Is the Tripartite Mission Still Valid? (Analyzing the Tripartite Terroir)

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Association of Professors of Dermatology
Chicago IL

Terroir

Terroir comes from the French word for earth or soil but in the wine world has taken on a quasi-mystical meaning to include not only the soil in a region, but also the climate, the weather, the location of the vineyards and anything else that can possibly differentiate one piece of land from another.

Terroir at Chateau Cheval Blanc St Emilion Bordeaux Summer 2015

Terroir and the Tripartite Mission

The Changing Terroir of Academic Dermatology in the United States

Increases in the NIH Budget and the Total Number of Medical School Basic Science and Clinical Faculty Members (1966-2006)

The New Terroir of Academic Medicine

Options for AMCs in Health System Formation

The Winds of War and German-American Dermatology
First of all, I had world class scientists as mentors. My first mentor won the Nobel Prize. Secondly, the colleagues coming through at the same time were all superb. Thirdly, there was such a critical mass that whenever you had a question, there was always somebody down the hall or in the next building that you could go to. Fourthly, there were seminars and courses to take that rivaled anything at any university. Finally, the people you were working with went out and pursued their careers so you had this whole cadre of people who you interacted with from the beginning.

Dr. Alan Schechter
With Jay Barnett and Ed Weisberg at UTAPAO
USAF SAC Base Circa 1969

Dining at Moissionnier ** in Cologne While Enjoying a
1996 Chateau Grand Puy-Lacoste

Goal: To Change the Standard of Care for Hereditary
Skin Cancer

- Cancer Prevention in High-Risk patients (XP, BCNS)
- Seeking Novel Drug to Enhance DNA repair
  *(Unsuccessful)*
- Low hanging fruit:
  - BCCs are driven by Hedgehog pathway
  - Genentech/Genetech had a Hedgehog inhibitor
  - Test this for BCC prevention

Yellow Berets and Other Physician-Scientists-
SID Meeting 2004

Jean Tang, M.D., Ph.D.
Training Trajectory and Protected Research Time

- East LA: customer service (mom and pop store)
- BA: UC Berkeley: Biochemistry, lipoprotein lab (Trudy Forte), 3
  yr (part time)
- MD/PhD: Stanford MSTP (Biophysics, NER repair, Gilbert Chu,
  Paul Berg, 4+4 yr)
- Internship: Guatemala, Xeroderma Pigmentosum (James
  Cleaver UCSF)
- FAAD: Stanford, Dermatology Residency, 2+1 (short track)
- MS Clinical Research: UCSF, KL2 CTSI; Post Doc (Ervin Epstein),
  GEMM and and Clinical Trials 3 yrs, K23 award
- Assistant Professor, Stanford: 2009, Damon Runyon (Philip
  Beachy), Bill Kaelin
- AMA (advanced maternal age): Kai age 7, Cory age 4
- Associate Professor, 2014: 90% research, 1 half-day/wk

Lesson #1: Brick Walls

“The brick walls are there for a reason. The brick
walls are not there to keep
us out. The brick walls are
there to give us a chance to
show how badly we want
something.”

- Randy Pausch

- No T32 funding
- UCSF had a new
  Clinical/Translational Training
  Program KL2
- Funding for 3-5 yrs
- Ervin Epstein Lab
- BCC Mouse Model and BCNS
  Patients
- Downside: Required to take 1 yr
  of Epidemiology and Biostatistics
  (Felt Like Homework)
Safe or Risky?

Lesson #2: Select a Feasible Research Question

“FINER Criteria For a Good Research Question”:
- Feasible
- Interesting (to you, follow your nose)
- Novel
- Ethical
- Relevant

-Steve Hulley, UCSF

Already Completed RCT in BCNS: Celecoxib for BCC Prevention

Clinical trial in 60 subjects: 2001-2004 (terminated early due to reports of potential cardiovascular events associated with celecoxib)

Data was sitting there: I entered the lab in 2006

Lesson #3: Biostatistics Can Be Your Friend

Lesson #4: Learn To Do Better Clinical Trials: Measuring the Target (Subgroup Analysis)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Celecoxib (mm²/year)</th>
<th>Placebo (mm²/year)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.8 (0.4, 1.3)</td>
<td>1.0</td>
<td>0.8 (0.5, 1.4)</td>
</tr>
<tr>
<td>High BCC</td>
<td>1.0 (0.5, 1.9)</td>
<td>2.0</td>
<td>0.5 (0.3, 0.9)</td>
</tr>
<tr>
<td>Low BCC</td>
<td>0.3 (0.1, 0.7)</td>
<td>0.5</td>
<td>0.6 (0.3, 1.1)</td>
</tr>
</tbody>
</table>

Vismodegib (GDC-0449) Was the First Hedgehog Pathway Inhibitor to Enter Clinical Trials

Vismodegib (OR:50%, PFS: 12 mon)

Baseline

At 3 months

OFF

Von Hoff et al., NEJM 2009, 361: 1164-1172
Sekulic A et al., NEJM June 2012
Randomized, Double-blinded Trial for 18 Months

Vismodegib 150mg pill vs Placebo (2:1)
41 patients with Basal Cell Nevus Syndrome (BCNS)
  • 3 clinical centers: Sept 2009 to Dec 2010
    (Vismodegib was FDA-approved in 2012)

Primary Endpoint: Prevention of New BCCs
Secondary endpoint:
  • Reduction in Size of Existing BCCs
  • Safety/Tolerability

You Can Get From Here to There

Lesson #5 Build Relationships with Patient Advocate Groups

Conclusions

1. Vismodegib has changed the standard of care for BCNS patients – no resistance seen even with intermittent dosage
2. In contrast, patients with advanced or metastatic BCCs develop resistance
3. Mutations in SMO (drug target) account for majority of drug resistant tumors

Give Yourself Enough Time

“80 percent of life/success is showing up”
- Woody Allen

“10,000 hour rule: the key to success is practicing and putting in the time”
(approximately 3yrs)

You Can Get From Here to There

Med School

Undergrad

Residency/Fellowship

Post-doc

Training

Life long career

You Can Get From Here to There
Genius is Made, Not Born

Sarasate, the great Spanish violinist of the nineteenth century, was once called a genius by a famous critic. Sarasate sharply replied, “Genius! For thirty-seven years I’ve practiced fourteen hours a day, and now they call me a genius.”

from The Power of Habit

What is Your Mindset

Carol Dweck, Stanford University  Mindset: The New Psychology of Success

Role of Ph.D. Scientists for Sustaining the Culture of Discovery in Academic Dermatology

PhD scientists are a major untapped resource in building and leading research divisions – look at the great PhDs behind many of the top programs who are leading the charge:

Dennis Roop at U of Colorado
Robert Lavker at Northwestern
Sarah Millar at Penn
Mohammad Athar at UAB
Hasan Mukhtar at U of Wisconsin
Molly Kulesz Martin at Oregon Health Sciences
Nicole Ward at Case Western

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Angela Christiano, Ph.D.
Columbia University
President, Society for Investigative Dermatology
2016-2017

NIAMS Columbia University
Skin Disease Resource-based Center

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Clinical Trials Unit with Focus on Translational Medicine

1. Design and conduct translational research in linked closely with the Basic Science Research Group (BSRG)

Currently Funded Grants:

- U01AR07173-01 Christiano NIH/NIAMS - Developing an Alopecia Areata Disease Activity Index (ALADIN)
  - Goal is to develop a new outcome instrument, the Alopecia Areata Disease Activity Index (ALADIN), which has the potential for use in the determination of clinically relevant endpoints for Alopecia Areata (AA)

- 1P30AR069632-01 Bickers (PI) NIH - Columbia University Skin Disease Resource-Based Core center at Columbia University epiCURE
  - This application supports the creation of a Skin Disease Resource-Based Core center at Columbia University epiCURE. The epiCURE is designed to address critical roadblocks on the Continuum of Translational research as defined by the National Academy of Medicine

- 1P50AR070588-01 Christiano (PI) NIH/NIAMS - Alopecia Areata Center for Translational Research (AACORT)
  - The mission of the AACORT is unravel the genetic basis of AA and exploit our discovery showing the role both innate and acquired immunity, and to synergize these findings into translational studies finding novel therapies for this disease, including the repurposing of existing drugs
Open-label Clinical Trial of the Jak-Stat Inhibitor Tofacitinib in Patients with Alopecia Areata

Columbia University Department of Dermatology, Clinical Trials Unit, Julian Mackay-Wiggan, MD, MPH, Director

Global Skin Diseases Research Consortium (GSDRC)

The long-term goal of this established collaborative agreement is to provide joint opportunities to foster the creation of novel approaches and insights into cutaneous biology, disease pathogenesis and clinical dermatology by coordinating multidisciplinary research aimed at finding innovative translational strategies to improve the care of patients with skin disease and to train tomorrow's scientific leaders.

Global Skin Diseases Research Consortium (GSDRC)

• Bi-annual symposium supported by one of the six Centers at their location
• Bi-annual GSDRC summer school for PhD and MD/PhD students and postdocs
• Exchange of PhD and MD/PhD students and postdocs to learn new techniques and approaches, and to promote collaborative projects between laboratories of the Centers
• Exchange of faculty for mini-sabbaticals
• Establish a web-based inventory to promote exchange of mouse models, other animal models, reagents and protocols

Herbert and Florence Irving

Herbert and Florence Irving

Alternative Sources of Funding in the New Terroir of Academic Dermatology

• Building consortia with industry sponsors, and health care insurers to achieve economies of scale
• Creating closer working relationships with community leaders as systems are created to promote population health
• Coordinating more effectively across government agencies
• Philanthropy $$$$$$$$$$$$$$$$$
Summary

Despite dire forecasts, dermatology departments at research-focused universities will continue to attract the shrinking pool of those seeking a career in academic dermatology. These departments may sustain the tripartite mission in the aggregate but at the level of individual faculty, there will be a growing bifurcation into clinician-educators on the one hand and physician scientists on the other.

Gary Wood, MD, U of Wisconsin

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