Research interests pursued by Arnold Levine at the Simons Center for Systems Biology take advantage of technologies that have generated enormous amounts of hitherto unseen biological data, and have allowed explorations into areas of genetics and genomics, molecular aspects of evolution, signal transduction pathways and networks, stress responses and pharmacogenomics in cancer biology. The tools of modern physics, mathematics, and computer science enable integration of such data, allowing scientists to draw conclusions that will result in leaps of fundamental understanding of evolution and basic molecular biology, and will reduce -- perhaps by years -- the time leading to significant breakthroughs in developing personalized approaches to diagnosis and treatment of cancer, viruses, and other diseases. Professor Levine and collaborators explore the linkage between theoretical and experimental biology. They have developed algorithms that have led to the discovery of correlations and signals that are characteristic of viruses, diseases such as cancer, and traits such as embryonic development and longevity. Using tools from statistical mechanics, information theory, theoretical computer science, researchers have addressed problems in population genetics and association studies, haplotype structure and gene selection in the p53 pathway, epistatic interactions between single nucleotide polymorphisms related to cell apoptosis, protocols for molecular profiling of cancer; evolutionary genetics, and patterns of mutations correlated with longevity, the bioinformatics of DNA and RNA sequences with applications including patterns of re-assortment in viruses.

The first publication from the Center, on genetic predispositions to cancer, *A Single Nucleotide Polymorphism in the MDM2 Promoter Attenuates the p53 Tumor Suppressor Pathway and Accelerates Tumor Formation in Humans*, appeared in the journal *Cell* in November 2004.

A selection of recent papers includes:

Levine AJ. The many faces of p53: something for everyone. J Mol Cell Biol. 2019 July 30; 11 (7): 524-530

Levine, AJ, Jenkins, NA, Copeland, NG. The Roles of Initiating Truncal Mutations in Human Cancers: The Order of Mutations and Tumor Cell Type Matters. Cancer Cell 2019 Jan 14; 35 (1): 10-15   NIHMSID: NIHMS1520982 (PMCID available on 2/17/2020)

Nogalski MT, Solovyov A, Kulkarni AS, Desai N, Oberstein A, Levine AJ, Ting DT, Shenk T, Greenbaum BD. A tumor-specific endogenous repetitive element is induced by herpesviruses. *Nature Communications* 2019 Jan 9; 10 (90):1-13

Baugh EH, Ke H, Levine AJ, Bonneau RA, Chan CS. Why are there hotspot mutations in the TP53 gene in human cancers? Cell Death Differ. 2018 Jan; 25(1):154-160 PMID: 29099487 PMCID: PMC5729537 [Available on 2019-01-01]

Levine AJ. Reviewing the future of the P53 field. Cell Death Differ. 2018 Jan; 25 (1):1-2. doi: 10.1038/cdd.2017.181. PMID: 29227987

Levine, AJ and Berger, SL. The interplay between epigenetic changes and the p53 protein in stem cells. Genes Dev. 2017 31: 1195-1200 PMID: 28765161 PMCID:PMC5558922

Levine, AJ. The Future of Systems Biology. Current Opinion in Systems Biology 2017; Feb 1: v–vii

Balachandran VP, Luksza M, Zhao JN, Makarov V, Moral JA, Remark R, Herbst B, Askan G, Bhanot U, Senbabaoglu Y, Wells DK, Ormsby Cary CI, Grbovic-Huezo O, Attiyeh M, Medina B, Zhang J, Loo J, Saglimbeni J, Abu-Akeel M, Zappasodi R, Riaz N, Smoragiewicz M, Z. Larkin Kelley, Basturk O, Australian Pancreatic Cancer Genome Initiative, Gonen M, Levine AJ, Allen PJ, Fearon DT, Merad M, Gnjatic S, Iacobuzio-Donahue CA, Wolchok JD, DeMatteo RP, Chan TA, Greenbaum BD, Merghoub T, Leach, SD "Identification of unique neoantigen qualities in long-term survivors of pancreatic cancer" Nature 2017, doi:10.1038/nature24462

Luksza M, Riaz N, Makarov V, Balachandran VP, Hellmann MD, Solovyov A, Rizvi NA, Merghoub T, Levine AJ, Chan TA, Wolchok JD, Greenbaum BD "A neoantigen fitness model predicts tumour response to checkpoint blockade immunotherapy" Nature 2017, doi:10.1038/nature24473

Sethna Z, Elhanati Y, Dudgeon CS, Callan CG Jr, Levine AJ, Mora T, Walczak AM. Insights into immune system development and function from mouse T-cell repertoires. PNAS 2017 Feb.14: 114(9):2253–2258. PMID: 28196891 PMCID: PMC5338539

Cámara PG, Levine AJ, Rabadán R. Inference of Ancestral Recombination Graphs through Topological Data Analysis. PLoS Comput Biol. 2016 Aug 17;12 (8):e1005071. doi: 10.1371/journal.pcbi.1005071.eCollection 2016. PMID:27532298 PMCID: PMC4988722

Pablo G. Camara, Daniel I. S. Rosenbloom, Kevin J. Emmett, Arnold J. Levine, Raul Rabadan. Topological data analysis generates high-resolution, genome-wide maps of human recombination. Cell Systems 2016 July 2; 2 (7): 1–12. PMID:27345159

Levine AJ, Ting DT, Greenbaum B. P53 and the defenses against genome instability caused by transposons and repetitive elements. Bioessays 2016 Jun; 38(6):508-13. doi: 10.1002/bies.201600031

Arnold J. Levine, Anna M. Puzio-Kuter, Chang S. Chan, and Pierre Hainaut. The Role of the p53 Protein in Stem-Cell Biology and Epigenetic Regulation. Cold Spring Harb Perspect Med. 2016 doi:10.1101/cshperspect.a026153

A.J Levine, C. Chan, C. Dudgeon, A. Puzio-Kuter, and P.Hainaut. The Evolution of Tumors in Mice and Humans with Germline p53 Mutations. Cold Spring Harbor Laboratory Press 2015 Dec 7. Cold Spring Harbor Symposium Quantitative Biology. Volume LXXX: 1-7

Antoine Tanne, Luciana R. Muniz, Anna Puzio-Kuter, Katerina I. Leonova, Andrei V. Gudkov, David T. Ting, Rémi Monasson, Simona Cocco, Arnold J. Levine, Nina Bhardwaj and Benjamin D. Greenbaum. Distinguishing the immunostimulatory properties of noncoding RNAs expressed in cancer cells. PNAS 2015, Dec 8;112(49):15154-15159. doi: 10.1073/pnas.1517584112. Epub 2015 Nov 2. PMCID: PMC4679042

Zhang X, Schulz R, Edmunds S, Krüger E, Markert E, Gaedcke J, Cormet-Boyaka E, Ghadimi M, Beissbarth T, Levine AJ, Moll UM, Dobbelstein M. MicroRNA-101 Suppresses Tumor Cell Proliferation by Acting as an Endogenous Proteasome Inhibitor via Targeting the Proteasome Assembly Factor POMP. Molecular Cell 2015 July 16. 59, 243–257 PMID: 26145175

AM Puzio-Kuter, SV Laddha, M Castillo-Martin, Y Sun, C Cordon-Cardo, CS Chan AJ Levine. Involvement of tumor suppressors PTEN and p53 in the formation of multiple subtypes of liposarcoma. Cell Death Differ. 2015 Nov; 22(11): 1785–1791. PMCID: PMC4648325

Dudgeon C, Chan C, Kang W, Sun Y, Emerson R, Robins H, Levine AJ. The evolution of thymic lymphomas in p53 knockout mice. Genes Dev. 2014 Dec 1;28(23):2613-20.doi: 10.1101/gad.252148.114 PMCID: PMC4248292

Ariffin H, Hainaut P, Puzio-Kuter A, Choong SS, Chan AS, Tolkunov D, Rajagopal G, Kang W, Lim LL, Krishnan S, Chen KS, Achatz MI, Karsa M5, Shamsani J, Levine AJ, Chan CS8. Whole-genome sequencing analysis of phenotypic heterogeneity and anticipation in Li-Fraumeni cancer predisposition syndrome. PNAS. 2014 Oct 28;111(43): 15497-501. doi: 10.1073/pnas.1417322111. Epub 2014 Oct 13. PMCID:PMC4217424 [Available on 2015/4/28]

Hait WN, Levine AJ. Genomic complexity: a call to action. Sci.Transl. Med. 2014 Sep 24;6(255):255cm10. doi: 10.1126/scitranslmed.3009148. PMCID: PMC25253671

Greenbaum BD, Cocco S, Levine AJ, Monasson R. Quantitative theory of entropic forces acting on constrained nucleotide sequences applied to viruses. PNAS. 2014 Apr 1; 111(13):5054-9. doi: 10.1073/pnas.1402285111. Epub 2014 Mar 17. PMCID: PMC3977288

Levine AJ, Greenbaum B "The Maintenance of Epigenetic States by p53: The Guardian of the Epigenome" Oncotarget 2012 Dec 11; 3 (12): 1503-1504. PMID: 23237909

Markert, EK, Levine, AJ, Vazquez A "Proliferation and tissue remodeling: the hallmarks revisited" Cell Death and Disease 2012. Oct 4; 3:e397. doi: 10.1038/cddis.2012.140. PMCID: PMC3481128

Xin Yu, Alexei Vazquez, Arnold J. Levine, Darren R. Carpizo. Allele-Specific p53 Mutant Reactivation. Cancer Cell, 2012 May 15; 21 (5): 614-625. PMCID: PMC3366694, NIHMSID: NIHMS372800

Greenbaum BD, Li OT, Poon LL, Levine AJ, Rabadan R.,Viral reassortment as an information exchange between viral segments. PNAS 2012 Feb 28; 109 (9):3341-6. PMCID: PMC3295259