Adenoid Cystic Carcinoma
Research Foundation

November 2018

ACCRF Overview

Jeff Kaufman, Executive Director

The Roots of ACCRF

ACCRF was founded by Marnie and Jeff Kaufman. Marnie was diagnosed with ACC at 38 years old when she had four boys under the age of 10.

ACCRF is a public charity established in December 2005 in Needham, Massachusetts, USA

ACCRF Overview

MISSION

Accelerate the development of **better treatments and a cure** for ACC patients

GOAL

Develop a **pipeline of clinical trials** based on the best available science

STRATEGY

Create a **community of researchers** following a **coordinated plan** that is driven by **supportive and supported patients**

ACCRF Research Agenda

ACC Patient Community

- **Donation of Specimens & Medical Records**
- **Funding**
- **Input on Key Challenges & Unmet Needs**
- **Clinical Trial Enrollment**

ACC Research Community

Building Blocks of Research

What can researchers work with to find answers?

- Biorepository & Registry
- Cell Lines
- Mouse Models

Mechanisms of Action

What biological processes make ACC possible?

- Genomics
- Pathway Identification
- Target Validation

Translational Research

What will hit the Achilles' heels of ACC?

- Functional Studies
- Drug Discovery
- Preclinical Screening

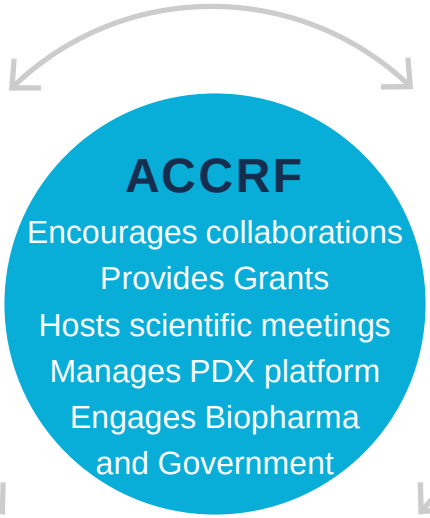
Clinical Research

What will work in actual patients?

- Approved Drugs
- Novel Drugs
- Radiation/Radiology

Better Therapies and Outcomes for Patients

ACCRF Research Network



Academic Institutions

MD Anderson
University of Virginia
Gothenburg University (Sweden)
University of Melbourne (Australia)
University of Munster (Germany)
Seoul National University (Korea)
Radboud University (Netherlands)
University of Manchester (UK)
Massachusetts General Hospital
Memorial Sloan-Kettering
Johns Hopkins
Dana-Farber Cancer Institute
University of New Mexico
Massachusetts Institute of Technology
Yale University

Government

National Institute of Dental and Craniofacial Research (NIDCR)
National Cancer Institute (NCI)

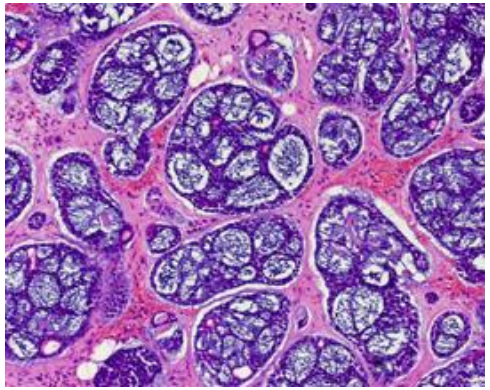
Private Industry

South Texas Accelerated Research Therapeutics (START)
Bethyl Labs
Cell Signaling Technology
Novartis
Pfizer
Eli Lilly
Merck
Bristol-Myers Squibb
Abbott
Bayer
Astra Zeneca
Glaxo Smith Kline
Ayala
Syndax

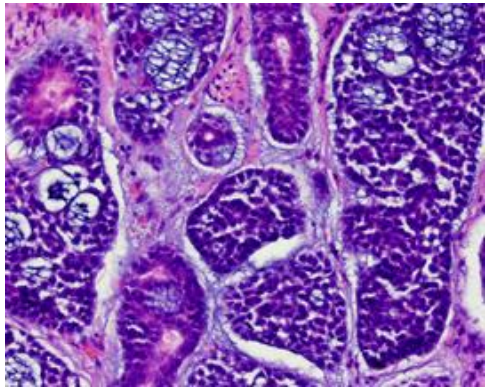
ACComplishments

	2005	2018
Biobanking	Limited	Repositories with hundreds of frozen tumor specimens
Cell Lines	Multiple invalid models	Misidentifications discovered; valid models developed
Animal Models	None	20+ mouse xenografts developed; first transgenic models
Genomics	Sporadic reports of translocations	• Discovery of recurrent MYB, MYBL1 and NFIB fusion genes • Identification of additional molecular targets with potential therapies: NOTCH, FGFR, IGF-1R, HDAC
Preclinical Drug Screens	None in valid models	• Open xenograft platform for academia and industry • Strong relationships with biopharmaceutical companies • 100+ anti-cancer compounds screened in mouse models
Mobilizing Patients	Limited	Tissue donations, clinical trial accrual and $15 million in donations
NIH Commitments	Negligible	Over $25MM for salivary gland tumor research (NIDCR)
Clinical Trials	Few, small & haphazard	Multiple science-driven trials with improved designs, enrollment, data quality and patient outcomes

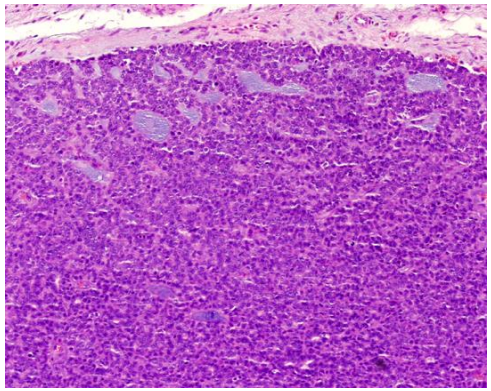
How we think ACC works



Grade 1
No solid component



Grade 2
<30% solid



Grade 3
>30% solid

MYB or *MYBL1*
fusion or overexpression
(90-95% of cases)

Secondary alterations in other genes
(*NOTCH1*, *FGFR*, *IGF*, *PI3K* and chromatin modifiers)
drive disease progression

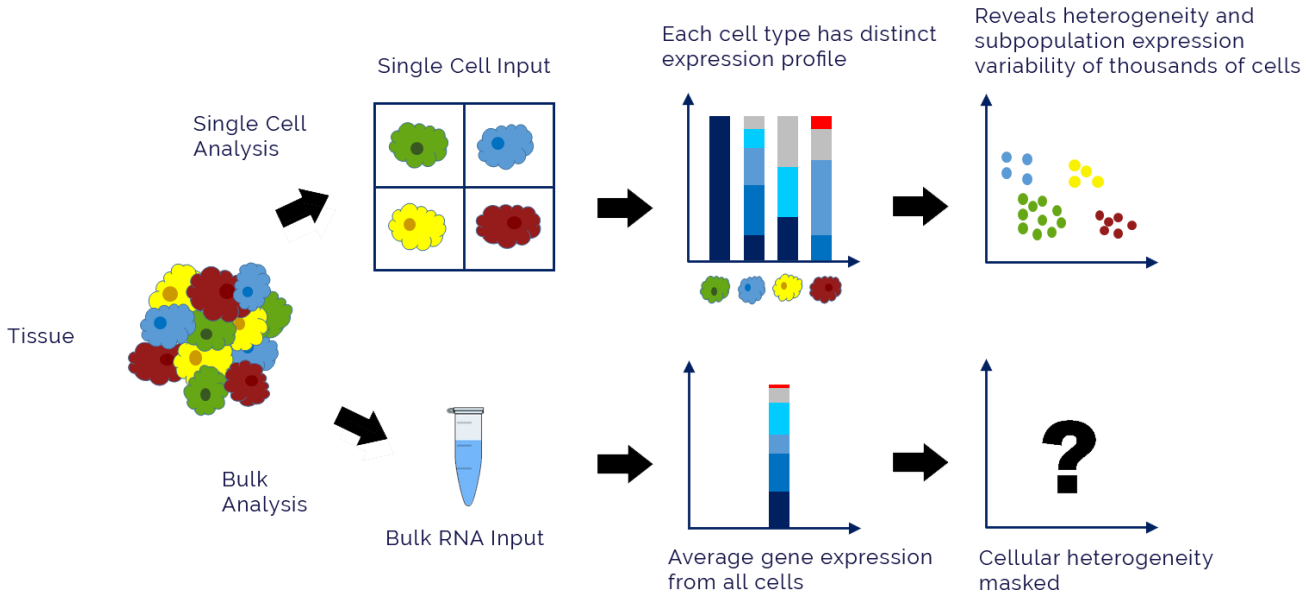
Therapies:

Research grants focused on finding MYB/L1 inhibitors

NOTCH inhibitors show early signal in NOTCH-mutant ACCs
Clinical trials are investigating other targeted and immune therapies in ACC

Some Basic Research Questions

- Do genes other than MYB or MYBL1 cause ACC?
- Do genes other than NOTCH1-4 cause ACC to be more aggressive?
- How do ACCs in various body sites differ?
- How do the 2 types of cells in ACC differ and interact?



2018 Reported ACC Trials

Drug	Targets	Study Location	ACC Patients	Partial Response	Progression Required
Lenvatenib (Lenvima)	VEGFR, FGFR, PDGFR, KIT	New York, USA	32	16%	Yes
Lenvatenib (Lenvima)	VEGFR, FGFR, PDGFR, KIT	Milan, Italy	28	11%	Yes
Apatinib	VEGFR	Shanghai, China	56	47%	No
Pembrolizumab (Keytruda) and Vorinostat (Zolinza)	PD-1, HDAC	Seattle, USA	12	8%	Yes

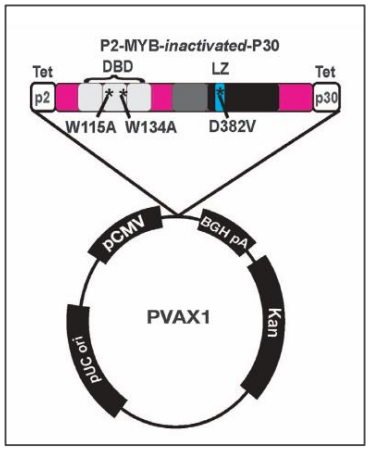
Partial Response is tumor shrinkage ≥30%

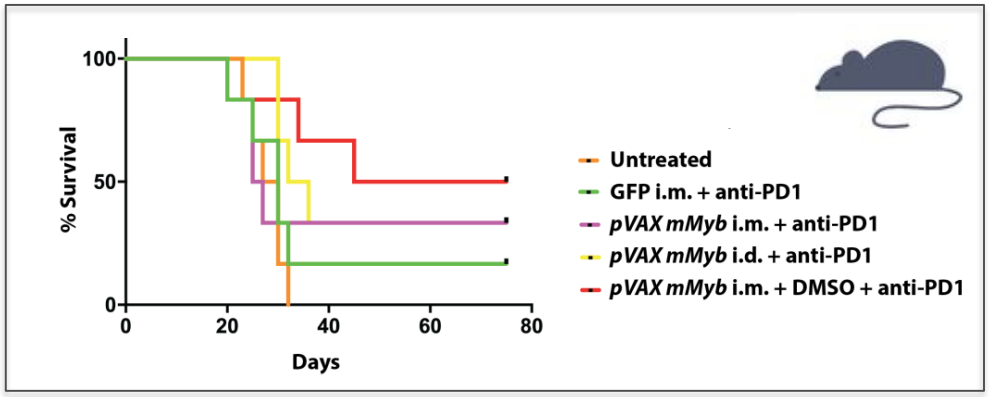
Open Trials

- **MYB**
  - **MYB vaccine and Tislelizumab (PD1 inhibitor)**, Phase I, Peter Mac Cancer Center, Melbourne, Australia
- **NOTCH**
  - **AL101 (NOTCH inhibitor)**, Phase II, Honor Health, Scottsdale, Arizona, with more sites to open through end of 2018/beginning 2019
  - **CB-103 (NOTCH inhibitor)**, Phase I, Netherlands, Spain, and Switzerland
- **Immunotherapy**
  - **Pembrolizumab (PD1 inhibitor) plus Docetaxel**, Phase II, U of Chicago, Chicago, IL
  - **Pembrolizumab (PD1 inhibitor) plus Radiation**, Phase II, DFCI, Boston, MA
  - **Nivolumab (PD1 inhibitor) plus Ipilimumab**, Phase II, Northwestern, Chicago, IL
- **HDAC**
  - **Chidamide (HDAC inhibitor) plus Cisplatin**, Phase II, Chinese Academy of Medical Sciences, Beijing, China

MYB DNA vaccine + PD-1 inhibitor

- ***Rationale:*** MYB is an oncogenic driver in several cancers (ACC, colon, T-ALL, etc.). 90-95% of ACC tumors overexpress MYB/L1.
- Vaccine designed to overcome the “self” antigen nature of MYB.
- Phase I trial opened for patients with advanced solid cancer including colon and ACC (Peter Mac Cancer Center, Australia).
- 1st metastatic ACC patient treated in September.



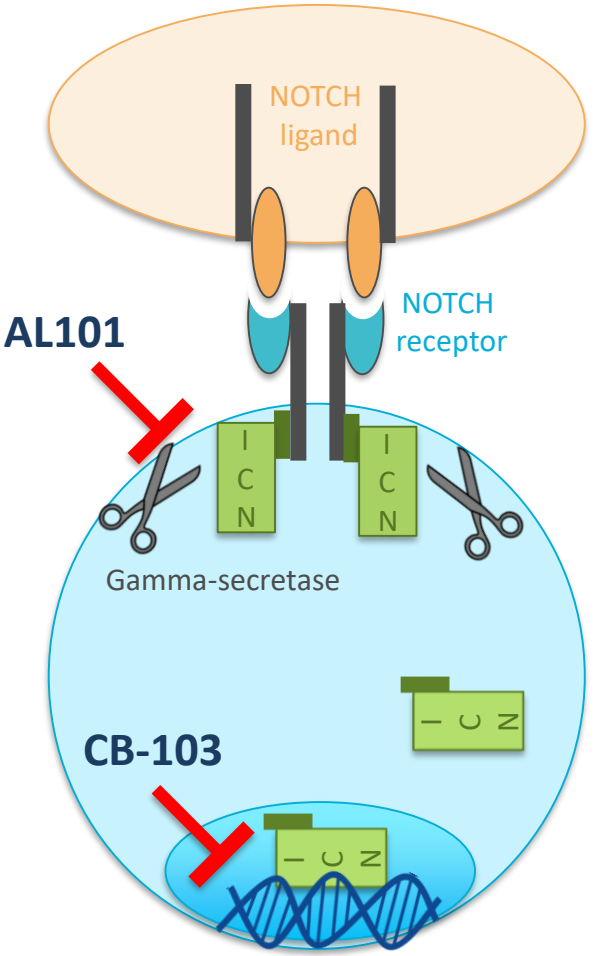


NOTCH inhibitors (AL101 and CB-103)

- ***Rationale:*** Activating NOTCH1 mutations are enriched in recurrent/metastatic ACC patients (22%) and define a subset of patients with poor prognosis

- **AL101 (GSI)** Phase II trial is open to ACC patients with activating mutations in NOTCH 1, 2 3 or 4. Open in US now, possibly in Europe late next year

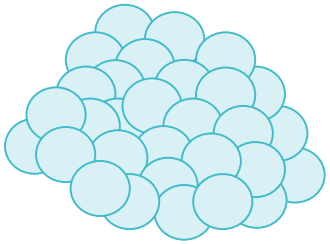
- **CB-103 (pan NOTCH inhibitor)** Phase I trial is now open to patients with solid tumors in Europe. ACC cohort tentatively scheduled to open in US and Europe in 2019.



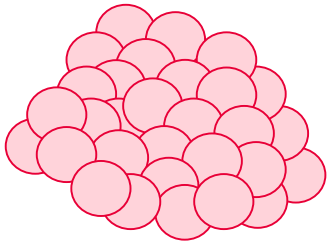
Immunotherapy Trials

Rationale:

"COLD"



"HOT"



NOT recognized by immune system
Low mutational burden
Microsatellite stable
Low immune cell infiltration
No PD-L1 (ACCs do have PD-1 and PD-L2)

Recognized by immune system
High mutational burden
Microsatellite unstable
High immune cell infiltration
High PD-L1 and PD-1

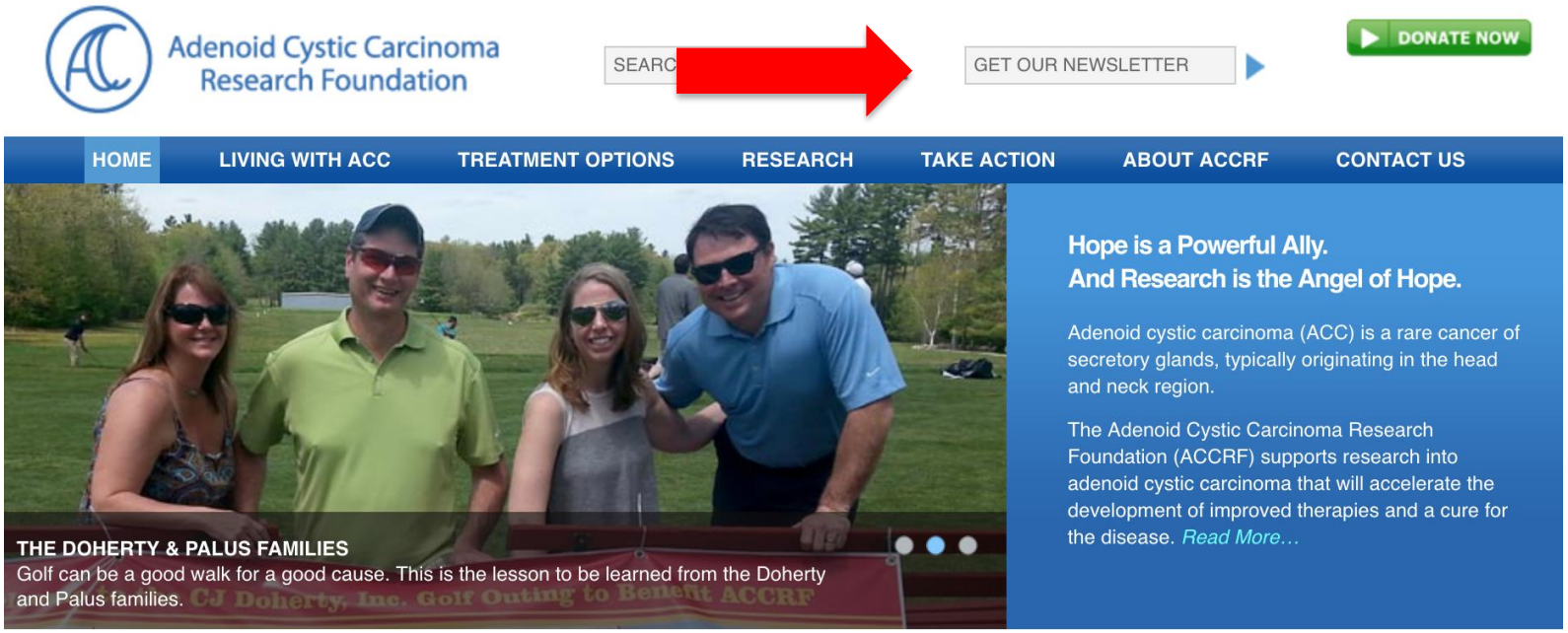
- **Pembrolizumab (PD1 inhibitor) plus Docetaxel**, Phase II, U of Chicago, Chicago, IL
- **Pembrolizumab (PD1 inhibitor) plus Radiation**, Phase II, DFCI, Boston, MA
- **Nivolumab (PD1 inhibitor) plus Ipilimumab (CTLA4 inhibitor)**, Phase II, Northwestern, Chicago, IL and MSK, New York, NY (recently completed)
- **What is different about ACC tumors from *exceptional responder* patients?**

Forthcoming Trial Concepts

- Combinations of immunotherapy with targeted drugs that are active in ACC
- MDM2 inhibitor
- Entinostat (HDAC inhibitor) plus Cisplatin
- Targeted delivery of radiation using PSMA radiolabeled drugs (for ACCs with high PSMA levels)
- ATRA
- Plus more in the pipeline…

Keep yourself updated…

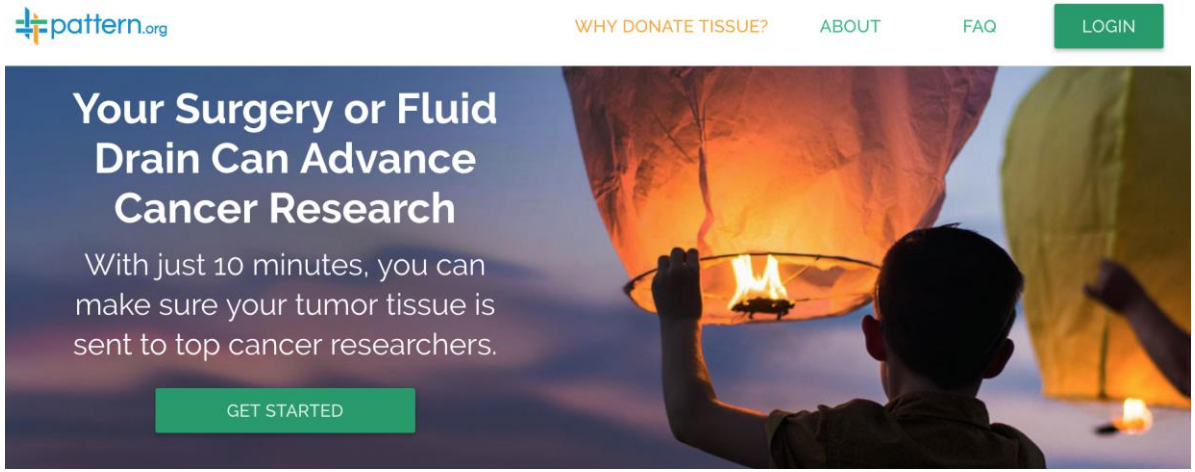
- Sign up to receive ACCRF research updates via email…



- Check the “Clinical Trials - Current Studies” section on our website!

Tumor donation options

- Online-consented tumor donation with *Pattern.org*



- The Christie NHS in Manchester, UK (Rob Metcalf's lab)

https://www.accrf.org/take-action/assist-in-research/

Summary

- ACCRF has jump-started the field of ACC research through:
  - World-class Scientific Advisory Board driving a directed agenda
  - Creation of biobanks, preclinical models and research network
  - Target discovery and validation leading to clinical trials

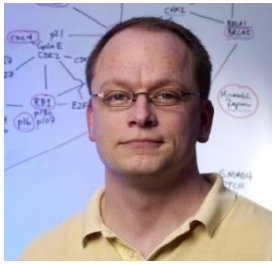
- ACCRF is prioritizing therapy discovery and innovative clinical trials, with several promising concepts in development

- We ask for your support to achieve our goal of having the **first approved therapy for ACC by 2020**


Adel El-Naggar


Chris Moskaluk

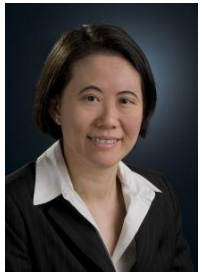

Göran Stenman


Andy Futreal


Michael Wick

Thanks to ACC Research Heroes!


David Sidransky


Lillian Siu


Bruce Chabner


Robert Haddad


Ned Sharpless


Gigi Lozano


Irwin & Joan Jacobs