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Title: Drug Repurposing to treat Asthma and Allergic Disorders: Progress and Prospects

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Abstract

Allergy and atopic asthma have continued to become more prevalent in modern society despite the advent of new treatments, representing a major global health problem. Common medications such as antihistamines and steroids may have undesirable long-term side effects and lack efficacy in some resistant patients. Biologic medications are increasingly given to treat resistant patients, but they can represent high costs, complex dosing and management, and are not widely available around the world. The field needs new, cheap and convenient treatment options in

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order to bring better symptom relief to patients. Beyond continued research and development of new drugs, a focus on drug repurposing could alleviate this problem by repositioning effective and safe small molecule drugs from other fields of medicine and applying them toward the treatment of asthma and allergy. Herein, preclinical models, case reports, and clinical trials of drug repurposing efficacy in allergic disease are reviewed. Novel drugs are also proposed for repositioning based on their mechanism of action to treat asthma and allergy. Overall, drug repurposing could become increasingly important as a way of advancing allergy and atopic asthma treatment, filling a need in treatment for patients today.

Keywords: Allergy – Asthma – Drug repositioning – Drug repurposing

Short title: Drug Repurposing in Asthma and Allergy

Introduction

Allergic disorders and atopic asthma are a major burden to patients causing decreased patient quality of life. Allergic disorders are being diagnosed with increasing frequency across the world. In the United States, a Center for Disease Control study found that food and skin allergy prevalence have increased from 3.4% to 5.1% and 7.4% to 12.5%, respectively, from 1997 to 2011 (1). In Europe, studies have estimated a prevalence of 20-25% allergic disease in adults, with many young people unaware of their disease (2).

Current drugs have limited ability to contain this growing allergic disease epidemic. Antihistamines are a mainstay in the treatment of various allergies, targeting signaling pathways in mast cells and airway epithelium, with routine prescriptions for loratidine and cetirizine providing daily allergy relief for millions of patients across the

world (3). Similarly, steroids are also used as generalized immunomodulators suppressing a variety of different types of immune cells. Inhaled steroids are important in treating atopic and non-atopic asthma, and topical steroids can be used to treat allergic skin flares. Most patients are able to control symptoms of their disease with these mainstay treatments. However, some patients can even be refractory to steroid therapy, with a small percentage of severe asthmatics contributing to the majority of morbidity and mortality associated with the disease, and thus require more potent therapies (4).

In order to provide symptom relief to treatment resistant patients, several biologic drug therapies have been developed with some showing marked benefits.

Prominently, antibodies targeting immunoglobulin E (IgE), such as omalizumab, are widely prescribed to many patients who fail conventional therapies (5). These antibodies work by preventing IgE binding to IgE receptors on the surface of mast cells and eosinophils, thereby preventing the cells' activation to cognate allergens (6). In addition to targeting IgE, several additional antibodies targeting IL-2, IL-13, IL-5, IL-1, C5a, and TNF- α are in clinical development for patients with severe asthma expanding the diversity of potential biologic interventions (7).

While treatments for asthma and allergic disorders have improved, their burdens continue to have enormous economic consequences. The costs of allergies to the United States each year were estimated at \$56 billion in 2007, a figure which includes direct medical costs and indirect productivity losses (8). Within the European Union, the cost estimates range from 55 and 151 billion per year, including indirect costs related to absence or reduced productivity at work (9).

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Severe asthmatics not controlled by medications contribute more than double the healthcare costs versus asthmatics controlled by medication (10). Though biologic therapies have provided many patient benefits, the costs versus benefits of biologics based on certain economic analyses limit their widespread use to restricted patient populations (11). Ideally, small molecules could be identified with different mechanisms of action than current allergic drug classes, while still delivering the same symptomatic improvements. These small molecule drugs might even have fewer side effects than the current mainstay drugs, particularly steroids.

Drug Repurposing

The development of new small molecule drugs, however, is a risky undertaking costing hundreds of millions of dollars and requiring years of research and clinical trials. This includes the challenge of target discovery, validation in animal models of disease, optimizing a lead candidate for pharmacokinetic properties for oral intake, safety testing in patients, and finally, trials for efficacy against the targeted disease, which can carry high failure rates even into Phase II and Phase III clinical trials (12). While the ultimate drug efficacy in these later phases will always be uncertain, many drugs initially fail during safety testing in a phase I trial, where a drug is tested in normal, healthy subjects at increasing doses and analyzed for any phenotypic changes or other abnormalities and toxicities (12). Before entering clinical trials and phase I testing, extensive data must be presented to the FDA demonstrating the safety of small molecules in mouse models, non-human primates, and other species, in order to get an investigational new drug (IND) application approved. This after spending the years of research necessary to identify the good lead drug candidate, which can prove challenging due to the difficulties finding targets, performing small molecule screens for activity, and most importantly, reproducing data across labs

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and experiments (13). All these steps mark a long wait (10+ years until approval) for those with uncontrolled symptoms of disease and no other treatment options.

In light of these challenges, there has been a growing movement for a new paradigm in drug development, where drugs already approved by the FDA, with well documented safety records that would not require phase I testing, are taken and tested for efficacy in other medical indications. Furthermore, these drugs in certain cases would be significantly cheaper than a new branded medicine, since they may be generic after many years on market representing another major advantage (14). This concept is known as “drug repurposing” (15) or “drug repositioning” (16). One recent example of drug repurposing is plerixafor, which is a CXCR4 antagonist. It was originally developed as an HIV entry inhibitor, but failed in that indication (17). A side effect during those trials was leukocytosis in the peripheral blood, including hematopoietic stem cells (HSCs) (17). This finding led to repurposing of plerixafor as a new agent to mobilize HSCs for bone marrow transplant (18).

Drug repurposing strategies can take many different forms, as reviewed in full in the enclosed reference (19). Sometimes, it is driven by clinical experience of physicians themselves, where the happenstance treatment of one indication in a patient leads to improvement in another seemingly unrelated disease process in the same patient. Often, it is led by deeper understanding of the biology of a disease through new basic research reports, observing that a protein or pathway targeted by the drug is a key component of an unrelated disease, either through new discoveries or bioinformatics data (20). More recently, scientists have started to employ high-throughput screening of libraries of FDA-approved drugs, affording an unbiased

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assay in cell culture whether a positive change in phenotype occurred, without a priori knowledge of the importance of the pathway in that disease (21). Another approach measures gene expression changes after FDA approved drug administration in diverse tissue types, forming a connectivity map of drug and gene outcomes, yielding the potential to computationally identify drug repurposing candidates (22). Automated reasoning algorithms have also been used to scan the words in research abstracts to identify new connections and potential drug indications (23). A recent study also suggested that analyzing social media data and patient commentary on drugs on WebMD could yield insights into novel beneficial uses for drugs and routes toward drug repurposing (24).

Once drug repurposing candidates are identified, electronic health records can be analyzed and responses for patients already on the drug assessed, in order to determine efficacy before ever doing a clinical trial. This leverages instances where patients are comorbid for the proposed indication and the current drug indication. An example of this strategy found that metformin could decrease mortality in cancer patients (25). Drug repurposing trials can also be more easily investigator-initiated at academic centers, with less complicated drug procurement for clinical trials, as the drug is already mass produced and often cheaply available. This compares to clinical trials with new chemical entities, where the amount of drug can be limiting and pharmaceutical companies largely control the trials. In that sense, drug repurposing allows physicians to move to the forefront of innovation in developing new medical therapies. Given that the safety record of the drugs is already established, physicians can anticipate the highest levels of drugs that patients can tolerate, and

go directly for efficacy testing in pilot studies of a small cohort of patients. These can then pave the way for larger, randomized control studies.

Drug repurposing has only begun to be explored in the fields of allergy and asthma, however, being more common in oncology, infectious disease, and autoimmune diseases. Herein, repurposed drugs that target the lymphocyte and myeloid cell populations, important in allergy and asthma pathogenesis, as well as agents with non-immune mechanisms will be reviewed. Initial reports of drugs repurposed in allergy and asthma animal models are evaluated. Finally, case reports and clinical trials utilizing repositioned drugs in patients with allergic disease treated are analyzed.

Lymphocyte Modulating Agents

Among the signaling molecules crucial for T cell activation, the janus kinase (JAK) / signal transducer and activator of transcription (STAT) pathway plays a crucial role. JAK/STAT is downstream of many important cytokine receptors that augment T cell activation (26). As a result, a number of different JAK and/or STAT inhibitors have been developed that might dampen T cell activation. An example is tofacitinib, an inhibitor to both JAK1 and JAK3, and currently approved for treatment in rheumatoid arthritis (27). Tofacitinib has also shown efficacy in a phase II trial to treat ankylosing spondylitis, improving severity and symptoms versus placebo after 12 weeks (28). Moving into allergic diseases, tofacitinib has been explored to treat atopic dermatitis (AD). The rationale was that T cells are also crucial to the inflammation in atopy, a chronic state with unclear environmental triggers. Tofacitinib therapy yields anti-pruritic and anti-inflammatory responses in a mouse model of allergic dermatitis

when applied topically (29). Extending into patients, oral tofacitinib in a clinical trial to treat recalcitrant AD found a significant decline in AD severity score (30). Exploring a different dermatological disease, tofacitinib is also being tested for treatment of psoriasis in Phase II clinical trials (31). Psoriasis is an autoimmune disease of the skin driven by T cells, and current clinical trial results suggest positive benefits for tofacitinib in this disease as well (31). Given the similarities of these diseases to allergic inflammation, it can easily be imagined that tofacitinib could find efficacy in clinical pilot studies.

Another small molecule in this class is ruxolitinib, which is a JAK1/2 inhibitor having a slightly different selectivity than tofacitinib. Ruxolitinib is currently approved for the treatment of intermediate or high-risk myelofibrosis, and for polycythemia vera in patients who do not respond to hydroxyurea treatment (32). Ruxolitinib has been found to potently suppress T cell functions *in vitro* and in myelofibrosis patients, inhibiting IL-2-dependent STAT5 activation and resultant pro-inflammatory cytokines secretion (33). Ruxolitinib has also shown promise in case reports in treating recalcitrant dermatomyositis (34) and chilblain lupus erythematosus (35), suggesting potential use in immunomodulation for other disorders. Extending into allergy, ruxolitinib was studied for repurposing to treat food allergies, which is driven in part by T cell inflammation in the gut. Oral administration of ruxolitinib into a food allergy mouse model found marked remission of symptoms (36). The finding has yet to be extended to humans, but demonstrates that the JAK/STAT pathway inhibitors may be exciting candidates for treatment of allergic disorders.

Pathogenic T cells can also be modulated by targeting interleukin-2-inducible T-cell kinase (ITK), which functions in promoting Th2 differentiation (37). A small molecule inhibitor, ibrutinib, has been developed that inhibits ITK and Th2 immunity, while sparing Th1 immunity (38). Ibrutinib also inhibits Bruton's tyrosine kinase (BTK), having efficacy in the treatment of B cell malignancies, where it holds FDA approval. Beyond cancer, BTK inhibitors also suppress normal B cell receptor signaling, which was used in animal models to successfully suppress auto-antibody production and the development of collagen-induced arthritis and lupus nephritis, respectively (39). Furthermore, ibrutinib can relieve different autoimmune arthritis mouse models, both those that are dependent on auto-antibody production, and surprisingly, in those models that do not depend on it (40). This indicates that beyond B cells, monocytes, macrophages, and mast cells may be inhibited by ibrutinib thereby relieving arthritic conditions (40). Treating allergic disease, IgE-mediated signaling and activation in human basophils was inhibited *in vitro* by ibrutinib (41). In a pilot study of patients already on ibrutinib for an underlying lymphoid malignancy, ibrutinib was found to cause sustained elimination of reactivity to cat or ragweed allergens by skin and basophil activation tests, through a mechanism thought to be mediated by inhibiting IgE-dependent basophil and mast cell activation (42). These promising results warrant further clinical exploration.

The mechanistic target of rapamycin (mTOR) pathway is recognized to modulate the signaling of both innate and adaptive immune cells (43). Rapamycin, the namesake inhibitor of mTOR, is approved for immunosuppression during organ transplants. While efficacious for general immunosuppression, it is possible that rapamycin could be harnessed in lower doses or locally applied doses in order to treat allergic

diseases. Investigators have found that rapamycin can attenuate allergic airway inflammation in a mouse model through inhibiting eosinophil differentiation (44). Similarly, bronchial hyperreactivity in a guinea pig model was successfully reduced by rapamycin via inhibiting leukocyte migration (45). Rapamycin was also able to attenuate airway hyperreactivity, goblet cells, and IgE levels in house dust mite induced mouse model of allergic asthma (46). However, when compared to dexamethasone treatment in an established model of allergic asthma, a different study found that rapamycin was less potent versus steroid treatment, suggesting that it needs to be dosed before the full onset of symptoms (47).

Bortezomib is a 26S proteasome inhibitor and approved for the treatment of mantle cell lymphoma and relapsing multiple myeloma (48). Bortezomib has also been shown to reduce the secretion of antibodies of various different classes, including IgE, by causing endoplasmic reticulum stress in plasma cells resulting in their death (49). This property was applied to abolish allergenic-specific IgE levels in a mouse model of hazelnut-induced intestinal anaphylaxis, with associated improvement in clinical symptoms (50). Thus, bortezomib could potentially reduce IgE levels similar to omalizumab. In an asthma mouse model, however, long-term bortezomib treatment was efficacious in decreasing the levels of allergen-specific IgE, but could not improve asthmatic symptoms in mice (51). Another study found contrasting results, as bortezomib alone or in combination with drugs enhancing protein phosphatase-2A effectively reduced inflammation and features of allergic airway disease in mice (52). More studies are needed to resolve this discrepancy.

A summary of repurposed drugs targeting lymphocytes is provided in **Figure 1**.

Myeloid Modulating Agents

Small molecules that inhibit myeloid cells are crucial in preventing allergic disease. Indeed, antihistamines counteract the effects of mast cells, but alternative molecules that inhibit their function might have more utility. One candidate molecule is imatinib, a tyrosine-kinase inhibitor, that heralded the era of targeted cancer therapy by inhibiting the fusion enzyme, BCR-ABL1, which drives the development of chronic myelogenous leukemia (CML) (53). While traditionally described as a targeted therapy, imatinib can inhibit various tyrosine kinases, including Flt-3, Lck and mitogen-activated protein kinase (MAPK), suppressing various functions in dendritic cells, macrophages, and T cells (54). Imatinib can also inhibit c-Kit receptor signaling, also known as mast cell growth factor receptor, thereby causing mast cell apoptosis in cell culture (55). Imatinib has been found to reduce T cell proliferation and activation through inhibiting T-cell receptor signaling in a dose-dependent manner, an additional mechanism useful for treating allergy (56). In a mouse model of allergic asthma induced with cockroach allergen, prior treatment with oral imatinib significantly alleviated symptoms, with decreased airway hyperreactivity, peribronchial eosinophil accumulation, and Th2 cytokines (57). Another supporting study discovered that imatinib can reduce airway hyperresponsiveness, smooth muscle thickening, and eosinophilic inflammation in an ovalbumin-challenged based chronic asthma mouse model (58).

Bringing these findings into human patients, studies have already found efficacy for imatinib in treating allergy and asthma. Imatinib has been shown to reverse aberrant leukotriene C4 production in neutrophils in patients with CML (59). While promoting myelogenesis and thus cancer in CML, leukotrienes are key mediators of asthma pathogenesis being potent bronchoconstrictors and inflammatory agents (60). Combining this information, in two patients with CML also having asthma-like lower airway symptoms, patients treated with imatinib to treat their cancer exhibited dramatic resolution of airway symptoms, suggesting targeted effects for asthma (61). In another case report, a 42-year-old man with chronic cough not responding to inhaled corticosteroid or leukotriene receptor antagonists diagnosed as hypereosinophilic syndrome successfully responded to imatinib treatment (62). The efficacy from these case reports were confirmed in a randomized, double-blind, placebo-controlled trial of 62 patients with poorly controlled severe asthma despite receiving maximal medical therapy. The patients receiving imatinib had significantly reduced airway hyperresponsiveness, mast-cell counts, and tryptase release compared to patients receiving placebo (63).

Tamoxifen is a revolutionary cancer drug for breast cancer patients, inhibiting the estrogen receptor in order to prevent tumor growth in certain types of breast cancer (64). Interestingly, estrogen also plays a role in the development of allergy and asthma. Estrogen has been shown in a mouse model of asthma to stimulate the production of Th2 cytokines, along with regulating the action of eosinophils during allergen challenge (65). Thus, inhibiting estrogen signaling could have benefits towards both cell types in asthma. This has been tested *in vitro* by demonstrating that mast cells can be inhibited by tamoxifen, limiting their proliferation and survival

(66). Similarly, tamoxifen can inhibit the maturation of dendritic cells into potent antigen presenting cells (67). These findings have been confirmed in an animal model of neutrophilic asthma, where horses treated with tamoxifen had reduced levels of bronchoalveolar lavage fluid neutrophils, comparable to dexamethasone treatment in the same animals (68).

Statins are a widely used class of medicine that lowers cholesterol levels by inhibiting HMG-CoA reductase. Some statins have also been noted to have some anti-inflammatory properties, and fluvastatin was found to be a potent suppressor of mouse mast cell activation, partly by inhibiting degranulation (69). A retrospective cohort study did find benefits of statins on asthma patients on inhaled corticosteroids, reducing odds of hospitalization or emergency room visits by almost half (70). However, a double-blind randomized control trial found that atorvastatin was not effective in reducing symptoms of persistent mild to moderate asthma (71). Further work is needed to clarify these discrepancies. Beyond statins, other approved drugs investigated as mast cell stabilizing drugs include nilotinib (tyrosine kinase inhibitor used in BCR-ABL1 positive CML therapy), ambroxol (a mucolytic agent), and loop diuretics (ex: furosemide) and are covered in depth in the enclosed review (72).

Metformin is a commonly prescribed medication for type II diabetic patients. It functions to suppress hepatic gluconeogenesis, but the exact molecular mechanism of action is unclear (73). One postulated mechanism is the activation of AMP-activated protein kinase (AMPK), and metformin has been shown to decrease airway remodeling and inflammation in a chronic asthma mouse model via AMPK activation

(74). Metformin also helped protect mice from bleomycin-induced lung injury in the same study, reducing eosinophilic inflammation, peribronchial fibrosis, and smooth muscle secretion. Given the link between asthma and obesity (75), an extension of these findings followed obese mice on a high fat diet that were then treated with metformin. Metformin reversed the insulin resistance in the mice, but also reduced eosinophilia in bronchoalveolar lavages upon ovalbumin challenge demonstrating a reduction in asthmatic symptoms (76). With these promising preclinical findings, a retrospective analysis was undertaken in order to assess among patients with diabetes and asthma, if metformin users were protected from asthma. Among 1,332 patients with both diseases, one-third were on metformin and those patients had a lower risk of asthma exacerbation and asthma related hospitalization, suggesting this might be an effective treatment for this patient population (77). This result contrasted with data evaluating metformin in a clinical trial to treat chronic obstructive pulmonary disease (COPD), finding that metformin had no effect on the COPD exacerbations in a randomized control trial (78), indicating that the positive effects may not extend to other lung diseases.

Pioglitazone is a PPAR- γ agonist that is important in the treatment of diabetes by decreasing insulin resistance in the liver and peripheral tissues. In a preclinical study in a cockroach allergen-induced mouse model of asthma, pioglitazone was found to be just as effective as dexamethasone in reducing airway hyperresponsiveness and inflammatory cell recruitment (79). Pioglitazone was also found to reduce NF-kappaB activity and IL-17 production in allergic airway mouse model (80). When these findings were translated in clinical trials, however, pioglitazone was found to have no therapeutic benefit in asthma patients in a double-blind randomized controlled trial

(81). Another randomized controlled trial testing pioglitazone to treat poorly controlled asthma in obese patients similarly found limited efficacy and even harm in this patient population (82). In a randomized, double-blind crossover trial with severe asthma resistant to inhaled corticosteroids, pioglitazone again showed no significant difference compared to steroids alone (83). The discrepancy between mouse and human studies suggest fundamental differences in the impact of PPAR- γ signaling on atopic pathways between species.

A summary of repurposed drugs targeting myeloid cells is provided in **Figure 2**.

Non-immune Targeting Agents

Endothelin-1 is important in controlling airway contraction, and may also play a role in some cancers (84). The competitive endothelin-1 antagonist, bosentan, on target receptors endothelin-A and endothelin-B receptors is currently approved for treating pulmonary artery hypertension (85). These same receptors for endothelin are also important in asthmatic individuals (86). However, when tested in poorly-controlled asthmatic patients, a double-blind, placebo-controlled crossover pilot study revealed no improvement versus placebo in FEV1, β -agonist use, asthma symptom score, or asthma control test (87). This suggests that endothelin-1 antagonism might be too far downstream in asthma pathogenesis as one of many effectors to have a large therapeutic effect.

Vascular endothelial growth factor (VEGF) is a significant protein in the pathogenesis of asthma, with genetic polymorphisms being associated to disease development (88). VEGF causes endothelial signaling for angiogenesis, and its levels are

increased in asthmatic patients, contributing to increased vascularity in airway remodeling and precipitating functional abnormalities (89). Pazopanib is an example of a small molecule that inhibits the VEGF receptor and resultant new vessel growth, which could be repurposed for asthma by inhibiting angiogenesis in the lung epithelium to alleviate symptoms and airway remodeling (90). Pazopanib carries the added benefit of inhibiting c-Kit (90), which is important for mast cell function and asthma pathology as discussed above. Among other drug classes investigated for asthma, the anesthetic ketamine has shown efficacy in treating intractable asthma (91). Antioxidants eliminating reactive oxygen species (ROS) are also a potential treatment for asthma. A ROS scavenger previously studied for acute myocardial infarction therapy was identified via a drug signature analysis for repurposing to treat neutrophilic bronchial asthma (92).

The antibiotic, azithromycin, has been extensively studied as an asthma therapy, with the idea that bacterial infection could worsen asthmatic symptoms and that azithromycin also has anti-inflammatory activities (93). In a clinical trial of children 1-3 years old, azithromycin decreased the duration of asthma-like symptoms in these pediatric patients (93). However, a large randomized clinical trial in an adult population comparing azithromycin versus placebo to treat acute asthma exacerbations found no clinically significant benefit (94). A placebo-controlled, randomized trial of azithromycin in pre-school children was similarly ineffective in treating wheezing (95). However, a different randomized control trial of 420 adults with persistent symptomatic asthma found a better quality of life with fewer exacerbations among patients treated with oral azithromycin (96). Thus, it remains

uncertain if azithromycin is truly of benefit toward treating asthma in children and adults.

Finally, a recent postulated mechanism for the pathogenesis of asthma has opened up a common class of drugs, antifungals, for their treatment of a disease traditionally treated with immunomodulatory drugs. Many common allergens contain proteases, and these proteases have been found to cleave fibrinogen, producing proteins that act as TLR4 agonists inducing inflammation (97). In particular, fungi can colonize the airway, secreting proteases that may play an important role in treatment resistant asthma patients (98). This suggests that using common antifungal agents such as oral triazoles and inhaled amphotericin B might be a promising strategy in treating asthma, in addition to immunomodulating agents (99).

Conclusion

Drug repurposing may play a key role in allergy and asthma treatment in the future, as molecular pathways important to these diseases continue to be elucidated, opening up the use of the armament of FDA approved drugs to target these pathways. While several candidates for drug repurposing are described in this review (summarized in **Table 1**), this represents only a small fraction of repositioning possibilities among all FDA drugs, meaning many more may find clinical utility going forward. Furthermore, many of these drugs were identified through rational selection based on known molecular pathways in allergy, but the future of allergy and asthma drug repurposing will also increasingly be based on high-throughput approaches and computational gene profiling. The challenge for these methods will be the multifactorial nature of allergy and asthma, where a nexus of cell types and pathways contribute to the disease. Animal models of allergic disease will be crucial

in order to validate new targets identified. In that regard, mining clinical data for drug effects in patients through retrospective analyses will also be extremely valuable in order to reduce costs and development risk of these new interventions.

Drug repurposing has unique advantages in allergic disorders, since the manifestations of these diseases often happen in local tissues that are susceptible to restricted application of therapy, namely inhaled or topical therapy. New formulations and delivery routes could facilitate clinical trial development. More importantly, the side effect profile of these drugs may be limited, while maintaining on target efficacy at perhaps higher concentrations and potencies than currently achieved from oral dosing. Of course, some candidate drugs might simply have a toxicity profile that while acceptable in cancer patients and feasible in animal models, might be unacceptable for an otherwise healthy individual with asthma and allergic disease. These limitations will be elucidated in testing over time.

Moving forward, several key challenges remain in order to facilitate continued drug innovation in allergy and asthma. Preclinical studies and case reports will need to be verified by multiple investigators in order to ascertain their robustness. Discrepancies between the potent effects of some candidates in mouse models versus their failures in human patients will need to be illuminated further to understand predictive paradigms in allergy and asthma research. Cocktail approaches of small molecules that could provide synergies should be explored in order to maximize clinical benefit toward patients. The costs of some specialty cancer drugs will need to decrease for allergic label indications in order for repurposing to become feasible. Finally, it is important for the field to continue to address the root cause of allergic disorders, in

addition to symptom suppression. In that regard, any small molecules that could stop the “atopic march” (100) and potentially shift immune phenotype permanently following a short term treatment course, similar to vaccines or allergy desensitization, would rise in priority and represent a paradigm shift in the management of these patients that is currently not achievable with current medications.

Figure Legends:

Figure 1. Summary of repurposed drugs targeting lymphocytes involved in allergic disease.

Lymphocytes consist of NK, B, and T cells, the latter two often implicated in allergy. Allergens recognized by the BCR or TCR can signal through BTK or ITK to activate B or T cells, but ibrutinib can inhibit this signaling. Similarly, various cytokines can activate mTOR or JAK proteins downstream of their receptors, but these signaling can be blocked by rapamycin and tofacitinib/ruxolitinib, respectively. The production of allergic antibodies may be decreased by inhibiting the 26S proteasome with bortezomib, which normally helps degraded unfolded proteins from the ER preventing cell death. Definitions: BCR (B-cell receptor); TCR (T-cell receptor); BTK (Bruton's tyrosine kinase); ITK (interleukin-2-inducible kinase); mTOR (mechanistic target of rapamycin); JAK1/2/3 (janus kinase)

Figure 2. Summary of repurposed drugs targeting myeloid cell populations involved in allergic disease.

Myeloid cells include mast cells, eosinophils, basophils, dendritic cells, and macrophages. The c-Kit receptor is important in mast cell growth, and the drug imatinib can block its signaling, in addition to blocking MAPK, which is also important in immune activation. Estrogen has been shown to promote inflammation, and the tamoxifen can be used to block the binding of estrogen to its receptor reducing inflammation. Pioglitazone is an agonist to PPAR- γ , which results in the reduction of pro-inflammatory signaling. Statins have shown some function to preventing degranulation in mast cells and basophils, among other hypothesized anti-inflammatory mechanisms. Finally, metformin has been shown to activate AMP-activated kinase, which can then reduce inflammation in myeloid cells by uncertain mechanisms. Definitions: MAPK (mitogen-activated protein kinases); PPAR- γ (Peroxisome proliferator-activated receptor-gamma); AMP-activated protein kinase (adenosine monophosphate activated protein kinase)

Declarations

Authors' contributions

RLK designed the study and drafted the manuscript. KV helped draft and revise the manuscript. Both authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Consent for publication

Article is a review, and contains no original studies with patients requiring informed consent.

Availability of data and materials

This article is a review and contains no original data and materials, but rather summarizes them.

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Table 1. Summary of Repurposed Drugs for Allergy and Asthma

Drug	Mechanism	Current FDA approved indication
Tofacitinib	JAK1/3 inhibitor	rheumatoid arthritis
Ruxolitinib	JAK1/2 inhibitor	myelofibrosis, polycythemia vera
Ibrutinib	inhibits ITK, BTK	B cell malignancies
Rapamycin	inhibits mTOR	organ transplant
Bortezomib	26S proteasome inhibitor	mantle cell lymphoma, relapsing multiple myeloma
Imatinib	tyrosine-kinase inhibitor, especially BCR-ABL1 fusion protein	Philadelphia chromosome positive CML
Tamoxifen	inhibits estrogen receptor	ER positive breast cancer
Statins	Inhibits HMG-CoA reductase	high cholesterol
Metformin	activation of AMP-activated protein kinase	type II diabetes
Pioglitazone	PPAR- γ agonist	Type II diabetes
Bosentan	endothelin-1 antagonist	pulmonary artery hypertension
Pazopanib	VEGFR2 inhibitor, several other receptor tyrosine kinases	advanced/metastatic renal cell carcinoma, advanced soft tissue sarcomas
Azithromycin	Inhibits 50S bacterial ribosome	antibiotic for gram + & - bacteria, some atypical bacteria
Oral triazoles, inhaled amphotericin B	Inhibit lanosterol 14 α -demethylase, form pores in fungal membrane	Antifungal, depending on strain sensitivity

Figure 1

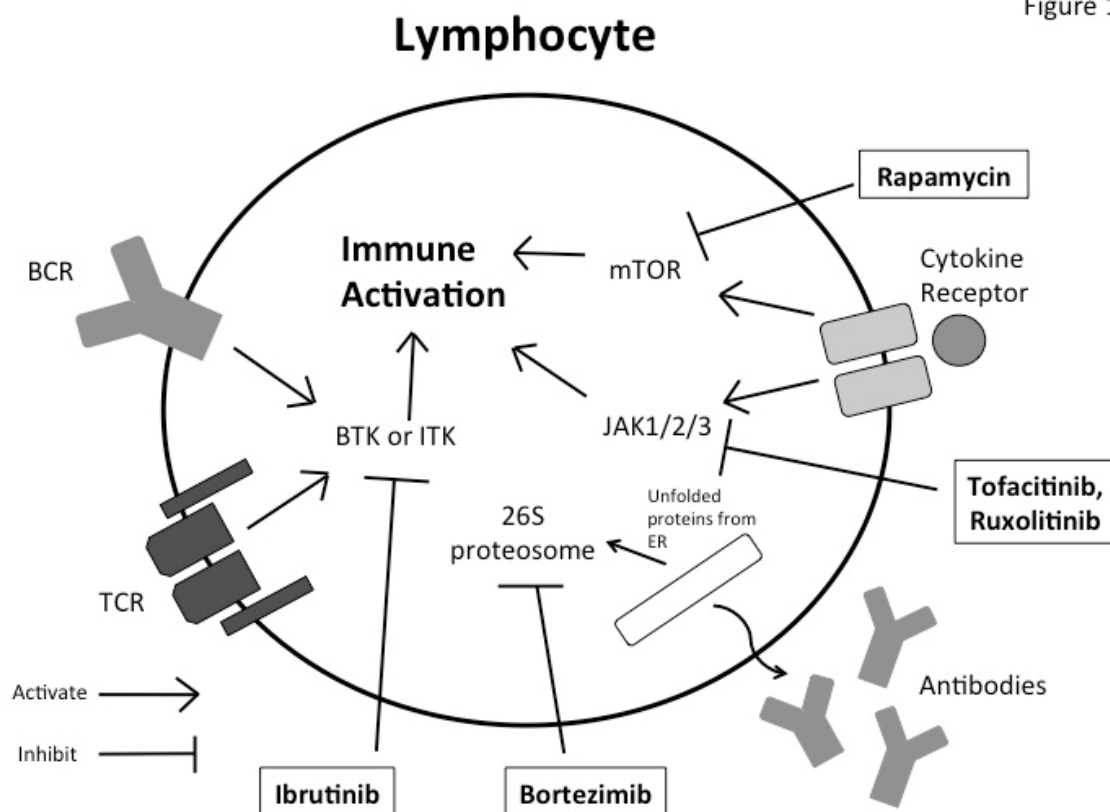


Figure 2

