

# How has the development of Poly-L-Lactic Acid as a wound sealant assisted medicine?

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PASS

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My research paper is about the use of poly-L-lactic acid – or PLLA – in the place of more traditional methods of closing wounds, such as suturing. I chose this to be the centre of my project because it is an extremely intelligent method that has only recently been discovered in 2008. I have examined the ethical issues, as well as comparing the method to those that would have traditionally been used by surgeons and medical professionals. I can conclude that PLLA is indeed an effective method, and could be extremely useful to medicine if only it wasn't quite so expensive – making it uneconomical for many of the state-funded hospitals. This is an area of nanotechnology that particularly interests me because it is not an area that would necessarily be thought of as an aspect of it; unlike mechanisms such as drug delivery systems, or uses like sunscreens that aren't immediately to do with medicine but are certainly health related. [1]

## **Introduction**

Nanotechnology is an area of science that has seen massive developments in the last fifty or so years. Since Feynman announced "The principles of physics, as far as I can see, do not speak against the possibility of manoeuvring things atom by atom." Scientists have sought to find a way to work things on an atomic level, particularly with a view to how this could revolutionise the way illness is treated in medicine.[2] The discovery of the Buckyball confirmed that this was an achievable dream, and it was later realised that the football shaped carbon molecule could in fact be used to 'block' the development of cancers and to inhibit basic processes in cells, to prevent illnesses like asthma [3]. An iconic achievement in nanotechnology, used to show the world just how precise using atoms could be was shown in 1989, when IBM was written in atoms, using a scanning tunnelling microscope [4]. Such technology has generated enormous interest and, as a result, vast financial backing – in 1991 MITI of Japan committed over \$200 million dollars to 'bottom-up atom factory', with endorsement from IBM. Such has the knowledge into nanotechnology improved, that by 1994 the first course in 'Nanosystems' was available at university [3]. This presumably led to the first Nanomedicine book being published in 1999, which focussed interest on how nanotechnology could help medicine.

As already mentioned, one of the most recent but most effective developments are "smart drugs" or targeted drug therapies – which are shown to be more effective and have less side effects than previous methods [5]. There have also been developments using transfer of drugs into the cytoplasm of cells through the cell membrane, which of course uses nanotechnology. Particularly with cancers in mind, there have been changes to traditional methods of radio and chemotherapy, by injecting the medicine instead. This is much more pleasant for the patient [6]. Recently zirconium oxide has been used for dental filling and even some bone replacement, demonstrating that nanotechnology can be useful in conjunction with medical problems other than cancer. Nanocrystal technology has made a cholesterol-lowering drug much more accessible. The colloidal dispersion or aqueous dispersion contains drug substances less than 1000 nanometres in diameter [7]. The effects of severe vasometer symptoms – or hot flushes – have been limited using a cream containing oestrogen and a drug delivery system developed by Novamax [8]. TiMesh has also used nanotechnology to create a mesh that has been designed for "repair of direct or indirect inguinal, femoral, umbilical and incisional hernias; rectal, vaginal and apical prolapses; and parietal reinforcement of tissues and abdominal wall repair" [9]. Particularly of interest to surgeons is the 'EnSeal Laparoscopic Vessel Fusion System' which can make operations such as bypasses much more precise and increase the chance of a successful process [10]. Extremely recently, Jason Halfner's Gold Nanostars have been used for sensing, imaging and measuring electrical fields inside the cell membranes, which are useful in many parts of medicine (including haematology, toxicology, etc.) [3].

Usually, when closing a wound, several things are taken into consideration: the depth of the wound, the scarring that is likely to result and the probability of infection [11]. Once these things have been considered, the doctor or surgeon can choose out of numerous ways of closing the wound. These methods include stitches, staples and a glue-like substance (usually consisting of PLLA) [12]. Where PLLA isn't used, suturing is often used instead. This can, in fact, lead to some problems. It is commonly agreed upon that there can be unwanted effects associated with the scars that form after skin incisions. Below, Table 1 shows the unwanted effects that can occur as a result of scars after suturing.

| <b>ORGAN/SYSTEM</b>    | <b>EFFECT</b>   |
|------------------------|---|
| Skin                   | Keloid; Hipertrophied scar; Burn contracture; Scleroderma |
| Gastrointestinal tract | Stricture; Adhesions; Chronic pancreatitis                |
| Liver                  | Cirrhosis; Biliary atresia                                |
| Lung                   | Intertiscial fibrosis; Bronchopulmonary dysplasia         |
| Heart                  | Rheumatic disease; Ventricular aneurysm                   |
| Eye                    | Retrolenthal fybroplasia; Diabetic retinopathy            |
| Nerve                  | Transmission loss   |
| Bone                   | Ankylosis; Osteoarthritis                                 |
| Kidney                 | Glomerulonephritis  |

Table 1 [13].

Therefore, it is clear that there are many negative effects associated with suturing.

To combat this, PLLA may be used and is a synthetic homopolymer. The nanosheets (about one centimetre long) can be used for plastic surgery, endoscopic surgery, regeneration medicine, external use (for the skin), as well as in place of suturing. The sheets have so far been proved to prevent the spread of infections around wounds. The Japanese researchers who discovered PLLA, have so far found it to have adhesiveness, high flexibility, and high transparency – all of which make it more useful than previous techniques [14].

There have been several studies to demonstrate how effective PLLA can be, usually involving mice. One of these Jiang *et al.* used PLLA as a scaffold to culture mouse foetal liver cells which produced albumin at levels comparable to adult mouse hepatocytes. In these experiments, it was found that sometimes PLLA can be subject to bulk degradation, surface erosion, hydrophobicity and degradation by hydrolysis. However, these difficulties can be easily overcome and reduced using photochemical modification and the incorporation of specific biochemical domains [15].

The PLLA molecule is mainly made up of a central carbon atom, surrounded by a hydrogen, a methyl group, carbon monoxide with an attached hydroxyl group and an oxygen atom [16].

## Discussion

It is sometimes remarked upon that, as a synthetic polymer, there are some ethical issues involved with PLLA. As a plastic being used in the body, it raises the issue that we could be evolving in a different way to before [17]. Prior to the new stage of human development, our bodies have been affected by the elements around us, as these would test our ability (as individuals and a species) to evolve, based purely on how we have evolved. Those who had evolved with individual mutations that were a benefit in the environment they lived in would survive, whilst those who had developed mutations that were a disadvantage – or who hadn't developed at all – were likely to be unable to beat the competition of others. However, due to our intelligence guaranteeing we can create situations that diminishes our reliance on our bodies, much of our evolutionary tendencies have been lost. As a result, the oldest skeleton in Britain – the Red Lady of Paviland [18] – has a skeletal structure that is almost exactly the same as ours today. For this reason, some people argue that in fact technology is evolving us, as we need the technology to make up for the things we have evolved to no longer need. For example, in the past homo sapiens would probably have had very strong immune systems that were capable of withstanding a small infection caused by a shallow skin wound. But, now, without treatment from antibiotics or from an effective way of closing the wound before infection becomes imminent, a small infection could in fact be extremely harmful. It is partly for this reason that PLLA is a more effective method of sealing wounds – as it vastly decreases the chances of infection. Ethically, some people think it's wrong that we have forsaken the way our bodies evolve to evolve with technology [19]. Thus, PLLA – as a plastic – is an artificial substance that reduces the bodies needs to fight day-to-day infections.

There are of course other methods used in medicine that are developing extremely quickly, but could also be looked at as less than ethical, for the same reason. Other developments that relate to the ethics of plastics and the body include relatives of PLLA; including lactic acids and glycolic acid and their copolymers with  $\epsilon$ -caprolactone [20]. As would be expected of such a chemically similar material, these constituents will also hydrolyse into safe end products within a few weeks or months.

However, there are other methods that do not involve synthetic plastics that will be used in the future to seal wounds. Instead of traditionally used staples and stitches, the nanotech wound closure technique uses dye, which coats the wound and is then exposed to light for two to three minutes. The dye absorbs the light and catalyses molecular bonds between the tissue's collagen [21]. This creates a bond that's watertight, prevents inflammation and the risk of infection – all qualities also attributed to PLLA.

In the future, PLLA could possibly be further developed to make it a more accessible resource to most hospitals. This would be difficult, as the technology involved in making it involves an electrospinning method that can use a lot of energy [22]. Therefore, it can be high in cost and difficult for hospitals to afford this method on a regular basis. It is fairly new technology and is still in the research phase of its development, so isn't actually available to be used as a sealant in most countries. Where it is used, it is effective, but not often able to be bought by state-owned hospitals – meaning it isn't available for most people, especially those who could need it more than others. However, it is usually used on wounds that could have a negative aesthetic effect (i.e. on the face) so is most often used by private plastic surgery clinics. The cost is only likely to rise, considering that the research will need to be done for

several years to gain a definitive result that allows the product to be used internationally and according to all laws aiming to preserve public health.

PLLA and other co-polymer polylactic acid nanotechnology can also be used in drug delivery systems and some methods of diagnostics [23]. This is a use of nanotechnology, PLLA and other co-polymer polylactic acids that could change how many of the current drug delivery systems are used – particularly in the areas of cardiovascular disease, cancer, vaccine and tissue engineering [24]. The combined scaffold and bioreactor design of the PLLA make it ideal for the differentiation of stem cells in hepatocytes. Obviously stem cells have a variety of uses in medicine – whether it's for research into genes and research into how genes can be 'switched on and off' or tested to see if they could be used to treat cancers and other diseases [25]. Thus, PLLA is an extremely useful resource for all kinds of people in many different cultures.

Another use of PLLA is for artificial valves in bypass surgery. Replacing or repairing diseased valves is extremely important in view of the illnesses that are plaguing our society today – heart disease is still the main cause of death in the UK today. PLLA can be used along with stents which are moulded to fit the aortic or mitral valves. They are effective and fit well into today's needs. Unfortunately, being made of plastic, it is necessary for the patient to take warfarin or coumadin to ensure that the blood is thinned, making it possible for the heart to work effectively without clotting – a common side effect of using a synthetic plastic in the heart [26].

Personally, I believe PLLA is most useful in areas that aren't directly involved with the aesthetics of sealed wounds, like plastic surgery. Instead, I believe it could be invaluable when used in areas of the world where resources are limited because it is in these areas that the prevention of infection is most important. The World Health Organisation showed that in the year 2002, 9.3% of deaths occurred in middle and low income countries as a result of perinatal conditions [27]. These would include infections caught due to lack of hygiene and blood loss due to haemorrhaging. Usually, women and babies in these situations can't be helped, as there is very little equipment with which to treat them, and unsanitary conditions mean that life threatening infections are rife. In my opinion, if it was economically viable (which, of course, it isn't at the moment) the use of PLLA would be much more suited to third-world countries than countries where it is used for its reducing scarring properties, not for its reduction in the risk of infection. An example of this is the very recent, devastating tsunami in Japan. As a result of it, many of the things that we take for granted in our everyday lives, like the electric and sewage systems, will have been removed. Often, diseases such as cholera flare up as a result, and the risk of infection rises hugely. There will be huge numbers of people, who became injured in the deluge, and sheer numbers will prevent medics from being able to treat everyone effectively; badly placed staples or messy suturing could be fatal.

## **Conclusion**

The uses of poly-l-lactic acids have affected many areas of science. The scaffold-like structure is perfect for the field of orthopaedics or heart bypass surgeries, as well as the use I have explained in above – for sealing wounds [28]. It is a basic polymer that is spread on incisions of the skin to seal them. There are several advantages to using it in place of suturing or staples – most importantly, it decreases the risk of infection and reduces scarring. Although only recently developed, I think it's most effective in many surgeries – particularly those which would have caused prominent and unattractive scarring. Despite

this, I think it could be used most effectively in areas where infection is rife, and the PLLA could significantly decrease deaths due to septicaemia and perinatal conditions. At this moment, it isn't an accessible resource for most hospitals and definitely could not be used widely in emergency situations and third world countries. However, after it has been researched more thoroughly by its creators and has been in circulation long enough for its price to drop so it can be in financial reach of most places, it would be extremely useful in third world countries.

So, the fact that it is uneconomical is one of its most potent disadvantages. It cannot be used in the parts of the world where it could possibly be most useful. However, it is quite often used in places where there is a higher level of disposable income and people are prepared to pay to ensure any scarring that occurs as a result of incisions to their skin is imperceptible. As a result, in future, the most likely development for PLLA would be to make it a financial option to all; scientifically, in terms of sealing wounds at least, it has very little development potential left.

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