CCR is the On-site Basic, Translational and Clinical Research Arm of the NCI

National Cancer Institute

Intramural Divisions
- Division of Cancer Epidemiology and Genetics

Extramural Divisions
- Division of Cancer Treatment and Diagnosis
- Division of Cancer Control and Population Sciences
- Division of Cancer Prevention
- Division of Cancer Biology
- Office of Centers, Training, and Resources
- Center to Reduce Cancer Health Disparities
History and Evolving Culture Shift Continuum for CCR

1994 Marks-Castle Report
1995 Bishop-Calabresi Report
2001 DCS DBS CCR formed

2009 Emphasize multidisciplinary research to solve complex problems: Faculties, Working Groups, Centers of Excellence

Continue shifting the culture in CCR

- Reengineering the IRP has been a dynamic process
- Encourage team science and collaboration while preserving and expanding outstanding PI-based research
- Strategies for rewarding team science have been implemented
- Faculty and working groups were formed, leading to the establishment of Centers of Excellence around areas of strength
- Closer ties between clinical and basic research have led directly to translational research advances and new opportunities
Integrate basic, translational, and clinical research to make cancer preventable, curable, or chronically manageable.
Distribution of Research Emphasis Across CCR

- Basic Research (30%)
- Translational and Clinical Research (55%)
- HIV/AIDS Research* (15%)

* About 50/50 Basic/Translational
Centers of Excellence serve as Focal Points for Bench to Bedside Translation

- Centers of Excellence serve to support the IRPs dedication to long-term, high-risk, innovative basic, and clinical research
  - Immunology - Robert Wiltrout, Head
  - Chromosome Biology – Gordon Hager, Head
  - HIV and Cancer Virology - Stuart LeGrice, Head
  - Molecular Oncology - Guiseppe Giaccone, Head
  - Integrated Cancer Biology and Genomics - Snorri Thorgeirsson, Head
  - **Genitourinary Malignancies- Marston Linehan and William Dahut, Co-Heads**

**Currently under development**
Distinctive Attributes of CCR’s Clinical Research Program

• Integrate basic and clinical research to accelerate translation of advances to benefit patients
• Integrate genetically engineered mouse models and methods with early drug development
• Discover and develop molecularly targeted agents and combinations of agents
• Conduct concept-based (science-driven) clinical trials to evaluate new therapies rather than test existing ones
• Develop and deliver novel technologies
• Study rare diseases and underserved cancers
• Provide translational research training
• Integrate personalized medicine into all clinical trials
A Shift Is Under Way

<table>
<thead>
<tr>
<th>Previous Approach</th>
<th>New Practices</th>
</tr>
</thead>
<tbody>
<tr>
<td>Descriptive medicine</td>
<td>Understanding of disease mechanisms</td>
</tr>
<tr>
<td>Empirical diagnosis</td>
<td>Mechanism-based diagnosis/treatment</td>
</tr>
<tr>
<td>Grouped by organ</td>
<td>Sub-grouped by molecular/biological classification</td>
</tr>
<tr>
<td>Uniform treatment</td>
<td>Individualized treatment</td>
</tr>
<tr>
<td>Retrospectively diagnose disease</td>
<td>Prospectively evaluate relative disease risk</td>
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<tr>
<td>Acute care</td>
<td>Early detection and intervention</td>
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</tbody>
</table>
Envisioning Personalized Care

- Earlier detection
- Cancer detected
- Today's cancer
- Personalized medicine
- Tomorrow's chronically managed cancer
- No cancer

Cancer burden

Clinical

Subclinical

Time
Reengineering the Clinical Trials Process at the NCI

Current NCI IRP clinical trials process evaluated based on data (2000-09)

- Recommendations were developed
- Presented to NCAB and BSC
- CCR implementing changes now including:
  - Developed Standard Operating Procedure for Scientific Review Groups (now at Lab/Branch level)
  - Identified 86 initial metrics for collection and completed necessary IT system changes
  - Establishing a central protocol support office
  - Established a CCR Clinical Research Strategic Planning & Monitoring Committee
    - Conducting visioning exercises
Investing in Programs to Bolster Discovery and Accelerate Translation

- Clinical Molecular Profiling Core
- Deep Sequencing Facility
- Trans-NIH program of large-scale RNAi screening based (NCGC)
- High-Resolution Imaging Facility
- NIH Mouse Imaging Facility - Bethesda Campus
- Small Animal Imaging Program – Frederick Campus
- Integrated Oncology Imaging Clinic
- NIH Center for Interventional Oncology
- Comparative Oncology Program
- Comparative Molecular Pathology Research Training Program
- Molecular Pathology
- Molecular Discovery Program
- Center for Advanced Preclinical Research
- NIH-Systems Biology
- Chemical Biology Consortium in Partnership with DCTD
- Centers of Excellence
Additions to Senior Leadership

• Joel Schneider, Chief, CBL (2009)
• J. Carl Oberholtzer, Chief, LP (2008)
• Crystal Mackall, Chief, POB (2008)
• Terry Van Dyke, Chief, MCGP (2007)
• Kevin Camphausen, Chief, ROB
• Giuseppe Giaccone, Chief, MOB (2007)
• Giorgio Trinchieri, Chief, LEI (2006)
• Paul Meltzer, Chief, GB (2006)

Other Appointments:
• R. Andrew Byrd, Acting Director, MDP
• William Dahut, Clinical Director
• Robert Yarchoan, Director for the NCI Office of HIV and AIDS Malignancies
• Michelle Bennett, Deputy Director
NCI’s IRP can rapidly redirect research efforts and resources to address encouraging public health issues; Xenotropic Murine Leukemia like Retrovirus (XMRV)

- Found in approximately two-thirds of chronic fatigue syndrome (CFS) patients and 4% of controls in clusters of cases in Nevada and Florida-South Carolina
  - *Science, 2009 Oct 8 online*

- The NCI IRP was able to rapidly assemble a multidisciplinary team to approach this public health concern. Experts in retrovirology, oncogenesis, cancer biology, epidemiology, and clinical research as well as others are actively engaged in advancing scientific knowledge of XMRV and the question of its possible impact on human health

- An intramural/extramural working group has been assembled to communicate findings and collaborate

- Is there a role for XMRV in either prostate cancer and/or lymphoma?
President Obama toured the NIH campus on September 30th. During his visit he stopped in the laboratory of Dr. Marston Linehan, Chief of the Urologic Oncology Branch, to talk about hereditary kidney cancer and advances being made in CCR.
CCR Labs and Branches Are Woven Together Around Strategic Priorities

- Understand the Cancer Process from Initiation to Metastasis
- **Interrogate the Molecular Genetics of Cancer**
- Improve Cancer Prevention, Early Detection, and Diagnostic Approaches
- Develop and Validate Novel Molecularly Targeted Interventions
- Harness the Immune System to Combat Cancer
- Discover and Develop Approaches to Combat HIV/AIDS and AIDS-associated Malignancies
CCR Scientific Presentations to the NCAB

- Shiv Grewal - RNAi-mediated epigenetic control of the genome
- Shyam Sharan - Understanding the functional significance of variants identified in human breast cancer susceptibility genes
- Pat Steeg - Brain metastasis of breast cancer: Molecular and preclinical advances
- Louis Staudt - RNA interference screens and cancer gene resequencing to discover the Achilles heel of cancer
- Marston Linehan - Genetic Basis of Kidney Cancer: Opportunity for Disease Specific Targeted Therapy
• What clinical initiatives are required to test emerging preclinical strategies?

• How do we get bench discoveries to the bedside more efficiently/effectively as well as address the "personalized aspect"?

• What clinical initiatives are required to test emerging preclinical strategies for brain metastases of breast cancer?
**Scientific Advances**

- Gene Therapy Method Slows Tumor Growth in Mice (Trinchieri/Blumenthal) *Cancer Gene Therapy* online October 9, 2009


- Gene Mutation Linked to Type of Childhood Cancer (Khan) *J Clin Invest* Online October 5, 2009


- NIH Study Reveals New Genetic Culprit in Deadly Skin Cancer (Rosenberg) *Nature Genetics* online: 30 August 2009

- Immunity to murine prostatic tumors: continuous provision of T-cell help prevents CD8 T-cell tolerance and activates tumor-infiltrating dendritic cells (Hurwitz) *Cancer Res.* 2009 Aug 1;69(15):6256-64


- Cancer Immunotherapy Can Use Small Numbers of Stem-Like Immune Cells to Destroy Large Tumors in Mice (Restifo) *Nature Medicine*. Online June 14, 2009
Chemical Biology Consortium (CBC)

**Vision**

- Develop an integrated network of chemists, biologists, and molecular oncologists, with synthetic chemistry support.
  - Active project management by NCI and external advisory boards.
  - Unified discovery with NCI preclinical and clinical development.
  - Link to other NCI initiatives with CCR as an integral partner.
  - Ongoing grant portfolio analysis.

- Focus on unmet needs in therapeutics such as “undruggable” targets and under-represented “orphan” malignancies.

- Enable a clear, robust pipeline from target discovery through clinical trials for academic, small biotech, and pharma investigators.

**High-throughput screening**

**Hit to lead**

**Lead optimization**

**Candidate seeking** (1-3 compounds)

**Preclinical development**

**Clinical development**

- Phase 0
- Phase I
- Phase II
- Phase III

- Phase III
Clinical trials performed using an exploratory investigational new drug (IND) will facilitate targeted therapies entering early phase evaluation where the target can be carefully monitored. The goal of this new guidance is to safely shorten the timeline for drug development. As part of the DCTD-CCR collaboration, novel agents for high-priority targets originating from academic and other extramural researchers will be eligible to take advantage of intramural resources.

Molecular Discovery Program

Build on the Strength of Biology in the CCR Mission / Founding Principles

- Enable collaborative, multi-disciplinary, basic research to advance mechanistic understanding
- Re-invigorate chemistry and chemical biology
- Facilitate the combinations of biological, chemical, and structural approaches to understanding human biology
- Enable the discovery of biological modulators and the verification of such modulators *in vitro* and *in vivo*
- Establish partnerships with the CBC and NCGC to share expertise and resources in areas such as Chemical Synthesis, Natural Products and Structure-based discovery
- Facilitate the transition of discoveries to the CBC development engine of DCTD and to Phase 0/1 trials
To facilitate the improvement of preclinical assessment and clinical trial design for effective cancer diagnosis and treatment

Terry van Dyke