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Chemical modulation of cell fates: *in situ* regeneration

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Chemical modulation of cell fates has been widely used to promote tissue and organ regeneration. Small molecules can target the self-renewal, expansion, differentiation, and survival of endogenous stem cells for enhancing their regenerative power or induce dedifferentiation or transdifferentiation of mature cells into proliferative progenitors or specialized cell types needed for regeneration. Here, we discuss current progress and potential using small molecules to promote *in vivo* regenerative processes by regulating the cell fate. Current studies of small molecules in regeneration will provide insights into developing safe and efficient chemical approaches for *in situ* tissue repair and regeneration.

small molecule, *in situ* regeneration, adult stem cells, somatic cells, dedifferentiation, transdifferentiation, reprogramming

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INTRODUCTION

The field of regenerative medicine has made tremendous progress in recent years owing to the advancement of stem cell biology. Regenerative medicine aims to replace or regenerate cells, tissues, or organs that are damaged or lost for restoring their normal functions. There are currently two main strategies to achieve regeneration. One is transplantation of exogenous cells that can release paracrine factors to protect the resident cells and tissues or directly home and engraft into damaged tissues and replace lost cells (Ti et al., 2016; Trounson and McDonald, 2015). Another one is to enhance the endogenous regeneration potential of stem cells and somatic cells by genetic, pharmaceutical, and engineering tools (Pacelli et al., 2017; Xie et al., 2018). The development of reprogramming approach provides new and innovative strategies to generate sufficient numbers of cells for transplantation (Papapetrou, 2016; Xu et al., 2015). The desired cell types can be produced from differentiation of induced pluripotent stem cells (iPSCs) or via direct cell conversion from other easily accessible cell types (e.g., skin fibroblasts) by genetic or chemical induction. Nevertheless, cell transplantation-based regeneration still has various challenging problems: how to efficiently deliver transplanted cells into the target tissues, to maintain their survival *in vivo*, and to engraft into the endogenous tissues.

Unlike mammals, lower animals like salamanders and zebrafish possess natural regeneration potential to regrow a range of their lost body parts, including hearts, limbs, tails, fins, and spinal cords. However, adult mammals are endowed with such limited regenerative capacity that they cannot restore the normal structure and function of diseased and injured tissues and organs (Sánchez Alvarado and Yamanaka, 2014). Several main reasons for low mammalian regeneration include intrinsically insufficient endogenous stem cells,

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the weak potential of terminally differentiated cells to dedifferentiate into proliferative progenitor/precursors or transdifferentiate into other cell types (Merrell and Stanger, 2016). Therefore, stimulating the endogenous adult stem cells and inducing the occurrence of dedifferentiation and transdifferentiation of terminally differentiated cells have attracted much attention for improving mammalian regeneration (Jopling et al., 2011; Sánchez Alvarado and Yamanaka, 2014).

Targeting the mobilization, proliferation, expansion, differentiation, and survival of endogenous stem cells with growth factors, chemokines, cytokines, biomaterials, and genetic manipulations has been shown to promote endogenous regeneration, as described thoroughly in previous reviews (Green and Lee, 2013; Lane et al., 2014). In addition, increasing studies have demonstrated the *in vitro* induction of dedifferentiation or transdifferentiation of terminally differentiated cells by growth factors, proteins, miRNAs and transcription factors, which has been illustrated elsewhere (Ebrahimi, 2017; Taguchi and Yamada, 2017). In current years, small molecules have been increasingly used to modulate the cell fate and plasticity of endogenous stem cells and mature cells and shown to improve tissue and organ regeneration. Moreover, small molecules have tremendous advantages over the approaches mentioned above. First, large libraries of small molecules can be synthesized cost-effective. Second, the biological activities of small molecules are reversible through "washout" and can be controlled temporally and precisely by restricting small-molecule exposure to a specific period and regulating their combinations and concentrations. Third, small molecules are relatively safe and thus make clinical translation more feasible (Zhang et al., 2012b). In this study, we focus on the *in vivo* chemical modulation of endogenous stem cells and terminally differentiated cells for improving tissue and organ regeneration (briefly described in Figure 1). We also provide new perspectives on using small molecules to achieve *in situ* regeneration suitable for clinical translation.

SMALL MOLECULES MODULATE HSCS: HEMATOPOIETIC REGENERATION

HSCs are multipotent cells within the bone marrow, with the

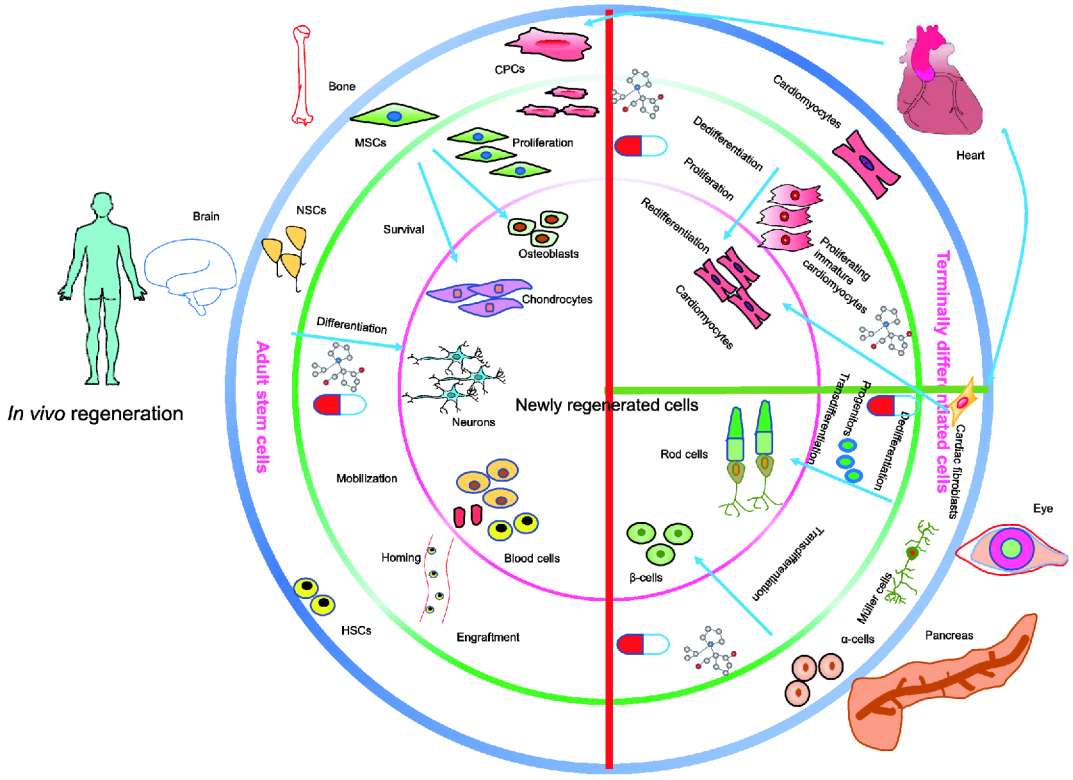

Figure 1 (Color online) Small molecules promote *in vivo* regeneration by targeting cell fates of endogenous stem cells and terminally differentiated cells. Small molecules can modulate the endogenous stem cell fates, including activation, proliferation, survival, differentiation, mobilization from the stem cell niche, homing, and engraftment into target tissues, thereby stimulating the regenerative responses in adult tissues and organs that have limited numbers of resident stem cells, like bone marrow MSCs, HSCs, and brain NSCs. As for adult tissues lacking endogenous stem cells, small molecules can induce dedifferentiation of terminally differentiated cells into proliferative progenitors/precursors capable of redifferentiating into the target cells, such as cardiomyocyte dedifferentiation; alternatively, small molecules induce transdifferentiation of terminally differentiated cells into the target cells for regeneration, for instance, transdifferentiation of α-cells into β-cells in pancreas. CPCs, cardiac progenitor cells; MSCs, mesenchymal stem cells; HSCs, hematopoietic stem cells; NSCs, neural stem cells.

potential to differentiate into all blood cell lineages (Crane et al., 2017). They reside in the stem cell niche of bone marrow, predominantly as a quiescent state (Crane et al., 2017). For maintaining hematopoietic homeostasis and initiating regenerative responses to injuries or diseases, HSCs must be mobilized from the stem cell niche (switching from the quiescent state to an active state) and undergo proliferation, migration, and differentiation to replenish or replace lost or died blood cells (Mendelson and Frenette, 2014). Although the hematopoietic system exhibits a highly regenerative capacity, the endogenous regeneration is still insufficient to restore the normal function of blood systems when injuries or diseases are extensive and irreversible. Chemical modulation of HSC fates, including mobilization, proliferation, migration, and differentiation, will be an attractive strategy to enhance the endogenous regenerative power of hematopoietic systems.

PROLIFERATION, SURVIVAL, REJUVENATION, AND DIFFERENTIATION OF HSCS

A few small molecules have been identified to support HSC maintenance and self-renewal *in vitro*. The synthetic adenine derivative, StemRegenin1 (SR1), was discovered to promote the self-renewal and expansion of HSCs *in vitro*, based on an image-based screen in primary $CD34^+$ HSCs (Boitano et al., 2010). Mechanical analysis disclosed that SR1 functions through antagonism of the aryl hydrocarbon receptor (AhR) (Boitano et al., 2010). Using a similar method, de Lichtervelde et al. identified a natural product eupalinilide E that can increase *ex vivo* expansion of HSCs by inhibiting AhR (de Lichtervelde et al., 2013). The small molecule-mediated promotion of HSC expansion may provide a large number of progenitors for therapeutic transplantation. Moreover, small molecules have been shown to enhance *in vivo* proliferation and regeneration of HSCs. Ca^{2+}/calmodulin (CaM)-dependent protein kinase kinase 2 (CaMKK2) is expressed in HSCs but inhibits HSC proliferation and regeneration *in vitro* and *in vivo*. Systemic administration of the CaMKK2 inhibitor STO-609 to irradiated mice enhanced HSC regeneration and prolonged survival of the animals (Racioppi et al., 2017). Therefore, targeting the CaMKK2 by small molecules may be a novel method to promote hematopoietic recovery from bone marrow injuries.

Small molecules can rejuvenate the aged HSCs. Aged tissues exhibit a lower regenerative capacity compared to younger tissues. RhoGTPase Cdc42 functions as a regulator of cell growth and development and contributes to the aging of HSCs. The tricyclic indolent CASIN, identified as an inhibitor of the Cdc42, was found to rejuvenate aged HSCs (Florian et al., 2012), providing a chemical tool to enhance hematopoietic recovery in elderly subjects.

Small molecules can direct the differentiation of HSCs into blood cells. Thrombopoietin (TPO) is a primary stimulator for megakaryopoiesis and thrombopoiesis from HSCs. TPO and TPO mimetics are capable of increasing the platelet counts and therefore applied to treat thrombocytopenia caused by different etiologies (Kuter and Begley, 2002). However, they would bring about severe complications, for instance, the development of cross-reacted antibodies against endogenous TPO can induce thrombocytopenia (Li et al., 2001). The TPO receptor agonist eltrombopag (SB-497115) is developed as a small molecule alternative for TPO and can be orally administered to increase platelet counts and treat thrombocytopenia (Bussel et al., 2007).

MOBILIZATION, HOMING, AND ENGRAFTMENT OF HSCS

Small molecules are capable of regulating the mobilization, homing, and engraftment of HSCs. For successful regeneration, stem cells must be mobilized from their niches and home into the damaged sites and engraft (or incorporate) into the resident tissues (Green and Lee, 2013). Granulocyte-colony stimulating factor (G-CSF) has been used to treat neutropenia in clinical patients by stimulating granulocyte production from bone marrow (Neidhart et al., 1989; Sheridan et al., 1989). However, G-CSF and its recombinant forms (such as lenograstim) show short plasma-life and chronic effects on the hematopoiesis, which limit their applications. Small molecule alternative would be highly advantageous. Small molecule SB-247464 was identified to increase granulocyte production from bone marrow in mice through activating G-CSF signaling pathways (Tian et al., 1998). Additional three small molecules (Filgrastim, SSCL02446, and SSCL02448) screened from 10,000 small compounds have a similar effect with G-CSF and increase peripheral blood neutrophil counts after subcutaneous injection into rats (Kusano et al., 2004). C-X-C chemokine receptor type 4 (CXCR4)/Stromal cell-derived factor 1 (SDF1) axis plays a crucial role in HSC cell trafficking. Liles et al. found that treatment with CXCR4 antagonist AMD3100 (plerixafor), an FDA-approved drug, can increase the mobilization of HSCs from bone marrows to peripheral blood in humans (Liles et al., 2003). Moreover, the combined use of plerixafor and G-CSF can significantly increase the production of HSCs for autologous transplantation (Flomenberg et al., 2005). The very late antigen 4, α4β1 integrin (VLA-4)/VCAM-1 axis is also associated with the mobilization of HSCs, and inhibition of this pathway by VLA-4 inhibitor BIO5192 can boost the mobilization of HSCs (Ramirez et al., 2009). Aside from mobilizing effects, the CXCR4/SDF-1 axis regulates homing and engraftment of

stem cells. Increasing the local SDF-1 levels by diprotin A, a small molecule that can inhibit membrane-bound dipeptidyl peptidase 4 (DPP-4) responsible for hydrolyzing SDF-1, promoted homing and engraftment of HSCs in mice (Christopherson et al., 2004).

SMALL MOLECULE-MEDIATED MODULATION OF CARDIAC PROGENITOR CELLS AND TERMINALLY DIFFERENTIATED CARDIOMYOCYTES: HEART REGENERATION

The adult mammalian heart possesses a very limited regenerative capacity, primarily due to the lack of CPCs and low turnover of adult cardiomyocytes. Unlike humans, zebrafish can completely regenerate its heart after injury mainly through dedifferentiation, proliferation, and redifferentiation of adult cardiomyocytes (Gemberling et al., 2013; Matrone et al., 2017). The recent discovery of resident CPCs in adult mammalian hearts offers a promising strategy to stimulate heart regeneration by stimulating the endogenous CPCs (Cahill et al., 2017). In fact, mammalian postmitotic cardiomyocytes retain a limited potential to reenter the cell cycle and proliferate, which provides an alternative approach to enhance heart regeneration by stimulating proliferation of terminally differentiated cardiomyocytes (Bergmann et al., 2009; Wang et al., 2017). More recently, direct conversion of cardiac fibroblasts into cardiomyocytes indicates the possibilities of regenerating cardiomyocytes via transdifferentiation or reprogramming mechanisms (Ieda et al., 2010; Murry and Pu, 2011). Chemically targeting of the activation of resident CPCs, the proliferation of terminally differentiated cardiomyocytes, the transdifferentiation of cardiac stromal cells such as cardiac fibroblasts is expected to promote heart regeneration, briefly summarized in Figure 2.

ACTIVATION OF CPCS

Since the number of CPCs in adult hearts are very limited, promoting the proliferation, expansion, survival, and differentiation of CPCs would produce sufficient cardiomyocytes for regeneration. Multiple signaling pathways have been shown to play critical roles in the proliferation and differentiation of CPCs, including Wnt signaling (Kwon et al., 2007), Akt signaling (Gude et al., 2006), Fgf signaling (Lin et al., 2010; Zhang et al., 2012a), Bmp signaling (de Pater et al., 2012), β2 adrenergic receptor (β2-AR) signaling (Khan et al., 2013), and Hippo signaling (Mosqueira et al., 2014). Chemical regulation of these signaling pathways may hopefully activate and enhance the intrinsic regenerative capacity of endogenous CPCs. For example, activation of Wnt signaling with a small molecule BIO (an activator of Wnt signaling) can expand CPCs (Qyang et al., 2007).

Russell and colleagues identified that a 3,5-disubstituted isoxazole, Isx1, can induce adult cardiomyocyte-like precursors from resident, multipotent Notch-activated epi-

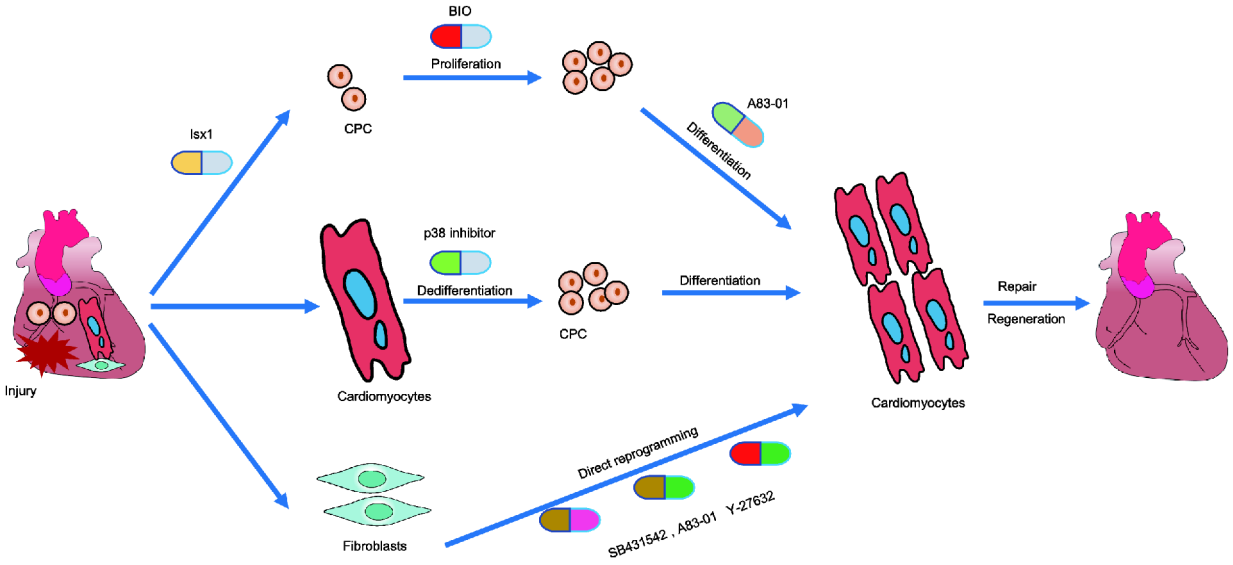

Figure 2 (Color online) Small molecule-based strategy for cardiac regeneration. Following heart injury, small molecules have been used to promote proliferation of CPCs and their differentiation into cardiomyocytes, facilitate the dedifferentiation and proliferation of differentiated cardiomyocytes and their redifferentiation into cardiomyocytes, or induce direct reprogramming or transdifferentiation of cardiac fibroblasts into cardiomyocytes. These three routes have the potential to produce new cardiomyocytes for repairing and regenerating injured heart. BIO, a small molecule activator of Wnt signaling, can promote CPC proliferation; Isx1, a 3,5-disubstituted isoxazole, can induce cardiac precursors ; A83-01, a small molecule inhibitor of TGF-β, can increase proliferation of cardioblasts; a p38 MAP kinase inhibitor can promote cardiomyocyte mitosis; SB431542, A83-01, and Y-27632 can promote the direct reprogramming of cardiac fibroblasts into cardiomyocytes induced by transcription factors.

cardium-derived cells (NECs) (Russell et al., 2012). However, myocardial infarction can abrogate the cardiogenic effects of Isx1 and direct NEC differentiation into fibroblasts, resulting in cardiac fibrosis (Russell et al., 2012). Nevertheless, this study suggests a new pharmaceutical approach to achieve safe, robust activation of endogenous CPCs for heart regeneration. Saraswati and co-workers demonstrated that intracardial injection of pyrvinium, an FDA-approved drug that activates Wnt signaling, increases the number of $Ki67^+$ cells in peri-infarct and distal myocardium, improves left ventricle internal dimension but does not alter heart function or infarction size in mice with myocardial infarction (Saraswati et al., 2010). ICG-01, a small molecule inhibitor of Wnt signaling, was found to improve ejection function in rat models of myocardial infarction (Sasaki et al., 2013). The cellular mechanisms of ICG-01 effects may be due to the activation of epicardial progenitor cells. Prostaglandin E2 (PGE2) production induced by myocardial infarction contributes to the protection of the heart (Degousee et al., 2008). Treatment with PGE2 was found to stimulate cardiac progenitor proliferation and cardiomyocyte regeneration in the infarcted heart of mice (Hsueh et al., 2014). Moreover, Pim-1 kinase, which is expressed explicitly on CPCs, plays a critical role in the proliferation and rejuvenation of CPCs (Cottage et al., 2010; Del Re and Sadoshima, 2012; Hariharan et al., 2015; Mohsin et al., 2013; Sundararaman et al., 2012). Therefore, activating or increasing Pim-1 kinase with small molecules will enhance the proliferation of CPCs and rejuvenate the aged CPCs from older patients. Targeting the CXCR4/SDF-1 axis by small molecule Sitagliptin has also been reported to improve the left ventricle function and overall survival in mouse model of myocardial infarction, possibly by activating resident CPCs, increasing angiogenesis, and reducing cardiac remodeling (Theiss et al., 2013; Zaruba et al., 2009). A83-01, a small molecule inhibitor of TGF-β, was demonstrated to increase proliferation of postnatal $Nkx2.5^+$ cardioblasts and their differentiation into cardiomyocytes *in vitro*. *In vivo* studies showed that A83-01 treatment enhanced proliferation of $Nkx2.5^+$ cardiomyoblasts in the mouse heart after myocardial infarction and increased newly formed cardiomyocytes, which led to the improvement of ventricular elastance and stroke work and contractility (Chen et al., 2015).

THE DEDIFFERENTIATION AND PROLIFERATION OF TERMINALLY DIFFERENTIATED CARDIOMYOCYTES

Adult mammalian is traditionally considered as postmitotic cells lacking the ability to undergo cell division. In recent years, studies show that human cardiomyocytes can reenter the cell cycle at a low rate (Bergmann et al., 2009). In rodent models of myocardial infarction, several studies have observed increased proliferative responses in pre-existing cardiomyocytes following heart injury (Porrello et al., 2011; Senyo et al., 2013). Cardiomyocyte proliferation is suggested to require a certain degree of dedifferentiation. These discoveries imply that cardiomyocytes may represent rich targets of small molecules to promote cardiac repair and regeneration by regulating dedifferentiation and proliferation processes (Matrone et al., 2017).

An initial study found that co-treatment with FGF1 growth factor and p38 MAP kinase inhibitor in rats after myocardial infarction could increase cardiomyocyte mitosis and improve cardiac function in rats after myocardial infarction (Engel et al., 2006). They seemed to have different effects: p38 MAP kinase inhibitor could increase cardiomyocyte proliferation, and FGF1 could enhance angiogenesis. Another early study identified a GSKβ inhibitor BIO, which could promote proliferation of neonatal and adult rat cardiomyocytes (Tseng et al., 2006). By using a high-content screening assay in mouse ESC-derived cardiomyocytes, Uosaki et al. found additional small molecules that could increase cardiomyocyte proliferation, including Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) inhibitors KN62 and KN93 and ERK inhibitors SU1498 and ZM336372 (Uosaki et al., 2013).

TRANSDIFFERENTIATION OF CARDIAC FIBROBLASTS INTO CARDIOMYOCYTES

Direct lineage conversion from one somatic cell into anther offers another promising way to generate target cell types. Ieda and colleagues first reported the direct conversion of mouse fibroblasts into functional cardiomyocytes by ectopic expression of three cardiac master transcription factors GATA4, MEF2C, and TBX5 (GMT) (Ieda et al., 2010). A later study found that addition of another transcription factor HAND2 to GMT (GHMT) could increase the conversion efficiency of mouse fibroblasts into cardiomyocytes (Song et al., 2012). Importantly, when the transcription factor genes (GMT or GHMT) were delivered into cardiac fibroblasts *in vivo*, they could reprogram resident cardiac fibroblasts into cardiomyocytes, even with higher efficiency than *in vitro* induction (Qian et al., 2012; Song et al., 2012). The *in vivo* induced cardiomyocytes were capable of improving cardiac function after myocardial infarction. Addition of small molecules can increase cardiac conversion efficiency from fibroblasts induced by master transcription factors. For example, *in vitro* supplementation of TGF-β inhibitors, SB431542 or A83-01, and ROCK inhibitor Y-27632 significantly enhanced the cardiac conversion efficiency in mouse fibroblasts induced by GMT or GHMT (Zhao et al., 2015). Noticeably, *in vivo* delivery of small molecules

(SB431542 and Wnt inhibitor XAV939) has been recently reported to increase GMT-induced cardiac reprogramming of cardiac fibroblasts and improve cardiac function in mouse models with myocardial infarction as compared to only GMT (Mohamed et al., 2017). To date, there is no report of only using small molecules to induce *in vivo* cardiac conversion from cardiac fibroblasts. However, several *in vitro* studies have identified different combinations of small molecules to induce direct cardiac conversion. Five small molecules (Forskolin, A83-01, SC1, CHIR99021, and BayK 8644), eight small molecules (CHIR99021, Repsox, Forskolin, VPA, Parnate, TTNPB, DZNep), and nine small molecules (CHIR99021, A83-01, BIX01294, AS8351, SC1, Y-27632, OAC2, SU16F, JNJ10198409) could reprogram mouse and human fibroblasts into cardiomyocytes (Cao et al., 2016; Fu et al., 2015; Park et al., 2015). For achieving *in vivo* chemical cardiac conversion, several challenges must be overcome, such as how to deliver small molecules into the target sites, how to control the release of small molecules and maintain an effective concentration, and even more challenging, how to target the small molecules only to cardiac fibroblasts for avoiding off-target effects.

SMALL MOLECULES INDUCE PANCREATIC REGENERATION AND IMPROVE DIABETES

The β-cell, the insulin-producing cells in the pancreas, is destroyed in the Type 1 diabetes mellitus (T1DM). As a result, insufficient insulin supply or insulin resistance leads to hyperglycemia. In Type 2 diabetes mellitus (T2DM), insulin resistance causes a deficiency of fully functional β-cells (Ashcroft and Rorsman, 2012). The expansion of β-cell mass has been thought to treat T1DM and T2DM. Several routes are proposed to increase β-cell mass, including the β-cell replication, transdifferentiation of other cells into β-cells, and β-cell dedifferentiation (Benthuysen et al., 2016).

PROMOTION OF β-CELL REPLICATION

Increasing the β-cell replication is a straightforward way to increase the β-cell mass. However, adult β-cells almost cannot divide. Therefore, the use of small molecules to enable β-cell replication is of great interest for increasing β-cell mass. Taking advantages of the existing islet culture techniques, researchers attempt to identify small molecules that can promote β-cell replication by high-throughput screening. Wang et al. identified GSK inhibitor and L-type calcium channel (LTCC) agonist BayK 8644 that promote β-cell replication from a library of 850,000 compounds (Wang et al., 2009). Another small molecule WS6 was found to increase β-cell proliferation in a mouse model that depletes β-cells (Shen et al., 2013). Moreover, administration of WS6 increased β-cell proliferation and restored the blood glucose level in a mouse model of T1DM (Shen et al., 2013). WS6 might increase β-cell proliferation by targeting the Erb3 binding protein-1 and the IκB kinase pathway (Shen et al., 2013).

Based on the zebrafish model of diabetes, Andersson and co-workers screened small molecules that can increase β-cell regeneration in the whole organism level and found that the adenosine agonist 50-*N*-ethylcarboxamidoadenosine (NECA) could simulate β-cell proliferation and accelerate the restoration of normoglycemia in zebrafish (Andersson et al., 2012). NECA was found to promote β-cell proliferation by acting through the adenosine A2a receptor. Injection of NECA in mice with diabetes caused by streptozotocin decreased the blood levels by 30% and increased the β-cell mass by 8-fold as compared to injection of the vehicle (Andersson et al., 2012). By contrast, another previous study showed that NECA ameliorated the glucose level in the mouse model of T1DM by promoting β-cell survival through adenosine A2b receptor (Németh et al., 2007). The two studies demonstrated that NECA could improve β-cell regeneration through increasing β-cell proliferation and survival. Two other adenosine kinase inhibitors 5-iodotubercidin and ABT-702 have been found to promote proliferation of primary β-cells from mice, rats, and pigs (Annes et al., 2012). Further studies of action mechanisms revealed that these inhibitors might act through the mTOR signaling pathways to promote β-cell proliferation (Annes et al., 2012). Using high-throughput small-molecule screening, Wang and colleagues identified harmine analogs as enhancers for human β-cell replication *in vitro*. Moreover, in the mouse and human islet *in vivo* models, harmine could increase β-cell replication and islet mass as well as improve the glucose homeostasis (Wang et al., 2015a). The action mechanisms of harmine might target the dual-specificity tyrosine-regulated kinase-1a (DYRK1A) (Wang et al., 2015a).

β-CELL REGENERATION VIA TRANSDIFFERENTIATION

Another route to increase β-cell regeneration is to transdifferentiate or to reprogram other cells in the pancreas into β-cells *in situ*. Transcription factors have been reported to transdifferentiate non-pancreatic cells (like fibroblasts) into β-cells *in vitro* (Li et al., 2014). More interestingly, pancreatic α-cells, acinar cells, and ductal cells could be directly converted into β-cells *in vivo* by ectopic expression of transcription factors (Demcollari et al., 2017). Extra-pancreatic tissue cells have also been reported to turn into β-cells *in vivo* upon genetic manipulation, including stomach, intestine, and

liver cells (Demcollari et al., 2017). However, a few studies have reported chemical generation of β-cells *in vivo*. Schreiber et al. identified a small molecule BRD 7389 from a library of 30,000 compounds, which could induce insulin expression in mouse α-cells by inhibiting the RSK kinase family, suggesting that this compound is capable of *in vivo* transdifferentiating mouse α-cells into β-cells (Fomina-Yadlin et al., 2010). Recently, long-term treatment with natural neurotransmitter gamma-aminobutyric acid (GABA) was able to induce α-cell conversion into β-cells *in vivo* in mice (Ben-Othman et al., 2017). Of great interest, activation of $GABA_A$ receptor signaling with small molecule artemisinins similarly converted α-cell into β-cells *in vivo*, resulting in regeneration of pancreatic β-cell mass (Li et al., 2017). The studies indicate that chemical modulation of key signaling pathways associated with α to β cell conversion may induce *in situ* cell conversion of non-insulin-producing pancreatic cells to insulin-producing β-cells for regenerative treatments for diabetes.

SMALL MOLECULES TARGET MESENCHYMAL STEM CELLS: PROMOTION OF ORTHOPEDIC TISSUE REGENERATION

Orthopedic tissue regeneration would benefit the patients with traumatic bone injury and degenerative bone and cartilage diseases. Although bone has a natural potential to regenerate and heal after injury, this regenerative potential progressively declines with increasing age (Jeon and Elisseeff, 2016). Therefore, it has tremendous interest to improve orthopedic regeneration in fractured bones or large bone defects from elderly patients. Transplantation of cells and delivery of growth factors and signaling proteins show beneficial effects on orthopedic regeneration, though their uses are high-priced and have other limitations, which restrict their therapies (Hankenson et al., 2015; Pacelli et al., 2017). Accordingly, the development of small molecules to trigger endogenous regeneration of bones and cartilages present a novel safe and cost-effective approach. Especially, small-molecule targeting of the proliferation, differentiation, and survival of endogenous adult stem cells in the orthopedic issues has drawn much attention.

MSCs mainly reside in the bone marrow and have the multipotent potential to produce osteoblasts, chondrocytes, adipocytes, and other cells (Uccelli et al., 2008). Chemical modulation of MSC differentiation toward a specialized cell type may be an attractive strategy to strengthen their therapeutic effects. Although MSCs have inherent capacities of differentiation into osteoblasts, strengthening this differentiation path will further improve their treatments for bone fracture and osteoporosis. For instance, the adenine derivative purmorphamine, an agonist for Shh signaling pathway, was discovered from a screen of 50,000 heterocyclic compounds as an inducer for osteoblast generation, and treatment with purmorphamine could promote bone regeneration *in vivo* (Wu et al., 2002). Systemic administration of the Wnt signaling agonist lithium could accelerate the distracted bone regeneration in rats (Wang et al., 2015b). Other small molecules have been developed and identified to stimulate MSC differentiation toward osteoblasts, including PPRR-γ agonist, rosiglitazone, ascorbic acid, vitamin D3, the glucocorticoid dexamethasone, the cyclooxygenase inhibitor indomethacin, and many more (Lyssiotis et al., 2011). Chemical promotion of chondrogenic differentiation of MSCs will reinforce their chondrogenic potentials. Schultz and coworkers identified chondrogenic compound kartogenin from a high-throughput screen (22,000 compounds) for chondrogenic nodule formation in primary human MSCs. Administration of kartogenin could protect cartilage *in vitro* and improve the cartilage repair in the collagenase- and surgery-induced mouse model of osteoarthritis *in vivo* (Johnson et al., 2012). This study suggests that small molecules have the potential to stimulate endogenous chondrogenesis for osteoarthritis repair. In addition, small molecule compounds such as simvastatin, lovastatin, and FTY720, have been reported to increase the chondrogenesis and osteogenesis in animal models (Jeon and Elisseeff, 2016; Laurencin et al., 2014).

However, the above small molecules only promote a single bone or cartilage regeneration. Given that the traumatic injuries or diseases often involve both bone and cartilages, the ideal small molecules would facilitate both bone and cartilage repair and regeneration. Several small molecules have been shown beneficial effects on both chondrogenesis and osteogenesis by regulating bone remodeling in animal models. For instance, teriparatide (Forteo), a recombinant form of parathyroid hormone, has bone anabolic effects and protect against cartilage degeneration in animal models of osteoporosis and osteoarthritis (Orth et al., 2014; Sampson et al., 2011). Some anti-resorptive small molecules such as osteoprotegerin (OPG) and strontium ranelate (both targeting RANKL pathway), cathepsin K inhibitors, and bisphosphonates can reduce osteoclastic bone resorption and inhibit cartilage degradation, which indirectly promotes bone and cartilage regeneration, as comprehensively reviewed by Jeon (Jeon and Elisseeff, 2016).

SMALL MOLECULES INDUCE MUSCLE DEDIFFERENTIATION: SKELETAL MUSCLE REGENERATION

In urodele amphibians, their limbs can regenerate mainly via dedifferentiation of skeletal muscle into progenitor cells (Wang and Simon, 2016; Zhao et al., 2016). However,

mammalian skeletal muscle represents a classic example of terminal differentiation and does not undergo dedifferentiation after injury. Many studies have attempted to induce mammalian terminally differentiated muscle cells to proliferative progenitors. Studies of C2C12 cell lines have demonstrated that some C2C12-derived myotubes can undergo dedifferentiation by newt extract, or overexpression of msx1 or twist (Frasch, 2016). Knockdown of pRb and Arf can also induce cell-cycle reentry in C2C12 myocytes but not in C2C12-derived myotubes (Pajcini et al., 2010). Increasing studies have demonstrated that treatment with small molecules can induce dedifferentiation of mammalian muscle. Mouse C2C12 myotubes were first reported to dedifferentiate into mononuclear cells after treatment with myoseverin (Rosania et al., 2000). Paliwal and Conboy demonstrated that small molecule inhibitors of tyrosine phosphatases (BpV) and apoptosis (Q-VD) dedifferentiated multinucleated myotubes into myogenic progenitor cells that can redifferentiate into myotubes *in vitro* and *in vivo* (Paliwal and Conboy, 2011). Another research group treated C2C12-derived myotubes with small molecule myoseverin B and induced them into proliferating, mononuclear cells. Followed by induction with small molecule reversine (2-(4-morpholinoanilino)-6-cyclohexylaminopurine), these proliferating cells can be further induced to multipotent stromal cells with the ability to undergo myogenic, adipogenic and osteogenic differentiation (Jung and Williams, 2011). Therefore, the chemical drugs induce mammalian skeletal muscle to obtain multipotency that is observed in urodele appendage regeneration. In another study, treatment with small molecules BIO (glycogen synthase-3 kinase inhibitor), lysophosphatidic acid (pleiotropic activator of G-protein-coupled receptors), SB203580 (p38 MAP kinase inhibitor), or SQ22536 (adenylyl cyclase inhibitor) induced C2C12 myotubes into proliferating, multipotent cells that can differentiate into mesodermal-derived cell lineages. Interestingly, sequential treatment with small molecules BIO, SB203580, or SQ22536 and the aurora B kinase inhibitor, reversine, dedifferentiated the muscle cellulate into cells with neurogenic potential (ectodermal lineage), indicating the acquirement of pluripotency (Kim et al., 2012). Intramuscular injection of small molecule 2-acetyl-4(5)-tetrahydroxybutyl imidazole (THI), a sphingosine-1-phosphate (S1P) lyase inhibitor, was able to promote muscle regeneration in acutely injured dystrophic muscles of *mdx* mice, as evidenced by increased muscle fiber size and increased muscle force (Ieronimakis et al., 2013). The regenerative effects of THI treatment were associated with increased numbers of myogenic cells. The small molecule THI may be developed into a therapeutic drug for treating Duchenne muscular dystrophy (DMD). Taken together, induction of skeletal muscle dedifferentiation with small molecules provides a novel approach for improving muscle regeneration after severe injuries or diseases.

SMALL MOLECULES ENHANCE APPENDAGE REGENERATION

Some regenerative animals can regenerate their appendages such as limbs, fins, and digits, which all consist of multiple tissues (bones, cartilages, muscle, vessels, nerves, and connective tissues) (Tanaka, 2016). By contrast, humans cannot regenerate the limb after traumatic injury. Using chemical compounds to modulate developmental signaling pathways has facilitated the discovery of key signaling pathways involved in the appendage regeneration processes, such as Wnt, Fgf, Notch and so on (Tanaka, 2016; Tornini and Poss, 2014). Chemical regulations of these key signalings may enhance appendage regeneration. Using the adult zebrafish model of fin amputation, Smith and colleagues screened a small molecule MSI-1463 that inhibits protein tyrosine phosphatase 1B, which could boost the fin regeneration after intraperitoneal injection (Smith et al., 2017). Some animals can regenerate their appendages at a restrictive time window after which their appendage regenerative potential declines rapidly. Small molecules targeting this regeneration-refractory period will rescue their appendage regeneration. Voltage-gated sodium channels are essential for the initial tail regeneration of *Xenopus laevis*. Transient activation of sodium ion influx by the small molecule activator monensin could trigger regeneration during the refractory period where tail regeneration does not normally happen (Tseng et al., 2010). This study highlights the use of small molecules to rescue and enhance appendage regeneration. The regenerative small molecules identified from lower regenerative animals may be useful for mammal limb regeneration or provide insights into the promotion of mammalian limb regeneration.

SMALL MOLECULES TARGET NSCS, AXONAL OUTGROWTH, AND REMYELINATION: CENTRAL NERVOUS SYSTEM REGENERATION

Discovery of chemical compounds that enhance neuronal regeneration can lead to the development of therapeutics to treat nervous system injuries and neurodegenerative diseases. Adult brain neural stem cells reside in two major regions of the subventricular zone (SVZ) and subgranular zone (SGZ) and primarily contribute to neurogenesis. Targeting the adult stem cells will promisingly enhance neural regeneration (Figure 3). Many molecular mechanisms and small molecules have been identified to modulate *in vitro* NSC self-renewal, proliferation, survival, and differentiation

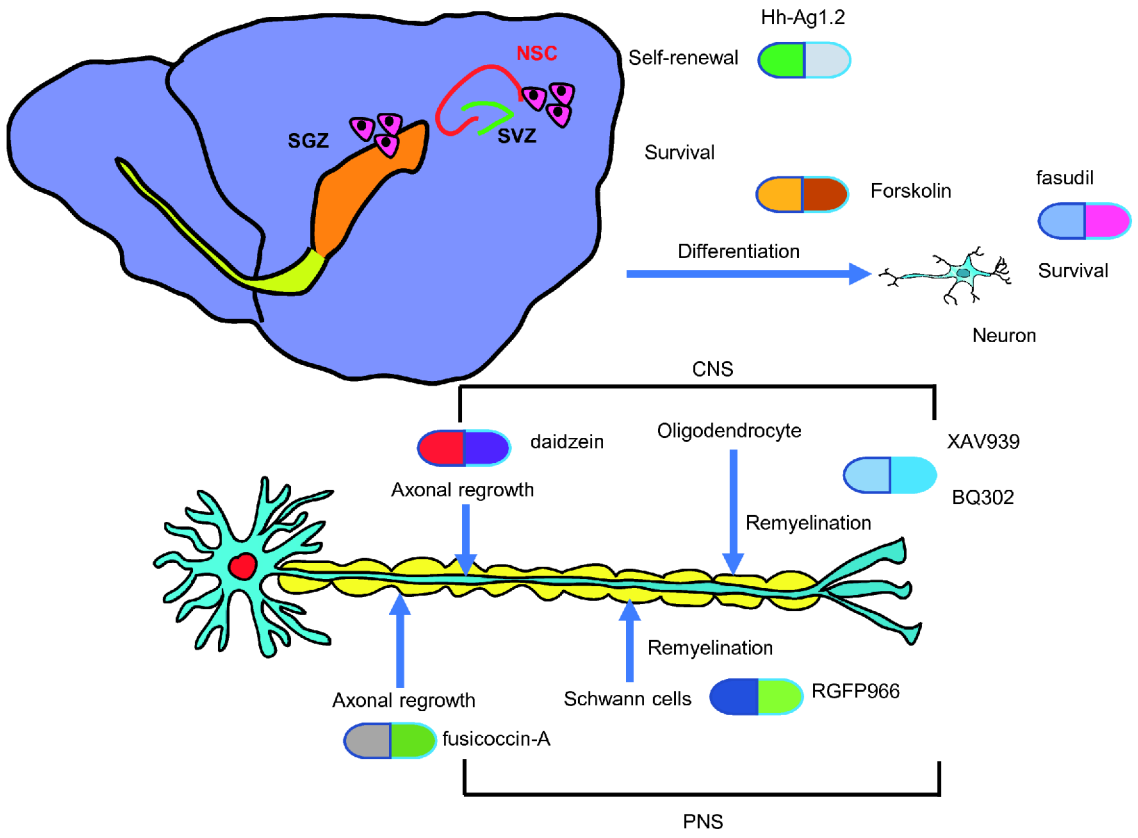

Figure 3 (Color online) Small molecules for promoting central nervous system (CNS) and peripheral nervous (PNS) regeneration. Small molecules can be applied to promote self-renewal, survival, and differentiation of NSC in the brain stem cell niches SVZ and SGZ. In addition, small molecules can provide neuroprotective effects on neurons and promote neuronal survival. Small molecules have been utilized to accelerate axonal regrowth and remyelination, which are important for nerve regeneration in the CNS and PNS. Hh-Ag1.2, an activator of Shh signaling, can increase CNS proliferation; Forskolin can elevate cAMP levels and enhance the differentiation of NSC; small molecule fasudil can enhance neuron survival; daidzein can increase neurite outgrowth; XAV939 and BQ302 promote differentiation of oligodendrocytes and remyelination; small molecule fusicoccin-A improve axonal outgrowth in the PNS; RGFP966 promotes differentiation of Schwann cells and remyelination.

(Xu et al., 2014). A variety of signaling pathways are involved in the self-renewal and differentiation of NSCs, including epidermal growth factors (EGFs), basic fibroblast growth factors (bFGFs), BMP signaling, LIF-JAK-STAT, Notch, Shh, and others (Xu et al., 2014). The use of small molecules to intervene these signaling pathways will regulate self-renewal and differentiation of NSCs. Androutsellis-Theotokis et al. reported that chemical inhibition of JAK or p38 could promote self-renewal of NSCs (Androutsellis-Theotokis et al., 2006). Activation of Shh signaling with small molecule Hh-Ag1.2 has been demonstrated to enhance proliferation of NSCs (Frank-Kamenetsky et al., 2002). Besides, small molecules can direct differentiation of NSCs. A typical example is the PKA signaling agonist Forskolin. *In vitro* treatment with Forskolin can increase neuronal differentiation by elevating intracellular cAMP level (Otte et al., 1989). Other compounds capable of inducing neural differentiation of NSCs have been discussed by Lyssiotis et al. (Lyssiotis et al., 2011). A recent study identified a catalog of small molecules that can manipulate SVZ microdomain-specific lineages *in vivo*. These small molecules can promote the generation of specific cell lineages from NSCs after *in vivo* treatment. This study unravels new strategies for using small molecules to direct the germinal activity in the SVZ, which has therapeutic potential in neurodegenerative diseases (Azim et al., 2017).

Small molecules can provide neuroprotective effects after nervous system injury and subsequently improve the neuronal survival. Pharmaceutical inhibition of Rho kinase with fasudil in a mouse model of Parkinson's diseases reduced the dopaminergic cell loss, preserved dopaminergic terminals, increased striatal fiber density, and dopamine level in the striatum, with the improvement of motor performance (Tönges et al., 2012). Intravenous administration of purmorphamine in the middle cerebral artery occlusion model of ischemic stroke can provide neuroprotection and restore neurological deficits and increase the amount of newly generated neurons in the peri-infarct and infarction area (Chechneva et al., 2014).

Promoting axonal outgrowth or regeneration is essential

for functional recovery after CNS injury. Small molecule-mediated modulation of axonal outgrowth and remyelination have been demonstrated to enhance axonal regeneration *in vivo* (Figure 3). Arginase 1 (Arg1) has been widely demonstrated to protect motor neurons and increase neurite outgrowth in sensory neurons. Small molecule daidzein acts as a transcriptional inducer of Arg1. Pretreatment with daidzein renders CNS and PNS neurons to overcome neurite outgrowth inhibition from the myelin-associated glycoprotein. More importantly, intraocular or subcutaneous injection of daidzein can efficiently promote axonal regeneration in an optic nerve crush model of rats (Ma et al., 2010). These suggest that daidzein may be an ideal candidate for development as a therapeutic for spinal cord injury. Using the laser neurosurgery model of *Caenorhabditis elegan*, Samara et al. identified PKC kinase inhibitor staurosporine dramatically increases neurite regeneration, and the other two PKC inhibitors also show similar effects (Samara et al., 2010).

Oligodendrocyte maturation plays a critical role in the remyelination of axons. Axin2 was expressed in immature oligodendrocyte progenitor cells in the brain white matter lesions of human newborns with neonatal hypoxic-ischemic and gliotic brain damage. Axin2 maintains normal remyelination by inhibiting Wnt signaling pathway. Treatment with small molecule XAV939 inhibiting tankyrase can stabilize Axin2 levels in oligodendrocyte progenitor cells from the brain and spinal cord and enhance their differentiation into mature oligodendrocyte and subsequently improve myelination after hypoxic and demyelinating injury (Fancy et al., 2011). Endothelin 2/endothelin receptor type B pathway is critical for remyelination of oligodendrocytes. Treatment with small molecule agonist BQ302 of endothelin receptor B in mouse cerebellar slice culture could increase remyelination, suggesting these agonists represent a promising therapeutic approach to promote myelin regeneration (Yuen et al., 2013). A cluster of κ-opioid receptor (KOR) agonist (±)U-50488 can promote oligodendrocyte differentiation and remyelination in purified rat oligodendrocyte cultures. The *in vivo* use of (±)U-50488 was able to accelerate remyelination after focal demyelination with lysolecithin. Consistently, treatment with (±)U-50488 enhanced differentiation of human oligodendrocyte precursor cells into mature oligodendrocytes (Mei et al., 2016). Other natural neurotrophic compounds and synthetic small molecules and their potential therapeutic application in the nervous system have been extensively reviewed by Xu et al. (Xu et al., 2014).

SMALL MOLECULES AND PERIPHERAL NERVE REGENERATION

Peripheral nerve regeneration contributes to functional recovery following peripheral nerve injury. Increasing studies have shown promoting effects of small molecules on peripheral nerve regeneration by increasing axonal regrowth and remyelination (Figure 3). By using small-molecule screening assay, He and colleagues found that histone deacetylase 3 (HDAC3) inhibitor RGFP966 or PDA106 can increase myelin growth and regeneration and improve functional recovery after sciatic nerve transection of the right hindlimb in mice (He et al., 2018). This study highlights the therapeutic potential of small molecule-mediated HDAC3 inhibition for improving peripheral nerve regeneration. 14-3-3s adaptors positively regulate axonal growth, small molecule fusicoccin-A (FC-A) can stabilize the 14-3-3 protein-protein interactions, stimulates axon growth *in vitro* and *in vivo* (Kaplan et al., 2017). Topical treatment with tropomyosin receptor kinase B (trkB) ligands, 7,8 dihydroxyflavone (7,8 DHF) and deoxygedunin, could enhance axon regeneration and muscle reinnervation in mice following peripheral nerve injuries (English et al., 2013).

SMALL MOLECULES ENHANCE TRANSDIFFERENTIATION AND DEDIFFERENTIATION: VISUAL SYSTEM REGENERATION

Amphibians can regenerate the retina by transdifferentiation of the retinal pigmented epithelium (RPE) into neural progenitors in responses to retinal injury. In the early embryonic chick, the RPE can also undergo similar transdifferentiation, but will soon lose this ability. Activin/TGF-β signaling plays a vital role in RPE development. Addition of activin can block transdifferentiation of chick RPE in an early stage, whereas a small molecule inhibitor of the activin/TGF-β signaling can reverse the developmental restriction in neural retinal regeneration from RPE in the later stage (Sakami et al., 2008). Moreover, small molecules can promote retinal regeneration by triggering dedifferentiation and proliferation. Similar to chick retina, inhibition of TGF-β signaling with a small molecule SB431542 accelerated functional recovery of zebrafish retinal degeneration induced by *N*-methyl-*N*-nitrosourea (MNU) (Tappeiner et al., 2016). By contrast, the beneficial effects of the small molecule may be associated with increased dedifferentiation and proliferation of Müller glia (Tappeiner et al., 2016). The dedifferentiation and proliferation of Müller glial cells are the major mechanisms of endogenous retinal regeneration in mammals. Shh is a potent mitogen for rat Müller glial cells and can dedifferentiate rat Müller glial cells into progenitor cells that can redifferentiate into rod photoreceptors. Purmorphamine, the small molecule activator of Shh signaling, was shown to promote proliferation of Müller glial cells, dedifferentiate them into neural progenitors that subsequently differentiate into rod-like photoreceptors (Gu et al., 2017). Noticeably,

intraocular injection of purmorphamine could activate Müller glial cells and increase the production of rod-like photoreceptors in the acutely damaged retina of rats (Gu et al., 2017). These results suggest treatment with small molecules can promote endogenous retinal regeneration.

CONCLUSIONS AND FUTURE PERSPECTIVES

We have made a systematic and comprehensive review of the chemical promotion of endogenous regeneration in various tissues and organs. Small molecules can target the activation, proliferation, differentiation, and survival of endogenous adult stem cells to enhance their regenerative responses to injuries and diseases. Moreover, small molecules can induce the *in vivo* dedifferentiation of differentiated cells into proliferative progenitors/precursors or transdifferentiation of adult differentiated cells into those lost or died cells, which both can produce new functional cells for regeneration. Currently, most studies focus on the promotion of endogenous regenerative capacity by chemical modulation of adult stem cells. For adult tissues and organs that are deficient in endogenous stem cells, the use of small molecules to trigger dedifferentiation and transdifferentiation of terminally differentiated cells may be more attractive approaches for increasing regeneration. The identification of small molecules that can promote regeneration is primarily based on the *in vitro* cell model by high-throughput screening from libraries of small molecule compounds. As a result, increasing small molecules have been discovered and developed to control stem cell fates and induce dedifferentiation, reprogramming, or transdifferentiation *in vitro* (Rennekamp and Peterson, 2015). However, *in vitro* effects of small molecules do not reflect the *in vivo* regenerative effects. The development of whole-organism high-throughput drug screening can be expected to drive the discovery of novel regenerative small molecules with beneficial effects *in vivo* (Rennekamp and Peterson, 2015). Moreover, future work needs to devise a safe and efficient delivery system for transporting regenerative small molecules into the target tissues. Because of lack of specificity, more efforts should be made to reduce the off-target effects and evaluate the tumorigenic risk while using small molecules to promote regeneration *in vivo* before clinical applications. Nevertheless, we hope that small molecules together with current biological technologies will enable *in situ* regeneration of tissues and organs and accelerate the progress in the regenerative medicine.

Compliance and ethics *The author(s) declare that they have no conflict of interest.*

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