STEPHEN HATFIELD, PhD

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 6250 – Ion Channel Physiology and Pharmacology (new course in Fall 2023)
  PMCL 6260 – Pharmacology I (retired in Spring 2023)
  PHSC 6216 – Human Physiology/Pathophysiology
  PHSC 6300 – Biomedical Sciences 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
- 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, SYMPOSIUMS AND AWARDS

1. ***Pharm Sci 360 Meeting. American Association of Pharmaceutical Scientists.*** Invited speaker. State-of-the-Art Tools for Basic Research and Early-Stage Drug Discovery. Targeting Hypoxia and Adenosine Mediated Immunosuppression to Improve Cancer Therapy Orlando, Florida: Oct. 22-26, *2023*
2. ***Cornell University Biomedical Sciences Seminar Series****.* Invited speaker. Targeting hypoxia-adenosinergenic immune-suppression to reprogram the tumor microenvironment and improve cancer immunotherapy. Ithaca, NY: Sept 21-22, 2023
3. ***2nd Annual Adenosine-Pathway Targeted Cancer Immunotherapy Summit****.* Invited speaker and pre-conference workshop leader. Harnessing Mono/Combo Adenosine Pathway Inhibition to Overcome Hypoxia & Immunosuppression in the Tumor Microenvironment. Boston, MA: June 20 - 22, 2023
4. ***2022 Gerald E. Schumacher Faculty Research Award Recipient***
5. ***American Association of Pharmaceutical Scientists Meeting.*** Invited speaker and Chair of Symposium; "Oncotargets: Challenges and Opportunities". Boston, MA: Oct. 14-20, 2022
6. ***1st annual Adenosine-Pathway Targeted Cancer Immunotherapy Summit****.* Invited speaker in two different symposiums: "Investigating Adenosine Signaling in the Context of the Hypoxic Tumor Microenvironment" and "Translating Key Fundamental Learnings from Non-Cancer Adenosine Biology to Inform Cancer Adenosine Biology". Boston, MA: May 10-12, 2022
7. ***NK2022 Society for Natural Immunity.*** Susceptibility of NK cells to hypoxia-adenosinergic immunosuppression. Poster Presentation. Bonita Springs, Florida: May 14-17, 2022.
8. ***Molecular Medicine Tri-Con, 2022****.* Elimination of Biochemical and Immunological Barriers in the TME to Improve Cancer Immunotherapy. Poster Presentation. San Diego, Ca: Feb. 21-23.
9. ***Tier 1 Award, 2021****:* CXCR4-targeted nanoparticles to eliminate hypoxia-adenosinergic immunosuppression in tumors: *July 1, 2021 to Sept 30, 2022*.
10. ***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*
11. ***Paris Redox, 2020****.* International Society of Anti-oxidants. Invited Speaker
12. ***Vaccine Forum, 2019****.* Valencia, Spain. May 8-9, 2019. Invited Speaker.
13. ***Drug Discovery Chemistry.*** San Diego, Ca: April 8-12, 2016. Invited Speaker.
14. ***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"
15. ***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**
16. ***Purines.*** Invited Speaker: "The anti-hypoxia adenosinergic approach to the immunotherapy of cancer". Bonn, Germany: July 23-27, 2014.
17. ***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"
18. ***BD Biosciences FACSAriaII / BD FACSAria III Operator Course****.* San Jose, California: Nov. 16-20, 2015.
19. ***Flocyte Regional Flow Cytometry Training Program.*** June 10-12, 2014. UMass Medical School.

PATENTS

- Issued USA Patent: **Method for generation of broadly neutralizing anti-pathogen antibodies**
  Inventors: Michail Sitkovsky, Robert Abbott, Stephen Hatfield

- Issued USA Patent: **Method for generation of oxygen-generating cryogels**
  Inventors: Sidi Bencherif, Thibault Colombani, Michail Sitkovsky, Adnan Memic, Stephen Hatfield

- Pending USA Patent: **Modified immune cells and methods.** Beam Therapeutics, Michail Sitkovsky, Stephen Hatfield

SUMMARY OF SCIENTIFIC AND SCHOLARLY ACTIVITY

- **PI - Sponsored Research Agreement w/ Bugworks Therapeutics:** Investigation of novel A2-adenosinergic drugs to improve cancer immunotherapy. *September 20, 2022 to September 19, 2024* **($300,000)**
- **PI – Tufts CTSI Pilot Award:** Preventing the oxygenation-associated inflammation and deaths of ventilated COVID-19 patients with ARDS: *June 1, 2022 to May 31, 2023* **($40,000)**
- **PI – Sponsored Research Agreement w/ Beam Therapeutics**: Characterization of CART cells genetically-resistant to hypoxia-adenosinergic immunosuppression: *February 1, 2021 to January 31, 2024.* **($900,000)**
- **PI** – **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)**
- **Co-PI** – **NEU Tier 1 Award:** CXCR4-targeted nanoparticles to eliminate hypoxia-adenosinergic immunosuppression in tumors: *July 1, 2021 to Sept 30, 2022*. **($50,000)**
- **Co-I** – **Sponsored Research Agreement with Juno Therapeutics** (Bristol Myers Squibb): Evaluation of the anti-tumor activities of JSMD026. *June 1, 2017 to May 31, 2020* **($998,085)**
- **Guest Editor** – 2020 'Cancer' section published in Current Opinion in Pharmacology
- **Chair of Symposium – Oncotargets: Challenges and Opportunities**. American Association of Pharmaceutical Scientists, 2022. Boston, MA: Oct. 14-20

DEPARTMENT SERVICE SUMMARY

2022-present – Chair of Self-Study Section (Standards #18-20)

2022-present – Graduate Committee

2022-present – Pharmacy Program Curriculum Revision Taskforce

2022-present – Tier 1 Award Reviewer

2020-present – Merit Review and Workload Policy Committee

2020-present – Assessment Committee

2020-present – Portfolio Advisor PharmD Student

2020-present – PharmD Capstone Student Advisor

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
14. Shivani Patel†

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

PUBLICATIONS

1. Murray R, Navarrete N, Desai K, Chowdhury R, Chilakapati S, Chong B, Messane A, Sobon H, Rocha J., Musenge F, Camblin A, Ciaramella G, Sikovsky M, Maldini C, **Hatfield SM.** Comprehensive genome editing confers 'off-the-shelf' CAR-T cells superior efficacy against solid tumors. BioRxiv [Preprint]. August 4, 2023. doi: https://doi.org/10.1101/2023.08.03.551705. Under Review at Nature Comm., Jan. 2024

2. Halpin-Veszeleiova K, Mallouh M, Apro A, Romero N, Bahr C, Shin M, Ward K, Rosenberg L, Sitkovsky M, Spiess B, **Hatfield SM**. Oxygen carrying nanoemulsions and respiratory hyperoxia eliminate tumor hypoxia-induced suppression and improve cancer immunotherapy. BioRxiv [Preprint]. Feb doi: https://doi.org/10.1101/2024.02.17.580835. Under Review at J Clin Invest: Insight, Oct. 2023

3. 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)*

4. 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)*

5. 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.

6. 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.

7. 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.

during cancer immunotherapy. Front Immunol. 2020; 11: 570041. Published online 2020 Sep 29. doi: 10.3389/fimmu.2020.570041

9. 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.

10. 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.

11. 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**

12. 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.

13. 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.

14. 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.

15. 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

16. 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

17. 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.

18. 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

19. 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)*

20. 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. **Systemic oxygenation weakens the hypoxia and hypoxia inducible factor 1α-dependent and extracellular adenosine- mediated tumor protection.** J Mol Med; 2014 Aug 15. PMID: 25120128

tumor biology as the next barrier to overcome for tumor immunologists. Cancer Immunol Res. 2014 Jul;2(7):598-605. PMID: 24990240

22. 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

23. 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

24. 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

25. 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

26. 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: 195