PÉCSI TUDOMÁNYEGYETEM
ÁLTALÁNOS ORVOSTUDOMÁNYI KAR
Immunológiai és Biotechnológiai Intézet

Biotechnology 2019

Biological therapies

Artificial and bioartificial organs & Brain-machine interface

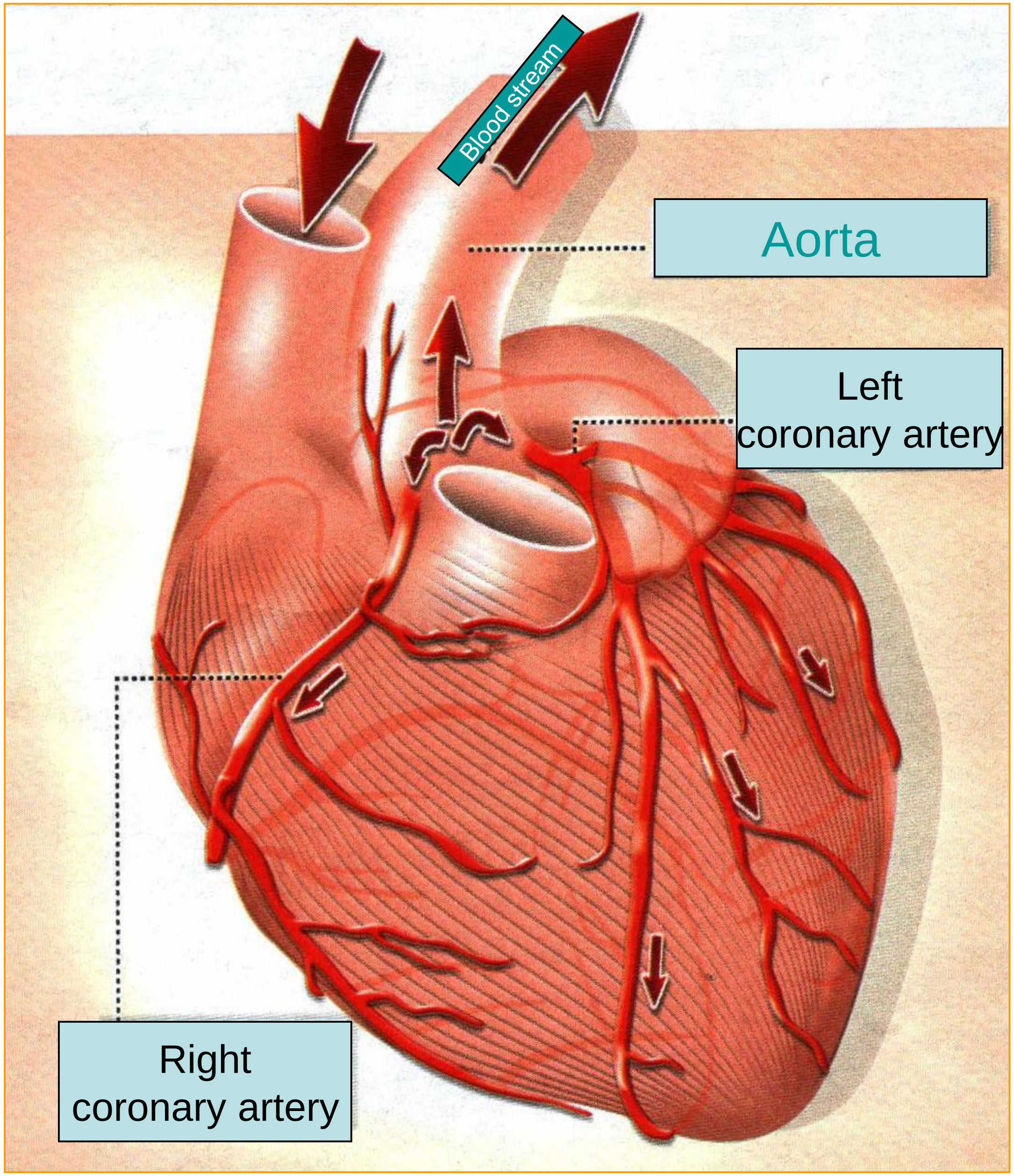
Najbauer József

Lectures 25-26; 2019. 05. 02.

Outline

1. ARTIFICIAL ORGANS AND ASSIST DEVICES
2. BIOARTIFICIAL ORGANS
3. NANOTECHNOLOGY AND ENGINEERING OF COMPLEX TISSUES
4. DEEP BRAIN STIMULATION
5. BRAIN-MACHINE INTERFACE
6. COGNITIVE NEURAL PROSTHETICS

1. ARTIFICIAL ORGANS AND ASSIST DEVICES



The Pumping Heart

(Cardiac Output):
>2l/min m²
300 L / h
7.200 L / day
2.628.000 L / year

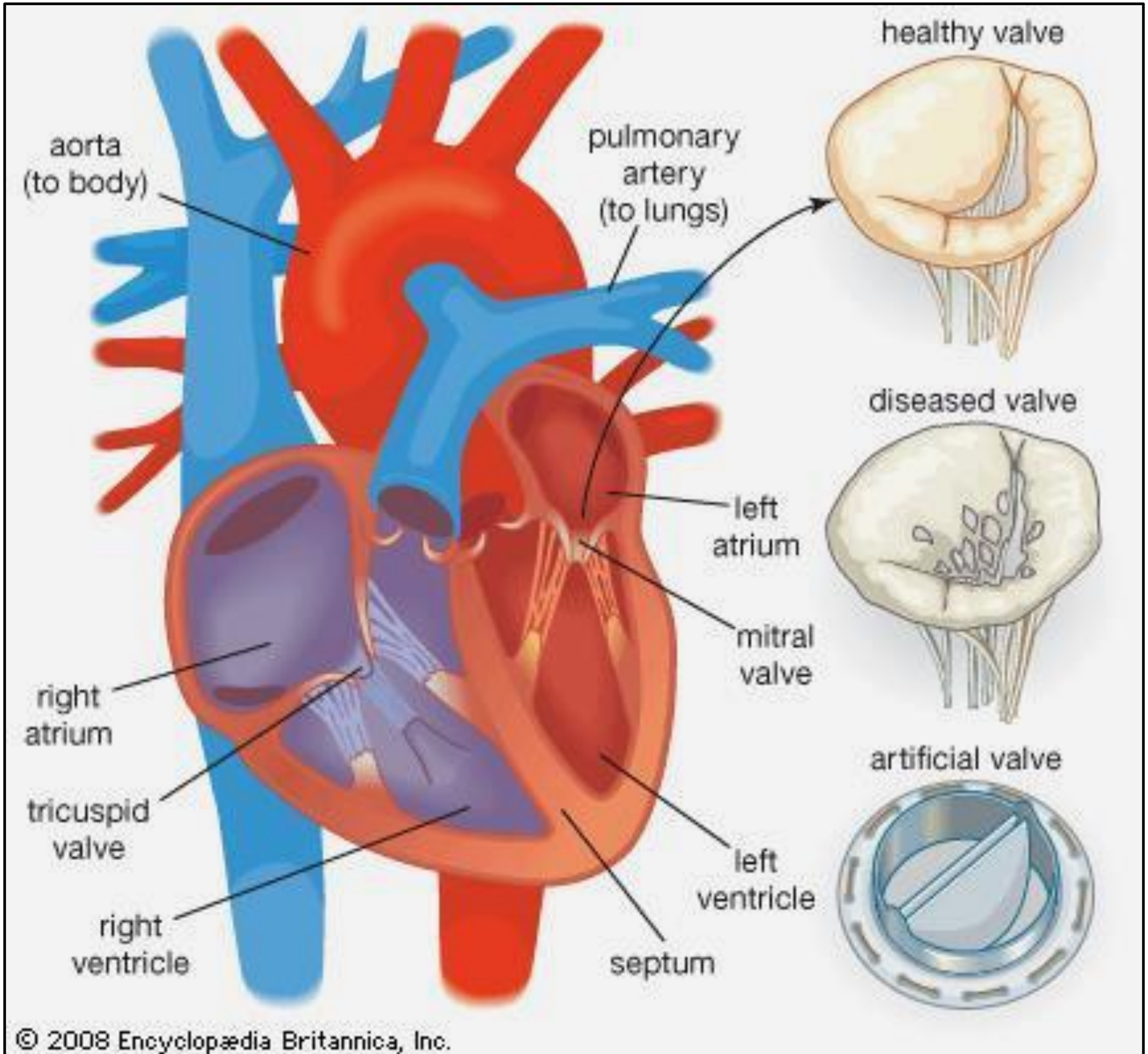
Resting Performance:
1,5 W

Slide: Vienken J, Bad Homburg, Germany

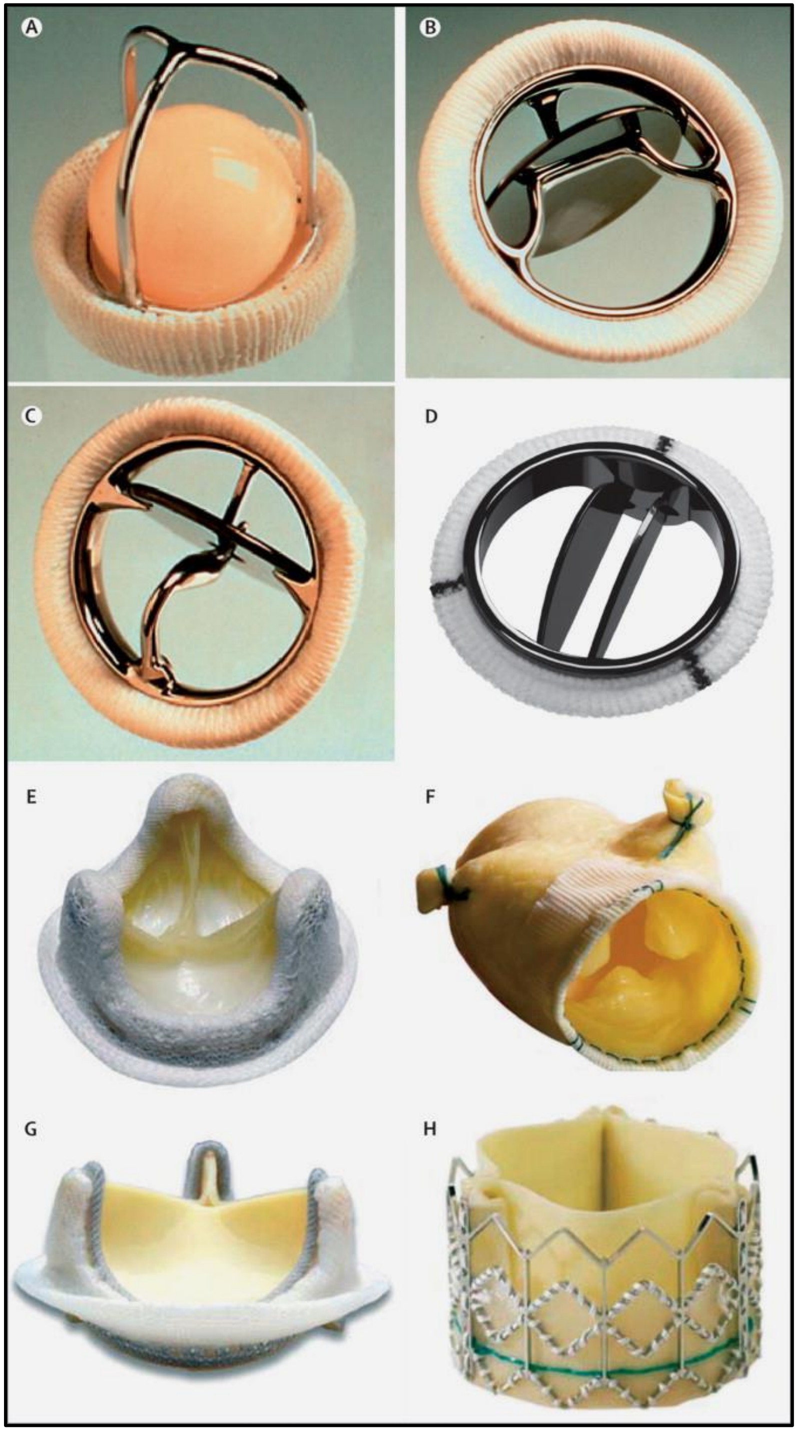
The Heart offers:

- High versatility of blood flow
  2l /min → 25l /min, stress dependent.
- Fast adaptation to load and strain.
- No clotting of blood in heartvalves and heart.
- Heart muscle accessible for training effects, capacity for moderate repair.
- Long lasting performance: > 80 years.

Heart valves



Open and close
~80,000 x
per day.



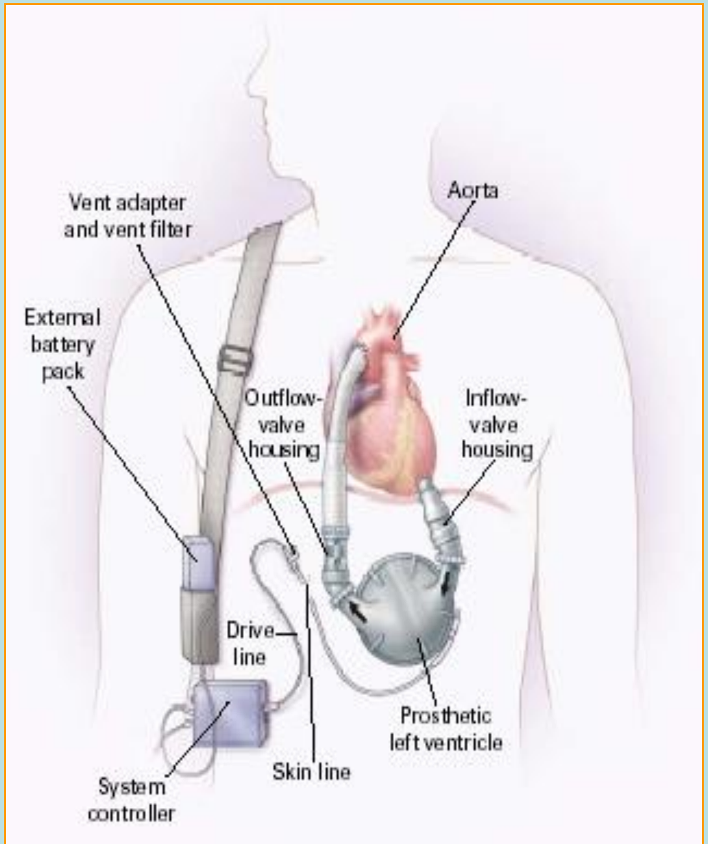
Different models of prosthetic heart valves

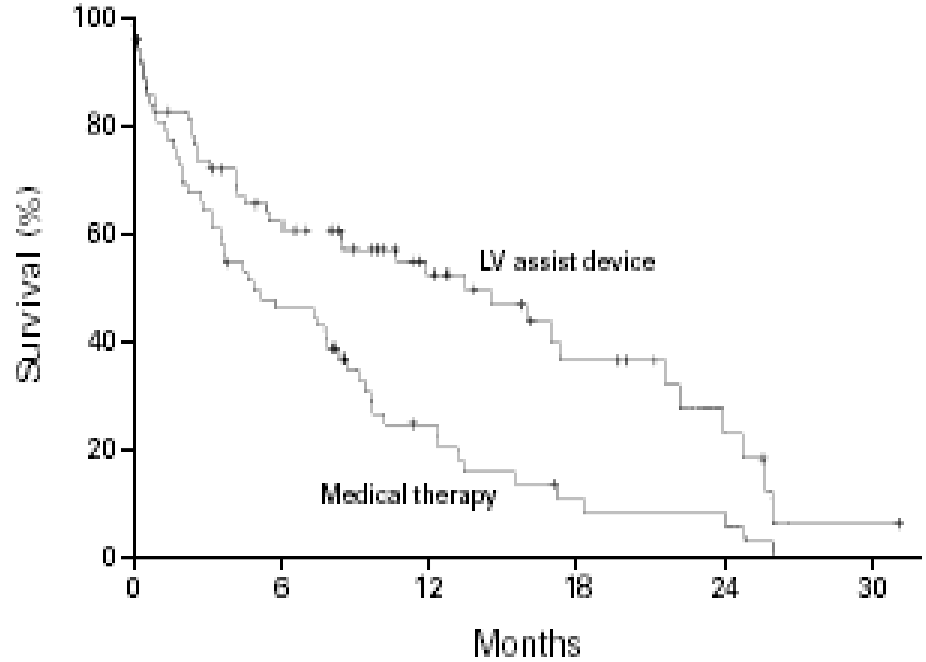
Over 4 million people worldwide have received a prosthetic heart valve, and an estimated 300 000 valves are being implanted every year.

Figure 1: Different models of prosthetic heart valves **(A)** Starr-Edwards caged-ball valve (courtesy of Edwards Lifesciences LLC, Irvine, CA, USA). **(B)** Bjork-Shiley tilting-disk valve (courtesy of Sorin Group of Canada Inc, Canada). **(C)** Medtronic Hall tilting-disk valve (with permission from Medtronic Inc, Canada). **(D)** St Jude Medical Regent bileaflet valve (courtesy of St Jude Medical Canada). **(E)** Medtronic HK II ultra porcine valve (with permission from Medtronic Inc). **(F)** Medtronic Freestyle porcine valve (with permission from Medtronic Inc). **(G)** Carpentier-Edwards Perimount bovine pericardial valve. **(H)** Edwards SAPIEN transcatheter pericardial aortic valve (courtesy of Edwards Lifesciences LLC, Irvine, CA, USA).

Sun JCJ et al, Lancet, 2009

‚Long-term use‘ of LVADs for ESHF



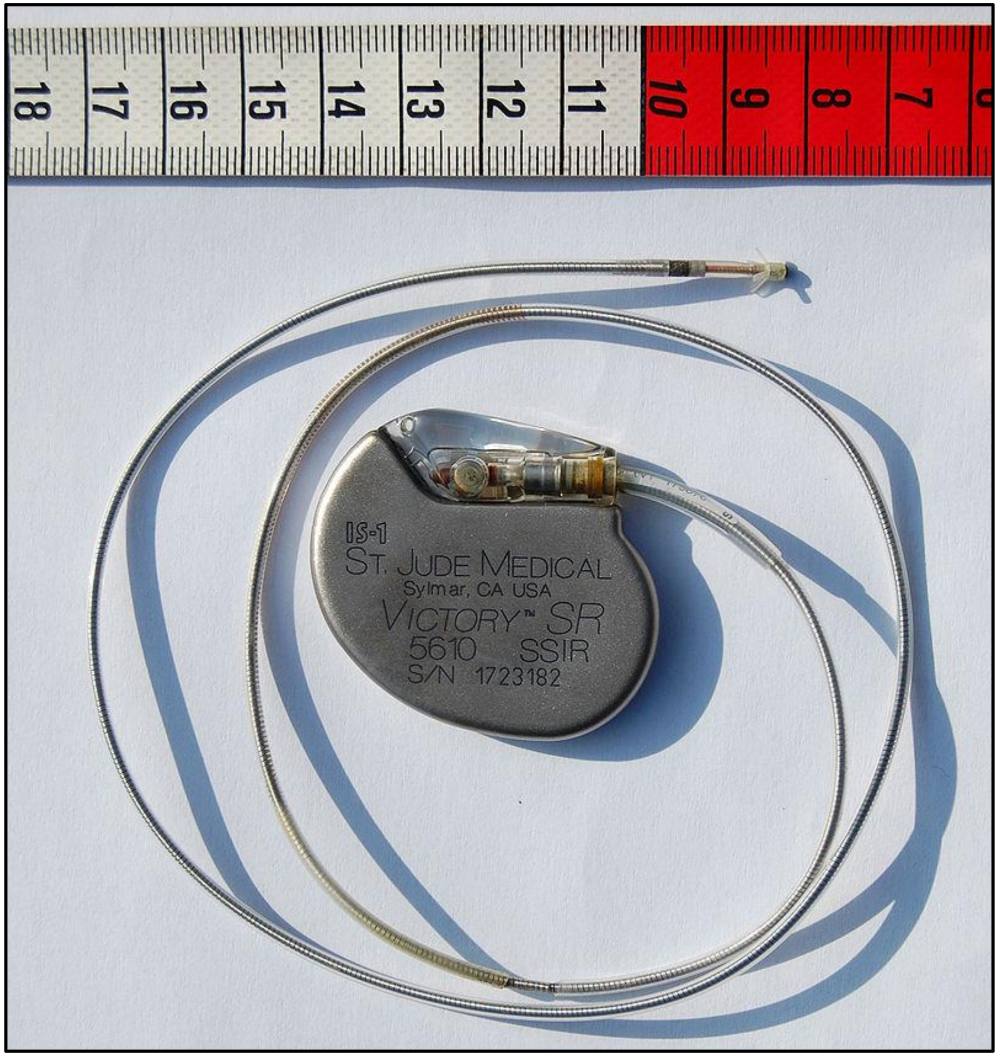


No. at Risk						
LV assist device	68	38	22	11	5	1
Medical therapy	61	27	11	4	3	0

ESHF, End-stage heart failure
LVAD, Left ventricular assist device

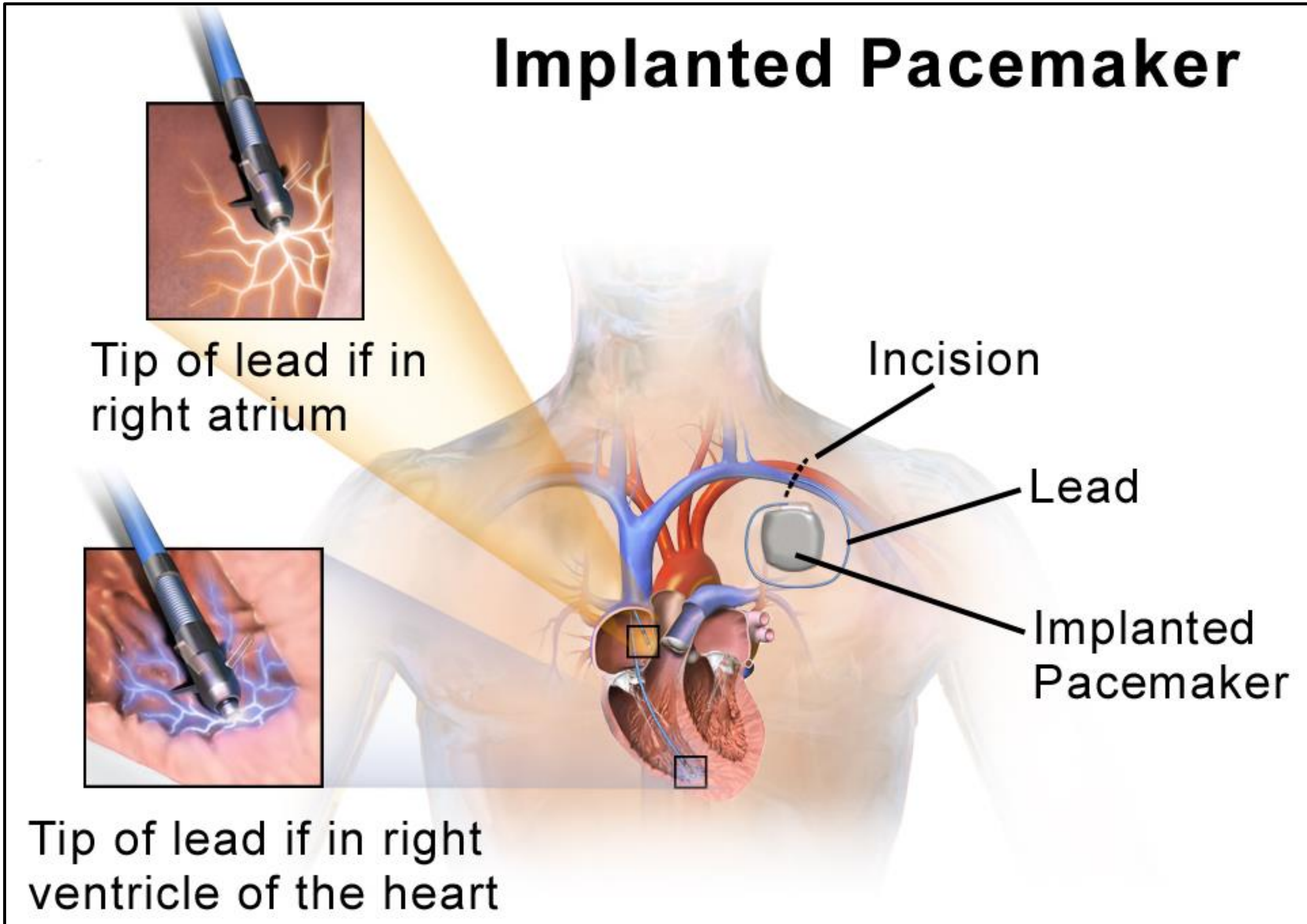
Rose et al, New Engl J Med, 345:1435-1443 (2001)

Pacemaker



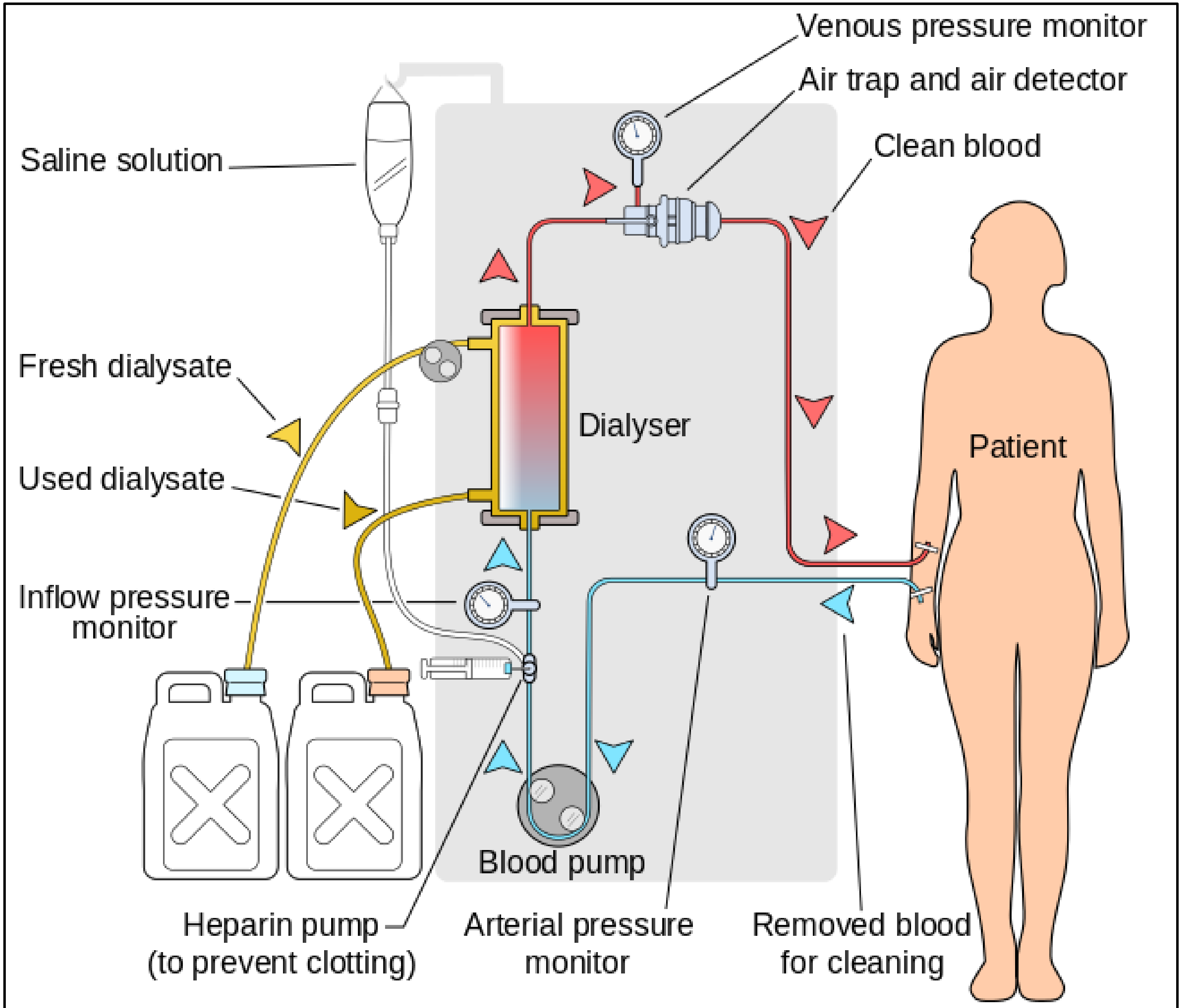
A **pacemaker** is a small device that's placed in the chest or abdomen to help control abnormal heart rhythms. This device uses low-energy electrical pulses to prompt the heart to beat at a normal rate. **Pacemakers** are used to **treat arrhythmias.** Arrhythmias are problems with the rate or rhythm of the heartbeat.

wikipedia.org

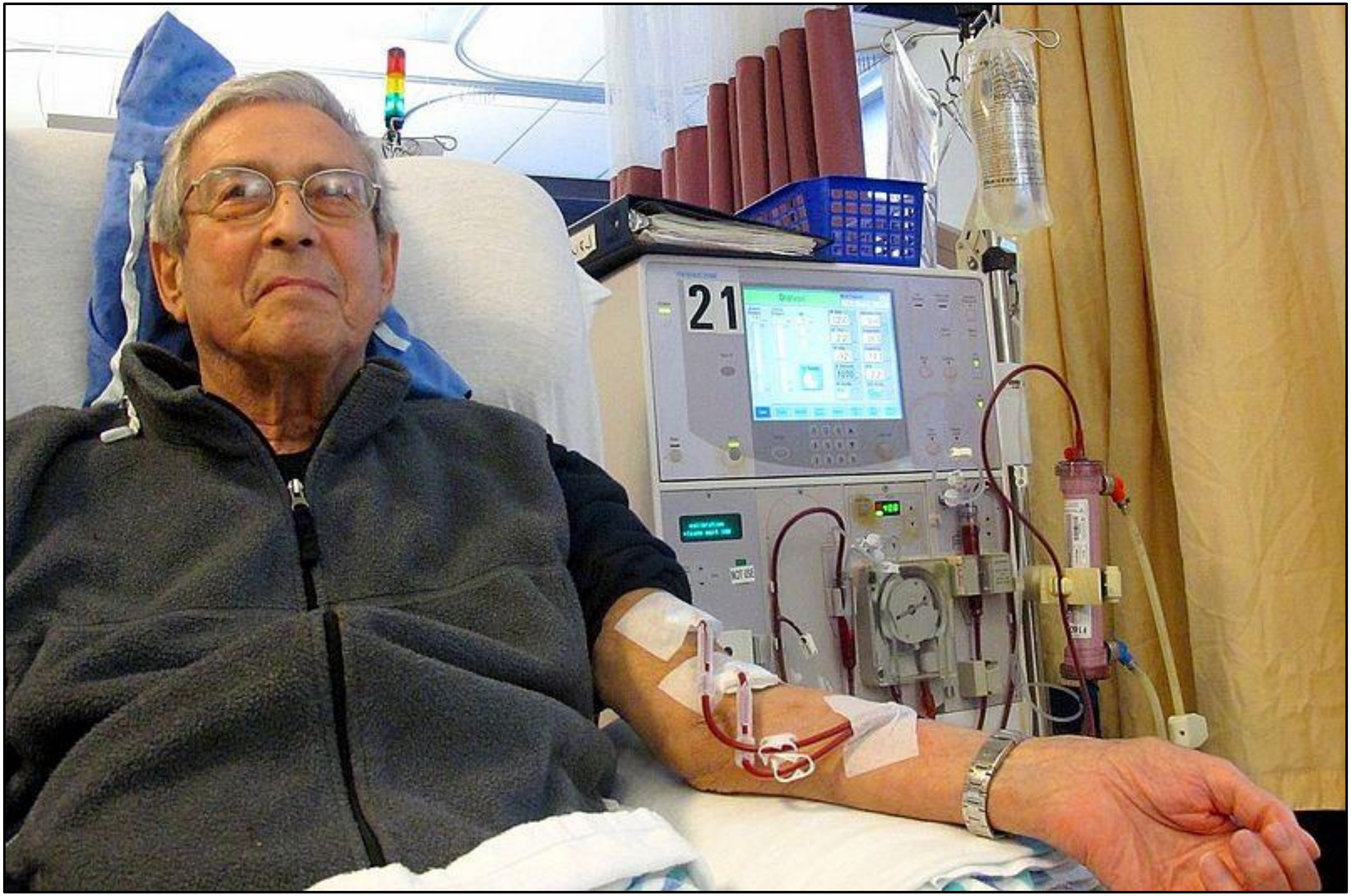


wikipedia.org

Hemodialysis schematic



Patient receiving dialysis



2. BIOARTIFICIAL ORGANS

Construction of engineered bladder

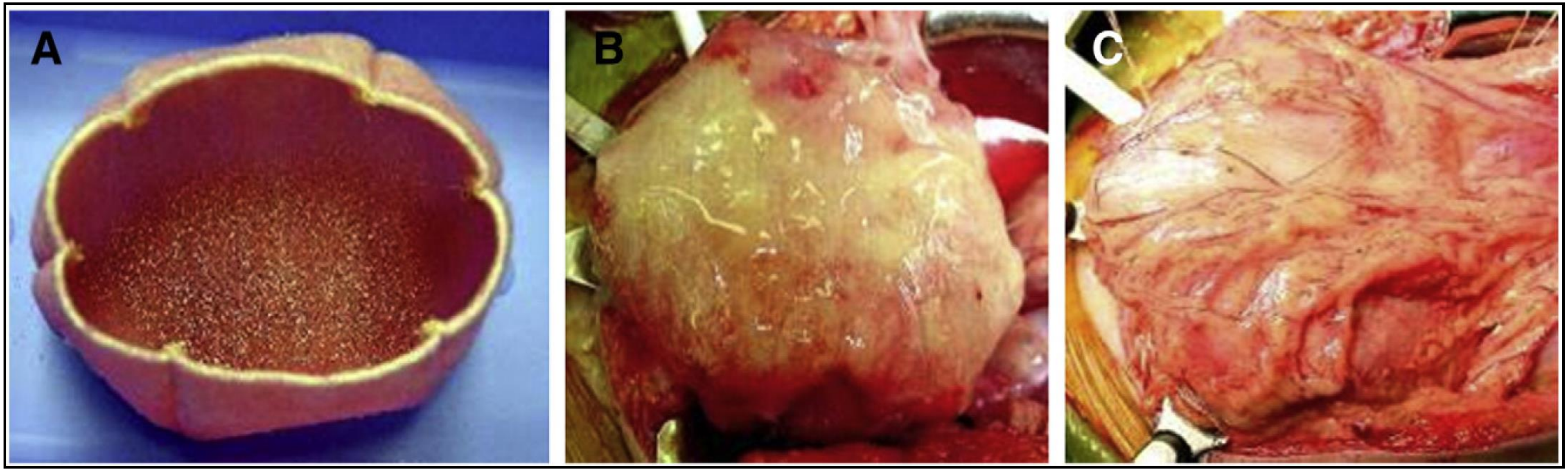


Fig. 3 A, **Scaffold material** seeded with cells for use in bladder repair.

B, The **seeded scaffold is anastamosed to native bladder** with running 4-0 polyglycolic sutures.

C, **Implant covered with fibrin glue and omentum.**

Atala A, Journal of Pediatric Surgery, 2012

Cystograms and urodynamic studies of a patient before and after implantation of the tissue engineered bladder

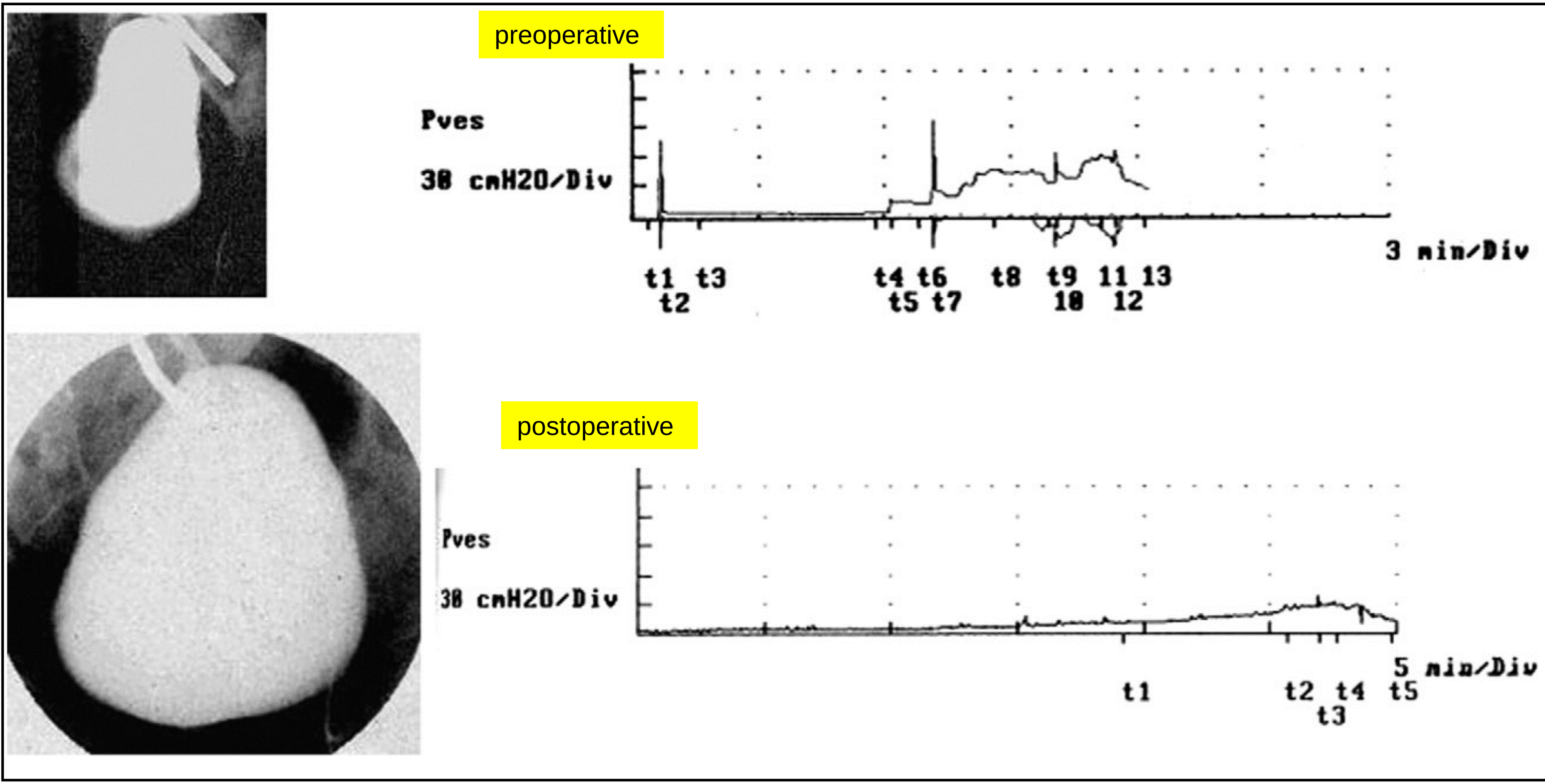


Fig. 4 A, Preoperative results indicate an irregular-shaped bladder in the cystogram (*left*) and abnormal bladder pressures as the bladder is filled during urodynamic studies (*right*).
B, Postoperatively, findings are significantly improved.

Atala A, Journal of Pediatric Surgery, 2012

Organ engineering based on decellularized matrix scaffolds

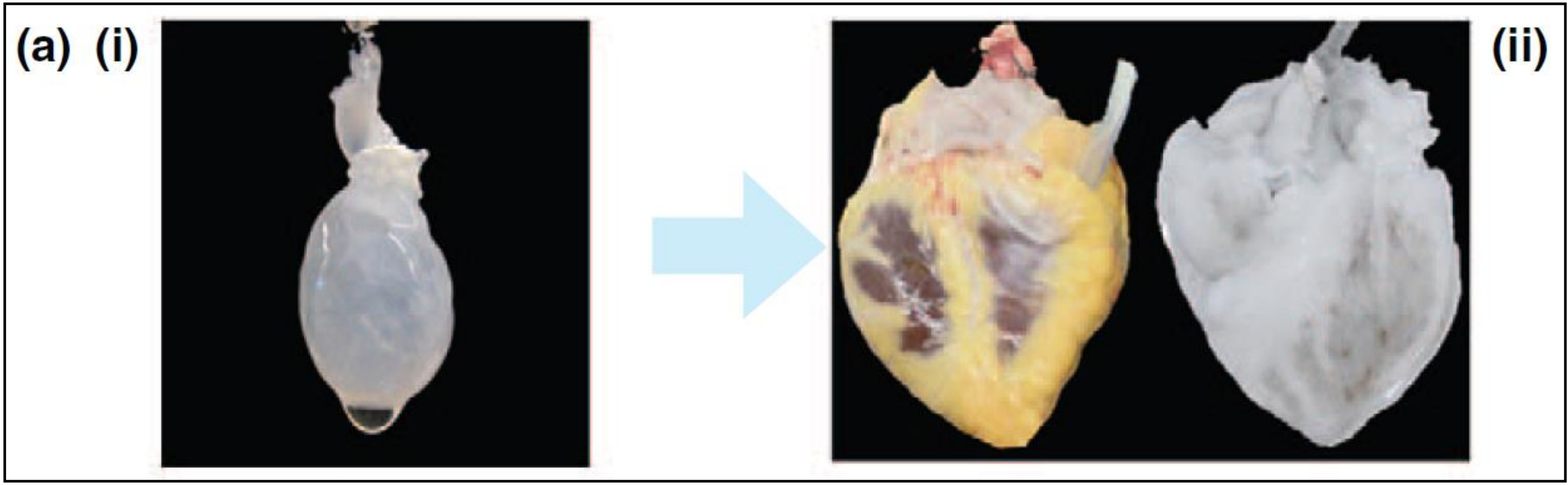
Song & Ott, Trends Mol Med, 2011

- End-organ failure is one of the major healthcare challenges in the Western world. Yet, donor organ shortage and the need for immunosuppression limit the impact of transplantation. The regeneration of whole organs could theoretically overcome these hurdles.

- Early milestones have been met **by combining stem and progenitor cells with increasingly complex scaffold materials** and culture conditions. Because the native extracellular matrix (ECM) guides organ development, repair and physiologic regeneration, it provides a promising alternative to synthetic scaffolds and a foundation for regenerative efforts.

- **Perfusion decellularization** is a novel technology that generates **native ECM scaffolds** with intact 3D anatomical architecture and vasculature. This review summarizes achievements to date and discusses the role of native ECM scaffolds in organ regeneration.

Perfusion-decellularized whole organ scaffolds
Heart scaffold

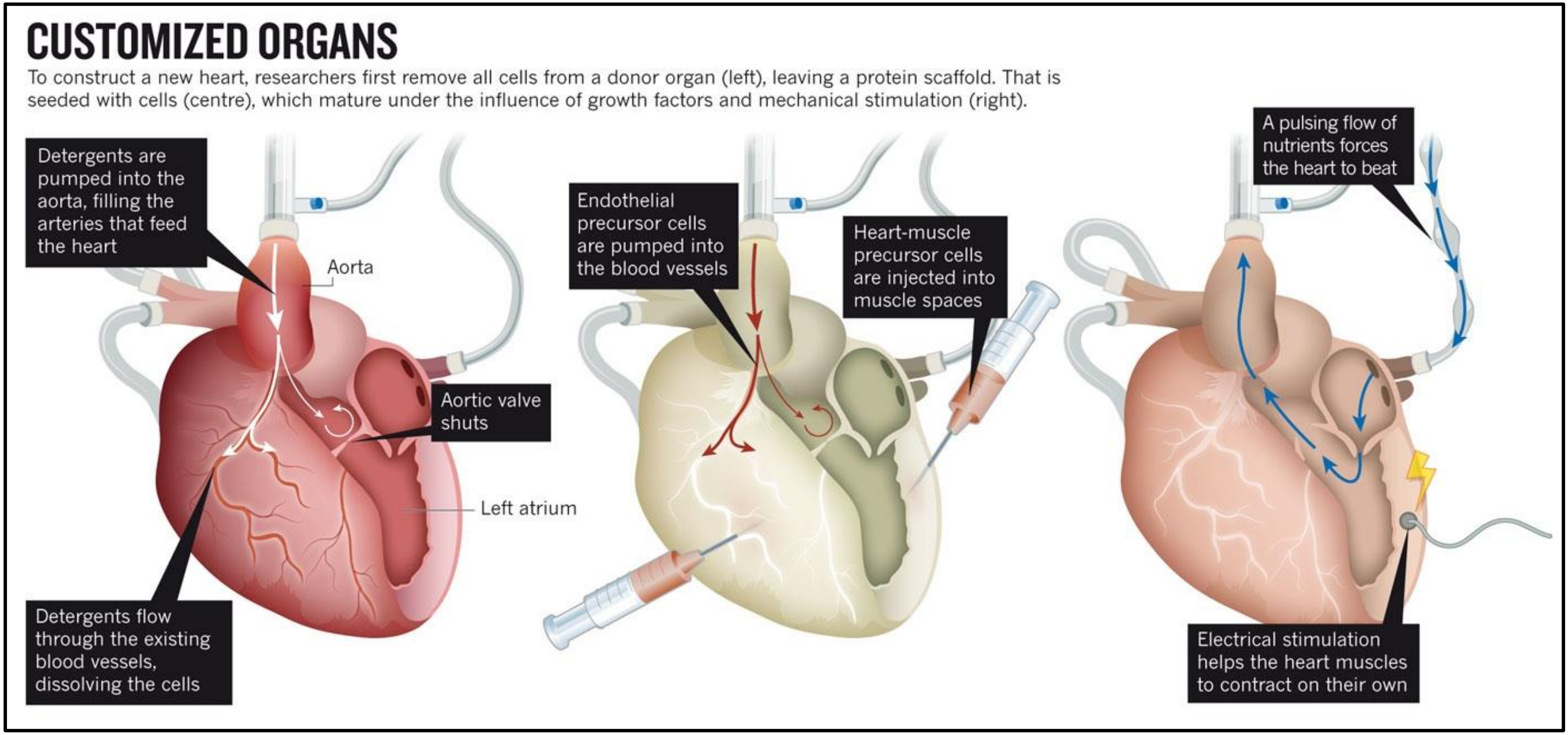


The native ECMs of cadaveric organs can be isolated by the perfusion of the native vascular system with detergent solutions. The resulting scaffolds are acellular, but maintain the structure of the native organ.

(a) Rat heart scaffold generated from cadaveric heart by perfusion decellularization (i). The ascending aorta was cannulated for perfusion. **Cadaveric human heart** before and after perfusion decellularization (ii).

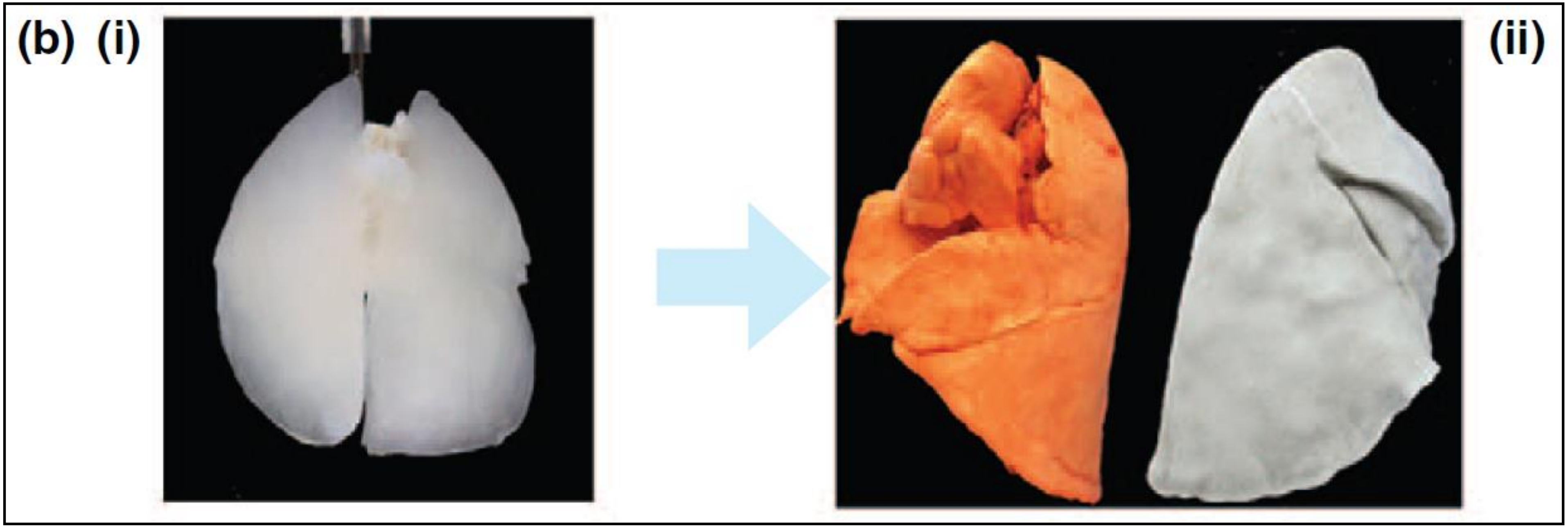
Song & Ott, Trends Mol Med, 2011

Building a heart



http://www.scientificamerican.com/media/inline/tissue-engineering-how-build-heart_3.jpg

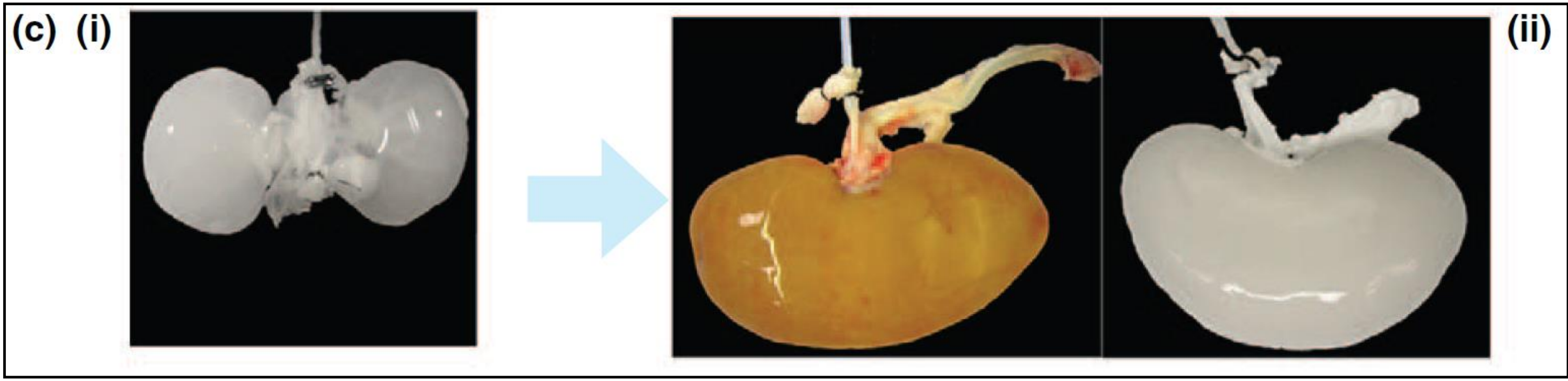
Lung scaffold



(b) Rat lung scaffold generated from cadaveric lung by perfusion decellularization (i). Perfusion was performed via the pulmonary artery. **Cadaveric sheep lung** before and after decellularization (ii).

Song & Ott, Trends Mol Med, 2011

Kidney scaffold



(c) Rat kidney scaffold generated from cadaveric kidney by perfusion decellularization (i). The abdominal aorta was cannulated for perfusion. **Porcine kidney** before and after perfusion decellularization (ii).

Song & Ott, Trends Mol Med, 2011

Ear

The synthetic scaffold of an ear sits bathed in cartilage-producing cells, part of an effort to grow new ears for wounded soldiers.

http://ngm.nationalgeographic.com/2011/03/big-idea/organ-regeneration-text

Box 2. Outstanding questions

- Organ Scaffolds:
  - type (engineered vs. native)
  - tissue source (human vs. animal)
  - standardized protocols for decellularization and sterilization

- Regenerative Cells:
  - type (adult derived vs. embryonic)
  - cell source (patient derived vs. banked)
  - standardized protocols for expansion, differentiation and purification

- Bioreactor Design and Organ Culture:
  - clinical grade bioreactors enabling safe and sterile whole organ culture
  - standardized culture protocols using clinically applicable growth factors

- Transplantation:
  - consensus on patient selection
  - identification of intermediate products
  - logistics of tissue/organ preservation and transport
  - understanding of immunologic response to a regenerated organ
  - optimization of graft longevity

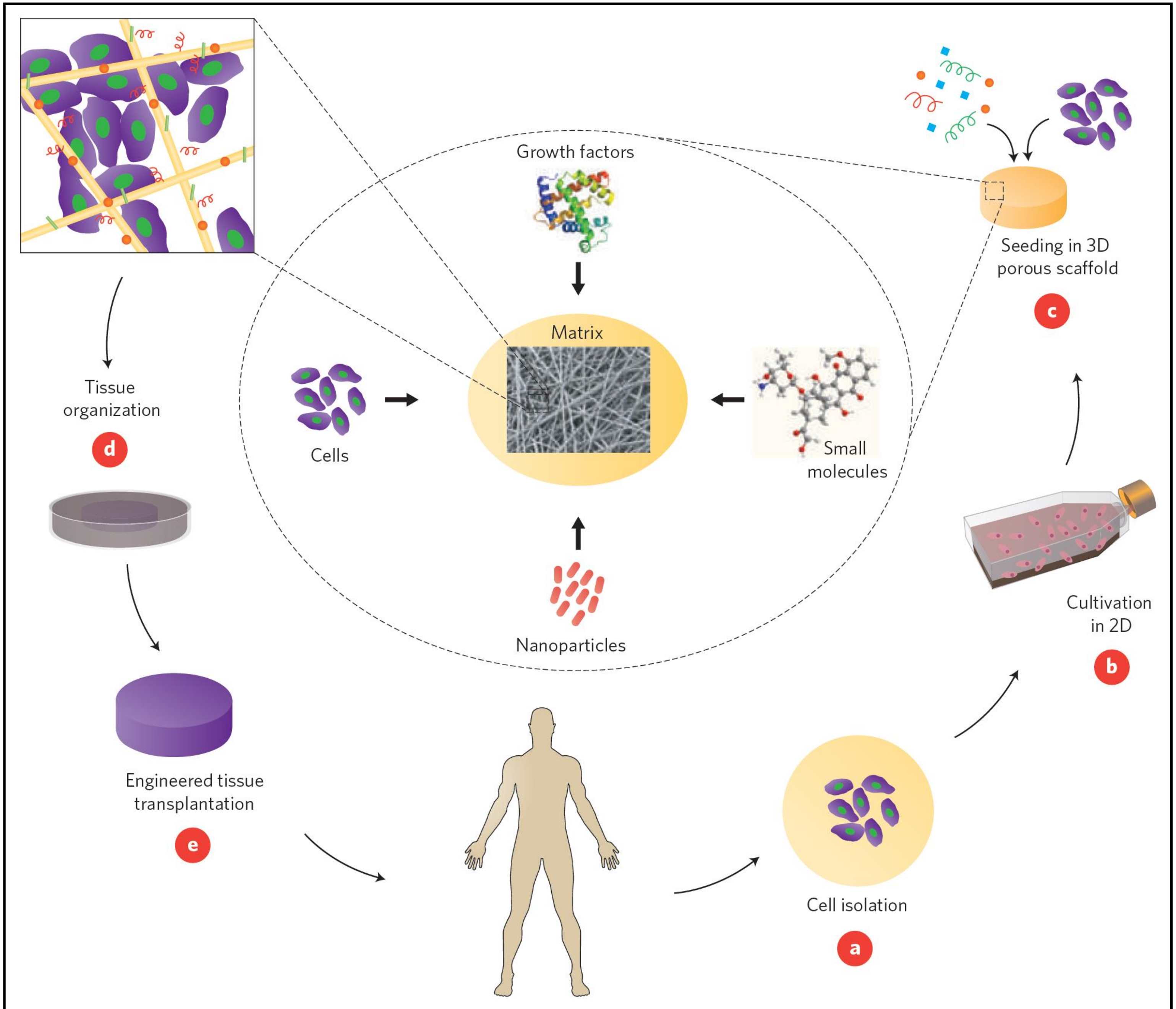
Song & Ott, Trends Mol Med, 2011

3. NANOTECHNOLOGY AND ENGINEERING OF COMPLEX TISSUES

Nanotechnological strategies for engineering complex tissues

- Tissue engineering aims at developing functional substitutes for damaged tissues and organs.
- Before transplantation, cells are generally seeded on biomaterial scaffolds that recapitulate the extracellular matrix and provide cells with information that is important for tissue development.

Dvir T et al, Nature Nanotechnology, 2011



Example of a <u>tissue engineering concept</u> that involves seeding cells within porous biomaterial scaffolds

Dvir T et al, Nature Nanotechnology, 2011

The information provided to cells by the extracellular matrix (ECM)

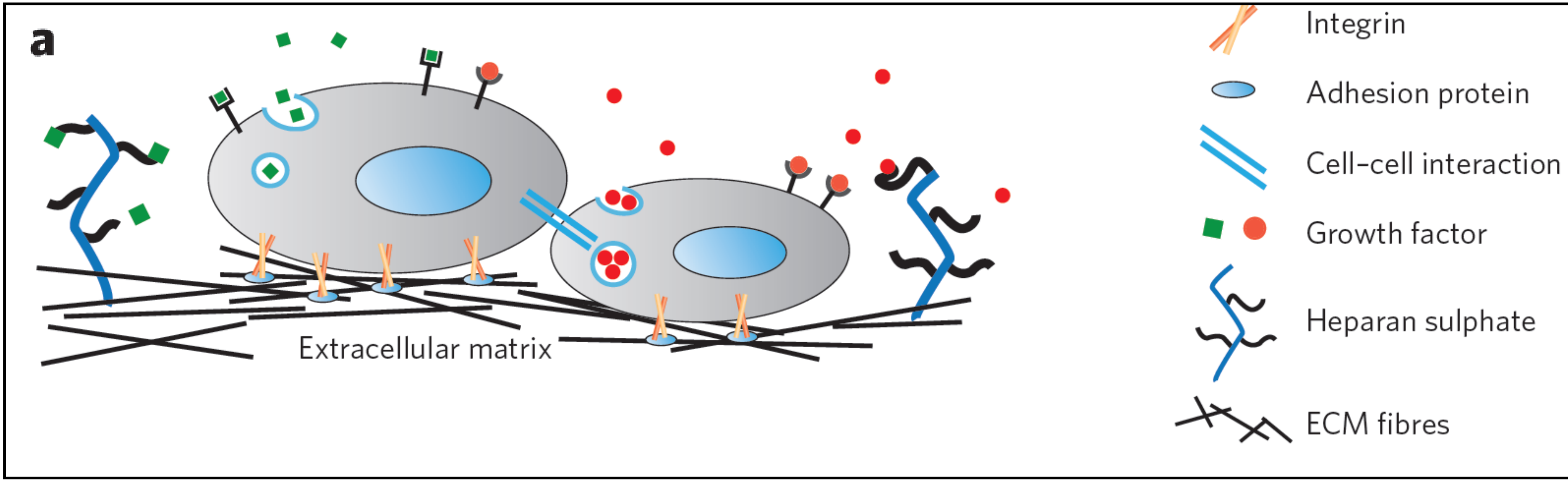


Figure 2 | a, ECM fibres provide cells with topographical features that trigger morphogenesis. Adhesion proteins such as fibronectin and laminin located on the fibres interact with the cells through their transmembrane integrin receptors to initiate intracellular signalling cascades, which affect most aspects of cell behaviour. Polysaccharides such as hyaluronic acid and heparan sulphate act as a compression buffer against the stress, or serve as a growth factor depot.

Dvir T et al, Nature Nanotechnology, 2011

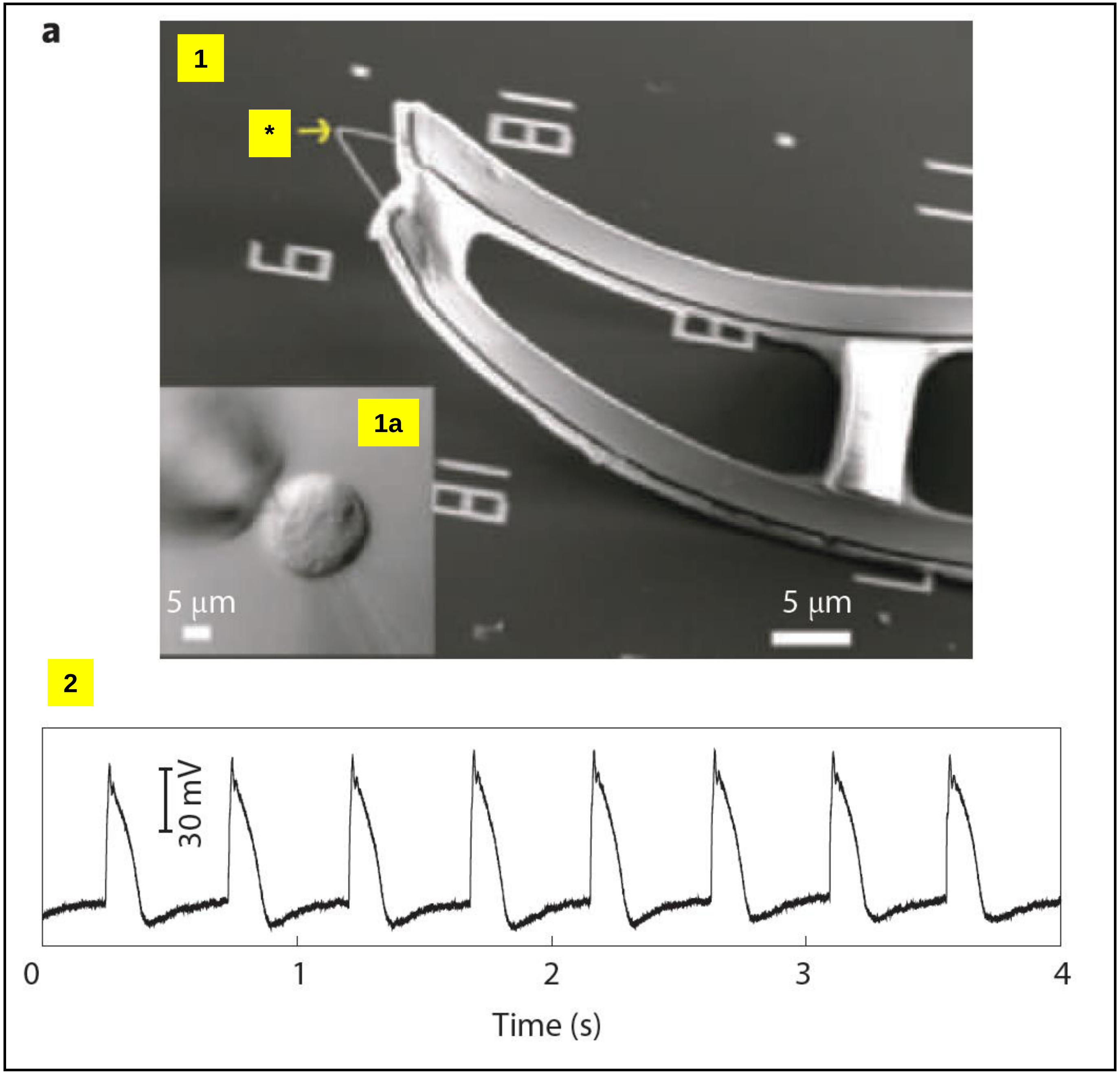


Figure 4 | Nanodevices in tissue engineering. **a**, Three-dimensional, free-standing nanowire transistor probe for electrical recording. The probe is composed of a kinked nanowire (yellow arrow) and a flexible substrate material. The device is used to penetrate the membrane of living cells (inset) and measure intracellular signals (lower panel).

Dvir T et al, Nature Nanotechnology, 2011

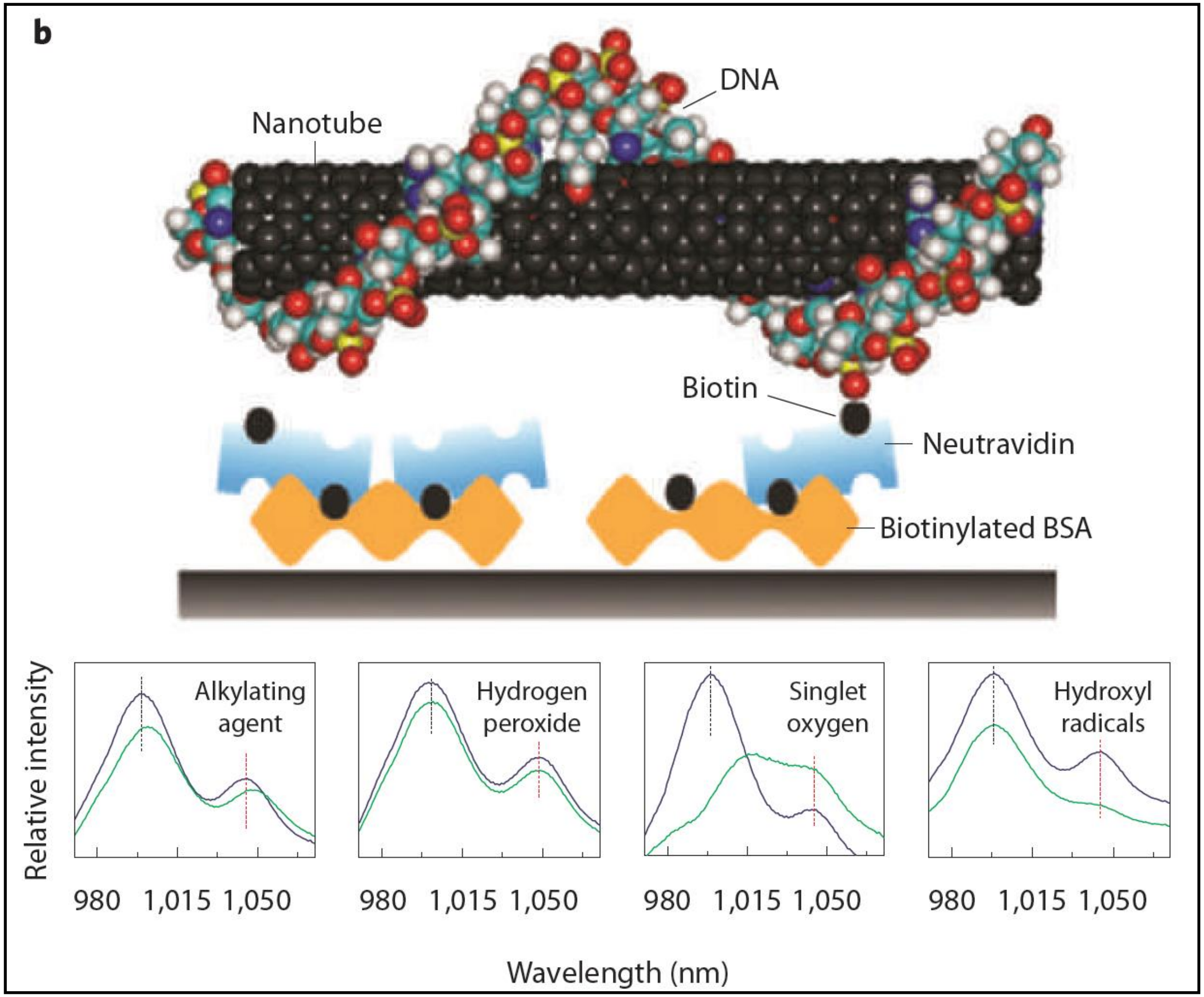
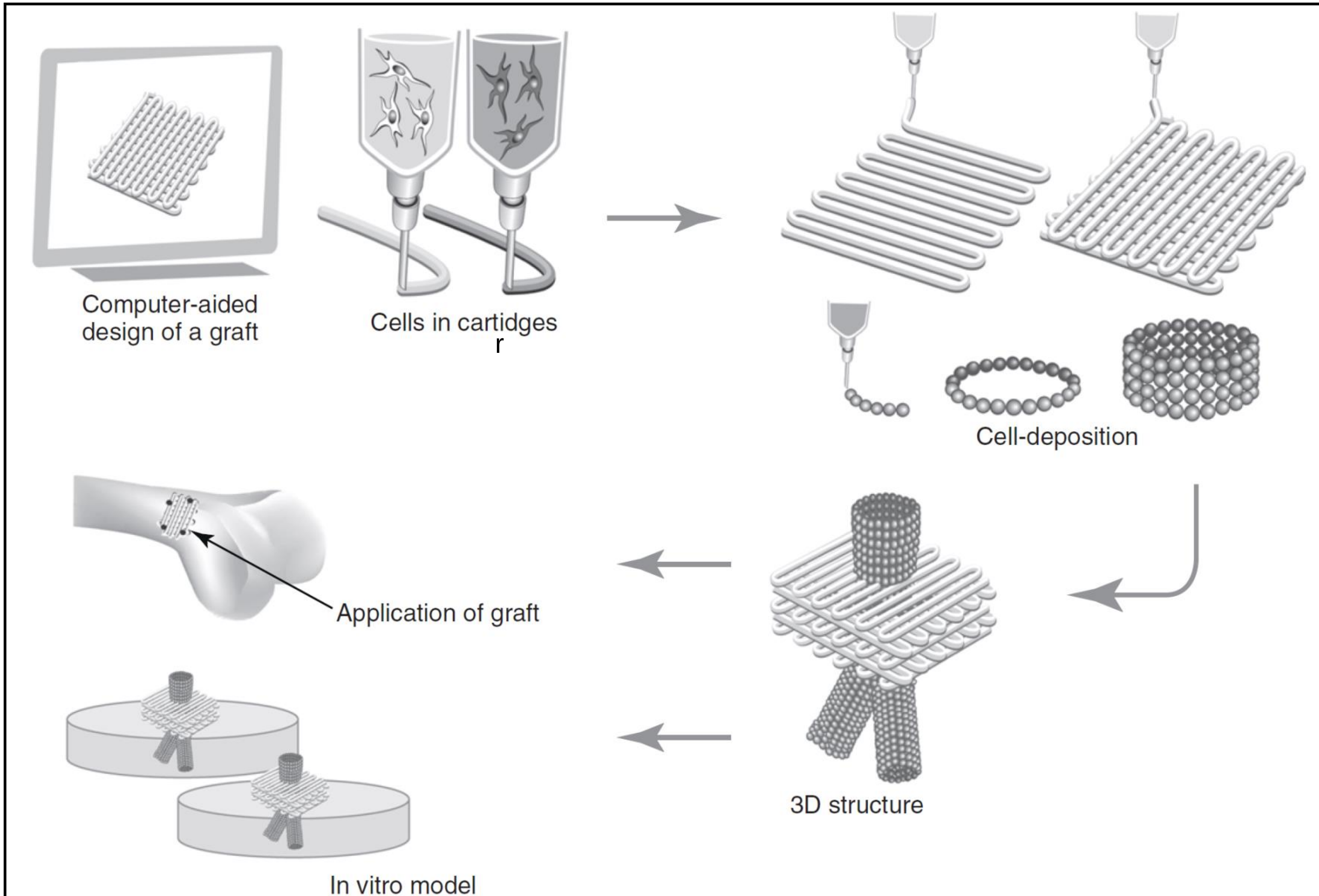


Figure 4 | Nanodevices in tissue engineering. b, Biosensors based on carbon nanotubes are used for the detection of genotoxic analytes, including chemotherapeutic drugs and reactive oxygen species. Upper figure shows a schematic of a **sensor made from a DNA and a single-walled carbon nanotube complex** bound to a glass surface through a biotin-BSA (orange) and neutravidin (blue) linkage. Lower figures reveal the spectral changes arising from the interaction of the nanotube sensor with (from left to right): a chemotherapeutic agent, hydrogen peroxide, singlet oxygen and hydroxyl radicals (blue curve, before addition of analytes; green curve, after addition of analytes).

Dvir T et al, Nature Nanotechnology, 2011

Organ printing



Fedorovich NE et al, Trends Biotech, 2011

Figure 1. Organ/tissue printing using fiber deposition. Computer-assisted design of the implant is translated by the rapid prototyping machine into a layered, cell-laden hydrogel structure with defined external shape and internal morphology, for use either in an in vitro model or in vivo grafting. The availability of multiple printing heads, each containing a specific cell type or hydrogel, enables printing of heterogeneous constructs.

4. DEEP BRAIN STIMULATION

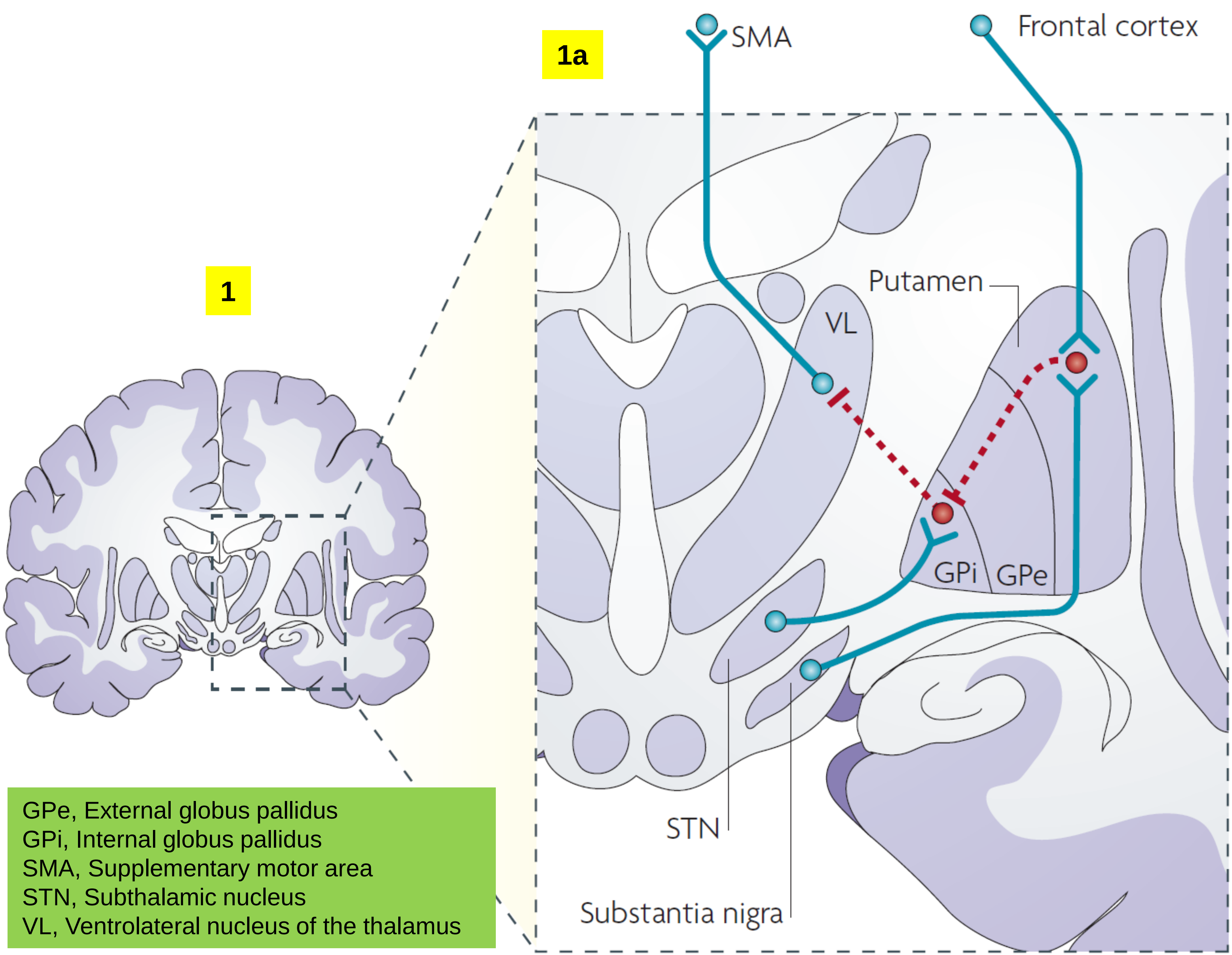
Deep brain stimulation (DBS)

Electrical signals generated in a central computing unit (CCU) placed subcutaneously are sent to electrodes implanted deeply in the brain to stimulate specific structures, such as the subthalamic nucleus in patients with Parkinson's disease.

Research directions:
DBS is being extended to earlier stages of Parkinson's disease and to some other neurological impairments, including epilepsy, minimally conscious states and psychiatric disorders.

Clausen J, Nature, 2009

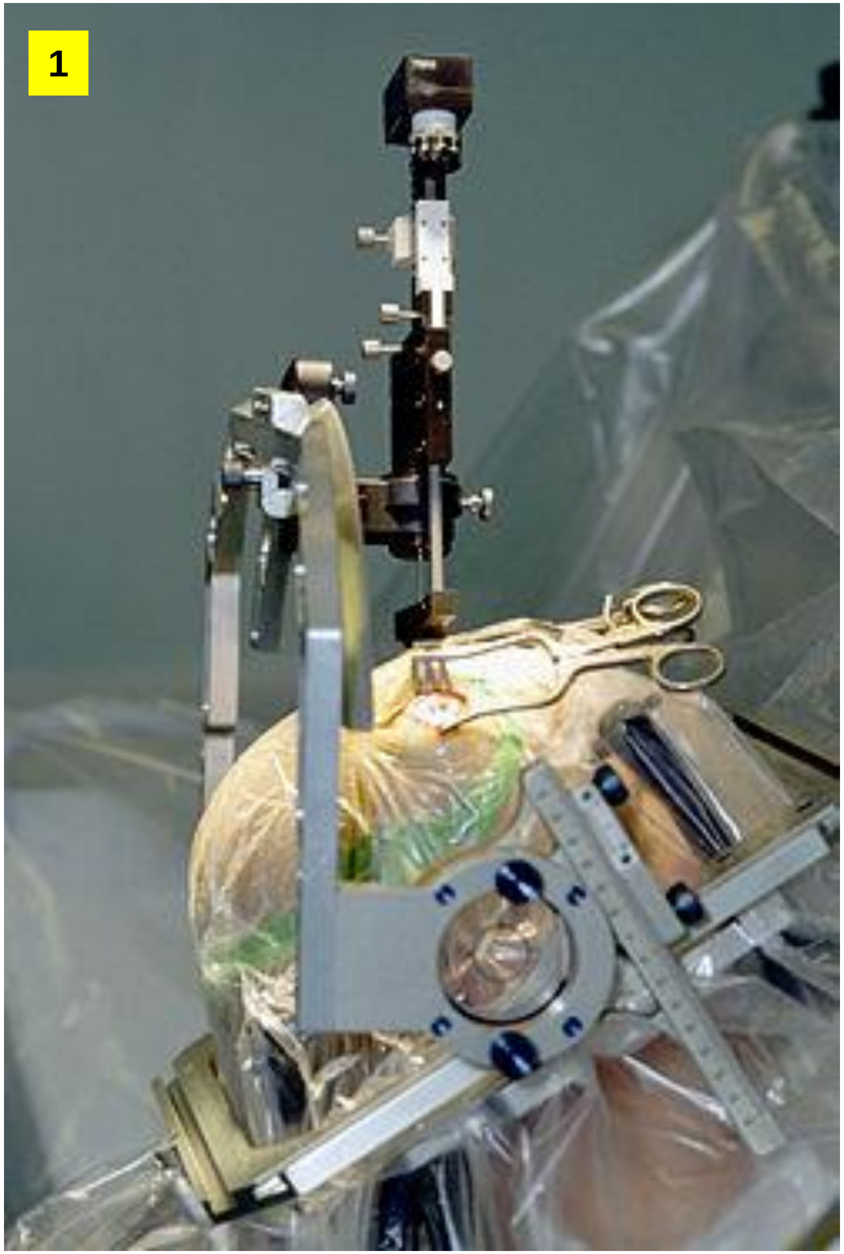
Deep brain stimulation (DBS) in movement disorders



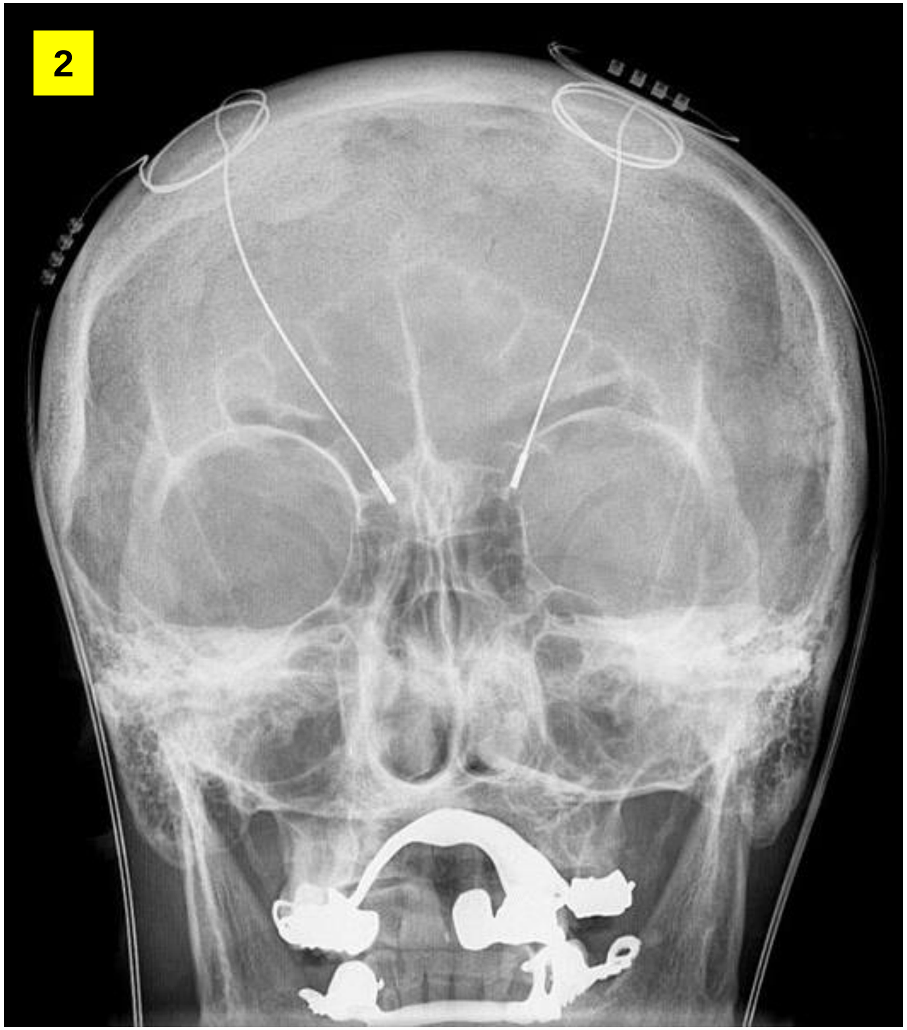
GPe, External globus pallidus
GPi, Internal globus pallidus
SMA, Supplementary motor area
STN, Subthalamic nucleus
VL, Ventrolateral nucleus of the thalamus

Kringelbach ML et al Nature Rev Neurosci, 2007

Insertion of electrode during surgery using a stereotactic frame



DBS-probes shown in X-ray of the skull



(white areas around maxilla and mandible represent metal dentures and are unrelated to DBS devices)

5. BRAIN-MACHINE INTERFACES

"Electronic devices can become our eyes and ears and even our arms and legs."

Clausen J, Nature, 2009

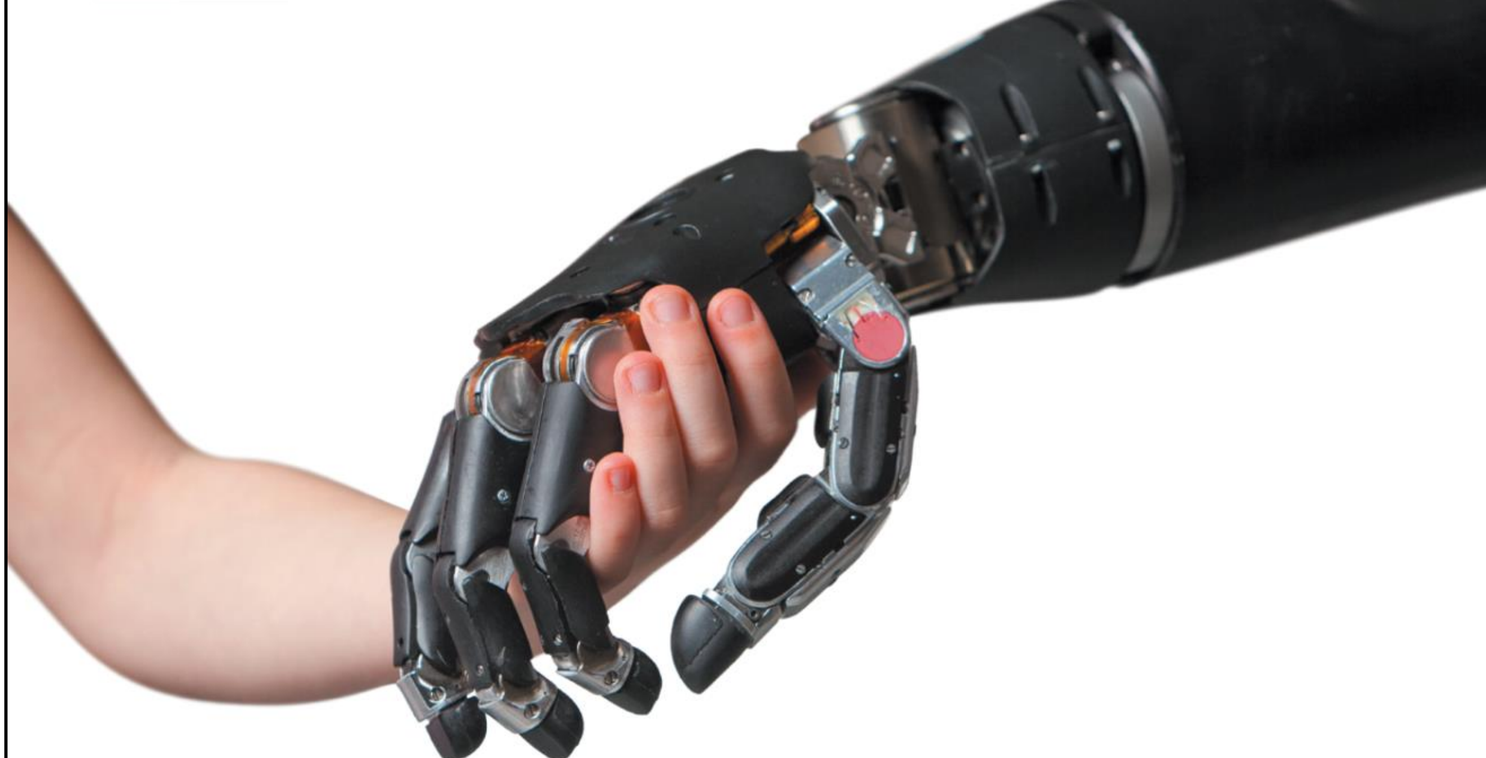
Brain–machine interface-based motor prostheses

Motor signals are recorded through electrodes implanted in the brain and sent to a CCU, which computes and generates signals to direct an artificial limb.

Research directions: animal experiments are becoming widespread. In experiments in patients with epilepsy, epicortical grid electrodes are placed on the surface of the brain to examine and improve decoding algorithms.

Clausen J, Nature, 2009

NEWS | FEATURE



Once more, with feeling

Prosthetic arms are getting ever more sophisticated. Now they just need a sense of touch.

BY ROBERTA KWOK

Kwok R, Nature, 2013

Sitting motionless in her wheelchair, paralysed from the neck down by a stroke, Cathy Hutchinson seems to take no notice of the cable rising from the top of her head through her curly dark hair. Instead, she stares intently at a bottle sitting on the table in front of her, a straw protruding from the top. Her gaze never wavers as she mentally guides a robot arm beside her to reach across the table, close its grippers around the bottle, then slowly lift the vessel towards her mouth. Only when she finally manages to take a sip does her face relax into a luminous smile.

Kwok R, Nature, 2013

<u>Skin prosthesis</u> using stretchable silicon nanoribbon electronics

- **Sensory receptors in human skin** transmit a wealth of **tactile and thermal signals** from external environments to the brain.

- Despite advances in understanding of mechano- and thermosensation, replication of these unique sensory characteristics in artificial skin and prosthetics remains challenging.

- The authors demonstrate a <u>smart prosthetic skin</u> instrumented with ultrathin, single **crystalline silicon nanoribbon strain, pressure and temperature sensor arrays, humidity sensors, electroresistive heaters and stretchable multi-electrode array**s for nerve stimulation.

- This collection of stretchable sensors and actuators facilitate highly localized mechanical and thermal skin-like perception in response to external stimuli, thus providing unique opportunities for emerging classes of prostheses and peripheral nervous system interface technologies.

Kim J et al, Nature Comm, 2014

a

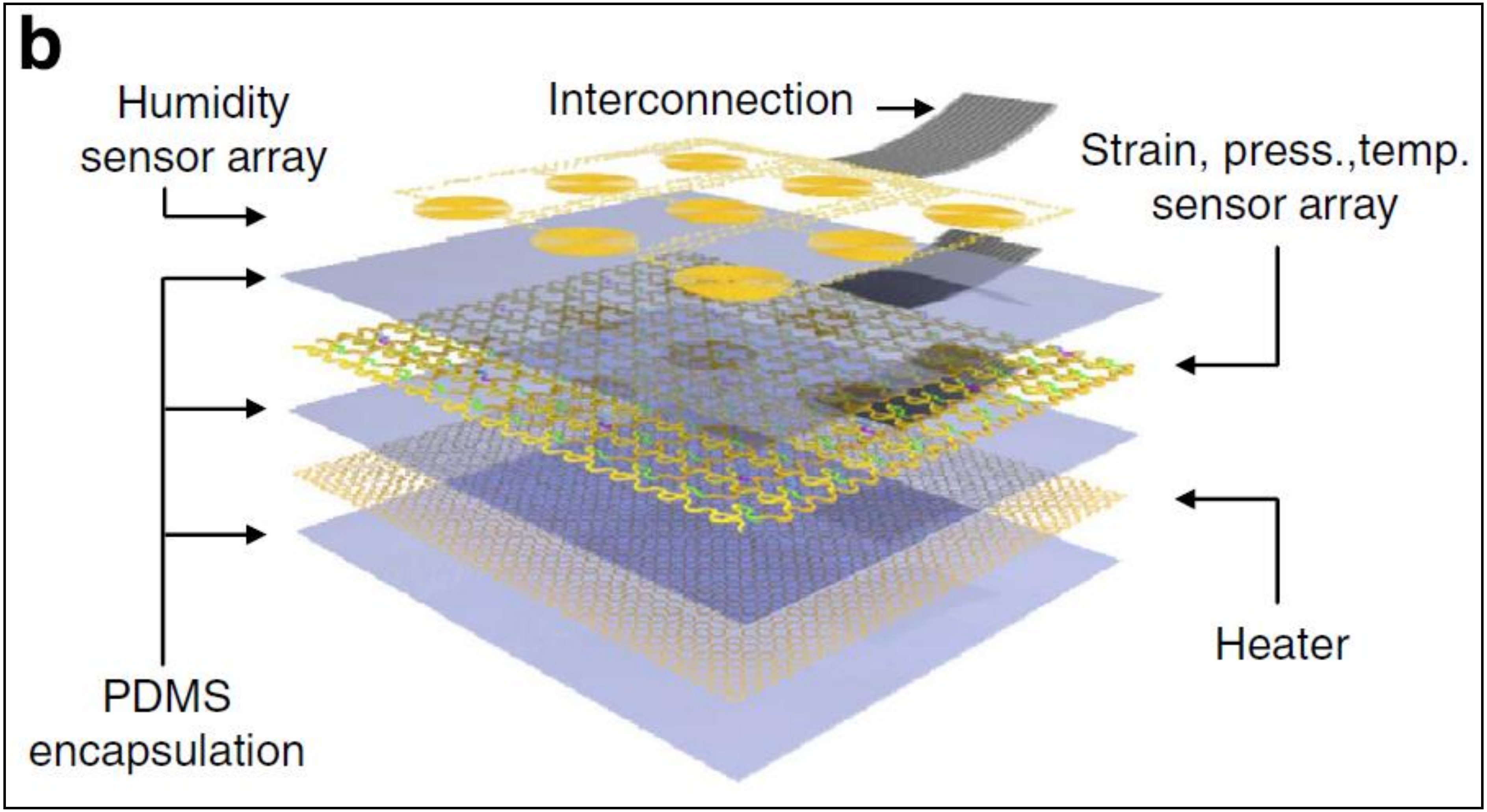
Skin prosthesis using stretchable silicon nanoribbon electronics

(a) Photograph of a representative smart artificial skin with integrated stretchable sensors and actuators covering the entire surface area of a prosthetic hand. Scale bar, 1 cm.

The inset shows the artificial skin stretched ~20%. Scale bar, 1 cm.

Kim J et al, Nature Comm, 2014

View of the artificial skin comprised of six stacked layers



(b) An exploded view of the artificial skin comprised of six stacked layers. Interconnected wires of each layer relay signals to external instruments.

PDMS, Polydimethylsiloxane

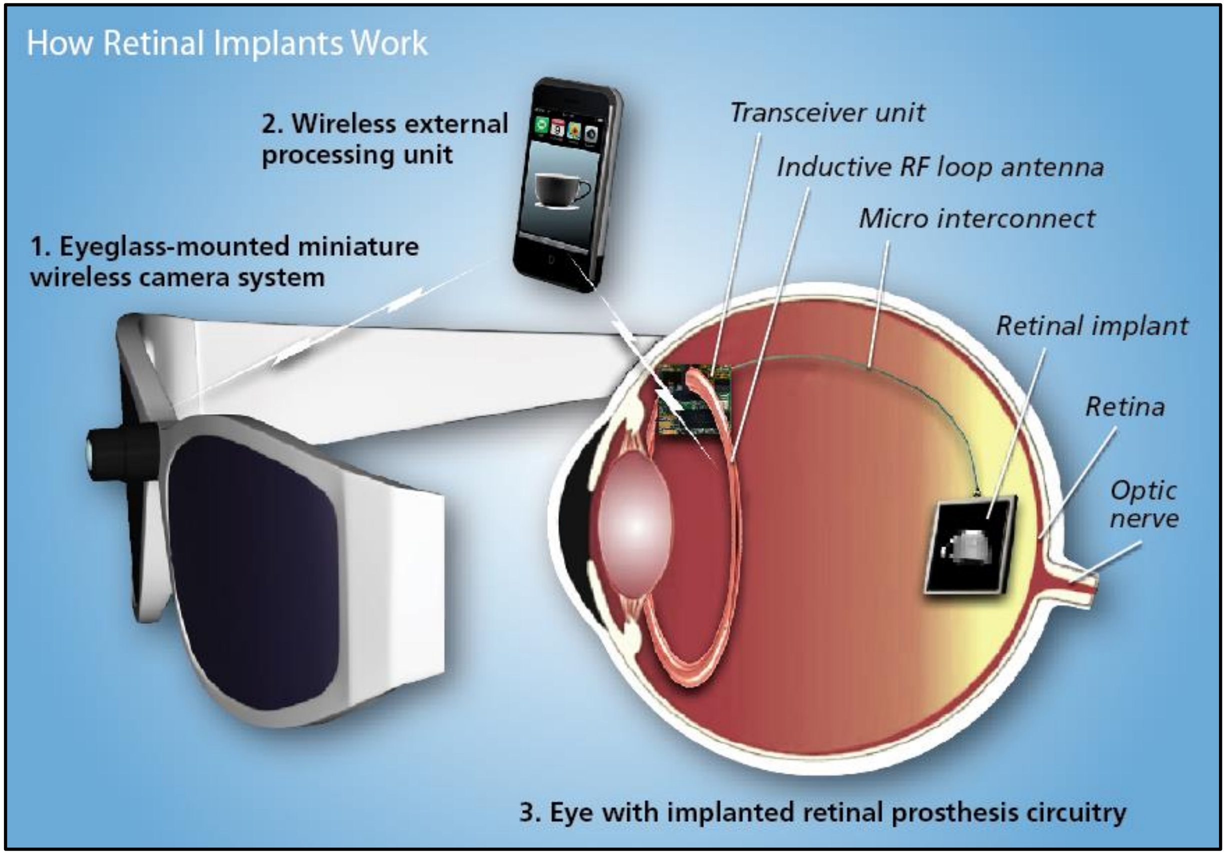
Kim J et al, Nature Comm, 2014

Retinal implants

Retinal implants
Visual signals are recorded through light-sensitive diodes that stimulate the remaining cells of the retina. Alternatively, external signals recorded by camera are sent to an implant directly interfaced with the optic nerve. Some visual prostheses bypass the retina and stimulate the visual cortex.

Research directions: external power sources may be needed to provide the electrical stimulation required by some of these implants. Technologies for providing this power are being investigated.

Clausen J, Nature, 2009



Wolfgang Fink and Mark Tarbell, Visual and Autonomous Exploration Systems Research Laboratory, Caltech and University of Arizona.

Jao C, Discover, 2014

Cochlear implant

A **cochlear implant** is an electronic medical device that replaces the function of the damaged inner ear. Unlike hearing aids, which make sounds louder, **cochlear implants** do the work of damaged parts of the inner ear (**cochlea**) to provide sound signals to the brain.

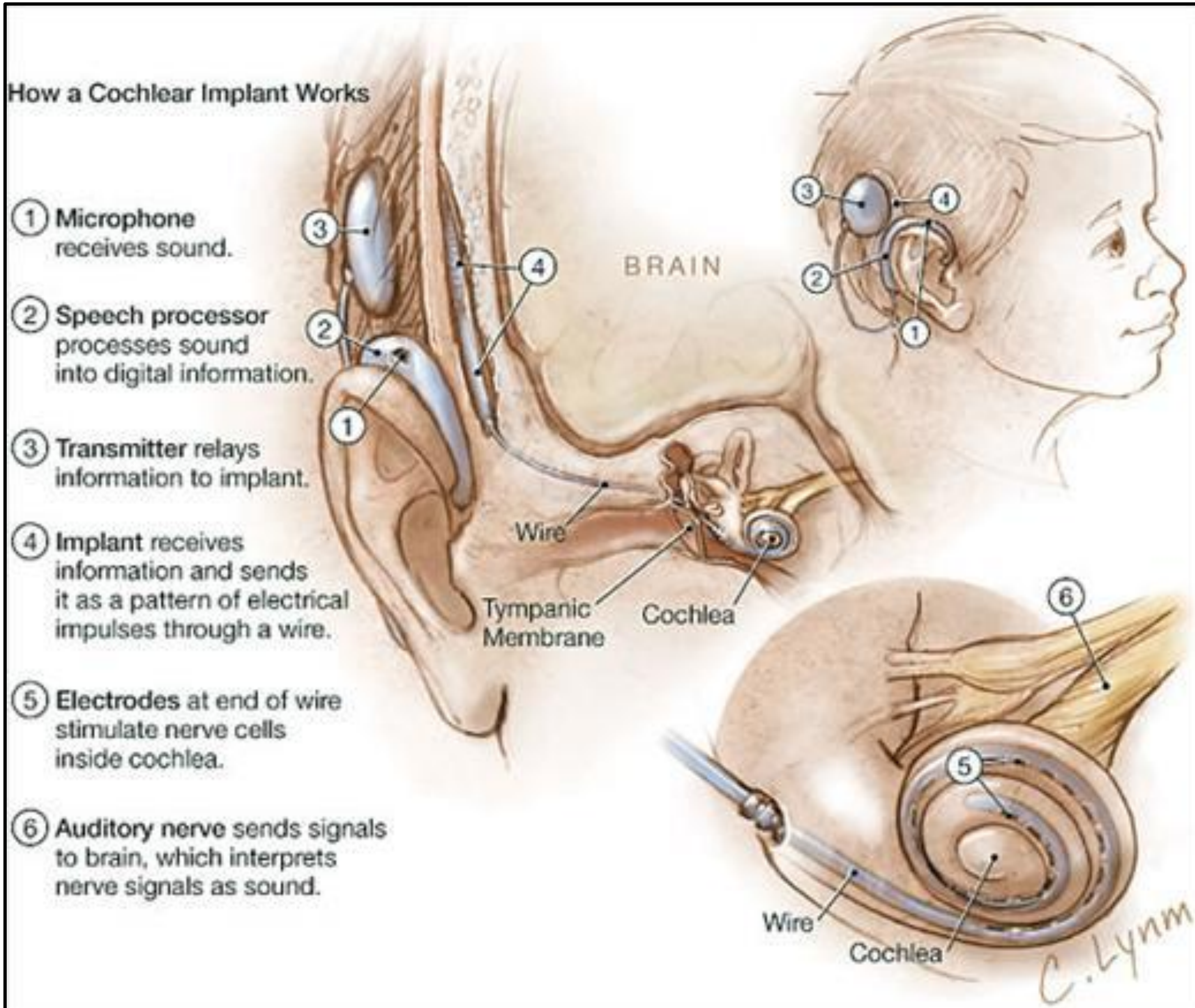
Cochlear implants

Acoustic signals are recorded by an external microphone and sent to a CCU placed outside the skull (containing a speech processor and a radio transmitter) to generate electrical impulses. These are sent wirelessly to a receiver inside the skull and stimulate the auditory nerve at the internal neural interface — an electrode implanted into the cochlea in the inner ear.

Research directions: for those whose auditory nerve is damaged, similar devices implanted into acoustically relevant areas of the brainstem or the midbrain are being tested clinically.

Clausen J, Nature, 2009

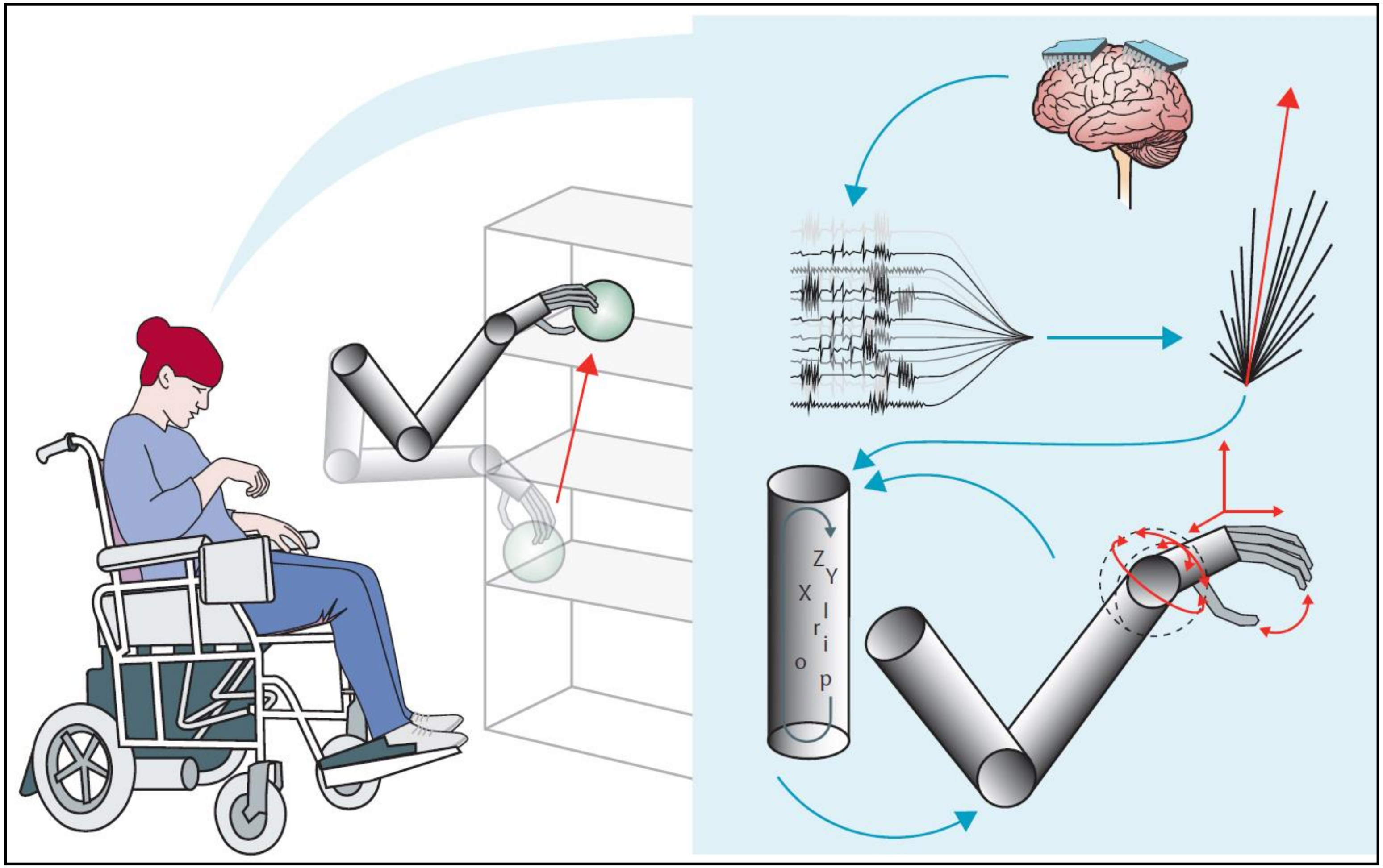
How a cochlear implant works



Parmet S et al, JAMA, 2004

6. COGNITIVE NEURAL PROSTHETICS

Brain–machine interface: closer to therapeutic reality?



Courtine G et al, Lancet, 2013

Turning thoughts into activities of daily living. The tetraplegic woman is sitting in her wheelchair with an anthropomorphic prosthetic arm on her side. Two silicon-substrate microelectrode arrays surgically implanted in the motor cortex allow recordings of ensemble neuronal activity. A population vector algorithm translates brain waves into intended movement commands. This brain-derived information is conveyed to a shared controller that integrates the participant’s intent, robotic position feedback, and task-dependent constraints. Using this bioinspired brain–machine interface, the paralysed woman could manipulate objects of various shapes and sizes in a three-dimensional workspace.

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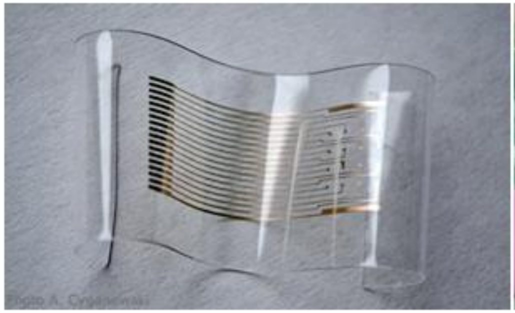
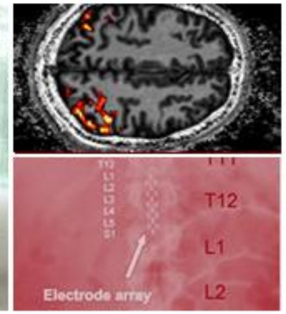




Ecole Polytechnique Fédérale de Lausanne

- **Walk again**
  Restoring sensorimotor functions after spinal cord injury

1

- **Bionic hand**
  Restoring sensory and motor functions after arm or hand amputation

2

- **Rehabilitation after vascular stroke**
  Providing neuro-technological tools for the rehabilitation of upper limb sensimotor loss

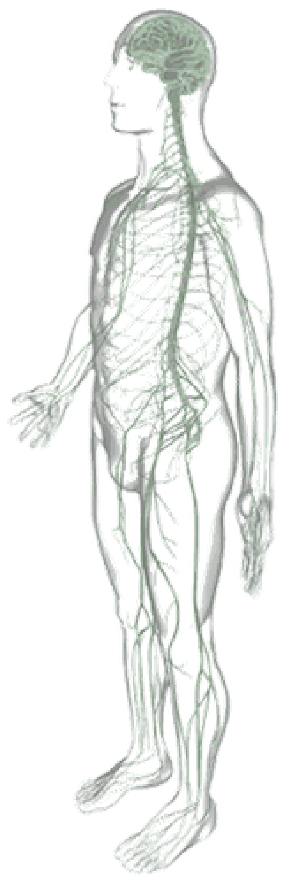
3

- **Human-computer confluence**
  Decoding brain activity for feeling and moving artificial bodies and robots

4

- **Hearing & Vestibular Research**
  development of a vestibular neuroprosthethis and auditory brainstem implants

5



http://cnp.epfl.ch/home
http://cnp.epfl.ch/page-87217-en.html

Abstract

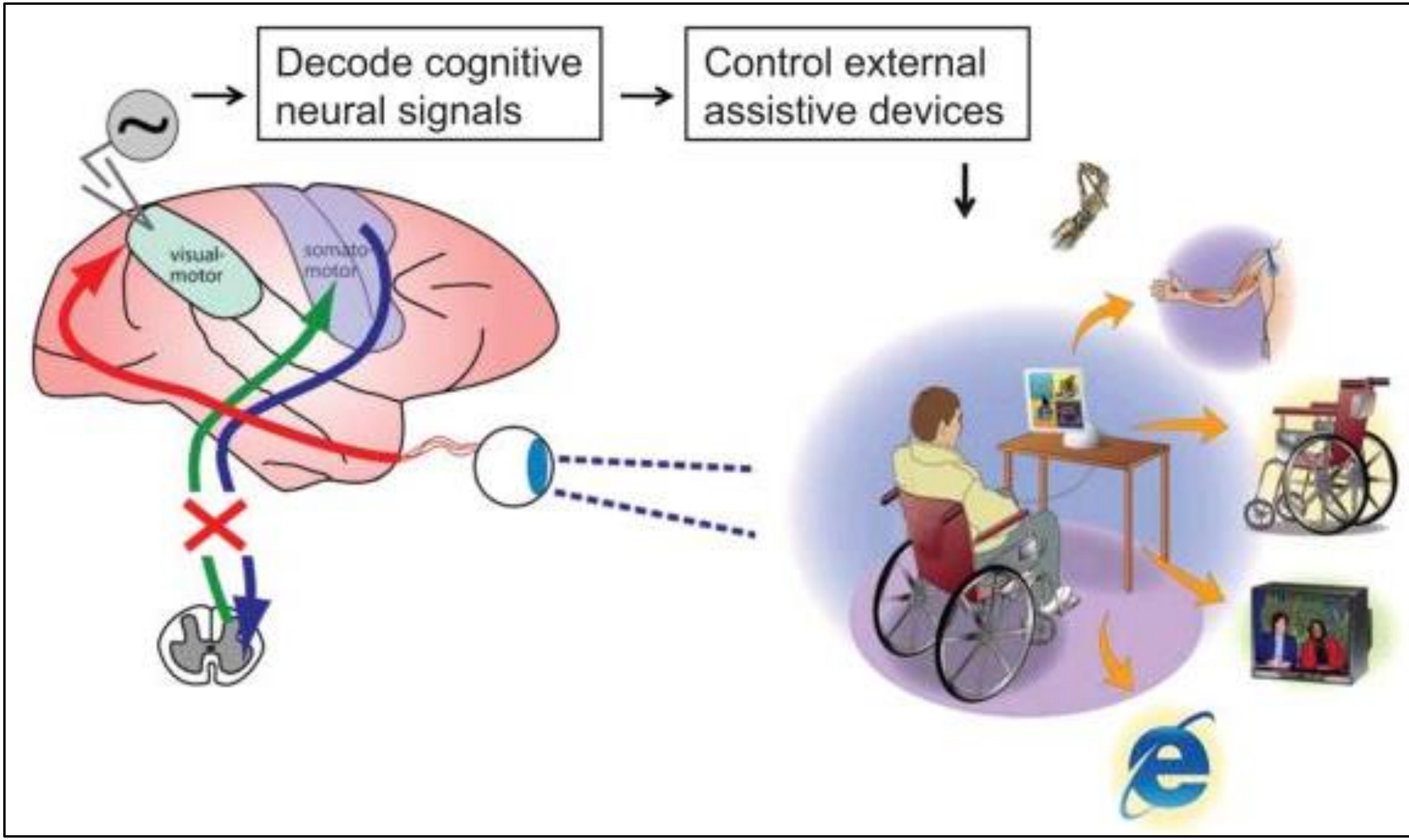
The **cognitive neural prosthetic (CNP)** is a very versatile method for assisting paralyzed patients and patients with amputations. The CNP records the cognitive state of the subject, rather than signals strictly related to motor execution or sensation. We review a number of high-level cortical signals and their application for CNPs, including intention, motor imagery, decision making, forward estimation, executive function, attention, learning, and multi-effector movement planning.

CNPs are defined by the cognitive function they extract, not the cortical region from which the signals are recorded. However, some cortical areas may be better than others for particular applications. Signals can also be extracted in parallel from multiple cortical areas using multiple implants, which in many circumstances can increase the range of applications of CNPs.

The CNP approach relies on scientific understanding of the neural processes involved in cognition, and many of the decoding algorithms it uses also have parallels to underlying neural circuit functions.

Andersen RA et al, Annu Rev Psychol, 2010

Schematic representation of a cognitive neural prosthetic



Andersen RA et al, Annu Rev Psychol, 2010

Schematic representation of a cognitive neural prosthetic. In this example, the patient has a lesion of the spinal cord, represented by the red X on the brain drawing on the left. The patient can still see the goal of a movement and can plan the movement, but cannot execute it.

The electrodes are positioned in sensorimotor cortex in the parietal reach region, which is involved in reach planning. The recordings are decoded to obtain the meaning of the cognitive signal and then transformed into processed control signals to operate an external device.

The schematic on the right indicates that this signal can be used, among other things, for controlling a robot limb, stimulating the muscles to animate the paralyzed limb, navigating a wheelchair, controlling a television, and using the Internet and email.

Andersen RA et al, Annu Rev Psychol, 2010

What phantom limbs and mirrors teach us about the brain

In a lab in southern California scientists are curing the previously incurable with little more than a mirror, and changing our understanding of the brain in the process

Vilayanur Subramanian Ramachandran
(born 1951), neuroscientist,
University of California San Diego

http://www.bbc.co.uk/news/magazine-15938103

http://cbc.ucsd.edu/ramabio.html

Mirror box

http://www.bbc.co.uk/news/magazine-15938103

Group Ehrsson

Brain, Body & Self Laboratory

"How do we recognise that our limbs are part of our own body, and why do we feel that our self is located inside the body?"

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About the Brain, Body and Self Laboratory

Out-of-body experiences are just part of Ehrsson's repertoire. He has convinced people that they have swapped bodies with another person, gained a third arm, shrunk to the size of a doll or grown to giant proportions.

Young E, Nature, 2011

http://www.ehrssonlab.se/index.php
http://www.ehrssonlab.se/publications.php

OPEN ACCESS Freely available online PLoS one

The Illusion of Owning a Third Arm

Arvid Guterstam*[9], Valeria I. Petkova[9], H. Henrik Ehrsson

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Abstract

Could it be possible that, in the not-so-distant future, we will be able to reshape the human body so as to have extra limbs? A third arm helping us out with the weekly shopping in the local grocery store, or an extra artificial limb assisting a paralysed person? Here we report a perceptual illusion in which a rubber right hand, placed beside the real hand in full view of the participant, is perceived as a supernumerary limb belonging to the participant's own body. This effect was supported by questionnaire data in conjunction with physiological evidence obtained from skin conductance responses when physically threatening either the rubber hand or the real one. In four well-controlled experiments, we demonstrate the minimal required conditions for the elicitation of this "supernumerary hand illusion". In the fifth, and final experiment, we show that the illusion reported here is qualitatively different from the traditional rubber hand illusion as it is characterised by less disownership of the real hand and a stronger feeling of having two right hands. These results suggest that the artificial hand 'borrows' some of the multisensory processes that represent the real hand, leading to duplication of touch and ownership of two right arms. This work represents a major advance because it challenges the traditional view of the gross morphology of the human body as a fundamental constraint on what we can come to experience as our physical self, by showing that the body representation can easily be updated to incorporate an additional limb.

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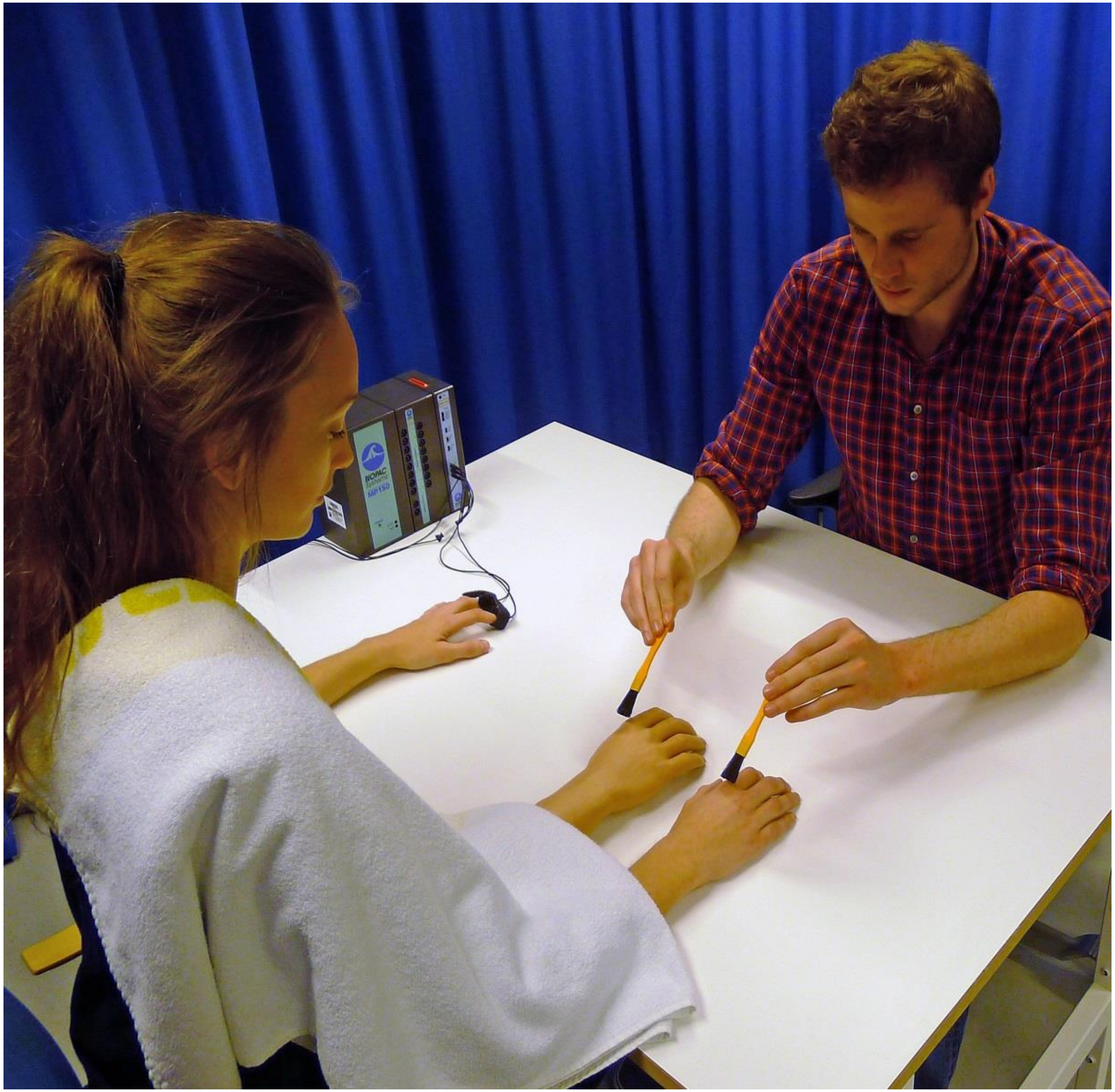
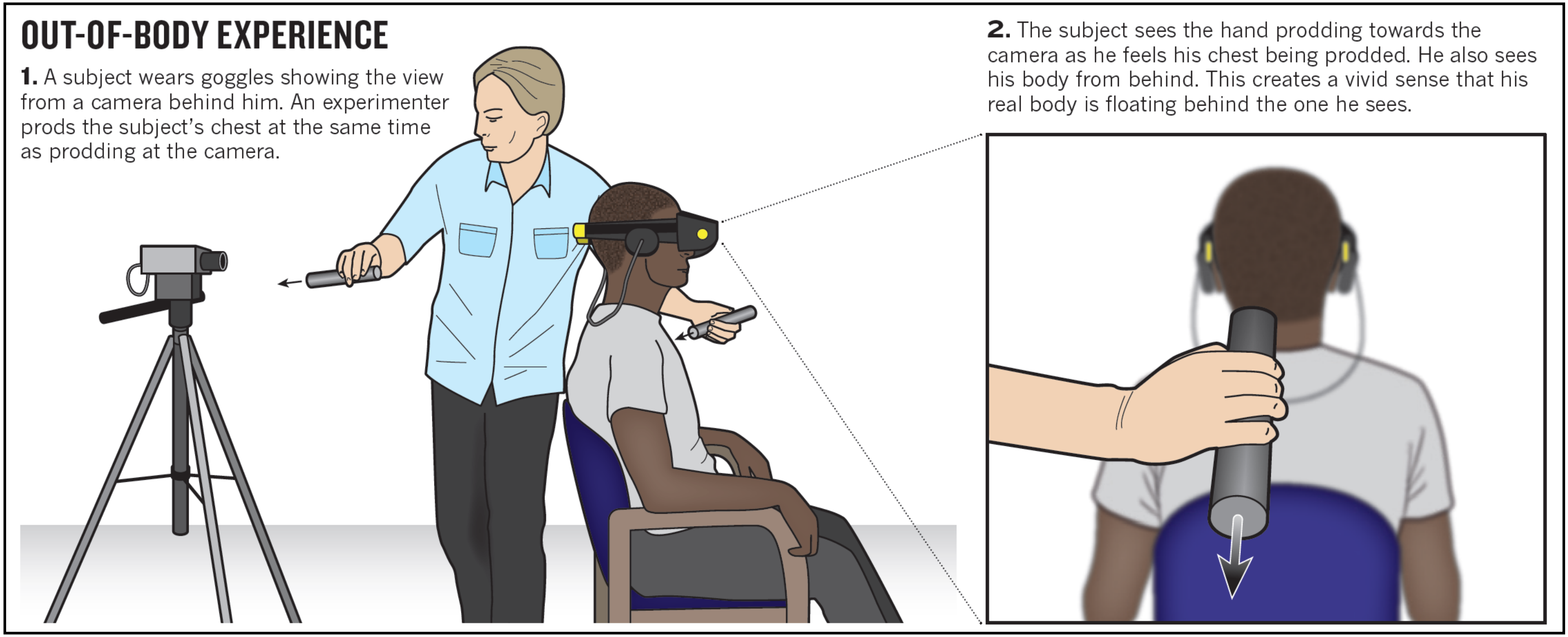
[9] These authors contributed equally to this work.

The illusion of owning and third arm



Guterstam A et al, PLoS ONE 2011

Out-of-body experience



Young E, Nature, 2011

“Henrik’s work speaks to the idea that there is no such thing as a soul or a self that’s independent of the brain.”

Young E, Nature, 2011

I assume that some people may argue with this idea.
Najbauer J