My journey from clinical lab scientist to commercial R&D to entrepreneurship: perspectives & lessons learned

Bob McCarthy
Bioman Conference
Bloomington, IN
13 July 2015
Building a career is a challenge in turbulent times

Where do I go???
My lessons/perspectives may serve as a guide to address these challenges.
Disruption of existing processes is the new normal
Driven by new biological eras

Each era driven by shift in ideas and/or technology

- Cell Theory (1860’s)
- Genetics (1900’s)
- Biochemistry (1920’s)
- Molecular Bio (1950’s)
- Biotechnology (1970’s)
- Genome/proteome (1990’s)
- Big Data (2002)
- Regen Medicine
How do we cope with the complexity of dynamic environments?

“Let’s not mince words: A strategic inflection point can be deadly when unattended to. Companies that begin a decline as a result of its changes rarely recover their previous greatness.” (p. 4, Only the Paranoid Survive)
Develop proactive orientation to address forces impacting career.
LESSONS LEARNED FROM EMPLOYMENT IN HEALTHCARE INDUSTRY
Core of Mayo’s approach to medicine is setting exceptional standards
No prima donnas at Mayo

Developed and implemented the concept of integrated, multispecialty group practice of medicine. This is Mayo Clinic’s most enduring and significant contribution to medicine.
Tight linkage of laboratory medicine to clinical practice

David Loegering & Robert A. Kyle
The Children’s Hospital Denver provided opportunity to broaden knowledge
Flow cytometry: a new tool for cellular analysis
Construction of a “Cytomutt” & application to clinical practice
Aneuploidy associated with improved prognosis in childhood acute lymphoblastic leukemia
Changes in healthcare reimbursement has a dramatic impact on medicine

...the single most influential postwar innovation in medical financing: Medicare's prospective payment system (PPS). Inexorably rising medical inflation and deep economic deterioration forced policymakers in the late 1970s to pursue radical reform of Medicare to keep the program from insolvency. Congress and the Reagan administration eventually turned to the one alternative reimbursement system that analysts and academics had studied more than any other and had even tested with apparent success in New Jersey: prospective payment with diagnosis-related groups (DRGs). Rather than simply reimbursing hospitals whatever costs they charged to treat Medicare patients, the new model paid hospitals a predetermined, set rate based on the patient's diagnosis. The most significant change in health policy since Medicare and Medicaid's passage in 1965 went virtually unnoticed by the general public. Nevertheless, the change was nothing short of revolutionary.

Old approach: fee for service
New approach: diagnosis related groups (DRGs)?
DRG’s radically changed the practice of medicine
Prepare for career change to business
TRANSITION TO COMMERCIAL SCIENCE
Boehringer Mannheim (BM): privately held German company with rich history in healthcare
Building a business for cell biology reagents

Biochemical reagents market circa 1987

- Molecular biology
  - Nucleic acid isolation
  - Restriction enzymes
  - RNA to DNA
  - Emergence of PCR
  - Nucleic acid manipulation
  - Nutridoma for hybridoma culture
  - Nucleic acid amplification
- Cell biology
  - Cell culture media
  - Antibody for cell antigens
  - Cell isolation media & devices
  - DOTMA, DOSPER
  - Transfection reagents
Developing a reagent business for rodent lymphocyte markers
Opportunity fora breakthrough product for managing type I DM

**Activity**

<table>
<thead>
<tr>
<th>Collagenase</th>
<th>BM</th>
<th>Sigma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type P</td>
<td>1.5-3.5</td>
<td>0.5-1.4</td>
</tr>
</tbody>
</table>

**Protease**

<table>
<thead>
<tr>
<th>Collagenase</th>
<th>Variable</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Variable</td>
<td>High</td>
</tr>
</tbody>
</table>

---

**HUMAN ISLET ISOLATION AND ALLOTRANSPLANTATION IN 22 CONSECUTIVE CASES**

Camillo Ricordi, Andreas G. Tzakis, Patricia B. Carroll, Yijun Zeng, Horacio L. Rodriguez Rilo, Rodolfo Alejandro, Ron Shapiro, John J. Fung, Anthony J. Demetris, Daniel H. Mintz, and Thomas E. Starzl

University of Pittsburgh, Transplant Institute, Pittsburgh, Pennsylvania 15213; and The Diabetes Research Institute, University of Miami, Miami, Florida 33101
Collagenase critical for cell release
Camillo Ricordi responsible for development of the islet isolation procedure routinely used today

From http://www.biorep.com
### Compare the Old with the New

<table>
<thead>
<tr>
<th></th>
<th>Crude collagenase</th>
<th>Liberase enzymes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enzyme activities</strong></td>
<td>&gt;15</td>
<td>3</td>
</tr>
<tr>
<td><strong>Endotoxin units / mg</strong></td>
<td>300-7000</td>
<td>&lt;50</td>
</tr>
<tr>
<td><strong>Lot-to-lot precision</strong></td>
<td>Low: Affected by conditions of fermentation</td>
<td>High: Formulation of purified enzymes</td>
</tr>
<tr>
<td><strong>How to get best results</strong></td>
<td>Screen different lots</td>
<td>Design optimal formulation: DOE</td>
</tr>
<tr>
<td><strong>Cell transplantation impact</strong></td>
<td>Dependent on availability of “magic lot”: reproducibility?</td>
<td>Minimized critical experimental variable, manipulate at will</td>
</tr>
</tbody>
</table>
R&D project leaders at Liberase launch event November, 1994
External, independent validation of performance by Linetsky et al (Miami) & Olack et al (St Louis)

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Center</th>
<th>Crude collagenase</th>
<th>Liberase HI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total IEQ/organ</td>
<td>Miami</td>
<td>$259.2K \pm 150.2K$ (n=50)</td>
<td>$487.4K \pm 343.9K$ (n=36)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>St Louis</td>
<td>$138.6K \pm 128.4K$ (n=10)</td>
<td>$389.6K \pm 191.2 K$ (n=13)</td>
<td></td>
</tr>
<tr>
<td>IEQ/g tissue</td>
<td>Miami</td>
<td>$3,245 \pm 2,041$</td>
<td>$6,698 \pm 4,920$</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>St Louis</td>
<td>$2,083 \pm 1,679$</td>
<td>$5,958 \pm 3,083$</td>
<td></td>
</tr>
</tbody>
</table>
Move from R&D to business development
Emergence of pharm-biotech ecosystem: deconstruction of value chain

**Discovery**
- Target Identification
- Target Validation
- Lead Generation & Optimization

**Development**
- Pre-Clinical Studies
- Clinical Trials

**Commercialization**
- Sales and Marketing

**BIG PHARMA**
- Outsource or in-house
- Core business

**TIER 1 VALUE ADDED SUPPLIERS**
- Core business
- Gene Hunters
- Animal Model
- Combi-Chem
- Synthetic Chemistry
- Small Biotech
- CRO’s

**TIER 2 PLATFORM & REAGENT SUPPLIERS**
- Core business
- Reagent
- Instrument
- Integrated System
Change in source of funding impacts business model

- Old model: academic users main source, purchasing weak
- New model purchasing stronger position
- Commercial firms will pay for innovation
- Must address needs of most demanding users to ensure success
Roadmaps to define areas for new product development

Market Trends
- M1
- M2

Root Needs
- RN1
- RN2
- RN3
- RN?

Technology
- T1
- T2
- T3
- T4
- T?

Competitive Assessment
- CA

Technology Projects
- P1
- P2
- P3
- P4

Planning to Time

Years
Licensing of a cell free protein expression system: success of realization
Licensing of a cell free protein expression system: failure of commerçilization

“There are only two important functions in business: marketing and innovation; everything else is cost.”

Peter Drucker
Innovation and Entrepreneurship, Practices and Principles, © 1985
PUTTING IT ALL TOGETHER:
FORMATION OF VITACYTE

Pure science, defined.
Success of islet transplantation

**A:** Survival analysis of C-peptide (blue) and insulin dependence (red) of patients receiving islet transplants

**B:** %HbA1c of islet transplant recipients whose:
- ● Transplant failed
- ○ Graft functional but had to resume insulin
- ◆ Graft functional and insulin independent

From: Merani & Shapiro, Clinical Science 110:611 (2006)
Lot variability with Liberase HI product
Key factors for success

- Industry knowledge
- Source of funding
- Stick to the knitting

Estimated that 90% of all high potential businesses founded by entrepreneurs who were in same or related industries (Bygrave)

SBIR/STTR awards
SBIR/STTR match funding from state government

More startups die of indigestion than starvation (Packard)
Carving out a defendable niche: focus on characterization of enzyme

Collagen degradation activity assay procedure

FITC (♦)-calf skin collagen fibrils + Collagenase
100 mM Tris 10mM CaCl₂ pH 7.5
60 min read at 35°C @ 2.5 min intervals
Ex 485/20 nm    Em 528/20 nm

Software calculates Vmax, maximal release of FU/minute during assay
One CDA unit = release of 1 FU/min
Correlation of enzyme activity to molecular form

Intact C2 $114 \text{ kDa}$ single CBD
- 9500 CDA U/mg

Intact C1 $116 \text{ kDa}$ double CBD
- 70,000 CDA U/mg

C1b single CBD C1 $100 \text{ kDa}$
- 9500 CDA U/mg

C1c single CBD C1 $100$ km
- 9500 CDA U/mg

Degraded C1 $<84 \text{ kDa}$ no CBD
- 0 CDA U/mg

Degraded C2 $<100 \text{ kDa}$ no CBD
- 0 CDA U/mg

Retention time: min
- 13.3
- 20.1
- 21.2
- 22.7
- 26.2
- 30.2

- Catalytic domain
- Linking domain
- Collagen binding domain

© 2015 VitaCyte LLC; All Rights Reserved
Manufactured first animal free enzyme mixture for cell isolation

NEM new enzyme mixture exposed to animal proteins
AFM animal free mixture no exposure to animal proteins
Development of AFM enables opportunity to expand to adjacent markets
Collagenase required to isolate and recover stem cells from cell culture
Potential uses of **Stem cells**

- Stroke
- Traumatic brain injury
- Learning defects
- Alzheimer's disease
- Parkinson's disease
- Missing teeth
- Wound healing
- Bone marrow transplantation (currently established)
- Spinal cord injury
- Osteoarthritis
- Rheumatoid arthritis
- Baldness
- Blindness
- Deafness
- Amyotrophic lateral sclerosis
- Myocardial infarction
- Muscular dystrophy
- Diabetes
- Crohn's disease
- Multiple sites: Cancers
LESSONS LEARNED FROM JOURNEY
Take home lessons

• Employment is a gift to build a career
• Initiate challenging projects that benefit employer
• Never stop learning, expand knowledge into adjacent areas aligned with strengths
• Be curious!
• Set a vision for goal whenever & wherever possible
• Opportunity abounds for technical firms that can provide value to ecosystem
Hurdle to overcome: funding critical path research

From 2004 FDA whitepaper: *Innovation or Stagnation*:
Open questions to improve success of manufacture of GMP islet product

- Donor criteria
- Organ procurement
- Organ transport
- Tissue dissociation
- Islet purification
- Islet characterization
- Islet release criteria
- Cell transplant
“An industry in flux creates vast opportunities. But to seize them, you have to understand how the current upheavals will create different sources of value – and reinvent your company to capitalize on them.”

Mark Levin
CEO, Millennium Pharmaceuticals