February 2022
Centre de Recherche des Cordeliers (CRC),
Paris, France,

Cover Letter
Hojjatollah Nozad Charoudeh
Tabriz University of Medical Sciences
Email: nozadh@tbzmed.ac.ir

Dear Recruitment Committee,

I am writing to express my interest in applying for a junior or senior group leader position (Based on evaluation) in the area of immuno-oncology with focus on Immunotherapy for Cancer.

I have completed my PhD in subject of hematopoietic stem cell biology in the Stem Cell Research Center at Lund University, Sweden (2006-2010). Subsequently I did my postdoctoral training in Immunotherapy field in the Biomedicine department, Basel University, Switzerland (2010-2011). I am currently an associate professor in the Department of Anatomical sciences in Tabriz University of Medical Sciences.

During my PhD training, I have worked on the molecular and cellular pathways of NK cell development and in postdoctoral, I extended my work on human NK cells. Those works led to the several highly cited publications. I have developed several cell lines, performed gene analysis, Flow cytometry and advanced molecular techniques.

Currently, I have my own PhD and master students and they are working on Leukemia stem cell markers and NK cell therapy for cancer (CD16 and KIR+ NK cells), which were published in several journals and also my research is ongoing in developing NK cell productivity in counter with different cancer stem cells like AML, Breast Cancer (TNBC) and colorectal cancer.

I am currently teaching anatomy, cancer and stem cell biology courses to postgraduate, undergraduate and medical students.

I am in the pipeline using AML, colorectal and breast cancer cell lines expressing CD34 markers. CD34 positive cells are evaluating for mitochondrial activity, telomere length, and telomerase activity and also for stem cell genes, anti-apoptotic, and pre-apoptotic genes. Our main goal is finding cancer stem cell biomarkers and targeting them with cord blood derived NK cells. We are stablishing Dendritic cells stimulation with Cancer RNA to personalize immunotherapy.

Centre de Recherche des Cordeliers (CRC) is well equipment for my work and also, outstanding researchers in the center would be benefit for developing my research in immunotherapy, therefore CRC is one of the elite scientific centers in the world and I believed my qualifications and experiences in research and teaching skills that I have obtained during the past years working with postgraduate and medical students would allow me to contribute to the permissive environment of this institute.

Based on my experiences in research and student training, I am fully convinced that I am able to fulfil the goals of research in the area of immuno-oncology and Immunotherapy.

I am looking forward to hearing from you and discuss these further in the near future. Meanwhile please don't hesitate to contact me if you have any further questions.

Yours Sincerely,

Hojjatollah Nozad Charoudeh PhD

CURRICULUM VITAE

Hojjatollah Nozad Charoudeh

I. Personal information

Name: Hojjatollah Nozad Charoudeh

Place & Date of Birth: Iran, 1969-05-23

Marital Status: Married & 2 children

Position: Associate professor, Tabriz University of Medical Sciences

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ORCID: http://orcid.org/0000-0003-4883-9924

Scopus ID: Scopus Author ID 26423470000

Research ID: Researcher L-6452-2017

II. Educational records:

2010- 2011: Postdoctoral, Immunotherapy laboratory, Biomedicine department, Basel University, Switzerland

2006-2010: PhD student, Stem cell centre, Lund University, Sweden

1994-1997: M.SC of Anatomy, Ahwaz University, Iran

1987-1991: B.SC of physiotherapy, Ahwaz University, Iran

III. Academic experiences:

2015-currently: Associate professor in anatomical Sciences Department, Stem Cell Biology

2014-2017: Head of Stem Cell Research Centre, Tabriz University of Medical Sciences, Iran

2012-2015: Assistant professor in Anatomy Department, Faculty of Medicine, Tabriz University of medical science, Iran

1998-2005: Instructor, Anatomical Department, Ardabil University of Medical science, Iran

2017- currently: Associate editor of Advanced Pharmaceutical Bulletin (APB)

IV. Teaching statement

Subject area competence and current teaching activity

1. Anatomical courses in Faculty of Medicine:
Gross anatomy (Trunk, head and neck, neuroanatomy), practical and theoretical courses, Advanced cellular and molecular techniques for PhD students
2. Stem cell biology and Cancer biology in Advanced Research school of Medical Sciences
3. Flow cytometry analysis course in Research centres

V. Supervision of Graduate student thesis and grants

1. KIR+ NK cells transplantation following GVHD in transplanted HSC patients, one PhD student (2020-2023)
2. Cord Blood derived KIR positive NK cells against cancers, one PhD student, 2 Master students (2019-2022)
3. Leukemia stem cell and Breast cancer stem cells, exploring Stemness context with inhibition of telomere and mitochondria, one PhD student, 3 Master students (2019-2023)
4. Evaluation of AML stem cell with inhibition of the mitochondria and telomeres activity, one master student (2017-2019)
5. Cord blood stem cell derived NK cell application for immune cell therapy for Leukemia (2016-2018)
6. Cord blood derived NK cells (CD16+ and KIR+ NK cells) properties, two PhD students (2015-2021)
7. Relationship between inhibition and activation of PI3K and AKT signaling with regulation of P53 and P10 genes, one PhD student, 3 Master students (2015-2017)
8. Evaluation of NK cells derived from cord blood CD34 positive cells, one master students (2015- 2018)
9. The effect of NF-KB and TDT inhibition on the leukemia stem cell derived acute lymphoblastic leukemia, one PhD student (2014-2016).
10. Evaluation of TDT expression and its inhibitor in cord blood CD34+ cells toward Lymphocytes, two Master students (2014-2015)
11. Evaluation of C-rel express and its inhibitor on lymphoid cell derive cord blood cells, two Master students (2014-2015).
12.Inhibition of SDF in liver cell development, apoptosis context of Anti SDF in Liver hepatocytes, two Master students. (2013-2014)

13. Evaluation of Cd26 population in cord blood stem cell, two Master students (2012-2013)

VI. Organizational contribution

1. Member of the Scientific committee of Anatomical sciences Department, Stem cell Research center and Biotechnology Research Center in Tabriz University of Medical Sciences(2014-currently)
2. Associate editor of Advanced Pharmaceutical Bulletin (APB)and consultant editor of Dove press journals
3. Supervision and evaluation of principal investigators reports of 3 national grants.
4. awarded 8 master students' theses from private universities (Bonab Azad university and Rabb Rashidi university)
5. Collaboration with Stem Cell Research center, Drug applied research center and Applied Cell Sciences department (5 PhD students' thesis in collaboration)
6. Collaboration with Sahand Technical University for establishing bioreactors for the expansion of cells for transplantation

VII. External Funding

1. National Research grant from council for development of stem cell sciences and technologies (2015-2017)
2. 5 Grants from private university (Bonab Azad University and Rabb Rashidi University) (2014-2020)

IIX. Conference and meetings:

1. ISEH, 38th Annual Scientific Meeting, Athens September 2009
2. Natural Killer Cell Symposium Mainz, Germany April 18 - 20, 2011
3. 11th International conference of Immunology & Allergy, IRAN, April 2012
4. NK2012 symposium Heidelberg, September 2012

IX. Awards:

2013: Short scholarship grant, EMBO
2012: Research fund in Tabriz University of Medical Sciences
2010: Postdoctoral, Immunotherapy Department, Basel university, Switzerland
2009: Short scientific grant for 6 months, Lund University.
2006: PhD scholarship, Ministry of Health of Iran

List of Publications:

1. Generated Cord Blood derived KIR+NK cells efficiently eradicated leukemia cells.
   Khadijeh Dizaji Asl, Ali Akbar Movassaghpour, Majid Mahdavi, Hamid Tayefi Nasrabadi, **Hojjatollah Nozad Charoudeh** (Submitted, 2022).

2. Inhibition of Telomerase and Mitochondria prohibited growth of Triple Negative Breast Cancer.
   Zeinab Mazloumi, Ali Rafat, Khadijeh Dizaji Asl, Mohammad Karimipour, Dariush Shanehbandi, Mehdi Talebi, Majid Montazer, Ali Akbar Movassaghpour, Alireza Dehnad, Raheleh Farahzadi, **Hojjatollah Nozad Charoudeh.** (Submitted, 2022)

3. Inhibition of telomerase increased the cytotoxicity of peripheral blood NK cell cytotoxicity against Breast Cancer Stem Cells.
   Zeinab Mazloumi, Ali Rafat, Khadijeh Dizaji Asl, **Hojjatollah Nozad Charoudeh** (Submitted, 2022)

4. Effect of Aberrant DNA Methylation on Cancer Stem Cell Properties
   Zeinab Mazloumi, Raheleh Farahzadi, Ali Rafat, Khadijeh Dizaji Asl, Mohammad Karimipour, Majid Montazer, Ali Akbar Movassaghpour, Alireza Dehnad, **Hojjatollah Nozad Charoudeh**. (Experimental and Molecular Pathology, 2022, Accepted)

5. Telomerase inhibition on Acute myeloid leukemia stem cell induced apoptosis with both intrinsic and extrinsic pathways.
   Ali Rafata, Raheleh Farahzadi, Zeinab Mazloumi, Ali Akbar Movassaghpour, Babak Nejati, **Hojjatollah Nozad Charoudeh** (Life Sciences, 2022, https://doi.org/10.1016/j.lfs.2022.120402)

6. Telomerase-based therapies in hematological malignancies.
   Ali Rafata, Khadijeh Dizaji Asl, Zeinab Mazloumi, Ali Akbar Movassaghpour, Raheleh Farahzadi, Babak Nejati, **Hojjatollah Nozad Charoudeh, ***Cell Biochemistry and Function, 2022, DOI: https://doi.org/10.1002/cbf.3687)

7. Performance evaluation of a novel conceptual bioprocess for clinically-required mass production of hematopoietic cells.
   Leila Shafiei Kaleybar, Ali Baradar Khoshfetrat, Reza Rahbarghazi, **Hojjatollah Nozad Charoudeh** (Biotechnology Letters, 2021, https://doi.org/10.1016/j.fbp.2020.04.012).

8. Profiling the expression of pro-metastatic genes in association with the clinicopathological features of primary breast cancer.
   Seyed-Mohammad Mazloomi, Mitra Foroutan-Ghaznavi, Vahid Montazeri, Gholamreza Tavoosidana, Ashraf Fakhrjou, **Hojjatollah Nozad-Charoudeh**, Saeed Pirouzpanah (Cancer Cell International, 2021, 21:6 https://doi.org/10.1186/s12935-020-01708-8).

9. The Role of KIR positive NK cells in diseases and its importance in clinical intervention.
   Khadijeh Dizaji Asl, Kobra Velaei, Ali Rafat, Hamid Tayefi Nasrabadi, Ali Akbar Movassaghpour, Majid Mahdavi, **Hojjatollah Nozad Charoudeh**.
   (International Immunopharmacology, Volume 92, March 2021, 107361)

10. Cord blood stem cell derived CD16+ NK cells eradicated acute lymphoblastic leukemia cells using with anti-CD47 antibody.
    Behnaz valipour, Ali Abedelahi, Elahe Nadeali, Kobra Velaei, Aliakbar Movassaghpour, Mehdi Talebi, Soheila montazersaheb, Hadi Chavoshi, and **Hojjatollah Nozad Charoudeh**, (Life Sciences,2020, 242:117223).

11. Modeling and performance prediction of a conceptual bioprocess for mass production of suspended stem cells.
    Shafiei Kaleybar, L., Khoshfetrat, A.B., Nozad Charoudeh, H., (Food and Bioproducts Processing, 2020, 122, 254-268)

12. Low-level laser irradiation modulated viability of normal and tumor human lymphocytes in vitro.
    Bagheri, H.S., Rasta, S.H., Mohammadi, S.M., Movassaghpour, A., Charoudeh, H.N. (Journal of Lasers in Medical Sciences, 2020, 11(2),174-180, 29).

13. Positive effects of PI3K/Akt signaling inhibition on PTEN and P53 in prevention of acute lymphoblastic leukemia tumor cells.
    Elahe Naderali, Behnaz Valipour, Amir Afshin Khaki, Jafar Soleymani Rad, Alireza Alihemmati, Mohammad Rahmati, **Hojjatollah Nozad Charoudeh***, (Adv Pharm Bull, 2019, 9(3), 473-486)

14. Telomere shortening as a hallmark of stem cell senescence.
    Fathi E, **Charoudeh HN**, Sanaat Z, Farahzadi R., (Stem Cell Investig. 2019 Mar 6:7. doi: 10.21037/sci.2019.02.04)

15. NK cells: An attractive candidate for cancer therapy.
    Valipour B, Velaei K, Abedelahi A, Karimipour M, Darabi M, **Charoudeh HN**. (J Cell Physiol. 2019 Nov;234(11):19352-19365)

16. Streptomyces Levis ABRIINW111 Inhibits SW480 Cells Growth by Apoptosis Induction.
    Behnaz Faramarzian Azimi Maragheh, Parisa Fatourachi, Seyede Momeneh Mohammadi, Behnaz Valipour, Meysam Behtari, Alireza Dehnad*, Hojjatollah Nozad Charoudeh*, (Adv Pharm Bull, 2018, 8(4), 675-682)

17. Prolonged incubation with Metformin decreased angiogenic potential in human bone marrow mesenchymal stem cells.
    Montazersaheb S, Kabiri F, Saliani N, Nourazarian A, Avci ÇB, Rahbarghazi R, **Nozad Charoudeh H**. (Biomed Pharmacother. 2018; 108:1328-1337)

18. Advances in nanomaterial based optical biosensing and bioimaging of apoptosis via caspase-3 activity.
Khalilzadeh B, Shadjou N, Kanberoglu GS, Afsharan H, de la Guardia M, **Charoudeh HN**, Ostadrahimi A, Rashidi MR, (Mikrochim Acta. 2018 Aug 29;185(9):434)

19. Culture filtrate ether extracted metabolites from Streptomyces levis ABRIINW111 increased apoptosis and reduced proliferation in acute lymphoblastic leukemia Behnaz Valipoura , Seyede Momeneh Mohammadi, Ali Abedelahi, Behnaz Faramarzian Azimi Maragheh, Elahe Naderali, Alireza Dehnad, **Hojjatollah Nozad Charoudeh**, (Biomedicine & Pharmacotherapy 108 (2018) 216–223)

20. Regulation and modulation of PTEN activity.
Naderali E, Khaki AA, Rad JS, Ali-Hemmati A, Rahmati M, **Charoudeh HN**, (Mol Biol Rep. 2018 Aug 25. doi: 10.1007/s11033-018-4321-6)

21. Extracted metabolite from *Streptomyces Levis* ABRIINW111 altered the gene expression in colon cancer.
Parisa Fatourachi, Behnaz Faramarziyan Azimi Maragheh, Seyede Momeneh Mohammadi, Behnaz Valipour, Alireza Dehnad, **Hojjatollah Nozad Charoudeh**, (Gastroenterol Hepatol Bed Bench, 2018, 11(1):34-41).

22. Telomerase activity and telomere on stem progeny senescence.
Balal Brazvan, Abbas Ebrahimi-Kalanb,, Kobra Velaei, Ahmad Mehdipour, Zeynab Aliyari serej, Ayyub Ebrahimi, Mohammad Ghorbani, Omid Cheraghih, **Hojjatollah Nozad Charoudeh**, (Biomedicine & Pharmacotherapy, 2018, 102: 9–17)

23. Farnesiferol C induces cell cycle arrest and apoptosis mediated by oxidative stress in MCF-7 cell line.
Davoud Hasanzadeh, Majid Mahdavia, Gholamreza Dehghan, **Hojjatollah Nozad Charoudeh**, (Toxicology Reports, 2017, 4: 420–426)

24. Rapamycin Inhibits Expansion of Cord Blood Derived NK and T cell.
Monireh Zare, Behnaz Valipour, Seyede Momeneh Mohammadi, Mohammad Nouri, Aliakbar Movassaghpour, **Hojjatollah Nozad Charoudeh**, (*Iran J Immunol. 2017; 14(3):192-199)*

25. Inhibition of c-REL using siRNA increased apoptosis and decreased proliferation in pre-B ALL blasts: Therapeutic implications.
Seyedeh Momeneh Mohammadi, Daryosh Mohammadnejad, Abbas Ali Hosseinpour Feizi,Ali Akbar Movassaghpour, Soheila Montazersaheba, **Hojjatollah Nozad Charoudeh**, (Leukemia Research, 2017, 61: 53-61)

26. Terminal Deoxynucleotidyl Transferase (TdT) Inhibition of Cord Blood Derived B and T Cells Expansion.
Sanaz Gholami, Seyede Momeneh Mohammadi, Aliakbar Movasaghpour Akbari, Ali Abedelahi, Alireza Alihemmati, Shirin Fallahi, **Hojjatollah Nozad Charoudeh**, (Adv Pharm Bull, 2017, 7(2), 215-220)

27. Regulation and roles of CD26/DPPIV in hematopoiesis and diseases.
Aliyari Serej Z, Ebrahimi Kalan A, Mehdipour A, **Nozad Charoudeh H**, (Biomed Pharmacother. 2017, Apr 24; 91:88-94)

28. Cord Blood Cells Responses to IL2, IL7 and IL15 Cytokines for mTOR Expression.
Anahita Mohammadian, Elahe Naderali, Seyedeh Momeneh Mohammadi, Aliakbar Movasaghpour, Behnaz Valipour, Mohammad Nouri, **Hojjatollah Nozad Charoudeh**, (Adv Pharm Bull, 2017, 7(1), 81-85)

29. Immunotherapy for B-acute Lymphoblastic Leukemia by Focusing on Monoclonal Antibody and CAR-T-cell Application.
Seyedeh M Mohammadi, Daryosh M Nejad, **Hojjatollah N Charoudeh**, (International Journal of Hematology and Oncology, 2017, 27(1), 227-238)

30. Genetic alterations in B-acute lymphoblastic leukemia.
Seyedeh Momeneh Mohammadi, Daryosh Mohammad Nejad, **Hojjatollah Nozad Charoudeh**, (Acta Haematologica Polonica, 2017, 48(1), 10-17)

31. Impact of C-rel Inhibition of Cord Blood-derived B-, T-, and NK cells.
Shirin Fallahi, Seyede Momeneh Mohammadi, Hamid Tayefi Nasrabadi, Alireza Alihemmati, Naser Samadi, Sanaz Gholami, Dariush Shanehbandi, and **Hojjatollah Nozad Charoudeh**, (Journal of Immunotoxiciology, 2017,14(1): 15–22)

32. L-carnitine contributes to enhancement of neurogenesis from mesenchymal stem cells through Wnt/β-catenin and PKA pathway.
Ezzatollah Fathi, Raheleh Farahzadi and Hojjatollah Nozad Charoudeh, (Experimental Biology and Medicine 2017; 0: 1–5. DOI: 10.1177/1535370216685432)

33. Platelet-Derived Ectosomes Reduce NK Cell Function.
Salima Sadallah, Laurent Schmied, Ceylan Eken, **Hojjatollah Nozad Charoudeh**, Francesca Amicarella, Jürg A Schifferli, (The Journal of Immunology, 2016: 1663-1671).

34. Key Immune Cell Cytokines affects the Telomere Activity of Cord Blood Cells In Vitro.
Balal Brazvan. Raheleh Farahzadi. Seyede Momeneh Mohammadi. Soheila Montazer Saheb. Dariush Shanehbandi. Laurent Schmied. Jafar Soleimani Rad Masoud Darabi. **Hojjatollah Nozad Charoudeh**, (Adv Pharm Bull. 2016; 6(2):153-161)

35. Morphine Inhibited the Rat Neural Stem Cell Proliferation Rate by Increasing Neuro Steroid Genesis.
Feizy N, Nourazarian A, Rahbarghazi R, **Nozad Charoudeh H**, Abdyazdani N, Montazersaheb S, Narimani M. (Neurochemical Research volume 2016, 41: 1410–1419)

36. , Ultrasensitive caspase-3 activity detection using an electrochemical biosensor engineered by gold nanoparticle functionalized MCM-41: Its application during stem cell differentiation.
Balal Khalilzadeh, **Hojjatollah Nozad Charoudeh**, Nasrin Shadjou, Rahim Mohammad-Rezaei, Yadollah Omidi, Kobra Velaei, Zeinab Aliyari, Mohammad-Reza Rashidi (Sensors and Actuators B: Chemical, 2016, 231, 561-575)

37. Cord blood mononuclear cells have a potential to produce NK cells using IL2Rg cytokines.
Nahid Khaziri, Momeneh Mohamadi, Zeinab Aliyari, Jafar Soleimani Rad, Hamid Tayefi Nasrabadi, **Hojjatollah Nozad Charoudeh**, (Adv Pharm Bull, 2016, 6(1), 5-8)

38. Indirect coculture of stem cells with fetal chondrons using PCL electrospun nanofiber scaffolds.
Parisa Nikpou, Jafar Soleimani Rad, Daryoush Mohammad Nejad, Nasser Samadi, Leila Roshangar, Amir Mohammad Navali, Hajar Shafaei, **Hojjatollah Nozad Charoudeh**, Neda Danandeh Oskoei, Sara Soleimani Rad, (Artificial Cells, Nanomedicine, and Biotechnology, 2016, ahead of publish)

39. Potent anti-angiogenic and cytotoxic effect of conferone on human colorectal adenocarcinoma HT-29 cells.
Omid Cheraghi, Gholamreza Dehghan, Majid Mahdavi, Reza Rahbarghazi, Aysa Rezabakhsh, **Hojjatollah Nozad Charoudeh**, Mehrdad Iranshahi, Soheila Montazersaheb, (Phytomedicine, 2016: (24)398–405)

40. Advantages of Sheep Infrapatellar Fat Pad Adipose Tissue Derived Stem Cells in Tissue Engineering. Parviz Vahedi, Jafar Soleimanirad, Leila Roshangar, Hajar Shafaei, Seyedhosein Jarolmasjed, **Hojjatollah Nozad Charoudeh**, (*Adv Pharm Bull*. 2016; 6(1): 105-110)

41. Hepatocyte differentiation of human induced pluripotent stem cells is modulated by stearoyl-CoA desaturase 1 activity.
Yaghoub Rahimi, Amir Mehdizadeh, **Hojjatollah Nozad Charoudeh**, Mohammad Nouri, Kobra Valaei, Shabnam Fayezi, Masoud Darabi, (Development, growth & differentiation, 2015: 667-674)

42. The roles of IL-2, IL-7, and IL15 Ligands in B Cells development from Cord Blood Mononuclear Cells.
Aliyari Z., Alami F., Mostafavi T., Taiefi Nasrabadi H., Soleimanirad J., **Nozad Charoudeh H.,** (Iranian Journal of Pediateric Hematology Oncology, 2015, 5(3): 156-162)

43. Reliable self-assembled peptide based electrochemical biosensor for detection of caspase 3 activity and apoptosis Khalilzadeh B., Shadjou N., Morteza Eskandani M., **Hojatollah Nozad Charoudeh,** Omidi Y., and Rashidi MA., (RSC Adv**.**, 2015,**5**, 58316-58326)

44. Key immune cell cytokines have a significant role in the expansion of CD26 population of cord blood mononuclear cells.
Aliyari Z., Khaziri, N., Brazvan B., Sayyah Melli M., Tayefi Nasrabadi H., Akbarzadeh, A., **Nozad Charoudeh H.** (Artificial Cells, Nanomedicine, and Biotechnology, 2016, 44(5), 1303-1310)

45. CD26+ Cord Blood Mononuclear Cells Significantly Produce B, T, and NK Cells.
Aliyari Z, Alemi F, Brazvan B, Tayefi Nasrabadi H, **Nozad Charoudeh H**., (Iran J Immunol. 2015 Mar;12(1):16-26).

46. IL2rg Cytokines Enhance Umbilical Cord Blood CD34+ Cells Differentiation to T Cells.
Aliyari Z., Soleimanirad S., Sayyah Melli M., Tayef Nasrabad H., **Nozad Charoudeh H.,** (Adv Pharm Bull, 2015 Dec;5(Suppl 1):615-9)

47. Modulation of KIR Repertoire by Cytomegalovirus Infection.
Hojjatollah Nozad Charoudeh, Karol Czaja, Asensio Gonsalez, Karin Schmitter, Martin Stern, (Eur J Immunol. 2013, 43(2):480-7.)

48. Quantity of HLA-C surface expression and licensing of KIR2DL+ natural killer cells.
Hojjatollah Nozad Charoudeh, Laurent Schmied, Asensio Gonzales, Grzegorz Terszowski, Karol Czaja, Karin Schmitter, Andreas Buser, and Martin Stern, (Immunogenetics, 2012, 64:739-745)

49. A polymorphism affecting HLA-C surface expression associates with herpes simplex virus and cytomegalovirus immunoglobulin G seropositivity.
Hojjatollah Nozad Charoudeh, Karin Schmitter, Andreas Buser, Asensio Gonsalez,Martin Stern, (Tissue Antigens, 2012, 80:263-264)

50. Emergence of NK cell progenitors and functionally competent NK cell lineage subsets in the early mouse embryo.
Yanjuan Tang*, Claudia Peitzsch*, **Hojjatollah Nozad Charoudeh** *, Min Cheng, Patricia Chaves, Sten Eirik W. Jacobsen and Ewa Sitnicka,(* Equal contribution), (Blood, 2012, 120:63-75)

51. Identification of a NK/T cell restricted progenitor in adult bone marrow contributing to bone marrow and thymic-dependent NK cells.
Hojjatollah Nozad Charoudeh, Yanjuan Tang, Min Cheng, Sten Erik W. Jacobsen and Ewa Sitnicka, (Blood, 2010, 116: 183-192)

52. Distinct and overlapping patterns of cytokine regulation of thymic and bone marrow derived NK cell development.
Min Cheng*, **Hojjatollah Nozad Charoudeh***, Petter Brodin, Yanjuan Tang, Tadepally Lakshmikanth, Petter Höglund, Sten Eirik W. Jacobsen and Ewa Sitnicka (* Equal contribution), (The journal of immunology, 2009, 182:1460-8)

53. FLT3 receptor and ligand are dispensable for maintenance and post-transplantation expansion of mouse hematopoietic stem cells.
Natalija Buza-Vidas, Min Cheng, Sara Duarte, **Hojjatollah Nozad Charoudeh**, Sten Eirik W. Jacobsen and Ewa Sitnicka, (Blood, 2009, 113:3453-60.)

54. IL-8 induces imbalances between nitric oxide and endothelin-1, and also between plasminogen activator inhibitor-1 and tissue-type plasminogen activator in cultured endothelial cells.
Min Cheng, Yi Li, Jiang Wu, Yongmei Nie, Liang Li, Xiaojing Liu, **Hojjatollah Nozad Charoudeh** and Huaiqing Chen, (Cytokine,2008 ,41:9-15)

55. Crucial role of FLT3 ligand in immune reconstitution after bone marrow transplantation and high-dose chemotherapy.
Natalija Buza-Vidas, Min Cheng, Sara Duarte, **Hojjatollah Nozad**, Sten Eirik W. Jacobsen, and Ewa Sitnicka, (Blood, 2007, 110: 424-432)

Research statement and Future Plan

Title: Immunotherapy for *Cancer Stem Cells*

Investigator: Hojjatollah Nozad Charoudeh

Background

Cancer stem cells (CSCs) are a small cell subpopulation within tumors that possess characteristics associated with normal stem cells with self-renewal, differentiation, and tumorigenicity properties when transplanted into an animal host. CSCs exhibit anti-cancer treatment resistance which can render conventional chemo- and radio-therapies ineffective. The most common preleukemic mutations as well as the mutations in breast cancer stem cells (BCSCs) occur in the DNA methyltransferase 3A (*DNMT3A*) and ten-eleven translocation 2 (*TET2*) genes. Additional genes mutated during the initiating phase include isocitrate dehydrogenase 1 and 2 (*IDH1/2*) and aldehyde dehydrogenase 1 (ALDH1) along with NF-κ B. In cancer stem cells, one important issue is maintaining the telomere activity. A critical length of telomere repeats is required to ensure proper telomere function and prevent the activation of DNA damage pathways which result in replicative senescence or cell death. Cancer stem cells (CSCs) have been suggested to be responsible for tumor re-growth and relapse. Energy metabolism and mitochondrial function are important factors for stemness maintenance and cell fate characteristics. Due to the role of mitochondria as central hubs in the overall cell metabolism as well as in death and survival pathways, research on their physiology in CSCs is highly important to decipher the mechanisms underlying their therapy-resistant phenotype.

These facts have prompted the investigation of alternative therapeutic strategies, particularly induction of immune responses against tumors. NK cells are a subset of lymphocytes that respond to IFN-γ and IL- 2 during infection with viruses and other intracellular pathogens. Functional variability in the NK cell repertoire is the result of clonally distributed expression of Killer cell Immunoglobulin-like Receptors (KIR). Patients treated with KIR ligand mismatched haploidentical grafts therefore benefit from a dramatically reduced incidence of disease relapse and increased survival (50% with KIR ligand mismatch versus 10% without). The relationship between telomere, mitochondrial activity, and altered genes in cancer stem cells is very important to find a key biomarker in cancer stem cells. Also, in parallel cord blood derived NK cells functionality and enrichment improvement would be helpful to find a cell therapy strategy.

Current research and Experimental plan

Our work focused on NK cells derived from cord blood stem cells. NK cell enrichment (both CD16+ and KIR+ NK cells) using combinations of different cytokines is established, and their cytotoxicity against tumors is tested. Evaluation of cord blood CD16+ NK cells against breast cancer and leukemia using CD47 antibody is under investigation. CD47 is overexpressed on both cancer and cancer stem cells. The CD47 receptor interacts with macrophages and calls them not to scavenge it. We seek to increase CD16+ NK cells cytotoxicity while also benefiting from macrophages against cancer. CD16+ NK cells generated efficiently from CD34 positive cord blood cells in vitro using IL-2, IL-15 and IL-21 cytokines and cord blood CD34 positive derived CD16+ NK cells with using anti CD47 blocking antibody eliminated cancer cells

(ADCC activity of NK cells) and efficiently increased apoptosis in ALL cells. We also evaluated KIR+NK cells for cytotoxicity. We established KIR+ NK cells expansion from cord blood stem cells and we are establishing its cytotoxicity against different leukemia. Maybe Could be use both benefits of cord blood derived NK cells (ADCC and KIR+ cytotoxicity) at the same time to prevent cancer progress.

Previously my laboratory evaluated c-Rel and TDT expression (part of NF-κB) in cord blood and leukemia (Leukemia research, 2017, 61: 53-61, Adv Pharm Bull, 2017, 7(2), 215-220 and Immunotoxicology, 2017,14(1): 15–22) and mTOR behavior in cord blood (Iran J Immunol. 2017; 14(3):192-199 and Adv Pharm Bull, 2017, 7(1), 81-85). Therefore, our main goal is finding cancer stem cell biomarkers and targeting them with cord blood derived NK cells. Our investigation illustrated that Telomerase inhibition induced intrinsic, extrinsic, and p53-mediated apoptosis and modulated DNMT3a and TET2 genes in Breast Cancer (TNBC) and Acute Myeloid Leukemia Cancer cells (Life Sciences, 2022). We are in a pipe line using AML and breast cancer cell lines expressing CD34 markers. CD34 positive cells enriched with MACS and both CD34+ and CD34- populations are evaluating for mitochondrial activity, telomere length, and telomerase activity and also for stem cell genes, anti-apoptotic, and pre-apoptotic genes. We are blocking telomere and mitochondrial activity with several inhibitors (e.g., Telemestate). Here, the main goal is finding a specific biomarker. The experiments will be applied for healthy CD34 positive cells to understand whether the behavior of both cancer stem cells and healthy stem cells would be different. These experiments will be performed in animal models. Therefore, our main goal is finding cancer stem cell biomarkers and targeting them with cord blood derived NK cells.

Future plan

1. Relationship between Telomere length, telomerase activity, mitochondrial activity and apoptotic/proliferation factors.

Cancer stem cells (like breast cancer) overexpress components of the nuclear factor-kappa B (NF-κB) signaling cascade and consequently display high NF-κB activity levels. Telomere length in both normal and cancer stem cells is significantly similar where an increase in abnormal mitosis is followed by massive apoptosis leading to the loss of the entire population. This cell death is telomere-length dependent, as cells with long telomeres are viable while exhibiting telomere shortening at a rate similar to that of mortal cells. It appears that telomerase inhibition in cells with short telomeres leads to chromosomal damage, which in turn triggers apoptotic cell death. In cancer cells, metabolism is elevated and mitochondrial activity grows in comparison to normal cells. Therefore, in this section we try to find a relationship between telomere, mitochondrial activity, and apoptosis as well as proliferation. We are continuing to use different inhibitors and activators to understand this relationship in different Leukemia (AML and ALL) and breast cancers.

2. Correlations between genes related to cancer stem cells (like DNMT3a, TET2, and ALDH/IDH,) and telomerase length as well as mitochondrial activity

Both stem cell related genes and telomere activity are age related genes, and as such there could be a relationship between sustaining telomere in cancer stem cells and upregulation of these genes

in tumors. In breast cancer and leukemia (in particular AML), genes like DNMT3a, TET2, and ALDH/IDH are mutated in cancer stem cells. It is important to understand the relationship between upregulation of cancer stem cell genes and mitochondrial activity as well as telomere context. In this section, we are trying to understand key biomarkers associated with increasing mutated cells.

3. Augmenting the cytotoxicity activity of CD16+ and KIR+ NK cells derived cord blood stem cells for killing cancer cells

Umbilical cord blood (UCB) has a greater proliferative and self-renewal capacity when compared to the other sources of HSCs. Importantly, they express very low HLA. Although the neutrophil recovery is slow and the most of derived B cells are immature following transplantation, cord blood stem cells could be a very important source for immunotherapy in future. Previous studies have shown that NK cells derived from cord blood could kill cancer cells, though its cytotoxicity is low. In parallel with previous sections, we would like to develop NK cells cytotoxicity against cancer cells. In this study, we evaluate and set up CD16+ enrichment and KIR+ NK cells using a combination of cytokines. We will evaluate CD16+ NK cells cytotoxicity (ADCC) against different leukemia and breast cancer using different antibodies against biomarkers which are well recognized and expressed on both cancer stem cells and cancer cells.

4. KIR+ NK cell education with different HLA cell lines

NK cells express different KIRs whose ligands are different HLA-C types (KIR2DL1, KIR2DL2/DL3, KIR3DL1, with their ligands HLA-C2, HLA-C2/C1, HLA-C1 respectively). The expression of self-HLA class I-reactive inhibitory receptors enhances the responsive potential of NK cells (licenses, arming, or disarming hypothesis). Therefore, NK cells developing in the absence of HLA class I are unable to kill HLA class I-deficient tumor cells (Hypo-responsive). NK cell education is a quantitative process whereby NK cell responsive capacity is determined by the frequency and strength of engagement of inhibitory receptors with self-MHC class (affinity and frequency of inhibitory receptors). Therefore, selecting KIR+NK cells from the donor is important in killing target cells. Since cord blood has very low HLA, derived KIR+ NK cells could be hyporesponsive in recipients. We will use different HLA cell lines to educate KIR+NK cells from cord blood based on recipients' HLA.

5. NK cell and macrophages co-operation in control of cancer cells expansion

In a recent study, we increased CD16+ NK cells cytotoxicity while benefiting from macrophages against cancer by using anti-CD47 receptor. This scenario increased inhibition of cancer cell expansion. In addition to this, I would like to establish the contribution of natural killer (NK) cells and inhibitory $CD163^{+}$ monocytes/macrophages in cancer inhibition. I think would be beneficial to improve the relationship of NK cells and macrophages in fighting with cancer cells.

Significances

My research goal is in line with the Centre de Recherche des Cordeliers (CRC), in the subject of Cancer immunology and Immunotherapy. My work will connect the most of scientific laboratory in the center to clinics. I am working on Breast cancer and Leukemia stem cell

biomarkers and potential targets for treatment of cancer stem cells. I could cooperate with people in the center to improve NK cell therapy in research and clinical application. Working on cancer biomarkers and target therapy would be an additional engine of productivity for NK cell therapy for cancer. Beatson institute is a particular chance for me to develop anti-tumor activity of NK cells and in following dendritic cells to overcome cancer cells. I would work with academic members of the institute to combine cellular therapy with NK cell therapy for cancer cells. This institute is particular chance to collaborate with scientists to improve immunotherapy for Cancer stem Cells. The investigators are well professional that would be helpful for me to improve my research significantly.

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