

STEM CELLS AND THEIR POSSIBILITIES IN THE TREATMENT OF FELINE  
CHRONIC RENAL FAILURE

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**PASS WITH DISTINCTION**

RESEARCH PAPER

BASED ON

PATHOLOGY LECTURES

AT VET-MEDLINK 2008

## ABSTRACT

Chronic Renal Failure (CRF) is one of the most common conditions diagnosed in elderly cats. However, it is also very difficult to manage and control, often leading to a slow decline in the cat's health and sometimes euthanasia if diagnosed too late, which can be distressing for both the pet and the owner. There is no absolute cure for the condition, so treatment is generally aimed at reducing symptoms and prolonging the cat's life. In this paper, I have discussed the topical issue of stem cells and how this developing technology can be applied to treating CRF, involving the regeneration of kidney tissues from undifferentiated stem cells as an alternative to existing drugs and transplant therapies.

## INTRODUCTION

A definition of stem cells from Biology-Online.org states that a stem cell is '(1) An unspecialized cell characterized by the ability to self-renew by mitosis while in undifferentiated state, and the capacity to give rise to various differentiated cell types by cell differentiation, or (2) A cell that has not yet acquired a special function.' This means they have the ability to become any type of cell in the body, given the correct signals, making them one of the most exciting discoveries in science and medicine in recent years. One of the biggest aims of current research is to identify these 'signals' and replicate them, in order to be able to control differentiation and unlock the massive potential of stem cells. The theoretical uses of these cells range from transplanting organs with minimal rejection risks to curing diseases such as Parkinson's Disease using stem cells to generate new dopamine-producing neurons in the brain.

The first mention of stem cells is attributed to a Russian histologist Alexander Maksimov in 1908, who proposed the existence of haematopoietic stem cells (pluripotent stem cells which can differentiate into any type of blood cell) at a meeting of a haematological society in Berlin. Scientists also began to consider bone marrow transplants, having discovered that mice with defective bone marrow could regain health with transfusions from other mice. Canadian scientists Ernest McCulloch and James Till proved the existence of these stem cells in 1963. They published many papers, including 'A direct measurement of the radiation sensitivity of normal mouse bone marrow cells.' (1961) and 'Cytological demonstration of the clonal nature of spleen colonies derived from transplanted mouse marrow cells.' (1963). They injected bone marrow cells into irradiated mice and many "nodules" were observed, which grew in proportion to the number of marrow cells injected. They called these "spleen colonies" and theorised that these colonies came from single bone marrow cells- stem cells. James Thomson (University of Wisconsin) succeeded in isolating embryonic stem cells from fertility clinics in 1998 and produced the world's first human embryonic stem cell line, which is still running.

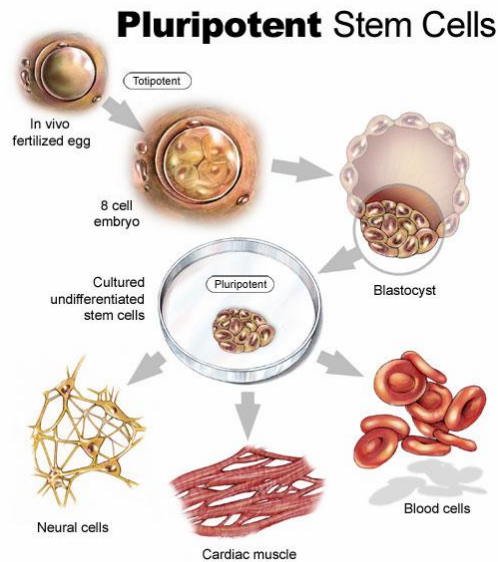


Fig. 1: derivation of stem cells  
(www.csa.com)

Stem cells are found in many different parts of the body. The most well-known, and controversial, is the embryonic stem cell, which is found in young embryos known as blastocysts, which consist of about 50-150 cells and are formed about 4 or 5 days after conception. They are pluripotent and can differentiate into almost any type of cell, as shown in Figure 1, making them one of the most useful types of stem cell discovered so far. Most of the research into stem cells done so far has been done using human or mouse embryonic stem cells. Adult (somatic) stem cells are not pluripotent, but multipotent, meaning that they can only differentiate into a limited number of cell types, which limits their usefulness; however their use is certainly less contentious in ethical debates.

Adult stem cells have now been identified in many tissues in the body, including bone marrow, which contains at least two types of stem cell: haematopoietic (able to turn into any type of blood cell) and bone marrow stromal cells (able to turn into bone, fat and cartilage). There is also a third type of stem cell derived from foetuses, which have intermediate properties to embryonic and somatic stem cells. A recently discovered phenomenon is plasticity- the ability of an adult stem cell to turn into a completely different type of cell to that of the tissue where it was produced. Therefore, somatic stem cells have become the main focus of many research experiments as an alternative to embryonic cells. In a study published in *Circulation Research* (Feb. 12 2009) from the UW-Madison School of Medicine and Public Health, a team of researchers were able to induce skin cells to become pluripotent stem cells. These were then differentiated to become beating heart muscle cells (cardiomyocytes). This research hopes to be able to extend to creating full sections of tissue, which could then be used to repair dying heart muscle. The team leader, Dr Tim Kamp is quoted as saying 'It's an encouraging result because it shows that those cells will be useful for research and may someday be useful in therapy... the speed at which knowledge is progressing is very encouraging.'

This research could theoretically be applied to produce working kidney cells, which could replace the dead kidney tissue after Chronic Renal Failure. There have already been

instances of transplants being done using stem cell technology. For example, in 2006, it was reported in the medical journal *The Lancet*, 7 children were given bladder transplants by Anthony Atala of Wake Forest University Medical School, using tissue made from their own stem cells. After removing diseased tissue from the bladder, muscle and bladder wall cells were grown on a biodegradable mould made of collagen (a structural protein found naturally in tendons and skin). This was the first time that a complex organ tissue had been grown from stem cells, rather than simple tissues such as skin or bone. Further proof of the possibilities came in 2008, when a Colombian woman suffering from a collapsed tracheal windpipe after contracting tuberculosis had a transplant using cartilage grown from her own stem cells. The following windpipe transplant used a donor piece of windpipe, which was treated with enzymes and detergent to remove all of the donor's cells, and induced stem cells from the patient's bone marrow into becoming cartilage. The operation was successful and five months later, there were still no signs of rejection by the body.

The concept of stem cells has a lot of potential in the medical and veterinary fields. I will now discuss how this could be used to combat the common problem of Feline Chronic Renal Failure.

## DISCUSSION

Chronic Renal Failure is a degenerative terminal condition that affects about 2% of all cats, with the risks increasing as the cat ages (10-30% of cats 10-15 yrs, 32% of cats over 15 yrs). There is no cure for CRF, and it can be very difficult to manage.

The kidneys maintain the homeostatic balance of the cat's body fluids, regulating the concentration of liquids to solids, or blood osmotic pressure regulation. Waste metabolites are filtered out of the blood and disposed of in urine to prevent build-up of these toxins, such as urea, a by-product of protein metabolism. If the waste products of metabolism build up in the blood stream, it can cause the animal to become uremic, as well as dehydration of the blood and cell cytoplasm. The kidneys also release some hormones, including erythropoietin, which is responsible for production of red blood cells.

The cortex (shown in Fig. 2) is the outer area of the kidney and contains most of the glomeruli- small bundles of capillaries where the majority of fluid and dissolved molecule exchange occurs. The medulla is supplied by tiny arterioles and any damage to the glomeruli in the cortex will have severe implications on the tubules of the medulla. The renal pelvis collects the filtrate of the kidneys and sends it down the ureter into the bladder. The renal artery and vein respectively take blood to and away from the kidneys to be filtered.

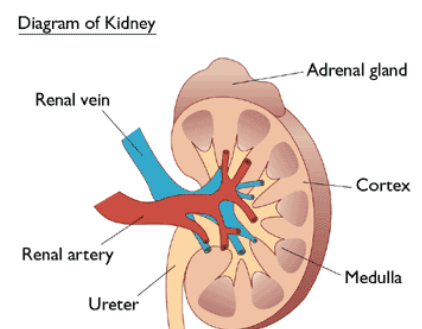


Figure 2: the simplified structure of a kidney (www.biologycorner.com)

Many diseases of the kidney involve the failure of nephrons, which are the main functional part of the kidney. The nephron has two parts- the renal corpuscle and the renal tubule.

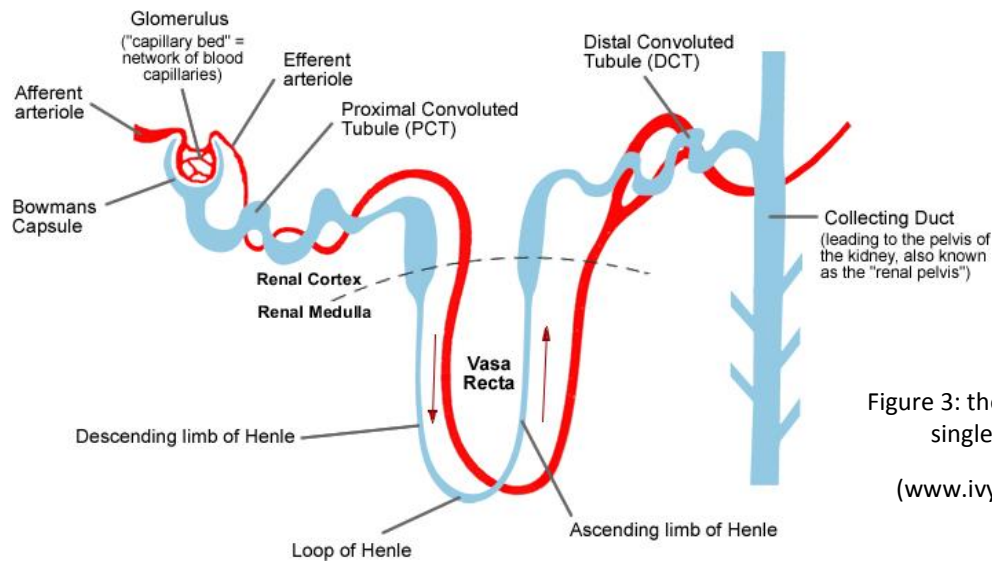


Figure 3: the structure of a single nephron

([www.ivy-rose.co.uk](http://www.ivy-rose.co.uk))

Blood is forced into the glomeruli of the renal corpuscle at high pressure, initiating a filtration process. Water and solutes (the glomerular filtrate) are able to pass through a filtration membrane between the glomerulus and Bowman's capsule and into the capsular space between the two walls of the Bowman's capsule. Some of the water and electrolytes are re-absorbed into the blood to maintain normal concentration levels. The glomerular filtrate then passes into the renal tubule, through the PCT, Loop of Henle and DCT. The DCTs of many nephrons join to a collecting duct where the fluid drains through; many of these ducts converge into the renal papilla. The fluid passes through more tubules of increasing size before passing into the renal pelvis, and finally out of the body through the ureter.

Damage to the nephrons is normally low-grade inflammation of the tissue, which accumulates over time in a condition called chronic nephritis. The toxins build up as they aren't removed quickly enough by the kidneys, and the body becomes increasingly acidic. Symptoms only appear once about 70% of the nephrons have been irreversibly damaged, which may be too late to provide adequate treatment. The fact that the disease only becomes diagnosable at a very late stage leads to it being incurable and an owner may choose to euthanase if they feel that the animal is in pain and isn't responding to, or is being distressed by, treatment. The first symptom is polydipsia, an increased need to consume water, and this may be noticed the owner. This is caused when the concentrated blood containing toxins and metabolites triggers sensors in the brain, causing the animal to feel dehydrated and it consequently drinks more. At the same time, the animal is losing more water than normal due to the kidneys being unable to retain water properly. This causes polyuria, or increased urination. Substances that are needed within the body such as proteins, glucose and vitamins may also be lost in urine, leading to weight loss and wasting. The kidneys also don't produce enough erythropoietin (which causes the body to produce red blood cells) leading to anaemia, so the cat appears lethargic and weak.

Sometimes the destruction of nephrons is through autoimmune diseases which attack the body's organs including the kidneys. Pyelonephritis is a bacterial infection which normally starts in the bladder and spreads to the kidneys as it becomes a chronic disease and the cat will then start to show further symptoms of kidney failure. Other causes of kidney failure may be through inherited genetic diseases, such as Polycystic Kidney Disease (PKD) and renal amyloidosis, both of which are commonly present in exotic breeds such as Persians. PKD involves the formation of cysts in the kidneys which enlarge the kidneys and destroy tissue, stopping them functioning. PKD normally presents itself fairly late in life (around 7 years), and is caused by a dominant gene, meaning that breeders can unknowingly breed kittens with PKD before a parent has shown symptoms.

The exact mechanisms of how Chronic Kidney Disease damages the nephrons are still largely unknown. As the disease progresses, scar tissue forms in the nephron system, making the damage irreversible, as the kidney is unable to repair itself. This is where stem cell technology could be used as a form of therapy for this disease, as transplants or tissue grafts become the only option to improve the pet's condition. At present, most treatments only aim to prolong the life of the animal through special diets, low in proteins and minerals such as phosphorous in order to reduce waste products in the blood, and progress is slow.

To produce a fully functioning kidney, many different types of tissue would have to be synthesised from stem cells, as the kidney is an extremely complex organ. The majority of the kidney is made from epithelial tissue, however every section of the kidney's functional tissue has its own unique cells, for example, principle cells and intercalated cells in the collecting duct. These are respectively responsible for sodium re-absorption and potassium secretion and acid-base homeostasis. It would be difficult to coax stem cells into becoming exactly the right type of kidney cell to form a whole kidney, but as stem cell technology advances, it is unlikely to be impossible. Once the correct cells were formed, they could be placed in a growth solution to rapidly produce more identical cells by mitosis.

Current transplants raise serious ethical issues as a healthy donor has to lose a kidney in order to supply an organ. The donor may sometimes be euthanised if a home can't subsequently be found. There is also the risk of rejection by the immune system due to non-self antibodies being present on the donated kidney, and immunosuppressive drugs need to be taken to prevent this. This incurs large costs for the owner and often a long and distressing hospital stay for the pet. The immunosuppressive drugs can cause further complications, such as urinary tract infections or hypertension leading to seizures. In addition, erythropoietin is normally taken to increase red blood cell production, which helps recovery and also lifts the pet's activity level, decreasing feelings of lethargy. Appetite stimulants, including certain anabolic steroids, are also given after a kidney transplant operation. If stem cells from healthy parts of the kidney could be used to grow renal tissue that is genetically identical to the original, and contains self antibodies. This would mean that there is a minimal chance of rejection.

The only other option currently available to treat kidney failure is dialysis which uses an 'artificial kidney' to filter the blood through a catheter. However, this is only viable for Acute Renal Failure, as a pet clearly can't be attached to a catheter all the time and have a good quality of life.

It is, of course, also important to discuss the controversial ethical issues surrounding stem cells. One of the biggest sources of stem cells is from discarded embryos from abortion and fertility clinics. Many anti-abortion groups, including the Catholic Church, feel that life begins at conception, so abortion is equal to murder. Then using these embryos for research is a further wrong, as we would not test on a human without their consent. An embryo can't consent, so it is felt that such research should not be taking place. Many people are even more disturbed by the fact that some scientists want to create embryos solely for the purpose of research, and argue that it doesn't promote the right values of human life- we would be de-sensitised to the destruction of human life.

A further argument laid out in a document prepared for the Australian Government in 2002 titled 'Key Ethical Issues in Embryonic Stem Cell Research' explores the issue of women being oppressed if eggs become seen as a commodity. It states that 'women who donate ova or embryos are at risk of exploitation to the extent that male-dominated medical practice appropriates their reproductive labour for commercial benefits'. It may seem far-fetched to think that, in the future, medical researchers may come to see women as 'egg machines', but nevertheless, steps must be taken to ensure this would never happen.

On the other side of the argument, the Human Fertilisation and Embryology Act of 1990 states that a foetus has rights, but not to the same extent as a living person. Embryos created for research from stem cell lines cannot, by law, be implanted into a womb, so they can never become babies. This would mean that an embryo is not a human, and that it isn't a moral crime to destroy it. Others believe that embryos have a status similar to that of a body part, since they haven't yet formed distinct organ systems, and are therefore the property of the body they came from. The potential gain from stem cells also has to be considered. If we develop stem cell therapy on a large scale, millions of people suffering from thousands of different diseases could be helped. Some argue that using embryos from fertility clinics would be much better than disposing of them- at least then we are using them for something that could potentially benefit people.

Adult stem cells are much less controversial in their use, as no embryos are used. They were originally thought to be much less versatile than embryonic cells, but research has discovered that they have many more uses than originally thought. In order to progress with stem cell research, it may be better to develop all possible uses of adult stem cells first, as there will be less legislation and laws about these cells.

In the end, the ethical decision has to be made on the basis of what value the embryo has- is it the same as a human, or just a body part? This question will have to be decided as countries settle on regulations for stem cell research.

## CONCLUSION

Stem cells have the potential to act as a type of therapy for many different diseases through transplantation, including for Feline Chronic Renal Failure, as outlined above. This could provide a real cure for kidney disease, without the issue of having to take organs from a donor. However, there are also many challenges to be faced first.

Firstly, there is the issue that as of yet, there is no reliable way to induce stem cells to become a particular type of cell. Clearly the signals that the body gives to stem cells to induce them to become the correct type of cell will have to be identified and replicated in laboratories before this technique is to be used on any large scale. In the study at the University of Wisconsin where functioning cardiomyocytes were produced, a virus was used to re-programme the genes of skin cells and induce them into becoming embryonic stem cell-like. This method in itself presents problems, as using a virus could cause the cells to become cancerous. Another method involved replacing an egg's nucleus with that of a somatic cell and stimulating it with an electric pulse to become an embryo, similar to therapeutic cloning.

There have been cases where treatments using stem cells have directly caused benign tumours local to the area of treatment. In 2001, an Israeli boy was given injections of foetal stem cells into his brain in an attempt to treat a degenerative brain disease called ataxia-telangiectasia. Two more such injections were given in 2002 and 2004, before a benign brain tumour was diagnosed in 2005, despite the condition appearing to improve. An important link to make is that stem cells are often found in the body in places where cancers are common, such as the blood and gut. By contrast, stem cells are rarely found in skeletal tissue and the heart- cancer of these organs is also uncommon. Clearly, this type of therapy has its own hazards, and trials would need to be thoroughly carried out in animals and humans to find out if organs formed from stem cells would carry the same sort of risks as the injections of stem cells. Further tests would need to be carried out to find out if immunosuppressant drugs would be needed after transplants since there are no non-self antigens, and if so, in what quantities.

Other obstacles to be overcome would be the how to produce a whole functioning kidney from sections of tissue. Possibly the best proposal would be of using a biodegradable scaffold made of proteins, similar to the bladder transplants. Again, tests would need to be done to either confirm or disprove this. Even though it might be possible to make a full kidney, there is no guarantee that it would function in the correct way.

As well as the practical challenges of making and transplanting a fully functioning kidney, there are major ethical obstacles to be overcome. The UK Stem Cell Initiative has laid down

11 recommendations for stem cell research, which include advice to continue funding from Research Councils and private sectors. Ultimately the ethical differences come from whether you see an embryo as a potential human or a potential organ. Adult stem cell research doesn't encounter nearly as many objections, so it might be advisable to discover all opportunities to use adult stem cells before using embryonic stem cells.

Stem cell research has such massive potential to be fulfilled, and could help many people if it is indeed feasible to produce fully working organs. Research is developing at an extremely rapid pace for such a new branch of science, and the medical benefits are considerable.

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