BIOGRAPHICAL SKETCH

NAME:	James A. DeCaprio, M.D.
eRA COMMONS USER NAME:	JAMES_DECAPRIO
POSITION TITLE:	Professor of Medicine

EDUCATION/TRAINING:

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
Wesleyan University, Middletown CT	B.A. with Honors	06/1977	Chemistry
New York University, New York NY	M.S.	06/1979	Biology
SUNY at Buffalo, Buffalo, NY	M.D. with Honors	06/1984	Medicine
University of Chicago, Chicago, IL	Residency	06/1986	Internal Medicine
Dana-Farber Cancer Institute, Boston, MA	Clinical Fellowship	06/1989	Medical Oncology
Dana-Farber Cancer Institute, Boston, MA	Research Fellowship	04/1992	Cancer Biology

A. Personal Statement

The DeCaprio Lab focuses on understanding the cooperative interactions between DNA tumor viruses and cellular host proteins that conspire to transform cells. We have made numerous fundamental discoveries that form major parts of our current molecular understanding of the role of tumor suppressor genes in malignant transformation and the still complex and incompletely understood transforming mechanism of the polyoma family of viruses including SV40 and Merkel cell polyomavirus. The DeCaprio Lab's overall strategy has been to identify cellular factors that bind specifically to the viral oncoproteins, determine their normal function, and gain insight into the biologic consequences that occur when they become mutated or perturbed by viruses.

The DeCaprio Lab has performed seminal studies that have led to a deeper understanding of the control of the mammalian cell cycle. These studies have led to a series of new insights into how cells regulate the cell cycle in both normal and malignant cells and what happens to those controls when transforming viruses are present. As part of this effort to discover cellular factors that bind to viral oncogenes, the DeCaprio Lab discovered the mammalian DREAM (DP, RB-related, E2F, and MuvB) complex and determined that DREAM serves as the master coordinator of cell cycle-dependent gene expression. We discovered the cullin-RING-ligase complex that contains CUL7, FBXW8, CUL9, and GLMN, and generated a mouse model that led to the discovery that CUL7 is mutated in the human 3-M short stature syndrome. The DeCaprio Lab revealed the molecular basis for the hereditary vascular disorder Glomuvenous Malformation (GVM). His laboratory identified FAM111A as an SV40 virus replication restriction factor. Remarkably, mutations in FAM111A have been described in the short stature Kenny-Caffey syndromes providing another connection between SV40 LT-host cell protein interactions linked to human disease.

Dr. DeCaprio has a long and extensive experience in mentoring and guiding trainees. In his laboratory, he has mentored 25 post-doctoral fellows, 18 PhD graduate students, and 14 undergraduate and post-baccalaureate research assistants, nearly all of whom have continued a career in science in academy or industry. He has trained 4 undergraduate students from Northeastern University sponsored by the NCI-supported CaNCURE (Cancer Nanomedicine Co-ops for Undergraduate Research Experiences) program. Currently, he directs a January term graduate level symposium on "Topics in Viral Oncology".

Dr. DeCaprio serves as the Program Director/Principal Investigator of the NCI sponsored training program "Graduate Training in Cancer Research" for Medical Oncology fellows (T32CA009172) and the "Young Empowered Scientists for ContinUed Research Engagement (YES for CURE)" program for under-represented minority college and high school students (R25 CA221738). He is co-director of the Harvard Medical School Poussaint Pre-Matriculation Summer Program (PPSP) designed to introduce topics in oncology to entering underrepresented medical students. Through coursework and seminars, clinical shadowing and mentorship, the PPSP scholars will gain a better understanding of the exciting career options in oncology.

B. Positions, Scientific Appointments, and Honors

Positions

1987-1992 Research Fellow, Laboratory of David Livingston, Dana-Farber Cancer Institute, Boston, MA
1989-1992 Instructor in Medicine, Dana-Farber Cancer Institute and Harvard Medical School
1989- Physician, Department of Medicine, Brigham & Women's Hospital, Boston, MA
1992-1998 Assistant Professor of Medicine, Dana-Farber Cancer Institute and Harvard Medical School
1998-2014 Associate Professor of Medicine, Dana-Farber Cancer Institute and Harvard Medical School
2003-2013 Director, Monoclonal Antibody Core, Dana-Farber/Harvard Cancer Center
2014- Professor of Medicine, Dana-Farber Cancer Institute and Harvard Medical School
2020- Chief, Division of Molecular & Cellular Oncology, Department of Medical Oncology, DFCI

Scientific Appointments

2003-2013 Director, Monoclonal Antibody Core, Dana-Farber/Harvard Cancer Center
2020- Chief, Division of Molecular & Cellular Oncology, Department of Medical Oncology, DFCI

Awards and Honors

1983 Elected member, Alpha Omega Alpha (AOA)
1998 Elected member, American Society for Clinical Investigation (ASCI)
2001 Harvard Medical School, Biological and Biomedical Sciences Award for Teaching
2002 The Leukemia & Lymphoma Society, Stohlman Scholar
2004 Harvard University Graduate School of Arts and Sciences, Excellence in Mentoring Award
2004 Elected member, Association of American Physicians (AAP)
2014 Master of Arts (Hon), Harvard University, Cambridge MA
2016 Elected Fellow, American Academy of Microbiology
2019 NIH/NCI Outstanding Investigator Award

C. Contributions to Science

The role of Merkel cell polyomavirus in Merkel cell carcinoma

Given our laboratory's experience in studying polyomavirus mediated transformation, we initiated studies of Merkel cell polyomavirus (MCPyV) LT and ST. We determined that MCPyV ST specifically recruits MYCL to the EP400 complex and transactivates a large number of downstream target genes. Importantly, there are several druggable downstream targets of the ST-MYCL-EP400 complex including MDM2 and LSD1. We have generated a mouse knock-in model capable of tissue specific expression of MCC tumor-derived, MCPyV truncated LT and intact ST and demonstrated their oncogenic potential *in vivo*.

1. Cheng J, Park EP, Berrios C, White EA, Arora R, Yoon R, Branigan T, Xiao T, Westerling T, Federation A, Zeid R, Strober B, Swanson SK, Florens L, Bradner JE, Brown M, Howley PM, Padi M, Washburn MP, **DeCaprio JA**. Merkel cell polyomavirus recruits MYCL to the EP400 complex to promote oncogenesis. PLOS Pathogens 2017 Oct 13;13(10):e1006668. PMID: 29028833 PMCID: PMC5640240
2. Park DE, Cheng J, Berrios C, Montero J, Cortés-Cros M, Ferretti S, Arora R, Tillgren ML, Gokhale PC and **DeCaprio JA**. Dual inhibition of MDM2 and MDM4 in virus-positive Merkel cell carcinoma enhances the p53 response. Proc Natl Acad Sci U S A. 2019 Jan 15;116(3):1027-1032. PMCID: PMC6338866
3. Starrett GJ, Thakuria M, Chen T, Marcelus C, Cheng J, Nomburg J, Thorner AR, Slevin MK, Powers W, Robert T. Burns RT, Caitlin Perry C, Adriano Piris A, Frank C. Kuo FC, Guilherme Rabinowits G, Giobbie-Hurder A, MacConaill LE, **DeCaprio JA**. Clinical and molecular characterization of virus-positive and virus-negative Merkel cell carcinoma. Genome Med. 2020 Mar 18;12(1):30. PMCID: PMC7081548
4. Park DE, Cheng J, McGrath JP, Lim MY, Cushman C, Swanson SK, Tillgren ML, Paulo JA, Gokhale PC, Florens L, Washburn MP, Trojer P, **DeCaprio JA**. Merkel cell polyomavirus activates LSD1-mediated blockade of non-canonical BAF to regulate transformation and tumorigenesis. Nat Cell Biol 2020 May;22(5):603-615. PMCID: PMC7336275

Identification of cancer-causing genes by study of Viral protein-Host cell protein interactions

The DeCaprio laboratory was a major contributor to an NHGRI-funded collaborative study with 7 independent laboratories and 50 scientists that performed a systematic analysis of more than 60 viral oncogenes. Significantly, we demonstrated that identification of cell proteins that interacted with viral oncoproteins was as effective at identifying cellular factors perturbed in cancer as other large-scale efforts including genome sequencing and genome wide association studies.

1. Rozenblatt-Rosen O, Deo RC, Padi M, Adelmant G, Calderwood MA, Rolland T, Grace M, Dricot A, Askenazi M, Tavares M, Pevzner S, Abderazzaq F, Byrdsong B, Carvunis AR, Chen AA, Cheng J, Correll M, Duarte M, Fan C, Ficarro SB, Franchi R, Garg B, Gulbahce N, Hao T, Holthaus AM, James R, Korkhin A, Litovchick L, Mar JC, R. Pak TR, Rabello S, Rubio R, Shen Y, Singh S, Spangle JM, Tasan M, Wanamaker S, Webber JT, Roecklein-Canfield J, Johannsen E, Barabási AL, Beroukhim R, Kieff E, Cusick ME, Hill DE, Münger K, Marto JA, Quackenbush J*, Roth FP*, **DeCaprio JA***, Vidal M*. *co-authors. Interpreting cancer genomes using systematic host perturbations by tumour virus proteins. Nature. 2012 Jul 26; 487 (7408):491-5. * co-corresponding author. PMCID: PMC3408847
2. Kim JW, Berrios C, Kim M, Schade AE, Adelmant G, Yeerna H, Damato E, Balboni Iniguez A, Florens L, Washburn MP, Stegmaier K, Gray NS, Tamayo P, Gjoerup O, Marto JA, **DeCaprio JA***, Hahn WC*. *co-authors. STRIPAK Directs PP2A Activity Toward MAP4K4 to Promote Oncogenic Transformation of Human Cells Elife. 2020 Jan 8;9:e53003. PMCID: PMC6984821

The DREAM (DP, RB-related, E2F and MuvB) complex

Dr. DeCaprio's lab identified an 8-protein complex that we termed DREAM based on its similarity to complexes previously identified by genetic and biochemical studies in *C. elegans* and *D. melanogaster*. We determined that the mammalian DREAM complex bound specifically to the promoters of all cell cycle regulated, E2F-dependent, genes and repressed their expression during cellular quiescence. They determined that the DYRK1A kinase was required for assembly of the DREAM complex during quiescence. They found that the DREAM complex underwent a metamorphosis during cell cycle progression with the MuvB component being released from p130, E2F4 and DP1 during the G1 phase of the cell cycle and subsequently binding to B-MYB (MYBL2) and FOXM1 to specifically activate expression of several hundred genes required for progression during G2 and M phase. The DeCaprio Lab established the foundation that the DREAM complex serves as a master coordinator of cell cycle gene expression.

1. Litovchick L, Sadasivam S, Florens L, Zhu X, Swanson SK, Velmurugan S, Chen R, Washburn MP, Liu XS, **DeCaprio JA**. Evolutionarily Conserved Multisubunit RBL2/p130 and E2F4 Protein Complex Represses Human Cell Cycle-Dependent Genes in Quiescence. Mol Cell. 2007;26(4):539-551. PMID: 17531812
2. Sadasivam S, Duan S, **DeCaprio JA**. The MuvB complex sequentially recruits B-Myb and FoxM1 to promote mitotic gene expression. Genes Dev. 2012 Mar 1;26(5):474-89. PMCID: PMC3305985
3. Schade AE, Fischer M, **DeCaprio JA**. RB, p130 and p107 differentially repress G1/S and G2/M genes after p53 activation. Nucleic Acids Res. 2019 Dec 2;47(21):11197-11208. PMCID: PMC6868438
4. Branigan TB, Kozono D, Schade AE, Deraska P, Rivas HG, Sambel L, Reavis HD, Shapiro GI, D'Andrea AD, **DeCaprio JA**. MMB-FOXM1-driven premature mitosis is required for CHK1 inhibitor sensitivity. Cell Rep. 2021 Mar 2;34(9):108808. PMCID: PMC7970065

Identification of human disease genes by study of Viral protein-Host cell protein interactions

The DeCaprio lab identified CUL7, CUL9, FBXW8, GLMN and FAM111A as specific interacting proteins with SV40 LT and generated knockout mice for *Cul7*, *Fbxw8*, *Cul9* and *Glmn* genes. They demonstrated that knockout of the Cul7 or the Fbxw8 gene in mice led to severe growth retardation that was recognized by an independent genetic study that determined that homozygous mutations in CUL7 were responsible for the human 3M short stature syndrome. They demonstrated that GLMN binds directly to RBX1 and inhibits the ubiquitin ligase activity of cullin RING ligases and revealed the molecular basis for Glomuvenous malformation, a human hereditary vascular malformation syndrome. Most recently, the DeCaprio laboratory identified FAM111A as an SV40 virus replication restriction factor. Remarkably, mutations in FAM111A have recently been described in the short stature Kenny-Caffey and osteocraniostenosis syndromes.

1. Arai T, Kasper JS, Skaar JR, Ali SH, Takahashi C, **DeCaprio JA**. Targeted disruption of p185/Cul7 gene results in abnormal vascular morphogenesis. Proceedings of the National Academy of Science U S A. 2003;100(17):9855-60. PMID: 12904573 PMCID: PMC187864
2. Tron AE, Arai T., Duda DM, Kuwabara H, Olszewski JL, Fujiwara Y, Bahamon BN, Signoretti S, Schulman BA, **DeCaprio JA**. The Glomuvenous Malformation Protein Glomulin Binds Rbx1 and Regulates Cullin RING Ligase-Mediated Turnover of Fbw7. Mol Cell. 2012 Apr 13;46(1):67-78. PMID: 22405651 PMCID: PMC3336104
3. Fine DA, Rozenblatt-Rosen O, Padi M, Khorkin A, James RL, Adelmant G, Yoon R, Guo L, Berrios C, Zhang Y, Calderwood MA, Velmurgan S, Cheng J, Marto JA, Hill DE, Cusick ME, Vidal M, Florens L, Washburn MP, Litovchick L, **DeCaprio JA**. Identification of FAM111A as an SV40 host range restriction factor. PLoS Pathog. 2012;8(10):e1002949 PMID: 23093934 PMCID: PMC3475652

4. Tarnita RM, Wilkie AR, **DeCaprio JA**. Contribution of DNA replication to the FAM111A-mediated simian virus 40 host range phenotype. J Virol. 2018 Oct 17. PMID: 30333173 PMCID: PMC6288344

Transforming activity of SV40 Large T antigen (LT)

As a postdoctoral fellow with David Livingston, Dr. DeCaprio demonstrated that SV40 LT could bind specifically to the product of the Retinoblastoma tumor suppressor gene (*RB1*). He also demonstrated that the residues contained in the LXCXE motif of SV40 LT were required for binding to RB and for cellular transformation. As an independent PI, his laboratory demonstrated that an intact LXCXE motif was required for SV40 LT mediated transformation of mouse embryo fibroblasts (MEFs) derived from *Rb1*-/- knockout mice. This was the first demonstration that the RB-related proteins p130 (*RBL2*) and p107 (*RBL1*) had growth suppressive functions and was one of the first published reports using MEFs derived from knockout mouse strains. This line of investigation led to the demonstration that all polyomavirus T antigens contain a functional, DNA J domain.

1. Zalvide J, **DeCaprio JA**. Role of pRb-related proteins in simian virus 40 large-T-antigen-mediated transformation. Mol Cell Biol. 1995;15(10):5800-10. PMID: 7565733 PMCID: PMC230832
2. Stubdal H, Zalvide J, Campbell KS, Schweitzer C, Roberts TM, **DeCaprio JA**. Inactivation of pRB-related proteins p130 and p107 mediated by the J domain of simian virus 40 large T antigen. Mol Cell Biol. 1997;17(9):4979-90. PMID: 9271376 PMCID: PMC232349
3. Campbell KS, Mullane KP, Aksoy IA, Stubdal H, Zalvide J, Pipas JM, Silver PA, Roberts TM, Schaffhausen BS, **DeCaprio JA**. DnaJ/hsp40 chaperone domain of SV40 large T antigen promotes efficient viral DNA replication. Genes Dev. 1997;11(9):1098-110. PMID: 9159391
4. Berrios C, Jung J, Primi B, Wang M, Pedamallu C, Duke F, Marcelus C, Cheng J, Garcea RL, Meyerson M, **DeCaprio** JA. Malawi polyomavirus is a prevalent human virus that interacts with known tumor suppressors. J Virol. 2015 Jan;89(1):857-62. PMID: 25320321 PMCID: PMC4301141

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/pubmed/?term=DeCaprio+JA%5BAuthor%5D