BIOGRAPHICAL SKETCH

Junior Trainer

NAME: Barak Blum

eRA COMMONS USER NAME (credential, e.g., agency login): BABLUM

POSITION TITLE: Assistant Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Ben-Gurion University of the Negev	B.Sc., ***cum laude***	06/2001	Life Sciences
The Hebrew University of Jerusalem	M.Sc., ***cum laude***	02/2004	Medical Biochemistry
The Hebrew University of Jerusalem	Ph.D.	06/2010	Genetics
Harvard University and Harvard Stem Cell Institute	Postdoc.	07/2015	Stem Cell and Regenerative Biology for Diabetes

A. Personal Statement

I have the expertise, leadership and training to successfully carry out the project described here. I performed my M.Sc. and Ph.D. research at the Hebrew University in Jerusalem, where I studied tissue-specific transcriptional regulation of metabolic genes and the organogenesis of *in vivo* differentiation of human pluripotent stem cells. From these studies I gained extensive experience in mouse genetics and stem cell biology, and developed my interests in stem cell approaches to treat diabetes. In my post-doctoral work with Dr. Douglas A. Melton at Harvard, I established the first coherent definition of the fully mature β cell state, and found the first genetic marker (the gene Ucn3) for the onset of functional β cell maturation (i). In subsequent work, I developed and used a novel maturation-sensitive reporter mouse line to identify factors that reverse β cell de-differentiation under diabetic stress (ii). These results, published in major scientific journals, expand our understanding of β cell maturation. As Assistant Professor of Cell and Regenerative Biology at the University of Wisconsin-Madison, I combine my extensive experience working with mouse models of diabetes, pluripotent stem cells and functional genomics and to tackle fundamental questions related to β cell maturation and organogenesis of the islets of Langerhans; this work builds on recent discoveries from my own lab pertinent to the role of the axon-guidance proteins Roundabout (Robo) receptors in islet organization and intra-islet cell-cell communication (iii). Since establishing my lab in July 2015, I have trained three graduate students (currently in their fourth and third year in the program), and nine undergraduate students. In the course of my work as an independent PI, I established excellent collaborations, including with Raghu Mirmira and Amelia Linnemann on intravital imaging of islet function, Richard Benninger on analyzing β cell connectivity in the islet, Michelle Kimple on G-protein signaling, Wei-Jun Qian on **islet proteomics**, and Jon Odorico on **human islets**. Thus, my prior experiences and skills, together with the strong and synergistic expertise of my collaborators, position me and my lab at an excellent place to contribute as a trainer in this training grant.

1. Blum, B. *et al*., Functional beta-cell maturation is marked by an increased glucose threshold and by expression of urocortin 3. *Nature biotechnology* 30, 261-264 (2012). PMID: 22371083
2. Blum, B*. *et al*., Reversal of beta cell de-differentiation by a small molecule inhibitor of the TGFbeta pathway. *eLife* 3, e02809 (2014). PMID: 25233132 *Corresponding Author.
3. Adams, M. T., Gilbert, J. M., Hinojosa Paiz, J., Bowman, F. M. & Blum, B., Endocrine cell type sorting and mature architecture in the islets of Langerhans require expression of Roundabout receptors in beta cells. *Scientific reports* 8, 10876, (2018). PMID: 30022126

B. Positions and Honors

Positions and Employment

2015-Present Assistant Professor, Dept. of Cell and Regenerative Biology, University of Wisconsin-Madison
2009-2015 Post-doctorate Fellow at the laboratory of Prof. Douglas A. Melton, Dept. of Stem Cell and Regenerative Biology and the Harvard Stem Cell Institute, Harvard University
2004-2009 Ph.D. candidate on “Cellular and molecular characterization of teratomas from human embryonic stem cells”. Under the supervision of Prof. Nissim Benvenisty, Dept. of Genetics, the Hebrew University of Jerusalem
2004-2009 Teaching assistant at the Life Sciences Institute, The Hebrew University of Jerusalem: General Genetics (Lab)
2001-2004 M.Sc. candidate on “The importance of PPARE response element for the PEPCK-C gene expression in liver and adipose tissue in vivo and the mechanism of glucocorticoids suppression of the gene transcription in adipose tissue”. Under the supervision of Prof. Lea Reshef, Dept. of Biochemistry, The Hebrew University, Hadassah Medical School, Jerusalem

Honors

2011-2014 JDRF Post-Doctoral Fellowship
2009-2011 EMBO Post-Doctoral Fellowship
2009 Menashe Marcus Prize for Excellent Graduate Student
2008 ISSCR Travel Award, for participation in the International Society for Stem Cell Research (ISSCR) 6th annual meeting, Philadelphia, USA
2008 Best Poster Presentation Award, The 2nd International Stem Cell Meeting of the Israel Stem Cell Society (ISCS), Tel-Aviv, Israel
2006 Russek Travel Award for excellent graduate students, for participation in the International Society for Stem Cell Research (ISSCR) 4th annual meeting, Toronto, Canada
2004 Faculty Prize for Best M.Sc. Thesis in Medical Sciences
2002 Scholarship from the Dr. Malka Wolf Foundation
2001 Dean's list for extreme excellence (summa cum laude)
2000 Awarded "Best Negev Industry Fellowship".

C. Contribution to Science

1. **Tumorigenicity and differentiation of human pluripotent stem cells:** Human pluripotent stem cells are an emerging hope for future regenerative medicine owing to their self-renewal and pluripotent differentiation potential. However, translation of this potential to the clinic is largely impeded by the fact that these cells are tumorigenic, and form teratomas upon transplantation. The teratoma formation capacity of pluripotent stem cells is an exceptional phenomenon because the tumors arise from cells that are otherwise normal; therefore understanding pluripotent stem cell tumorigenicity is critical for regenerative medicine and may reveal insights into the basic principles of tumor initiation. Additionally, pluripotent stem cell-induced teratomas provide an excellent tool for understanding spontaneous differentiation *in vivo*. During my PhD, I used functional genomics, cell biology and physiology to analyze the genetic basis of this unique tumorigenic phenomenon. I identified a gene, BIRC5, which is expressed in most cancers, but also in normal early stage embryos, and is almost completely absent from mature normal tissues. By neutralizing the activity of BIRC5 in the undifferentiated cells as well as in the tumors, I was able to initiate apoptosis in those normal, yet tumorigenic cells. I further showed that different cell lines mutually contribute to the same distinctive tissue structures, suggesting that during the *in vivo* differentiation of human pluripotent stem cells within the teratoma the differentiating cells are affected by neighboring cells. These results elucidate the generation of differentiated structures from human pluripotent stem cells *in vivo*, stressing the need for a three dimensional growth in order to achieve complex differentiation of these cells.

a. Blum, B., and Benvenisty, N., Clonal analysis of human embryonic stem cell differentiation into teratomas. *Stem Cells*, 25:1924-1930, (2007).

b. Blum, B.*, and Benvenisty, N.*, The tumorigenicity of human embryonic stem cells. *Adv. Cancer Res.*, 100:133-158, (2008) *Corresponding Author. (Invited Review). NIH Policy Exempt – Published with non-U.S. Gov't funds.

c. Blum, B., Bar-Nur, O., Golan-Lev, T. and Benvenisty, N., Involvement of the anti apoptotic gene Survivin in the tumorigenicity of human embryonic stem cells. *Nat. Biotechnol.*, 27:281-287, (2009). NIH Policy Exempt – Published with non-U.S. Gov't funds.

d. Blum, B.*, and Benvenisty, N., The tumorigenicity of diploid and aneuploid human pluripotent stem cells. *Cell Cycle*, 8:3822-3830, (2009) *Corresponding Author. (Invited Review). NIH Policy Exempt – Published with non-U.S. Gov't funds.

2. **Functional maturation and de-differentiation of pancreatic β cells:** In my post-doctoral work with Dr. Melton, I have established the first coherent definition of the fully mature β cell state, and found the first genetic marker (the gene Ucn3) for the onset of functional β cell maturation. In subsequent work, I discovered that the expression of Ucn3 is lost in the earliest stages β cell degeneration in diabetes. I used a novel maturation-sensitive reporter mouse line to screen for factors that reverse β cell de-differentiation under diabetic stress, and found several new compounds controlling this process. These results expand our understanding of the establishment, maintenance and collapse of the terminally-differentiated cell state, may lead to the first drugs directly aimed to reverse and recover the loss of β cell maturation during diabetes, and help establish functional maturation in pluripotent stem-cell-derived β cells.

a. Blum, B., Hrvatin, S., Schuetz, C., Bonal, C., Rezania, A., Melton, D.A., Functional beta-cell maturation is marked by an increased glucose threshold and by expression of urocortin 3. *Nat. Biotechnol.*, 30:261-264, (2012). PMCID:PMC4617627

b. Blum, B.*, Roose, A.N., Barrandon, O., Maehr, R., Arvanites, A.C., Davidow, L.S., Davis, J.C., Peterson, Q.P., Rubin, L.L., Melton, D.A*., Reversal of β cell de-differentiation by a small molecule inhibitor of the TGFβ pathway. *eLife*, e02809, (2015). *Corresponding Author. PMCID:PMC4204634

3. **Organogenesis of the islets of Langerhans:** Pancreatic islets of Langerhans display characteristic spatial architecture of their endocrine cell types. This architecture is critical for cell-cell communication and coordinated hormone secretion. In my own lab at UW-Madison, we found that formation of mature islet architecture require the expression of Roundabout (Robo) receptors in β cells. We showed that mice with whole-body deletion of *Robo1* and conditional deletion of *Robo2* either in all endocrine cells or selectively in β cells show complete loss of endocrine cell type sorting, highlighting the importance of β cells as the primary organizer of islet architecture. Conditional deletion of *Robo* in mature β cells subsequent to islet formation results in a similar phenotype. We provided evidence to suggest that the loss of islet architecture in *Robo KO* mice is not due to β cell transdifferentiation, cell death or loss of β cell differentiation or maturation. This suggests that Robo signaling could be harnessed to regulate islet organization and cell-cell communication.

a. Gilbert, J.M. and Blum, B., Synaptotagmins tweak functional β cell maturation. *Dev Cell.* 7;45(3):284-286. (2018). PMID: 29738707

b. Adams, M.T., Gilbert, J.M., Paiz, J.H., Bowman, F.M., and Blum, B., Endocrine cell type sorting and mature architecture in the islets of Langerhans require expression of Roundabout receptors in beta cells. *Scientific reports* 8, 10876, (2018). PMID: 30022126

Complete List of My Published Work: https://www.ncbi.nlm.nih.gov/pubmed/?term=barak+blum

D. Research Support

Ongoing

NIH/NIDDK 1R56DK115837
08/01/18 – 07/31/19
Genetic control of beta cell maturation and dedifferentiation
Role: PI

Juvenile Diabetes Research Foundation Strategic Research Agreement (SRA)
06/01/2018 – 05/31/2020

2-SRA-2018-621-S-B
Regulation of human beta cell maturation
Role: PI

Wisconsin Alumni Research Foundation Fall Competition Award
MSN215659
07/01/2018 – 06/30/2019
Genetic control of beta cell dediferentiation in diabetes
Role: PI

Pending

DoD PRMRP
IIRA PR181766
02/01/2019 – 01/31/2022
Role of Robo Receptors in the Islet of Langerhans
Role: PI

NIH/NIDDK
1R01DK121706
07/01/2019 – 06/30/2024
Regulation of spatial organization and cell-cell communication in the islet of Langerhans
Role: PI

Completed
WU-Madison - Washington University Diabetes Research Center Pilot & Feasibility Award
06/01/2018 – 08/31/2020
P30DK020579
Robo receptors control the organization and function of the islets of Langerhans
Role: PI

UW-Madison ICTR Basic & Clinical Pilot Award
09/01/2017 – 08/31/2018
Robo signaling controls the cellular organization of the islets of Langerhans in development and diabetes – implications to regenerative biology and tissue engineering
Role: PI

Juvenile Diabetes Research Foundation
09/01/2011 – 08/31/2014
3-2011-347
Functional maturation of beta-cells
Role: PI

EMBO
09/01/2009 – 08/31/2011
ALTF 515-2009
Analysis of beta-cell regeneration in mice using direct cell cycle visualization
Role: PI