

LUDWIG CENTER | MIT

Ludwig Center for Molecular Oncology Updates—2018

The **Ludwig Center for Molecular Oncology at MIT** is focused on the processes associated with malignant progression, specifically on the mechanisms that allow cancer cells originating in primary tumors to disseminate and ultimately form metastatic colonies. This multi-step process involves a series of cell-biological and biochemical changes in malignant cells, which are being investigated at several levels. Our research includes the biological determinants that allow disseminated cancer cells to gain a foothold in foreign tissue microenvironments, where they can succeed in spawning rapidly growing metastatic colonies.

The **Ludwig Center for Molecular Oncology at MIT** continues to support the research of 12 Koch Institute faculty members whose work focuses on the critical problems of cancer progression and metastasis. These include Drs. Weinberg and Jacks who serve as co-leaders of the Center. They are joined by Drs. Amon, Bhatia, Gertler, Hemann, Hynes, Lees, Manalis, Regev, and Vander Heiden, who are all full members; and, Dr. Gupta, who received Pilot Project funding in 2018. Of note: Dr. Angelika Amon was awarded full membership in 2018.

Examples of faculty awards and honors received by Ludwig Center Members over the past year:

| Name | Awards and Honors |
|-----------------|---|
| Angelika Amon | Inducted into the American Academy of Arts & Sciences and received the Breakthrough Prize in Life Sciences |
| Sangeeta Bhatia | Inducted into the National Academy of Science and received the Xconomy 'Innovation at the Intersection' Award and the Science Club for Girls 'Catalyst' Award |
| Richard Hynes | Received the David Rall Medal from the National Academy of Medicine |
| Aviv Regev | Received the Paul Marks Prize and the International Society for Computational Biology Innovator Award |
| Robert Weinberg | Received the NIH Outstanding Investigator Award |

Following are some structural highlights from the year:

- The annual **Ludwig Center for Molecular Oncology at MIT Retreat** was held at MIT's Endicott House on May 30, 2018. This is an outstanding opportunity for Ludwig Center PIs and researchers to share updates, shape future directions and explore opportunities for collaborations through scientific presentations and a poster session; 77 faculty and researchers were in attendance.
- **Ludwig Center Principal Investigator Meetings** Ludwig faculty meet on a quarterly basis throughout the year to discuss ongoing research. There are also multiple opportunities to discuss Ludwig-supported research including weekly "floor meetings" and "Friday Focus."
- **Ludwig Graduate Fellowships** were awarded to four students.

| Name | Project Title |
|--------|--|
| Xin Gu | "Identification and validation of SAMTOR as an S-adenosylmethionine sensor linking mTORC1 and one-carbon metabolism" |

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|----------------------|--|
| Cynthia Hajal | "Tumor cell extravasation in an <i>in vivo</i> blood-brain barrier microvascular network model" |
| Bashar Hamza | "Optofluidic platform for longitudinal and dynamic circulating tumor cell studies in mouse models of cancer" |
| Elaine Kuo | "Role of BMI1 in colon tumorigenesis and metastasis" |

- **Ludwig Center Postdoctoral Fellowships** were awarded to ten postdoctoral associates.

| Name | Project Title |
|-----------------------------|---|
| Genevieve Abbruzzese | "Regulation of growth factors by the Extracellular matrix in cancer metastasis" |
| Banu Eskiocak | "Deciphering the tumor-natural killer cell interactions during development and metastasis of lung adenocarcinoma" |
| Liangliang Hao | "Protease-activated detection and imaging of tumor progression and metastasis" |
| Brendan Horton | "Interrogating tissue-specific immune responses against metastatic pancreatic cancer" |
| Augusto Tentori | "Quantitative, multiplex microRNA heterogeneity profiling in tumor sections using microwell arrays" |
| Elen Torres | "The role of Mena in local mRNA translation in breast cancer metastasis" |
| Marianna Trakala | "Relevance of the aneuploid microenvironment in cancer progression and metastasis" |
| Nicholas Truex | "Delivering cancer vaccines with a protective antigen delivery system" |
| Bert van de Kooij | "Delineating the function of mitotic serine/threonine kinases in adhesion site signaling and cell migration" |
| Jacomina Zweemer | "Is apoptosis-induced migration via the AXL-receptor leading to <i>in vivo</i> metastasis?" |

Most important is the research that comes from Ludwig Center members as demonstrated in the following publications since our last report:

Publications

Tang YC, Yuwen H, Wang K, Bruno PM, Bullock K, Deik AA, Santaguida S, Trakala M, Pfau SJ, Zhong N, Huang T, Wang L, Clish CB, **Hemann MT, Amon A**. Aneuploid cell survival relies upon sphingolipid homeostasis. *Cancer Res*, 77:5272-5286, 2017. PMID28775166; PMC5772763; 10.1158/0008-5472.CAN-17-0049

Lo JH, Hao L, Muzumdar MD, Raghavan S, Kwon EJ, Pulver EM, Hsu F, Aguirre AJ, Wolpin BM, Fuchs CS, Hahn WC, **Jacks T, Bhatia SN**. iRGD-guided tumor-penetrating nanocomplexes for therapeutic siRNA delivery to pancreatic cancer. *Mol Cancer Ther*, *In process*, 2018. PMID30097486; N/A; 10.1158/1535-7163.MCT-17-1090

Chen PY, Muzumdar MD, Dorans KJ, Robbins RA, Bhutkar A, Del Rosario AM, Mertins P, Qiao J, Schafer C, **Gertler FB, Carr SA, Jacks T**. Adaptive and reversible resistance to Kras inhibition in pancreatic cancer cells. *Cancer Res*, 78:985-1002, 2018. PMID29279356; PMC5837062; 10.1158/0008-5472.CAN-17-2129

Gocheva V, Naba A, Bhutkar A, Guardia T, Miller KM, Li CM, Dayton TL, Sanchez-Rivera FJ, Kim-Kiselak C, Jaiikhani N, Winslow MM, Del Rosario A, **Hynes RO, Jacks T**. Quantitative proteomics identify Tenascin-C as a promoter of lung cancer progression and contributor to a signature prognostic of patient survival. *Proc Natl Acad Sci U S A*, 114:E5625-E5634, 2017. PMID28652369; PMC5514763; 10.1073/pnas.1707054114

Lee JH, Tammela T, Hofree M, Choi J, Marjanovic ND, Han S, Canner D, Wu K, Paschini M, Bhang DH, **Jacks T, Regev A, Kim CF**. Anatomically and Functionally Distinct Lung Mesenchymal Populations Marked by Lgr5 and Lgr6. *Cell*, 170:1149-1163.e12, 2017. PMID28886383; PMC5607351; 10.1016/j.cell.2017.07.028

Parisi T, Balsamo M, **Gertler F, Lees JA**. The Rb tumor suppressor regulates epithelial cell migration and polarity. *Mol Carcinog*, *In process*, 2018. PMID30084175; N/A; 10.1002/mc.22886

Romero R, Sayin VI, Davidson SM, Bauer MR, Singh SX, LeBoeuf SE, Karakousi TR, Ellis DC, Bhutkar A, Sanchez-Rivera FJ, Subbaraj L, Martinez B, Bronson RT, Prigge JR, Schmidt EE, Thomas CJ, Goparaju C, Davies A, Dolgalev I, Heguy A, Allaj V, Poirier JT, Moreira AL, Rudin CM, Pass HI, **Vander Heiden MG, Jacks T**, Papagiannakopoulos T. Keap1 loss promotes Kras-driven lung cancer and results in dependence on glutaminolysis. *Nat Med*, 23:1362-1368, 2017. PMID28967920; PMC5677540; 10.1038/nm.4407

Dayton TL, Gocheva V, Miller KM, Bhutkar A, Lewis CA, Bronson RT, **Vander Heiden MG, Jacks T**. Isoform-specific deletion of PKM2 constrains tumor initiation in a mouse model of soft tissue sarcoma. *Cancer Metab*, 6:6, 2018. PMID29854399; PMC5977456; 10.1186/s40170-018-0179-2

Qi R, Wang Y, Bruno PM, Xiao H, Yingjie Y, Li T, Lauffer S, Wei W, Chen Q, Kang X, Song H, Yang X, Huang X, Detappe A, Matulonis U, Pepin D, **Hemann MT**, Birrer MJ, Ghoroghchian PP. Nanoparticle conjugates of a highly potent toxin enhance safety and circumvent platinum resistance in ovarian cancer. *Nat Commun*, 8:2166, 2017. PMID29255160; PMC5735131; 10.1038/s41467-017-02390-7

Tao Z, Muzumdar MD, Detappe A, Huang X, Xu E, Yu Y, Mouhieddine TH, Song H, **Jacks T**, Ghoroghchian PP. Differences in Nanoparticle Uptake in Transplanted and Autochthonous Models of Pancreatic Cancer. *Nano Lett*, 18:2195-2208, 2018. PMID29533667; PMC5957485; 10.1021/acs.nanolett.7b04043

Roper J, Tammela T, Akkad A, Almeqdadi M, Santos SB, **Jacks T**, Yilmaz OH. Colonoscopy-based colorectal cancer modeling in mice with CRISPR-Cas9 genome editing and organoid transplantation. *Nat Protoc*, 13:217-234, 2018. PMID29300388; N/A; 10.1038/nprot.2017.136

Chen MB, Hajal C, Benjamin DC, Yu C, Azizgolshani H, **Hynes RO**, Kamm RD. Inflamed neutrophils sequestered at entrapped tumor cells via chemotactic confinement promote tumor cell extravasation. *Proc Natl Acad Sci U S A*, 115:7022-7027, 2018. PMID29915060; N/A; 10.1073/pnas.1715932115

Haber AL, Biton M, Rogel N, Herbst RH, Shekhar K, Smillie C, Burgin G, Delorey TM, Howitt MR, Katz Y, Tirosh I, Beyaz S, Dionne D, Zhang M, Raychowdhury R, Garrett WS, Rozenblatt-Rosen O, Shi HN, Yilmaz O, Xavier RJ, **Regev A**. A single-cell survey of the small intestinal epithelium. *Nature*, 551:333-339, 2017. PMID29144463; PMC6022292; 10.1038/nature24489

Wyant GA, Abu-Remaileh M, Wolfson RL, Chen WW, Freinkman E, Danai LV, **Vander Heiden MG**, Sabatini DM. mTORC1 Activator SLC38A9 Is Required to Efflux Essential Amino Acids from Lysosomes and Use Protein as a Nutrient. *Cell*, 171:642-654.e12, 2017. PMID29053970; PMC5704964; 10.1016/j.cell.2017.09.046

Yamanaka K, Chatterjee N, **Hemann MT**, Walker GC. Inhibition of mutagenic translesion synthesis: A possible strategy for improving chemotherapy? *PLoS Genet*, 13:e1006842, 2017. PMID28817566; PMC5560539; 10.1371/journal.pgen.1006842

Rizzo AA, Vassel FM, Chatterjee N, D'Souza S, Li Y, Hao B, **Hemann MT**, Walker GC, Korzhnev DM. Rev7 dimerization is important for assembly and function of the Rev1/Polzeta translesion synthesis complex. *Proc Natl Acad Sci U S A*, 115:E8191-E8200, 2018. PMID30111544; PMC6126741; 10.1073/pnas.1801149115

Frose J, Chen MB, Hebron KE, Reinhardt F, Hajal C, Zijlstra A, Kamm RD, **Weinberg RA**. Epithelial-Mesenchymal Transition Induces Podocalyxin to Promote Extravasation via Ezrin Signaling. *Cell Rep*, 24:962-972, 2018. PMID30044991; N/A; 10.1016/j.celrep.2018.06.092

Kauke MJ, Tisdale AW, Kelly RL, Braun CJ, **Hemann MT**, Wittrup KD. A Raf-competitive K-Ras binder can fail to functionally antagonize signaling. *Mol Cancer Ther*, 17:1773-1780, 2018. PMID29720559; N/A; 10.1158/1535-7163.MCT-17-0645

Knouse KA, Lopez KE, Bachofner M, **Amon A**. Chromosome Segregation Fidelity in Epithelia Requires Tissue Architecture. *Cell*, *In process*, 2018. PMID30146160; N/A; 10.1016/j.cell.2018.07.042

Geller LT, Barzily-Rokni M, Danino T, Jonas OH, Shental N, Nejman D, Gavert N, Zwang Y, Cooper ZA, Shee K, Thaisz CA, Reuben A, Livny J, Avraham R, Frederick DT, Ligorio M, Chatman K, Johnston SE, Mosher CM, Brandis A, Fuks G, Gurbatri C, Gopalakrishnan V, Kim M, Hurd MW, Katz M, Fleming J, Maitra A, Smith DA, Skalak M, Bu J, Michaud M, Trauger SA, Barshack I, Golan T, Sandbank J, Flaherty KT, Mandinova A, Garrett WS, Thayer SP, Ferrone CR, Huttenhower C, **Bhatia SN**, Gevers D, Wargo JA, Golub TR, Straussman R. Potential role of intratumor bacteria in mediating tumor resistance to the chemotherapeutic drug gemcitabine. *Science*, 357:1156-1160, 2017. PMID28912244; PMC5727343; 10.1126/science.aah5043

Ren Y, Sagers JE, Landegger LD, **Bhatia SN**, Stankovic KM. Tumor-Penetrating Delivery of siRNA against TNFalpha to Human Vestibular Schwannomas. *Sci Rep*, 7:12922, 2017. PMID29018206; PMC5635039; 10.1038/s41598-017-13032-9

Gilles ME, Hao L, Huang L, Rupaimoole R, Lopez-Casas PP, Pulver E, Jeong JC, Muthuswamy SK, Hidalgo M, **Bhatia SN**, Slack FJ. Personalized RNA Medicine for Pancreatic Cancer. *Clin Cancer Res*, 24:1734-1747, 2018. PMID29330203; N/A; 10.1158/1078-0432.CCR-17-2733

Viswanathan SR, Nogueira MF, Buss CG, Krill-Burger JM, Wawer MJ, Malolepsza E, Berger AC, Choi PS, Shih J, Taylor AM, Tanenbaum B, Pedamallu CS, Cherniack AD, Tamayo P, Strathdee CA, Lage K, Carr SA, Schenone M, **Bhatia SN**, Vazquez F, Tsherniak A, Hahn WC, Meyerson M. Genome-scale analysis identifies paralog lethality as a vulnerability of chromosome 1p loss in cancer. *Nat Genet*, 50:937-943, 2018. PMID29955178; N/A; 10.1038/s41588-018-0155-3

Dudani JS, Ibrahim M, Kirkpatrick J, Warren AD, **Bhatia SN**. Classification of prostate cancer using a protease activity nanosensor library. *Proc Natl Acad Sci U S A*, 115:8954-8959, 2018. PMID30126988; PMC6130343; 10.1073/pnas.1805337115

Feng YX, Jin DX, Sokol ES, Reinhardt F, Miller DH, **Gupta PB**. Cancer-specific PERK signaling drives invasion and metastasis through CREB3L1. *Nat Commun*, 8:1079, 2017. PMID29057869; PMC5651903; 10.1038/s41467-017-01052-y

Miller DH, Jin DX, Sokol ES, Cabrera JR, Superville DA, Gorelov RA, Kuperwasser C, **Gupta PB**. BCL11B Drives Human Mammary Stem Cell Self-Renewal In Vitro by Inhibiting Basal Differentiation. *Stem Cell Reports*, 10:1131-1145, 2018. PMID29503088; PMC5918530; 10.1016/j.stemcr.2018.01.036

Ramos A, **Hemann MT**. Drugs, Bugs, and Cancer: *Fusobacterium Nucleatum* Promotes Chemoresistance in Colorectal Cancer. *Cell*, 170:411-413, 2017. PMID28753421; N/A; 10.1016/j.Cell.2017.07.018

Qi R, Wang Y, Bruno PM, Xiao H, Yu Y, Li T, Lauffer S, Wei W, Chen Q, Kang X, Song H, Yang X, Huang X, Detappe A, Matulonis U, Pepin D, **Hemann MT**, Birrer MJ, Ghoroghchian PP. Publisher Correction: Nanoparticle conjugates of a highly potent toxin enhance safety and circumvent platinum resistance in ovarian cancer. *Nat Commun*, 9:628, 2018. PMID29416025; PMC5803230; 10.1038/s41467-018-02963-0

Wagner FF, Benajiba L, Campbell AJ, Weiwer M, Sacher JR, Gale JP, Ross L, Puissant A, Alexe G, Conway A, Back M, Pikman Y, Galinsky I, DeAngelo DJ, Stone RM, Kaya T, Shi X, Robers MB, Machleidt T, Wilkinson J, Hermine O, Kung A, Stein AJ, Lakshminarasimhan D, **Hemann MT**, Scolnick E, Zhang YL, Pan JQ, Stegmaier K, Holson EB. Exploiting an Asp-Glu "switch" in glycogen synthase kinase 3 to design paralog-selective inhibitors for use in acute myeloid leukemia. *Sci Transl Med*, *In process*, 2018. PMID29515000; N/A; 10.1126/scitranslmed.aam8460

Fiedler ERC, Bhutkar A, Lawler E, Besada R, **Hemann MT**. In vivo RNAi screening identifies Pafah1b3 as a target for combination therapy with TKIs in BCR-ABL1(+) BCP-ALL. *Blood Adv*, 2:1229-1242, 2018. PMID29853524; PMC5998924; 10.1182/bloodadvances.2017015610

Naba A, Pearce OM, Del Rosario A, Ma D, Ding H, Rajeev V, Cutillas PR, Balkwill FR, **Hynes RO**. CHARACTERIZATION OF THE EXTRACELLULAR MATRIX OF NORMAL AND DISEASED TISSUES USING PROTEOMICS. *J Proteome Res*, 16:3083-3091, 2017. PMID28675934; N/A; 10.1021/acs.jproteome.7b00191

Benjamin DC, **Hynes RO**. Intravital imaging of metastasis in adult Zebrafish. *BMC Cancer*, 17:660, 2017. PMID28946867; PMC5613480; 10.1186/s12885-017-3647-0

Engblom C, Pfirschke C, Zilionis R, Da Silva Martins J, Bos SA, Courties G, Rickelt S, Severe N, Baryawno N, Faget J, Savova V, Zemmour D, Kline J, Siwicki M, Garris C, Pucci F, Liao HW, Lin YJ, Newton A, Yaghi OK, Iwamoto Y, Tricot B, Wojtkiewicz GR, Nahrendorf M, Cortez-Retamozo V, Meylan E, **Hynes RO**, Demay M, Klein A, Bredella MA, Scadden DT, Weissleder R, Pittet MJ. Osteoblasts remotely supply lung tumors with cancer-promoting SiglecF(high) neutrophils. *Science*, *In process*, 2017. PMID29191879; N/A; 10.1126/science.aal5081

Steigedal TS, Toraskar J, Redvers RP, Valla M, Magnussen SN, Bofin AM, Opdahl S, Lundgren S, Eckhardt BL, Lamar JM, Doherty J, **Hynes RO**, Anderson RL, Svineng G. Nephronectin is Correlated with Poor Prognosis in Breast Cancer and Promotes Metastasis via its Integrin-Binding Motifs. *Neoplasia*, 20:387-400, 2018. PMID29539586; PMC5909680; 10.1016/j.neo.2018.02.008

Muzumdar MD, Chen PY, Dorans KJ, Chung KM, Bhutkar A, Hong E, Noll EM, Sprick MR, Trumpp A, **Jacks T**. Survival of pancreatic cancer cells lacking KRAS function. *Nat Commun*, 8:1090, 2017. PMID29061961; PMC5653666; 10.1038/s41467-017-00942-5

Perez DE, Henle AM, Amsterdam A, Hagen HR, **Lees JA**. Uveal melanoma driver mutations in GNAQ/11 yield numerous changes in melanocyte biology. *Pigment Cell Melanoma Res*, *In process*, 2018. PMID29570931; N/A; 10.1111/pcmr.12700

Cetin AE, Stevens MM, Calistri NL, Fulciniti M, Olcum S, Kimmerling RJ, Munshi NC, **Manalis SR**. Determining therapeutic susceptibility in multiple myeloma by single-cell mass accumulation. *Nat Commun*, 8:1613, 2017. PMID29151572; PMC5694762; 10.1038/s41467-017-01593-2

Luskin MR, Murakami MA, **Manalis SR**, Weinstock DM. Targeting minimal residual disease: a path to cure? *Nat Rev Cancer*, 18:255-263, 2018. PMID29376520; N/A; 10.1038/nrc.2017.125

Zhou F, Liu Y, Rohde C, Pauli C, Gerloff D, Kohn M, Misiak D, Baumer N, Cui C, Gollner S, Oellerich T, Serve H, Garcia-Cuellar MP, Slany R, Maciejewski JP, Przychodzen B, Seliger B, Klein HU, Bartenhagen C, Berdel WE, Dugas M, Taketo MM, Farouq D, Schwartz S, **Regev A**, Hebert J, Sauvageau G, Pabst C, Huttelmaier S, Muller-Tidow C. AML1-ETO requires enhanced C/D box snoRNA/RNP formation to induce self-renewal and leukaemia. *Nat Cell Biol*, 19:844-855, 2017. PMID28650479; N/A; 10.1038/ncb3563

Habib N, Avraham-Davidi I, Basu A, Burks T, Shekhar K, Hofree M, Choudhury SR, Aguet F, Gelfand E, Ardlie K, Weitz DA, Rozenblatt-Rosen O, Zhang F, **Regev A**. Massively parallel single-nucleus RNA-seq with DroNc-seq. *Nat Methods*, 14:955-958, 2017. PMID28846088; PMC5623139; 10.1038/nmeth.4407

Stubbington MJT, Rozenblatt-Rosen O, **Regev A**, Teichmann SA. Single-cell transcriptomics to explore the immune system in health and disease. *Science*, 358:58-63, 2017. PMID28983043; PMC5654495; 10.1126/science.aan6828

Puram SV, Tirosh I, Parikh AS, Patel AP, Yizhak K, Gillespie S, Rodman C, Luo CL, Mroz EA, Emerick KS, Deschler DG, Varvares MA, Mylvaganam R, Rozenblatt-Rosen O, Rocco JW, Faquin WC, Lin DT, **Regev A**, Bernstein BE. Single-Cell Transcriptomic Analysis of Primary and Metastatic Tumor Ecosystems in Head and Neck Cancer. *Cell*, 171:1611-1624.e24, 2017. PMID29198524; PMC5878932; 10.1016/j.cell.2017.10.044

Filbin MG, Tirosh I, Hovestadt V, Shaw ML, Escalante LE, Mathewson ND, Neftel C, Frank N, Pelton K, Hebert CM, Haberler C, Yizhak K, Gojo J, Egervari K, Mount C, van Galen P, Bonal DM, Nguyen QD, Beck A, Sinai C, Czech T, Dorfer C, Goumnerova L, Lavarino C, Carcaboso AM, Mora J, Mylvaganam R, Luo CC, Peyrl A, Popovic M, Azizi A, Batchelor TT, Frosch MP, Martinez-Lage M, Kieran MW, Bandopadhyay P, Beroukhi R, Fritsch G, Getz G, Rozenblatt-Rosen O, Wucherpfennig KW, Louis DN, Monje M, Slavc I, Ligon KL, Golub TR, **Regev A**, Bernstein BE, Suva ML. Developmental and oncogenic programs in H3K27M gliomas dissected by single-cell RNA-seq. *Science*, 360:331-335, 2018. PMID29674595; PMC5949869; 10.1126/science.aao4750

Ji Z, He L, Rotem A, Janzer A, Cheng CS, **Regev A**, Struhl K. Genome-scale identification of transcription factors that mediate an inflammatory network during breast cellular transformation. *Nat Commun*, 9:2068, 2018. PMID29802342; PMC5970197; 10.1038/s41467-018-04406-2

Chihara N, Madi A, Kondo T, Zhang H, Acharya N, Singer M, Nyman J, Marjanovic ND, Kowalczyk MS, Wang C, Kurtulus S, Law T, Etmnan Y, Nevin J, Buckley CD, Burkett PR, Buenrostro JD, Rozenblatt-Rosen O, Anderson AC, **Regev A**, Kuchroo VK. Induction and transcriptional regulation of the co-inhibitory gene module in T cells. *Nature*, 558:454-459, 2018. PMID29899446; PMC6130914; 10.1038/s41586-018-0206-z

Olivares O, Mayers JR, Gouirand V, Torrence ME, Gicquel T, Borge L, Lac S, Roques J, Lavaut MN, Berthezene P, Rubis M, Secq V, Garcia S, Moutardier V, Lombardo D, Iovanna JL, Tomasini R, Guillaumond F, **Vander Heiden MG**, Vasseur S. Collagen-derived proline promotes pancreatic ductal adenocarcinoma cell survival under nutrient limited conditions. *Nat Commun*, 8:16031, 2017. PMID28685754; PMC5504351; 10.1038/ncomms16031

Ebot EM, Gerke T, Labbe DP, Sinnott JA, Zadra G, Rider JR, Tyekuceva S, Wilson KM, Kelly RS, Shui IM, Loda M, Kantoff PW, Finn S, **Vander Heiden MG**, Brown M, Giovannucci EL, Mucci LA. Gene expression profiling of prostate tissue identifies chromatin regulation as a potential link between obesity and lethal prostate cancer. *Cancer*, 123:4130-4138, 2017. PMID28700821; PMC5802874; 10.1002/cncr.30831

Muir A, Danai LV, Gui DY, Waingarten CY, Lewis CA, **Vander Heiden MG**. Environmental cystine drives glutamine anaplerosis and sensitizes cancer cells to glutaminase inhibition. *Elife, In process*, 2017. PMID28826492; PMC5589418; 10.7554/eLife.27713

Luengo A, Gui DY, **Vander Heiden MG**. Targeting Metabolism for Cancer Therapy. *Cell Chem Biol*, 24:1161-1180, 2017. PMID28938091; PMC5744685; 10.1016/j.chembiol.2017.08.028

Sayin VI, LeBoeuf SE, Singh SX, Davidson SM, Biancur D, Guzelhan BS, Alvarez SW, Wu WL, Karakousi TR, Zavitsanou AM, Ubriaco J, Muir A, Karagiannis D, Morris PJ, Thomas CJ, Possemato R, **Vander Heiden MG**, Papagiannakopoulos T. Activation of the NRF2 antioxidant program generates an imbalance in central carbon metabolism in cancer. *Elife, In process*, 2017. PMID28967864; PMC5624783; 10.7554/eLife.28083

Graff RE, Ahearn TU, Pettersson A, Ebot EM, Gerke T, Penney KL, Wilson KM, Markt SC, Pernar CH, Gonzalez-Feliciano AG, Song M, Lis RT, Schmidt DR, **Vander Heiden MG**, Fiorentino M, Giovannucci EL, Loda M, Mucci LA. Height,

obesity, and the risk of TMPRSS2:ERG-defined prostate cancer. *Cancer Epidemiol Biomarkers Prev*, 27:193-200, 2018. PMID29167279; PMC5809280; 10.1158/1055-9965.EPI-17-0547

Hosios AM, **Vander Heiden MG**. The redox requirements of proliferating mammalian cells. *J Biol Chem*, 293:7490-7498, 2018. PMID29339555; PMC5961062; 10.1074/jbc.TM117.000239

McKenney AS, Lau AN, Somasundara AVH, Spitzer B, Intlekofer AM, Ahn J, Shank K, Rapaport FT, Patel MA, Papalex E, Shih AH, Chiu A, Freinkman E, Akbay EA, Steadman M, Nagaraja R, Yen K, Teruya-Feldstein J, Wong KK, Rampal R, **Vander Heiden MG**, Thompson CB, Levine RL. JAK2/IDH-mutant-driven myeloproliferative neoplasm is sensitive to combined targeted inhibition. *J Clin Invest*, 128:789-804, 2018. PMID29355841; PMC5785272; 10.1172/JCI94516

Pakula H, Linn DE, Schmidt DR, Van Gorsel M, **Vander Heiden MG**, Li Z. Protocols for Studies on TMPRSS2/ERG in Prostate Cancer. *Methods Mol Biol*, 1786:131-151, 2018. PMID29786791; N/A; 10.1007/978-1-4939-7845-8_8

Muir A, **Vander Heiden MG**. The nutrient environment affects therapy. *Science*, 360:962-963, 2018. PMID29853672; N/A; 10.1126/science.aar5986

Danai LV, Babic A, Rosenthal MH, Dennstedt EA, Muir A, Lien EC, Mayers JR, Tai K, Lau AN, Jones-Sali P, Prado CM, Petersen GM, Takahashi N, Sugimoto M, Yeh JJ, Lopez N, Bardeesy N, Fernandez-Del Castillo C, Liss AS, Koong AC, Bui J, Yuan C, Welch MW, Brais LK, Kulke MH, Dennis C, Clish CB, Wolpin BM, **Vander Heiden MG**. Altered exocrine function can drive adipose wasting in early pancreatic cancer. *Nature*, 558:600-604, 2018. PMID29925948; PMC6112987; 10.1038/s41586-018-0235-7

Sullivan LB, Luengo A, Danai LV, Bush LN, Diehl FF, Hosios AM, Lau AN, Elmiligy S, Malstrom S, Lewis CA, **Vander Heiden MG**. Aspartate is an endogenous metabolic limitation for tumour growth. *Nat Cell Biol*, 20:782-788, 2018. PMID29941931; PMC6051729; 10.1038/s41556-018-0125-0

Vandekeere S, Dubois C, Kalucka J, Sullivan MR, Garcia-Caballero M, Goveia J, Chen R, Diehl FF, Bar-Lev L, Souffreau J, Pircher A, Kumar S, Vinckier S, Hirabayashi Y, Furuya S, Schoonjans L, Eelen G, Ghesquiere B, Keshet E, Li X, **Vander Heiden MG**, Dewerchin M, Carmeliet P. Serine Synthesis via PHGDH Is Essential for Heme Production in Endothelial Cells. *Cell Metab*, *In process*, 2018. PMID30017355; N/A; 10.1016/j.cmet.2018.06.009

Muir A, Danai LV, **Vander Heiden MG**. Microenvironmental regulation of cancer cell metabolism: implications for experimental design and translational studies. *Dis Model Mech*, *In process*, 2018. PMID30104199; PMC6124553; 10.1242/dmm.035758

Alkan HF, Walter KE, Luengo A, Madreiter-Sokolowski CT, Stryeck S, Lau AN, Al-Zoughbi W, Lewis CA, Thomas CJ, Hoeffler G, Graier WF, Madl T, **Vander Heiden MG**, Bogner-Strauss JG. Cytosolic Aspartate Availability Determines Cell Survival When Glutamine Is Limiting. *Cell Metab*, *In process*, 2018. PMID30122555; N/A; 10.1016/j.cmet.2018.07.021

Shibue T, **Weinberg RA**. EMT, CSCs, and drug resistance: the mechanistic link and clinical implications. *Nat Rev Clin Oncol*, 14:611-629, 2017. PMID28397828; PMC5720366; 10.1038/nrclinonc.2017.44

Dongre A, Rashidian M, Reinhardt F, Bagnato A, Keckesova Z, Ploegh HL, **Weinberg RA**. Epithelial-to-mesenchymal Transition contributes to Immunosuppression in Breast Carcinomas. *Cancer Res*, 77:3982-3989, 2017. PMID28428275; PMC5541771; 10.1158/0008-5472.CAN-16-3292

Rashidian M, Ingram JR, Dougan M, Dongre A, Whang KA, LeGall C, Cragnolini JJ, Bierie B, Gostissa M, Gorman J, Grotenbreg GM, Bhan A, **Weinberg RA**, Ploegh HL. Predicting the response to CTLA-4 blockade by longitudinal noninvasive monitoring of CD8 T cells. *J Exp Med*, 214:2243-2255, 2017. PMID28666979; PMC5551571; 10.1084/jem.20161950

Ye X, Brabletz T, Kang Y, Longmore GD, Nieto MA, Stanger BZ, Yang J, **Weinberg RA**. Upholding a role for EMT in breast cancer metastasis. *Nature*, 547:E1-E3, 2017. PMID28682326; N/A; 10.1038/nature22816

Aiello NM, Brabletz T, Kang Y, Nieto MA, **Weinberg RA**, Stanger BZ. Upholding a role for EMT in pancreatic cancer metastasis. *Nature*, 547:E7-E8, 2017. PMID28682339; PMC5830071; 10.1038/nature22963

Ye X, **Weinberg RA**. The SUMO guards for SNAIL. *Oncotarget*, 8:97701-97702, 2017. PMID29231927; PMC5716684; 10.18632/oncotarget.22432

Brabletz T, Kalluri R, Nieto MA, **Weinberg RA**. EMT in cancer. *Nat Rev Cancer*, 18:128-134, 2018. PMID29326430; N/A; 10.1038/nrc.2017.118

Krall JA, Reinhardt F, Mercury OA, Pattabiraman DR, Brooks MW, Dougan M, Lambert AW, Bierie B, Ploegh HL, Dougan SK, **Weinberg RA**. The systemic response to surgery triggers the outgrowth of distant immune-controlled

tumors in mouse models of dormancy. *Sci Transl Med, In process*, 2018. PMID29643230; N/A; 10.1126/scitranslmed.aan3464

Binnewies M, Roberts EW, Kersten K, Chan V, Fearon DF, Merad M, Coussens LM, Gabrilovich DI, Ostrand-Rosenberg S, Hedrick CC, Vonderheide RH, Pittet MJ, Jain RK, Zou W, Howcroft TK, Woodhouse EC, **Weinberg RA**, Krummel MF. Understanding the tumor immune microenvironment (TIME) for effective therapy. *Nat Med*, 24:541-550, 2018. PMID29686425; PMC5998822; 10.1038/s41591-018-0014-x

Zhang Y, **Weinberg RA**. Epithelial-to-mesenchymal transition in cancer: complexity and opportunities. *Front Med*, 12:361-373, 2018. PMID30043221; N/A; 10.1007/s11684-018-0656-6

Li J, Choi PS, Chaffer CL, Labella K, Hwang JH, Giacomelli AO, Kim JW, Ilic N, Doench JG, Ly SH, Dai C, Hagel K, Hong AL, Gjoerup O, Goel S, Ge JY, Root DE, Zhao JJ, Brooks AN, **Weinberg RA**, Hahn WC. An alternative splicing switch in FLNB promotes the mesenchymal cell state in human breast cancer. *Elife, In process*, 2018. PMID30059005; PMC6103745; 10.7554/eLife.37184

Castano Z, San Juan BP, Spiegel A, Pant A, DeCristo MJ, Laszewski T, Ubellacker JM, Janssen SR, Dongre A, Reinhardt F, Henderson A, Del Rio AG, Gifford AM, Herbert ZT, Hutchinson JN, **Weinberg RA**, Chaffer CL, McAllister SS. IL-1beta inflammatory response driven by primary breast cancer prevents metastasis-initiating cell colonization. *Nat Cell Biol*, 20:1084-1097, 2018. PMID30154549; N/A; 10.1038/s41556-018-0173-5

Expenditures

Use of **Ludwig Center for Molecular Oncology at MIT** funds are focused on Faculty Research including direct support for research through use of the Koch Institute Swanson Biotechnology Center Core Facilities, Pilot Projects to support novel research projects and fellowships for graduate students and postdoctoral associates. Support for the Ludwig Center in Fiscal Year 2018 was broken down as indicated in the chart below.

