

# University of the Sciences in Philadelphia

## Annual Progress Report: 2011 Formula Grant

### Reporting Period

July 1, 2013 – June 30, 2014

### Formula Grant Overview

The University of the Sciences in Philadelphia received \$32,583 in formula funds for the grant award period January 1, 2012 through December 31, 2015. Accomplishments for the reporting period are described below.

### Research Project 1: Project Title and Purpose

*Integrated Behavioral Treatment for Co-Morbid Obesity and Chronic Pain* – Evidence suggests individuals with co-morbid chronic pain and obesity experience reduced treatment success in traditional programs designed to address either pain or obesity in isolation. Little is known about how to successfully treat individuals with co-morbid pain and obesity, and to date no programs are available to simultaneously treat pain and obesity. To address this deficiency, the proposed program will compare traditional self-management approaches to treat chronic pain and obesity with an integrated program designed to simultaneously treat pain and obesity. The primary hypothesis is that individuals enrolled in an integrated program will experience increased treatment success compared to those enrolled in a traditional program.

### Anticipated Duration of Project

1/1/2012 – 12/31/2015

### Project Overview

The *primary objective* of the project is to determine whether obese individuals with chronic pain who are randomized to receive an evidence-based, integrated cognitive-behavioral program simultaneously promoting self-management of chronic pain and obesity will lose more weight and experience greater reduction in pain intensity immediately post-treatment and show greater maintenance of weight loss and pain reduction 3 months post-treatment than those randomized to receive a standard care treatment approach that addresses pain or obesity in isolation. *Secondary objectives* are to determine whether obese individuals with chronic pain who are randomized to receive the integrated treatment will show significantly improved quality of life and greater treatment adherence as compared to those randomized to standard care treatments.

This project is a three-group prospective randomized clinical trial comparing the effects of an integrated cognitive-behavioral intervention that simultaneously addresses both chronic pain and obesity as compared to standard care interventions designed to treat obesity and chronic pain in

isolation. The design involves three intervention conditions (combined treatment for chronic pain and obesity, standard treatment for obesity, standard treatment for chronic pain) and three repeated assessment intervals (pre-treatment, post-treatment, 3 month follow-up). The intervention involves five in-person sessions delivered on a biweekly basis with a trained interventionist combined with five telephone sessions delivered between in-person sessions by the same trained interventionists. Primary dependent measures will be percent weight lost, pain intensity, and pain disability. Secondary dependent measures will be health related quality of life and treatment adherence. Additional measures will be designed to assess pain beliefs, self-efficacy, and stages of change as potential mediators of the relationship between treatment condition and behavioral outcome. Finally, measures of treatment fidelity and treatment credibility will be used to assess treatment feasibility.

### **Principal Investigator**

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### **Other Participating Researchers**

Florda Priftanji, Megan Fritz, Brittany Haltzman, Christina Hopkins, Elizabeth Jones, Patricia Turo, Alesha Huskra, Shaun Nisani, Kaitlyn Schmidt, Nathaniel Arrington – students employed by the University of the Sciences

### **Expected Research Outcomes and Benefits**

This novel examination of an integrated treatment approach stands to make a significant impact on the health and quality of life of those suffering with pain and obesity. First, it emphasizes collaboration and promotes community involvement by providing a much needed clinical service (pain/obesity treatment) to the local community. The intervention to be tested will target a common co-morbidity that is often resilient to treatment—both chronic pain and obesity are two prevalent and significant clinical conditions, yet little empirical literature is available to inform successful treatment when they co-occur. Insights gained from this study will add to the evidence base in this area and inform research designs, grant applications, and clinical implementation of best practices to treat co-occurring pain and obesity. Dissemination will occur at the local level (through discussion of findings with clinical providers and local research presentations) as well as the national/international level (through publication and presentation of study findings). Second, the project will increase research and training capacity at University of the Sciences by increasing opportunities for on-campus student research involvement and clinical training for graduate students who will be involved in intervention delivery and undergraduates who will be involved in other project activities. Thus, the grant will aid in training the ‘next generation’ of clinicians and scientists. Finally, as both pain and obesity are conditions that occur in minority populations at higher rates (and, specifically at higher rates in the state of Pennsylvania) and

recruitment will occur in clinics serving mostly minority populations, the proposal will contribute to research that directly addresses disparities in health status among Commonwealth populations.

### **Summary of Research Completed**

The study procedures are approved by the Institutional Review Board at the University of the Sciences, and the procedures have undergone oversight and annual continuing review. In keeping with the goals of increasing transparency in clinical trials, we have registered our trial with ClinicalTrials.gov (NCT02100995).

Participants are recruited from the local community directly by advertisement, by health provider referral, and by viewing our study/lab information on an online resource (such as clinicaltrials.gov or our lab website). A brief telephone assessment screens candidates for study entry and eligible individuals are scheduled for a baseline session that includes additional in-person assessment. At the conclusion of baseline, the participant is scheduled for their first treatment session during the upcoming 7 days. Randomization occurs immediately prior to the first scheduled treatment session. Participants are randomly assigned to one of three groups: behavioral weight loss (Standard Weight), behavioral chronic pain management (Standard Pain), or integrated treatment for weight loss and chronic pain (Integrated Treatment).

Each intervention consists of 11 sessions delivered during one-hour individual meetings with a study therapist. Interventionists are the PI and/or graduate-level masters students in the Health Psychology program at University of the Sciences who have specific training in the topics listed and how to achieve healthful behavior change. To assure treatment fidelity, treatment manuals have been designed describing each treatment. Furthermore, each session is recorded and monitored for fidelity to the manualized treatment and weekly meetings take place to supervise and discuss treatment fidelity.

Participants in the Standard Weight Loss and Integrated Treatments are assigned daily calorie goals at their first treatment session. Caloric targets are established using the Harris-Benedict equation to calculate an individual's basal metabolic rate and daily calorie requirements assuming a sedentary activity level, subtracting 500 calories from this calculated figure. If, after meeting their calorie goals daily for two consecutive weeks, participants do not lose weight, they are instructed to reduce their caloric intake in 200 kcal increments until they reach a calorie intake that yields a weight loss rate of approximately .5 to 1% of their current weight each week. No patient will be given an intake goal below 1200 kcal per day. Conversely, if weight loss occurs at > 3 pounds/week for 3 consecutive weeks, the calorie intake goal will be increased in 100 kcal increments until weekly weight loss goals are achieved for two consecutive weeks.

Participants are randomized to one of three treatments (see Table 1 for intervention details). The weight loss intervention includes content focused around nutrition and eating habits, stimulus control and behavioral change, and physical activity. The chronic pain intervention is focused around reconceptualization of pain, decreasing catastrophizing, and increasing self-efficacy for pain. The Integrated Treatment includes content designed to simultaneously and explicitly target both chronic pain and obesity. Participants complete assessments at the end of treatment, 3

months after treatment (6 month follow-up), and we have added an additional 12-month follow-up assessment point at which time we repeat the end of treatment assessment battery to assess long term treatment outcomes.

Accomplishments during the past year have focused around achieving tasks necessary to maintain subject recruitment and enrollment. As this is an ongoing randomized clinical trial, preliminary outcomes are not available. Proposed milestones for the past year included:

Maintain study databases and tracking mechanisms, commence data entry and checking: Ongoing. Current study staff has been trained on use of study databases and tracking mechanisms. Data entry and data checking has begun and will continue.

Conduct community outreach to ensure adequate patient referral: Ongoing. Local providers who treat individuals with chronic pain and obesity have been contacted about referring eligible participants for treatment. Providers include those from the Hospital of the University of Pennsylvania, Philadelphia Veterans Affairs Hospital, and Mercy Health Hospital in Lansdowne. Outreach has also been made to community providers of mental health services, such as The Consortium, Inc. Study staff has utilized multiple media sources to educate the community about study goals and treatment offered including social media (e.g., Twitter, Facebook) and local community resource blogs and newspapers. Study staff has established an ongoing relationship with members of the West Philadelphia YMCA whereby we offer periodic education about chronic pain and obesity to the local community. We also have established and offered care to patients not eligible for this study through our community outreach clinic.

Recruit 15+ participants and administer experimental therapy, focusing on providing service to minority populations: Ongoing. Since opening the study for subject recruitment in November 2012, 73 individuals have inquired about participating. Of these, 31 were screened for participation and a total of 21 eligible and interested individuals have been randomized to treatment. See Figure 1 for diagram tracking participant progress to date. Of note, our clinic draws heavily from the surrounding urban area. Accordingly, our patient population is one that is meeting the needs of a local underserved minority population (with current study enrollment > 80%), in accordance with our planned goals.

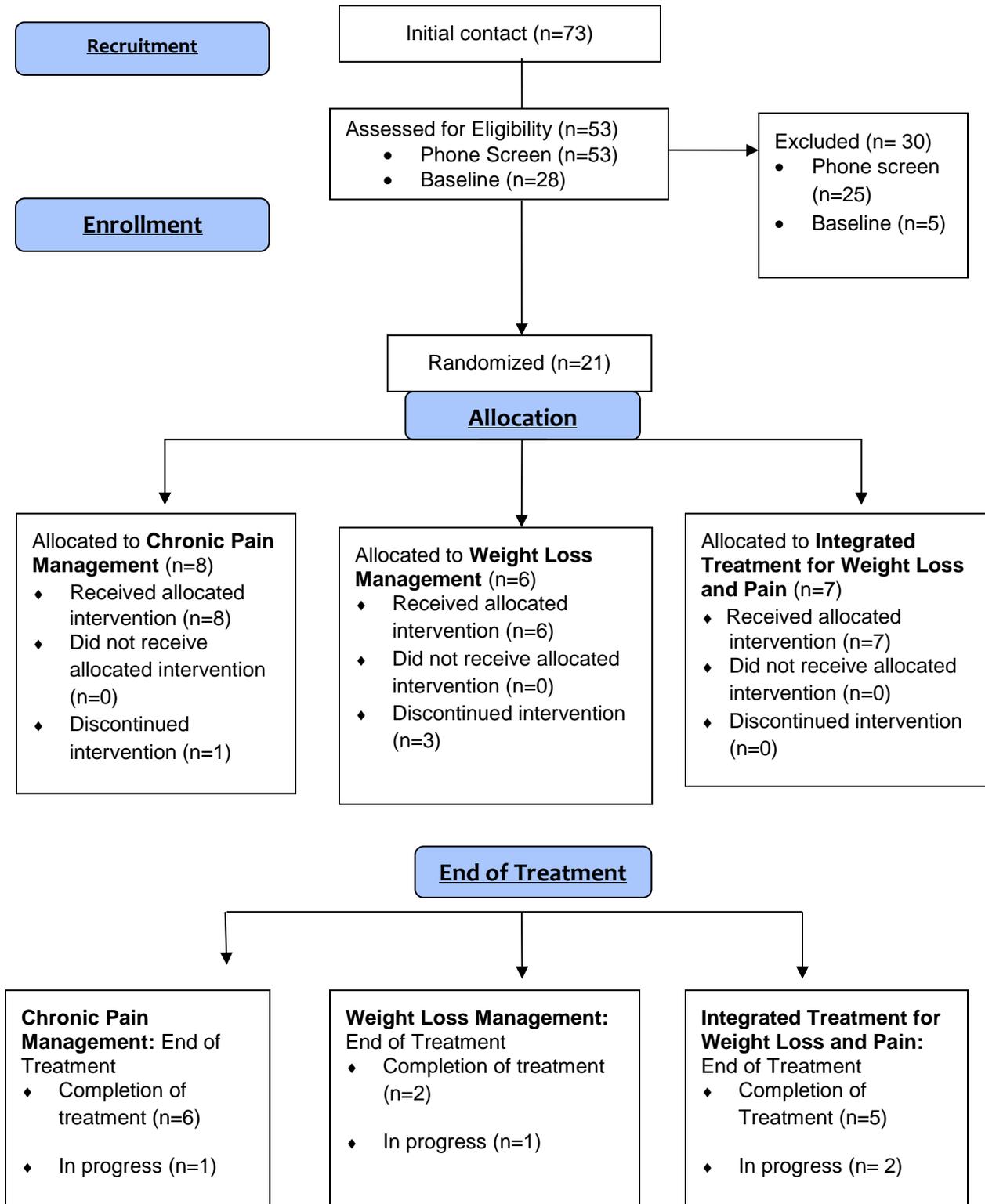
Students trained: Ongoing. During the past year, both undergraduate and graduate students served as research coordinators. A total of 10 students worked on the project including 5 undergraduates who provided research support, 4 graduate students who served as study therapists under the PI's supervision, and another graduate student who served as data manager. Students assist in all aspects of project management, and the project has served as an important forum for training.

Manuscripts prepared, submitted, and published: Completed for study protocol paper. During the past year, we prepared, submitted, and in June 2014 published the study protocol paper in *BMC Public Health* (doi:10.1186/1471-2458-14-621).

Table 1. Intervention Content by Treatment Arm

	Standard Care Weight Loss (SCW)	Standard Care Pain Management (SCP)	Integrated Treatment
	Baseline Goals Setting		
1	Psychoeducation about Weight; Introduction to Calorie Restriction and Self-Monitoring	Psychoeducation about Pain and Theories about Pain	Psychoeducation about Pain and Weight, Self-monitoring
2	Review of Calorie Counting, Nutrition Information, and Self-Monitoring	Pleasant Activity Scheduling	Review of Calorie Counting, Nutrition Information, and Self-monitoring
3	Stimulus Control and Dietary Behaviors	Understanding Automatic Thoughts and Health, Identifying Automatic Thoughts	Activities Reframed: Pleasant Activities and Physical Activity
4	Guiding Thoughts, Motivation, and Problem Solving	Evaluating and Challenging Automatic Thoughts	Time-based Activity Pacing
5	Physical Activity	Cognitive Restructuring: Identifying 'Shoulds' and Core Beliefs	Stimulus Control, Dietary Behaviors
6	Reviewing Weight and Primary Goals	Cognitive Restructuring: Identifying and Challenging Core Beliefs	Thoughts and Health: Identifying Automatic Thoughts and Cognitive Errors
7	Identifying and Modifying Automatic Thoughts	Relaxation Techniques	Evaluating and Challenging Automatic Thoughts
8	Evaluating and Challenging Automatic Thoughts	Time-based Activity Pacing	Cognitive Restructuring: Identifying and Challenging "Should" Beliefs
9	Targeting Thoughts, Feelings, and Behaviors that Influence Diet and Activity	Stress Management and Coping Self-Statements	Cognitive Restructuring: Identifying and Challenging Core Beliefs
10	Relaxation Techniques	Assertiveness, Anger Management, Communication	Relaxation Techniques
11	Review and Planning for Weight Maintenance	Review, Relapse Prevention, Flare Up Planning	Review, Weight Maintenance, Relapse Prevention, Flare Up Planning

Figure 1. Consort Diagram of Participant Status



## **Research Project 2: Project Title and Purpose**

*Experimental and Computational Analysis of GPCR Phosphoregulation* – This project will use a combination of experimental and computational biochemical studies to investigate the invasive function and structural dynamics of phosphorylated CXCR4, a chemokine G protein-coupled receptor (GPCR) known to play a critical role in cancer metastasis and HIV-1 infection. The molecular understanding of CXCR4 phosphorylation-dependent functions and conformational changes will aid in the rational design of novel therapeutics that target CXCR4 for anti-cancer and anti-HIV properties.

### **Anticipated Duration of Project**

7/1/2012 – 12/31/2014

### **Project Overview**

*Objective:* To investigate the invasive function (Aim 1) and structural dynamics (Aim 2) of phosphorylated CXCR4, a GPCR known to play a critical role in cancer metastasis and HIV-1 infection. The molecular understanding of CXCR4 phosphorylation-dependent functions will aid in the rational design of novel therapeutics that target CXCR4 for anti-cancer and anti-HIV properties. We hypothesize that the invasive function of CXCR4 in cancer cells is modulated by receptor phosphorylation. We further hypothesize that receptor phosphorylation leads to a conformational change in the C-tail, which influences the binding to select signaling scaffolds required for invasion.

*AIM 1:* Experimentally determine the effects of receptor phosphorylation on CXCR4-mediated invasive capacity of metastatic breast cancer cells.

*Research Design and Method:* We will generate a CXCR4 phosphorylation-specific antibody and a corresponding point mutant of CXCR4. We will characterize the phosphosignature of the CXCR4 mutant and the utility of the new antibody by a mobility shift assay that we developed. We will generate preliminary data on the effects of mutation on CXCR4 binding to Arf6 signaling complexes which we have shown to play a critical role in cancer cell invasion. We will determine the effects of phosphorylation-directed antibody on the invasive capacity of metastatic breast cancer cells.

*AIM 2:* Computationally determine the effects of receptor phosphorylation on dynamic CXCR4 structure using molecular dynamics (MD) simulations.

*Research Design and Method:* We will generate MD simulations of native and phosphorylated CXCR4 and characterize the structure by RMSD, SASA, and helical motion metrics. Specifically, we will determine the motion of transmembrane helices (twisting, pistoning, flexing, translation) and the structure of the C-tail and critical residues (registration and orientation relative to the bilayer interface, distance between atoms,  $\phi/\psi$  torsion angles, and solvent accessible surface areas).

## **Principal Investigator**

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## **Other Participating Researchers**

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## **Expected Research Outcomes and Benefits**

Metastasis is the leading cause of death in cancer patients. This research will provide mechanistic insight into the acquisition of a metastatic phenotype, and will advance the establishment of CXCR4 as a novel therapeutic target in aggressive metastatic breast cancers. Aberrant CXCR4 expression was initially identified in breast carcinoma, and now has been observed in 23 different cancers including prostate carcinoma and melanoma, greatly broadening the implications on improving health status among cancer patients.

## **Summary of Research Completed**

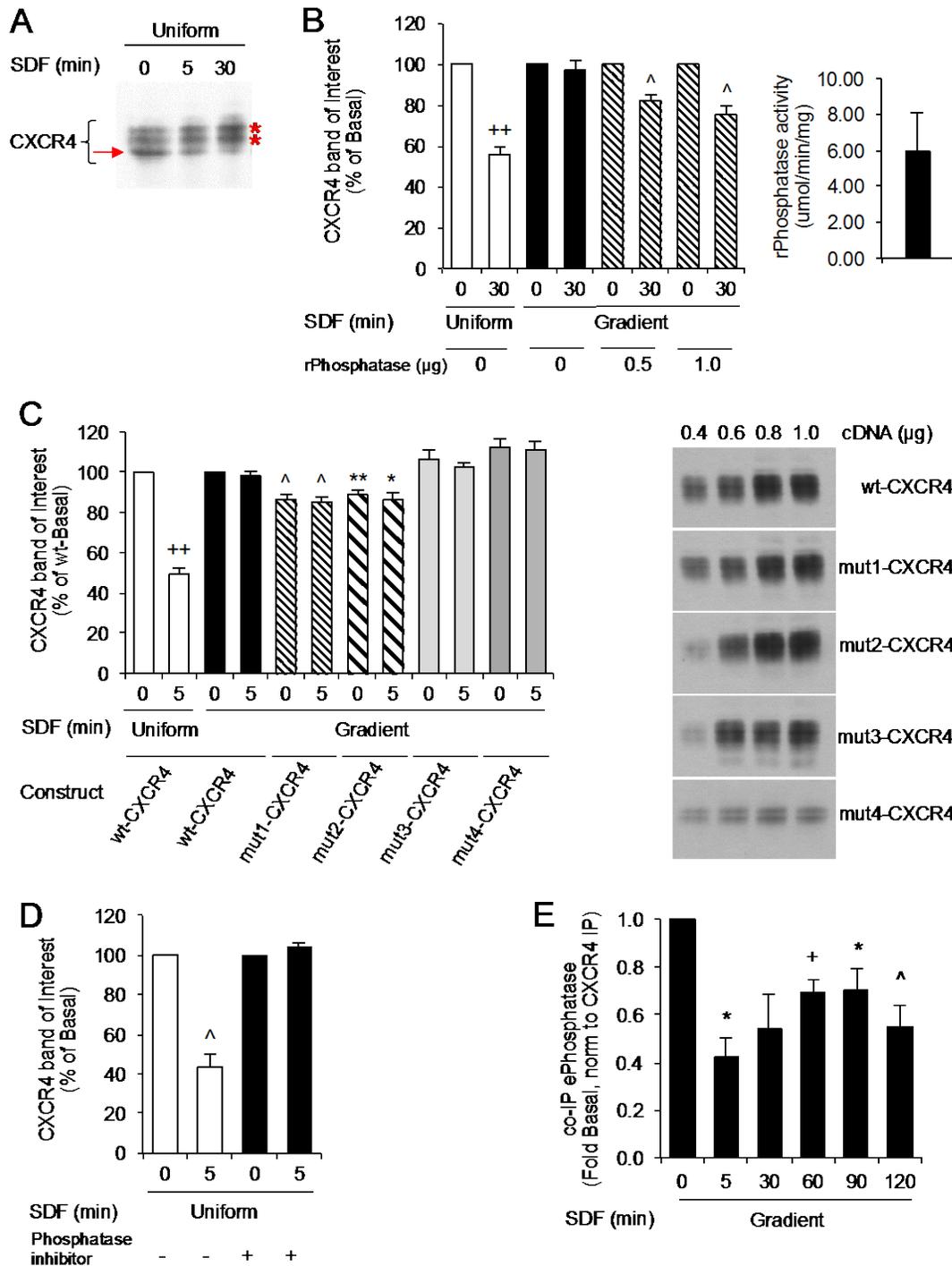
During this reporting period, we focused on experimental studies using the methodology established in the prior reporting period to investigate phosphorylated CXCR4, a chemokine G protein-coupled receptor (GPCR) known to play a critical role in cancer metastasis and HIV-1 infection. Most GPCRs undergo phosphorylation-dependent desensitization, but an emerging theme is phosphorylation-dependent signaling and function, which we hypothesize contributes to the invasive capacity imparted by aberrant CXCR4 expression in cancer cells. The molecular understanding of CXCR4 phosphorylation-dependent function and structure will aid in the rational design of novel therapeutics that target CXCR4 for anti-cancer and anti-HIV properties.

AIM 1: Experimentally determine the effects of receptor phosphorylation on CXCR4-mediated invasive capacity of metastatic breast cancer cells.

Milestones accomplished: We extended the use of a mobility shift assay (developed last reporting period) to assess the phosphosignature of CXCR4 after activation of the receptor with gradient SDF (condition that induces invasion). We identified that in contrast to the robust mobility shift that occurs following uniform SDF, CXCR4 mobility shift is inhibited upon gradient SDF conditions. A lower band of interest is maintained, similar to the phosphosignature we observed following Arf6 activation (protein that drives invasion). Interestingly, this band of interest is sensitive to select recombinant phosphatase treatment as well as select mutations of potential phospho-acceptor sites, suggesting that it contains previously unidentified CXCR4 phospho-species. Antibodies against these novel phospho-sites 1 and 2 are being developed.

Notably, the identified sites are also being assessed via computational molecular dynamic (MD) simulations.

Research Summary: Previously we identified Arf6 as a novel regulator of the SDF-CXCR4 axis, whereby it is required for CXCR4-mediated invasion of metastatic breast cancer cells. Last reporting period, we confirmed the use of a nonradioactive phosphorylation assay to assess the global phosphosignature of CXCR4, and identified that Arf6 (protein that drives invasion) modulates CXCR4 phosphorylation. Here, we identified potential phospho-sites regulated by Arf6 and are developing phospho-directed antibodies accordingly. Specifically, we assessed CXCR4 phosphosignatures after gradient SDF stimulation (condition that induces invasion), select recombinant phosphatase treatment, or mutation of CXCR4 at potential phospho-sites. CXCR4 mobility on SDS-PAGE gels was compared to those observed after uniform SDF-dependent mobility shift, from a predominant lower band [arrow], to two shifted upper bands (Fig. A). We observed that in contrast to uniform SDF (white bars), gradient SDF led to maintenance of a lower band of interest (black bars) which was sensitive to treatment with a select *recombinant (r) active phosphatase* (hatched bars) (Fig. B). Similarly, in contrast to uniform SDF (white bars), gradient SDF led to maintenance of a lower band of interest (black bars), which was sensitive to selective *mutations* at potential CXCR4 phospho-acceptor sites (hatched bars) (Fig. C). As control, construct expression levels were assessed (right panel), and experiments were conducted under conditions of equal expression. These data suggest that the band of interest, which is induced by gradient SDF that stimulates invasion (this reporting period) and induced by an Arf6 protein that drives invasion (last reporting period), contains previously unidentified CXCR4 phospho-species. Consistent with this, treatment of cells with the corresponding selective *phosphatase inhibitor* recapitulates the observed phosphosignature (Fig. D). Interestingly, gradient SDF leads to rapid dissociation of the select *endogenous (e) phosphatase* from CXCR4 as measured by co-immunoprecipitation (Fig. E). Taken together, these data suggest previously unidentified CXCR4 phospho-species are regulated by Arf6, which may play a role in Arf6 regulation of the SDF-CXCR4 axis during invasion of metastatic breast cancer cells. Antibodies against novel CXCR4 phospho-sites 1 and 2 are being developed.



**Figure. Aim I Progress.** Data are representative immunoblots or average  $\pm$  SEM for multiple independent experiments (A, n=3; B, n=5-6; C, n=4-10; D, n=4; E, n=3-9). Statistical significance was assessed using one sample t-test (\*,  $P < 0.05$ ; \*\*,  $P < 0.01$ ; ^,  $P < 0.005$ ; +,  $P < 0.001$ ; ++,  $P < 0.0001$ ).