GRAND ROUNDS CLINICI DEL MERCOLEDÌ
con il Policlinico San Matteo

Sistema Socio Sanitario
Regione Lombardia

Fondazione IRCCS Policlinico San Matteo

ATS Pavia

Aula Magna "C. Golgi"
& WEBINAR

22 Marzo 2023

Patrizia Comoli

SSD Cell Factory e Centro Terapie Cellulari Avanzate

Le terapie cellulari in Fondazione: dalla produzione alla gestione multidisciplinare

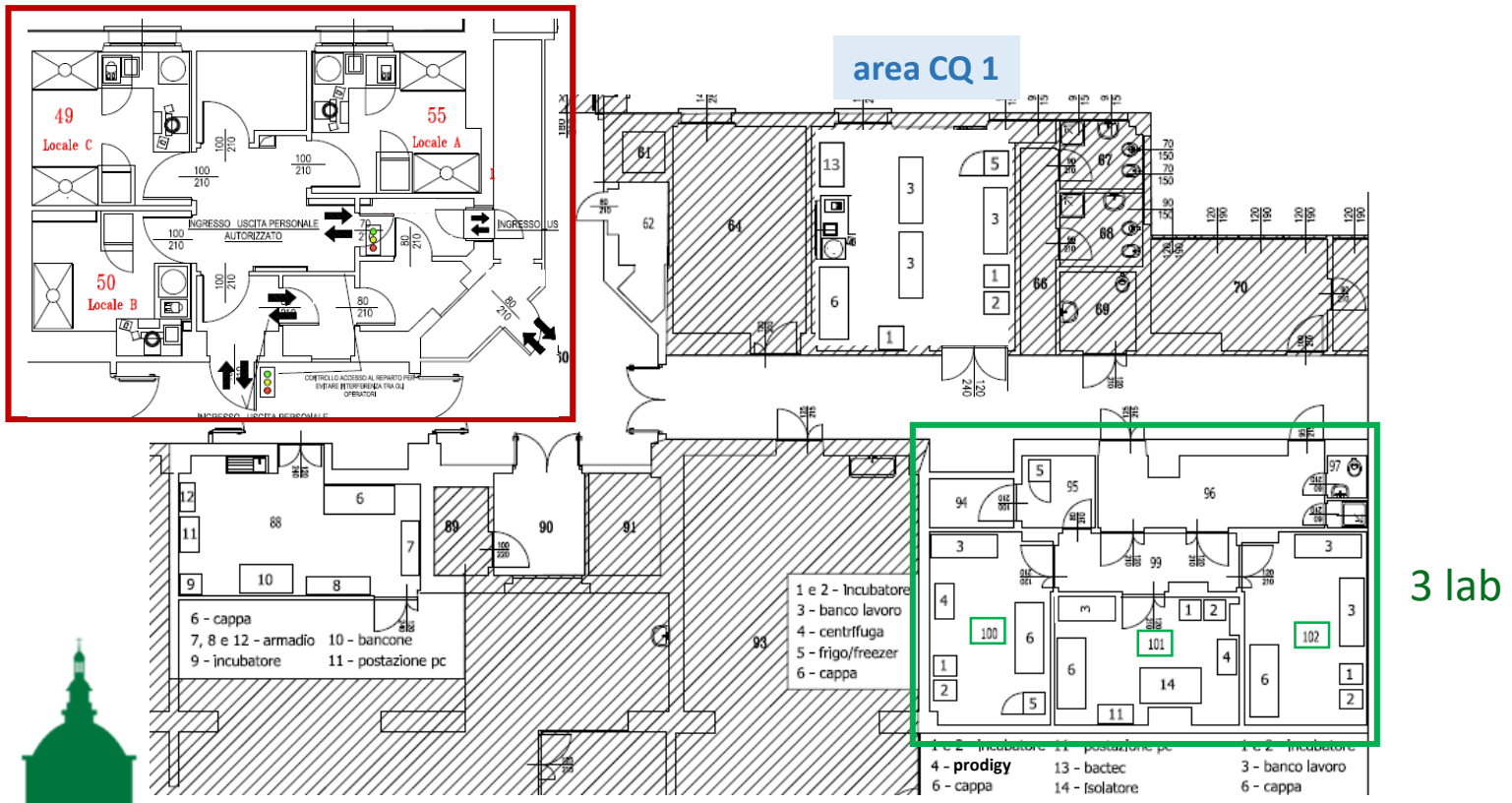
Terapie cellulari in Fondazione – Cell Factory

Officina farmaceutica autorizzata da AIFA, in attività dal 1997 (nella forma attuale, 2005)

La sua struttura attuale include:

- area di produzione a **pressione positiva** (rossa: produzione di ATMP per terapia cellulare somatica)
- area di produzione a **pressione negativa** (verde: produzione di ATMP per terapia genica)

3 lab

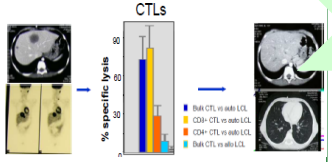


3 lab

Cell Factory – il passato

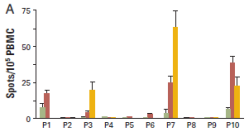
- E’ nata per trattare le malattie linfoproliferative post-trapianto con linfociti anti-EBV
- La sua attività si è poi estesa a diverse applicazioni cliniche grazie al lavoro dei laboratori di ricerca ad essa afferenti

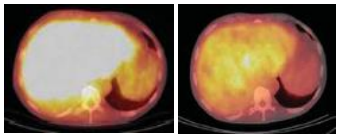
Terapia cellulare dei linfomi EBV post-trapianto



Blood 2002
AJT 2005
AJT 2007

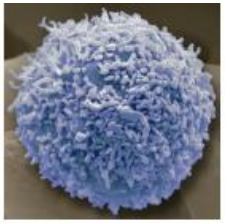
Terapia cellulare dei tumori testa-collo EBV-correlati





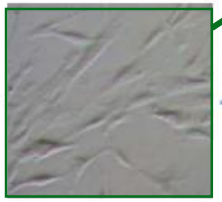
Ann Oncol 2004
J Clin Oncol 2005

1996 — 2005 — 2010



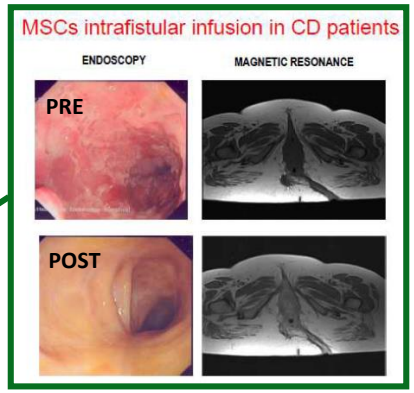
Linfociti

Leucemie
Infezioni
} **Trapianti**



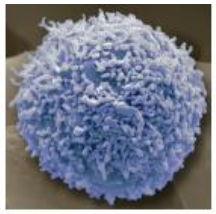
Cellule stromali mesenchimali

Trapianti
Medicina riparativa
Malattie (auto) immuni



Cell Factory – Il presente

- produzione/distribuzione linfociti anti-infettivi, anti-leucemia/tumore e MSC
- conduzione/partecipazione a sperimentazioni cliniche di terapia cellulare



Linfociti

Leucemie
Infezioni
} **Trapianti**

Tumori solidi

Cellule stromali Mesenchimali

Trapianti

Malattie immuni

Medicina riparativa

ATTIVITÀ NEL PERIODO 2017-22

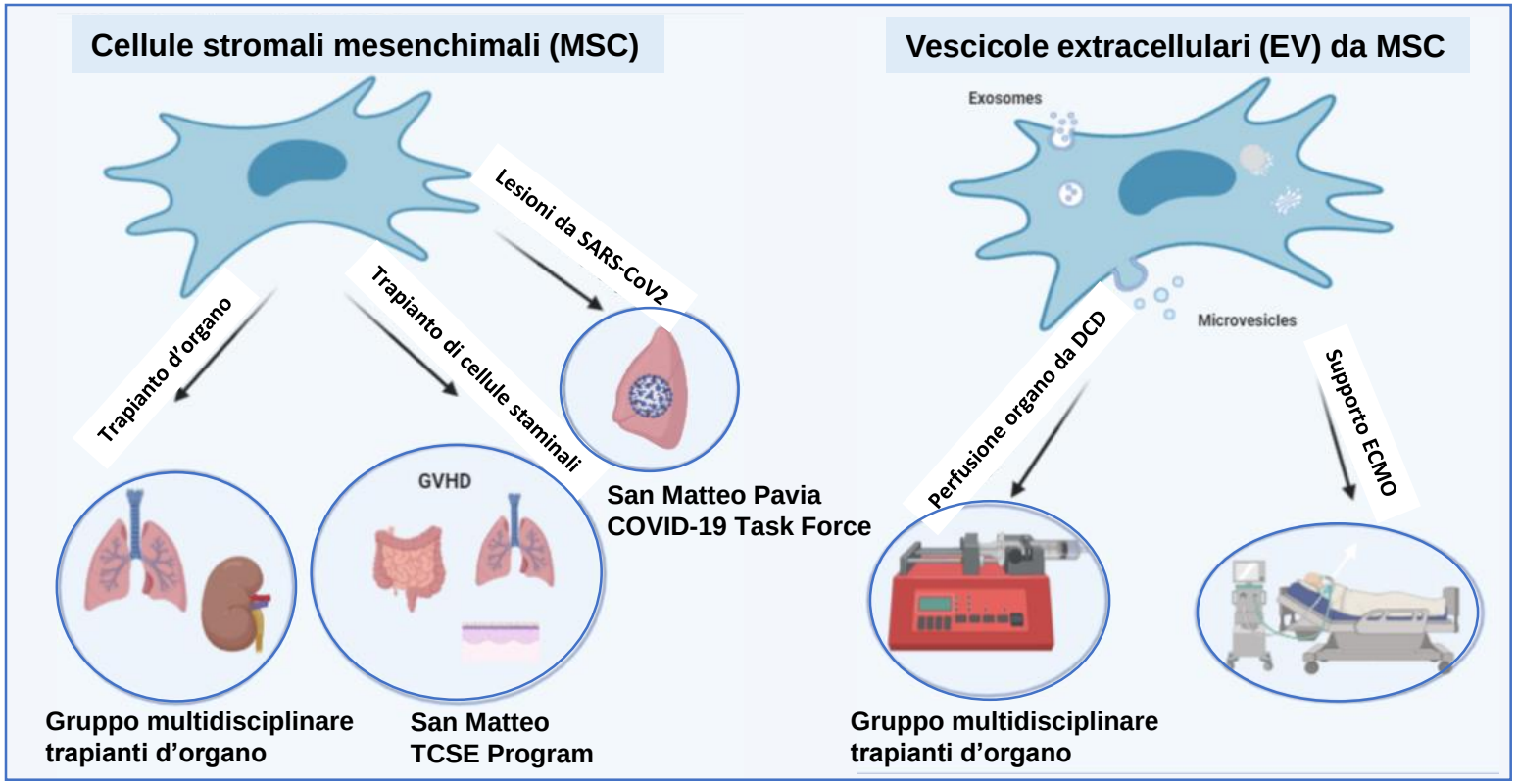
	2017	2018	2019	2020	2021	2022
Numero lotti prodotti	48	46	37	46	49	41
Numero unità bancate	220	420	316	408	479	466
Numero unità cedute*	73	140	106	156	174	220

* ad unità della Fondazione o ad altri ospedali nazionali e internazionali

Cell Factory – Programma MSC

APPLICAZIONI ATTUALI

APPLICAZIONI FUTURE

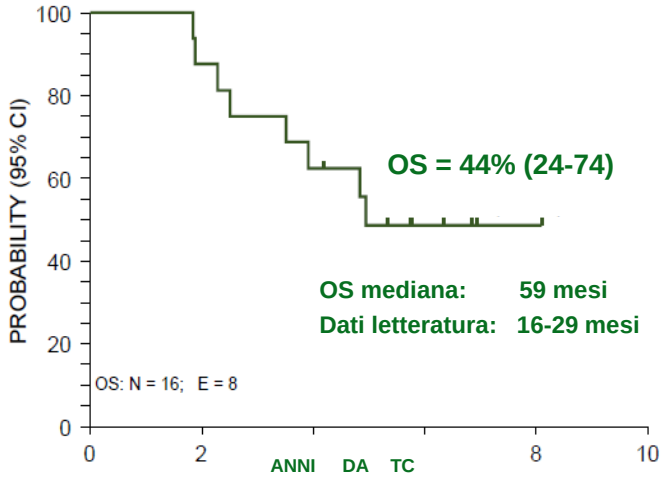


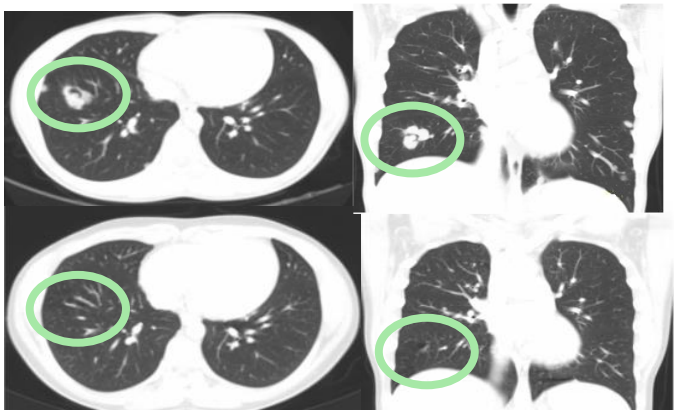
Cell Factory – Gruppo MSC: team leader dott.ssa M.A. Avanzini

ricercatori: S Croce, E Lenta, C Valsecchi

Cell Factory –Programma terapia antivirale

- **Prodotti antivirali:**
  - Linfociti T citotossici EBV-specifici: trattamento dei tumori EBV-associati





PRE-TC

POST-TC

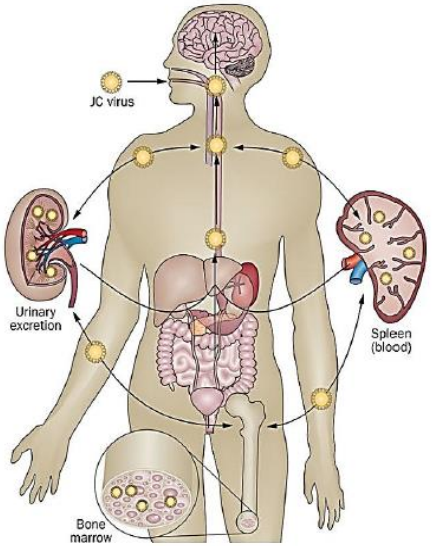
Dott.sse S. Basso (Cell Factory) e S. Secondino (SC Oncologia)
con Gruppo multidisciplinare tumori testa-collo San Matteo

Cell Factory –Programma terapia antivirale

- **Prodotti antivirali:**
  - Linfociti T citotossici EBV-specifici: trattamento dei tumori EBV-associati
  - Linfociti T multivirus-specifici (specificità per EBV, CMV, adenovirus, HHV6, PyVBK): prevenzione o trattamento delle complicanze virali dopo trapianto di CSE o organo solido
  - Linfociti T specifici per polyomavirus JC: trattamento della leucoencefalopatia multifocale progressiva

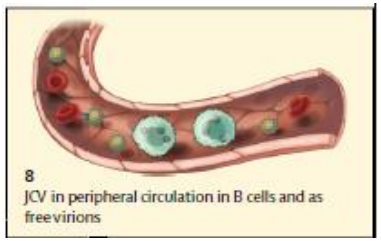
Cell Factory –
Gruppo LTC antivirali-antitumor Ag: team leader dott.ssa S. Basso
ricercatori: M. De Cicco, A. Bianco, S. Muscianisi, C. Pulvirenti, M. Siciliano, J. Bagnarino, S. Di Vincenzo

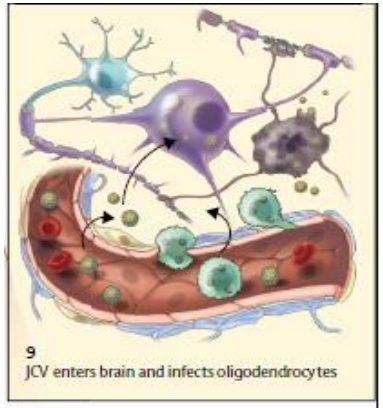
Cell Factory – Trattamento della PML

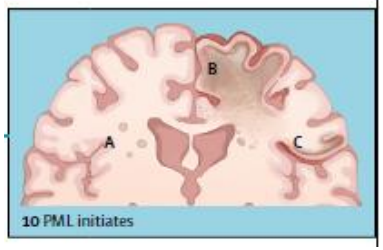


PML is a rare demyelinating disease of CNS caused by JCPyV

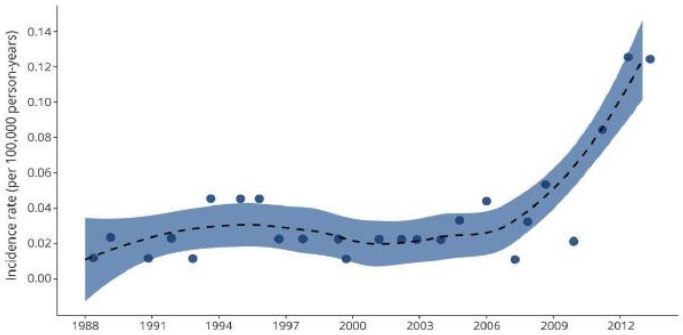
- primary infection in tonsil stroma cells
- JCPyV-related PML:
  - reactivation of virus in peripheral blood B lymphocytes;
  - B cells carry the virus to CNS: lytic infection of oligodendrocytes

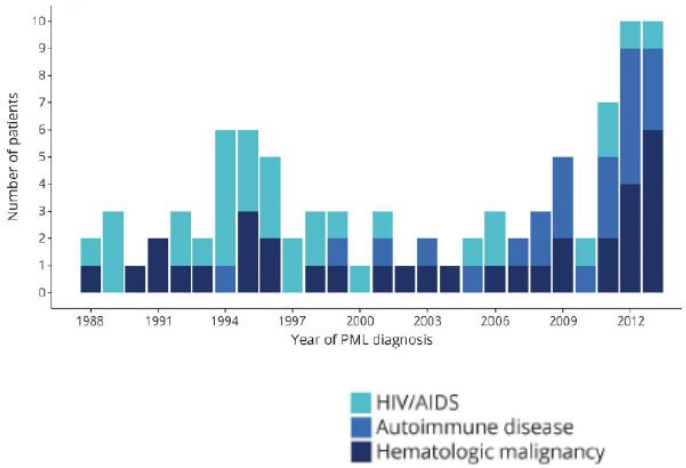






PML incidence is increasing…

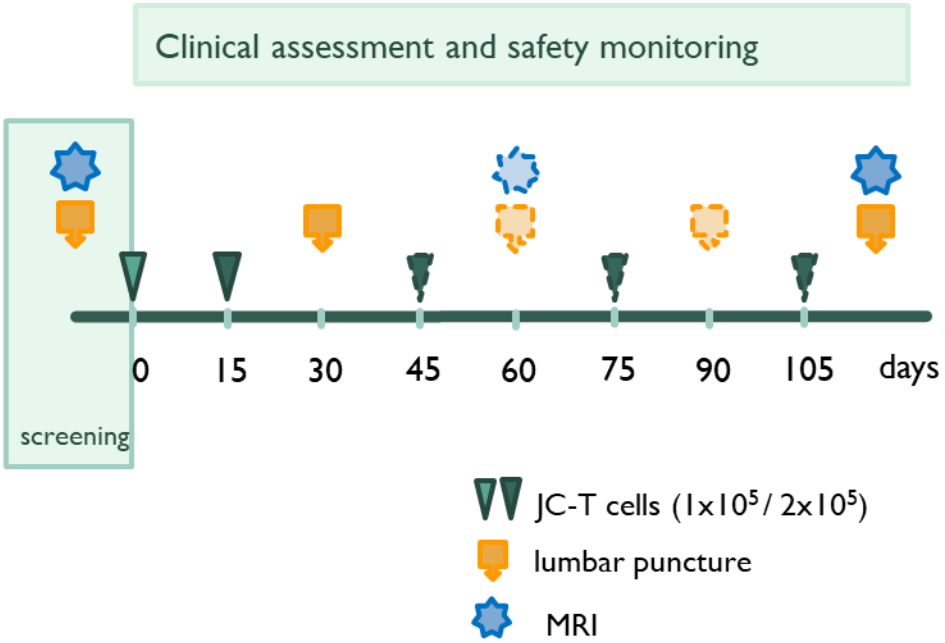




Cell Factory –Trattamento della PML

Between 2014 and 2019

- 9 HIV-negative patients treated for PML
- underlying condition:
  - hematologic malignancy treated with biologicals
  - HSCT recipients
  - immunodeficiency



- median delay PML diagnosis – CT: 2.6 months
- lymphocyte source:
  - autologous: 4 pts
  - allogeneic family donor (haplo): 3 pts
  - allogeneic unrelated third-party donor: 2 pts
- median number of infusions: 4 (range 1-6)

Berzero et al. Ann Neurol 2021

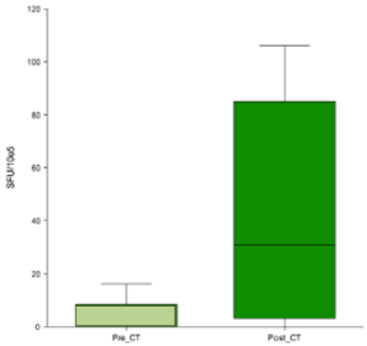
Cell Factory –Trattamento della PML

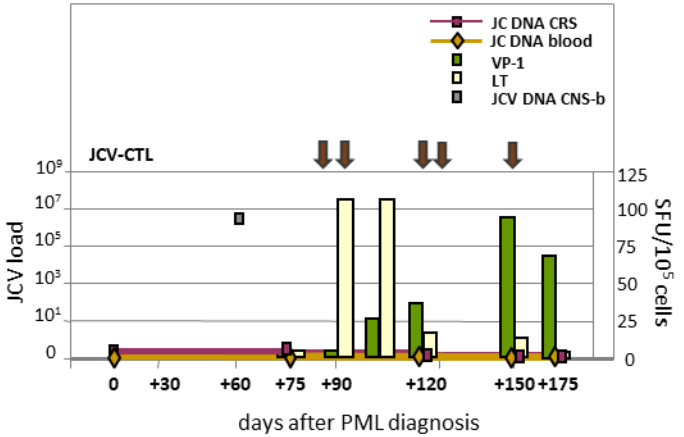
- Median follow-up in surviving patients: 51 (28-81) months
  - JC DNA CSF: marked reduction/clearance in the 4 evaluable pts
  - JC-specific T cell immunity pre-post CT: early increase in JC LT-specific T cells

JC-specific T cell immunity post CT:

- median 47 (6-106) SFU/10^5 cells

JCPyV immune recovery:





Berzero et al. Ann Neurol 2021

Cell Factory –Trattamento della PML

FOLLOW-UP		
FU duration from diagnosis (months)	Patient status at last FU	Neurological status at last FU (residual deficits)
69,0	Alive	severe hemiparesis, aphasia (mRS 4)
27,7	Alive	no residual deficit (mRS 1)
3,6	Deceased (PML)	-
4,4	Deceased (VZV encephalitis)	-
19,3	Alive	mild cognitive impairment, LHH (mRS 2)
5,0	Deceased (PML)	-
6,0	Deceased (PML)	-
50,3	Alive	mild dysarthria and gait ataxia (mRS 2)
12	Alive	mild ataxia and tremor (mRS 2)

Clinical response:
5/9 pts
55%

- 5 patients achieved long-term survival :
  - 4 pts: clinical improvement (mRS 1-2)
  - 1 pt: clinical stabilization (mRS 4, wheelchair bound)
- 1 patient had disease stabilization:
  - died of VZV encephalitis
- 3 patients progressed and died of PML

Berzero et al. Ann Neurol 2021

Cell Factory –Trattamento della PML

- 30 year-old woman
- cystic fibrosis
- 2015: lung transplantation
  - complications
    - chronic lung allograft disfunction
    - infections:
      - chronic cavitary Aspergillosis
      - lung colonization with Pseudomonas aeruginosa XDR

  → End stage organ disease
- 2019: retransplantation
  - induction: thymoglobulin
  - IS: Micophenolate, Tacrolimus, PDN

Peghin et al. J Heart LungTranspl 2022

Cell Factory –Trattamento della PML

- 30 year-old woman
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End stage organ disease

- 2019: retransplantation
  - induction: thymoglobulin
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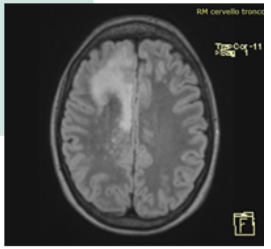
Jan 20, 2020:

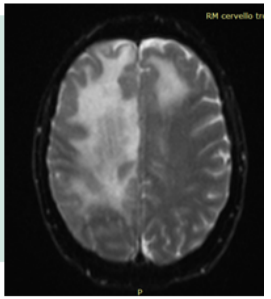
- Abrupt onset of headache, postural instability, vomit, and partial seazures
- JCPyV DNA in CSF: 208.596 copies/mL
- MRI: right frontal lobe cerebritis



↓ IS + adjuvant treatment

Feb 2020:

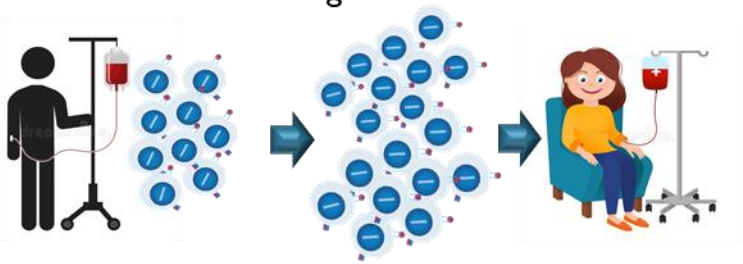
- Dyspnea, fever, hypoxia
- Left body complete hemiparesis
- Sudden disphagya
- Multiple temporal and frontal epileptic spikes



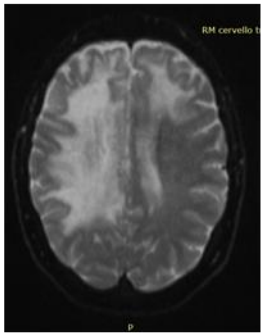
Peghin et al. J Heart LungTranspl 2022

Cell Factory –Trattamento della PML

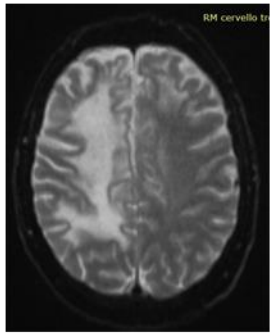
Donor: HLA-identical sibling



Before treatment



After treatment



Month +2

- Intensive rehabilitative therapy → ability **to sit without support**
- **VII nerve palsy disappeared**
- EEG: reduction in epilectic spikes

Month +4

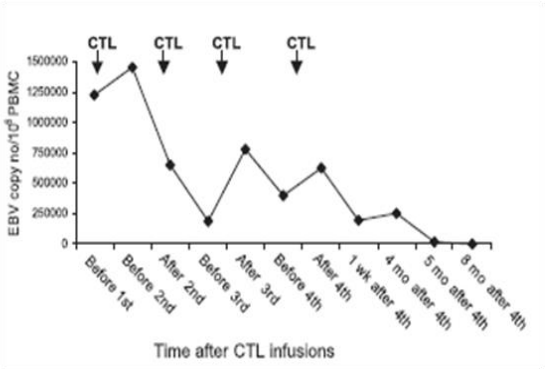
- Slowly **re-gaining ability to walk** with support
- Left arm persistently paralized
- EEG: **no more epilectic** spikes

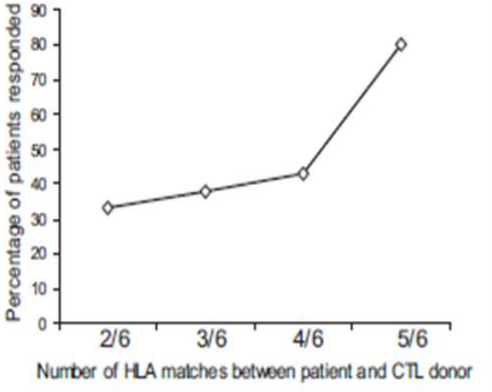
What about the organ?

- Good lung function
- IS: Tac restarted + everolimus + PDN
- Additional: ECP

Peghin et al. J Heart LungTranspl 2022

ATMP antivirali: impiego prodotti bancati «terza parte»



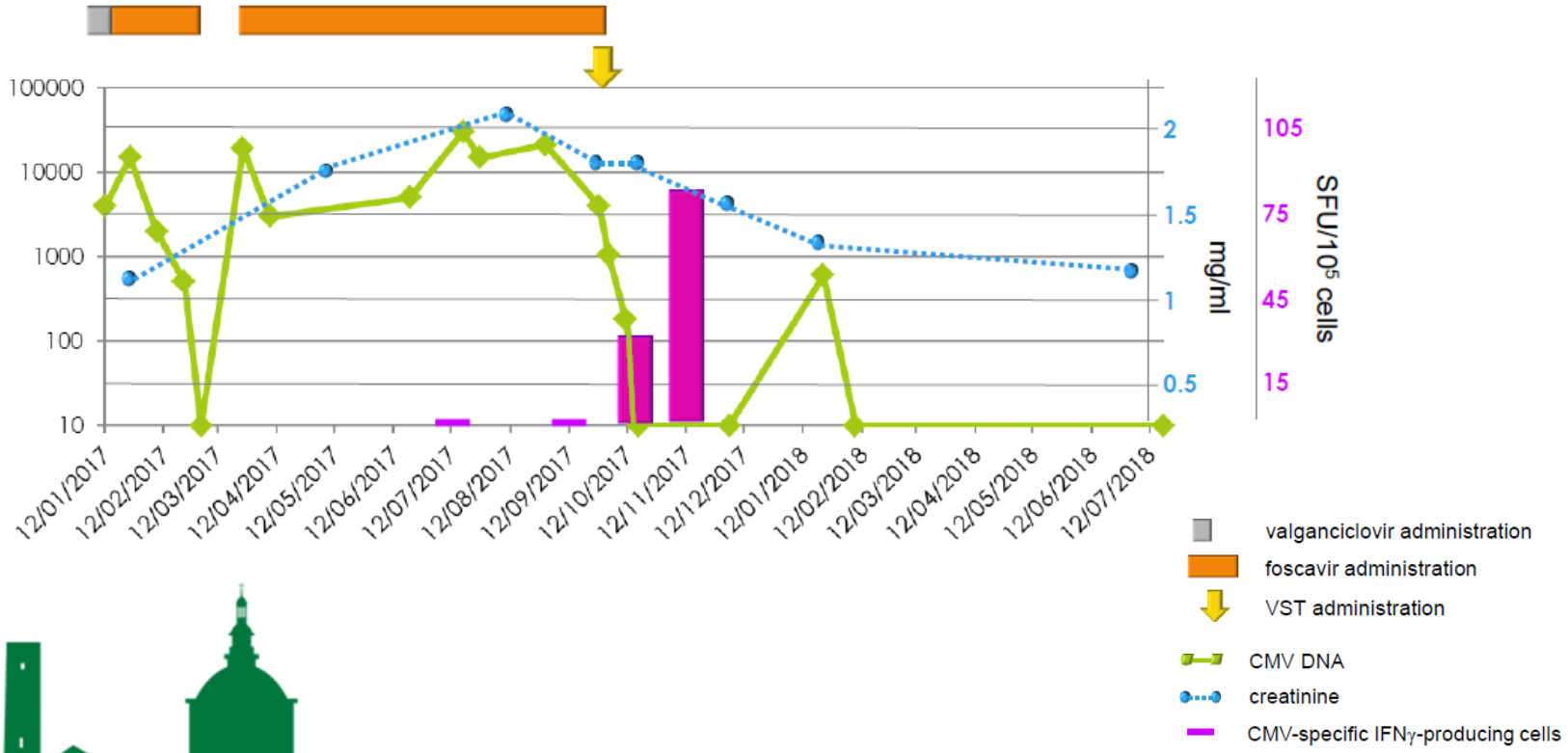


Haque et al. *Blood* 2007

	Patient nr.	Response	GVHD/toxicity
Single 3rd party VST			
Haque, *Blood 2007*	39	49% (19/39) achieved CR	1 grade I aGVHD
Barker, *Blood 2010*	5	80% (4/5) achieved CR	none
Uhlin, *CID 2013*	1	CR, recurrence then response to 2nd dose	none

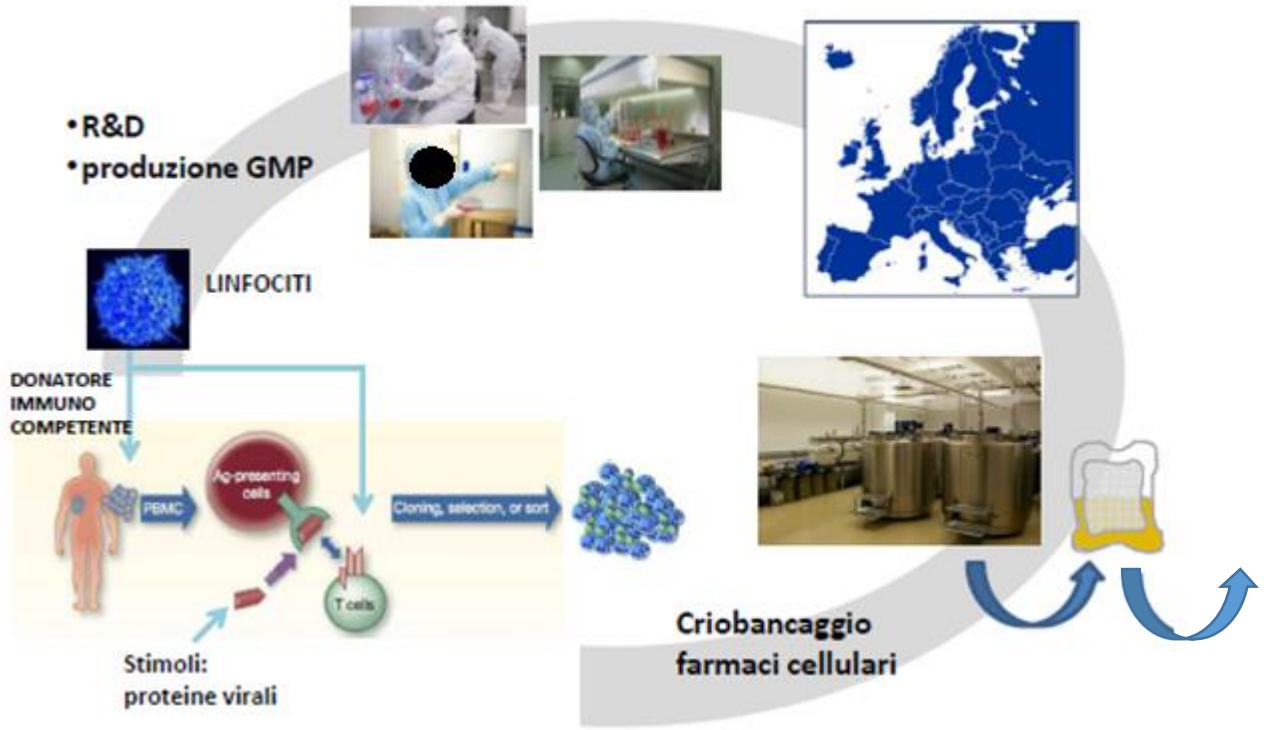
ATMP antivirali: impiego prodotti bancati «terza parte»

HSCT recipient with relapsing-refractory CMV infection and renal dysfunction: treatment with HLA-partially matched banked VSTs



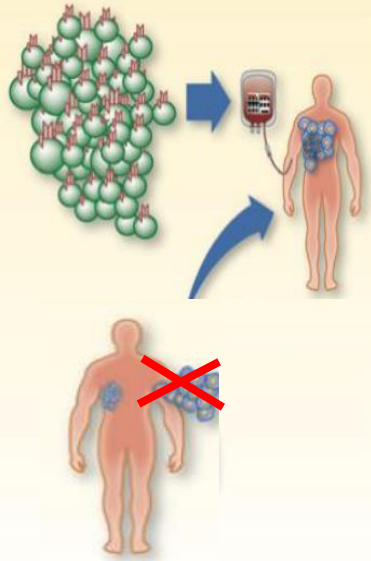
Cell Factory – Programmi

Cellule di donatori sani, da impiegare come prodotto «pronto all'uso» in malati con infezioni resistenti



MALATTIA DA PATOGENO REFRATTARIO/RESISTENTE:

Citomegalovirus
Virus di Epstein-Barr (EBV)
Adenovirus
Polyomavirus
… SARS-CoV2



MALATO IMMUNODEFICIENTE

Cell Factory – Trattamento con ATMP terza parte

- linfociti anti-infettivi e MSC per GVHD o ARDS

Centro TMO Pediatrico e Mal. infettive
AO San Gerardo e FMBBM, Monza

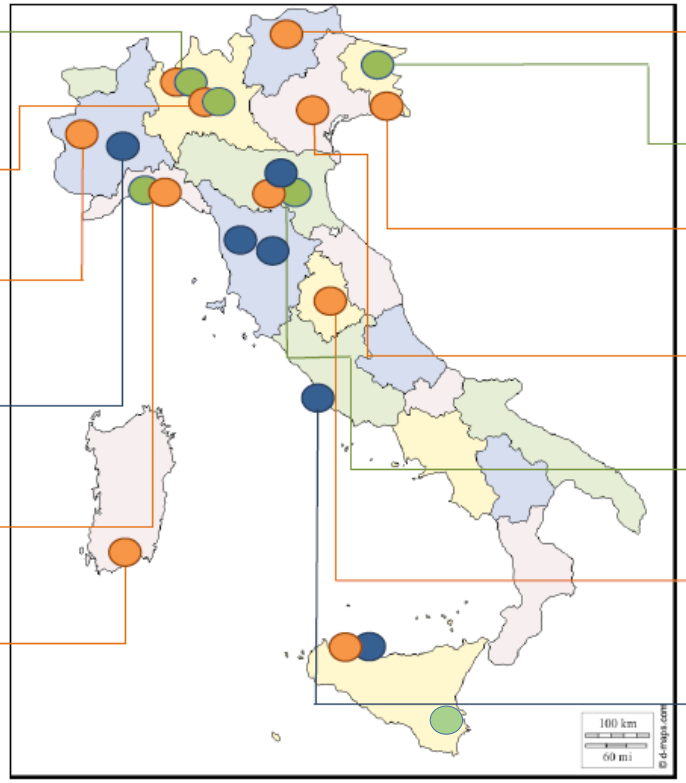
Centro TMO e Mal. Infettive
Ospedale San Raffaele, Milano

Oncoematologia Pediatrica
Ospedale Regina Margherita, Torino

Centro TCSE
AO SS Antonio e Biagio e C. Arrigo
Alessandria

Centro TMO – Istituto G. Gaslini
Genova

Centro TMO Adulto - Pediatrico
Cagliari



Centro TMO - Ematologia
Bolzano

Mal. Infettive e CT Polmone
Ospedale di Udine

Centro TCSE Pediatrico
Trieste

Centro TCSE Pediatrico
Padova

Centro TMO - Ematologia
Bologna

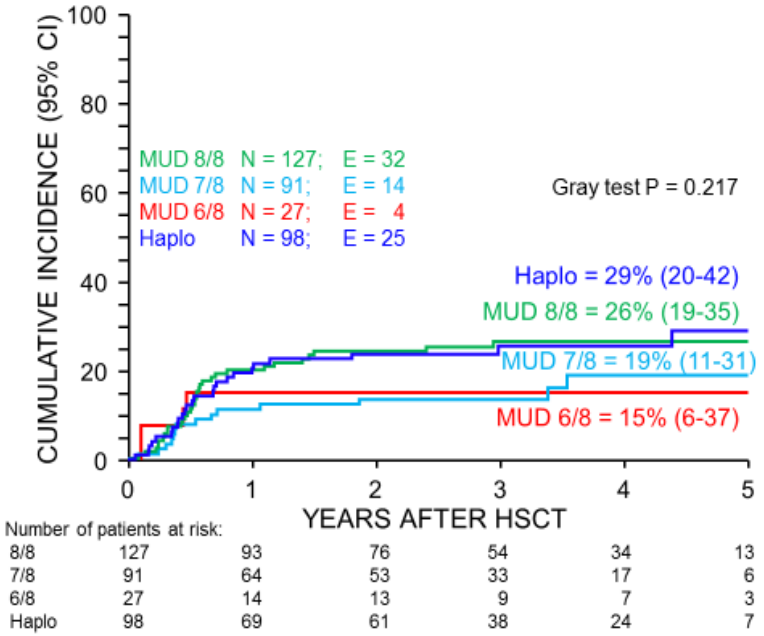
Centro TMO - Ematologia
Perugia

Centro TCSE
Ospedale Bambino Gesù
Roma

CMV – AdV - EBV
PyVJC

Terapia cellulare post-TCSE: controllo antitumorale

RELAPSE



Means to improve GvL are needed to reduce relapse rate:

- T cells play a major role in GvL effect: adoptive T-cell therapy strategies have arisen out of the need to improve GvL.
- Our αβ/CD19 cell depleted Haplo-HSCT is an ideal platform for cell therapy:

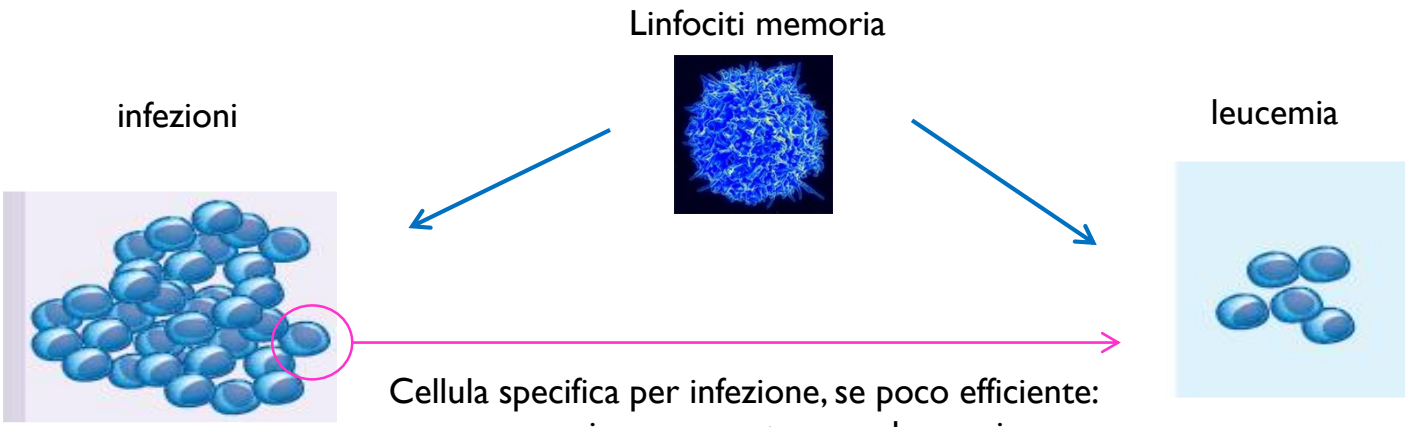
no post-transplant immunosuppression

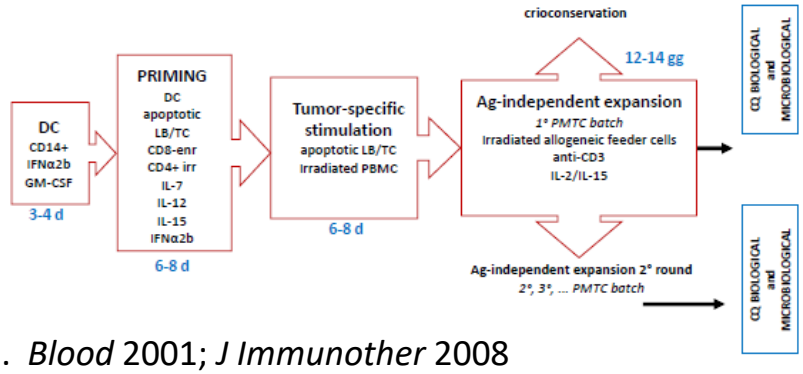
Bertaina A*, Zecca M*, Buldini B, et al, *Blood* 2018

Terapia cellulare post-TCSE: controllo antivirale vs antitumorale

Donatori sani:

- circa il 60-80% sono positivi per CMV o EBV: hanno circa 1:3.000 – 1:6.000 cellule memoria per questi virus
- nessun soggetto sano ha incontrato la leucemia: cellule potenzialmente in grado di rispondere 1:500.000 – 1:10^6

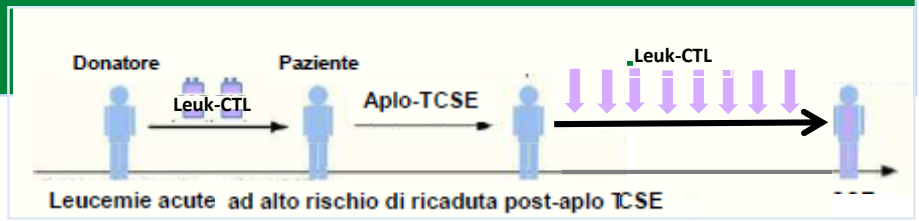




Montagna et al. *Blood* 2001; *J Immunother* 2008

Cell Factory – Programma antileucemia

Leuk-CTL-001 trial: PI M. Zecca
Co-PI D. Montagna

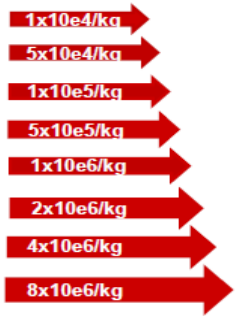


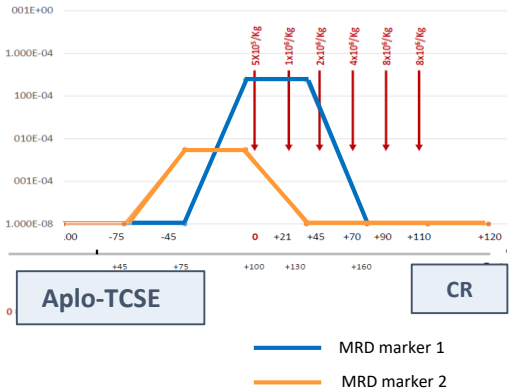
Impiego preventivo di CTL antileucemia dopo TCSE aploidentico per prevenire recidiva di leucemia acuta pediatrica

DOSE
Escalating doses of donor leuk-CTL
from 10^4 cells/dose, ½ log every 3 wks, to $8x10^6$ cell/dose

ADMINISTRATION
i.v. infusion in saline solution and human albumin

PACKAGING
2 ml cryovials preserved in nitrogen vapour until final formulation.

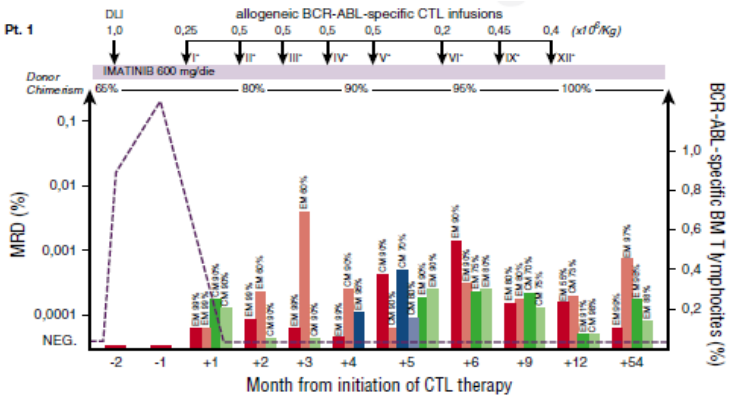


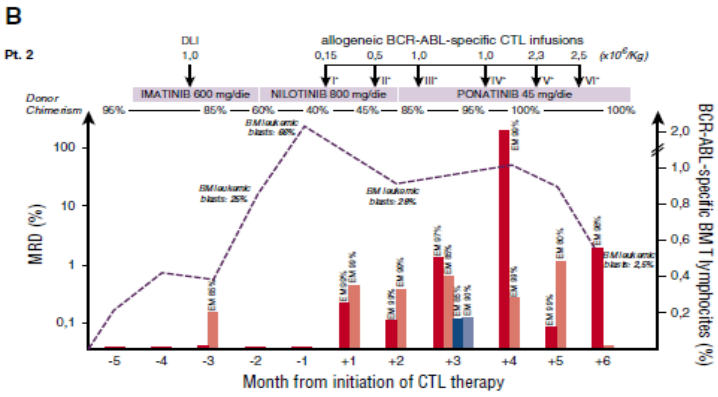


Cell Factory –
Gruppo CTL antileucemia/cellule NK: team leader dott.ssa D. Montagna
ricercatori: M. Tanzi, E. Montini, A. Rumolo

Cell Factory – Programma antileucemia

- Abbiamo però una necessità clinica: produrre CTL per i pazienti che non hanno blasti criopreservati
- Stiamo lavorando all'identificazione di bersagli leucemici per la terapia cellulare, e sull'ottimizzazione di protocolli di espansione di CTL utilizzando peptidi sintetici per la stimolazione.
  - Recentemente, abbiamo espanso CTL specifici per ^{p190}BCR/ABL stimolando con peptidi derivati dalla regione di fusione BCR/ABL





Cell Factory –
Gruppo LTC antivirali-antitumor Ag: team leader dott.ssa S. Basso
ricercatori: M. De Cicco, A. Bianco, S. Muscianisi, C. Pulvirenti

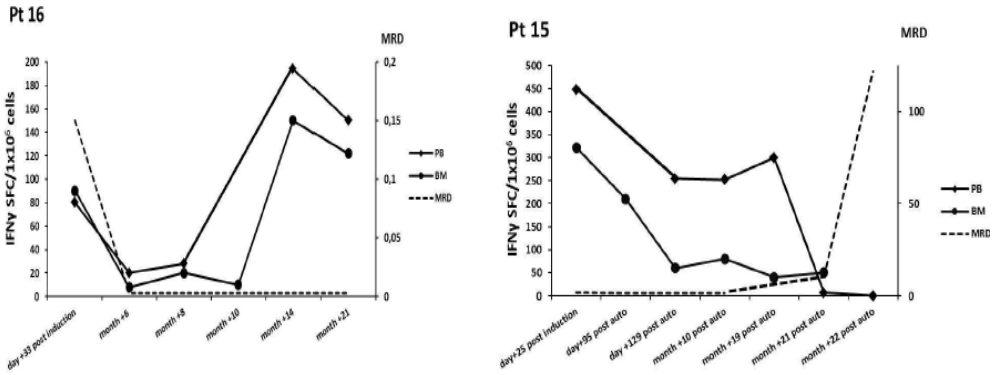
Issue Highlights

BCR-ABL-specific T-cell therapy in Ph$^+$ ALL patients on tyrosine-kinase inhibitors
Blood 2017 129:582-586;

Cell Factory – Programma antileucemia

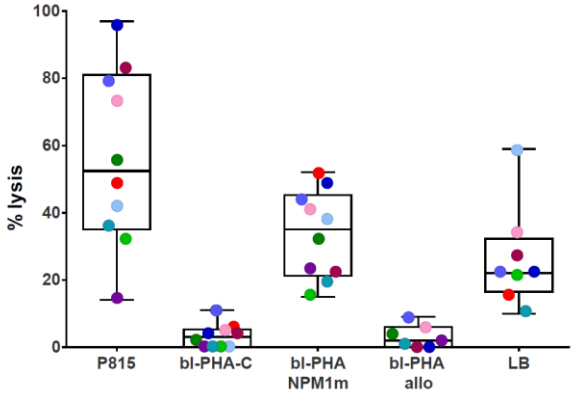
- Ora ci stiamo focalizzando sull'identificazione di bersagli presenti su leucemie mieloidi da utilizzare per terapie cellulari
  - Neoantigene NPM1-mutato (35% AML nell'adulto)

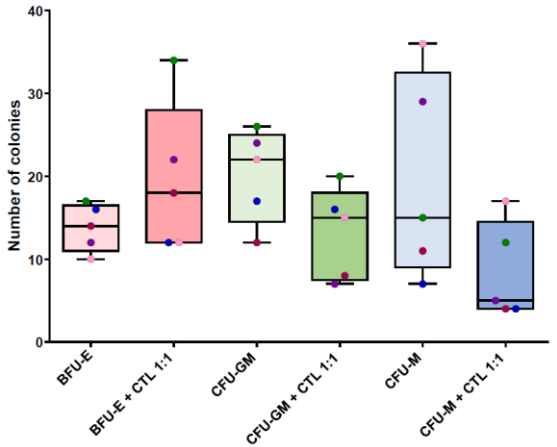
- Relazione tra MMR e immunità NPM1^{mut}-specifica



Correlazione **inversa** tra la cinetica della MMR e la cinetica delle cellule T specifiche anti-leucemiche

Forghieri et al. Oncotarget 2019



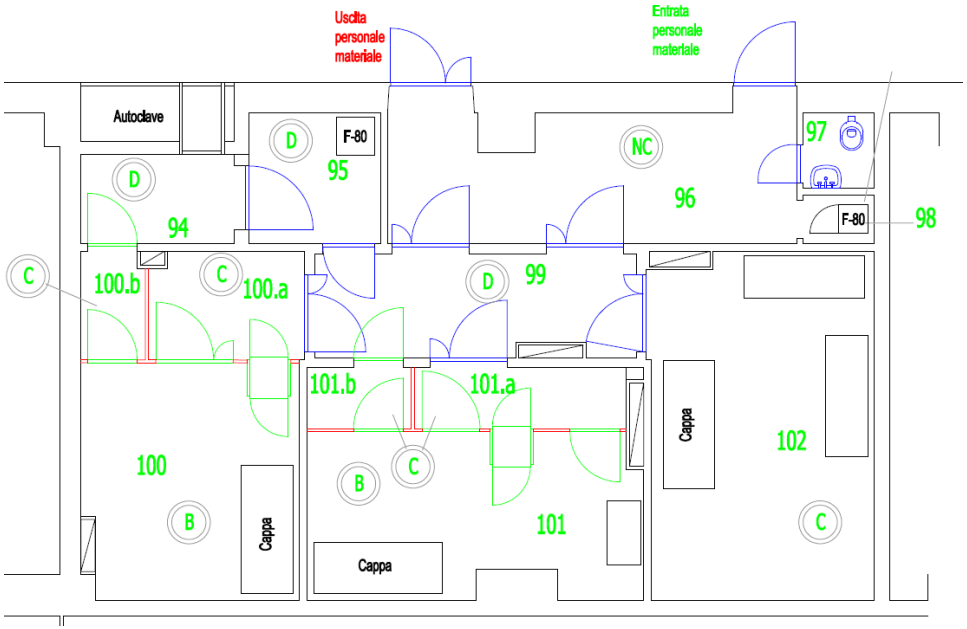


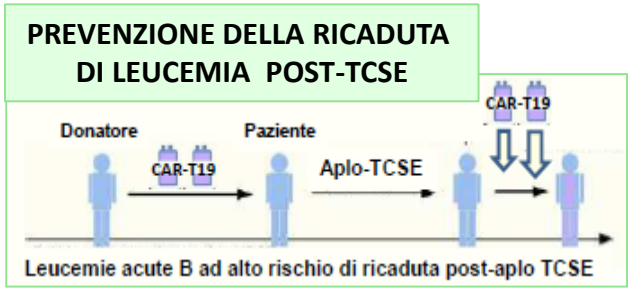
De Cicco et al. submitted

Cell Factory – Programmi futuri

e se non abbiamo cellule del paziente o del donatore in grado di attivarsi?

- Programmi di terapia delle leucemie acute B-cellulari e di tumori solidi con cellule CAR-T





San Matteo Transplant Program – OEPed

Collaborazioni per attività di produzione

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SC Microbiologia: P Cambieri, F Baldanti

SC Farmacia: B Croesi, M Tizzoni, M Calvi

SC Tecnico-Patrimoniale, SC Ingegneria Clinica, SC Sistemi Informativi, SC Fisica Sanitaria, SC DMP-Servizio Sterilizzazione

Cell Factory

AQ: **A. Moretta**, L Catenacci, D Sapuppo

CQB: G Acquafredda, J Rotella

CQM: **D Barbarini**, J Bagnarino, M Siciliano