UMC Utrecht

Potential for HIV Cure by stem cell transplantation

IciStem

Monique Nijhuis
University Medical Center Utrecht
the Netherlands

Stem cell transplantation in HIV patients

- People living with HIV have a higher risk for hematological malignancies, such as acute myeloid leukemia (AML), or lymphoma‘s and often require a transplantation with donor stem cells (allogeneic stem cell transplantation, allo-SCT)
- People living with HIV have an lower overall survival rate after allo-SCT as compared to a matched control group of HIV negative individuals

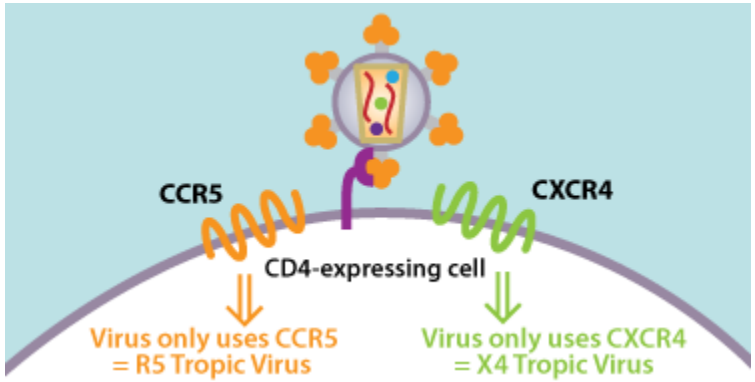
→ Timothy Brown, the so called “Berlin patient” was cured from both AML and HIV-infection after allo-SCT with CCR5Δ32 donor cells (12 years ago)

↑ Special about these cells?

Sutton et al, Br J Hematol 2001; Hutter et al, aids Res Ther 2016; Kaner et al, Blood 2016; Aboulafia et al, AIDS 2002; Ryu Intern Med 2001

HIV cell entry: CCR5WT cells

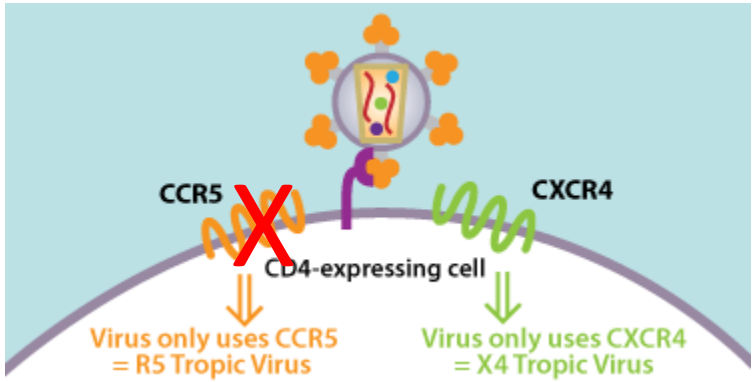
Cell entry in CCR5WT cells:



Dominant route of infection

HIV cell entry: CCR5Δ32 cells

Cell entry in CCR5Δ32 cells:



Dominant route of infection

Alternative route of entry

Treatment interruption in HIV patients transplanted with CCR5Δ32stem cells

- "Berlin patient": diagnosed with AML and transplanted **twice** with CCR5Δ32 donor cells[1]
  - Transplanted in 2007, received total body irradiation and severe chemotherapy
  - Stopped cART at the moment of the first allo-SCT and no viral rebound occurred
  - Prior to allo-SCT a few virus variants predicted to use the CXCR4 coreceptor
  - Laboratory analyses demonstrated that these variants still depended on CCR5 for viral entry and could not infect the donor cells of the "Berlin Patient[2]

→ One other patient described, the so called "Essen patient" who stopped cART during allo-SCT using CCR5Δ32 donor cells[3]

[1]Hutter et al, NEJM, 2008; [2]Symons et al, CID, 2014; [3]Kordelas et al, NEJM, 2014

Treatment interruption in HIV patients transplanted with CCR5Δ32stem cells (peri-SCT)

- "Essen patient": diagnosed with anaplastic large-cell lymphoma and transplanted with **CCR5Δ32** donor cells[1]
    - 27 year old HIV-1 infected patient transplanted in 2012
    - Successful engraftment
    - cART interruption 7 days before transplantation
    - Rebound of virus **3 weeks** after transplantation
    - Laboratory analyses revealed this was related to **pre-existing CXCR4-tropic**[4]

[1]Kordelas et al, NEJM, 2014; [4]Verheijen et al, CID, 2018

Treatment interruption in HIV patients transplanted with CCR5WT stem cells (post-SCT)

- Boston Patients: transplanted with **CCR5WT** donor cells[1]

  - After allo-SCT: no HIV DNA and infectious virus detected in blood and rectal tissue
  - 2.6 - 4.3 years: ATI and viral rebound was observed after **12**, **32 weeks**
  - Rebound virus was related to viral PBMC DNA sequences observed before allo-SCT

- Minnesota Case: transplanted with **CCR5WT** donor cells[2]

  - After allo-SCT: HIV DNA +/- detectable in PBMCs, no infectious virus detected in blood
  - In situ hybridization was negative in colon
  - 2.1 years: ATI and viral rebound was observed after **41 weeks**
  - Rebound virus is phylogenetic distinct from circulating PBMCs prior to allo-SCT

[1]Henrich et al, Ann. Intern. Med., 2014; [2]Cummins et al, PLoS Medicine, 2017

What were the determinants for cure in the “Berlin Patient”

•Raising the Question: What were the determinant for cure in the “Berlin Patient”

- “Berlin Patient” had inherited already one CCR5Δ32 gene defect from one of his parents
- CCR5Δ32 donor cells
- Received two transplants
- Total body irradiation
- Conditioning regime, severe chemotherapy
- Mild Graft versus Host Disease

IciStem Consortium

International collaboration to guide and investigate the potential for HIV cure in HIV-infected patients requiring allogeneic stem cell transplantation for hematological disorders

AIM 1

To guide clinicians involved in allogeneic SCT procedures in HIV infected individuals

AIM 2

To better understand the underlying biological processes leading to viral reservoir reduction and potential cases of HIV-1 eradication/remission.

Principal Investigators:

Javier Martinez Picado

Annemarie Wensing

www.icistem.org

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Overview of CCR5Δ32 donor search

Cord Blood Bank	Samples Tested	CCR5 Δ32/Δ32	%	Sponsor
Spain	25.720	157	0,61	ONT
UK (NHS)	3.053	31	1,02	amfAR
Finland	783	9	1,15	
Germany (JCarreras)	1796	17	0,95	
Sweeden	847	16	1,89	
TOTAL	**32,199**	**230**		

Adult donors	Samples Tested	CCR5 Δ32/Δ32	%	Sponsor
Germany*	**2.242.462**	~22.000	~1%	DKMS

** Also some donors from UK and Poland*

Overview of registration

- 45 patients registered from 9 different countries
- 39 patients have been transplanted; 26 patients are still alive
- Median follow-up: 1707 days (>4.5 years)
  19 patients beyond 1th year post-SCT

	CCR5WT or heterozygous	CCR5Δ32		alive
Adult donor	29	7	36 →	25
Umbilical Cord	1	2	3 →	1
	30	9		
alive	22	4		

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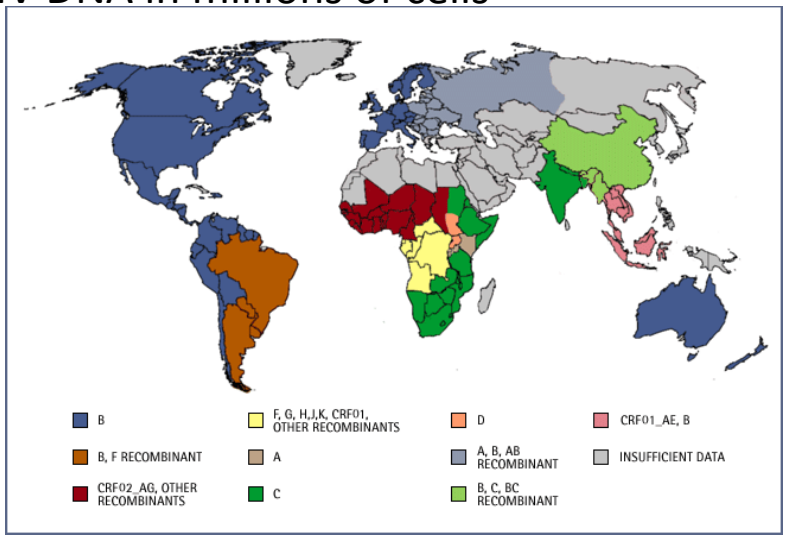
Development of ultra-sensitive techniques

- Many different HIV-1 variants can be observed worldwide and have a slightly different genome; important for all the genome based detection methods
- Single copy of HIV RNA in 10 mL of plasma or CSF[1]
- Single copy of HIV DNA in millions of cells[2]



- Single infectious virus in millions of cells (PBMC or humanized mouse viral outgrowth assay)[3]

[1]Duarte et al, Lancet HIV, 2015; [2]Bosman et al, JIAS, 2018 ; Metcalf et al, JID, 2015

HIV Reservoir

Leukapheresis

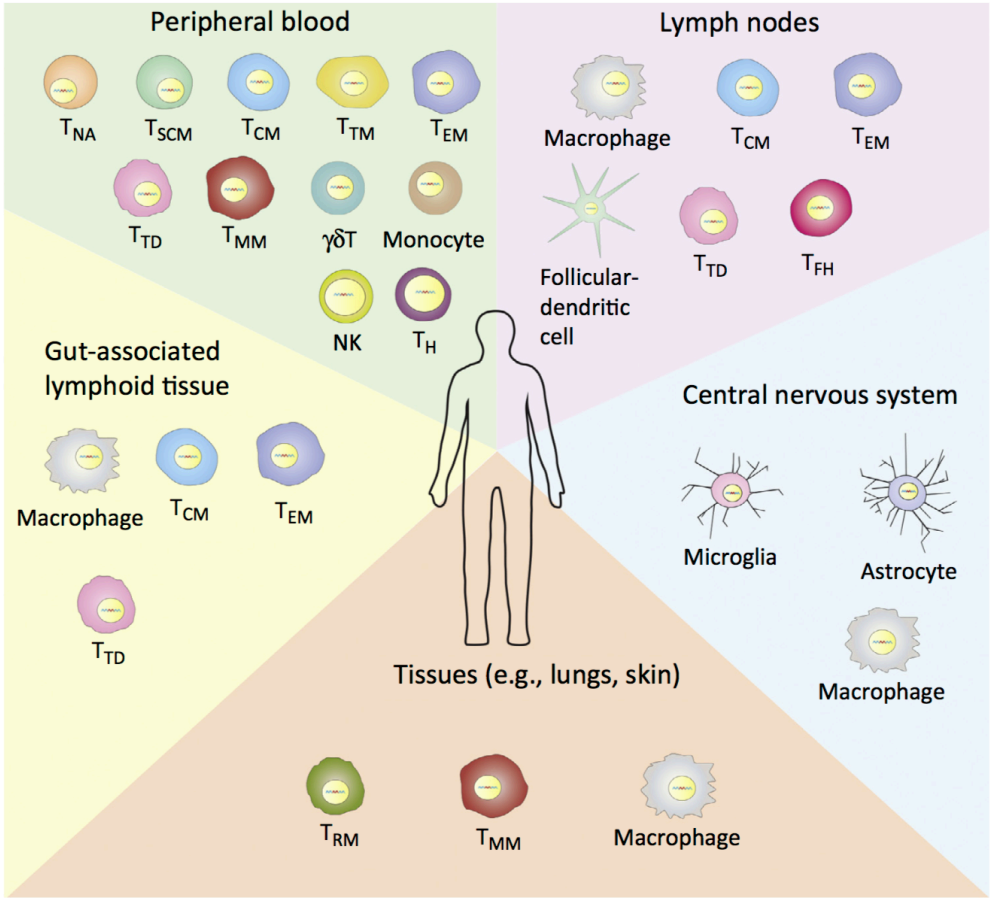
Bone Marrow

Blood

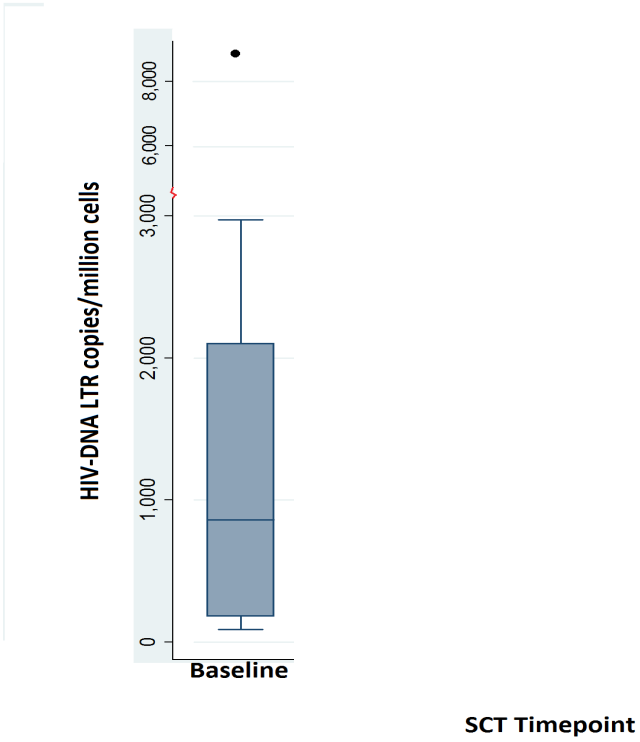
Lymph node

Ileum biopsy

CSF



Analyses of the dynamics of the viral reservoir



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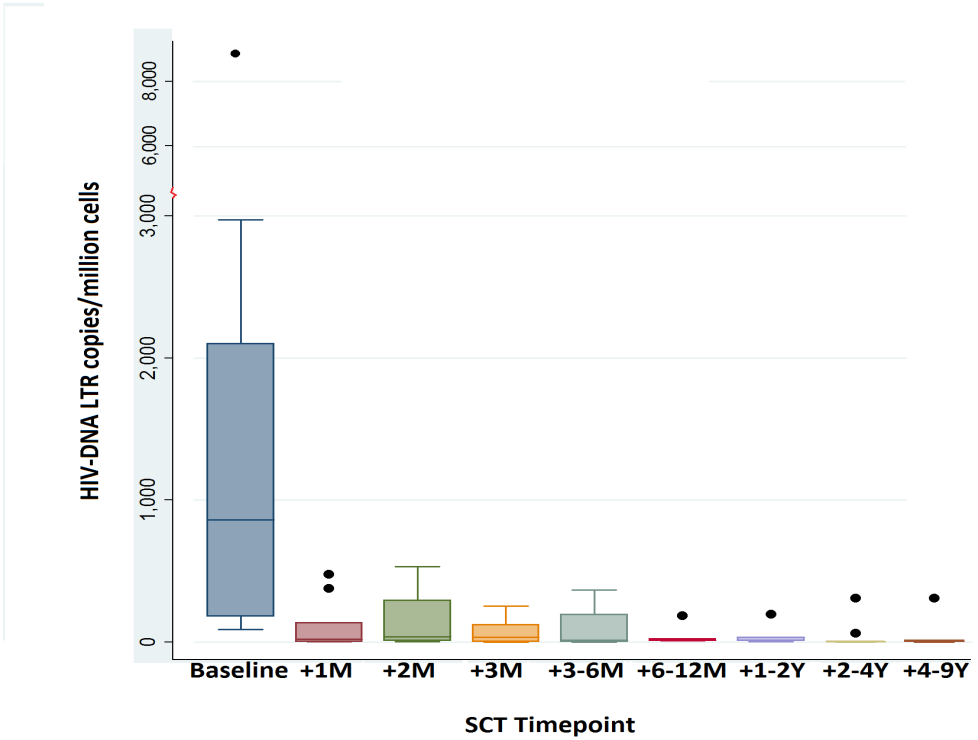

- Only curative intervention in which a reduction of the viral reservoir is observed
- In the presence of antiretroviral therapy
- No difference between patients received CCR5WT cells or CCR5Δ32 donor cells

IciStem Patient	HSCT	Year of transplant	Single copy assay (HIV-RNA cp/ml)	Total DNA (cp/ 10^6 CD4)	qVOA in CD4 (IUPM)	Ileum, CSF, LN, BM
1	CCR5WT	2012				
3	CCR5WT	2013				
6	CCR5WT	2014				
17	CCR5WT	2010				
27	CCR5WT	2009				
28	CCR5WT	2013				

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1	CCR5WT	2012	5	25		
3	CCR5WT	2013	undetectable	undetectable		
6	CCR5WT	2014	undetectable	undetectable		
17	CCR5WT	2010	undetectable	undetectable		
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Summary

- IciStem has identified >22.000 CCR5Δ32 donors that can be used for allo-SCT
- IciStem has compiled the largest registry of allo-transplants in people living with HIV
  - Clinical information
  - Clinical samples
- Developed an array of ultra-sensitive techniques to analyse the viral reservoir
- After allo-SCT, a sharp decline in HIV DNA in the blood, CSF and tissue is observed to below the level of detection in most transplanted patients

Directions:

- Patients transplanted with **CCR5WT** donor cells are candidates for ATI with cure intervention
  - Clinically stable; > 2 years post transplant; > 1 year post immune-suppression
  - Undetectable viral reservoir in blood, CSF and tissue
  - 2019: include 5 patients who will receive broadly neutralizing antibodies for 8 months
  - Additional follow-up of 10 months

- Patients transplanted with **CCR5Δ32** donor cells
  - Four patients are alive
  - Data on two patients are going to be presented at CROI as late breaker abstracts

    - IciStem patient #36, oral presentation 5th March 11.45 hours, room 6E
    - IciStem patient #19, poster presentation, 6th March, 14.30 hours, 4EF

Acknowledgement

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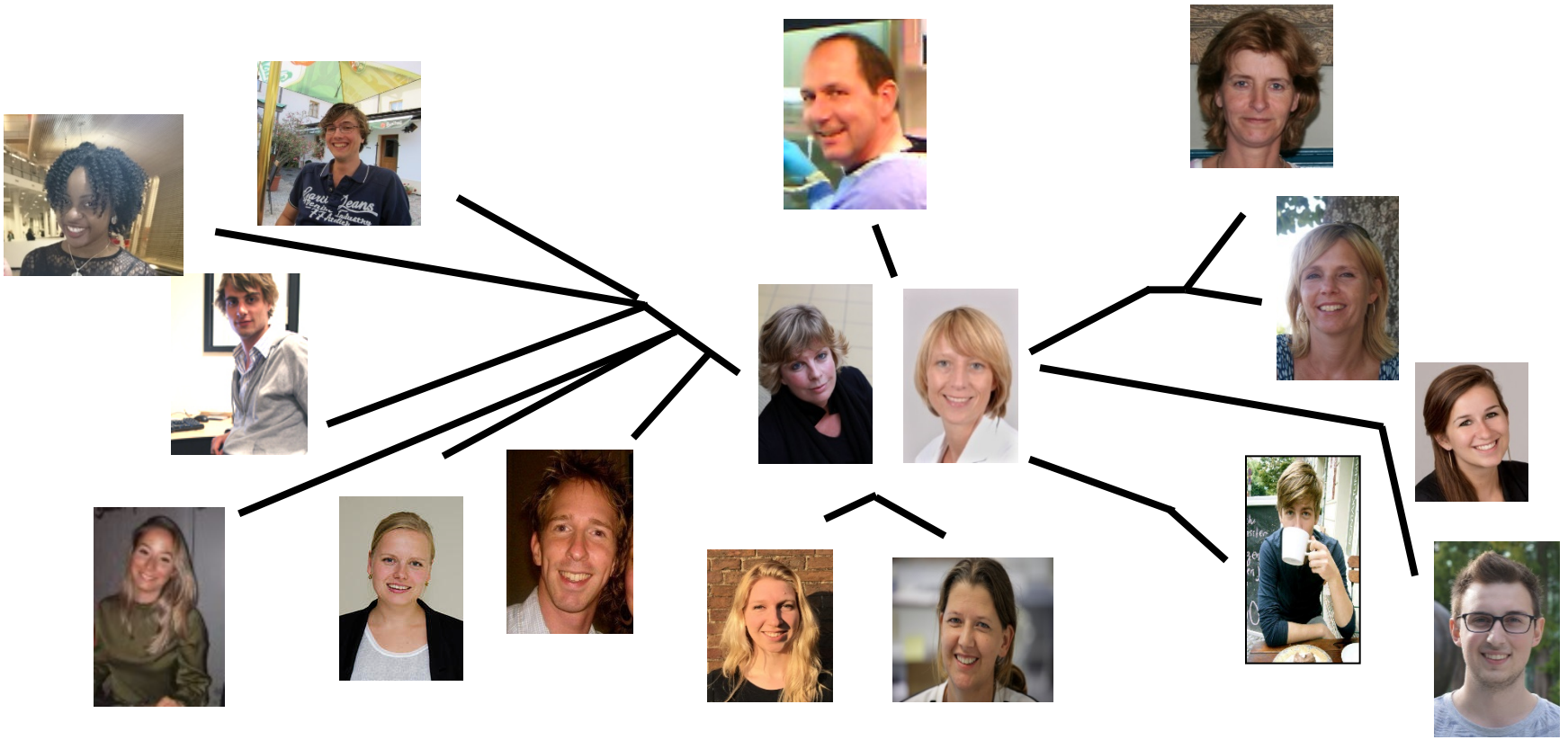

Acknowledgements

The IciStem consortium

Javier Martinez-Picado (Co-PI, Virologist, AIDS Research Institute IrsiCaixa, Barcelona)

Annemarie Wensing (Co-PI, Clinical Virologist, University Medical Center Utrecht)

Jose L. Díez Martin (Hematologist, Hospital Gregorio Marañón, Madrid)

Gero Hütter (Hematologist, Cellex Dresden)

Jürgen Kuball (Hematologist, University Medical Center Utrecht)

Monique Nijhuis (Virologist, University Medical Center Utrecht)

Vanderson Rocha (Hematologist Cord Blood Bank Specialist Oxford University)

Asier Sáez-Cirión (Immunologist,Pasteur Institute, Paris)

Julian Schulze zur Wiesch (Infectious disease specialist, UMC Hamburg-Eppendorf)

patients

IciStem research workgroup: Julià Blanco Institute IrsiCaixa, Barcelona), Jorge Carrill Institute IrsiCaixa, Barcelona), Johanna Eb Medical Center Hamburg-Eppendorf), Mi Kwon (Hematologist, Hospital Gregorio Marañón), **María Salgado** (Virologist, AIDS Research Institute IrsiCaixa, Barcelona)

Management team: Tineke Johnston and Josien Straver (Financial management/project assistance University Medical Center Utrecht), Laura Huyveneers (Medical coordination/IRB University Medical Center Utrecht), Pascual Balsalobre (Gregorio Marañón, Madrid), Judith Dalmau (AIDS Research Institute IrsiCaixa, Barcelona)

Scientific Advisors: Koen van Besien (New York-Presbyterian hospital)

IciStem participants

Belgium: Linos Vandekerckhove, Marie-Angélique de Scheerder, Eva Steel (University of Ghent)

Canada: Lisa Barrett, Sharon Oldford, Jill Moore, Clarissa Brisseau (NSHA/ Dalhousie University, Halifax)

Germany: Dieter Häussinger, Guido Kobbe, Björn Jensen (University

ena Knops (University of Cologne) Medical Center Hamburg-Eppendorf)

Italy: Alessandra Bandera, Antonio Muscatello and Alessandro Soria (San Gerardo Hospital, Monza, Italy), Gabriella Scarlatti, Simona Piemontese (Istituto Scientifico San Raffaele)

Netherlands: Pauline Ellerbroek, Lodewijk Brosens, Anke Bruns, Erik van Maarseveen (UMC Utrecht) Jan van der Meer, Sacha Zeerleder (AMC), Jaap Jan Boelens (University Medical Center Utrecht/Memorial Sloan Kettering Cancer Center, New York)

Spain: Jon Badiola, Manuel Jurado Chacón (Complejo Hospitalario Universitario de Granada), Raquel Saldana (Hospital General de Jerez de la Frontera), Luz Martín Carbonero (La Paz Hospital), Ildefonso Espigado (University Hospital Virgen del Rocío, Seville)

Sweden Piotr Nowak (Karolinska Institutet)

Switzerland Mitja Nabergoj, Alexandra Calmy (Hôpitaux Universitaires de Genève)

United Kingdom: Kavita Raj, Fabio Cruciani, Varun Mehra, Carmel Rice (Kings College Hospital, London) Angela Bailey (Imperial College Healthcare NHS Trust, London), Waseem Qasim (Institute of Child Health & Great