James Dalton
2018

Slide 1: Thank you!

I'm humbled to be here today to deliver the Rho Chi Lecture. I'd like to thank Dr. Karen Farris who nominated me (I think), the five unknown people who apparently were willing to stretch the truth and write letters of endorsement, the members of Rho Chi Lecture Award Committee and the Rho Chi Executive Council who selected me from what I am sure was a stellar group of other nominees. It's a great honor to be recognized by one's peers and I hope that my talk today lives up to your expectations. Thank you!

Slide 2: Climbing the Stairway to Success

My talk today is part career advice and part history lesson, viewed through the lens of my personal experiences in academic drug discovery and development.

It's not uncommon for us to think about our goals, careers, and lives as linear marches through time, proceeding from point A to point Z through an orderly sequence of steps that will carry us from our starting point to success.

We think about where we are today and where we want to be in the future.

We consider our options, make a plan, get started, work hard, perhaps overcome a setback or two, and achieve a series of goals that carry us toward what we define as success.

Hard work, persistence, intelligence, a good sense of humor, mentors, and a robust network of peers are among the many essential attributes for climbing the stairs to success.

However, the stairs from start to finish are seldom straight in my experience {CLICK}

Challenges, discoveries, new people and new opportunities are always entering and exiting your personal life and career and altering your path in unexpected ways.

Being curious, being creative, being adaptable, and accepting risks along the way are equally necessary and common traits of some of the most successful people that I've met along my journey.

Slide 3: Trivia Question

Before I tell you my story and the importance of stairs to my career, I'd like to start with a trivia question.

By a show of hands, how many of you have used margarine? How many of you have used mayonnaise? How many are students or faculty members at a College with a chapter of Rho Chi?

Ok, we've covered most of the people in the room with the first three items shown on this slide.

So, my trivia question is this: what do all of these things have in common?

Slide 4: Dr. Hans Vahlteich

The answer is Dr. Hans Vahlteich.

Hans was born in Chicago in 1896 and grew up working in his father's pharmacy.

In his own words and he (and I quote) "was practically born and raised in a drug store."

He ran "...chores and ... errands when in grade school" and the drugstore was his home between 1915 and 1918 while a student in pharmaceutical chemistry at the University of Illinois at Chicago.

He opened the store at 7:30 a.m., left for the day to attend pharmacy school, then returned to the store where his mother brought him dinner. He closed the store at 10 p.m. and slept in the back room.

After finishing his degree at UIC, he enrolled at the University of Michigan College of Pharmacy where he completed his BS and MS degrees in pharmacy in 1920 and 1921, respectively.

While a student at Michigan, he and colleagues founded The Rho Chi Society and established its Alpha chapter at the University of Michigan.

Hans left Michigan in 1921, earned a PhD at Columbia in 1923, and became the first employee in a new enterprise that Mr. Richard Hellman was starting in Long Island. Mr. Hellman was a successful delicatessen owner who had developed a new and award winning salad dressing (Blue Ribbon Mayonnaise) and was now interested in increasing its production to commercial scale.

Hans led the commercial scale-up of Hellman's mayonnaise and spent his entire career in the new company, Best Foods, eventually retiring as VP for Research and Quality Control in 1961.

Along the way, he made an important discovery and patented the chemical process for hydrogenation of vegetable oil in 1934, paving the way for commercial production of margarine.

He passed away at the age of 93 in 1989 and his estate funded substantial gifts to the University of Illinois and Columbia University and a $3.4M gift to the University of Michigan, endowing professorships at all three universities and also establishing the Vahlteich Medicinal Chemistry Core at Michigan.

Slide 5: Vahlteich's Stairway

We can arrange Vahlteich's education and accomplishments in an orderly timeline of steps from his humble beginnings pharmacy student to VP of Research and the creation of endowments that will sustain medicinal chemistry research in perpetuity.

However, I think that it's reasonable to guess than young Hans didn't lie awake in the back of his father's pharmacy dreaming about building a factory that would supply the world with the perfect dressing for a BLT, creating a replacement for butter, or founding a pharmacy honor society that would bring us all together here today.

Hans was strong believer in the value of pharmacy education, and saw that it could be successfully adapted into other areas. I imagine that his friends and perhaps even his parents were astounded to hear that he would be transitioning from his multiple pharmacy degrees to food science and then go into the mayonnaise business, but he didn't see it that way. He saw an opportunity and seized it!

In a 1977 interview, he said: "I could go into food chemistry and have certain advantages that someone who had never had any pharmacy would not have had...". Most people were thinking about salad dressing, and he was thinking about how to apply the knowledge of oil and water emulsions that he had learned in pharmacy school to the technical problem in front of him.

The pictures in the bottom right of this slide are Hans' graduation picture from our 1921 composite photo and a hard copy of his dissertation from Columbia that stored in our College archive. {CLICK}

Slide 6: Vahlteich's Stairway #2

It's fair to say that Hans' stairway to success was a crooked one. His stairway to success is unlike anyone else's that I've seen, but in my experience crooked stairways are more common than not. Vahlteich's took a turn when he saw an opportunity in food science.

Before leaving the Vahlteich story, I want to share some other personal aspects of the story that make it special for me. On the bottom right of this slide is the original framed certificate establishing the Rho Chi Society. It is signed by Vahltiech and hangs outside my office door in the College of Pharmacy at the University of Michigan.

Lastly, one of my favorite parts of being dean is the opportunity to meet and learn about some of our most successful alumni and families, who through their accomplishments and generosity have made the world a better place.

The woman shown in the upper right hand corner of this slide is Mrs. Beverly Delaney, Hans Vahlteich's only child. Beverly is 82 years old, one of the kindest people that you will ever meet, and voraciously reads every update that we send her from the Vahlteich professorship and core lab. I imagine that her father viewed her as his greatest success and contribution to the world.

Slide 7: Drug Discovery and Development

As pharmacists, we often think of the drug discovery and development process as a linear one as well.

A new drug is discovered, studied extensively in batteries of in vitro tests and animal studies to understand its pharmacology, toxicology, physical and chemical properties, formulated, and then advanced to clinical development.

Phase I studies in healthy volunteers, Phase II studies in the chosen patient population, and ultimately pivotal Phase III studies are completed, with the ultimate hope that the safety and efficacy of the drug are proven, that a new drug application can be submitted and approved by regulatory authorities, and that it will be a therapeutic success for patients and a commercial success for the company.

However, it's an expensive and risky process. A 2016 study by Tufts Center for the Study of Drug Development estimated the out-of-pocket costs to develop a new drug at $1.4 billion dollars and the overall probability that a drug that enters clinical testing will eventually be approved at 11.8%!

However, like careers, drug discovery and development rarely proceeds as expected. Unexpected clinical results, newly found therapeutic effects or side effects when tested in larger and larger patient populations, the changing clinical landscape, patient variability, financial considerations, and even shifting expectations of the FDA and other regulatory bodies require the pharmaceutical industry to change direction in order to seize opportunities and overcome the challenges ahead. {CLICK}

As such, the path from discovery to therapeutic success for a drug is often crooked at best and more often than not is a dead end.

Slide 8: Career Paths in Academia

It might not surprise you given the title of my talk and the discussion so far, that the steps that I've taken on my way from my early pharmacy education to being on the stage today, didn't proceed in a straight line either.

Sure, I've taken the traditional steps along the way: finishing pharmacy school at the University of Cincinnati in 1986, earning my PhD at Ohio State in 1990, and developing an extramurally-funded research program that helped me train graduate students, publish papers, and ascend the stairs from assistant professor in 1992 to dean in 2014.

{CLICK} But as you might guess from these two pictures, one in full blown Ohio State gear with my daughter Ava and another several years later standing in the Big House at Michigan, there have been some unexpected developments along the way. There have been many decision points, opportunities seized, and setbacks along the way that have made my stairway to the podium today a crooked one. {CLICK}

Instead of pursuing a PharmD or going to work as a pharmacist when I finished pharmacy school, I decided to pursue my PhD and do a postdoctoral fellowship at a different school. I took my first faculty position at University of Tennessee in 1992 and moved back to Ohio State as an associate professor in 2000, where I was promoted to chair and full professor.

Now it might already be apparent to you, but a major deviation from the traditional academic path was already afoot before I moved back to Columbus.

In 1997, we discovered a new class of drugs known as selective androgen receptor modulators (or SARMs) in my lab at Tennessee. We patented it, licensed it to GTx three years later, and began development, with me serving as a consultant to the company's three employees.

Opportunity had already knocked and I was soon going to go sprinting through the door!

I left Ohio State on an entrepreneurial leave-of absence in 2005, and spent the next nine years of my career leading the development of this exciting new class of drugs as our company grew from three people to a high of about 160 employees.

But as we discussed on the previous slide, it was one of those unexpected turns in new drug discovery and development for our SARM in 2013 that prompted my decision to throw my hat in the ring for the deanship at the University of Michigan.

And with that introduction, I'd like to tell you about my work with SARMs and how stairs are an important part of the SARM story too.

Slide 9: What is a SARM?

We discovered our first SARM in 1997 and filed a patent through the University of Tennessee.

We were working at the time to make irreversible antiandrogens, drugs that prevent the actions of testosterone in prostate cancer. We had developed a cellular assay to determine whether or not the novel drugs that we were making were able to inhibit the ability of testosterone to stimulate the androgen receptor.

A graduate student of mine, Arnab Mukherjee, came into my office with some surprising data. Several of the nonsteroidal compounds that we had designed to inhibit the androgen receptor (analogs of R-1 shown here) were actually stimulating it just as well as known anabolic steroids.

This was the world's first evidence that a nonsteroidal compound could mimic the effects of testosterone on the androgen receptor and we thought that it might open the door to a wide variety of therapeutic applications.

Drawing the analogy to selective estrogen receptor modulators (or SERMs) which bind to estrogen receptor alpha and beta, and have the ability to act differently in bone, breast, and uterus, we hypothesized that SARMs might have the ability to bind to the androgen receptor and act differently in muscle, bone, and prostate.

Slide 10: Anabolic/androgenic steorids

Let's quickly review how testosterone and the anabolic and androgenic steroids work.

Slide 11: Enoboarm is Anabolic and Selective

Slide 12: SARMs Molecular Mechanisms

Slide 13: Small Pharma Discovery and Development

Slide 14: Publication versus Patent

Slide 15: Industry/Academia Collaboration

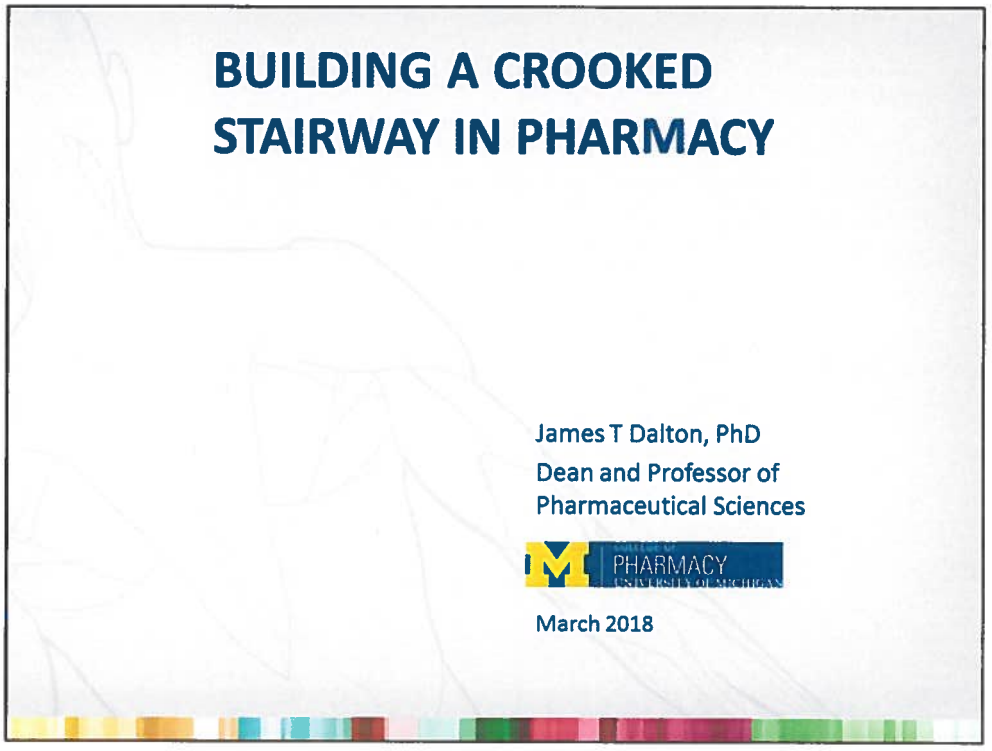
Slide 16: Science and Financing

Slide 17: Partnerships: The Good, The Bad, and The Ugly

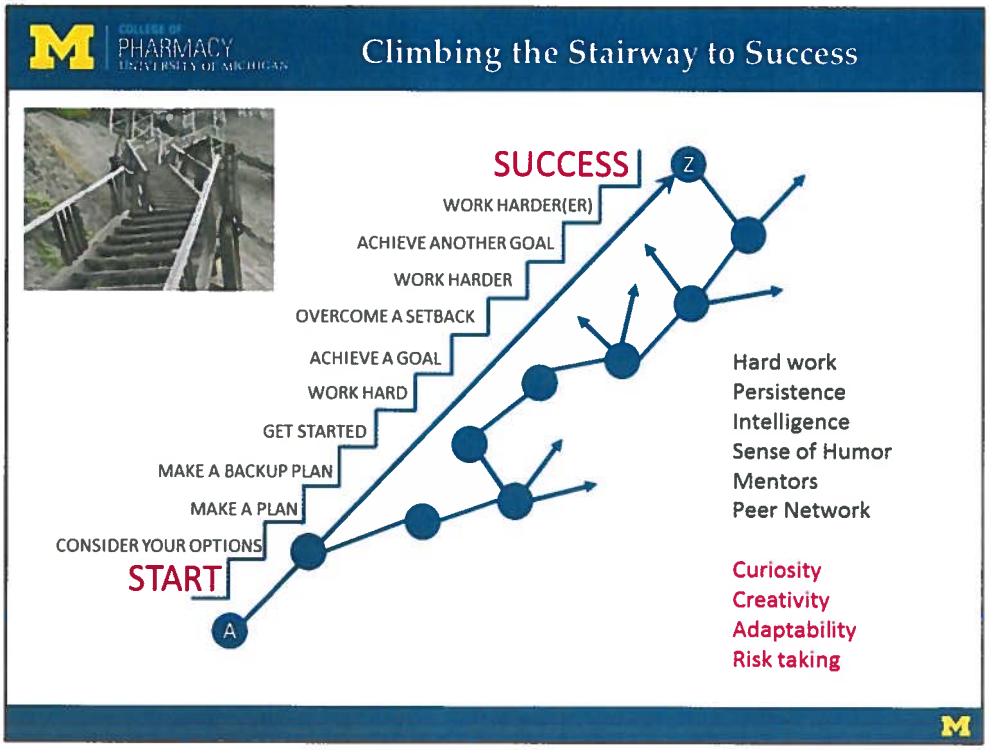
Slide 18: SARM Potential Clinical Applications

Slide 19: Cancer-Induced Muscle Wasting

2018
James Dalton



I'm humbled to be here today to deliver the Rho Chi Lecture. I'd like to thank Dr. Karen Farris who nominated me (I think), the five unknown people who apparently were willing to stretch the truth and write letters of endorsement, the members of Rho Chi Lecture Award Committee and the Rho Chi Executive Council who selected me from what I am sure was a stellar group of other nominees. It's a great honor to be recognized by one's peers and I hope that my talk today lives up to your expectations. Thank you!



My talk today is part career advice and part history lesson, viewed through the lens of my personal experiences in academic drug discovery and development.

It's not uncommon for us to think about our goals, careers, and lives as linear marches through time, proceeding from point A to point Z through an orderly sequence of steps that will carry us from our starting point to success.

We think about where we are today and where we want to be in the future.

We consider our options, make a plan, get started, work hard, perhaps overcome a setback or two, and achieve a series of goals that carry us toward what we define as success.

Hard work, persistence, intelligence, a good sense of humor, mentors, and a robust network of peers are among the many essential attributes for climbing the stairs to success.

However, the stairs from start to finish are seldom straight in my experience {CLICK}

Challenges, discoveries, new people and new opportunities are always entering and exiting your personal life and career and altering your path in unexpected ways.

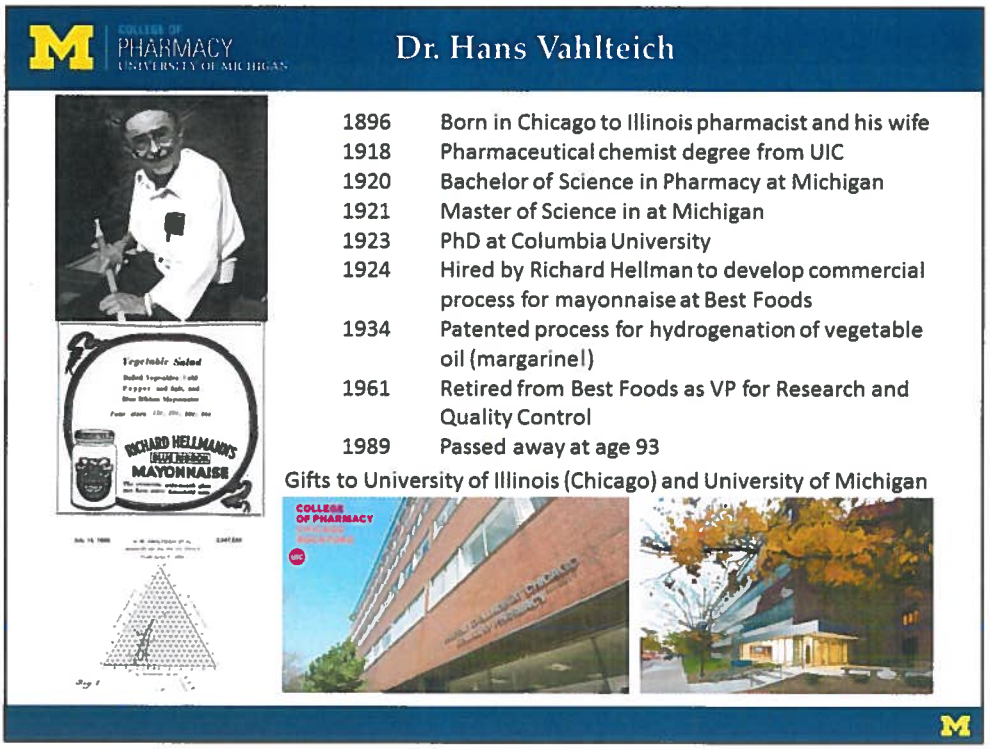
Being curious, being creative, being adaptable, and accepting risks along the way are equally necessary and common traits of some of the most successful people that I've met along my journey.

Before I tell you my story and the importance of stairs to my career, I'd like to start with a trivia question.

By a show of hands, how many of you have used margarine? How many of you have used mayonnaise? How many are students or faculty members at a College with a chapter of Rho Chi?

Ok, we've covered most of the people in the room with the first three items shown on this slide. The last three images on this slide refer to The University Of Michigan and UIC Colleges of Pharmacy, and the Teachers College at Columbia University.

So, my trivia question is this: what do all of these things have in common?



The answer is Dr. Hans Vahlteich.

Hans was born in Chicago in 1896 and grew up working in his father's pharmacy.

In his own words and (and I quote) he "was practically born and raised in a drug store."

He ran "...chores and ... errands when in grade school" and the drugstore was his home between 1915 and 1918 while a student in pharmaceutical chemistry at the University of Illinois at Chicago.

He opened the store at 7:30 a.m., left for the day to attend pharmacy school, then returned to the store where his mother brought him dinner. He closed the store at 10 p.m. and slept in the back room.

After finishing his degree at UIC, he enrolled at the University of Michigan College of Pharmacy where he completed his BS and MS degrees in pharmacy in 1920 and 1921, respectively.

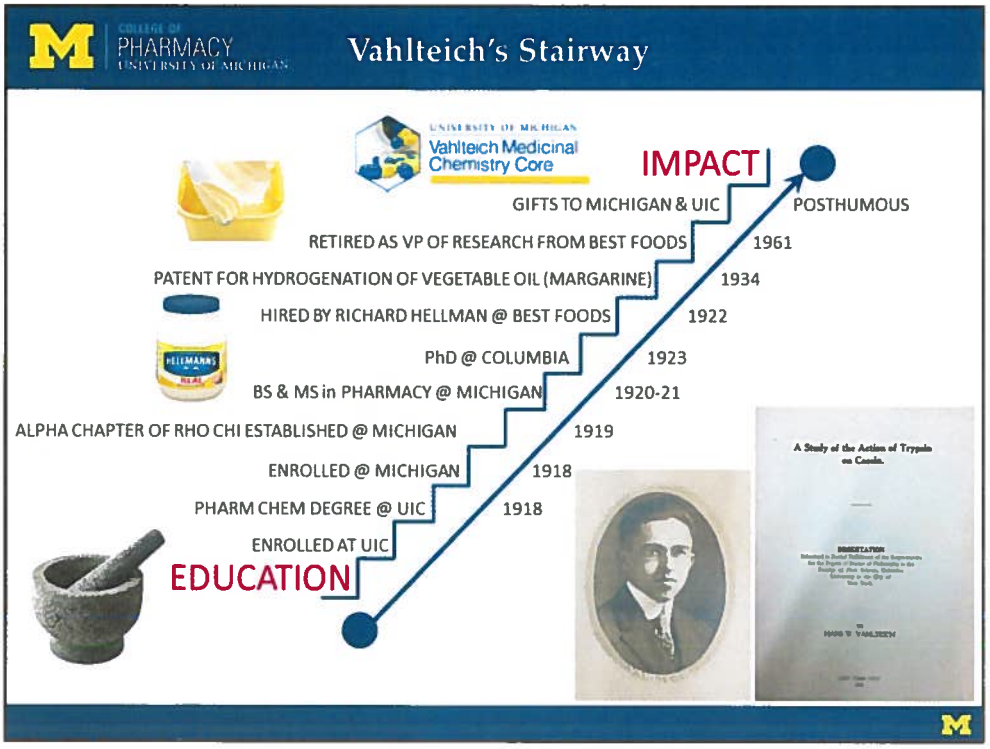
While a student at Michigan, he and colleagues founded The Rho Chi Society and established its Alpha chapter at the University of Michigan.
Hans left Michigan in 1921, earned a PhD at Columbia in 1923, and became the first employee in a new enterprise that Mr. Richard Hellman was starting in Long Island. Mr.

Hellman was a successful delicatessen owner who had developed a new and award winning salad dressing (Blue Ribbon Mayonnaise) and was now interested in increasing its production to commercial scale.

Hans led the commercial scale-up of Hellman's mayonnaise and spent his entire career in the new company, Best Foods, eventually retiring as VP for Research and Quality Control in 1961.

Along the way, he made an important discovery and patented the chemical process for hydrogenation of vegetable oil in 1934, paving the way for commercial production of margarine.

He passed away at the age of 93 in 1989 and his estate funded substantial gifts to the University of Illinois and Columbia University and a $3.4M gift to the University of Michigan, endowing professorships at all three universities and also establishing the Vahlteich Medicinal Chemistry Core at Michigan.



We can arrange Vahlteich's education and accomplishments in an orderly timeline of steps from his humble beginnings pharmacy student to VP of Research and the creation of endowments that will sustain medicinal chemistry research in perpetuity.

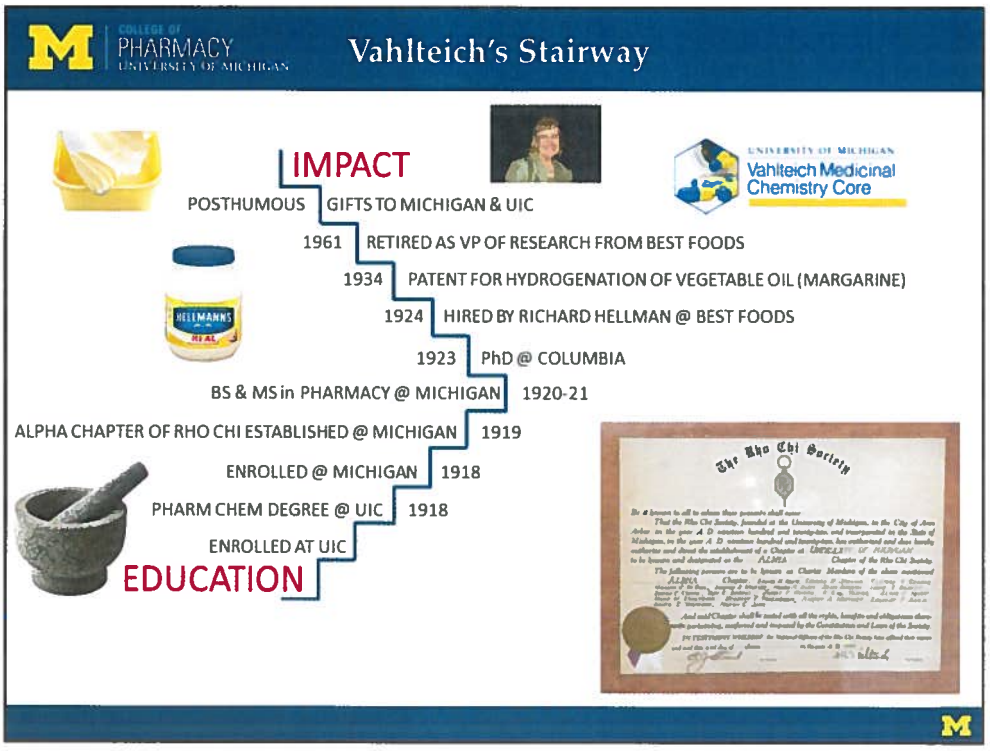
However, I think that it's reasonable to guess than young Hans didn't lie awake in the back of his father's pharmacy dreaming about building a factory that would supply the world with the perfect dressing for a BLT, creating a replacement for butter, or founding a pharmacy honor society that would bring us all together here today.

Hans was strong believer in the value of pharmacy education, and saw that it could be successfully adapted into other areas. I imagine that his friends and perhaps even his parents were astounded to hear that he would be transitioning from his multiple pharmacy degrees to food science and then go into the mayonnaise business, but he didn't see it that way. He saw an opportunity and seized it!

In a 1977 interview, he said: "I could go into food chemistry and have certain advantages that someone who had never had any pharmacy would not have had...". Most people were thinking about salad dressing, and he was thinking about how to apply the knowledge of oil and water emulsions that he had learned in pharmacy school to the technical problem in front of him.

The pictures in the bottom right of this slide are Hans' graduation picture from our

1921 composite photo and a hard copy of his dissertation from Columbia that stored in our College archive. {CLICK}

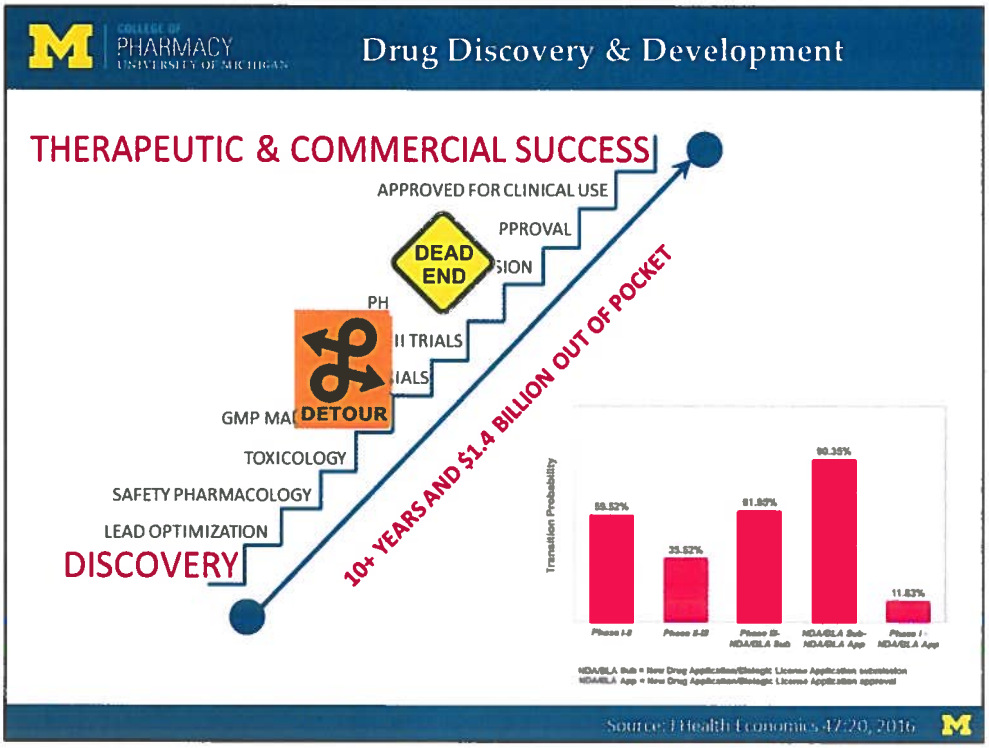


It's fair to say that Hans' stairway to success was a crooked one. Vahlteich' stairway to success is unlike anyone else's that I've seen, but in my experience crooked stairways are more common than not.
Vahlteich's stairway to success took a turn when he saw an opportunity in food science.

Before leaving the Vahlteich story, I want to share some other personal aspects of the story that make it special for me. On the bottom right of this slide is the original framed certificate establishing the Rho Chi Society. It is signed by Hand Vahlteich and hangs outside my office door in the College of Pharmacy at the University of Michigan.

Lastly, one of my favorite parts of being dean is the opportunity to meet and learn about some of our most successful alumni and their families, who through their accomplishments and generosity have made the world a better place.

The woman shown in the upper right hand corner of this slide is Mrs. Beverly Delaney, Hans Vahlteich's only child. Beverly is 82 years old, one of the kindest people that you will ever meet, and voraciously reads every update that we send her from the Vahlteich professorship and core lab. I imagine that her father viewed her as his greatest success and contribution to the world.



As pharmacists, we often think of the drug discovery and development process as a linear one as well.

A new drug is discovered, studied extensively in batteries of in vitro tests and animal studies to understand its pharmacology, toxicology, physical and chemical properties, formulated, and then advanced to clinical development.

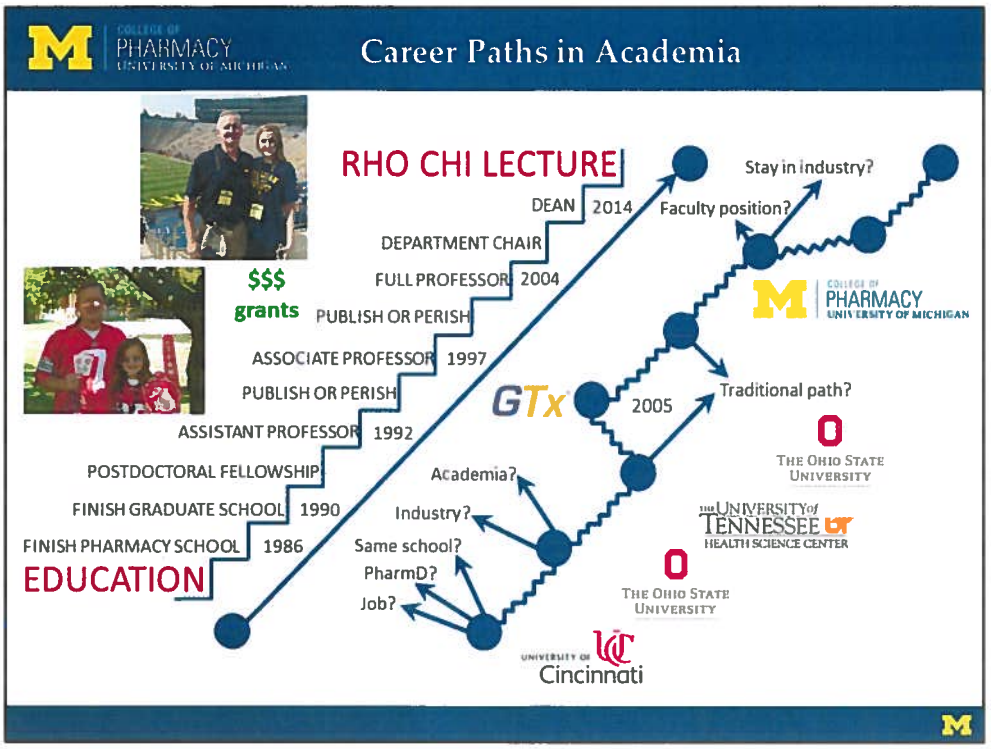
Phase I studies in healthy volunteers, Phase II studies in the chosen patient population, and ultimately pivotal Phase III studies are completed, with the ultimate hope that the safety and efficacy of the drug are proven, that a new drug application can be submitted and approved by regulatory authorities, and that it will be a therapeutic success for patients and a commercial success for the company.

However, it's an expensive and risky process. A 2016 study by Tufts Center for the Study of Drug Development estimated the out-of-pocket costs to develop a new drug at $1.4 billion dollars and the overall probability that a drug that enters clinical testing will eventually be approved at 11.8%!

Like careers, drug discovery and development rarely proceeds as expected. Unexpected clinical results, newly found therapeutic effects or side effects when tested in larger and larger patient populations, the changing clinical landscape, patient variability, financial considerations, and even shifting expectations of the FDA and other

regulatory bodies require the pharmaceutical industry to change direction in order to seize opportunities and overcome the challenges ahead. {CLICK}

CLICK
As such, the path from discovery to therapeutic success for a drug is often crooked at best and more often than not is a dead end.



It might not surprise you given the title of my talk and the discussion so far, that the steps that I've taken on my way from my early pharmacy education to being on the stage today, didn't proceed in a straight line either.

Sure, I've taken the traditional steps along the way: finishing pharmacy school at the University of Cincinnati in 1986, earning my PhD at Ohio State in 1990, and developing an extramurally-funded research program that helped me train graduate students, publish papers, and ascend the stairs from assistant professor in 1992 to dean in 2014.

{CLICK}
But as you might guess from these two pictures, one in full blown Ohio State gear with my daughter Ava and another several years later standing in the Big House at Michigan, there have been some unexpected developments along the way. There have been many decision points, opportunities seized, and setbacks along the way that have made my stairway to the podium today a crooked one.

{CLICK}
Instead of pursuing a PharmD or going to work as a pharmacist when I finished pharmacy school, I decided to pursue my PhD and do a postdoctoral fellowship at a different school. I took my first faculty position at University of Tennessee in 1992 and moved back to Ohio State as an associate professor in 2000, where I was promoted to chair and full professor.

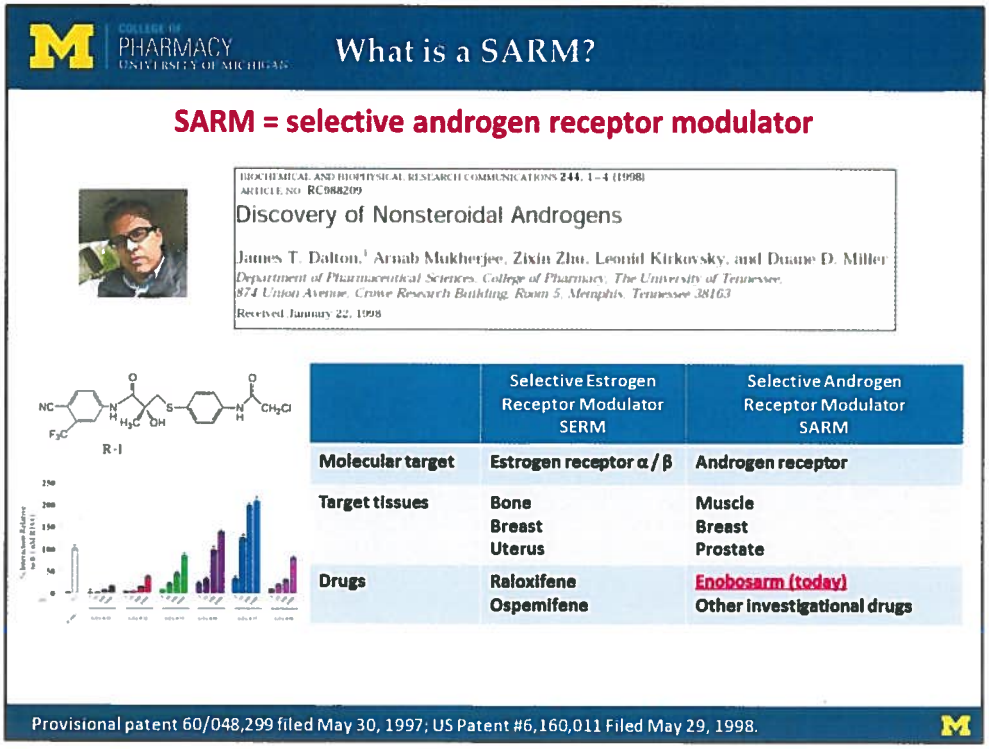
Now it might already be apparent to you, but a major deviation from the traditional academic path was already afoot before I moved back to Columbus.
In 1997, we discovered a new class of drugs known as selective androgen receptor modulators (or SARMs) in my lab at Tennessee. We patented it, licensed it to GTx three years later, and began development, with me serving as a consultant to the company's three employees.

Opportunity had already knocked and I was soon going to go sprinting through the door!

I left Ohio State on an entrepreneurial leave-of absence in 2005, and spent the next nine years of my career leading the development of this exciting new class of drugs as our company grew from three people to a high of about 160 employees.

But as we discussed on the previous slide, it was one of those unexpected turns in new drug discovery and development for our SARM in 2013 that prompted my decision to throw my hat in the ring for the deanship at the University of Michigan.

And with that introduction, I'd like to tell you about my work with SARMs and how stairs are an important part of the SARM story too.



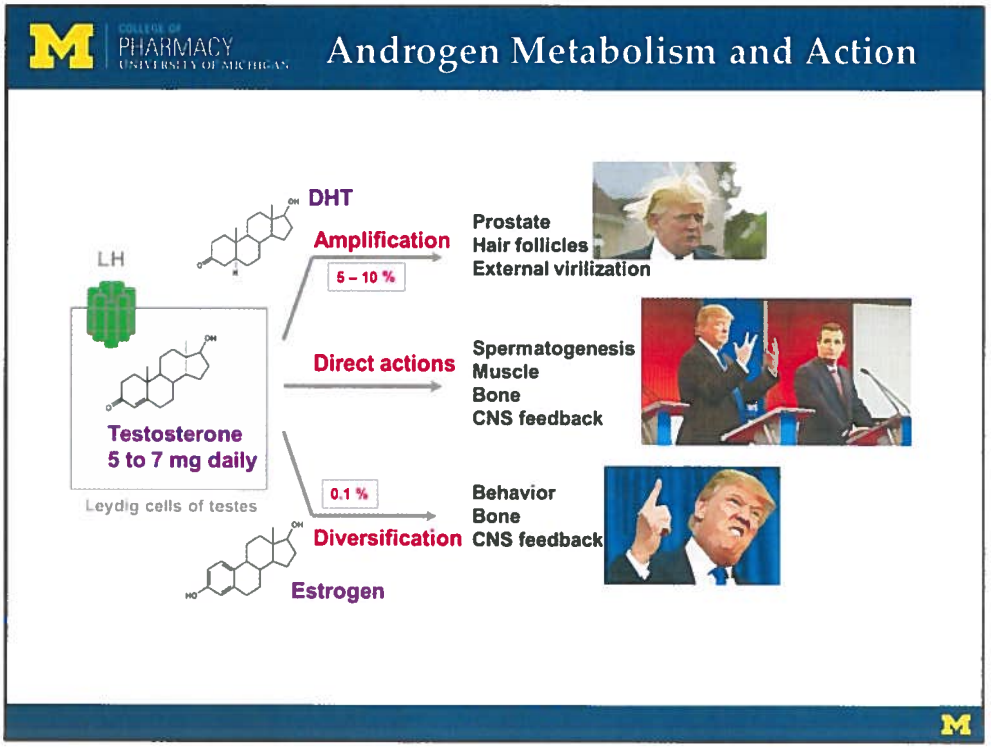
We discovered our first SARM in 1997 and filed a patent through the University of Tennessee.

We were working at the time to make irreversible antiandrogens, drugs that prevent the actions of testosterone in prostate cancer. We had developed a cellular assay to determine whether or not the novel drugs that we were making were able to inhibit the ability of testosterone to stimulate the androgen receptor.

A graduate student of mine, Arnab Mukherjee, came into my office with some surprising data. Several of the nonsteroidal compounds that we had designed to inhibit the androgen receptor (analogs of R-1 shown here) were actually stimulating it just as well as known anabolic steroids.

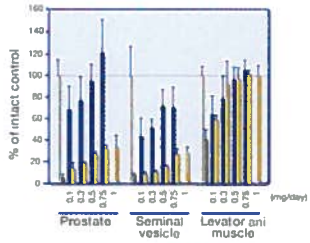
This was the world's first evidence that a nonsteroidal compound could mimic the effects of testosterone on the androgen receptor and we thought that it might open the door to a wide variety of therapeutic applications.

Drawing the analogy to selective estrogen receptor modulators (or SERMs) which bind to estrogen receptor alpha and beta, and have the ability to act differently in bone, breast, and uterus, we hypothesized that SARMs might have the ability to bind to the androgen receptor and act differently in muscle, bone, and prostate.



Let's quickly review how testosterone and the anabolic and androgenic steroids work.

Enobosarm is Anabolic and Selective



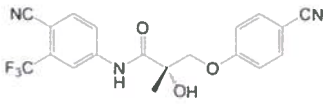
Intact control
Castrated control (vehicle)
Testosterone propionate treated
SARM treated (S-4)

MUSCLE

Testosterone = SARM

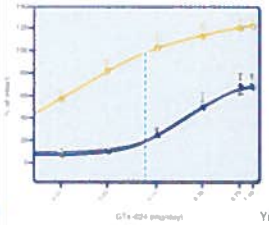
PROSTATE

Testosterone >> SARM



ENOBOSARM

Invented in 2004



Enobosarm Dose Response and Tissue Selectivity

	Prostate	Seminal vesicles	Levator ani
E_{max}	75 ± 8	73 ± 3	126 ± 4
ED_{50}	0.22 ± 0.05	0.21 ± 0.02	0.01 ± 0.01

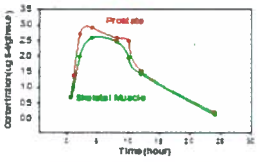
Yin D, Gao W, Kearbey JD, Xu H, Chung K, He Y, Marhefka CA, Veverka KA, Miller DD, Dalton JT. J Pharmacol Exp Ther. 304(3):1334, 2003; Kim J, Wu D, Hwang DJ, Miller DD, Dalton JT. J Pharmacol Exp Ther. 315(1):230, 2005

SARMs: Molecular Mechanisms of Tissue Selectivity

Ligand-specific differences in:

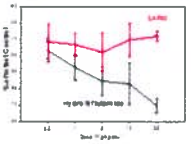
- AR conformation (x-ray)
- Tissue accumulation
- Lack of 5α-reductase amplification
- Gene regulation
- N/C interactions
- Non-genomic signaling
- Coactivator/corepressor interactions

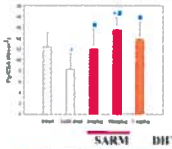
DHT, SARM, AF-2



SARM Tissue Concentrations after Oral Dosing

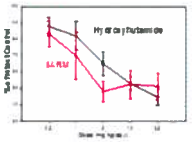
Levator Ani weight

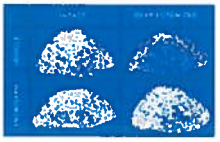




Soleus muscle strength

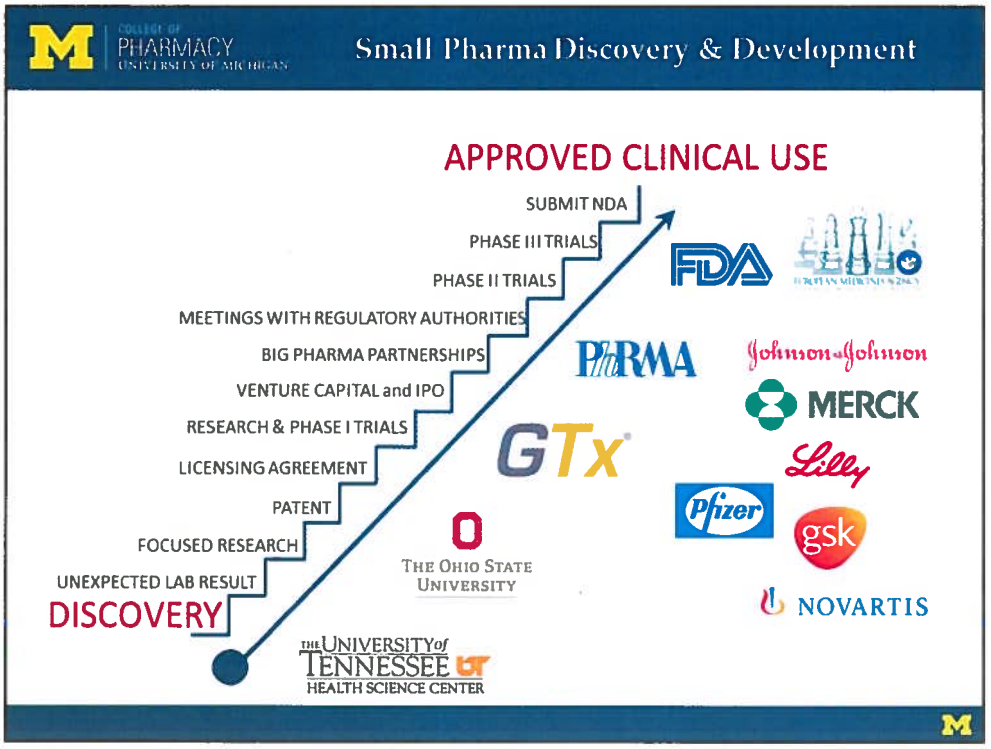
Prostate weight



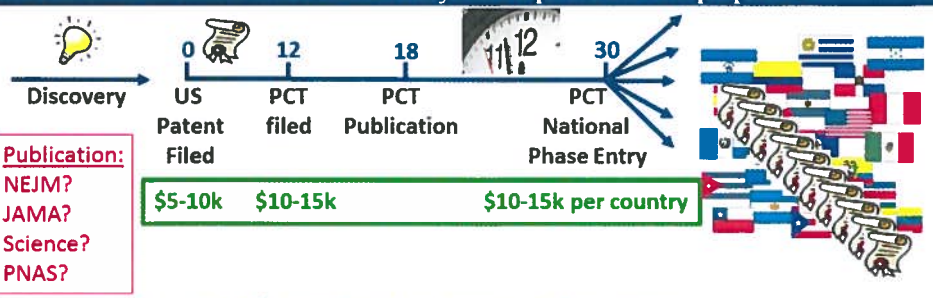


Bone µCT

PNAS 2005, 102 6201; Journal of Biological Chemistry 2005, 280 37747 and 2007, 282 13468, Endocrinology 2005, 146(11) 4887-97 and 2004, 145(12) 5420-8, Molecular Endocrinology 2008, 22 2448


PHARMACY
UNIVERSITY OF MICHIGAN
Small Pharma Discovery & Development
APPROVED CLINICAL USE
SUBMIT NDA
PHASE III TRIALS
PHASE II TRIALS
MEETINGS WITH REGULATORY AUTHORITIES
BIG PHARMA PARTNERSHIPS
VENTURE CAPITAL and IPO
RESEARCH & PHASE I TRIALS
LICENSING AGREEMENT
PATENT
FOCUSED RESEARCH
UNEXPECTED LAB RESULT
DISCOVERY
FDA
PhRMA
Johnson & Johnson
MERCK
GTx
Lilly
Pfizer
gsk
NOVARTIS
THE OHIO STATE UNIVERSITY
THE UNIVERSITY of TENNESSEE HEALTH SCIENCE CENTER

Publication versus Patent
(tenure system prioritizes papers)



Publication:
NEJM?
JAMA?
Science?
PNAS?

1. University files on behalf of academic inventors.
2. University searches for partner interested in licensing & developing.

3a. If successful, licensee assumes future costs.

3b. If unsuccessful or delayed, PCT and/or international patent costs present financial challenge to university.

1997	First SARM patent filed by University of Tennessee
2000	Licensed SARMs to GTx
2004	Enobosarm invention and US Patent

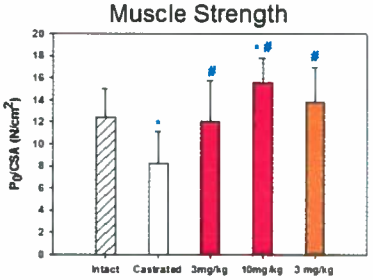
437 total SARM patents: 269 pending, 168 issued/allowed applications

Industry/Academia Collaboration to IND

August 2000

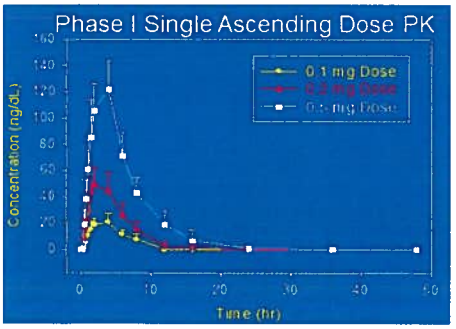
UT: synthesis of drug substance, licensing & inter-institutional agreements
OSU: in vitro and in vivo pharmacology, pharmacokinetics, metabolism
GTx: GMP synthesis, GLP safety & toxicology, regulatory, patents

Muscle Strength



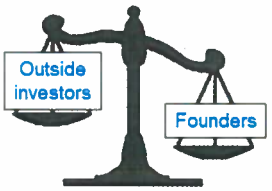
Male Rats: ORX and untreated for 12 weeks, then treated with SARM or DHT for 8 weeks (n=7-8/group)

Phase I Single Ascending Dose PK



Science and Financing

- GTx, Inc founded in September 1997
  - IPO in 2004 of 5.4M shares @ $14 = ~$70M
  - 2010, 2011 & 2012 R&D expenses were ~$42M, 44M, and $50M
  - Raised $600M since inception
- Cost to bring NCE market estimated at $1.4B (PhRMA)
- Constant effort to prioritize R&D and assure that resources devoted to studies that answer essential medical questions and prove safety and efficacy of drug in target indication



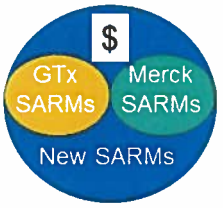
"If you want advice, ask for money"

Partnerships: The Good, The Bad and the Ugly

License to andarine in March 2004.

Advantages:
- J&J resources to advance toward cancer cachexia indication
- $7.2M cash & milestone payments as Phase II, Phase III, NDA achieved
- Freedom to develop other SARMs from our library

Disadvantages:
- Loss of control
- Bureaucracy / redundancy
- Competition with J&J internal SARM program



Cross license to each other's SARMs in Dec 2007

Advantages:
- Open competition to identify best SARM (Phase II "beauty contest")
- Merck intent to advance toward chronic sarcopenia indication (~$10B)
- $85M cash, research support & milestone payments as Phase II, Phase III, NDA achieved regardless of whether Merck or GTx SARM

Disadvantages:
- Cancer cachexia a lower Merck priority (silos)
- Bureaucracy / redundancy

SARM Potential Clinical Applications

- Chronic Muscle Wasting
  - Sarcopenia (age-related muscle wasting) - Long & Expensive Clinical Trials
  - Stress Urinary Incontinence - Intermediate Length Clinical Trials
  - Duchenne Muscular Dystrophy
- Acute Muscle Wasting
  - Cancer cachexia
  - HIV
  - End-stage renal disease
  - Burns

Serious Un-met Medical Need
Non-Small Cell Lung Cancer
Almost 200,000 new cases per year
Significant Muscle Wasting Early in Disease
Associated with Deficits in Physical Function

- Hormonal therapy for breast cancer - Intermediate Length Clinical Trials and Lots of Competition
  - ER+ and AR + metastatic breast cancer
  - Triple negative, AR+ metastatic breast cancer
- Osteoporosis

Cancer –Induced Muscle Wasting

- Cancer induced muscle wasting results in accelerated muscle loss and decline in physical function.
- Up to 50-85% of patients with cancer have muscle wasting at diagnosis, and this muscle loss increases throughout the course of the malignancy.
- Pancreatic & Upper GI > Lung > Colorectal & Prostate >> Breast & NHL
- Occurs also due to cancer treatment (chemotherapy, radiation).
- Body weight and BMI can mask the underlying deficit in muscle

BMI=16.4 BMI=24.8 BMI=40.2

Sarcopenic Obesity

390 days before 58 days before death

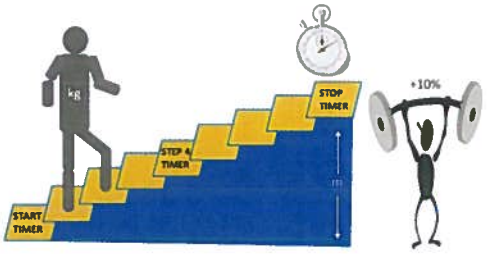
Skeletal muscle (red) loss in patient with lung cancer

Vickie Baracos (Alberta), J Clin Oncol 2013

Stairway to Success for SARMs?

- Efficacy Endpoint?
  - LBM (FDA: hGH experience)
  - Physical Function
    - Stair climb, hand grip, gait speed, 6 minute walk

$$\text{Stair Climb Power (watts)} = \frac{\text{weight (kg)} \cdot \text{distance (m)} \cdot 9.8\ \text{m/s}^2}{\text{time (sec)}}$$

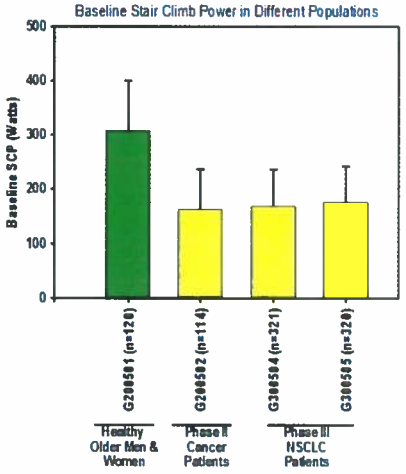


- Nutritional supplementation
- Oxandrolone
  - Weight gain* after extensive surgery, chronic infection, or severe trauma
  - Off label (oxymetholone, nandrolone): HIV wasting, burn injury, delayed growth
- Somatropin (hGH)
  - HIV wasting*
- Megestrol (progestin)- used off label as appetite stimulant

- *FDA Approvals: primary endpoint of body weight
  - LBM (measured by DEXA) was 2° endpoint for hGH
  - Confounded by edema

Why NSCLC?

NSCLC patients have already lost substantial physical function at the time of diagnosis



- About 50% of the NSCLC patients in GTx phase III studies had lost >5% of their body weight in the 6 months prior to randomization
- Baseline SCP in NSCLC patients in GTx phase III studies was about 40-45% lower than that observed in otherwise healthy elderly men and women
- Further declines in physical function (SCP), LBM, and weight were observed in chemotherapy alone groups in both phase III studies over 5 months.

COLLEGE OF PHARMACY UNIVERSITY OF MICHIGAN

Enobosarm Clinical Trial Overview (24 completed/ongoing trials, > 1700 subjects)

Study #	Title	Subjects
G100401	Single ascending dose study in healthy, young male volunteers (0,1, 3, 10, 30 and 100 mg)	96
G100402	Multiple ascending dose study in healthy, young males and elderly males (14 days)	71
G100503	Divided dose study in healthy elderly male and female volunteers (14 day)	36
G100506	Relative bioavailability and food effect study in healthy male volunteers	27
G100507	Phase I Study to Assess the Pharmacokinetics and Absolute Oral Bioavailability of GTx-024 in Caucasian and African American Men and Postmenopausal Women	48
G100508	Phase I Study to Assess the Effect of Mild and Moderate Hepatic Impairment on Pharmacokinetics of GTx-024	24
G100509	Phase I Mass Balance Study to Determine the Metabolism and Excretion of Radiolabeled GTx-024	6
G100510	A Single-dose, Randomized, Double-Blind, Comparative, Positive and Placebo-Controlled, Four-Period Crossover Study to Define the ECG Effects of GTx-024: A Thorough ECG Trial	54
G100511	Phase I Study to Assess the Effect of Severe Renal Impairment on Pharmacokinetics of GTx-024	16
G100512	Phase I Study to Assess the Effects of Ketoconazole on the Pharmacokinetics of GTx-024	24
G100513	Phase I Study to Assess the Effects of Rifampicin on the Pharmacokinetics of GTx-024	24
G100514	Phase I Study to Assess the Effects of GTx-024 on the Pharmacokinetics of Celecoxib	24
G100515	Phase I Study to Assess the Effects of Probenecid on the Pharmacokinetics of GTx-024	24
G100516	Phase I Study to Assess the Effects of GTx-024 on the Pharmacokinetics of Rosuvastatin	50

COLLEGE OF PHARMACY UNIVERSITY OF MICHIGAN

Enobosarm clinical trial overview

Study	Design	Duration	Total	Treatment
Study 003 (Phase Ib)	Head-to-head comparison of GTx-024 to MK-3984 in postmenopausal women	12 weeks	88	3 mg
Study 006 (Phase Ib)	Pharmacokinetic study in postmenopausal Japanese women	10 days	12	1, 3, 10 mg
G200501 (Phase II)	Proof of concept study in healthy older men & postmenopausal women	12 weeks	120	0.1, 0.3, 1, 3 mg
G200502 (Phase II)	Cancer cachexia study in males ≥45 & post-menopausal women with cancer	16 weeks	159	1, 3 mg
G300504 (Phase III)	Effect of GTx-024 on Muscle Wasting in Patients With Non-Small Cell Lung Cancer (NSCLC) on First Line Platinum + Taxane	21 weeks	330	0, 3 mg
G300505 (Phase III)	Effect of GTx-024 on Muscle Wasting in Patients With Non-Small Cell Lung Cancer (NSCLC) on First Line Platinum + Non-Taxane	21 weeks	330	0, 3 mg
G200517 (Phase II)	Efficacy and Safety of GTx-024 in Patients With ER+/AR+ Breast Cancer	24 weeks	88	9, 18 mg
G200518 (Phase II)	Efficacy and Safety of GTx-024 in Patients With AR +Triple Negative Breast Cancer (AR+ TNBC)	24 weeks	55	18 mg
G200519 (Phase II)	GTx-024 as a Treatment for Stress Urinary Incontinence in Women	12 weeks	35	3 mg

Enobosarm consistently increased LBM & improved physical function in Phase IIs

Phase IIb cancer cachexia trial:

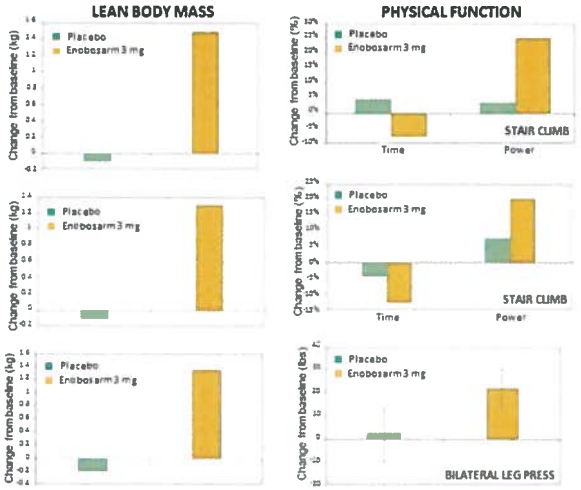
159 subjects with cancer cachexia,
4 months tx

Phase II POC clinical trial:

120 elderly men and postmenopausal women,
3 months tx

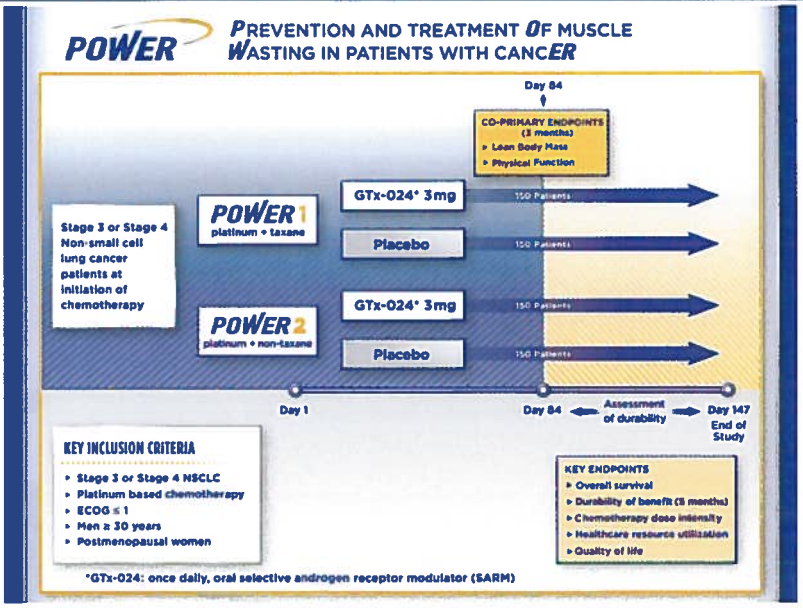
Phase Ib sarcopenia trial:

88 postmenopausal women, 3 months tx



J Cachexia Sarcopenia Muscle 2(3):153-161, 2011; Lancet Oncology, 14(4):335-45, 2013; Endocrine Reviews 31(3):(suppl 1)S872, 2010.

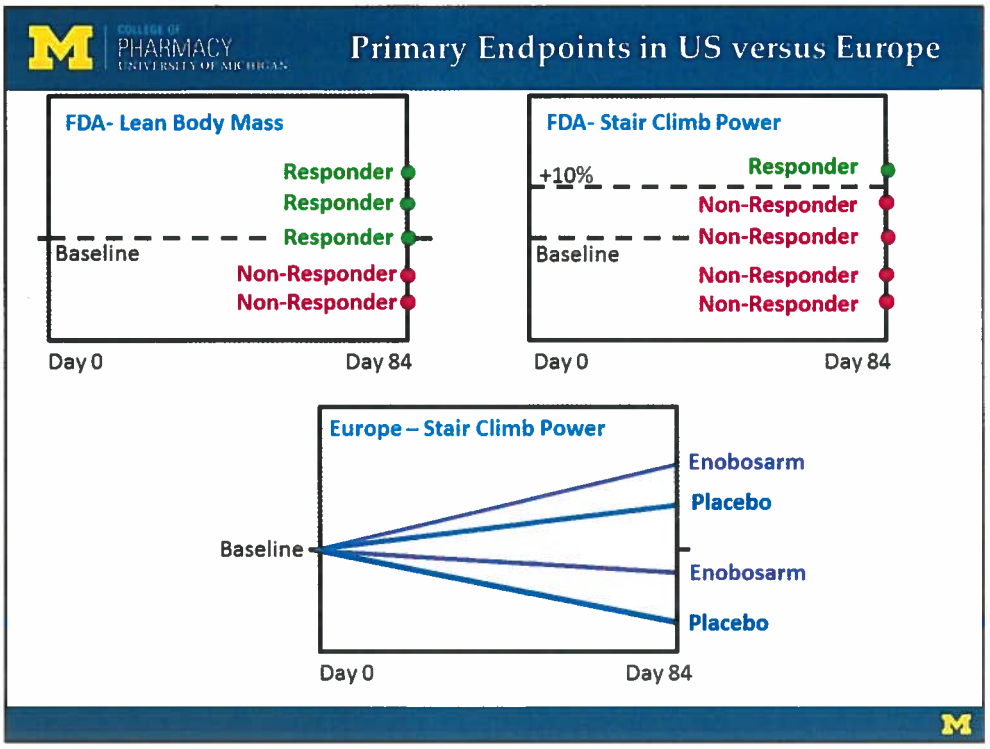
Phase III Trial Design for Enobosarm



Crawford J, Prado CM, Johnston MA, Gralla RJ, Taylor RP, Hancock ML, Dalton JT. Current Oncology Reports 18(6):37, 2016

Primary Endpoint in US versus Europe

- **FDA: Responders Analyses**
  - **Success defined as more Responders in Treatment Group as Compared to Placebo**
  - Lean body mass (LBM): $p < 0.05$
    - Responder defined as a subject that maintained or demonstrated an increase in LBM at Day 84 as compared to baseline
  - Stair climb power (SCP): $p < 0.05$
    - Responder defined as subject that demonstrated a 10% or greater increase at Day 84 as compared to baseline
- **European authorities (MHRA, MPA): Continuous Variable Analyses**
  - **Success defined as statistically and clinically meaningful difference in slope**
  - Change in Stair Climb Power through Day 84: $p < 0.05$
  - LBM considered as a key secondary endpoint


PHARMACY
Primary Endpoints in US versus Europe
FDA- Lean Body Mass
Responder
Responder
Responder
Baseline
Non-Responder
Non-Responder
Day 0
Day 84
FDA- Stair Climb Power
+10%
Responder
Non-Responder
Non-Responder
Baseline
Non-Responder
Non-Responder
Day 0
Day 84
Europe – Stair Climb Power
Enobosarm
Placebo
Baseline
Enobosarm
Placebo
Day 0
Day 84

COLLEGE OF PHARMACY UNIVERSITY OF MICHIGAN

Platinum+Taxane Phase III Trial
Efficacy endpoints

FDA Analyses

		% Responders (n)		
		Placebo (N=161)	GTx-024 (N=160)	p-value
LBM	Day 84	30.4% (49)	41.9% (67)	0.036
SCP	Day 84	24.2% (39)	29.4% (47)	0.315

European Analyses

Statistical hierarchy			Slopes		
			Placebo	GTx-024	p-value
1	SCP*	Day 84	-0.0773 %/day	+0.0443 %/day	0.0147
2	LBM	Day 84	-0.011 kg/day	+0.0049 kg/day	0.0002

* Primary endpoint for Europe

Platinum+Nontaxane Phase III Trial
Efficacy endpoints

FDA Analyses

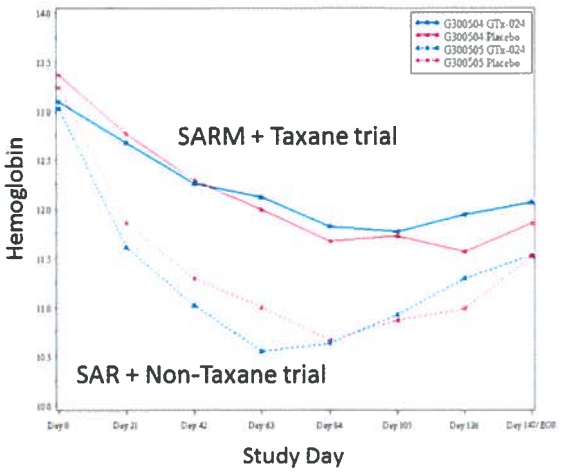
		% Responders (n)		
		Placebo (N=161)	GTx-024 (N=159)	p-value
LBM	Day 84	37.9% (61)	46.5% (74)	0.113
SCP	Day 84	24.8% (40)	19.5% (31)	0.289

European Analyses

Statistical hierarchy			Slopes		
			Placebo	GTx-024	p-value
1	SCP*	Day 84	-0.0245 %/day	-0.0305 %/day	0.8877
2	LBM	Day 84	-0.0044 kg/day	+0.0056 kg/day	0.0111

* Primary endpoint for Europe

Confounding Effects of Chemotherapy-Induced Anemia



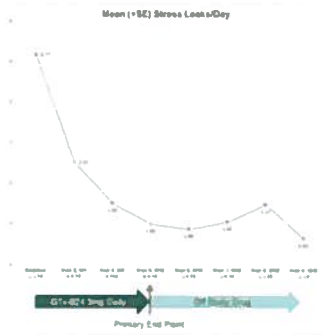
- Hemoglobin values were similar at baseline in both studies
- Hemoglobin concentrations were markedly lower at Day 84 in G300505 (gemcitabine) versus G300504 (taxane)
- Translating more muscle mass to more muscle strength was likely confounded by low hemoglobin (oxygenation) in gemcitabine study

Stress Urinary Incontinence

- Planned enrollment: ~ 30 patients
  - Enrollment closed at 19 patients
- Open label, multi-center (3 US centers)

Primary Endpoint
- 12 weeks
- Number of stress incontinence episodes/day
- Assessed by 3-day voiding diary

Key Secondary Endpoints
- Daily voids
- Pad weight
- Bladder stress test
- Change in pelvic floor muscles by MRI
- QOL: MESA, PGI-S, PGI-I, UDI-6, IIQ-7, FSFI



Primary Endpoint Results were Positive

Mean Stress Leaks Decreased by 81%

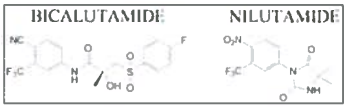
- Mean stress leaks decreased from 5.17 to 1.0 per day
- All 18 patients were responders*
- Up to 7 months durability in reduction in stress incontinence episodes (N=9)

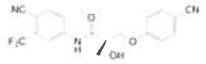
* Responders: 50% or greater reduction in number of stress leaks/day, considered clinically meaningful

SARMs in Development

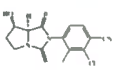
Compound	Clinical status
Enobosarm (GTx)	Phase III (NCT01355497 and NCT01355484)
GSK2849866 (GSK)	Phase I (NCT01696604)
MK-0773 (Merck)	Phase I (NCT00529659)
GLPG0634 (Galapagos)	Phase I (NCT01820806)
LGD-4033 (Ligand)	Phase I
S-101479 (Kaken)	Phase I
BMS-564929 (BMS)	Phase I
LY2452473 (Eli Lilly)	Phase I
PF-05314882 (Pfizer)	Phase I

Antiandrogens

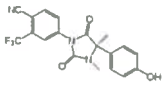




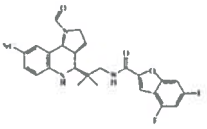
ENOBOSARM



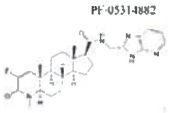
BMS-564929

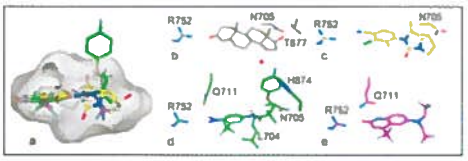


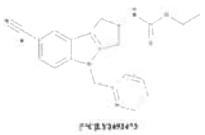
Galapagos



S-101479

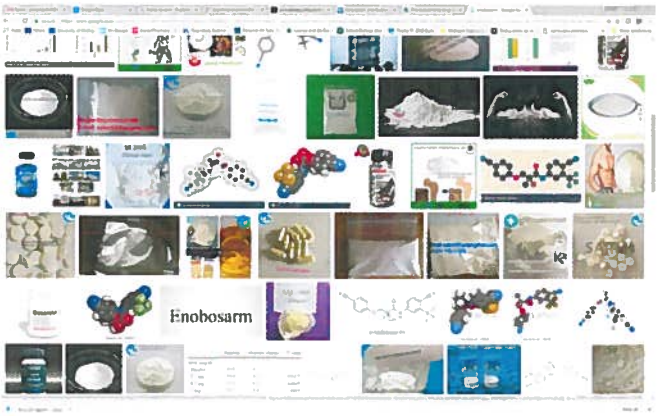




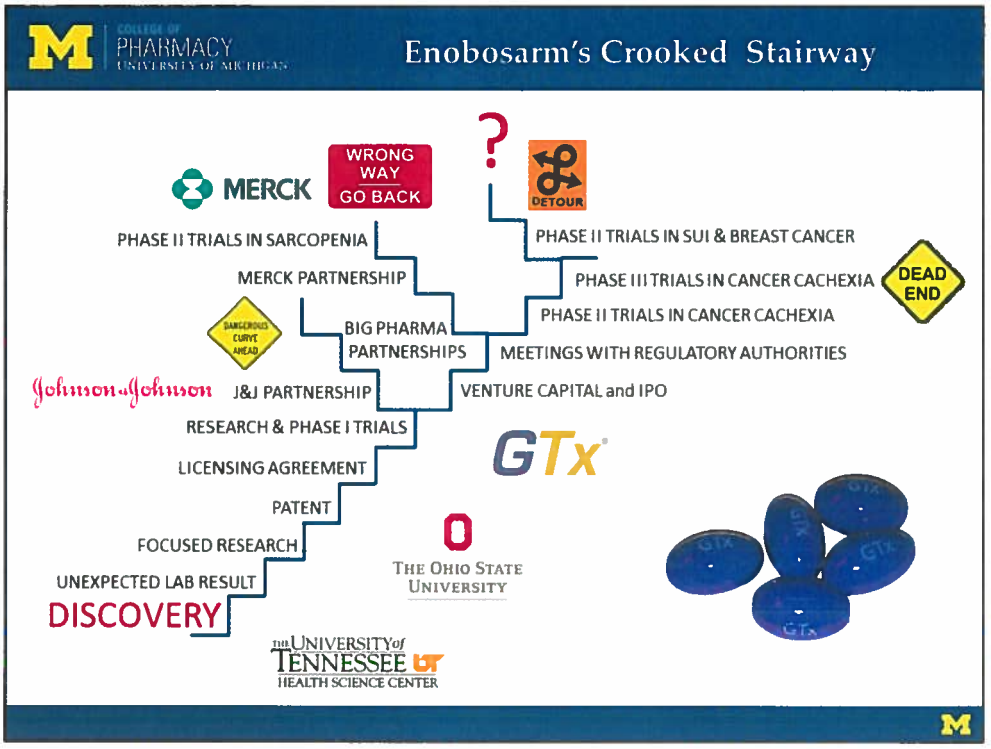


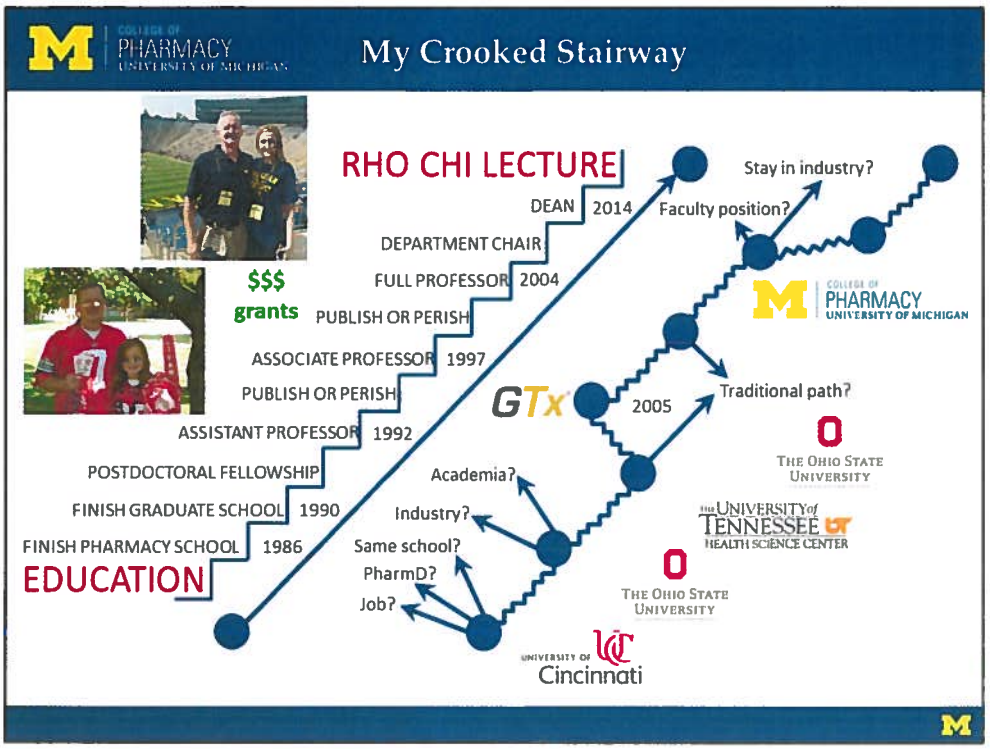
Lab Bench to Bench Press?

- Not approved for human use by FDA or others
- Increasing numbers of positive tests in athletes
- Purposeful consumption of illegal products
- Unexpected consumption in dietary supplements (creatine)
- WADA reported 28 cases gobally in 2015
- USADA reported 17 suspensions since 2014
- Currently 36 products on High Risk List
- FDA Office of Criminal Investigations initiated prosecutions of companies



Track & Field
Weightlifters
Major League Baseball
Paralympians
Volleyball
MMA
NCAA Basketball
Russian and American Olympian


PHARMACY
Enobosarm's Crooked Stairway
MERCK
WRONG WAY GO BACK
?
DETOUR
PHASE II TRIALS IN SARCOPENIA
PHASE II TRIALS IN SUI & BREAST CANCER
MERCK PARTNERSHIP
PHASE III TRIALS IN CANCER CACHEXIA
DEAD END
DANGEROUS CURVE AHEAD
BIG PHARMA PARTNERSHIPS
PHASE II TRIALS IN CANCER CACHEXIA
MEETINGS WITH REGULATORY AUTHORITIES
Johnson & Johnson
J&J PARTNERSHIP
VENTURE CAPITAL and IPO
RESEARCH & PHASE I TRIALS
GTx
LICENSING AGREEMENT
PATENT
FOCUSED RESEARCH
THE OHIO STATE UNIVERSITY
UNEXPECTED LAB RESULT
DISCOVERY
THE UNIVERSITY of TENNESSEE HEALTH SCIENCE CENTER


COLLEGE OF PHARMACY UNIVERSITY OF MICHIGAN
My Crooked Stairway
RHO CHI LECTURE
DEAN 2014
DEPARTMENT CHAIR
FULL PROFESSOR 2004
PUBLISH OR PERISH
ASSOCIATE PROFESSOR 1997
PUBLISH OR PERISH
ASSISTANT PROFESSOR 1992
POSTDOCTORAL FELLOWSHIP
FINISH GRADUATE SCHOOL 1990
FINISH PHARMACY SCHOOL 1986
EDUCATION
$$$
grants
Stay in industry?
Faculty position?
COLLEGE OF PHARMACY UNIVERSITY OF MICHIGAN
GTx
2005
Traditional path?
THE OHIO STATE UNIVERSITY
Academia?
Industry?
Same school?
PharmD?
Job?
THE UNIVERSITY of TENNESSEE HEALTH SCIENCE CENTER
THE OHIO STATE UNIVERSITY
UNIVERSITY OF Cincinnati

What Will Your Stairs Look Like?

JOB, RESIDENCY, FELLOWSHIP (Z)

PAY OFF LOANS

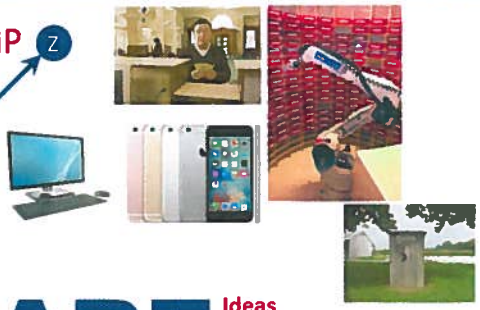
PASS NAPLEX & MJPE

APPLY

GRADUATE

P1, P2, P3, P4

PHARMACY SCHOOL (A)



SHARE X

- Ideas
- The Work
- The Credit
- Connections
- Opportunities

Changing State & Laws
- Affordable Care Act
- Robotics
- Technicians
- Provider Status

Disrupters
- Amazon
- Telehealth
- Wearables
- 3D Printers

Job Market
- Chain Consolidation
- # of Pharmacy Graduates
- # of Jobs, Fellowships, Residencies

Almost everything we do now will be done differently 50 years from now

Thank You!




"Nothing in this world can take the place of persistence. Talent will not: nothing is more common than unsuccessful [people] with talent. Genius will not; unrewarded genius is almost a proverb. Education will not: the world is full of educated failures. Persistence and determination alone are omnipotent."
- Calvin Coolidge

- Mitch Steiner, M.D.
- Duane Miller, Ph.D.
- Juhyun Kim, Ph.D.
- Chris Coss, Ph.D.
- Amanda Jones, Ph.D.
- Ramesh Narayanan, Ph.D.
- Yali He, Ph.D.
- Seoung-Soo Hong, Ph.D.
- Mike Mohler, Pharm.D., Ph.D.
- Domingo Rodriguez, M.D.
- Mary Ann Johnston, Pharm.D.
- Michael Hancock
- Matt Gosnell, Ph.D.