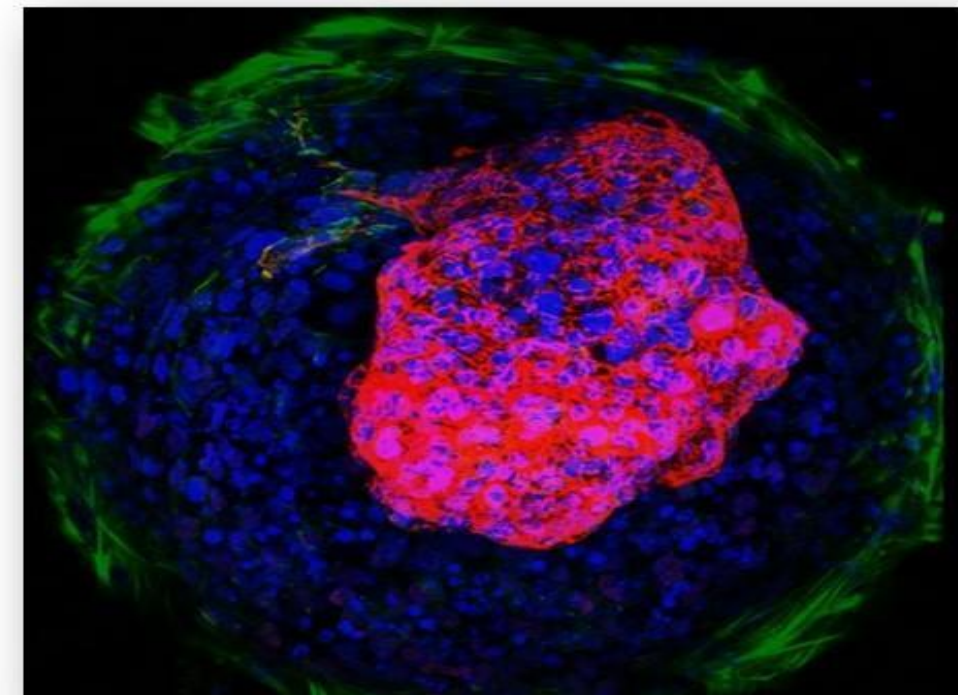
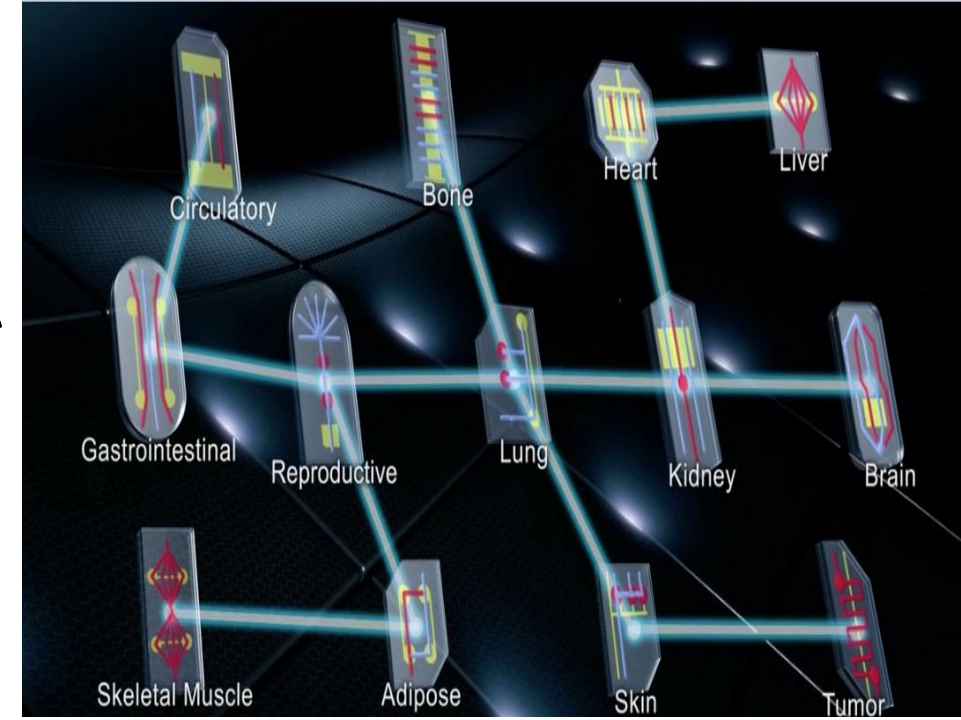
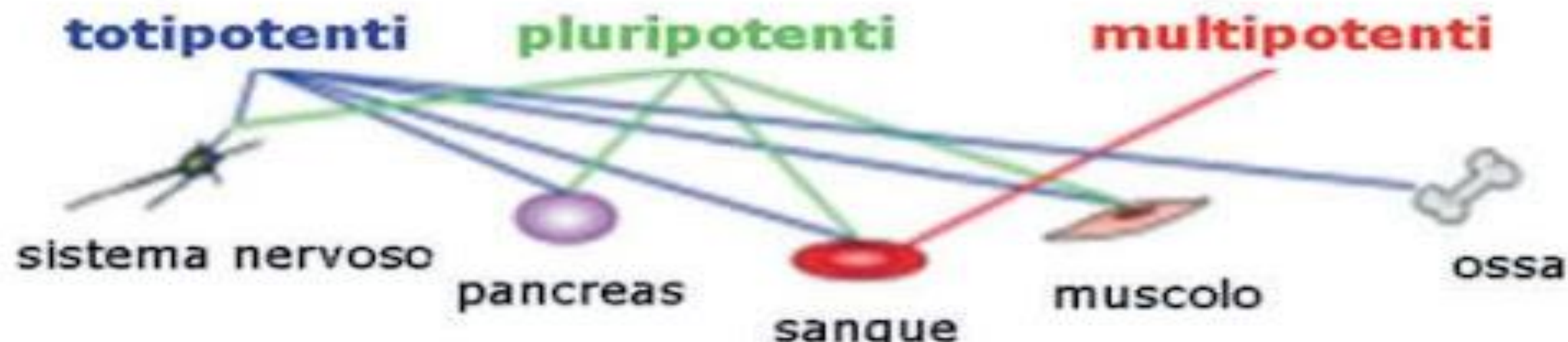
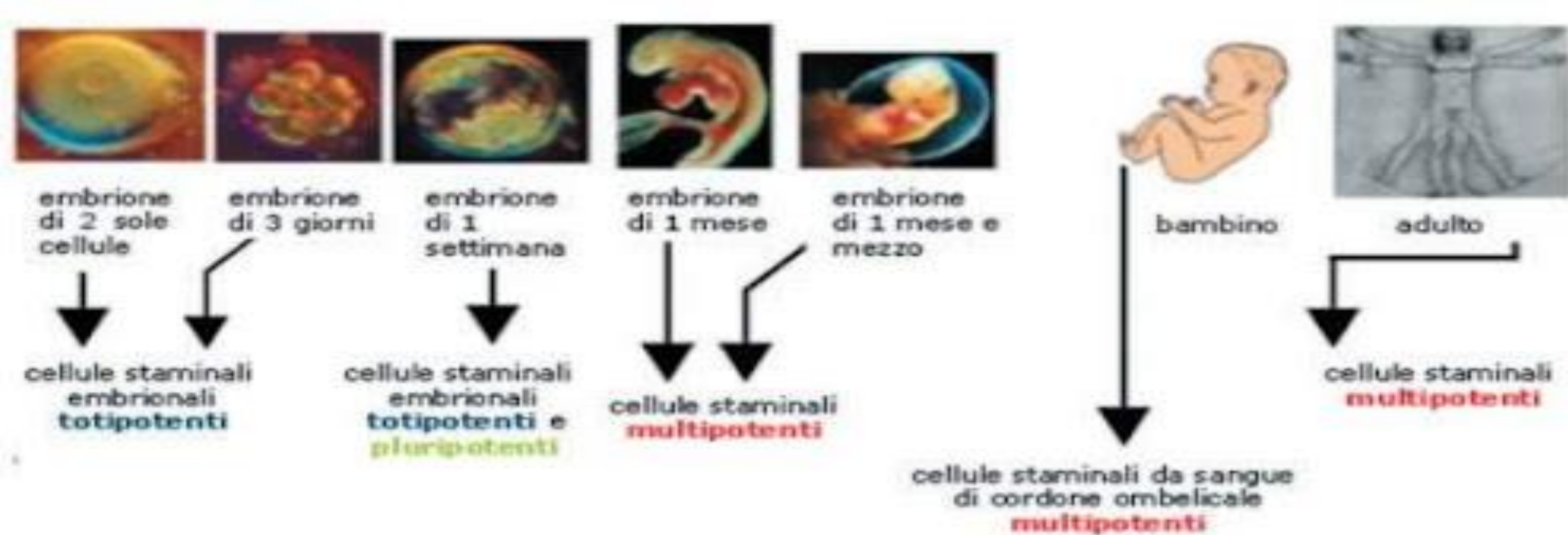


LA TERAPIA CELLULARE IN CARDIOLOGIA RIGENERATIVA COME CONTRIBUTO INNOVATIVO ALLA MEDICINA CLINICA DALLA RICERCA BIOMEDICA BASATA SULLA BIOLOGIA UMANA.

- ***DOTT.SSA GABRIELLA ERRICO***
- ***PEDIATRA***
- ***SOCIA ISDE, SOCIA SIOoC***
- ***VICEPRESIDENTE O.S.A.***
(Oltre la Sperimentazione Animale)

gabriella.errico@libero.it

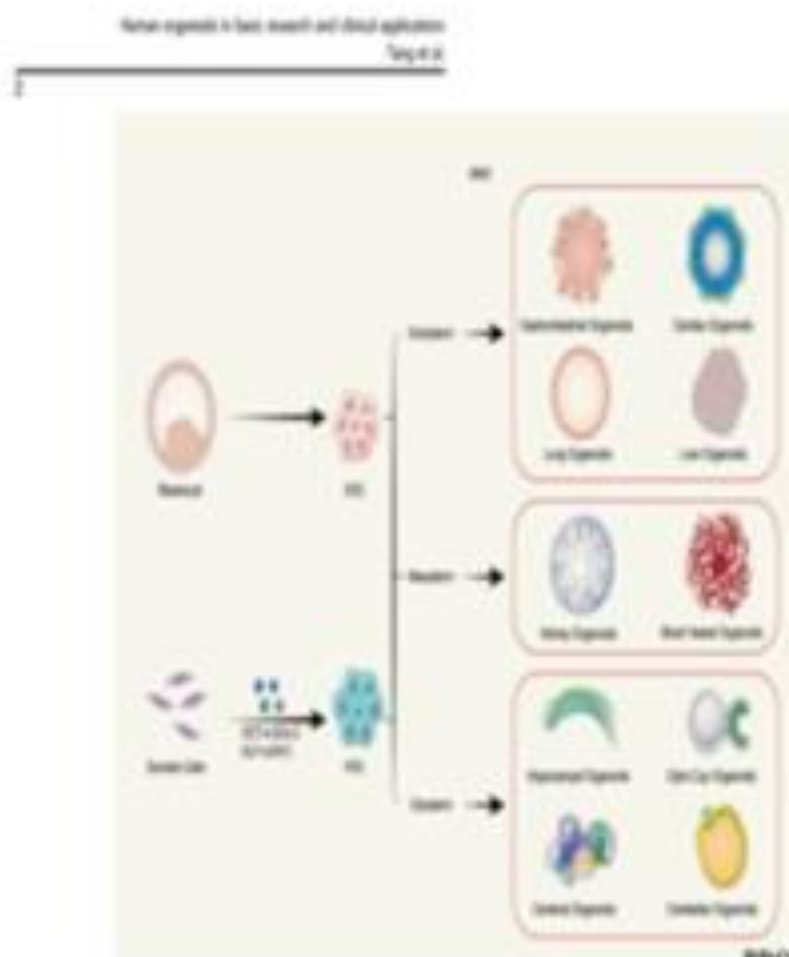




ORGANOIDI UMANI

TECNICA DEGLI ORGANOIDI:

a partire dal 2009, grazie agli studi dei Ricercatori H. Clevers e T. Sato e del premio Nobel giapponese S. Yamanaka, è diventato possibile riprodurre in laboratorio, partendo da cellule staminali adulte pluripotenti indotte (iPS) ed impiegando sistemi di stampa 3D, diversi tessuti cellulari di origine umana che sono in grado di produrre versioni in miniatura (circa 10000 volte più piccole del tessuto originale) di tessuto epatico, polmonare, intestinale, cerebrale, pancreatico, retinico, renale, cardiaco, vescicale, cutaneo e tessuti specifici di orecchio interno, lingua, denti, mammelle, ipofisi, tiroide e prostata. Tali versioni miniaturizzate degli organi originali prendono il nome di organoidi e sono in grado di ricapitolare la funzione e la struttura citoarchitettonica dell'organo originale.



PROF. SHENYA YAMANAKA



PROF. HANS CLEVERS



COMPLESSITA' DELLA RIPROGRAMMAZIONE

- La demetilazione del DNA sblocca l'epigenoma repressivo che mantiene statico il DNA
- Induzione alla pluripotenza tramite il supporto dei fattori genetici di pluripotenza classici (OSKM) oppure miRNA o modificatori epigenetici
- Tale sequenza modifica in modo profondo la struttura della cromatina e dell'epigenoma cellulare con conseguente cambiamento in tutti gli aspetti della biologia cellulare: metabolismo, signalling intercellulare, trasporto intracellulare, proteosintesi
- Criticità: durante tale processo si formano cellule in stato intermedio di maturazione che non completano fino in fondo la riprogrammazione conferendo, almeno potenzialmente, caratteristiche di instabilità genetica, pertanto è essenziale che ci sia un approfondito controllo di qualità degli iPSCs e delle cellule loro derivate per essere certi che il prodotto cellulare ottenuto sia normofunzionale e non contenga mutazioni patologiche o tumorigene.

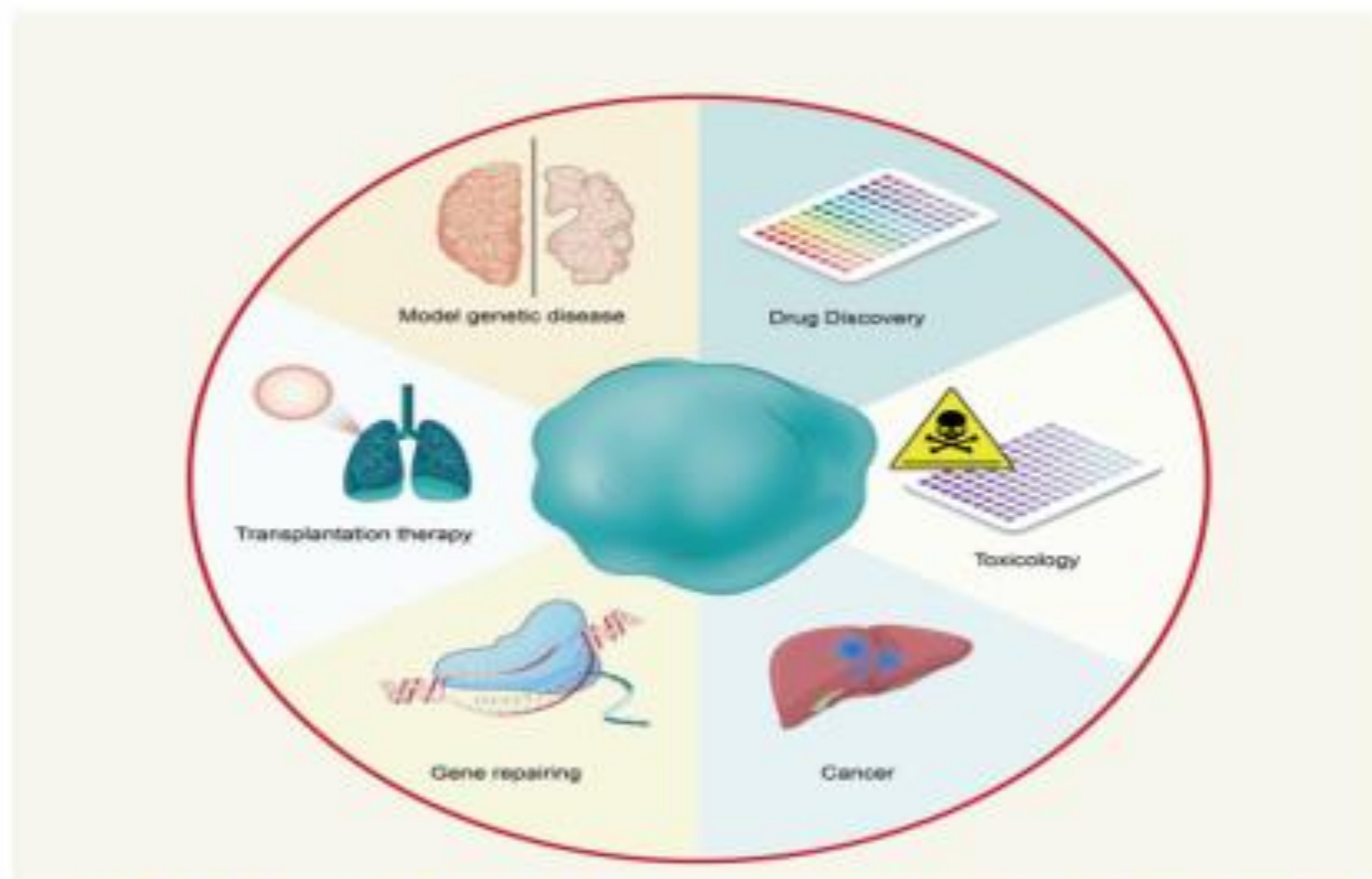
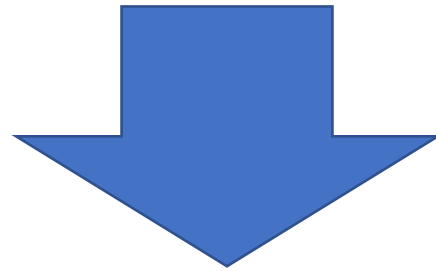


Fig. 5 Various applications of organoid technology. Schematic depiction of various applications of organoid technology based on the studies mentioned above. Organoid technology provides ideal models mimicking human genetic diseases caused by induced mutations. By using gene editing techniques such as CRISPR/Cas9, researchers could investigate some diseases associated with genetic defects. Organoid technology has also provided a potential tool for high-throughput drug discovery and enables accurate toxicity testing and preclinical studies. Recent advances in cancer research within organoids are opening the way for promising organoid transplantation therapy in the future

Applicazioni dei prodotti cellulari derivati da h iPSCs

- **Approccio innovativo per riparare o sostituire un tessuto danneggiato o per montare una risposta immune volta a contrastare una patologia (es recettore chimerico CAR-T per LLA e Linfoma B)**
- **Xenotrapianti con cellule specializzate derivate da hiPSC in grado di mitigare disfunzioni tissutali e recuperare l'omeostasi funzionale dell'ospite(isole pancreatiche da hiPSC secernenti insulina in Topi e Macachi diabetici ;2022)**
- **Recupero della mielinizzazione con dimostrazione che la tecnologia hiPSC può validamente vicariare l'ottenimento di tipologie cellulari di difficile accesso quanto a colture primarie**



31 TRIAL CLINICI ATTUALI

Table 1. Selected interventional clinical trials of iPSC-based cell therapy

Organ	Indication	Cell Product	Phase	Study Type	Primary Outcome	Location	Trial ID
Brain	Parkinson's disease	Allogeneic iPSC-derived dopaminergic progenitor cells	Phase I/II	Single-arm, open-label	Safety & graft expansion	Japan	JPRN-jRCT2090220384
		Allogeneic iPSC-derived dopaminergic progenitor cells	Phase III	Single-arm, open-label	Non-rejection rate	Japan	JPRN-jRCT2091220385
		Autologous iPSC-derived dopaminergic progenitor cells	N/S	Crossover, non-randomized, single-blind	Safety	China	NCT06145711
	Chronic ischemic stroke	Allogeneic iPSC-derived neural progenitor cells	Phase I	Single-arm, open-label	Safety	China	NCT06299033
	Acute ischemic stroke	Allogeneic iPSC-derived endothelial progenitor cells	Phase I	Parallel, randomized, double-blind	Safety	China	NCT05993884
Spinal cord	Spinal cord injury	Allogeneic iPSC-derived neural progenitor cells	Phase I/II	Single-arm, open-label	Safety	Japan	JPRN-jRCTa031190228
Eyes	Age-related macular degeneration	Allogeneic iPSC-derived RPE cells	N/S	Single-arm, open-label	Safety	Japan	JPRN-UMIN000026003
		Autologous iPSC-derived RPE cell sheet	N/S	Parallel, non-randomized, open-label	Safety	Japan	JPRN-UMIN000011929
		Autologous iPSC-derived RPE	Phase I/II	Single-arm, open-label	Safety & visual acuity change	United States	NCT04339764
		Autologous iPSC-derived RPE	Phase I	Single-arm, open-label	Safety	China	NCT05445063
	Retinitis pigmentosa	Allogeneic iPSC-derived retinal sheets	Phase I	Single-arm, open-label	Safety & increase in retinal thickness	Japan	JPRN-jRCTa050200027
	RPE-related impairment	Allogeneic iPSC-derived RPE cells	Phase I/II	Single-arm, open-label	Reduction of the window defect area	Japan	JPRN-jRCTa050200122
Bone marrow	Thrombocytopenia	Autologous iPSC-derived platelets	Phase I	Single arm, open-label	Safety	Japan	JPRN-jRCTa050190117
	Acute myeloid leukemia	Allogeneic iPSC-derived NK cells	Phase I	Sequential, non-randomized, open-label	Safety	United States	NCT04714372
Heart	Congenital heart disease	Autologous iPSC-derived cardiac lineage cells	Phase I	Parallel, non-randomized, open-label	Short term safety & feasibility	United States	NCT05647213
	Ischemic cardiomyopathy	Allogeneic iPSC-derived cardiomyocyte sheet	Phase I	Single-arm, open-label	Safety & improvement in LVEF	Japan	NCT04696328
	Heart failure	Allogeneic iPSC-derived engineered human myocardium	Phase I/II	Single-arm, open-label	Target heart wall thickness & heart wall thickening fraction	Germany	NCT04396899
		Allogeneic iPSC-derived cardiomyocyte spheroids	Phase I/II	Sequential, non-randomized, open-label	Safety	Japan	NCT04945018
		Allogeneic iPSC-derived cardiomyocytes	Phase I/II	Parallel, randomized, double-blind	Safety	China	NCT03763136
		Allogeneic iPSC-derived cardiomyocytes	Phase I	Parallel, randomized, double-blind	Safety	China	NCT04982081
Lungs	Respiratory failure	Allogeneic iPSC-derived mesenchymal stem cells	Phase I	Parallel, randomized, open-label	Assessment of respiratory dysfunction	Australia	NCT04537351
	COVID-19 in patients with hypoxia	Allogeneic iPSC-derived NK cells	Phase I	Sequential, non-randomized, open-label	Safety	United States	NCT04363346
Ovaries	Ovarian cancer	Allogeneic iPSC-derived NK cells	Phase I	Sequential, non-randomized, open-label	Safety	United States	NCT04630769

Table 1. continued

Organ	Indication	Cell Product	Phase	Study Type	Primary Outcome	Location	Trial ID
Systemic	Systemic lupus erythematosus	Allogeneic iPSC-derived CAR NK cells	Phase I	Sequential, non-randomized, open-label	Safety & recommended phase II regimen	United States	NCT06255028
	B cell cancers	Allogeneic iPSC-derived CAR NK cells	Phase I	Sequential, non-randomized, open-label	Safety & recommended phase II regimen	United States	NCT05336409
	Advanced solid tumors	Allogeneic iPSC-derived CAR T cells	Phase I	Parallel, non-randomized, open-label	Safety	United States	NCT06241456
	Advanced solid tumors	Allogeneic iPSC-derived NK cells	Phase I	Parallel, non-randomized, open-label	Safety	United States	NCT03841110
	Steroid-resistant acute GvHD	Allogeneic iPSC-derived mesenchymal stem cells	Phase I	Sequential, non-randomized, open-label	Safety	Australia, United Kingdom	NCT02923375
	High-risk acute GvHD	Allogeneic iPSC-derived mesenchymal stem cells	Phase II	Parallel, randomized, quadruple-blind	Overall response rate	United States, Australia	NCT05643638

CAR chimeric antigen receptor, COVID-19 coronavirus disease 2019, GvHD graft-versus-host disease, HIV human immunodeficiency virus, iPSCs induced pluripotent stem cells, LVEF left ventricular ejection fraction, N/S not specified, NK natural killer, RPE retinal pigment epithelium

Clinical Problem: ischemic heart disease

Valeria Chiono

THE URGENT NEED

TERAPIE POSSIBILI

- FARMACOLOGICA
- CARDIOLOGIA INTERVENTISTICA
- CARDIOCHIRURGICA
- **TERAPIA CELLULARE!**



1 heart attack every
40 seconds



Someone dies of a
stroke every 4 minutes

HEART DISEASE 1 KILLER

disorders of the heart and blood vessels,
and **stroke**.



>75%

of CVD deaths take place in low-
and middle-income countries

➤ Myocardial infarction (MI) causes **85% of all CVDs** deaths worldwide.

Courtesy from Prof. ssa V. Chiono, Bioingegneria Politecnico Torino
1°Congresso Nazionale O.S.A. 2025

Transplantation of Human Embryonic Stem Cell-derived Progenitors in Severe Heart Failure [J Am Coll Cardiol 2018;71:429–38) © 2018 by the American College of Cardiology Foundation

ABSTRACT

BACKGROUND In addition to scalability, human embryonic stem cells (hESCs) have the unique advantage of allowing their directed differentiation toward lineage-specific cells.

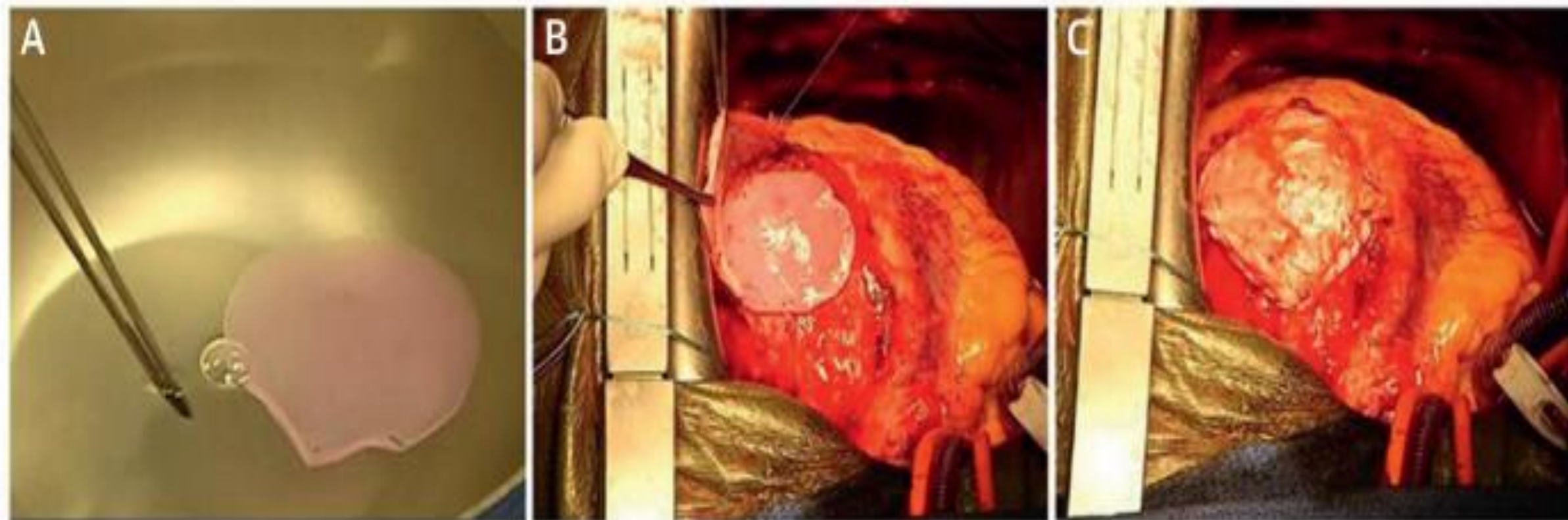
OBJECTIVES This study tested the feasibility of leveraging the properties of hESCs to generate clinical-grade cardiovascular progenitor cells and assessed their safety in patients with severe ischemic left ventricular dysfunction.

METHODS Six patients (median age 66.5 years [interquartile range (IQR): 60.5 to 74.7 years]; median left ventricular ejection fraction 26% [IQR: 22% to 32%]) received a median dose of 8.2 million (IQR: 5 to 10 million) hESC-derived cardiovascular progenitors embedded in a fibrin patch that was epicardially delivered during a coronary artery bypass procedure. The primary endpoint was safety at 1 year and focused on: 1) cardiac or off-target tumor, assessed by imaging (computed tomography and fluorine-18 fluorodeoxyglucose positron emission tomography scans); 2) arrhythmias, detected by serial interrogations of the cardioverter-defibrillators implanted in all patients; and 3) alloimmunization, assessed by the presence of donor-specific antibodies. Patients were followed up for a median of 18 months.

RESULTS The protocol generated a highly purified (median 97.5% [IQR: 95.5% to 98.7%]) population of cardiovascular progenitors. One patient died early post-operatively from treatment-unrelated comorbidities. All others had uneventful recoveries. No tumor was detected during follow-up, and none of the patients presented with arrhythmias. Three patients developed clinically silent alloimmunization. All patients were symptomatically improved with an increased systolic motion of the cell-treated segments. One patient died of heart failure after 22 months.

CONCLUSIONS This trial demonstrates the technical feasibility of producing clinical-grade hESC-derived cardiovascular progenitors and supports their short- and medium-term safety, thereby setting the grounds for adequately powered efficacy studies. (Transplantation of Human Embryonic Stem Cell-derived Progenitors in Severe Heart Failure [ESCORT];

FIGURE 1 Intraoperative Views of Implantation of the Cardiovascular Progenitor-Loaded Fibrin Patch (the "Kangaroo" Procedure)



(A) The cell-loaded fibrin patch during a final wash in a physiological serum-filled container, immediately before its implantation onto the infarcted area. **(B)** The fibrin patch delivered onto the epicardium of the infarct area and its immediate surroundings. **(C)** The autologous pericardial flap, sutured around the infarct area and folded over the fibrin patch, thereby sandwiching it between the pericardial sheet and the underlying epicardium to provide cells with pericardium-associated supportive cells and growth factors.

VESCICOLE EXTRACELLULARI E SECRETOMA

- Il termine vescicole extracellulari (EV) è il nome generico dato alle particelle rilasciate naturalmente dalle cellule, caratterizzate da un doppio strato lipidico e incapaci di replicarsi in quanto prive di un nucleo funzionale. La composizione biochimica delle EV è costituita principalmente da lipidi, proteine e acidi nucleici ed è denominata **SECRETOMA**.
- Giocano un ruolo fondamentale nella comunicazione intercellulare e sono coinvolte in importanti processi biologici: rigenerazione tissutale e cellulare, risposta immune, angiogenesi, apoptosi, modulazione infiammatoria e rilascio di molecole terapeutiche.
- Sono già state impiegate in trial clinici riguardanti malattie oncologiche, respiratorie e diabete, ulteriori indicazioni al loro impiego riguardano l'area cardiovascolare in modo specifico.

First-in-man use of a cardiovascular cell-derived secretome in heart failure. Case report *www.thelancet.com Vol 103 May, 2024*

Summary

Background There is increased evidence that the effects of stem cells can mostly be duplicated by administration of their secretome which might streamline the translation towards the clinics.

Methods The 12-patient SECRET-HF phase 1 trial has thus been designed to determine the feasibility and safety of repeated intravenous injections of the extracellular vesicle (EV)-enriched secretome of cardiovascular progenitor cells differentiated from pluripotent stem cells in severely symptomatic patients with drug-refractory left ventricular (LV) dysfunction secondary to non-ischemic dilated cardiomyopathy. Here we report the case of the first treated patient (baseline NYHA class III; LV Ejection Fraction:25%) in whom a dose of 20×10^9 particles/kg was intravenously infused three times three weeks apart.

Findings In addition to demonstrating the feasibility of producing a cardiac cell secretome compliant with Good Manufacturing Practice standards, this case documents the excellent tolerance of its repeated delivery, without any adverse events during or after infusions. Six months after the procedure, the patient is in NYHA Class II with improved echo parameters, a reduced daily need for diuretics (from 240 mg to 160 mg), no firing from the previously implanted automatic internal defibrillator and no alloimmunization against the drug product, thereby supporting its lack of immunogenicity.

Interpretation The rationale underlying the intravenous route is that the infused EV-enriched secretome may act by rewiring endogenous immune cells, both circulating and in peripheral organs, to take on a reparative phenotype. These EV-modified immune cells could then traffic to the heart to effect tissue repair, including mitigation of inflammation which is a hallmark of cardiac failure.

CONSIDERAZIONI BASATE SUI RISULTATI OTTENUTI

- Dopo la valutazione dell'efficacia clinica a breve termine in ambito di terapia cellulare saranno necessari anche follow-up a medio/lungo termine per valutare con maggior precisione il rischio oncologico eventualmente collegato a tale trattamento.
- E' fondamentale proseguire nella creazione e diffusione di biobanche di iPSCs (specie HLA omologhe).
- Qualora fosse confermata la fondatezza dell'azione terapeutica del «secretoma» del prodotto cellulare derivato da iPSCs si aprirebbe la strada per nuove terapie cell-based ma a-cellulari, con significativo miglioramento gestionale in termini di costi di produzione, controllo di qualità, disponibilità e somministrazione.

CONCLUSIONI

- **Allo stato attuale la terapia cellulare derivata da iPSCs, in paragone con la classica terapia farmacologica, si è rivelata più complessa e sfidante in termini di sicurezza ed organizzazione produttiva.**
- **L'esito dei recentissimi trials già avviati nei pazienti indica l'efficacia clinica di tale trattamento innovativo.**
- **Anche se gli attuali risultati preliminari vanno implementati tramite un campione più ampio e un follow-up più esteso sono, comunque, sicuramente incoraggianti.**