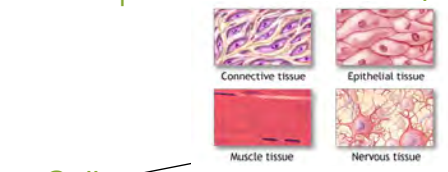
Tissue Engineering

What is it?

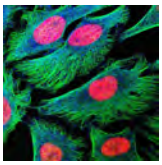
– Is a technology where artificial organs and tissues are constructed in vitro and transplanted in vivo for the recovery of lost or malfunctioned organs or tissues.

– Is the use of a combination of cells, engineering methods and materials, and suitable biochemical factors to improve or replace biological functions.

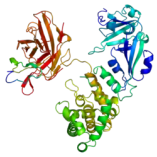
Tissue engineering starts from components of biological tissues



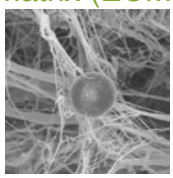
Cells



Growth factors



Extracellular matrix (ECM)



Cell Sources

Autologous: Come from the person that needs the new cells.

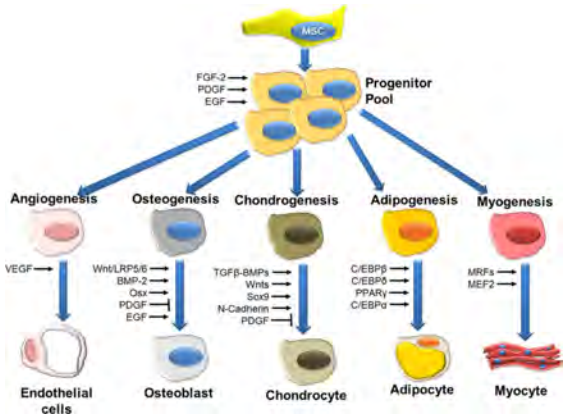
Allogeneic: Come from a body from the same species.

Xenogenic: Come from a different species then the organism they're going into.

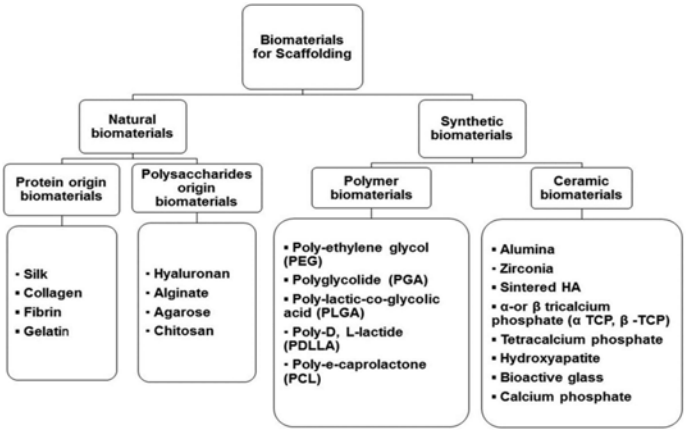
Isogenic (Syngenic): Come from identical twins.

Stem cells: Undifferentiated cells with the ability to divide in culture and give rise to different forms of specialized cells

The most common cells in tissue engineering are mesenchymal stem (stromal) cells - MSCs

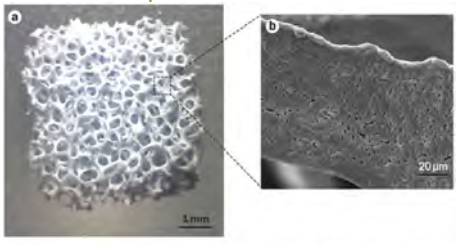


Scaffolds



Scaffold Requirements

1. Biocompatible
2. Bioabsorbable
3. Degrade with healing
4. Highly porous
5. Correct pore size for cell penetration
6. Permeable for nutrient delivery and gas exchange
7. Provide appropriate stress environment
8. Surface conducive to cell attachment
9. Promote extracellular matrix production and deposition
10. Carry and transmit biomolecular signals

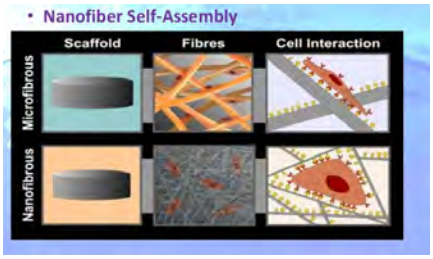


Nature Reviews | Rheumatology

Scaffolds Synthesis

Nanofiber self-assembly:

Molecular self-assembly is one of the few methods for creating biomaterials with properties similar in scale and chemistry to that of the natural in vivo extracellular matrix (ECM), a crucial step toward tissue engineering of complex tissues. Moreover, these **hydrogel** scaffolds have shown superiority in in vivo toxicology and biocompatibility compared to traditional macro scaffolds and animal-derived materials



Scaffolds Synthesis

Textile technologies:

These techniques include all the approaches that have been successfully employed for the preparation of non-woven meshes of different polymers. In particular, non-woven **polyglycolide** structures have been tested for tissue engineering applications: such fibrous structures have been found useful to grow different types of cells. The principal drawbacks are related to the difficulties in obtaining high porosity and regular pore size

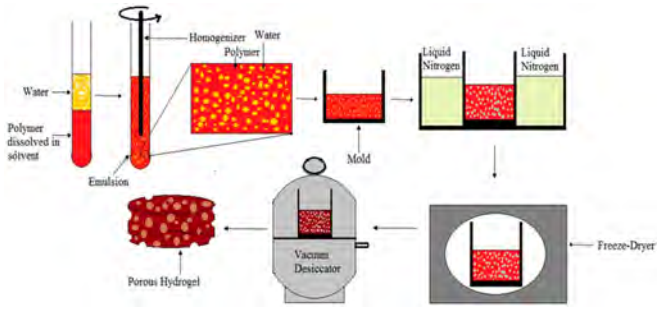
Scaffolds Synthesis

Freeze- drying:

First, a synthetic polymer is dissolved into a suitable solvent (e.g. polylactic acid in dichloromethane) then water is added to the polymeric solution and the two liquids are mixed in order to obtain an **emulsion**.

Before the two phases can separate, the emulsion is cast into a mold and quickly frozen by means of immersion into liquid nitrogen.

The frozen emulsion is subsequently freeze-dried to remove the dispersed water and the solvent, thus leaving a solidified, porous polymeric structure.

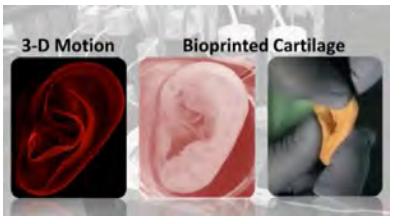


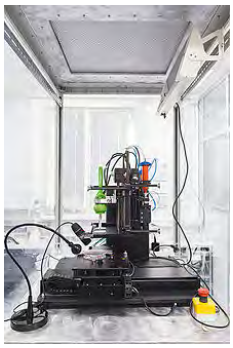
Scaffolds Synthesis

CAD/CAM (3D-Printing):

3D bioprinting is the process of creating cell patterns in a confined space using 3D printing technologies, where cell function and viability are preserved within the printed construct. Generally, 3D bioprinting utilizes the **layer-by-layer method** to deposit materials known as Bioinks (cells, matrix and nutrients) to create tissue-like structures that are later used in medical and tissue engineering fields.

Bioprinting covers a broad range of materials. The first patent related to this technology was filed in the United States in 2003 and granted in 2006.



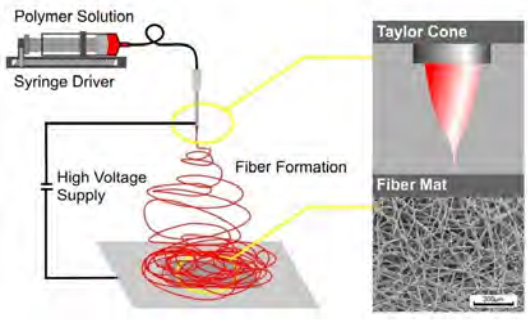


Scaffolds Synthesis

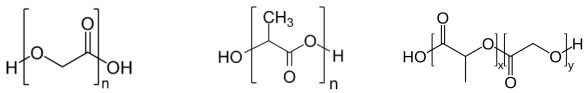
Electrospinning

Can be used to produce continuous fibers from submicrometer to nanometer diameters. A solution is fed through a spinneret and a high voltage is applied to the tip. Electrostatic repulsion within the charged solution, causes it to eject a thin fibrous stream. A mounted collector plate with an opposite or grounded charge draws in the continuous fibers, which arrive to form a highly porous network.

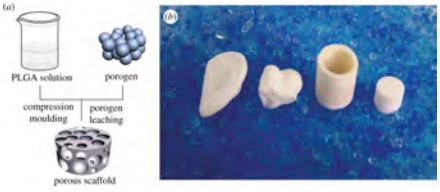
Advantages: simplicity and ease of variation (by modifying distance to collector, magnitude of applied voltage, or solution flow rate, the scaffold architecture changes dramatically).



Poly-α-hydroxy acid (PLGA)

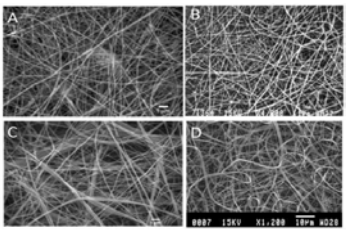


- Extensive research has been performed in developing a full range of PLGA polymers.
- Both L- and DL-lactides have been used for co-polymerization.
- The ratio of glycolide to lactide at different compositions allows control of the degree of crystallinity of the polymers.
- When the crystalline PGA is co-polymerized with PLA, the degree of crystallinity is reduced and as a result this leads to increases in rates of hydration and hydrolysis.
- In general, the higher the content of glycolide, the quicker the rate of degradation. However, an exception to this rule is the 50:50 ratio of PGA: PLA, which exhibits the fastest degradation.



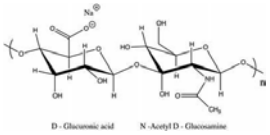
Natural Polymers

- Blends of **collagen** and **glycosaminoglycans** (GAG) have been used extensively for dermal regeneration.
- **Chondroitin sulfate** has been added to collagen type I for dermal regeneration templates and aggrecan (chondroitin sulfate/dermatan sulfate/keratin sulfate) to collagen type II for articular cartilage tissue engineering

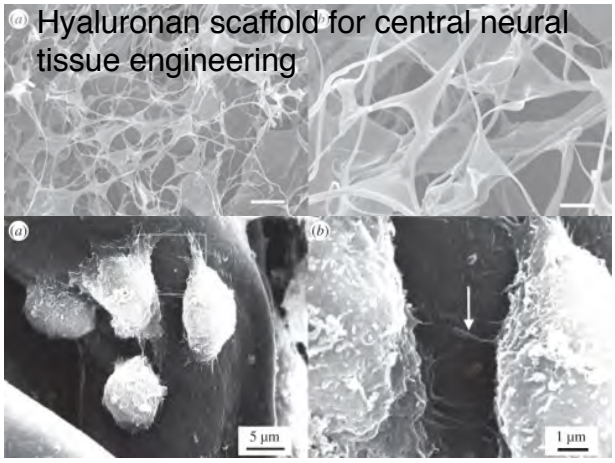


Hyaluronan

- Composed of repeated disaccharide units of D-glucuronic acid and Nacetylglucosamine
- The unique properties of HA are manifested in its mechanical function in the synovial fluid, the vitreous humor of the eye, and the ability of connective tissue to resist compressive forces, as in articular cartilage.
- Plays a fundamental role during embryonic development and in wound healing



Hyaluronan scaffold for central neural tissue engineering



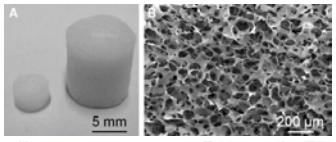
Neural cells that adhered to HA–PDL hydrogel. Boxed section in (*a*) is enlarged in (*b*) to show the connection (white arrow) between neurons

Collagen

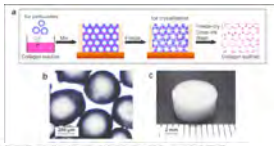
In the form of collagen sponge

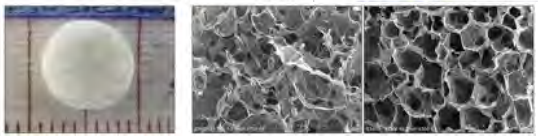
- Porosity, biodegradability, and biocompatibility
- Can be modified using growth factors or other manipulations to promote chondrocyte growth and cartilage matrix formation
- Scaffolds made from a single collagen type or composites of two or more types
- Disadvantages

Poor dimensional stability. Variability in drug release kinetics
Poor mechanical strength.



Jellyfish collagen scaffolds for cartilage tissue engineering

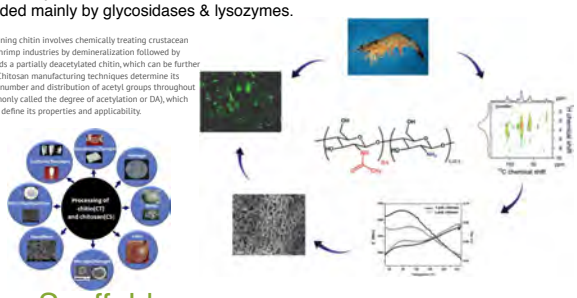




Chitosan

- It consists of β-1-4 linked 2 amino-2-deoxy gluco – pyranose moieties.
- Commercially manufactured by N-deacetylation of **Chitin from Mollusc shells**.
- It is soluble only in acidic pH i.e. when amino group is protonated.
- Thereby it readily adheres to bio membranes.
- It is degraded mainly by glycosidases & lysozymes.

The usual method of obtaining chitin involves chemically treating crustacean shells from the crab and shrimp industries by demineralization followed by deproteinization. That yields a partially deacetylated chitin, which can be further deacetylated to chitosan. Chitosan manufacturing techniques determine its molecular weight and the number and distribution of acetyl groups throughout the backbone chain (commonly called the degree of acetylation or DA), which are essential features that define its properties and applicability.



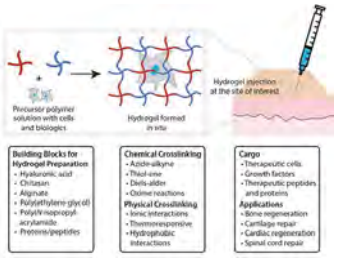
Chitosan Scaffold

- Freezing of a chitosan-acetic acid solution, followed by lyophilization

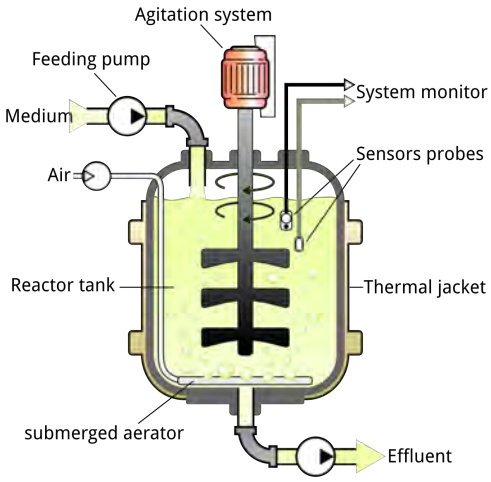
Scaffold microstructure will depend on the shape of the mold used for freezing and on the freezer temperature.

Hydrogels as scaffold

- Cells are suspended within or adhered to the 3D hydrogel framework during or after formulation as scaffolds
- RGD (arginine–glycine–aspartic acid) adhesion peptide sequence. Inclusion of these RGD domains in hydrogels has shown improved cellular migration, proliferation, growth, and organization in tissue regeneration applications.
- Cells have been shown to favorably bind to the RGD-modified hydrogel scaffolds. These cells include endothelial cells (ECs), fibroblasts, smooth muscle cells (SMCs), chondrocytes and osteoblasts.



A **bioreactor** may refer to any manufactured or engineered device or system that supports a biologically active environment

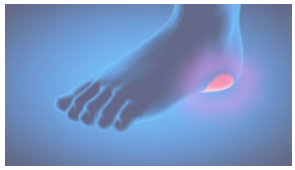


PREFER
"Sviluppo di un PRodotto biocompatibile per la tErapia delle FERite difficili"

3% INCIDENZA NELLA POPOLAZIONE OLTRE

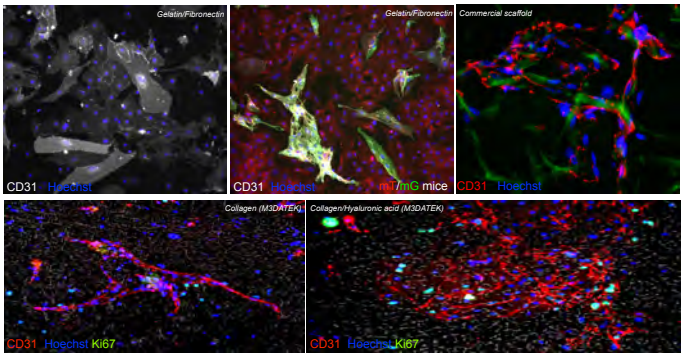
65 ANNI

30 MESI	1.102.085 BUDGET TOTALE	4 PARTNER

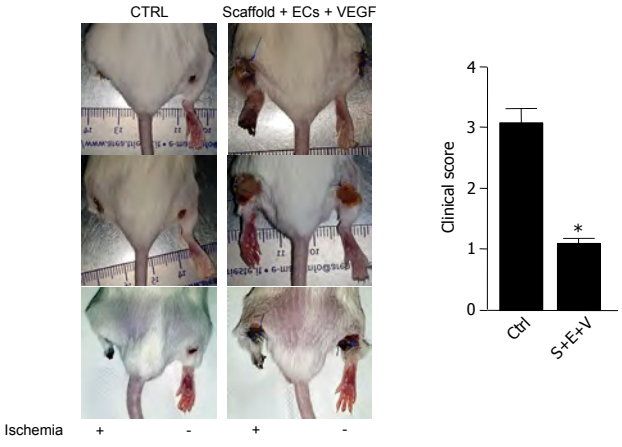


VivaBioCell — UNIVERSITÀ DEGLI STUDI DI TRIESTE — RESEARCH — ICGEB

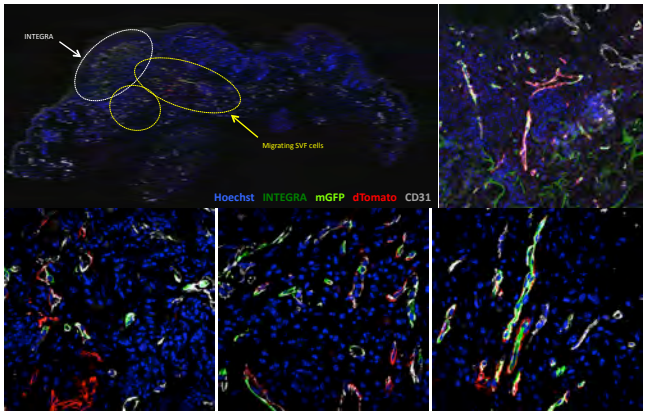
Endothelial cells can be efficiently cultured on various substrates and 3D scaffolds



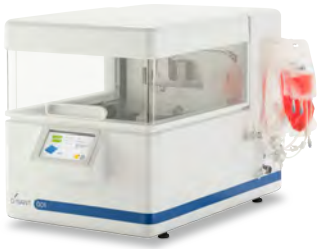
Scaffold+ECs+VEGF is effective in mice

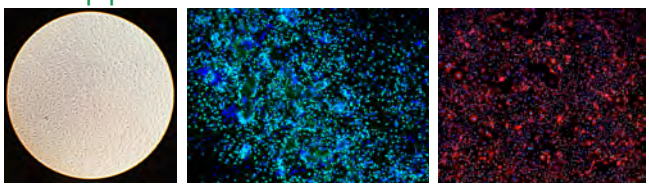


Scaffold+ECs+VEGF induces neovascularization



Endothelial cells can be efficiently efficiently expanded using a bioreactor - toward the clinical application

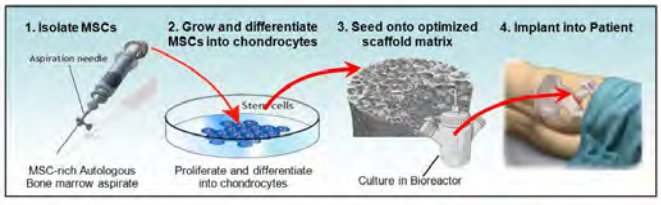




Engineering cartilage

Objectives
Immediate functionality (mechanical, metabolic); capacity for further development and integration

Culture requirements
High initial cell density
Nutrient and gas exchange
Growth factors (TGFbeta, IGF… sequential application)
Hydrodynamically active environment



Engineering cartilage

Cartilage is avascular, aneural, and alymphatic, and contains only a sparse population of a single cell type (chondrocyte):

- no spontaneous regeneration
- suitable for tissue engineering

1. Orthopaedic applications: the engineered cartilage is used to repair defects in an articular joint or in a meniscus in order to restore the joint's load-bearing function and relieve pain
2. Head and neck applications: the cartilage is engineered for the repair or reconstruction of an auricle, trachea, nose, larynx, or eyelid for an aesthetic or functional purpose

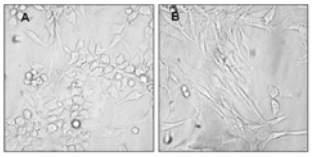
Engineering cartilage

No consensus on the optimal cell source for current orthopedic cartilage engineering. The most clinically applicable seed cell sources are chondrocytes and MSCs.

Since the most important function of orthopedic cartilage is to bear weight, engineered neocartilage should be able to:
1. integrate with the subchondral bone, but also with the adjacent cartilage for stable load distribution and mechanotransduction;
2. match the mechanical properties of the adjacent native cartilage in order to avoid tissue degradation caused by strain disparity;
3. be resistant to load under large deformations and motions;
4. recapitulate the distinct zonal architecture in order to recreate the structure-function relationship of the native cartilage.

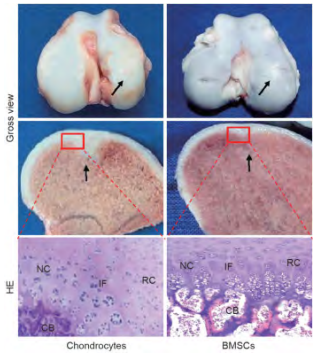
Chondrocytes for cartilage engineering

- logical choice of seed cells for cartilage engineering
- isolating chondrocytes from the joint surface is difficult, and would cause secondary injury leading
- non-articular "heterotopic" chondrocytes are easier to harvest, associated with lower donor-site morbidity, and possess a higher proliferation rate. However, it remains unclear whether heterotopic chondrocytes would produce cartilage with a desired type (such as hyaline cartilage) and function during defect healing
- chondrocytes tend to de-differentiate in culture



MSCs for cartilage engineering

MSCs
- can be harvested from a number of sources that do not affect cartilage activity,
- maintain multipotency after numerous expansions,
- can be differentiated to generate both cartilage and bone, making the tissue-specific repair of osteochondral defects possible



Repair of autologous osteochondral defects by polyglycolic acid (PGA) scaffold loaded with chondrocytes or bone marrow stromal cells (BMSCs), respectively. Both cells realized cartilage repair with a smooth surface. Chondrocytes failed to realize tissue-specific repair in the subchondral region. HE: haemotoxylin and eosin; NC: native cartilage; IF: interface; RC: regenerated cartilage; CB: subchondral bone.

Scaffold options for tissue-engineered cartilage for orthopedic reconstruction

- *Hydrogel scaffolds*: similar mechanical, swelling, and lubricating behavior to articular cartilage; their viscoelastic nature facilitates the transfer of mechanical loading; they allow their loaded cells to take on a spherical morphology, which is characteristic of the chondrogenic phenotype

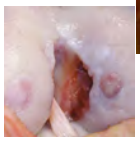
- *Solid scaffolds*: natural (collagen sponges, decellularized cartilage, small intestinal submucosa)

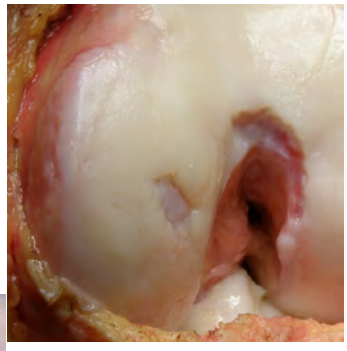
Engineering cartilage: products on the market

maci
autologous cultured chondrocytes on porcine collagen membrane

MACI® (autologous cultured chondrocytes on porcine collagen membrane) is an autologous cellularized scaffold product that is indicated for the repair of single or multiple symptomatic, full-thickness cartilage defects of the adult knee, with or without bone involvement.

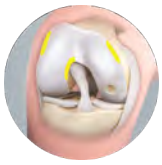
DEFECT WITH BONE INVOLVEMENT
DEFECT:
2.5cm x 1.5cm = 3.75cm2 (0.8cm depth)
PATIENT:
22 years old, gymnast, sports injury at 15 years old





MEDIAL FEMORAL CONDYLE
DEFECT:
2.7cm x 1.3cm = 3.51cm2
PATIENT:
28 years old, occupational therapist, runner

MACI PROCEDURE

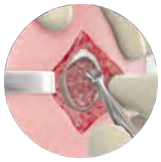


STEP 1: BIOPSY TAKEN
A small biopsy of healthy cartilage is taken arthroscopically from a non weight-bearing area of the patient's knee.
Typical harvest sites include the **intercondylar notch and the proximal aspect of the medial and/or lateral femoral condyle.**

STEP 2: BIOPSY PROCESSED
The biopsy is sent to the Vericel cell-processing facility in Cambridge Massachusetts.
A **state-of-the-art cell-processing facility** provides optimal product quality and safety.

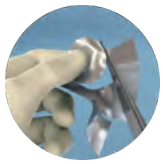
STEP 3: CHONDROCYTES EXTRACTED AND LOADED
Chondrocytes are extracted from the biopsy, expanded, and, using proprietary methods are uniformly seeded onto a resorbable Type I/III collagen membrane.
MACI delivers a **controlled, uniform dose of cells** with a density of at least 500,000 cm² on a Type I/III collagen membrane.

STEP 4: MACI DELIVERED
MACI is **delivered via courier to the treatment facility** for the procedure.

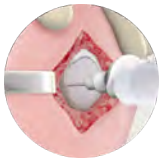


STEP 5: DEFECT DEBRIDED
The defect area is debrided back to **healthy, stable cartilage.**

STEP 6: TEMPLATE CREATED
To ensure precise sizing, use sterile materials to **create a template** of the defect.



STEP 7: MACI IMPLANTED
The MACI implant is secured in place using fibrin sealant. Suture fixation is not required.
The MACI implant can be **easily cut and shaped** to the appropriate size.



Engineering cartilage: products on the market

Hyalograft-C HS

CellMatrix has licensed the Hyalograft-C technology from Fidia Advanced Biopolymers (FAB), Abano Terme Italy for the Scandinavian market. Hyalograft C is a hyaluronan based biocompatible and biodegradable scaffold that was the first three-dimensional cell culture matrix specifically developed for use in cartilage repair and that is currently a market leader in the field in Europe.

The Hyalograft-C HS service provided by CellMatrix uses the patients autologous serum for the expansion of the patients own chondrocytes as well as for the matrix-cell culture for 5 weeks.

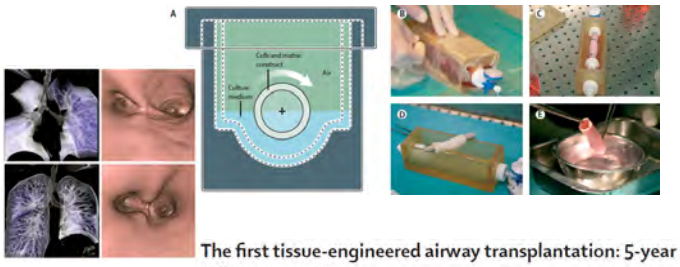
The Hyalograft-C HS membrane enables the surgeon to treat the cartilage injury either artroscopically if the injury is accessible or through a miniarthrotomy.

Engineering cartilage for head and neck defects

Clinical transplantation of a tissue-engineered airway

Paolo Macchiarini, Philipp Jungebluth, Tetsuhiko Go, M Adelaide Asnaghi, Louisa E Rees, Tristan A Cogan, Amanda Dodson, Jaume Martorell, Silvia Bellini, Pier Paolo Parnigotto, Sally C Dickinson, Anthony P Hollander, Sara Mantero, Maria Teresa Conconi, Martin A Birchall

Lancet 2008; 372: 2023–30



The first tissue-engineered airway transplantation: 5-year follow-up results

Alessandro Gonfiotti, Massimo O Jaus, Daniel Barale, Silvia Baiguera, Camilla Comin, Federico Lavorini, Giovanni Fontana, Orief Sibila, Giovanni Rombolà, Philipp Jungebluth, Paolo Macchiarini

Lancet 2014; 383: 238–44

Paolo Macchiarini: A surgeon's downfall

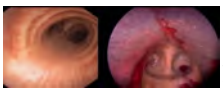
Ground-breaking work on synthetic organ transplants made Paolo Macchiarini one of the most famous doctors in the world. But some of his academic research is now seen as misleading, and most of the patients who received his revolutionary treatment have died. What went wrong?

BBC World Service, September 2016

A few questions have dogged Paolo Macchiarini

1. **Decision-making around operations.** Had the risk of each operation been properly assessed? Were the patients ill enough to require such drastic intervention? Did the patients understand the risks involved?
2. **Academic publications.** Footage from surgical cameras conflicted with the descriptions of the patient in published articles. Was the success of the operations misrepresented, omitting or even fabricating data in his published articles?
3. **Absence of pre-clinical large animal studies**

Patient	Location	When operated	Outcome
Andemariam Beyene	Stockholm	June 2011	Deceased Jan 2014
Keziah Shorten	London	Sept 2011	Deceased Jan 2012
Christopher Lyles	Stockholm	Nov 2011	Deceased March 2012
Julia Tuulik	Krasnodar	June 2012, Aug 2013	Deceased Sept 2014
Alexander Zozulya	Krasnodar	June 2012, Nov 2013	Deceased Feb 2014
Yasim Cetir	Stockholm	Aug 2012, July 2013	Survives (remains hospitalised)
Hannah Warren	Peoria, US	April 2013	Deceased July 2013
Sadiq Kanaan	Krasnodar	Aug 2013	Deceased (date unknown)
Dmitri Onogda	Krasnodar	June 2014	Survives (synthetic trachea removed)

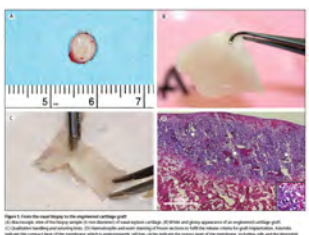
published result  footage from surgical cameras

Engineering cartilage for nose reconstruction

Engineered autologous cartilage tissue for nasal reconstruction after tumour resection: an observational first-in-human trial

Engineered autologous cartilage tissue for nasal reconstruction after tumour resection: an observational first-in-human trial

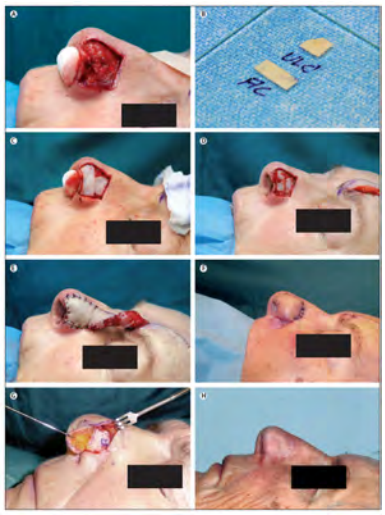
Ilario Fulco*, Sylvie Miot*, Martin D Haug, Andrea Barbero, Ankie Wimmerten, Sandra Feliciano, Francine Wolf, Garnot Jundt, Anna Marsano, Jian Farhadi, Michael Heberer, Marcel Jakob, Dirk J Schaefer, Ivan Martin



Lancet 2014; 384: 337–46
Published Online
April 11, 2014
http://dx.doi.org/10.1016/S0140-6736(14)60544-4
See Comment page 288
*Contributed equally

Department of Surgery and Department of Biomedicine
(I Fulco MD, S Miot PhD, M D Haug MD, A Barbero PhD, A Wimmerten MSc, S Feliciano BSc, F Wolf BSc, A Marsano PhD, Prof M Heberer MD, Prof M Jakob MD, Prof D J Schaefer MD, Prof I Martin PhD), and Institute of Pathology (Prof G Jundt MD), University Hospital Basel, University of Basel, Basel,

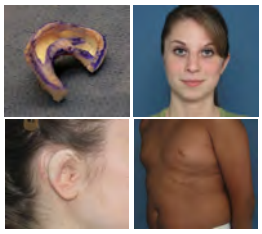
Figure 3: Surgical procedure in one patient
(A) Two-layer defect after wide local excision of the skin cancer on the alar lobule. (B) Tissue engineered cartilage cut to the right shape and ready for implantation; this patient needed cartilage support to achieve stability in the alar lobule (labelled AC) and at the upper lateral site (labelled ULC). (C,D) Tissue engineered cartilage was inserted to replace the structural support and secured by absorbable sutures. (E) Reconstruction of the outer layer with a paramedian forehead flap. (F) Division of the flap pedicle 2 weeks after reconstruction. (G) Intra-operative appearance of the implanted engineered tissue during refinements 6 months after reconstruction. (H) Follow-up 1 year after reconstruction.



Engineering cartilage for ear reconstruction

MEDPOR: the patient's own skin is grafted over a polyethylene framework

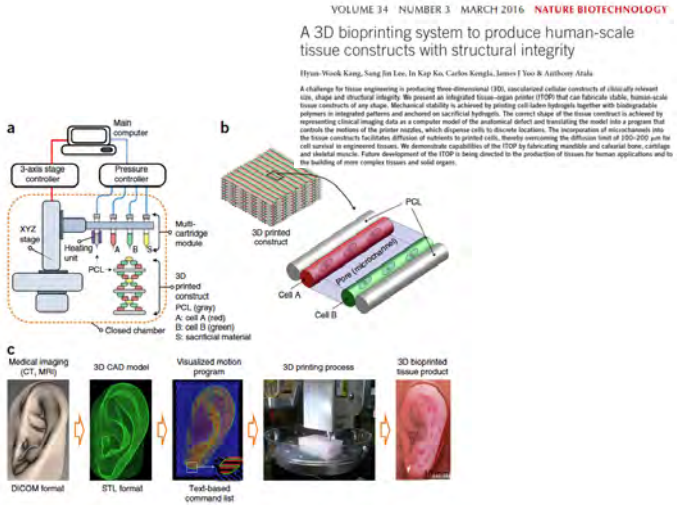
Rib Cartilage Ear Construction



Tissue engineering

Since the early 1990s, tissue engineering has become increasingly popular in the field of reconstructive surgery. In particular, when an in-vitro-manufactured auricular-shaped cartilage implant was implanted on the back of a nude mouse, reconstructive surgeons were intrigued and patients' expectations were raised.

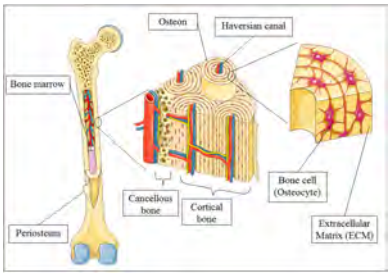
Figure: Image-based tissue engineering of human ear cartilage. Comparison of photograph (left), digitized image (middle), and tissue engineered ear cartilage after two weeks in culture.

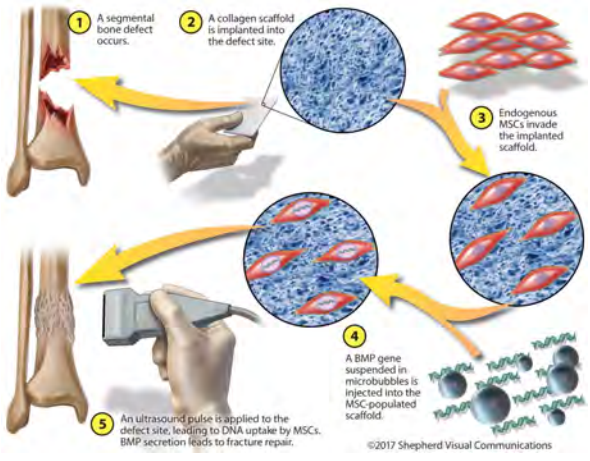


Engineering bone

Objectives
Immediate functionality (mechanical, metabolic)
Capacity for further development and integration
Functional hierarchy

Culture requirements
Nutrient and gas exchange
Regulatory molecules (dex, BMP-2, etc)
Hydrodynamically active environment (interstitial flow)



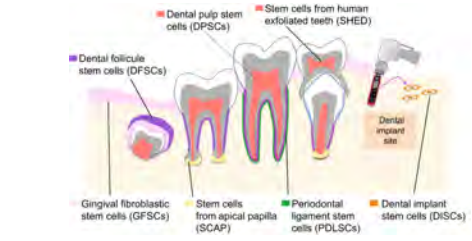


"In situ bone tissue engineering via ultrasound-mediated gene delivery to endogenous progenitor cells in mini-pigs," *Science Translational Medicine* (2017).

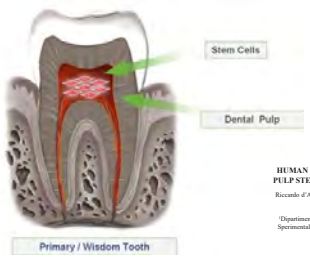
MSCs of oral origin

Table 1: Mesenchymal Stem Cells from dental tissues

Name	Site	Date of discover	Authors	Country	Institution
DPSCs	Dental Pulp	2000	S. Gronthos, M. Mankani, J. Brahim, P.G. Robey, S. Shi	USA. Bethesda, Maryland	National Institute on Dental Research, National Institutes of Health
SHED	human Exfoliated Deciduous Teeth	2003	M. Miura, S. Gronthos, M. Zhao, B. Lu, L.W. Fisher, P. G. Robey, S. Shi	USA. Bethesda, Maryland	National Institute on Dental Research, National Institutes of Health
PDLSCs	Periodontal Ligament	2004	B. M. Seo, M. Miura, S. Gronthos, P.M. Bartold, S. Batouli, J. Brahim, M. Young, P.G. Robey, C.Y. Wang, S. Shi	USA. Bethesda, Maryland	National Institute on Dental Research, National Institutes of Health
SCAP	Apical Papilla	2006	W. Sonoyama, Y. Liu, D. Fang, T. Yamaza, B.M. Seo, C. Zhang, H. Liu, S. Gronthos, C.Y. Wang, S. Wang, S. Shi	USA. Los Angeles, California JAPAN. Okayama	University of Southern California School of Dentistry; Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences
DFSCs	Dental Follicle	2005	C. Morsczeck, W. Götz, J. Schierholz, F. Zeilhofer, U. Kühn, C. Möhl, C. Sippel, K.H. Hoffmann	GERMANY. Bonn	Stiftung Caesar, Center of Advanced European Studies and Research
hPCy-MSCs	human Periapical Cyst	2013	M. Marrelli, F. Paduano, M. Tatullo	ITALY. Crotone	Calabrodental, Unit of Maxillofacial Surgery; Tecnologica Research Institute, Biomedical Section



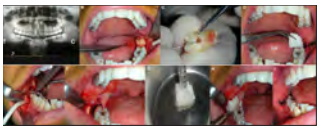
Dental pulp stem cells for bone regeneration

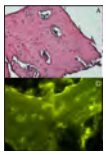


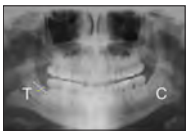
HUMAN MANDIBLE BONE DEFECT REPAIR BY THE GRAFTING OF DENTAL PULP STEM/PROGENITOR CELLS AND COLLAGEN SPONGE BIOCOMPLEXES

Riccardo d'Aquino[1,2], Alfredo De Rosa[1], Vladimiro Lanza[1], Virginia Tirino[1], Luigi Laino[1], Antonio Graziano[1], Vincenzo Desiderio[1], Gregorio Laino[1] and Gianpaolo Papaccio[1]*

[1]Dipartimento di Discipline Odontostomatologiche, Ortodontiche e Chirurgiche, [2]Dipartimento di Medicina Sperimentale, Sezione di Istologia ed Embriologia, Tissue Engineering and Regenerative Medicine (TERM) Division, Secondo Ateneo di Napoli, Naples, Italy







European Cells and Materials Vol. 18 2009 (pages 75-83) DOI: 10.22203/eCM.v018a07

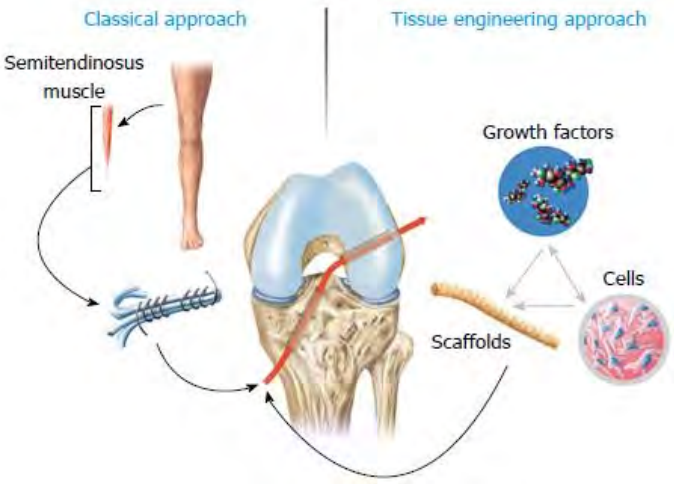
Engineering ligament

Objectives
Immediate functionality (mechanical, metabolic)
Capacity for bonding with adjacent bones

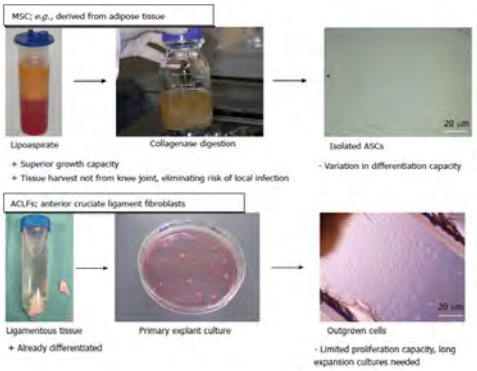
Culture requirements
High initial cell density
Nutrient and gas exchange
Physical signals
Perfusion
Mechanical stimulation (ligament-like)

Need for Ligament Tissue Engineering

- Knee ligaments cannot self repair
- High injury rate, especially the anterior cruciate ligament (ACL)
  - > 200,000 ACL surgeries/year
  - > 5 billion dollars
- Surgery options
  - Disease transfer
  - Tissue rejection
  - Poor mechanical strength (current synthetic grafts)

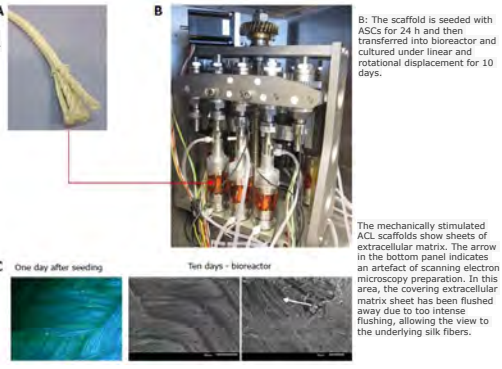


Primary choice of cells for ACL regeneration:
1. mesenchymal stem cells (MSC)
2. ACL fibroblasts



Mechanical stimulation of silk grafts with a bioreactor system

A: The silk-based anterior cruciate ligament (ACL) scaffold is produced of *Bombyx mori* silk fibers in a wire-rope design

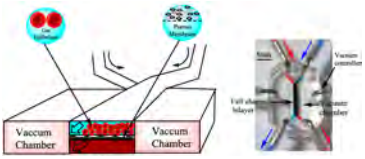


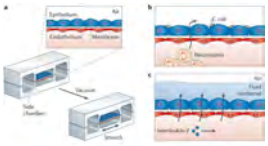
B: The scaffold is seeded with ASCs for 24 h and then transferred into bioreactor and cultured under linear and rotational displacement for 10 days.

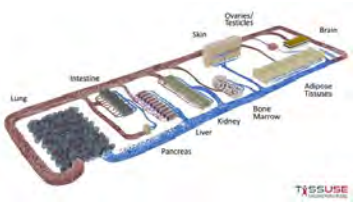
The mechanically stimulated ACL scaffolds show sheets of extracellular matrix. The arrow in the bottom panel indicates an artefact of scanning electron microscopy preparation. In this area, the covering extracellular matrix sheet has been flushed away due to too intense flushing, allowing the view to the underlying silk fibers.

Adipose-derived stem cells cultured on silk-based ligament grafts produce sheets of extracellular matrix proteins under mechanical stimulation *via* a bioreactor system

Organs on chip

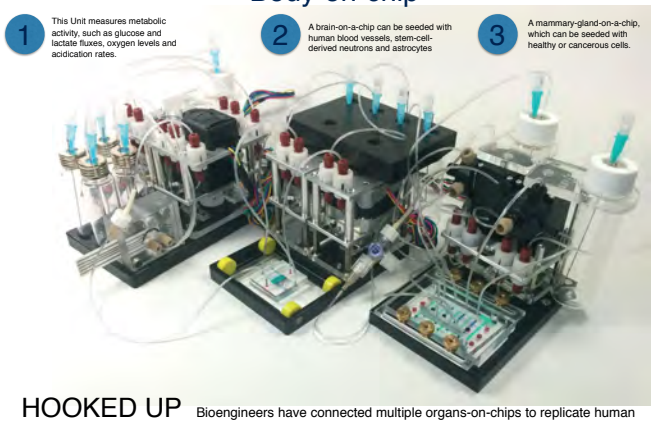






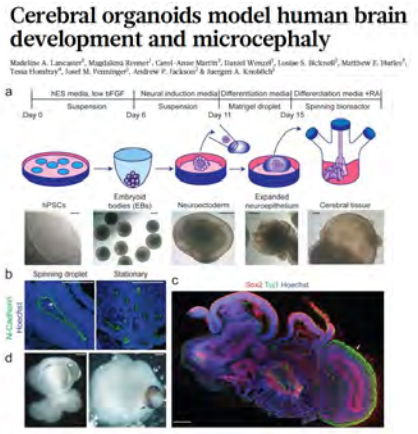
German spin-off TissUse is producing chips with two or four organs on each.

Tissue Engineering for Precision Medicine in Cancer Body-on-chip



HOOKED UP Bioengineers have connected multiple organs-on-chips to replicate human physiology. They hope to use the set-up to study the spread of metastatic breast cancer to the brain.

Tissue Engineering, Organoids and Precision Medicine



Cerebral organoids model human brain development and microcephaly

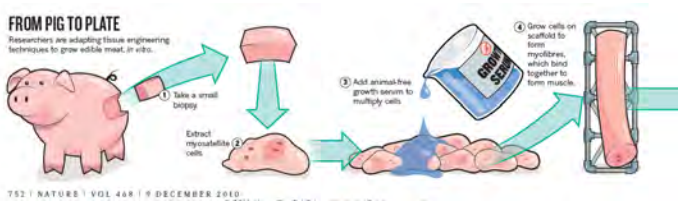
Madeline A. Lancaster[1], Magdalena Renner[1], Carol-Anne Martin[2], Daniel Wenzel[3], Louise S. Bicknell[4], Matthew E. Hurles[3], Tessa Homfray[4], Josef M. Penninger[2], Andrew P. Jackson[3] & Juergen A. Knoblich[1]

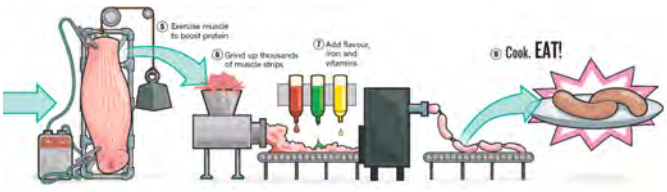
In vitro or cultured meat

Cultured meat, also called **clean meat** or ***in vitro* meat**, is meat grown in cell culture, using many of the same tissue engineering techniques traditionally used in regenerative medicine, instead of inside animals.

- first peer-reviewed journal article published in 2005 in *Tissue Engineering*.
- in 2008, PETA (People for the Ethical Treatment of Animals) offered a $1 million prize to the first company to bring lab-grown chicken meat to consumers by 2012
- as of 2012, 30 laboratories from around the world have announced that they are working on cultured meat research.

In vitro or cultured meat





In vitro or cultured meat

The first cultured beef burger patty, created by Dr. Mark Post at Maastricht University, was eaten at a demonstration for the press in London in August 2013.

Science & Environment BBC

World's first lab-grown burger is eaten in London

5 August 2013

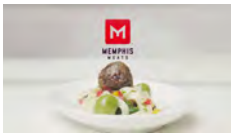
On August 6, 2013, the world's first lab-grown burger was cooked and eaten at a news conference in London. Scientists from Maastricht University in the Netherlands, led by professor Mark Post, had taken stem cells from a cow and grown them into strips of muscle which they then combined to make a burger. The burger was cooked by chef Richard McGeown of Couch's Great House Restaurant, Polperro, Cornwall, and tasted by critics Hanni Ruetzler, a food researcher from the Future Food Studio and Josh Schonwald.

…There is really a bite to it, there is quite some flavour with the browning. I know there is no fat in it so I didn't really know how juicy it would be, but there is quite some intense taste; it's close to meat, it's not that juicy, but the consistency is perfect. This is meat to me... It's really something to bite on and I think the look is quite similar…

Challenges associated with scaling and cost-reduction
Not yet commercialized
Will consumers accept cultured meat?

Start-ups producing cultured meat

1. Memphis meat (San Francisco, Silicon Valley)



- beef metballs
- chicken tenders
- duck à l'orange

2. Supermeat (Israel)