CURRICULUM VITAE

STEPHEN M. HATFIELD, Ph.D.

IMPACT - SUMMARY OF MAJOR ACCOMPLISHMENTS

- Provided proof of principle that drug-mediated elimination of tumor-protecting hypoxic areas enables anti-tumor T cells to reject tumors.
- Publications in ***Science Translation Medicine*** and the ***Journal of Molecular Medicine*** were the first genetic and pharmacological in vivo evidence of a novel method to weaken immunosuppressive intratumoral hypoxia by oxygenation of tumors.
- The impact of these studies established the industry of repurposing anti-hypoxia and oxygenation agents for cancer immunotherapy to oxygenate tumors directly or to target hypoxic areas.
- These studies generated great excitement by experts and public interest as reflected in press releases, editorials, commentaries and subsequent evaluations in Nature Reviews Cancer, describing the work as *"groundbreaking"* and *"landmark"*. Commentaries appeared in top-tier journals and major media outlets including: Nature Reviews Cancer, Cancer Cell, Science cover (online), Associated Press "The Big Story", NY Times, Washington Post, BBC, NBC, NPR, and others.
- This research served as proof of principle justifying the follow up clinical trial entitled *"Immunotherapy Study of Evofosfamide in Combination With Ipilimumab"*. ClinicalTrials.gov NCT03098160

EXPERIENCE

01/2020-present

NORTHEASTERN UNIVERSITY Boston, MA

ASSISTANT PROFESSOR, **Department of Pharmaceutical Sciences, Bouvé College of Health Sciences**

- Improving cancer immunotherapies by preventing immunosuppression of tumor reactive immune cells in the tumor microenvironment using novel strategies to target tumor hypoxia and adenosinergic signaling
- Investigating and developing novel treatments for infectious diseases in emerging animal models including humanized hamsters for COVID-19
- Recipient of the 2022 Gerald E. Schumacher Faculty Research Award
- PI on 3-year sponsored research agreement with Beam Therapeutics on the characterization of CART cells genetically-resistant to hypoxia-adenosinergic immunosuppression
- PI on 2-year sponsored research agreement with Bugworks Therapeutics on the investigation of novel A2-adenosinergic drugs to improve cancer immunotherapy
- Recipient of Tufts Clinical and Translational Science Institute Pilot Study Grant
- Recipient of Northeastern COVID-19 Research Award: Preventing supplemental oxygen mediated exacerbation of lung damage of ventilated COVID-19 patients
- Recipient of Northeastern University Tier 1 award
- Editor of 2020 'Cancer' section published within *Current Opinion in Pharmacology*

- **Current Courses:**
  PMCL 6260 – Pharmacology I
  PHSC 6216 – Human Physiology/Pathophysiology
  PHSC 6300 – Pharmaceutics Seminar
  PHSC 6300 – Pharmacology Seminar
  PHSC 2650 – Intro to Health Science Research
  PHSC 2330 – Immunology* (developed all new course material in 2021)
  PHSC 1001 – Intro to Contemp. Pharm Sci* (new course in Fall 2021)

03/2017-01/2020

NORTHEASTERN UNIVERSITY Boston, MA
PRINCIPAL RESEARCH SCIENTIST, **New England Inflammation & Tissue Protection Institute**

- Lead investigator on *in vivo/in vitro/ex vivo* tumor immunology assays of immune suppression in the tumor microenvironment (TME) with particular focus on T cells, NK cells, T regulatory cells, and MDSCs
- Led and supervised all projects and collaborations, performed and analyzed experiments, and authored manuscripts resulting in peer-reviewed publications in top-tier journals
- Selected, recruited and trained talented and competitive graduate and undergraduate students for research within the institute
- Leveraged unique expertise in the design and performance of assays of tumor immunology in combination with anti-hypoxia-adenosinergic treatments to develop creative reasoning to increase the probability of receiving grants and funding from industry
- Provided and analyzed key data resulting in sponsored research agreements with major biopharmaceutical companies
- Developed models to recapitulate the hypoxic and adenosine-rich TME in 2-D and 3-D cultures

01/2012-03/2017

NORTHEASTERN UNIVERSITY Boston, MA
ASSOCIATE RESEARCH SCIENTIST, **New England Inflammation & Tissue Protection Institute**

- Led projects and collaborations, performed and analyzed experiments, and authored manuscripts resulting in peer-reviewed publications in high impact journals
- Critical member of the team establishing that immune suppression can be prevented pharmacologically by selective antagonism of the A2A adenosine receptor (A2AR) using small molecule drugs
- Provided detailed proposals, experimental design, reasoning, and preliminary data to funding institutions
- Co-authored, served as Key Personnel, processed grant submissions and prepared all grant progress reports
- Developed and reviewed all IACUC animal protocols
- Supervised graduate and undergraduate student researchers

COURSE LECTURER

- Developed and instructed both traditional lecture and online courses at the undergraduate and graduate level

Biotechnology/Bioinformatics Program
- Molecular Cell Biology for Biotechnology (Traditional and online course)
- Molecular Cell Biology for Bioinformatics (Online course)

Biology Department
- Introduction to Immunotherapies of Cancer
- Cell and Molecular Biology
- Genetics and Molecular Biology Laboratory
- Biochemistry Methods Laboratory
- Microbiology Laboratory (I ,II, III)

09/06-01/2012

NORTHEASTERN UNIVERSITY Boston, MA
GRADUATE STUDENT/LAB MANAGER, **New England Inflammation & Tissue Protection Institute**

- Investigated anti-hypoxia-adenosinergic approaches to cancer immunotherapy including physiological and immunological checkpoint inhibitors
- Examined the role of respiratory hyperoxia in preventing the inhibition of endogenous or adoptively transferred T cells and NK cells
- Established and maintained long-term interactions with key collaborating scientists
- Managed lab inventory, safety protocols, radiation and hazardous waste, general lab maintenance, etc.
- Supervised undergraduate researchers

06/05-09/06

THE UNIVERSITY OF NEW HAMPSHIRE Durham, NH
ASSISTANT RESEARCH SCIENTIST/TECHNICIAN
Laboratory of Dr. Estelle Hrabak

- Investigated the sub-cellular localization of calcium-dependent protein kinases in *Arabidopsis Thaliani*
- Managed lab supply inventory, radiation and hazardous waste and general lab maintenance
- Supervised undergraduate researchers

EDUCATION

NORTHEASTERN UNIVERSITY Boston, MA
Ph.D. in Biology
Jan, 2012

UNIVERSITY OF NEW HAMPSHIRE Durham, NH
B.S. in Molecular, Cellular, and Developmental Biology
May, 2005

CONFERENCES AND AWARDS

1. ***Gerald E. Schumacher Faculty Research Award Recipient, 2022***
2. ***American Association of Pharmaceutical Scientists, 2022.*** Invited speaker and Chair of Oncotargets: Challenges and Opportunities Symposium. Boston, Ma: Oct. 14-20
3. ***NK2022 Society for Natural Immunity.*** Susceptibility of NK cells to hypoxia-adenosinergic immunosuppression. Bonita Springs, Florida: May 14-17, 2022.
4. ***Molecular Medicine Tri-Con, 2022***. Elimination of Biochemical and Immunological Barriers in the TME to Improve Cancer Immunotherapy. San Diego, Ca: Feb. 21-23.
5. ***Tier 1 Award, 2021****:* CXCR4-targeted nanoparticles to eliminate hypoxia-adenosinergic immunosuppression in tumors: *July 1, 2021 to Sept 30, 2022*.
6. ***Northeastern University COVID-19 Research Award, 2020****:* Preventing supplemental oxygen mediated exacerbation of lung damage of ventilated COVID-19 patients: *June 30, 2020 to June 30, 2021*
7. ***Paris Redox, 2020***. International Society of Anti-oxidants. Invited Speaker
8. ***Vaccine Forum, 2019***. Valencia, Spain. May 8-9, 2019. Invited Speaker.
9. ***Drug Discovery Chemistry.*** San Diego, Ca: April 8-12, 2016. Invited Speaker.
10. ***4th Annual Immuno-Oncology Summit.*** Boston, Ma: Aug 29-Sep. 2, 2016. Invited Speaker: "Anti-Hypoxia-A2-Adenosinergic Co-Adjuvants to Enable the Full Anti-Tumor Capacities of T- and Natural Killer Cells During Immunotherapies of Cancer"
11. ***The New England Immunology Conference***. Woods Hole, Ma: October 17-18, 2015. Invited Speaker: "Respiratory hyperoxia reprograms the immunosuppressive metabolism in the hypoxic tumor microenvironment and enhances T and NK cell responses". NEIC 2015 Young Investigator Award
10. ***Purines.*** Bonn, Germany: July 23-27, 2014. Invited Speaker: "The anti-hypoxia adenosinergic approach to the immunotherapy of cancer"
9. ***Tumor Models for Cancer Immunotherapy.*** World Pharma Congress. Boston, Ma: May 21-23, 2014. Presentation: "A2A adenosine receptor gene-deletion or selective antagonism liberates anti-tumor CD8 T cells from tumor-induced suppression"

PATENTS

- Issued Patent: **Method for generation of broadly neutralizing anti-pathogen antibodies**
  Inventors: Michail Sitkovsky, Robert Abbott, Stephen Hatfield
- Issued Patent: **Method for generation of oxygen-generating cryogels**
  Inventors: Sidi Bencherif, Thibault Colombani, Michail Sitkovsky, Adnan Memic, Stephen Hatfield
- Pending Patent: **Modified immune cells and methods.** Ryan Murray, Michail Sitkovsky, Stephen Hatfield

FUNDING

ACTIVE

Title: *Preventing the oxygenation-associated inflammation of ventilated COVID-19 patients with ARDS*
Contact PI: Hatfield
Sponsor: Tufts CTSI
Period of Performance: 05/1/2022-05/31/2023
Effort: 0.16 Summer months
Total Costs: $ 39,994
Goal: Dr. Hatfield will assume oversight responsibility for all assays investigating bacterial-induced ARDS models in hamsters. In addition, Dr. Hatfield's group will be responsible for the immunological, biochemical, and molecular biological analyses of samples from SARS-CoV-2 infected hACE2 hamsters collected at USU BSL3 facilities. With expertise in adenosinergic drugs and hyperoxia, Dr. Hatfield will provide insights on experiments using adenosine analogues and supplemental oxygenation conducted at USU. These analyses will be done in parallel with samples from bacterial-induced ARDS.
Grant Officer:
Role: PI

Title: *Design and characterization of CART cells genetically-resistant to hypoxia-adenosinergic immunosuppression*
Contact PI: Hatfield
Sponsor: Beam Therapeutics
Period of Performance: 02/01/2021-01/31/2024
Effort: 3.2 summer months
Total Costs: $ 956,593
Goal: This work will focus on fully characterizing the T cell anti-tumor response in both mouse and hamster with respect to immunosuppressive barriers commonly seen in the TME, namely inhibition via checkpoint inhibitors (CTLA4, PD1) and hypoxia-driven extracellular adenosine that leads to accumulation of suppressive cAMP[7]**.** Overcoming these barriers can be mitigated by genetic ablation of hypoxia inducible factor 1-alpha (HIF1a) and adenosine A2A receptor via base editing to rescue T cell hypo-functionality in the TME.
Grant Officer:
Role: PI

Title: *Investigations of the anti-tumor effects of a dual A2AR/A2BR antagonist*
Contact PI: Hatfield
Sponsor: Bugworks, LLC
Period of Performance: 07/01/2022-06/29/2024
Effort: 0.20 academic months
Total Costs: $ 294,800
Goal: In vitro assays to compare novel BW-A_{2A}R/A_{2B}R antagonist with other leading adenosine receptor antagonists in their ability to improve T cell effector functions across a range of activation inputs. To determine whether novel BW-A_{2A}R/A_{2B}R antagonist alone or in combination with adoptive T cell therapy induces the regression of pulmonary tumors.
Aim 3. To determine whether administration of BW-A_{2A}R/A_{2B}R can improve the efficacy immune checkpoint blockade (monoclonal antibody therapy to PD1 and CTLA4).
Grant Officer:
Role: PI

PENDING

Title: *Understanding the mechanism(s) by which hypoxia-adenosinergic signaling during EMT mediates cross-protective effects in heterogeneous breast tumors*
Contact PI: Hatfield (Partner PI)
Sponsor: Department of Defense
Period of Performance: 05/01/2023- 04/30/2026
Effort: 1.6 summer months

Total Costs: $ 613,180
Goal: To determine whether the cross-protective effects observed in mixed tumors are mediated by the action of qM-derived adenosine on Epithelial carcinoma cells and whether the cross-protective effects observed in mixed tumors are mediated by the action of qM-derived adenosine on immune cells.
Grant Officer:
Role: Partner PI

PREVIOUS

Northeastern University COVID-19 Research Award: Preventing supplemental oxygen mediated exacerbation of lung damage of ventilated COVID-19 patients: June 30, 2020 to June 30, 2021. ($30,000)

NEU Tier 1 Award: CXCR4-targeted nanoparticles to eliminate hypoxia-adenosinergic immunosuppression in tumors: July 1, 2021 to Sept 30, 2022. ($50,000)

DEPARTMENT SERVICE SUMMARY

2022 – Chair of Self-Study Section

2022 – Graduate Committee

2022 – Pharmacy Program Curriculum Revision

2022 – Tier 1 Award Reviewer

2020-present – Merit Review and Workload Policy Committee

2020-present – Assessment Committee

2020-present – Portfolio Advisor PharmD Students

2020-2021 – Bachelor of Science in Pharmaceutical Sciences (BSPS) Curriculum Revision Taskforce

2020-2021 – Pharmaceutical Sciences PlusOne Master's Program Taskforce

RESEARCH MENTORING (Students Since 2020)

PH.D/M.S MENTORING

1. Art Groy
2. Bradley Delaney
3. Katarina Halpin-Veszeleiova
4. Joseph Steingold
5. Ryan Murray
6. Reed Masakayan
7. Christina Blackwell
8. Kashvi Desai
9. Neha Parth Gokhale
10. Hiral Parag Gujar
11. Mayuri Shukla
12. Divya Parikh
13. Monica Kavarthapu
14. Somya Jain

UNDERGRADUATE MENTORING

1. Angela Liu†
2. Natalie Desilet
3. Liliana Lachnace
4. Kelly Ward†
5. Kai Beattie
6. Jack Schaeffer
7. Brian Chong
8. Nuria Romero†
9. Camille Bahr
10. Ashley Apro
11. Alexis Bloedel
12. Laura Rosenberg
13. Michael Mallouh

† *Project-Based Exploration for the Advancement of Knowledge (PEAK) Award Recipient*

PUBLICATIONS

1. Katarina Halpin-Veszeleiova, Stephen Hatfield. **Therapeutic Targeting of Hypoxia-A2-Adenosinergic Pathway in COVID-19 Patients.** Physiology (Bethesda). 2022 Jan 1;37(1):46-52. doi: 10.1152/physiol.00010.2021. *(*Selected for Journal Cover)*

2. T. Colombani, S.M. Hatfield, M. Rezaeeyazdi, L.J. Eggermont, A. Memic, M.V. Sitkovsky, S.A. Bencherif. **Oxygen-generating cryogels restore T cell-mediated antitumor cytotoxicity in hypoxic tumors.** Advanced Functional Materials. 2021, doi: 10.1002/adfm.202102234. *(*Selected for Journal Cover)*

3. Hatfield S, Sitkovsky M**. Antihypoxic oxygenation agents with respiratory hyperoxia to improve cancer immunotherapy.** J Clin Invest 2020 Sep 28;137554. doi: 10.1172/JCI137554.

4. Paul A Beavis, Stephen M Hatfield. Editorial overview: **Cancer 2020 current mechanistic insights into the hypoxia-adenosine-A2A adenosinergic immunosuppressive axis in cancer immunotherapies**. Curr Opin Pharmacol. 2020 Aug;53:iii-v. doi: 10.1016/j.coph.2020.10.012.

5. Veszeleiova K, Hatfield S. **Oxygenation and A2AR blockade to eliminate hypoxia/HIF-1α-adenosinergic immunosuppressive axis and improve cancer immunotherapy**. Curr Opin Pharmacol. 2020. 22;53:84-90. doi: 10.1016/j.coph.2020.07.005.

6. Steingold J, Hatfield S. **Targeting hypoxia-A2A adenosinergic immunosuppression of antitumor T cells during cancer immunotherapy**. Front Immunol. 2020; 11: 570041. Published online 2020 Sep 29. doi: 10.3389/fimmu.2020.570041

7. Hatfield S, Veszeleiova K, Steingold J, Sethuraman J, Sitkovsky M. **Mechanistic Justifications of Systemic Therapeutic Oxygenation of Tumors to Weaken the Hypoxia Inducible Factor 1α-Mediated Immunosuppression.** Adv Exp Med Biol. 2019;1136:113-121. doi: 10.1007/978-3-030-12734-3_8.

8. Sorrentino C, Hossain F, Rodriguez PC, Sierra RA, Pannuti A, Hatfield S, Osborne BA, Minter LM, Miele L, Morello S.. **Adenosine A2A Receptor Stimulation Inhibits TCR-Induced Notch1 Activation in CD8+T-Cells.** Front Immunol. 2019 May 3;10:935. doi: 10.3389/fimmu.2019.00935. eCollection 2019.

9. Kjaergaard J[1]*, Hatfield SM[1]*, Jones G[2], Ohta A[1] and Sitkovsky M[1] **A2A adenosine receptor gene-deletion or synthetic A2A antagonist liberate tumor-reactive CD8+ T-cells from tumor-induced immunosuppression.** J Immunol. 2018 Jul 15;201(2):782-791. doi: 10.4049/jimmunol.1700850. Epub 2018 May 25.
   ***Authors contributed equally**

10. Silva M, Nguyen TH, Philbrook P, Chu M, Sears O, Hatfield S, Abbott RK, Kelsoe G, Sitkovsky MV. **Targeted Elimination of Immunodominant B Cells Drives the Germinal Center Reaction toward Subdominant Epitopes.** Cell Rep. 2017 Dec 26;21(13):3672-3680. doi: 10.1016/j.celrep.2017.12.014.

11. Yuan G, Jankins TC, Patrick CG Jr, Philbrook P, Sears O, Hatfield S, Sitkovsky M, Vasdev N, Liang SH, Ondrechen MJ, Pollastri MP, Jones GB. **Fluorinated Adenosine A2A Receptor Antagonists Inspired by Preladenant as Potential Cancer Immunotherapeutics.** Int J Med Chem. 2017;2017:4852537. doi: 10.1155/2017/4852537. Epub 2017 Oct 19.

12. Sethumadhavan S, Silva M, Philbrook P, Nguyen T, Hatfield SM, Ohta A, Sitkovsky MV. **Hypoxia and hypoxia-inducible factor (HIF) downregulate antigen-presenting MHC class I molecules limiting tumor cell recognition by T cells.** PLoS One. 2017 Nov 20;12(11):e0187314. doi: 10.1371/journal.pone.0187314. eCollection 2017.

13. Abbott RK, Silva M, Labuda J, Thayer M, Cain DW, Philbrook P, Sethumadhavan S, Hatfield S, Ohta A, Sitkovsky M. **The GS Protein-coupled A2a Adenosine Receptor Controls T Cell Help in the Germinal Center.** J Biol Chem. 2017. PMID: 27974461

14. Abbott RK, Thayer M, Labuda J, Silva M, Philbrook P, Cain DW, Kojima H, Hatfield S, Sethumadhavan S, Ohta A, Reinherz EL, Kelsoe G, Sitkovsky M. **Germinal Center Hypoxia Potentiates Immunoglobulin Class Switch Recombination.** J Immunol. 2016 Nov. PMID: 27798169

15. Hatfield SM, Sitkovsky M. **A2A Adenosine Receptor antagonists to weaken the hypoxia-HIF-1α driven immunosuppression and improve immunotherapies of cancer.** *Curr. Op. in Pharmacology*, 2016 Aug;29:90-6. doi: 10.1016/j.coph.2016.06.009. Epub 2016 Jul 17.

16. Hatfield SM, Sitkovsky M**. Oxygenation to improve cancer vaccines, adoptive cell transfer and blockade of immunological negative regulators.** Oncoimmunology. May 2015 doi:10.1080/2162402X.2015.1052934

17. Hatfield SM, Kjaergaard J, Lukashev D, Schreiber TH, Belikoff B, Abbott R, Sethumadhavan S, Philbrook P, Ko K, Cannici R, Rodig S, Kutok JL, Karger B, Podack ER, Ohta A, Sitkovsky M. **Immunological mechanisms of the anti- tumor effects of supplemental oxygenation.** *Science Translational Medicine*, 2015 Mar 4;7(277):277ra30. doi: 10.1126/scitranslmed.aaa126 *(*Selected for Cover - Online)*

18. Hatfield SM, Kjaergaard J, Lukashev D, Belikoff B, Schreiber TH, Sethumadhavan S, Abbott R, Philbrook P, Thayer M, Shujia D, Rodig S, Kutok JL, Ren J, Ohta A, Podack ER, Karger B, Jackson EK, Sitkovsky M. S**ystemic oxygenation weakens the hypoxia and hypoxia inducible factor 1α-dependent and extracellular adenosine- mediated tumor protection.** J Mol Med; 2014 Aug 15. PMID: 25120128

19. Sitkovsky MV, Hatfield S, Abbott R, Belikoff B, Lukashev D, Ohta A**. Hostile, hypoxia-A2-adenosinergic tumor biology as the next barrier to overcome for tumor immunologists.** Cancer Immunol Res. 2014 Jul;2(7):598-605. PMID: 24990240

20. Georgiev P, Belikoff BG, Hatfield S, Ohta A, Sitkovsky MV, Lukashev D. **Genetic deletion of the HIF-1α isoform I.1 in T cells enhances antibacterial immunity and improves survival in a murine peritonitis model.** Eur J Immunol 2013; 43:655-66. PMC 3757952

21. Thomas R, Lee J, Chevalier V, Sadler S, Selesniemi K, Hatfield S, Sitkovsky M, Ondrechen MJ, Jones GB. **Design and evaluation of xanthine-based adenosine receptor antagonists: potential hypoxia targeted immunotherapies.** Bioorg Med Chem 2013; 21:7453-64. PMID: 24126093

22. Belikoff B, Hatfield S, Georgiev P, Ohta A, Lukashev D, Buras JA, Remick DG, Sitkovsky M. **A2B Adenosine Receptor Blockade Enhances Macrophage-Mediated Bacterial Phagocytosis and Improves Polymicrobial Sepsis Survival in Mice.** J Immunol 2011;186:2444-53. PMC 3708265

23. Belikoff B, Hatfield S, Sitkovsky M, Remick DG. **Adenosine negative feedback on A2A adenosine receptors mediates hyporesponsiveness in chronically septic mice.** Shock 2011;35:382-7. PMC 3693562

24. Hatfield S, Belikoff B, Lukashev D, Sitkovsky M, Ohta A. **The antihypoxia-adenosinergic pathogenesis as a result of collateral damage by overactive immune cells.** J Leukoc Biol 2009;86:545-8. PMID: 1956