University of Sassari

Istituto Nazionale Biostrutture Biosistemi
I.N.B.B.
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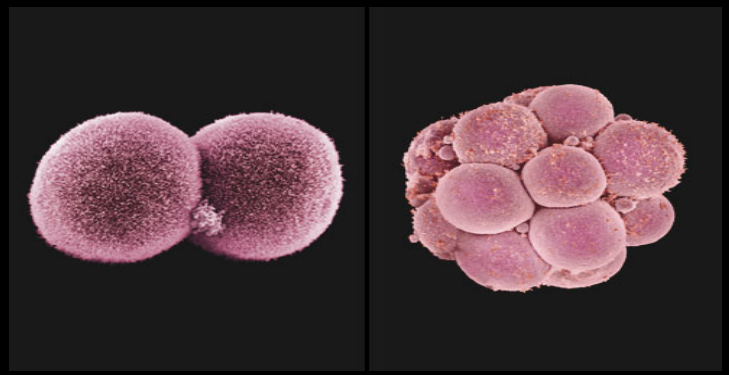
Biomaterials and advanced physical techniques for regenerative cardiology and neurology



Prof. Margherita Maioli,PhD

School of Medicine, Department of Biomedical Sciences
University of Sassari-Italy
Head of CEDEBIOR (Center for Developmental Biology and Reprogramming), University of Sassari-Italy

Expertise of our group

Stem cell differentiation
Regenerative Medicine
Definition of novel conditioned media
Obtain a high yield of a specific cell line, to replace damaged elements
From cardiovascuar phenotype to osteogenesis

- Drugs, nutraceuticals
- Viral vectors
- Physical energy

Which strategies????

The use of chemistry to drive the molecular signals underlying stem cell commitment and/or pluripotentiality have represented the focus of scientists in the last decade

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Butyric and Retinoic Mixed Ester of Hyaluronan

A NOVEL DIFFERENTIATING GLYCOCONJUGATE AFFORDING A HIGH THROUGHPUT OF CARDIOGENESIS IN EMBRYONIC STEM CELLS*

Carlo Ventura‡§, Margherita Maioli¶, Yolande Asara¶, Daniela Santoni¶, Ignazio Scarlata‖, Silvia Cantoni‖, and Alberto Perbellini‡

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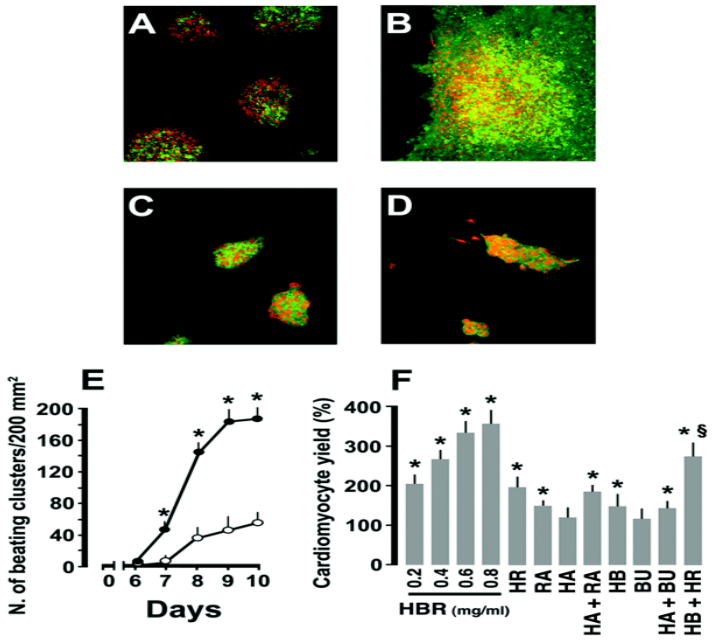
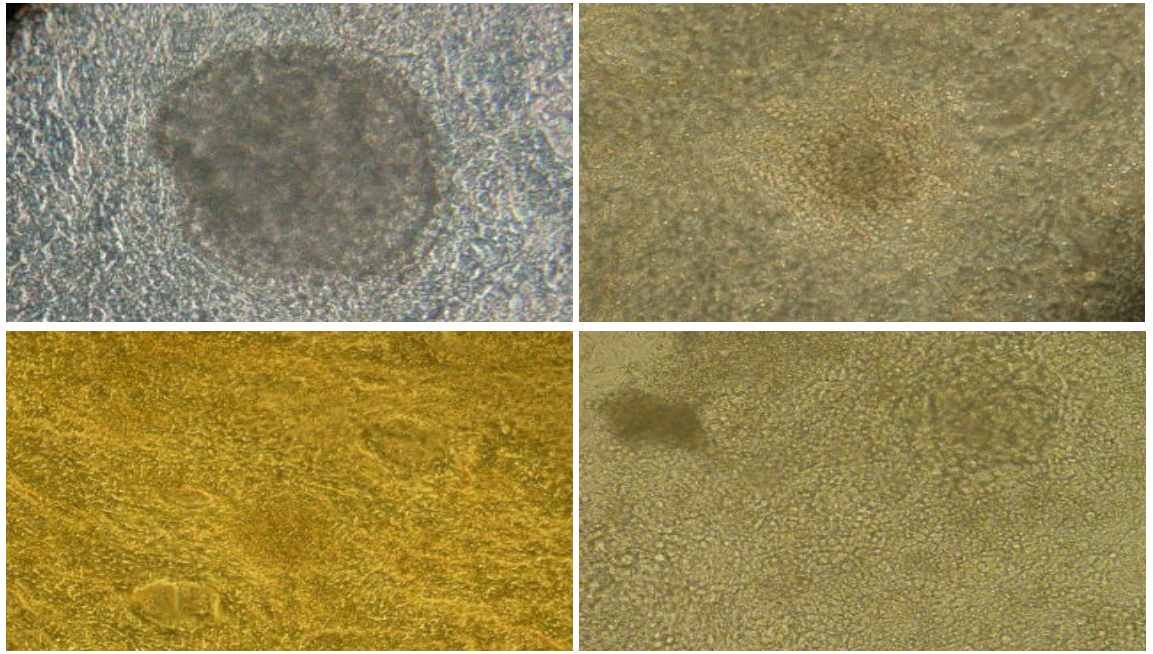
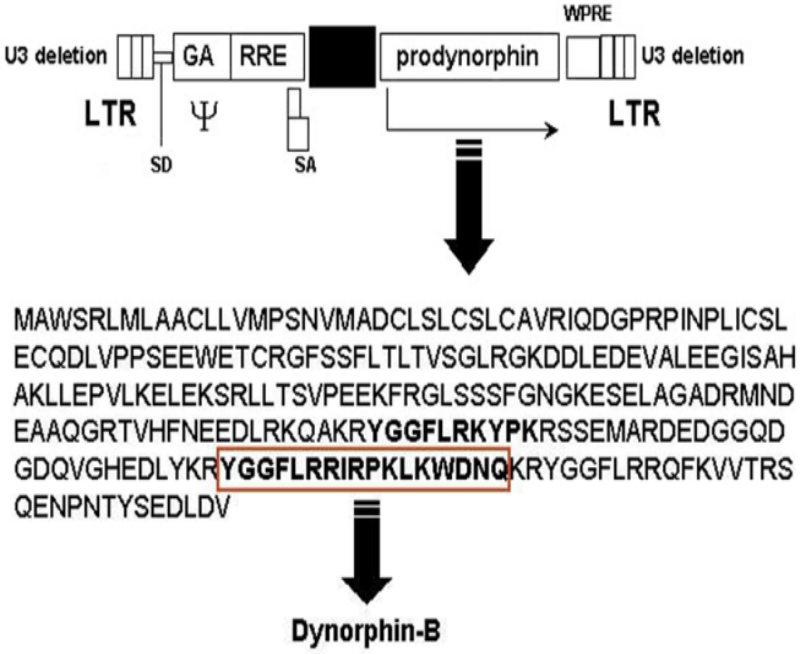


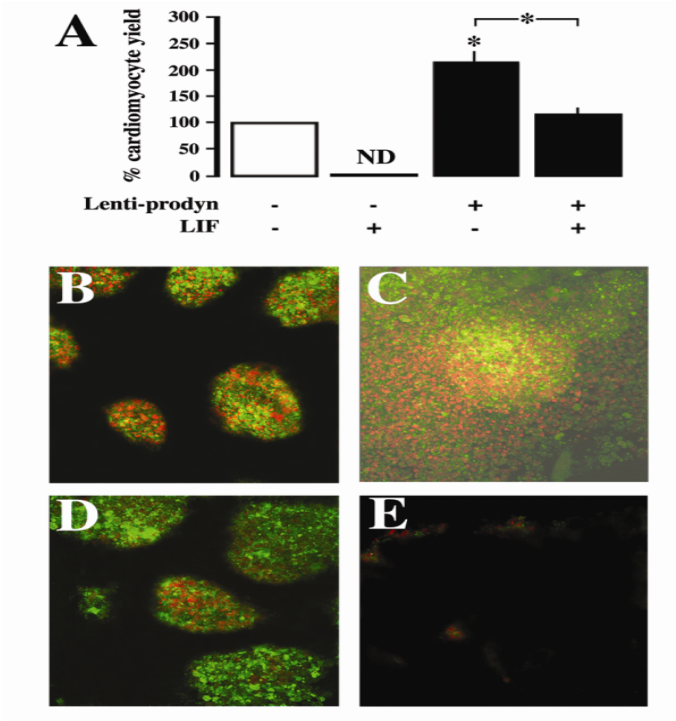


Opioid Peptide Gene Expression Primes Cardiogenesis in Embryonal Pluripotent Stem Cells

Carlo Ventura, Margherita Maioli

Abstract—Zinc finger–containing transcription factor GATA-4 and homeodomain Nkx-2.5 govern crucial developmental fates and have been found to promote cardiogenesis in embryonic cells exposed to the differentiating agent DMSO. Nevertheless, intracellular activators of these transcription factors are largely unknown. In this study, pluripotent P19 cells expressed the prodynorphin gene, an opioid gene encoding for the dynorphin family of opioid peptides. P19 cells were also able to synthesize and secrete dynorphin B, a biologically active end product of the prodynorphin gene. DMSO-primed GATA-4 and Nkx-2.5 gene expression was preceded by a marked increase in prodynorphin gene expression and dynorphin B synthesis and secretion. The DMSO effect occurred at the transcriptional level. In the absence of DMSO, dynorphin B triggered GATA-4 and Nkx-2.5 gene expression and led to the appearance of both α-myosin heavy chain and myosin light chain-2V transcripts, two markers of cardiac differentiation. Moreover, dynorphin B–exposed cells were positively stained in the presence of MF 20, a mouse monoclonal antibody raised against the α-myosin heavy chain. Opioid receptor antagonism and inhibition of opioid gene expression by a prodynorphin antisense phosphorothioate oligonucleotide blocked DMSO-induced cardiogenesis, suggesting an autocrine role of an opioid gene in developmental decisions. (***Circ Res*. 2000;87:189-194.**)





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Regenerative Med. (2007) 2(2), 193–202

RESEARCH ARTICLE

Creating prodynorphin-expressing stem cells alerted for a high-throughput of cardiogenic commitment

Margherita Maioli[1], Yolande Asara[1], Antonella Pintus[1], Stefania Ninniri[1], Saverio Bettuzzi[2], Maurizio Scaltriti[2], Francesco Galimi[1†] & Carlo Ventura[3]

†Author for correspondence

Background: The development of cell therapy for the rescue of damaged heart muscle is a major area of inquiry. Within this context, the establishment of a cardiogenic cell line may remarkably facilitate the molecular dissection of cardiac fate specification, a low-efficiency and still poorly understood process, paving the way for novel approaches in the use of stem cells for cardiac repair. **Methods & results:** We used GTR1 cells, a derivative of mouse R1 embryonic stem cells bearing the puromycin-resistance gene driven by the cardiomyocyte-specific α-myosin heavy chain promoter, affording a gene trapping selection of a virtually pure population of embryonic stem cell-derived cardiomyocytes. Third-

NOT ONLY MOLECULES!

BUT…

The FASEB Journal express article 10.1096/fj.04-2695fje. Published online October 26, 2004.

Turning on stem cell cardiogenesis with extremely low frequency magnetic fields

Carlo Ventura,* Margherita Maioli,† Yolande Asara,† Daniela Santoni,† Pietro Mesirca,‡ Daniel Remondini,‡ and Ferdinando Bersani‡

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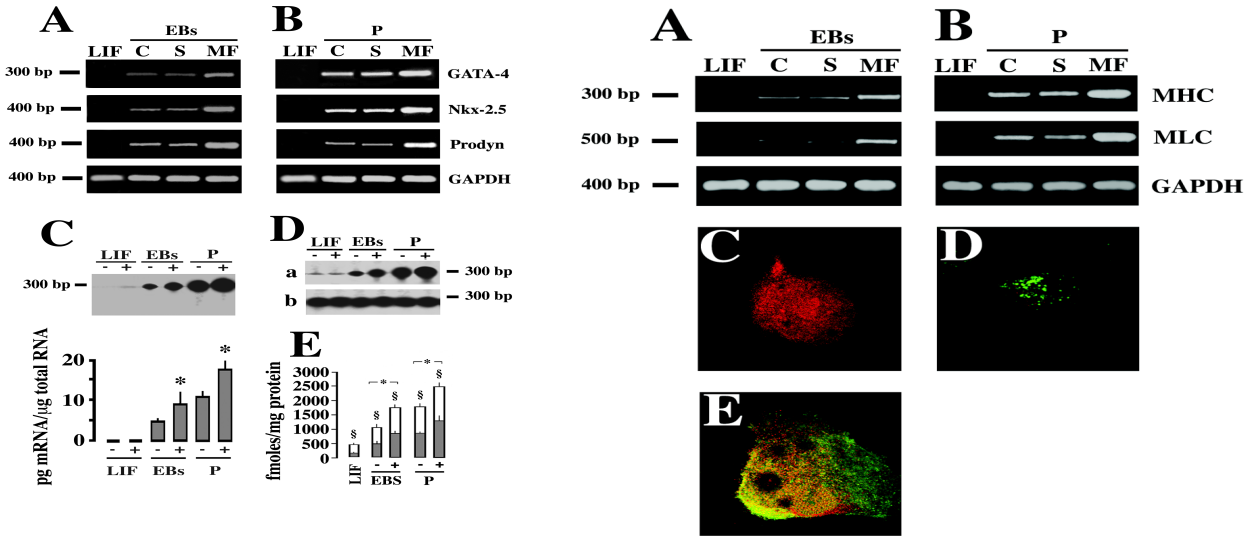

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Radio Electric Conveyed Fields Directly Reprogram Human Dermal Skin Fibroblasts Toward Cardiac, Neuronal, and Skeletal Muscle-Like Lineages

Margherita Maioli,*† Salvatore Rinaldi,‡ Sara Santaniello,*† Alessandro Castagna,‡ Gianfranco Pigliaru,*† Sara Gualini,*† Claudia Cavallini,†§ Vania Fontani,‡ and Carlo Ventura†§

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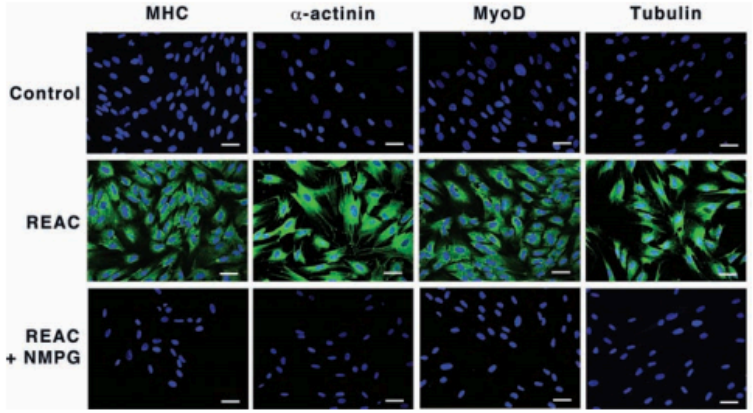

Figure 4. REAC induces fibroblast commitment toward cardiac, neuronal, and skeletal muscle lineages. The expression of α-myosin heavy chain (MHC), α-sarcomeric actinin (α-actinin), MyoD, and β-3-tubulin (tubulin) was assessed by confocal microscopy in fibroblasts cultured for 72 h in the absence or presence of REAC and then left unexposed for additional 4 days. In separate experiments, cells were preincubated for 2 h prior to REAC treatment with the free radical scavenger *N*-(2-mercapto-propionyl)-glycine (NMPG) (100 μM). Scale bars: 40 μm. Nuclei are labeled with DAPI (blue). Representative of five separate experiments.

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SCIENTIFIC REPORTS

OPEN

Neurological morphofunctional differentiation induced by REAC technology in PC12. A neuro protective model for Parkinson's disease

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Margherita Maioli[1,2,3,*], Salvatore Rinaldi[3,4,*], Rossana Migheli[6], Gianfranco Pigliaru[1,2], Gaia Rocchitta[6], Sara Santaniello[1,2], Valentina Basoli[3], Alessandro Castagna[3,4], Vania Fontani[3,4], Carlo Ventura[2,5] & Pier Andrea Serra[6]

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SCIENTIFIC REPORTS

OPEN

REAC technology and hyaluron synthase 2, an interesting network to slow down stem cell senescence

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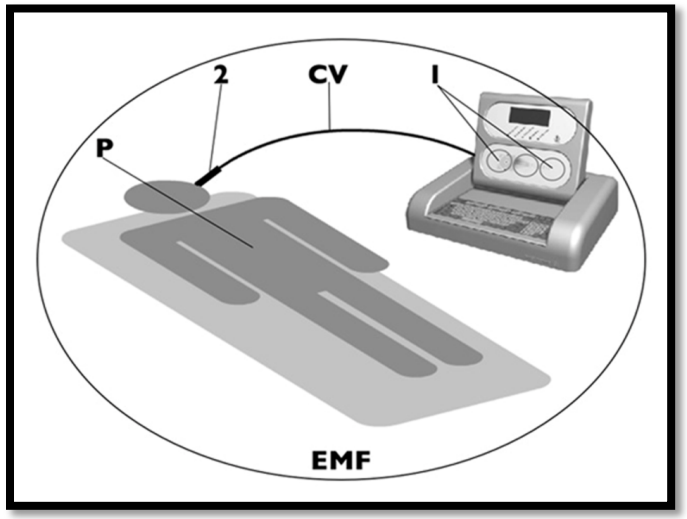
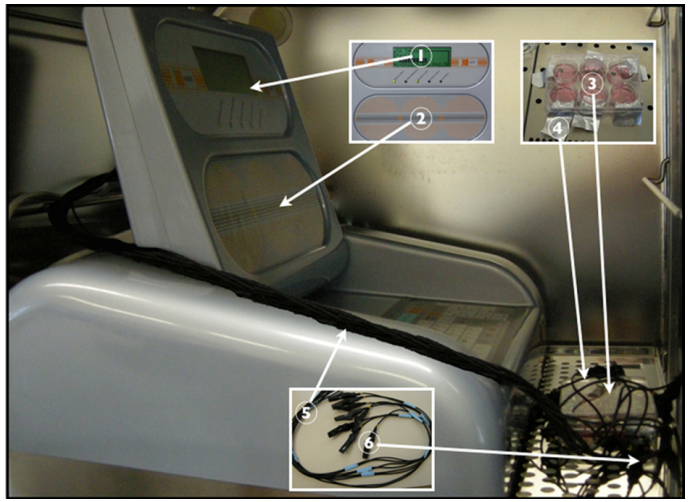
Margherita Maioli[1,2,3,4,*], Salvatore Rinaldi[3,5,6,*], Gianfranco Pigliaru[1,4], Sara Santaniello[1,4], Valentina Basoli[1,6,7], Alessandro Castagna[3,5,6], Vania Fontani[3,5] & Carlo Ventura[4,8]





Radio Electric Asymmetric Conveyer (REAC)
(Drs. Salvatore Rinaldi and Vania Fontani, Patented)

The REAC apparatus adapted to an embryonic stem (ES) cell culture system within a CO_2 incubator.

1: **Display;**
2: **Emitter;**
3: **Tissue culture dishes containing medium with ES cells;**
4: **Laminar Probes;**
5: **Cables;**
6: **Probes.**

One or more radiofrequency generators and one or more irradiating antennas *(1)* are able to create a radiofrequency field (EMF); one or more electrodes *(2)* connected through a Cable (CV). The radio frequency field (EMF) induces radiofrequency currents in the body, conveyed by the electrodes *(2)*.

POTENTIAL CONTRIBUITION TO BIONECA

- Test novel molecules and biomaterials in vitro for regenerative process as cardiogenesis, neurogenesis, but not only.
- Study of cell proliferation, cell senescence in a conditioned environment, biocompatibility, gene expression and epigenetic analysis
- We can also apply physical stimuli as REAC (Radio Electric Asymmetric Conveyer) or electromagnetic fields for tissue regenerationa
- We can isolate different adult mesenchymal stem cells from different sources (dental pulp, adipose tissue, fetal membrane, amniotic fluid, cord blood, oral mucose and skin) and obtain patient's derived IPSCs

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- Dott.ssa Vania Fontani, IRF Firenze
- Dott.Alessandro Castagna, IRF Sassari
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