



## **ACCRF'S RESEARCH AGENDA (September 2009)**

ACCRF's Research Agenda represents the best efforts of the best minds at the best cancer institutions in the world to find a cure for adenoid cystic carcinoma (ACC). As with many rare diseases, ACC poses some peculiar challenges for researchers. The lack of ACC specimens and models – the building blocks of research – has been accompanied by the lack of a logically-sequenced plan to access the most promising technological platforms of scientific discovery. These challenges must be met with ingenuity and determination in order to gain more widespread focus, greater resources and new insights. With the support of many patients and scientists, ACCRF is accelerating the development of improved treatments for ACC through this Research Agenda.

### **Guiding Principles**

Certain principles underlie the manner in which ACCRF has developed the overall Research Agenda as well as the individual research projects:

- Venture Philanthropy Approach – The gaps in medical research are well known. Private firms do not find it financially rewarding, especially for rare diseases, to undertake the basic and pre-clinical translational research that eventually results in candidate drugs. Academic and government investigators receive less funding than pharmaceutical investigators and typically are less focused on developing novel treatments. **ACCRF sees its role as a provider of seed capital to advance pre-clinical drug discovery and development to the point where clinical trials are supported by the National Institutes of Health (NIH) and private sponsors.**
- Portfolio Management Perspective – ACC, like other cancers, is a varied and complex disease that will be understood more quickly by gathering together a wide variety of different perspectives. Rather than focus on just one approach, **ACCRF seeks to build a diversified portfolio of promising research projects.** Each project represents one fragment in a mosaic that will create a clearer picture of ACC.
- Multi-Institutional Cooperation – No single institution has the resources or the expertise to carry out all the necessary research projects for ACC. **The specimens and models are too rare, the technology platforms are too expensive, and the leading experts are too dispersed for any one institution to carry the burden alone.** ACCRF's greatest impact is in fostering multi-institutional collaboration.
- Proactive Project Selection – ACCRF is fortunate to benefit from the insights of an exceptional Scientific Advisory Board. It would be a waste of outstanding talent to limit its participation to the passive review of investigator-initiated proposals (the traditional model for most foundations in



which researchers tell project funders what they would like to study). Instead, in consultation with top researchers from around the world, **ACCRF's Scientific Advisory Board proactively drives the Research Agenda, suggesting high-impact projects and identifying the leading researchers with the capacity and interest to carry them out.** Certainly, ACCRF welcomes investigator-initiated proposals, but does not rely upon them as the primary engine of progress.

- Accelerating Practices – The need for rigor and validation in scientific research often obscures and occasionally blunts the sense of urgency among researchers. However, ACCRF believes that there are ways the research process may be accelerated responsibly:
  - ACCRF pushes for **rapid and wide dissemination of research findings** to avoid unnecessarily duplicative work and to attract new researchers.
  - ACCRF delineates **expectations for deliverables and timeframes in each project** and uses contracts in place of grants where appropriate.

Based upon these principles, and benefitting from the input of many researchers at numerous scientific meetings, ACCRF has created this Research Agenda. It is a living document that will change as circumstances and feedback warrant.

### Project Categories

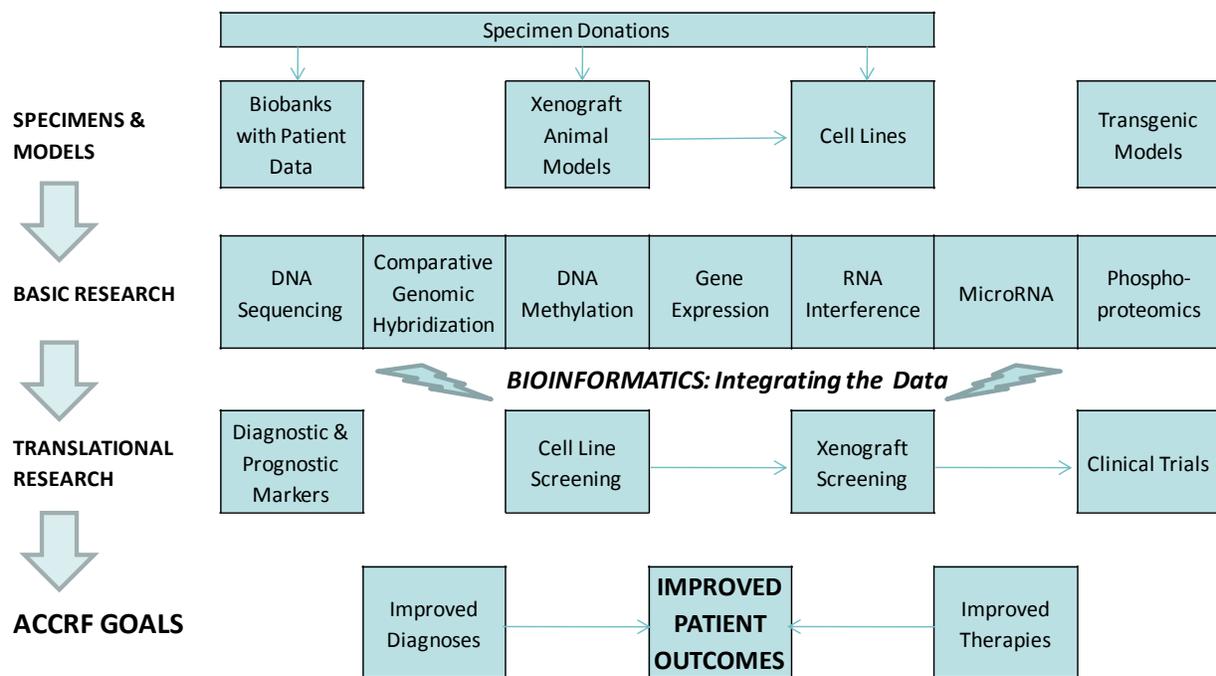
The projects supported by ACCRF fall into three broad categories:

1. Specimens & Models – Researchers investigating ACC need certain building blocks as the foundation of their experiments. Biobanks (repositories for tumors, saliva, plasma and other specimens), cell lines (tumor cells grown in dishes) and animal models (tumors grown typically in mice) are readily available for researchers looking at common cancers. Unfortunately, these specimens and models are very difficult to obtain for researchers looking at rare cancers. ACCRF is committed to increasing the availability of – and access to – these **crucial building blocks of research**.
2. Basic Research – In order to accelerate the development of improved therapies, it is prudent to invest in projects that **reveal the mechanisms of action that are driving the genesis, development and progression of ACC**. By understanding which genes, proteins and/or environmental factors are leading to the cancer, researchers will be in a better position to propose and develop effective treatments. ACCRF and its Scientific Advisory Board believe that supporting basic research is a necessary and pivotal step in hastening the discovery of improved therapies.

3. Translational Research – **The eventual goal of all research is to get treatment ideas from “the bench” (the research laboratory) to “the bedside” (patients in the clinic).** Before a novel therapy can reach the bedside, however, it must pass many tests of safety and efficacy. ACCRF is preparing an open and efficient infrastructure to conduct high-throughput screening of compounds in cell lines and animal models. In addition, ACCRF is exploring ways to support clinical trials for ACC patients, whether for novel compounds or drugs already approved for other indications.

In summary, the Research Agenda focuses on putting in place the building blocks of research and then finding the most capable researchers with the available capacity to carry out rapidly the highest-impact basic and translational research projects. The various components are depicted below and described thereafter.

### Schematic Diagram of ACCRF’s Research Agenda



ACCRF has methodically pursued parallel progress in the various components of the Research Agenda. In many projects, multiple investigators across multiple institutions are collaborating and contributing to progress. Currently, approximately 50 projects are under way with

investigators representing 25 institutions. A partial listing of ACCRF-affiliated institutions – organized by their involvement in research projects – includes the following:

Specimens and Models		Basic Research		Translational Research	
Biobanking	University of Virginia MD Anderson NIDCR	DNA Sequencing	Sanger Institute MD Anderson University of Virginia	Diagnostics/Imaging	UCLA
Xenograft Development	University of Virginia Johns Hopkins Dana-Farber Mass. General Hosp. Mass. Eye & Ear	DNA Rearrangements	Sanger	Xenograft Screens	START
Cell Line Development	MD Anderson Brigham & Women's Johns Hopkins INCELL University of Virginia Dana-Farber Mass. General Hosp.	CGH	Sahlgrenska Academy MD Anderson	Cell Line Screens	Mass. General Hosp. National Insts. Of Health
Model Characterization	UCSF University of Virginia	Methylation	Johns Hopkins MD Anderson	Clinical Trials	National Insts. Of Health
		Mitochondrial Mutations	Johns Hopkins		
		Transcriptome Seq.	Sanger Institute		
		RNAi	Harvard		
		MicroRNA	MD Anderson		
		Phosphoproteomics	Cell Signaling Tech. University of Virginia Mass. General Hosp.		
		Bioinformatics	MD Anderson University of Virginia		

### Specimen Donations

The entire research endeavor is based upon the support of patients. By consenting to provide tumor specimens, patients jumpstart the entire process of developing biobanks, animal models and cell lines – the building blocks upon which improved therapies may be discovered. Indeed, tumor donations permit patients to take an active role in eventually helping other patients – and perhaps themselves.

The most useful specimens for research are those that are made available to researchers within hours of surgery (fresh or frozen). So it is imperative that patients inform their surgeons ahead of time that they would like to donate for research any excess tumor that won't be required for their own follow-up care.

For more information on how patients may donate tumor specimens, please click [here](#).

### Biobanks and Patient Databases

Biobanks are crucial to the research endeavor in two ways. First, they provide the inputs for the gene-based and protein-based studies that are involved in developing targeted therapies and improved diagnostics. Second, if they are combined with patient records, they provide an invaluable resource from which to undertake correlative studies on patient outcomes.

- **M.D. Anderson Cancer Center** – ACCRF has provided support for a Lab Technician to harvest, process and distribute ACC samples. In addition, pathologic, clinical and follow-up information on ACC cases are maintained.



- **University of Virginia** – ACCRF has provided support for a Lab Technician to harvest, process and distribute ACC samples. Specimens are banked with available clinical information.
- **NIDCR Salivary Gland Tumor Biorepository (SGTB)** – Sponsored by the National Institute of Dental and Craniofacial Research (NIDCR) and supported by ACCRF, the SGTB consortium includes six academic medical centers: MD Anderson, the University of Virginia, Johns Hopkins University, the University of Pittsburgh, the University of California, San Francisco and Brown University. Standardized protocols ensure that patients at these institutions may provide their informed consent to donate specimens and help build a shared resource for all researchers with an interest in salivary gland cancers.

### **Model Development (Cell Lines and Animal Models)**

**Cell lines** (human tumor cells grown in dishes) are helpful to researchers in understanding the basic biology of a disease as well as for initial screening of drugs. Unfortunately, researchers have found it very difficult to create ACC cell lines. ACCRF is attempting to remedy the situation.

- ACCRF supports the efforts of researchers at the **University of Virginia, the Dana-Farber Cancer Institute, the M.D. Anderson Cancer Center, Johns Hopkins University, INCELL, Massachusetts General Hospital and Brigham & Women's Hospital** to grow new ACC cell lines from fresh tumor donations and animal models.
- ACCRF and affiliated investigators collected from labs around the world several cell lines that were purported to be derived from ACC tumors. As the investigators analyzed the cell lines at a molecular level, it became clear that they were derived from non-ACC tumors (see [http://www.accrf.org/pdf/accrf\\_cellupdate\\_mar09.pdf](http://www.accrf.org/pdf/accrf_cellupdate_mar09.pdf)) As a result, the research community no longer relies upon invalid models for ACC experiments. An affiliated investigator at the **University of California, San Francisco** has published on the misidentification issue: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2698276>.

**Animal models** (typically mice with implanted human tumors, called **xenografts**) help researchers better understand the mechanisms of action, effectiveness, dosing and toxicity of new treatments. In addition, they facilitate the creation of new cell lines.

- ACCRF supports the efforts of researchers at the **University of Virginia, the Dana-Farber Cancer Institute, the M.D. Anderson Cancer Center, Massachusetts General Hospital and Johns Hopkins University** to create new animal models of ACC. Several xenografts have been created, and more are under development.

ACCRF is committed to making as many models available to researchers as possible. However, it is important that the models are validated and well characterized before they are distributed.

Accordingly, ACCRF is working to ensure the quality control of ACC cell lines and xenografts used by affiliated researchers.

### **Basic Research (Genomics and Proteomics)**

Genomics and proteomics involve the study of genes (DNA), RNA and proteins in living cells. Genetic abnormalities are often implicated in the development and progression of cancer. In addition, the RNA and protein products of those genes may be different in tumors than in normal tissues. By identifying the mutated genes, RNA and proteins that are peculiar to ACC, researchers may be able to diagnose patients better and use targeted treatments more effectively.

- **DNA Sequencing** – ACCRF has a Research Collaboration Agreement with the **Wellcome Trust Sanger Institute** in the United Kingdom to sequence DNA from ACC samples. The Sanger Institute was the leading contributor of finished sequence to the Human Genome Project, and its Cancer Genome Project maintains the pre-eminent public database of cancer genes and somatic mutations (<http://www.sanger.ac.uk/genetics/CGP/>). A pilot ACC sequencing project has identified the somatic mutations in 400 genes across 25 specimens; an extension of the project will sequence all exons (gene regions with the code to make proteins). In addition, paired-end sequencing will identify translocations in the chromosomes of ACC tumors. For more information on the Sanger Institute's efforts in ACC, please follow this link: [http://www.accrf.org/pdf/accrf\\_spotlight\\_futreal.pdf](http://www.accrf.org/pdf/accrf_spotlight_futreal.pdf).
- **Comparative Genomic Hybridization (CGH)** – ACCRF supported the expansion of an array CGH study to identify genetic imbalances and novel target genes in ACC. The study is being conducted at the **Sahlgrenska Academy at the University of Gothenburg** in Sweden.
- **Methylation** – ACCRF is facilitating a study of the methylation status of ACC specimens to determine which genes are turned on or off as the disease progresses. The study is being conducted at **Johns Hopkins University**.
- **RNAi** – ACCRF has a Research Collaboration Agreement with the **Harvard Medical School** to identify genes that are essential for the proliferation and/or survival of ACC cells through RNA interference (RNAi) studies. Utilizing short hairpin RNAs (shRNA), researchers will identify potential drug targets to halt or reverse the progression of ACC. For more information on the laboratory conducting the study, please follow this link: <http://www.hms.harvard.edu/dms/bbs/fac/harlow.html>
- **Phosphoproteomics** – ACCRF is supporting a study of the phosphorylation status of genes in ACC. By identifying those proteins that are particularly active (rather than merely present), researchers may learn of cell signaling pathways to disrupt in ACC. **Cell Signaling Technology** is performing the study with the collaboration of the **University of Virginia** and **Massachusetts General Hospital**.



- **MicroRNA** – ACCRF will support studies into microRNAs, cellular molecules whose importance in cancer have become more apparent recently. Depending upon their significance in ACC, microRNA profiling may indicate additional targets for therapy.
- **Bioinformatics** – ACCRF will support an open and consistent data platform from which affiliated researchers may analyze the large and growing ACC-specific data sets generated by ACCRF's basic research projects. In most cases, the same specimens and models have been used in the studies, leading to a particularly rich data set to mine. Computational Biologists at the **University of Virginia, MD Anderson** and the **Sanger Institute** will join others in gathering, curating and disseminating data sets from affiliated researchers.

### **Diagnostic and Prognostic Biomarkers**

Biomarkers are biochemical features that can be used to measure the progress of disease or the effects of treatment. ACCRF's basic research into mechanisms of action in ACC may well uncover biomarkers that will prove helpful in diagnosing patients earlier and guiding treatment for individual patients based on the prognosis indicated by their particular biomarkers.

- ACCRF will support the development of diagnostic and prognostic tests for ACC as appropriate biomarkers are discovered.
- Magnetic Resonance Imaging (MRI) – ACCRF supports researchers at the **University of California, Los Angeles** in their efforts to study perineural invasion (PNI) in ACC patients with high-resolution MRI. ACC has a peculiar propensity to grow along nerves, so a better understanding of that PNI process may improve the diagnosis, surgical treatment and outcomes for ACC patients.

### **Drug Screening**

Before a new treatment for ACC may reach patients through clinical trials, it must be subjected to rigorous screening for toxicity and efficacy *in vitro* (in cell lines) and *in vivo* (in animal models). Screens may be conducted with clinically-relevant drugs (those currently available to patients) or even with libraries that comprise hundreds of thousands of compounds. By correlating the genomic profiles of the cell lines or animal models with their sensitivity to the drugs, researchers may be able to identify subsets of patients for whom treatments are particularly effective.

- **Clinically-Relevant Drug Screens** – ACCRF is facilitating the provision of ACC cell lines to the Center for Molecular Therapeutics at the **Massachusetts General Hospital**. Drug screening with approximately 110 clinically-relevant compounds is being carried out on the cell lines, providing information on their sensitivity to drugs and perhaps leading to the optimization of molecularly-targeted therapies for ACC. For more information, please follow this link: <http://www2.massgeneral.org/cancer-research/groups.aspx?id=66>.



- High-Throughput Screens – ACCRF is collaborating with the **NIH Chemical Genomics Center (NCGC)** to conduct high-throughput screening (HTS) on ACC cell lines with their library of over 300,000 compounds. Of particular interest will be the 2,000+ FDA-approved compounds as well as the 14,000 compounds with annotated bio-activity. In addition to the prospect of finding promising drugs directly, the project may permit researchers to induce the mechanisms of action in ACC. For more information on the NCGC, please follow this link: <http://www.ncgc.nih.gov/>
- Xenograft Screening – Drug screening in mouse models typically precedes the movement of novel therapies into clinical trials. ACCRF is consolidating the animal models developed by its affiliated researchers at one institution, **South Texas Accelerated Research Therapeutics (START)**. This program permits cost-effective drug screening that will be made available to all researchers, whether from academic, government or private institutions. The information gleaned from the genomic, proteomic and HTS studies will help researchers decide upon the most promising compounds to screen in the animal models. For more information on START, please follow this link: <http://www.startthecure.com/>

## Clinical Trials

The goal of the Research Agenda is to get effective drugs to patients. Clinical trials are the testing ground for effectiveness and toxicity in humans. They may involve a drug that has already been approved for another cancer or condition, or a novel drug that has yet to receive regulatory approval for any indication.

Clinical trials are particularly difficult to organize for rare conditions such as ACC because multiple clinical institutions must coordinate in order to enroll sufficient patients. It is far simpler to plan the scientific, logistical, regulatory and statistical elements of a clinical trial within one hospital or cooperative group. And private pharmaceutical firms may not be willing to finance the high cost of clinical trials for a small patient population that may not generate much revenue.

- By supporting the generation of data on biological mechanisms of action and pre-clinical drug efficacy, ACCRF is providing rationales for designing ACC-specific clinical trials that are more likely to yield improved therapies. Patients are more likely to enroll in such trials and the NIH and private pharmaceutical firms are more likely to sponsor such clinical trials.
- ACCRF communicates regularly with the medical oncologists at the leading head & neck cancer institutions who treat most ACC patients. These relationships will be crucial as multi-institutional groups are formed to push clinical trials forward for ACC patients.
- ACCRF Co-Founder Marnie Kaufman is serving a 3-year term on the **National Cancer Institute's Head & Neck Steering Committee (HNSC)**. The HNSC's role is to prioritize and design large Phase 2 and Phase 3 clinical trials in cancers of the Head and Neck. The 22-member Steering Committee will benefit from the work of four Task Forces: (1) Metastatic/Recurrent Disease, (2) Rare Tumors, (3) Previously-untreated Locally



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Advanced Disease, and (4) Tumor Biology and Imaging. As a voting member, Marnie Kaufman is well positioned to learn of all new drugs and trials being considered for NCI funding. In addition, she will serve as a strong advocate for clinical trials in under-researched rare tumors like ACC.

ACCRF constantly seeks to improve its Research Agenda and to learn about new avenues of research that might benefit ACC patients. All comments and suggestions are welcome, and may be directed to [info@accrf.org](mailto:info@accrf.org).