Is it time to perform the first human head transplant? Comment on the CSA (cephalosomatic anastomosis) paper by Ren, Canavero, and colleagues

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In November 2017, SNI published another article in the series of scientific papers on basic science studies leading to the first transplant of a Human Head to a donor body (CSA) by an international team of scientists led by Ren and Canavero. The latest paper was on the trial using cadavers to perfect the details of the complex surgical transplant procedure to be performed in the future.[21]

The reasons to perform such a healthy head transplant to a healthy body was well described by Ren et al.[22]

“Composite tissue allo-transplantation (CTA) involves the grafting of limbs or other complex tissues from an unrelated donor and recipient. In the 1990s, animal studies helped to pave the way for the first successful human hand transplantation in United States, which was performed at the University of Louisville and Christine M. Kleinert Institute for Hand and Microsurgery in 1999. This patient recovered fully, and continues to work and lead a normal social life. Studies in small animals and a porcine model allowed for optimization of the immunosuppressive regimen, as well as a system for characterizing the degree of immune rejection of transplanted tissues. Facial tissue transplantation has also become a clinical reality, and worldwide there have been more than 100 completed cases of the CTA operation. However, there is no effective way to save a surviving healthy mind when there is critical organ failure in the body, such as complete cervical spinal cord injury with paraplegia, tumor metastatic disease, hereditary body muscle atrophy, and others.”[22]

There are three major parts of this CTA, head to body transplant, that represent the significant components of this transplantation of a human head from one person to the body of a second person (1) reconnection of a severed spinal cord to produce a functional outcome; (2) the actual steps in a complex surgical procedure to complete the transplantation; (3) the potential transplant rejection. The work on these steps will be discussed in the following paragraphs.

Reconnection of a severed spinal cord
It is generally believed by almost all neuroscientists that a severed spinal cord cannot be reconnected to yield a functional recovery below the severed level.[2,5,7] Many attempts using various biological combinations have been tried without success.[5,7] However, this long held viewpoint has been found not to be true based on historical observations and the experimental work of Canavero, Ren, and their colleagues worldwide and the observations of others.[3,5,7]

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Early evidence for spinal cord repair in humans and animals

In their in-depth review of the literature on spinal cord repair, Canavero and Ren describe two case reports in the literature from 2005 and 2014.

In the first case, “a 24-year-old woman sustained a traumatic spinal cord injury and transection at T6-T7. After 39 months as a paraplegic with no motor or sensory activity below the level of the injury, Goldsmith removed the scarred portion of the spinal cords proximal and distal leaving a 4-cm gap. He then placed a collagen bridge between the two spinal cord segments and placed an omentum pedicle to cover the operative site of the severed spinal cord and collagen bridge. At 6 months, the patient could move her legs on command, and in 4 years she was able to walk long distances.” There was no detailed independent neurological examination of her status at 4 years to evaluate the extent of the patient’s recovery. But, the fact that she regained function after being paraplegic for 39 months is remarkable. I know Dr. Goldsmith personally and believe he is a credible surgeon and observer.[5]

In a second case, a 38-year-old man sustained a traumatic transection of his spinal cord at T9. “Using one of the patient’s olfactory bulbs, a cell culture containing olfactory ensheathing cells and olfactory nerve fibroblasts was developed. After operative resection of the glial scar in the patient’s spinal cord, the cultured cells were transplanted into the spinal cord stumps above and below the site of injury, and the 10-mm gap between the stumps of the spinal cord was bridged with 4 strips of autologous sural nerve.” After 19 months of rehabilitation, the patient had partial recovery of voluntary movements and superficial and deep sensation below the level of the spinal cord transection.[5]

Canavero and Ren describe the work of Freeman who in the 1950s and 60s sharply transected the spinal cords of rats and dogs and then re-approximating them. The animals re-established function below the transection site, which could be seen in 7–14 months after the operation. Electrical activity and nerve growth across the repaired site was seen and recorded.[5]

Two neuronal systems that regulate sensory and motor behavior

The pyramidal tract and the Cortico-trunco-reticulo-propriospinal pathway (CTRPS)

How could this spinal cord recovery in man and animals be explained in view of the belief in the scientific community that the long fiber tracts, which course from the brain’s cortex to the spinal cord, cannot re-grow across a severed cord?

In a detailed explanation, Canavero cites known evidence that there are two sets of fiber tracts from the brain to the spinal cord that regulate voluntary function of the extremities. The first system is a multisynaptic pathway from the brain to the spinal cord that connects many neurons in sequence over short segments from the brain cortex to the spinal cord to provide movement to the extremities. This is the remnant of the primitive spinal cord system in lower species, as worms or centipedes, which have a segmental nervous system. However, as the species evolved, a faster conducting system, consisting of long fast signal transmitting neurons connecting the brain cortex nerve cells to the spinal cord nerve cells allowed for rapid transmission of volitional signals. This long fiber tract is called the pyramidal tract. When the spinal cord is transected, the long neuron tracts, which are cut, are slow to recover because the re-growth of the nerve must be from the brain to the spinal cord. However, with the short multineuron pathway that travels short segments from the brain to the spinal cord, the short neurons can quickly re-grow and establish connections to the spinal segment below the transection re-establishing the multineuronal pathway that controls movement and sensation. This multi-synaptic motor system, called the Cortico-trunco-reticulo-propriospinal pathway (CTRPS), re-establishes the integrity of this duplicate motor system to allow voluntary movement of the extremities to occur.[3,5,20]

How to get neurons to grow across the severed cord ends

Fusogens / Sealants

With the evidence from animals and humans that the spinal cord could indeed be repaired, Canavero and Ren believed it was important to speed up the repair process in the severed spinal cord. It was important to improve the rate of growth of the short nerves across the sectioned spinal cord so that motor and sensory function can occur more quickly. Numerous molecular agents have been tested in different models of acute and chronic spinal cord injury. They include Chitosan nanospheres, PEG-polyethylene glycol biopolymer matrix, IKVAV membrane spanning peptide, and olfactory mucosa autograft. All were used in different chronic cord injury models, and neuronal growth occurred with all. PEG was used more commonly and allowed nerve growth to occur before scar formation. None have been compared with each other. Canavero and Ren used the PEG fusogens to accomplish the goal of fusion of sharply cut spinal cord ends that would have less tissue damage.[3,5,7]

Properties of Fusogens

“Fusogens/sealants, are molecules that can reconstitute the integrity of the neural membranes and nerve fibers and restore electrophysiologic conduction when applied to the cut spinal cord ends shortly after severance. Fusogens were discovered in 1986 but were not used in medicine until these spinal cord fusion experiments. Fusogens allowed nerve axon growth to occur at 1 week post treatment. This growth increased steadily over time, and was long
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Critical time for fusogens to act
However, time is critical in allowing this fusion to happen. As Canavero and Ren state, “The ends of the transected spinal axons remain stable for only about 10–20 minutes before they undergo fragmentation (the first step before classic Wallerian degeneration, or dieback) at both cut ends of the spinal cord or nerve. These cut cells and neurons span 0.3 mm, only to stabilize and persist for 3–7 days; about 30% of proximal axons then start regrowing within 6–24 hours. Thus, the fusogens must be brought into the site of anastomosis within minutes (certainly <10 minutes). As for the axons that do not get re-fused, dieback is on average 0.5–2.5 mm in rat models and is short-lived (1 month). Considering a 1 mm/day regrowth rate, even these axons would reach the point of section within 3 days (with the minority, within 3 weeks).”[3,5,7]

Electrical stimulation to accelerate nerve growth
A final step in promoting a faster spinal cord fusion process is the use of electrical stimulation of the spinal cord.

Electrical stimulation of the spinal cord and peripheral nerves has been found to accelerate nerve growth in animals and is used in the fusion process.[3,4,7]

Now the stage was set for the judicious use of animals to prove that spinal cord repair can be achieved before its use in humans.

Experiments reconnecting the sharply severed spinal cords of animals-acute spinal cord injury
In a series of experiments in mice,[15] rats,[16] and a dog,[11] first reported in SNI, the spinal cords of these animals were sharply transected in the cervical region and then re-approximated with the fusogen, PEG, in the interface between the transected upper and lower cords. The animals regained their function within 24 hours and improved over 4 weeks of observation. The videos accompanying these papers show the animals regaining function.[13,15,16]

In the mouse experiment performed by Kim et al. in Korea, fusogens (PEG) were not used in the control animals but were used in the treated group. In the 5 control animals, there was some recovery of function after 2 weeks. The PEG-fusogen treated mice recovered some function in 24 hours and moved all four limbs in 4 weeks after the surgery, indicating that the fusogens allowed faster recovery and likely growth of neurons.[15]

In another experiment by Kim et al. using rats, PEG–GNR was used as the fusogen scaffolding for nerve fiber growth. Somatosensory evoked potentials (SSEP) were recorded from the scalp after stimulation of the sciatic nerve as a measure of electrical transmission across the severed spinal cord. In all 5 of the PEG–GNR treated rats, the SSEPs were recorded 24 hours after the surgery indicating a transmission of electrical stimulus from the sciatic nerve to the rat cortex. None of the 5 control animals, which had saline instead of a fusogen at the site of spinal cord section, showed any SSEPs. Because 4 of the treated rats died in an unexpected laboratory flooding, long-term assessment of recovery of function was only possible in one rat. In that animal, there were steady signs of functional recovery after 24 hours with the rat being able to stand and walk in 2 weeks. This was a remarkable achievement in spinal cord injury research.[16]

Kim also reported recovery of function from spinal cord transection in 7 more rats using PEG in 2016.[14]

Kim et al. sectioned the spinal cord of a dog nearly completely and re-approximated the cut ends in a PEG solution so that the ends were touching. The animal was followed with videos of its function twice a week. The dog recovered at least 90% of his normal function by 3 weeks postsurgery. No further experiments were conducted on the dog.[15]

Ren and colleagues reported on a more detailed experiment in another set of rats in China.

Using 15 rats with 6 as controls, the scientists used a specially designed sapphire knife to make a sharp cut at the T10 spinal cord level that produced a minimum of cell and fiber damage. The control animals had saline placed in the cut area while the 9 treated animals were given a PEG fusogen mixture between the cut ends of the spinal cord. “After 4 weeks, the treated group had recovered ambulation vs. none in the control group “…All animals were studied with SSEP [measuring an electrical impulse that travelled from the leg though the sectioned spinal cord level to the sensory cortex recorded from the scalp of the rat-Ed] …” The SSEP recovered postoperatively only in the PEG-treated rats, indicating the recovery of electric conduction across the treated spinal cords. Using magnetic resonance imaging technique which demonstrates nerve fiber tracts, called diffusion tensor imaging (DTI), the
DTIs showed disappearance of the transection gap in the treated animals vs. an enduring gap in the controls. “On qualitative visual inspection, the extent of re-growth of the imaged nerve fibers correlated with behavioral recovery, with near-normal rats with a more normal fiber pattern vs. no or little change in controls.”[20]

In the Discussion section of the paper, the authors continue, “The minimally disruptive (nanometers) severance of the cord [by the sapphire knife] damages a very thin layer of these inter-neurons: PEG reseals their membranes and curbs cell death. These same cells, along with others in proximity, which were not damaged by the extra-sharp blade, can immediately re-grow (sprout) their appendages and reestablish contact between the apposed interfaces. Consequently, the gray matter neuropil is restored by spontaneous re-growth of the severed axons/dendrites over very short distances at the point of contact between the apposed cords” [These conclusions-Ed] “were recently suggested by an immuno-histochemical study of PEG-treated mice submitted to 100% cervical transection” by Kim et al. on their mouse experiment tested groups which showed axonal growth across the severed part of the cord.[17]

In communication with Canavero, he reports that the same observations that are described above in the mouse, rat, and dog using PEG have been duplicated in the primate. Ren and colleagues will report in the journal Surgery a recent randomized controlled study in dogs comparing control animals with T10 sectioned spinal cords with dogs having PEG-treated T10 sectioned spinal cords. Most of the motor recovery occurred in the PEG treated dogs after 60 days compared with no recovery in the control dogs. The work was further enhanced with evidence of electrical conduction across the severed cord in the treated dogs and DTI evidence of nerve fiber growth across the severed cords compared with none in the control animals. These observations will expand the success of spinal cord fusion to higher order mammals. We await the publication of the primate studies in this singularly important landmark research. For information, the observations of spinal cord repair recorded in human case reports are not as thoroughly investigated as the animal models.

Finally, in this superbly conceived and executed experiment in rats (and now dogs) the authors concluded, “We show for the first time, in an adequately powered study, that the paralysis attendant to a acute complete transection of the spinal cord can be reversed. This opens the path to a severance-reapposition cure of spinal paralysis…”[20]

Perfection of the surgical transplant procedure

As the next step toward CSA, Ren and Canavero wanted to perfect the technical aspects of the CSA in cadavers before the actual human trial. This concept is the substance of their most recent paper published in SNI.[21] The appropriate consents were obtained in the country of China and the deceased patients families. Working at Harbin University in China, Ren and Canavero assembled a team of scientists and surgeons who worked to develop the plan for the transfer of a cadaver head to a second cadaver patient’s body in a trial run of the actual live human operation. This report by Ren and colleagues and Canavero is the first publication of that work of a human CSA.[21] The experiment was a trial for perfection of the techniques that will be used in an actual human CSA in the future.

The paper on CephaloSomatic Ansatomosis (CSA)[21] was the product of a combined team effort of many specialists and others. Many experiments were unreported and were conducted in animals and cadavers to answer all the technical questions posed by this huge experimental project before the first cadaver surgical CSA was performed. Most of these experiments dealt with choosing the proper routes to the various surgical targets in the transplant, which were to be carried out simultaneously in two cadavers by multiple teams of surgeons.

I will not detail the various aspects of the procedure but will highlight some. For a complete understanding of how the investigators have planned and performed this operation, I refer the reader to the actual paper.

In an operative approach that included many standard operations that are done around the world from spine surgery, to trachea[19,27] and esophagus repair, and including vascular reanastomosis, the surgeons developed an extremely clever operative plan to achieve the removal of the head from the first cadaver and then to attach the recipient cadaver’s head to the donor cadaver’s body in a complex operation using multiple teams of surgeons. According to the authors, more steps will be necessary to perfect the procedures in CSA in cadavers before the first CSA can be performed in the live patient. This undertaking has all the aspects of a well-planned surgical approach.

To ensure that the patient will be able to talk after the head transplant, his head and cervical spine to C3 will be removed from his diseased body. However, the entire trachea and its recurrent laryngeal nerve supply will be transplanted with the patient’s head so that the patient’s speech, or phonations, can be obtained after the procedure. Hopefully, the scientists will be able to communicate with the patient as he experiences recovery from the transplantation.

The patient’s head will be cooled by hypothermia during the surgery to preserve brain function at the time of transfer. The circulation between the donor body and the recipient head will be established initially along with external carotid vertebral ansatomoses to limit the
The subject of personality change

The crucial step, taken from the experimental work outlined previously above, will be the re-fusion of the two spinal cords. The donor and recipient bodies will be in the sitting positions. The donor body’s spine will be fused with instrumentation from in front early on in the procedure on the donor body. Posteriorly, lateral mass screws will be placed in the donor cervical and recipient cervical laminae so that an immediate posterior instrumented fusion will be ready for fusion of the recipient head and donor body cervical vertebrae. A specially designed lift that will take the recipient head and move it to the donor body for the fusion of the cervical vertebrae and spinal cords has been developed. The next immediate need will be to sharply cut and fuse the spinal cords in bath of PEG achieving a time limit of less than 20 minutes for the fusion of the spinal cords to be achieved from the time the recipient head was detached from its body and transferred to the donor body. The fusion site will be encased in a vacuum apparatus containing the PEG. The negative pressure will keep the cord ends apposed. This work has been validated in animal models. An electrical grid will be placed across the fusion site to provide the electrical current to promote the nerve growth also, another aspect of the procedure that was worked out in animals. The goal is to provide maximum stability without motion to the fusion site so that a successful fusion can proceed. The vagus nerve end will be anastomosed to the donor vagus using the fusogen techniques described above and in the literature. Transplantation of tracheal parts between the donor and recipient has already been reported in the literature during tracheal repair surgery. The remaining closure of the incisions and surgical sites will complete the procedure. Many more aspects of this challenging feat are presented in the Discussion of the paper.

Composite tissue allo-transplantation experience

Relating to the allo-head and body transplantation

Ren has stated, “There is no effective way to save a surviving healthy mind when there is critical organ failure in the body. The next frontier in CTA (composite tissue allo-transplantation) is allo-head and body reconstruction (AHBR), and just as animal models were key in the development of CTA, they will be crucial in establishing the procedures of AHBR for clinical translation.”

Transplantation of organs, or solid organ transplantation (SOT), is practiced around the world. Kidney, heart, pancreas, intestine, lung, and liver transplantation are well known SOTs and practiced successfully. SOT is performed when organ failure threatens survival. SOT success is based on the functioning of the organ transplanted.

In almost three decades, we have seen transplantation of hands and facial tissue. This reconstructive transplantation (RT) is performed in physically healthy individuals except for the defect in the body part that is affected. The reasons for the RT become complicated with psychological and other factors and may not be life threatening but are related to quality of life. According to Hautz et al., an in-depth psychological assessment including the patient’s coping mechanisms need to be explored. Side-effects of immunosuppressants, metabolic complications, infections, and tissue rejections occur with RT. “The question whether risks associated with indefinite immuno-suppressive treatment are justified for a non-lifesaving procedure in an otherwise physically uncompromised patient still remains unanswered. [The body of the recipient head in this case is significantly compromised-Ed]. While the risks must be weighed against psychological and social benefits, individual outcomes differ significantly and make conclusions and generalizations difficult. In contrast to SOT, decision making in RT, therefore, remains more on an individual basis, and careful patient selection, comprehensive patient information, and an individualized approach seem most suitable currently.”

The subject of personality change in accepting a new body and in treating central pain if it should occur have also been addressed by the authors. The literature indicates that the SOT transplantations are successful in more than 50% of the cases depending upon the organ and recipient. The results are improving with knowledge of the immunologic resistance. Hands have been successfully transplanted for 10 years, but still with RT there is a 60% success rate on a smaller total number of cases than have undergone SOT.

Harbin Medical University (HMU) in Harbin China, where the CSA will be done by Ren and Canavero and the team of doctors, according to Wikipedia, is known for its excellence in allogeneic organ transplantation. “Allogeneic organ transplantation is a specialty of HMU. Allogeneic spleen transplantation, allogeneic both-hands transplantation, and allogeneic single-forearm transplantation have reached international renown. Patients who receive allogeneic heart transplantation go on to enjoy the best life quality in Asia.” At Harbin Medical University there exists a team of people apparently well qualified to do CSA transplantation.

CONCLUSION

It appears to me, after reviewing the extensive literature surrounding the fusion of the spinal cords the transplant of the recipient head to a donor body and the problems faced with transplant rejection, that the authors and their multinational team of basic and clinical scientists...
have done a superb job of establishing the foundation for this operation to proceed. It would be important to the worldwide audience to read the reports of the primate work they and others have done to complete the scope of the project. It would also be important for scientists to read the literature quoted in this review and the CSA paper[21] to gain a personal understanding of this important work.

In my opinion, this body of work represents a quantum leap in medical science in which many hypotheses in regard to spinal cord repair, including the use of fusogens to enable faster spinal cord recovery, the chance to offer paralyzed patients hope that they can regain recovery of their inactive limbs, the ability to grant a patient suffering from a terrible disability of the body to have a new body that hopefully should function, to maintain a functioning human brain under hypothermia, and other hypotheses can be proven. Without the observations of many in medical history and the ability to test these hypotheses thoughtfully in animals, none of these advances with potential benefit to thousands of people worldwide would have been possible. Also, I would expect challenging issues to be uncovered that will take more creativity to resolve.

As Ren and Canavero have stated:

“There is no effective way in which to save a survival healthy mind when there is critical organ failure in the body, such as complete cervical spinal cord injury with paraplegia, tumors and metastatic disease, hereditary body muscle atrophy, and others... The next frontier in CTA is allo-head and body reconstruction (AHBR), and just as animal models were key in the development of CTA, they will be crucial in establishing the procedures of AHBR for clinical translation.”[22]

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