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Editorial

The rise of transplantation neurosurgery: Spinal cord, eye, brain

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TO THE MEMORY OF VD DEMIKHOV (1916–1998)

Since 1954, almost any organ or tissue or body part of the human body has been transplanted, with the notable exception of the central nervous system (CNS).[1] While cell graft trials into diseased brains, spinal cords, and retinas have been conducted since the end of the XX century,[17,19,32,46] transplantation of segments of the spinal cord (SC) to treat spinal cord injury (SCI) or transplantation of the whole brain tout court is considered out of reach, due to impassable biologic and – in the case of the brain – ethical hurdles (e.g. Newcombe[30]).

Nerve fusion technology developed over the past 40 years, including the GEMINI SC fusion (SCF) protocol,[3-5,37] aims at enabling spinal cord transplantation (SCT) and optic nerve (ON) reconstruction in the setting of eye transplantation. Brain transplantation is discussed elsewhere.[6,7]

MENDING NEURAL DAMAGE

The GEMINI SCF protocol, first introduced in 2013, has been reviewed in depth in several publications to which the interested reader is referred (e.g., Canavero *et al*. and Canavero and Ren[4,5]). Briefly, whereas it is commonly thought that the brain sends out motor commands through long-range fibers coursing only in the white matter (pyramidal tract, lemnisci, etc.), neuroanatomic evidence proves that there is another pathway, phylogenetically older but equally, or even more, vital for physiologic motor functioning. This path, named the cortico-trunco-reticulo-propriospinal pathway, originates in the brainstem, where corticofugal fibers from motor areas reach it and descend within the gray matter of the brainstem and SC. These cells are joined by very short-range fibers that, once severed, can regrow and quickly reestablish a functional link. The GEMINI protocol exploits this fact. Using a minimally traumatic transection of the SC, this cellular network is left mostly unscathed and allows quick, functional reconnection.

GEMINI exploits the rapid application of special substances that act as Fusogens or Sealants (e.g., Polyethylene Glycol [PEG] and Chitosan) (reviewed in Ryan and Henderson[37]): The sealing affects the cells whose membranes were injured by the advancing scalpel, both neuronal, glial, and vascular; simultaneously, they fuse a certain number of long axons in the white matter (e.g., pyramidal tract, posterior columns). Animal studies in rodents, canines, primates, and swine from independent laboratories around the world confirmed that, even as a stand-alone strategy, fusogens could quickly lead to near complete recovery of sensori-motor function,[22,24,25,33] with the first signs visible within 48 h. Most relevantly, a comparison of all strategies adopted

in rodent models after full spinal transection proves that fusogens afford the best and fastest recovery of all, including stem cells, scaffolds, growth factors, gene therapy, and others.[34] Recently,[26] rabbits submitted to complete dorsal SC transection recovered from paralysis faster when a mixture of topical PEG-Chitosan was boosted with IV PEG 400 (20% solution/5 mL) immediately after the surgery and then once daily for 40 days: Basso-Beatty-Bresnahan (BBB) scores at 40 days were 12 versus 17 (controls: 1; normal: 20).

The final result is further accelerated by combined electrical stimulation (ES) of the SC overlying the fusion interface and the primary motor cortex (M1). This can be effected either invasively by positioning electrodes over MI and the SC or noninvasively by combining Transcranial Magnetic Stimulation of MI and simultaneous Trans Spinal Direct Current Stimulation. Protocols already exist.[8,43] ES also facilitates the excitation of propriospinal neurons: this approach supports the propagation of the voluntary command to the central pattern generators (i.e., the neuronal networks responsible for locomotion) at the cervical and lumbar levels.[4] Finally, prolonged electrical positivity during spinal shock hinders repair of the human SC: injecting negative charges is thus indicated to support recovery.[4] Importantly, peripheral motor axons deteriorate, often irreversibly, after SCI and may become completely inexcitable. A 6-week program of early, percutaneous peripheral nerve stimulation (TENS) over the median nerve at the wrist and common peroneal nerves around the fibular head helped conserve peripheral nerve function in the early phases of SCI and improved long-term outcomes of neurorehabilitation.[27] Similarly, ES accelerates nerve regeneration.

During SC, eye, and brain transplantation, cranial nerves and spinal roots will have to be reconnected. The olfactory nerve and the ON, unlike the other ten cranial nerves and the spinal roots, are considered to be extensions of the CNS because oligodendrocytes myelinate them, whereas the ten other cranial nerves and the spinal roots are myelinated by Schwann cells.[36]

As such, one would consider standard microsurgical suturing of these nerves as the preferred option. Unfortunately, as De Medinaceli, the surgeon who introduced the concept of cell surgery for the repair of peripheral nerves in the 1970s, noted: [16] "*The use of operating microscopes and microsurgical techniques has not fundamentally changed the prognosis of nerve injuries…exacting efforts of the surgeon are not always rewarded with good functional recovery while imperfect repairs and dubious coaptions oftentimes have satisfactory results…even in the best cases, recovery is seldom perfect.*" The reasons are multiple and the interested reader is referred to his monumental *opus magnum*.[16] Importantly, regenerated neurites after microsuturing do not regain normality; the caliber of the new fibers is generally smaller than normal, and their myelination is weaker. Moreover, by the time the new fibers reach the periphery, the target is usually modified: for instance, muscle atrophy begins almost immediately after nerve injury and worsens with time. However, as he wrote, "*In the case of sharply divided nerves without associated lesions, excellent surgical repair is theoretically possible. The truncated neurites in the proximal stump may be positioned properly, facing their former pathway in the distal stump with little interposition of debris. Sprout regeneration may take place with minimal branching and wrong-ways, and a large number of regenerated neurites may reach their appropriate targets.*" He thus developed methods to address these issues (reviewed in[16]). Most importantly, he wrote: "*…an injury to the nerve fiber produces an extraordinary situation, unique in biology, i.e., the cutting of a cell in two pieces. The divided segments survive, the proximal one indefinitely and the distal one for 1 or 2 days. This exceptional condition makes it possible to envision an exceptional treatment. Divided cells should be repaired by primary fusion of their fragments…this method represents the ideal treatment of nerve injuries.*"

Starting with Bittner's demonstration in 1986 that a severed axon can be refused with PEG, the promise of fusogens in restoring lost function after peripheral nerve section is becoming a clinical reality (reviewed in Bittner *et al*.[2]). Specifically, fusion technology exploits so-called fusogens, such as PEG and chitosan (reviewed in Ryan and Henderson[37]). *Within minutes*, successful PEG-fusion restores gross anatomical and electrophysiological continuity across severed nerves. At 6 weeks, many fused axons are morphologically similar to intact axons; that is, do not undergo Wallerian degeneration and remain connected to a nerve cell body. Survival of successfully PEG-fused axons leads to behavioral recovery starting at *3 days postoperatively* up to 1–4 weeks. This recovery is sustained over time. Not all axons undergo fusion, as this requires precise alignment, but those that do so are enough to ensure the return of function, also supported by CNS reorganization. Other forms of fusion include electrofusion and electroacoustic fusion.[4-6] Importantly, a custom-made circular-snare blade that first sections the tougher outer layer of a nerve and only then the axonal proper is a key to avoid crush damage of the axons to be fused [Figure 1].[4-6] Such technology is part and parcel of SC, eye, and brain transplantation.

SCT

As is well known, SCI is generally due to localized tissue disruption at C4–5 or T11–12; multilevel injuries are a distinct minority.[18] The lost function might thus be recovered by replacing the injured segment. The idea of replacing a damaged portion of the SC with a healthy one is not new. In 1905, Shirres reported his attempt to graft a segment of a healthy canine cord in a human paraplegic patient:

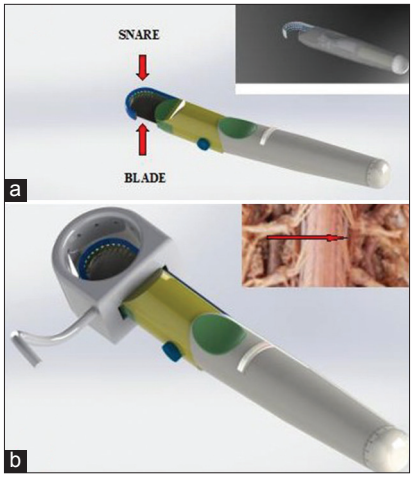

Figure 1: (a) The GEMIN-o-tome. (b) Site of spinal cord section (from ref,[5,7] with permission).

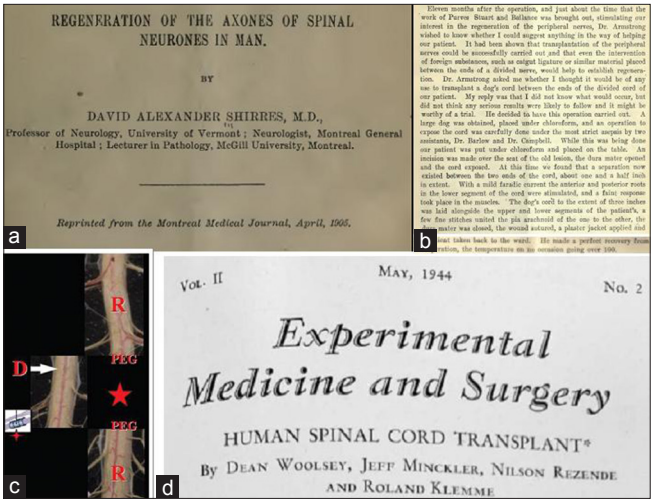

Figure 2: (a-b and d) The title pages of Shirres (1905) and Woolsey *et al.* (1944);[40,44] inset: Depiction of spinal cord transplantation. (c): Inset D: Donor R: Recipient; Arrow: Donor segment moved to fill the gap; Asterisk: After removal of damaged cord in recipient.

initial sensory recuperation was observed at 3 months, but the patient succumbed to infection; of relevance, autopsy showed clear signs of neuroregeneration.[40] This idea bred no further attempts until 40 years later. In 1944, Woolsey et al.[44] operated on a 16-year-old Black male with complete loss of sensorimotor function after he was shot in his right shoulder with the bullet reaching the superior border of T4. Following laminectomy, the injured SC was completely transected and replaced with a cadaveric SC (approximate length: 3 inches) that had been fixed in 10% formalin for 12 days and cleaned and sterilized with running and distilled water and 70% alcohol. No improvement in the patient's condition was noted, and the patient died almost 4 months after the surgery. The autopsy showed exceptional preservation of the transplanted graft, although with restricted regeneration and limited tissue reaction. The preservation was attributed to the preoperative use of formalin, and no explanations or related conclusions on the microscopic findings could be made [Figure 2]. In the XXI century, cord segments matching the injured patient's cord can be harvested from brain-dead organ donors (BDOD) at the same level, thereby matching the intrinsic anatomy of the damaged cord.[9] Actually, a BDOD's SC can service several patients at the same time (cervical, dorsal, and lumbar). A special instrument (GEMIN-o-tome) would allow for quick dissection.[4-6] Alternatively, many converging lines of evidence show that cadaveric neural tissue can be salvaged up to 6 h (and perhaps more) postmortem in human bodies.[10] This approach is a mere extension of current efforts aimed at harvesting organs (but also bone marrow) from circulatory-determined death donors (DCD), namely hyper-fresh cadavers. Cadaveric SC qualifies as a further extension of this contemporary paradigm (Canavero *et al.*[9]). Finally, the two ends of the graft would be exposed to GEMINI fusion. This would be followed by reconnection of the dorsal and ventral roots and revascularization of the transplanted segment (discussed in Canavero *et al.*[9]). As per other transplant procedures, immunosuppression is indicated, at least initially.

The feasibility of SCT has been confirmed recently. A Chinese group[20] transected the SC at T8 in rats with a #11 surgical blade and removed the T8–9 segment; bleeding was controlled with gelatin sponges. Simultaneously, a T8–9 allogenic segment was harvested from donor rats, rinsed in saline, dryed with a gelatin sponge, and then grafted into the gap; 40 µL of prefabricated collagen gel was slowly injected at the two stump interfaces. In a further group, collagen was mixed with NT-3 (1 µg), BDNF (1 µg), and VEGF (0.5 µg). At 12 weeks, mean BBB scores were 8 and <6 in controls. While clearly rats showed signs of recovery, the technology was not yet mature for SCT. Kim *et al.* (*unpublished observations, 2022*) [Figure 3] removed a segment of the dorsal cord in rats and inserted a segment of equal length harvested from a donor without revascularization or immunosuppression. At 18 postoperative days, rats treated with PEG 600 showed clear signs of motor recovery versus none in controls. Zhang *et al.*,[45], after confirming the feasibility in rats, submitted 24 female beagles to SCT. The recipient beagles were treated with oral tacrolimus (0.1 mg/kg/day) plus IM methylprednisolone (1.0 mg/kg/day) postsurgery. Donor SC tissue was harvested at T9–T11 levels, along with the radicular artery (RA), dorsal intercostal artery (DIA), and accompanying vein at the T10 level, serving as its vascular pedicle. The graft was enveloped in ice-cold saline-soaked gauze (hypothermic preservation). Simultaneously, longitudinal incisions were made in the skin and subcutaneous soft tissue at T9–T11, allowing for the exploration and exposure of the muscle perforators of the DIA at the T10 level within the paravertebral region on the

Figure 3: Fusogen-supported spinal cord transplantation in rats (credit: HEAVEN/GEMINI/Kim).

same side as the donor SC graft vascular pedicle. The vascular pedicle of the donor SC graft was meticulously anastomosed with the muscle perforator and the accompanying vein of the recipient DIA. After confirming blood flow in the donor SC graft, a T10 laminectomy was performed along with the lower edge of T9 and the upper edge of T11 of the recipient SC. A "H" shape incision was made in the dura mater, and a segment of SC tissue at the T10 level was excised with an extremely sharp knife to create a 1.5 cm SC defect. The length of the donor SC graft was appropriately tailored to match the extent of the SC defect, and it was meticulously bridged at both the distal and proximal ends of the recipient SC. 2 mL of PEG-600 (100%) was applied topically to the two contact interfaces of the SC after the transplantation. Antibiotic treatment and IV heparin (100 IU/kg/day) were administered postoperatively. In the experimental group, two beagles exhibited voluntary movement in the hind limb joints Canine BBB (cBBB 1) 12 days postsurgery. At 6 months, two beagles demonstrated frequent plantar stepping and consistent forelimbs-hindlimbs coordination, scoring 14. The average cBBB score for beagles in the experimental group was 10.63 at 6 months (versus 0 in controls). A significant disparity ($P < 0.05$) in cBBB scores between the experimental and control groups was noted from day 22 postsurgery. Electrophysiology and neuroimaging confirmed restoration of anatomo-electrical continuity.

However, this study has several shortcomings. First, the time to revascularize the transplanted segment was 2 h, during which ischemia exerts deleterious effects. Although extreme damage is seen at 4 h, 2 h is still excessive.[1] Ischemia-reperfusion damage would have added further insult, as no therapy was instituted. Second, after removal, the neural elements at the sectional interface undergo a degenerative process within minutes, which would compromise the fusion process: as suggested elsewhere,[3-5] nerve structures must be excised beyond the point of final fusion and then trimmed back at the moment of fusion so that the neural interface is pristine. This was not done. Third, direct application of ice-cold saline can, in fact, be insufficient to neuroprotect the cord. A superselective injection of cooled saline through spinal angiography would have been much more effective. Fourth, while it is true that tacrolimus has neuroprotective properties, only a comparative study with other immunosuppressants would have helped in selecting the correct regimen; moreover, it is well known that tacrolimus may be toxic on both the ON and the retina, while cyclosporine has rare ophthalmic toxicity.[47]

In light of these data, a human trial of SCT incorporating the above suggestions is warranted. Actually, over the past few decades, attempts have been made to remove the damaged segment of the cord and replace it with segments of peripheral nerves, e.g., the sural nerve, both in animals and men, with some level of recovery. However, it was only with the deployment of fusogens that a recent study in swine led to remarkable motor recovery in animals[31] and humans[35] treated with excision of the injured level and insertion of segments of the sural nerve along with PEG. Nonetheless, only a healthy segment of cord properly fused and reconnected can afford full restoration of sensory, motor, sexual, and sphincter functions.

EYE TRANSPLANTATION

On May 27, 2023, a human eye transplantation took place as part of a facial transplant.[12] However, the optic and other cranial nerves were not functionally reconnected, and the patient did reacquire neither his sight nor eye motility.

The combined whole eye and face transplant procedure commenced with donor and recipient surgical procedures performed simultaneously in adjacent operating rooms. Induction immunosuppression was initiated with thymoglobulin and rituximab. Among other steps, the left-sided vascular dissection in the donor also included harvesting a long anterior branch of the superficial temporal artery and vein in continuity with the left external carotid and internal jugular vascular system. This was followed by entry into the cranial vault and orbital dissection with identification of the ophthalmic artery, internal carotid artery, ophthalmic veins, and the motor nerves to the extraocular muscles. The ON was dissected all the way back to the optic chiasm, where it was divided. The origins of the ophthalmic artery and superior ophthalmic vein were then each divided and anastomosed to the left superficial temporal artery and vein, respectively. Significant back bleeding from the divided ophthalmic artery end, which was attached to the eye, suggested significant collateral flow and, hence, oxygenation to the retina, likely from branches of the facial artery. Total warm ischemia time (or low flow) from division to completion of the anastomosis

was 25 min. Robust perfusion of the anterior and posterior tissues of the allograft, including the globe, was confirmed. The allograft anastomosis of the superficial temporal artery to the ophthalmic artery was intact. Concurrently, after isolation of the recipient vessels for allograft anastomosis and resection of craniofacial bone, the orbit of the recipient was debrided of scarred tissue, and the intraorbital ON end was identified and dissected free up to the optic canal. The allograft was then brought into the recipient field, followed by bony fixation of the geniotomy segment and coaptation of the ON ends with interrupted 8–0 nylon epineural sutures through the nerve sheath. Prior traumatic injury, subsequent enucleation, and resultant scar precluded precise fascicular alignment to the recipient ON end. Previously processed donor-derived CD34+ enriched bone marrow stem/progenitor fraction was then directly injected into the ON epineurium proximal and distal to the coaptation as a neuroprotectant. The allograft was then revascularized, and the remainder of the allograft components were attached to the recipient in a standard fashion. Total cold ischemia time for the facial allograft (and of the retina) was 2 h 59 min, with a total operative time of approximately 21 h. Postoperative maintenance immunosuppression consisted of standard triple therapy with tacrolimus, mycophenolate mofetil, and prednisone with infectious prophylaxis.

In reality, this cannot be construed as the first true human eye transplantation but more like a surgical experiment, as the nerves were not functionally reconnected. Actually, the first such experiment took place in Paris on May 5, 1885, when Chibret transplanted a rabbit eye to a young girl who had lost her left eye. No return of sight was mentioned.[13] Ever since, a large number of eye transplantations in mammals have been reported, and eye viability and retinal function in the perfused eyes have been confirmed (e.g.[38]). However, ON regeneration has not been achieved yet, although we know that the best results are seen when the ON is sectioned intracranially rather than intraorbitally. We also know that the ischemia time has to be <30 min before irreparable damage to the retina ensues.

In 1992, one of us (SC) published a cadaveric-based protocol for whole eye transplantation that also included the tubulization of the ON stump with segments of the sural nerve to boost Schwann cell-enabled growth and avoid shrinkage, infusion of growth factors through a minipump directly into the tubular guide and ES through embedded wires attached to an external battery.[11] Very recently, a graft of sural nerve has been employed to fill a gap of the rabbit ON, with promising results.[39]

That early work has been recently expanded with cadaveric rehearsals by another group[14,15] [Figure 4]. It is worth repeating the procedure which is very similar to the proposed decades ago.[11] As they write, "*donor procurement requires combined transorbital, endonasal, and transcranial approaches to allow for 360° decompression of the bony structure of the orbit and orbital apex. First, endonasal resection of middle turbinate, maxillary enterostomy, total ethmoidectomy, and bilateral sphenoidotomy are performed to gain access to the medial and inferior orbit, orbital apex, and canalicular segment of the ON. Then, a small posterior septectomy is created to allow for binarial access. The lamina papyracea and medial orbital floor, orbital apex, and bony optic canal are decompressed, keeping the periorbita intact. An endoscopic endonasal transplanum approach is performed to gain access to the optic chiasm, ophthalmic artery, and carotid artery. Initially, the dura is preserved to minimize the duration of the associated Cerebrospinal fluid (CSF) leak during the procedure. Subsequently, with a coronal incision, the temporalis is reflected and an extended pterional craniotomy is made. Extradural dissection of the anterior and middle cranial fossae provides access for the removal of the orbital roof and lateral orbital wall. After transection of the meningo-orbital band, the superior orbital fissure and lateral wall of the cavernous sinus are exposed. The roof of the optic canal is drilled out all the way to the medial wall where the dura had been previously exposed from the endonasal approach. The anterior clinoid process is removed to provide access to the lateral optic canal. At this point, the frontotemporal dura is opened in a curvilinear fashion. The ON and internal carotid artery are identified after opening the opticocarotid cistern. Transorbital exenteration is then performed to include globe, muscles, fat, suspensory ligaments, and trochlea within the periosteum of the orbit. The lateral orbital apex is decompressed, the superior orbital vein is identified and preserved, and the canthal tendons are disarticulated on each side. Next, the dura of the planum sphenoidale is opened to the suprasellar cistern endonasally. The optic chiasm, medial ON, ophthalmic artery, and carotid artery are identified. The medial dural ring of the medial clinoid is incised to allow separation of the ON from the internal carotid artery. Returning transcranially, the ON is followed posteriorly and transected before it reaches the optic chiasm. The oculomotor nerve is identified at its entrance into the oculomotor triangle of the cavernous sinus; the oculomotor triangle dura is opened to expose the oculomotor nerve traveling at the roof of the cavernous sinus; the transection of the nerve is completed before entering the triangle to maximize its length. Similarly, the trochlear nerve is sectioned at its cisternal segment before entering the cavernous sinus, the ophthalmic nerve is transected right after the trigeminal ganglion as it enters the cavernous sinus, and the abducens nerve is sectioned at the distal Dorello canal. The ophthalmic artery is not transected, but the internal carotid artery is ligated proximally at the paraclival-petrous segment and distally at the supraclinoidal segment just before the origin of the posterior communicating artery. Finally, en bloc mobilization of the cavernous sinus and superior orbital fissure, along with the*

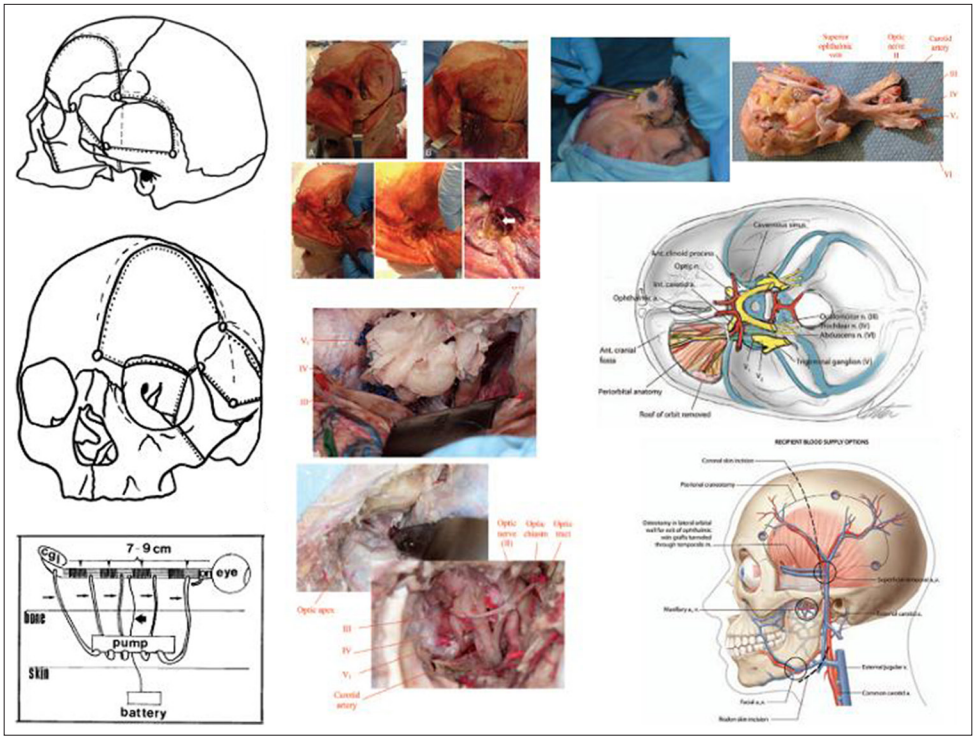

Figure 4: Eye transplantation. Surgical approach (left panels: From ref[11]) and cadaveric rehearsal (right panels: From refs[14,15]).

orbital apex and full globe-periorbita-orbital contents, are obtained to deliver the donor specimen. A similar approach is utilized in the recipient, with combined transorbital, endonasal, and transcranial orbital apex decompression and exenteration, such that cranial nerves III, IV, V1, and VI are isolated at the entrance into the cavernous sinus, and the ON is isolated at the cisternal space before joining the chiasm. Similarly, the ophthalmic artery is not directly ligated, but the carotid artery is isolated proximal and distal to the ophthalmic artery origin. The recipient procedure thereafter requires the harvesting of vein grafts for both arterial and venous anastomoses, recipient vessel exposure, inset of donor tissue, arterial and venous anastomoses, and sequential coaptation of cranial nerves. Candidate recipient vessels exposed include (1) the superficial temporal artery and vein (however, their small caliber creates a size mismatch), (2) the internal maxillary artery exposed by the coronal incision and turndown of the temporalis muscle with an extended lateral orbitotomy approach as in middle cerebral artery bypass (however, even then, the artery is positioned deep, rendering anastomosis technically challenging and the accompanying venous plexus here is not amenable to venous anastomosis and thus would require exposure of a vein at another site), (3) the facial artery and vein exposed through a Risdon submandibular incision (however, they require long vein grafts). Anyway, vein grafts from recipient facial vessels are tunneled through the temporalis. All candidate recipient vessels would require vein grafting to provide sufficient length for anastomosis to the donor pedicle. Vein graft anastomoses to recipient artery and vein are performed before insertion of donor tissue, which is secured with 3–0 permanent Prolene sutures parachuted into drill holes in four orbital quadrants. Arterial anastomosis is then performed from vein grafted recipient vessel to donor carotid artery transcranially using standard microsurgical techniques with 9–0 Ethilon sutures. Similarly, venous anastomosis to the donor superior ophthalmic vein is performed transcranially using standard microsurgical techniques with 9–0 Ethilon sutures. Then, sequential coaptation of cranial nerves from deep to superficial (cranial nerves VI, V1, IV, III, and II) is performed. Finally, the bone graft is replaced, the temporalis resuspended, and the coronal incision closed. Endoscopic endonasal nasoseptal flap repair of the skull base can then aid in CSF leak prevention. Notably, mean donor ophthalmic artery pedicle length and caliber were 13.5 ± 0.5 and 1± 0.04 mm, respectively; however, with a stem of paraclival internal carotid artery, these values can be increased to 33 ± 1.6 and 3 ± 0.2 mm. Mean ON was 25 ± 1.5 mm from the orbital apex to the annulus of Zinn and 14 ± 0.4 mm from the annulus of Zinn to the optic chiasm, essentially 14 mm of mobile pedicle. Similarly, cranial nerves III to VI had mobile pedicle lengths of 10–14 mm. In sum, recipient internal maxillary and facial artery were the closest size match to donor ophthalmic artery with supraclinoidal carotid artery origin. The internal maxillary artery required the shortest vein graft but had no accompanying usable vein

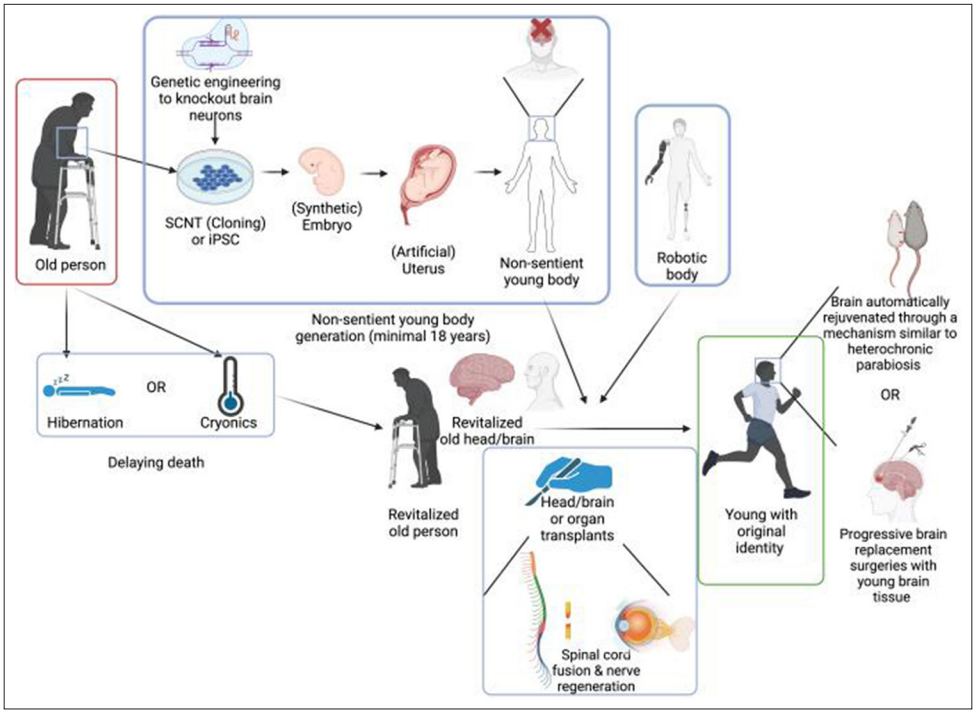

Figure 5: A plan to achieve extreme rejuvenation by combining brain transplantation, cloning, heterochronic parabiosis, and progressive brain replacement (credit: PERSEUS project).

for venous anastomosis. Facial vessels required the longest vein grafts. Superficial temporal vessels were the smallest in caliber. Of note, the extended pterional craniotomy allows for considerable access to coapt the cranial nerves; given its deeper anatomical location, the abducens nerve must first be coapted, followed sequentially by cranial nerves V1, IV, III, and II working deep to superficial. Finally the timings in donor cadavers is ca 3 h (cranial nerve coaptation being about 1 h) and a little more in recipients."

In conclusion, eye transplantation is surgically feasible. Coaptation of the cranial nerves is carried out as discussed earlier in this article.

CONCLUSION

It is clear from the above discussion that both SC and eye transplantation represent the low hanging fruit of nerve fusion waiting for someone to start a clinical trial. The surgical approaches are clear. As regards cranial nerves and nerve roots, microsuturing remains burdensome and, as De Medinaceli so poignantly wrote, suboptimal. Instead, recent work shows that nerve fusion can be effected successfully by simple approximation with just two epineural sutures.[41] Alternatively, Photochemical Tissue Bonding is a very quick way to approximate a nerve and does not interfere with fusion.[7]

Brain transplantation[6,7] has been the Holy Grail of every neurosurgeon since the start of this specialty. But why would anyone consider such exacting surgery? In the XXI century, thanks in large part to the efforts of Aubrey DeGrey, a new field has emerged: longevity science.[23] Current efforts to expand the human lifespan have yet to deliver on their promises and extreme rejuvenation is still out of reach. At the same time, the cloning of primates has become a reality.[28,29] This would allow the transfer of an elderly brain into the younger cloned body, making sure that a nonsentient clone is the actual body donor. At that point, heterochronic parabiosis, with young blood flowing 24/7 into the old brain[5] initially and progressive brain replacement later on[21], is potentially well placed to rejuvenate the brain [Figure 5]. Equally relevant, it has become clear that outer space is toxic to the human body (e.g., Tomsia *et al.*[42]). Transplanting the brains of future space colonizers whose bodies have been ravaged by a combination of cosmic radiation and the absence or reduced gravity on their healthy clones could offer a potential therapeutic option.

As the father of astronautics, Konstantin Ėduardovič Tsiolkovsky (1857–1935), once said, "*The impossible today will be the possible of tomorrow.*" For transplantation neurosurgery, the future is now.

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