AWARD NUMBER: W81XWH-19-1-0666

TITLE: Transferrin Receptor Identifies a Comprehensive Pool of Circulating Tumor Cells with Unique Molecular Features from Metastatic Prostate Cancer Patients

PRINCIPAL INVESTIGATOR: Paraskevi Giannakakou

CONTRACTING ORGANIZATION:
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13. SUPPLEMENTARY NOTES

14. ABSTRACT Metastatic castration resistant prostate cancer (CRPC) is currently incurable, due to treatment resistance. Elucidation of resistance mechanisms requires frequent tumor sampling to monitor tumor evolution and tailor treatments to the individual. Circulating tumor cells (CTCs) represent a non-invasive, accessible "liquid biopsy" source of tumor cells, allowing for longitudinal molecular disease profiling. Due to limitations with existing EpCAM-based CTC isolation assays we have identified and clinically tested Transferrin Receptor (TfR) as a novel cell-surface antigen that enables capture of all CTCs across the EMT gradient from metastatic patients. Mining large datasets (TCGA, SU2C) revealed **TfR enrichment in metastatic patients,** which significantly correlated with advanced state from localized PC to CRPC to the aggressive neuroendocrine NEPC. RNA-seq analysis indicates that TfR^+-CTCs possess unique expression profile and are enriched in EMT and tumor progression pathways, as compared to $EpCAM^+$- CTCs. Expression of androgen receptor (AR) splice variants (AR-Vs) is known to drive disease progression. We have developed a highly sensitive—down to single cell—digital droplet PCR assay for the quantitation of AR-Vs in patient CTCs. Isolation of TFR^+ vs $EpCAM^+$ CTCs from metastatic patients, revealed significant AR-V **enrichment in TFR^+ CTCs,** while AR-FL expression was similar. When we analyzed **single CTCs** using the same ddPCR assay, we observed even more striking enrichment, with AR-Vs detected in 21% of single TFR^+-CTCs vs 0% in $EpCAM^+$-CTCs. These data support our **hypothesis** that *TfR can identify a comprehensive pool of CTCs (not limited to the epithelial-only phenotypes) and provide an accurate representation of metastatic disease burden*. To test this, we propose to **prospectively** collect peripheral blood from CRPC and NEPC patients to **1**. Molecularly profile TFR^+-CTCs and $EpCAM^+$-CTCs, and matching tumor biopsies, by RNA-Seq to identify the driving oncogenic pathways that correlate with clinical outcomes **2.** Characterize heterogeneity and clinical impact of AR-V expression, assessed by ddPCR, in single TFR^+- and $EpCAM^+$-CTCs from CRPC patients. In addition, we propose to **3**. Explore the functional relationship between TfR and Myc in patient-derived tumor and animal models.

15. SUBJECT TERMS NONE LISTED

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Introduction

Metastatic castration resistant prostate cancer (CRPC) is currently incurable, due to treatment resistance. Elucidation of resistance mechanisms requires frequent tumor sampling to monitor tumor evolution and tailor treatments to the individual. Circulating tumor cells (CTCs) represent a non-invasive, accessible "liquid biopsy" source of tumor cells, allowing for longitudinal molecular disease profiling. Due to limitations with existing EpCAM-based CTC isolation assays we have identified and clinically tested Transferrin Receptor (TfR) as a novel cell-surface antigen that enables capture of all CTCs across the EMT gradient from metastatic patients. Mining large datasets (TCGA, SU2C) revealed **TfR enrichment in metastatic patients,** which significantly correlated with advanced state from localized PC to CRPC to the aggressive neuroendocrine NEPC, as compared to no changes in EpCAM expression. CTC enumeration shows that TfR^+-CTC counts are significantly higher than $EpCAM^+$-CTCs in patients with mCRPC. RNA-seq analysis indicates that TfR^+-CTCs possess unique expression profile and are enriched in EMT and tumor progression pathways, as compared to $EpCAM^+$-CTCs. Expression of androgen receptor (AR) splice variants (AR-Vs) is known to drive disease progression. We have developed a highly sensitive—down to single cell—digital droplet PCR assay for the quantitation of AR-Vs in patient CTCs. Isolation of TFR^+ vs $EpCAM^+$ CTCs from metastatic patients, revealed significant AR-V **enrichment in TFR^+ CTCs,** while AR-FL expression was similar. Taken together these data led us formulate the following hypothesis:

Hypothesis *TfR can identify a comprehensive pool of CTCs (not limited to the epithelial-only phenotypes) and provide an accurate representation of metastatic disease burden*.

To address this hypothesis, we proposed to **prospectively** collect peripheral blood from CRPC and NEPC patients and

Specific Aim 1. Molecularly profile TFR^+-CTCs and $EpCAM^+$-CTCs, and matching tumor biopsies, by RNA-Seq to identify the driving oncogenic pathways that correlate with clinical outcomes

Specific Aim 2. Characterize heterogeneity and clinical impact of AR-V expression, assessed by ddPCR, in single TFR^+- and $EpCAM^+$-CTCs from CRPC patients.

Specific Aim 3. Explore the functional relationship between TfR and Myc in patient-derived tumor and animal organoids.

2. Keywords: Prostate Cancer, castration resistant prostate cancer (CRPC), neuroendocrine prostate cancer (NEPC), circulating tumor cells (CTCs), Transferrin Receptor (TfR), androgen receptor (AR), AR splice variants (AR-Vs), epithelial cell adhesion molecule (EpCAM)

3. **Accomplishments:**

- **What were the major goals of the project?**

Specific Aim 1. Molecularly profile TFR^+-CTCs and $EpCAM^+$-CTCs, and matching tumor biopsies, by RNA-Seq to identify the driving oncogenic pathways that correlate with clinical outcomes

Specific Aim 2. Characterize heterogeneity and clinical impact of AR-V expression, assessed by ddPCR, in single TFR^+- and $EpCAM^+$-CTCs from CRPC patients.

Specific Aim 3. Explore the functional relationship between TfR and Myc in patient-derived tumor and animal organoids.

- **What was accomplished under these goals?**

Specific Aim 1. Identify clinically meaningful genes/oncogenic pathways associated with disease progression and/or response to therapy by molecular profiling of TfR+ -CTCs and EpCAM+ -CTCs from CRPC patients and NEPC patients using serial sampling at baseline and progression and correlate with clinical outcomes.

The *working hypothesis* of this aim is that TfR+-CTCs will provide a more accurate representation of metastatic disease burden and include a more comprehensive spectrum of CTCs, whose molecular analysis will be clinically informative. In addition, we hypothesize that TfR+-CTCs will contribute to the diagnosis and molecular phenotyping of NEPC.

In this Aim we have been collecting peripheral blood from patients with metastatic CRPC receiving treatment with AR-targeted therapies (abiraterone/enzalutamide) (IRB0707009283, PI Tagawa) and from patients with NEPC (at Dana Farber, IRB19883, PI: Beltran) and enriching for circulating tumor cells (CTCs) by depleting the contaminating CD45$^+$ leukocytes (RosetteSep human CD45 depletion cocktail, STEMCELL™ technologies). CTCs were collected at baseline and at the time of progression to AR-Signaling Inhibitors (ARSI), abiraterone and enzalutamide. After enrichment, TfR$^+$ and EpCAM$^+$ CTCs were isolated utilizing the automated micromanipulator CellCelector (Automated Lab Solution, Germany). Matching leucocytes (peripheral blood mononuclear cells, PBMCs) were also collected to assess crosstalk between CTCs and the circulating tumor macroenvironment. We first showed that TfR mRNA was significantly enriched in metastatic patients compared to the ones with primary localized disease, in contrast to EpcAM distribution which was similar in both cohorts.

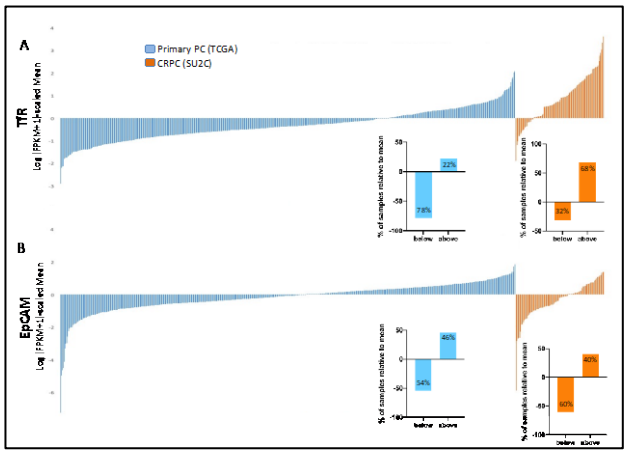

*Figure 1. Prevalence and distribution of TfR and EpCAM expression in large clinical datasets from patients with localized or metastatic prostate cancer (**A**) Expression of TfR (**A**) or EpCAM (**B**) was determined in primary prostate cancer samples (TCGA, blue, n=505) and metastatic CRPC (SU2C, orange, n=98) by mining RNA-seq data. The waterfall plots display the expression of the two transcripts relative to the mean. The mean expression of each transcript (scaled mean) was calculated across the two cohorts of samples and set as 0. The enclosed bar graphs show the percent distribution of each transcript relative to the scaled mean. TfR mRNA expression levels (top panel) increase from 22% above the mean in primary prostate cancer to 68% in mCRPC; on the contrary, EpCAM mRNA expression levels did not vary.*

(**Figure 1**). These data strongly suggested that in patients with metastatic disease where tumor cells undergo epithelial to mesenchymal transition (EMT) EpCAM expression may be downregulated. To test this hypothesis we assessed TfR and EpCAM expression in a preclinical model of prostate cancer cells engineering to undergo EMT upon Snail induction. Upon EMT induction we observed complete loss of EpCAM expression while TfR expression remained unaltered (**Figure 2**). Taken together these data suggest that TfR-based capture could identify a more comprehensive pool of CTCs from metastatic patients, in which EpCAM expression is lost or downregulated.

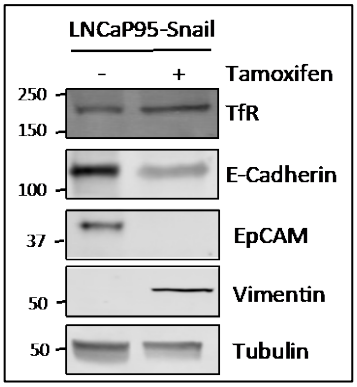

Figure 2. Modulation of TfR expression upon induction of epithelial-to-mesenchymal transition (EMT). Prostate cancer cell line LNCap95 stably expressing tamoxifen-inducible Snail were used to induce partially EMT. LNCaP95 were treated with tamoxifen or ethanol (vehicle) for 14 days. Cells were then harvested, and protein was collected for quantification of TfR, epithelial (E-cadherin, EpCAM (epithelial markers) and vimentin (mesenchymal markers) by western blot

Next, we sought to compare head-to-head TfR-*vs* EpCAM-based CTC enumeration in a cohort of patients with mCRPC (n=32) using the same blood draw. CTCs were enriched via negative depletion of CD45$^+$-cells and labeled live with antibodies against the cell surface proteins, TfR, EpCAM and CD45. CTCs were enumerated based on their respective immunophenotypes as TfR$^+$/EpCAM$^-$/CD45$^-$ (hereafter TfR$^+$), EpCAM$^+$/TfR$^-$/CD45$^-$ (hereafter EpCAM$^+$) and TfR$^+$/EpCAM$^+$/CD45$^-$ (double positive). Our analysis showed that TfR$^+$-CTCs (mean= 593 CTCs; median= 370 CTCs, range= 0-3299) were significantly more abundant than EpCAM$^+$-CTCs (mean= 36

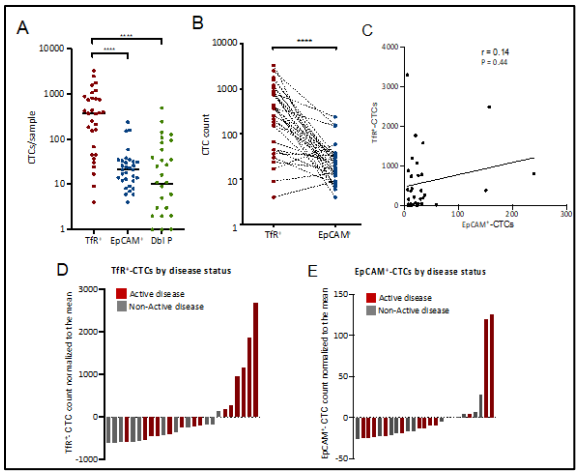

*Figure 3. Enumeration of different TfR$^+$-versus EpCAM$^+$-CTC subpopulations isolated in patients with mCRPC. CTCs were identified based on size and shape (bright field) and assigned into three immunophenotypic categories as TfR$^+$/EpCAM$^-$ (hereafter TfR$^+$), EpCAM$^+$/TfR$^-$ (hereafter EpCAM$^+$) and TfR$^+$/EpCAM$^+$ (Double positive). CTCs were enumerated using the automated microscopy-based single cell selection platform CellCelector (**A, B**) Dot plots show the CTC counts per patient for each subpopulation, and paired TfR$^+$- CTCs and EpcAM$^+$-CTC counts for each patient; Mann Whitney and Wilcoxon statistical tests were used.****=p<0.0001. (**C**) Linear correlation between TfR$^+$-CTCs and EpCAM$^+$-CTCs in patients with mCRPC. (**D, E**) Waterfall plots show the distribution of TfR$^+$- and EpCAM$^+$-CTC counts from 25 patients with mCRPC for whom disease status at the time of blood draw was available. Disease status at the time of blood draw is color coded as red (active disease) or grey (inactive).*

CTCs; median= 21 CTCs, range= 5-240; p <0.0001) (**Figure 3A).** Double positive TfR$^+$/EpCAM$^+$ CTCs were also detected in several samples, but they were the least abundant of the three CTC subpopulations (mean= 49 CTCs, median= 10 CTCs, range: 0-491). Direct comparison of matching TfR$^+$ *vs* EpCAM$^+$-CTCs in each individual patient, revealed that TfR$^+$-CTCs were the predominant CTC subpopulation with TfR$^+$-CTCs counts being up to 550-fold (mean 43-fold) higher than EpCAM$^+$-CTCs (**Figure 3B).** In addition, there was no correlation between TfR$^+$ and EpCAM$^+$ CTC counts, and both appeared to be independent of disease burden (**Figure 3C**). Notably, patients with active disease at the time of blood draw had the highest TfR$^+$-CTC counts, a pattern that was not observed with EpCAM$^+$-CTC counts (**Figure 3D and E**). These data suggest that TfR$^+$-CTCs positively correlate with disease progression.

CTCs were molecularly profiled by RNA-Sequencing. RNA-Seq raw reads were trimmed and aligned to the human reference genome (hg38). Transcriptomic analysis of the enriched CTCs was performed before treatment initiation (baseline) to identify clinically meaningful genes/molecular pathways associated with intrinsic response/resistance to treatment. Analysis of CTCs at disease progression will be informative of genes/pathways associated with acquired resistance. As we reported in the Year 2 technical report of this grant, GSEA analysis at baseline showed enrichment of oncogenic pathways previously associated with resistance to ARSI treatment in prostate cancer, such as RB-loss and E2F activation (E2F targets). **Interestingly, the gene encoding for TfR (TFRC) was found among the leading-edge genes of the E2F targets pathway** (data not shown), supporting an association between the expression of TfR, the activation of the RB-E2F axis and intrinsic resistance to ARSI treatment in prostate cancer. Mechanistic studies to explore this relationship are currently undergoing in the lab.

In addition, GSEA analysis of CTCs isolated at ARSI progression showed the significant enrichment of several pathways associated with the inflammatory process and the immune response, as compared to baseline CTCs (**Figure 1B**). Previous results have also shown significant enrichment of TFRC-related pathways enriched at progression (**Figure 4**).

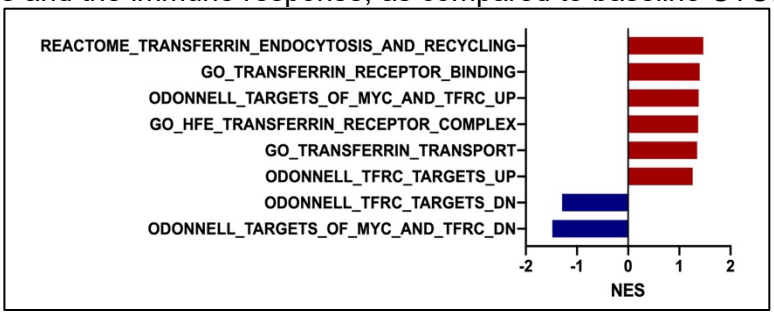

Figure 4 GSEA of CTCs isolated at ARSI progression as compared to baseline. Red bars indicate TFRC-related pathways significantly enriched at progression; blue bar indicate TFRC-related pathways significantly enriched at baseline. NES: normalized enrichment score.

Transcriptomic analysis of the matched TfR$^+$ CTCs isolated at baseline and at progression is currently ongoing and will be informative to understand the association between TFRC-related pathways and the pathways associated with resistance to ARSI treatment. Analysis of matching PBMCs will inform on potential crosstalk between TfR$^+$ CTCs and the circulating macroenvironment.

Specific Aim 2. Characterize heterogeneity and clinical impact of AR-V expression, assessed by ddPCR, in single TFR$^+$- and EpCAM$^+$-CTCs from CRPC patients.

In this Aim, we examined AR variant expression in TfR$^+$- versus EpCAM$^+$-CTCs. To that end, we isolated single CTCs (sCTCs) based on their respective immunophenotypes, as TfR$^+$/EpCAM-/CD45$^-$ (TfR+) or EpCAM$^+$/TfR-/CD45$^-$ (EpCAM+) and subjected them to ddPCR to quantify AR, AR-V7 and ARv567 mRNA expression, as we recently described. We analyzed a total of 165 single CTCs (TfR+, n=102 or EpCAM$^+$, n=63) isolated from 3 different patients with mCRPC. Surprisingly, the EpCAM$^+$-CTCs did not express AR-V7 (0/21 sCTCs) or ARv567 (0/21 sCTCs) while TfR$^+$-CTCs expressed both variants with AR-V7 detected in 7/34 sCTCs (21%) and AR-v567es in 6/34 sCTCs (18%). As expected, AR-fl was detected in both CTC subpopulations at the same rate (24%) (**Figure 5**).

AR-V ddPCR in single CTCs (sCTCs)		
AR-V	TfR$^+$ (n=34)	EpCAM$^+$ (n=21)
AR-FL	24% (8/34)	24% (5/21)
AR-V7	21% (7/34)	0% (0/21)
AR-v567	18% (6/34)	0% (0/21)

Figure 5 *Single TfR$^+$-CTCs (n=102) or EpCAM$^+$-CTCs (n=63) were isolated from 3 patients with mCRPC using the microscopy-based CellCelector micromanipulator and processed by ddPCR for expression of AR-FL, AR-V7 or AR-v567 transcripts (one cell/transcript) as previously described (Gjyrezi A et al. Commun Biol 2021). Equal groups of single TfR$^+$-CTCs (n=34) or single EPCAM$^+$-CTCs (n=21) were analyzed by ddPCR for each of the three transcripts.*

Taken together these results demonstrate that, compared to EpCAM, TfR^+-CTCs represent the predominant CTC subpopulation, and that high TfR^+-CTCs correlate with active disease status. Importantly, TfR^+-CTCs are enriched in AR-V7 expression, which is a clinically actionable biomarker.

These results are now published in:

- Gjyrezi, A, Galletti, G, Zhang, J, Worroll D, Sigouros M, Kim S, Cooley V, Ballman KV, Ocean AJ, Shah MA, Scandura JM, Sboner A, Nanus DM, Beltran H, Tagawa ST, Giannakakou P. **Androgen receptor variant shows heterogeneous expression in prostate cancer according to differentiation stage**. *Commun Biol* 4, 785 (2021). https://doi.org/10.1038/s42003-021-02321-9

Specific Aim 3. Explore the functional relationship between TfR and Myc in patient-derived tumor and animal organoids.

In the preliminary data presented earlier, we identified enrichment for RB-loss pathway in CTCs from patients with mCRPC who did not respond to ARSI treatment and who also displayed enrichment in TFRC-pathways. In addition, at disease progression we found enrichment (upregulation) of TFRC-related pathways. To start exploring the functional relationship between TfR and Myc we took advantage of already established GEMs with MYCN overexpression in combination with loss of Rb1, to recapitulate the gene expression clinical associations between RB-loss, treatment resistance and disease progression, presented in Aim 1. Using organoids isolated from these animal models we are currently performing mechanistic studies to determine the role of N-Myc binding at the TFRC promoter and the mechanism by which N-Myc activity leads to upregulation of TFRC and its role in NEPC development.

- **What opportunities for training and professional development has the project provided?**

Drs Giannakakou, Beltran, Tagawa and Rickman are fully committed to furthering the training and professional development of the postdoctoral fellows and students affiliated to this project. Due to the unexpected COVID-19 crisis we had limited opportunities to present our preliminary data. Parts of the data were presented at the scientific conferences and internal research progress meetings mentioned in the following section.

- **How were the results disseminated to communities of interest?**

Prostate Cancer Foundation, Carlsbad, CA (Annual Scientific Retreat, October 2022)

Annual Scientific Retreat

Belfer Basic Research Working Group, New York, NY (May 2021)

Internal research in progress meeting in the Meyer Cancer Center at Weill Cornell Medicine.

- **What do you plan to do during the next reporting period to accomplish the goals?**

In the next reporting period, we plan to continue our investigations in all 3 Aims. In **Specific Aims 1** and **2** we will expand the molecular profiling of CTCs in additional patients with mCRPC and NEPC, as outlined in the original application. We will isolate pools of TfR+ and EpcAM+ CTCs and perform differential gene expression and pathway analyses to identify genes/pathways that are significantly associated with clinical outcomes. Along these lines we will perform single CTC analyses to determine the heterogeneity and clinical impact of AR-V expression using our established AR-V ddPCR assay. We have also published a manuscript as part of **Specific Aim 2** (see section 6. Products). In **Specific Aim 3** we will determine if C-Myc and N-Myc are bone fide regulators of TFRC expression and will also determine the impact of TFRC depletion on the landscape of N-Myc binding, N-Myc target genes and associated epigenomic alterations during the transformation from CRPC to NEPC phenotype.

4. Impact

- **What was the impact on the development of the principal discipline(s) of the project?**

  Nothing to Report

- **What was the impact on other disciplines?**

  Nothing to Report

- **What was the impact on technology transfer?**

  Nothing to Report

- **What was the impact on society beyond science and technology?**

  Nothing to Report

5. Changes/Problems

Nothing to Report

6. Products

Publications, conference papers, and presentations

Gjyrezi, A, Galletti, G, Zhang, J, Worroll D, Sigouros M, Kim S, Cooley V, Ballman KV, Ocean AJ, Shah MA, Scandura JM, Sboner A, Nanus DM, Beltran H, Tagawa ST, Giannakakou P. **Androgen receptor variant shows heterogeneous expression in prostate cancer according to differentiation stage**. *Commun Biol* 4, 785 (2021). https://doi.org/10.1038/s42003-021-02321-9 (published). Acknowledgement of federal support: yes.

Zhang J, Zimmermann B, Galletti G, Halabi S, Gjyrezi A, Yang Q, Gupta S, Verma A, Sboner A, Anand M, George D, Gregory S, Hong S, Pascual V, Mavragani C, Antonarakis ES, Nanus DM, Tagawa ST, Elemento O,. Armstrong AJ, Giannakakou P. **Transcriptomic profiling of tumor and immune-macroenvironment cells from liquid biopsies identifies the molecular determinants of clinical resistance to Androgen Receptor Signaling Inhibitors in Prostate Cancer** (submitted). Acknowledgement of federal support: yes.

Website(s) or other Internet site(s)
Nothing to report

Technologies or techniques
Nothing to report

Inventions, patent applications, and/or licenses
Nothing to report

Other Products
Nothing to report

7. Participants & Other Collaborating Organizations

- **What individuals have worked on the project?**

Name:	Paraskevi Giannakakou
Project Role:	PI
Contribution to Project:	No Change
Name:	Ada Gjyrezi
Project Role:	Lab Manager
Nearest person month worked:	5
Contribution to Project:	Ada was involved in CTC processing and the molecular analysis of the isolated CTCs. In addition, she was responsible of the quantification of AR-variants in the TfR^+ and $EpCAM^+$ CTCs for Aim 2.
Name:	Jiaren Zhang
Project Role:	Research Associate
Nearest person month worked:	6
Contribution to Project:	Jiaren performed the computational analyses that revealed the transcriptomic profiles of the isolated CTCs
Name:	Lucie Van Emmenis
Contribution to Project:	No Change
Name:	Robert Zimmerman
Contribution to Project:	No Change

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?** Nothing to Report

- **What other organizations were involved as partners?**

    - **Organization Name:** Dana Farber Cancer Institute

        - **Location of Organization:** Boston, MA

        - **Partner's contribution to the projec**t

            - Subaward

Other Support – Project/Proposal

*Title: Molecular and Translational Oncology Research

*Major Goals: The Molecular and Translational Oncology Research (MTOR) Training Program will provide postdoctoral fellows with rigorous, multidisciplinary, state-of-the-art training in translational oncology. The ultimate goal of MTOR is to equip excellent young researchers with the knowledge and skills required to accelerate the translation of basic science discoveries into true clinical gains and help realize Precision Medicine in the USA.

*Status of Support: Active

Project Number: T32 CA203702

Name of PD/PI: Giannakakou / Blenis

*Source of Support: NIH/NCI

*Primary Place of Performance: Weill Cornell Medicine, New York, NY

Project/Proposal Start and End Date: (MM/YYYY) (if available): 07/01/17 – 06/30/22 **NCE**

*Total Award Amount (including Indirect Costs):

*Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
5. 2022	1.20 calendar

*Title: Transferrin Receptor Identifies a Comprehensive Pool of Circulating Tumor Cells with Unique Molecular Features from Metastatic Prostate Cancer Patients

*Major Goals: The goal of this project is to use a precision medicine approach to interrogate the molecular characteristic of the TfR+ CTCs to identify novel mechanisms implicated in resistance to treatment, and uncover new genes/ pathways to target in the challenging to treat NEPC.

*Status of Support: Active

Project Number: W81XWH-19-1-0666

Name of PD/PI: Giannakakou

*Source of Support: U.S. Department of Defense

*Primary Place of Performance: Weill Cornell Medicine, New York, NY

Project/Proposal Start and End Date: (MM/YYYY) (if available): 08/15/19 – 08/14/22

*Total Award Amount (including Indirect Costs):

*Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
4. 2022	1.20 calendar

*Title: A novel, short isoform of the +TIP microtubule (MT) binding protein CLIP170 confers taxane resistance by obstructing the MT pore

*Major Goals: The goal of this project is to elucidate clinically meaningful mechanisms underlying taxane resistance in order to develop novel therapeutic strategies and identify patients that will most benefit from taxane chemotherapy.

*Status of Support: Active

Project Number: R01 CA228512

Name of PD/PI: Giannakakou

*Source of Support: NIH/NCI

*Primary Place of Performance: Weill Cornell Medicine, New York, NY

Project/Proposal Start and End Date: (MM/YYYY) (if available): 04/19/18-3/31/23

*Total Award Amount (including Indirect Costs):

*Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
6. 2023	1.92 calendar

*Title: Developmental Research Program (DRP)

*Major Goals: The goal of this project is to take a novel precision medicine approach to PCA patient care, by aligning translational research goals with the care of men across the PCA spectrum. The Developmental Research Program (DRP) will act as an incubator for high-risk/high-gain and novel collaborative projects within the Weill Cornell Medicine (WCM) SPORE in Prostate Cancer.

*Status of Support: Active

Project Number: P50 CA211024

Name of PD/PI: Loda

*Source of Support: NIH/NCI

*Primary Place of Performance: Weill Cornell Medicine, New York, NY

Project/Proposal Start and End Date: (MM/YYYY) (if available): 08/30/17-07/31/22 **NCE**

*Total Award Amount (including Indirect Costs):

*Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
5. 2022	0.30 calendar

*Title: Targeting the novel MT +TIP variant CLIP-170S to reverse taxane resistance in Gastric Cancer

*Major Goals: In Aim 1 we propose to identify proteins which will likely lead to the discovery of novel druggable targets to reverse taxane resistance. In Aim 2 we will elucidate the mechanism underlying Imatinib/Cediranib synergistic interaction with DTX in vitro and in vivo against CLIP-170S-expressing GC xenograft and PDX models

*Status of Support: Active

Project Number: n/a

Name of PD/PI: Giannakakou

*Source of Support: DeGregorio Family Foundation

*Primary Place of Performance: Weill Cornell Medicine, New York, NY

Project/Proposal Start and End Date: (MM/YYYY) (if available): 09/15/21 – 09/14/23

*Total Award Amount (including Indirect Costs):

*Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
3. 2023	0.60 calendar

*Title: Enhancing the Efficacy of Docetaxel in Prostate Cancer

*Major Goals: Identify the impact ofFOXJ1-TPPP3 axis on the microtubule cytoskeleton and taxane resistance using in vitro and in vivo models.

*Status of Support: Pending

Project Number: R01 CA249395

Name of PD/PI: Bhatt

*Source of Support: NIH

*Primary Place of Performance: Beth Israel Deaconess Medical Center, Inc.

Project/Proposal Start and End Date: (MM/YYYY) (if available): 07/01/22 – 06/30/27

*Total Award Amount (including Indirect Costs):

*Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
2. 2023	1.20 calendar
3. 2024	1.20 calendar
4. 2025	1.20 calendar
5. 2026	1.20 calendar
6. 2027	1.20 calendar