SCENARI DI SVILUPPO DELLA TERAPIA CELLULARE: FRA SFIDE E OPPORTUNITA'

•**Kymriah** is for pediatric and young adult patients age 25 or younger with B-cell acute lymphoblastic leukemia. It has also been approved for adult patients with certain types of large B-cell non-Hodgkin's lymphoma who have relapsed on not responsed to standard treatments.

•**Yescarta** has been approved for patients with large B-cell non-Hodgkin's lymphoma that has relapsed or does not respond to standard treatments.

TASSI DI SVILUPPO ATTESI PER CELLULE CAR-T

- **IN USA**
- **IN ITALIA**
- **IN SICILIA**

USA

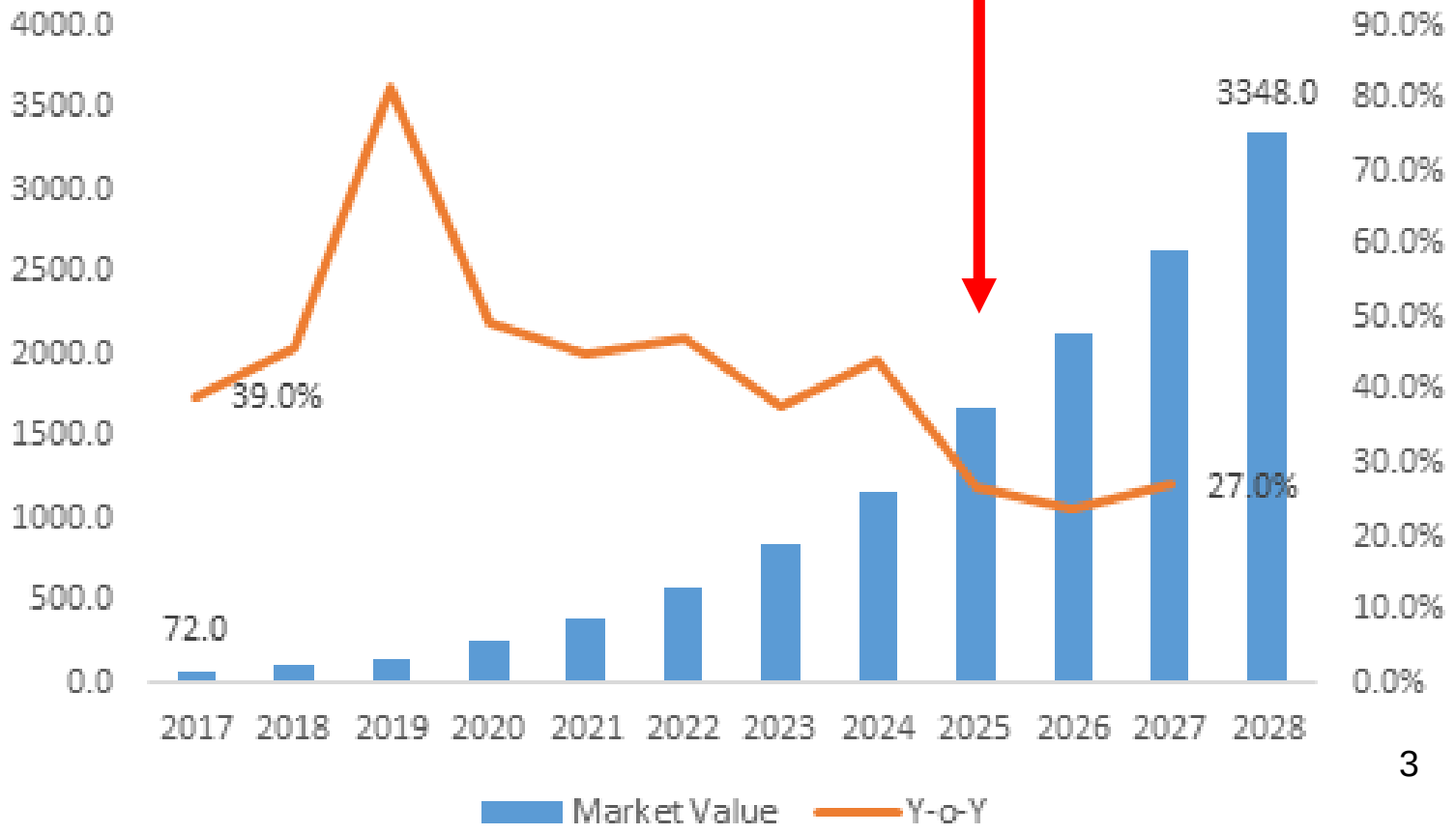
1,5 miliardi $ /anno
=1500 milioni $ anno
3.000 paz

ITALIA
(1/5 abitanti
Rispetto USA)
300 milioni
di euro Anno
600 paz

Sicilia (1/10 di abitanti Rispetto a ITALIA)

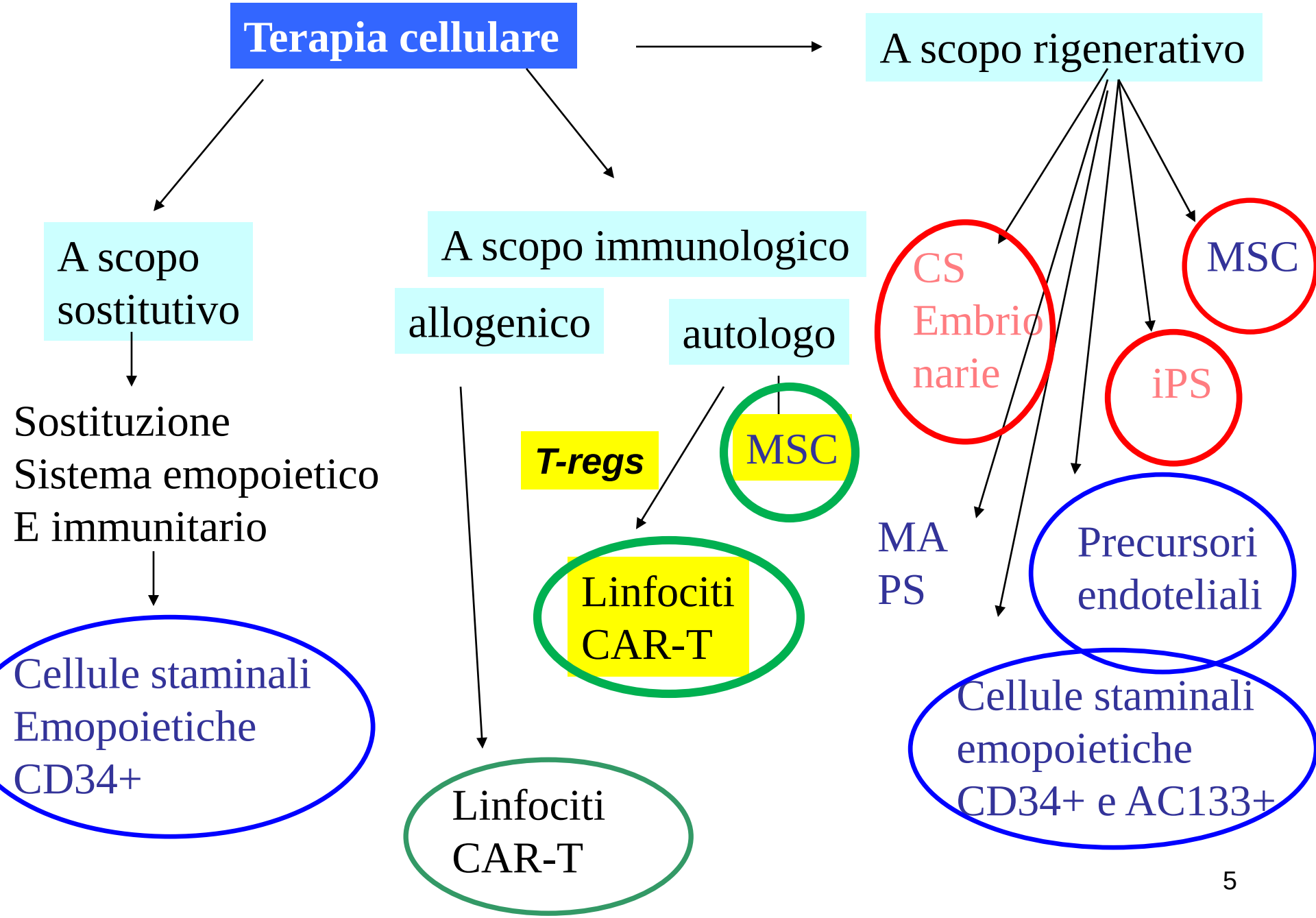
15-30 milioni di euro/anno
60 paz

Milioni di dollari



TERAPIA CELLULARE

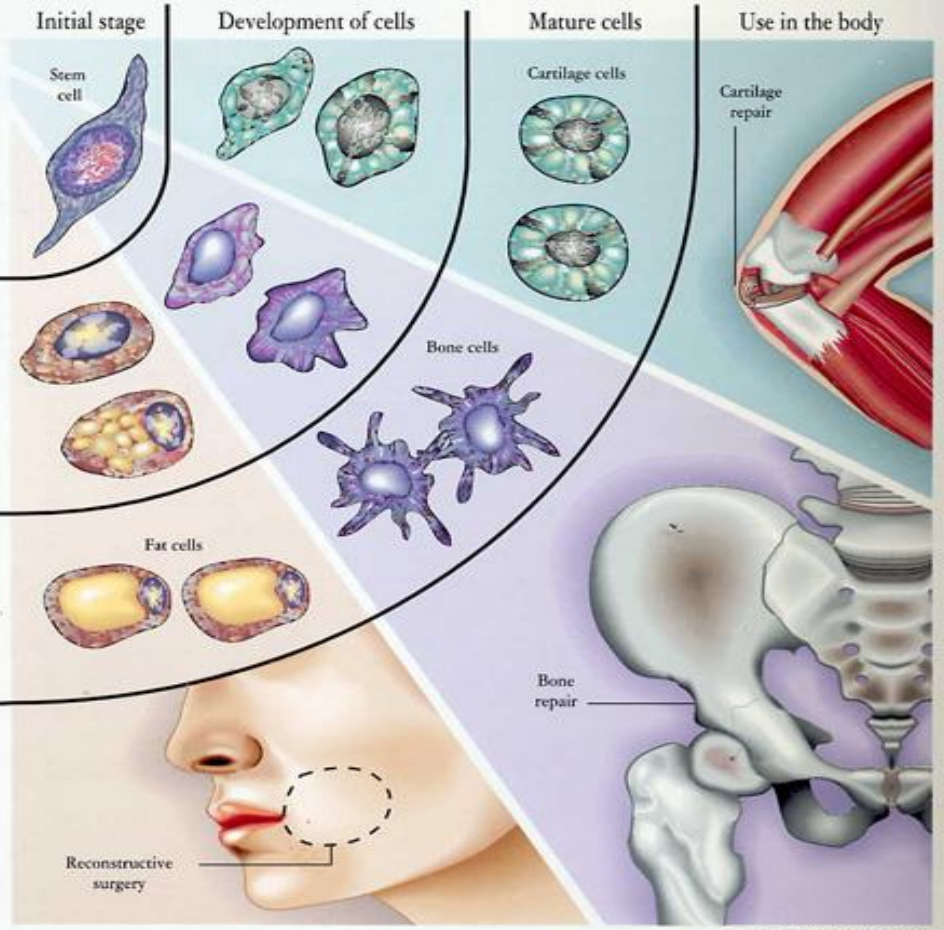
- IMMUNOATTACCO SPECIFICO CELLULE TUMORALI (CAR-T CELLS)
- TRAPIANTO CELLULARE E DI TESSUTI
- RIGENERAZIONE TISSUTALE
- IMMUNOMODULAZIONE IMMUNOSOPPRESSIONE E TOLLERANZA INDOTTA


Terapia cellulare
A scopo rigenerativo
A scopo sostitutivo
A scopo immunologico
allogenico
autologo
Sostituzione
Sistema emopoietico
E immunitario
T-regs
MSC
CS Embrionarie
MSC
iPS
MA
PS
Precursori endoteliali
Linfociti CAR-T
Cellule staminali Emopoietiche CD34+
Linfociti CAR-T
Cellule staminali emopoietiche CD34+ e AC133+

ACCANTO ALLE CELLULE CAR-T ANCHE LE CELLULE MESENCHIMALI SONO UNA FONTE DI TERAPIA

Mesenchymal Stem Cells for Regenerative Medicine

Scientists at Osiris Therapeutics Inc. in Baltimore have begun to manipulate master cells, known as stem cells, to develop medical treatments which would regenerate damaged or diseased bone, cartilage and other tissues. Here's a look at how stem cells can develop into cartilage, fat and bone.



1 In their earliest form, stem cells ...e the potential to ...ome virtually any ...e of cell in a certain "family."

2 By re-creating microenvironments found within the body, Osiris coaxes the cells to differentiate into cells with specific tasks.

3 Once the cell's role is designated, it has data needed to form bonds with similar cells in its environment.

4 Initially, cultured cells might be used for regenerating areas of injured hips and knees, and for reconstructive surgery.

Illustration: Emily Holmes, Baltimore Sun

OSIRIS THERAPEUTICS

Leading the Way In Cell Therapy

Osiris Therapeutics is engaged in the development and commercialization of cellular therapeutic products for the regeneration and functional restoration of damaged or diseased tissues. Osiris has developed proprietary technology to isolate and expand Mesenchymal Stem Cells for their use as cell therapeutic products for the regeneration of tissues damaged through injury, aging or degenerative disease.

TRAPIANTI CELLULARI E TESSUTI

Midollo, Cute, Pancreas

- **Trapianto CSE Autologo, Autologo dopo modifica Genetica (thalassemia)**
- **Trapianto** allogenico.

Terapia cellulare

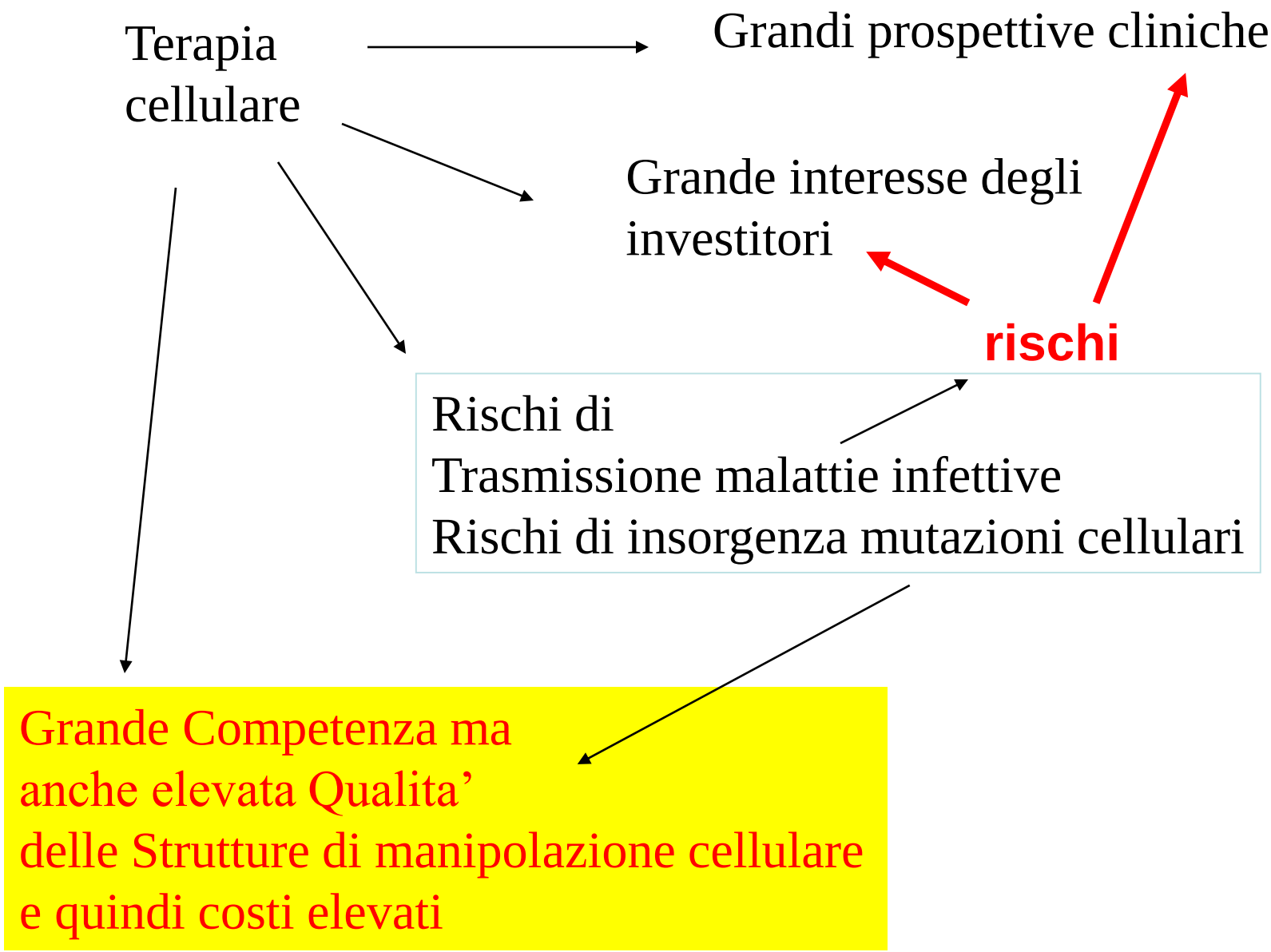
Effetti terapeutici non farmacologici di **RIGENERAZIONE** basati su **fenomeni biologici complessi** ed in buona parte sconosciuti

Ricostruzione in laboratorio Di organo o di tessuto (osso, miocardio, cute, cartilagine)

"**IMMUNOTERAPIA** adottiva Allogenica Anti-neoplastica" (riconoscimento da parte di Linfociti **geneticamente modificati** delle Cellule tumorali e loro attacco) CAR T

Immunoterapia autologa non specifica, LAK e CIK cells

ASPETTI ECONOMICI DEL MERCATO DELLE CSE



ASPETTI REGOLATORI CSE

Controllo e autorizzazione delle proposte

Terapia cellulare

Necessita'
Di rigide regole

EC 17
EC 86
EC 23
EC 83
EC 94

Sorveglianza
Di cio' che accade
"Registrazione"

Certificazione di
Qualita'
ISO –JACIE- FACT
GMP

La terapia cellulare è un settore
In crescita,
ma la cui crescita puo'
Essere assicurata solo dalla
Osservazione di elevati
Standard di qualita'

SCHEMA DELLE TAPPE NECESSARIE ALL'UTILIZZO IN CLINICA DELLE CAR-T

Patient selection

Clinical specialist (disease specific)

--CELLULAR HARVEST

LOCAL JACIE ACCREDITED CELL MANIPULATION LABORATORY

GMP CENTRALIZED LABORATORY FOR CELL MANUFACTORING

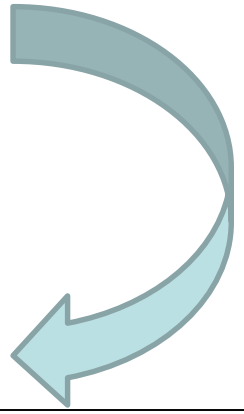
BMT UNIT
LYMPHODEPLETION TREATMENT
INFUSION OF CAR T
POST- INFUSION FOLLOW-UP

CONTROL OF ADVERSE EVENTS (CLS, CRS, Neurological Toxicity)

MULTIDISCIPLINARY STAFF, INPATIENT ICU
(ICU, Neurologist, Infectious disease Specialist) BEDS, NURSES,

COMINCIARE CON IL PASSO GIUSTO E' IMPORTANTE

Provisional authorization to start activity to some center with minimal requirement (Scientific Society advices)
--JACIE accreditation,
-- High transpllant activity
-- ICU available .



but in 3-4 years **higher requirement will be required**

Center selection **will** be based on:

--MINIMUM YEAR CELL THERAPY ACTIVITY
--SUCCESSFUL DEVELOPMENT OF A SPECIFIC QUALITY SYSTEM
-- TAKING PART OF AN ACCREDITED TRANSPLANT PROGRAM
--FULLFILLMENT OF FACT STANDARD ON IMMUNE EFFECTOR CELLS

STANDARDS FOR IMMUNE EFFECTOR CELLS

FOUNDATION FOR THE ACCREDITATION OF CELLULAR THERAPY
AT THE UNIVERSITY OF NEBRASKA MEDICAL CENTER

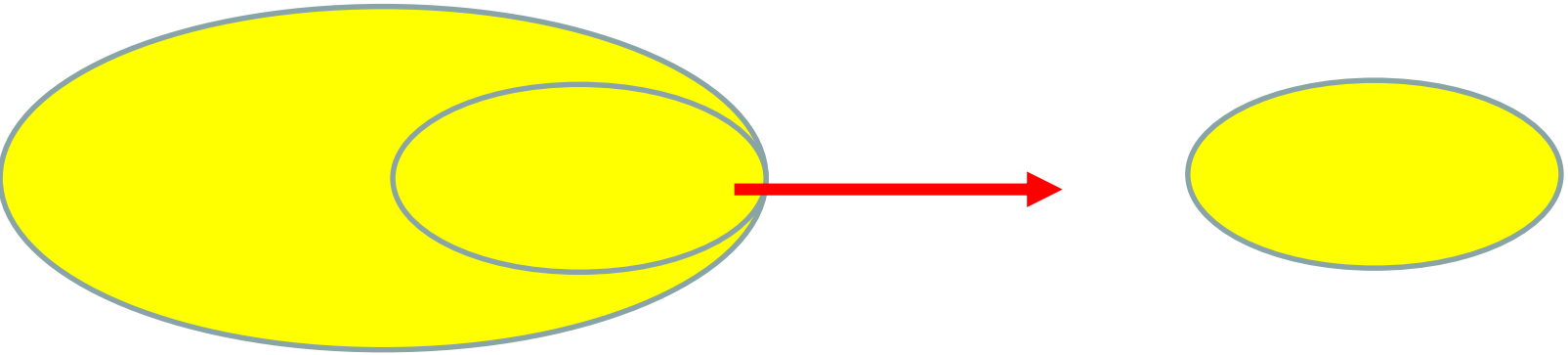
Regole internazionali
Per il funzionamento
Dei centri che vogliano fare
Terapia con CAR T cells
Già esistono=
FACT STANDARD FOR IMMUNE EFFECTOR CELL THERAPY

First Edition
Version 1.1
March 2018

Jacie=

JOINT ACCREDITATION COMMISSION ISCT-EUROPE EBMT

LE MODALITA' ORGANIZZATIVE DEI CENTRI PER LA TERAPIA CON CELLULULE CAR-T SONO GIA' SCRITTE E SONO STATE ESTRAPOLATE DA QUELLE PER I CENTRI DI TRAPIANTO ACCREDITATI SEC JACIE

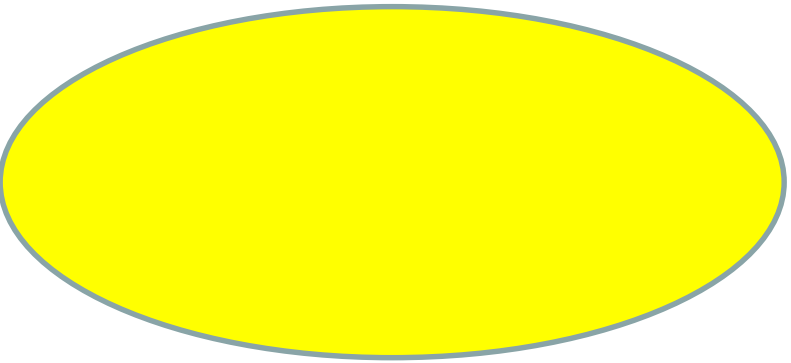


Regole di qualita'
Per i Programma di Trapianto

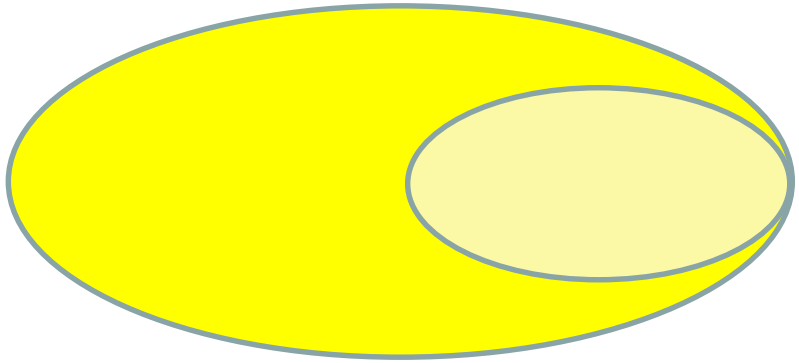
Regole di qualita'
Per Le cellule CAR-T

FIRST STEP IS TO START CAR-T THERAPY WITHIN ACCREDITED BMT PROGRAM

BMT UNITS ALREADY EXISTING AND JACIE ACCREDITED REQUIRE ONLY TO IMPLEMENT MANIPULATION LAB QUALITY

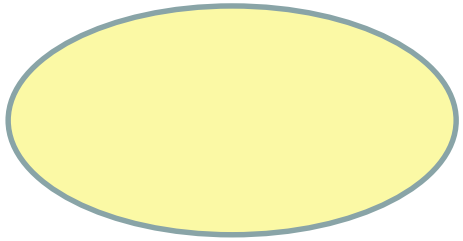


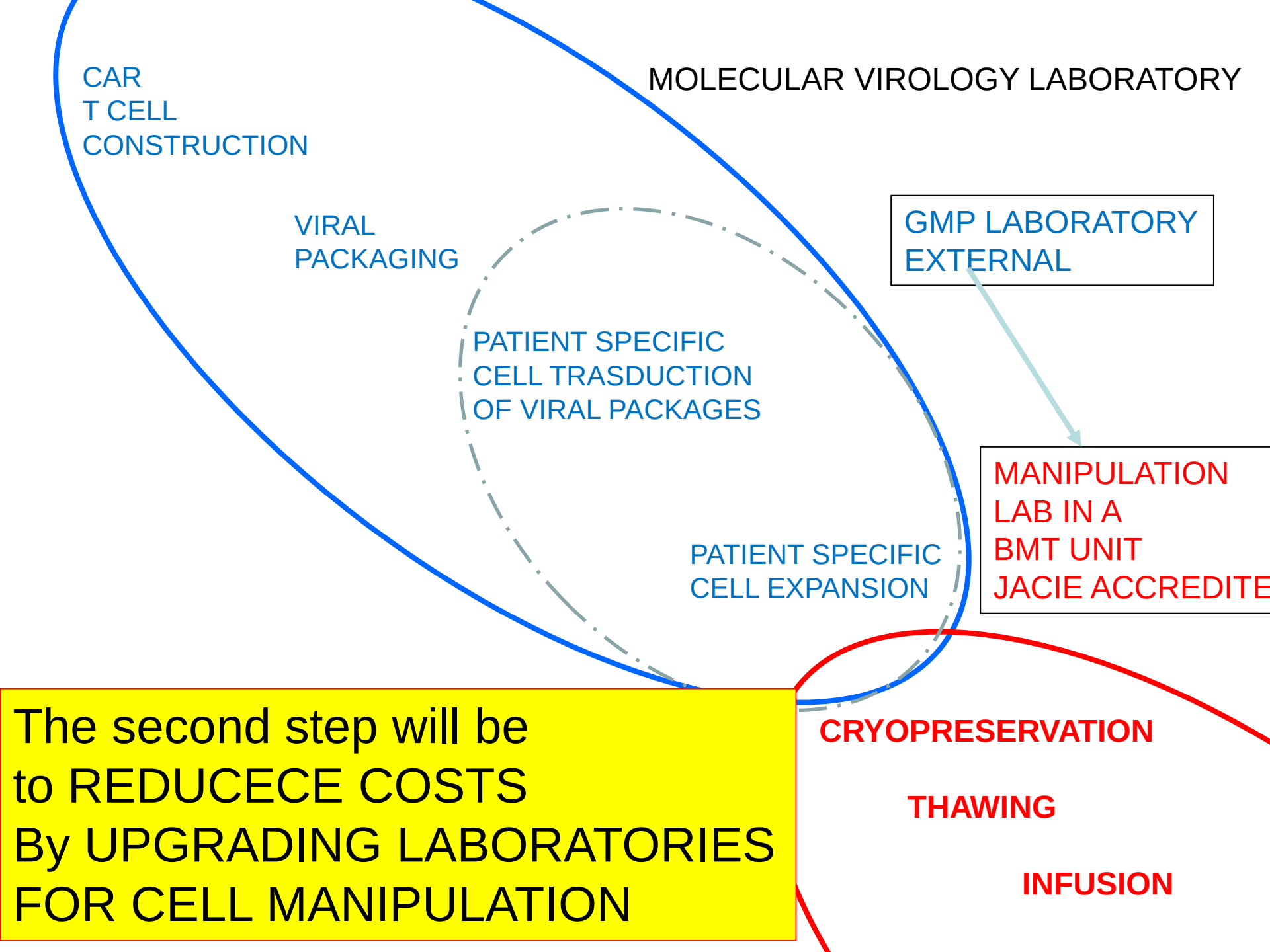
IEC AS PROGRAM WITHIN A BMT CENTER

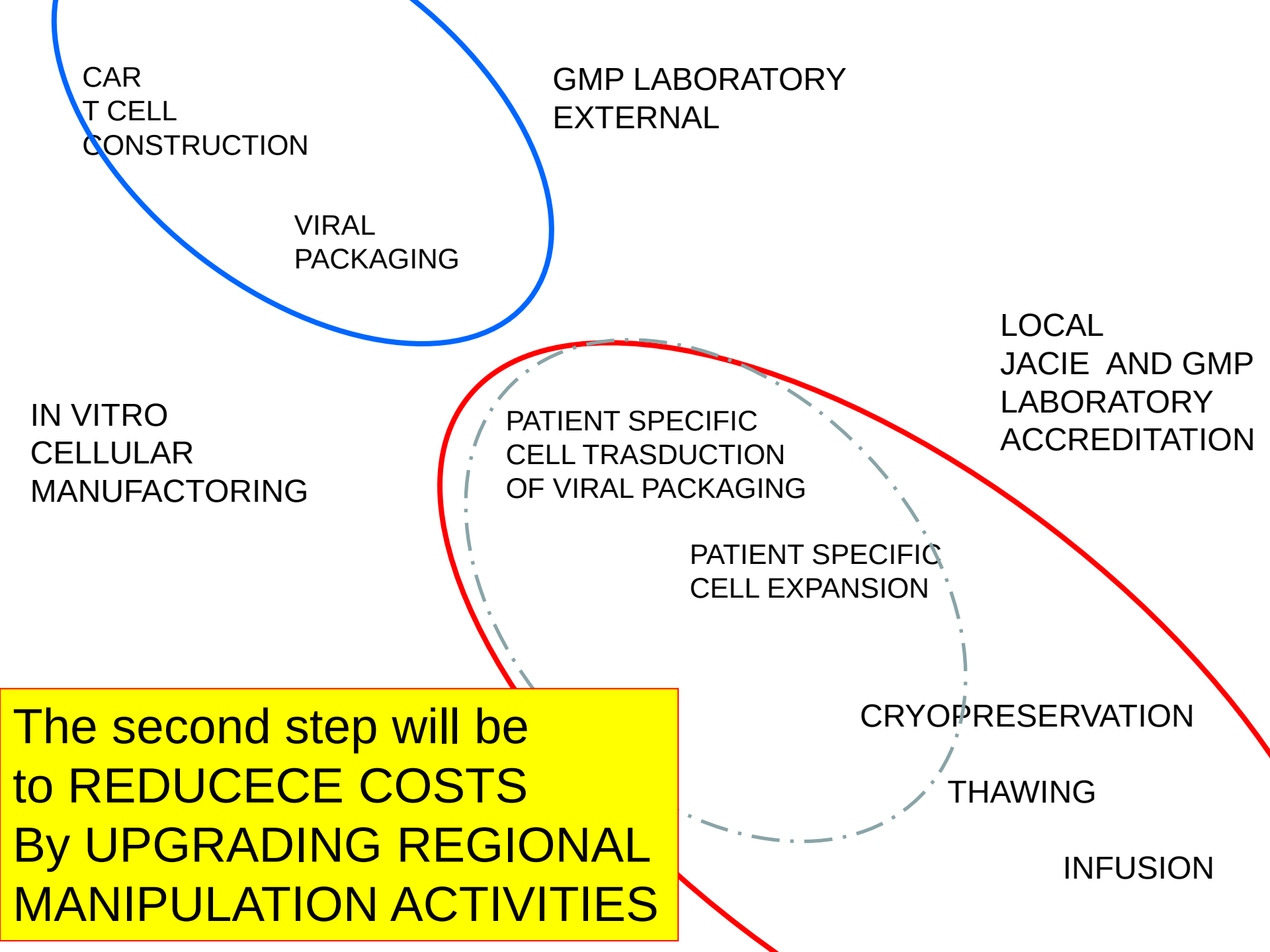


In a Hospital that do not have a BMT UNIT JACIE-accredited
For HSC TRANSPLANTATION =

IEC AS STAND ALONE PROGRAM




CAR
T CELL
CONSTRUCTION
MOLECULAR VIROLOGY LABORATORY
VIRAL
PACKAGING
GMP LABORATORY
EXTERNAL
PATIENT SPECIFIC
CELL TRASDUCTION
OF VIRAL PACKAGES
MANIPULATION
LAB IN A
BMT UNIT
JACIE ACCREDITE
PATIENT SPECIFIC
CELL EXPANSION
CRYOPRESERVATION
THAWING
INFUSION
The second step will be
to REDUCECE COSTS
By UPGRADING LABORATORIES
FOR CELL MANIPULATION


CAR
T CELL
CONSTRUCTION
VIRAL
PACKAGING
GMP LABORATORY
EXTERNAL
LOCAL
JACIE AND GMP
LABORATORY
ACCREDITATION
IN VITRO
CELLULAR
MANUFACTORING
PATIENT SPECIFIC
CELL TRASDUCTION
OF VIRAL PACKAGING
PATIENT SPECIFIC
CELL EXPANSION
CRYOPRESERVATION
THAWING
INFUSION
The second step will be
to REDUCECE COSTS
By UPGRADING REGIONAL
MANIPULATION ACTIVITIES

IL LABORATORIO DI PROCESSING E' CENTRALE PER L'ACCREDITAMENTO DELLE ATTIVITA' CAR-T CELLS

FACT Standards
for **IMMUNE EFFECTOR CELLS**
FIRST EDITION 1.1

D1.3 The Processing Facility shall have a Processing Facility Director, a Processing Facility Medical Director, a Quality Manager, and at least one designated staff member actively performing cellular therapy product processing. This team shall have been in place for at least twelve (12) months preceding initial accreditation.

D2: PROCESSING FACILITY

D2.1 The Processing Facility shall be of adequate space, design, and location for the intended procedures.

D2.1.1 The Processing Facility shall provide adequate lighting, ventilation, and access to sinks to prevent the introduction, transmission, or spread of communicable disease.

D2.1.2 Oxygen sensors shall be appropriately placed and utilized in areas where liquid nitrogen is present.

D2.1.3 The Processing Facility shall be secure to prevent the entrance of unauthorized personnel

B3.1.4 The Clinical Program Director shall be responsible for all elements of the design of the Clinical Program including quality management, the selection and care of patients and donors, and cell collection and processing, whether internal or contracted services.

B3.1.5 The Clinical Program Director shall have oversight of the medical care provided by all members of the Clinical Program.

B3.1.5.1 The Clinical Program Director or designee shall be responsible for verifying the knowledge and skills of members of the Clinical Program once per accreditation cycle, at minimum.

B3.10 QUALITY MANAGER

B3.10.1 There shall be a Clinical Program Quality Manager to establish and maintain systems to review, modify, and approve all policies and procedures intended to monitor compliance with these Standards and/or the performance of the Clinical Program.

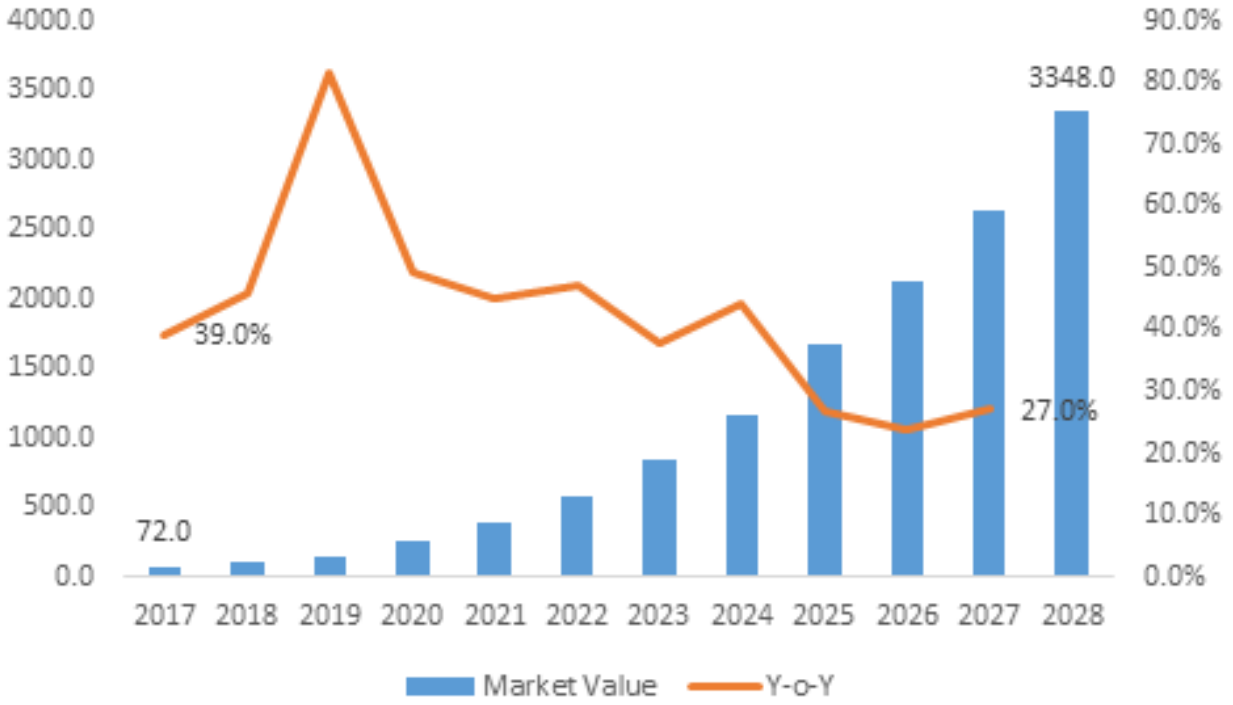
B3.10.2 The Clinical Program Quality Manager should have a reporting structure independent of cellular therapy product manufacturing.

B3.10.3 The Clinical Program Quality Manager shall participate in ten (10) hours of educational activities related to cellular therapy and/or quality management annually at a minimum.

TO ENHANCE EFFICIENTLY THE START OF CAR-T CELL THERAPY

1) WE HAVE TO SUPPORT JACIE ACCREDITATION OF HSC TRANSPLANT PROGRAM ALREADY PRESENT IN THE REGION IMPROVING QUALITY OF THE CLINICAL UNIT AND OF THE COLLECTION UNIT.

2) TO IMPLEMENT CELL MANIPULATION LABORATORY ALREADY PRESENT SO THAT IN A NEAR FUTURE THEY CAN BE UPGRADED AND ABLE TO MEET ALSO GMP ACCREDITATION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70.0%
60.0%
50.0%
40.0%
30.0%
20.0%
10.0%
0.0%
72.0
39.0%
27.0%
3348.0
2017
2018
2019
2020
2021
2022
2023
2024
2025
2026
2027
2028
Market Value
Y-o-Y

RISCHI DELLA TERAPIA GENICA E DELLE TERAPIE CELLULARI

Insertional mutagenesis combined with acquired somatic mutations causes leukemogenesis following gene therapy of SCID-X1 patients
Steven J. Howe

Stem Cells. 2010 Sep;28(9):1568-70.
Human induced pluripotent stem cells develop teratoma more efficiently and faster than human embryonic stem cells regardless the site of injection.
Gutierrez-Aranda I, Ramos-Mejia V, Bueno C, Munoz-Lopez M, Real PJ, Mácia A, Sanchez L, Ligero G, Garcia-Parez JL, Menendez P.

l Transplant. 2011;20(6):883-91. Epub 2010 Nov 5.

Tumorigenic development of induced pluripotent stem cells in ischemic mouse brain.

Yamashita T, Kawai H, Tian F, Ohta Y, Abe K.
Department of Neurology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan.

Abstract

Induced pluripotent stem (iPS) cells may provide cures for various neurological diseases. However, **undifferentiated iPS cells have high tumorigenicity**, and evaluation of the cells fates, especially in pathologic condition model, is needed.

These results suggest that the transcriptional factors might increase expression of MMP-9 and activate VEGFR2, promoting teratoma formation in the ischemic brain. We strongly propose that the safety of iPS cells should be evaluated not only in normal condition, but also in a pathologic, disease model.

Int J Clin Exp Med. 2010 Sep 7;3(4):248-69.

Bone marrow and umbilical cord blood human mesenchymal stem cells: state of the art.

Malgieri A, Kantzari E, Patrizi MP, Gambardella S.

Abstract

Mesenchymal stem cells (MSCs) **are multipotent adult stem cells present in all tissues,** as part of the perivascular population. are an excellent candidate for cell therapy because they are easily accessible, their isolation is straightforward, they can be bio-preserved with minimal loss of potency, and they have shown no adverse reactions to allogeneic versus autologous MSCs transplants.

Therefore, MSCs are being explored to regenerate damaged tissue and Treat

1. inflammation,
2. cardiovascular disease and myo-cardial infarction (MI),
3. brain and spinal cord injury,
4. stroke,
5. diabetes,
6. cartilage and
7. bone injury,
8. Crohn's disease and graft versus host
9. disease (GvHD).

I RISCHI DELLE TERAPIE CELLULARI DIPENDONO DALLE MANIPOLAZIONI EFFETTUATE FUORI DAL CORPO (IN VITRO) E DALLA SEDE DI REITRODUZIONE

Terapia cellulare

Cellule introdotte in tessuti non originari: ove
Assumono una funzione nuova
Non fisiologica
(Es. Cellule midollare introdotte Nel cuore)

RISCHIO

Cellule Reintrodotte Dopo "Manipolazione in vitro"
Per correggerle
Per differenziarle,
Per moltiplicarle
Per selezionarle
Per attivarle

RISCHIO

Cellule introdotte nei tessuti Originari ove riprendono la loro funzione originaria
(trapianti di cellule)
(es. cellule midollari Introdotte nel Midollo) autotrapianto di midollo autologo o da donatore HLA identico
Trapianto di cellule pancreatiche

(a) 'Advanced therapy medicinal product' means any of the following medicinal products for human use:

— a gene therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC,

— a somatic cell therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC,

— a tissue engineered product as defined in point (b).

(c) Cells or tissues shall be considered 'engineered' if they fulfil at least one of the following conditions:

— the cells or tissues have been subject to substantial manipulation, so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved. The manipulations listed in Annex I, in particular, shall not be considered as substantial manipulations,

— the cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor.

The manufacture of advanced therapy medicinal products should be in compliance with the principles of good manufacturing practice, as set out in Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use (3), and adapted, where necessary, to reflect the specific nature of those products. Furthermore, guidelines specific to advanced therapy medicinal products should be drawn up, so as to properly reflect the particular nature of their manufacturing process.