Acquisition of functional neurons by direct conversion: Switching the developmental clock directly

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A R T I C L E   I N   P R E S S

Journal of Genetics and Genomics xxx (xxxx) xxx

Contents lists available at ScienceDirect

Journal of Genetics and Genomics

Journal homepage: www.journals.elsevier.com/journal-of-genetics-and-genomics/

ARTICLE IN PRESS

Abstract

Identifying approaches for treating neurodegeneration is a thorny task but is important for a growing number of patients. Researchers have focused on discovering the underlying molecular mechanisms of reprogramming and optimizing the technologies for acquiring neurons. Direct conversion is one of the most important processes for treating neurological disorders. Induced neurons derived from direct conversion, which bypass the pluripotency stage, are more effective, more quickly obtained, and are safer than those produced via induced pluripotent stem cells (iPSCs). Based on iPSC strategies, scientists have derived methods to obtain functional neurons by direct conversion, such as neuron-related transcriptional factors, small molecules, microRNAs, and epigenetic modifiers. In this review, we discuss the present strategies for direct conversion of somatic cells into functional neurons and the potentials of direct conversion for producing functional neurons and treating neurodegeneration.

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1. Introduction

Reprogramming is the process of turning back a cell’s developmental clock, and it has been studied for 60 years (Gurdon JB, 1958; Haag et al., 2018). Takahashi and Yamanaka (2006) first used four transcriptional factors (TFs), Oct4, Sox2, Klf4, and c-Myc, to successfully reprogram fibroblasts into induced pluripotent stem cells (iPSCs). Although iPSCs provide a solution for ethical concerns and immunological rejection, many problems are still present, such as tumorigenesis, inefficiency, and instability (Jaenisch and Young, 2008; Polo et al., 2010).

Direct conversion, a process directly converting terminal, fully differentiated cells to another type of terminal special cells that not only bypasses the pluripotency stage but also simplifies the transdifferentiation procedure, is an attractive approach for generating specific cell types (Vierbuchen et al., 2010; Velasco et al., 2014). This process allows for conversion between two totally unrelated cell types, providing an interesting approach for repairing or replacing injured organs and curing neurodegenerative diseases (Ebrahimi, 2016).

Various neurological diseases are caused by injury to specific subtypes of neurons; thus, there is a demand for various subtypes of neurons. In fact, the earliest transdifferentiation originated in 1987. Using the TF MyoD, researchers were able to derive myoblasts from mouse embryonic fibroblasts (Davis et al., 1987). Nevertheless, this technology did not advance rapidly until iPSCs emerged. In 2010, induced neurons (iNs) were first derived from mouse fibroblasts by Vierbuchen et al. (2010) through the use of three neuron-related TFs (Brn2, Ascl1, and Myt1L; BAM) (Vierbuchen et al., 2010). When NeuroD1 was added to the three TFs, human fibroblasts were able to be converted into neurons (Pang et al., 2011). Subsequently, the field of direct conversion has grown. Many strategies for achieving specific cell types, such as neurons, neural progenitors, neural crest, pancreatic β cells, myocardial cells, chondrocytes, hepatocytes, endotheliocytes, and epithelial cells, have been introduced (Ieda et al., 2010; Kim et al., 2011a, 2014a, 2014b; Jayawardena et al., 2012; Kulangara et al., 2014; Lee et al., 2015, 2017; Kaminski et al., 2016; Van Pham et al., 2017).

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https://doi.org/10.1016/j.jgg.2019.10.003

Please cite this article as: Chen, S et al., Acquisition of functional neurons by direct conversion: Switching the developmental clock directly, Journal of Genetics and Genomics, https://doi.org/10.1016/j.jgg.2019.10.003
Theoretically, direct conversion can provide a safer and quicker method for addressing neurological disorders. This method has great implications for the clinical treatment of neurodegeneration. In this review, we focus on the recent advancements in the acquisition of functional neurons through direct conversion.

2. Strategies for direct conversion of fibroblasts into functional neurons

2.1. Transcription factors

In different neurological diseases, different subtypes of neurons are impaired and need to be targeted for repair. Originally, studies on direct conversion activated “master control genes (MCGs)” to control cell fate (Lewis, 1992). The earliest evidence of direct conversion was in 1987, when Davis et al. (1987) converted fibroblasts into myoblasts using the MCG MyoD. However, in 2010, Vierbuchen et al. (2010) reported that transdifferentiation of fibroblasts into functional neurons can be achieved using three neuron-related TFs (Brn2, Ascl1, and Myt1L). They demonstrated that these three neuron-related TFs can directly convert mouse fibroblasts into functional neurons. The iNs exhibit features of functional membranes, namely action potentials (APs) and spontaneous APs (Vierbuchen et al., 2010). One or few TFs whose encoding genes act as MCGs are sufficient to trigger the activation of many other genes, leading to cell fate changes (Nizzardo et al., 2013).

In fact, subsequent research has shown that overexpression of three TFs Ascl1, Brn2, and Ngn2 can also induce the transdifferentiation of fibroblasts into functional neurons (Meng et al., 2012). Furthermore, researchers have demonstrated that the single reprogramming factor Ascl1 can generate iNs (Chanda et al., 2014). In addition, human fibroblasts can also be converted into neurons by the combination of the neural differential-related TF NeuroD1 with the three TFs Brn2, Ascl1, and Myt1L (Pang et al., 2011). Moreover, patient-specific iNs can be generated by a direct conversion strategy (Wang et al., 2014), and Ngn2 can enhance the generation of patient-specific iNs (Zhao et al., 2015), providing more approaches for treating degenerative diseases.

Another way to activate neuron-related TFs is by inhibit the RNA binding protein PTB, which results in the expression of neuron-related TFs and microRNAs (Xue et al., 2013). In addition, the non-neural progenitor TF Ptf1a is sufficient to convert mouse and human fibroblasts into induced neural stem cells (iNSCs) (Xiao et al., 2018). Thus, focusing on non-neural TFs is also a new idea for transdifferentiation.

Based on the preceding studies, many researchers have successfully derived various types of specific functional neurons, such as motor neurons, medium spiny neurons, peripheral sensory neurons, and dopaminergic neurons, via transdifferentiation (Table 1) (Caiazzo et al., 2011; Kim et al., 2011b; Blanchard et al., 2015; Hu et al., 2015; Tian et al., 2015).

Compared with the use only TFs, the combination of TFs and small molecules is more convenient and provides more advantages (Ladewig et al., 2012; Pfister et al., 2016; Smith et al., 2016). For example, Ladewig et al. (2012) showed that three small molecules, CHIR99021 (an inhibitor of GSK3), SB431542 (an inhibitor of the TGF-β receptor), and LDN193189 (an inhibitor of the BMP receptor), increase the efficiency of generating Ascl1/Ngn2-iNs from human fibroblasts. Smith et al. (2016) reported that small molecules facilitate Ngn2-mediated transdifferentiation via modulating chromatin accessibility. The combination of TFs and small molecules also facilitates the generation of target cells, such as striatal neurons, serotonergic neurons, cholinergic neurons, and cortical pyramidal neurons, from human fibroblasts (Berry et al., 2011; Pfister et al., 2011, 2016; Ladewig et al., 2012; Liu et al., 2013; Victor et al., 2014; Dai et al., 2015; Xu et al., 2016; Miskinyn et al., 2017).

2.2. Small-molecule compounds

Compared with other strategies, small molecules hold many unique advantages. As drugs, they are acceptable for clinical use. They can modulate specific targets, including transcription, metabolism, signaling, and epigenetic modification, which represent valuable approaches for probing cell fate determinants and generating specific functional neurons (Schug et al., 2008).

As compounds, small molecules exhibit distinct advantages in the process of direct reprogramming (Table 1). First, they are convenient to use for direct conversion. They provide rapid and reversible effects. Meanwhile, their effects are confined to target cells or tissues and do not act on other cells or tissues. Second, they are cost-effective. The preparation of TFs requires more time and relatively complex procedures. Small molecules are easier to manufacture, quantify, and produce. Third, they allow a high degree of temporal and spatial control. In addition, the compounds are highly permeating, which allows their effects to be reversible. The concentration and combination can be fine-tuned (Yu et al., 2014; Xie et al., 2017). Different concentrations and combinations can be used for various approaches for specific demands (Li et al., 2015).

Small molecules normally promote the expression or activation of master neuronal TFs, such as ISX9 (an isoaxizole), which is necessary to induce the activation of neuronal genes (Ngn2, Neurod1, NF-H, Tau, and Syn2) in fibroblasts by regulating signaling pathways that facilitate neural differentiation via neurotransmitter-evoked Ca2+ signaling pathways (Schneider et al., 2008; Li et al., 2015). Dai et al. (2015) reported a highly efficient approach based on inhibition of the SMAD signaling and the MEK-ERK pathway to directly convert human fibroblasts into functional neurons using a chemical cocktail of six types of small molecules, namely, CHIR99021 (an inhibitor of GSK3β), SB431542 (a TGF-β receptor inhibitor), LDN193189 (a BMP receptor inhibitor), PD0325901 (a MEK-ERK inhibitor), pifithrin-α (a p53 inhibitor), and forskolin. Another study revealed that forskolin and dorsomorphin can increase Ngn2-based direct reprogramming by increasing H3K27 acetylation and chromatin accessibility (Smith et al., 2016). Stimulating Wnt signaling with CHIR99021 and inhibiting TGF-β signaling with SB431542 significantly enhance the conversion of fibroblasts into neurons after the transduction of Ngn2 and Ascl1 (Ladewig et al., 2012). CHIR99021 has been previously shown to be critical for the phosphorylation of Ngn2 and motoneuron specification (Ma et al., 2019). When CHIR99021 is combined with Ngn2 for transdifferentiation, no HB9-positive cells are detected (Liu et al., 2013). Therefore, small-molecule compounds may contribute to the acquisition of specific neurons.

Using a cocktail of four chemicals (forskolin, CHIR99021, ISX9, and I-BET151), Li et al. (2015) successfully generated functional neurons (also called chemically induced neurons) from mouse fibroblasts. Hu et al. (2015) reported that direct neuronal conversion from human fibroblasts can be achieved with a chemical cocktail (named VCRFSGY) including seven types of small-molecule compounds (V, VPA; C, CHIR99021; R, RepSox; F, forskolin; S, SP600625; G, GO6983; Y, Y-27632) and iNs need to be cultured in CDF (C, CHIR99021; F, forskolin; D, dorsomorphin) for maturation. Furthermore, a strategy was derived to generate human functional neurons from patients with familial Alzheimer’s disease, which provides a promising clinical approach for modeling neurological disorders and for regenerative medicine (Hu et al., 2015).

As a nascent approach for direct conversion, small molecules present significant challenges, but they are valuable for facilitating the application of molecule-based neuronal differentiation for the treatment of degenerative diseases.
2.3. Epigenetic modifications

There have been extensive studies on DNA methylation by DNA methyltransferases (Smith and Meissner, 2013), which exerts a profound effect on the stability of genomes, transcriptional processes, development, and reprogramming (Ko et al., 2010). A previous report has shown that primary neurons exhibit extensive DNA demethylation (Yu et al., 2015). Although there are some reports focusing on the relationship between epigenetic modifications and reprogramming, fewer focus on the relationship between epigenetic modifications and direct conversion (Table 1) (Gu et al., 2011; Gao et al., 2013; Yu et al., 2015).

### Table 1

<table>
<thead>
<tr>
<th>Donor cells</th>
<th>Target neuronal type</th>
<th>Factors in direct conversion</th>
<th>Efficiency (yielda or purityb)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strategy: transcription factors (TFs)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mouse fibroblasts</td>
<td>Unidentified type</td>
<td>Ascl1, Brn2, Myt1L</td>
<td>Yield: 19.5%</td>
<td>Vierbuchen et al. (2010)</td>
</tr>
<tr>
<td>Human fibroblasts</td>
<td>Ascl1</td>
<td>N/A</td>
<td>Yield: 10%</td>
<td>Chanda et al. (2014)</td>
</tr>
<tr>
<td>Human astrocytes</td>
<td>Neuroblasts</td>
<td>Sox2</td>
<td>N/A</td>
<td>Matsuda et al. (2019)</td>
</tr>
<tr>
<td><strong>Strategy: small-molecule compounds + TFs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mouse fibroblasts</td>
<td>Nociceptor, mechanoreceptor, proprioceptor neurons</td>
<td>Ngn1 or Ngn2, Brn3a</td>
<td>Purity: 4.5%</td>
<td>Blanchard et al. (2015)</td>
</tr>
<tr>
<td>Human fibroblasts</td>
<td>Ascl1, Ngn2, Myt1L, LHx3, Is1</td>
<td>N/A</td>
<td>Yield: 14%</td>
<td>Wainger et al. (2015)</td>
</tr>
</tbody>
</table>

### Footnotes

- a Yield, numbers of iNs divided by numbers of plated cells.
- b Purity, numbers of iNs divided by numbers of DAPI.
- c N/A, not available.

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Zhang et al. (2016) presented a new strategy for direct conversion. Their research suggests that DNA demethylation contributes to direct conversion of fibroblasts into functional neurons. 5hmC is correlated with neuron-specific gene expression in the central nervous system (Kriaucionis and Heintz, 2009; Mellen et al., 2012). Epigenetic modification mediated by 5hmC is critical in neurodevelopment (Szulwach et al., 2011). Thus, the generation of 5hmC may be pivotal for the modification of neuronal differentiation by epigenetics (Zhu et al., 2016). Tet3, which is well known for its functional role in DNA demethylation, has been shown to guide the development of neuronal differentiation (Zhang et al., 2016).

In addition to DNA demethylation, DNA methylation is essential for iN generation. De novo methylation by DNMT3A suppresses the donor fibroblast and the competing myogenic programs, which is necessary for TF-induced direct reprogramming (Luo et al., 2019).

2.4. MicroRNAs

Because neuron-related TFs can convert fibroblasts into functional neurons, scientists have developed neuron-related microRNA approaches. The neuronal-specific microRNAs miR-9/9* and miR-124 can promote the transdifferentiation of human fibroblasts into neurons. Although the induced cells only express the neuronal marker MAP2, this approach widens the field of direct conversion (Yoo et al., 2011). Combined with TFs, microRNAs can facilitate efficiency and maturation (Table 1) (Ambasudhan et al., 2011; Pang et al., 2011; Yoo et al., 2011). Reports have also shown that the repression of the release of a single RNA binding protein, PTB, silences neuronal lineage-specific genes, including microRNAs (Xue et al., 2013). Inhibiting PTB-mediated effects of microRNAs on multiple components of the REST complex is a key event in neuronal cell generation (Xue et al., 2013).

2.5. Others

In addition to the major factors aforementioned, other indirect paths can be used to achieve direct conversion. For example, Li et al. (2017) reported that chemically induced cells in an extraembryonic endoderm (XEN)-like state derived from fibroblasts can be directly converted into functional neurons without entering the pluripotent stage. They improved the previous protocol for inducing chemically induced pluripotent stem cells from fibroblasts; VCGTFAE, which contains seven types of small-molecule compounds (VPA, TD114-2, 616452, tranylcypromine, forskolin, AM580, and EPZ004777), was used to generate the desired cell type (Li et al., 2017). Yoo et al. (2017) found that, in addition to chemical and biological methods, electromagnetic fields (EMFs) can be used for direct reprogramming. Gold nanoparticles (AuNPs) can facilitate the conversion of fibroblasts and astrocytes into iNSs under specific EMF frequencies (Yoo et al., 2017). The EMF system is a noninvasive method and thus may be more suitable for application. EMFs combined with a small-molecule strategy may be an ideal approach for reprogramming somatic cells into neurons.

In addition to fibroblasts, astrocytes and microglia are good donor cells for generating iNSs. In 2007, Berninger et al. (2007) determined that astrocytes can be converted into functional neurons. Generation of subtype-specific neurons, such as glutamatergic and GABAergic neurons, from astrocytes can also be achieved through overexpression of the neurogenic TFs Neurog2 and Dlx2 (Heinrich et al., 2010). Gong Chen’s group demonstrated that after brain injury, reactive astrocytes can be reprogrammed into functional neurons in vivo through overexpression of a single TF, NeuroD1 (Guo et al., 2014). To improve the in vivo glia-to-neuron conversion for therapeutic applications, they used an adeno-associated virus Cre-FLEX system to express NeuroD1 and regenerated 30%–40% of lost neurons in an ischemic injury mouse model (Chen et al., 2019). Recently, Matsuda et al. (2019) demonstrated that mouse microglia can be converted into neurons both in vitro and in vivo through expression of NeuroD1 (Matsuda et al., 2019). Glia cells, the major cells in the brain, accumulate at injured sites in the central nervous system. They may be suitable for restoring neurons through direct conversion in vivo without exhausting resources (Zhang et al., 2018). Further work is needed to address the functionality of these converted neuronal cells and to improve the conversion efficiency in mouse models of neurodegeneration.

The model of direct conversion strategies shown in Fig. 1 illustrates approaches for directly converting mouse and human fibroblasts into functional neurons. Various combinations of TFs, small molecules, epigenetic modifiers, and microRNAs may produce a number of new cell types. On the other hand, iNSCs or astrocytes can also differentiate into target neurons. These strategies are derived from practices and new discoveries. As these strategies are developed, the field of direct conversion may be used for clinical applications.

3. Discussion

Achieving functional target cell types and promising safe and effective clinical treatments are fundamental to regenerative medicine. Cell lineage reprogramming brings promise to the neurodegenerative diseases, especially those that require neuronal-specific cell types.

Researchers have described methods that drive the transdifferentiation of fibroblasts into neurons (Yang et al., 2011). They have further explored the hierarchical mechanism of direct conversion from fibroblasts into neurons through the use of Ascl1, Brn2, and Myt1L: Ascl1 first occupies the genomic sites of fibroblasts and then recruits Brn2 to these sites; Zfp238 is the target gene of Ascl1, which induces transdifferentiation (Wapinski et al., 2019).
2013). In recent years, Ascl1 have been studied very frequently in the field of neuronal induction. During neurogenesis, Ascl1 can bind to closed chromatin to promote chromatin accessibility and then activate gene expression (Raposo et al., 2015). For transdifferentiation, neuronal and cell cycle genes are also activated by Ascl1 overexpression in fibroblasts. The initial transcriptional response of all cells to Ascl1 is nearly homogenous; however, the later events play a main role in reprogramming efficiency (Treutlein et al., 2016). The study of single-cell RNA sequencing at multiple time points during conversion of fibroblasts into neurons has suggested that the molecular reprogramming path is remarkably continuous. Cells go through a unique intermediate transcriptional stage that is unrelated to donor and target cell programs rather than a canonical neural progenitor cell stage (Treutlein et al., 2016).

It seems difficult to achieve highly efficient conversion with the use of only TFs compared with other methods for reprogramming fibroblasts into neurons (Table 1). The main reason may be that most research uses viruses to ectopically express TFs. Thus, it is impossible to control the expression levels and temporal effects of TFs in donor cells. In addition, signaling pathways, metabolome, and proteome are dramatically changed during transdifferentiation. TFs cannot reprogram cells in multiple “dimensions” at once. Moreover, using viruses as an application of iNs in translational medicine for safety reasons. The combination of TFs with microRNAs or small molecules can significantly increase the conversion efficiency of iNs and even some specific neuronal subtypes (Ambasudhan et al., 2011; Yoo et al., 2011; Ladewig et al., 2012; Liu et al., 2013; Victor et al., 2014). Thus, regulating donor cells in multiple dimensions is more advantageous for the acquisition of iNs. Recent studies have demonstrated the mechanism of transdifferentiation by small molecules that target metabolic processes, epigenetic modifications, and signaling pathways. However, the precise targets of most small-molecule compounds during transdifferentiation remain unclear. In addition, one small molecule may have multiple targets in different donor cells. For example, forskolin is a very common small molecule used for reprogramming. Smith et al. (2016) revealed that forskolin can promote chromatin remodeling and enhance H3K27 acetylation. However, another group found that forskolin improves the neural transdifferentiation of mesenchymal stem cells through downregulation of the neuron restrictive silencer factor (Thompson et al., 2019). Using pure chemical compound cocktails is an ideal way to safely obtain neuronal cells, which can generate reprogrammed functional neurons from normal fibroblasts as well as from fibroblasts of Alzheimer’s patients (Hu et al., 2015; Li et al., 2015). Ma et al. (2019) used RNA sequencing to explore the transcriptome dynamics of chemical reprogramming of human astrocytes into neurons. They identified several signaling pathways that might be critical during conversion process, and also identified several new genes, such as neuronatin (NNAV), jagged canonical notch ligand 1 (JAG1), and repulsive guidance molecule A (RGMA), which are critical to coordinate the chemical reprogramming process.

Generation of some neuronal subtypes via these similar approaches is possible. miR-9/9* and miR-124 (miR-9/9*–124) promote the conversion of human fibroblasts into glialmatogenic neurons (Yoo et al., 2011); when miR-124 is combined with Myt1L and Brn2, the induction of glialmatogenic neurons from human fibroblasts can also be achieved (Ambasudhan et al., 2011). The combination of Bcl11b (also called Ctip2), Myt1L, Dlx1, and Dlx2 can guide the transdifferentiation of human postnatal and adult fibroblasts into striatal neurons (Victor et al., 2014). Dopaminergic neurons derived from mouse and human fibroblasts can be obtained by overexpression of three TFs, Ascl1, Nurr1 (also called Nr4a2), and Lmx1a (Caiazzo et al., 2011). Seven TFs (Ascl1, Brn2, Myt1L, Hb9, Is1l, Lhx3, and Ngn2) have been identified to facilitate the production of spinal motor neurons from both mouse and human fibroblasts (Son et al., 2011).

Great achievements in neuronal direct conversion have been made since 2010. Different approaches, including TFs, microRNAs, and small-molecule cocktails, have been used to change the fate of cells from fibroblasts to neurons (Vierbuchen et al., 2010; Pang et al., 2011; Yoo et al., 2011; Hu et al., 2015; Li et al., 2015). However, some questions still exist. Although the hierarchical mechanism of direct conversion has been clarified (Wapinski et al., 2013), the underlying mechanism of direct reprogramming still needs to be better understood (Xu et al., 2015). It is more difficult to transdifferentiate human cells into neurons than to transdifferentiate mouse cells into neurons. In addition, the conversion efficiency decreases as the age of the donor increases (Tanabe et al., 2015). Furthermore, for clinical application, high-quality and high-pure human-derived iNs must be acquired. The safety of the cell source used for transplantation for the treatment of neurodegenerative diseases should be considered a main concern (Xu et al., 2015).

It is difficult to ensure that all transplanted induced cells are integrated into local neural circuits. According to previous studies, grafted iNs can reverse symptoms in mouse model of some diseases, such as Parkinson’s disease. These iNs are able to integrate into and survive in brain networks and have also been characterized by electrophysiological examination, immunostaining, etc. However, few studies have determined the efficiency of iN survival in iN-grafted brains, and the interaction between the microenvironment and iNs has not been fully elucidated (Caiazzo et al., 2011; Kim et al., 2011b; Torper et al., 2013; Cassidy et al., 2014; Tian et al., 2015). In addition, different molecules and factors that affect grafted cell fate are largely unidentified. Direct conversion from fibroblasts into functional neurons provides us with a good model for drug screening and for the study of neurodegenerative diseases (Graf, 2011). However, potential risks should be avoided. There is still a long journey to clinical application in this field.

Acknowledgments

This work was supported by grants from the CAS Strategic Priority Research Program (XDA16020602), the National Key R&D Program of China (2019YFA0110300), the National Science Foundation of China (81825006, 31730033 and 31621004), and the K.C.Wong Education Foundation.

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Please cite this article as: Chen, S et al., Acquisition of functional neurons by direct conversion: Switching the developmental clock directly. Journal of Genetics and Genomics, https://doi.org/10.1016/j.jgg.2019.10.003


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Please cite this article as: Chen, S et al., Acquisition of functional neurons by direct conversion: Switching the developmental clock directly, Journal of Genetics and Genomics, https://doi.org/10.1016/j.jgg.2019.10.003


Please cite this article as: Chen, S et al., Acquisition of functional neurons by direct conversion: Switching the developmental clock directly, Journal of Genetics and Genomics, https://doi.org/10.1016/j.jgg.2019.10.003