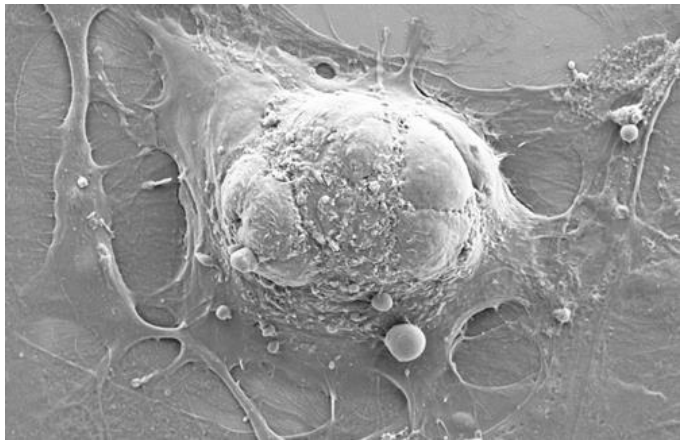

FOCAL POINT

BIOCHEMISTRY OF STEM CELLS

Fakultät für Chemie und Biochemie

Fakultät für Biologie und Biotechnologie

Fakultät für Medizin

Ruhr-Universität Bochum

Focal Point: Biochemistry of Stem Cells

Stem cell research is central to our understanding how human life develops as well as leads us to the discovery of novel drugs using stem-cell based disease models and cellular therapies in regenerative medicine.
Cellular reprogramming of somatic cells to induced, pluripotent stem (iPS) cells as well as direct cell transdifferentiations using combinations of transcription factors are the latest developments in these directions.

We predict that in the near future a strong demand of educated biochemists with backgrounds in stem cell biology and regenerative medicine will find their places in basic research, medical research institutions, biotechnology and pharmaceutical industry.

This demands in turn an advanced interdisciplinary educational approach starting in the field of chemistry of small molecules, bioinformatics of nucleic acids and protein networks, biochemistry of transcription factors, genetics and epigenetics, systems biology as well as nanotechnology and material sciences combined with molecular developmental and stem cell biology training.

Focal Point: Biochemistry of Stem Cells

Members

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PD. Dr. Holm Zähres	holm.zaehres@rub.de	(Speaker / Chair)

Focal Point: Biochemistry of Stem Cells

Lectures / Seminars

Wintersemester

203010	Stem Cell Physiology I	Brand-Saberi
203021	Pathology of Degenerative Diseases	Lecture series
203011	Stem Cell Lecture Series I	Lecture series
203020	Advances in Stem Cell Research	Lectures series

Sommersemester

203000	Stem Cell Physiology II	Faissner, Wiese
203002	Molecular Genetic Methods	Zähres
203100	Molecular Tracing	Theiss, Bühler
203003	Tissue Engineering	Lecture series
203001	Stem Cell Lecture Series II	Lecture series

Focal Point: Biochemistry of Stem Cells : Practicals

Adamietz / Bühler: Tumor stem cells

Brand-Saberi / Balakrishnan-Renuka: Myogenic stem cell biology

Brand-Saberi: In situ hybridization

Heumann / Neumann: Protein purification and transduction

Heumann / Pape: Adult hippocampal neurogenesis in transgenic mice

Jakobsen: Regenerative medicine in plastic surgery

Köller / Sengstock: Mesenchymal stem cells for regenerative medicine

Napirei: Isolation and culturing of embryonic stem cells

Petrasch-Parwez: Immunohistochemisty of neural stem cells in the SVZ

Wiese: Culture and differentiation of neural precursor cells

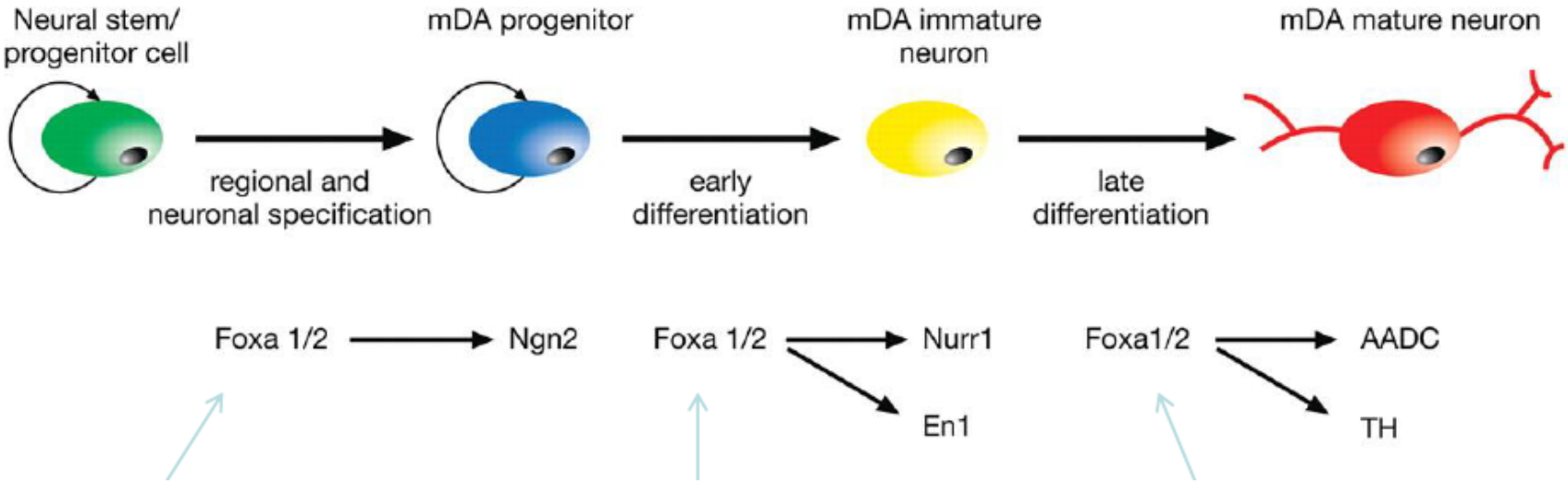
Zähres: Molecular cloning

Zähres: Genome editing

Zähres: Reprogramming to induced, pluripotent stem (iPS) cells

Faculty of Chemistry and Biochemistry

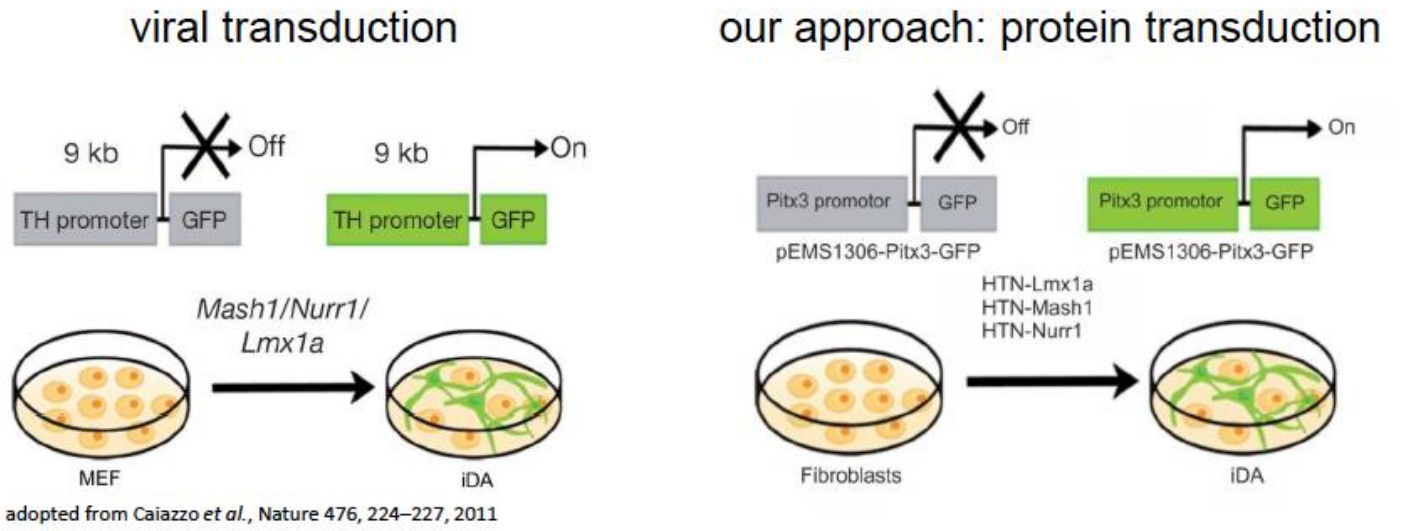
Prof. Dr. Rolf Heumann



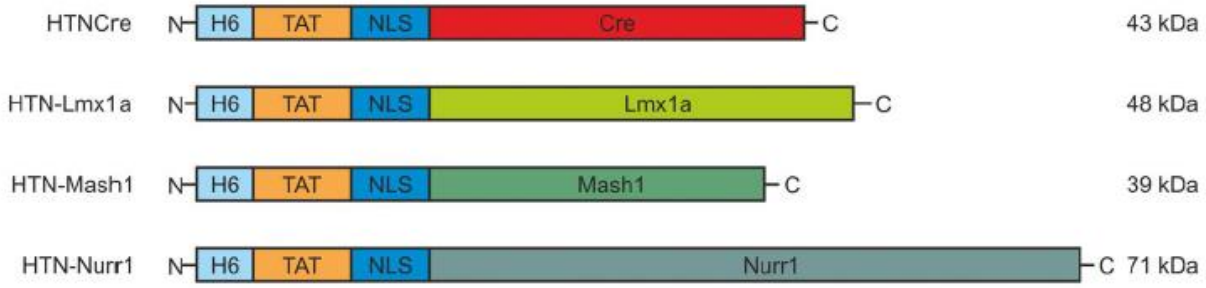
Faculty of Chemistry and Biochemistry

Prof. Dr. Rolf Heumann / Dr. Sebastian Neumann

Reprogramming of stem cells to induced dopaminergic neurons (iDA) by protein transduction

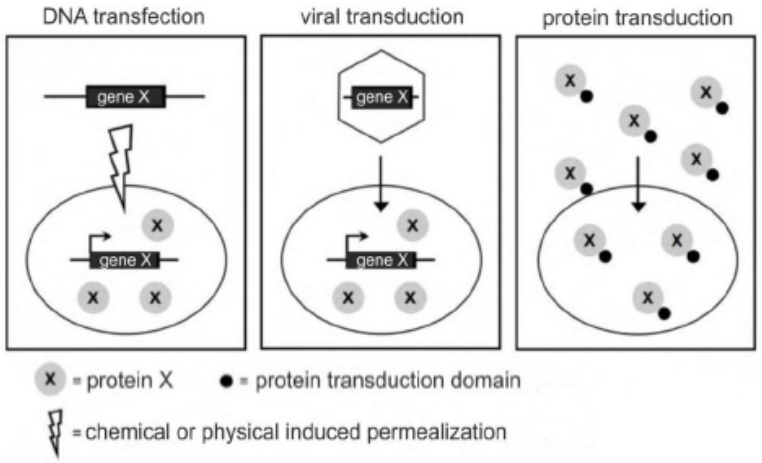


adopted from Caiazzo *et al.*, Nature 476, 224–227, 2011



Faculty of Chemistry and Biochemistry

Prof. Dr. Rolf Heumann / Dr. Sebastian Neumann



adopted from Peitz 2007

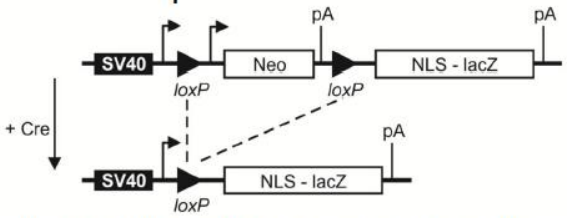
Name	Sequence / Structure
TAT	YGRKKRRQRRR
Antp (Penetratin)	RQIKIWFQNRRMKWKK
Transportan	GWTLNSAGYLLGKINKALAALAKKIL
K-FGF	AAVLLPVLLAAP
Oligoarginine	R_n (n = 4-12)

Edenhofer, Curr Pharm Des. 14, 3628-3636, 2008

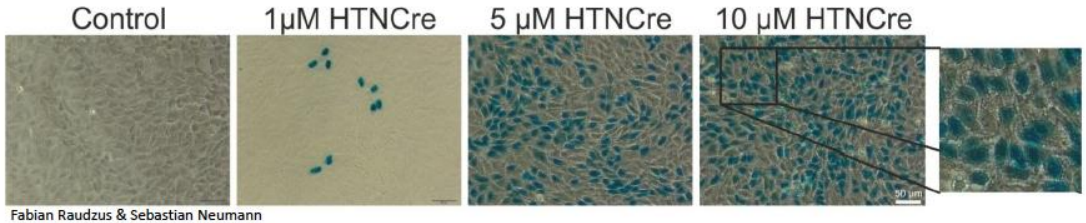
Cell permeable Cre recombinase: HTN-Cre

adopted from Peitz *et al.*, PNAS 99(7), 4489–4494, 2002

Cre reporter cell line: CV1-5B



adopted from Kellendonk *et al.*, Nucleic Acids Research 24(8), 1404–1411, 1996

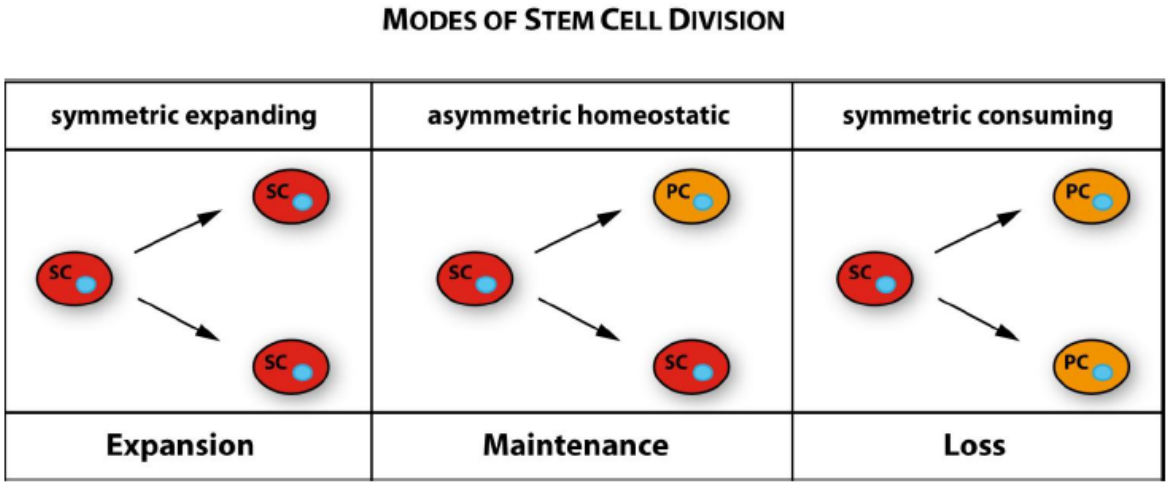


Fabian Raudzus & Sebastian Neumann

Faculty of Biology and Biotechnology, Molecular Neurobiology

Prof. Dr. Andreas Faissner

NEURAL STEM CELLS, GLIAL PROGENITORS AND THEIR NICHES



When do neural stem cells divide ?

What controls the cell fate of the daughter cells ?

How is neurogenesis regulated as opposed to gliogenesis ?

What is the role of the immediate environment – the neural stem cell niche -

In these cellular processes ?

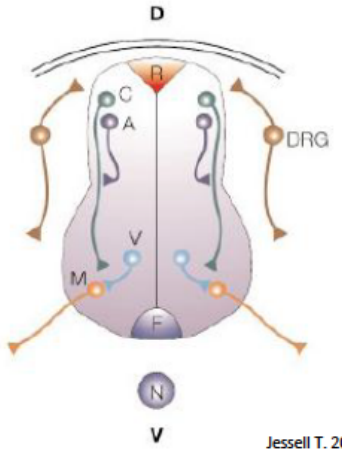
How do neural stem cells integrate environmental information ?

Faculty of Biology and Biotechnology, Molecular Neurobiology

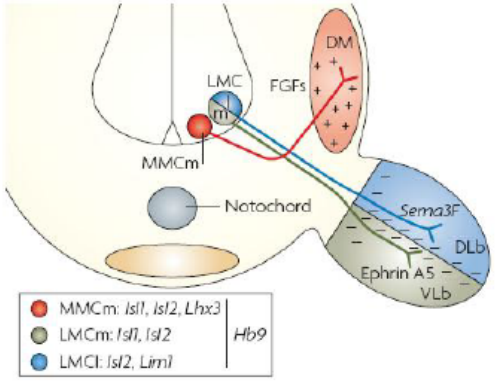
Prof. Dr. Stefan Wiese

The Extracellular matrix influences differentiation and neurite growth of embryonic motoneurons

- cells migrate laterally from the ventricular zone and turn along the dorso-ventral axis
- commissural (C) and association (A) neurons differentiate in the dorsal part
- dorsal root ganglion (DRG) neurons differentiate from neural crest progenitors
- motor neurons (M) and ventral interneurons (V) develop in the ventral half
- Motor axons emigrate from spinal cord to innervate their muscle target
- On their way to their targets they traverse a dense jungle of many different cells, expressing a variety of different molecular guidance cues



Jessell T. 2000

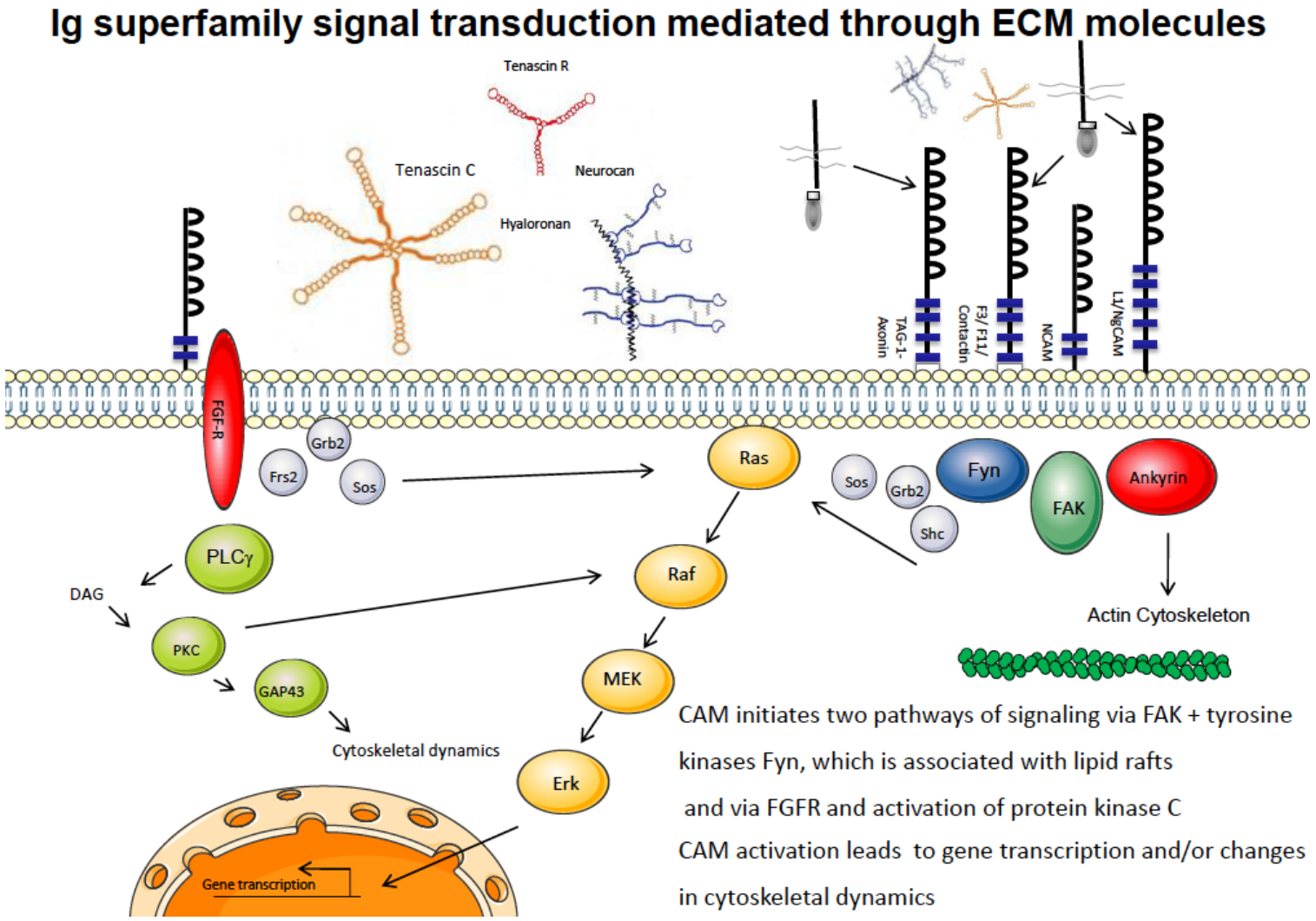


(Polleux F. 2007)

Questions:
What are the ECM guidance cues that help motoneurons to differentiate from stem cells?
What are the intracellular signaling events?

Faculty of Biology and Biotechnology, Molecular Neurobiology

Prof. Dr. Stefan Wiese



Surgical Research

Prof. Dr. Manfred Köller

Bergmannsheil
Berufsgenossenschaftliches Universitätsklinikum
UK RUB UNIVERSITÄTSKLINIKUM DER RUHR-UNIVERSITÄT BOCHUM

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Mesenchymal stem cells for regenerative medicine

Harvest and cultivation of mesenchymal stem cells

Differentiation of MSC

Interaction of MSC with biomaterials

Autologous plasma clot carrier matrices for bone fracture healing and neuroregeneration

Interaction of MSC with nanoparticles

Surgical Research

Prof. Dr. Manfred Köller

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Berufsgenossenschaftliches Universitätsklinikum
UK RUB UNIVERSITÄTSKLINIKUM DER RUHR-UNIVERSITÄT BOCHUM

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Mesenchymal stem cells for regenerative medicine

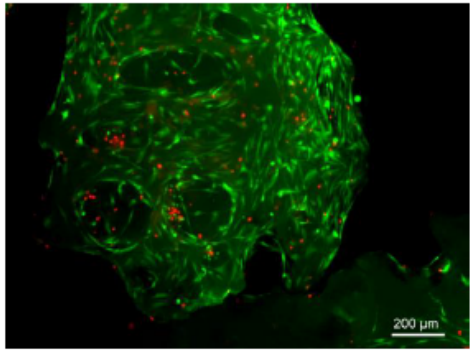
Clinical success of stem cell research is related to clinically important answers

How to make stem cells morph into the cell type needed (is that really needed ??)

How to ensure the survival of stem cells ?

How to home stem cells to sites of injury ?

What is the optimal application method under clinical conditions ?



MSC cultured on a porous calcium phosphate particle for fracture healing (calcein-AM / PI- stain)

Surgical Research

Prof. Dr. Manfred Köller

Bergmannsheil
Berufsgenossenschaftliches Universitätsklinikum
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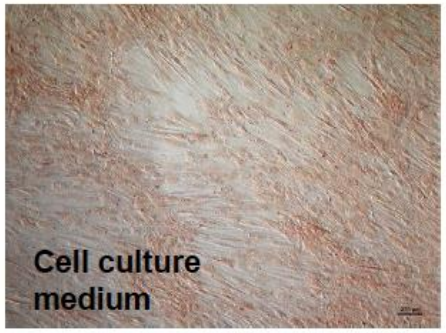
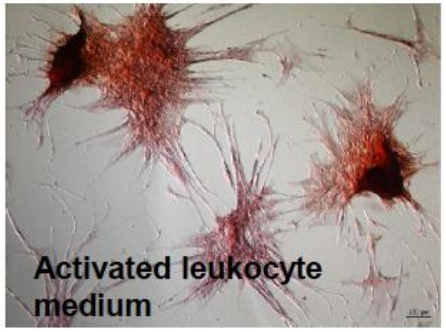
Mesenchymal stem cells for regenerative medicine

Example: Osteogenic differentiation of MSC induced by supernatants of activated leukocytes (Alizarin red staining)





Plastic Surgery Research

Dr. Frank Jakobsen

Bergmannsheil
Berufsgenossenschaftliches Universitätsklinikum
UK RUB UNIVERSITÄTSKLINIKUM DER RUHR-UNIVERSITÄT BOCHUM

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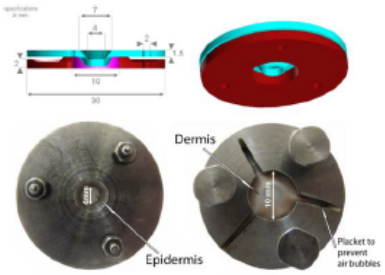
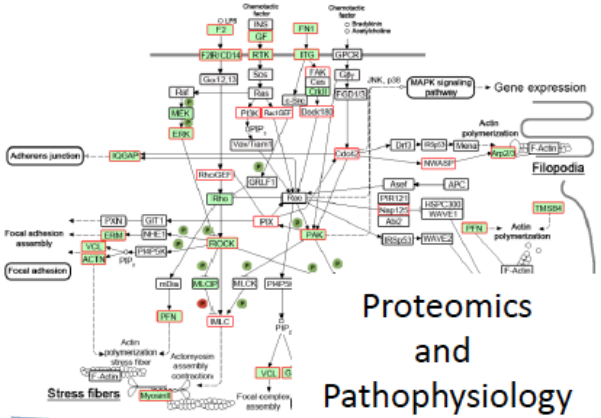
In vivo Models:
- Rat
- Mouse
- Pig

Human full skin model

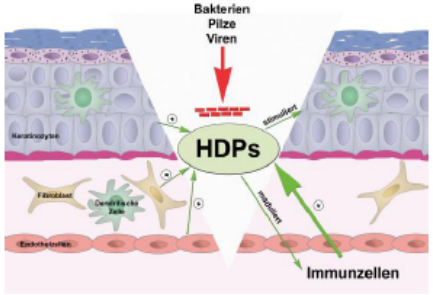


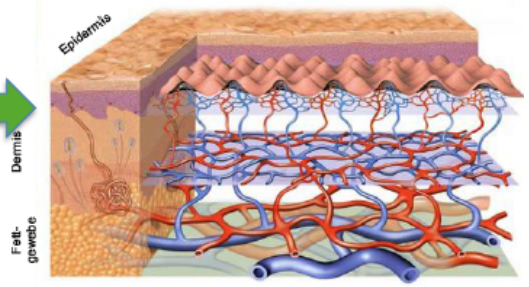


Proteomics
and
Pathophysiology

Wound healing

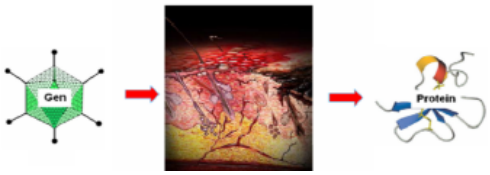
Host Defense Peptides





Cell seeded scaffolds
Artificial skin

Gene therapy approach



Plastic Surgery Research

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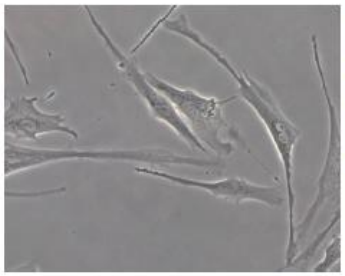
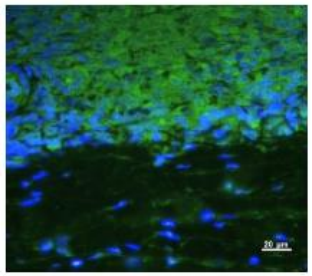
In vivo Models:
- athymic mice
- syngenic (BFS-1) mice

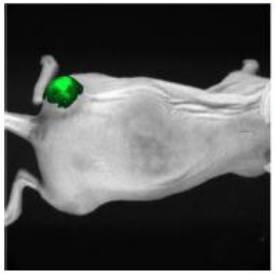




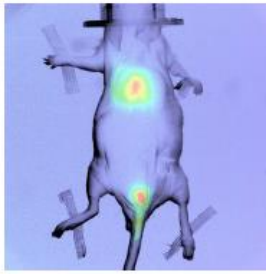
In vitro and *ex vivo* tissue analysis

Oncology of soft tissue sarcoma

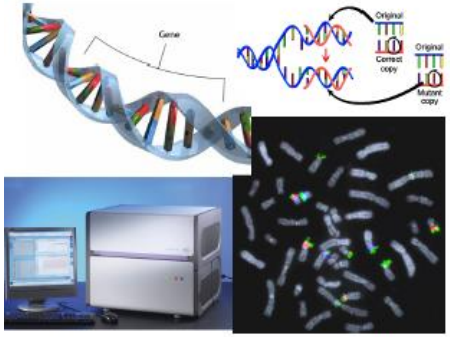
Oncolytic peptides as an alternative for sarcoma treatment



Primary sarcoma



Metastasis



Gene expression profiles,
Mutation analysis, chromosome profiling

Strahlentherapie, Universitätsklinikum

Prof. Dr. Irenäus Adamiez / Dr. Helmut Bühler

Katholisches Klinikum Bochum®

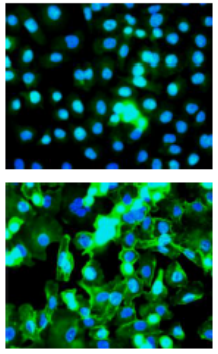
RUB

Ionophores as selective inhibitors of tumor stem cells and first approaches to clarify the underlying mechanisms.

Na^+K^+ATPase activity might be the crucial factor.

Dr. H. Bühler, Institut für Molekulare Onkologie, Strahlenbiologie und Experimentelle Strahlentherapie (IMOSES), Klinikum Marienhospital

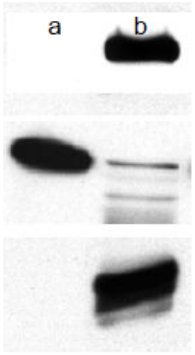
The stem cell hypothesis in cancer:
„Tumors and recurrences originate from tumor stem cells“
We need specific therapeutic agents!



CD24 negative

CD44 positive

breast cancer stem-like cells



<- E-cadherin

<- vimentin

<- keratin 18

a= wild type; b= epithelial)

<u>Test system for selective inhibitors:</u>

two subclones from a breast cancer cell line:

- isolated stem cells
- epithelial clone via the transfection of keratin 18

IMOSES

Strahlentherapie, Universitätsklinikum

Prof. Dr. Irenäus Adamiez / Dr. Helmut Bühler

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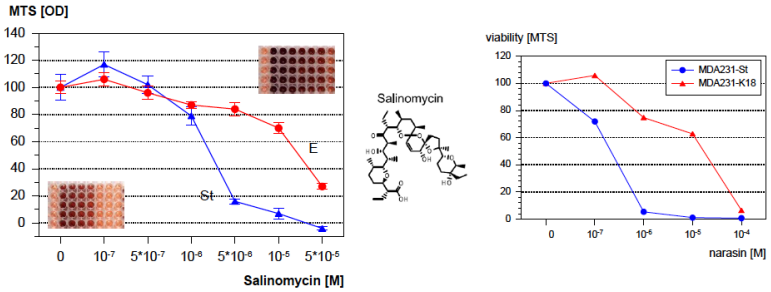
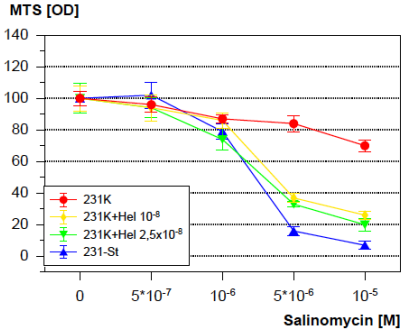
The viability of cancer stem cells is strongly reduced by salinomycin or narasin, whereas the epithelial clone is only marginally affected.



- both are **ionophors** for monovalent kations, e.g. Na^+ und K^+
- intracellular K^+ ist essential for the cell
- a Na^+/K^+-gradient has to be maintained against the interstitial fluid
- the main player is the enzyme **Na^+-K^+-ATPase**

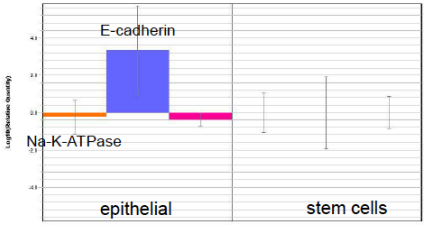
Hypothesis:
Tumor stem cells are more sensitive to salinomycin, due to a less active Na+-K+-ATPase compared to somatic cells.

Adding hellebrin to the epithelial cells brings both graphs in line.

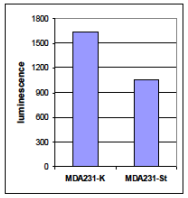


Hellebrin is a potent inhibitor of the Na^+-K^+-ATPase

But qRT-PCR of Na^+K^+ATPase expression revealed no significant difference between stem cells and the epithelial clone.



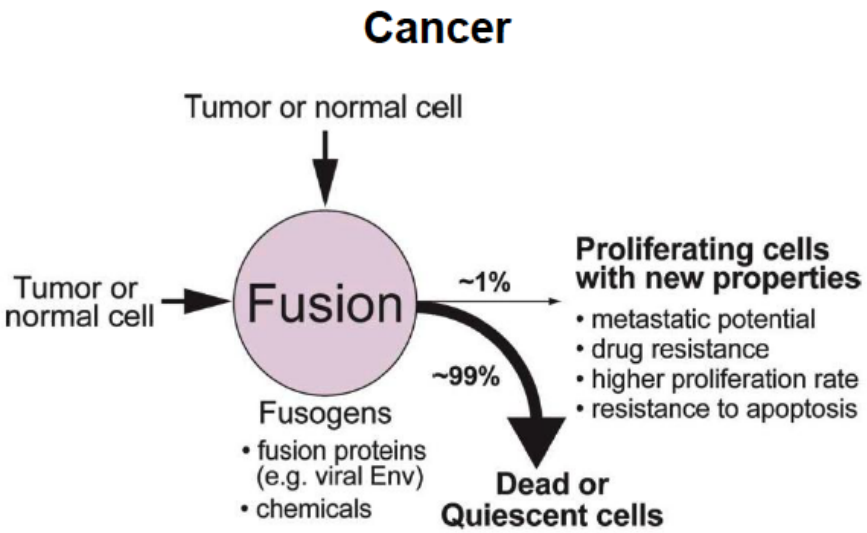
However, a significantly lower concentration of ATP was observed in the stem cells.



The Na+K+ATPase membrane transport is very energy consuming:
3 ATP are needed for every pair of kations.

Institute for Immunology

Prof. Dr. Thomas Dittmar



Duelli & Lazebnik Cancer Cell 2003; 3:445-448

Fusion of tumor cells with normal cells, e.g., adult stem cells, can give rise to hybrid cells exhibiting novel properties, such as:

- an enhanced metastatic potential (due to an altered migratory activity)

- an increased drug resistance

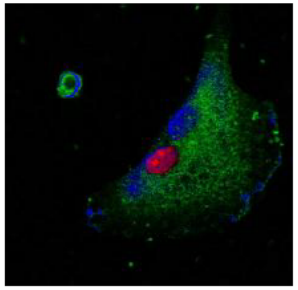
- a higher proliferation rate

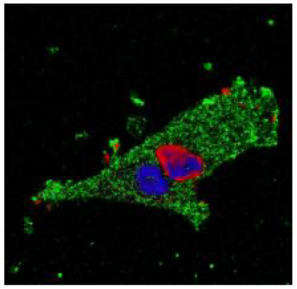
- an increased resistance to apoptosis

Institute for Immunology

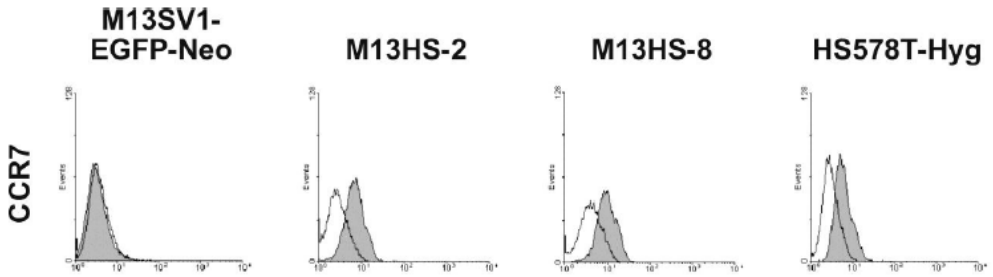
Prof. Dr. Thomas Dittmar

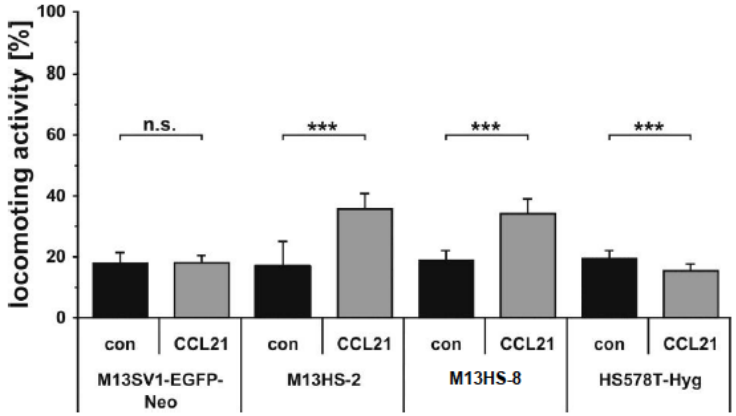
Breast stem/ breast cancer hybrids are sensitive to the lymph node metastasis directing chemokine CCL21





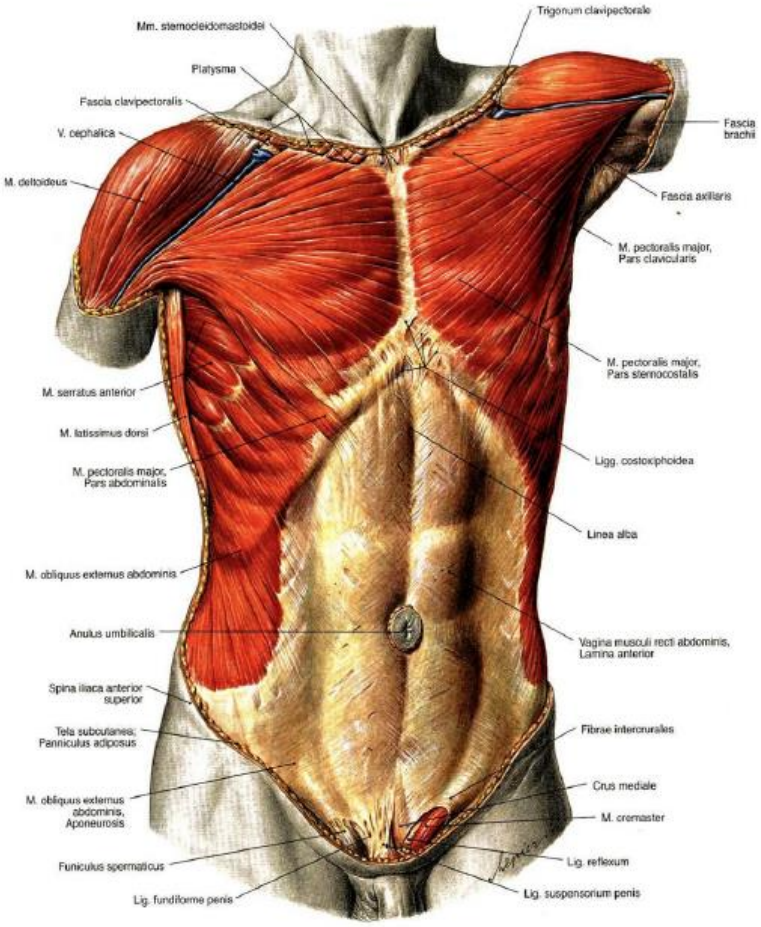
Green: EGFP (breast epithelial cell)
Red: BrdU (tumor cell)
Blue: Syto60 (nuclear stain)





Faculty of Medicine, Anatomy and Molecular Embryology

Prof. Dr. Beate Brand - Saberi



How do complex tissues form from a few cells?

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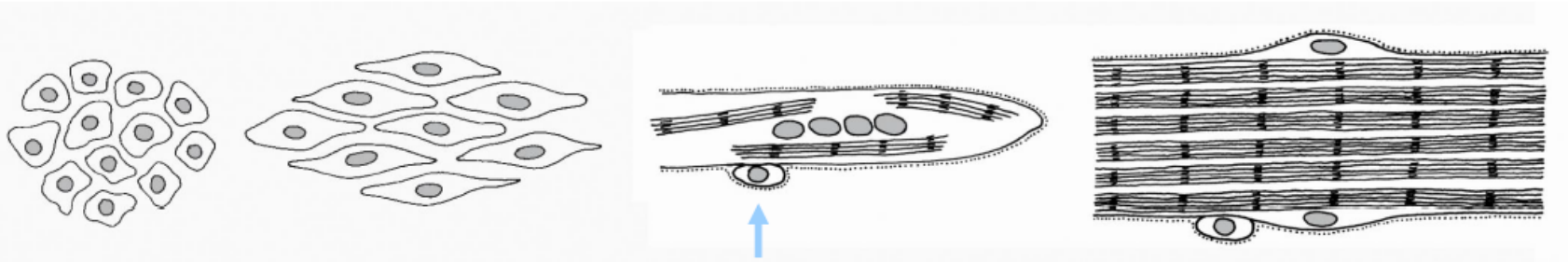
SKELETAL MUSCLE DEVELOPMENT

Mesodermal stem cells	Myoblasts	Myotubes, Satellite cells	Muscle fibers



Pax3 Pax7 Myf5 CXCR4	Myf5 MyoD Mef2	Mrf4 Myogenin Pax7 (in satellite cells) Muscle-specific proteins	Myosin heavy chain Desmin

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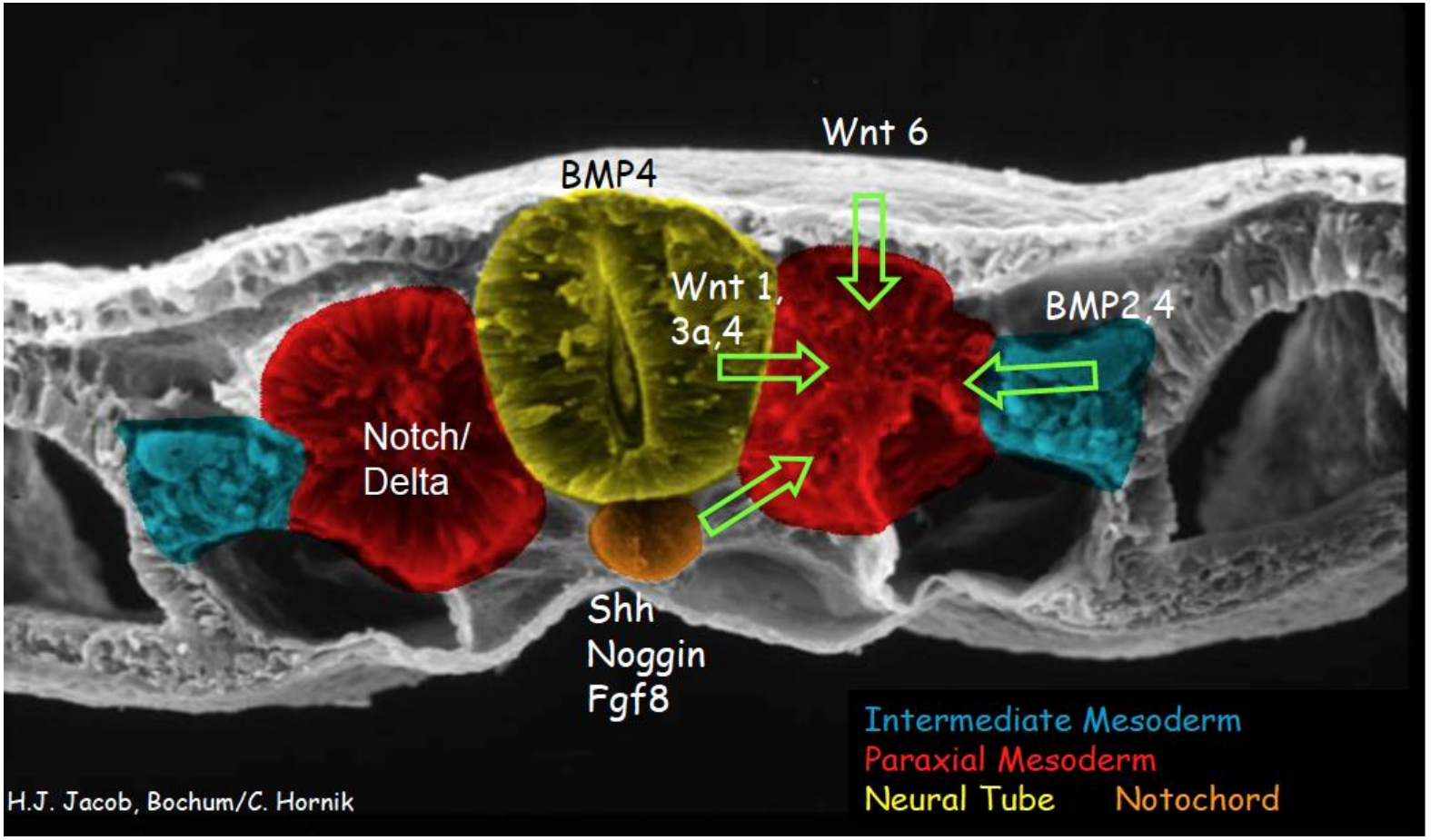
SKELETAL MUSCLE DEVELOPMENT



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Prof. Dr. Beate Brand - Saberi

SKELETAL MUSCLE DEVELOPMENT

CXCR4/SDF-1 axis is involved in the migration of muscle precursor cells into the limb bud

SDF-1:

- Stromal-cell derived factor 1
- Alpha-chemokine

CXCR4:

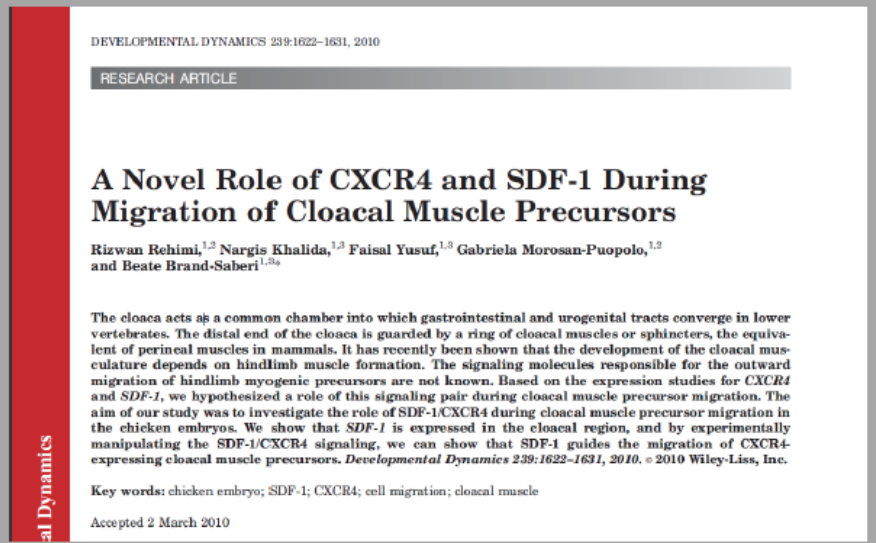
- G protein-coupled receptor
- SDF-1 is its sole ligand

CXCR4 and *Gab1* cooperate to control the development of migrating muscle progenitor cells

Elena Vasyutina,[1] Jürg Stebler,[2] Beate Brand-Saberi,[3] Stefan Schulz,[4] Erez Raz,[2] and Carmen Birchmeier[1,5]

[1]Max-Delbrück-Center for Molecular Medicine, 13125 Berlin, Germany; [2]Max Planck Institute for Biophysical Chemistry, 37077 Göttingen, Germany; [3]Institute of Anatomy and Cell Biology, University of Freiburg, 79104 Freiburg, Germany; [4]Department of Pharmacology and Toxicology, Otto-von-Guericke University, 39120 Magdeburg, Germany.

GENES & DEVELOPMENT 19:2187–2198 © 2005



DEVELOPMENTAL DYNAMICS 239:1622–1631, 2010

RESEARCH ARTICLE

A Novel Role of CXCR4 and SDF-1 During Migration of Cloacal Muscle Precursors

Rizwan Rehimi,[1,2] Nargis Khalida,[1,3] Faisal Yusuf,[1,3] Gabriela Morosan-Puopolo,[1,2] and Beate Brand-Saberi[1,3]*

The cloaca acts as a common chamber into which gastrointestinal and urogenital tracts converge in lower vertebrates. The distal end of the cloaca is guarded by a ring of cloacal muscles or sphincters, the equivalent of perineal muscles in mammals. It has recently been shown that the development of the cloacal musculature depends on hindlimb muscle formation. The signaling molecules responsible for the outward migration of hindlimb myogenic precursors are not known. Based on the expression studies for *CXCR4* and *SDF-1*, we hypothesized a role of this signaling pair during cloacal muscle precursor migration. The aim of our study was to investigate the role of SDF-1/CXCR4 during cloacal muscle precursor migration in the chicken embryos. We show that *SDF-1* is expressed in the cloacal region, and by experimentally manipulating the SDF-1/CXCR4 signaling, we can show that SDF-1 guides the migration of CXCR4-expressing cloacal muscle precursors. *Developmental Dynamics 239:1622–1631, 2010.* © 2010 Wiley-Liss, Inc.

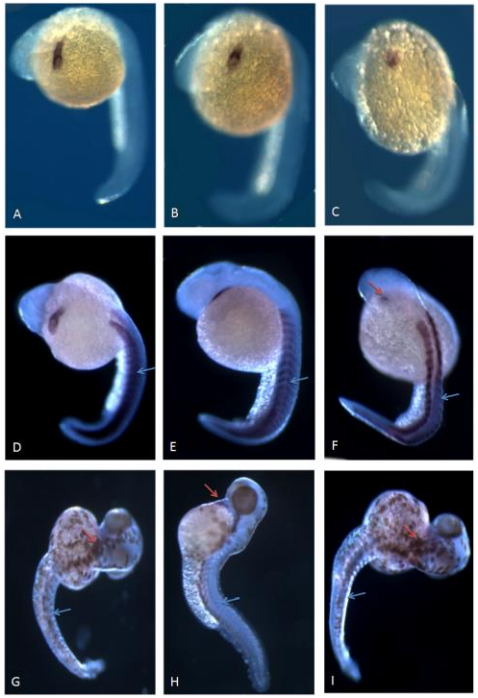
Key words: chicken embryo; SDF-1; CXCR4; cell migration; cloacal muscle

Accepted 2 March 2010

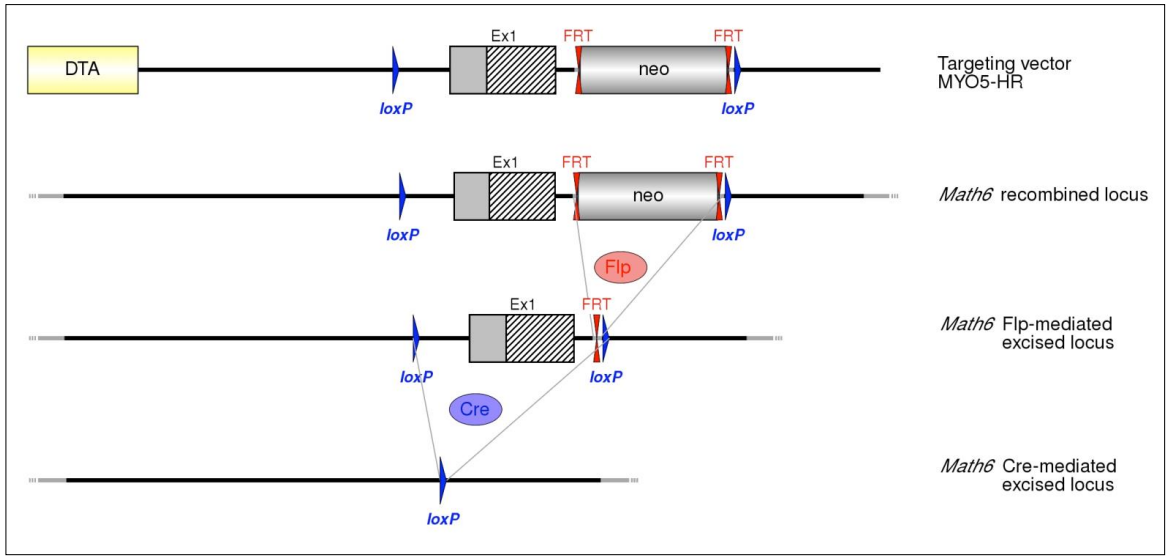
Faculty of Medicine, Anatomy and Molecular Embryology

Prof. Dr. Beate Brand - Saberi

TRANSCRIPTION FACTOR ATOH8 IN MYOGENESIS



Scheme of Cre- or Flp-excision at the recombined *Math6* locus



Morphanten- und Mutanten-Analyse beim Zebrafisch
Bockholt/Brand-Saberi

Generierung einer murinen ATOH8 (MATH6) Mutante

In Kollaboration mit Firma Genoway unterstützt durch MYORES NoE FP6

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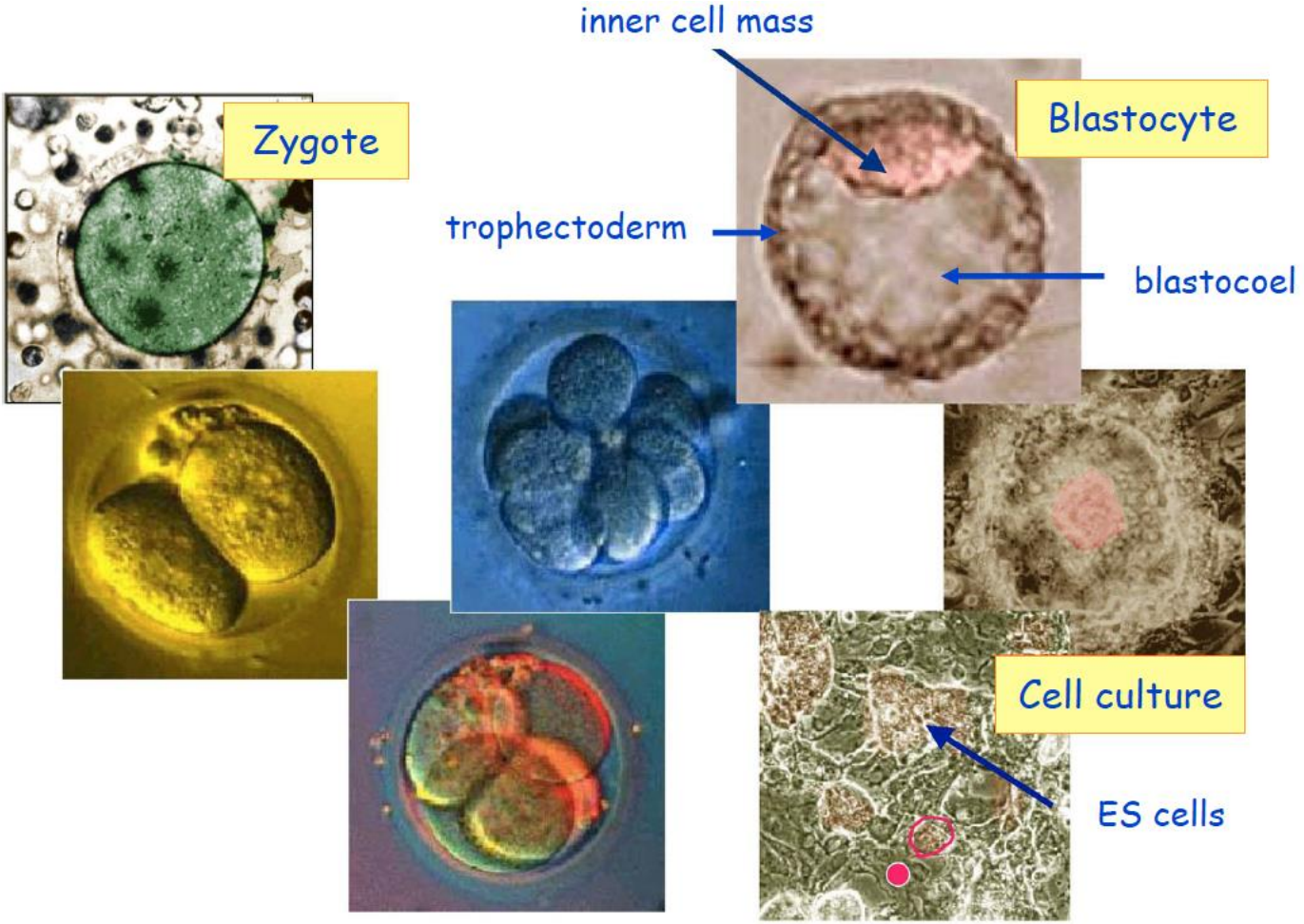
Dr. Markus Napirei

ISOLATION AND CULTURING OF EMBRYONIC STEM CELLS



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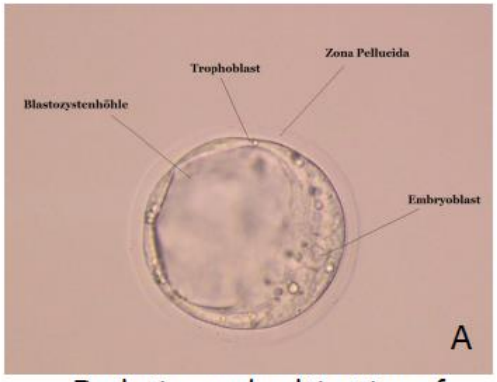
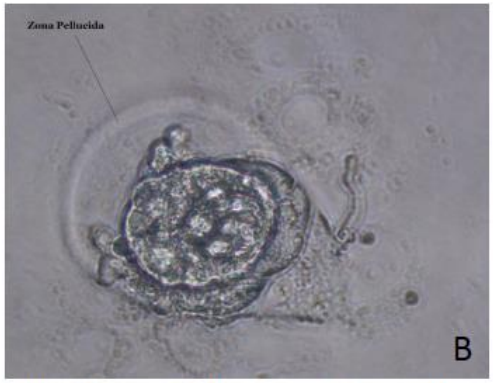
Dr. Markus Napirei

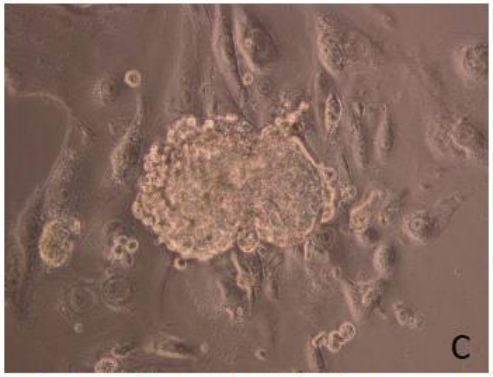
ISOLATION AND CULTURING OF EMBRYONIC STEM CELLS



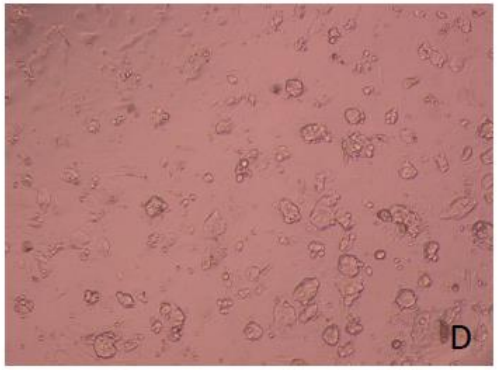
Isolation and cultivation of blastocytes on mitotically arrested murine embryonic fibroblasts (feeder cells)



Hatching of blastocyst from the zona pellucida and subsequent fast upgrowth of the inner cell mass



Inner cell mass ready for trypsin treatment and transfer into the 24 well plate



Establishment of ES cell lines by picking out and culturing the colonies separately

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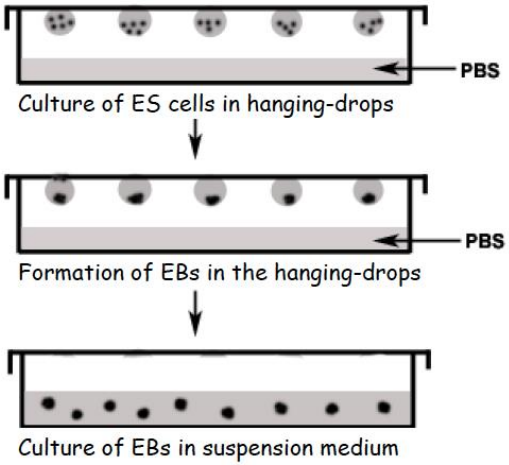
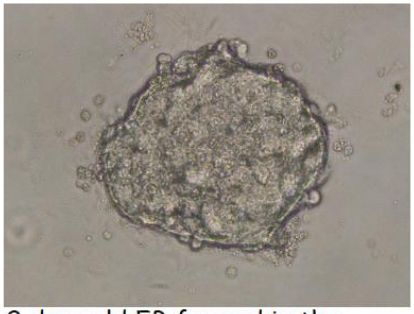
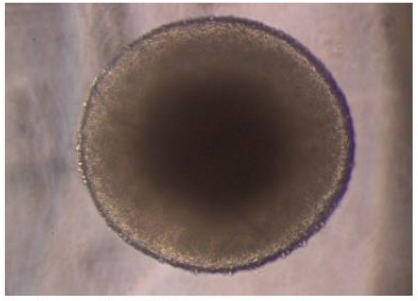
ISOLATION AND CULTURING OF EMBRYONIC STEM CELLS

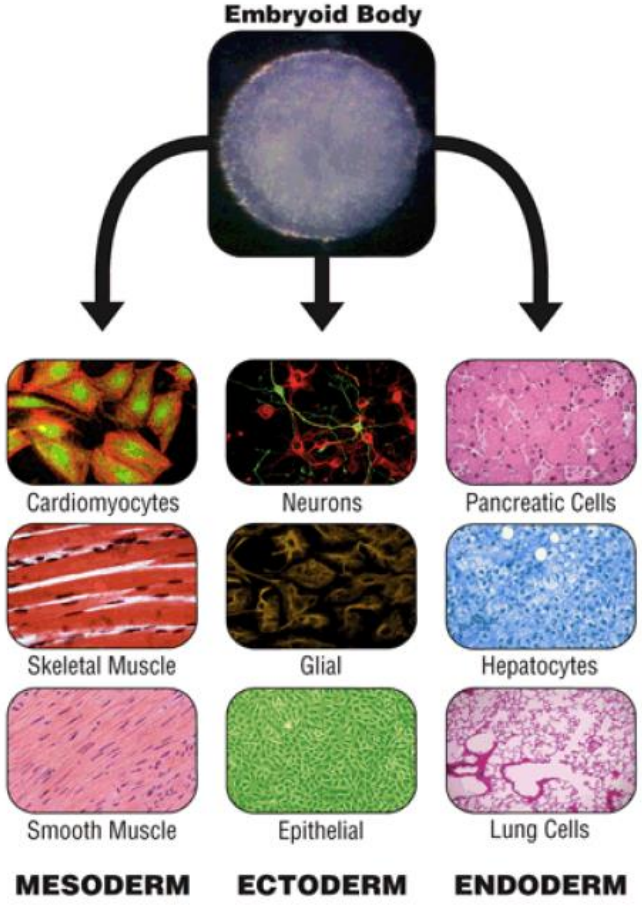




2 days old EB formed in the hanging-drop culture



4 days old EB in the static suspension culture



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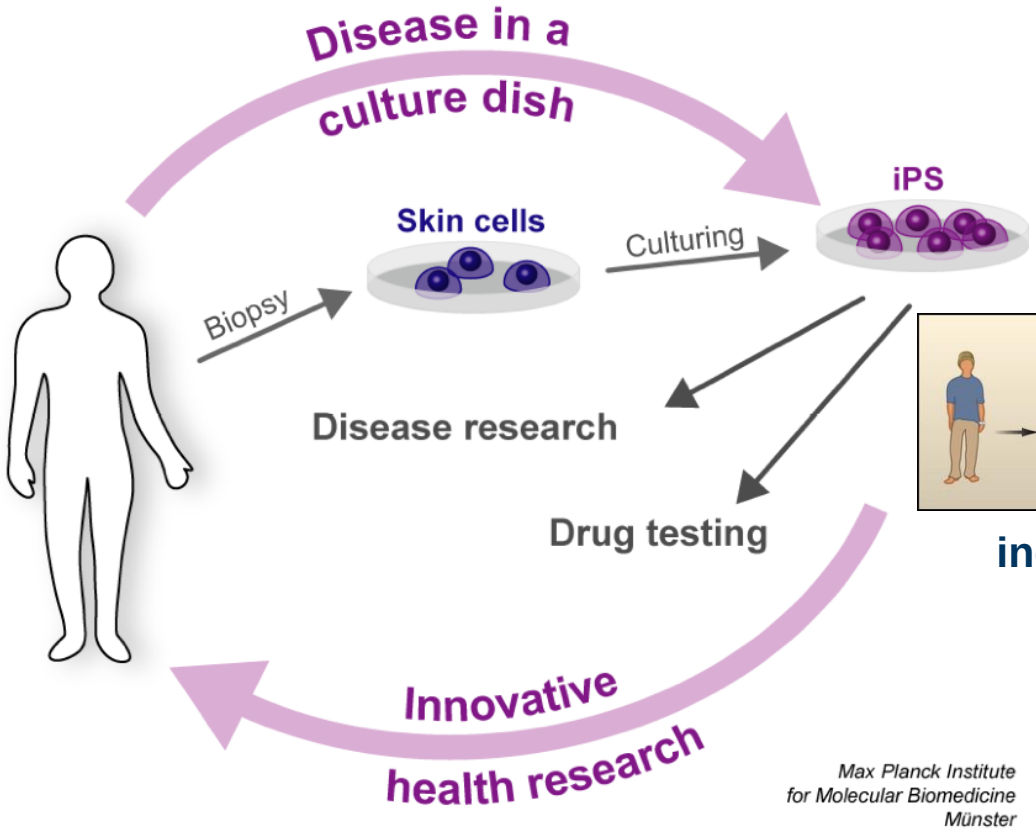
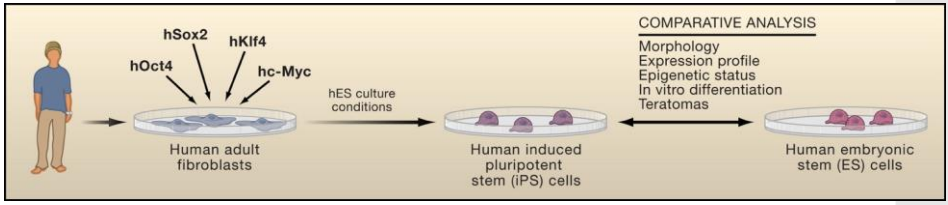
DISEASE MODELING WITH HUMAN iPSC





induced, pluripotent stem (iPS) cells

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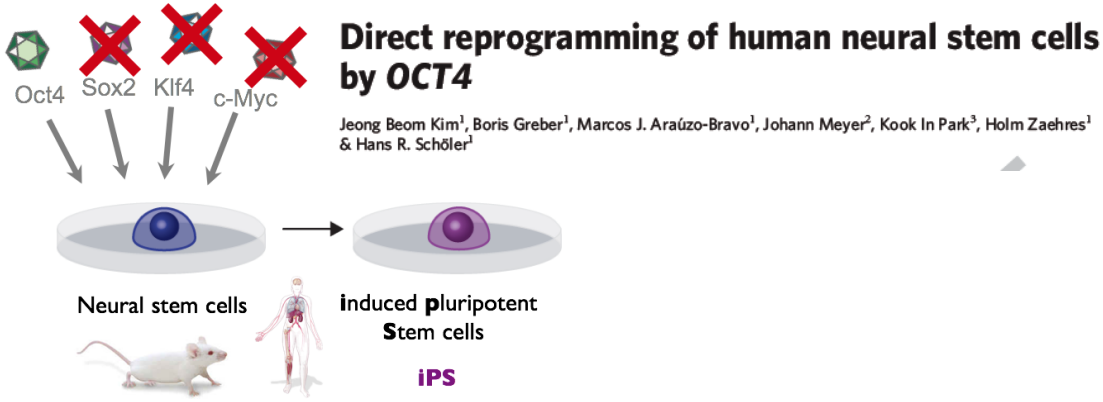
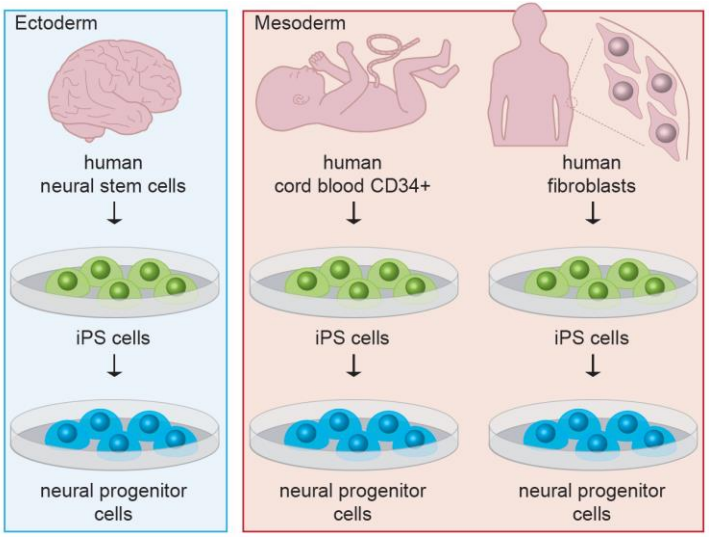
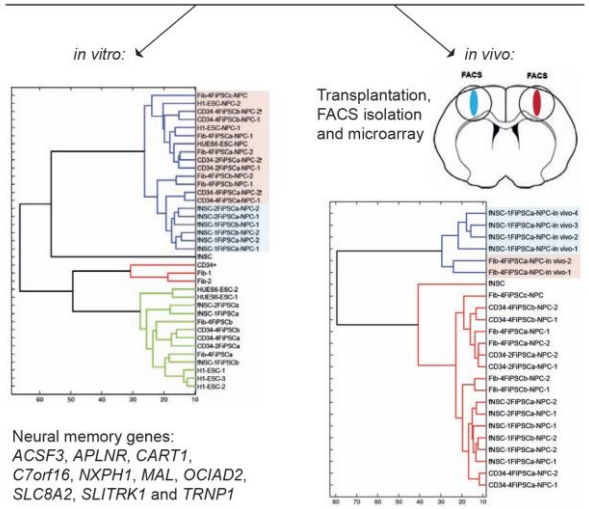
NEURO DISEASE MODELING WITH HUMAN iPSC







Hargus et al.

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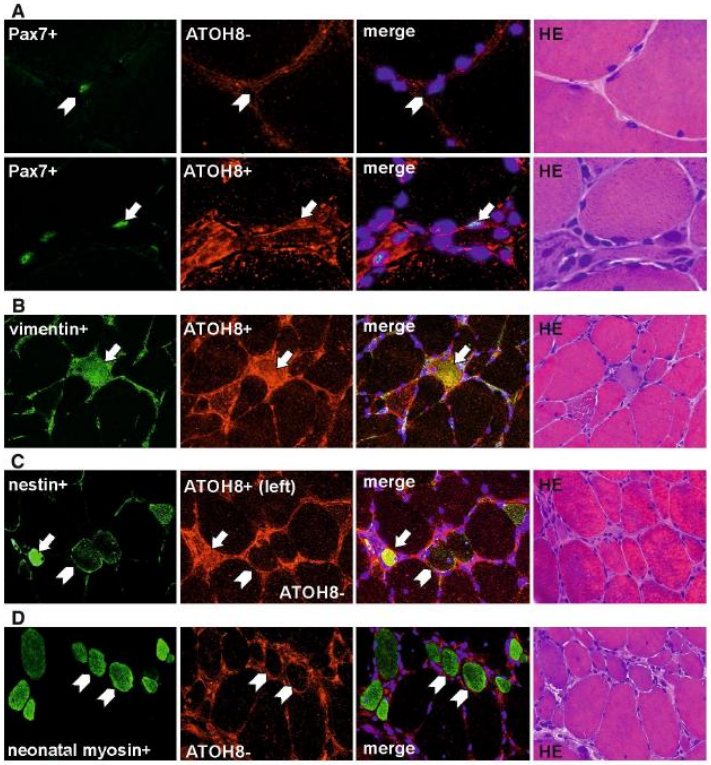
MUSCLE DISEASE MODELING WITH HUMAN iPSC

Claudia Weise · Fangping Dai · Felicitas Pröls
Uwe-Peter Ketelsen · Ulrike Dohrmann
Mathias Kirsch · Beate Brand-Saberi

Myogenin (_Myf4_) upregulation in trans-differentiating fibroblasts from a congenital myopathy with arrest of myogenesis and defects of myotube formation



ATOH8: a novel marker in human muscle fiber regeneration

Anne-K. Güttsches · Ajeesh Balakrishnan-Renuka ·
Rudolf André Kley · Martin Tegenthoff ·
Beate Brand-Saberi · Matthias Vorgerd

UK RUB UNIVERSITÄTSKLINIKUM DER RUHR-UNIVERSITÄT BOCHUM

MUSKELZENTRUM RUHRGEBIET

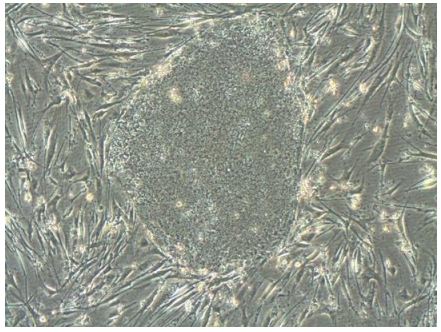
Faculty of Medicine, Anatomy and Molecular Embryology

METHODS

Klassische Embryologie

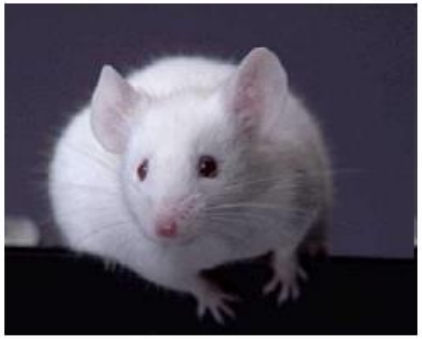
Transmissions-
elektronenmikroskopie
Rasterelektronen-
mikroskopie

Molekularbiologie
Konfokalmikroskopie



Entwicklungsbiologie am Tiermodell

Hühnerembryo
Zebrafisch
Maus

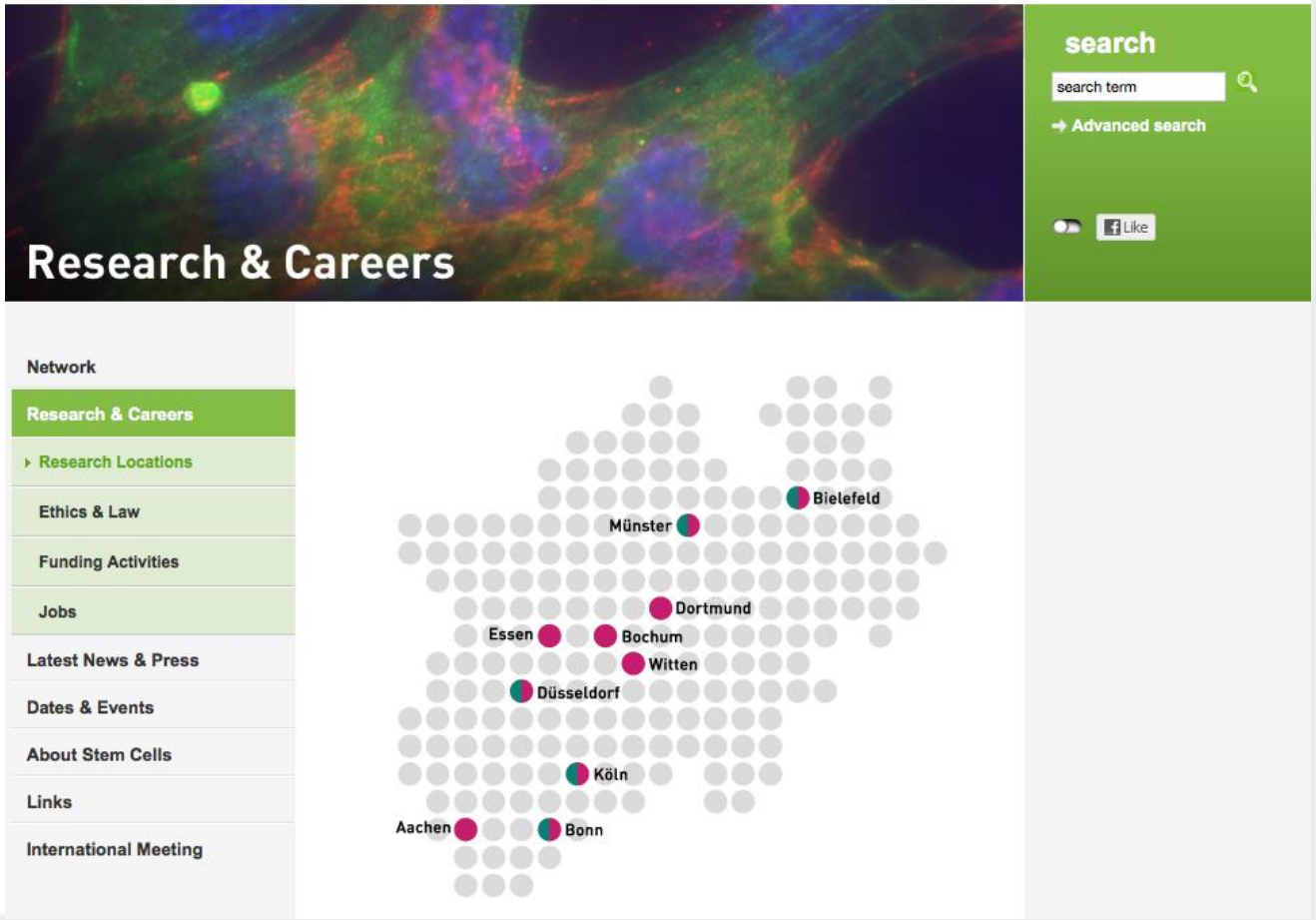


Entwicklungsbiologie an humanen, pluripotenten Stammzellen

Stem Cell Network NRW

Stem Cell Network
North Rhine Westphalia

funded by
Ministry of Innovation, Science and Research of the German State of North Rhine-Westphalia

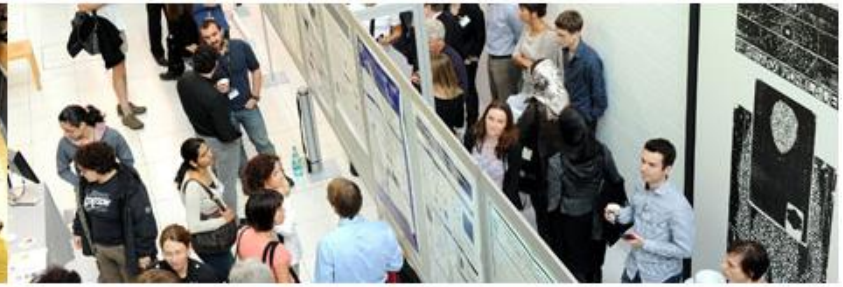


German Stem Cell Network

GermanStemCellNetwork

NETWORK FOR BASIC AND APPLIED STEM CELL RESEARCH IN GERMANY

THE GSCN | GSCN MEMBERSHIP | ANNUAL CONFERENCE | WORKING GROUPS | FOR THE PUBLIC | EVENTS | RESOURCES



Upcoming events

→ 4th Annual GSCN Conference
12 - 14 September 2016
Hannover, Germany

GSCN Humhub

GSCN members discuss new

GSCN NEWS

4th Annual GSCN Conference

→ Conference Website

GSCN Members

→ CURRENT MEMBERS

Max-Planck-Institut für Herz- und Lungenforschung
W.G. Kerckhoff-Institut

BI Biological Industries
Culture of Excellence

International Society for Stem Cell Research

Members Public Media

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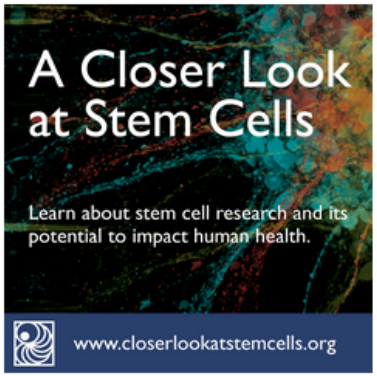
GUIDELINES FOR STEM CELL RESEARCH AND CLINICAL TRANSLATION

MEMBERSHIP INFORMATION

For the Public



What's New?

Nominations for the ISSCR Board of Directors now being accepted

18 August, 2016

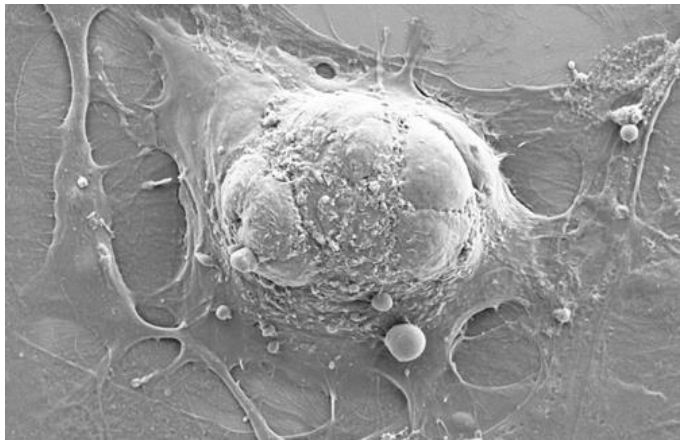
Nominations will be accepted through midnight (CDT) 15 September 2016.

Read more

The ISSCR Congratulates George Q. Daley on Being Named Dean of Harvard Medical School

10 August, 2016

The ISSCR congratulates George Q. Daley, MD PhD, on his selection as the next dean of Harvard Medical School (HMS). Daley is a long-time member of the ISSCR leadership, having served in several capacities, including as president (2007-08) and chair of the inaugural guidelines task force (2005-06). He is currently a member of the ISSCR Board of Directors.



FOCAL POINT

BIOCHEMISTRY OF STEM CELLS

Fakultät für Chemie und Biochemie

Fakultät für Biologie und Biotechnologie

Fakultät für Medizin

Ruhr-Universität Bochum