4º CIMES
CONGRESSO DE INOVAÇÃO EM MATERIAIS E EQUIPAMENTOS PARA SAÚDE

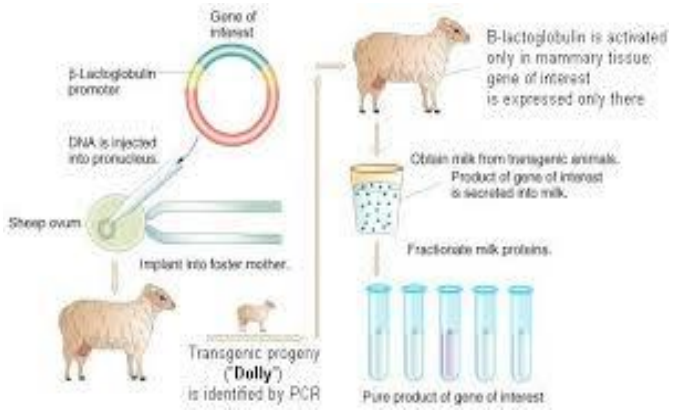
Novas Alternativas Terapêuticas em Odontologia

Profa. Dra.Monica Talarico Duailibi

REALIZAÇÃO: ABIMO Associação Brasileira da Indústria de Artigos e Equipamentos Médicos, Odontológicos, Hospitalares e de Laboratórios
PATROCÍNIO GOLD: BNDES
PATROCÍNIO: SEBRAE
APOIO: GOVERNO FEDERAL BRASIL PÁTRIA EDUCADORA

Novas Alternativas Terapêuticas em Odontologia

1865	1944	1953	1977	1996	2000
Mendel: trabalha na Rep. Tcheca com ervilhas e descobre as leis da herança genética	Estudos sobre Herança genética identifica o DNA como material que permite a herança genética	Drs.James Watson e Francis Crick descrevem a dupla hélice do DNA com o alinhamento das bases nitrogenadas	Primeiro genoma completo proveniente de uma bactéria foi sequenciado	Nasce a ovelha DOLLY, fruto de clonagem – núcleo de cél. Adulta + DNA →óvulo = cópia geneticamente identica a mãe.	*Anúncio de conclusão do sequenciamento completo do genoma humano unido Primeiro Ministro UK –Tony Blair e o Presidente dos USA, Bill Clinton*



2000-2015 mutações podem ser identificadas em genes chave para resposta imunológica de diversas doenças – Exame de sequenciamento

Projeto genoma humano original custou US$ 2,7 bilhões e hoje para se realizar um sequenciamento humano custa a partir de R$ 10.000,00

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GENOMA - estudo do código genético – genes – DNA

ERA PÓS GENÔMICA

TRANSCRIPTOMA – estudo dos transcritos – expressão genes – RNA

PROTEÔMICA – estudo em larga escala das proteínas por métodos bioquímicos

METABOLÔMICA – estudo que delimita o perfil molecular de determinada doença – espectroscopia de massa

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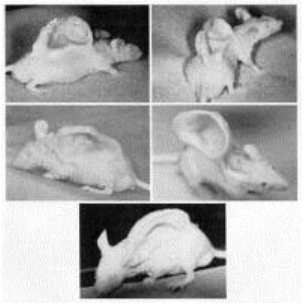
1938	1950	1967	1988	1997	2002
Publicação de Alexis Carrel (médico) e Lindbergh (aviador): *The Culture of Organs*	Estudos com Células-tronco em cães que foram expostos em altas doses de radiação (Medicina Regenerativa)	Dr. Christian Barnard Primeiro transplante de coração entre humanos de doador vivo	Dr. Skalak define "Tissue Engineering" confirmado mais tarde pelo relatório da ITRI e NSF	Joseph Vacanti e col. Publica na *Plastic and Reconstructive Surgery*	*Conceitos de Engenharia Tecidual consolidado na reunião da International Technology Research Institute – ITRI National Science Foundation*



Consolidação da TE como uma ciência Inter, trans e multi disciplinar

Polímero biodegradável (ác. poliglicólico) semeado com condrócito de boi e implantado nas costas de rato atímico.

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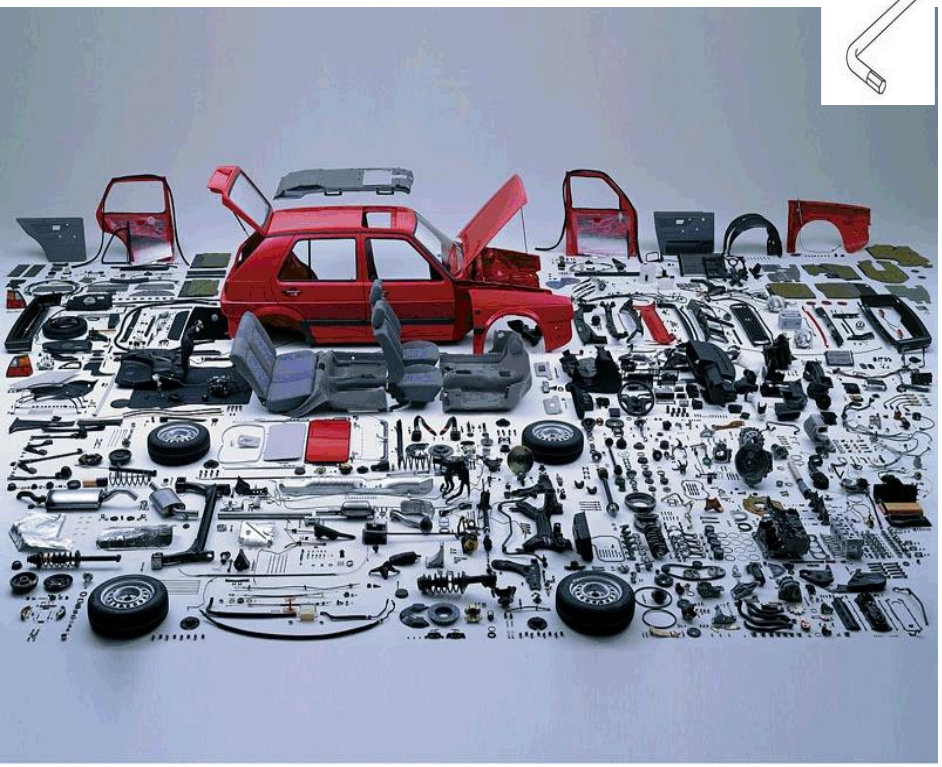
Engenharia Tecidual



Biofabricação

TEMPs - Tissue Engineering Medical Products
ABNT – CB26:070.03- Implantes e Substitutos Biológicos
ASTM- F04
ISO- TC 150/SC7

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índice geral São Paulo, sexta-feira, 20 de janeiro de 2012 FOLHA DE S.PAULO saúde

Texto Anterior | Próximo Texto | Índice | Comunicar Erros

FOCO

Coreia aprova droga feita com células-tronco de humanos

Medpost/France Presse

Cientista sul-coreana mostra droga produzida com células-tronco coletadas de humanos

DAS AGÊNCIAS DE NOTÍCIAS

A agência que regula medicamentos na Coreia do Sul anunciou ontem a aprovação da primeira droga do mundo que utiliza células-tronco coletadas de outras pessoas que não próprio paciente.

O medicamento, batizado de Cartistem, foi desenvolvido com células-tronco obtidas de cordão umbilical.

A droga, que é injetável, ajudará na regeneração da cartilagem dos joelhos.

O desenvolvimento do fármaco começou em 2001 e custou cerca de US$ 23 milhões, obtidos de investidores privados e do governo.

Os testes em humanos começaram no ano passado e devem seguir até 2015.

Dez laboratórios estão negociando a licença mundial para produzir a droga.

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SUBSTITUTOS BIOLÓGICOS
APROVADOS PELO FDI E DISPONÍVEIS NO MERCADO

Table 85.1. FDA-Approved Human Cellular- and Tissue-Based Products (HCT/Ps)

Skin Applications			
Product	*Sponsor*	*Intended Use*	*Approval*
Carticel (Autologous Cultured Chondrocytes)	Genzyme Corporation	Repair of femoral condyle caused by acute or repetitive fracture	1997-Biologic (BLA)
Apligraf (Viable Allogeneic Fibroblasts/Keratinocytes On Type-1 Bovine Collagen)	Organogenesis Inc.	Standard therapeutic compression for treatment of non-infected partial and full-thickness skin ulcers	1998-Device (PMA)
Dermagraft (Cryopreserved Dermal Substitute; Allogeneic Fibroblasts, Extracellular Matrix, Bioabsorbable Scaffold)	Advanced Tissue Sciences, Inc.	Treatment of full-thickness diabetic foot ulcers	2001-Device (PMA)
Composite Cultured Skin (Viable Allogeneic Fibroblasts/ Keratinocytes On Collagen Matrix)	Ortec International, Inc.	Adjunct to standard autograft procedures for covering wounds and donor sites after surgical release of hand contractions in Recessive Dystrophic Epidermolysis Bullosa patients	2001-Device (HDE)
Dermagraft (Cryopreserved Dermal Substitute; Allogeneic Fibroblasts, Extracellular Matrix, Bioabsorbable Scaffold)	Smith and Nephew Wound Management	Treatment of wounds related to Recessive Dystrophic Epidermolysis Bullosa	2003-Device (HDE)

SUBSTITUTOS BIOLÓGICOS
APROVADOS PELO FDI E DISPONÍVEIS NO MERCADO

Musculoskeletal Applications			
Product	*Sponsor*	*Intended Use*	*Approval*
OP-1 Implant (Recombinant Human Osteogenic Protein (rh OP-1), Type-1 Bovine Bone Collagen Matrix)	Stryker Biotech	Alternative to autograft in recalcitrant long bone non-unions	2002-Device (PMA)
In FUSE Bone Graft/LT-Cage Lumbar Tapered Fusion Device (Recombinant Human Bone Morphogenetic Protein-2, Type-1 Bovine Bone Collagen, Titanium Alloy Cage)	Medtronic	Spinal fusion for degenerative disc disease	2002-Device (PMA)
OP-1 Putty (Recombinant Human Osteogenic Protein (rh OP-1), Type-1 Bovine Bone Collagen Matrix, Putty Additive — Carboxymethyl Cellulose Sodium)	Stryker Biotech	Alternative to autograft in compromised patients requiring revision posterolateral lumbar spinal fusion for whom autologous bone and bone marrow-harvest are not feasible or expected to promote fusion	2004-Device (HDE)
GEM 21S™ (Growth Factor Enhanced Matrix) (Recombinant Human Platelet Derived Growth Factor, Synthetic Beta Tricalcium Phosphate)	Biomimetic, Pharmaceuticals, Inc.	Treatment for periodontally-related defects; intrabony defects; furcation defects; gingival recession associated with periodontal defects.	2005-Device (PMA)

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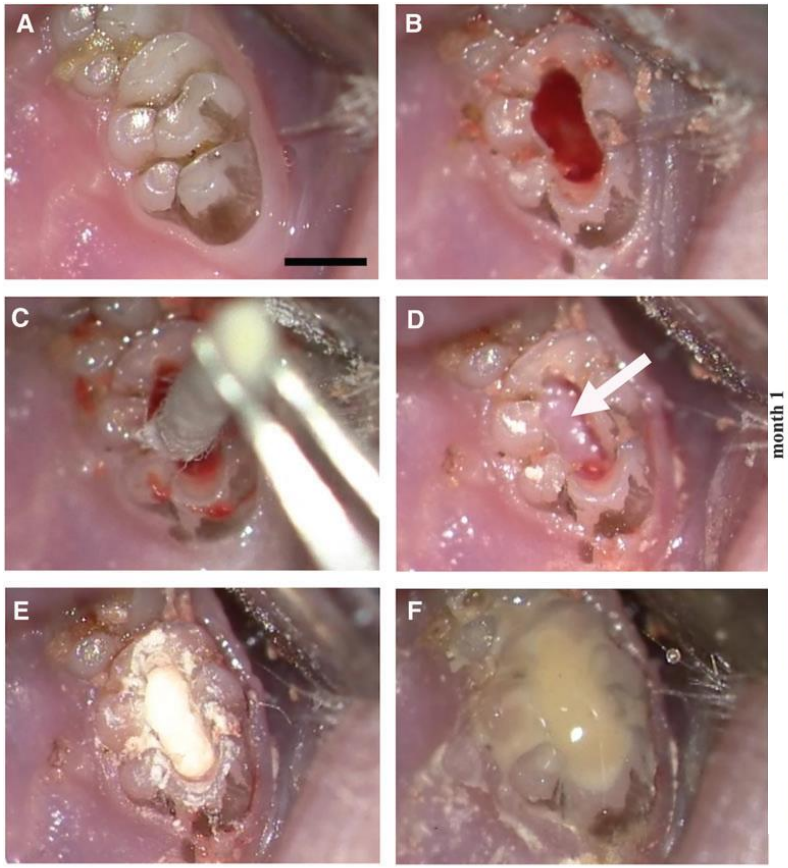

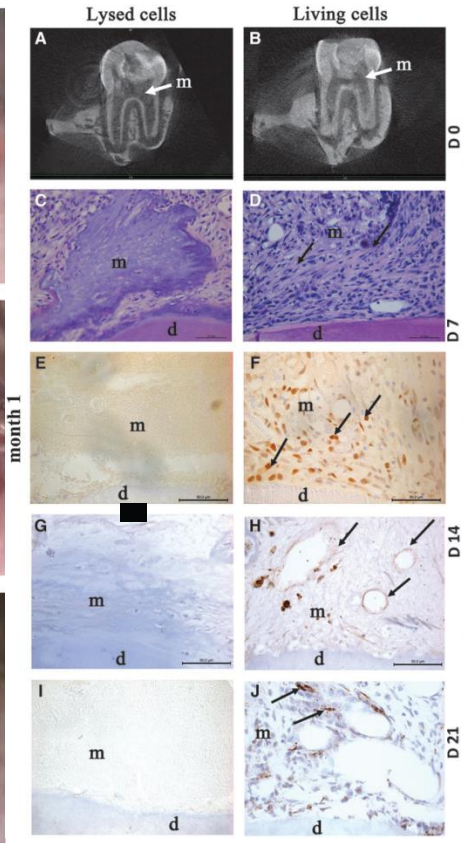

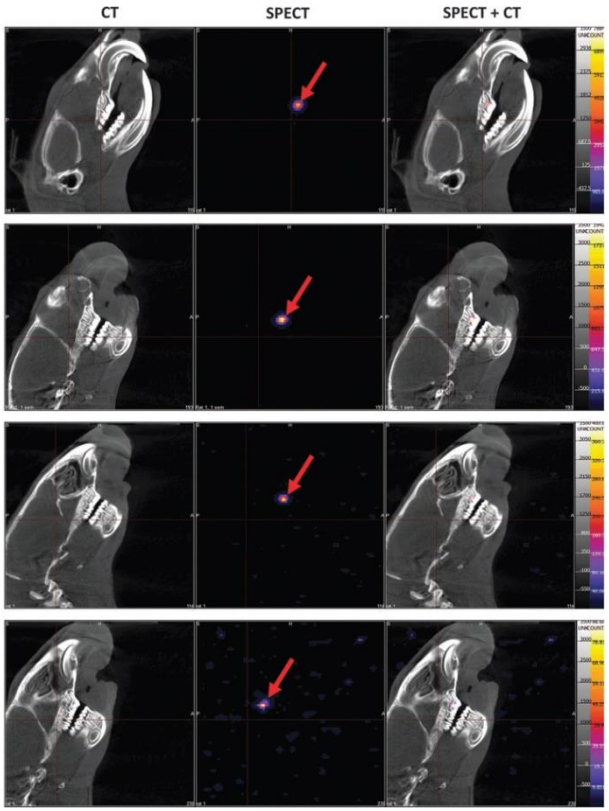

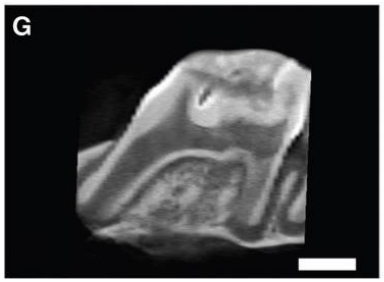

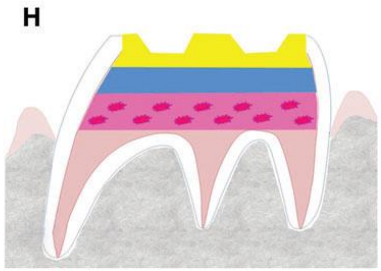

Souron et al., Tissue Engineering, Part C Methods, 2014

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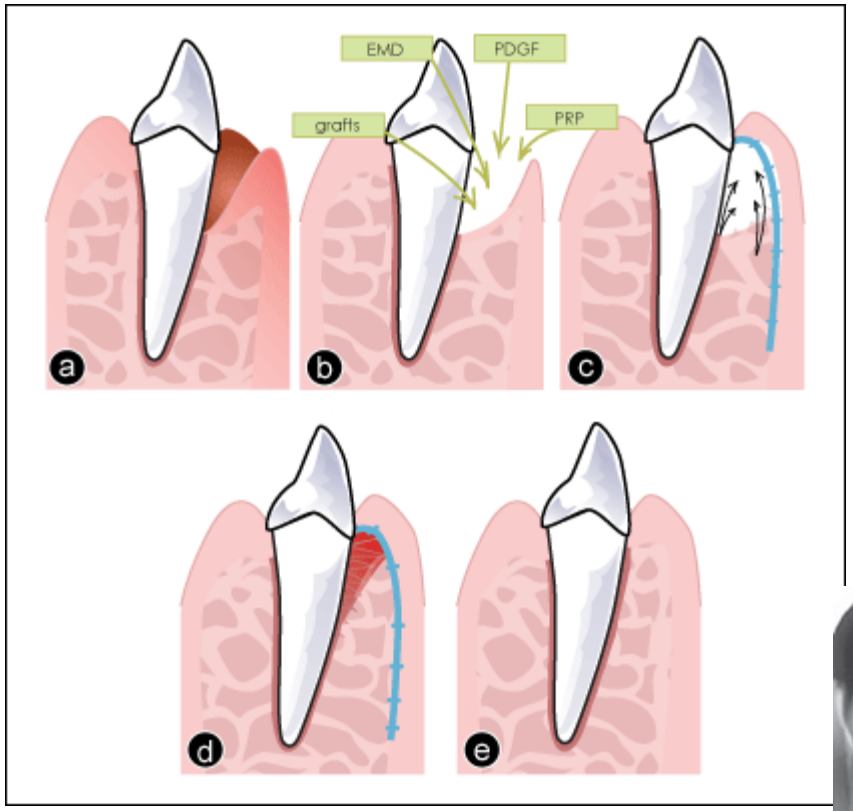
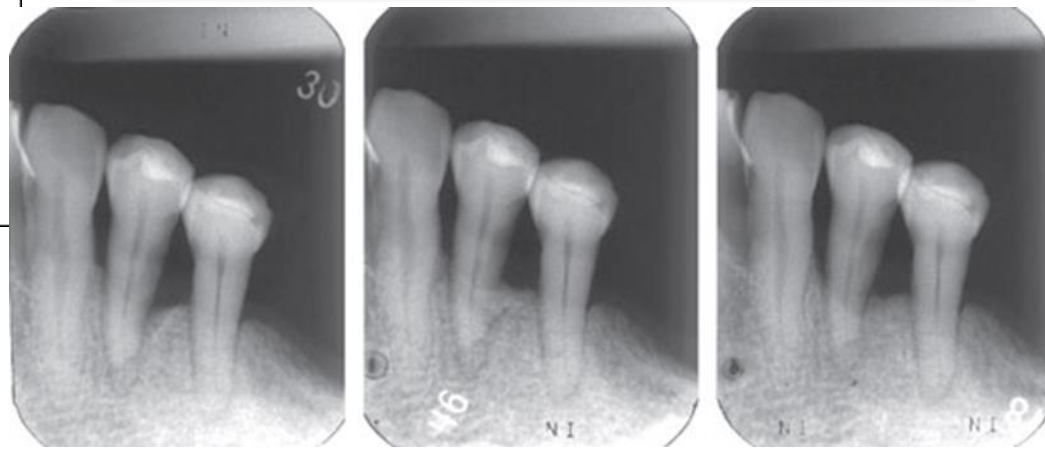




Izume et al , 2011

Engenharia por camada celular

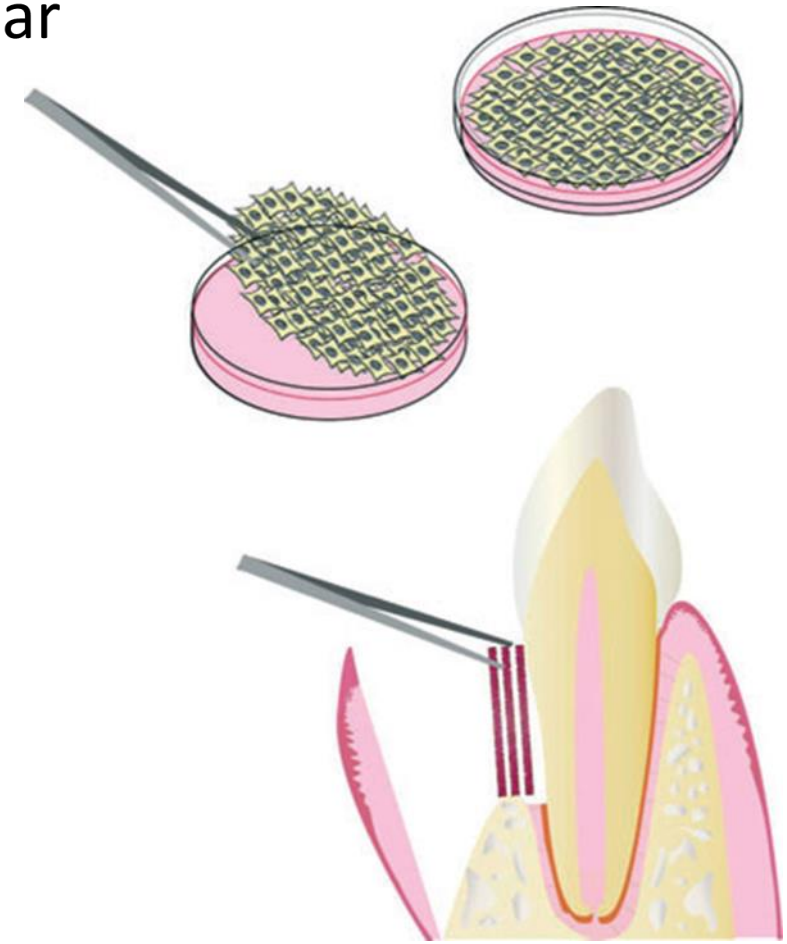
CELL SHEETS

Produzir uma camada celular funcional.

Vários tipos de transplantes sem arcabouço tem sido desenvolvidos.

Reconstrução de córnea, tratamento de ulcera esofágica, incremento da função ventricular esquerda em pacientes com cardiomiopatia isquêmica e dilatada.

UpCeLL ™ (CellSeed Inc. Toquio, Japão)



Novas Alternativas Terapêuticas em Odontologia

RESEARCH REPORTS
Biomaterials & Bioengineering

M.T. Duailibi[4], S.E. Duailibi[4], C.S. Young[2], J.D. Bartlett[2], J.P. Vacanti[3], and P.C. Yelick[2]*

[1]University Federal of São Paulo, Department of Otorhinolaryngology and Human Communication Disorders, São Paolo, Brazil; [2]Department of Cytokine Biology, The Forsyth Institute, 140 The Fenway, and Department of Oral and Developmental Biology, Harvard Medical School, Boston, MA 02115, USA; and [3]Department of Surgery, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA; [4]authors contributing equally to this paper; *corresponding author, pyelick@forsyth.org

J Dent Res 83(7):523-528, 2004

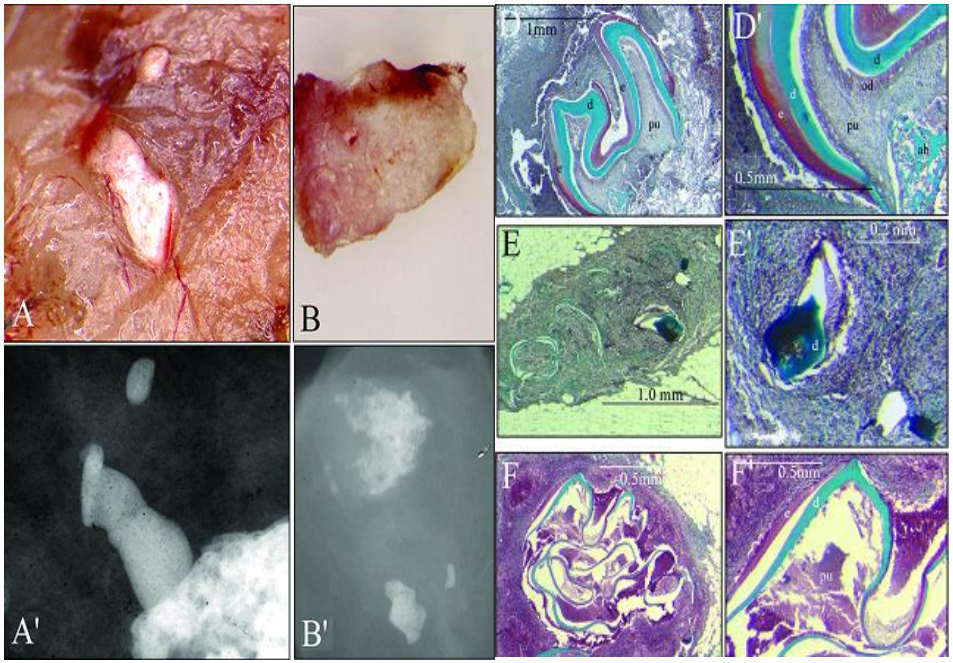
Bioengineered Teeth from Cultured Rat Tooth Bud Cells

ABSTRACT

The recent bioengineering of complex tooth structures from pig tooth bud tissues suggests the potential for the regeneration of mammalian dental tissues. We have improved tooth bioengineering

INTRODUCTION

The incidence of children born with missing primary and/or adult teeth is significant (Nunn *et al.*, 2003), and tooth loss in aged populations is also a prevalent health problem. Current replacement tooth methods use synthetic materials that can elicit an immune induced host rejection response. The ability to generate biological tooth substitutes from autologous human tissues would be a valuable clinical tool. Tissue



RESEARCH REPORTS
Biomaterials & Bioengineering

S.E. Duailibi[1†], M.T. Duailibi[1†], W. Zhang[2], R. Asrican[3], J.P. Vacanti[4], and P.C. Yelick[2*]

[1]University Federal of São Paulo, Department of Plastic Surgery, UNIFESP-CINTERGEN, Interdisciplinary Center of Gene Therapy, São Paulo, Brazil; [2]Division of Craniofacial and Molecular Genetics, Department of Oral and Maxillofacial Pathology, Tufts University, Boston, MA 02111, USA; [3]Department of Cytokine Biology, The Forsyth Institute, and Department of Developmental Biology, Harvard School of Dental Medicine, [4]Laboratory for Tissue Engineering and Organ Fabrication, Massachusetts General Hospital and Department of Surgery, and Harvard Medical School, Boston, MA, USA; [†]authors contributing equally to this manuscript; *corresponding author, Division of Craniofacial and Molecular Genetics, Department of Oral and Maxillofacial Pathology, Tufts University, 136 Harrison Avenue, Room M824, Boston, MA 02111, USA, pamela.yelick@tufts.edu

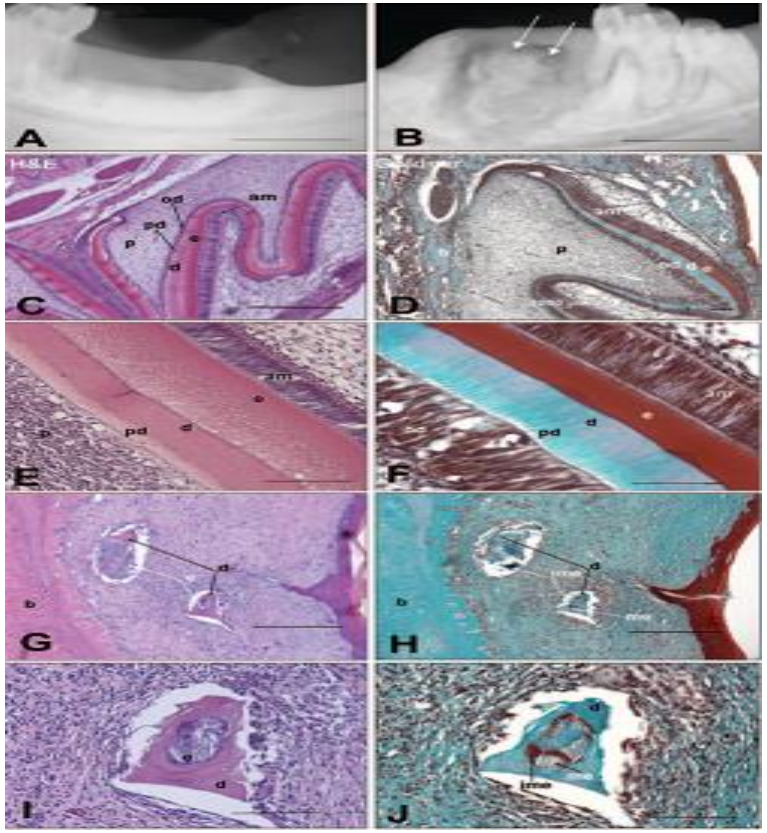
J Dent Res 87(8):745-750, 2008

Bioengineered Dental Tissues Grown in the Rat Jaw

ABSTRACT

INTRODUCTION

Recent advances in materials science and tissue engineering have created opportunities for the development of methods to bioengineer tissue and organ replacements, including highly mineralized craniofacial and dental tissues. Current methods to repair and/or replace dental tissues principally use synthetic materials, whose physical and mechanical properties are quite distinct from those of naturally formed teeth. The need for alternative



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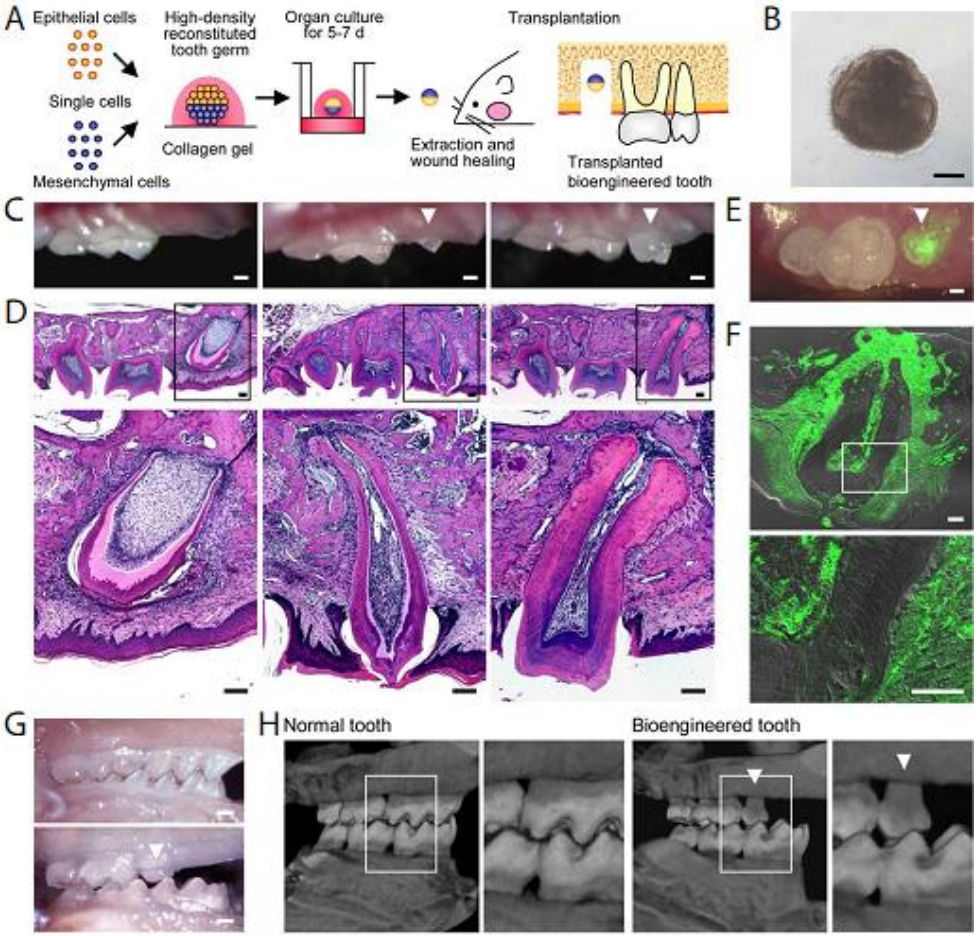
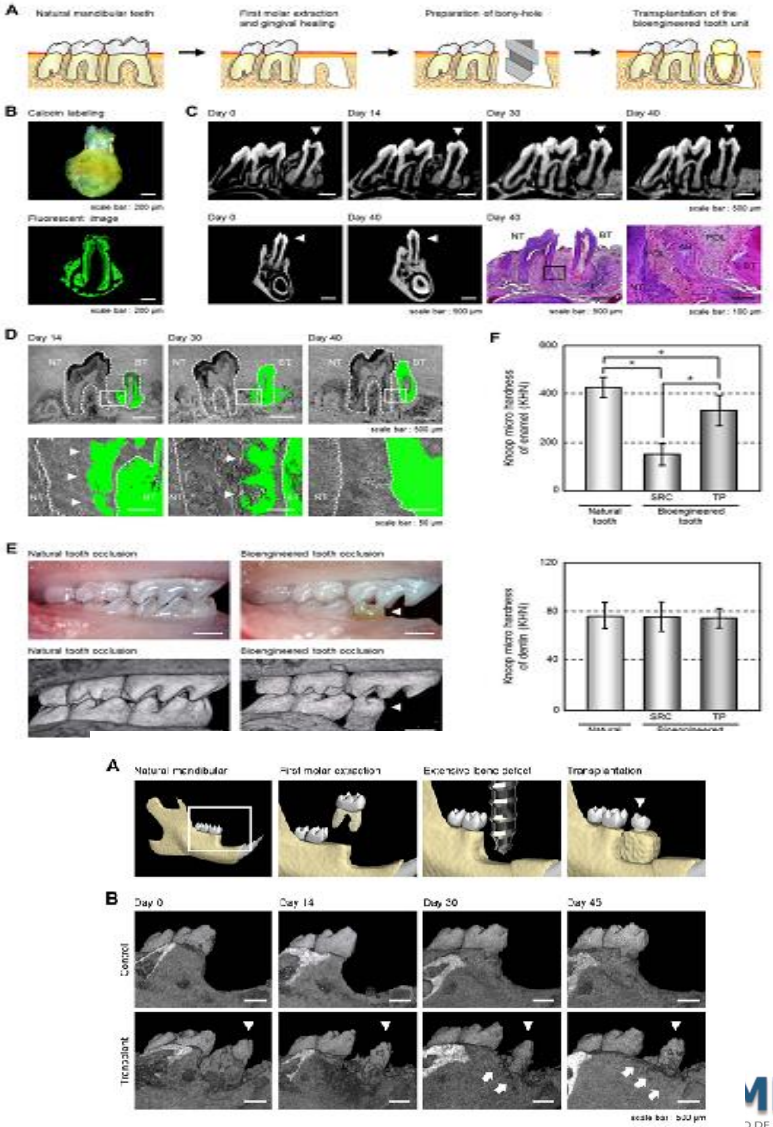


Ikeda et al., 2009 *PNAS*



Oshima et al., 2011 *Plos One*

MES
DE INOVAÇÃO EM MATERIAIS E EQUIPAMENTOS PARA SAÚDE

Novas Alternativas Terapêuticas em Odontologia

Estratégias para a Engenharia Tecidual do Dente Inteiro

Translational Studies

Terapia Celular

Biomimetismo dos eventos celulares e moleculares

Protocolos para o controle do número, tamanho, forma e cor.

BMP4 (incisors)

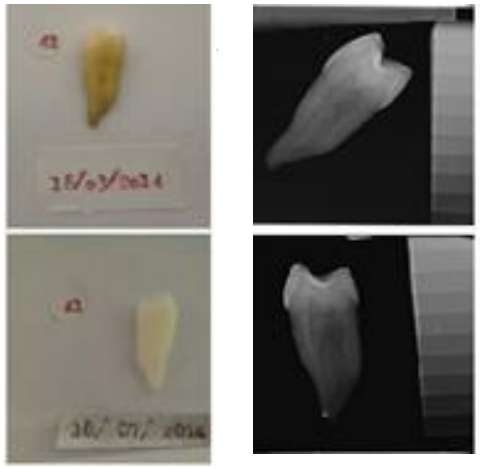
Msx1
Msx2

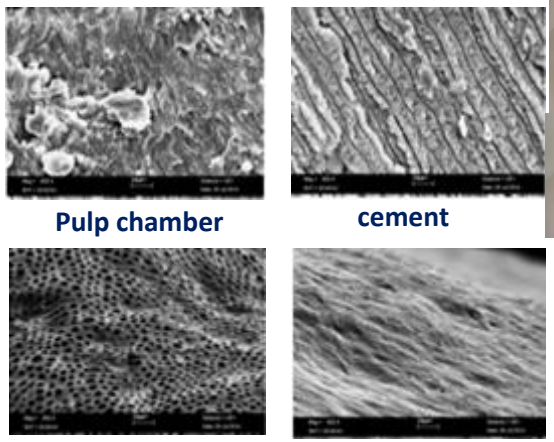
FGF8 (molars)

Dlx1
Dlx2
Barx1

Descelularização Tecidual

Scaffold Natural



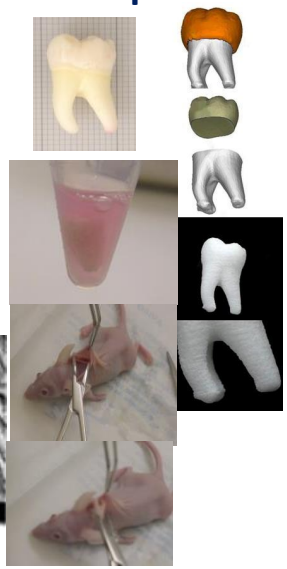


TTE Tranplantação celular

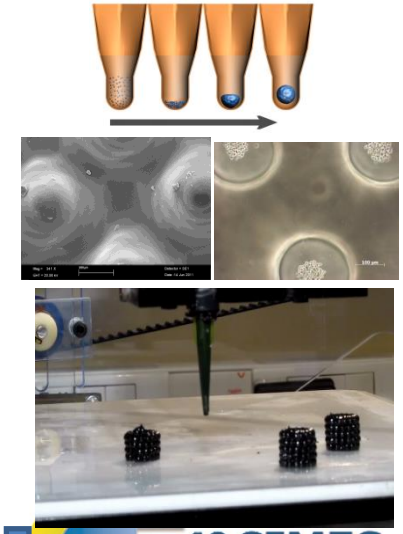
Construct or TEMPs

Fonte celular

Expansão de células primárias



esferóides ou micro tecidos (cultura 3D)



SCAFFOLDS

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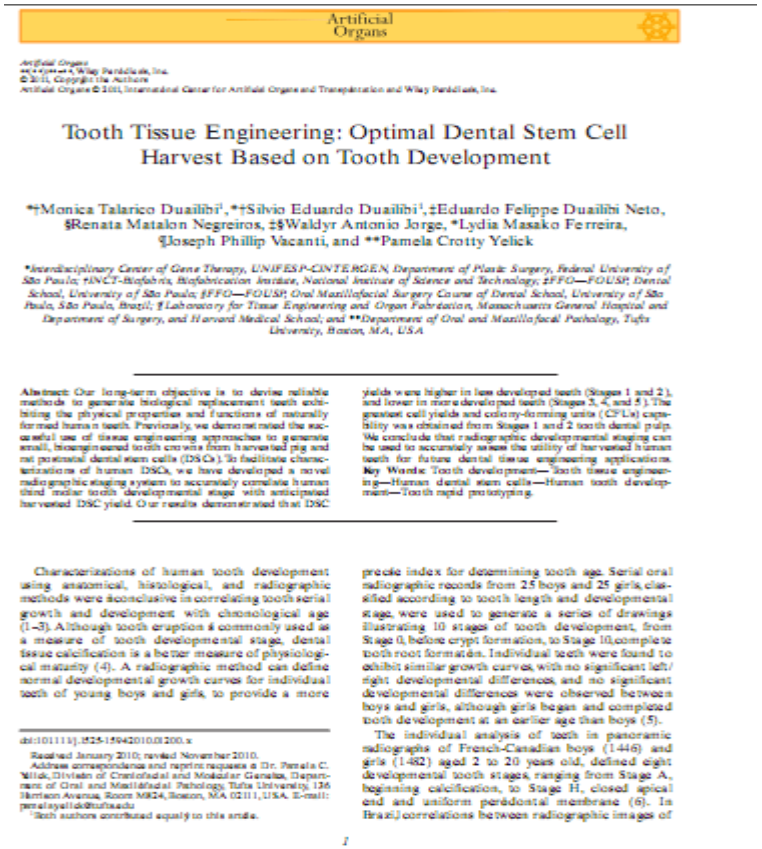

Artificial Organs

Artificial Organs
Wiley Periodicals, Inc.
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Tooth Tissue Engineering: Optimal Dental Stem Cell Harvest Based on Tooth Development

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*Interdisciplinary Center of Gene Therapy, UNIFESP-CINTERGEN, Department of Plastic Surgery, Federal University of São Paulo; †INCT-Biofabris, Biofabrication Institute, National Institute of Science and Technology; ‡FFO—FOUSP, Dental School, University of São Paulo; §FFO—FOUSP, Oral Maxillofacial Surgery Course of Dental School, University of São Paulo, São Paulo, Brazil; ¶Laboratory for Tissue Engineering and Organ Fabrication, Massachusetts General Hospital and Department of Surgery, and Harvard Medical School; and **Department of Oral and Maxillofacial Pathology, Tufts University, Boston, MA, USA

Abstract: Our long-term objective is to devise reliable methods to generate biological replacement teeth exhibiting the physical properties and functions of naturally formed human teeth. Previously, we demonstrated the successful use of tissue engineering approaches to generate small, bioengineered tooth crowns from harvested pig and rat postnatal dental stem cells (DSCs). To facilitate characterizations of human DSCs, we have developed a novel radiographic staging system to accurately correlate human third molar tooth developmental stage with anticipated harvested DSC yield. Our results demonstrated that DSC yields were higher in less developed teeth (Stages 1 and 2), and lower in more developed teeth (Stages 3, 4, and 5). The greatest cell yields and colony-forming units (CFUs) capability was obtained from Stages 1 and 2 tooth dental pulp. We conclude that radiographic developmental staging can be used to accurately assess the utility of harvested human teeth for future dental tissue engineering applications.
Key Words: Tooth development—Tooth tissue engineering—Human dental stem cells—Human tooth development—Tooth rapid prototyping.

Characterizations of human tooth development using anatomical, histological, and radiographic methods were inconclusive in correlating tooth serial growth and development with chronological age (1–3). Although tooth eruption is commonly used as a measure of tooth developmental stage, dental tissue calcification is a better measure of physiological maturity (4). A radiographic method can define normal developmental growth curves for individual teeth of young boys and girls, to provide a more precise index for determining tooth age. Serial oral radiographic records from 25 boys and 25 girls, classified according to tooth length and developmental stage, were used to generate a series of drawings illustrating 10 stages of tooth development, from Stage 0, before crypt formation, to Stage 10, complete tooth root formation. Individual teeth were found to exhibit similar growth curves, with no significant left/right developmental differences, and no significant developmental differences were observed between boys and girls, although girls began and completed tooth development at an earlier age than boys (5).

The individual analysis of teeth in panoramic radiographs of French-Canadian boys (1446) and girls (1482) aged 2 to 20 years old, defined eight developmental tooth stages, ranging from Stage A, beginning calcification, to Stage H, closed apical end and uniform periodontal membrane (6). In Brazil, correlations between radiographic images of

doi:10.1111/j.1525-1594.2010.01200.x
Received January 2010; revised November 2010.
Address correspondence and reprint requests to Dr. Pamela C. Yelick, Division of Craniofacial and Molecular Genetics, Department of Oral and Maxillofacial Pathology, Tufts University, 136 Harrison Avenue, Room M824, Boston, MA 02111, USA. E-mail: pamela.yelick@tufts.edu
[1]Both authors contributed equally to this article.

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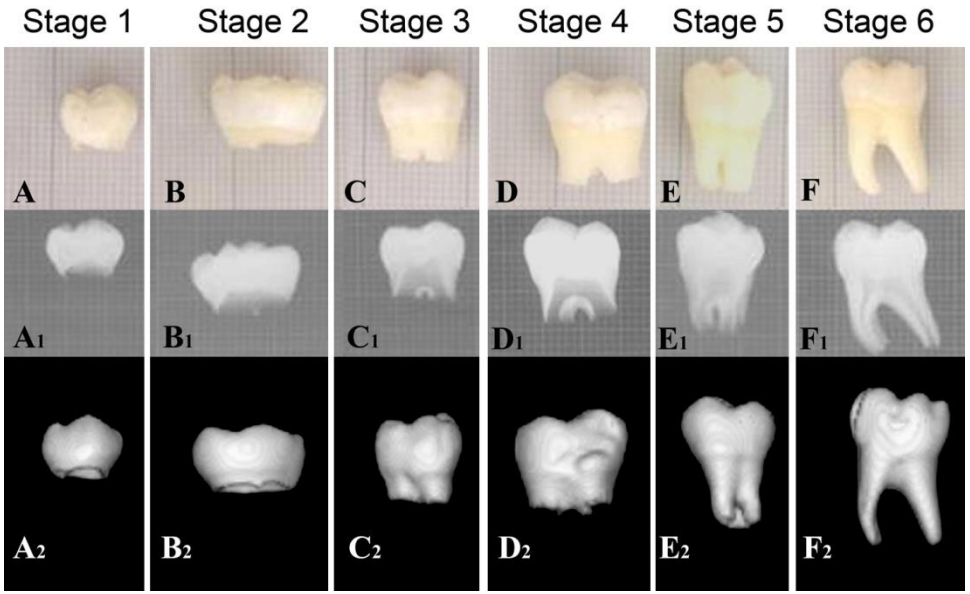

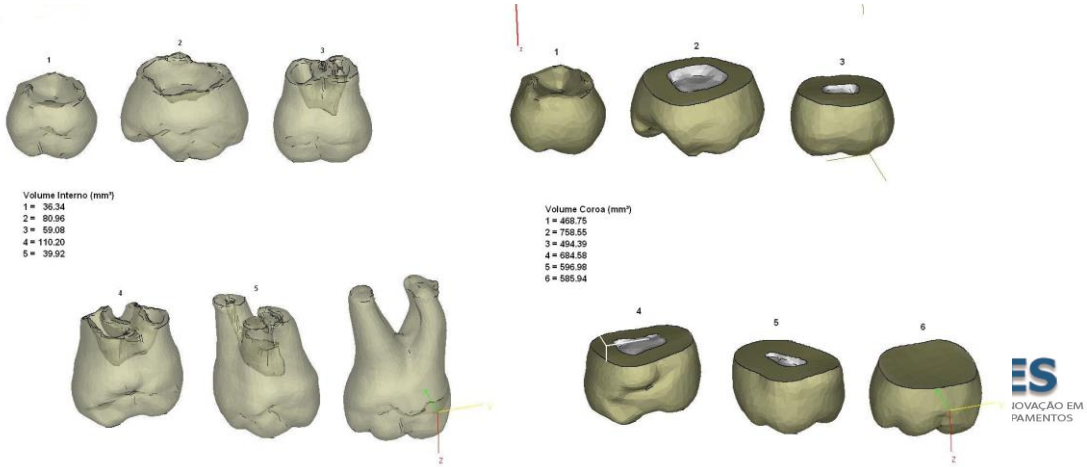

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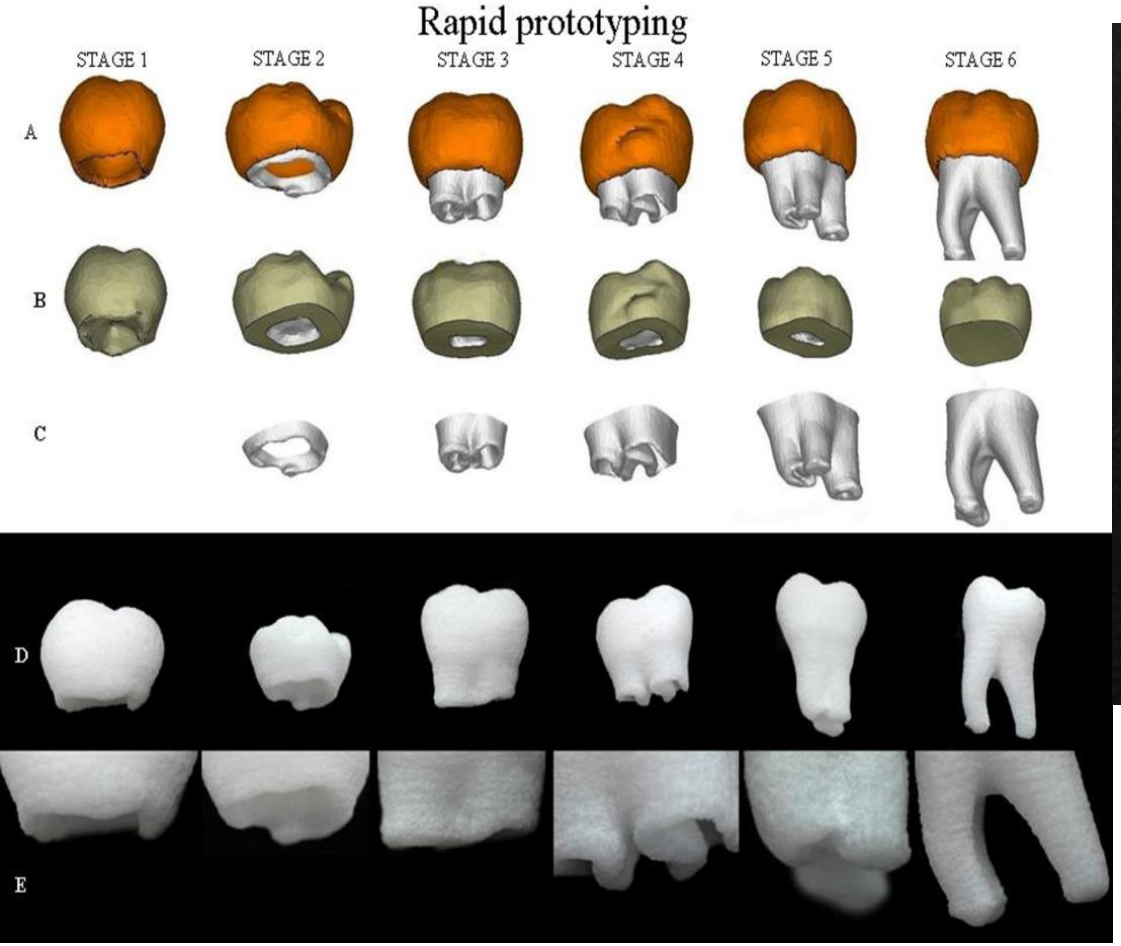

Duailibi et al., 2011 *Artificial Organs*

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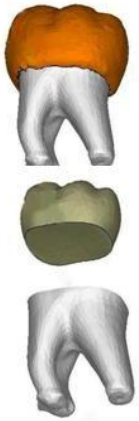
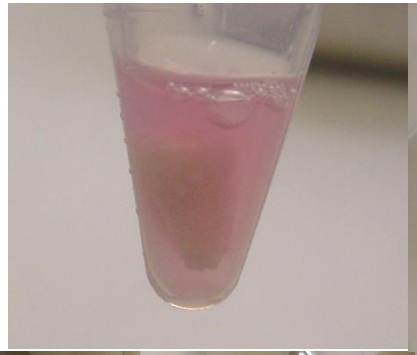
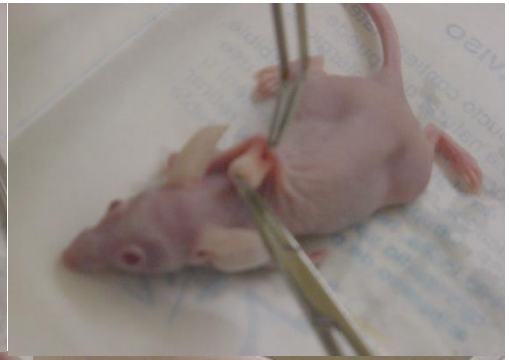
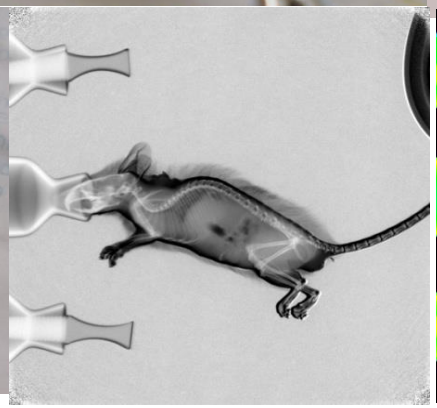
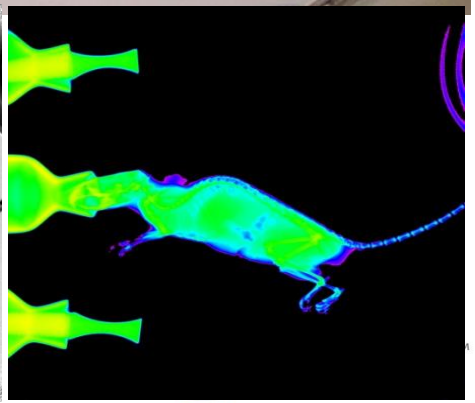


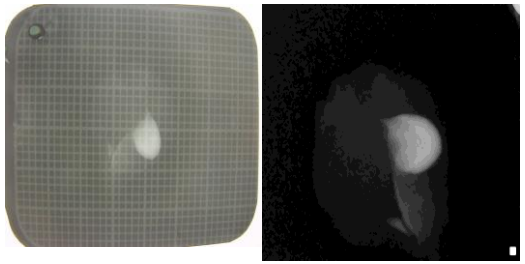








Novas Alternativas Terapêuticas em Odontologia
Estudo translacional

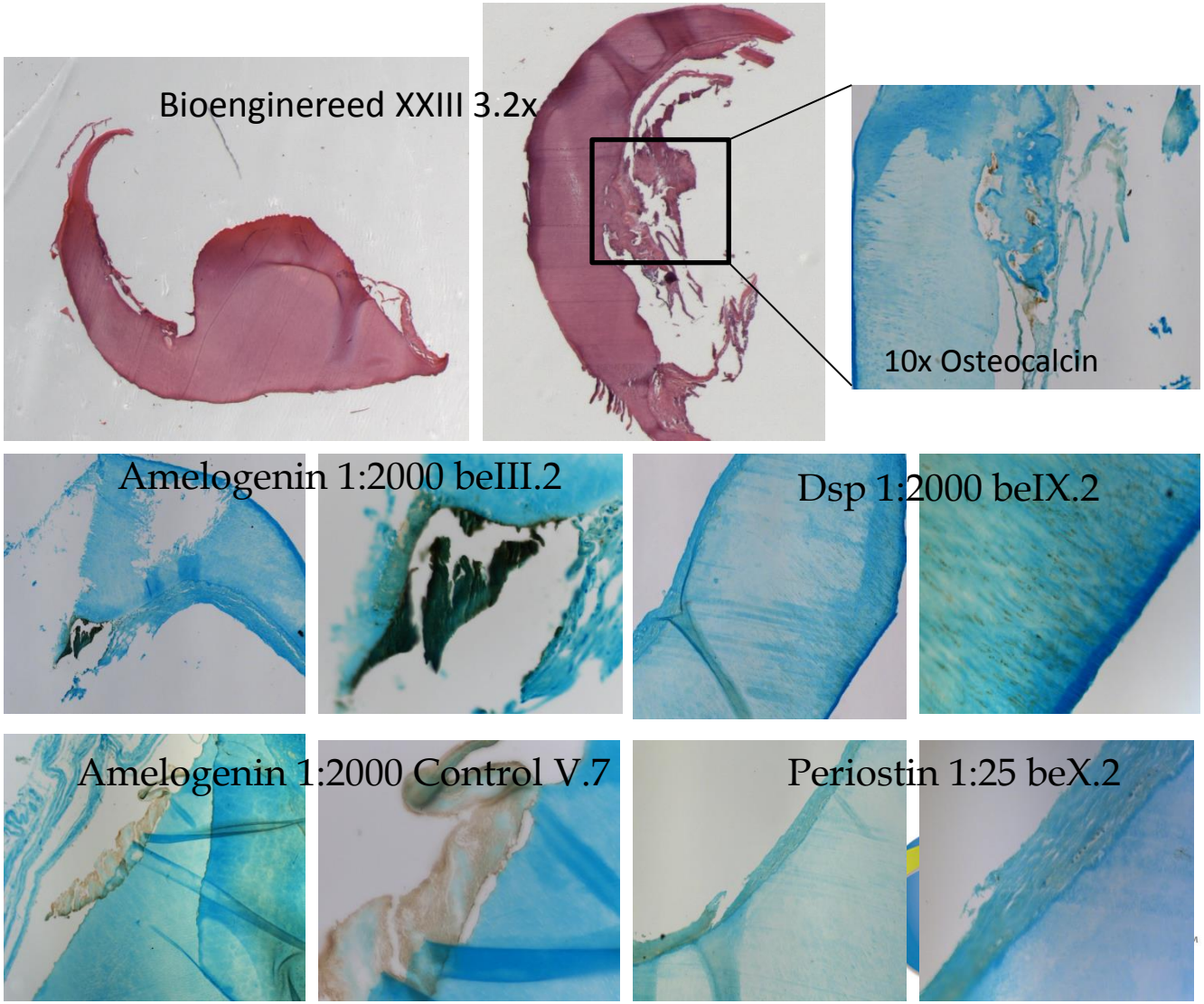


Micro CT

sagital

ventral

lateral



Duailibi et al., 2015Submmited *Tissue Engineering Part A*

Como otimizar o processo para garantir a segurança e o controle na aplicação clínica??

ASPECTOS RELACIONADOS AO MATERIAL BIOLÓGICO:

- Fonte celular – autóloga X alogênica
- Controle da migração celular
- Manutenção da Integridade tecidual – Estrutura X Funcionalidade
- Métodos de armazenagem – condições específicas para cada tipo de tecido
- Testes de validação – fundamentados pela ISO/ ASTM/ DIN/ ABNT etc…
- Controle de tamanho e cor - customização

ASPECTOS RELACIONADOS A COMPLEXIDADE DOS SCAFFOLDS:

- Macro e Micro geometria – Biomimetismo
- Controle da biodegradabilidade
- Conhecimento de Interfaces – Biomaterial X Material Biológico
- Método ideal de esterilização TEMPs para ser posteriormente implantado

Novas Alternativas Terapêuticas em Odontologia

J Mol Hist
DOI 10.1007/s10735-011-9373-z

ORIGINAL PAPER

Cytogenetic instability of dental pulp stem cell lines

Monica Talarico Duailibi · Leslie Domenici Kulikowski · Silvio Eduardo Duailibi · Monica Vannucci Nunes Lipay · Maria Isabel Melaragno · Lydia Masako Ferreira · Joseph Phillip Vacanti · Pamela Crotty Yelick

Received: 18 August 2011 / Accepted: 9 November 2011
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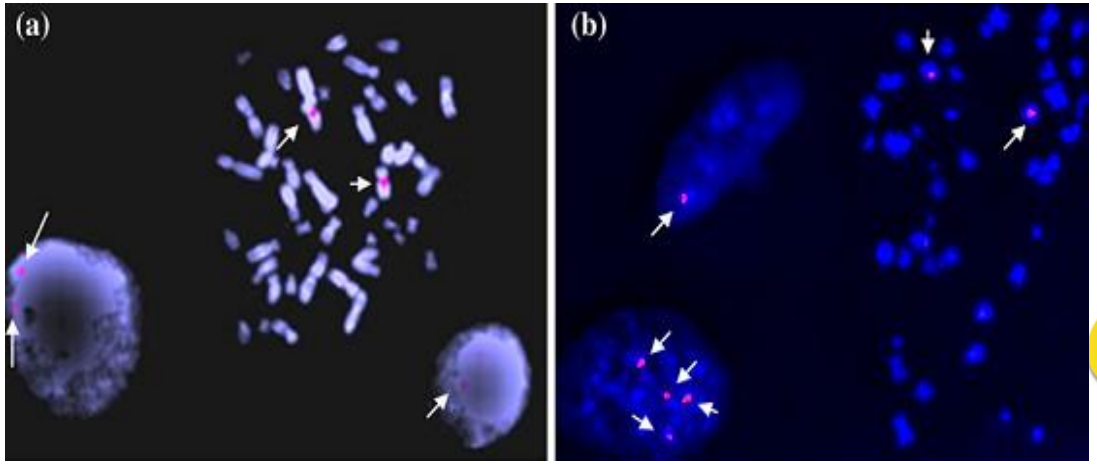
Abstract Human adult stem cells (hASCs) offer a potentially renewable source of cell types that are easily isolated and rapidly expanded for use in regenerative medicine and cell therapies without the complicating ethical problems that are associated with embryonic stem cells. However, the eventual therapeutic use of hASCs requires that these cells and their derivatives maintain their genomic stability. There is currently a lack of systematic studies that are aimed at characterising aberrant chromosomal changes in cultured ASCs over time. However, the presence of mosaicism and accumulation of karyotypic four expanded hDSC cultures using classical G banding and fluorescent in situ hybridisation (FISH) with X chromosome specific probe. Our preliminary results revealed that about 70% of the cells exhibited karyotypic abnormalities including polyploidy, aneuploidy and ring chromosomes. The heterogeneous spectrum of abnormalities indicates a high frequency of chromosomal mutations that continuously arise upon extended culture. These findings emphasise the need for the careful analysis of the cytogenetic stability of cultured hDSCs before they can be used in clinical therapies.



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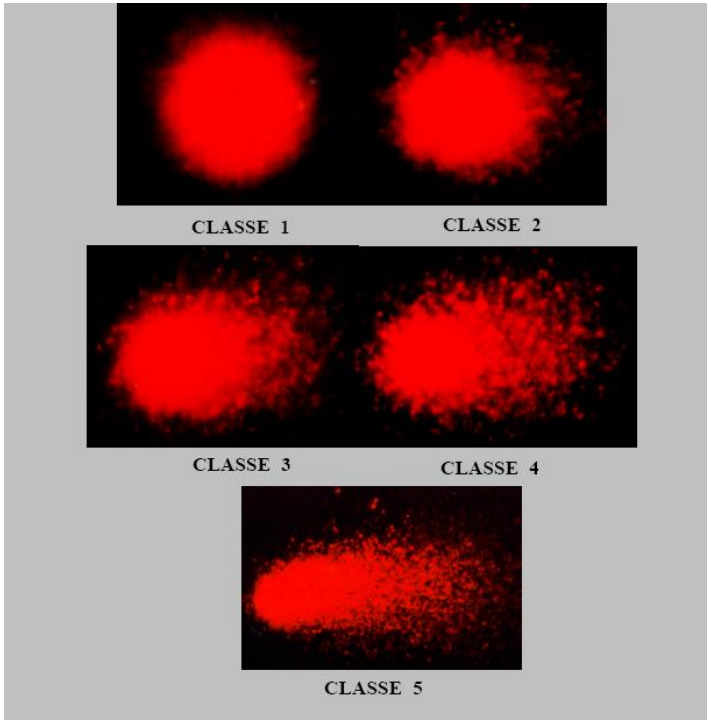
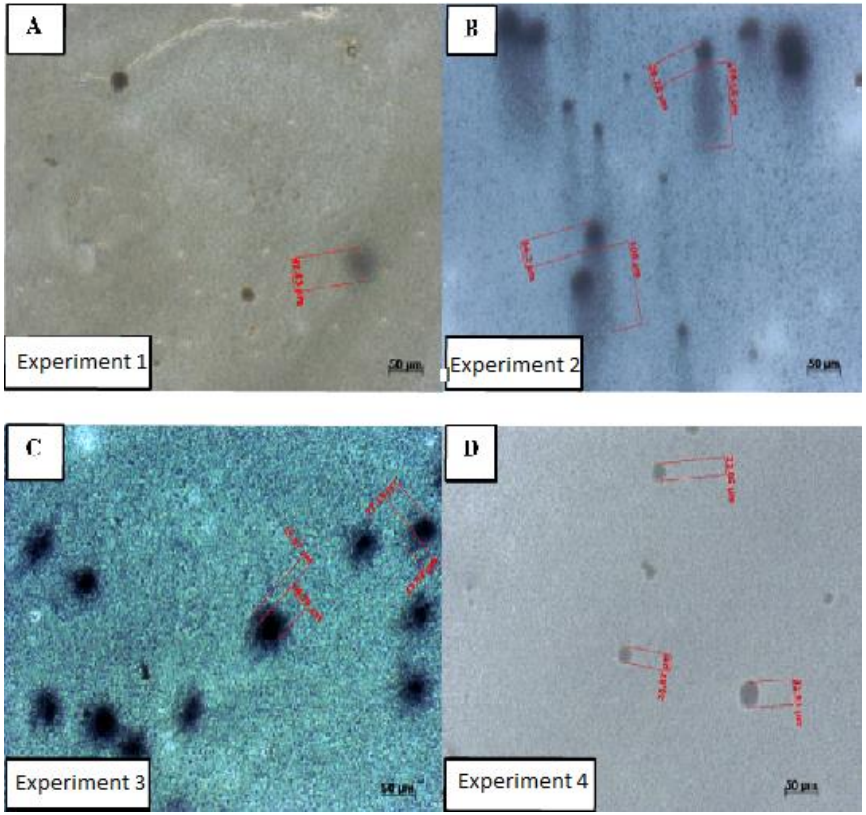
Tissue Eng Part A. 2015 Sep 28. [Epub ahead of print]

Tooth Tissue Engineering: The importance of blood products as a supplement in tissue culture medium for human Pulp Dental Stem Cells.

Pisciolaro RL[1], Duailibi MT[2], Novo NF[3], Juliano Y[4], Pallos D[5], Yelick PC[6], Vacanti J[7], Ferreira LM[8,9], Duailibi SE[10].





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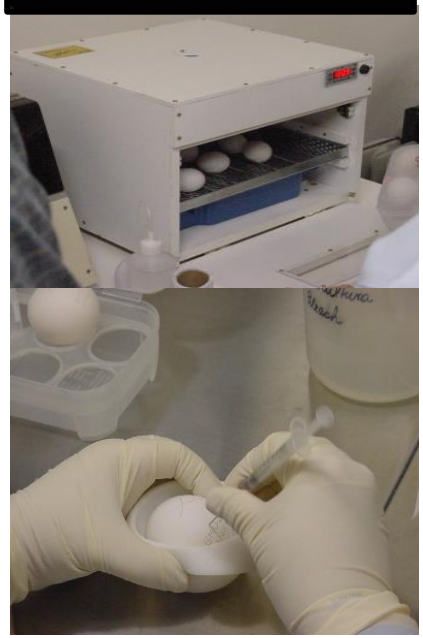
TTE: *Gallus domesticus,* rastreamento das hDSC , modelo *in vivo*
CEP – 1879/11



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Duailibi et al.,2015 in submission

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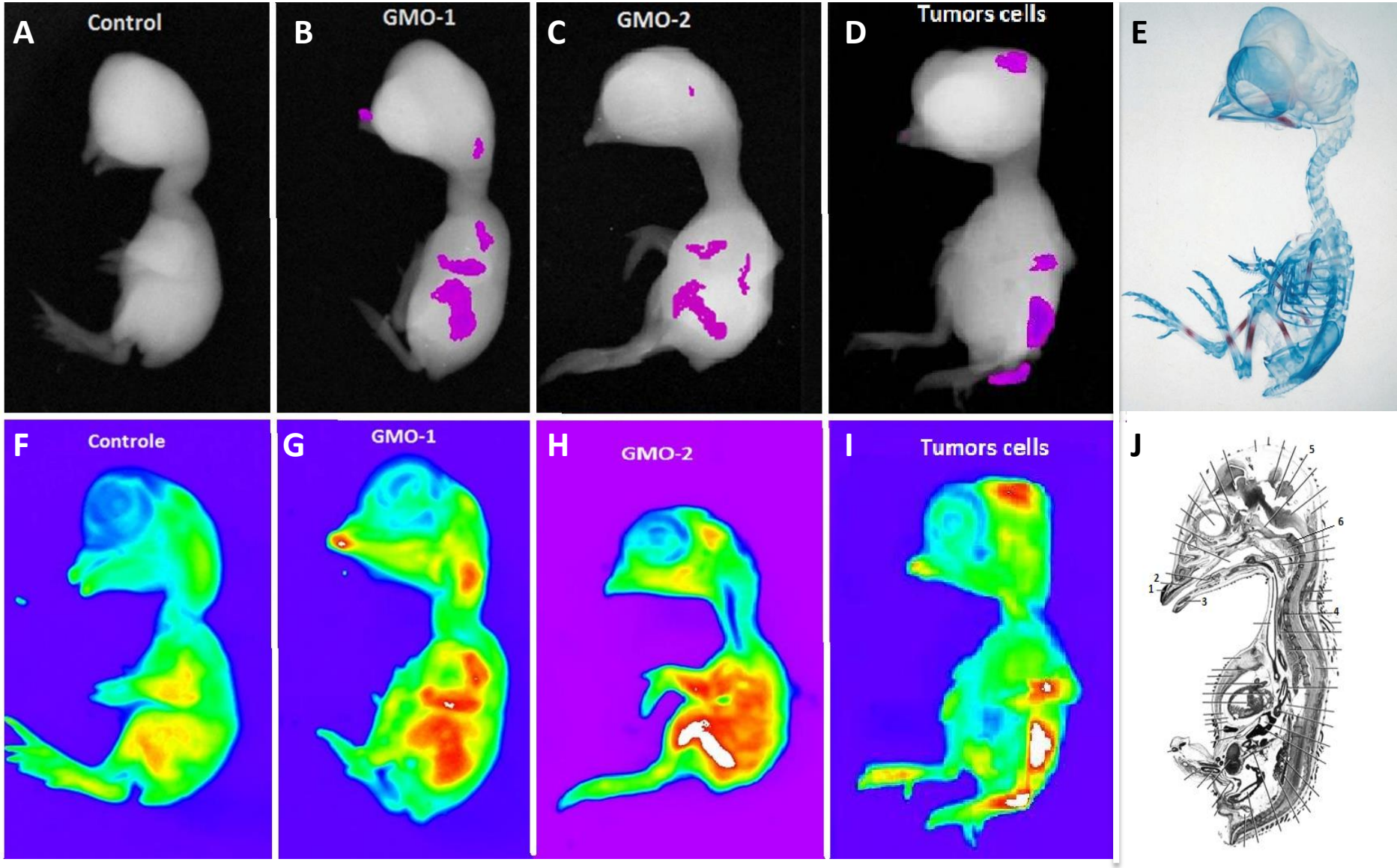

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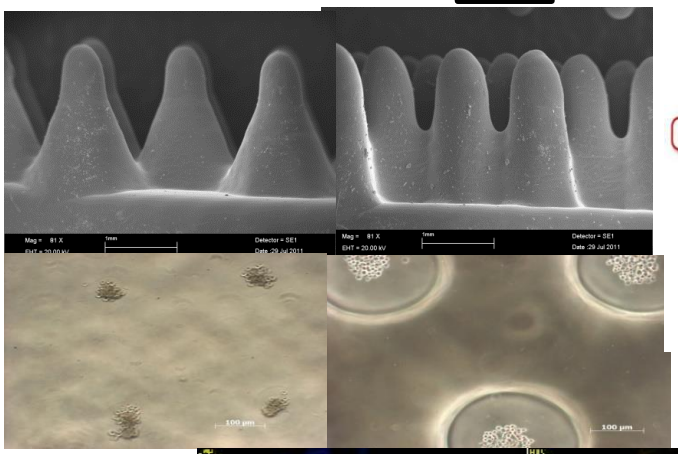
SISTEMAS DE CULTURA DE CÉLULAS:

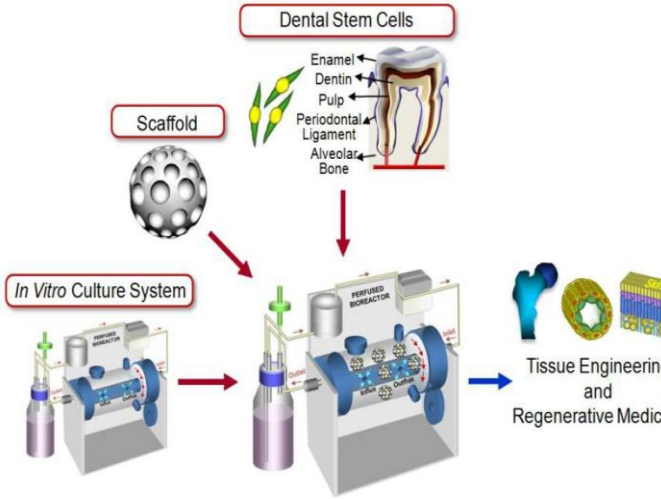
estático ou contínuo

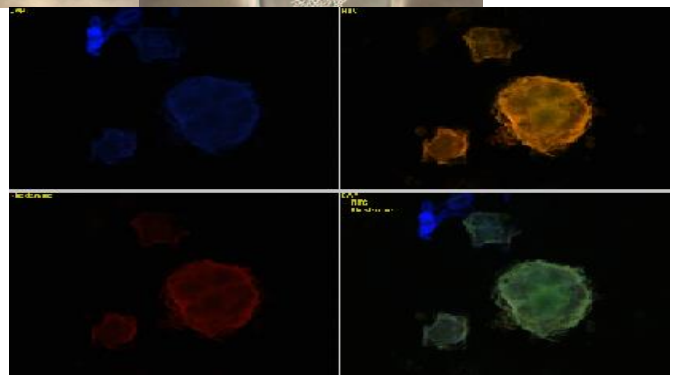
2D

Duailibi et al., 2015 *Biofabrication* (in preparation)

3D







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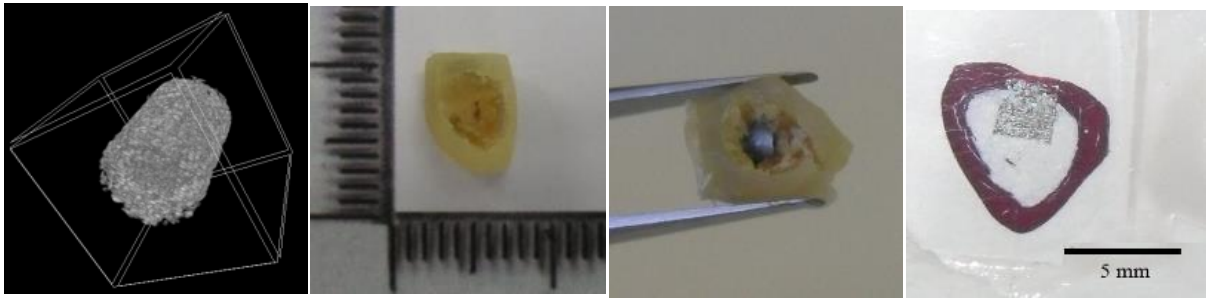
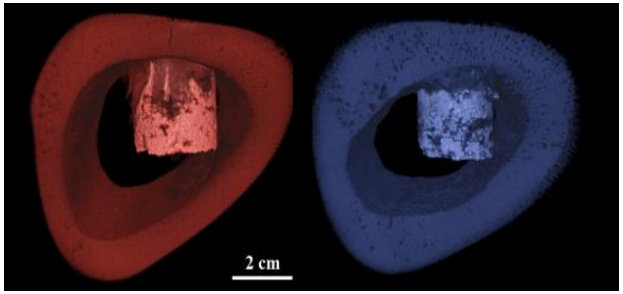
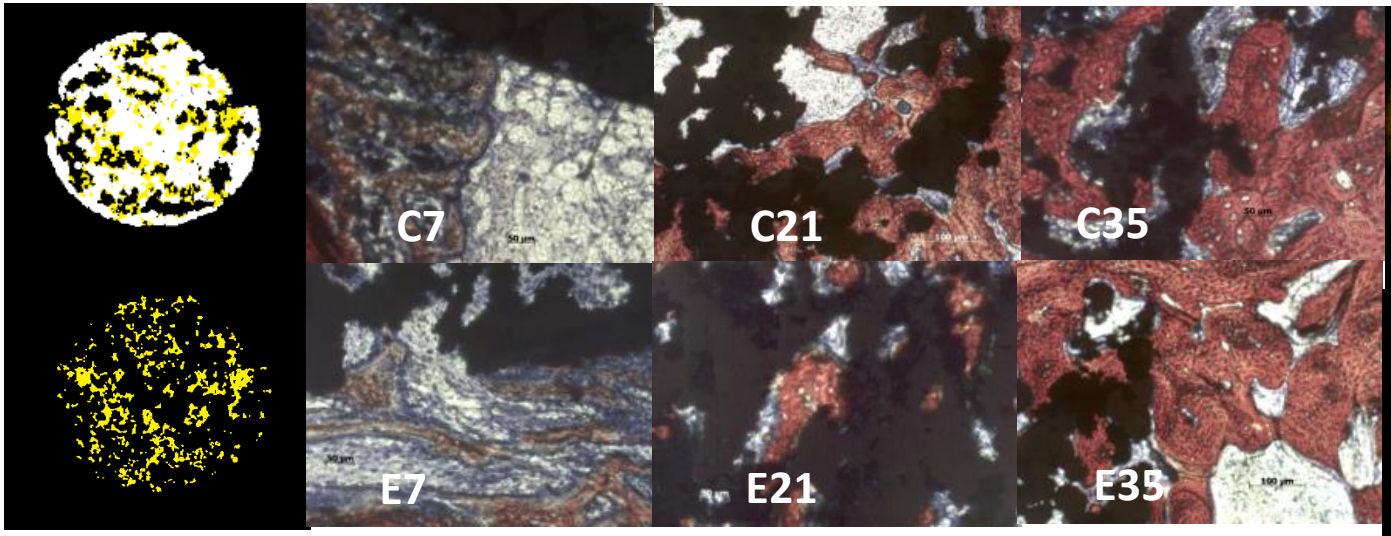
Complexidade dos scaffolds

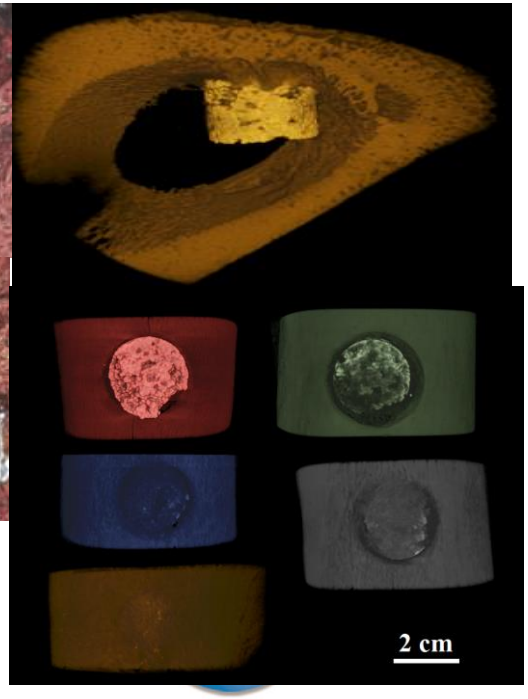
Controle da Macro and Microgeometria

TITANIUM POROSIDADE IRREGULAR x REGULAR









ANÁLISE DE IMAGEM : MICROTOMOGRAFIA

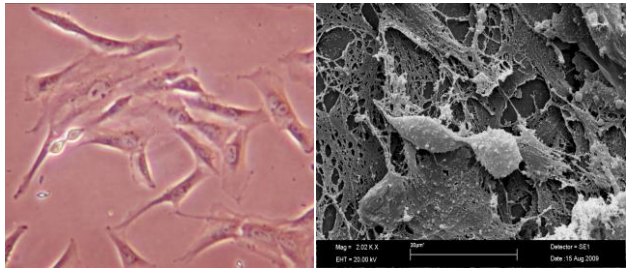
Duailibi et al., *Tissue Engineering Part C Methods submmited*

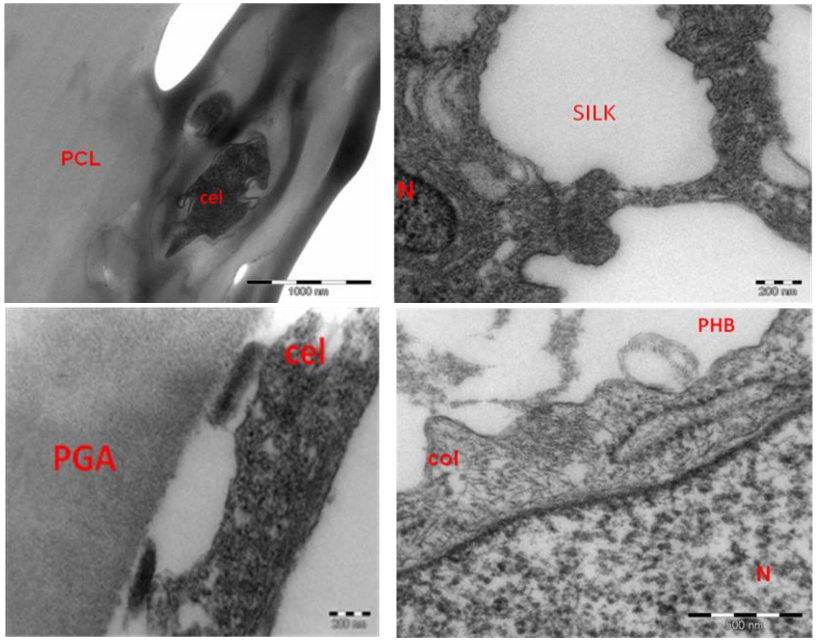
Novas Alternativas Terapêuticas em Odontologia

Complexidade dos scaffolds

Estudo de interface com material biológico

ADESÃO CELULAR → TRATAMENTO DE SUPERFÍCIE





- **TRATAMENTO FÍSICO**
  - MECÂNICO
  - PLASMA
  - BOMBARDEAMENTO DE ELECTRONS
  - LUZ UV
- **TRATAMENTO BIOLÓGICO**
  - COLAGENO
  - PROTEINA
  - FATOR DE CRESCIMENTO

Duailibi et al, 2011
Inovative Developments

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Agências de Fomento

CNPq
Conselho Nacional de Desenvolvimento Científico e Tecnológico

CAPES

NATIONAL INSTITUTES OF HEALTH

Ciência e Tecnologia
Ministério da Ciência e Tecnologia

FAPESP

Agências de Apoio

UNIFESP
UNIVERSIDADE FEDERAL DE SÃO PAULO
1933

PROGRAMA IBEROAMERICANO
CYTED
CIENCIA Y TECNOLOGIA PARA EL DESARROLLO

UNIFESP Fap

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Parcerias Nacionais

Centro de Tecnologia da Informação Renato Archer

UFF

ipen

Engenharia Mecânica
USP - São Carlos
SEM

LIM 60 – FMUSP

USP
ESALQ

PUC-SP

UFRGS
UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

INSTITUTO NACIONAL DE TECNOLOGIA
INT

biofabris

UNICAMP

instituto de ortopedia e traumatologia

NAP/MEPA
ESALQ/USP

Parcerias Internacionais

Universitat de Girona

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Rede Iberoamericana de Biofabricação:
Materiais, Processos e Simulação
CYTED

MASSACHUSETTS GENERAL HOSPITAL
MGH 1811

IPL
instituto politécnico de leiria

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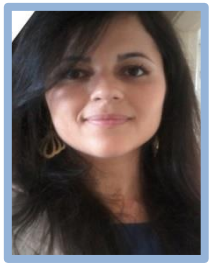
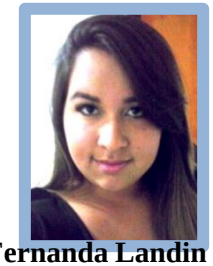


Samara Ribeiro
DDS – CI



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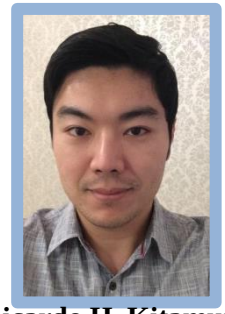
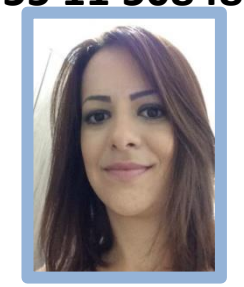
DDS – CI

Márcia Regina Alves
MD – Ms Candidade



Ricardo H. Kitamura
MD – Ms Candidade



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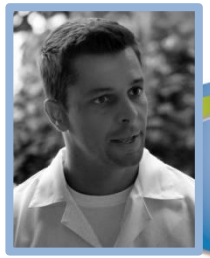
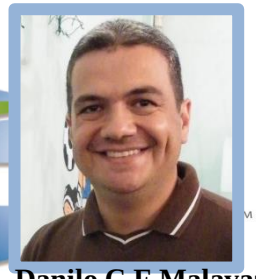
DDS – Ms Candidate



Renato
VET– Ms Candidate



Danilo C.F.Malavazi
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Obrigado!

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BNDES

PATROCÍNIO:
SEBRAE

APOIO:
GOVERNO FEDERAL
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