Impediments to eye transplantation: ocular viability following optic-nerve transection or enucleation

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ABSTRACT

Maintenance of ocular viability is one of the major impediments to successful whole-eye transplantation. This review provides a comprehensive understanding of the current literature to help guide future studies in order to overcome this hurdle. A systematic multistage review of published literature was performed. Three specific questions were addressed: (1) Is recovery of visual function following eye transplantation greater in cold-blooded vertebrates when compared with mammals? (2) Is outer retina function following enucleation and reperfusion improved compared with enucleation alone? (3) Following optic-nerve transection, is there a correlation between retinal ganglion cell (RGC) survival and either time after transection or proximity of the transection to the globe? In a majority of the studies performed in the literature, recovery of visual function can occur after whole-eye transplantation in cold-blooded vertebrates. Following enucleation (and reperfusion), outer retinal function is maintained from 4 to 9 h. RGC survival following optic-nerve transection is inversely related to both the time since transection and the proximity of transection to the globe. Lastly, neurotrophins can increase RGC survival following optic-nerve transection. This review of the literature suggests that the use of a donor eye is feasible for whole-eye transplantation.

Approximately 37 million people worldwide suffer from blindness, with up to 20% or 7.4 million having vision of only light perception or less.[1 2] Much of this irreversible blindness is due to age-related diseases such as macular degeneration, diabetic retinopathy and glaucoma,[3–5] as well as trauma and ocular tumours.[6–8] The irreversible nature of these diseases is a result of permanent optic-nerve damage. Irreversibly damaged axons of retinal ganglion cells (RGCs)—the output neurons from the retina that pass through the optic nerve—do not regain their function. Potentially, whole-eye transplantation can provide a blind recipient with viable RGCs capable of regeneration, as well as the optical system necessary for forming a retinal image.

In 1977, a 17-member advisory council for the National Eye Institute (NEI) called for a "limited and thoughtful laboratory effort" in the area of eye transplantation. However, the council acknowledged that "at present, any effort to transplant a mammalian eye is doomed to failure by the ganglion cell axon's inability to withstand cutting, by the difficulty of insuring adequate circulation of blood to the transplanted eye during or shortly after operation, and lastly by immune rejection of foreign tissue."[9]

Here we provide a comprehensive understanding of the current literature regarding ocular viability of the donor eye. Throughout this review, ocular viability will be defined in one of three ways: capacity for visual recovery, maintenance of outer retina function (measured using an electroretinogram (ERG)) or RGC survival. The following three questions relating to ocular viability were addressed: (1) Is recovery of visual function following eye transplantation greater in cold-blooded vertebrates when compared with mammals? (2) Is outer retina function following enucleation and reperfusion improved compared with enucleation alone? (3) Following optic-nerve transection, is there a correlation between RGC survival and either time after transection or proximity of the transection to the globe? To answer these questions, we systematically reviewed the published literature to determine the outcome of whole-eye transplantation in animals, outer retina function after enucleation and RGC survival after optic-nerve transection.

LITERATURE SOURCES AND EVALUATION

Pertinent articles were identified through a multi-stage systematic approach. In the first stage, a computerised search of MEDLINE database (National Library of Medicine, Bethesda, Maryland) was performed. The search-terms "optic nerve regeneration," "eye transplantation," "isolated perfused eye," retinal ganglion cell survival axotomy" and "circulatory revascularisation of the eye" from the Medical Subject Headings (MeSH0 supplement to *Index Medicus* (National Library of Medicine, Bethesda, Maryland) were used for a broad search. This search produced 702 unique citations. Commercial internet search engines were queried for additional unique references. In the second stage, all abstracts were carefully scanned to identify articles that pertained to ocular viability. Whole copies of 153 articles were obtained. Bibliographies of the retrieved articles were manually searched for additional articles. In the third stage, complete articles were reviewed to identify those that discussed eye transplantation, ocular viability, retinal function in the isolated perfused eye or RGC survival following optic-nerve transection. The search was limited to English language articles.

Articles were grouped into three categories for further data abstraction: (1) articles that described in vivo whole-eye transplantation, (2) articles that described in vivo and ex vivo whole-eye reperfusion and (3) articles that described in vivo RGC survival and factors that increase RGC survival. Data were

abstracted from identified articles to determine ocular viability in each of the above three categories and for factors that improve ocular viability.

For evidence of visual function, only articles in which the eye was completely enucleated and reimplanted were included. Articles in which the optic nerve was transected but the eye was not enucleated were excluded. We relied on each identified article's conclusion to assess evidence of visual function. Outcome of whole-eye transplantation in cold-blooded vertebrate was compared with outcome in mammals. In total, 17 articles regarding whole-eye transplantation in both cold-blooded vertebrate and mammals satisfied our inclusion criteria.

For evidence of preserved outer retina function, only articles that evaluated outer retina function (with ERG) at greater than one time point were included. Articles, in which an enucleated eye was perfused, but maintenance of ocular viability at greater than one time point was not evaluated, were excluded. Articles in which there was no attempt to evaluate retina function were also excluded. In total, eight articles regarding ex vivo perfused eyes satisfied our inclusion criteria.

For RGC survival, articles were divided into two categories based upon the location of optic-nerve transection—intraorbital or intracranial. Articles that evaluated RGC survival at (at least) two of the following three time points were included: 1–3 days post-transection, 10–15 days post-transection and 26–30 days post-transection. Only articles in which complete optic-nerve transection (one optic-nerve crush article was included) was performed and in which quantification of RGC survival at more than one time point was assessed were included. In total, 12 articles regarding survival of RGC after optic-nerve transection satisfied our inclusion criteria.

Finally, articles that demonstrated factors that improved RGC survival were included. The effect of the positive factors is reported as the percentage difference of RGC survival between the eye that was treated with the factor, and the eye that was not treated. This percentage difference was calculated by subtracting the percentage (of healthy control) of RGC survival in the untreated eye from the percent (of healthy control) of RGC survival in the treated eye. The result of this calculation yielded the ''percentage survival difference.'' In total, 45 articles regarding factors that increase RGC survival satisfied our inclusion criteria.

A total of 82 articles were included in the study, and a total of 93 articles are referenced. A total of 60 articles were excluded based on our exclusion criteria.

RESULTS

Whole-eye transplantation

In defining ocular viability as recovery of visual function following transplantation, it is necessary to review attempts at whole-eye transplantation, which date back to 1885 when a rabbit eye was transplanted into a human orbit.[10] Over the subsequent 10 years, several attempts at mammalian eye transplantation followed;[10 11] however, by the early to mid 20th century, most of the attempts at eye transplantation were performed in cold-blooded vertebrates, and much of our knowledge is obtained from these studies. In total, we have reviewed 17 articles regarding whole-eye transplantation.[10–26] Figure 1 outlines eye transplantations performed from the years 1880 until 2000 (962 in total).

A total of seven articles describing 173 mammalian eye transplantations were reviewed.[10–13 15 17 18] Of the seven studies, only two have demonstrated recovery of visual function.[13 15] In 1925, Koppanyi and Baker reported the recovery of visual function in three out of 25 rats in which autograft transplantation (excision and reimplantation) was performed.[15] Doubts have since been raised regarding the accuracy of the tests Koppanyi used to demonstrate visual function and whether the rats ever truly recovered vision.[9 14] The only other study that shows recovery of visual function in mammals was performed by Freed and Wyatt in 1980.[13] They demonstrated that following transplantation of fetal eyes directly into the brains of adult rats, surviving ocular tissue could be identified. Visual evoked responses were positive in nine out of 10 rats in which surviving ocular tissue was identified. Although some of the remaining studies establish ''success'' in other capacities, no visual function was recovered following transplantation.

We have reviewed a total of 10 articles,[15 16 19–26] eight of which describe 789 eye transplantations in cold-blooded vertebrates.[16 19–25] In the remaining two articles, recovery of visual function was reported, but the number of experimental models was not given.[15 26] One of the eight articles describes 296 transplantations, but the specific number in which recovery of visual function was tested is not given.[23] In the remaining seven articles,[16 19–22 24 25] of the 493 transplantations that were recorded, 180 were tested for visual recovery, and 95 demonstrated recovery of visual function. Table 1 describes the 10 articles in greater detail.

Many more eye transplantations were performed in cold-blooded vertebrate than in mammals. Furthermore, maintenance of ocular viability was more successful in cold-blooded vertebrates when compared with mammals.

Outer retina function after enucleation

In assessing ocular viability of the donor eye as it pertains to whole-eye transplantation, one of the primary concerns is the ability for the retina to maintain function following enucleation. Throughout this section, ocular viability will be defined as maintenance of outer retina function following enucleation as measured using ERG. An excellent model for assessing retina function after enucleation ex vivo is the isolated, perfused eye that was originally used in 1970.[27] Even though this model was employed prior to 1970, it was not for the purposes of assessing retinal function.[28 29] In this system, the eye is enucleated and immediately (usually within less than 10 min) reperfused with an artificial perfusate designed to maintain retina function for as long as possible. In this review, a total of eight articles describing outer retina function in a perfused eye are reviewed.[27 30–36]

All eight of the articles regarding outer retina function in an isolated perfused eye identified a period of time in which outer retina function was maintained after enucleation and reperfusion.[27 30–36] Maintenance of outer retina function was determined by the presence of a stable ERG response as determined by each individual study. Of the eight studies, seven used flash ERG,[27 30–33 35 36] and one used multifocal ERG (mfERG).[34] Two of the eight studies reported that without reperfusion, ERG activity is greatly decreased or absent within 5 min after enucleation.[27 32] In the eight studies, the period in which outer retina function was maintained following enucleation and reperfusion ranged from 4 h to more than 9 h. Table 2 outlines these eight studies in greater detail.

RGC survival following optic-nerve transection

The third area of importance regarding maintaining ocular viability is RGC survival as assessed by histological analysis of the retina following optic-nerve transection. Specifically, we

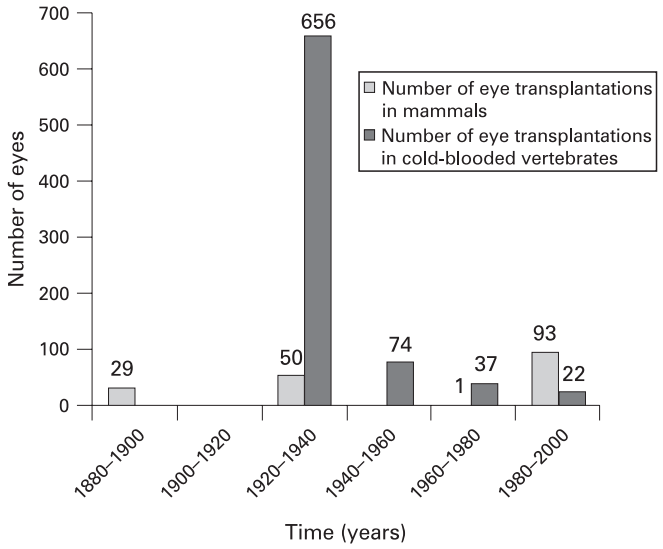

Figure 1 Timeline of whole-eye transplantations performed between the years 1880 and 2000.

evaluated the correlation between RGC survival and both time after optic-nerve transection and distance of transection from the globe. We also evaluated factors that increase RGC survival after optic-nerve transection. In total, 12 articles describing RGC survival after optic-nerve transection were reviewed.[37–48] An additional 45 articles identifying factors that increase RGC survival were reviewed.[38 39 42 43 46 49–88]

In nine of the 12 studies that evaluated RGC survival at the above-mentioned time points, an intraorbital injury was performed,[38–40 42–46 48] in two studies, both an intraorbital and intracranial injury was performed,[37 47] and in one study, only an intracranial injury was performed.[41] The injuries were divided into two categories—intraorbital injury (11 studies) and intracranial injury (three studies).

The results of the studies using intraorbital injuries were as follows: eight studies evaluated RGC survival at the 1–3 day time point with survival ranging from 72 to 100%;[37 40 42–46 48] 11 studies evaluated RGC survival at the 10–15 day time point with results ranging from 5.8 to 27%;[37–40 42–48] and six studies evaluated RGC survival at the 26–30 day time point with results ranging from "negligible" to 7.5%.[37–40 46 47]

The results of the intracranial injuries were as follows: two studies evaluated RGC survival at the 1–3 day time point with survival ranging from 90 to 100%;[37 41] four studies (three articles) evaluated RGC survival at the 10–15 day time point with results ranging from 57.4 to 68%;[37 41 47] and four studies (three articles) evaluated RGC survival at the 26–30 day time point with results ranging from 49 to 71.4%.[37 41 47] Table 3 outlines these studies in greater detail. An inverse relationship between RGC survival following optic-nerve transection, and both time after transection and proximity of transection to the globe is clearly demonstrated.

A total of 45 articles that describe factors that increase RGC survival after optic-nerve transection were reviewed.[38 39 42 43 46 49–88] In these articles, 31 individual factors, six combined factors and 17 gene modifications are discussed. In the 45 articles, some of the factors that are studied include brain-derived neurotrophic factor (BDNF),[39 61 68 74 76 78 85] ciliary neurotrophic factor (CNTF),[46 82 83] glial-derived neurotrophic factor (GDNF),[64 66 68 82 85] neurturin,[68] nerve growth factor (NGF)[51] and many others. Tables 4–6 list the factors along with details for each study.

DISCUSSION

Whole-eye transplantation may prove to be the ultimate treatment for irreversible causes of blindness. The three main impediments to transplanting a human eye are:[9 89] maintenance of donor eye viability, optic-nerve regeneration and restoration of topographic organisation, and avoidance of immunological rejection. We have systematically reviewed the first impediment to eye transplantation, which is maintenance of donor eye viability. Three measurable characteristics defining ocular viability that are of particular importance to whole-eye transplantation are recovery of visual function after eye transplantation, outer retina function after enucleation, and RGC survival after optic-nerve transection. The method in which ocular viability was determined and defined was specific to the individual factors and is clearly delineated in the introduction of this article. Our review of the literature concluded that recovery of visual function can occur after whole-eye transplantation in cold-blooded vertebrates. However, limited information is available regarding recovery of visual function after whole-eye transplantation in mammals. In mammals, following enucleation and reperfusion, outer retinal function is maintained from 4 to 9 h. RGC survival following optic-nerve transection is inversely related to both the

Table 1 Whole-eye transplantation in cold-blooded vertebrates

Animal	No of eyes transplanted	No of eyes tested for vision	Method of testing	No of eyes that recovered visual function	Study
Bombinator (European toad)	NR	NR	Skin colour (visual controlled)	"Many"	Koppany and Baker[15]
Salamander	NR	NR	Behavioural response	"Many"	Stone and Ussher[26]
Salamander	82	6	Behavioural response	All 6	Stone[20]
Salamander	296	NR	Behavioural response	"Many specimens"	Stone and Cole[23]
Salamander	186	31	Behavioural response	All 31	Stone *et al*[25]
Salamander	33	9	Behavioural response	6 of 9	Stone and Zaur[24]
Salamander	59	4	Behavioural response.	NR	
Frog	32 (16 animals)	All (16 animals)	Behavioural response	2 of 16 frogs	Sperry[19]
Salamander	42 (21 animals)	All (21 animals)	Behavioural response	12 of 21 salamanders	
Salamander	11 eyes	10	Behavioural response	7 of 10	Stone[22]
Salamander	26 (13 animals)	24 (12 animals)	Behavioural response	9 of 12 salamanders	Stone[21]
Salamander	22	22	Recovery of visual activated skin camouflage	18 of 22	Pietsch and Schneider[16]

NR, not recorded.

Table 2 Eye viability and retinal function in the perfused eye

Animal	Eye viability (hours postenucleation)	Measurement of eye viability	Study
Cat	6–8	Stable ERG response	Gouras and Hoff[27]
Bovine	5–6* (>10)	Stable ERG response (small negative deflection)	Tazawa and Seaman[35]
Cat	8–10	Stable ERG response	Niemeyer[31]
Frog	>9	Stable ERG response	Friedman and Marchese[30]
Cat	4.5	Stable ERG response	Sandberg *et al*[33]
Bovine	8*	Stable ERG response	Tseng *et al*[36]
Cat	7–9	Stable ERG response	Peachey *et al*[32]
Bovine	4	mfERG (multifocal) response	Shahidullah *et al*[34]

*Oxygenated blood was used instead of artificial perfusate.

time since transection and the proximity of transection to the globe. Neurotrophins can increase RGC survival following optic-nerve transection. Taken together, these findings suggest the feasibility of using the donor eye for possible whole-eye transplantation.

One of the primary concerns regarding maintenance of ocular viability is the ability to preserve or recover retinal function of the donor eye following enucleation. Of particular concern are the photoreceptor cells that are responsible for absorbing the light and initiating signal transduction to the higher visual centres. An ideal system for assessing this function is the isolated perfused eye.[27] Following enucleation of a cat eye, the ophthalmic artery was immediately cannulated, and artificial perfusion was initiated. ERG responses were obtained over several hours in order to demonstrate that the eye remained viable. The presence of ERG responses demonstrated that the photoreceptors were still functioning. Several additional researchers adopted and improved the perfused eye technique.[30 31 33 35 36] Although most researchers used this method to assess the toxicity of certain substances, its use provides excellent information regarding the length of time an eye can remain viable following enucleation. This is of particular importance with regards to eye transplantation, as it would be absolutely necessary to maintain the retina function of the donor eye in order to allow transplantation to the recipient.

RGC survival after optic-nerve transection is another major concern when evaluating ocular viability. It is well known that following optic-nerve transection, RGCs undergo degeneration.[89] It is important, however, to identify the extent of RGC loss and survival as well as what additional factors affect RGC survival. For successful transplantation to occur, RGCs must survive in order to regenerate the optic nerve. We conclude from the literature review that transection of the optic nerve at a point that is more distal from the globe produces far less RGC loss than an injury that is proximal to the globe. Additionally, we were able to summarise many factors that are useful in augmenting RGC survival after optic-nerve transection. Another promising finding regarding RGC survival was demonstrated in cold-blooded vertebrates. In 1985, Scalia *et al* performed a quantitative analysis of RGC survival following optic-nerve injury and regeneration. Scalia was able to demonstrate that even though the animal fully recovered vision, only 29% of the RGCs remained after 50 weeks.[90] Others have since noted survivals of 60%,[91] 50%[92] and 40%[93] at different time points after injury. Although these results are somewhat variable, we can easily conclude that considerably less than 100% RGC survival is sufficient for visual recovery. The evidence from cold-blooded vertebrates along with the increasing ability to maintain RGC survival in mammals provides us with very promising evidence regarding RGC survival in eye transplantation.

The ability to successfully reperfuse the enucleated eye after reanastomosis to a different blood supply is integral to maintaining ocular viability following enucleation and transplantation. Herman Sher was the first and one of the only researchers to report the surgical feasibility of reanastomosing the enucleated eye and to assess the presence of reperfusion following the reanastomosis. In one experiment, Sher attempted to reanastomose the ciliary artery of dogs to the femoral artery in rats.[18] In a second experiment, Sher

Table 3 Retinal ganglion cell survival following axotomy in mammalian eyes

Distance from eye	1–3 days postinjury (%)	10–15 days postinjury (%)	26–30 days postinjury (%)	Study
Intraorbital (<5 mm)	NA	24.7	18.2	Villegas-Perez *et al*[47]
	72	23.6	NA	Takano and Horie[45]
	100	5.8	Negligible	Berkelaar *et al*[37]
	NA	26	5	Di Polo *et al*[39]
	100	19	NA	Watanabe *et al*[48]
	85	24	NA	Manabe *et al*[44]
	NA	9.6	2	Cheng *et al*[38]
	97	14.9	7	van Adel *et al*[46]
	88	27	7.54	Germain *et al*[40]
	100	19	NA	Hou *et al*[42]
	98	16.3	NA	Kretz *et al*[43]
Intracranial (>8 mm)	90	68	64	Grafstein and Ingoglia[41]
	NA	57.4	54.5	Villegas-Perez *et al*[47]
	NA	65.6	71.4	
	100	63	49	Berkelaar *et al*[37]

NA, not applicable.

Table 4 Factors and details for each study: single factors that have been shown to increase retinal ganglion cell (RGC) survival following axotomy

Factor*	Animal	No of days postaxotomy	Percentage survival difference†	Administration
aFGF[80]—postinjury	Rat	Day 30	24.5%	PN
Antisemaphorin 3A Ab[79]—postinjury	Rat	Day 8	79%	IO
Aurintricarboxylic acid(ATA)[58]—postinjury	Rat	Day 14	45%	IO
BDNF[74 78 85 68 82]—postinjury	Rat	Day 7–14	51.1–30% –	IO
	Cat	Day 14	12%	IO
bFGF[80]—postinjury	Rat	Day 30	20.5%	PN
CNTF[82 46]—postinjury	Cat	Day 14	14%	IO
	Rat	Day 14	14.8%	IO
Collicular proteoglycan[60]—postinjury—intraocular	Rat	Day 7, 14	26%, 48%	IO
Cortisol[59]—postinjury	Rat	Day 14	33%	IO
Donepezil (AchE inhibitor)[75]—postinjury	Rat	Day 7	9.5%	Orally
Electrical stimulation[77]—postinjury	Rat	Day 7	29%	Nerve stump
Erythropoietin (EPO)[84]—postinjury	Rat	Day 14	872 and 455 RGC/mm^2‡	IO
Fibroblasts[72]—preinjury	Rat	Day 7	11.8%	IO
Flunarizine[57]—postinjury	Rat	Day 14	5%	SubQ
GDNF[64 66 68 82 85]—postinjury	Rat	Day 7–14	37–18%	IO
	Cat	Day 14	13%	IO
GM1[54]—preinjury	Rat	Day 14	18.87%	IO
IGF-1[62]—postinjury	Rat	Day 14	14%	IO
IL-1β[55]—postinjury	Rat	Day 14	39.4%	IO
Inosine[42]—postinjury	Rat	Day 14	5.9%	Intraperitoneal
Latanoprost[70]—preinjury	Rat	Day 10	31.8%	IO
Leukaemia inhibitory factor[46]—postinjury	Rat	Day 14	9%	IO
L-NAME (NO inhibitor)[67]—postinjury	Rat	Day 10, 14	21%, 22.4%	IO
Minocycline[49]—pre- and postinjury	Rat	Day 7	23%	Intraperitoneal
Neurturin[68]—postinjury	Rat	Day 14	16%	IO
NGF[51]—postinjury	Rat	Week 5, 7	16.7%, 16.9%	IO
NOLA (NO inhibitor)[67]—postinjury	Rat	Day 10, 14	29.2%, 32%	IO
NT-4 (neurotrophin)[78 82]—postinjury	Rat	Day 7, 14	38.2%, 13.2%	IO
	Cat	Day 14	8%	IO
Optic-nerve graft[53]—preinjury implantation	Hamster	Day 7	15%	IO
Rifampicin[63]—postinjury	Mice	Day 14	25.9%	Intraperitoneal
Schwann cells[72]—pre injury	Rat	Day 7	16.1%	IO
Simvastatin[43]—postinjury	Rat	Day 7, 14	40.9%, 16.2%	IO
TNF-α[56]—postinjury	Rat	Day 14	35.1%	IO

*The time the factor was given is listed along with the factor.
†Results are calculated as the percentage difference of RGC survival (compared with healthy retina) in the retina of treated eyes versus the untreated eye (ie, percentage of surviving RGC in the treated eye minus the percentage of surviving RGC in the untreated eye).
‡No controls were used numbers are reported as actual numbers.
Ab, antibodies; aFGF, acidic fibroblast growth factor; BDNF, brain-derived neurotrophic factor; bFGF, basic fibroblast growth factor; CNTF, ciliary neurotrophic factor; GDNF, glial derived neurotrophic factor; GM1, monosialotetrahexosylganglioside; IGF, insulin like growth factor; IL, interleukin; IO, intraocular; L-NAME, N-nitro-L-arginine methyl ester; NGF, nerve growth factor; NOLA, Nω-nitro-L-arginine; PN, perineural; TNF, tumour necrosis factor.

contralaterally transplanted sheep eyes.[17] For each transplanted eye, eight vascular anastomoses were performed (two arterial and six venous). In both experiments, anastomotic patency and reperfusion were demonstrated by microscopic examination and fluorescein angiography, respectively.

Although much significant research with regards to whole-eye transplantation has been performed, much additional research is still necessary. Future research on eye transplantation should focus on promoting optic-nerve regeneration, as well as further enhancing ocular viability.

Table 5 Factors and details for each study: combined factors that have been shown to increase retinal ganglion cell (RGC) survival following axotomy

Factor*	Animal	No of days postaxotomy	Percentage survival difference†	Administration
Aurintricarboxylic acid+cortisol[59]—postinjury	Rat	Day 14	44	IO
BDNF+CNTF[82]—postinjury	Cat	Day 14	12	IO
BDNF+GDNF[68 85]—postinjury	Rat	Day 14	65.2–59.6	IO
BDNF+Neurturin[68]—postinjury	Rat	Day 14	65.1	IO
BDNF+S-PBN (N-tert-butyl-(2-sulfophenyl)-nitrone)[65]—postinjury	Rat	Day 14	56.4	IO
GDNF+Neurturin[68]—postinjury	Rat	Day 14	37	IO

*The time the factor was given is listed along with the factor.
†Results are calculated as the percentage difference of RGC survival (compared with healthy retina) in the retina of treated eyes versus the untreated eye (ie, percentage of surviving RGC in the treated eye minus the percentage of surviving RGC in the untreated eye).
BDNF, brain-derived neurotrophic factor; CNTF, ciliary neurotrophic factor; GDNF, glial derived neurotrophic factor.

Table 6 Factors and details for each study: gene modifications that have been shown to increase retinal ganglion cell (RGC) survival following axotomy

Factor*	Animal	No of days postaxotomy	Percentage survival difference†	Administration
Anti-Apaf-1 RNA inhibitor[73]—postinjury	Rat	Day 14	200 and 423 RGC/mm^2‡	Nerve stump
Anti-c-Jun RNA inhibitor[73]—postinjury	Rat	Day 14	200 and 520 RGC/mm‡	Nerve stump
Bcl-2 overexpression[50]	Neonatal mice	24 h	50%	Transgenic mice
Bcl-2 overexpression[52]	Mice	2–3.5 months‡	58%	Transgenic mice
Ad-BDNF—postinjury[39 61]	Rat	Day 10, 14	39%, 7%	IO-Ad vector
BDNF cDNA+electroporation[76] —postinjury	Rat	Day 14	57.9%	IO cDNA injection
Ad-CNTF[83 46]—postinjury	Rat	Day 7–21	40.1–7%	IO-Ad vector
Ad-CNTF[71]—postinjury	Rat	Day 14	19.5%	Nerve stump
Lv-CNTF[81]—postinjury	Rat	Day 14	53.1%	IO-Lv vector
Ad-IL-10[69]—postinjury	Rat	Day 14	18%	IO-Ad vector
Ad-IL-4[69]—postinjury	Rat	Day 14	5.4%	IO-Ad vector
Ad-p53[71]—postinjury	Rat	Day 14	17.4%	Nerve stump
Trk oncogene[88]—preinjury	Rat	Day 7	37%	Superior colliculus
TrkB gene[38]—preinjury	Rat	Day 7, 14, 28	25%, 17%, 5%	IO
TrkB gene transfer (preinjury)+BDNF (postinjury)[38]	Rat	Day 7, 14, 28	47%, 66%, 15%	IO
Ad-XIAP[87]—postinjury	Rat	Day 14	16.9%	Nerve stump
VEGF overexpression[86]	Mice	Day 14	13.3%	Transgenic mice

*The time the factor was given is listed along with the factor.
†Results are calculated as the percentage difference of RGC survival (compared with healthy retina) in the retina of treated eyes versus the untreated eye (ie, percentage of surviving RGC in the treated eye minus the percentage of surviving RGC in the untreated eye).
‡Wild type was evaluated at 2 months and Transgenic was evaluated at 3.5 months.
Ad, adenoviral; BDNF, brain-derived neurotrophic factor; CNTF, ciliary neurotrophic factor; IL, interleukin; IO, intraocular; Lv, lentiviral; VEGF, vascular endothelial growth factor; XIAP, X-linked inhibitor of apoptosis.

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