

Implants: the biodegradable future

Dr Joachim Kohn of Rutgers University in the USA tells Jim Banks how a new device for hernia treatment has opened the door to a faster development and approval process for biodegradable polymer implants.



There is much excitement around the potential capabilities of synthetic biodegradable polymers and the effect they will have on the design and function of implanted devices. Whether they are used to facilitate a controlled drug delivery function within the body or to reduce the amount of material left inside a patient's body, these materials are crucial to a paradigm shift that is currently taking place. The current trend suggests that, in the next few years, some permanent prosthetic implants will give way to fully degradable devices. However, the slow evolution of synthetic degradable polymers has so far put the brakes on this transition.

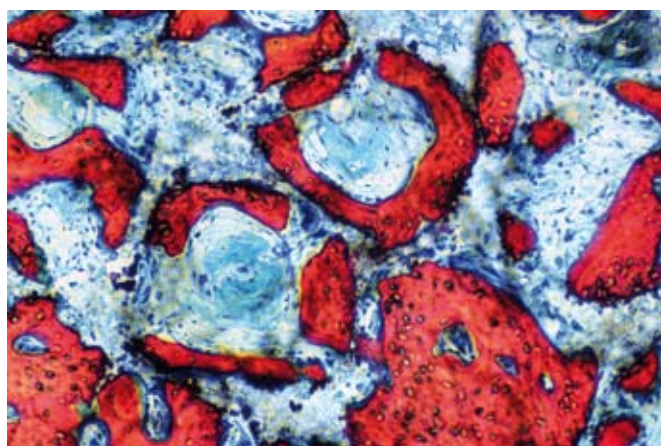
The year 1969 saw the first approval of a synthetic degradable suture made of poly(glycolic acid). In 1971, an improved suture, containing poly(lactic acid) was approved. Then there was a long wait until polydioxanone appeared as a material for biodegradable sutures and bone pins in the early 1980s. The next fundamental advance came in 1996 with the development of an implantable drug delivery system using degradable polyanhydrides.

Dr Joachim Kohn, director of the New Jersey Center for Biomaterials and board of governors professor of chemistry and chemical biology at Rutgers, The State University of New Jersey, says: 'There have been many variations around these themes, but relatively few fundamentally new, synthetic degradable polymer systems have come through as platform technologies. In this sense, the rate of development is very slow - maybe one new polymer system per decade.'

Kohn believes that this rate of development must accelerate to allow the wide use of synthetic degradable polymers to impact the performance of a range of existing medical implants. Ultimately, synthetic degradable polymers may become the sole material for the manufacture of medical implants.

'People think that we are now seeing a paradigm shift from using permanent prosthetic implants that replace damaged tissue to biodegradable devices that help the body regenerate damaged

- Synthetic polymers are being used in the development of biodegradable implants.
- A helpful regulatory framework is ensuring that the development and approval process for biodegradable implants is free from unnecessary obstacles.
- Innovations in the way biodegradable polymers are developed is leading to the creation of exciting new materials.



Growth of bone within a degradable bone regeneration scaffold (Courtesy: TyRx Pharma)

tissue,' Kohn says. 'My basic hypothesis is that we will need many more synthetic degradable polymers to match the large number of specific applications such a shift would require. For now, the choice of synthetic degradable polymers is too limited and their rate of innovation is too slow.'

Hernia device

A biodegradable tyrosine-derived polyarylate is a critical component of a new hernia repair device marketed by TyRx Pharma, Inc, a firm that focuses on the development of new drug-eluting medical devices. TyRx uses a combinatorially designed library of tyrosine-derived polyarylates developed by Dr Kohn's team at Rutgers.

These polymers were developed after a thorough examination of the body's natural metabolites, which highlighted that derivatives of tyrosine dipeptide were a close natural, non-toxic mimic to diphenols used in industrial plastics. The resulting tyrosine-derived polyarylates have shown strong structural and drug delivery capabilities for implants, and in vivo animal testing suggests minimal tissue and blood response, even at full degradation.

FDA clearance has been granted for a new device that incorporates these polymers as a coating on a surgical mesh. The polymer improves the handling capabilities of the mesh to facilitate precise placement during surgery. The coating is then reabsorbed, leaving a smaller amount of material in the body. While this partially degradable implant represents a step forward in the use of biodegradable polymers, perhaps the most significant factor is the route by which the polymer has become part of an approved medical device.

The hernia device was granted clearance by the FDA using the 510(k) mechanism. Using 510(k) involves showing that a new device is equivalent to an existing device. If this equivalence can be demonstrated, the FDA responds more rapidly and may decide that it does not require the complex and costly process of establishing safety through extensive clinical trials.

Kohn believes that the successful use of the 510(k) approval mechanism by TyRx is highly significant, marking a breakthrough in regenerative medicine. 'The approval of the TyRx hernia device is a unique event,' Kohn says. 'The industry has an example of a successful marketing strategy using the 510(k) mechanism, which suggests that, in certain circumstances, FDA is open to new synthetic degradable polymers as part of devices without requiring extensive clinical trials prior to market approval. I can't overemphasise how important this is.'

He believes that this is a major staging post on the road to fully degradable implant technology, as it will encourage medical device developers to invest in synthetic degradable polymer research. This in turn could lead to the rapid development of products, provided that the companies behind them accept that innovations must be introduced in stages. Kohn says: 'The 510(k) mechanism can shorten development times, but at the cost of fundamental innovation being replaced with incremental development. A fundamentally new device can take a long time to get approval which is necessary to safeguard patients.' TyRx, for example, developed around a device that was already approved by the FDA by simply adding a novel polymer coating.

Accelerating the development cycle

Taking this incremental approach could well speed the industry along the development curve for devices incorporating synthetic degradable polymers. A classic example of how this development is expected to progress can be seen by looking at stent technology, as it moves along the curve from permanent implant to fully biodegradable device. In their first generation, stents were bare metal devices. The second generation saw them coated with a non-degradable polymer coating for drug release. The third generation would see them coated with a degradable coating that would improve the controlled drug release function. Ultimately, they would become totally degradable, leaving the body entirely once the necessary remodelling of the blocked blood vessel was complete.

'Right now, we are at the middle stage of this process, and we are working with combination devices - traditional implants enhanced with a drug delivery function. The advantage of biodegradable polymers is that they help the drug delivery function to operate over a limited period of time,' says Kohn.

A similar development path could be envisaged for the hernia repair devices marketed by TyRx. Indeed, the firm has recently highlighted the FDA's decision to treat a drug delivering hernia repair implant as a device rather than as a drug under its approval

processes. In this sense, TyRx is a pioneer, opening the door for the next generation of medical devices.

Polymer library

The FDA's seemingly favourable disposition to the wider use of synthetic degradable polymers will no doubt be encouraging to developers, but the medical device industry also needs a broader palette of polymers to choose from if the rate of innovation is truly to accelerate. Significant breakthroughs in polymer technology have traditionally come one at a time, with a new platform polymer inspiring variations that find uses over time. However, work at Rutgers suggests that this discovery format could change. In making the hernia device, TyRx did not license the rights to a single polymer from Rutgers. Instead, it bought a license to a library of novel tyrosine-derived polyarylates that arose from an adaptation of combinatorial chemistry to biomaterials. Rutgers used two sets of starting materials and produced all possible combinations thereof, creating a library of 112 related polymers. Drawing structure-function correlations from these materials enabled TyRx to quickly predict characteristics such as modulus, glass transition temperature, hydrophobicity and degradation time, and then select suitable polymers from the library for specific applications.

At Rutgers, the focus is now on producing very large polymer libraries, sometimes containing ten thousands of individual compositions. For such large polymer libraries, it is no longer possible to synthesize each polymer composition contained in these libraries. Therefore Kohn's team makes use of computational modeling techniques to create 'virtual' libraries. So far, this technique has found limited use in the biomaterials field, given the difficulty of establishing appropriate models to describe the interaction between biomaterials and living tissue. However, advances in computational modeling techniques may now allow for the elimination of much detailed characterisation of individual polymers by high-throughput screening. For example, predicting the glass-transition temperature of individual polymers contained within Rutgers' library of polyarylates was based on the 'total flexibility index', which is an empirically derived parameter that can be calculated from a polymer's chemical structure. The overall effect of starting the discovery process with a visit to a virtual polymer library, Kohn believes, will be to enhance the pace at which new biomaterials can be discovered. Rutgers has already provided a license to REVA Medical, Inc for a second combinatorially designed polymer library. This library was designed to facilitate the development of degradable stents, which could be a \$4bn market, and Rutgers expects more development projects to come online swiftly. 'In the next five years, we will see many pioneering efforts around the addition of drug delivery capability through synthetic degradable polymer coatings. In five to ten years we will see a larger number of efforts to replace permanent prostheses with degradable tissue regeneration devices,' Kohn says. If the favourable regulatory attitude towards degradable polymers persists and the necessary investment is found, such a short timescale is certainly achievable. ●

profile Joachim Kohn

Professor Joachim Kohn is the board of governors professor of chemistry and chemical biology at Rutgers university and an adjunct associate professor of orthopedics at the New Jersey Medical School. He has served as director of the New Jersey Center for Biomaterials since its establishment in 1997.