Space R & D; How does it complement ground research – an example in the bone/tissue-engineering field

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What do we know?

- load-bearing lower extremities most subject to bone loss during space exposure,
- by contrast some increase of the skull mass has been mentioned,
- recovery is a long-lasting process,… [if at all possible!]

Hence

- efficient countermeasures is essential for the long-duration flights

because of likely multifactorial origin of bone homeostasis, i.e.
mechanical,
nutritional,
physical activity, i.e. muscular, vascular, systemic factors,
possibly stress effects.

====> general understanding instead of "single path"

Therefore

===> traditional human and mammalian animal physiology models,
====> plus cell, tissue, and other animal models.

Bone quality assessment

Largest changes of bone mass after exposure to microgravity for lower extremities ((Vico *et al*., 2000; Lang, *et al*., 2004)

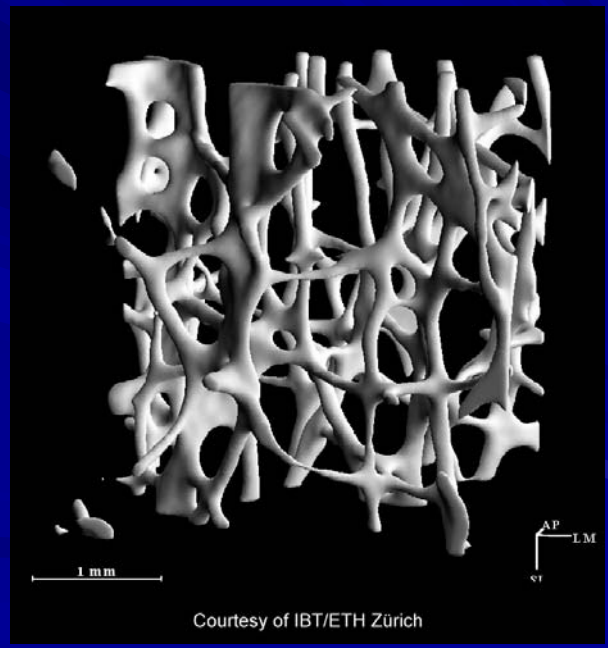
in line with clinical and animal studies

===> immobilization or skeletal unloading results in a loss of bone mass and bone strength (Krølner & Toft, 1983).

Accurate **risk** assessment:

➔knowledge on
- loss of structural elements, and
- of connectivity [trabecular bone]

(ESA supported development 3D-µCT / Scanco)



Efficiency of post-recovery measures or of countermeasures

===> recovery or conservation of a **bone microstructure efficient in a mechanical sense**

i.e. "accumulating bone mass without proper mechanically efficient tridimentional structure ====> no advantage in terms of bone resistance"

Problem in the assessment of bone quality evolution

Variability between sites in the same bone and, for animal experiments, between individuals (C.M. Davies *et al*., 2006) prevents accurate assessment of a change in bone structure with use of classical invasive method (histomorphometry on sections of bone biopsies).

===> High costs
===> Infection risks
===> Ethical aspects

ADOQ project (**A**dvance **D**etection of b**O**ne **Q**uality)

In vivo quantitative computed tomography (QCT)

(joint activity with the European Commission 5th Framework Programme "Quality of Life"; start Jan. 2003)

"potential of the analysis of bone quality based on three dimensional peripheral quantified computed tomography and micro finite element modelling for risk prediction"

European multi-centric clinical study (Geneva, Berlin, Cambridge, and St-Etienne) on a general population from young age groups up to elderly, and different physical training patterns, from sedentary to semi-professional sporters

XtremeCT developed for measurements on the radius and the tibia sites with a resolution of 100*100*100µm:

- multi-centric clinical testing (Geneva, Cambridge, St-Etienne, Berlin)

- additional unit at WISE long-duration bed rest in Toulouse in 2005, along with QCT, DEXA, and an ultra-sonic device; on reference and countermeasure groups ===> sensitivity and capability for early detection of changes in the bone mass and bone quality,

-EDOS experiment ===> normative data on astronauts/cosmonauts pre- and post-flights,

- Relation between reconstructed 3D microarchitecture based on CT measurements and mechanical performances by measures of complexity experimentally confirmed by Max Planck Inst. Potsdam.

Bone homeostasis, a multi-factorial mechanism

ESA favours an integrated multi-disciplinary approach encompassing nutrition, hormonal regimen, exercise with endurance/strength/frequency components, inter-tissular muscle/bone and vascular system/bone signalling, stress/psychosomatic effects, and genetic determinants. Drug therapies are additional experimental components to this integrated approach.

===> space oriented research very relevant to the general public health research where impact of lifestyles is estimated to account for over 25% of disability-adjusted life years lost in developed regions such as Europe (F.C. Bijnen *et al*., 1999; M.Aijo *et al*., 2002).

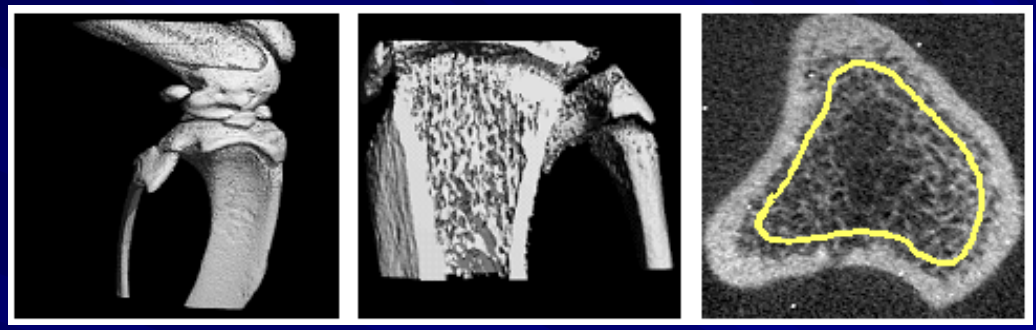
Simplified animal and biological models

- Faster (and less expensive) animal models: for remodelling studies, rat model replaced by mice (mature skeleton in about 4 months for the BL/6); tail suspension µg simulation model adapted to mice.

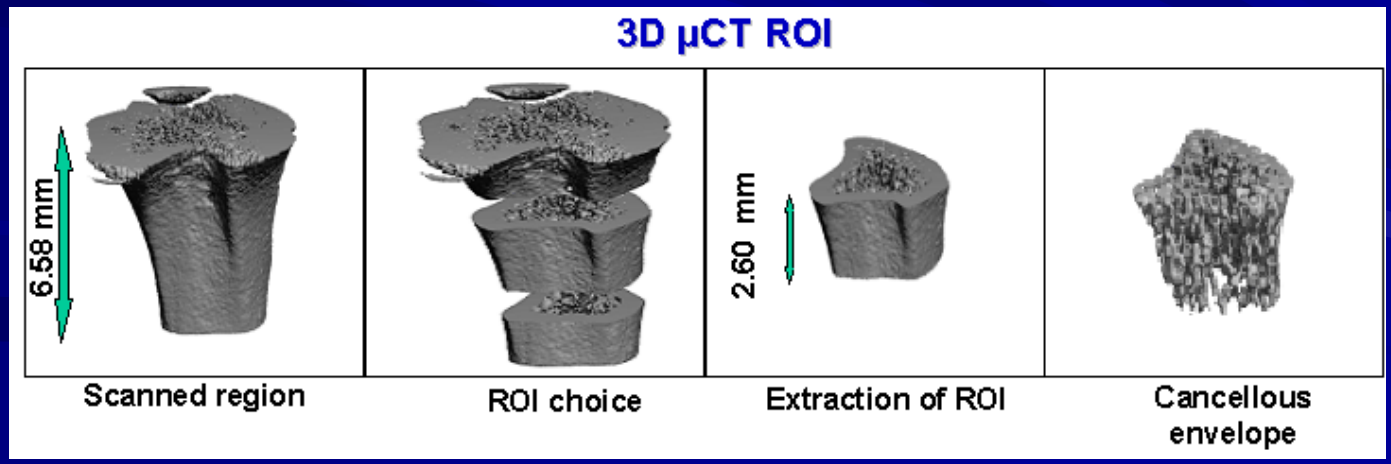
- Longitudinal survey in the hind limb unloaded rodent model have shown the sensibility of the vascular system to µg simulation and its possible role in the induced accelerated bone resorption (O. Barou et al., 2002)

- A **non-invasive/in vivo technique** (3D-pQCT / Viva CT) **for the longitudinal survey of trabecular bone microstructure** for rodents experiments (developed and validated)

Longitudinal non-invasive survey / in vivo technique (3D-pQCT / Viva CT)



Rat: Image acquisition and ROI Choice - Spatial Resolution of 20µm in X/Y and 40µm in Z.



Simplified animal and biological models

- Model fishes Medaka and Zebrafish to understand in vivo regulation of gene expression under different gravity conditions or following drug treatment (M.Muller Uni. Liege et al., MAP-99-LSS-003).

-*In vitro* cellular and tissular models to complement the human and animal physiological models by simplified engineered models (systemic vs. local regulation mechanisms); control the mechanical and biochemical stimuli in bioreactor

- on *ex vivo* bone samples (Z'Tos, Biotechnology Mammalian Tissue Culture facility, ...),

- with deterministic 3D-multi-cells constructs: 3D mineral or organo-mineral "bone" matrix hosting OB, OC, OCy plus BMSC and submitted to biochemical and/or mechanical stimulation

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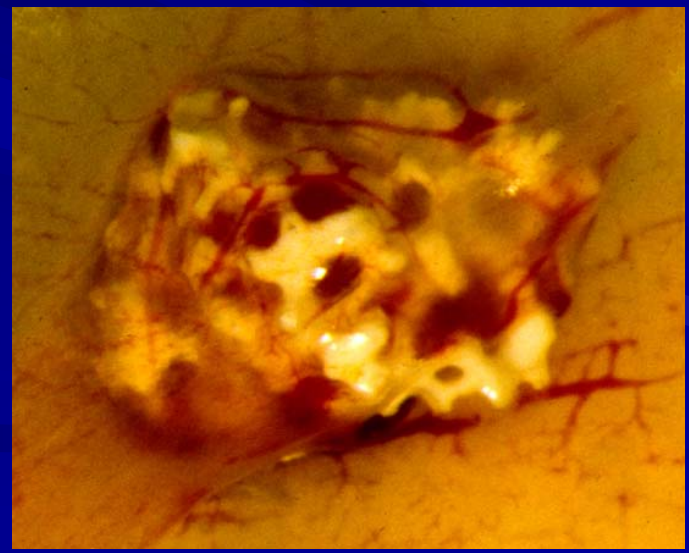
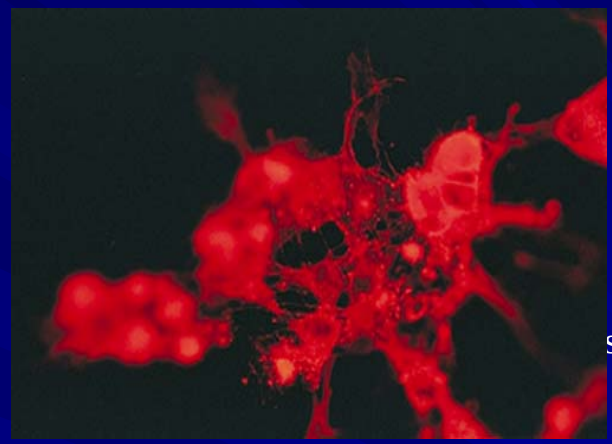


Courtesy R.Cancedda, Genoa /
Vascularisation of vitalised bone matrix

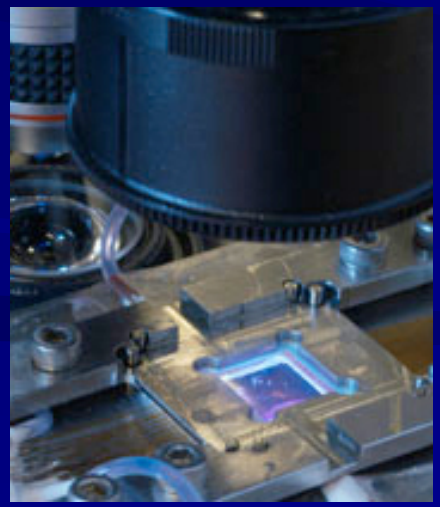
Models to favour basic understanding: tissue engineering

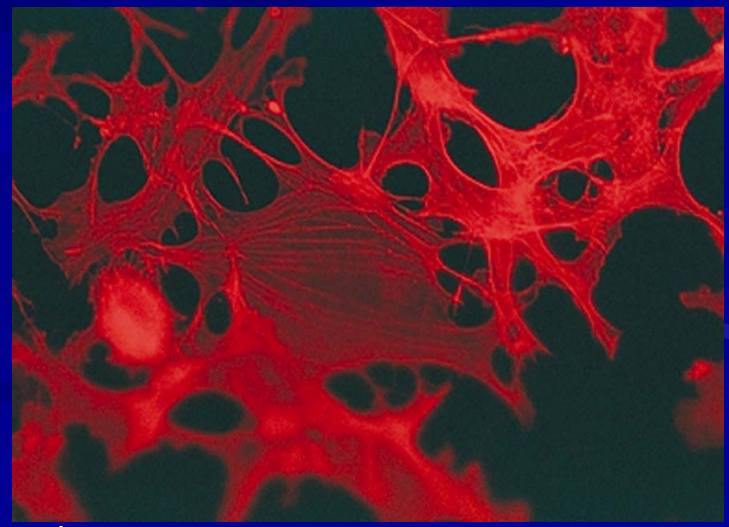
What makes environmental conditions organotypical? … and how to reproduce it in bioreactors?



Chondrocytes: osmotic shock protection by FSC **gradient**; courtesy I.Walther, ETH

…among other: concentration gradients in signalling molecules…





Conclusion: Maintaining Bone Quality - a space and societal challenge for science

Similar objectives for long-duration stay in space, later for human exploration of space, and today for an ageing European population

===> maintenance of bone quality.

Very strong rationale and justifications to have "space bone research" programmes not developing in isolation, but deeply relying and integrated with on-going general programmes at national, European, and international level.

and, if you still believe that space research just remains a dream for you,…

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TGFβ_3 and loading increases osteocyte survival in human cancellous bone cultured *ex vivo*

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