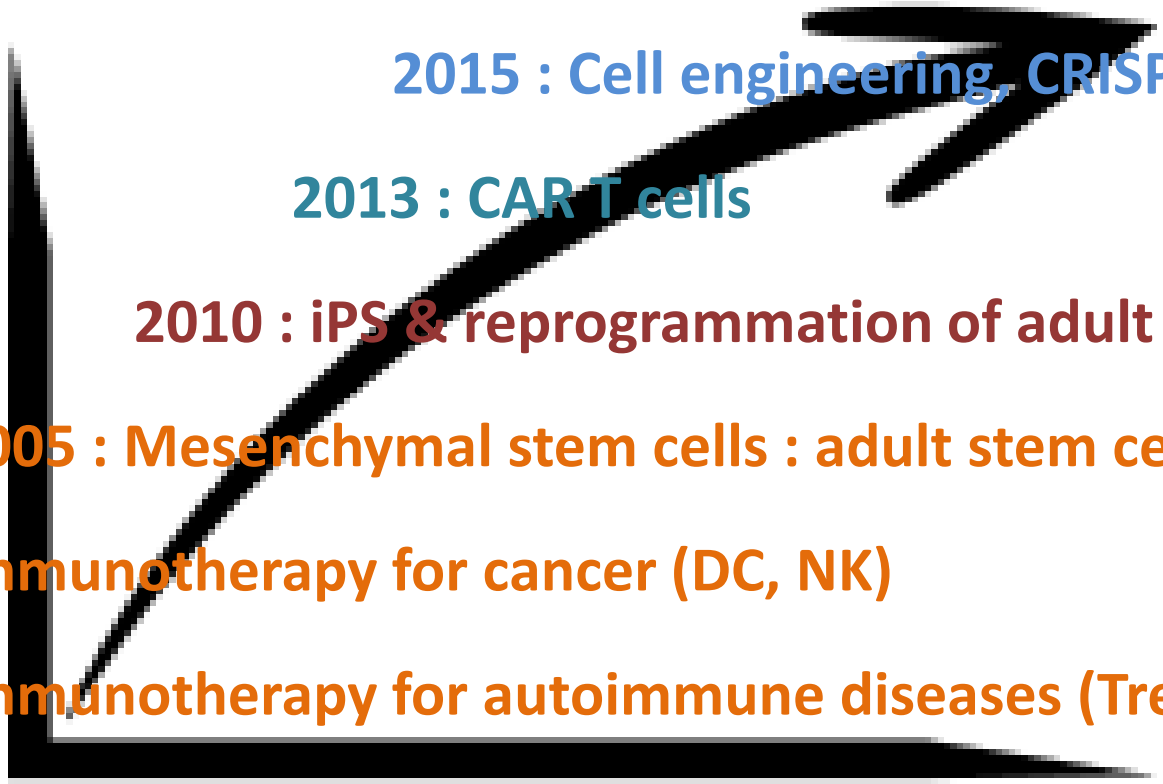
ADIPOA-2

IRMB
Institute For Regenerative Medicine & BIOTHERAPY

How to bring Advanced Therapy Medicinal Product to clinical practice in Europe ?

Institute for Regenerative Medicine & Biotherapy
Montpellier France
christian.jorgensen@inserm.fr

Cell therapy : innovative medicine



2015 : Cell engineering, CRISPR/CAS technology

2013 : CAR T cells

2010 : iPS & reprogrammation of adult cells for pluripotenty

2005 : Mesenchymal stem cells : adult stem cells (MSC, ASC)

Immunotherapy for cancer (DC, NK)

Immunotherapy for autoimmune diseases (Treg, DC)

Cell therapy in EU

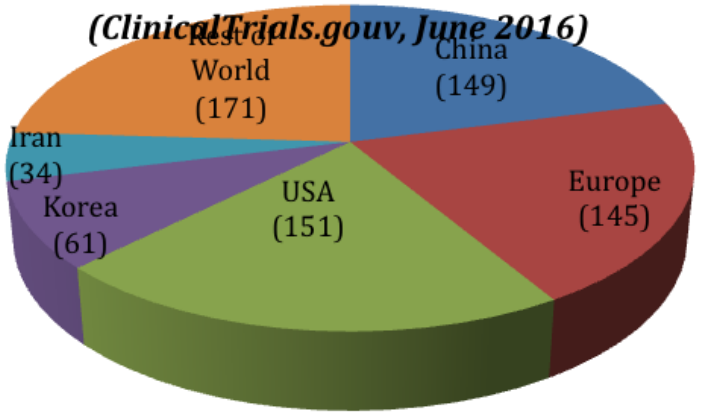
- Innovative medicine
- Powerful
- Adaptative
- 20% of clinical trials led in EU

But:

- Need for GMP platforms for safe production
- Preclinical needs humanized models (biodistribution, toxicology …)
- Regulatory : Cells are ATMP
- Cost & new business model

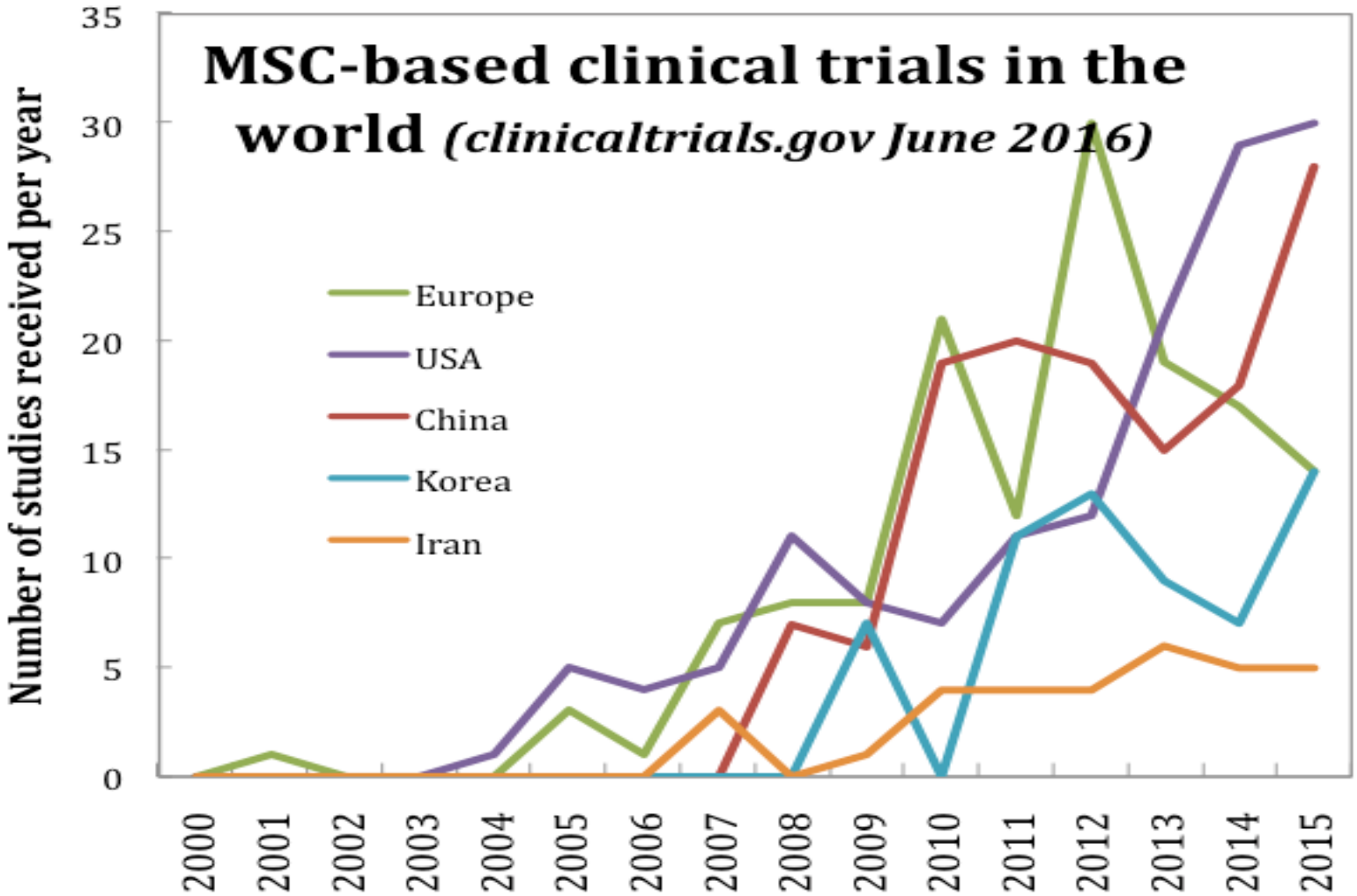
MSC-based clinical trials in the world

(ClinicalTrials.gouv, June 2016)

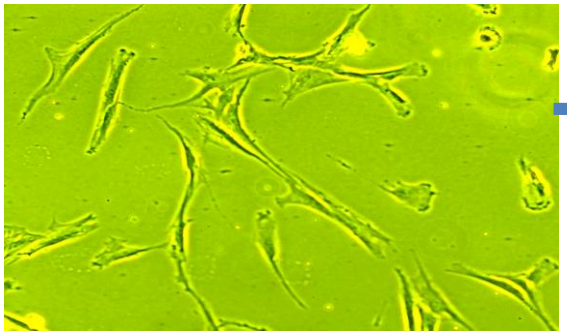


Country/continent	# Studies	% Studies
USA	151	21%
China	149	21%
Europe	145	20%
Korea (republic of)	61	9%
Iran	34	5%
"Rest of the world"	171	24%
South America	25	4%
India	15	2%
Israel	12	2%
Russian Federation	17	2%
Canada	13	2%

Cell therapy in EU



MSC for cell mediated therapy



Self renewal

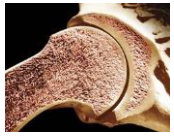
migration

Secreted factors:
Anti inflammatory
Growth factors
Metabolism : glycolysis
Prevent apoptosis
Prevent fibrosis

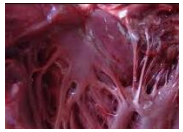
differentiation


Cartilage


muscle


osseux


adipeux

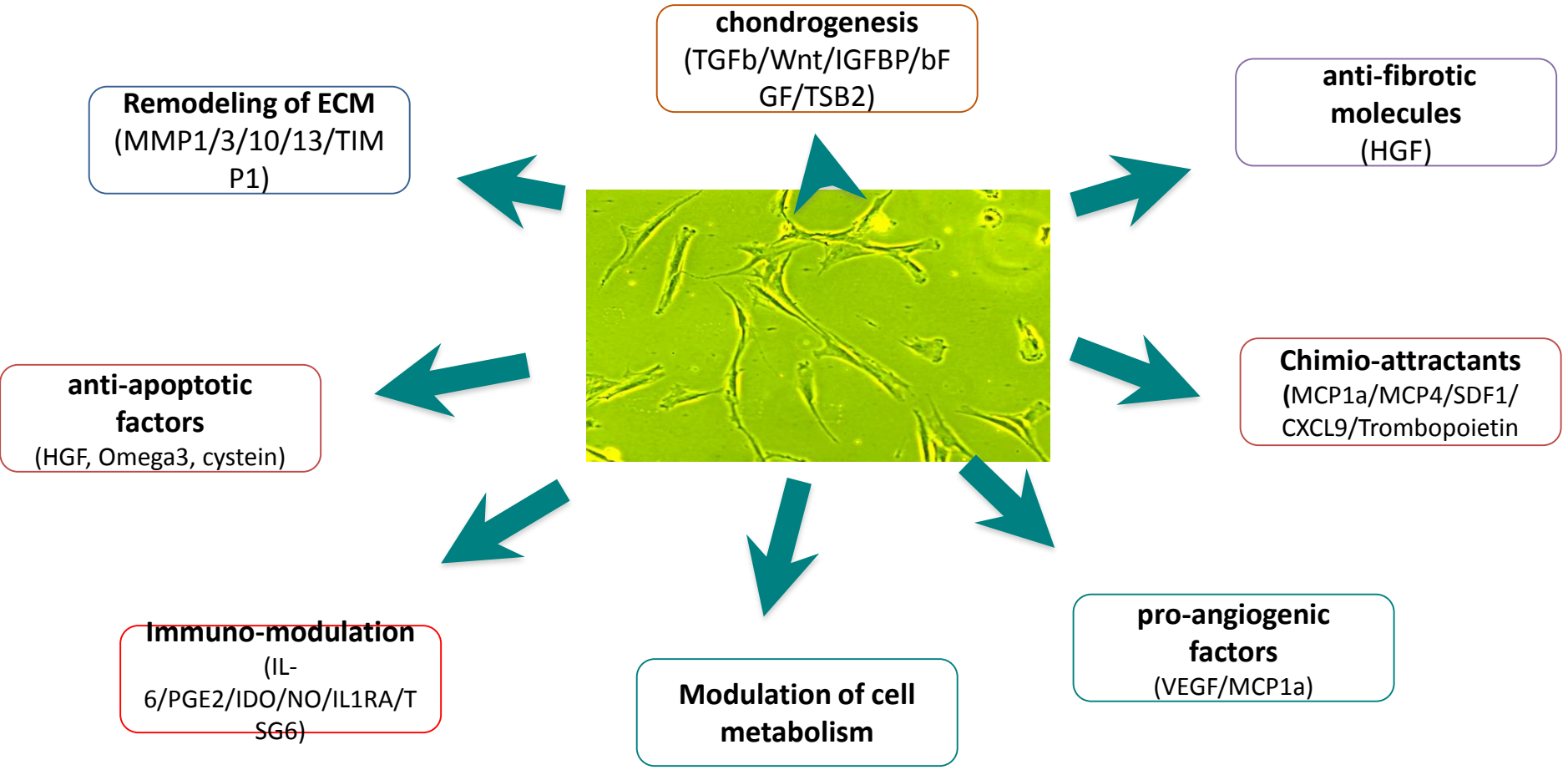

cardiomyocytes

Exosomes : miR

Nanotubes: mitochondria

tissue regeneration

ASC for cell mediated therapy



Allogenic or autologous cells?

Allogenic process

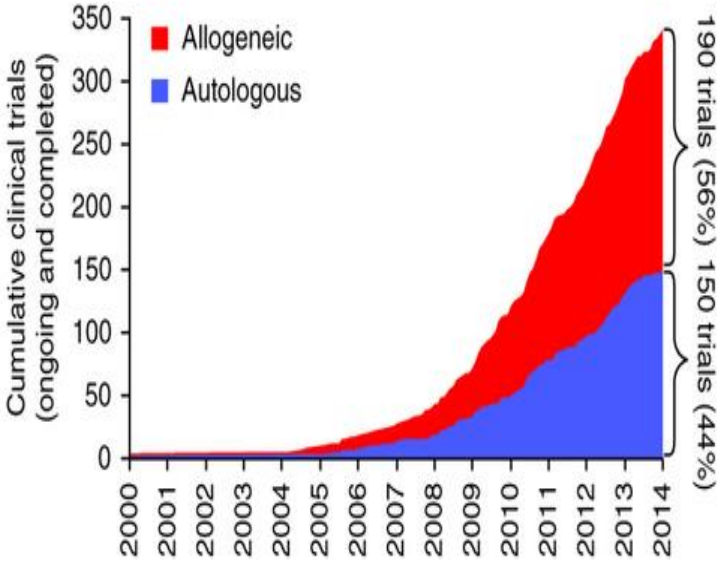
- biodistribution
- Anti-HLA response
- Reduction in cost production
- « on the shelf » product
- Young donor
- May be encapsulated
- May be genetically modified

autologous process

- safety
- Time for expansion
- cost
- Possible repeated administration

Allogenic or autologous cells?

- Today, 463 trials based on MSC
- Allogenic 56% & Autologous 44%
- MSC are immunoevasive but not immuno-privileged : mMSC persist >40 days in syngenic recipient, but 20 days in allogenic setting.
- 13% of patients developed anti-HLA response, not correlated to clinical response or safety
- All biotech cell product are allogenic



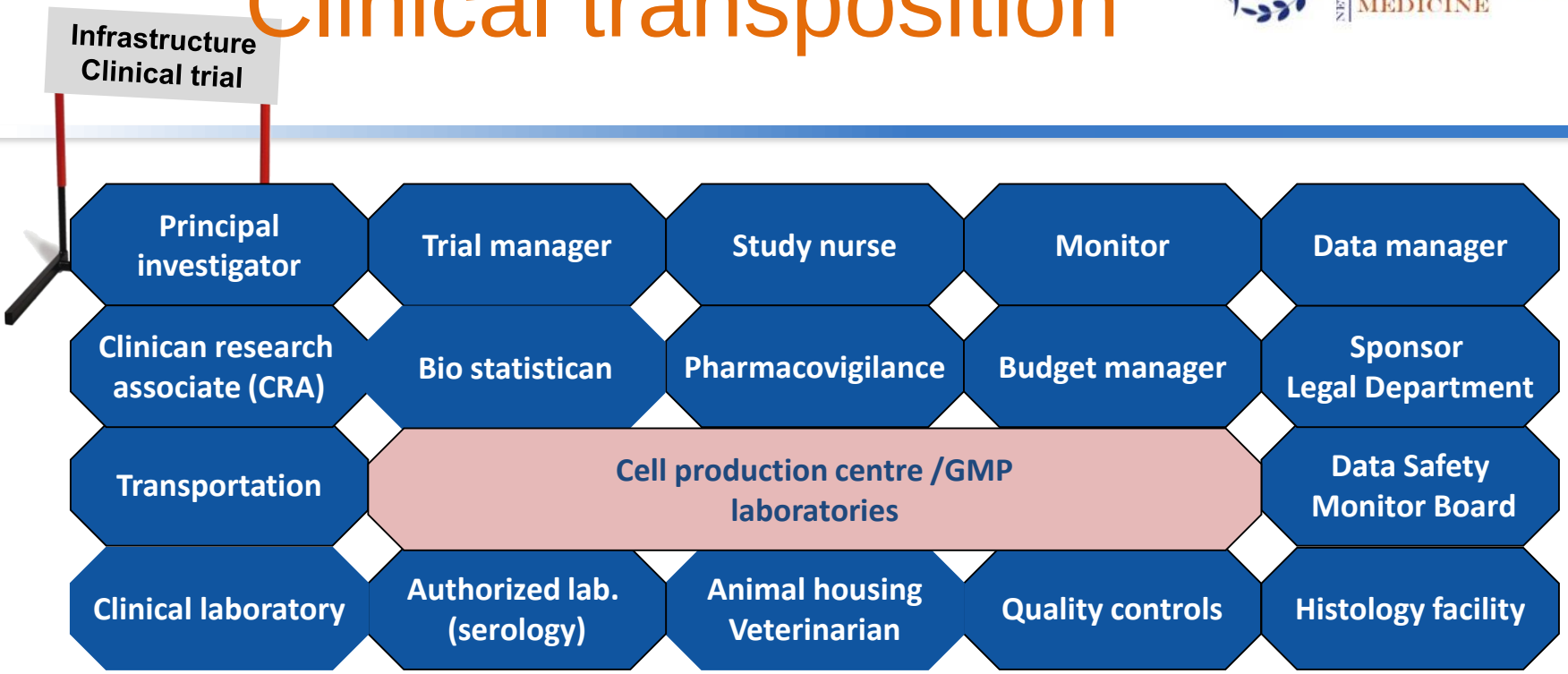
✓Mesoblast Prochymal
✓Athersys Multistem
✓Stemedica Stemdyne
✓Tigenix Cx611
✓Stempentic Stempencel
✓Medipost Pharmicell

Imran Ullah et al. Biosci. Rep. 2015

regulatory

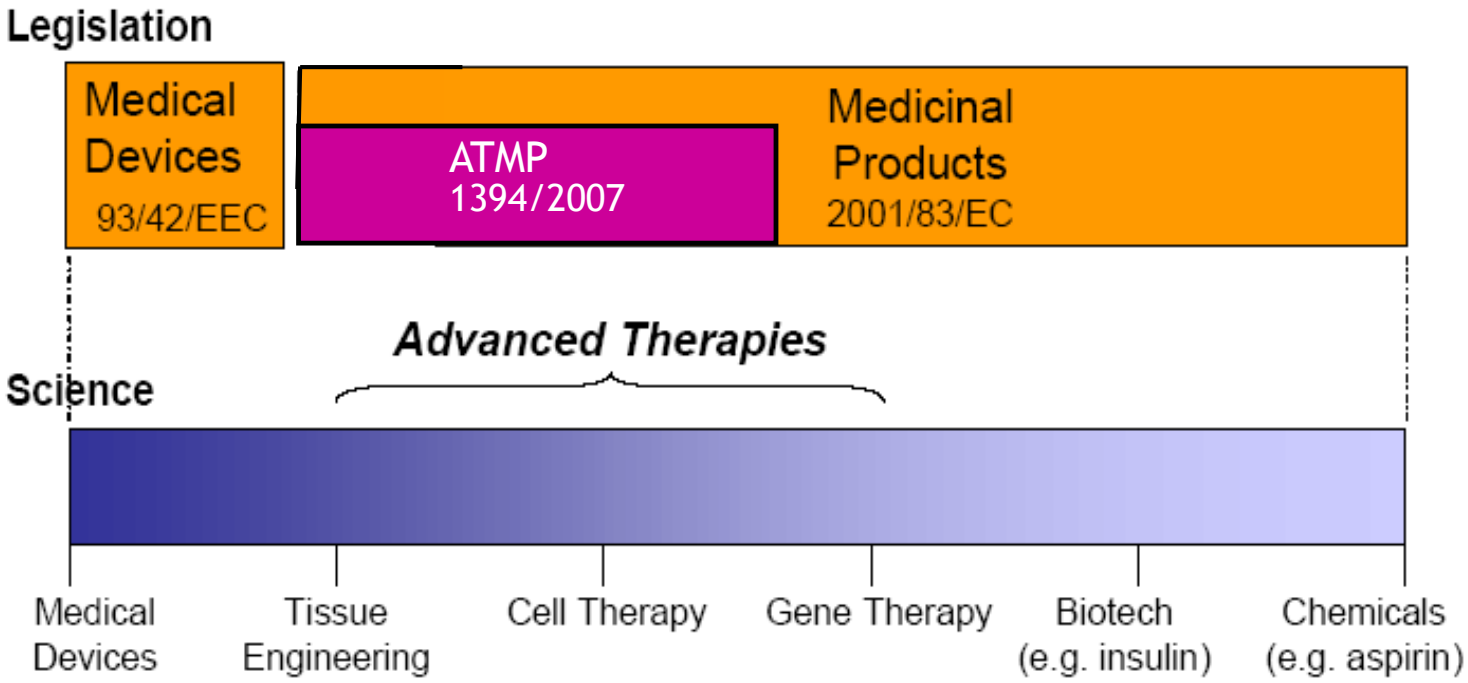
EUROPEAN MEDICINES AGENC
SCIENCE MEDICINES HEALTH

Clinical transposition



- ✓ Dossier include:
  - ✓ Core Clinical Trial Application (CTA) & EudraCT form
  - ✓ Insurance
  - ✓ IMPD, IB, protocol
- ✓ Approved by EMEA through VHP procedure
- ✓ Ethical committee approval

Advanced Therapy Medicinal Products



Somatic Cell Therapy Medicinal Products

- ✓ consists of **cells or tissues** that have been subject to **substantial manipulation** so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered,
- ✓ cells or tissues that **are not intended to be used for the same essential function** in the recipient and the donor;
- ✓ to treat a disease through the pharmacological, immunological or metabolic action of its cells or tissues.

[Directive 2001/83/EC annex 1, Part IV; amended by 2009/120/EC]

→ Cells = medicinal product

Cell products that are not ATMP: Exceptions to Substantial Manipulations

- cutting
- grinding
- shaping
- centrifugation
- soaking in antibiotic or antimicrobial solutions
- sterilization,irradiation
- cell separation, concentration or purification
- filtering
- lyophilization
- freezing
- cryopreservation,

How are ATMP's regulated?

EMA centralized assessment through the Committee on Advanced Therapy (CAT)

- the follow-up of efficacy of ATMPs and of adverse reactions are required;
- Draft opinions on the Quality, and Safety of each ATMP for final approval by the Committee for medicinal Products for Human Use (CHMP)
- Advice on whether the product falls within the definition ATMP
- Control of traceability requirement for the hospital, institution or private practice where the product is used. data kept for 30 years

✓ **Approval of the Investigational Medicinal Product Dossier (IMPD) and administration to patients in clinical trials**

✓ **VHP procedure**

How are the cell or ATMP produced?

- Producing cells in pharmaceutical standards to obtain efficient Advanced Therapy Medicinal Products (European Commission [EC] No. 1394/2007)
- Large scale GMP platforms
  - Class A clean rooms
  - Bioreactors
  - Obtain authorization for ATMP production by national regulatory agency (ANSM, PEI …)
- pharmaceutical structure:
  - Pharmacist
  - reproducibility and traceability of processes with quality assurance (QA)
  - SOP for quality controls (QC)

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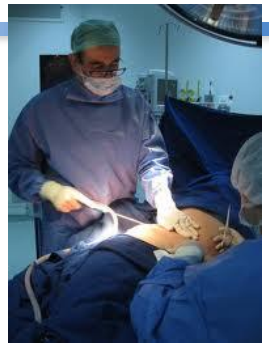
cGMP MSC production platform

Donor eligibility tests



ADIPOSE tissue aspiration

GMP Cell culture / expansion bioreactor

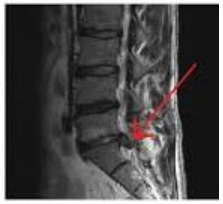
Harvest banking

Drug Order

Filling / Release testing

MSC

Clinical injection site

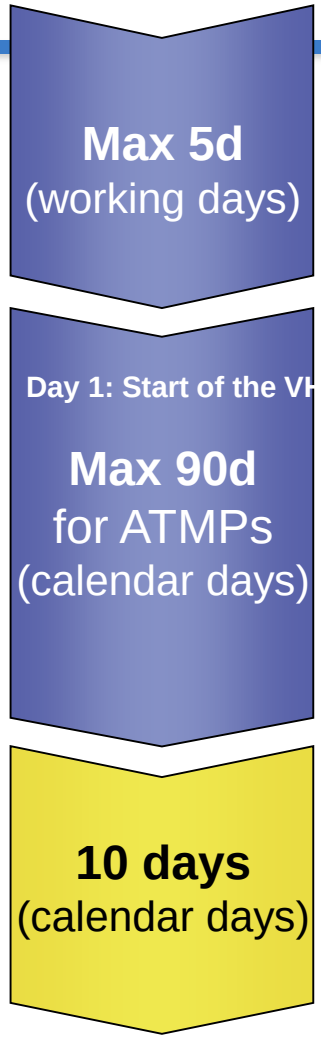


Regulatory submission (VHP)

- At least 2 countries, Voluntary basis
- **VHP-Phase 1: Request for a VHP and validation of the application**
- **VHP-Phase 2: The assessment step**

  Review of the Clinical Trial Application (CTA) by the National Competent Authorities of the participating Member States
- **VHP-Phase 3: the national step with formal CTAs to all concerned NCAs**

  Within 20 days following the VHP approval
- 2014-2015 : 416 applications by 130 different sponsors (academic applicants: 10%)
- Average time used for a VHP: 53,1 days (0 to 75)



Examples of clinical applications

FP7 program: preclinical

Stellar — Identify kidney MSC and benefit in renal diseases

VISICORT — Immune response and prevent rejection in corneal transplant

MERLIN — MSC for primary sclerosing cholangitis

REDDSTAR — preclinical phase : benefit of ORB1+ SSC in diabetic models.

Reborne — advanced biomaterials and cells triggering for bone healing

ADIPOA — Phase 1 for ASC in ostearhritis

ADIPOA

ADIPOA: phase 1 clinical trial of autologous stromal cell from adipose tissue in osteoarthritis

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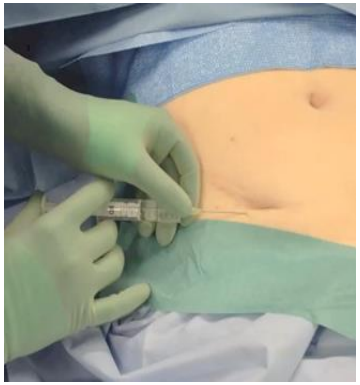
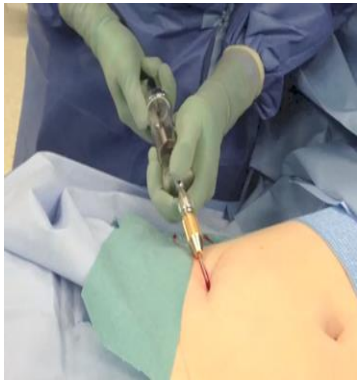
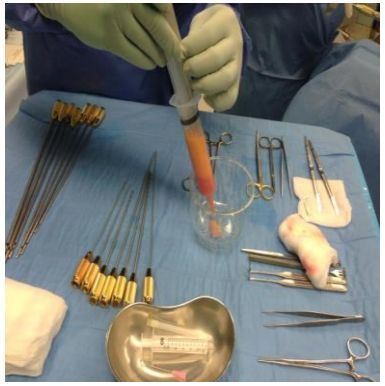

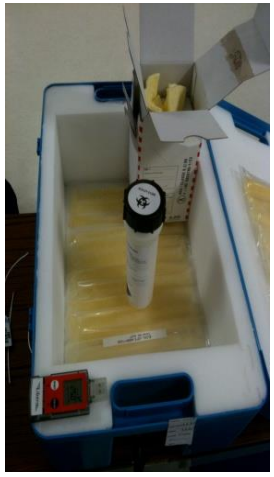

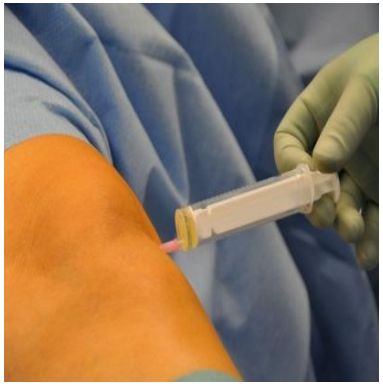
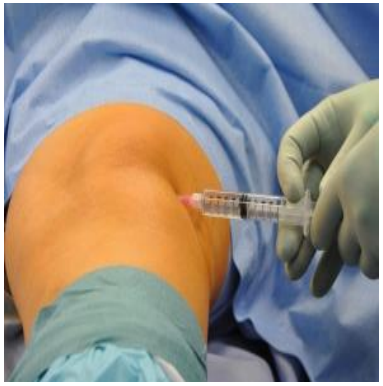

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Patients caracteristics

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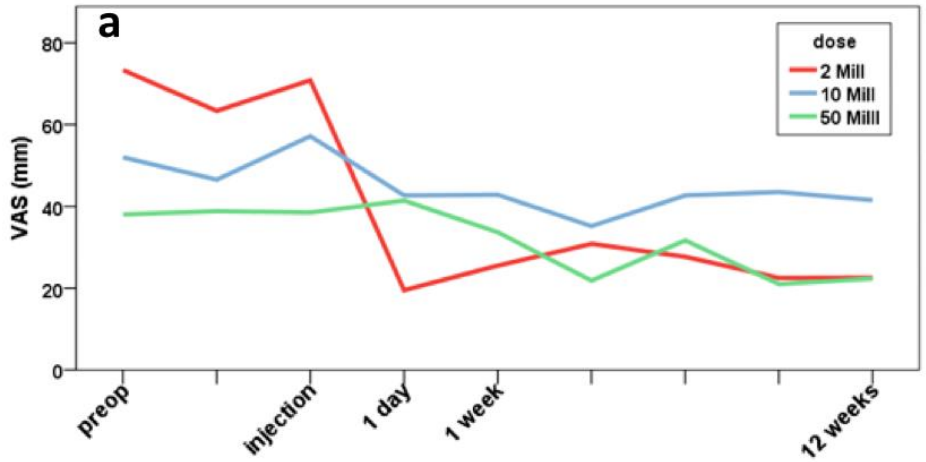
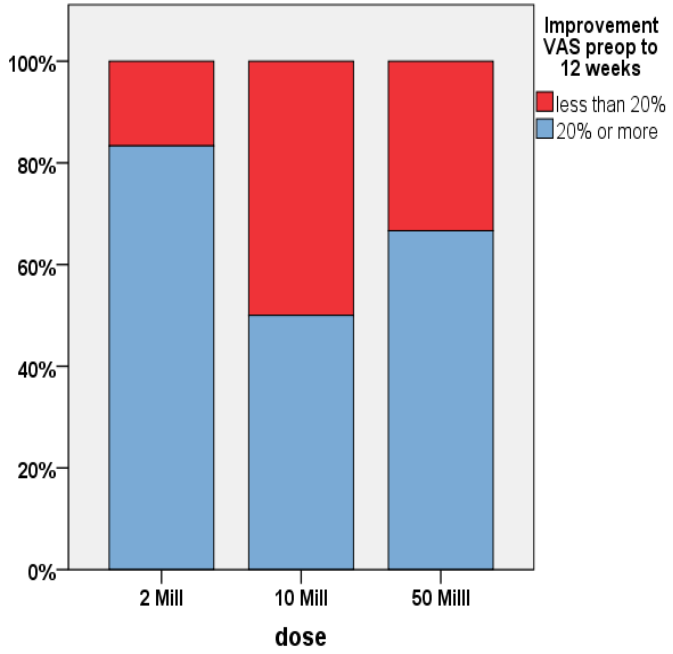
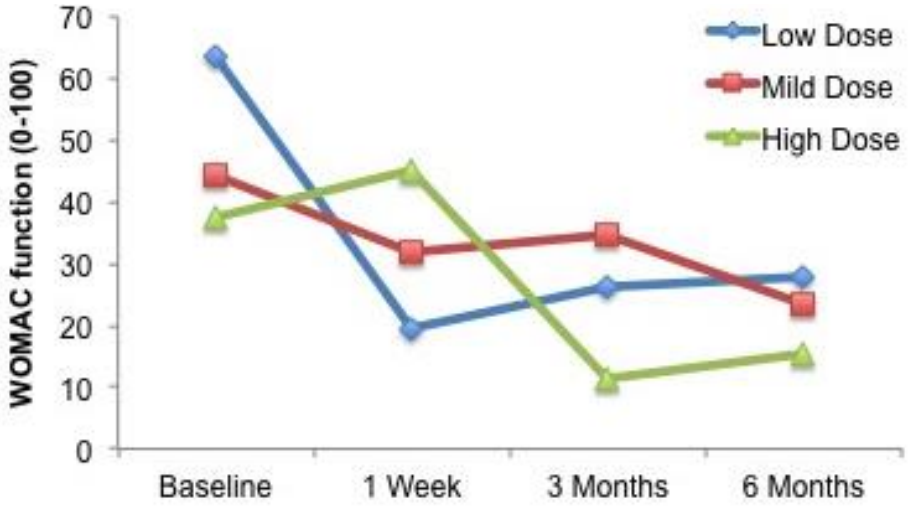
- n= 18
- 50 % of patients were women
- Age: 61,83(±7,13) years
- mean duration OA was 10,8 (±6) years
- mean stage KL : 62,5% stage IV and 37,5% stage III
- initial WOMAC score : 68,05 (±18,07)
- mean initial VAS score : 50,18 (±12,52)

Clinical assessment months 6

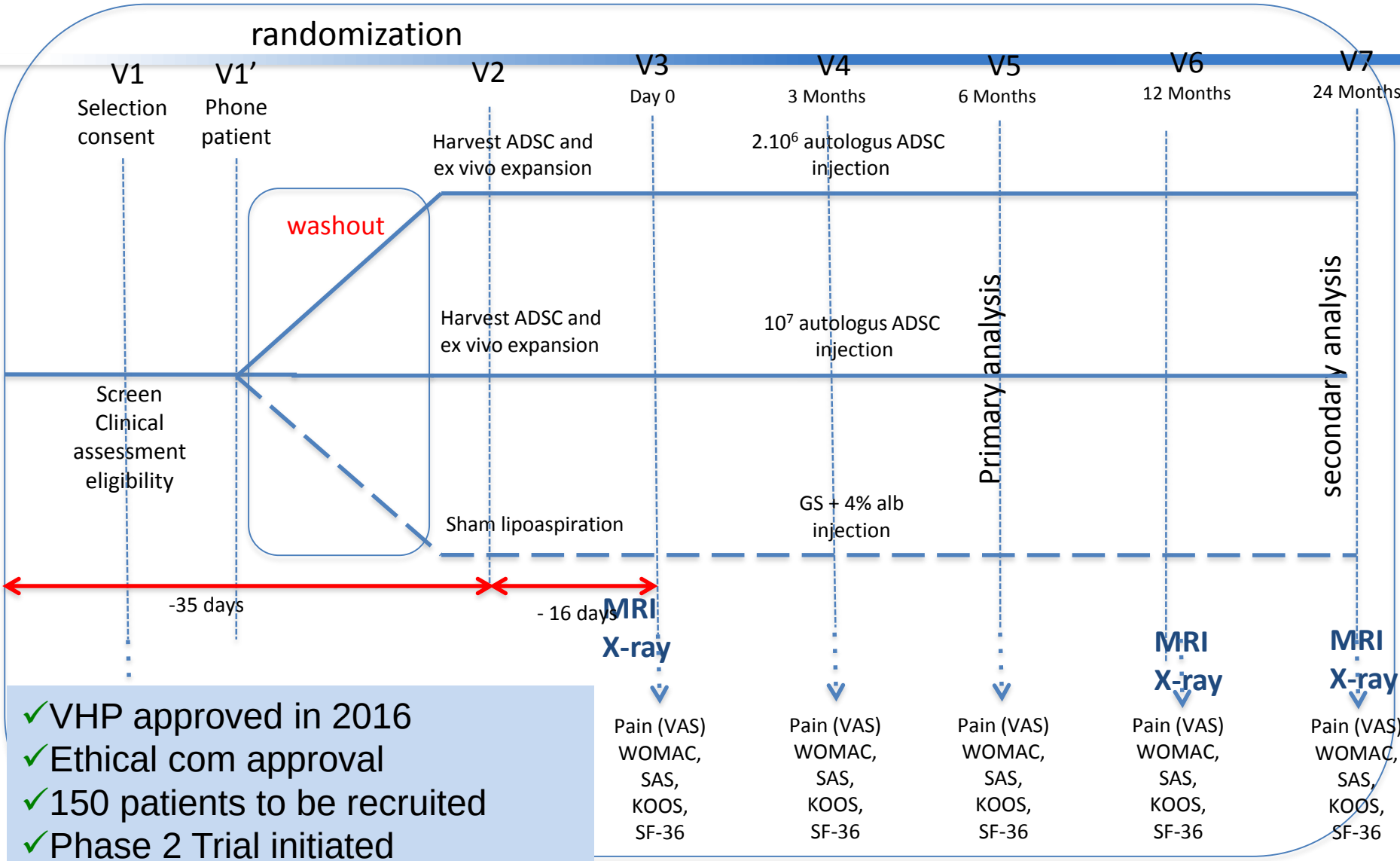






Pers et al, Stem cell Trans Med, 2016

ADIPOA2 : phase 2 trial of autologous stromal cell from adipose tissue



- ✓VHP approved in 2016
- ✓Ethical com approval
- ✓150 patients to be recruited
- ✓Phase 2 Trial initiated

RETHRIM coord. W Fibbe

RE THR IM
Regeneration through Immune Modulation

- Indication : steroid-resistant visceral GVHD
- Methodology : placebo controlled randomized phase III trial using MSC regenerative therapy for the treatment of GvHD.
- 150 patients to be recruited.
- Status: No VHP. National approval Germany, Netherlands, Sweden, Spain.
- Trial initiated : 10 patients recruited.

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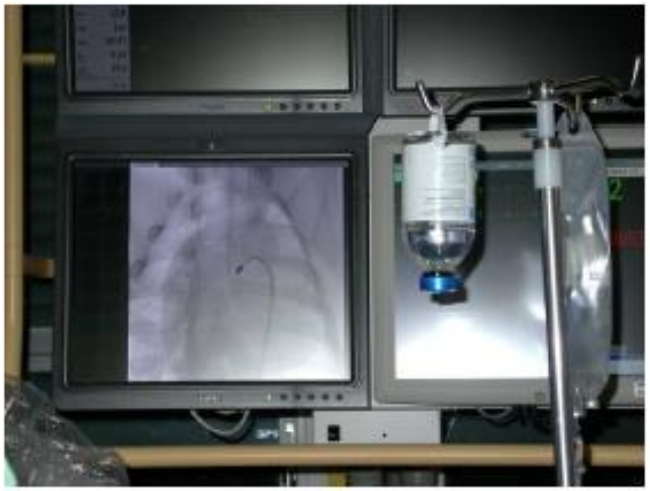
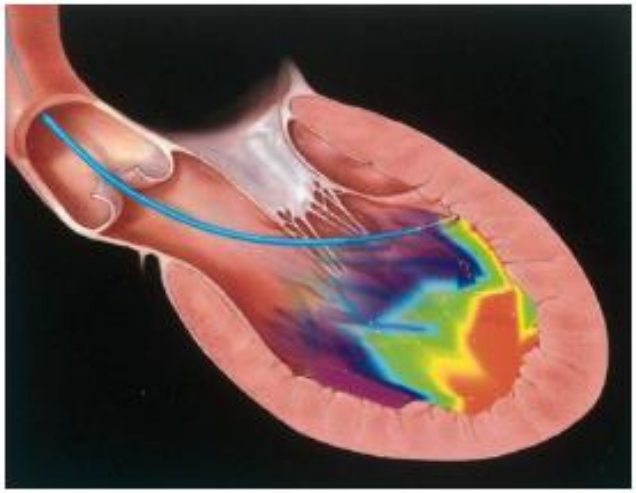
The SCIENCE Project coord J kastrup

- Indication: ischemic heart disease and heart failure
- Methodology: double-blind placebo controlled trial with allogeneic adipose-derived stromal cells (CSCC-ASCs) to improve myocardial function
- N=138
- establish a manufacture facility for centralised production of allogeneic CSCC_ASCs
- Status VHP approved. Recruitment initiated

Stem cell treatment – NOGA XP® method

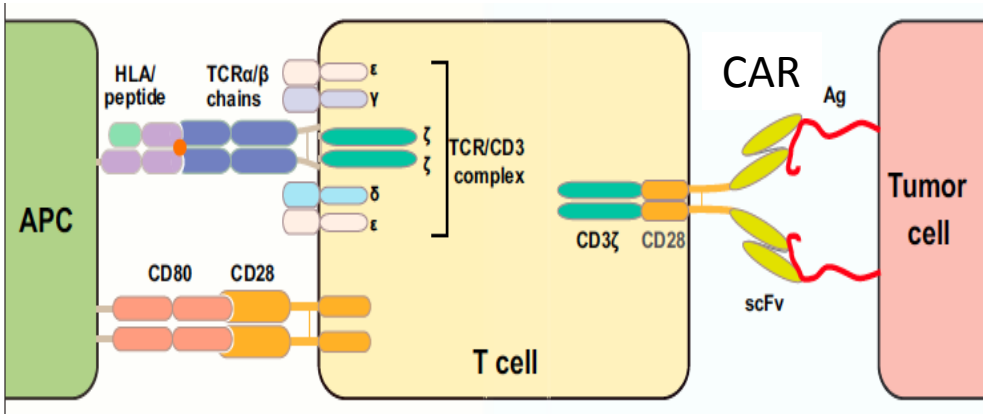


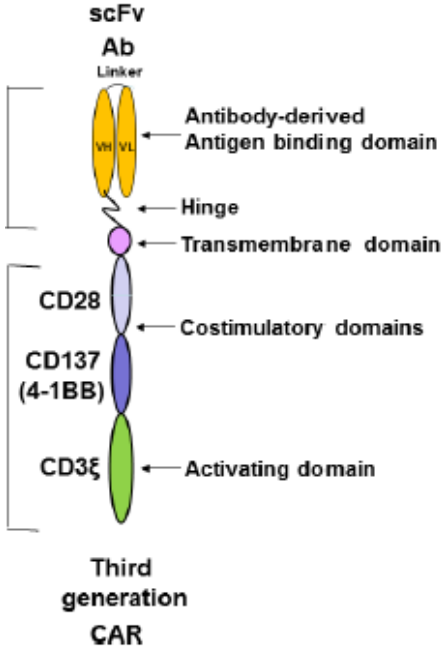


Cell Engineering

T cell engineering with CAR

- Expression of chimeric receptor on T cells
- Tumor recognition through scFv
- Independently from HLA/APC
- Second generation: enhance function through CD28





Brentjens R, Sci Trans Med, 2013

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Clinical results with therapeutic T CAR cells B cell hemopathies

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Publication/Meeting Date	Number/Age of Subjects	Complete Remission Rate
Brentjens, *Sci Transl Med*[17] March 21, 2013	5 (adults)	100%
Grupp, *N Engl J Med*[18] April 18, 2013	2 (children)	100%
Davila, *Sci Transl Med*[19] February 19, 2014	16 adults	88%
Lee, *Lancet*[20] October 13, 2014	21 (children)	67%
Maude, *N Engl J Med*[21] October 16, 2014	30 (25 children, 5 adults)	90%
Park, ASCO-2015 May 30, 2015	33 adults	91%

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iPS & reprogrammation

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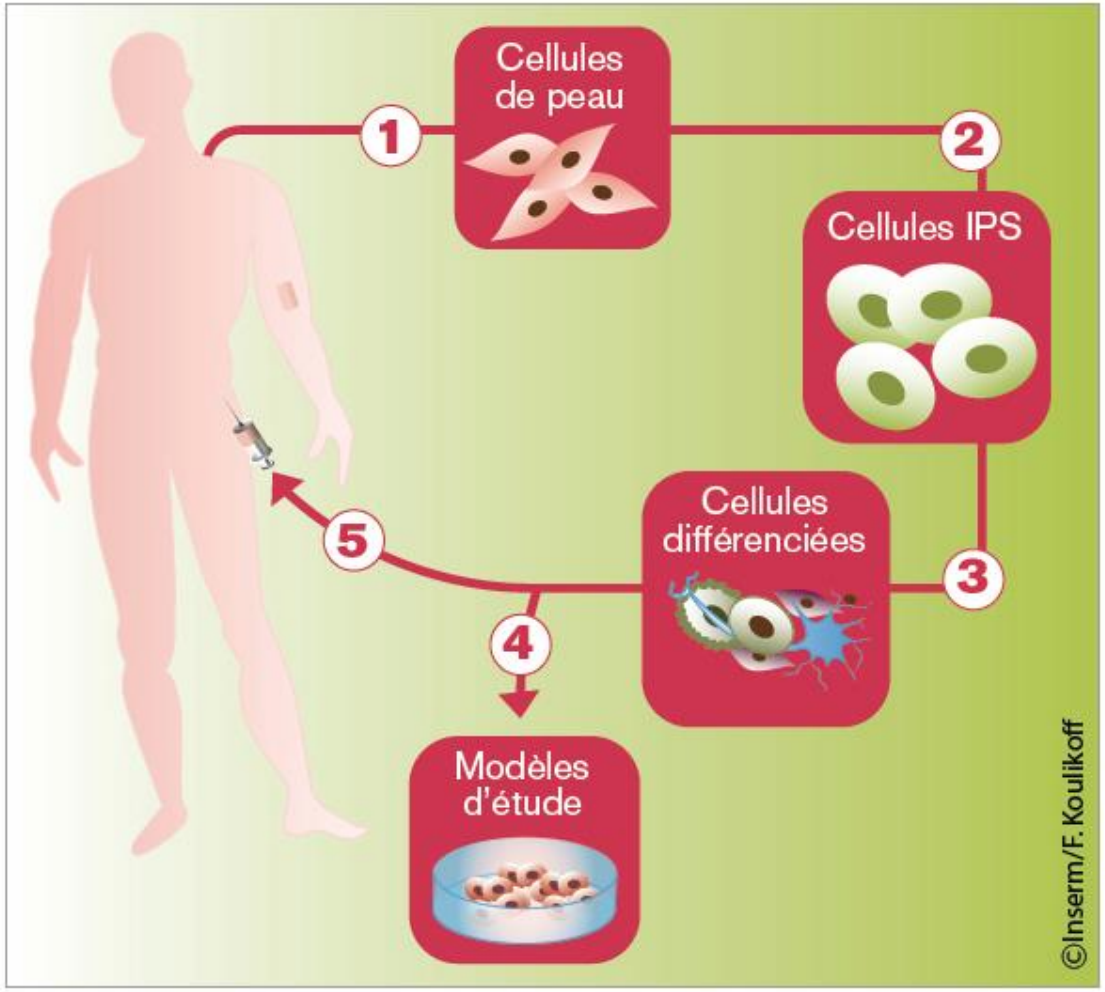


1 – Biopsy derived fibroblasts

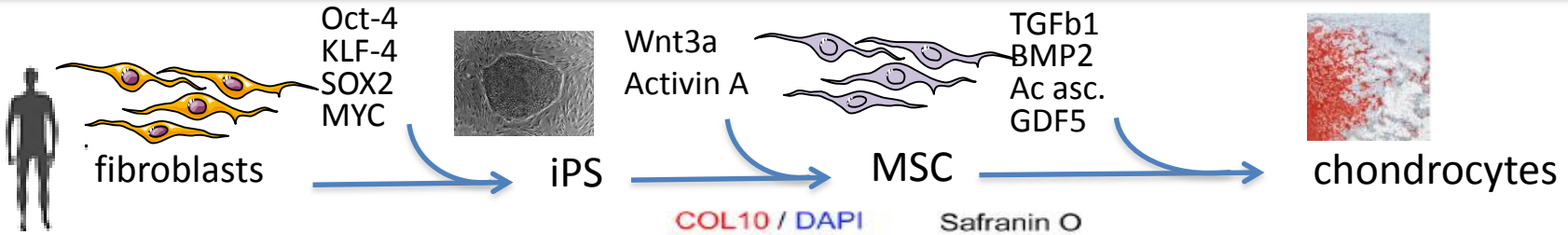
2 – Derivation of iPSC
. reprogrammation
. qualification
. banking

3 – Differentiation

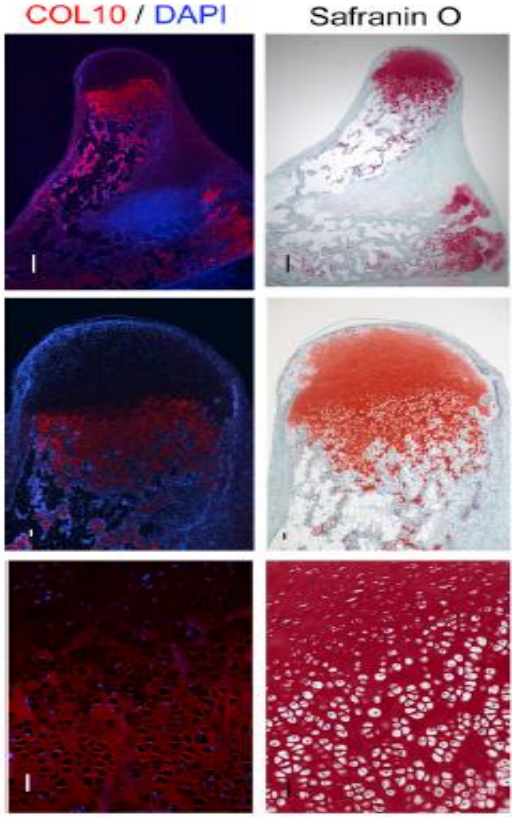
4 – Disease modelling, toxicology, drug screen

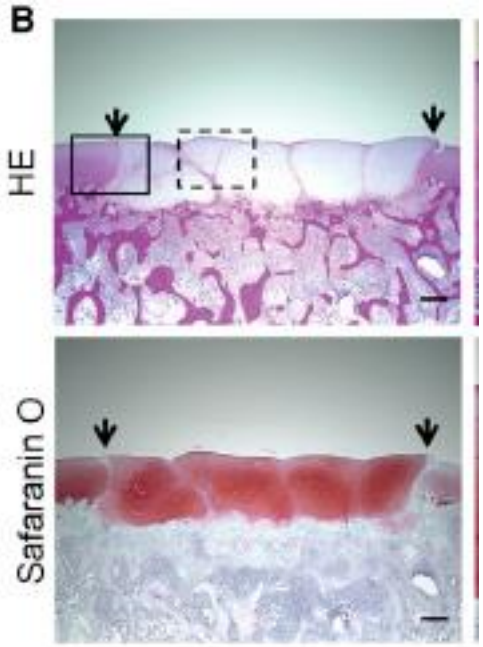
5 – Cell therapy

iPS as a source for cartilage tissue



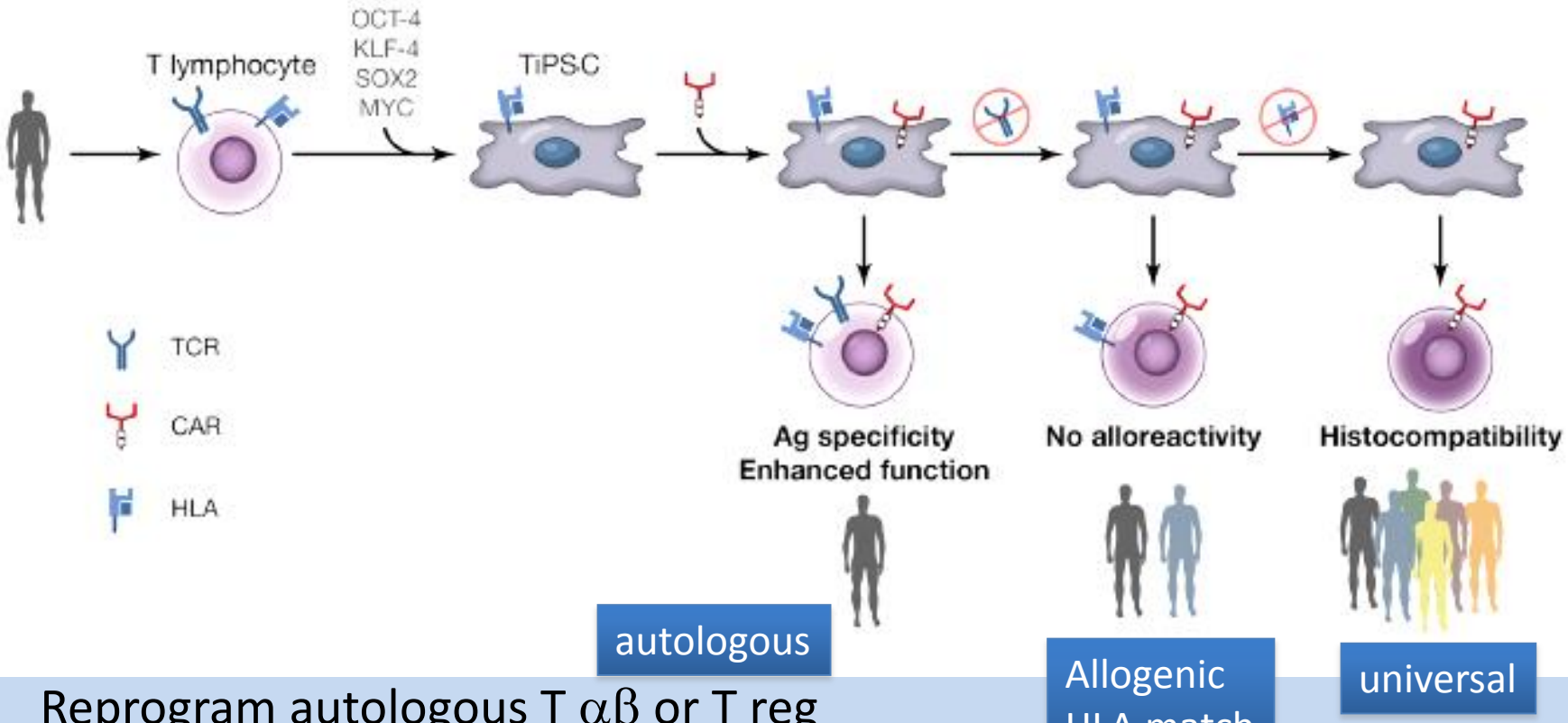
- Reprogram fibroblast
- Step 1: mesodermal progenitor
- Step 2: form pellets in suspension
- Step 3: chondroblasts
- In vivo :hyaline cartilage, integrated to adjacent native cartilage
- No hypertrophy





Akihiro Yamashita, Stem cell report , 2015

Perspective: iPS as a source of therapeutic T cells



- Reprogram autologous T αβ or T reg
- Lentiviral vectors to express CAR or scFV anti col 2
- CRISPR/CAS9 to delete HLA expression or TCR
- Results in CD3+ CD56+ CD4−CD8− T cells with original TCRαβ

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Challenge of ATMP development in EU

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- Concept of cell therapy
- Preclinical : efficiency in 2 models, safety, biodistribution, toxicology…
- ATMP authorization, VHP
- Phase 1 : feasibility, safety
- Phase 2 : randomized study, dose escalation
- Phase 3 : large randomized trial : efficiency
- EMA Approval
- Commercialisation: reimbursement, approval by the payers, pricing
- Public access !

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EU perspectives

ECellFrance NETWORK FOR REGENERATIVE MEDICINE

- Encouraging research & innovation on cell products
- Continue to support phase 1 studies (POC)
- Improving cell technology (iPS, CAR, CRISPR/CAS…)
- Automatisation of cell production (bioreactors) , share cGMP platforms, support for regulatory issues
- Use of allogenic cells “on the shelf”
- need long term randomized controlled trials
- Stem cells are the new biologics!

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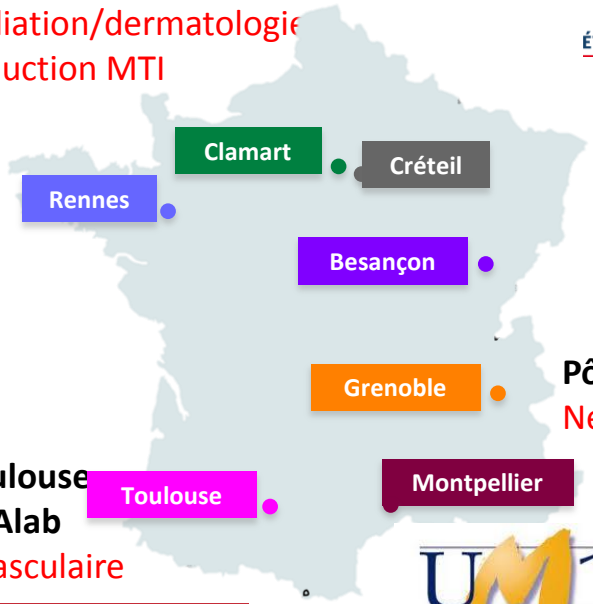
Pôle Clamart (CTSA)
Irradiation/dermatologie
Production MTI



EFS
ÉTABLISSEMENT FRANÇAIS DU SANG

Pôle EFS : 5 centres
Production MTI
Immuno-monitoring

Pôle Grenoble (CHU) CHU GRENOBLE
Neurovasculaire

Pôle Toulouse
STROMAlab
Cardiovasculaire

Université de Toulouse
Université Paul Sabatier TOULOUSE III

UM1 Université Montpellier I

Pôle Montpellier
Clinical coordination
Osteoarticular diseases
autoimmunity
Immuno-monitoring

INVESTISSEMENTS D'AVENIR

Infrastructure biologie santé ECELLFRANCE
Staff: G Robin
Head: C Jorgensen

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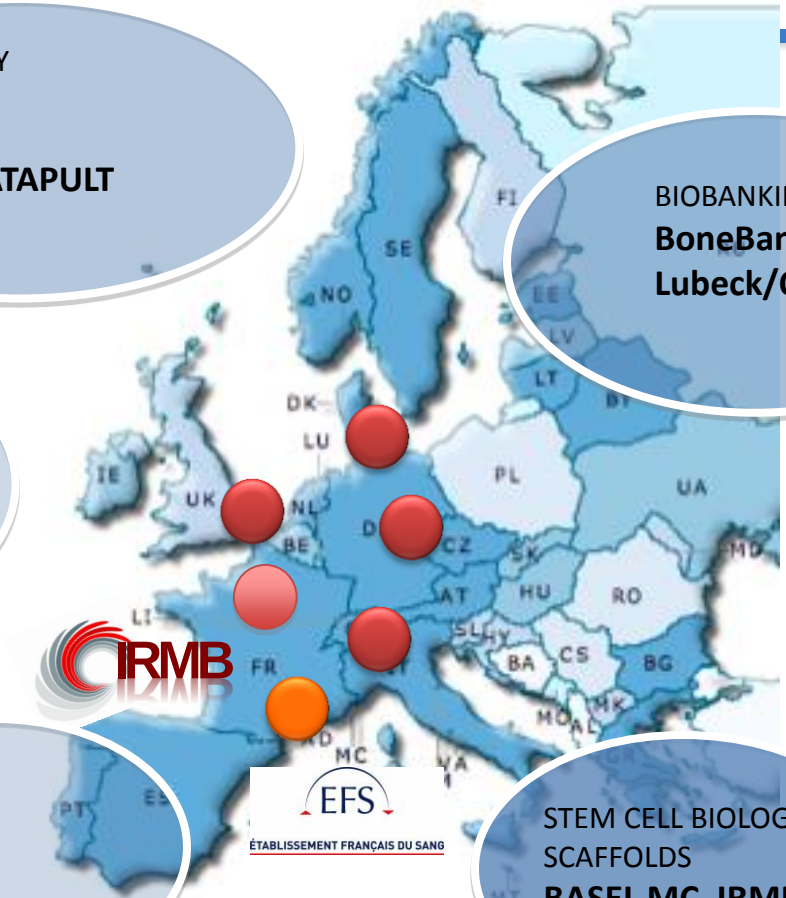
EUROCELL: EU infrastructure

E Cell France NETWORK FOR REGENERATIVE MEDICINE

REGULATORY
SOP
Guidelines
EATRIS, CATAPULT UK

BIOBANKING
BoneBank, BBMRI Lubeck/Odense

CELL PRODUCTION
ECELL, DRK, CATAPULT, EFS



CLINICAL
ECRIN

STEM CELL BIOLOGY, SCAFFOLDS
BASEL MC, IRMB

HORIZON 2020

Inserm

Institut national
de la santé et de la recherche médicale

E Cell France
NETWORK FOR REGENERATIVE MEDICINE

INVESTISSEMENTS D'AVENIR

IRMB
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ROAD
Research on
Osteo Arthritis Diseases

IRMB Inserm, Montpellier

F. Djouad
C. Bony
I. Richard
P. Louis-Plence
D. Noel
ML Vignais
F. Apparailly
JM Lemaitre
J. Pene
P Luz-Crawford
YM Pers
JM Brondello