

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



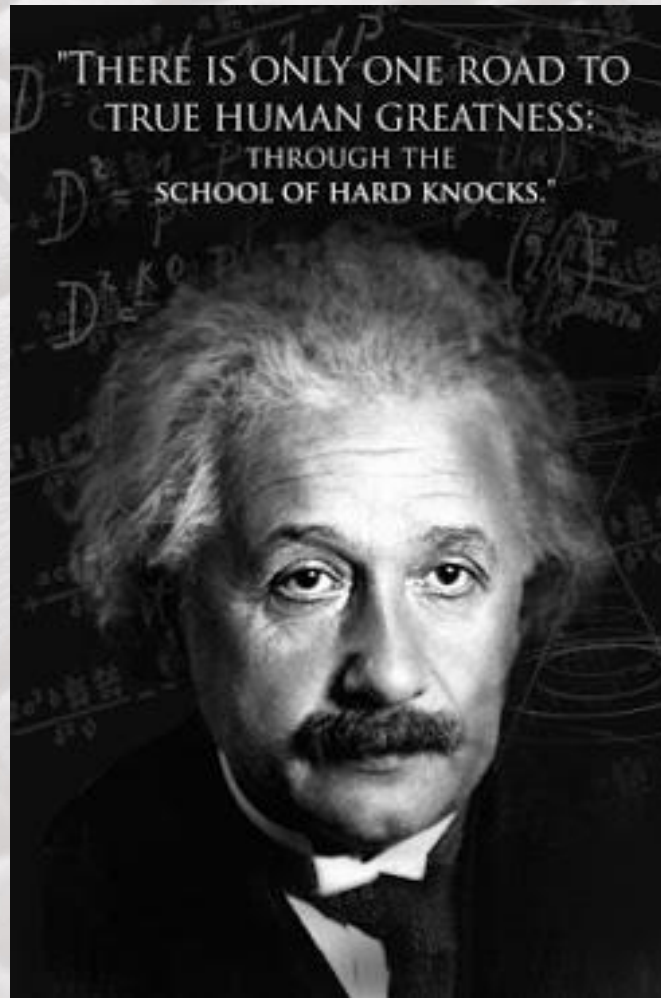
Bob McCarthy
Bioman Conference
Bloomington, IN
13 July 2015

Building a career is a challenge in
turbulent times

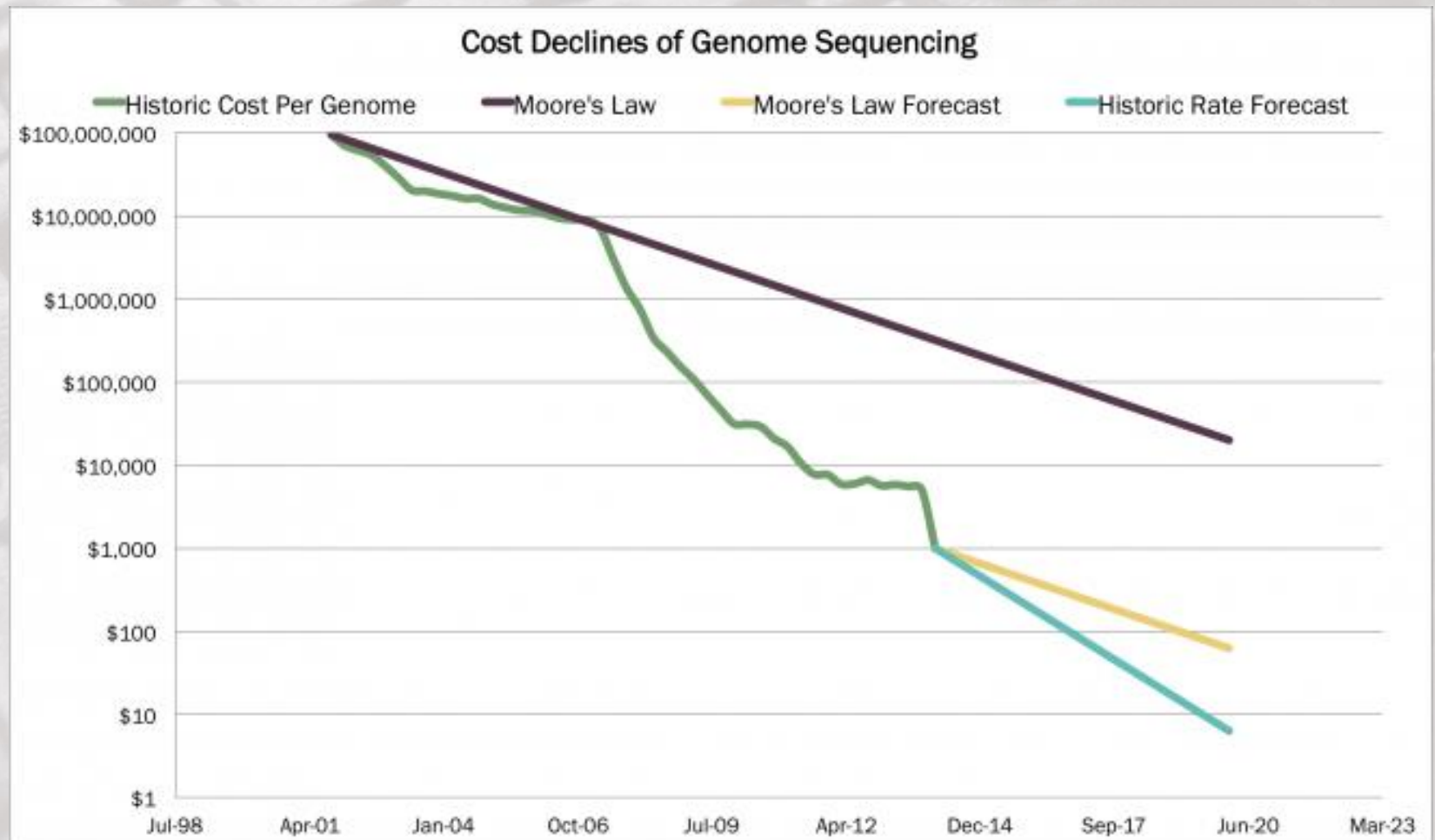


Where do I go???

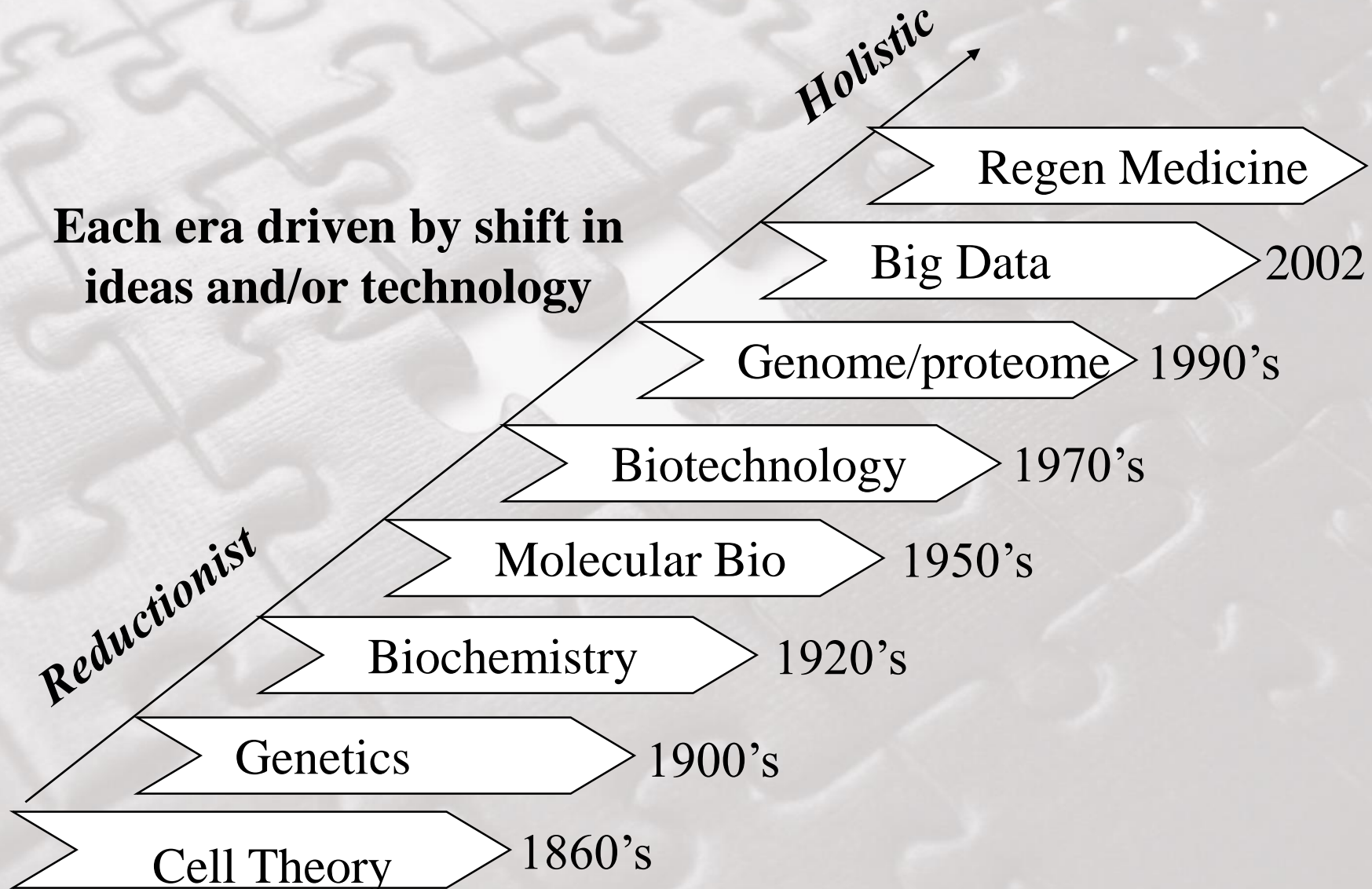
My lessons/perspectives may serve as
a guide to address these challenges



Disruption of existing processes is the new normal



Driven by new biological eras



How do we cope with the complexity of dynamic environments?

Business goes to
new heights

**Inflection
Point**

Big Data

Regenerative Medicine

Business
declines

“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

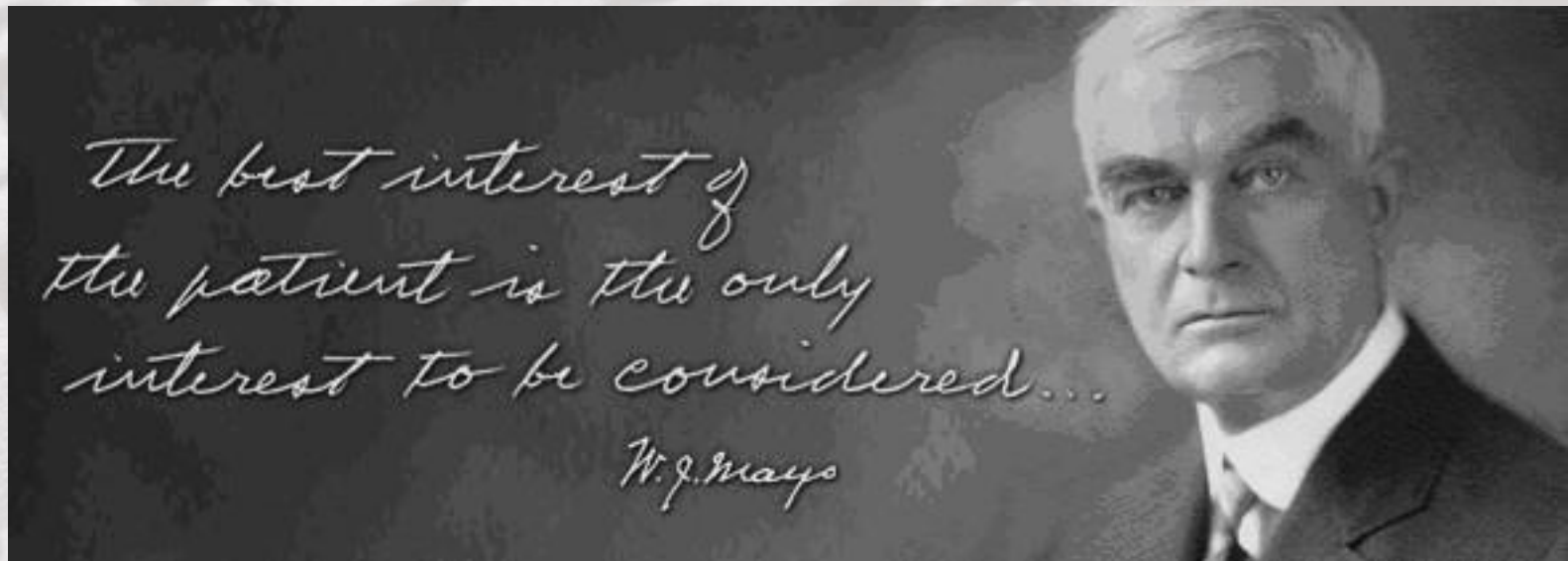


The Children's Hospital

Core of Mayo's approach to medicine is
setting exceptional standards



No prima donnas at Mayo

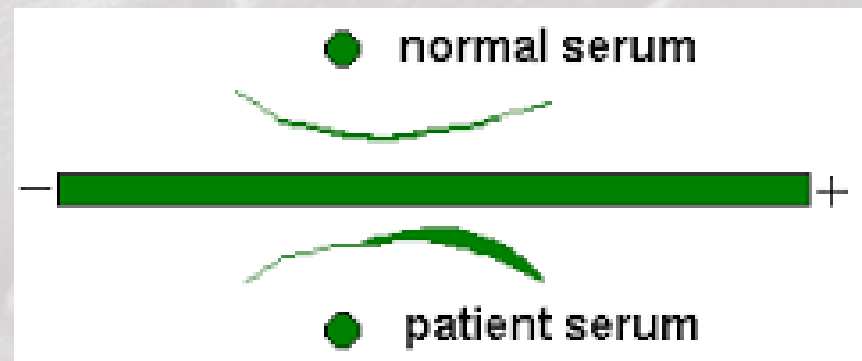
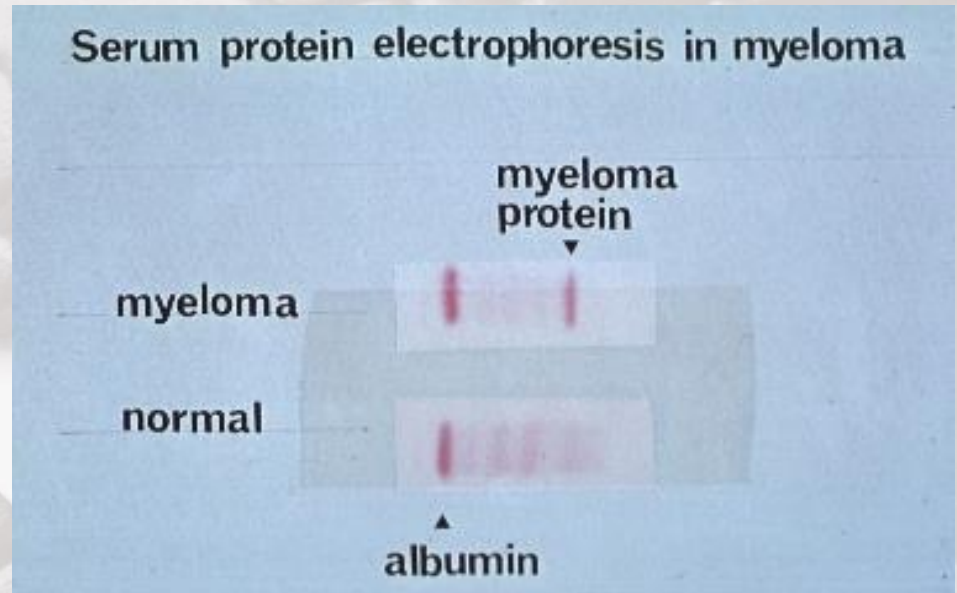


Developed and implemented the concept of integrated, multispecialty group practice of medicine. This is Mayo Clinic's most enduring and significant contribution to medicine.

Tight linkage of laboratory medicine to clinical practice



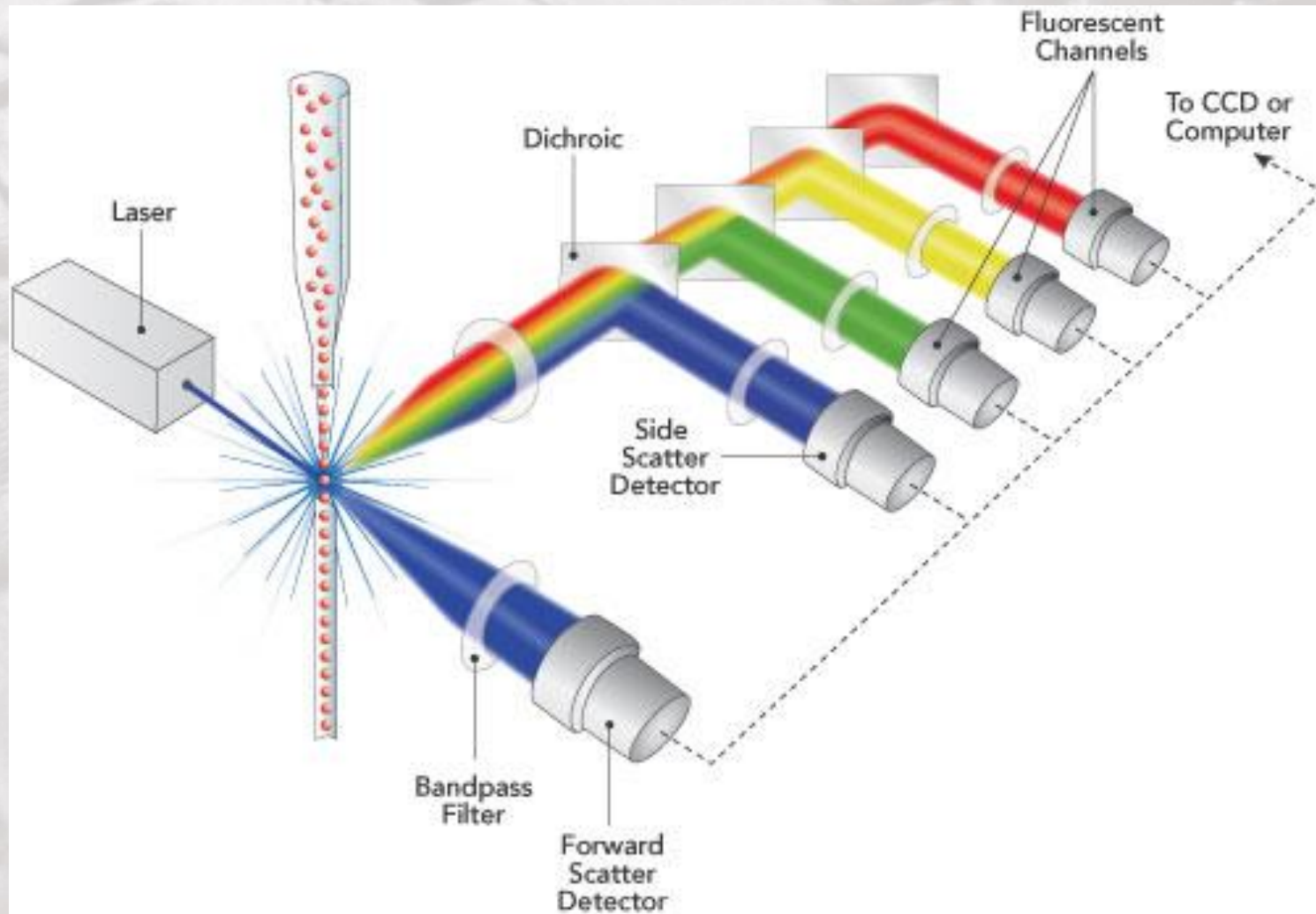
David Loegering & Robert A. Kyle



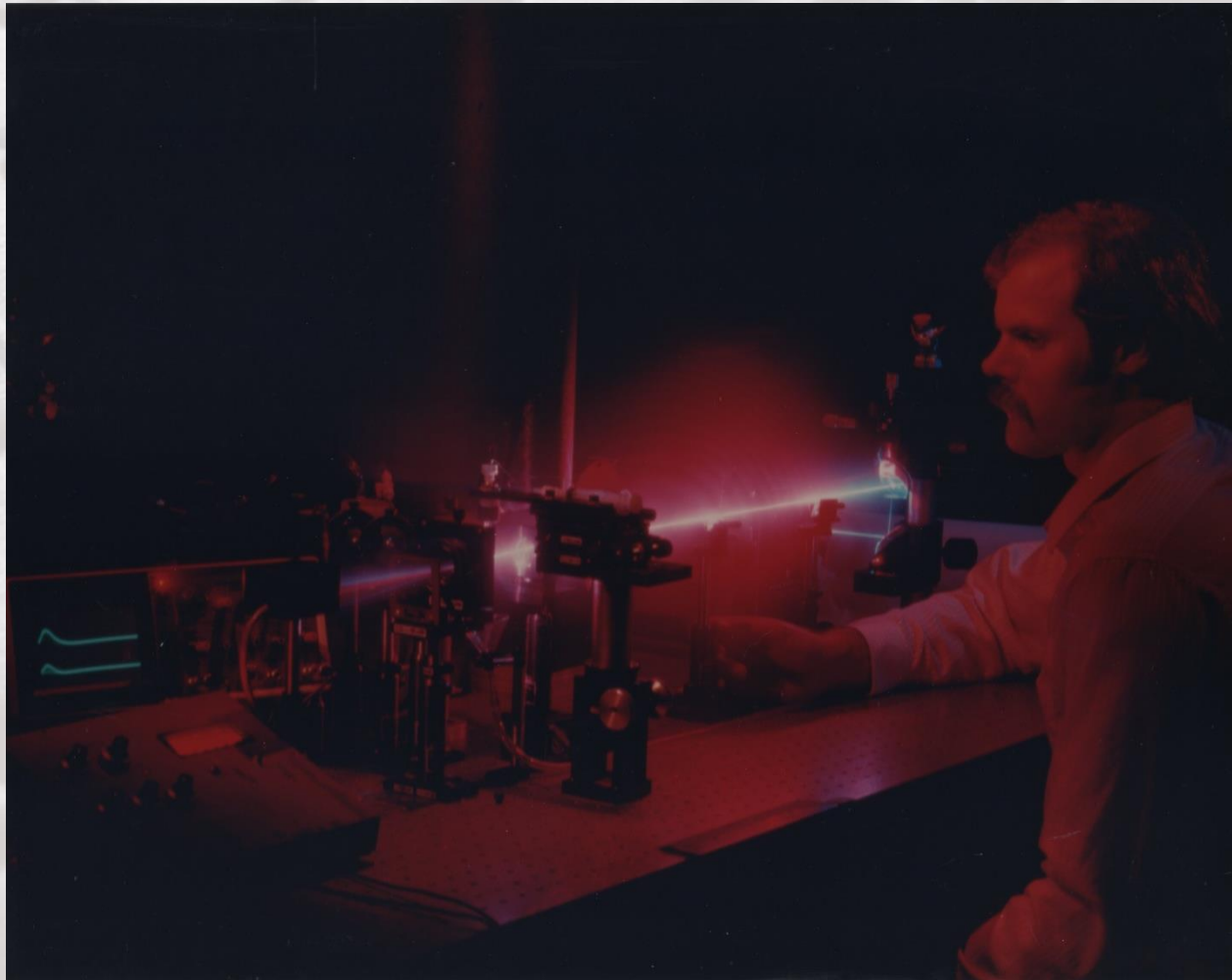
The Children's Hospital Denver provided opportunity to broaden knowledge



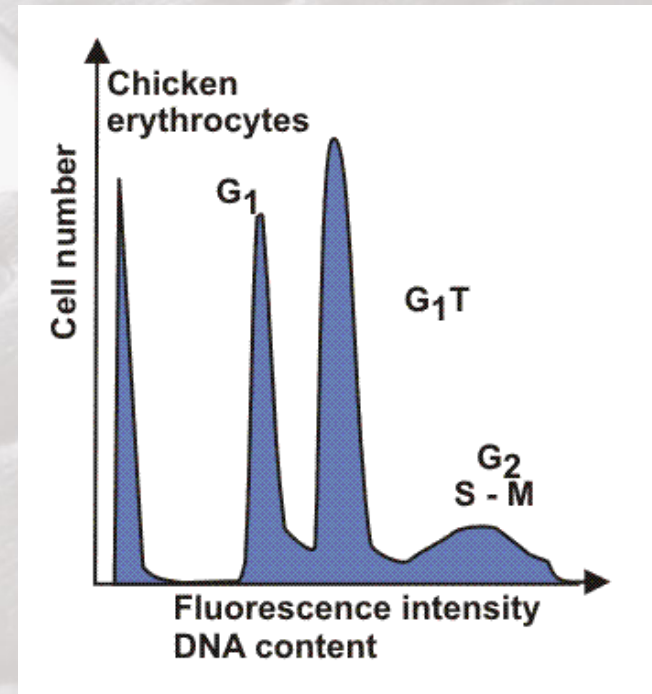
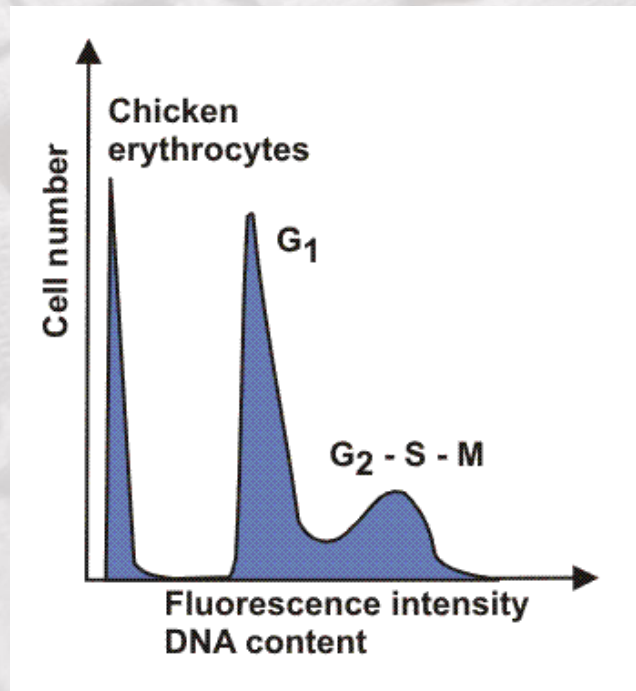
Flow cytometry: a new tool for cellular analysis



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

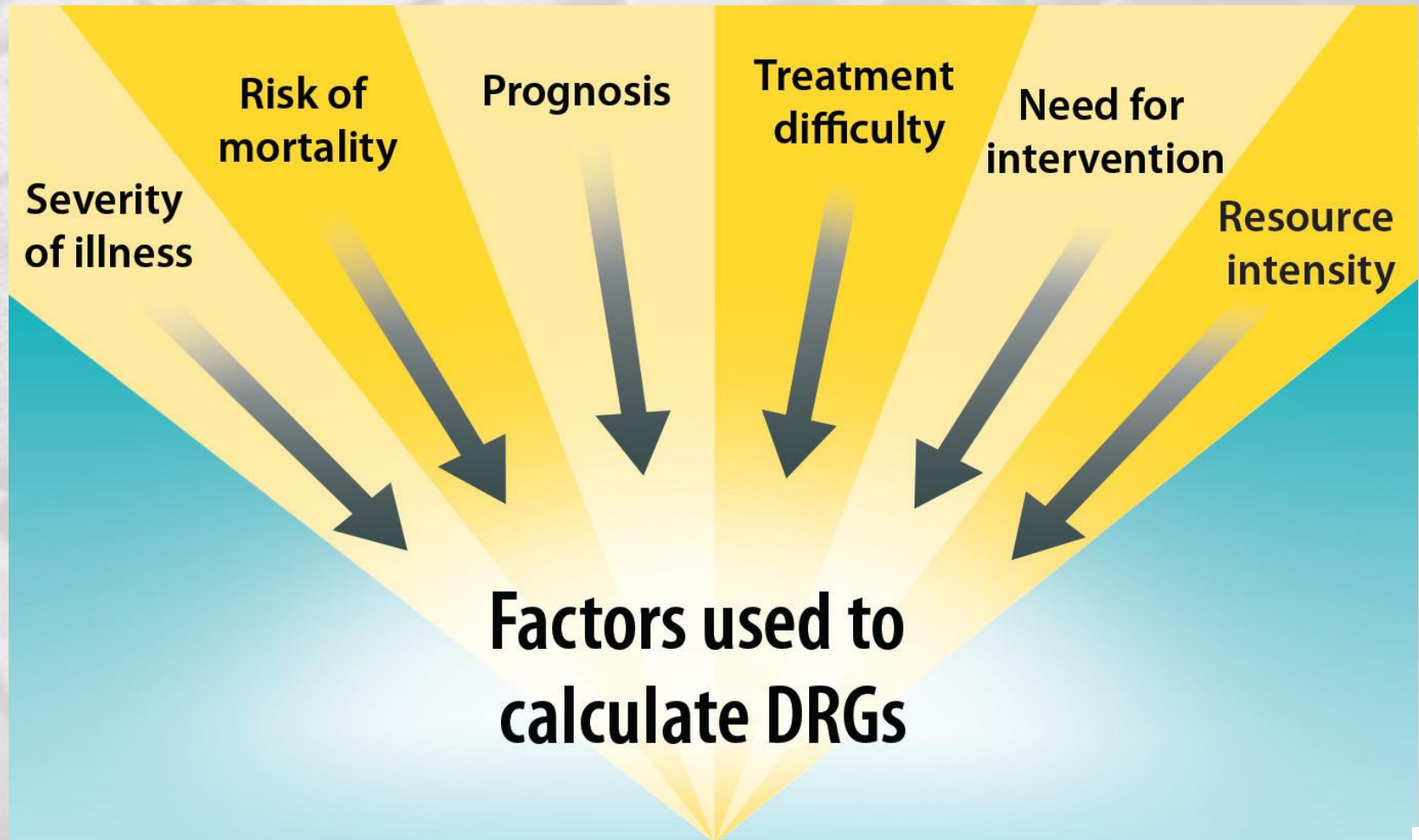
...the single most influential postwar innovation in medical financing: Medicare's prospective payment system (PPS). Inexorably rising medical inflation and deep economic deterioration forced policymakers in the late 1970s to pursue radical reform of Medicare to keep the program from insolvency. Congress 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.**

Mayes, Rick, "The Origins, Development, and Passage of Medicare's Revolutionary Prospective Payment System" *Journal of the History of Medicine and Allied Sciences* Volume 62, Number 1, January 2007, pp. 21–55

Old approach: fee for service



New approach: diagnosis related groups (DRGs)?

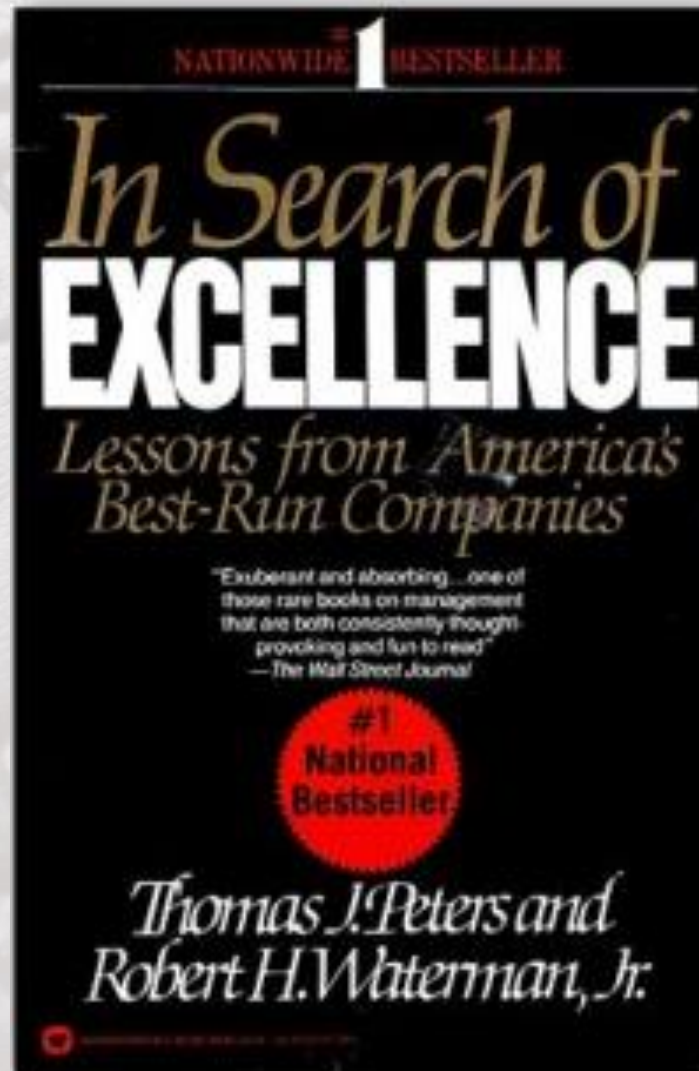


DRG's radically changed the practice of medicine

Figure 6: Percent Change in Medicare Total Costs and GDP in Nominal Dollars for 1967-97



Prepare for career change to business



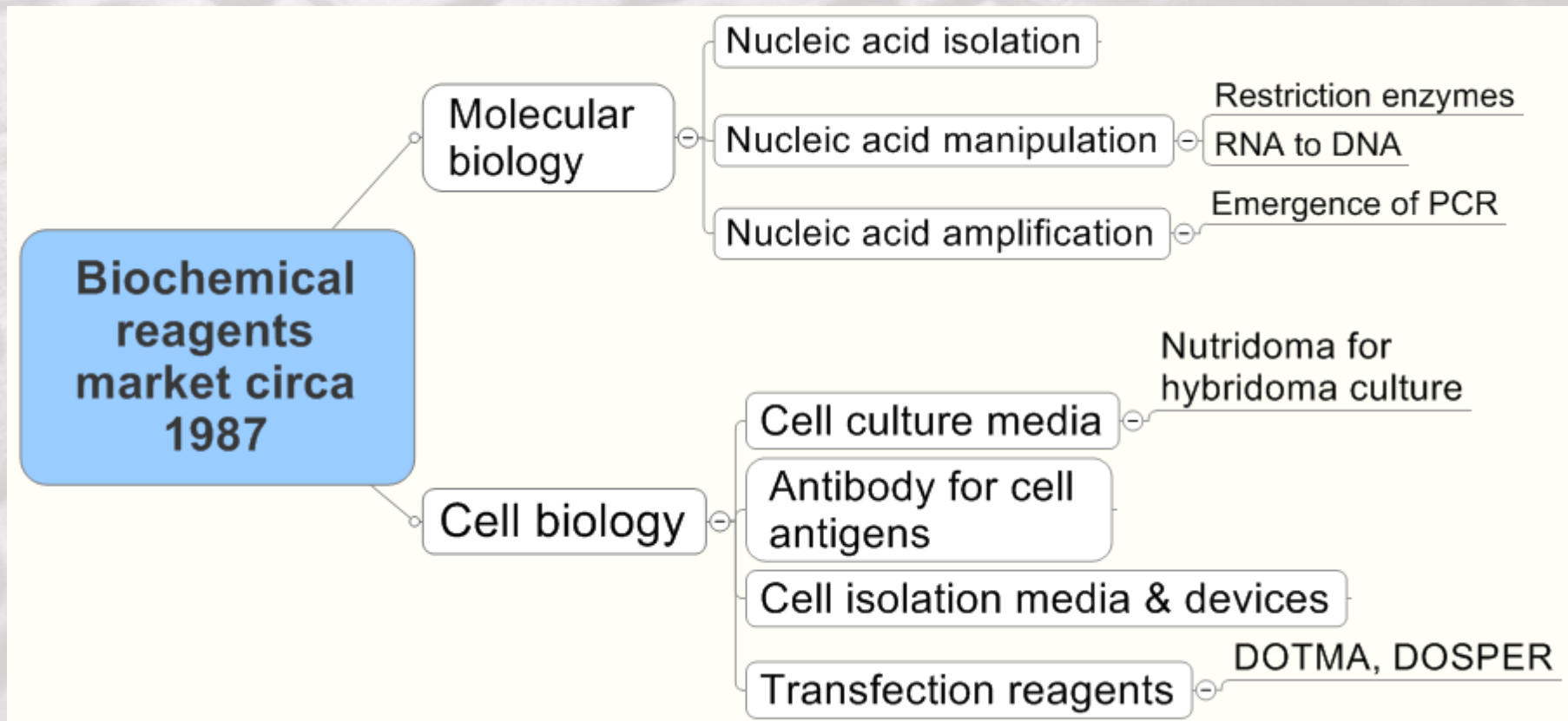
TRANSITION TO COMMERCIAL SCIENCE



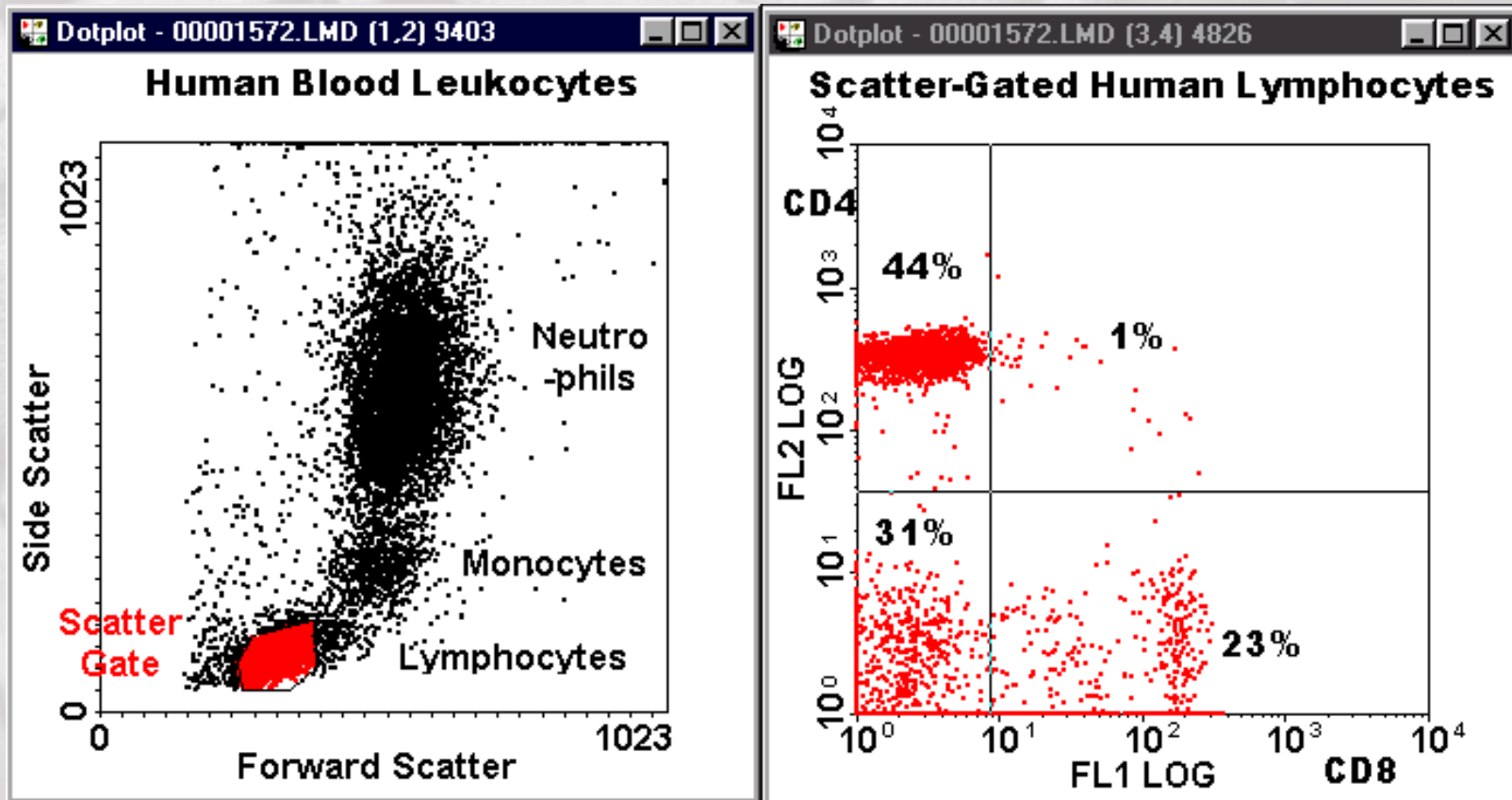
Boehringer Mannheim (BM): privately held German company with rich history in healthcare



Building a business for cell biology reagents



Developing a reagent business for rodent lymphocyte markers



Opportunity for a breakthrough product for managing type I DM



Activity

Collagenase

	BM Type P	Sigma Type XI
Wunsch	1.5-3.5	0.5-1.4
Protease	Variable Low	Variable High

0041-1337/92/5302-0407\$03.00/0
TRANSPLANTATION
Copyright © 1992 by Williams & Wilkins

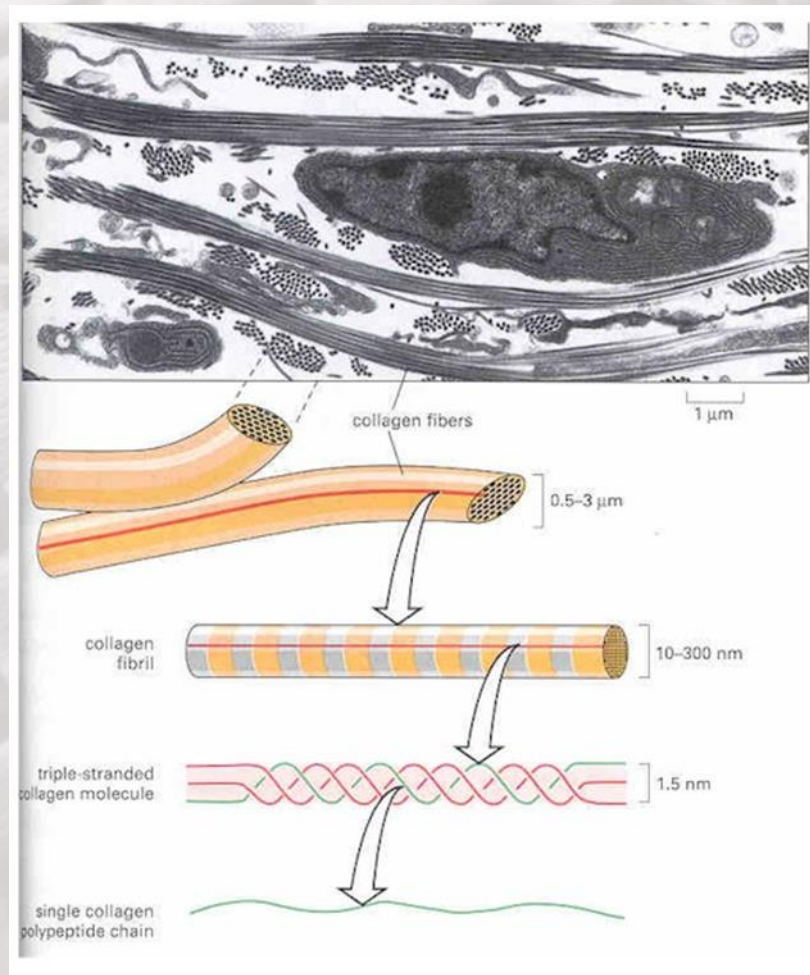
Vol. 53, 407-414, No. 2, February 1992
Printed in U.S.A.

HUMAN ISLET ISOLATION AND ALLOTRANSPLANTATION IN 22 CONSECUTIVE CASES^{1,2}

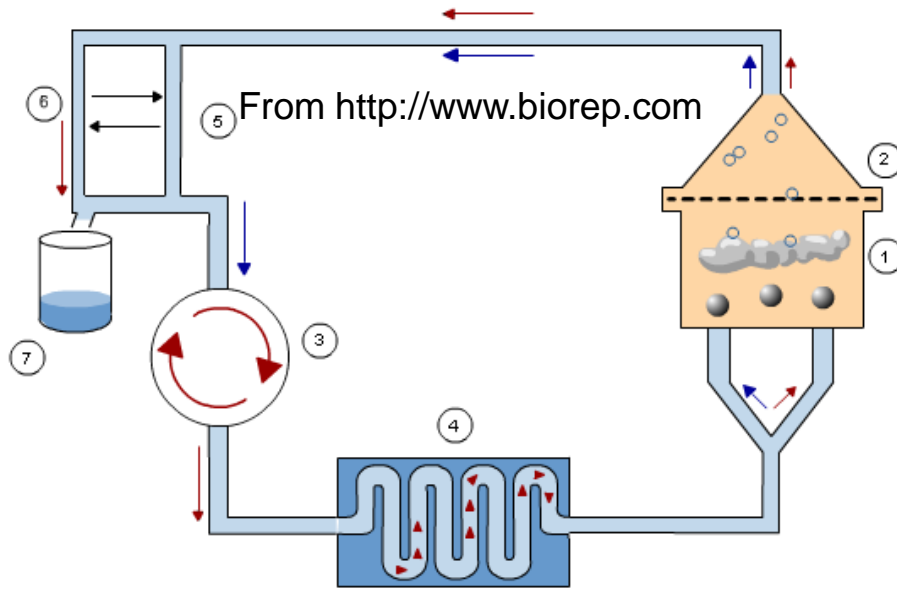
CAMILLO RICORDI,³ ANDREAS G. TZAKIS, PATRICIA B. CARROLL, YIJUN ZENG,
HORACIO L. RODRIGUEZ RILO, RODOLFO ALEJANDRO, RON SHAPIRO, JOHN J. FUNG,
ANTHONY J. DEMETRIS, DANIEL H. MINTZ, AND THOMAS E. STARZL

University of Pittsburgh, Transplant Institute, Pittsburgh, Pennsylvania 15213; and The Diabetes Research Institute, University of Miami, Miami, Florida 33101

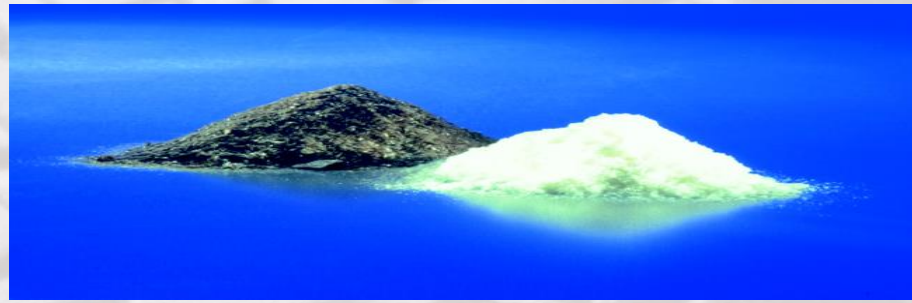
Collagenase critical for cell release



Camillo Ricordi responsible for development of the islet isolation procedure routinely used today



Compare the Old with the New



Crude collagenase

Liberase enzymes

Enzyme activities

>15

3

Endotoxin
units / mg

300-7000

<50

Lot-to-lot precision

Low: Affected by
conditions of
fermentation

High: Formulation of
purified enzymes

How to get best
results

Screen different lots

Design optimal
formulation: DOE

Cell
transplantation
impact

Dependent on
availability of "magic
lot": reproducibility?

Minimized critical
experimental
variable, manipulate
at will

R&D project leaders at Liberase launch event November, 1994



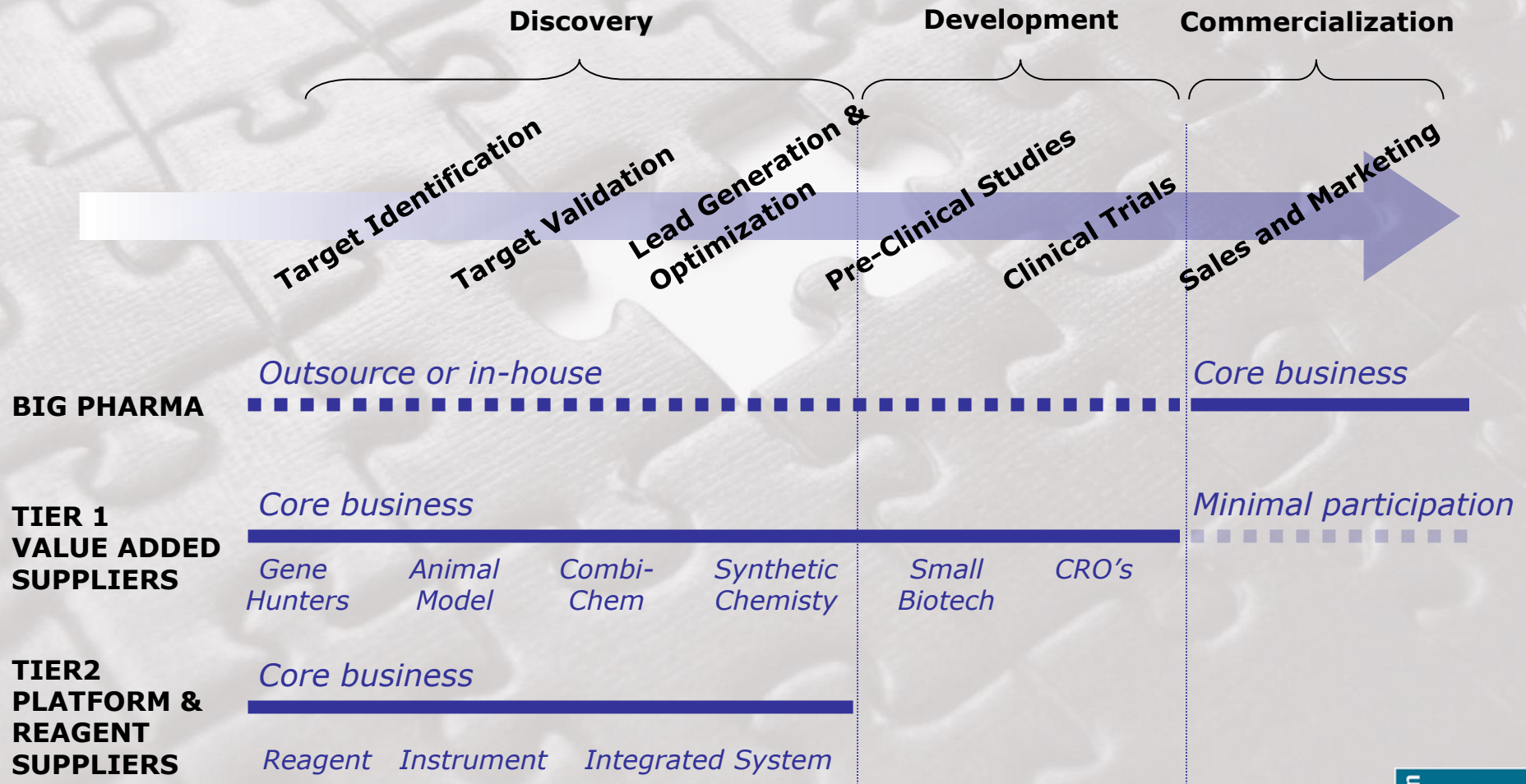
External, independent validation of performance by Linetsky et al (Miami) & Olack et al (St Louis)

Analysis	Center	Results		P
		Crude collagenase	Liberase HI	
Total IEQ/organ	Miami	259.2K \pm 150.2K (n=50)	487.4K \pm 343.9K (n=36)	< 0.001
	St Louis	138.6K \pm 128.4K (n=10)	389.6K \pm 191.2 K (n=13)	
IEQ/g tissue	Miami	3,245 \pm 2,041	6,698 \pm 4,920	< 0.001
	St Louis	2,083 \pm 1,679	5,958 \pm 3,083	

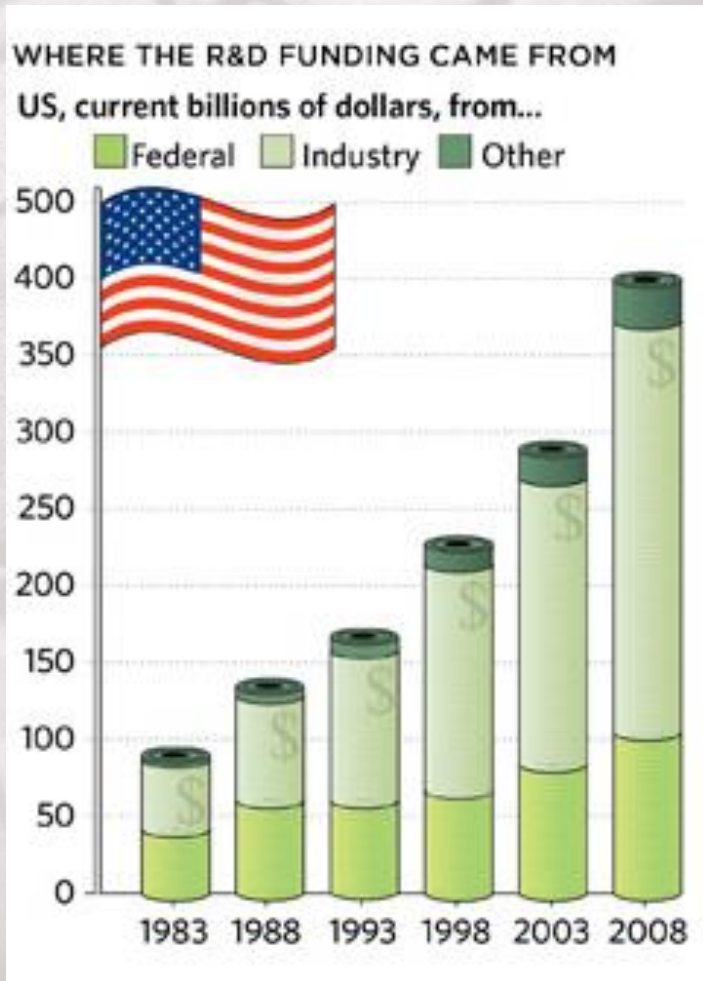
Move from R&D to business development



Emergence of pharm-biotech ecosystem: deconstruction of value chain



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



Root Needs



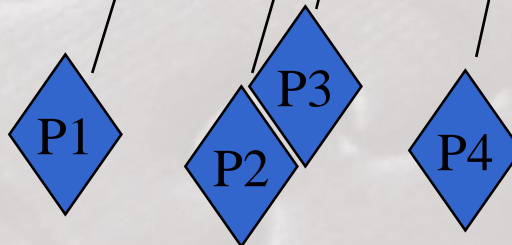
Technology



Competitive Assessment



Technology Projects



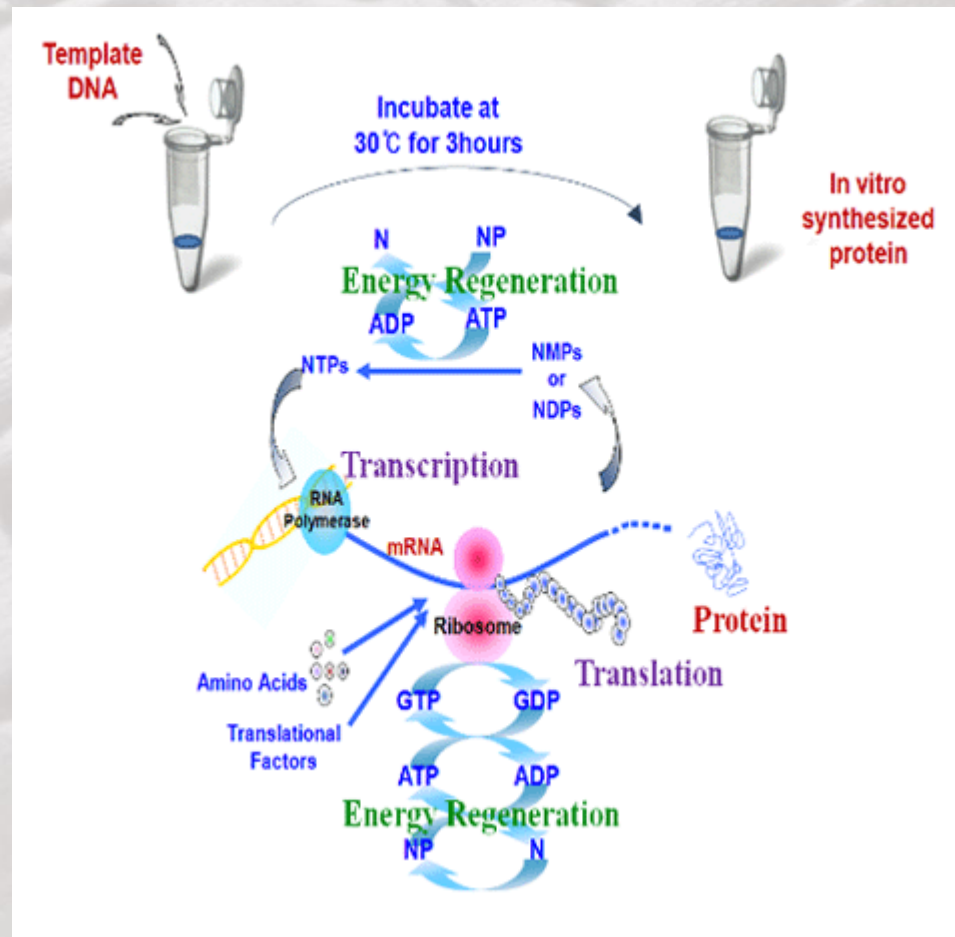
Planning

Time

Years



Licensing of a cell free protein expression system: success of realization



Licensing of a cell free protein expression system: failure of commercialization



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

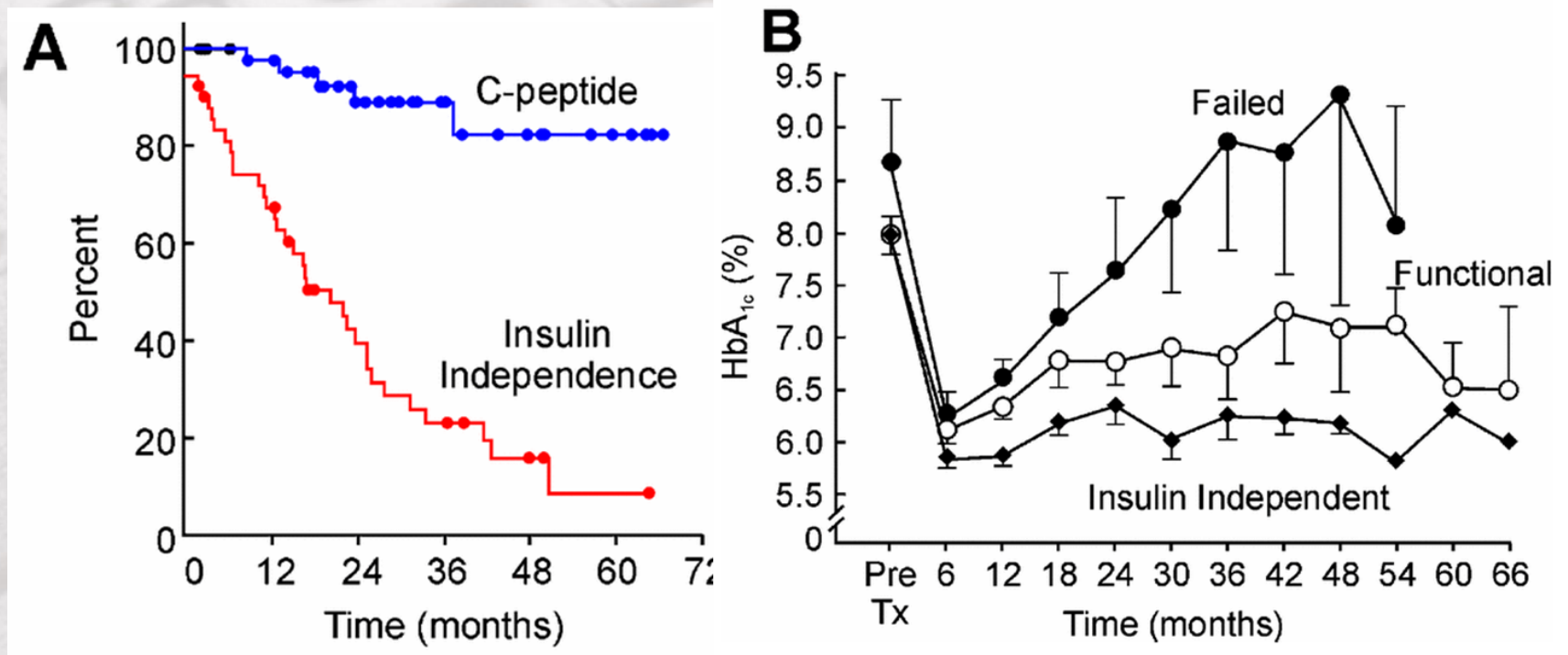
Peter Drucker

Innovation and Entrepreneurship,
Practices and Principles, © 1985

**PUTTING IT ALL TOGETHER:
FORMATION OF VITACYTE**



Success of islet transplantation



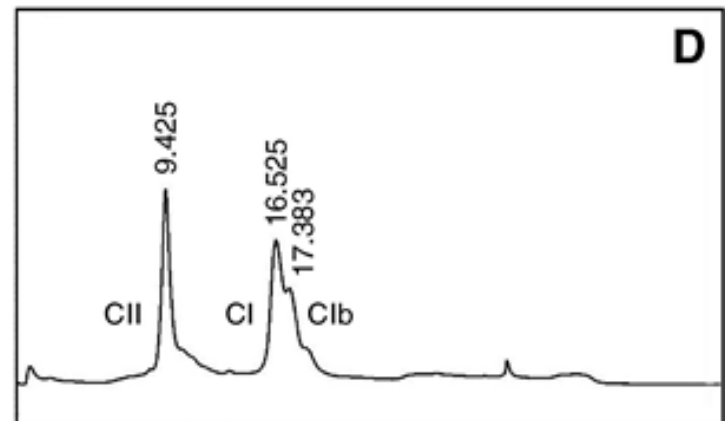
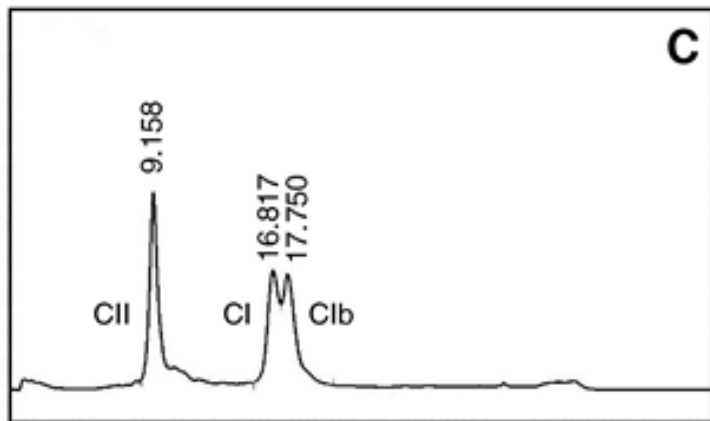
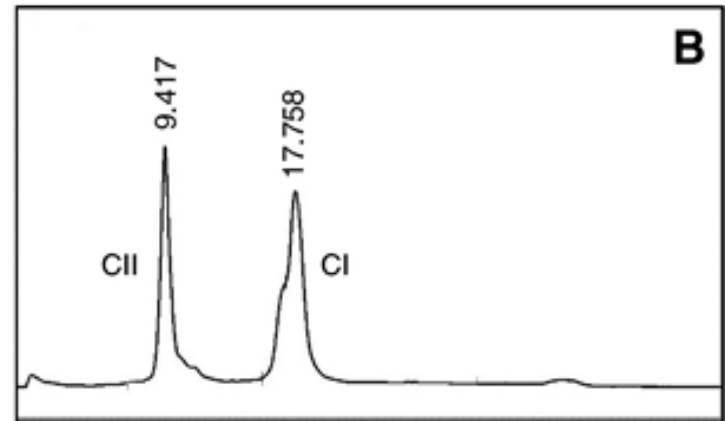
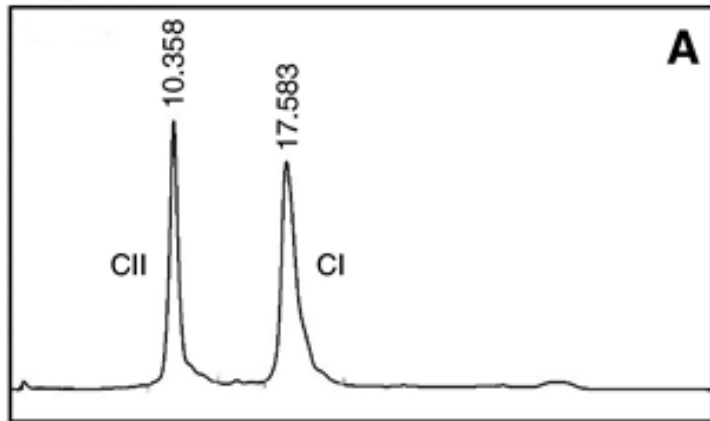
A: Survival analysis of C-peptide (blue) and insulin dependence (red) of patients receiving islet transplants

B: %HbA_{1c} of islet transplant recipients whose:

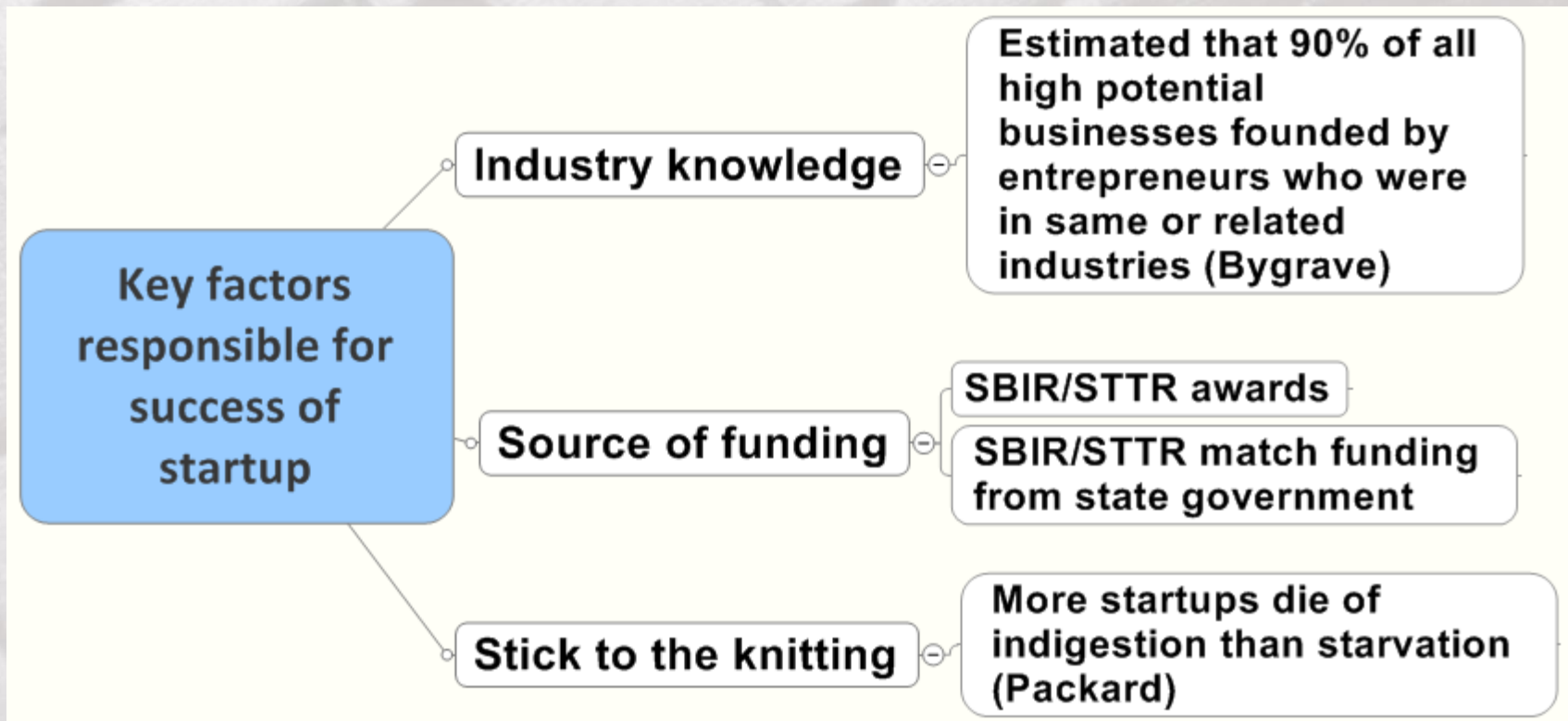
- Transplant failed
- Graft functional but had to resume insulin
- ◆ Graft functional and insulin independent

Lot variability with Liberase HI product

Formulation Analysis by HPLC



Key factors for success



Carving out a defensible niche: focus on characterization of enzyme

Collagen degradation activity assay procedure



FITC (★)-calf skin collagen fibrils
+

Collagenase

100 mM Tris 10mM CaCl₂

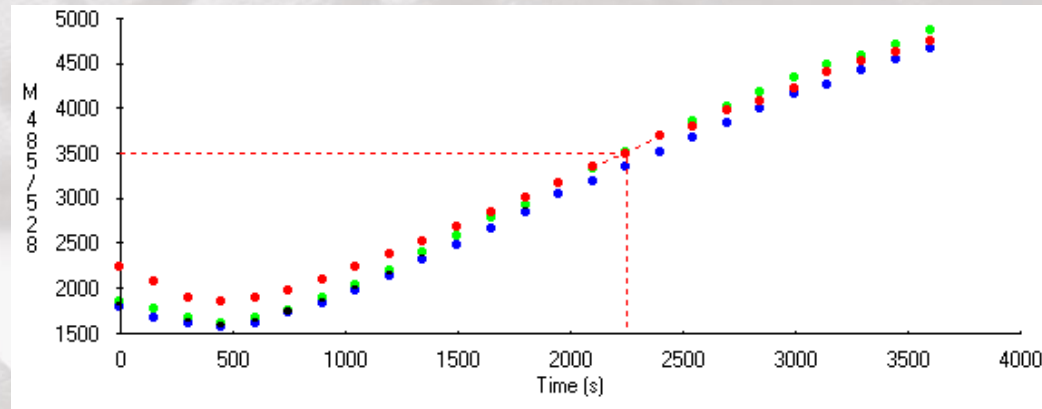
pH 7.5



60 min read at 35°C

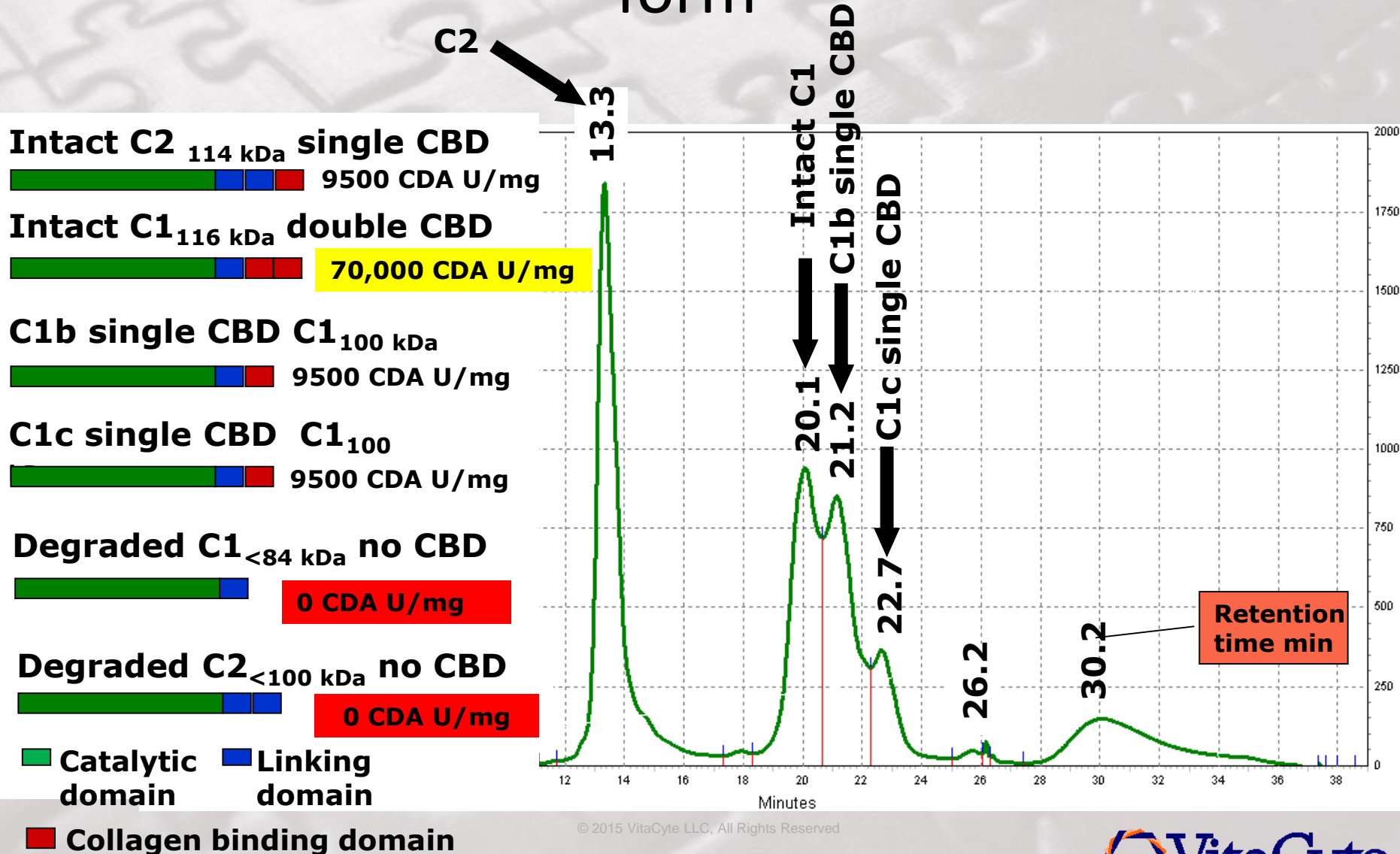
@ 2.5 min intervals

Ex 485/20 nm Em 528/20 nm

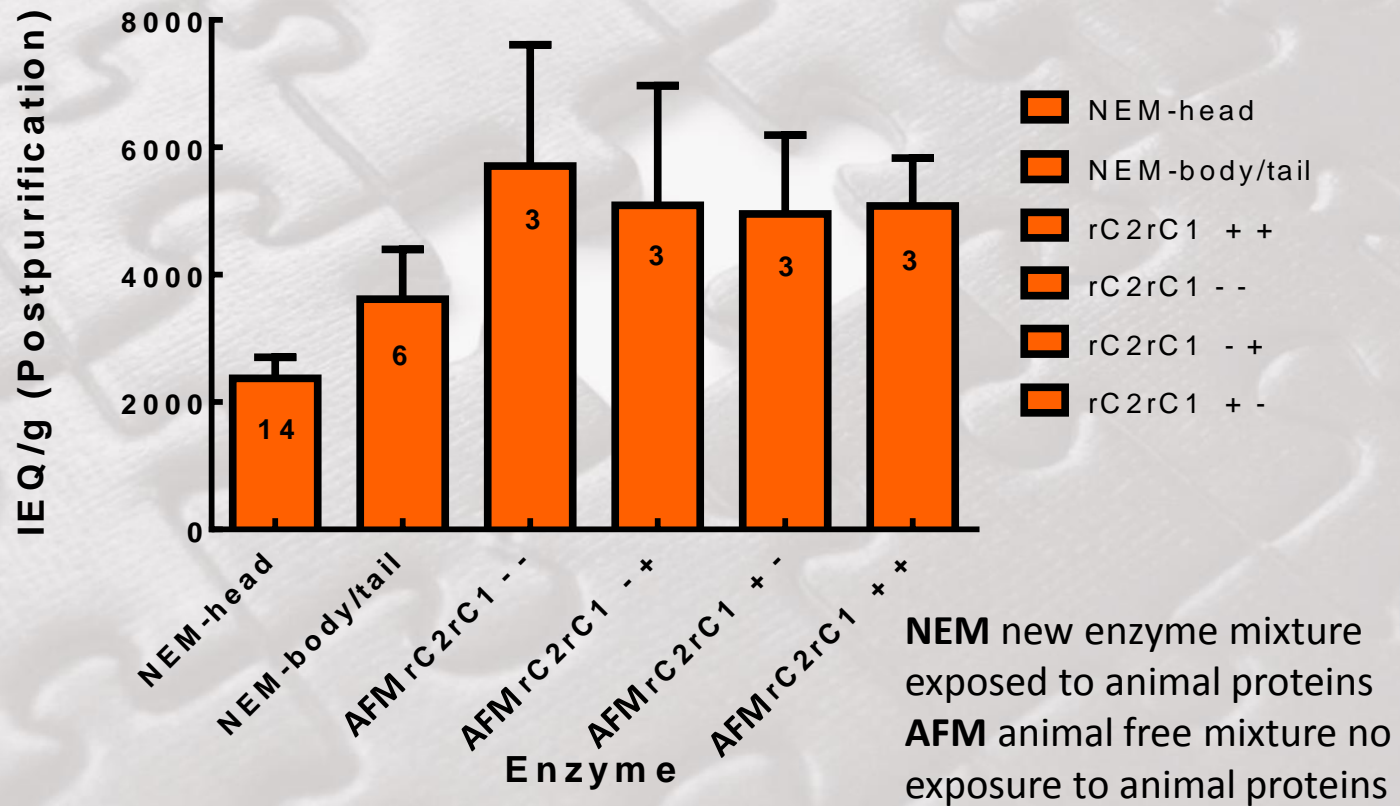


- ⊕ Software calculates Vmax, maximal release of FU/minute during assay
- ⊕ One CDA unit = release of 1 FU/min

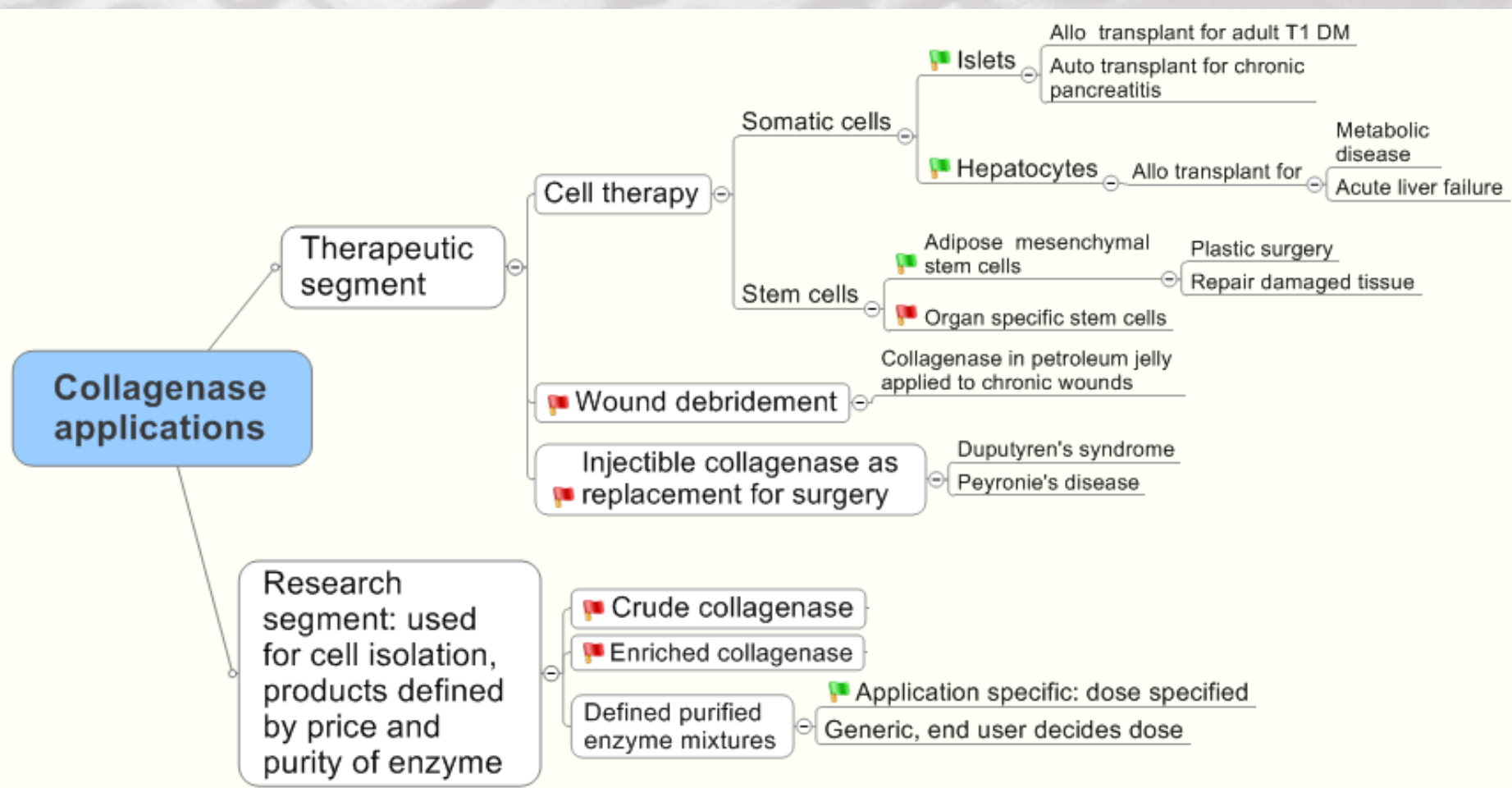
Correlation of enzyme activity to molecular form



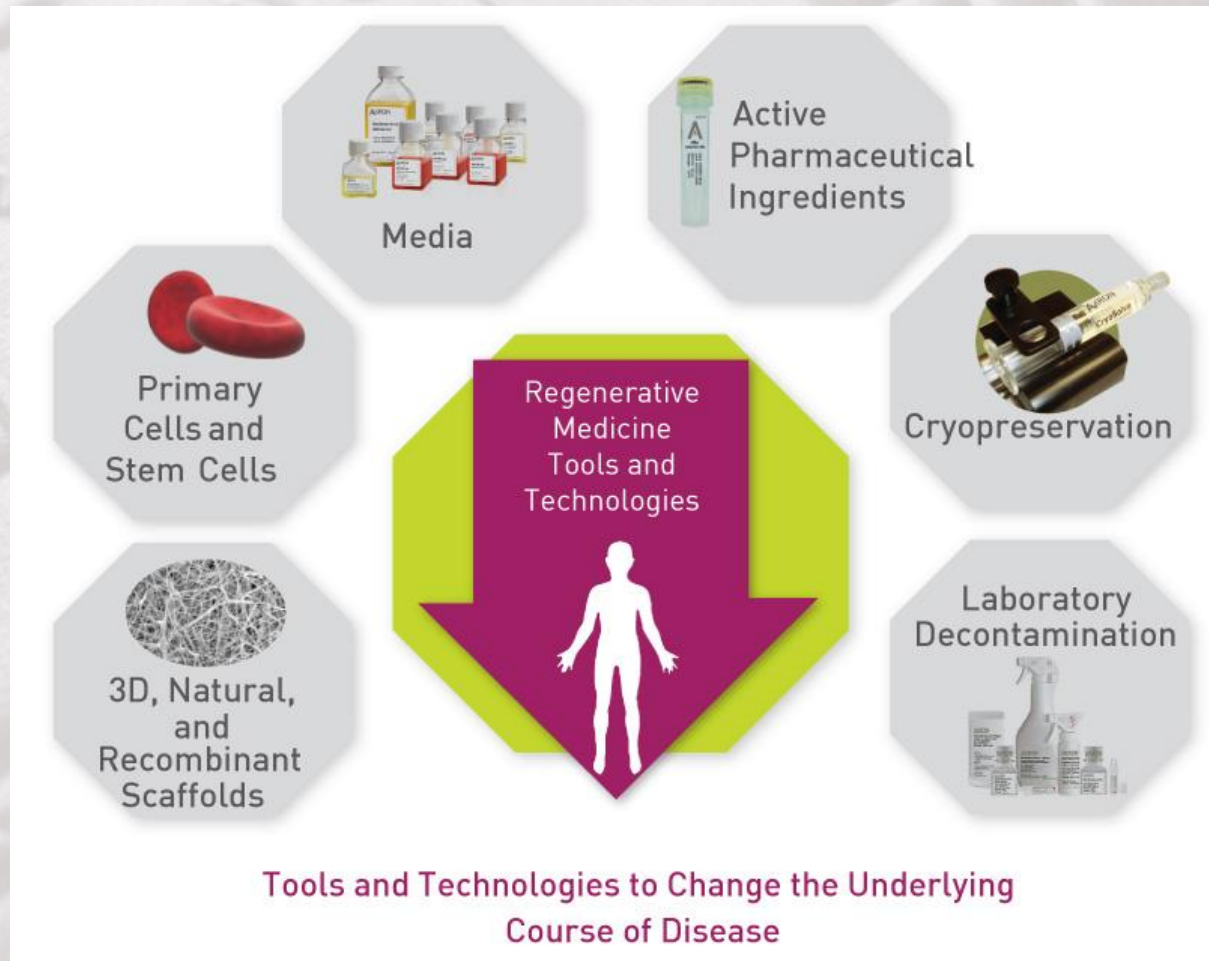
Manufactured first animal free enzyme mixture for cell isolation



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**





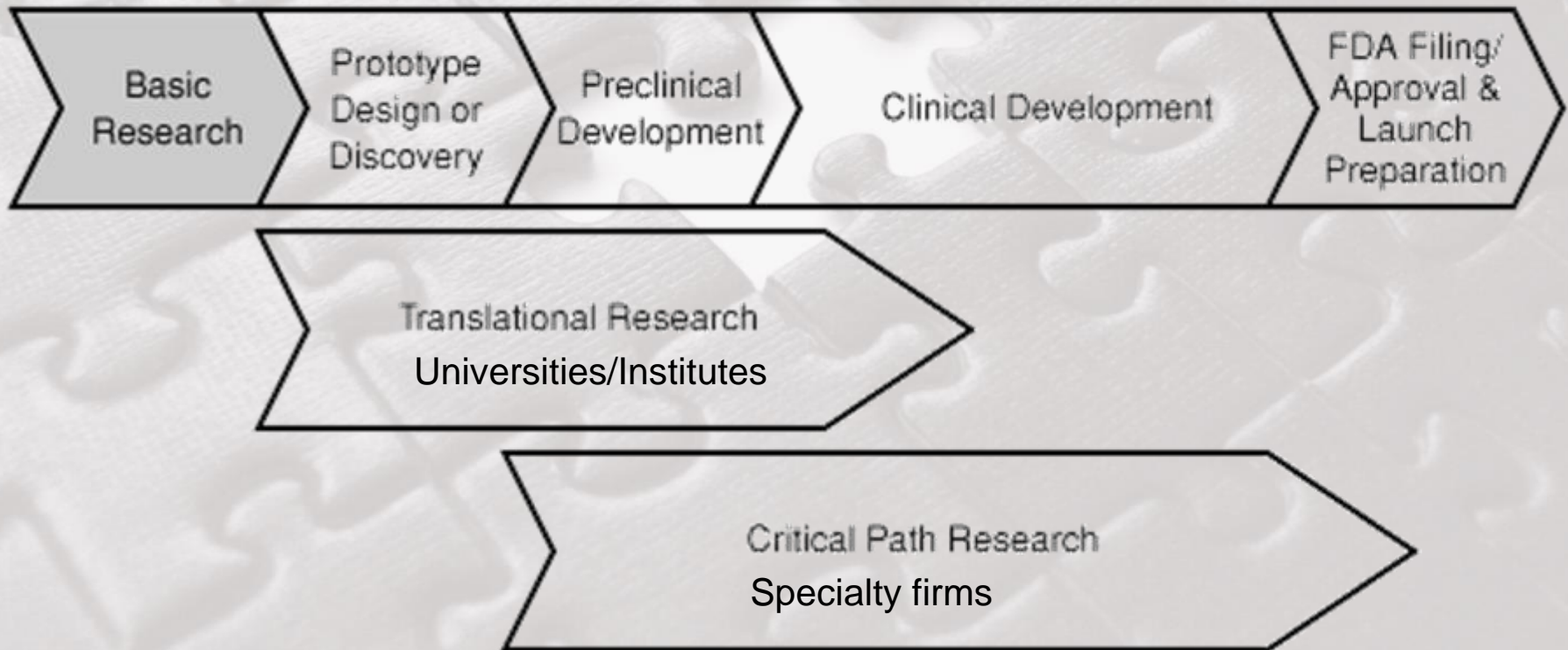
LESSONS LEARNED FROM JOURNEY

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

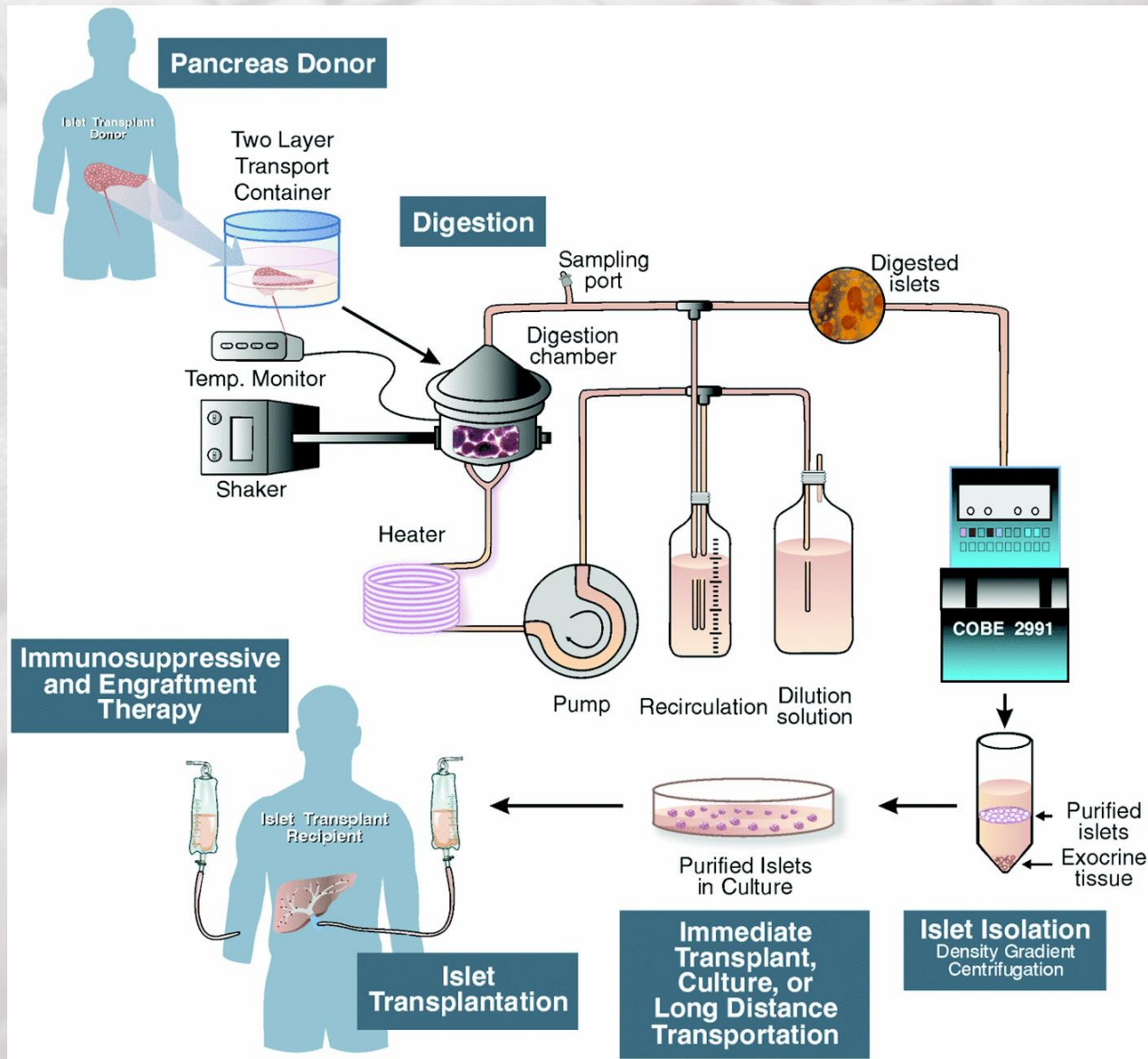
Hurdle to overcome: funding critical path research

Figure 5: Research Support for Product Development



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
Harvard Business Review, June 2001

