Adenoid Cystic Carcinoma
Research Foundation

November 2019

ACCRF Research Update

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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 STRATEGY

ACC Patient Community

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

ACC Research Community

Building Blocks of Research

What tools do researchers have 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

How can we stop ACC tumor cells from growing?

- Functional Studies
- Drug Discovery
- Preclinical Screening

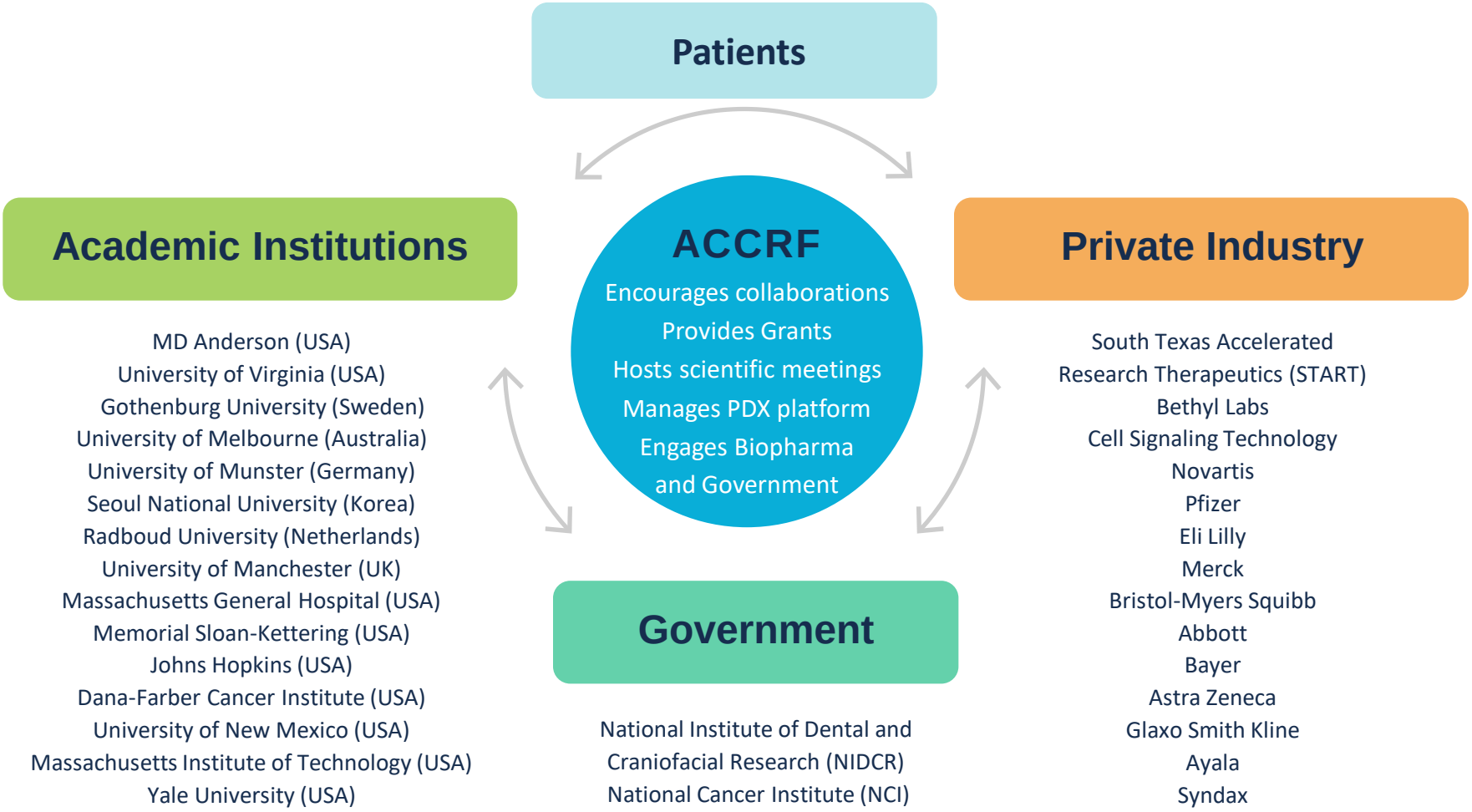
Clinical Research

What will work in actual patients?

- Approved Drugs
- Novel Drugs
- Radiation/Radiology

Better Therapies and Outcomes for Patients

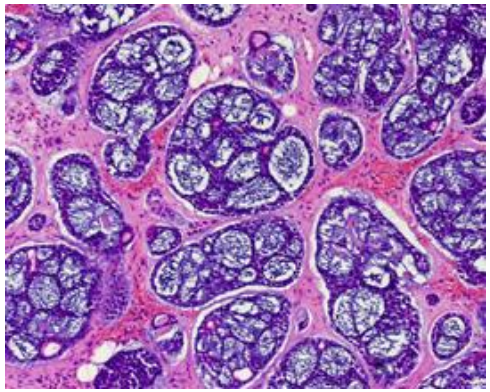
ACCRF RESEARCH NETWORK



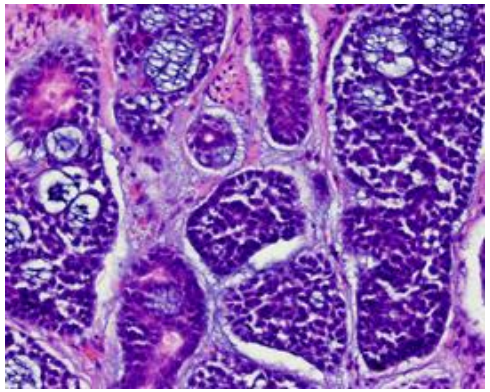
ACCOMPLISHMENTS

	2005	2019
Mobilizing Patients	Limited	Tissue donations, clinical trial accrual and $18+ million in donations
Mobilizing Funders	Negligible	$25+ milliion for salivary gland tumor research
Biobanking	Limited	Repositories with hundreds of frozen tumor specimens
Cell Lines	Multiple invalid models	Misidentifications discovered; valid cell line published
Animal Models	None	20+ mouse xenografts developed; first transgenic models
Genomics	Sporadic reports of translocations	• Discovery of recurrent t(6;9) and MYB-NFIB fusion gene • Identification of additional molecular targets with potential therapies: NOTCH, VEGFR, FGFR, HDAC
Preclinical Drug Screens	None in valid models	• Patient-derived xenograft platform open to academia and industry • Strong relationships with 30+ biopharmaceutical companies • 100+ anti-cancer compounds screened in xenografts
Clinical Trials	Few, small & haphazard	Multiple science-driven trials with improved designs, enrollment, data quality and patient outcomes

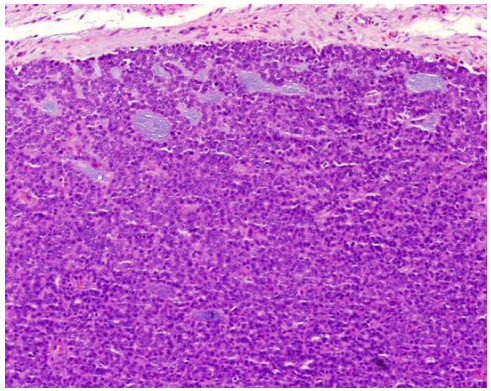
HOW WE THINK ACC WORKS



Grade 1
No solid component



Grade 2
<30% solid



Grade 3
>30% solid

MYB/MYBL1
DNA fusion and overexpression

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

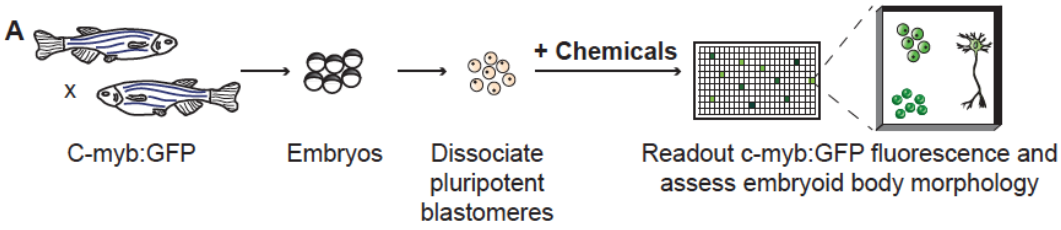
Therapies:

- ATRA clinical trial
- MYB DNA vaccine
- Drugs that go after MYB targets

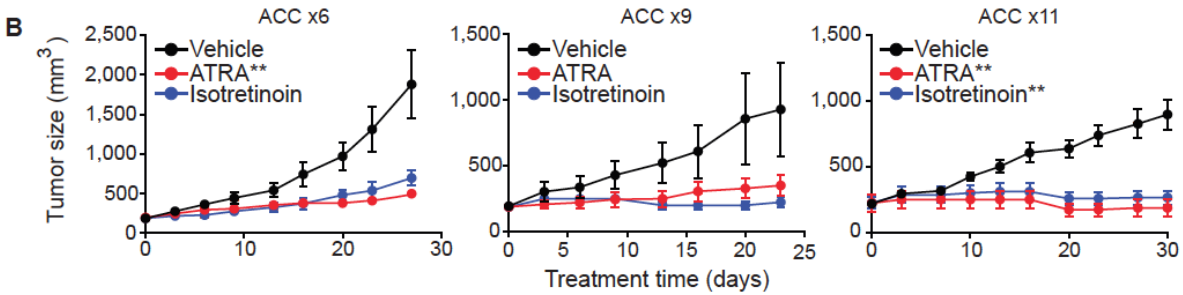
- Active phase II trial of AL101 in NOTCH-mutant ACC
- Active clinical trials are investigating other targeted and immune therapies in ACC

ACCRF SUPPORT: LAB TO CLINIC

ACCRF grant to screen for MYB inhibitors



ATRA inhibits tumor growth in ACC models



ACCRF co-funds ATRA clinical trial (currently recruiting)

OPEN AND PENDING CLINICAL TRIALS I

MAKING SENSE OF THE "MOLECULAR TARGETS"

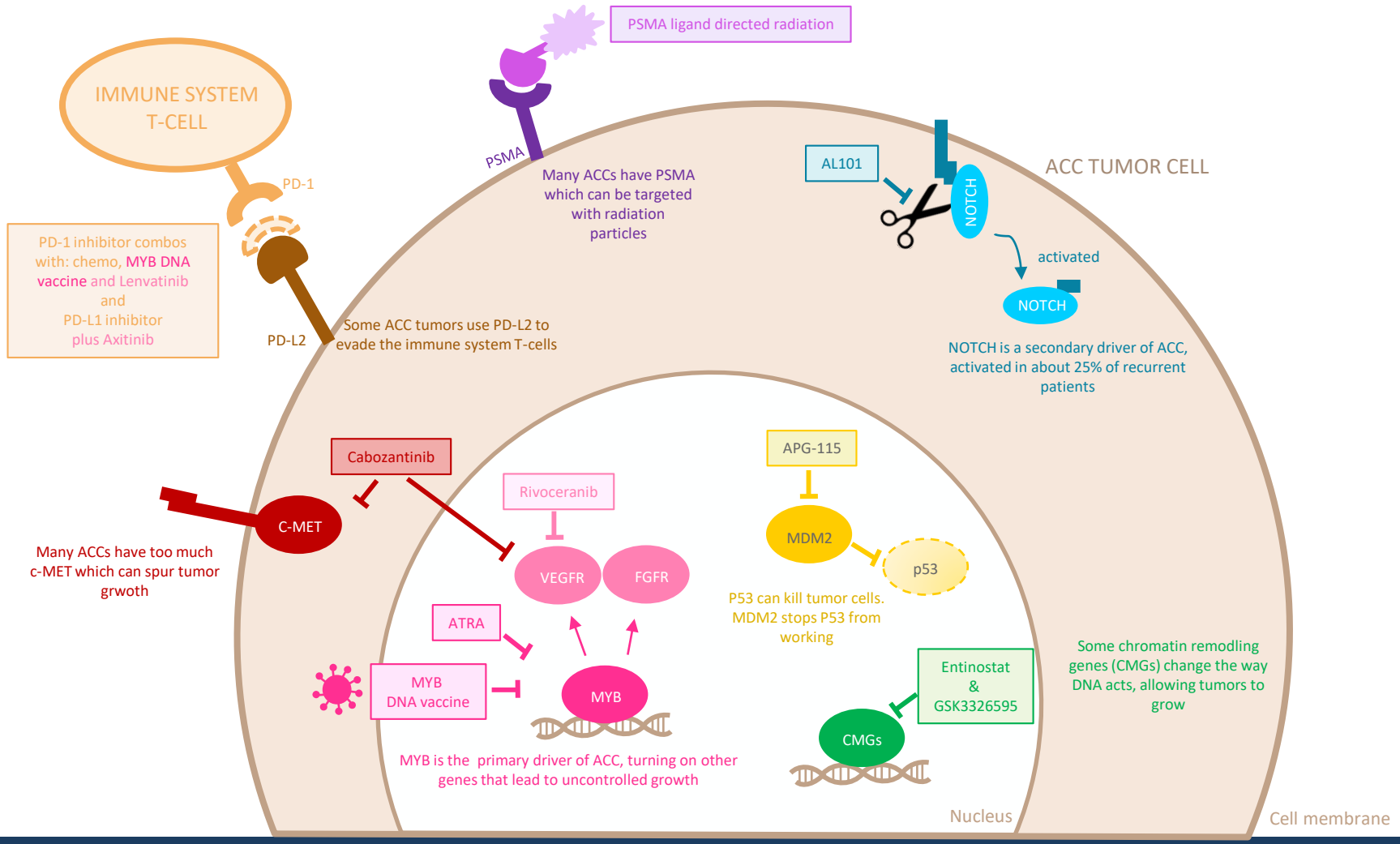
- **MYB – Primary driver of ACC of that leads to uncontrolled tumor growth**
  - **MYB vaccine and Tislelizumab (PD-1 inhibitor)**, Phase I, Peter Mac Cancer Center, Melbourne, Australia
  - **ATRA**, Phase II, Dana-Farber Cancer Institute, Boston, MA, USA
- **KINASES – Downstream mechanisms turned on by MYB**
  - **Cabozantinib (C-MET, VEGFR, AXL and RET inhibitor)**, Phase II, Nijmegen, Netherlands
  - Rivoceranib/Apatinib (VEGFR inhibitor) – PENDING
- **NOTCH – Secondary driver of aggressive ACC ~ 25% of metastatic patients**
  - **AL101 (NOTCH inhibitor)**, Phase II, Moffitt CC, MGH, MSKCC, MDACC, Fred Hutchinson CC and more (full site list on clinicaltrials.gov and ACCRF's website)
  - **CB-103 (NOTCH inhibitor)**, Phase I, Netherlands, Spain, and Switzerland
- **MDM2 – Stops tumor suppressor gene from killing ACC**
  - **APG-115 (MDM2-p53 inhibitor)**, Phase II, U of Michigan, Ann Arbor, MI, USA

OPEN AND PENDING CLINICAL TRIALS II

MAKING SENSE OF THE "MOLECULAR TARGETS" (continued)

- **HDAC – Disrupts normal chromatin (DNA strands)**
  - **Chidamide (HDAC inhibitor)**, Phase II, Fudan University, Shanghai, China
  - **Chidamide (HDAC inhibitor) plus Cisplatin**, Phase II, Chinese Academy of Medical Sciences, Beijing, China
  - Entinostat (HDAC inhitor) plus Cisplatin - PENDING
- **PRMT5 – Disrupts normal chromatin (DNA strands)**
  - GSK3326595 (PRMT5 inhibitor) - PENDING
- **PD-1 (IMMUNOTHERAPY) – Turns off the T cells that kill tumors**
  - **Axitinib (Tyrosine Kinase Inhibitor) plus Avelumab (PD-L1 inhibitor)**, Phase II, Houston, TX, USA
  - **Pembrolizumab (PD-1 inhibitor) plus Docetaxel**, Phase II, U of Chicago, Chicago, IL, USA
  - **Nivolumab (PD-1 inhibitor) plus Ipilimumab (CTLA-4 inhibitor)**, Phase II, Northwestern, Chicago, IL, USA
  - Pembrolizumab (PD-1 inhibitor) plus Lenvatinib (VEGFR inhibitor) - PENDING
- **PSMA – Coincidental marker found in ACC and prostate**
  - PSMA ligand-directed radiation - PENDING

ACC CLINICAL TRIAL LANDSCAPE (Fall 2019)



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 and drug discovery leading to clinical trials

- ACCRF is prioritizing new therapies and innovative clinical trials, with many promising concepts in the clinic and preclinical development

- We ask for your support to achieve our objective of having the **<u>first</u> approved systemic therapy for ACC within 1-2 years**

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Thanks to ACC Research Heroes!

ACCelerate the CURE