



# REPURPOSING OF MULTIPLE SCLEROSIS (MS) AND GRAFT VERSUS HOST DISEASE (GVHD) THERAPEUTICS TO INHIBIT CHRONIC REJECTION OF TRANSPLANTED ORGANS



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**Abstract:** Chronic rejection of transplanted organs is an incurable event in transplantation. Macrophages infiltrating allograft induce vessel occlusion and tissue fibrosis, which over the months-years post-transplantation cause organ failure. Patients require re-transplantation, which is extremely problematic because of the permanent lack of organ donors. Our studies showed that chronic rejection depends on the function of macrophages and the RhoA/ROCK pathway. Genetic (RhoA knockout) or pharmacologic (ROCK inhibitors) interference with the RhoA pathway inhibits macrophage functions and prevents chronic rejection in the rodent transplantation model. Most commercially available RhoA pathway inhibitors are not approved for clinical use. However, we found two compounds: fingolimod (Gilenya, FTY720) and belumosudil (Rezurock), which are clinically approved for relapsing multiple sclerosis (MS) and chronic graft versus host disease (cGVHD), respectively, which also inhibit the RhoA pathway. We tested these two drugs in the rodent transplantation model, and both inhibited chronic rejection. Thus, we proposed to repurpose these drugs for organ transplantation. A clinical trial on the effect of fingolimod in kidney transplant patients is ongoing, and the belumosudil trial is pending.

**Keywords:** organ transplantation, macrophage, fingolimod, belumosudil, RhoA pathway.

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## Introduction

Despite enormous progress in medicine, the obesity, lengthening of the human lifespan, side effects of over-medication, and environmental factors increase the number of terminally ill patients. For many of them, the only chance for survival is organ transplantation. According to the 2021 statistics, there were over 144,000 transplantations performed worldwide [1]. Unfortunately, lifesaving organ transplantation is limited by the lack of organ donors. Currently, in the USA only, over 100,000 people are on the transplant waiting list, and every 10 minutes, a new patient is added to the list. Because of this huge demand, there is an urgent need to find new therapies that would improve transplanted organ health and longevity. All transplanted organs, if they do not derive from genetically identical donors, such as identical twins, undergo a process of immune rejection. There are two main phases of organ rejection: acute and chronic rejection [2]. While acute rejection occurs a few days after transplantation, chronic rejection develops much later, usually months or years post-transplantation. Ten years after transplantation approximately 70% of all organs fail because of chronic rejection. Nowadays, acute rejection, which is T- and B cell-dependent, can be successfully managed by a variety of available immunosuppressive drugs [3]. Unfortunately, there is no cure for chronic rejection, which mainly depends on the activity of macrophages

[4]. In this essay, we describe our research in the chronic rejection field and our most recent efforts in repurposing the existing clinically approved therapies from other diseases to clinical transplantation.

## Chronic rejection of transplanted organs is driven by macrophages

Chronically rejected organs display two main signs of chronic rejection: vessel occlusion and fibrosis. Occlusion of the blood vessel lumen cuts off the blood flow to the transplant, and tissue fibrosis destroys organ architecture resulting in organ failure. Our laboratory has studied chronic rejection of transplanted organs for over a decade. We use a rodent (rat and mouse) cardiac transplantation model and the *in vitro* cultures of isolated mouse monocyte/macrophages and mouse macrophage cell line RAW 264.7. In a rodent transplantation model, the transplanted heart from a genetically different donor is placed in the abdominal cavity of the recipient and anastomosed to its circulatory system via the infrarenal aorta and *vena cava*. Subsequently, the development of chronic rejection is monitored within 100 days post-transplantation. Using such transplantation models, we showed that the allograft is infiltrated by the recipient macrophages and that the application of RhoA pathway inhibitors (in conjunction with the inhibitors of acute rejection: the low dose cyclosporin or mTOR inhibitor

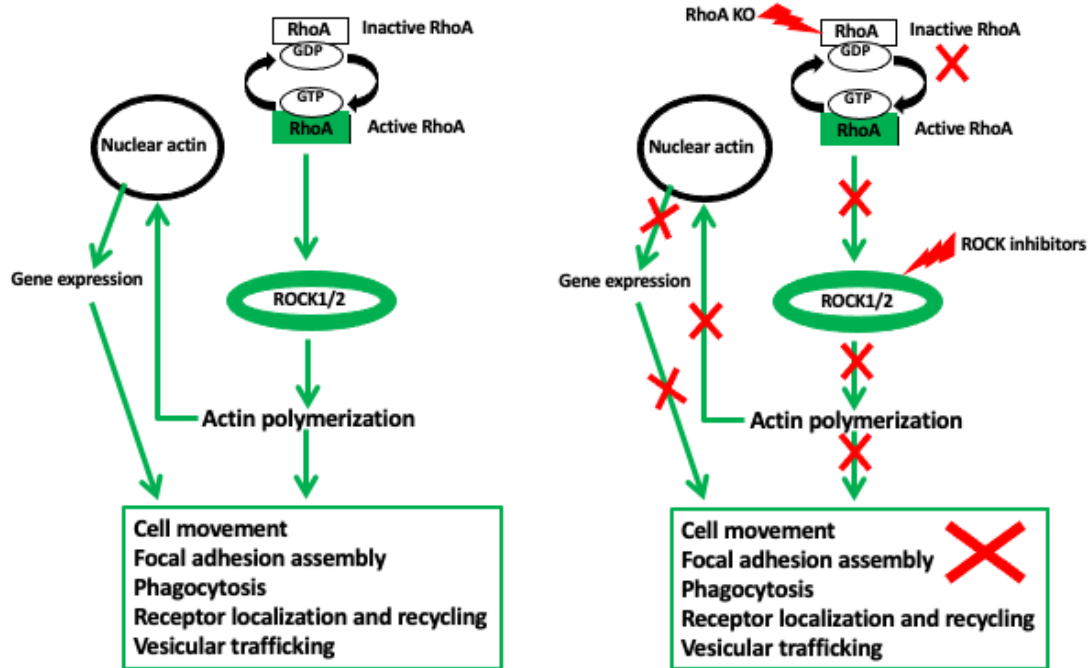
(everolimus) in rats and CTLA4-Ig in mice) within the first week after transplantation inhibits macrophage infiltration and reduces or prevents subsequent chronic rejection [5-7]. The RhoA is a small GTPase that, through its downstream effector ROCK1/2 kinases, regulates actin polymerization, actin cytoskeleton, and all actin-dependent cell functions, such as cell shape, motility, receptor expression and recycling, phagocytosis, vesicular trafficking, and organelle positioning and integrity. It also controls the expression of pro- and anti-inflammatory genes in macrophages by affecting the nuclear actin (which regulates chromatin structure) and the nuclear influx of unpolymerized G actin (Fig. 1).

**Mechanism of macrophage entry into the graft**

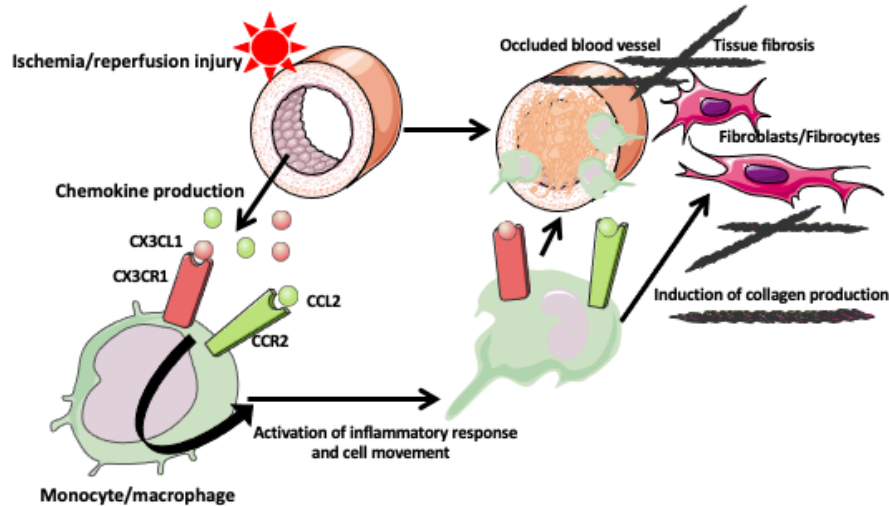
From the moment the organ is procured from the donor and connected to the recipient circulation, it undergoes ischemia/reperfusion injury that causes cell death and the production of inflammatory factors. The injured endothelium of the graft blood vessels produces chemokines such as fractalkine (CX3CL1) and monocyte chemoattractant protein (CCL2), which are the ligands for their respective receptors: CX3CR1 and CCR2 expressed at the surface of monocytes and macrophages [8]. The binding of these chemokines to their receptors activates monocyte/macrophage movement into the graft and their aggregation around the injured blood vessels. While both pathways operate in targeted macrophage migration, the CX3CL1/CX3CR1 pathway dominates in chronic rejection scenario [9, 10]. While in the graft, macrophages induce the over-proliferation of muscle cells in the artery walls, causing, over time, a decrease

and, eventually, total occlusion of the arteries' lumen. Additionally, activated macrophages induce the fibrotic pathways that produce collagen within the graft tissues (Fig. 2, Fig. 3). We showed that in the rodent model system, the application of RhoA/ ROCK inhibitor Y27632 (in conjunction with the T cell inhibitors to prevent acute rejection) to the graft recipient within the first week after transplantation inhibited monocyte/macrophage movement to the graft [5-7]. To confirm the involvement of RhoA in macrophage movement, we created the knockout (KO) mouse with the RhoA gene deleted in the macrophages, and we used these KO mice as the graft recipients [11]. These studies showed that macrophage-specific deletion of RhoA inhibited macrophage infiltration, abrogated vessel occlusion and fibrosis, and inhibited chronic rejection of the graft [11]; (Fig.3). The question was why and how the pharmacologic (Y27632 inhibitor) or genetic (RhoA deletion) interference with the RhoA pathway prevents macrophage movement to the graft. Knowing that the RhoA pathway regulates actin, we studied the effects of RhoA interference on macrophage actin-dependent features and functions. We showed that macrophages treated *in vitro* with Y27632 inhibitor and RhoA-deleted macrophages from the KO mice were abnormally elongated, and their organelles, such as Golgi, mitochondria, and nuclei, were displaced from their proper locations within the cell. While the average length of mouse macrophages is ~ 50µm, the RhoA-inhibited macrophages were over 700µm length [11]. The macrophage movement forward depends on a cyclical attachment/detachment of the end of the tail to the substrate, which is facilitated by the cyclical formation/disassembly of focal adhesions in

Figure 1. RhoA/ROCK pathway and actin-dependent cell functions.



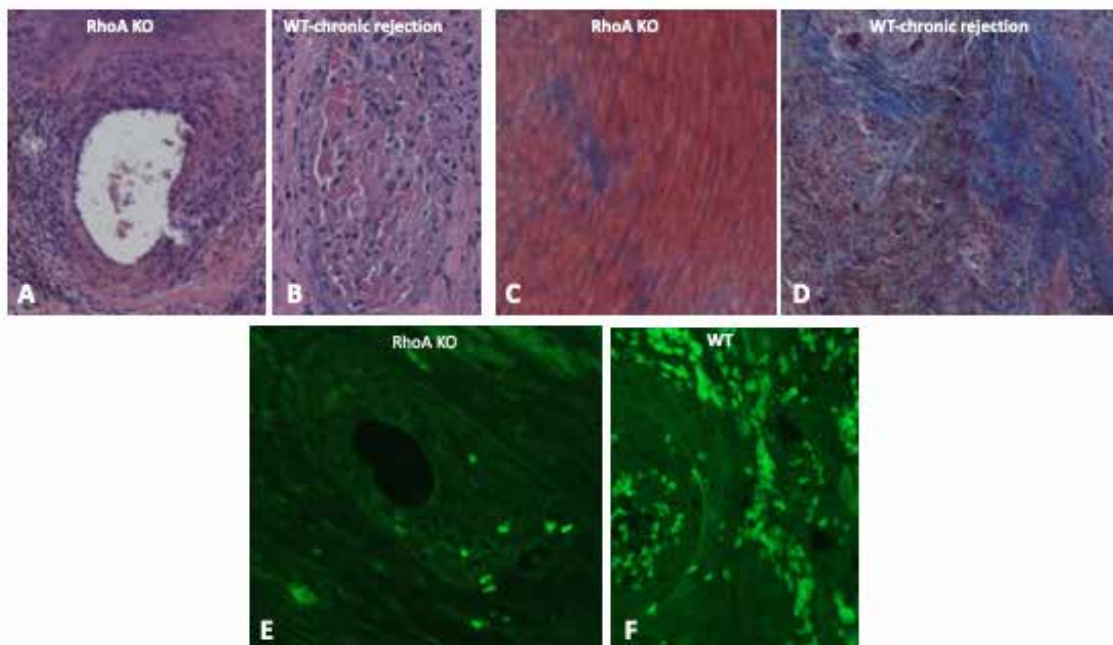
Exchange of GDP to GTP activates RhoA. Active RhoA, through its downstream effector ROCK kinase 1 and 2, activates actin polymerization and dynamics between globular (G) and filamentous (F) actin and thus regulates all actin-dependent cell functions, such as cell movement, focal adhesion assembly/disassembly, phagocytosis, vesicular trafficking, receptor localization at the cellular membrane, and receptor recycling. It also regulates influx of G actin to the nucleus, where actin regulates chromatin condensation and gene transcription. Interference with the RhoA pathway, either by RhoA knockout or pharmacologic inhibition of ROCK1/2 dysregulates actin polymerization and all actin-dependent cell functions.

**Figure 2.** Mechanism of macrophage movement to the allograft.

Procurement of an organ causes ischemia/reperfusion injury. After transplantation, the chemokines produced by the endothelium of injured blood vessels, such as CXCL1 and CCL, bind to their respective receptors CX3CR1 and CCR2 on monocytes and macrophages, which activates inflammatory response and initiate targeted movement toward the injured blood vessels. Macrophages aggregated around the arteries induce the over-proliferation of smooth muscle cells in the arterial wall causing vessel lumen occlusion. Additionally, activated macrophages induce fibroblasts/fibrocytes to produce collagen, causing tissue fibrosis.

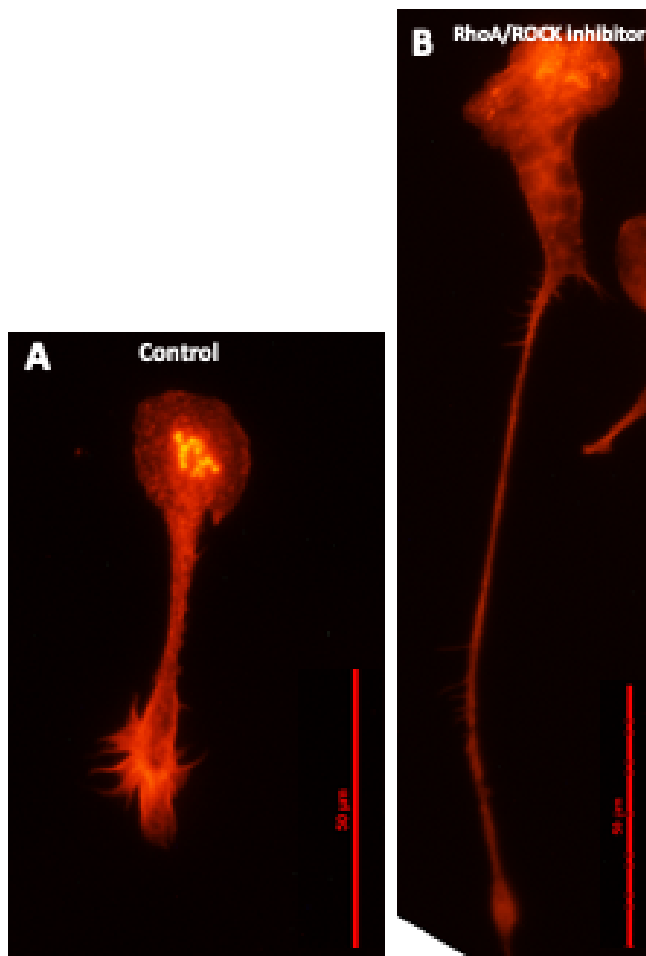
the tail. We showed that in the RhoA-inhibited macrophages, the focal adhesions do not disassemble, thus, the tail remains permanently attached to the substrate while the macrophage front is trying to move forward until physical overstretching causes the tail to break. Because such a futile movement forward with the attached tail mimics the movements of the feeding hummingbird, we called this macrophage phenotype “the

hummingbird phenotype” [11]; (Fig.4). We also showed that the expression and localization of the fractalkine receptors CX3CR1 (which direct macrophages to the blood vessels of the graft) were abnormal in the RhoA-deleted macrophages. We concluded that interference with the RhoA pathway affects actin-dependent targeted cell movement and prevents macrophage infiltration to the graft [11].

**Figure 3.** RhoA pathway interference inhibits macrophage infiltration and chronic rejection.

Microscope images of the cross-sections of control and chronically rejecting mouse hearts. A) Non-occluded blood vessel in the mouse heart transplanted to the recipient whose macrophages the RhoA deletion (RhoA KO). B) Occluded blood vessel in the heart transplanted to the wild-type recipients. C) Fragment of tissue with very little collagen (stained blue) in the heart transplanted to the RhoA KO recipient. D) heart transplanted to the wild-type recipient shows massive disposition of collagen. E) Heart transplanted to the RhoA KO recipient shows very low number of macrophages (immunostained green with F48 macrophage marker). F) Heart transplanted to the wild-type recipient shows massive infiltration of macrophages (green).

**Figure 4.** Hummingbird phenotype of RhoA-inhibited macrophages.



A) The macrophage from a control mouse is around 50 $\mu$ m long.  
B) Incubation of macrophages with RhoA/ROCK inhibitor Y27632 causes extreme elongation, the so-called hummingbird phenotype.

### Results of screening RhoA/ROCK inhibitors for the ability to prevent chronic rejection

To further confirm that, besides the Y27632, other ROCK inhibitors also abrogate chronic rejection, we tested several commercially available inhibitors in mouse cardiac transplantation model. We found that out of four tested RhoA/ROCK inhibitors, fasudil and azaindole, inhibited vessel occlusion, tissue fibrosis, decreased macrophage infiltration, and abrogated chronic rejection of mouse cardiac allografts. The remaining inhibitors, SAR-407899 and SLX-2119 (belumosudil), decreased tissue fibrosis, and, at least at the tested doses, were less effective in inhibiting vessel occlusion [5]. Although these studies confirmed that RhoA/ROCK inhibition abrogates chronic rejection in the mouse model, we do not know if this also will be true for human transplantation. Thus, the next step should be the clinical trials testing these inhibitors in transplantation patients. The Y27632 was tested in clinical trials without success due to severe side effects, yet it is approved in Japan for ocular diseases treatment. Other ROCK inhibitors available for the clinical use outside of the USA are: fasudil, approved in Japan and China

to treat cerebral vasospasm ischemic symptoms [12], and ripasudil, a derivative of fasudil, approved in Japan for the treatment of ocular hypertension and glaucoma [13, 14]. Fortunately, we found two RhoA/ROCK inhibitors clinically approved in the USA for treatments irrelevant to chronic rejection of transplanted organs, fingolimod and belumosudil.

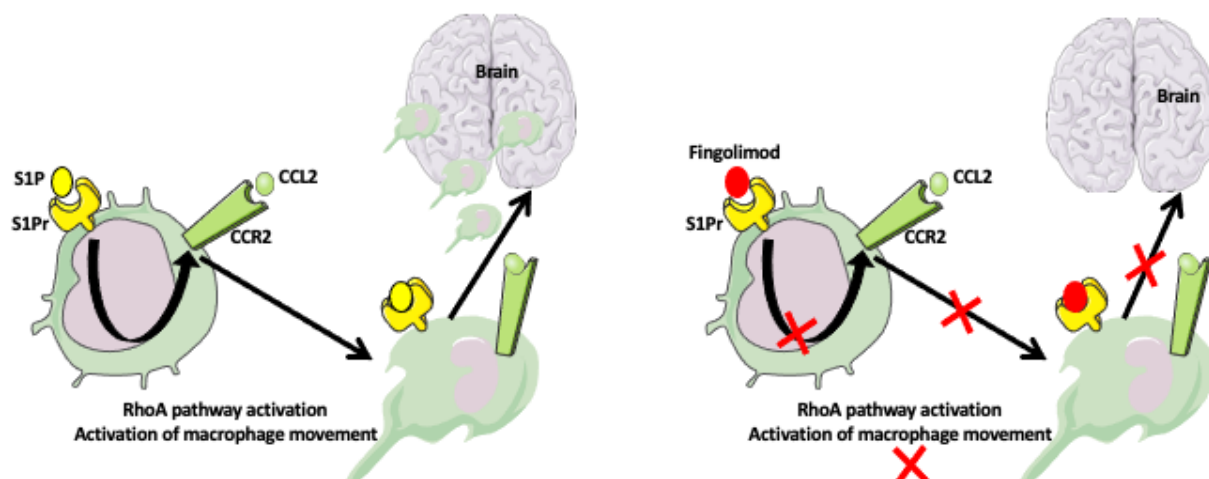
### Clinically approved therapies with fingolimod and belumosudil

Fingolimod (Gilenya, FTY720) is a derivative of fungal metabolite myriocin, which structure resembles sphingosine (15, 16). Fingolimod (Gilenya, FTY720) and its familial compound siponimod (Mayzent) are used for the treatment of multiple sclerosis (MS) [17, 18]. MS is a chronic and debilitating autoimmune disease of the central nervous system. It causes inflammation and damage to the myelinating cells - oligodendrocytes, myelin, and nerve fibers. MS affects over 2.5 million people worldwide, with the highest prevalence in North America and Europe. There are three main forms of MS: primary progressive MS (PPMS), characterized by a rapid progression, affects only 10–15% of MS patients, the relapsing-remitting MS (RRMS) consists of episodes of deterioration interrupted by periods of partial or complete recovery and affects ~85% of MS population, and the secondary progressive MS, (SPMS) characterized by a steady deterioration, which usually develops after two decades of RRMS [19]. In MS, the immune cells exit from the blood and lymphoid organs and enter the central nervous system (CNS), causing inflammation and damage. The movement of immune cells, including macrophages, to CNS depends on the sphingosine 1-phosphate (S1P) and CCL2/CCR2 pathway. S1P binding to its receptors expressed on the surface of immune cells activates chemokine CCL2 pathway signaling. The binding of CCL2 to its receptor CCR2 induces translocation of immune cells to CNS. Fingolimod binds to S1P receptors, inhibiting the activation of CCL2 signaling and preventing immune cell translocation (Fig.5). While fingolimod binds to four out of five S1P receptors, the S1P1, S1P3, S1P4, and S1P5, [20]. Siponimod is selective for S1P1 and S1P5 receptors, and this specificity decreases adverse effects of the drug [18]. Beside inhibiting S1P pathway, fingolimod also inhibits RhoA/ROCK pathway [21].

Belumosudil (Rezurock) is used for the treatment of the chronic graft versus host disease (cGVHD), (22). The cGVHD is a long-term (beyond 100 days) complication following allogeneic hematopoietic cell transplantation. The hallmark of chronic GVHD is inflammatory fibrosis of skin, joints, and internal organs (mostly the lungs). While acute form of the GVHD is caused by the T cells, B cells, the chronic GVHD mostly depend on macrophages. Activated macrophages infiltrate various organs and tissues and produce transforming growth factor-  $\beta$  (TGF- $\beta$ ), leading to fibroblast activation and overproduction of collagen [23-25]. Belumosudil, through inhibition of the RhoA/ROCK pathway, reduces cGVHD fibrosis by downregulating TGF- $\beta$  signaling and inhibiting the expression of profibrotic genes and collagen production [26].



Figure 5. Fingolimod effect on macrophages.



In multiple sclerosis (MS), the binding of the S1P ligand to its S1P receptor activates CXCL1/CCL and RhoA pathways in macrophages and induces macrophage movement to the central nervous system. Fingolimod, because of its similarity to S1P, binds to the S1P receptor. Fingolimod – S1Pr binding prevents the activation of RhoA and CXCL1/CCL pathways, preventing macrophage movement to the central nervous system. Thus, fingolimod therapy is beneficial for MS patients.

### Repurposing fingolimod and belumosudil therapies from MS and cGVBD to transplantation

Because fingolimod and belumosudil inhibit RhoA/ROCK pathway and affect macrophage migration and activation, we hypothesized that they might also inhibit chronic rejection of transplanted organs and, because they are clinically approved, they can be repurposed from MS and cGVHD applications to clinical transplantation. However, before starting relevant clinical trials, we wanted to be sure that these drugs could inhibit chronic rejection in animal models. Animal studies showed that fingolimod inhibited vessel occlusion and allografts' fibrosis, and belumosudil (the Rezurock) (at least at the tested dose) was especially effective in inhibiting fibrosis but less effective in preventing vessel occlusion [21, 27]. We also performed a global transcriptome analysis of mouse macrophages treated with fingolimod and belumosudil. This analysis showed that both drugs downregulated GTPase and actin pathway genes involved in cell migration and immune response, but they differentially affected the fibrotic pathway genes. Belumosudil specifically downregulated fibrotic pathway genes, pentraxin 3 (PTX3, which promotes fibrocyte differentiation), CCR2, and CCL2, while fingolimod specifically downregulated NOTCH1, which is a known target of many antifibrotic therapies [28, 29]. All these studies strongly suggested that fingolimod and belumosudil should be tested in clinical trials in transplanted, and possibly, also COVID-19 patients [30]. Currently, in the Methodist Hospital in Houston, Texas, USA, we have ongoing fingolimod clinical trials in kidney transplant recipients, and the belumosudil clinical trials are pending. The next step would be to test the effect of fingolimod with belumosudil combination on macrophage infiltration, fibrosis, vessel occlusion, and inhibition of chronic rejection in animal models and, ultimately, in clinical trials.

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