2019). Neuberger et al.'s results show that fewer than 20% of candidate drugs evaluated outside their original therapeutic context were successfully repurposed and fewer than 30% of drugs evaluated within their original therapeutic area were successfully repurposed (2019). Our results emphasize this problematic trend in *in vitro* research and by connecting it to trends in clinical trials, elevates the level of urgency concerning the use of relevant drug concentrations in preclinical studies.

While our findings have support from existing literature, this meta-analysis has several limitations that are important to consider. In terms of surveyed clinical trials, we did not look at "Completed, With No Results" trials for erlotinib. This may have decreased the number of

diseases that erlotinib was truly tested in. However, the same search for imatinib only added one more unique disease which potentially predicts that an insignificant number of diseases would be added to the erlotinib results. Furthermore, the timeline to efficiently review hundreds of imatinib clinical trials from the "Completed, With No Results" search only included trials starting after 2008 and completed by 2015 which may have excluded relevant trials and therefore, unique diseases. However, in a retrospective check, we found only one relevant clinical trial testing imatinib in a hypereosinophilic syndrome that was excluded which shows that overall, our timeline based on the history of clinicaltrials.gov was effective to sort through many trials (NCT00787384).

Furthermore, in terms of finding supporting *in vitro* studies, many of the clinical trials did not have publications of results or had an abstract without accessible references. And in some cases, clinical trials had publications but cited *in vivo* rationale only or *in vitro* rationale with different drugs/non-disease models. Without direct citations, we assumed that clinical trial initiators were aware of *in vitro* studies found on the MEDLINE database that were contemporaneous to or before the start of a trial or we included *in vitro* studies after the start of a trial when none existed before. This choice could have potentially skewed the overall trends in our collected *in vitro* concentrations. In terms of limitations in analysis, imatinib is approved for doses ranging from 300 mg once a day up to 400 mg twice a day, but for comparison, we used an effective C_{ave} for the standard dose of 400 mg once a day. Our results would have still shown similar trends, but further nuance could have been added by comparing a disease's lowest efficacious *in vitro* concentration against an effective C_{ave} that represented the dosage used in trials to test that disease. For erlotinib, a 100 mg once a day dose is only approved for pancreatic

cancer, and otherwise, 150 mg once a day dose was used for all other diseases, and so the effective C_{ave} for a 150 mg dose was a consistent comparator.

Even considering choices in our methodology, the trends of failed drug repurposing with an underlying body of *in vitro* studies mainly using clinically irrelevant concentrations are still visible, significant, and supported. Our findings highlight the need to improve preclinical development for cancer drugs at the *in vitro* level, so researchers can better direct their efforts towards success. This is especially important when considering the huge and continually rising financial costs demanded by the drug development process along with the impact on the lives of patients who join cancer trials which may be set up to fail due to incomplete or misleading preclinical rationale. Specifically, as kinase inhibitors continue to be touted for their safe and cost-effective repurposing potential – ex. imatinib is currently being clinically tested in COVID-19 (NCT04394416) – a renewed focus on bettering preclinical development along with other data-driven approaches may allow for successful repurposing efforts in the future (Pushpakom et al. 2018). To continue to provide evidence to and support for calls to better translational cancer research with clinical relevance in mind, future follow-up research should examine the clinical trials and supporting *in vitro* studies of more kinase inhibitors. Future examinations of *in vitro* experimental design in other aspects – ex. incubation times, choice of assays, exaggeration of synergy, etc. – should also be pursued to build a comprehensive picture of how preclinical development can be improved to enhance the translation of novel and repurposed cancer drugs. We anticipate that these collective efforts can lead to more positive cancer clinical trials.

Chapter 4

Methods

This meta-analysis methodology was developed and conducted with the input of and peer-review of Dr. Justin Pritchard, Kady Dennis, and Anushka Shah. All recorded data on each of the clinical trials can be found in detail on the "Imatinib Clinical Trial Analysis" and "Erlotinib Clinical Trial Analysis" spreadsheets. Furthermore, the "Imatinib Summary Tables" and "Erlotinib Summary Tables" spreadsheets provide detail into the grouping and summary of the raw data from the "Analysis" spreadsheets. For all parts of this methodology, please refer to the aforementioned spreadsheets to gather more specific information.

Initial collection of Imatinib and Erlotinib clinical trials

Imatinib and erlotinib clinical trials for the meta-analysis were found with term-specific searches on the clinicaltrials.gov results database. On May 18th, 2020, a search with "imatinib, sti-571, gleevec" in the Other Terms search bar was run to account for trials using imatinib's generic, original, and brand names respectively. The search was filtered for Completed and With Results because only trials that had concluded and had published results could be analyzed for their outcomes. This search yielded 87 trials (Figure 4). Retrospectively after the analysis of imatinib trials, it was understood that the clinicaltrials.gov database automatically searches for trials linked to a drug's synonymous names during drug-based searches. This sometimes means that a search with more name terms can result in an insignificant, but a slightly lesser number of trials compared to a search with just the generic name. And so, to make sure the greatest number of erlotinib trials was brought up, the erlotinib analysis initiated on August 19th, 2020 began with

a search with only “erlotinib” in the Other Terms search bar. After the search was filtered for Completed and With Results trials, it yielded 231 trials (Figure 5). For each imatinib and erlotinib trial, the following types of data were recorded: study ID (NCT number), start date, enrollment, phase, dosage tested, disease tested, primary endpoint, rationale, etc.

Additionally, for erlotinib trials testing in non-small cell lung cancer (NSCLC), information about molecular hypotheses was collected. Given that the most recent approvals for erlotinib is in NSCLC with specific EGFR mutations and only about 30% of all NSCLC cases fall into this category, it was necessary to indicate if trials tested an unstratified or stratified molecular hypothesis at enrollment (Supplementary Table 2; Zhang et al. 2016). An unstratified molecular hypothesis means that patients did not receive treatment based on their mutational status and/or patients’ molecular statuses were examined retrospectively; a stratified molecular hypothesis means that patients received treatment based on their mutational status. This was not necessary for imatinib trials because the Philadelphia (Ph) chromosome or *bcr-abl* fusion gene is associated with almost all cases of chronic myeloid leukemia (CML) and imatinib has only been approved in Ph+ acute lymphoblastic leukemia (ALL) (Kolenova et al. 2016).

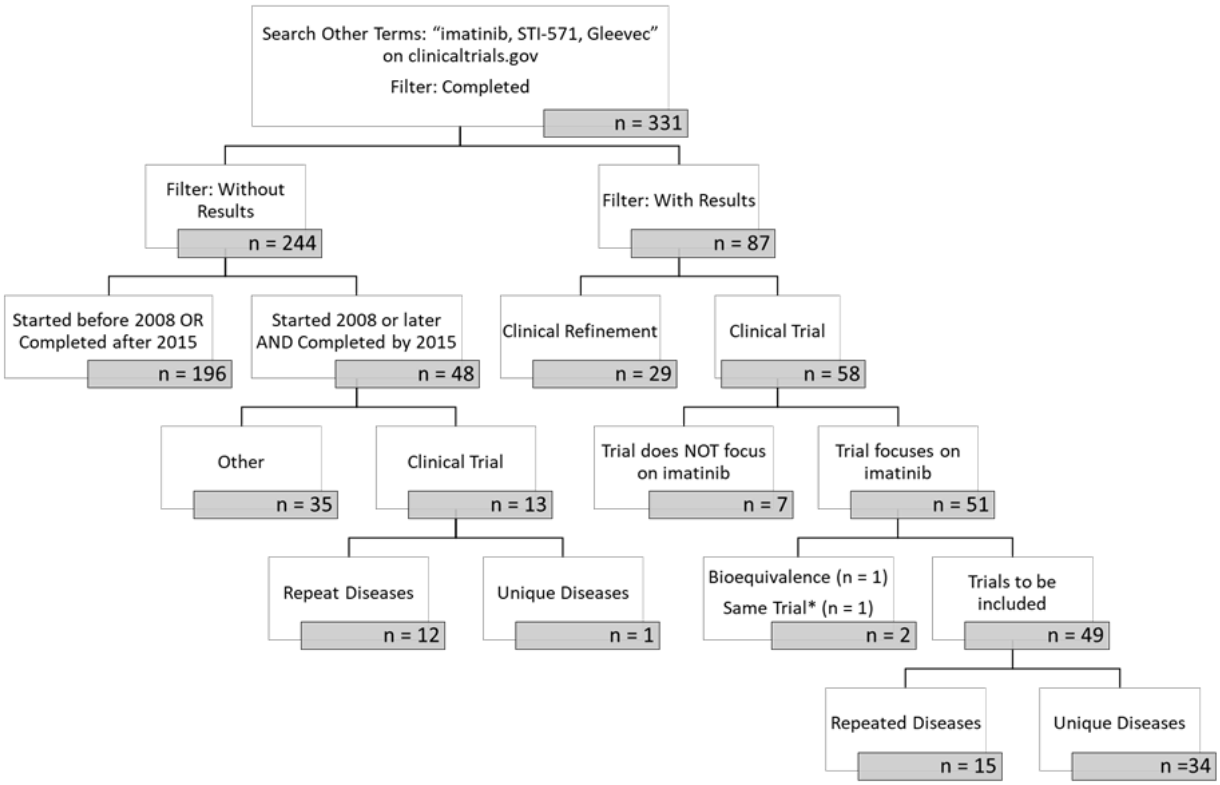

Figure 4. Flow chart of imatinib meta-analysis trial selection methodology
Imatinib trials that were included, excluded, and the number of unique diseases imatinib was tested in from the searches on clinicaltrials.gov results database

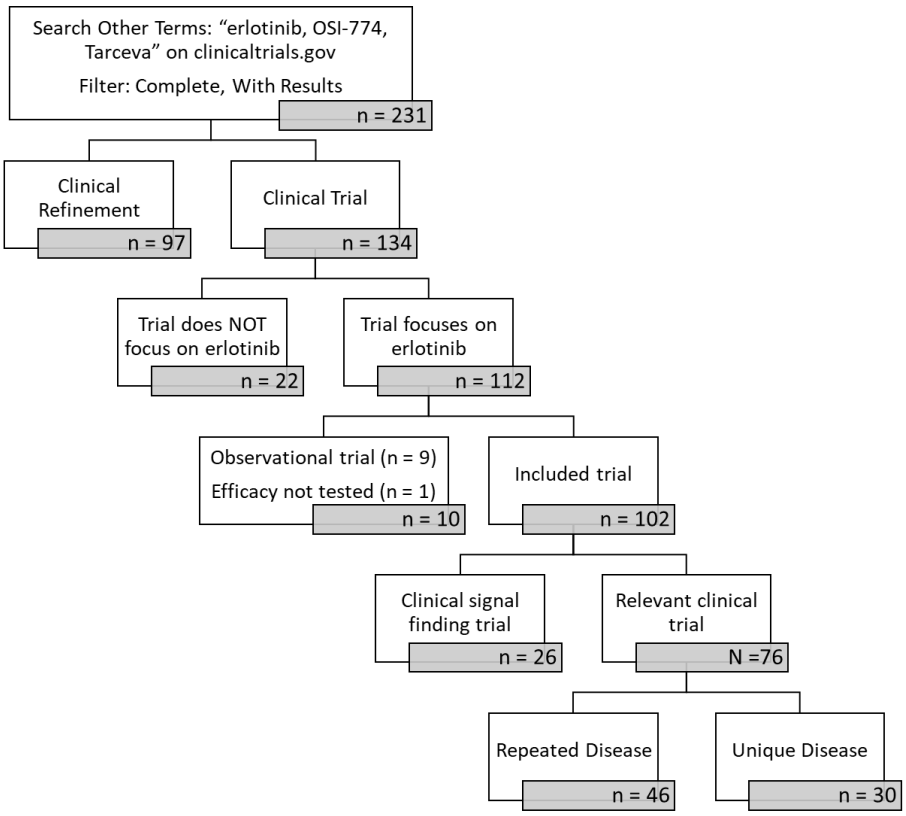

Figure 5. Flow chart of erlotinib meta-analysis trial selection methodology
Erlotinib trials that were included, excluded, considered relevant for analysis, and the number of unique diseases imatinib was tested in from the searches on clinicaltrials.gov results database

Exclusion criteria

To ensure that only clinical trials where imatinib and erlotinib were tested for their respective efficacies in diseases were included in the meta-analysis, exclusion criteria were established to funnel down the searches (Figs. 4 & 5). First, clinical refinement trials were excluded. Clinical refinement trials were defined as trials that were run on previously approved indications for the drug after its approval date, or were testing for something other than the approved treatment, (i.e. either dose adjustments, treatment time adjustments, the addition of other drugs), or were targeting a specific subset of patients outside of what was approved (i.e

trials focused on children, the elderly, a certain demographic, patients who had received the drug previously and failed or were resistant/intolerant) (Supp. Figs. 2 & 3).

Trials were also excluded for not being focused on the drug. This aspect of the exclusion criteria was defined as trials in which patients were already receiving the drug before the trial, trials where another drug's efficacy was focused on, trials comparing imatinib/erlotinib against another drug or treatment that was not the standard of care. Finally, non-interventional trials or trials not testing a drug's efficacy were excluded (i.e bioequivalence and observational trials, trials testing feasibility). Any redundant trials were also excluded which was the case in the imatinib analysis. Using these step-wise exclusion criteria, 49 trials for imatinib and 102 trials for erlotinib were included in the meta-analysis (Figs. 4 & 5).

Further collection of imatinib clinical trials

Unlike the initial search for erlotinib, the initial search for imatinib clinical trials did not yield trials for all of the diseases imatinib is approved in. To attempt to account for all completed clinical trials that could test more unique diseases, the initial search was filtered for "Completed, Without Results". Only trials starting after 2008 and completed by 2015 were reviewed and considered for analysis based on the following assumptions: 1. The clinicaltrials.gov results database was not established until 2008 and perhaps trials started before then may not have been able/required to report results 2. Trials completed by 2015 would be assumed to have reported results by the time of the meta-analysis five years later (U.S. National Library of Medicine 2021). Of the 48 trials fitting this timeline, only 13 did not fall under our exclusion criteria and the term "Other" on the flowchart encompasses these excluded trials: clinical refinement,

observational, bioequivalence, pharmacokinetic, drug interaction, not focused on imatinib, healthy patient trials (Fig. 4). Of the 13 trials that could be potentially included in our analysis, only one trial involved a unique disease and the remaining 12 were trials for diseases already captured from the trials collected in the initial search. Thus, that singular trial was included in the analysis to result in a total of 35 unique diseases, of which 34 came from the sorting of the trials from the initial search.

Clinical signal finding trials in erlotinib meta-analysis

A further step was taken in the erlotinib meta-analysis because it was found that many trials fell under the clinical refinement criteria, but did not fit the criteria's time requirement of testing post-approval of erlotinib in the disease indication. These trials were labeled as clinical signal finding trials because they ultimately led to the approvals of erlotinib in NSCLC and pancreatic cancer, but they were not the key trials testing typical molecular stratifications and patient populations nor testing later approved first- or second-line treatments. The separation of clinical signal finding from key and other trials, labeled as relevant trials, allowed for a more focused examination and analysis of the included trials. These relevant trials were analyzed to determine the number of unique diseases erlotinib was tested in and examined for the *in vitro* rationale behind each trial and disease. At the end of this sorting process, 30 unique diseases were found from the 76 relevant trials of the 102 included erlotinib trials (Fig. 5).

Clinical trial primary endpoints to clinical outcomes of imatinib/erlotinib in diseases

The collection and categorization of each trial's primary endpoint as being met or unmet was integral to determining the success of imatinib/erlotinib's clinical outcome in each disease. The primary endpoint of each trial was assessed with comprehensive criteria to determine its ultimate status. First, it was noted whether the trial had been published as a paper and whether the paper indicated positive or negative results. If the paper indicated negative results, the primary endpoint was marked as not met. If the paper indicated positive results, the primary endpoint was marked as met. However, for trials with met primary endpoints, additional searches of the disease and drug(s) in clinicaltrials.gov were conducted to see if there were any follow-up or currently active trials in the same disease and if the results of any follow-up trials were better than the current standard of care. This information on imatinib and erlotinib's ongoing or lack of potential in a disease was additionally noted. If a trial did not have a published paper, then its primary endpoint was solely judged by its results in comparison to the standard of care and the results of follow-up/existence of active trials. In finding trials' published papers, some trials linked the publication from results directly on clinicaltrials.gov, while others needed to searched on the MEDLINE database and Google using keywords such as imatinib/erlotinib, the disease, title, and name of the primary investigator if available, etc.

After establishing whether each trial's primary endpoint was met, all trials for a unique disease were analyzed. If all trials did not meet their primary endpoint, the drug had an obvious failed clinical outcome in the disease. If all trials met their primary endpoint, the drug had an obvious successful clinical outcome in the disease. Ultimately, all currently approved diseases were given a label of a successful clinical outcome for the drug. In the instances of a unique

disease having trials with varying levels of success through their primary endpoints, an individual decision was made on whether to label them as ongoing, successful, or failed.

In vitro rationale

A detailed process was established to collect and characterize each trial's *in vitro* rationale which was then grouped to represent *in vitro* rationale supporting the testing of a drug in a disease. Ultimately, the following three labels were developed to characterize rationale: clear *in vitro* rationale in a disease model, clear *in vitro* rationale in a non-disease model, no *in vitro* rationale but some available. For the analysis of erlotinib trials specifically, the aforementioned set of labels were modified to note if *in vitro* rationale with gefitinib, the earliest EGFR inhibitor, was originally cited by a trial and if *in vitro* rationale with erlotinib was available. To determine the label a trial received, the following steps were followed. First, if a trial had a published paper, this was examined to see if any *in vitro* rationale in a disease model was present and cited either in the abstract, introduction, or discussion. If there were no *in vitro* studies cited, but rather other clinical trials cited as rationale, those referenced trials were then opened to see if any of them cited any *in vitro* rationale in a disease model. These trials were labeled as having clear *in vitro* rationale in a disease model. If the directly and indirectly cited *in vitro* studies were in a non-disease model and/or used gefitinib (in erlotinib trials), this was noted and additional searches were prompted.

If no *in vitro* rationale was present in the paper and a trial the paper referenced, or the rationale was done in a non-disease model, or if the rationale was gefitinib-based over erlotinib, then a MEDLINE search was conducted to find any *in vitro* evidence showing that the drug had

an *in vitro* effect (specifically on proliferation or cell viability) in a disease model preferably before and/or at the year the trial started. The MEDLINE search typically included keywords such as imatinib/erlotinib, the disease of interest, and *in vitro*. If a study/studies with *in vitro* evidence in a disease model was/were found, the trial was given the label no *in vitro* rationale, but some available. However, it was also noted if the trial originally had clear *in vitro* rationale in a non-disease model and *in vitro* evidence in a disease model was found. In instances where no *in vitro* evidence was available in a disease model, these diseases remained labeled as clear *in vitro* rationale in a non-disease model. These trials were ultimately excluded from the analysis of the relationship between *in vitro* rationale and clinical outcome, as their *in vitro* data was inaccurate in predicting the success or failure of a trial.

Next, if no paper was published for a trial, and no *in vitro* rationale was present on the registered trial on clinicaltrials.gov (or was present but not referenced), a MEDLINE search was again conducted to find whether *in vitro* studies were available for the disease model preferably before and/or at the start trial. If found, the trial was labeled no *in vitro* rationale, but some available (if *in vitro* rationale present but not referenced, and the evidence found matched rationale present, then it was labeled clear *in vitro* rationale in disease model). In general, all searches on MEDLINE were first filtered for studies that were published at the start of the clinical trial and before and if none were found, then studies after the trial start date were reviewed. However, overall, the main intention was to find any supporting *in vitro* study rationalizing the drug being tested in each disease to overall analyze trends in drug concentrations *in vitro* studies and so the timing of each study was not of utmost importance.

After finding the studies acting as the *in vitro* rationale for a trial, whether it was through a paper or a MEDLINE search, the IC_{50} or listed effective concentration(s) that imatinib/erlotinib

caused an effect was recorded. For trials with combination drug treatments, *in vitro* studies that matched the combination was attempted to be found, but if only some with the erlotinib/imatinib or only some part of the combination was able to be found, that was also recorded. The analysis and summary spreadsheets for each kinase inhibitor provide further details on the collection and labeling process for *in vitro* data.

Data Representation and Analysis

All results figures were made on the program GraphPad Prism. In Figures 2 and 3, the lowest efficacious concentration used in a disease model as represented from the collected *in vitro* rationale for each disease was considered against each kinase inhibitor's effective C_{ave} at a standard, prescribed dose. This allowed the most equitable comparison between a drug's claims of *in vitro* activity and its average human serum concentration possible. In these same figures, some diseases were excluded in this representation of the data and analysis compared to Figure 1 looking solely at clinical outcomes in tested unique diseases. This is due to the diseases not having any *in vitro* rationale in appropriate disease models cited by the trial/its publication of results nor any found on the MEDLINE database or the *in vitro* rationale did not have a lowest efficacious concentration. The "Summary Table" spreadsheets show for which diseases this was the case. To evaluate the significance of correlations, one-tailed Fisher's exact tests were run on the erlotinib and imatinib results alone and combined on an online calculator (Lowry 2021).

Appendix

Supplementary Tables and Links

Supplementary Table 1. Fisher's exact test contingency tables for imatinib and erlotinib results alone

		Successful clinical outcome in disease	Failed clinical outcome in disease
Imatinib	*In vitro* concentration above C_{ave}	1	22
	In vitro concentration below C_{ave}	5	1
Erlotinib	*In vitro* concentration above C_{ave}	1	16
	In vitro concentration below C_{ave}	1*	4

* = NSCLC EGFR+ is counted as one data point because it is one disease supported by 2 *in vitro* concentrations both under the erlotinib C_{ave}

Supplementary Table 2. Approval history of erlotinib

Disease and Dose	Line of Therapy	Approval date
Locally advanced or metastatic non-small cell lung cancer (NSCLC) → 150 mg orally, once daily	After failure of ≥ 1 prior chemotherapy regimen	11/18/2004
	Maintenance after disease has not progressed after 4 cycles of platinum-based 1st line chemotherapy	4/6/2010
	1st line for tumors expressing EGFR exon 19 deletion or exon 21 (L858R) substitution mutations	5/14/2013
	All lines of therapy (maintenance or 2nd line or greater) for tumors expressing EGFR exon 19 deletion or exon 21 (L858R) substitution mutations	10/18/2016
Locally advanced, unresectable, or metastatic pancreatic cancer → 100 mg, orally, once daily	1st line in combination with gemcitabine	11/2/2005

Supplementary Table 3. Approval history for imatinib

Disease and Dose	Line of Therapy	Approval date
Chronic myeloid leukemia (CML) → 400 mg, orally, once a day for Ph+ CP in adults 600 mg, orally, once a day for Ph+ AP or BC in adults 340 mg/m2/day or 260 mg/m2/day intravenously for Ph+ in pediatrics	In blast crisis (BC), accelerated phase (AP), or in chronic phase (CP) after failure of interferon-alpha therapy	5/10/2001
	1st line in adult patients with Philadelphia Chromosome positive (Ph+) CML	12/20/2002
	Pediatric patients with Ph+ CML whose disease has recurred after stem cell transplant or who are resistant to interferon-alpha therapy	5/20/2003
	1st line as single agent for pediatric patients with newly diagnosed Ph+ CML	9/27/2006
Gastrointestinal stromal tumors (GIST) → 400 mg, orally, once a day for adults	Kit+ (CD117) unresectable and/or metastatic malignant GIST	2/1/2002
	Adjuvant treatment for adult patients following complete gross resection of Kit+ (CD117) GIST (accelerated approval)	12/19/2008 - Accelerated approval 1/31/2012 - Regular approval
Unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP) → 800 mg, orally, 400 mg twice a day for adults	For adult patients	10/19/2006
Hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) → 100 mg or 400 mg, orally, once a day for adults	For adult patients who are FIP1L1-PDGFRα fusion kinase positive, negative, or unknown (positive had first approval)	10/19/2006
Myelodysplastic/ myeloproliferative diseases (MDS/MPD) → 400 mg, orally, once a day	For adult patients with MDS associated with PDGFR (platelet-derived growth factor receptor) gene rearrangements	10/19/2006
Acute lymphocytic leukemia → 600 mg, orally, once a day	For adult patients with relapsed or refractory Ph+ ALL	10/19/2006

	1st line in combination with chemotherapy for pediatric patients with newly diagnosed Ph+ ALL	1/25/2013
Aggressive systemic mastocytosis (ASM) → 100 mg or 400 mg, orally, once a day	For adult patients who are without D816V c-Kit mutation or with c-Kit mutational status unknown	10/19/2006

Imatinib Clinical Trial Analysis Spreadsheet:
https://docs.google.com/spreadsheets/d/10gZHQsOKMNqYdqy34iieRLS127I6ROhY010WD5OVVPI/edit?usp=sharing
Erlotinib Clinical Trial Analysis Spreadsheet:
https://docs.google.com/spreadsheets/d/1hF3J27SAJnS5kO0hDCTrXib77QbM6A8k5ZhcDyMC7JA/edit?usp=sharing

Imatinib Summary Tables Spreadsheet:
https://pennstateoffice365-my.sharepoint.com/:x:/g/personal/kad5963_psu_edu/EQPR2i-QKGhCsUC-ZhxLXOUBR5n8L9JnSRF7sPLotQx9-g?e=vMTsfo
Erlotinib Summary Tables Spreadsheet:
https://pennstateoffice365-my.sharepoint.com/:x:/g/personal/ams8561_psu_edu/EZf5LWsBxNJEranVmHBLCBIBsbeLuw8n5Mx38kKn0GhcBw?e=r5e3jP

REFERENCES

Begley, C. G., & Ellis, L. M. (2012). Drug development: Raise standards for preclinical cancer research. *Nature*, *483*(7391), 531-533. https://doi.org/10.1038/483531a

Ben-David, U., Ha, G., Tseng, Y. Y., Greenwald, N. F., Oh, C., Shih, J., McFarland, J. M., Wong, B., Boehm, J. S., Beroukhim, R., & Golub, T. R. (2017). Patient-derived xenografts undergo mouse-specific tumor evolution. *Nature Genetics*, *49*(11), 1567–1575. https://doi.org/10.1038/ng.3967

Björkhem-Bergman, L., Lindh, J. D., & Bergman, P. (2011). What is a relevant statin concentration in cell experiments claiming pleiotropic effects? *British Journal of Clinical Pharmacology*, *72*(1), 164–165. https://doi.org/10.1111/j.1365-2125.2011.03907.x

Ferreira D, Adega F, & Chaves R. (2013). The importance of cancer cell lines as *in vitro* models in cancer methylome analysis and anticancer drugs testing. In C. Lopez-Camarillo & E. Arechaga-Ocampo (Eds.), *Oncogenomics cancer proteomics: Novel approaches in biomarkers discovery and therapeutic targets in cancer* (vol 3., p. 139–166). InTech. https://doi.org/10.5772/ 53110.

DiMasi, J. A., Feldman, L., Seckler, A., & Wilson, A. (2010). Trends in Risks Associated With New Drug Development: Success Rates for Investigational Drugs. *Clinical Pharmacology & Therapeutics*, *87*(3), 272-277. https://doi.org/https://doi.org/10.1038/clpt.2009.295

Eastman, A. (2017). Improving anticancer drug development begins with cell culture:

misinformation perpetrated by the misuse of cytotoxicity assays. *Oncotarget*, *8*(5), 8854-8866. https://doi.org/10.18632/oncotarget.12673

Gao, H., Korn, J. M., Ferretti, S., Monahan, J. E., Wang, Y., Singh, M., Zhang, C., Schnell, C., Yang, G., Zhang, Y., Balbin, O. A., Barbe, S., Cai, H., Casey, F., Chatterjee, S., Chiang, D. Y., Chuai, S., Cogan, S. M., Collins, S. D., Dammassa, E., … Sellers, W. R. (2015). High-throughput screening using patient-derived tumor xenografts to predict clinical trial drug response. *Nature Medicine*, *21*(11), 1318–1325. https://doi.org/10.1038/nm.3954

U.S. National Library of Medicine. (2021). *History, Policies, and Laws*. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/about-site/history.

Johnson, J. I., Decker, S., Zaharevitz, D., Rubinstein, L. V., Venditti, J. M., Schepartz, S., Kalyandrug, S., Christian, M., Arbuck, S., Hollingshead, M., & Sausville, E. A. (2001). Relationships between drug activity in NCI preclinical *in vitro* and *in vivo* models and early clinical trials. *British Journal of Cancer*, *84*(10), 1424–1431. https://doi.org/10.1054/bjoc.2001.1796

Karaman, M. W., Herrgard, S., Treiber, D. K., Gallant, P., Atteridge, C. E., Campbell, B. T., Chan, K. W., Ciceri, P., Davis, M. I., Edeen, P. T., Faraoni, R., Floyd, M., Hunt, J. P., Lockhart, D. J., Milanov, Z. V., Morrison, M. J., Pallares, G., Patel, H. K., Pritchard, S., Wodicka, L. M., & Zarrinkar, P. P. (2008). A quantitative analysis of kinase inhibitor selectivity. *Nature Biotechnology*, *26*(1), 127–132. https://doi.org/10.1038/nbt1358

Kolenova, A., Maloney, K. W., & Hunger, S. P. (2016). Philadelphia Chromosome-positive

Acute Lymphoblastic Leukemia or Chronic Myeloid Leukemia in Lymphoid Blast Crisis. *Journal of Pediatric Hematology/Oncology*, *38*(6).

Leighow, S. M. et al. (2021). Unprincipled preclinical drug dosing is a common source of failure in clinical drug repositioning (Unpublished manuscript). Department of Biomedical Engineering, Pennsylvania State University.

Lowry, R. (2021). *2x2 Contingency Table with Odds Ratios*. VassarStats: Website for Statistical Computation. http://vassarstats.net/odds2x2.html.

McIlroy, K. (2020). Modeling Serum-Drug Kinetics for the Prediction of Cancer Resistance to Second Line Therapeutics (Undergraduate honors thesis). Retrieved from https://honors.libraries.psu.edu/files/final_submissions/6201

Neuberger, A., Oraiopoulos, N., & Drakeman, D. L. (2019). Renovation as innovation: is repurposing the future of drug discovery research?. *Drug Discovery Today*, *24*(1), 1–3. https://doi.org/10.1016/j.drudis.2018.06.012

Novartis Pharmaceuticals Corp. (2018). *Gleevec (imatinib mesylate).* East Hanover, NJ: Novartis Pharmaceuticals Corp.

OSI Pharmaceuticals. (2016). *Tarceva (erlotinib).* South San Francisco, CA: Genentech Inc.

Pushpakom, S., Iorio, F., Eyers, P. et al. Drug repurposing: progress, challenges and recommendations. Nat Rev Drug Discov 18, 41–58 (2019). https://doi.org/10.1038/nrd.2018.168

Rubin, E. H., & Gilliland, D. G. (2012). Drug development and clinical trials—the path to an

approved cancer drug. *Nature Reviews Clinical Oncology*, *9*(4), 215-222. https://doi.org/10.1038/nrclinonc.2012.22

Smith, M. A., & Houghton, P. (2013). A Proposal Regarding Reporting of *In vitro* Testing Results. *Clinical Cancer Research*, *19*(11), 2828-2833. https://doi.org/10.1158/1078-0432.ccr-13-0043

Zhang, Y. L., Yuan, J. Q., Wang, K. F., Fu, X. H., Han, X. R., Threapleton, D., Yang, Z. Y., Mao, C., & Tang, J. L. (2016). The prevalence of EGFR mutation in patients with non-small cell lung cancer: a systematic review and meta-analysis. *Oncotarget*, 7(48), 78985–78993. https://doi.org/10.18632/oncotarget.12587

ACADEMIC VITA

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EDUCATION

The Pennsylvania State University | Schreyer Honors College | Aug. 2017 – May 2021 University Park, PA
B.S. in Biology (Neurobiology Focus)
B.A. in English (Creative Writing Focus)
Honors: Braddock Scholar, Paterno Fellow, National Merit Scholar, President's Freshman Award, Dean's List (all semesters)
The Pennsylvania State University | The Graduate School | Aug. 2020 – May 2021 University Park, PA
M.A. in Creative Writing (Poetry Focus)

EXPERIENCE

Pritchard Lab | Penn State Department of Biomedical Engineering University Park, PA
Undergraduate Research Assistant Jan. 2019 – May 2021

- Conducted meta-analysis of clinical trials involving kinase inhibitors to examine drug repurposing patterns and preclinical rationale to understand clinical trial failure rates
- Applied computational and systems biology methods to understand patterns of drug resistance variability in clonal populations of and mutants from different cancer cell lines

Creative Writing Department | Penn State Department of English University Park, PA
Public Relations Intern and Recipient of Emma J. and Edward F. Campbell Internship Fund Aug. 2019 – May 2020

- Wrote and distributed press releases and created promotional posts for department's blog and social media for Mary E. Rolling Reading series and Emily Dickinson lecture to advertise these events to Penn State and local communities
- Updated design, organizational, and informational aspects of blog to improve aesthetic and accessibility of interface

Department of Pediatric Radiology | UPMC Children's Hospital of Pittsburgh Lawrenceville, PA
Student Research Assistant (Summer of 2019) and SRIP Intern (Summer of 2018) June 2018 – Aug. 2019

- Applied manual segmentation methods and volumetric analyses to generate and organize olfactory bulb and hippocampal volumetric data of congenital heart disease (CHD) and control cases to contributed to research on links between (CHD) and poor neurodevelopmental outcomes
- Presented on associations between hippocampal volumes and ciliary dysfunction data in SRIP poster symposium

LEADERSHIP AND SERVICE

Schreyer for Women (SfW) University Park, PA
President (April 2020 – April 2021) and Special Projects (SP) Director & Chair (May 2019 – March 2020) Aug. 2017 – May 2021

- Led and coordinated executive board operations and general body meetings, while maintaining a larger vision and tone within in all SfW initiatives and communications (President)
- Organized and facilitated unique events that fostered personal development for members and promoted collaboration within SfW pillars and SfW with the Schreyer and Penn State communities (SP Director and Chair)

Penn State Arts for Health Initiative University Park, PA
Founder and Director (Jan. 2020 – Dec. 2020) Jan. 2020 – May 2021

- Coordinated initiative's operations to maintain and curate a social media gallery project that aims to share and support how professional and casual artists in the community are engaging with arts for their wellbeing

Penn State Remote Area Medical (RAM) University Park, PA
General member January 2019 – May 2020

- Volunteered as general support to help facilitate free medical services at local healthcare clinics

Schreyer Honors College Recruitment University Park, PA
Scholar Ambassador Team (August 2018 – December 2019) August 2017 – December 2019

- Served on student panels and led tours for prospective students and parents and represented the honors college at alumni and donor events to give insight on the honors experience

WRITING AWARDS

- 2021: American Academy of Poets Steinberg Prize (2021) & Mihelcic Poetry 1st Prize
- 2020: Edward Nichols Creative Nonfiction 1st & Mihelcic Poetry 2nd Prize
- 2019: Cranage Poetry 2nd Prize
- 2018: Mihelcic Poetry Award 1st Prize