



Host responses to implants and challenges

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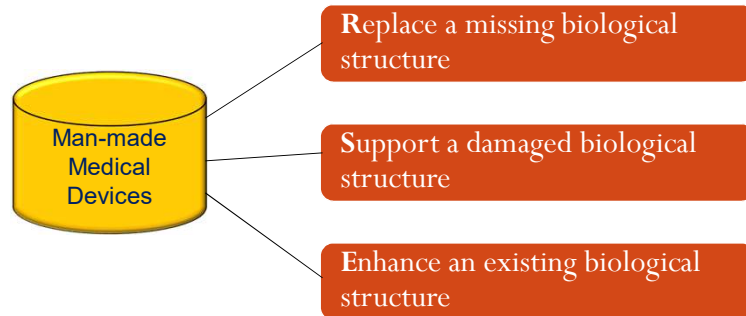
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Overview

- **Implants**
- **Host responses to implants**
- **Evaluation of host responses to implants**
- **Summary**

Implant



Some implants are bioactive, such as subcutaneous drug delivery devices or drug-eluting stents.

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Implant categories

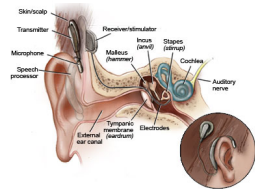
Implants can be categorized into groups by application:

- **Sensory and neurological implants**, e.g. cochlear implant, intraocular lens, or neurostimulator.
- **Cardiovascular medical devices**, e.g. stents or vascular prostheses
- **Orthopedic implants**, e.g. pins, rods, screws, and plates
- **Contraceptive implants**, e.g. copper-and hormone-based intrauterine devices
- **Cosmetic implants**, e.g. breast implants, injectable filler
- **Biomaterials/Tissue engineered implants**, e.g. fibrin, collagen, biomaterials seeded with cells

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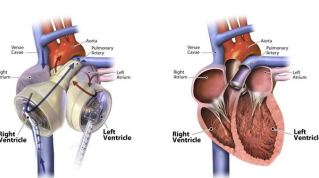
Implants

Cochlear implant



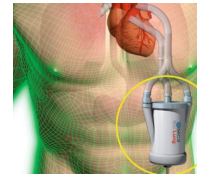
http://kidshealth.org/EN/images/illustrations/cochlear Implant_420x315_rd1_enIL.jpg

Artificial heart



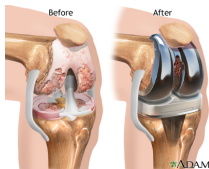
http://cms.ipressroom.com.s3.amazonaws.com/173/files/20155/559323366eafb57f0500bba4_Total+Artificial+Heart/Total+Artificial+Heart_mid.jpg

Artificial lung



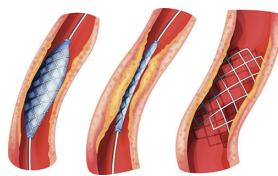
<https://theoraclemagazine.wordpress.com/2014/11/30/looking-for-a-new-lung/>

Artificial knee joint



<https://www.nlm.nih.gov/medlineplus/ency/images/ency/fullsize/9494.jpg>

Cardiovascular stents



<https://www.herzbewusst.de/herzinfarkt-therapie/invasive-therapie/stents-lebensrettende-metallroehrchen>

Dental implants



http://paulkorb.com/?page_id=293

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Host response to material implantation

Implantation of a material is an invasive procedure that initiates a series of events whose outcome ultimately determine the biocompatibility of the material.

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Effect of material on host tissue

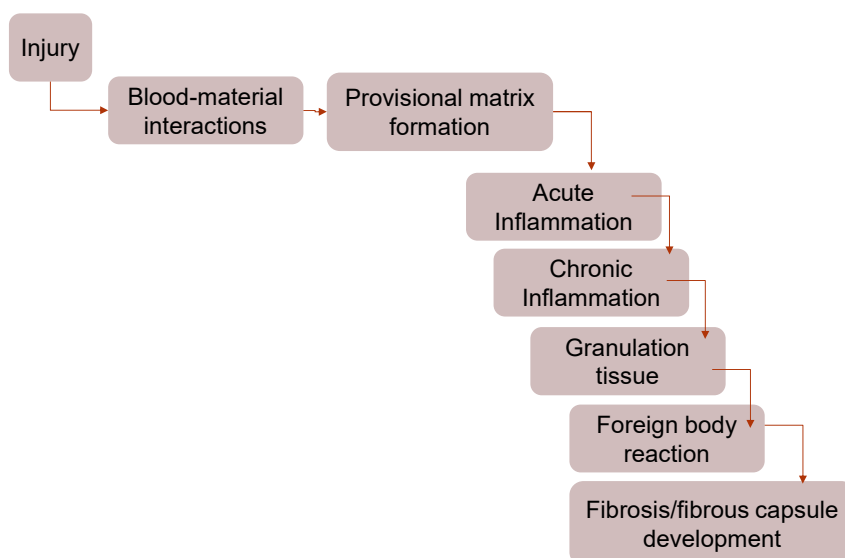
The implantation of a biomaterial, prosthesis, or medical device results in injury to tissues or organs.

Main cellular host responses to injury are:

- Inflammation
- Wound healing response
- Foreign body reaction

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The sequence of host reactions upon implantation of medical devices or biomaterials in vivo



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Blood material interactions and provisional matrix formation

Regardless of the tissue or organ into which a biomaterial is implanted, the initial inflammatory response is activated by injury to vascularized connective tissue

→ **Blood clotting**

and

→ **Formation of fibrin network** on the surface of the implant (this process is described as provisional matrix formation)

These events occur within minutes to hours following implantation of a medical device

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Blood material interactions and provisional matrix formation

Activated platelets release amongst others PDGF and TGF β

→ Leads to fibroblast recruitment

The complex 3D structure of the fibrin network provides a substrate for cell adhesion and migration

The presence of mitogens, chemoattractants, cytokines, and growth factors within the provisional matrix control wound healing process

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Acute inflammation

Main characteristics of acute inflammation are:

- The exudation of fluid and plasma proteins (edema)
- The emigration of leukocytes (predominantly neutrophils and monocytes)

It is of relatively short duration from minutes to days

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Chronic Inflammation

Characterized by the presence of macrophages, monocytes, and lymphocytes, with the proliferation of blood vessels and connective tissue

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Granulation Tissue

Granulation tissue is characterized by a pebbly, granular appearance caused by the creation of many vascular buds sprouting from existing blood vessels. This process is called angiogenesis.

Histological features include:

proliferation of new small blood vessels and fibroblasts

Granulation tissue can be detected 3 to 5 days following implantation of a material.

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Foreign Body Reaction (FBR)

FBR is an inflammatory reaction evoked by the presence of a foreign material in the tissues.

The FBR is characterized by:

- **Formation of foreign body giant cells (FBGCs)**
- Formation of granulation tissue that consists of macrophages, fibroblasts and capillaries.
- Encapsulation of the foreign object

FBR occurs usually a few weeks after implantation

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Foreign Body Reaction (FBR)

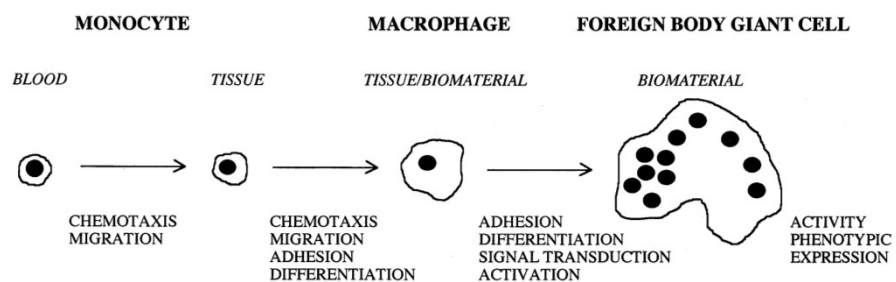
When macrophages encounter a foreign object too large to be phagocytosed, such as an implant, it is thought that the macrophages experience “frustrated phagocytosis.”

Macrophages fuse to form large **foreign body giant cells** composed of up to a few dozen individual macrophages.

<https://www.youtube.com/watch?v=SzNd0KYpyLk>

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Foreign Body Reaction (FBR)

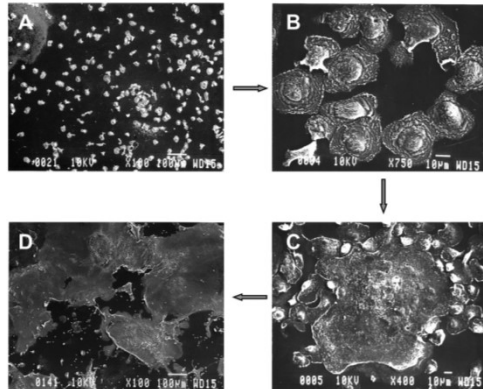


Anderson J.M., et al., 2001, Biological Responses to Materials

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Foreign Body Reaction (FBR)

Adhesive Events at Implanted Biomaterial Surface



Scanning electron microscopy images of an Elasthane 80A polyurethane surface from an *in vivo* cage study showing the morphological progression of the foreign body reaction.

(A) monocyte adhesion (0 days),
(B) monocyte-to-macrophage development (3 days),
(C) ongoing macrophage-macrophage fusion (7 days),
(D) foreign body giant cells (14 days).

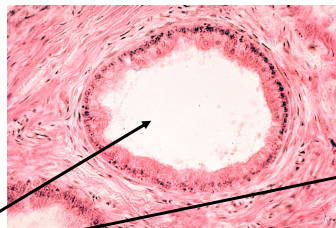
Anderson J.M., et al., 2008, Foreign body reaction to biomaterials.

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Foreign Body Reaction (FBR)

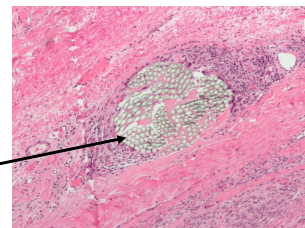
Very large foreign body giant cells containing large numbers of nuclei are typically present on the surface of biomaterials (implants) and they can persist for the lifetime of the implant.

Foreign body giant cell surround the foreign material



Foreign material

Micrograph of a suture with a foreign body giant cell reaction. H&E stain.



https://commons.wikimedia.org/wiki/File:Suture_micrograph.jpg#/media/File:Suture_micrograph.jpg

[http://portal.unimap.edu.my/portal/page/portal30/Lecturer%2520Notes/KEJUR
UTERAAN_MEKATRONIK/SEM1_08_09/ENT311BIOMATERIALS/LECTURE
NOTES/LECTURE_7.PPT](http://portal.unimap.edu.my/portal/page/portal30/Lecturer%2520Notes/KEJUR%20UTERAAN_MEKATRONIK/SEM1_08_09/ENT311BIOMATERIALS/LECTURE%20NOTES/LECTURE_7.PPT)

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Foreign Body Reaction (FBR)

The surface chemistry, form, and topography of material surfaces determine the composition and severity of the foreign body reaction.

High surface-to-volume implants such as porous materials show higher ratios of macrophages and foreign body giant cells than the smooth-surface implants.

The foreign body reaction can lead to chronic pain and device rejection and failure.

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Fibrosis and Fibrous Encapsulation

The final stage healing response for implants made of nondegradable materials.

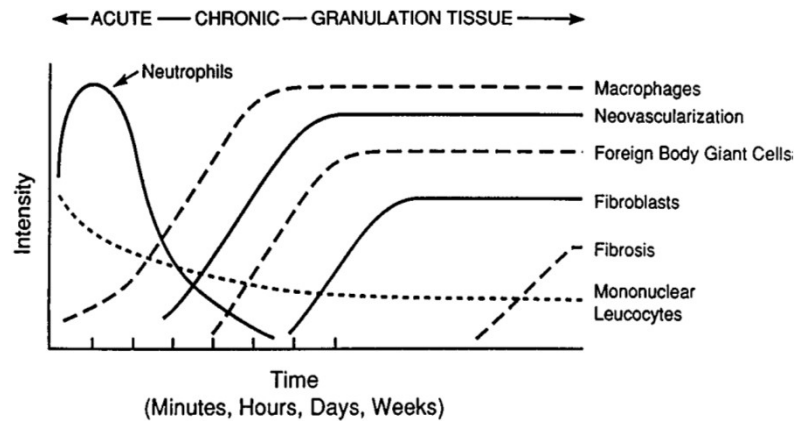
- Type I collagen is mainly synthesized by fibroblasts and forms a fibrous capsule.
- The firm, generally avascular collagen capsule around the foreign body effectively isolates it from the host tissues. This response is developed as a protective measure.

Encapsulation is especially problematic for devices designed to interact with the body, such as glucose sensors.

Occurs usually four or more weeks after implantation

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Sequence of events following implantation



Anderson J.M., et al., 2001, Biological Responses to Materials

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Implant response resolution

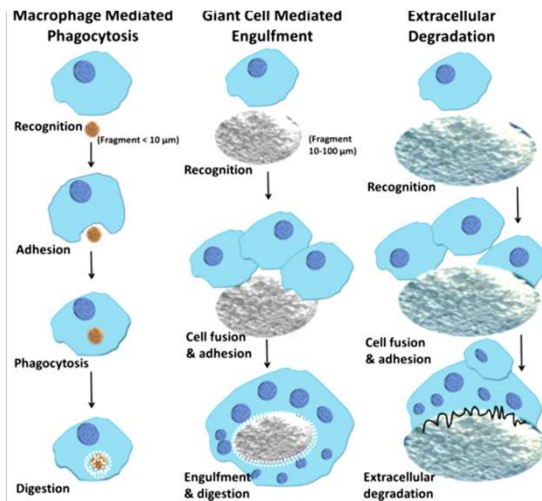
Four types of implant response resolution:

- Extrusion: material forced out of the body (e.g. splinter)
- Resorption: material biodegrades, no fibrous capsule forms
- Integration: implant and host tissue grow together (e.g. porous titanium implant in bone)
- Encapsulation: implant surrounded by fibrous tissue

Resolution: Attainment of a final steady-state condition after implantation

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Macrophage response depending on size of the implanted materials



Sheikh Z. et al. *Materials* 2015, 8, 5671-5701

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Small fragments and particles (<10 μm): internalization via phagocytosis and intracellular digestion.

Particles larger than 10 μm and smaller than 100 μm : the macrophages fuse together, forming giant cells which in turn engulf the particles and digest them.

Larger particles: the bulk digestion is carried out via extracellular degradation by macrophages and foreign body giant cells through the release of enzymes and/or pH lowering mechanisms.

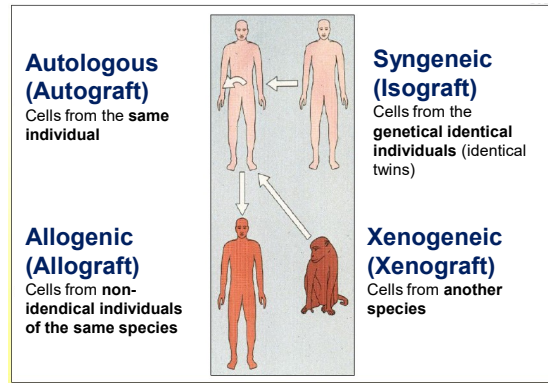
Macrophage-Mediated Extracellular Degradation

Macrophages and FBGCs release mediators of degradation such as: Reactive oxygen intermediates (ROIs), enzymes, and acid between the cell membrane and biomaterial surface.

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Tissue engineered implants

Biomaterials are combined with cells, proteins, and/or other biological components for regeneration of diseased and damaged tissues.



http://141.83.55.222/media/custom/1595_1005_3.PDF, Folie 9

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Tissue engineered implants

- Interactions between the host and the implanted cells
- Interactions between the host and the implanted biomaterial

At the implant site:

inflammatory mediators and signaling molecules, e.g. cytokines, growth factors, and low pH, ROS, and degradative enzymes, can generate an environment, which is different than the native environment of the incorporated cells

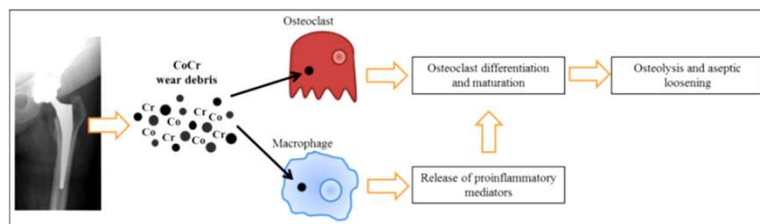
→ Undesired activation, differentiation, proliferation, or migration of cells can be triggered.

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Example: Main challenge with joint implants

Wear debris, primarily generated from the prosthetic joint articular surface, lead to a foreign body inflammatory reaction.

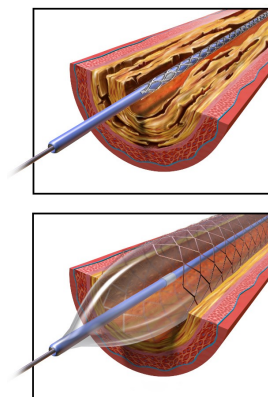
- Metallic debris induce macrophage activation and trigger immune responses resulting in the release of an array of proinflammatory mediators.
- These mediators induce osteoclast differentiation and maturation, which lead to bone resorption and, ultimately, aseptic loosening.
- Resulting in implant failure (10 to 20 years after joint replacement surgery)



Olga M. Posada, et al. *Lubricants* 2015, 3, 539-568

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Example: Challenges with cardiovascular stents



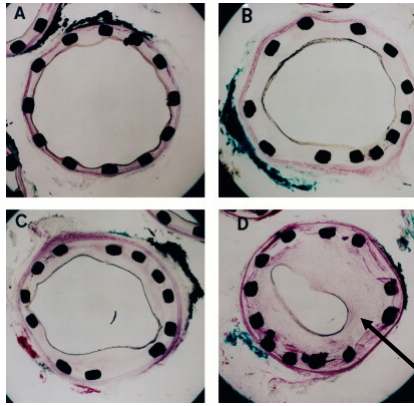
https://en.wikipedia.org/wiki/Angioplasty#/media/File:Angioplasty_-_Balloon_Inflated_with_Stent.png

Angioplasty is used to reopen narrowed or obstructed blood vessels.

- The balloon catheter is passed over a wire into the narrowed vessel and inflated.
- The balloon pushes the plaque against the wall of the artery.
- A stent is inserted to ensure that the vessel remains open
- Blood flow is restored.

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Example: Challenges with cardiovascular stents



Due to injury and the presence of a foreign material

- Thrombosis can occur
- Inflammation is induced
- SMCs proliferate and lead to in stent hyperplasia
- Can result in occlusion of the blood vessel

Van Belle E., et al. *J Am Coll Cardiol.* 1997;29(6):1371-1379.

Intimal Hyperplasia

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Evaluation of responses to implants

Safety data can be obtained by testing according to recommended guidelines:

- ISO 10993 standard, Biological Evaluation of Medical Devices
- Blue Book Memorandum #G95-1 guidance document, an FDA -modified version of ISO 10993, "Biological Evaluation of Medical Devices - Part 1."
- From the Ministry of Health, Labour and Welfare (MHLW) (Japan)

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Evaluation of responses to implants

Tests required for tissue compatibility:

- Cytotoxicity
- Sensitization
- Irritation or intradermal reactivity
- Systemic toxicity (acute toxicity) / pyrogenicity
(adverse effects within 24 h after implantation)
- Subacute toxicity
(adverse effects during a period of 14 to 28 days after implantation)
- Subchronic toxicity
(adverse effects up to 90 days after implantation)
- Genotoxicity
(DNA effects, gene mutations, and chromosomal aberrations)

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Evaluation of responses to implants

Tests required for tissue compatibility:

- Implantation
(to assess the local pathological effects)
- Hemocompatibility:
evaluation of thrombosis, coagulation, platelets, hematology, and immunology (complement and leukocytes)
- Chronic toxicity
(adverse effects over 90 days after implantation)
- Carcinogenicity (determine tumorigenic potential of implants)
- Biodegradation
(determination of kinetics of biodegradation, nature of degradation products, etc.)
- Immune response

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Selection of animal models for in vivo tests

TABLE 8 Animal models for the in vivo assessment of medical devices

Device classification	Animal
Cardiovascular	
Heart valves	Sheep
Vascular grafts	Dog, pig
Stents	Pig, dog
Ventricular assist devices	Calf
Artificial hearts	Calf
Ex-vivo shunts	Baboon, dog
Orthopedic/bone	
Bone regeneration/substitutes	Rabbit, dog, pig, mouse, rat
Total joints—hips, knees	Dog, goat, non-human primate
Vertebral implants	Sheep, goat, baboon
Craniofacial implants	Rabbit, pig, dog, non-human primate
Cartilage	Rabbit, dog
Tendon and ligament substitutes	Dog, sheep
Neurological	
Peripheral nerve regeneration	Rat, cat, non-human primate
Electrical stimulation	Rat, cat, non-human primate
Ophthalmological	
Contact lens	Rabbit
Intraocular lens	Rabbit, monkey

Anderson J.M., et al., 2001, Biological Responses to Materials

Animal models are used to predict clinical behavior, safety, and biocompatibility of implants in humans.

Choice of Animal:

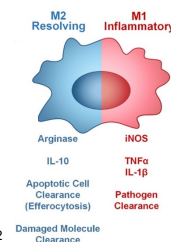
Select on similarity of physiology and healing response to that of humans in a given application

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Future prospects

The development of new implants requires an in-depth understanding of the biological responses to implanted materials.

- Selection of materials that evoke less macrophage response
- Generation of surface coatings to prevent recognition
- Further research to understand the mechanisms of macrophage mediated biomaterial degradation is required
- Modulation of macrophage reaction to the implant



Bohlson S.S. et al. Front. Immunol., 2014, <http://dx.doi.org/10.3389/fimmu.2014.00402>

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Summary

The biological reaction to an artificial implant

Foreign body response

Foreign giant cells

Required tests for evaluation of biocompatibility

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Thank you for your attention!

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