PROGRAM GOALS AND CHARACTERISTICS

The themes, emphases, and goals of the Cell Response and Regulation (CRR) Program remain the same as those described in HCI’s 2014 CCSG competitive application and site visit. These remain our key interest areas, and we continue to strengthen these Program pillars as well as to capitalize on the synergism between them.

1. Mechanisms underlying cell turnover, including cell division, checkpoints, and cell death
2. Aberrant signaling in cancer and mechanisms of drug resistance

**CRR 2015 PROGRAM CHARACTERISTICS**

| MEMBERS                        | # | %   | FUNDING (TC)          | # | $(%)
|-------------------------------|---|-----|-----------------------|---|-------
| Total                         | 28| 100%| NCI                   | 11| 2,424,192
| Full                          | 25| 89% | Other NIH             | 11| 2,500,752
| Associate                     | 3 | 11% | Other PR              | 6 | 1,411,170
| Departments                   | 12|     | Total PR              | 28| 6,336,114
| Schools/Colleges              | 3 |     | Industry              | 1 | 26,166
| Members with Funding          | 17| 61% | Other PR              | 9 | 1,592,121
| Full Members with Funding*    | 17| 68% | Total Non-PR          | 10| 1,618,287
| Full Members with PR Funding* | 17| 68% | Grand Total           | 38| 7,954,401

| DEGREES                       |     |     | PUBLICATIONS          |     |     
|-------------------------------|-----|-----|-----------------------|-----|-------
| MD                            | 6  | 21% | Total                 | 50 | 100%
| MD/PhD                        | 3  | 11% | High-impact           | 13 | 26%
| PhD                           | 19 | 68% | Intra-Program         | 5  | 10%
| RANK                          |     |     | Inter-Program         | 22 | 44%
| Assistant Professor           | 9  | 32% | HCI Collab            | 25 | 50%
| Associate Professor           | 7  | 25% |                       |     |       
| Professor                     | 12 | 43% |                       |     |       
| Visiting Instructor           | 0  | 0%  |                       |     |       

**CLINICAL TRIALS --- not applicable**

Program Leadership

Leadership of CRR has undergone a significant transition with Douglas Grossman, MD, PhD, stepping down as co-leader to put his efforts into co-leading the Melanoma Disease-Oriented Research Team (DOT). Katharine Ullman, PhD, is currently serving as the sole CRR leader. Her previous role as CRR co-leader has allowed continuity and momentum toward CRR strategic goals. In the longer term, a co-leader with complementary expertise will be appointed during year 27.

Program Membership

Recruitment of new CRR members has been a key accomplishment of this past year and helps to position CRR for future success. Specifically, Martin McMahon, PhD, and June Round, PhD, have joined the program, and Alana Welm, PhD, was reinstated on her return to Utah. Dr. McMahon brings expertise in pre-clinical models of melanoma and lung cancer and Dr. Round studies the microbiome and how it can influence the microenvironment, immune status, and tumorigenesis. Dr. Welm studies Ron signaling in breast cancer, with a specific interest in metastasis to the bone. Michelle Mendoza, PhD, a new recruit to the Department of Oncological Sciences (December 2015), studies signaling pathways that control cell motility. Some members have transitioned out of the program, including Ricardo Baron, PhD, who relocated; Gerald Spangrude, PhD, who retired; and Matthew Sigman, PhD, whose research became focused in new directions. Michael Cohen, MD, who is a pathologist and previously ran a research laboratory, is busy in his role as the University of Utah
Health Sciences Ombudsman. We highly value his perspective and advice on grants, but since he is not engaged actively in research, his status will be changed to affiliate membership.

Awards to Members; Member Leadership Roles

Many CRR members hold important leadership positions. This includes a cadre of members who are leaders of Disease-Oriented Research Teams (Grossman, Holmen, O’Hare, Murtaugh). Dr. McMahon is Senior Leader of Pre-Clinical Translation at HCI. It will be very beneficial to have his expertise and perspective in this arena embedded within our Program. In addition to her role as Director/CEO of the Cancer Center, Mary Beckerle, PhD, continues as Associate Vice President of Cancer Affairs at the University of Utah, and has taken on new roles as a member of an NCI Cancer Center Review Subcommittee, as well joining the Howard Hughes Medical Institute Medical Advisory Board. Dean Li, MD, PhD, is Associate VP for Research at the University of Utah Health Sciences and Director of the Molecular Medicine Program. Jody Rosenblatt, PhD, was honored this past year by being named a recipient of a H.A. and Edna Benning Presidential Endowed Chair at the University of Utah. She is also playing a lead role as chair of the Molecular Biology Graduate Program curriculum committee and is helping to spearhead a new and innovative core curriculum for this graduate program, which supplies the majority of graduate student trainees in CRR labs. Dr. Ullman was recently elected to serve on the Medical School Curriculum Committee and is Director of Graduate Affairs in Oncological Sciences. Dr. Welm has been a member of the DOD Breast Cancer Research Program Integration Panel since 2012. It is also noteworthy that both Adam Frost, MD, PhD, and Dr. Round are funded by prestigious NIH New Innovator awards.

With Center-wide strategic planning underway, eight CRR members took part in a strategic planning retreat held in November, where there was opportunity to interact across Programs and to help articulate priorities and initiatives for HCI as we move forward into the next phase of development.

2015 KEY SCIENTIFIC ACCOMPLISHMENTS

Cell division: new insight into the machinery and regulation of cytokinetic abscission

Wesley Sundquist, PhD (CRR), Adam Frost, MD, PhD, and Katharine Ullman, PhD (CRR)

The final step of cell division is the process of cell separation, or cytokinesis. This step is a transition during cell proliferation where surveillance mechanisms tie different types of quality control into the decision to complete division. A host of proteins, known as ESCRT factors, participate in the process of cell separation—or cytokinetic abscission. CRR member Wesley Sundquist, PhD, is a leading expert on the structure and biology of the ESCRT machinery, which he has studied in the context of HIV budding and intracellular trafficking. CRR funds have been used to bolster Dr. Sundquist’s growing interest in cell division and regulatory mechanisms that take place at the time of cytokinesis. In FY12, the CRR Program funded an award to support collaboration between Drs. Sundquist and Adam Frost, MD, PhD, a CRR member with expertise in electron microscopy (EM). This project came to fruition this past year with exciting discoveries published in Science. There, the authors report the higher order organization of an ESCRT-III complex (between IST1 and CHMP1B). Using cryo-EM reconstruction, they were able to understand how these proteins interface in a polymeric assembly and how this assembly drives membrane dynamics. The complex they studied unexpectedly showed an ability to shape membranes into tubules. These polymeric structures not only bring new insight into a novel role for ESCRT factors, but also shed light on general features of ESCRT interactions and membrane dynamics that underpin further opportunities to elucidate molecular steps in the execution of cytokinetic abscission. The Sundquist lab was also involved in a project that identified a new regulator of abscission, the kinase ULK3. This kinase was found to target IST1 as a key step in the abscission checkpoint. Drs. Sundquist and Katharine Ullman, PhD (CRR), have also been building on collaborative opportunities that were reinforced by CRR Program meetings and CRR funding. They now jointly mentor a graduate student who is using a system developed in the Ullman lab to synchronize cells with an abscission checkpoint in order to understand precisely how ESCRT factor localization and activity is altered by Aurora B and ULK3 kinases. Synergisms fostered by CRR funding are currently being leveraged toward a PPG application, with projects from Drs. Sundquist, Frost, Martin-Serrano (King’s College, UK), and Ullman. This group effort includes a focus on the ESCRT factor CHMP4C, which was identified in GWAS studies as a gene with variants linked to ovarian cancer. Such variants may disable the abscission checkpoint, thereby allowing cells to progress prematurely when mis-segregated chromosomes or nuclear formation defects are present, in turn resulting in genomic damage and instability. This research is an example of CRR’s strength in the mechanistic biology of cell division and underscores how CRR Program leaders have promoted research aimed both at understanding how cancer develops and revealing new opportunities to consider for therapeutic strategies.
Aberrant signaling in cancer: a developmental regulator suppresses KRAS-driven pancreatic cancer
Charles Murtaugh, PhD (CRR), Raymond MacDonald, PhD, UT Southwestern, and Mary Bronner, MD (ET)

CRR member Charles Murtaugh, PhD, has a long-standing interest in pancreatic cancer. Striving to understand the early steps in tumor development is particularly relevant in the context of pancreatic cancer as the etiology of this disease suggests that pancreatic ductal adenocarcinoma (PDAC) arises after a long course of evolution, which may provide the opportunity to detect and halt the process before it becomes an intractable disease. Dr. Murtaugh previously made the discovery that pancreatic acinar cells are reprogrammed in a process that gives rise to pancreatic intraepithelial neoplasia (PanINs) and PDAC. In a paper published this past year, he reports that PTF1A, known as a master regulator of acinar differentiation, is a key suppressor of PDAC initiation. They found that deletion of this transcription factor resulted in conditions highly sensitized to KRAS transformation, accelerating development of PDAC. This study was accomplished by inter-institutional collaboration with Raymond MacDonald, PhD, who is a member of the Harold C. Simmons Comprehensive Cancer Center at UT Southwestern Medical Center. Drs. MacDonald and Murtaugh have a multi-PI collaborative R01 and are pursuing additional grant opportunities together. Archival human tumor specimens, obtained from the Biorepository and Molecular Pathology Shared Resource, helped to bolster this study. Mary Bronner, MD, a pathologist in HCI’s Experimental Therapeutics Program, played a key role in the histological analysis of tissue from both a mouse model, as well as human tumors. Dr. Murtaugh also credits the Bioinformatics Section of the High-Throughput Genomics and Bioinformatic Analysis Shared Resource, which provided critical advice on resources for learning data analysis techniques. This research highlight illustrates how CRR members often capitalize on the interface between developmental biology and tumorigenesis to gain new insight into specific steps in disease. This study also exemplifies the great training environments in CRR member laboratories; the first author of the study is an MD/PhD student in Murtaugh’s lab. This work has been presented at a Gordon Conference on Pancreatic Diseases, the AACR Pancreatic Cancer conference, and the PancWest Symposium. Dr. Murtaugh’s excellence in and commitment to pancreatic cancer research are reflected in his recent appointment to co-lead the HCI Pancreatic Cancer DOT. The CRR Program has fostered Dr. Murtaugh’s pancreatic cancer focus via a past mini-grant award and will continue to identify ways to bolster this research area.


Signaling and chemoresistance: novel strategies to inhibit BCR-ABL1 kinase
Carol Lim, PhD (CRR), Thomas O’Hare, PhD (CRR), and Michael Deininger, MD, PhD (ET)

Carol Lim, PhD (CRR), is interested in using dimerizing peptide motifs designed to selectively inhibit the function of proteins of interest as a therapeutic strategy. She has optimized a peptide that dimerizes with BCR-ABL1, the oncogenic kinase that drives chronic myelogenous leukemia (CML). The most recent iteration of the engineered peptidomimetic (CCmut3) favors heterodimerization with BCR-ABL1 over non-productive homodimerization, increasing the efficacy of interference with BCR-ABL dimerization and consequently potently inhibiting its enzymatic activity. Although BCR-ABL1 has been successfully targeted by small molecule inhibitors, chemoresistance remains a serious problem. CRR Program activities and program leader introductions brought Dr. Lim together with CRR member Thomas O’Hare, PhD, and ET member Michael Deininger, MD, PhD. Together, these investigators tested whether delivery of CCmut3 has the potential to combat relapsed cases, by ectopically expressing either BCR-ABL1 or TKI-resistant mutant BCR-ABL1 in Ba/F3 cells. In each case, CCmut3 expression resulted in increased apoptosis and decreased colony formation. Moreover, using patient-derived CML cells from both newly-diagnosed and chemo-resistant
patients, they found that introduction of CCmut3 suppressed colony formation. Though this strategy holds promise as a complementary tactic to target CML, delivery of therapeutic peptides must be addressed before movement toward clinical application. Dr. Lim explored the feasibility of peptide delivery by fusing a leukemia-specific cell-penetrating peptide to CCmut3. This strategy was effective at delivering peptide to cultured cells at levels that had specific inhibitory effects. With feasibility established, the Lim lab is currently pursuing additional methods to enhance delivery, such as PEGylation and hydrocarbon peptide stapling. She has ideal collaborators in the ET Program with whom to work on such approaches, including ET members Sung Wan Kim, PhD, and Danny Chou, PhD. In a CRR-funded project from FY14, funds were supplied to test the delivery of peptides. This was in the context of a different biological target (ovarian cancer), but will more generally push forward progress toward peptide delivery methods. These research accomplishments and plans reflect our Program’s aspiration to find new ways to interfere in key cell signaling mechanisms that underlie oncogenesis, particularly in the context of chemoresistance, and to work collaboratively to move these strategies toward clinical applications. We will further enhance Dr. Lim’s research efforts in the coming year by integrating her in a group working toward a grant focused on Drug Development and Delivery.

Bruno BJ, Lim CS (CRR) Inhibition of bcr-abl in human leukemic cells with a coiled-coil protein delivered by a leukemia-specific cell-penetrating Peptide. Mol Pharm. 2015 12:1412-21


**Metastasis: signaling pathways that promote the development of brain metastasis in melanoma.**

Sheri Holmen, PhD (CRR), Matthew VanBrocklin, PhD (CRR), and Martin McMahon, PhD (CRR)

An understanding of the signaling network that underlies metastasis in melanoma is an important step in improving clinical outcomes in this disease. The Sheri Holmen, PhD (CRR), lab, along with CRR members Matthew VanBrocklin, PhD, and Martin McMahon, PhD, as well as MD/PhD student, Joseph Cho, made progress on this front in a project at the intersection of our Program themes focused on signaling and metastasis. Dr. Holmen, who is an expert at the development of preclinical mouse models of cancer, engineered a melanoma mouse model with lesions in genes frequently altered in this disease context. Specifically, mice were induced to express BRAFV600E within melanocytes regionally and simultaneously to lose expression of Cdkn2A. Though these mice frequently develop melanoma, no metastases were observed under these circumstances. Concurrent loss of the tumor suppressor PTEN decreased mean survival time, but did not significantly increase metastases. Although PTEN is thought to work in a pathway that influences Akt activity, previous studies have distinguished Akt activation from PTEN loss. Here, when activated (myristoylated) Akt1 was expressed in the context of this genetic landscape, metastases significantly increased; moreover, Dr. Holmen and her colleagues were able to demonstrate cooperation between loss of PTEN and activation of Akt1 in the incidence of brain metastases. They pursued the question of how PTEN loss compares to Akt1 activation and found a notable difference in the mTOR pathway (mTOR decreased in tumors with PTEN loss and increased in tumors with Akt1 activation). In turn, a test of an mTOR inhibitor indicated an important role for this pathway in cell migration. This study paves the way to a better understanding of the role of Akt—including its additional isoforms and patient-derived mutations—in melanoma metastasis, as well as an opportunity to further explore whether manipulation of this signaling network can be strategically targeted to ameliorate clinical outcomes for melanoma patients. This melanoma model will soon be included in the expanding repertoire of HCI’s Preclinical Research Resource, a developing Shared Resource headed by Dr. McMahon and dedicated to facilitating the use of pre-clinical mouse models for translational cancer research. The CRR Program provided an opportunity for Dr. Holmen to design a mini-symposium agenda centered on the topic of metastasis. In collaboration with Douglas Grossman, MD, PhD (CRR), she organized a transdisciplinary program that included talks by many CRR members (Rosenblatt, Stewart, Factor) as well as Cancer Center members with clinical perspectives to share (Akerley, Sharma, and Khong, all members of the ET Program). This successful mini-symposium also featured the outside speaker Dr. Kay Macleod and a dinner for further discussion and interaction between speakers and CRR members.

RESEARCH AND/OR INITIATIVES FOCUSED ON THE NEEDS OF HCI'S CATCHMENT AREA.

With eight members involved in melanoma research (Grossman, Holmen, McMahon, Moos, Li, Stewart, VanBrocklin, and Williams), CRR is tightly linked to the efforts of HCI to improve outcomes in this disease, which occurs at heightened frequency in the Utah population. This past year, CRR co-funded a mini-grant with the Melanoma DOT (MDOT) that supported a collaboration between CRR member Dr. Grossman and CCPS member Lisa Cannon-Albright, PhD. This project is aimed at understanding how a mutation in a newly-discovered disease-associated gene in familial melanoma disrupts function at a molecular level. Dr. Ullman has monthly meetings with MDOT co-leader Dr. Grossman to remain up-to-date on the research projects of a working group of Cancer Center members in this area, who seek to submit a collaborative grant. This group will present their plans at a CRR Program meeting this Spring, where ways to further bolster these efforts will be explored.
SELECTED CRR PUBLICATIONS YEAR 26

The journal articles listed below are selected from a total of 50 Program-related publications. Publications for dual members are reported in only one Program.

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Combined STAT3 and BCR-ABL1 inhibition induces synthetic lethality in therapy-resistant chronic myeloid leukemia. Leukemia 29:586-97. PMCID: PMC4334758


