2016

Earle A. Chiles Research Institute 2015 Year In Review

Earle A. Chiles Research Institute

Follow this and additional works at: https://digitalcommons.psjhealth.org/publications
Part of the Oncology Commons

Recommended Citation
https://digitalcommons.psjhealth.org/publications/352

This Book is brought to you for free and open access by Providence St. Joseph Health Digital Commons. It has been accepted for inclusion in Journal Articles and Abstracts by an authorized administrator of Providence St. Joseph Health Digital Commons. For more information, please contact digitalcommons@providence.org.
Advancing Cancer Immunotherapy
Through State-of-the-Art Translational Research

2015 YEAR IN REVIEW

Earle A. Chiles Research Institute, a division of Providence Cancer Center

Advancing Cancer Immunotherapy Through State-of-the-Art Translational Research
The Earle A. Chiles Research Institute is a world-class research facility located within Providence Cancer Center in Portland, Ore. Home to a team of internationally-recognized scientists and physicians, the main area of investigation is cancer immunotherapy.

Location & Contact

Earle A. Chiles Research Institute
Providence Portland Medical Center
4805 NE Glisan Street, 2N35
Portland, OR 97213
503-215-6588
www.chilesresearch.org

@ChilesResearch
@providencecancercenter

<table>
<thead>
<tr>
<th>TABLE OF CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>MESSAGE FROM THE DIRECTOR</td>
</tr>
<tr>
<td>FACTS &amp; FIGURES</td>
</tr>
<tr>
<td>NEW &amp; NOTEWORTHY</td>
</tr>
<tr>
<td>New Faculty Appointments</td>
</tr>
<tr>
<td>Noteworthy Achievements</td>
</tr>
<tr>
<td>Harder Family Endowed Chair</td>
</tr>
<tr>
<td>A PATIENT’S JOURNEY</td>
</tr>
<tr>
<td>FACULTY MEMBERS</td>
</tr>
<tr>
<td>CORE FACILITIES</td>
</tr>
<tr>
<td>Immune Monitoring Laboratory</td>
</tr>
<tr>
<td>Flow Cytometry Core</td>
</tr>
<tr>
<td>Molecular Pathology Core</td>
</tr>
<tr>
<td>EDUCATION &amp; TRAINING</td>
</tr>
<tr>
<td>Graduate Education</td>
</tr>
<tr>
<td>Postdoctoral Fellowships</td>
</tr>
<tr>
<td>Summer Research Program</td>
</tr>
<tr>
<td>EVENTS &amp; ENGAGEMENT</td>
</tr>
<tr>
<td>Creating Hope Luncheon</td>
</tr>
<tr>
<td>Finish Cancer Campaign</td>
</tr>
<tr>
<td>Providence Hood-To-Coast Relay</td>
</tr>
<tr>
<td>White Out Cancer Day</td>
</tr>
<tr>
<td>FRANZ LEADERSHIP CABINET</td>
</tr>
<tr>
<td>SELECT PUBLICATIONS</td>
</tr>
</tbody>
</table>
For the past 23 years, our major focus has been cancer immunotherapy – the hypothesis that the immune system can be activated to recognize and kill cancer cells.

Immunotherapy is not a new concept. It has been the subject of investigation for more than 100 years. There has always been a strong scientific rationale for immunotherapy, but until recently there was little evidence of clinical benefit. Tumor regressions were so uncommon that, when we started 23 years ago, the idea that physicians would be able to harness the body’s immune system to fight cancer was met with skepticism.

Nevertheless, we believed in the power of the immune system and refused to abandon what we thought was a promising strategy. With the support of Providence Health & Services, philanthropists, public and private grants, and industry partners, we built a great team and continued to learn more about the immune system and cancer biology. Armed with this knowledge, we were able to move our innovations from the laboratory to the patient bedside.

The best example of our novel approach is the OX40-based translational research led by Andrew D. Weinberg, Ph.D., (page 25) and Brendan D. Curti, M.D. (page 15). The OX40 discovery research performed at our institute was fueled by local philanthropy, which allowed us to initiate the first-in-human OX40 trial at Providence Cancer Center, and led to the formation of the biotechnology company, AgonOx. Providence licensed the technology to AgonOx, who sublicensed OX40 to one of the largest pharmaceutical companies in the world. What began as a philanthropy-driven 30-patient trial in a single hospital in Portland, Ore. is now being tested in hundreds of patients in multiple cancer centers around the world.

We are also proud of our contribution to the development of ipilimumab – the first immunotherapy drug to improve survival in patients with advanced melanoma. I was honored to serve as the principal investigator for the international clinical trial that led to ipilimumab’s FDA approval in 2011, distinguishing the Earle A. Chiles Research Institute as a leader in cancer immunotherapy.

In the past 10 years, we have witnessed more progress in cancer care than in the previous 100 years. When we began, immunotherapy was the focus of only a handful of centers. Now it is a major program in every cancer center in the United States and a top priority in every major drug company. There is no denying that this is a very exciting time in cancer research. However, despite the significant progress that has been made, substantial challenges remain because only a minority of patients with advanced cancer benefit from current therapy.

Every advance in the treatment of cancer is the result of our investment in research, the teams of scientists and physicians attempting new approaches and the incredibly brave patients who volunteer to help move us forward. We are grateful for our many supporters who have partnered with us, and we invite you to help us achieve our goal of increasing the number of cancer survivors through immunotherapy. Together, we can finish cancer.
FACTS & FIGURES

Investigators & Personnel
- Faculty Members: 18
- Clinical Researchers: 32
- Lab Researchers: 46

Grant Funding, Sponsored Research & Philanthropy
- $3.4 million annually in federal, private and sponsored research funding
- Providence Foundations Center of Hope Campaign raised over $12 million for cancer research, including a gift of $5.5 million
- Providence Guest House opened to patients and their families through philanthropic support

Memberships & Collaborations
- Bristol Myers-Squibb International Immuno-Oncology Network
- NCI Cancer Immunotherapy Trials Network
- NCI Community Oncology Research Program
- Partnership with MedImmune / AstraZeneca for the clinical development of anti-OX40

Institute Publications
- Journal Articles: 44
- Book Chapters: 8
- Abstracts: 56

Clinical Trials
- 214 cancer clinical trials open for enrollment, including 174 therapeutic trials and 51 Phase I trials
- 1,238 total enrollments
NEW & NOTEWORTHY

New Faculty Appointments

Kristina H. Young, M.D., Ph.D., and David B. Page, M.D., are the two newest physician researchers to join the Earle A. Chiles Research Institute, and both have received national recognition. In 2015, they were among 58 recipients worldwide to be honored with a Young Investigator Award from the American Society of Clinical Oncology.

Dr. Young is a radiation oncologist with a laboratory research focus on the tumor microenvironment. She completed her medical education, residency and doctoral degree in cellular and developmental biology at Oregon Health & Science University, and completed a Holman Research Pathway Fellowship in the investigation of radiation oncology and basic science at the Earle A. Chiles Research Institute. Read more about Dr. Young on page 26.

Dr. Page is a medical oncologist specializing in new immunotherapies for women with breast cancer. After completing his medical education at Northwestern University Feinberg School of Medicine and residency at New York Presbyterian Hospital / Columbia University Medical Center, he completed a medical oncology fellowship at Memorial Sloan Kettering Cancer Center. Read more about Dr. Page on page 22.

Noteworthy Studies & Publications

In collaboration with Dung Le, M.D., of Johns Hopkins University, Todd S. Crocenzi, M.D., was co-investigator on a Phase II study of PD-1 inhibition in patients with metastatic colorectal cancer. This landmark study showed that anti-PD-1 was effective in this subset of patients with advanced colon cancer and defects in mechanisms of DNA repair. This research helped make the important correlation between mutational burden and efficacy of immunotherapy (N Engl J Med. 2015; 372(26):2509). Read more about Dr. Crocenzi on page 14.

Bernard A. Fox, Ph.D, with Carlo B. Bifulco, M.D., led an international task force evaluating the prognostic value of the immune score in patients with colorectal cancer. With the aid of his graduate student, Zipei Feng, multispectral imaging was used to predict the ability to culture tumor-infiltrating lymphocytes and the results were presented at major scientific conferences. Learn more about Dr. Fox on page 16 and Dr. Bifulco on page 11.

Brendan D. Curti, M.D., was co-author on the seminal publication Talimogene Laherparepvec Improves Durable Response Rate in Patients with Advanced Melanoma, which led to FDA approval of this innovative oncolytic therapy in October 2015 (J Clin Oncol. 2015; 33(25):2780). Read more about Dr. Curti on page 15.

Rachel E. Sanborn, M.D., served as the Providence Cancer Center site principal investigator for the clinical trial testing anti-PD-1(nivolumab) in patients with advanced squamous non-small cell lung cancer. Following successful trial results, nivolumab received FDA approval in March 2015, earlier than... continued
anticipated, culminating in the first immunotherapy drug approval for lung cancer. Later in October, the FDA expanded approval of nivolumab to include previously treated patients with advanced non-squamous non-small cell lung cancer. Read more about Dr. Sanborn on page 24.

Preclinical work from the laboratory of William L. Redmond, Ph.D., has shown the benefit of combining checkpoint inhibitors, such as anti-CTLA-4 or anti-PD-1, with a galectin-3 inhibitor (GR-MD-02). This led to two translational clinical trials testing the galectin inhibitor in combination with checkpoint inhibitors, supported in part by an R21 grant award from the National Cancer Institute. Read more about Dr. Redmond on page 23.

Harder Family Endowed Chair in Cancer Research bestowed on Bernard A. Fox, Ph.D.

On March 5, 2015, family, friends, colleagues and supporters joined Dr. Bernard Fox in Palm Desert, Calif., for a celebratory reception in recognition of his contributions to immunotherapy and global efforts to cure cancer. Presented with the Harder Family Endowed Chair in Cancer Research by the Providence Portland Medical Foundation, Dr. Fox received messages of support and congratulation, including the following selected remarks:

“I’ve known Bernie and supported his research efforts for 20 years. He’s been a key to the growth of the Earle A. Chiles Research Institute. He’s made me and the Chiles Foundation proud. And the most exciting part of all this is the fact that he has so much more to offer us all. As the holder of the Harder Chair, he will continue with new discoveries. He will continue to publish his findings. He will continue on the path to cure cancer.” - Earle M. Chiles & The Chiles Foundation

“Bernie is a world-recognized scientist who is frequently called upon by granting agencies, such as the NIH and FDA, academic institutions, biotechnology and pharmaceutical companies to provide expert opinion and serve as a subject matter expert in the immunotherapy of cancer.” – Raj K. Puri, M.D., Ph.D., director, Division of Cellular and Gene Therapies, Center for Biologics Evaluation and Research, U.S. Food & Drug Administration
“Thank you, Bernie, for leading me and others along the path to finding a cure for cancer. Congratulations to you as you receive this prestigious honor.” – Tara Withington, executive director, Society for Immunotherapy of Cancer.

“Your vision of cancer immunology and immunotherapy, and your passion and tireless efforts at realizing its success in our lifetime (who would have ever thought we would witness it from our days together at the NCI so many years ago!), will forever set apart the Earle A. Chiles Research Institute as one of the leaders in our field.” – James J. Mulé, Ph.D., associate center director for Translational Science, Moffitt Cancer Center.

Learn more about Dr. Fox on page 16.
A PATIENT’S JOURNEY

Steve Smith had few options for surviving stage IV colon cancer, but he entered a Phase I trial at Providence Cancer Center and gained a new lease on life.

Steve Smith, 63, sits by the fire in the main floor of Providence Guest House after flying in from Montana the night before and receiving his infusions of varilimumab and nivolumab that morning. He quips, “I already had an expiration date.”

It’s an amusing joke for the 29-year career salesman in grocery products for Proctor & Gamble. He’s in a good mood and explains why.

In February 2014, shortly after retiring and moving with his wife back to his boyhood home in Great Falls, Smith was diagnosed with stage IV colon cancer with liver metastases. He underwent chemotherapy for a year, a colectomy, seven tumor resections and removal of 24 lymph nodes. His cancer was stable for six months and then progressed.

With limited options in Montana, Smith and his oncologist began searching the Web and determined an immunotherapy trial offered the best hope. They found clinical trials that looked promising in Seattle, Phoenix and Minneapolis, among other cities, but decided on Portland because of the pioneering work performed at Providence Cancer Center and for its proximity to Vancouver, Wash., where Smith lived for much of his working career.

Screening Period

In April 2015, Smith visited Providence Cancer Center for a consultation with Todd S. Crocenzi, M.D., to see if he qualified for a Phase I/II trial combining two immunotherapy agents, varilimumab and nivolumab, in patients with advanced cancers. The screening included urine testing, electrocardiogram, chest X-ray, tumor biopsy, CT scans of his chest, abdomen and pelvis, and brain and blood draws to verify the absence of complicating factors.

A screen for biomarkers such as the non-mutated KRAS gene provided data to help investigators determine whether Smith might respond to the drugs.

“Fortunately for me, I met the requirements. As a cancer patient, you have to investigate what’s out there or miss an opportunity,” he says.

When Smith enrolled in the trial, he was among a small cohort of patients who have received a mid-range dose of medication. By 2020, the target end date of the trial, approximately 190 patients are expected to be enrolled at up to 15 sites in the country. This is the first time varilimumab and nivolumab have been tested together in humans.
**Home Away From Home**

While the costs of the drugs are covered for Smith, he figures he’d spend about $30,000 on travel. Early on, no stranger to a lot of miles on the road in his job, Smith didn’t mind driving himself to his infusions every two weeks – a 700 mile trip. He says he used the time to turn on the music and let it all go. “Once I started to feel the results, a lot of my anxiety was taken care of,” he says.

Being able to stay at the Providence Guest House close to the hospital has made a huge difference to Smith. He doesn’t feel as transient as he did hopping around from one budget hotel to another like he and his wife did earlier in the trial. He uses some of his free time seeing a brother who lives in Vancouver.

“We are very pleased that we could offer Mr. Smith a therapeutic trial that was not available in his home state, and that he has shown a positive response to treatment. We are also grateful that he and his family are able to stay at the Providence Guest House during his treatment,” says Dr. Crocenzi.

**Results**

At the end of June 2015, two months after his screening visit, a CAT scan showed a 30 percent reduction in Smith’s tumors; by August, 43 percent; October, 60 percent; December, 75 percent; and at the end February 2016, Smith’s tumors had reduced by 84 percent.

“I could be totally clear,” Smith says. “I’m not the only one who’s shaking his head.”

While reading the long list of possible side effects was intimidating, Smith shrugs off what he has experienced as mild – irritability at the site of his chest infusion port, joint pain and diarrhea. “You work it out when it’s all compared to staying alive,” he says.

Also, there has been the improvement in his quality of life. Smith has been enjoying spending time with his family, which includes nine grandchildren and 12 great-grandchildren. Among hobbies he’s taken up is panning for gold.

“I’m healthy enough to enjoy retirement,” he says.

Feature courtesy of Providence inScope.
R. Bryan Bell, M.D.,
D.D.S., FACS
Assistant member and medical director,
Providence Oral, Head & Neck Cancer
Program and Clinic
Head and Neck Oncologic Surgery

Dr. Bell’s research interest is in the characterization and
manipulation of the tumor microenvironment in head
and neck cancer. He seeks to develop novel clinical trials
and treatment strategies to stimulate pre-surgical immune
responses in patients with head and neck squamous
cell carcinoma.

Since joining Providence Cancer Center in 2010, Dr. Bryan Bell
has been instrumental in expanding clinical research for patients
with oral, head and neck cancer. Working closely with Rom S.
Leidner, M.D., the portfolio of clinical trials has grown from one
cooperative group trial in 2010 to more than 25 investigator-
initiated, industry-funded and cooperative group trials in 2015.
Dr. Bell serves as the principal investigator on a Phase Ib
investigator-initiated trial of anti-OX40 prior to surgical resection,
as well as an industry-sponsored Phase II trial of IRX-2, which
contains interleukin-2 and various cytokines, administered at
pre- and post-surgical resection. Nationally, Dr. Bell is among the
highest accruing surgeons in a Phase II cooperative group trial
(ECOG 3311) investigating transoral robotic surgery in head
and neck squamous cell carcinoma (HNSCC). In August 2015,
Drs. Bell and Leidner hosted the inaugural New Horizons in
Immunotherapy for Head and Neck Cancer Symposium held
in Newberg, Ore., bringing together leading investigators in
HNSCC immunotherapy.

In collaboration with the Integrated Therapies Laboratory led by
Marka R. Crittenden, M.D., Ph.D., and Michael J. Gough, Ph.D.,
Dr. Bell seeks to develop a perioperative immunotherapy strategy
to clear residual cancer cells in the surgical site without impacting
normal tissues, anatomic structures or wound healing. “Such
an intervention may also increase the number of patients eligible
for surgical resection, since patients whose tumors have invaded
critical structures may become eligible for surgery if we are able
to eliminate remaining cancer cells,” says Dr. Bell.

Dr. Bell has also engaged in a next generation immunoprofiling
collaboration with Bernard A. Fox, Ph.D., whose laboratory
has established a head and neck cancer tumor bank and
cryopreserved more than 250 tissue samples from Dr. Bell’s
patients. Multispectral imaging analyses of tumors from a cohort
of patients with HNSCC has resulted in the development of a
potential prognostic biomarker for oral cancer that may be
used in the future to direct conventional treatment as well as
immunotherapy.

Another intramural collaboration includes Dr. Bell’s partnership
with Andrew D. Weinberg, Ph.D., to examine the expression
of immune modulatory proteins, OX40, PD-1, and CTLA-4, in
HNSCC and to see whether these proteins could be targeted
alone or in combination for future clinical trials. Further studies
are centered on evaluating the primary tumor, metastatic
and non-metastatic draining lymph nodes to identify novel
immunotherapy targets, biomarkers of response, and how
to best use immunotherapy combinations with the goal of
translating their findings into innovative clinical trials.
Carlo B. Bifulco, M.D.

Member and director, Translational Molecular Pathology and Informatics Anatomic and Molecular Pathology

As a pathologist with subspecialty training and expertise in molecular genetic pathology and hemato-pathology, Dr. Bifulco serves as director of the Molecular Pathology Core at the Earle A. Chiles Research Institute. He also serves as co-leader of the Biospecimen Core for the Pacific Cancer Research Consortium, a community site of the NCI Community Oncology Research Program.

“Medicine is undergoing a major shift toward personalized health care, a model in which preventive and therapeutic practices are custom designed for each patient’s specific needs,” says Dr. Carlo Bifulco. “For cancer, personalized treatment is made possible by rapid and dramatic advances in DNA sequencing, which enables us to decode tumor genomes, and by new drugs that selectively target cells with damaged or mutated genes. These developments allow us to match drugs to patients with specific tumors, resulting in better outcomes, less toxicity and lower costs.”

The Molecular Pathology Core plays an important role in detecting tumor-driver mutations and tumor pathways that will respond well to certain drugs. It performs or coordinates tests for several molecular targets in multiple tumor types, including breast, colon, lung and hematologic malignancies.

Test results are routinely incorporated into diagnostic pathology reports. “Now we’re preparing for the next leap forward in personalized care,” says Dr. Bifulco. “We’re transitioning from single gene mutation testing – that is, focusing on one gene at a time for specific targetable mutations – to mapping and decoding whole genomes. By comparing the patient’s normal DNA to the tumor DNA, we can identify all the potentially actionable mutations. This allows for more targeted, personalized treatment.”

At Providence Cancer Center, this process will be developed in stages through a multiphase approach. “First we’ll focus on characterizing cancers through next-generation sequencing of gene groups currently associated with specific tumor types. Later, as the technology and data interpretation become standardized and increasingly robust, we’ll extend this approach to the whole exome – the part of the genome most frequently altered in tumor-driving mutations. The ultimate goal is complete genetic profiling of tumors with the sequencing of whole tumor genomes,” says Dr. Bifulco.

This shift in cancer diagnostics and treatment approach will result in better and more affordable diagnostics and, most importantly, in improved clinical outcomes. Because there is an important role for personalized immunotherapy to complement the advancements in medical genomics and bioinformatics, Dr. Bifulco’s team is developing tests to characterize a patient’s immune response to a tumor. “We’re hopeful that this immunoprofiling approach will allow for further personalized use of immunotherapeutic agents in cancer treatment.”
Alison K. Conlin, M.D., MPH

Associate member and medical director, Providence Breast Cancer Program and High-Risk Breast Clinic
Medical Oncology

As a medical oncologist with training in population health and health outcomes, Dr. Conlin specializes in breast cancer clinical research as well as breast cancer risk evaluation, screening, and clinical and lifestyle interventions.

Since her arrival at Providence Cancer Center in 2008, Dr. Alison Conlin has been an active clinical investigator. She serves as a member of the Alliance for Breast Cancer Committee. She is a member of the Southwest Oncology Group Breast Committee and Breast Cancer Working Group, in which she founded and co-chairs the Brain Metastasis Working Group.

“Currently, I am on the advisory board of the Providence Breast Health Registry – a database of patients’ screening, diagnostic, treatment, and follow-up information,” says Dr. Conlin. “Additionally, I am the medical director of our high-risk breast clinic where we evaluate women for their breast cancer risk and counsel them to consider medications to reduce risk, such as tamoxifen, raloxifene, or exemestane, appropriate screening and testing practices, and lifestyle modifications that may reduce risk of future breast cancer.”

In late 2014, Dr. Conlin became the co-principal investigator for the Providence Portland Medical Center site of the Pacific Cancer Research Consortium (PCRC), a community site of the NCI Community Oncology Research Program (NCORP). Comprising three major community cancer centers in the Western United States, PCRC includes Swedish Cancer Institute in Seattle, Mountain States Tumor Institute in Boise, and Providence Portland Medical Center, home to Providence Cancer Center and the Earle A. Chiles Research Institute. Along with their sub-components and 27 other participating components across Alaska, Washington, Oregon, Idaho, and California, PCRC-NCORP is a consortium of 48 sites designed to conduct multi-site cancer clinical trials and cancer care delivery research through a 5-year grant award from the NCI.

Dr. Conlin is the leader of the PCRC Research Base Core which oversees the selection of PCRC cooperative group trials and represents PCRC to the National Clinical Trials Network Research Base. “The function of the PCRC Research Base Core is to ensure that we screen and select appropriate protocols for our PCRC sites and that we achieve accrual requirements,” says Dr. Conlin. “This is done through engaging and capitalizing on our investigators’ disease-specific expertise to review and select clinical trials from the participating research base portfolios.”
Marka R. Crittenden, M.D., Ph.D.
Assistant member, Integrated Therapies Laboratory
Director, Translational Radiation Research
Radiation Oncology

As a physician scientist trained in both radiation oncology and immunology, Dr. Marka Crittenden has a strong interest in the development of immunotherapy approaches for the treatment of cancer.

“In my role as director of Translational Radiation Research, I am involved in multiple investigator-initiated Phase I and Phase II clinical studies combining immunotherapy with radiation therapy in melanoma, breast cancer, pancreatic and prostate cancer,” says Dr. Marka Crittenden. “I also co-lead with Michael J. Gough, Ph.D., the Integrated Therapies Laboratory which studies the integration of immunotherapy approaches targeting the immune environment within the tumor and conventional therapies such as chemotherapy and radiation.” Learn more about the Integrated Therapies Laboratory on page 18.

In 2015, Dr. Crittenden contributed to numerous publications with intramural and extramural collaborators. She co-authored six journal articles and seven abstracts, including a first author publication entitled Current Clinical Trials Testing Combinations of Immunotherapy and Radiation (Semin Radiat Oncol. 2015;25(1):54). At the 2015 annual meeting of the American Society of Clinical Oncology, she gave poster presentations on a Phase II study of stereotactic body radiation therapy in combination with a monoclonal antibody to OX40 in patients with metastatic breast cancer and a Phase I study of safety and immunogenicity of a Listeria monocytogenes vaccine, ADU-623, in patients with WHO grade III/IV astrocytomas. She served as institutional principal investigator on clinical trials for patients with glioblastoma and other tumor types, including a first-in-human study of a monoclonal antibody to PD-1 administered alone and in combination with other anti-cancer therapies in patients with advanced malignancies.

Additionally, Dr. Crittenden served as an expert discussant for the Immunotherapy and Radiation Therapy session of the American Society of Therapeutic Radiation Oncology 2015 annual meeting in San Antonio, and co-chair of the Immune Therapy and Immune Modulation Workshop at the NRG Oncology Semi-Annual Meeting in Denver. She attended the 2015 annual meeting of the American College of Radiation Oncology in Washington, D.C., where she presented on “Radiation and Immunotherapy: A Primer,” as well as the 2015 annual meeting of the Radiation Research Society in Weston, Fla., where she presented on myeloid response to radiation therapy. Dr. Crittenden was also an active participant in the Radiation and Immune Modulation Working Group and Lung Cancer Working Group of the National Cancer Institute and engaged in collaborations with UC Davis, Sanford Health and Baylor College of Medicine.
Todd S. Crocenzi, M.D.

Associate member and director, Gastrointestinal Oncology Research
Medical Oncology

As a medical oncologist with a strong interest in the immunologic aspects of cancer biology, Dr. Crocenzi’s ongoing professional goal is to develop methods of redirecting the immune system as a cancer therapeutic.

As an oncology fellow at Dartmouth Hitchcock Medical Center, Dr. Todd Crocenzi was mentored by Marc Ernstoff, M.D., in the clinical care of patients with advanced melanoma and renal cell carcinoma undergoing standard and investigational immunotherapy regimens. He also gained experience in translational research and was a co-principal investigator on an institutional grant which funded a clinical trial of a novel dendritic cell vaccine for metastatic melanoma and renal cell carcinoma. It was this training and experience in investigational immunotherapy which led to Dr. Crocenzi’s directorship of Gastrointestinal Oncology Research at the Earle A. Chiles Research Institute, where he seeks to improve immunotherapeutics for patients with gastrointestinal cancers.

“As a physician scientist developing novel cancer therapy, I believe immunotherapy can integrate with current conventional therapies to optimize effectiveness. To this end, I designed and conducted two clinical trials evaluating the safety and feasibility of chemo-immuno-radiotherapy in patients with locally advanced or borderline resectable pancreatic cancer. I continue to work with Michael J. Gough, Ph.D., and Marka R. Crittenden, M.D., Ph.D, to analyze blood and tissue samples from these patients to formulate other translational research projects in pancreatic, liver and colorectal cancer,” says Dr. Crocenzi.

Dr. Crocenzi has collaborated with Duke University on a multi-institutional clinical trial to explore a multi-peptide, viral vector delivered vaccine in patients with resected, metastatic colorectal cancer. Most recently, Dr. Crocenzi collaborated with Dung Le, M.D., of Johns Hopkins University in the clinical trial demonstrating the efficacy of PD-1 inhibition in patients with metastatic colorectal cancer and mismatch repair deficiency (N Engl J Med. 2015; 372(26):2509). “Dr. Le and I were also awarded a PANCAN-AACR Research Acceleration Network Grant, a $1 million award to support our ongoing clinical trial exploring a prime-boost vaccination strategy in combination with anti-PD-1 antibody for second line treatment of metastatic pancreatic adenocarcinoma,” says Dr. Crocenzi.

Dr. Crocenzi is an active investigator on several other investigator-initiated clinical trials combining immunotherapy, chemotherapy and radiation therapy as well as multi-center studies through the Cancer Immunotherapy Trials Network and the cooperative group system of the NCI.
Brendan D. Curti, M.D.

Member and director, Genitourinary Oncology Research
Director, Cytokine and Adoptive Immunotherapy Program
Co-director, Providence Melanoma Program
Medical Oncology

Dr. Curti is a principle investigator on numerous translational clinical trials and a recognized leader in melanoma, genitourinary and interleukin-2 (IL-2) immunotherapy.

Dr. Brendan Curti served as the principal investigator on the first-in-human OX40 study that was performed at Providence Cancer Center. Based on the promising results of the Phase 1 trial, new OX40 agonists and combinations are being investigated in the clinic in conjunction with collaborators at MedImmune, which acquired the rights to develop OX40 agonists. This includes several in-house studies testing the immunological effects in the tumor specimens of pre-operative administration of anti-OX40 in patients with advanced oral, head and neck cancer, and in patients with liver metastases from colorectal cancer.

Intratumoral therapy for melanoma has been a longstanding clinical research interest of Dr. Curti’s. Providence Cancer Center enrolled the first patient on the Phase III talimogene laherparepvec trial that was the basis for its FDA approval (J Clin Oncol 2015, 33(25):2780). Dr. Curti is an active collaborator on clinical research studies investigating another oncolytic virus, CAVATAK (Coxsackie Virus CVA-21). Presentations of this research were given at the 2015 annual meetings of the American Society of Clinical Oncology and American Association for Cancer Research. “Based on pre-clinical data showing synergy with anti-CTLA-4, I authored a clinical trial studying the combination of CAVATAK and ipilimumab in patients with advanced melanoma and a subcutaneous melanoma deposit suitable for intratumoral vaccination,” says Dr. Curti. Four of the first five patients have achieved a partial regression of disease. Detailed analysis of immune parameters including immunoscore is being performed. Collaborators include the John Wayne Cancer Institute and the Huntsman Cancer Institute.

Galectins are proteins with immune suppressive properties produced in excess by many malignancies. William L. Redmond, Ph.D., studied galectin inhibitors in conjunction with T-cell costimulatory antibodies and demonstrated enhanced anti-tumor activity in pre-clinical tumor models. To translate this work to the clinical setting, Dr. Curti authored two clinical trials, one combining the galectin inhibitor, GR-MD-02, with the anti-CTLA-4 agent, ipilimumab, and another combining it with the anti-PD-1 agent, pembrolizumab. Both are first-in-human studies conducted at Providence Cancer Center. An R21 NIH grant award for immune monitoring on these trials was funded in 2015.

Dr. Curti’s investigations of stereotactic body radiation therapy (SBRT) plus IL-2 in collaboration with Marka R. Crittenden, M.D., Ph.D., are ongoing. The randomized Phase II study in melanoma, which opened in 2012, is nearing completion. The results are still preliminary; however, the probability of objective response in patients who received SBRT plus IL-2 was 30 percent and those receiving IL-2 monotherapy was approximately 15 percent. Another randomized Phase II comparison of SBRT plus IL-2 and IL-2 began enrolling in 2015 in patients with advanced renal cancer. A biomarker study of the immunomodulatory effects of IL-2 in these patients was published (Immunity 2015, 43(2):240). Other Cytokine Working Group members will become collaborators on the SBRT plus IL-2 trial in renal cancer in 2016.
Bernard A. Fox, Ph.D.

Member, Molecular and Tumor Immunology Laboratory
Harder Family Endowed Chair in Cancer Research

Dr. Fox and his laboratory seek to improve the effectiveness of cancer immunotherapy. This includes a preclinical effort to develop strategies to increase efficacy and a clinical effort to translate these findings into clinical trials for patients with cancer.

“My lab is interested in assessing the immune infiltrate that exists within the tumor microenvironment, also known as immunoscore, and how we might increase the number and augment the function of immune cells in that environment through various immunotherapeutic strategies. Patients with a positive immunoscore have fared well on checkpoint inhibitors such as anti-PD-1, but patients with a negative immunoscore require other immunotherapeutic modalities to increase their immunoscore, and this is a major focus of my research,” says Dr. Bernard Fox. The immunoscore research by the Fox Laboratory has led to a biotechnology collaboration with PerkinElmer enabling the use of multispectral imaging to assess five to eight markers on a single tumor section. This has allowed a greater understanding of cell types, functionality, and cell-to-cell interactions within the tumor microenvironment. This work was performed with samples from both pre-clinical models and samples from clinical trials, and was presented at the American Association of Immunologists and the Society for Immunotherapy of Cancer (SITC) 2015 annual meetings.

The future of immuno-oncology lies in combination immunotherapies, and Dr. Fox’s laboratory is studying the impact of combining various reagents to improve anti-tumor efficacy. “We have found that the sequence of how antibodies for OX40 and PD-1 are administered is important in determining whether combination treatment is effective,” says Dr. Fox. “We have partnered with a major pharmaceutical company to examine novel reagents targeting immune function, and our research was cited as part of the technical brochure for FDA approval of the first-in-human clinical trial of anti-VISTA. Our hope is that this combination approach will lead to more effective cancer therapies for patients.”

An additional focus of the laboratory is assessing antibody responses both as an effector function as well as surrogates of T-cell immunity in both human and murine systems. “Previously, we observed in a clinical trial of combination immunotherapy for men with advanced prostate cancer, those who had increased PSA doubling time had increased number of strong antibody responses to antigens on circulating tumor cells,” says Dr. Fox. “We extended this research in a pre-clinical model demonstrating that our autophagosome vaccine, DRibbles, plus poly-IC produced antibody responses against antigens within the vaccine.” This work was also presented at the 2015 SITC annual meeting, where Dr. Fox was honored with a SITC Visionary / Legacy Award in recognition of his ingenuity and steadfast commitment to advancing cancer immunotherapy. Earlier in the year, Dr. Fox was awarded The Harder Family Endowed Chair in Cancer Research by the Providence Portland Medical Foundation in honor of his distinguished record of leadership and scientific contributions (see page 6).
John E. Godwin, M.D., MS

Member and program leader, Hematologic Malignancies
Medical Oncology

Dr. Godwin’s research interest is in clinical immunotherapy of hematologic malignancies, also known as blood cancers. This entails understanding the various mechanisms of immune resistance and suppression in hematologic malignancies.

Through intramural and extramural collaborations, Dr. John Godwin seeks a greater understanding of immune system functionality in hematologic malignancies for the development of more effective cancer therapeutics. In 2015, Dr. Godwin’s activities were devoted to several areas of hematological research. “Firstly, I have brought about unique investigator-initiated studies,” says Dr. Godwin. One is a tissue collection protocol for bone marrow samples in Myelodysplastic Syndromes (MDS) patients, specifically evaluating the presence of myeloid derived suppressor cells in MDS.

“Secondly, we have enhanced our clinical trial portfolio by opening several novel immunotherapy trials in hematologic malignancies,” says Dr. Godwin. These include the chimeric antigen receptor (CAR) T cell therapy from Kite Pharma for mantle cell Non-Hodgkin Lymphoma (NHL) and the bispecific antibody therapy for Acute Myeloid Leukemia (AML), MGD006. A trial investigating the anti-CD30 immunoconjugate in combination with anti-PD-1 (nivolumab) through Bristol-Myers Squibb and Seattle Genetics has also been opened, and activation of a trial of the anti-CD33 immunoconjugate from Seattle Genetics, SGN33, for AML and MDS is in process. “We are one of only a few sites in the country working with Kite CAR T cells and the MGD bispecific antibody,” says Dr. Godwin.

Additionally, Dr. Godwin is responsible for the continued development of the hematologic malignancies program in the Providence Oregon Region. “We have an active tumor board that has increased presentations, and our enrollment in clinical trials in hematologic malignancies has increased in the past year,” says Dr. Godwin. In 2015, Providence Health & Services established a system-wide Clinical Program Group focused on hematologic malignancies, of which Dr. Godwin is a co-leader. Through this group, Dr. Godwin has been active in establishing a system-wide pathology report which includes specific tumor markers in NHL.
Michael J. Gough, Ph.D.

Assistant member, Integrated Therapies Laboratory

The Integrated Therapies Laboratory is a collaborative research effort between Michael J. Gough, Ph.D., and Marka R. Crittenden, M.D., Ph.D. It encompasses their overlapping research interest into the ability of cytotoxic therapy to provide large-scale cancer cell death in vivo, while modifying the immune cell profile within the tumor.

“This year was an important year for the laboratory,” says Dr. Michael Gough. “Firstly, we expanded. We acquired a second post-doctoral fellow and two additional research associates in 2015. Secondly, our projects based around the STING sensor have matured. We have successfully published our first paper on this topic in Cancer Research, which also resulted in an image of ours being selected as cover art for the January 2016 issue,” says Dr. Gough (Cancer Res. 2016 Jan 1;76(1):50. Epub 2015 Nov 13).

Subsequent manuscripts are in progress and three grant awards to continue investigation of the STING sensor were received: a postdoctoral fellowship from the American Cancer Society; an award from the Oral Maxillofacial Surgery Foundation with R. Bryan Bell, M.D., D.D.S., to initiate a preclinical surgical model; and an award from the Heath Foundation to apply findings to pre-malignant disease.

A collaboration with Victor DeFilippis, Ph.D., at the Vaccine and Gene Therapy Institute to investigate a collection of novel small molecule STING ligands is underway. The laboratory's collaboration with Jacob Raber, Ph.D., at Oregon Health & Science University has continued to earn grant awards, most recently resulting in a prestigious Howard Hughes Medical Institute Medical Research Fellows Award for a second-year medical student under Dr. Gough’s mentorship.

The laboratory has developed a strong pipeline of new areas of investigation. Much interest has been shown in its project investigating the role of macrophage phagocytic receptors in the response to radiation therapy. Manuscripts describing one candidate pathway and findings from the laboratory’s first clinical trial testing pancreatic cancer patients are in development.

National recognition has brought Dr. Gough invitations to speak at medical, scientific and industry conferences and meetings. Presentations were given at Thomas Jefferson University, Rigel Pharmaceuticals, Bristol Meyers-Squibb, and New Horizons in Immunotherapy for Head and Neck Cancer Symposium with additional presentations at universities and conferences planned in 2016. See page 13 to learn about Dr. Crittenden’s activities.
Hong-Ming Hu, Ph.D.

Associate member, Cancer Immunobiology Laboratory

The long-term goal of the Cancer Immunobiology Laboratory is to understand how the immune system senses tumor cells and to develop effective cancer vaccines and other immunotherapy strategies.

Dr. Hong-Ming Hu leads the Cancer Immunobiology Laboratory in productive, innovative research with a special interest in the development of therapeutic cancer vaccines. He is both knowledgeable and well versed in molecular and cellular immunology studies and is directly involved in the clinical translation of ideas and concepts that originate from his laboratory. “My laboratory investigates how tumor cells, live or dead, are sensed by the immune system. A better understanding of how the immune system recognizes tumor cells will lead to the design of more effective cancer vaccines and immunotherapy strategies,” says Dr. Hu.

Dr. Hu’s interest in autophagy, the mechanism by which cells dispose of unnecessary or dysfunctional components, and its role in regulating antitumor immune responses has spawned several areas of investigation. “Our research in antigen cross-presentation led to an original finding that cross-presentation of tumor-associated antigen is regulated by autophagy in tumor cells. We have also made several new discoveries that uncover the mechanisms by which autophagy regulates the efficiency of cross-presentation and antitumor immune responses,” says Dr. Hu. “Based on these exciting discoveries, we seek to develop a deeper understanding and clearer picture of how autophagy regulates antitumor immune response.”

Another major focus of Dr. Hu’s laboratory is the research and development of DRibble vaccines, a novel therapeutic cancer vaccine platform based on tumor-derived autophagosomes developed in collaboration with Bernard A. Fox, Ph.D. DRibbles have been shown to induce a strong tumor-specific immune response and mediate tumor regression in several tumor models. Using pre-clinical models of breast and lung cancer, Dr. Hu’s laboratory has determined that the effect of a combination of agonist antibodies against T-cell costimulatory molecules (OX40, CD27, GITR) and/or immune checkpoint blockade (PD-1 or PD-L1) could boost T-cell mediated immune responses induced by vaccination with DRibbles. “We generated preliminary data showing such combinations are therapeutically more effective than either vaccine or antibody alone,” says Dr. Hu. “Ongoing experiments are underway to determine the antitumor effects and mechanisms of these combinations. Results from these studies could form the basis for multiple clinical trials.”
Rom S. Leidner, M.D.

Assistant member and co-director, Providence Oral, Head and Neck Cancer Program
Medical Oncology

Dr. Leidner has pioneered the expansion of immunotherapy in head and neck cancer, applying knowledge gained from lung cancer and melanoma studies to patients with head and neck cancer.

The success of immunotherapy in melanoma has inspired many researchers to test the impact of boosting the immune system against other cancer types. As a physician scientist with an interest in head and neck cancer, Dr. Rom Leidner has been at the leading edge of applying various immunotherapy agents to head and neck cancer patients, including immune checkpoint inhibitors, combination therapies, and adoptive transfer of tumor infiltrating lymphocytes (TIL). Through philanthropic support from Providence Portland Medical Foundation, Dr. Leidner treated the first oral squamous cell carcinoma (SCC) patient with adoptive TIL plus tumor-derived, autophagosome-enriched DRibbles vaccine (DPV-001). His group was the first to enroll SCC patients in trials of both pre-operative murine OX40 agonist (MEDI6469) and pre-operative anti-PD-L1 (durvalumab). “We ran the first-in-human Phase I trial of a humanized monoclonal OX40 agonist antibody, MEDI0562, in patients with head and neck squamous cell carcinoma,” says Dr. Leidner. “We are at the national forefront in this capability.”

Dr. Leidner authored and presented five abstracts at international meetings and co-authored two articles in 2015, including a publication with R. Bryan Bell, M.D., D.D.S., on effective immunotherapies in oral, head and neck cancer (J Oral Maxillofac Surg. 2015;73(12 Suppl):S107). Together with Dr. Bell, he organized the inaugural New Horizons in Immunotherapy for Head and Neck Cancer Symposium, bringing together leading investigators in the field of head and neck squamous cell carcinoma (HNSCC) immunotherapy.

An active member of the Providence Portland Medical Center Institutional Review Board, Dr. Leidner serves as the site principal investigator on 10 Phase I/II clinical trials, including a newly-opened investigator-initiated trial using liquid biopsy to analyze circulating tumor DNA in plasma from head and neck cancer patients. Another trial testing a human monoclonal anti-PD-1 treatment for cutaneous SCC will begin recruiting patients in 2016. Additional industry-sponsored studies are in development, testing intra-tumoral modeling directly at the level of cancer cells and TIL in HNSCC patients.

Dr. Leidner values the collaborative environment of the Earle A. Chiles Research Institute. Through multiple intramural collaborations, he has helped build a database of more than 100 samples from HNSCC patients for the creation of autologous TIL and multiplex immunohistochemical analyses of immune infiltration in primary tumors. These tissue libraries have potential as future discovery platforms for adoptive transfer and aid in predicting patient responders. Ongoing intramural collaborations will focus on both human and pre-clinical studies of combination immunotherapies for head and neck cancer. Dr. Leidner hopes to expand his clinical research endeavors in glioblastoma, gastroesophageal, thyroid, salivary, and other rare tumors in the future.
Philippa H. Newell, M.D.

Assistant member and medical director, Providence Liver Cancer Clinic
Liver and Pancreas Surgery

Dr. Newell is pursuing new combination therapies for patients with hepatocellular carcinoma, the most common type of primary liver cancer. By combining traditional liver-directed therapies with immunotherapy, she hopes to provide a wider range of effective treatment options for this patient population.

Many patients with hepatocellular carcinoma (HCC) have underlying chronic liver disease and recurrence rates following standard treatment are high. Radiofrequency ablation (RFA) for HCC involves a specialized needle that is placed in the center of the tumor to destroy tumor cells with high temperature, also known as thermal ablation. By removing a small piece of the tumor from the needle, Dr. Philippa Newell can analyze the molecular pathways that are altered in response to RFA. She has found an increase in heat shock proteins, which mediate the cellular response to protein damage and are indicators of cellular stress. “The big challenge with these molecular approaches is teasing out the effects of the tumor, compared to the treatments, when the liver itself is also highly diseased,” says Dr. Newell.

Dr. Newell is principal investigator or co-principal investigator on multiple clinical trials. She co-authored and presented five posters at international research conferences in 2015 and was first author on the article Multimodal Treatment of Unresectable Hepatocellular Carcinoma to Achieve Complete Response Results in Improved Survival (HPB 2015, 17(5):454).

Dr. Newell is investigating combinations of the immune checkpoint inhibitor anti-PD-1 plus stereotactic radiation and RFA in a Phase III safety and feasibility trial for HCC patients. She is also investigating the molecular pathways affected by these combinations in pre-clinical models of liver cancer with Marka R. Crittenden, M.D., Ph.D., and Michael J. Gough, Ph.D. Additionally, Dr. Newell has started a Phase I safety trial with Brendan D. Curti, M.D., testing pre-operative anti-OX40 immunotherapy plus RFA in patients with colorectal cancer that has metastasized to the liver.

Dr. Newell’s clinical interests also include pancreatic cancer, with projects that focus on prognostic approaches to support informed clinical decision making for these patients. At the 2015 annual meeting of the Society for Immunotherapy of Cancer, she described an analysis of circulating immune cells as potential biomarkers for malignancy of pancreatic tumors. She also gave an oral presentation at the North Pacific Surgical Association conference on results from a retrospective analysis of the use of pre-operative CT scans to predict the development of post-operative pancreatic fistula after pancreatectomy, accepted for publication in the American Journal of Surgery. With the recent push to use personalized medicine to predict which patients will benefit from specific therapies, she is collaborating with Rom S. Leidner, M.D., to perform whole-exome sequencing in patients with head and neck cancer and pancreatic adenocarcinoma.

Community outreach and collaboration are important to Dr. Newell. She organizes a Portland city-wide HCC meeting that brings together specialists from multiple disciplines to discuss the latest updates on management of hepatocellular carcinoma. The conference includes providers from many different hospital systems and private clinics in Portland.
David B. Page, M.D.

Assistant member, Breast Cancer Immunotherapy
Medical Oncology

As a newly-appointed faculty member, Dr. Page seeks to explore novel combination strategies, identify immune-based biomarkers of response, and develop cancer immunotherapies to improve outcomes for patients with breast cancer.

Dr. David Page joined the Earle A. Chiles Research Institute in July 2015 after completing a medical oncology fellowship at Memorial Sloan Kettering Cancer Center. His research focuses on the clinical development of immunotherapy in breast cancer. Dr. Page serves the Portland breast cancer advocacy community as a clinician, researcher, and educator. He is a board member of the Breast Friends Foundation, Medical Advisory Committee member for the Ore. and SW Washington Chapter of the Susan G. Komen Foundation and a frequent peer-reviewer for grant agencies and academic journals.

“My primary research focus is to develop and implement clinical trials that evaluate novel combination strategies designed to overcome immunologic tolerance in breast cancer,” says Dr. Page. Since his arrival, Dr. Page has developed several investigator-initiated clinical trials for both early stage breast cancer and metastatic disease. These include a study combining cytotoxic chemotherapy with immunologic checkpoint blockade to characterize the immunologic effects of chemotherapy, a study to evaluate whether next-generation immune-based assays, such as T-cell receptor sequencing or RNA transcriptional profiling, can predict clinical response in early stage breast cancer, and studies evaluating pre-operative immunotherapy in early stage breast cancer.

“My secondary focus is to develop novel immune-based biomarkers that may one day be used to guide treatment with immunotherapy,” says Dr. Page. “I have expertise in flow cytometry, seromics, and cytokine array platforms, as well as next-generation sequencing assays including Nanostring and T-cell clonal repertoire analysis.” Grant funding from the Terri Brodeur Breast Cancer Foundation supports Dr. Page’s research to evaluate clonal repertoire analysis as a novel predictive biomarker in the setting of neoadjuvant pertuzumab-based chemotherapy to facilitate disease control in women with brain metastases. A Carol Litwin Memorial Fellowship from the SASS Foundation supports his Phase Ib study of peri-operative cryo-immunotherapy and candidate immune-based predictive biomarkers to harness the curative potential of lymphocytes in women with early stage breast cancer.

In 2015, Dr. Page was honored with a Young Investigator Award from the American Society of Clinical Oncology, one of 58 award recipients worldwide, to investigate T-cell receptor DNA deep sequencing as a novel immune-based biomarker in early stage breast cancer. He also received a Clinical Research Excellence Award from the Immuno-Oncology Young Investigator’s Forum, a program of the Academic Research Coalition, and a Breast Symposium Merit Award from the Society for Immunotherapy of Cancer.
William L. Redmond, Ph.D.

Associate member, Cancer Immunotherapy Laboratory

Dr. Redmond and his laboratory seek to elucidate the mechanisms by which T cell co-stimulation through ligation of the TNF receptor family member OX40 (CD134) boosts CD8 T cell survival, differentiation, and the efficacy of tumor immunotherapy.

“We are exploring how specific combinations of immunotherapy agents can be used to boost the function of specialized white blood cells, known as killer T cells, which have the ability to detect and eliminate malignant cells,” says Dr. Redmond. “By understanding the mechanisms by which these drugs regulate tumor-specific immunity, we hope to develop more effective cancer therapeutics capable of harnessing the power of the immune system.”

One area of active investigation is how combinatorial approaches to immunotherapy can synergize to increase anti-tumor immunity. These studies helped demonstrate how two different immune-boosting drugs, anti-OX40 antibody plus interleukin-2, could be combined to induce more robust tumor regression than either agent alone. Research conducted by Dr. Redmond’s laboratory has also revealed a unique synergy between OX40-specific immunotherapy and blockade of the immune checkpoint CTLA-4. “This approach was the equivalent of stepping on the gas pedal while taking your foot off the brakes,” said Dr. Redmond.

Another major focus of the laboratory is investigating the mechanisms by which tumor-specific vaccines plus combination immunotherapy can revive killer T cells that had been suppressed by the tumor. “We are studying how dual anti-OX40/anti-CTLA-4 therapy plus vaccination rescues killer T cells that have been shut down by progressively growing tumors so that they can be reactivated to destroy the cancer,” says Dr. Redmond.

Key accomplishments in 2015 include receiving a Career Catalyst Research Grant from the Susan G. Komen Foundation and an R21 grant award from the National Cancer Institute with Brendan D. Curti, M.D., to fund an on-going phase I clinical trial of Ipilimumab (anti-CTLA-4) plus a Galectin-3 inhibitor (GR-MD-02) in patients with metastatic melanoma. Additionally, there were three publications from Dr. Redmond’s team in 2015, highlighted by a forthcoming article in Proceedings of the National Academy of Sciences entitled Combination OX40 Agonism/CTLA-4 Blockade with HER2 Vaccination Reverses T-cell Anergy and Promotes Survival in Tumor-Bearing Mice. Four poster presentations were made by Redmond Laboratory postdoctoral fellows and research associates at the Society for Immunotherapy of Cancer 2015 annual meeting.
Rachel E. Sanborn, M.D.

Associate member, Phase I Clinical Trials Program
Co-director, Providence Thoracic Oncology Program
Medical Oncology

Dr. Sanborn’s research interests and clinical practice include clinical and translational research in thoracic oncology, and the development of new agents via the Phase I Clinical Trials Program at Providence Cancer Center.

The primary focus of Dr. Rachel Sanborn’s clinical and translational research involves the investigation of immunotherapy or in combinations of immunotherapy agents with standard therapy. “This entails partnering with pharmaceutical companies in novel clinical trials, as well as partnering with other institutions across the country in the conduct of research,” says Dr. Sanborn. “This also includes collaborating with the immunologists at our institution investigating novel agents, such as the DRibble vaccine, in ongoing clinical trials, and in the active process of developing new clinical trials.”

The Phase I Clinical Trials Program has expanded significantly over the past year, dramatically increasing the number of available Phase I clinical trials to more than 50 by year-end 2015. “The reputation of the Earle A. Chiles Research Institute as a referral center for early-phase and innovative research has grown commensurately, with a steady increase in referrals from across the region and out of state,” says Dr. Sanborn. Dr. Sanborn opened and initiated accrual to an investigator-sponsored Phase I/II trial of MK-3475 with gemcitabine in patients with previously-treated advanced non-small cell lung cancer.

In 2015, Dr. Sanborn was elected by colleagues to serve as medical director for the Cancer Research and Biostatistics (CRAB) Clinical Trials Consortium Lung Cancer Research team. This is a four-year term, which will involve working with the multi-institution consortium in developing and expanding the clinical research portfolio and memberships.

Dr. Sanborn also served as a peer reviewer for grant applications for the Department of Defense Lung Cancer Research Program and as a panel member for the American Lung Association Take Action Network. She was co-chair of the American Lung Association’s Lung Force Expo held in Portland, Ore., where she presented on “Lung cancer screening: Evidence, benefits, and pitfalls from a high-volume program’s perspective.” She also serves as a member of Free to Breathe’s Medical Advisory Workgroup, which consists of a panel of physicians focused on thoracic oncology nationally.

Within Providence Health & Services, Dr. Sanborn is a member of the Thoracic Oncology Clinical Focus Group, and acts as co-chair for its thoracic medical oncology working group subcommittee. She is also a member of the Genomics Clinical Focus Group.
Andrew D. Weinberg, Ph.D.

Member, Basic Immunology Laboratory

Dr. Weinberg and his laboratory focus on cellular and molecular mechanisms of action of OX40 agonists. OX40-based therapy leads to tumor regression in cancer-bearing mice, both as monotherapy or when combined with other immunotherapy modalities. Their pre-clinical research has shown that OX40-based therapy leads to tumor regression, both as monotherapy and when combined with other immunotherapy modalities.

The Basic Immunology Laboratory led by Dr. Andrew Weinberg uses pre-clinical models to study the molecular pathways involved in co-stimulation of T cells using agonist anti-OX40 antibodies. “Using an immunization model in the lab, we examined changes that occur in phospho-protein levels within antigen-stimulated T cells comparing anti-OX40 to the immune check-point inhibitor anti-CTLA-4. We found that anti-OX40 treatment led to increased T cell survival and production of memory T cells,” says Dr. Weinberg. In the MCA205 pre-clinical tumor model, anti-OX40 was found to bind to regulatory T cells (Tregs) from the tumor microenvironment. To characterize how OX40 agonists affect Treg function, gene array experiments were performed to analyze the molecular changes of Tregs from tumors treated with and without anti-OX40. “Several transcripts within tumor-isolated Tregs were consistently altered with OX40 agonists. We are currently confirming these changes on the protein level,” says Dr. Weinberg.

Dr. Weinberg is engaged in multiple preclinical and clinical intramural collaborations with the Providence Oral, Head and Neck Cancer Program, Breast Cancer Program, Radiation Oncology, and Cytokine and Adoptive Immunotherapy Program, as evident in his co-authorship of the review article OX40 Signaling in Head and Neck Squamous Cell Carcinoma: Overcoming Immunosuppression in the Tumor Microenvironment (Oral Oncology. 2016;52:1; Epub 2015 Nov 21). Examinations by his laboratory of immune response to combination anti-OX40 and TGFβ receptor blockade resulted in a publication for which he was senior author (Cancer Immunol Res 2015, 3(5):526).

In recognition of his seminal contributions to the emerging field of T-cell agonist immunotherapy, Dr. Weinberg was selected to serve as a co-organizer for the Society for Immunotherapy of Cancer 30th Anniversary Annual Meeting held in National Harbor, Md. He also served as co-chair for the meeting’s Coinhibition and Costimulation Session which focused on new costimulation (OX40) and coinhibition (VISTA) pathways of T cells, and combination therapy with anti-CTLA-4 and anti-PD-1.

Dr. Weinberg also co-chaired the inaugural Cambridge Health Institute Agonist Immunotherapy Targets stream at the 11th Annual Protein Engineering Summit held in Boston. He served as a moderator of the Combinations in Cancer Immunotherapy Session and also presented on OX40 Agonist Combined with PD-1 and TGFβ Receptor Blockade. Additional speaking invitations brought Dr. Weinberg to the 8th Annual Canadian Cancer Immunotherapy Consortium Symposium, the inaugural New Horizons in Immunotherapy for Head and Neck Cancer Symposium held in Newberg, Ore., and to South Korea for seminars given to the Korean Society for Immunology and Academy of Immunology and Microbiology.
Kristina H. Young, M.D., Ph.D.

Assistant member, Tumor Microenvironment Laboratory
Radiation Oncology

Dr. Kristina Young joined the faculty of the Earle A. Chiles Research Institute to pursue translational cancer immunotherapy research with a focus on the tumor microenvironment and radiation oncology.

Dr. Kristina Young’s research interests include the role of cancer-associated fibroblasts on immune-mediated radiation resistance in the treatment of pancreatic cancer. Her laboratory is investigating how inhibition of the fibroblast activation protein (FAP) combined with radiation can delay or impede tumor growth. “Thus far we have found that FAP inhibition with radiation results in two separate tumor growth delays in pre-clinical models. We observed an early delay approximately seven days following radiation therapy, and a second delay approximately three weeks following last therapy,” says Dr. Young. Additional experiments are planned to determine the mechanism of action and enhance these findings. The laboratory is also investigating the direct and indirect inhibition on radiation efficacy. “Based on our previously published data demonstrating enhanced radiation efficacy in pre-clinical models, we are performing further experiments to determine if the improved response to radiation was a direct effect of CD8 T cells,” says Dr. Young.

Dr. Young is also an active clinical investigator. She is principal investigator of an investigator-initiated Phase II clinical trial testing TGFβ inhibition in patients undergoing neoadjuvant chemoradiation for locally advanced rectal cancer, and is engaged in intramural collaborations with Todd S. Crocenzi, M.D., and Philippa H. Newell, M.D., on a multi-institution Phase I trial of stereotactic body radiation therapy (SBRT) plus nivolumab in patients with hepatocellular carcinoma not eligible for other liver-directed therapies. Additionally, her collaborations with Marka R. Crittenden, M.D., Ph.D., and Michael J. Gough, Ph.D., resulted in the journal article, Comparing Equals When Evaluating Immunotherapy with Different Doses and Fractions of Radiation Therapy (Immunotherapy. 2015;7(8):847).

In 2015, Dr. Young was honored by the American Society for Clinical Oncology as one of 58 young investigators worldwide to receive its prestigious Young Investigator Award. The award will fund her translational research proposal, entitled Targeting the Tumor Stroma to Enhance Radiation Efficacy, to advance state-of-the-art cancer immunotherapy through improving the immune response to cancer among patients receiving radiation therapy. She was also awarded a Research and Education Foundation Seed Grant from the Radiologic Society of North America for her proposal Targeting Cancer-Associated Fibroblasts to Enhance Radiation Efficacy.
Peripheral Blood Mononuclear Cells (PBMC) and serum (left) are isolated and stored in liquid nitrogen tanks for use on subsequent assays (right).

The Robert W. Franz Cancer Research Center, founded in 1993 by Walter J. Urba, M.D., Ph.D., and a small team of scientists, is part of the Earle A. Chiles Research Institute at Providence Cancer Center.

Research laboratories of the Earle A. Chiles Research Institute are in close proximity to the oncology clinics and patient rooms within Providence Cancer Center so that scientists never lose sight of the people their research is intended to serve. This environment encourages translational research, also known as bench-to-bedside research, where scientists and physicians partner to translate the most promising discoveries from the laboratory into novel treatments for patients in Oregon and throughout the country.

The Earle A. Chiles Research Institute is home to state-of-the-art core facilities offering the latest in immunological monitoring, flow cytometry and molecular pathology and informatics services. These facilities are available to both intramural and extramural investigators.

Immune Monitoring Laboratory

Established in 2000, the mission of the Immune Monitoring Laboratory (IML) is to support clinical investigators and research scientists at Providence Cancer Center and throughout the United States by providing real-time, state-of-the-art monitoring of cancer patients’ immune responses during immunotherapy clinical trials. The IML is also the archival and disbursement center for the acquisition, processing, cryopreservation and cataloguing of all peripheral blood mononuclear cells and serum collected during the course of cancer clinical trials.

The IML team is among the nation’s leaders in developing and implementing immune monitoring assays for the evaluation of anti-tumor immune responses in cancer patients receiving immunotherapy. They measure patients’ immune responses to different anti-cancer immunotherapy interventions, such as checkpoint inhibitors, T-cell agonists, and experimental cancer vaccines, to assess their effectiveness. They use a variety of standardized assays specifically designed and optimized to monitor changes and detect responses in cancer patients’ immune systems throughout the course of their treatments.
Flow Cytometry Core

The IML encompasses the Flow Cytometry Core, a valuable resource to all intramural investigators. Highly sophisticated polychromatic flow cytometry techniques allow investigators to measure anti-tumor immune responses on a cellular level. The results help researchers refine their studies and improve immunotherapy strategies for patients at Providence Cancer Center and throughout the world. The Flow Cytometry Core provides sample processing, staining, data acquisition and analysis under the supervision of experienced research personnel who assist in the design and execution of multi-color flow cytometry and all sorting experiments.

The Flow Cytometry Core is equipped with a BD LSRII, BD FACS Aria II Cell Sorter with BSL2 Containment System, BD FACS Calibur, CTL ImmunoSpot ELISpot, Bio-Plex 100 and Guava PCA-96, among other state-of-the-art immunological monitoring and flow cytometry resources.

Molecular Pathology Core

The Molecular Pathology Laboratory (MPL) is a fundamental and strong component of translational research of the Earle A. Chiles Research Institute. The MPL provides translational immunologists with molecular correlates to their research questions. The MPL leverages shared clinical infrastructures dedicated to the deployment of a system-wide personalized medicine program enabling high-throughput “-omics” projects with clinically validated bioinformatics pipelines supported by a dedicated in-house software development team. All applications include data security, access logs, data storage, and backup and are built to operate in the clinical setting.

The MPL is part of Providence Health and Services laboratories, licensed by the Oregon State Health Division and accredited by various agencies such as the College of American Pathologists, Joint Commission, Accreditation of Hospitals Organization, American Association of Blood Banks and FDA. The MPL maintains a significant and diverse sequencing infrastructure including the latest Illumina and Ion Torrent instrumentation as well as instruments for performing Sanger sequencing and quantitative polymerase chain reaction (PCR). The large-capacity HiSeq 2500 is devoted to exome sequencing, RNA-seq and other genomics applications.
EDUCATION & TRAINING

GRADUATE EDUCATION
Since 1994, the Earle A. Chiles Research Institute has trained the next generation of tumor immunologists.

Through a partnership with Oregon Health & Science University School of Medicine, graduate students conduct research under the mentorship of a faculty member with a joint appointment at the School of Medicine and the Earle A. Chiles Research Institute. Students accepted into doctoral programs in Molecular Microbiology and Immunology, Molecular and Cellular Biosciences, and Cancer Biology attend university courses and conduct research at the Earle A. Chiles Research Institute in the laboratory of their faculty advisor. Students have the opportunity to give poster presentations at national conferences and present their research at department seminars while advancing to doctoral candidacy. Faculty advisors serve as members of the students’ thesis committees, guiding them through thesis defense to degree completion. Upon receipt of their doctoral degrees, previous students have been accepted to postdoctoral fellowships at the National Cancer Institute, INSERM (French National Institute of Health and Medical Research) and within the biotechnology industry.

POSTDOCTORAL FELLOWSHIPS
Earle A. Chiles Research Institute provides a rich postdoctoral training environment that stimulates creativity and nurtures professionalism for fellows pursuing careers in cancer immunotherapy.

Postdoctoral fellowships serve as training periods of scholarly, mentored research for doctoral degree holders seeking to acquire the professional skills and experience necessary for independent scientific careers. With input and guidance from their faculty mentors at the Earle A. Chiles Research Institute, fellows develop individualized development plans to identify professional development opportunities and career objectives which serve to guide them through their fellowships.

In addition to discipline-specific expertise, conceptual knowledge and research skill development, fellows are also mentored in leadership, management, communication, and the responsible conduct of research. Fellows are encouraged to obtain external funding and develop a strong publication record to provide a solid foundation for transitioning to an independent scientific career. Previous postdoctoral fellows have received funding from the NIH Pathway to Independence Award (K99), American Cancer Society Postdoctoral Fellowship Award, and Prostate Cancer Foundation Young Investigator Award, and obtained appointments at Rush University, Oregon Health & Science University, Legacy Research Institute and the Earle A. Chiles Research Institute upon completion of their training fellowships.
SUMMER RESEARCH PROGRAM
The Earle A. Chiles Research Institute offers a summer research program for undergraduate students pursuing a career in biomedical sciences.

Research projects and poster presentations from the 2015 cohort include:

- Sting Ligand and its Effect on SOCS Production
- Soluble Intercellular Signaling Factors in the Tumor Microenvironment
- Different Therapeutic Anti-PD-1 Clones Prevent or Allow the Detection of PD-1 via Flow Cytometry
- Cross Presentation of DRibble Vaccine Independent of MyD88 Adaptor Protein
- OX40 Immunotherapy Effect on Tumor Resident Regulatory T cell Function and Phenotype

Past interns have been accepted to Oregon Health & Science University School of Medicine, Northwestern University School of Medicine, and The Mayo Clinic Graduate School.

The intensive nine-week internship is designed to provide direct, hands-on research experience and mentorship for undergraduate students who are interested in biomedical research. Under the guidance of a faculty mentor, interns complete an independent research project and present their findings at a capstone poster session. Interns also attend regular bioinformatics classes, institute-wide research seminars, and Journal Club meetings.
CREATING HOPE LUNCHEON

2015 marked the 17th anniversary of the Creating Hope for Cancer Patients Luncheon, the signature fundraising event of Providence Cancer Center benefitting the Earle A. Chiles Research Institute.

With more than 540 guests in attendance and a $100,000 matching challenge, the 17th Annual Creating Hope Luncheon garnered a record-breaking $620,000 in contributions. Emceed by Matt Zaffino of KGW Channel 8 News, the program included remarks from cancer patients and survivors, including a keynote address from cancer survivor, cartoonist and author of Cancer Vixen, Marisa Acocella Marchetto. Survivors shared stories of their treatment and care at Providence Cancer Center and inspired hope in others. Walter J. Urba, M.D., Ph.D., director of cancer research at the Earle A. Chiles Research Institute, was joined by Nick Morris, Ph.D., cancer survivor and senior research scientist, in conveying the importance of philanthropy in advancing cancer research and immunotherapy.

FINISH CANCER CAMPAIGN

The 2015 Creating Hope Luncheon served as the launch of Providence Cancer Center’s award-winning #FINISHCANCER campaign.

Honored with a 2015 Gold Award by the Cancer Awareness Advertising Awards Program, the #FINISHCANCER campaign aims to raise awareness of recent advancements in cancer research – namely immunotherapy – and the need for continued funding. The campaign emphasizes the “I CAN” in “FINISHCANCER,” calling on all to help finish the fight against cancer. Whether through volunteering, advocacy, donations or promoting cancer screenings and prevention, all have a role to play in finishing cancer. Visit www.finishcancer.org to learn more.
PROVIDENCE HOOD-TO-COAST RELAY

More than $565,000 was raised for cancer research at Providence Cancer Center by participants and supporters of the 2015 Hood-To-Coast Relay.

For the second year in a row, Providence Health & Services was the title sponsor of the world's largest relay race, Providence Hood-To-Coast Relay, spanning 198 miles from Timberline Lodge on Mt. Hood to the coastal town of Seaside, Ore. Considered the “mother of all relays,” this two-day event included 12,600 runners comprising 1,050 teams supported by 3,600 volunteers.

Several teams from Providence Health & Services competed, including Providence Cancer Center team “Runners For Research” led by team captain Samantha Kaiser, director of cancer research operations at the Earle A. Chiles Research Institute. Fellow teammates included researchers, administrators, providers, advocates, patients and Providence Oregon CEO, Dave Underriner.

Runners For Research Van 1 at Timberline Lodge.

Runners For Research Van 2 at Providence Cancer Center.

WHITE OUT CANCER DAY

A day devoted to raising awareness of cancer immunotherapy, the Earle A. Chiles Research Institute joined institutions across the world in celebrating #WhiteOutCancerDay.

On June 12, 2015, Providence researchers stood side by side with oncologists, nurses, fundraising officers, administrators and support staff to show support for cancer immunotherapy, shared via Providence Cancer Center social media using hashtags #WhiteOutCancer and #FinishCancer.

Researchers, clinicians, advocates, administrators and support staff wear white in support of #WhiteOutCancerDay.
FRANZ LEADERSHIP CABINET

The Robert W. Franz Leadership Cabinet comprises men and women with a strong desire to connect our local community with dedicated teams of researchers at the Earle A. Chiles Research Institute working to finish cancer.

Founded in 2001, the leadership cabinet has a strong and loyal membership representing a broad spectrum of the community.

2015 CABINET MEMBERS

Charlie Engleberg, Chair
Flo Atkinson
Stephen Bader, M.D.
Mark Beckius
Walter Bowen
Earle M. Chiles
Maxine Cracraft
Dan Floyd
Robert W. Franz
Diana Hall
Cindy Harder

Tyler Johnson
Sheryl Langerman Rosenfeld
Lynn Loacker
TJ O’Connor
Linda Read
James F. Robb, Ph.D.
Linda Smiley
Jim Snow
Judi Swift
Mark Williams
Linda Yoshida

At the Earle A. Chiles Research Institute, scientists work in lockstep with physicians to discover ways to harness our own immune systems in the fight against cancer. “I continue to be amazed by the number of times researchers at the Earle A. Chiles Institute have been first in Oregon, first in the country, even first in the world, to deliver novel treatments to patients,” says Charlie Engleberg. “Cancer immunotherapy is proving to save lives!”

2015 Franz Leadership Cabinet with ex-officio members Bernard A. Fox, Ph.D., and Walter J. Urba, M.D., Ph.D., pictured second row far left and far right, respectively. Not all members pictured.
SELECT PUBLICATIONS


Linch SN, McNamara MJ, Redmond WL. OX40 Agonists and Combination Immunotherapy: Putting the Pedal to the Metal. Frontiers in Oncology 2015, 5: 34.


Our Mission
As people of Providence, we reveal God’s love for all, especially the poor and vulnerable, through our compassionate service.

Our Core Values
Respect, Compassion, Justice, Excellence, Stewardship

www.providencefoundations.org