

Biomedical Technologies and Innovation Doctoral Programme (BIOTIN)



Title of the PhD Project	Characterizing the regulatory roles of long-noncoding RNAs in tumor immunity
Acronym	LNCTIMM
Research Fields of the Project	Tumor biology, immunology, bioinformatics, computational biology
Keywords	Noncoding RNA, immunoevasion, immunity
Host Institution, Department and Campus Location	İzmir Institute of Technology, Department of Molecular Biology and Genetics, Urla, İzmir
PhD Awarding Institution and Graduate Programme	İzmir Institute of Technology, Graduate School, PhD in Molecular Biology and Genetics
Name and Affiliation of Main Supervisor	Asst. Prof. H. Atakan Ekiz (IZTECH)
Name and Affiliation of Co-supervisors	Prof. Bünyamin Akgül (IZTECH) Assoc. Gökhan Karakulah (IBG)
Research Environment and Infrastructure	<p>Host institution Izmir Institute of Technology (IZTECH) and participating institution Izmir Biomedicine and Genome Center (IBG) offer excellent infrastructures to perform cutting edge scientific research and world-class graduate training programs. Multinational faculty in these institutions carry out highly collaborative research spanning a wide range of disciplines including cancer biology, immunology, bioinformatics, and therapeutics development. Laboratories in both institutions are fully equipped with basic molecular biology equipment and there are advanced core facilities with expert staff including small animal and zebrafish vivaria, flow cytometry and sorting, cell imaging, bioinformatics, and structural protein biochemistry cores. IZTECH and IBG have been beneficiaries of multiple national and international grants including the TUBITAK, TUBA, TUSEB, ERC, EMBO Installation Grants, Marie Curie Sklodowska Action Grants. Thus, this proposal will be carried out at institutions that are fully integrated with the research circles of the EU at the highest standards. Importantly, the faculty in the participating institutions have a wide range of scientific research interests and areas of expertise which will allow pursuing science in every direction as well as generating new collaborative projects.</p> <p>https://www.atakanekiz.com/en/lab/</p>

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<p>Scientific Context of the Project</p>	<p>Immunotherapy has changed the outlook in advanced cancers, but not all patients benefit from the treatment. Although the correlates of a productive antitumor immune response have been recently reported, ultimately it remains unknown why some patients fail to respond immunotherapeutics, suggesting key regulatory mechanisms within the tumor immune microenvironment remains to be determined. This project will focus on long non-coding RNAs (lncRNAs), a major component of human transcriptome, as predictors of immunotherapy response and clinical outcome in cancer. By using large amounts of publicly available data and various machine learning algorithms, we will investigate molecular patterns that are strongly associated with clinically relevant parameters in human cancers of various origins, and experimentally study particular lncRNA candidates in order to reveal novel mechanisms of antitumor immunity. This work will advance our knowledge of how the immune system responds to cancer and it will have applications in predictive biomarker development and therapeutic target discovery in cancer. Importantly, trainees participating into this project will strongly enhance their professional competitiveness by gaining essential skills at the intersection of tumor biology, immunology, and computational biology, and they will be able to prepare themselves for a successful career in science. Excellent mentors and the advanced infrastructures of two collaborating biomedical research institutions will optimally position trainees to investigate clinically important mechanisms while residing in a vibrant city that offers many exciting opportunities for extracurricular activities.</p>
<p>Brief Workplan</p>	<p>(1-3 months) This project requires students to know coding for high throughput data analysis as well as molecular tumor immunology research techniques. To that end, students will take didactic courses and attend intensive laboratory hands-on trainings as they are introduced to their thesis topics.</p> <p>(3-12 months) High throughput gene expression data from cancer biopsies will be obtained from public databases and recently published studies. Long noncoding RNA (lncRNA) expression profiles will be investigated in various contexts. We will examine lncRNA signatures in immune-enriched vs immune-devoid cancer biopsies first by focusing on melanoma, an aggressive form of skin cancer, and expand our search to other cancer types. Researchers will utilize various statistical modeling and machine learning approaches to investigate relationships between lncRNAs and clinical parameters such as tumor stage, survival, and immunotherapy response.</p> <p>(12-18 months) In silico work from the previous step will result in candidate lncRNAs that will be further investigated experimentally. Prior work we conducted already have identified a few target lncRNAs (including NRAV, DANCR, HCP5 and others) and our efforts as part of this project will lead to multiple other candidate lncRNAs. To be able to study the function of these lncRNAs we will generate overexpression (cDNA expression or CRISPRa) and suppression vectors (shRNA or CRISPRi) and validate these tools.</p> <p>(18-24 months) We will utilize various cancer cell lines and test the immunomodulatory effects of manipulating selected lncRNAs. To that end, we will set up cultures in which cells are treated with pro-inflammatory cytokines such as</p>

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	<p>type-I (IFNa, IFNb) and type-II (IFNg) interferons and tumor necrosis factor alpha (TNFa) in the presence or absence of the lncRNA expression. In these experiments we will assess the impact on proliferation and cell death and examine the transcriptomic and proteomic landscape of the cancer cells to characterize the affected pathways. Our findings here will uncover previously unknown immunomodulatory players that are clinically relevant in cancer.</p> <p>(24-48 months) In this section, further mechanistic studies will be performed to characterize the cellular interaction partners of selected immunomodulatory RNAs. As part of the proposed experiments, lncRNA cellular localization will be assessed and lncRNA interaction partners will be examined through various transcriptomic and proteomic approaches. Findings here will enable us to delineate how lncRNAs are involved in tumor immunoevasion.</p>
<p>Innovative Aspects of the Project</p>	<p>This project brings together experts in multiple disciplines: noncoding RNA biology, immunology, and bioinformatics. The multifaceted research design involves state of the art methodologies and will generate impactful findings. We propose an innovative approach that is powered by big biological data analysis followed by rigorous validation studies and mechanistic characterization. In that sense, this project will integrate cutting-edge innovations across multiple disciplines to address important questions in biomedical cancer research.</p>
<p>Training Opportunities of the Project</p>	<p>This project will give trainees an unparalleled opportunity to learn from and work with leading scientists in a highly competitive research arena. Participants to this program will take advanced graduate-level courses in IZTECH and IBG, develop hands-on experimentation skills in world-class laboratories while having access to sophisticated core facilities. PhD students in this program will develop a strong understanding of high throughput biological data analysis, machine learning, molecular and functional characterization of lncRNAs. Both IZTECH and IBG have strong mentorship programs in place to monitor the progress of its students and ensure the research and training milestones are reached properly. Importantly, the skills that the trainees will learn through their thesis studies are heavily sought after in both academia and industry. These skills include bioinformatics, big biological data analysis, CRISPR-genome editing, in vitro and in vivo study models Therefore, the graduates of this program will be prepared and optimally positioned for a fulfilling scientific career.</p>
<p>Interdisciplinary Aspects</p>	<p>Our proposal involves multiple disciplines that have had a transformative impact on biomedical research in the last two decades. This project will integrate bioinformatics, computational biology, tumor immunology, noncoding RNA biology, and cancer biology. Therefore, the findings of this study will contribute to multiple scientific arenas and open new research avenues.</p>
<p>Intersectoral Mobility</p> <p><input checked="" type="checkbox"/> Short Visit</p> <p><input type="checkbox"/> Secondment</p>	<p><i>Host: AMGEN Türkiye</i></p> <p><i>Context of Mobility: Management for the Pharmaceutical Industry</i></p>

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<p>Intersectoral Mobility</p> <p><input checked="" type="checkbox"/> Short Visit</p> <p><input type="checkbox"/> Secondment</p>	<p><i>Host: Istanbul Health Industry Cluster (ISEK)</i></p> <p><i>Context of Mobility: Entrepreneurship Training, Thematic Pre-incubation Program</i></p>												
<p>International Academic Secondment</p>	<p><i>Host Supervisor: Prof. Daniel Gautheret</i></p> <p><i>Host Institution: French National Centre for Scientific Research (CNRS), Paris, France</i></p> <p><i>Host Department: Institute for Integrative Biology of the Cell</i></p> <p><i>Duration: 6 months</i></p> <p><i>Estimated Time of Mobility: 2nd Year</i></p>												
<p>Main Supervisor:</p>													
<p>Brief CV</p>	<p>Asst. Prof. H. Atakan Ekiz</p> <p>E-mail: atakanekiz@iyte.edu.tr</p> <p>ACADEMIC DEGREES</p> <table border="0"> <tr> <td>Ph.D.</td> <td>Molecular Biology</td> <td>University of Utah, USA</td> <td>2018</td> </tr> <tr> <td>M.Sc.</td> <td>Clinical Investigation</td> <td>University of Utah, USA</td> <td>2018</td> </tr> <tr> <td>B.Sc.</td> <td>Molecular Biology and Genetics</td> <td>Izmir Institute of Technology, Turkey</td> <td>2009</td> </tr> </table> <p>Google Scholar: https://scholar.google.com/citations?hl=tr&user=KdejXWcAAAAJ</p> <p>https://orcid.org/0000-0001-7718-6841</p>	Ph.D.	Molecular Biology	University of Utah, USA	2018	M.Sc.	Clinical Investigation	University of Utah, USA	2018	B.Sc.	Molecular Biology and Genetics	Izmir Institute of Technology, Turkey	2009
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<p>Brief CV</p>	<p>Prof. Bünyamin Akgül</p> <p>E-mail: bunyaminakgul@iyte.edu.tr</p> <p>ACADEMIC DEGREES</p> <table border="0"> <tr> <td>Ph.D.</td> <td>Genetics</td> <td>Pennsylvania State University, USA</td> <td>2001</td> </tr> <tr> <td>M.Sc.</td> <td>Genetics</td> <td>Pennsylvania State University, USA</td> <td>1995</td> </tr> <tr> <td>B.Sc.</td> <td>Veterinary</td> <td>Ankara University, Turkey</td> <td>1991</td> </tr> </table> <p>Google Scholar: https://scholar.google.com/citations?hl=tr&user=55y3LvkAAAAJ</p> <p>https://orcid.org/0000-0001-9877-9689</p>	Ph.D.	Genetics	Pennsylvania State University, USA	2001	M.Sc.	Genetics	Pennsylvania State University, USA	1995	B.Sc.	Veterinary	Ankara University, Turkey	1991
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<p>Brief CV</p>	<p>Assoc. Prof. Gökhan Karakülah</p> <p>E-mail: gokhan.karakulah@ibg.edu.tr</p> <p>ACADEMIC DEGREES</p> <table border="0"> <tr> <td>Ph.D.</td> <td>Bioengineering</td> <td>Dokuz Eylül University, Turkey</td> <td>2014</td> </tr> <tr> <td>M.Sc.</td> <td>Medical Informatics</td> <td>Dokuz Eylül University, Turkey</td> <td>2009</td> </tr> <tr> <td>B.Sc.</td> <td>Biology</td> <td>Ege University, Turkey</td> <td>2005</td> </tr> </table> <p>Google Scholar: https://scholar.google.com/citations?hl=tr&user=ac2JQN8AAAAJ</p> <p>https://orcid.org/0000-0001-6706-1375</p>	Ph.D.	Bioengineering	Dokuz Eylül University, Turkey	2014	M.Sc.	Medical Informatics	Dokuz Eylül University, Turkey	2009	B.Sc.	Biology	Ege University, Turkey	2005
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