PERSONAL INFORMATION

Bernhard R. GENTNER

Affiliation: Centre Hospitalier Universitaire Vaudois (CHUV), Department of Oncology
Address: Rue du Bugnon 25a, 1005 Lausanne (VD), Switzerland

+41 79 556 90 20

bernhard.gentner@chuv.ch

https://www.unil.ch/dof/en/home/menuinst/research-labs/hi-tide--gentner.html

Sex Male| *Nationality* German

Enterprise	University	EPR
☐ Management Level	☐ Full professor	☒ Research Director and 1st level Technologist / First Researcher and 2nd level Technologist / Principal Investigator
☐ Mid-Management Level	☒ Associate Professor	☐ Level III Researcher and Technologist
☐ Employee / worker level	☐ Researcher and Technologist of IV, V, VI and VII level / Technical collaborator	☐ Researcher and Technologist of IV, V, VI and VII level / Technical collaborator

WORK EXPERIENCE

2022-current

Oak Professor in Immune- Stem Cell Engineering, University of Lausanne

- Attending Physician, Immuno-oncology Service, CHUV, Lausanne
- Group Leader, Human Integrated Tumor Immunology Discovery Engine (Hi-TIDe), Ludwig Institute for Cancer Research, Lausanne
- Translational Advisor & EU X-PAND Consortium Task Leader, San Raffaele Telethon Institute for Gene Therapy (SR-Tiget), Milano

2015-2022

Physician Scientist

San Raffaele Hospital and Telethon Institute for Gene Therapy

- Staff Haematologist & Independent Group Leader
- Determinants of treatment resistance in acute leukaemia (AIRC IG 2019-2023)
- Ex vivo expansion of hematopoietic stem and progenitor cells (TELETHON Core Grant)
- Clinical translation of novel gene transfer technologies (Project Leader and Co-PI, MPSIH gene therapy clinical study; NCT03488394)
- Development of gene therapy approaches for cancer (Phase I studies in Glioblastoma multiforme: NCT03866109)

Business or sector: Medicine, Biotechnology, Science (Academic)

2009-2015

Project Leader

San Raffaele Telethon Institute for Gene Therapy

- Study the biological role of microRNAs in hematopoietic stem cells and leukaemia
- Improved gene transfer into hematopoietic stem cells and its translation into the clinics
- Preclinical development of a cancer gene therapy protocol based on genetically engineered hematopoietic stem and progenitor cells

Business or sector: Biotechnology, Science (Academic)

EDUCATION AND TRAINING

2009-2014 **Specialist in Haematology** *70/70 (lode)*
Vita-Salute University, San Raffaele Hospital, Milan, Italy. Prof. Claudio Bordignon, Fabio Ciceri

2006-2009 **Post-Doctoral Training**
San Raffaele Telethon Institute for Gene Therapy, Milan, Italy. Prof. Luigi Naldini

EDUCATION AND TRAINING

2003-2006 **Internal Medicine Clinical Training**
University of Erlangen, Germany. Prof. Eckhart Hahn, Wolfgang Brueckl

1999-2004 **Doctoral Degree in Medicine (Ph.D. equivalent)** *Summa cum laude*
University of Heidelberg and German Cancer Research Center (DKFZ), Germany. Prof. Wolfgang Zeller, Stefan Fruehauf

1996-2003 **Medical School, M.D. Degree** *1.0, top 1% of students*
University of Heidelberg, Germany. MD Anderson Cancer Center & Baylor College of Medicine, Houston, TX, USA.

WORK ACTIVITIES

Awards ESGCT Young Investigator Award 2011, multiple best abstract awards and travel grants by ASH, ASGCT & EHA.

Editorial activity Regular peer reviewer for Nature Communications, Blood, Molecular Therapy and National & European granting agencies

Invited presentations >25 invited talks at European and International Symposia in the field of Gene Therapy, Hematology and Cancer.

Grants EIC Pathfinder Challenge X-PAND (2022-2026); AIRC IG (2019-23); TELETHON Core Grant (2016-21 & 2022-27), EHA Research Fellowship (2015-18)

Patents WO2010125471 (A2) - GENE VECTOR (granted and licensed to Genenta Science). Other 3 patent applications pending.

ADDITIONAL INFORMATION

Publications Scopus Author ID: 6507111312. Orcid ID: http://orcid.org/0000-0001-6024-4718
Selected publications (* shared first/last authorship)

Caserta C*, Nucera S*, […], Gentner B. miR-126 identifies a quiescent and chemo-resistant human B-ALL cell subset that correlates with minimal residual disease. **Leukemia**. 2023 Oct;37(10):1994-2005. doi: 10.1038/s41375-023-02009-5. PMID: 37640845

Naldini MM, […], Gentner B. Longitudinal single-cell profiling of chemotherapy response in acute myeloid leukemia. **Nat Commun**. 2023 Mar 8;14(1):1285.

Gentner B et al, Hematopoietic Stem and Progenitor Cell Gene Therapy for Hurler Syndrome**. N Engl J Med**. 2021 Nov 18;385(21):1929-1940. doi: 10.1056/NEJMoa2106596. PMID: 34788506. Impact Factor: 91.25. Citations: 2. Field-Weighted Citation Impact: 2.27.

Capo V, […], Gentner B & Villa A. Expanded circulating hematopoietic stem/progenitor cells as novel cell source for the treatment of TCIRG1 osteopetrosis. **Haematologica**. 2021 Jan 1;106(1):74-86. doi: 10.3324/haematol.2019.238261. PMID: 31949009. Impact Factor: 9.94. Citations: 7. Field-W. Citation Impact: 2.90.

Zonari E, […], Gentner B. Efficient Ex Vivo Engineering and Expansion of Highly Purified Human Hematopoietic Stem and Progenitor Cell Populations for Gene Therapy. **Stem Cell Reports**. 2017 Apr 11;8(4):977-990. doi: 10.1016/j.stemcr.2017.02.010. PMID: 28330619. Impact Factor: 7.77. Citations: 87. Field-W. Citation Impact: 5.19.

Chiriaco M et al, Gentner B*, Aiuti A*. Dual-Regulated Lentiviral Vector for Gene Therapy of X-linked Chronic

Granulomatosis. **Mol Ther**. 2014 Aug;22(8):1472-83. doi: 10.1038/mt.2014.87. PMID: 24869932. Impact Factor: 11.45. Citations: 50. Field-Weighted Citation Impact: 2.45.

Lechman ER*, Gentner B* et al. Attenuation of miR-126 activity expands HSC in vivo without exhaustion. **Cell Stem Cell**. 2012 Dec 7;11(6):799-811. doi: 10.1016/j.ccell.2015.12.011. doi: 10.1016/j.stem.2012.09.001. PMID: 23142521. Impact Factor: 24.63. Citations: 147. Field-Weighted Citation Impact: 3.74

Gentner B et al. Identification of Hematopoietic Stem Cell-specific miRNAs Enables Gene Therapy of Globoid Leukodystrophy. **Sci Transl Med**. 2010 Nov 17;2(58):58ra84. doi: 10.1126/scitranslmed.3001522. PMID: 21084719. Impact Factor: 18.00. Citations: 160. Field-Weighted Citation Impact: 15.65.

Brown BD*, Gentner B* et al. Endogenous microRNA can be broadly exploited to regulate transgene expression according to tissue, lineage and differentiation state. **Nat Biotechnol**. 2007 Dec;25(12):1457-67. doi: 10.1038/nbt1372. PMID: 18026085. Impact Factor: 54.91. Citations: 437. Field-Weighted Citation Impact: 10.3.

Contributions to Science (narrative)

Early career achievements: As a medical student, I established methods that allowed to determine retroviral integration sites in the genome of human hematopoietic stem cells (HSC). My work was one of the first to suggest that retroviral vector integration in repopulating HSC occurred semi-randomly, with demonstration of several chromosomal hotspots before this concept became known in the gene therapy community. This work was published as Laufs*, Gentner* et al., ***Blood*** 2003 (co-first author) and Gentner et al., ***Gene Therapy*** 2003. As a Post-Doc in Luigi Naldini's lab, I developed novel lentiviral vector tools, which allowed single cell miRNA expression profiling and stable miRNA gain- and loss-of-function studies. These tools were then applied to study the function of miRNAs in the hematopoietic system, and to identify HSC-specific miRNAs that could be exploited to eliminate ectopic transgene expression and hence, toxicity, in stem and progenitor cells. Such regulated vectors form the basis for an HSC gene therapy approach against cancer, developed by Genenta Science. Major publications emerging from this work include Brown*, Gentner* et al., ***Nat Biotechnol*** 2007, Gentner et al, ***Nat Methods*** 2009, Gentner et al., ***Sci Transl Med*** 2010 (* co-first author).

Achievements as a TIGET Project Leader (transition phase towards independence): In parallel to my clinical training in Hematology, I coordinated a research group focused around elucidating the biological function of microRNAs in hematopoietic cells. In collaboration with Dr. John Dick, we defined the role of microRNA-126 as a regulator of the self-renewal-quiescence equilibrium in normal HSC (Lechman*, Gentner* et al, ***Cell Stem Cell*** 2012- co-first author), while its quiescence-inducing effect is crucial for leukemic stem cells to support AML persistence and chemotherapy-resistance (Lechman*, Gentner* et al, ***Cancer Cell*** 2016- co-first author). Opposing outcomes of miR-126 inhibition in normal versus malignant stem cells, i.e. expansion versus exhaustion, respectively, highlighted the therapeutic potential of this approach. Other studies focused on functional aspects of miR-155 (Zonari et al, ***Blood*** 2013- co-last author) and miR-223 biology in steady state and stress hematopoiesis, such as the presence of a tumor. I also performed translational gene therapy research, designing the culture conditions that allowed the first demonstration of relevant levels of site-specific gene targeting in human long-term repopulating HSC (Genovese et al, ***Nature*** 2014- collaborator). I contributed to the development of safe and effective gene therapy for chronic granulomatous disease (Chiriaco et al, ***Mol Ther*** 2014- co-last author) applying the miRNA-de-targeting strategy, which also emerged as a key strategy to expand the therapeutic window of a cancer gene therapy approach based on tumor-targeted type 1-interferon delivery through genetically engineered HSC (Escobar et al, ***Sci Transl Med*** 2014- collaborator).

Achievements as an independent Group Leader Physician Scientist: Following up on the miR-126 studies, my group demonstrated that its uncontrolled expression in HSPC causes B-ALL in mice, where it orchestrates a comprehensive oncogenic program and its experimental downregulation leads to complete leukemia regression and cure of the mice (Nucera et al., ***Cancer Cell*** 2016- co-last and corresponding author). Further studies in human primary B-ALL and AML are highlighting the involvement of miR-126 in chemotherapy resistance (Caserta et al, ***Leukemia*** 2023- last author; Naldini et al, ***Nat Commun*** 2023- last author). *Ex vivo* hematopoietic stem cell gene therapy has become a major translational focus of my group. We have developed next-generation lentiviral protocols based on short culture, transduction enhancers, highly purified HSC and *ex vivo* expansion (Zonari et al., ***Stem Cell Reports*** 2017- last and corresponding author). I was leading the preclinical and manufacturing studies to translate a next-generation ex vivo HSC transduction protocol to the clinics, in the framework of a Phase I/II first in human gene therapy study for patients affected by Mucopolysaccharidosis type 1 Hurler (Gentner et al, ***N Engl J Med*** 2021). Currently, I am leading the development of a first-in-man study employing genetically-engineered, *ex vivo* expanded HSC for the treatment of infantile malignant osteopetrosis (Phase I/II study to open in 2025). Moreover, exploiting the miRNA de-targeting technology, I developed HSC gene therapy approaches against cancer based on the local delivery of type I or type II interferon (Escobar et al, ***Nat Commun*** 2018- co-last and corresponding author; Mucci et al, ***EMBO Mol Med*** 2021- last author). A clinical trial exploring HSC-based Interferon gene therapy in patients with glioblastoma multiforme is showing feasibility, safety and signs of biological activity (Gentner et al, *manuscript in preparation*).