Jiekun (Jackie) Yang

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Education

University of Virginia (Ming Li lab, UVa) 2013-2016
Ph.D., Biomedical Sciences (Bioinformatics)
Dissertation URL: http://libra.virginia.edu/catalog/libra-oa:11462
Reviewer of *Nucleic Acids Research*, *Genome Research*, *Bioinformatics*, *Genome Medicine*
Classes: Certified Data Science Specialization with Johns Hopkins University on Coursera
Grade: 4.0/4.0 (1/25)

University of Wisconsin-Madison (UW-Madison) 2009-2011
Master, Information Science
Grade: 4.0/4.0 (1/72)

Renmin University of China (Renmin U)
Bachelor, Information Management and Information System 2005-2009

Professional Experience

Incoming Assistant Professor at Rutgers University Department of Genetics start date: January 1, 2024

Research Scientist (Manolis Kellis lab) at MIT Computer Science & Artificial Intelligence Lab and Broad Institute 2019-

- *Obesity:* Dissect single-cell multi-tissue multi-omics obesity-exercise interaction
- *Cancer:* Investigate cell-type-specific and cell communication alterations underlying heterogeneous responses of metastatic melanoma to immune checkpoint inhibitors
- *Down Syndrome:* Determine susceptible cell types, genes, pathways, and master regulators for Alzheimer's Disease in Down Syndrome (DS) using single-cell dissection of postmortem human brains
- *Deep learning:* Infer sample-specific contextualized graphical models using clinical, genetics, metabolomics and transcriptomics data to reveal gene regulatory network heterogeneity in obesity, cancer and DS
- *Leadership:* Strategic planning of projects and grant writing with collaborators from Joslin Diabetes Center, Massachusetts General Hospital, Dana-Farber Cancer Institute, MD Anderson, University of California-Irvine & Novo Nordisk
- *Mentorship:* Mentor graduate and undergraduate students for cancer, metabolism, DS, and method development projects

Postdoctoral Research Fellow (Sunney Xie lab) at Boston Children's Hospital and Harvard Medical School 2019 (PI moved to China)

- Developed a single-cell mass spectrometry project, designed synthetic peptides and conducted preliminary data analysis
- Wrote a computational program for a novel single-cell methylation technique
- Collaborated on computational analysis for non-invasive preimplantation genetic tests of mono- and poly-genic diseases

Postdoctoral Researcher (Mazhar Adli lab) at UVa Biochemistry and Molecular Genetics 2016-2019

- Conceived, developed, and conducted independent research on the association of transcription factor (TF) binding and somatic mutations in breast and prostate cancers, which generated a $25K grant award
- Co-led studies of pancreatic and ovarian cancers by focusing on hypothesis generation using ChIP-seq, ATAC-seq, RNA-seq, and CROP-seq data
- Established computational strategies and analysis of bulk and single-cell high-throughput sequencing data for multiple collaborative labs

• Designed CRISPR-STOP and CRISPR screening libraries and optimized screening strategies
• Mentored graduate and undergraduate students

Research Specialist (Ming Li lab) at UVa Psychiatry and Neurobehavioral Sciences 2011-2013
• Designed analytical and computational pipelines for terabyte-scale genetics datasets
• Conceived and performed statistical analysis for family and case-control studies with thousands of subjects

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Grant Writing Experience

NIH NCI K22 Transition Career Development Award – pending 2023-
The development of immune checkpoint inhibitors (ICIs) targeting the co-inhibitory receptors CTLA-4 and PD-1 have revolutionized the treatment of over a dozen different tumor types. However, only a subset of patients maintains durable responses. Identifying novel and synergistic immune targets remains a critical and unresolved issue. Among the players in cancer immunity, dendritic cells (DCs) are the key link between innate immunity and adaptive immunity, holding promise to improve T cell-mediated immune response in cancer immunotherapy. Based on our preliminary result, an increased density of mature and activated conventional DCs (cDCs) within the tumor microenvironment (TME) is associated with improved prognosis and responsiveness to anti-PD-1 immunotherapy in patients with metastatic melanoma. The guiding hypothesis of this proposal is that (a) the different proportion of mature/activated cDCs in the TME is mediated by cDC intrinsic and extrinsic mechanisms, some of which may be elucidated by systematic single-cell molecular analysis of the cDC and TME; (b) applying epigenetic CRISPR screening approaches to a 3D in vitro model will inform molecular targets mediating cDC activation; and (c) heterogeneous cDC inactivation mechanisms exist within and among cancer types, partially reflected by sample-specific gene regulatory networks (GRNs) associated with cDC activation as inferred from large human cancer cohorts.

NIH T32-DK110919 (Harvard training program in bioinformatics applied to diabetes, obesity and metabolism) – awarded 2020-2021
Obesity is a complex, multifactorial disease that is causally associated with insulin resistance, type 2 diabetes, hyperlipidemia and increased cardiovascular risk. Current treatment options are limited and new therapies for these conditions are desperately needed. Importantly, regular physical activity, or exercise training, is a well-established tool to prevent and treat chronic conditions such as diabetes and obesity. However, the mechanisms through which exercise training affects molecular and metabolic functions across multiple tissues at single-cell resolution is currently not known. Here I use an integrated computational approach across multiple tissues in mouse, in four interventional conditions, to elucidate and validate the molecular mechanisms, genes, pathways, cell types, and tissues mediating the beneficial effects of exercise in subcutaneous and visceral adipose tissues and skeletal muscle. The study includes single-cell and bulk transcriptomics. Integration of data at different resolutions leads to discovery of cell-type and tissue-specific exercise-induced cellular pathways in health and obesity, which enables preclinical studies in the future.

MIT Alana Fellowship (Single-cell transcriptomic and epigenomic dissection of Alzheimer's Disease in Down Syndrome) – awarded 2019-2020

Down syndrome (DS) is the most common chromosomal condition diagnosed in the U.S. According to the Centers for Disease Control and Prevention, about 6,000 babies with DS are born in the U.S. each year. However, remarkably little is known about the condition, which has impeded the ability to design new therapeutic interventions to improve the health and well-being of people with DS. The observed transcriptional and genomic heterogeneity in diverse brain cell types may well explain both mechanisms underlying the condition and phenotypic variability among individuals with DS. Here we generate single-cell transcriptomics and epigenomics datasets for DS with and without Alzheimer's Disease in two brain regions, prefrontal cortex and amygdala (n=24, age- and gender-matched). This study allows us to create molecular signatures of AD in DS, through which we will be able to unravel the contributions of cell-type specific factors that play a decisive role in the development of AD in DS and its associated transcriptional and epigenomic characteristics. Such knowledge has the potential to unravel new translational opportunities.

UVa Cancer Center Trainee RFA (Identifying and validating androgen receptor induced somatic mutations in prostate cancer) – awarded $25K 2018-2019

Somatic mutations are the driving force for cancer cell evolution. Large-scale sequencing efforts have revealed that somatic mutation burden largely resides within non-coding genomic regions. However, the mutational processes underlying non-coding cancer mutations are poorly understood. Our previous research has shown that regardless of chromatin states, a large fraction of non-coding somatic mutations in Estrogen Receptor (ER) positive breast cancer are confined to ER binding sites. To further investigate the role of transcription factor (TF) binding in tumor mutagenesis, we 1) systematically characterize the mutational landscape of Androgen Receptor (AR) binding sites in prostate cancer by integrating whole-genome sequencing and AR ChIP-seq data using clinical samples. We determine the top 100 genomic sites with both AR binding and excessive number of somatic mutations. 2) We perform targeted sequencing for the 100 genomic sites after treating AR-positive and -negative prostate cancer cell lines with two different doses of androgen for 7 and 30 days. We then compare the somatic mutations discovered in samples with and without AR activity. This proposal empowers us to experimentally test the causal relationship between TF binding and mutagenesis in prostate cancer.

Project Leadership Experience

Problem-solving, detail-oriented, open-mindedness, teamwork (strong collaboration skills), multi-tasking, strong written and oral presentation skills, paper and grant writing.

Multi-tissue dissection of obesity-exercise interaction in mouse and human, Head 2019-

Tumor microenvironment analysis of metastatic melanoma treated with immune checkpoint inhibitor, Head 2019-

Single-cell molecular changes associated with Alzheimer's Disease in Down Syndrome, Head 2020-

Publications

14. **Yang, J.***, Vamvini, M.*, Nigro, P.*, Ho, L.-L., Galani, K., Alvarez, M., Tanigawa, Y., Renfro, A., Carbone, N.P., Laakso, M., Agudelo, L.Z., Pajukanta, P., Hirshman, M.F., Middelbeek, R.J.W., Grove, K., Goodyear, L.J., Kellis, M., 2022. Single-cell dissection of the obesity-exercise axis in adipose-muscle tissues implies a critical role for mesenchymal stem cells. *Cell Metabolism* 34, 1578-1593.e6. https://doi.org/10.1016/j.cmet.2022.09.004

13. Nigro, P.*, Vamvini, M.*, **Yang, J.**, Caputo, T., Ho, L., Carbone, N.P., Papadopoulos, D., Conlin, R., He, J., Hirshman, M.F., White, J.D., Robidoux, J., Hickner, R.C., Nielsen, S., Pedersen, B.K., Kellis, M., Middelbeek, R.J.W., Goodyear, L.J., 2023. Exercise Training Remodels Inguinal White Adipose Tissue through Adaptations in Innervation, Vascularization, and the Extracellular Matrix. *Cell Reports* 42, no. 4. https://doi.org/10.1016/j.celrep.2023.112392.

12. Maitituoheti, M.*, Shi, A.*, Tang, M.*, Ho, L.-L., Terranova, C., Galani, K., Keung, E.Z., Creasy, C.A., Singh, A.K., Chaudhri, A., Anvar, N.E., **Yang, J.**, Raman, A.T., Sarkar, S., Jiang, S., Malke, J., Haydu, L., Burton, E., Davies, M.A., Gershenwald, J.E., Hwu, P., Lazar, A., Liu, D., Cheah, J.H., Soule, C.K., Bernatchez, C., Wargo, J., Boland, G.M., Kellis, M., Rai, K., 2023. Enhancer Reprogramming in Melanoma Immune Checkpoint Therapy Resistance. *Cancer Cell* (In Review).

11. Ozturk, H.*, Cingoz, H.*, Tufan, T.*, **Yang, J.***, Adair, S.J., Tummala, K.S., Kuscu, C., Kinali, M., Comertpay, G., Nagdas, S., Goudreau, B.J., Luleyap, H.U., Bingul, Y., Ware, T.B., Hwang, W.L., Hsu, K., Kashatus, D.F., Ting, D.T., Chandel, N.S., Bardeesy, N., Bauer, T.W., Adli, M., 2022. ISL2 is a putative tumor suppressor whose epigenetic silencing reprograms the metabolism of pancreatic cancer. *Developmental Cell* 57, 1331-1346.e9. https://doi.org/10.1016/j.devcel.2022.04.014

10. Wei, X.*, **Yang, J.***, Adair, S.J., Ozturk, H., Kuscu, C., Lee, K.Y., Kane, W.J., O'Hara, P.E., Liu, D., Demirlenk, Y.M., Habieb, A.H., Yilmaz, E., Dutta, A., Bauer, T.W., Adli, M., 2020. Targeted CRISPR screening identifies PRMT5 as synthetic lethality combinatorial target with gemcitabine in pancreatic cancer cells. *Proceedings of the National Academy of Sciences* 117, 28068–28079. https://doi.org/10.1073/pnas.2009899117

9. Shang, S., **Yang, J.**, Jazaeri, A.A., Duval, A.J., Tufan, T., Fischer, N.L., Benamar, M., Guessous, F., Lee, I., Campbell, R.M., Ebert, P.J., Abbas, T., Landen, C.N., Difeo, A., Scacheri, P.C., Adli, M., 2019. Chemotherapy-Induced Distal Enhancers Drive Transcriptional Programs to Maintain the Chemoresistant State in Ovarian Cancer. *Cancer Res* 79, 4599–4611. https://doi.org/10.1158/0008-5472.CAN-19-0215

8. **Yang, J.**, Adli, M., 2019. Mapping and Making Sense of Noncoding Mutations in the Genome. *Cancer Research* 79, 4309–4314. https://doi.org/10.1158/0008-5472.CAN-19-0905

7. **Yang, J.***, Wei, X.*, Tufan, T., Kuscu, C., Unlu, H., Farooq, S., Demirtas, E., Paschal, B.M., Adli, M., 2018. Recurrent mutations at estrogen receptor binding sites alter chromatin topology and distal gene expression in breast cancer. *Genome Biology* 19, 190. https://doi.org/10.1186/s13059-018-1572-4

6. Szlachta, K., Kuscu, C., Tufan, T., Adair, S.J., Shang, S., Michaels, A.D., Mullen, M.G., Fischer, N.L., **Yang, J.**, Liu, L., Trivedi, P., Stelow, E.B., Stukenberg, P.T., Parsons, J.T., Bauer, T.W., Adli, M., 2018. CRISPR knockout screening identifies combinatorial drug targets in pancreatic cancer and models cellular drug response. *Nature Communications* 9, 4275. https://doi.org/10.1038/s41467-018-06676-2

5. Kuscu, C., Parlak, M., Tufan, T., **Yang, J.**, Szlachta, K., Wei, X., Mammadov, R., Adli, M., 2017. CRISPR-STOP: gene silencing through base-editing-induced nonsense mutations. *Nat Meth* 14, 710–712. https://doi.org/10.1038/nmeth.4327

4. **Yang, J.**, Li, M.D., 2016. Converging findings from linkage and association analyses on susceptibility genes for smoking and other addictions. *Molecular Psychiatry* 21, 992–1008. https://doi.org/10.1038/mp.2016.67

3. **Yang, J.***, Wang, S.*, Yang, Z., Hodgkinson, C.A., Iarikova, P., Ma, J.Z., Payne, T.J., Goldman, D., Li, M.D., 2015. The contribution of rare and common variants in 30 genes to risk nicotine dependence. *Mol Psychiatry* 20, 1467–1478. https://doi.org/10.1038/mp.2014.156

2. **Yang, J.**, Li, M.D., 2014. Association and interaction analyses of 5-HT3 receptor and serotonin transporter genes with alcohol, cocaine, and nicotine dependence using the SAGE data. *Hum Genet* 133, 905–918. https://doi.org/10.1007/s00439-014-1431-7

1. Cui, W.Y., Wang, S., **Yang, J.**, Yi, S.G., Yoon, D., Kim, Y.-J., Payne, T.J., Ma, J.Z., Park, T., Li, M.D., 2013. Significant association of CHRNB3 variants with nicotine dependence in multiple ethnic populations. *Molecular Psychiatry* 18, 1149–1151. https://doi.org/10.1038/mp.2012.190

Invited Talks

2.Single-cell epigenomic and transcriptomic dissection of melanoma immunotherapy response.9th International Cancer Metastasis Congress, San Francisco, CA. May 4, 2023.

1. Using Single-cell computation and biology to overcome tissue and disease boundaries. INSERM MD PHD program conference (virtual). March 19, 2023.

Oral Presentations

6. Ellington, C., Lengerich, B., Watkins, T., **Yang, J.**, Kellis, M., Xing, E. (2022). Sample-specific contextualized graphical models using clinical and molecular data reveal transcriptional network heterogeneity across 7000 tumors. Presented at the Graph Learning for Industrial Applications virtual NeurIPS workshop, December 9.

5. Ellington, C., Lengerich, B., Watkins, T., **Yang, J.**, Kellis, M., Xing, E. (2022). Sample-specific contextualized graphical models using clinical and molecular data reveal transcriptional network heterogeneity across 7000 tumors. Presented at CSHL Biological Data Science, November 9-12.

4. **Yang, J.***, Vamvini, M.*, Nigro, P.*, Galani, K., Ho, L., Agudelo, L., Middelbeek, R., Goodyear, L.†, and Kellis, M†. (2022). Single-cell dissection of the obesity-exercise axis in adipose-muscle tissues infers a critical role for mesenchymal stem cells. Presented at Keystone Symposia Adipose Tissue and Metabolic Health, August 7-10.

3. **Yang, J.***, Vamvini, M.*, Nigro, P.*, Galani, K., Ho, L., Agudelo, L., Middelbeek, R., Goodyear, L.†, and Kellis, M†. (2021). Single-cell multi-tissue dissection of obesity-exercise circuitry in mouse. Presented at CSHL The Biology of Genomes, May 11-14.

2. **Yang, J.***, Vamvini, M.*, Nigro, P.*, Galani, K., Ho, L., Agudelo, L., Middelbeek, R., Goodyear, L.†, and Kellis, M†. (2020). Single-cell dissection of obesity-exercise interaction across four tissues. Presented at Annual Meeting of the American Society of Human Genetics (ASHG), October 27-30.

1. **Yang, J.** (2016). Determination of genetic mechanisms underlying smoking addiction. Presented at Graduate Biosciences Society (GBS) Symposium, Charlottesville, Virginia, March 21.

Poster Presentations

7. **Yang, J.***, Fu, D.*, Galani, K., Ho, L., Robitschek, E., Frederick, D.T., Yadav, S.K., Deng, W., Singh, A.K., Burke, K.P., Wang, C., Sharova, T., Liu, D., Rai, K., Boland, G.M., Kellis, M. (2023). Single-cell transcriptomic and epigenomic landscapes of innate and adaptive immune cells in metastatic melanoma treated with immunotherapy. Presented at the American Association for Cancer Research (AACR) annual meeting, April 19.

6. Huang, A., Vokes, N., Ricker, C., Aprati, T., Robitschek, E., **Yang, J.**, Ho, L., Galani, K., Burke, K.P., Tarantino, G., Chen, J., Sharpe, A., Van Allen, E., Kellis, M., Boland, G.M., Liu, D. (2023). Transcriptional meta-analysis of immune-dependent clinical response to PD-1 and CTLA-4 blockade in metastatic melanoma. Presented at the American Association for Cancer Research (AACR) annual meeting, April 17.

5. Ellington, C., Lengerich, B., Watkins, T., **Yang, J.**, Kellis, M., Xing, E. (2022). Sample-specific contextualized graphical models using clinical and molecular data reveal transcriptional network heterogeneity across 7000 tumors. Presented at the Machine Learning for Health (ML4H), November 28.

4. **Yang, J.**, Wei, X., Tufan, T., Kuscu, C., Unlu, H., Farooq, S., Demirtas, E., Paschal, B.M., and Adli, M. (2018). Recurrent mutations at estrogen receptor binding sites alter chromatin topology & distal gene expression in breast cancer. Presented at Cell Symposia: The TCGA Legacy: MultiOmic Studies in Cancer, Washington D.C., September 27-29.

3. **Yang, J.**, Payne, T. J., Ma, J. Z., and Li, M.D. (2014). Association and interaction analyses of 5-HT3 receptor and serotonin transporter genes with alcohol, cocaine, and nicotine dependence using the SAGE

data. Presented at 20th Annual Meeting of the Society for Research on Nicotine and Tobacco (SRNT), Seattle, Washington, February 5-8.

2. Wang, S., **Yang, J.**, Yang, Z., Ma, J. Z., Payne, T. J., Hodgkinson, C. A., Iarikova, P., Goldman, D., and Li, M. D. (2012). Rare variants discovery for candidate genes related to nicotine dependence through deep sequencing approach. Presented at 62nd Annual Meeting of the American Society of Human Genetics (ASHG), San Francisco, California, November 6-10.

1. **Yang, J.**, Wang, S., Ma, J. Z., Payne, T. J., and Li, M.D. (2012). Determination of a rare variant and common variants in *COMT* for their involvement in the etiology of smoking dependence. Presented at 62nd Annual Meeting of the American Society of Human Genetics (ASHG), San Francisco, California, November 6-10.

Honors and Awards

Alana Postdoctoral Fellowship, MIT	2019
Outstanding Student Award of Biochemistry & Molecular Genetics, UVa	2016
International Student Academic Achievement Award, UW-Madison	2011
James Krikelas Award for Innovative Use of Information Technology, UW-Madison	2011
Valmai Fenster Memorial Scholarship, UW-Madison	2009, 2010
First Chinese National Scholarship, Renmin U	2008
Sony Scholarship, Renmin U	2007

Computational Experience

- Environments: High Performance Clusters, Linux, Mac, Windows
- Programming: Bash scripting, Python (Spyder & Jupyter), R (Rstudio), git
- Databases: MySQL, Oracle, Microsoft SQL Server
- Graphic design: Adobe Illustrator, PRISM, Circos, GIMP
- Modelling: R (Bioconductor), SAS, SPSS, Machine Learning (Octave), Matlab
- Data resources: dbGaP, NCI data commons (TCGA), ICGC, GEO
- Bioinformatics tools:
    - Sequence QC & processing: FastQC, Cutadapt, Samtools, Bedtools, deepTools, Picard, liftOver
    - Alignment: Bowtie2, HISAT2, BWA, STAR
    - RNA-, ATAC- & ChIP-seq: StringTie, EdgeR, DESeq2, PEPATAC, MACS2, diffBind, GREAT, GSEA
    - Single cell assays: cellranger, CROP-seq pipeline, Seurat, Monocle, Liger, scVelo
    - Mutation/variant calling & annotation: GATK, ANNOVAR, HaploReg, SIFT, PolyPhen
    - Variant imputation: IMPUTE2, SHAPEIT, MACH, PLINK
    - Data visualization: UCSC genome browser, IGV