Detailed Curriculum vitae for AXA Research Fund

PERSONAL INFORMATION

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Date prepared:	**October 2, 2023**

URL for web site: http://www.ttk.hu/ei/en/epigenetic-and-genome-editing-research-group/

URL for publications: https://scholar.google.com/citations?user=Yb_J2UoAAAAJ&hl=hu

URL for detailed CV: http://www.ttk.hu/wp-content/uploads/SpisakDetailedCV.pdf

EDUCATION

2011 PhD in Gastroenterology
Semmelweis University, Budapest, Hungary
Dr. Bela Molnar, Prof. Dr. Zsolt Tulassay

2004 M.Sc. in Biotechnology and Molecular Genetics
Szent Istvan University, Godollo, Hungary

CURRENT POSITION

2022- Principal Investigator, group leader – Epigenetics and Genome Editing Research Group, RCNS - TTK, Institute of Enzymology, Budapest, Hungary

PREVIOUS POSITIONS

2020-2022 Instructor with Dr. Nilay Sethi
Sethi lab, Dana-Farber Cancer Institute, Harvard University, Boston, MA, USA

2013-2020 Postdoctoral Fellow with Dr. Matthew Freedman
Freedman lab, Dana-Farber Cancer Institute, Harvard University, Boston, USA

2012-2013 Postdoctoral Fellow with Dr. Barry Karger
Barnett Institute, Northeastern University, Boston, MA, USA

2011-2012 Postdoctoral Fellow with Dr. Bela Molnar
2nd Department of Internal Medicine, Semmelweis University, Budapest, Hungary

FELLOWSHIPS AND AWARDS

2023-2025 Bolyai Scientific Award and Scolarship (Hungarian Scientific Academy)
2021 ASHG Best Poster Award/ASHG Annual meeting/USA (spatial transcriptomics)
2011 First Prize, Pancreatic Oncology Award/Simor Pal Foundation/Hungary
2010 Dr. Farkas Zsolt Award/Veritas et Virtus Foundation/Hungary
2008 Markusovszky Prize/Lajos Markusovszky Foundation/Hungary
2004 Award of Young Biotechnologists/Hungarian National Scientific Council/Hungary
2002-2003 Jozsef Beres Scholarship/Jozsef Beres Foundation/Szent Istvan University/Dept. Biotechnology

TEACHING ACTIVITIES

2022- Lecturer – Genetics/Eotvos Lorand University/Biology Doctoral School/Budapest/Hungary

2011- Lecturer – Molecular biology/Semmelweis University/Clinical Doctoral School, Budapest/Hungary

INSTITUTIONAL RESPONSIBILITIES

2022- Member of the Genetic Core Facility/RCNS-TTK/Institute of Enzymology/Hungary

MEMBERSHIPS OF SCIENTIFIC SOCIETIES

2007- Hungarian Transplantation Association
2006- Hungarian Bioinformatics Association
2004- Hungarian Gastroenterology Association
2000- Association of Hungarian Geneticists

PERSONAL STATEMENT

My decision to pursue a scientific career was profoundly influenced by various experiences. Growing up in an environment that encouraged curiosity laid the foundation for my love of biology and passion for problem-solving. My initial exposure to academic science occurred when I met with my supervisor, Dr. Andras Holczinger, and professors, Prof. Tibor Sik and Prof. Laszlo Orosz, at Szent István University. Under their guidance, I delved into the fundamentals of bacterial genetics and biotechnology, exploring a robust bacteria-bacteriophage system. This experience not only taught me the intricacies of genetics but also highlighted how careful and precise investigative research can answer important questions.

Following my undergraduate studies, I directed my focus towards human genetics, spurred by the desire to apply it to unravel cancer mechanisms. The decision took a deeply personal turn when a family member was diagnosed with colon cancer. This fueled my determination to delve into cancer research. Embarking on my Ph.D. journey at Semmelweis Medical University, I naturally gravitated towards colorectal cancer research. During this period, I gained invaluable experience in various facets, including gastroenterology under Zsolt Tulassay, virtual microscopy and laser microdissection with Prof. Bela Molnar, pathology with Prof. Karoly Lapis, and computational science with Prof. Istvan Csabai.

Continuing my research journey, I became a postdoctoral fellow in Prof. Barry Carger's laboratory at Northeastern in Boston, where I explored cutting-edge technologies in glycobiology and mass spectrometry. Although intriguing, I missed the direct application to human disease and genetics. Fortunately, a turning point came when I joined Dr. Matthew Freedman's lab, focusing on human molecular genetics and epigenetics during my postdoctoral work. This period was transformative, allowing me to specialize in the functional evaluation of germline noncoding variants and their association with prostate cancer risk. Additionally, I gained extensive experience in epigenetics and genome editing, including functional CRISPR screens. Venturing into independent research, I eagerly applied my expertise in epigenomic investigation to colorectal cancer, collaborating with Dr. Nilay Sethi, a physician-scientist at Dana-Farber Cancer Institute, who combines clinical work with gastrointestinal cancer patients and conducts research in the laboratory.

In 2022, I received an invitation to establish the Epigenetics and Genome Editing Research Group at the Enzymology Institute of the Research Centre of Natural Sciences in Budapest, Hungary. Leading a team of motivated researchers, we directed our focus towards unraveling early events in colon cancer biology. Our achievements have been acknowledged through initial findings and publications, further reinforced by collaborations.

As a devoted scientist, my commitment lies in gaining a profound understanding of specific genomic alterations and fundamental molecular mechanisms driving gastrointestinal cancers. I aspire to translate this understanding into clinical advancements. My enthusiasm for investigative research is driven by the desire to enhance our knowledge of human disease and, ultimately, contribute to the effective diagnosis and treatment of colon cancer. I am eager to collaborate with like-minded individuals to make meaningful strides in the field of cancer research.

CONTRIBUTION TO SCIENCE

Graduate Career: Colorectal Cancer Biomarker Discovery

I investigated colorectal cancer development and biomarker discovery during graduate school. While high-throughput molecular biological methods have advanced our understanding of tumor molecular processes, numerous questions remain regarding early diagnosis. For my Ph.D. thesis, I identified and validated biomarkers for CRC development and progression. I determined genes regulated by methylation based on altered mRNA expression and then analyzed the effect of chemo preventive agents using a cell culture model. I established that laser capture microdissected (LCM) samples are suitable for whole genomic microarray analysis. Using LCM samples, I identified differentially expressed genes during the progression of the colorectal adenoma-carcinoma sequence. Furthermore, I determined the tissue-specific expression of biomarkers from biopsy and surgical studies using LCM samples. I demonstrated that methylation-regulated genes could be identified through the examination of gene expression, including the methylation locus of the PTGDR gene. Additionally, I assessed molecular processes in CRC carcinogenesis that can be reversed by selective COX2 inhibitor treatment.

1. **Spisak S**, Tulassay Z, Molnar B, Guttman A. Protein microchips in biomedicine and biomarker discovery. **Electrophoresis**. 2007 Dec;28(23):4261-73. Review.

2. Galamb O*, **Spisák S***, Sipos F, Tóth K, Solymosi N, Wichmann B, Krenács T, Valcz G, Tulassay Z, Molnár B. Reversal of gene expression changes in the colorectal normal-adenoma pathway by NS398 selective COX2 inhibitor. **Br J Cancer**. 2010;102(4):765-73. PMCID: PMC2837560. *** =** joint first authorship

3. **Spisák S**, Galamb B, Sipos F, Galamb O, Wichmann B, Solymosi N, Nemes B, Molnár J, Tulassay Z, Molnár B. Applicability of antibody and mRNA expression microarrays for identifying diagnostic and progression markers of early and late stage colorectal cancer. **Dis Markers**, 2010;28(1):1-14. PMCID: PMC3833602.

4. **Spisák S**, Kalmár A, Galamb O, Wichmann B, Sipos F, Péterfia B, Csabai I, Kovalszky I, Semsey S, Tulassay Z, Molnár B. Genome-wide screening of genes regulated by DNA methylation in colon cancer development. **PLoS One**. 2012;7(10):e46215. PMCID: PMC3462205.

Early Detection of Cancer using Epigenomics

During my graduate studies, I also participated in early colon cancer detection projects with an Epigenomics company that developed ProClolon, Epi proColon® and Septin 9 Methylation (mSEPT9) Detection kit. We set up cell-free DNA (cfDNA) isolation protocols and tested the kit on patient samples, demonstrating that Septin9 is methylated during the normal adenoma-carcinoma transition using laser capture microdissection (LCM).
A couple of years ago, our lab at the Dana-Farber Cancer Institute started a collaboration with Daniel De Carvalho's research group from Princess Margaret Cancer Centre in Toronto, Canada, to use their approach for the early detection of tumors from circulating cell-free DNA (cfDNA). Based on my previous experiences, we were able to successfully establish this technique in our lab. In an early detection effort, we have begun testing clinical samples for the presence of cfDNA from genitourinary cancers. The novelty of our approach lies in successfully implementing the first example of using urine DNA to determine its DNA methylation pattern for the early detection of kidney cancer. Now, my lab is eager to apply other novel epigenetic-related techniques, including plasma chromatin immunoprecipitation (ChIP) and DNA evaluation of fragments for early interception (DELFI), to implement them in early cancer detection.

1. Wasserkort R, Kalmar A, Valcz G, **Spisak** S, Krispin M, Toth K, Tulassay Z, Sledziewski AZ, Molnar B. Aberrant septin 9 DNA methylation in colorectal cancer is restricted to a single CpG island. **BMC Cancer**. 2013 Aug 30;13(1):398.

2. Nuzzo PV*, Berchuck JE*, Korthauer K*, **Spisak S***, Nassar AH, Abou Alaiwi S, Chakravarthy A, Shen SY, Bakouny Z, Boccardo F, Steinharter J, Bouchard G, Curran CR, Pan W, Baca SC, Seo JH, Lee GM, Michaelson MD, Chang SL, Waikar SS, Sonpavde G, Irizarry RA, Pomerantz M, De Carvalho DD, Choueiri TK, Freedman ML. Detection of renal cell carcinoma using plasma and urine cell-free DNA methylomes. **Nat Med.** 2020 Jul;26(7):1041-1043.
   *** =** joint first authorship

3. Berchuck JE, Baca SC, McClure HM, Korthauer K, Tsai HK, Vitale Nuzzo P, Kelleher KM, He M, Steinharter JA, Zacharia S, **Spisak S**, Seo JH, Conteduca V, Elemento O, Auh J, Sigouros M, Corey E, Hirsch MS, Taplin ME, Choueiri TK, Pomerantz MM, Beltran H, Freedman ML. Detecting neuroendocrine prostate cancer through tissue-informed cell-free DNA methylation analysis. **Clin Cancer Res**. 2021 Dec 14. PMID: 34907080

Therapeutic Vulnerabilities in different Cancers

During the first part of my postdoctoral training, I joined a research project that focused on DNA repair related questions. By targeted sequencing of cancer-related genes, we found that germline *BRCA2* mutations are enriched (~6%) in aggressive prostate cancer. Once this mutation is present, the probability that patients will develop aggressive castrate-resistant prostate cancer (CRPC) is higher than if the mutation were not present. Notably, we found that majority of the BRCA2 mutant patients had response to platinum-based therapies. These results suggested that BRCA2 mutation status can serve as a predictive biomarker for platinum response. In other studies, we used deep sequencing and/or genome editing approaches to better understand genomic alterations and drug sensitivity in homologues directed repair (HDR) deficient cancers. I also contributed to a study that demonstrated en bloc transmission of extracellular vesicles through the plasma membrane between tumor cells. Immunofluorescent-based detection of these vesicles in archived pathological samples may represent a novel and unique opportunity which enables analysis of EV release in situ in human tissues. Recently, I contributed to a study in colon cancer, where we interrogated the role of SOX9 as a key molecule of stem cell program. The major finding of this study, that SOX9 blocks differentiation via an enhancer-mediated stem-cell like epigenetic program. Genetic inactivation of SOX9 can be reversed this process and initiate cellular differentiation.

1. Pomerantz MM*, **Spisák S***, Jia L, Cronin AM, Csabai I, Ledet E, Sartor AO, Rainville I, O'Connor EP, Herbert ZT, Szállási Z, Oh WK, Kantoff PW, Garber JE, Schrag D, Kibel AS, Freedman ML. The association between germline BRCA2 variants and sensitivity to platinum-based chemotherapy among men with metastatic prostate cancer. **Cancer**. 2017 Jun 13. doi: 10.1002/cncr.30808. * = joint first authorship

2. Valcz G, Buzás EI, Kittel Á, Krenács T, Visnovitz T, **Spisák S**, Török G, Homolya L, Zsigrai S, Kiszler G, Antalffy G, Pálóczi K, Szállási Z, Szabó V, Sebestyén A, Solymosi N, Kalmár A, Dede K, Lőrincz P, Tulassay Z, Igaz P, Molnár B. En bloc release of MVB-like small extracellular vesicle clusters by colorectal carcinoma cells. J **Extracell Vesicles**. 2019 Apr 8 PMID: 31007874

3. Póti Á, Gyergyák H, Németh E, Rusz O, Tóth S, Kovácsházi C, Chen D, Szikriszt B, **Spisák S**, Takeda S, Szakács G, Szallasi Z, Richardson AL, Szüts D. Correlation of homologous recombination deficiency induced mutational signatures with sensitivity to PARP inhibitors and cytotoxic agents. **Genome Biol**. 2019 Nov 14;20(1):240. PMID: 31727117

4. Sztupinszki Z, Diossy M, Krzystanek M, Borcsok J, Pomerantz MM, Tisza V, **Spisak S**, Rusz O, Csabai I, Freedman ML, Szallasi Z. Detection of Molecular Signatures of Homologous

Recombination Deficiency in Prostate Cancer with or without BRCA1/2 Mutations. **Clin Cancer Res**. 2020 Feb 18. PMID: 32071115

5. Liang X, Duronio GN, Yang Y, Bala P, Hebbar P, **Spisak S**, Sahgal P, Singh H, Zhang Y, Xie Y, Cejas P, Long HW, Bass AJ, Sethi NS. An Enhancer-Driven Stem Cell-Like Program Mediated by SOX9 Blocks Intestinal Differentiation in Colorectal Cancer. **Gastroenterology**. 2022 Jan;162(1):209-222. PMID: 34571027

Investigating the functional non-coding genome, focusing on germline variants, transcription factors and enhancers

I have dedicated a substantial portion of my research to developing strategies for functionally characterizing the non-protein coding genome. One notable innovation is CAUSEL, short for Characterization of Alleles Using Editing of Loci. This pioneer approach leverages genome and epigenome editing tools to introduce precise base pair changes. CAUSEL is designed to efficiently handle challenges such as single-cell cloning and genotyping thousands of clones.
Additionally, I have applied epigenomic techniques, including the analysis of open chromatin regions, histone modifications, transcription factor binding, and DNA methylation, to comprehend the development of aggressive metastatic castration-resistant prostate cancer. In the realm of prostate cancer (PCa), where the androgen receptor (AR) is a pivotal driver and therapeutic target, the transcriptional regulation of this crucial gene remains incompletely understood. Utilizing epigenetic and genetic approaches, we identified candidate AR regulators and employed a CRISPR interference screen to functionally validate enhancer candidates. Our research successfully demonstrated that a distant enhancer on chromosome X regulates AR expression. Subsequent work will focus on identifying the specific transcription factor that binds to this enhancer, with the goal of paving the way for a novel approach to treating advanced PCa.

1. **Spisak S***, Lawrenson K*****, Fu Y*****, Csabai I, Cottman RT, Seo JH, Haiman C, Han Y, Lenci R, Li Q, Tisza V, Szállási Z, Herbert ZT, Chabot M, Pomerantz M, Solymosi N; GAME-ON/ELLIPSE Consortium, Gayther SA, Joung JK, Freedman ML. CAUSEL: an epigenome- and genome-editing pipeline for establishing function of noncoding GWAS variants. **Nat Med.** 2015 Sep 23.
*** =** joint first authorship

2. Takeda DY*, **Spisak S***, Seo JH, Bell C, O'Connor E, Korthauer K, Ribli D, Csabai I, Solymosi N, Szállási Z, Stillman DR, Cejas P, Qiu X, Long HW, Tisza V, Nuzzo PV, Rohanizadegan M, Pomerantz MM, Hahn WC, Freedman ML. A Somatically Acquired Enhancer of the Androgen Receptor Is a Noncoding Driver in Advanced Prostate Cancer. **Cell.** 2018 Jun 9. PMCID: PMID29909987, *** =** joint first authorship

3. Guo H, Wu Y, Nouri M, **Spisak S**, Russo JW, Sowalsky AG, Pomerantz MM, Wei Z, Korthauer K, Seo JH, Wang L, Arai S, Freedman ML, He HH, Chen S, Balk SP. Androgen receptor and MYC equilibration centralizes on developmental super-enhancer. **Nat Commun.** 2021 Dec 15;12(1):7308. PMID: 34911936

4. Lu X, Fong KW, Gritsina G, Wang F, Baca SC, Brea LT, Berchuck JE, **Spisak S**, Ross J, Morrissey C, Corey E, Chandel NS, Catalona WJ, Yang X, Freedman ML, Zhao JC, Yu J. HOXB13 suppresses de novo lipogenesis through HDAC3-mediated epigenetic reprogramming in prostate cancer. **Nat Genet.** 2022 Apr 25.

5. **Spisak S**, Tisza V, Nuzzo PV, Seo JH, Pataki B, Ribli D, Sztupinszki Z, Bell C, Rohanizadegan M, Stillman DR, Alaiwi SA, Bartels AB, Papp M, Shetty A, Abbasi F, Lin X, Lawrenson K, Gayther SA, Pomerantz M, Baca S, Solymosi N, Csabai I, Szallasi Z, Gusev A, Freedman ML. A biallelic multiple nucleotide length polymorphism explains functional causality at 5p15.33 prostate cancer risk locus. **Nat Commun.** 2023 Aug 23;14(1):5118.

CURRENT RESEARCH GRANTS

Starting grant, RCNS-TTK, Enzymology Institute, grant no. : 0006-22 418 AT
Establishment of the Epigenetic and Genome Editing Research Group at RCNS-TTK
09/2022-08/2025, € 250 000, Principal Investigator, grant holder

National Research Development and Innovation Office Hungary, grant no. : FK142835 (OTKA)
Detection of early disease recurrence using plasma cell-free DNA methylome from liquid biopsy of early-stage lung adenocarcinoma patients
10/2022-09/2026, € 120 000, Principal Investigator, grant holder

Additional Information: Research Support and/or Scholastic Performance

Friends of Dana Farber Foundation 10/01/2018 – 09/30/2019
Targeting The Transcriptional Regulation of The Androgen Receptor In Advanced Prostate Cancer
The overall goal of this proposal is to mechanistically understand the epigenetic activation of a somatically acquired enhancer in prostate cancer, which regulates the Androgen receptor gene. This work could serve a basis to find potential drug targets to develop a fundamentally new way to treat aggressive metastatic castration resistant prostate cancers (CRPC).

Role: Principal Investigator

LIST OF PUBLICATIONS

Peer-reviewed publications

Research Investigations

* = co first author

1. Galamb O, Sipos F, Dinya E, **Spisák S**, Tulassay Z, Molnar B. mRNA expression, functional profiling and multivariate classification of colon biopsy specimen by cDNA overall glass microarray. World J Gastroenterol. 2006 Nov 21;12(43):6998-7006. PMID: 17109495
2. Galamb O, Sipos F, Molnar B, Szoke D, **Spisák S**, Tulassay Z. Evaluation of malignant and benign gastric biopsy specimens by mRNA expression profile and multivariate statistical methods. Cytometry B Clin Cytom. 2007 Sep;72(5):299-309. PMID: 17366642
3. Galamb O, Gyorffy B, Sipos F, **Spisák S**, Németh AM, Miheller P, Dinya E, Molnár B, Tulassay Z. [Identification of colorectal cancer, adenoma, and inflammatory bowel disease specific gene expression patterns using whole genomic oligonucleotide microarray system]. Orv Hetil. 2007 Nov 4;148(44):2067-79. PMID: 17959550 Hungarian.
4. Galamb O, Sipos F, Dinya E, **Spisák S**, Somorácz A, Molnár B, Tulassay Z. [Functional mRNA expression analysis and classification of colonic biopsy samples using overall cDNA microarray technique]. Orv Hetil. 2008 Feb 3;149(5):219-32. PMID: 18218589 Hungarian.
5. Galamb O, Győrffy B, Sipos F, Dinya E, Krenács T, Berczi L, Szőke D, **Spisák S**, Solymosi N, Németh AM, Juhász M, Molnár B, Tulassay Z. Helicobacter pylori and antrum erosion-specific gene expression patterns: the discriminative role of CXCL13 and VCAM1 transcripts. Helicobacter. 2008 Apr;13(2):112-26. PMID: 18321301
6. Galamb O, Györffy B, Sipos F, **Spisák S**, Németh AM, Miheller P, Tulassay Z, Dinya E, Molnár B. Inflammation, adenoma and cancer: objective classification of colon biopsy specimens with gene expression signature. Dis Markers. 2008;25(1):1-16. PMID: 18776587
7. Galamb O, Sipos F, Solymosi N, **Spisák S**, Krenács T, Tóth K, Tulassay Z, Molnár B. Diagnostic mRNA expression patterns of inflamed, benign, and malignant colorectal biopsy specimen and their correlation with peripheral blood results. Cancer Epidemiol Biomarkers

Prev. 2008 Oct;17(10):2835-45. PMID: 18843029

8. Galamb O, Sipos F, **Spisák S**, Galamb B, Krenács T, Valcz G, Tulassay Z, Molnár B. Potential biomarkers of colorectal adenoma-dysplasia-carcinoma progression: mRNA expression profiling and in situ protein detection on TMAs reveal 15 sequentially upregulated and 2 downregulated genes. Cell Oncol. 2009;31(1):19-29. PMID: 19096147

9. Szoke D, Molnar B, Solymosi N, Racz K, Gergics P, Blasko B, Vasarhelyi B, Vannay A Mandy Y, Klausz G, Gyulai Z, Galamb O, **Spisák S**, Hutkai B, Somogyi A, Berta K, Szabo A, Tulassay T, Tulassay Z. Polymorphisms of the ApoE, HSD3B1, IL-1beta and p53 genes are associated with the development of early uremic complications in diabetic patients: results of a DNA resequencing array study. Int J Mol Med. 2009 Feb;23(2):217-27. PMID: 19148546

10. **Spisák S**, Galamb B, Wichmann B, Sipos F, Galamb O, Solymosi N, Nemes B, Tulassay Z, Molnár B. [Tissue microarray (TMA) validated progression markers in colorectal cancer using antibody microarrays]. Orv Hetil. 2009 Aug 23;150(34):1607-13. PMID: 19648079 Hungarian.

11. Galamb O*, **Spisák S***, Sipos F, Tóth K, Solymosi N, Wichmann B, Krenács T, Valcz G, Tulassay Z, Molnár B. Reversal of gene expression changes in the colorectal normal-adenoma pathway by NS398 selective COX2 inhibitor. Br J Cancer. 2010 Feb 16;102(4):765-73. PMID: 20087348

12. **Spisák S**, Galamb B, Sipos F, Galamb O, Wichmann B, Solymosi N, Nemes B, Molnár J, Tulassay Z, Molnár B. Applicability of antibody and mRNA expression microarrays for identifying diagnostic and progression markers of early and late stage colorectal cancer. Dis Markers. 2010;28(1):1-14. PMID: 20164542

13. **Spisák S**, Kalmár A, Galamb O, Sipos F, Wichmann B, Molnár B, Tulassay Z. Identification of methylation related genes from laser capture microdissected colon samples during investigation of adenoma-carcinoma sequence. Orv Hetil. 2010 May 16;151(20):805-14. PMID: 20442051 Hungarian.

14. Tóth K, Galamb O, **Spisák S**, Wichmann B, Sipos F, Valcz G, Leiszter K, Molnár B, Tulassay Z. The influence of methylated septin 9 gene on RNA and protein level in colorectal cancer. Pathol Oncol Res. 2011 Sep;17(3):503-9. PMID: 21267688

15. Kalmar A, Wichmann B, Galamb O, **Spisák S**, Tóth K, Leiszter K, Tulassay Z, Molnár B. Gene expression analysis of normal and colorectal cancer tissue samples from fresh frozen and matched formalin-fixed, paraffin-embedded (FFPE) specimens after manual and automated RNA isolation. Methods. 2013 Jan;59(1):S16-9. doi: 10.1016/j.ymeth.2012.09.011. PMID: 23036325

16. **Spisák S**, Kalmár A, Galamb O, Wichmann B, Sipos F, Péterfia B, Csabai I, Kovalszky I, Semsey S, Tulassay Z, Molnár B. Genome-wide screening of genes regulated by DNA methylation in colon cancer development. PLoS One. 2012;7(10):e46215. PMID: 23049694

17. Galamb O, Wichmann B, Sipos F, **Spisák S**, Krenács T, Tóth K, Leiszter K, Kalmár A, Tulassay Z, Molnár B. Dysplasia-carcinoma transition specific transcripts in colonic biopsy samples. PLoS One. 2012;7(11):e48547. PMID: 23155391

18. Kiss O, Tőkés AM, **Spisák S**, Szilágyi A, Lippai N, Szász AM, Kulka J. MicroRNA-profiling in breast- and salivary gland-derived adenoid cystic carcinomas. Orv Hetil. 2013 Jun 23;154(25):963-8. doi: 10.1556/OH.2013.29643. PMID: 23774803 Hungarian.

19. **Spisák S**, Solymosi N, Ittzés P, Bodor A, Kondor D, Vattay G, Barták BK, Sipos F, Galamb O, Tulassay Z, Szállási Z, Rasmussen S, Sicheritz-Ponten T, Brunak S, Molnár B, Csabai I. Complete genes may pass from food to human blood. PLoS One. 2013 Jul 30;8(7):e69805. PMID: 23936105

20. Wasserkort R, Kalmar A, Valcz G, **Spisák S**, Krispin M, Toth K, Tulassay Z, Sledziewski AZ,

Molnar B. Aberrant septin 9 DNA methylation in colorectal cancer is restricted to a single CpG island. BMC Cancer. 2013 Aug 30;13(1):398. PMID: 23988185

21. Fűri I, Sipos F, **Spisák S**, Kiszner G, Wichmann B, Schöller A, Tulassay Z, Műzes G, Molnár B. Association of self-DNA mediated TLR9-related gene, DNA methyltransferase, and cytokeratin protein expression alterations in HT29-cells to DNA fragment length and methylation status. ScientificWorldJournal. 2013 Dec 29;2013:293296. PMID: 24459426

22. Sipos F, Műzes G, Fűri I, **Spisák S**, Wichmann B, Germann TM, Constantinovits M, Krenács T, Tulassay Z, Molnár B. Intravenous administration of a single-dose free-circulating DNA of colitic origin improves severe murine DSS-colitis. Pathol Oncol Res. 2014 Oct;20(4):867-77. PMID: 24723054

23. Andocs G, Meggyeshazi N, Balogh L, **Spisák S**, Maros ME, Balla P, Kiszner G, Teleki I, Kovago C, Krenacs T. Upregulation of heat shock proteins and the promotion of damage-associated molecular pattern signals in a colorectal cancer model by modulated electrohyperthermia. Cell Stress Chaperones. 2015 Jan;20(1):37-46. doi: 10.1007/s12192-014-0523-6. PMID: 24973890

24. Sipos F, Germann TM, Wichmann B, Galamb O, **Spisák S**, Krenács T, Tulassay Z, Molnár B, Műzes G. MMP3 and CXCL1 are potent stromal protein markers of dysplasia-carcinoma transition in sporadic colorectal cancer. Eur J Cancer Prev. 2014 Sep;23(5):336-43. PMID: 24999605

25. Műzes G, Sipos F, Fűri I, Constantinovits M, **Spisák S**, Wichmann B, Valcz G, Tulassay Z, Molnár B. Preconditioning with intravenous colitic cell-free DNA prevents DSS-colitis by altering TLR9-associated gene expression profile. Dig Dis Sci. 2014 Dec;59(12):2935-46. doi: 10.1007/s10620-014-3325-x. PMID: 25217236

26. Kiss O, Tőkés AM, **Spisák S**, Szilágyi A, Lippai N, Székely B, Szász AM, Kulka J. Breast- and salivary gland-derived adenoid cystic carcinomas: potential post-transcriptional divergencies. A pilot study based on miRNA expression profiling of four cases and review of the potential relevance of the findings. Pathol Oncol Res. 2015 Jan;21(1):29-44. doi: 10.1007/s12253-014-9770-1. PMID: 25240490

27. Valcz G, Patai AV, Kalmár A, Péterfia B, Fűri I, Wichmann B, Műzes G, Sipos F, Krenács T, Mihály E, **Spisák S**, Molnár B, Tulassay Z. Myofibroblast-derived SFRP1 as potential inhibitor of colorectal carcinoma field effect. PLoS One. 2014 Nov 18;9(11):e106143. doi: 10.1371/journal.pone.0106143. PMID: 25405986

28. Kiss K, Baghy K, **Spisák S**, Szanyi S, Tulassay Z, Zalatnai A, Löhr JM, Jesenofsky R, Kovalszky I, Firneisz G. Chronic hyperglycemia induces trans-differentiation of human pancreatic stellate cells and enhances the malignant molecular communication with human pancreatic cancer cells. PLoS One. 2015 May 26;10(5):e0128059. PMID: 26010611

29. Fűri I, Kalmár A, Wichmann B, **Spisák S**, Schöller A, Barták B, Tulassay Z, Molnár B. Cell Free DNA of Tumor Origin Induces a 'Metastatic' Expression Profile in HT-29 Cancer Cell Line. PLoS One. 2015 Jul 2;10(7):e0131699. doi: 10.1371/journal.pone.0131699. eCollection 2015. PMID: 26133168

30. Kalmár A, Wichmann B, Galamb O, **Spisák S**, Tóth K, Leiszter K, Nielsen BS, Barták BK, Tulassay Z, Molnár B. Gene-expression analysis of a colorectal cancer-specific discriminatory transcript set on formalin-fixed, paraffin-embedded (FFPE) tissue samples. Diagn Pathol. 2015 Jul 25;10:126. PMID: 26208990

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Preprints (bioRxiv)

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Manuscripts under preparation

1. Miklos Diossy M, Tisza V, Li H, Zhou J, Sztupinszki Z, Young D, Nousome D, Kuo C, Chen Y, Ebner R, Sesterhenn IA, Moncur JT, Chesnut GT, Petrovics G, Klus GT, Valcz G, Nuzzo PV, Ribli D, Schina A, Börcsök J, Prosz A, Krzystanek M, Ried T, Szuts D, Kaochar S, Pathania S, D'Andrea AD, Csabai I, Srivastava S, Dobi A, Freedman ML, **Spisak S**[#], Szallasi Z. Increased frequency of CHD1 deletions in prostate cancers of African American men is associated with distinct homologous recombination deficiency associated DNA aberration profiles. Nat. Common. under revision, [#] = co-corresponding author

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2. Nuzzo PV, **Spisák S**, Chakravarthy A, Shen SY, Berchuck JE, Nassar A, Abou Alaiwi S, Steinharter JA,Bakouny Z, Boccardo F, Sonpavde G, Mary Lee GS, Chang SL, Pomerantz M, De Carvalho D, Freedman M, Choueiri TK. Cell-free methylated DNA (cfMeDNA) immunoprecipitation and high throughput sequencing technology (cfMeDIP-seq) in patients with clear cell renal cell carcinoma (ccRCC). ASCO 2019, Chicago, CA, USA.

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5. Freedman ML, **Spisák S**, Seo JH., Zarif TE., He S., Phan J., Lee I., Jenkins J., Piazza E., Kim D., Beechem J., Highly sensitive transcriptomic-based pooled CRISPR screening enabled by Spatial Molecular Imager (SMI), 2021, Advances in Genome Biology and Technology (AGBT), St. Louis, MO, Virtual Meeting

6. **Spisak S**, Freedman ML, Seo JH, Kim D, Pimentel H, He S, Piazza E, Danaher P, Lee I, Jenkins J, Liu R, Joseph Beechem J. Highly sensitive transcriptomic-based pooled CRISPR screening enabled by Spatial Molecular Imager (SMI). 2021 Annual Meeting - ASHG (online)

TEN SELECTED PUBLICATIONS

1. **Spisak S**, Tisza V, Nuzzo PV, Seo JH, Pataki B, Ribli D, Sztupinszki Z, Bell C, Rohanizadegan M, Stillman DR, Alaiwi SA, Bartels AB, Papp M, Shetty A, Abbasi F, Lin X, Lawrenson K, Gayther SA, Pomerantz M, Baca S, Solymosi N, Csabai I, Szallasi Z, Gusev A, Freedman ML. A biallelic multiple nucleotide length polymorphism explains functional causality at 5p15.33 prostate cancer risk locus. **Nat Commun.** 2023 Aug 23;14(1):5118.

2. Nassar A, Alaiwi SA, Baca SC, Corona RI, Seo JH, Adib E, Fonseca MAS, **Spisak S**, Braun DA, Du H, He M, Flaifel A, Denize T, Shukla SA, Hou Y, Bouchard G, Berchuck JE, Nuzzo PV, Lee GSM, Signoretti S, Pomerantz MM, Henske E, Gusev A, Lawrenson K, Choueiri TK, Kwiatkowski DJ (2023). Leveraging the Epigenomic Landscape to identify Histology-Specific Master transcription factors and to functionally annotate risk loci in renal cell carcinoma. **Nat. Commun**. 14(1):346

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4. Lu X, Fong KW, Gritsina G, Wang F, Baca SC, Brea LT, Berchuc JE, **Spisak S**, Ross J, Corey E, Chandel N, Catalona WJ, Yang X, Freedman ML, Zhao1 JC, Yu J (2022). HOXB13 suppresses de novo lipogenesis through HDAC3-mediated epigenetic reprogramming. **Nat Genet**. 54(5):670-683

5. Liang X, Duronio GN, Yang Y, Bala P, Hebbar P, **Spisak S**, Sahgal P, Singh H, Zhang Y, Xie Y, Cejas P, Long HW, Bass AJ, Sethi NS (2022). An Enhancer-Driven Stem Cell-Like Program Mediated by SOX9 Blocks Intestinal Differentiation in Colorectal Cancer. **Gastroenterology**.162(1):209-222.

6. Guo H, Wu Y, Nouri M, **Spisak S**, Russo JW, Sowalsky AG, Pomerantz MM, Wei Z, Korthauer K, Seo JH, Wang L, Arai S, Freedman ML, He HH, Chen S, Balk SP (2021). Androgen receptor and MYC equilibration centralizes on developmental super-enhancer. **Nat. Commun**. 12(1):7308.

7. Nuzzo PV*, Berchuck JE*, Korthauer K*, **Spisák S***, Nassar AH, Abou Alaiwi S, Chakravarthy A, Shen SY, Bakouny Z, Boccardo F, Steinharter J, Bouchard G, Curran CR, Pan W, Baca SC, Seo JH, Lee GM, Michaelson MD, Chang SL, Waikar SS, Sonpavde G, Irizarry RA, Pomerantz M, De Carvalho DD, Choueiri TK, Freedman ML (2020). Detection of renal cell carcinoma using plasma and urine cell-free DNA methylomes. **Nat Med**. (7):1041-1043.

8. Takeda DY*, **Spisák S***, Seo JH, Bell C, O'Connor E, Korthauer K, Ribli D, Csabai I, Solymosi N, Szállási Z, Stillman DR, Cejas P, Qiu X, Long HW, Tisza V, Nuzzo PV, Rohanizadegan M, Pomerantz MM, Hahn WC, Freedman ML (2018). A somatically acquired enhancer of the androgen receptor is a noncoding driver in advanced prostate cancer. **Cell**.174(2):422-432.

9. Pomerantz MM*, **Spisák S***, Jia L, Cronin AM, Csabai I, Ledet E, Sartor AO, Rainville I, O'Connor EP, Herbert ZT, Szállási Z, Oh WK, Kantoff PW, Garber JE, Schrag D, Kibel AS, Freedman ML (2017). The association between germline BRCA2 variants and sensitivity to platinum-based chemotherapy among men with metastatic prostate cancer. **Cancer**. 123(18):3532-3539.

10. **Spisák S***, Lawrenson K*, Fu Y*, Csabai I, Cottman RT, Seo JH, Haiman C, Han Y, Lenci R, Li Q, Tisza V, Szállási Z, Herbert ZT, Chabot M, Pomerantz M, Solymosi N; GAME-ON/ELLIPSE Consortium, Gayther SA, Joung JK, Freedman ML (2015). CAUSEL: an epigenome- and genome-editing pipeline for establishing function of noncoding GWAS variants. **Nat Med**. (11):1357-63.

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DOCTORAL THESIS

Spisák S. Characteristic molecular changes during colorectal carcinogenesis and progression [dissertation]. 2011, Semmelweis University, 2nd Department of Internal Medicine, Budapest

Full thesis in English:

http://phd.sote.hu/mwp/phd_live/vedes/export/spisaksandor.e.pdf

PATENT

Sethi NS, **Spisak S**. Compositions and Methods for Treating and/or Identifying an Agent for Treating Intestinal Cancer. US Patent Application 63/208,313, filed June 8, 2021, Patent pending.
(Related to SOX9 applicability in colon cancer)

INSTITUTIONAL BACKGROUND AND SUPPORT

My host institute, the Research Centre for Natural Sciences (RCNS) stands out as one of Hungary's largest research complexes, encompassing four departments dedicated to molecular life sciences, chemistry, and neuro science, thus offering numerous opportunities for emerging researchers. Boasting 300 well-equipped labs, the RCNS institute is positioned not only for cutting-edge national research but also on the international stage. Within the Department of Enzymology, there are 13 research groups, with a predominant focus on cancer biology and oncology-related subjects. This emphasis on cancer research was a key factor that drew me to consider the Department of Enzymology as the host institute for my research group. The robust institutional structure provides a solid foundation for sustaining the momentum of my research and pursuing promising research directions.

Crucially, the Institute of Enzymology furnishes all the necessary laboratory equipment and infrastructure essential for the successful execution of the proposed "**Understanding Early Molecular Events in Colorectal Cancer for Innovative Therapeutics and Precision Prevention**" AXA Research Fund project. The institute is equipped with high-performance computing (HPC) capacity, ensuring ample server space for data storage and computing - a critical pillar of this project, given the high-quality data it will generate. Additionally, the Genetic and Sequencing core facility at the Institute of Enzymology, further supported by the Flow Cytometry and Mass Spectrometry Core Facility at RCNS, will play a vital role in facilitating our research endeavors.

COLLABORATION AND NETWORKS

I have curated a multidisciplinary team with diverse expertise in genetics, epigenetics, tumor biology, bioinformatics, and clinical oncology at the Institute of Enzymology, RCNS. The core team includes two Postdoctoral scientists, Dr. Viktoria Tisza, a molecular biologist and expert in epigenetics and genome editing with postdoctoral training at Boston Children's Hospital and

Dana-Farber Cancer Institute, and Dr. Laura Vizkeleti, an expert in gene expression and DNA sequencing analysis with years of experience at Semmelweis University, 2nd Department of Pathology. Additionally, two lab technicians and a Ph.D. student, Csaba Kiss, who focuses on the functional understanding of the non-coding genome in colorectal cancer from a computational standpoint, form integral parts of the team.

For computational analysis, we have the expertise of Dr. István Csabai and Dr. Lorinc Pongor from Eotvos Lorand University and HCEMM, respectively. Dr. Bela Molnar, my former mentor at Semmelweis University, significantly contributes to clinical data, sample collection processes, sequencing projects, and tissue digitalization through his virtual microscopy lab. This collaborative effort ensures a comprehensive and diverse skill set, encompassing sequencing projects and tissue digitalization processes through his virtual microscopy lab, to effectively address the complexities of our research goals.

MAJOR COLLABORATORS

Istvan Csabai, computer science, machine learning, Eotvos Lorand University, Budapest, Hungary

Bela Molnar, gastroenterology, Semmelweis University, Budapest, Hungary

Lorinc Pongor, computer science, bioinformatics, epigenetics, Cancer Genomics and Epigenetics Research Group, HCEMM, Szeged, Hungary

Gyorgy Keseru, organic chemistry, drug screens, Institute of Organic Chemistry, RCNS-TTK, Budapest

Gergely Szakacs, cell biology, Medical University of Vienna, Austria

Nikolaus Fortelny, cell morphology, Dept. of Computational Biology, University of Salzburg, Austria

Pier Vitale Nuzzo, liquid biopsy, Deptartment of Pathology and Laboratory Medicine, Weill Cornell Medical College, New York, NY, USA

Gergely Rona, cell biology, cell differentiation, NYU School of Medicine and HHMI, New York, NY, USA

Ramesh Shivdashani, colon biology, Dana-Farber Cancer Institute, Harvard University, Boston, USA

Rinath Jesselson, clinical genomics, Dana-Farber Cancer Institute, Harvard University, Boston, USA

Shanshan He, Joseph Beechem, spatial transcriptomics, Nanostring Inc., Seattle, WA, USA

Harold Pimentel, computer science, single cell transcriptomics, UCLA, Los Angeles, CA, USA

SCIENTOMETRIC DATA

Total number of scientific papers = 64

Number of first/co-firs author papers = 15

Number of corresponding/co corresponding author papers = 8

Total citations = 3180 (Google Scholar)

Cumulative impact factor: IF = 554.440

h-index = 31

Number of book chapters = 1

Number of patents = 1