ÖZGEÇMİŞ VE ESERLER LİSTESİ

ÖZGEÇMİŞ

Adı ve Soyadı: Erhan Keleş

Akademik Unvanı: Assistant Professor

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Bildiği Yabancı Diller: İngilizce (Profesyonel Yetkinlik), Almanca (Başlangıç), Fransızca(Başlangıç)

Aldığı Sertifikalar:

- Animal Experimentation Licence (Theoretical and Practical)
- Advanced Mouse Phenogenomics
- Hands-on Imaging on 3D/4D-Visualization and Analysis for Gigabyte-sized Images

Uzmanlık Alanı: Moleküler Biyoloji ve Genetik, Hücre Biyolojisi, Biyokimya, Sinyal Yolakları, İlaç Keşfi (Kovalent Bağlanan İnhibitörler)

Eğitim:

Derece	Bölüm/Program	Üniversite	Yıl
Lisans (BSc)	Bioengineering	Montana State University & İstanbul Teknik Üniversitesi (Uluslararası Ortak Lisans Programı	2014
Y. Lisans (MSc)	Bioengineering	Washington State University	2016
Doktora (PhD)	Genetics	University of Basel	2021

Yüksek Lisans Tez Başlığı (özeti ekte) ve Tez Danışman(lar)ı:

- *Recent progress in nanomaterials for gene delivery applications*

Prof. Dr. Wen-Ji Dong (Washington State University)

Doktora Tezi/S.Yeterlik Çalışması/Tıpta Uzmanlık Tezi Başlığı (özeti ekte) ve Danışman(lar)ı:

- *Novel PI3K and mTOR selective inhibitors to deconvolute PI3K signaling*

Prof. Dr. Matthias P. Wymann (University of Basel)

Prof. Dr. Gerhard M. Christofori (University of Basel)

Dr. Jens Petersen (AstraZeneca)

Görevler:

Görev Unvanı	Görev Yeri	Yıl
Assistant Professor	Bogazici University	28 Nisan 2025-current
Scientist	Swiss Federal Institute of Technology Lausanne (EPFL)	Ocak 2024 - Eylül 2025
Postdoctoral Researcher	Stanford University	Ekim 2021-Kasım 2022
Pre-doctoral Researcher	University of Basel	Eylül 2016 - Temmuz 2021
Graduate Research Assistant	Washington State University	Ağustos 2014 - Ağustos 2016
Research Assistant	Montana State University	Ocak 2014 - Mayıs 2014
Intern	Harvard Medical School	Haziran 2013 - Ağustos 2013
Research Assistant	İstanbul Teknik Üniversitesi	Ocak 2013 - Nisan 2013

Yönetilen Yüksek Lisans Tezleri :

- Developing NanoBiT assay platforms to study dynamic interactions of PI3Kγ and p84
    - Marco Beger successfully defended his Master's thesis at the University of Basel in 2021.

Yönetilen Doktora Tezleri/Sanatta Yeterlik Çalışmaları :

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Projelerde Yaptığı Görevler:

- Group Leader, TÜBİTAK BİDEB 2232 International Fellowship for Early-Stage Researchers, Fellowship and Start-up Funding, 2025 – 2028 (Awarded in July 2024):
    - Artificial Intelligence-powered Phosphoinositide-3-Kinase (PI3K) Drug Discovery for Precision Cancer Treatment
- Postdoctoral Researcher, Swiss Federal Institute of Technology Lausanne (EPFL) funded by Swiss National Science Foundation (SNF), Ocak 2024-Eylül 2025:
    - Discovery and Characterisation of Chromatin States in Notch-driven T cell acute lymphoblastic leukaemia (T-ALL) and development of novel therapeutics.
    - Investigating genetic and epigenetic functions of transcription factors including c-Myc, Tcf1, and Lef1 in Notch1-driven T-ALL during disease progression and maintenance.
- Postdoctoral Researcher, Stanford Cancer Institute, Stanford University, Oct. 2021 – Nov. 2022
    - Development of small molecule inhibitors and targeted protein degraders (TPD) as novel therapeutics for MYC-driven cancers:
    - Discovering novel pharmacological intervention strategies to modulate c-Myc proteome interactions in order to inhibit c-Myc oncogenic functions.
- Doctoral Researcher, University of Basel funded by European Union Horizon 2020 Marie Skłodowska-Curie Actions, Eylül 2016-Temmuz 2021

- Development of a covalent inhibition strategy to minimize side effects of phosphoinositide-3-kinase (PI3K) inhibitor cancer therapy.
- Developed a rational drug-design approach to provide prolonged inhibition of PI3K-driven cancers by exploiting a covalent binding of inhibitors targeting PI3K isoform-specific nucleophilic amino acid side chains.

- Graduate Research Assistant, Washington State University, Chemical Engineering and Bioengineering Department, Aug. 2014 – Aug. 2016
  - Studied effects of cardiomyopathy-causing mutations on cardiac myofilament regulation.
  - Trained in application of photonics and biophysical principles to elucidate protein-protein interactions and functional properties of cardiac myofilament proteins.
- Harvard Stem Cell Institute Intern, Molecular Neurotherapy and Imaging Laboratory, Harvard Medical School/Massachusetts General Hospital, USA, 10 June - 16 August 2013
  - Characterization of therapeutic stem cells and profiling host immune response to tumor growth in a syngeneic mouse Glioblastoma Multiforme (GBM) resection model:
  - Trained in tumor (GBM) implantation and surgical resection into/from mouse brain through the intracranial window, immunohistochemistry (IHC), hematoxylin & eosin (H&E) staining, bioluminescence imaging (BLI), and stem cell encapsulation into hyaluronic acid-based polymer.
- Research Assistant, Nano/Micro ElectroMechanical Systems Laboratories, Advisor: Prof. Dr. Huseyin Kizil, Istanbul Technical University –Turkey, 14 January - 5 April 2013
  - Studied photolithography techniques to create microfluidic devices and appropriate nanotopographies:
  - Trained in scanning electron microscopy and photolithographic fabrication techniques including e-beam evaporator, thermal evaporator, mask aligner, plasma cleaner, and photoresist spinner.
- Research Assistant, Department of Chemistry and Biochemistry, Advisor: Prof. Dr. Brian Bothner, Montana State University –USA, 14 May-3 August 2012 and continued between Jan. 8-May 2, 2014
  - Studied assembly, stability, and dynamics of Hepatitis B Virus (HBV) envelope protein.
  - Trained in high-performance liquid chromatography (HPLC), mass spectrometry (MS), and differential scanning fluorimetry (DSF).

İdari Görevler:

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Bilimsel Kuruluşlara Üyelikler:

- American Association for Cancer Research (AACR) Membership
- Tau Beta Pi (TBP), the engineering honor society, Membership

Ödüller:

• *TÜBİTAK BİDEB 2232* - International Fellowship for Early-Stage Researchers, Fellowship and Start-up Funding for the Group Leader, 2025 – 2028 (Awarded in July 2024)

• *Marie Skłodowska-Curie Fellowship* for Ph.D. Studies, 2016 – 2019

• *International Student Scholarship*, Washington State University, 2015

Son iki yılda verdiği lisans ve lisansüstü düzeydeki dersler (Açılmışsa, yaz döneminde verilen dersler de tabloya ilave edilecektir)**:**

Akademik Yıl	Dönem	Dersin Adı	Haftalık Saati		Öğrenci Sayısı
			Teorik	Uygulama	
2023-2024	Güz	Intracellular protein transport and vesicular transport	1.45		60
	Bahar				

ESERLER

A. <u>Uluslararası hakemli dergilerde yayımlanan makaleler:</u>

A1. **Keles, E.***; Bissegger L.*; Constantin, T.A.*; Raguz, L.; L.; Barlow-Busch, I.; Orbegozo, C.; Schaefer, T.; Sriramaratnam, R.; Schaefer, A.; Gstaiger, M.; Burke, J.E.; Borsari, C.*, Wymann, M.P*. Rapid, Potent, and Persistent Covalent Chemical Probes to Deconvolute PI3Kα Signaling. Chemical Science, https://doi.org/10.1039/D4SC05459H (2024) (*Joint 1st authors).

A2. **Keles, E.***; Borsari, C.*; McPhail, J.A.; Schaefer, A.; Sriramaratnam, R.; Schaefer, T.; Gstaiger, M.; Burke, J.E.; Wymann, M.P. Covalent Proximity Scanning of a Distal Cysteine to Target PI3Kα. J. Am. Chem. Soc. 144, 6326−6342 (2022). (*Joint 1st authors) https://doi.org/10.1021/jacs.1c13568

A3. **Keles, E.***; Borsari, C.*; Treyer, A.; De Pascale, M.; Hebeisen, P.; Hamburger, M.; Wymann, M.P. Second-generation tricyclic pyrimido-pyrrolo-oxazine mTOR inhibitor with predicted blood-brain barrier permeability. RSC Med. Chem., 12, 579–583 (2021) (* Joint 1st authors). https://doi.org/10.1039/D0MD00408A

A4. Borsari, C.; **Keles, E.**; Rageot, D.; Treyer, A.; Bohnacker, T.; Bissegger, L.; De Pascale, M.; Melone, A.; Sriramaratnam, R.; Beaufils, F.; Hamburger, M.; Hebeisen, P.; Löscher, W.; Fabbro, D.; Hillman, P.; Wymann, M.P. 4-(Difluoromethyl)-5-(4-((3R,5S)-3,5dimethylmorpholino)-6-((R)-3- methylmorpholino)-1,3,5-triazin-2-yl)pyridin-2-amine (PQR626), a Potent, Orally Available, and Brain-Penetrant mTOR Inhibitor for the Treatment of Neurological Disorders. J. Med. Chem. 63, 13595-13617 (2020). https://dx.doi.org/10.1021/acs.jmedchem.0c00620

A5. Rageot, D.; Bohnacker, T.; **Keles, E.**; McPhail, J.A.; Hoffmann, R.M.; Melone, A.; Borsari, C.; Sriramaratnam, R.; Sele, A.M.; Beaufils, F.; Hebeisen, P.; Fabbro, D.; Hillman, P.; Burke, J.E.; Wymann, M.P. (S)-4-(Difluoromethyl)-5-(4-(3-methylmorpholino)-6-morpholino-1,3,5-triazin-2-yl)pyridin-2-amine (PQR530), a Potent, Orally Bioavailable, and Brain-Penetrable Dual Inhibitor of Class I PI3K and mTOR Kinase. J. Med. Chem. 62, 13, 6241-6261 (2019). https://doi.org/10.1021/acs.jmedchem.9b00525

A6. Borsari, C.; Rageot, D.; Beaufils, F.; Bohnacker, T.; **Keles, E.**; Buslov, I.; Melone, A.; Sele, A.M.; Hebeisen, P.; Fabbro, D.; Hillman, P.; Wymann, M. P. Preclinical Development of PQR514, a Highly Potent PI3K Inhibitor Bearing a Difluoromethyl-

Pyrimidine Moiety. ACS Med. Chem. Lett. 10, 1473-1479 (2019). https://doi.org/10.1021/acsmedchemlett.9b00333

A7. Choi, S.H.; Stuckey, D.W.; Pignatta, S.; Reinshagen, C.; Khalsa, J.K.; Roozendaal, N.; Martinez-Quintanilla, J.; Tamura, K.; **Keles, E**; Shah, K. Tumor Resection Recruits Effector T Cells and Boosts Therapeutic Efficacy of Encapsulated Stem Cells Expressing IFNβ in Glioblastomas. Clin. Cancer Res. 23, 22, 7047-7058 (2017). https://doi.org/10.1158/1078-0432.CCR-17-0077

A8. Keles, E; Song, Y; Du, D; Dong, W-J; Yuehe, L. Recent Progress in Nanomaterials for Gene Delivery Applications. Biomater. Sci. 4, 1291-1309 (2016). https://doi.org/10.1039/C6BM00441E

B. Uluslararası bilimsel toplantılarda sunulan ve bildiri kitaplarında (*proceedings*) basılan bildiriler:

B1. **Keles, E.***; Borsari, C.*; Sriramaratnam, R.; Schaefer, T.; Wymann, M.P. A novel, highly potent PI3Kα covalent inhibitor deconvolutes class I PI3Ks isoforms in cancer cells. Cancer Research 81 (13 Supplement):Abstract nr 1378. (2021). (*Joint 1-st authors). https://cancerres.aacrjournals.org/content/81/13_Supplement/1378

B2. Borsari, C.*; **Keles, E.***; McPhail, J.A.; Schaefer, A.; Sriramaratnam, R.; De Pascale, M.; Gstaiger, M.; Burke, J.E.; Wymann, M.P. Volume scanning, a rational approach to covalent PI3Kα inhibitors. Cancer Research 81 (13 Supplement):Abstract nr 1377. (2021). (*Joint 1-st authors). https://cancerres.aacrjournals.org/content/81/13_Supplement/1377

B3. Borsari, C.*; **Keles, E.***; Treyer, A.; De Pascale, M.; Hebeisen, P.; Hamburger, M.; Wymann, M.P. Second-generation tricyclic pyrimido-pyrrolo-oxazine mTOR inhibitors suitable for the treatment of CNS disorders. Cancer Research 81 (13 Supplement):Abstract nr 293. (2021). (*Joint 1-st authors). https://cancerres.aacrjournals.org/content/81/13_Supplement/293

B4. De Pascale, M.; Borsari, C.; **Keles, E.**; McPhail, J.A.; Schaefer, A.; Sriramaratnam, R..; Gstaiger, M.; Burke, J.E.; Wymann, M.P. Development of optimized chemical probes targeting PI3Kα to deconvolute the role of class I PI3K isoforms in insulin signaling. Cancer Research 81 (13 Supplement):Abstract nr 291. (2021). (*Joint 1-st authors). https://cancerres.aacrjournals.org/content/81/13_Supplement/291

B5. Borsari, C.; **Keles, E.**; Rageot, D.; Melone, A.; Bohnacker, T.; Batchelor, L.K.; De Pascale, M.; Hebeisen, P.; Hillmann, P.; Fabbro, D.; Wymann, M.P. Discovery and preclinical characterization of PQR626: A potent, orally available, and brain-penetrant mTOR inhibitor for the treatment of tuberous sclerosis complex. Cancer Research 80 (16 Supplement), 665-665 (2020). https://cancerres.aacrjournals.org/content/80/16_Supplement/665

G1. Patentler:

Keles, E.; Wymann, M.P.; Borsari, C. (2024) Method for identifying PI3 Kinase-alpha Inhibitors. (Equal Contribution) (Reference: UZ474WO-EP; Patent No.: 4320261) Access Link: https://register.epo.org/ipfwretrieve?apn=US.202218554638.A&lng=en

EKLER:

Doktora Tezi (Özet):

Novel PI3K and mTOR selective inhibitors to deconvolute PI3K signaling

Phosphoinositide 3-kinase (PI3K) signaling has key roles in the regulation of cellular processes such as cell growth, proliferation, and metabolism. Constitutive activation of PI3K in tumors is frequent and drives cancer progression. Considering the contribution of aberrant PI3K signaling in cancer progression, pharmacological intervention strategies to inhibit PI3K-driven malformations have been broadly explored as a therapeutic target, but many pan-PI3K inhibitors displayed a low response rate in clinical trials mainly due to on target metabolic side effects. Acute pan-PI3K inhibition triggers a rapid increase in blood glucose and insulin level since PI3Kα and PI3Kβ isoforms have redundant roles in insulin signaling in the hepatocyte, and acute inhibition of the both isoforms impairs glucose homeostasis. Given that, isoformselective PI3Kα inhibition may alleviate hyperglycemia and hyperinsulinemia. However, the selectivity of the claimed PI3Kα-specific drugs is currently limited at their physiologically effective concentrations.

Herein, this project aimed to develop a rational drug design approach to increase target selectivity of a pan-PI3K inhibitory scaffold, PQR514, by its covalent attachment to an isoform-specific non-conserved nucleophilic amino acid side chain, Cys862 in PI3Kα. PQR514 reversible scaffold was derivatized to attach an electrophilic moiety (warhead) after adjusted improvements in warhead stability and warhead intrinsic chemical reactivity. The warhead proximity and its orientation to the covalent anchor site were optimized through our "active volume scanning" strategy to promote isoform-selective covalent attachment on the target site.

In order to validate the target using the active volume scanning strategy, a highly reactive warhead was utilized to scan the dynamic protein space and generate "reactive hits" in terms of successful covalent labeling of the target. If a covalent bond was formed between the warhead and the targeted amino acid side chain in the target protein of interest, further modifications were carried out using the steric modifications to optimize warhead proximity and the nucleophilic attack vector in order to maximize covalent bond formation efficiency. Accordingly, the highly reactive warhead was exchanged with a moderately reactive, drug like warhead in order to minimize unwanted side reactions and promote its metabolic stability. Our novel covalent inhibitors already containing drug-like warheads were metabolically stable and outperformed CNX1351, the only reported PI3Kα-selective covalent inhibitor, in terms of biochemical and cellular potency, physicochemical properties, and metabolic stability. Concerning "drug-likeness" of the currently available PI3K covalent inhibitors, the only covalent PI3K inhibitor in clinical trials was a pan-PI3K covalent inhibitor, PX866, which had been tested in clinical trials for 15 years but failed due to poor clinical outcome. Its labile wortmannin core and unstable Schiff-base forming warhead with the targeted amino acid side chains were not optimal for in vivo efficacy. Although there are many reversible class I PI3K inhibitors that have been already tested in the clinics, the isoform-selective covalent inhibition strategy is not thoroughly exploited in order to improve the isoform-selectivity profile of the currently available reversible PI3K inhibitors. Therefore, there is a need to develop isoform selective, highly potent, and metabolically stable drug-like covalent PI3K inhibitors not only to treat PI3Kα-driven malignancies but also to deconvolute class I PI3K signaling activities in cells in order to unravel redundant and non-redundant functions of PI3K isoforms.

Our covalent inhibition strategy based on a covalent PI3Kα/non-covalent (reversible) pan-PI3K inhibition approach could allow novel scenarios to reversibly target class I PI3Ks (PI3Kβ, PI3Kδ, PI3Kγ), while only PI3Kα isoform is irreversibly inhibited for a prolonged period of time. Even tumors with loss of PTEN can be transiently targeted, while PI3Kα inactivation will persist for a prolonged period of time after systemic

elimination of the drug. This mode of action is more suitable for intermittent dosing suggested by a clinical trial with PQR309 (Bimiralisib). In intermittent treatment regimen, PQR309 maintained the suppression of tumor growth with lessened on-target metabolic side effects in rodents and patients [NCT02249429, NCT03740100]. Therefore, a covalent inhibition strategy may introduce an improved therapeutic window.

Through a structure-activity relationship (SAR) study, highly potent, metabolically stable, and drug-like PI3Kα-selective covalent inhibitors were developed as a tool to fine-tune pharmacology in PI3K inhibitor cancer therapy. Optimization of linker length and warhead proximity toward the nucleophilic Cys862 side chain in PI3Kα promoted increased covalent bond formation efficiency up to a two-order of magnitude without modifying the electrophilicity (or intrinsic reactivity) of warheads. Rigorous cellular characterizations pinpointed low nanomolar potency in inhibition of PI3K downstream activity in cancer cells and prolonged inhibitory activity after drug washout. Moreover, Nano Bioluminescence Resonance Energy Transfer (NanoBRET) experiments exploiting PI3Kα Cys862Ser genetic point mutation confirmed the involvement of Cys862 in drug action in intact HEK293 cells. In agreement with this, X-ray crystal structures of PI3Kα in complex with our novel covalent inhibitors validated the covalent modification of Cys862 in PI3Kα. Our lead compounds outperformed the rapidly metabolized CNX1351, which is the only reported PI3Kα irreversible inhibitor. Moreover, our inhibitors exhibited excellent cellular activity with a superior physicochemical profile compared to CNX1351. Our results represent a step towards an increased local and temporal control of 10 PI3K inhibition, and our rational covalent inhibitor design strategy paves the way to a more efficient targeting of a broader panel of cysteines in the human kinome.

In addition to the development of novel PI3K targeting pharmacological probes, a dual pan PI3K/mTOR-selective inhibitor (PQR530) and an mTOR-selective inhibitor (PQR626) were developed to deconvolute PI3K and mTOR signaling and to evaluate novel treatment modalities against epileptic seizures occurring due to loss of tuberous sclerosis complex (TSC) function. TSC2 (tuberin) together with its binding partner TSC1 (hamartin) have key functions to integrate multiple inputs from PI3K, ERK, Wnt, and energy signals through the attenuation of mTORC1 activity. Given that, TSC1 and TSC2 function as tumor suppressors, and genetic mutations disrupting TSC function cause a malformation called tuberous sclerosis complex (TSC) disease, which is manifested by the formation of cysts and benign tumors in vital organs such as brain and kidney. Targeting mTOR in the treatment of epileptic seizures using blood-brain barrier (BBB) permeable, orally bioavailable, and mTOR-selective drug-like small molecule inhibitor, PQR626, reduced the loss of TSC1- caused mortality in a TSC1GFAPCKO mouse model and did not induce metabolic side effects including hyperglycemia and hyperinsulinemia. mTOR-selective/PI3K-sparing inhibition strategy with PQR626 introduced certain advantages over dual mTOR/pan-PI3K inhibition strategy with PQR530 in order to circumvent on target metabolic side effects of pan-PI3K inhibition.

Yüksek Lisans Tez (Özet):

Recent progress in nanomaterials for gene delivery applications

Nanotechnology-based gene delivery is the division of nanomedicine concerned with the synthesis, characterization, and functionalization of nanomaterials to be used in targeted-gene delivery applications. Nanomaterial-based gene delivery systems hold great promise for curing fatal inherited and acquired diseases, including neurological disorders, cancer, cardiovascular diseases, and acquired immunodeficiency syndrome (AIDS). However, their use in clinical applications is still controversial. To date, the Food and Drug Administration (FDA) has not approved any gene delivery system because of the unknown long-term toxicity and the low gene transfection efficiency of nanomaterials in vivo. Compared to viral vectors, nonviral gene delivery vectors are characterized by a low

preexisting immunogenicity, which is important for preventing a severe immune response. In addition, nonviral vectors provide higher loading capacity and ease of fabrication. For these reasons, this review article focuses on applications of nonviral gene delivery systems, including those based on lipids, polymers, graphene, and other inorganic nanoparticles, and discusses recent advances in nanomaterials for gene therapy. Methods of synthesizing these nanomaterials are briefly described from a materials science perspective. Also, challenges, critical issues, and concerns about the in vivo applications of nanomaterial-based gene delivery systems are discussed. It should be noted that this article is not a comprehensive review of the literature.