

A Career Analysis in the Pharmaceutical Industry

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Boston University Women in Chemistry Meeting

April 28, 2006

Agenda

Careers **Happen** and Most Often are Not **Planned**...

My Background

Educational Opportunities

Personal Career Opportunities

Balancing Personal Life

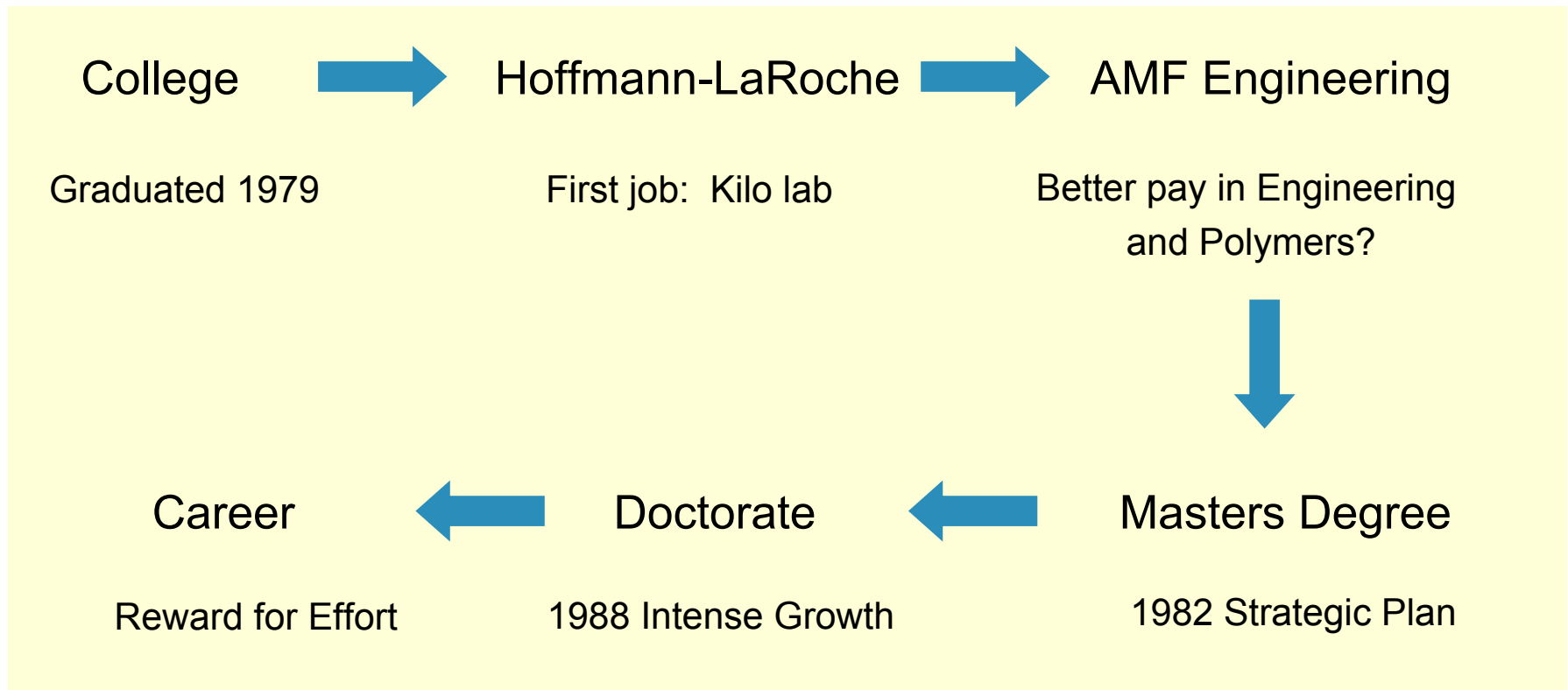
Modern Life in the Pharmaceutical Industry

Some Advice...

General Discussion on your questions

Early Days...

Science sparked my imagination in 6th grade...



Key people played an encouraging role at each step

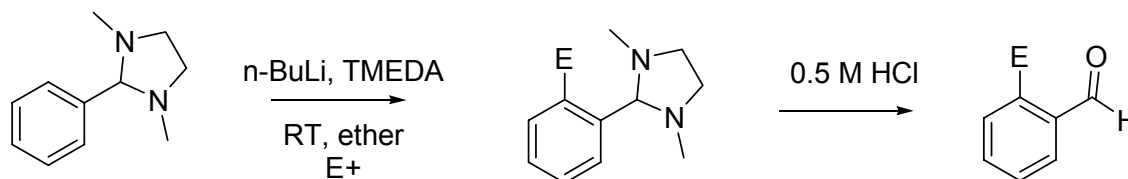
Decision Factors

Rationale

College: Furthest from home
In-state School
Initial major: Forestry and Field Biology
Final major: Chemistry and Biology

Opportunity

Undergraduate research program
Every lab course possible



J. Org. Chem. 1979, 44, 2004

Preview to Dan Comins Chemistry!

It's important to start mentoring undergraduates (not slave labor!)

Motivated me to get further in to chemistry

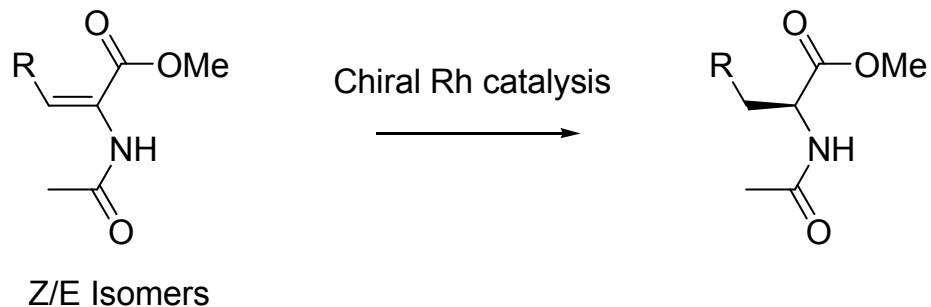
Decision Factors

Rationale

HLR: First and only interview / First job
Close to home
Immersed in synthesis up to 1 kg

Opportunity

Side project
Challenging chemistry
Learned about 'the industry'



J. Org. Chem. 1981, 46, 5086

Start of a life long network: “6 degrees of separation concept”

First met Prof. Al Meyers

Decision Factors

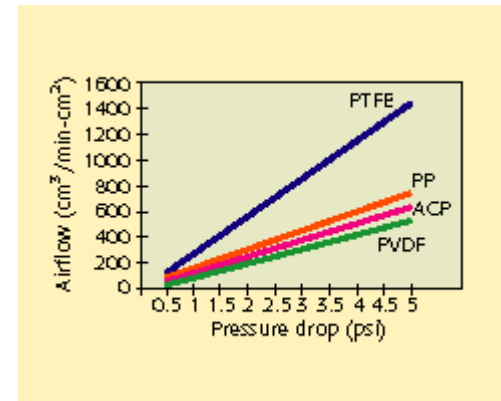
Rationale

AMF: Needed more Money / Apartment
Applied vs. Basic Research
Harley-Davidson Motorcycles!



Opportunity

Test engineering skills
Challenging problems
'Think Tank' mentality



Reinforced my personal motivation for obtaining an Advanced Degree

Very supportive supervisor pushing me back to school

Academics



Targeted MS in Chemistry (2 years)
Familiar with Faculty and School
Completed undergraduate project
Strategy: Fortify knowledge to target any
PhD granting institution in the country

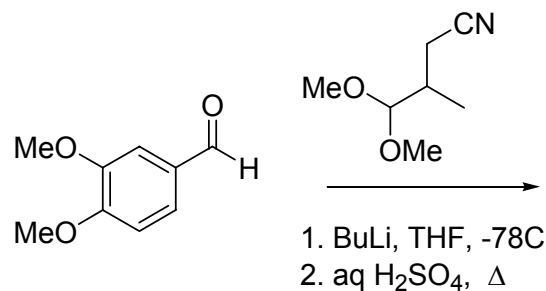


Last School visited (March 1984)
Prof. Meyers offered RA position
Said **yes** on the spot!
Factors: High pressure recruiting + Colorado
Top 5 synthesis group in world
Asymmetric Synthesis (80 hours a week)

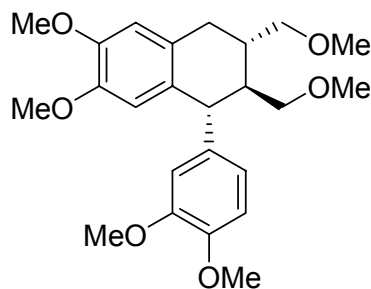
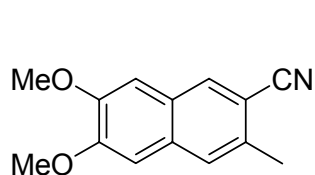
Round Two Academics...

MS: Fine tuned laboratory skills and core courses

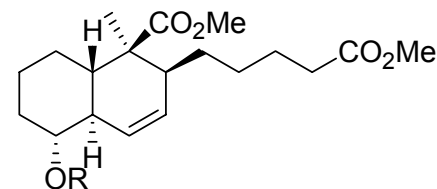
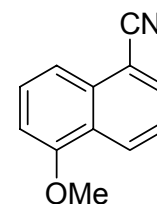
PhD: Focused on problem solving and scientific accomplishment



Synthesis 1986, 427
J. Am. Chem. Soc 1988, 110, 4611
Tetrahedron 1989, 45, 6949



(+)- Phyltetralin



Chlorothricolide 'Bottom Half'

Tandem additions to Naphthyloxazolines

Career Choices

Bristol-Myers



Bristol-Myers Squibb

Process Research (Syracuse NY)
1988-1990

Post Merger Restructuring
Medicinal Chemistry (Wallingford CT)
1990-1994



Abbott Bioresearch Center



Boehringer Ingelheim

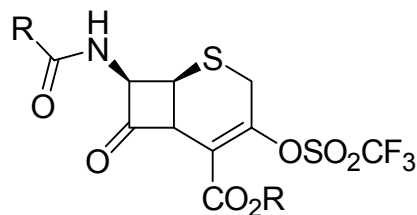
Medicinal Chemistry 2003-2005
Exploratory Research 2005-2006
Restructuring

Process Research (Ridgefield CT)
Combinatorial Chemistry
Medicinal Chemistry 1994-2003
International Experience

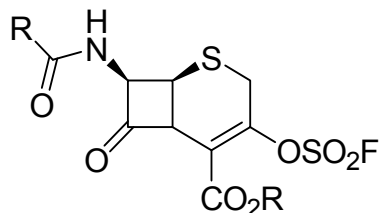
Events and Opportunities were not planned...

Chemistry Highlights

Bristol-Myers (Squibb)



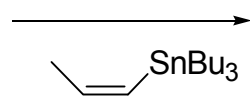
Syn Comm. 1990, 20, 2185



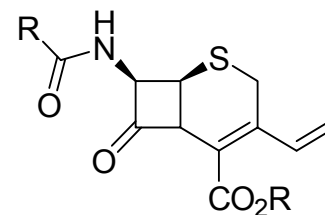
US Patent
general methodology

Adventures in Palladium Chemistry

$\text{Pd}(\text{OAc})_2$, solvent, 5 min



> 95%



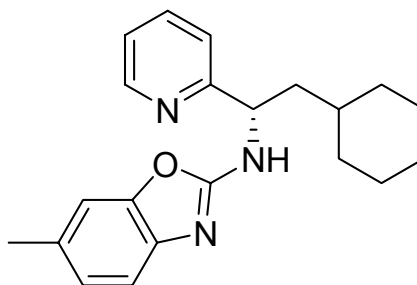
Cefprozil

J. Org. Chem. 1991, 56, 3493
Tett. Lett. 1991, 32, 4243
Tett. Lett. 1991, 32, 4073
Tett. Lett. 1992, 33, 1959 (with Jeanine)
Tett. Lett. 1993, 34, 7229
Tett. Lett. 1993, 34, 5925 (with Bruce Lipshutz)
J. Org. Chem. 1993, 58, 5434
Book Chapter

Project afforded 'Recreational Chemistry' opportunity...

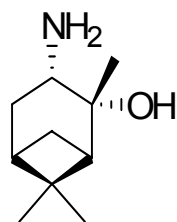
Chemistry Highlights

Boehringer Ingelheim



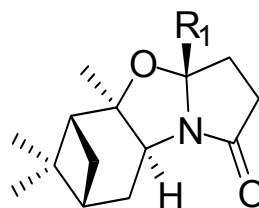
Idea → 20 kg

Ontazolast (LTB₄ Inhibitor)
Org. Proc. Res. Dev. 1997, 1, 331

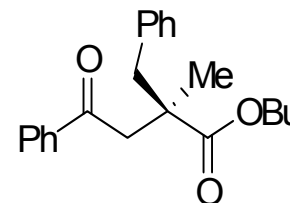


Process Byproduct

J. Org. Chem. 1996, 61, 5710



Meyers Bicyclic Lactam

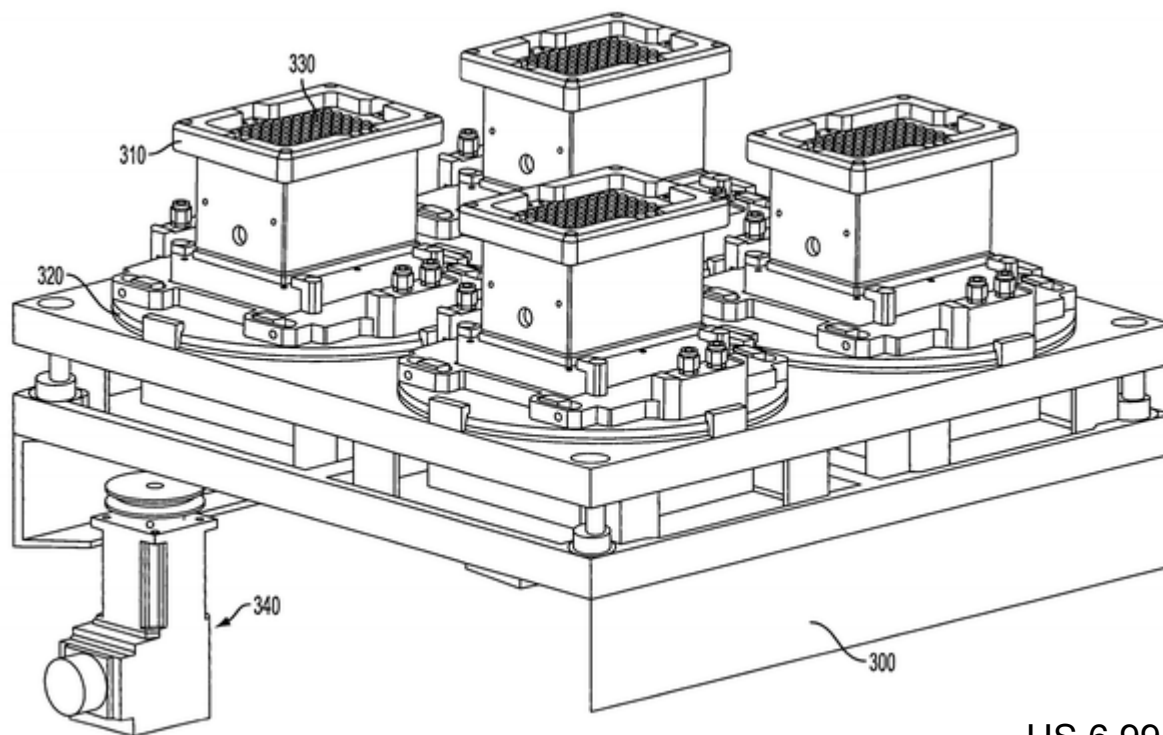


Opposite facial
selectivity for same
relative stereochemistry
 α vs β attack

90% de at RT !

Challenge yourself with the 'unknown'...
Recognize and capitalize on opportunities

Synthesis Technology



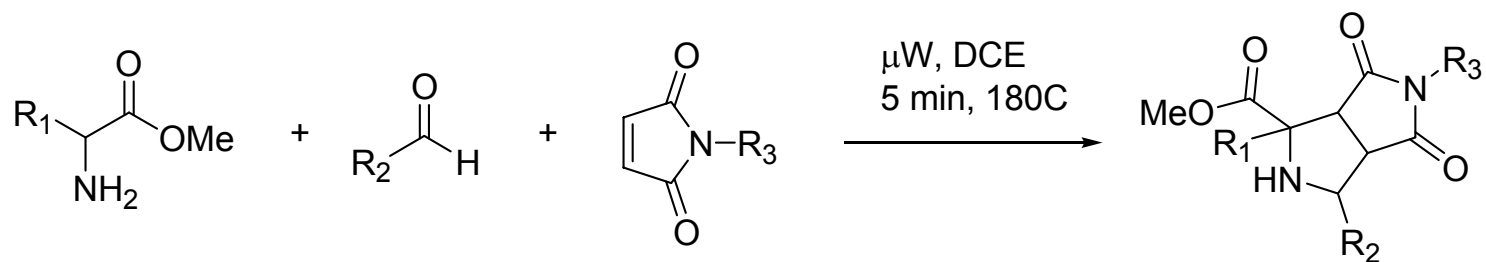
US 6,991,766 B2

Participation in and Management of External Collaborations

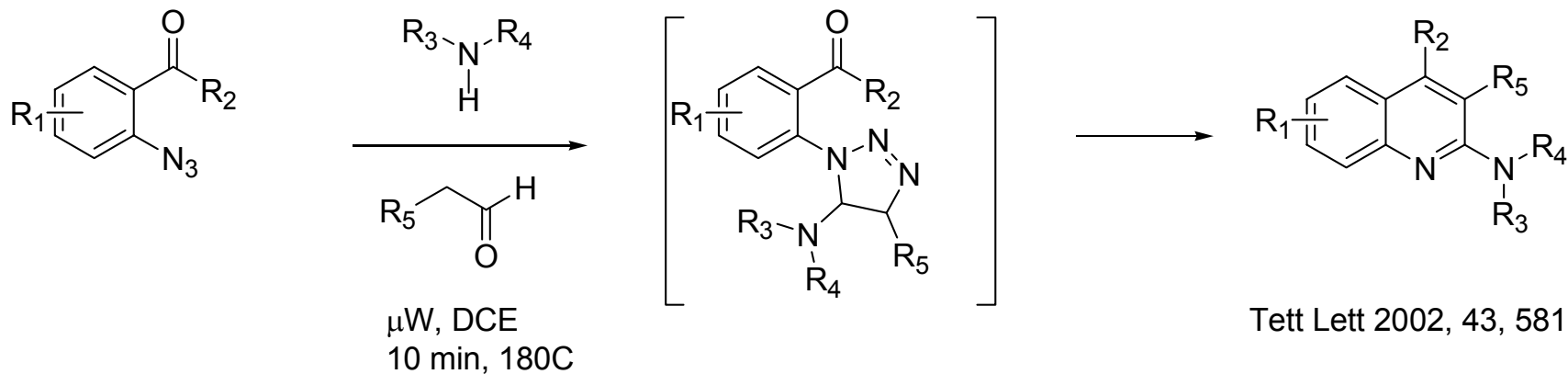
Ontogen, Charybdis Technologies, 3D Pharmaceuticals, Albany Molecular Research

Microwave Technology

Multicomponent Condensation Reactions



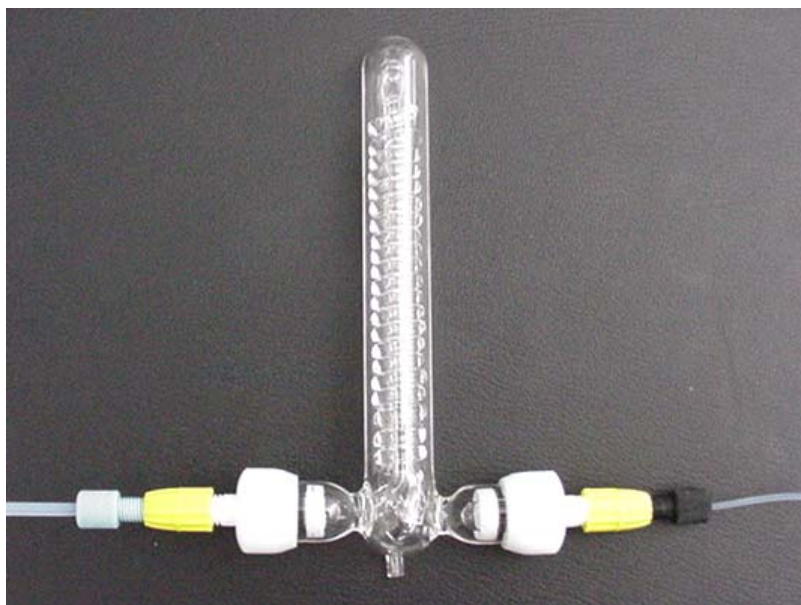
Tett Lett 2001, 42, 8939



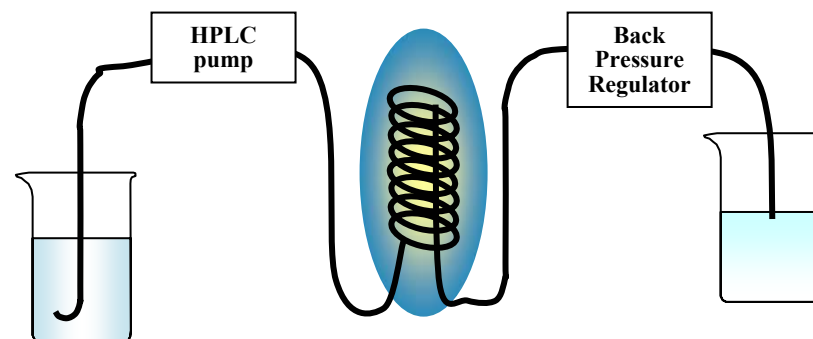
Tett Lett 2002, 43, 581

Enabled synthesis of 800-1000 member libraries

Microwave Flow-Cell Technology



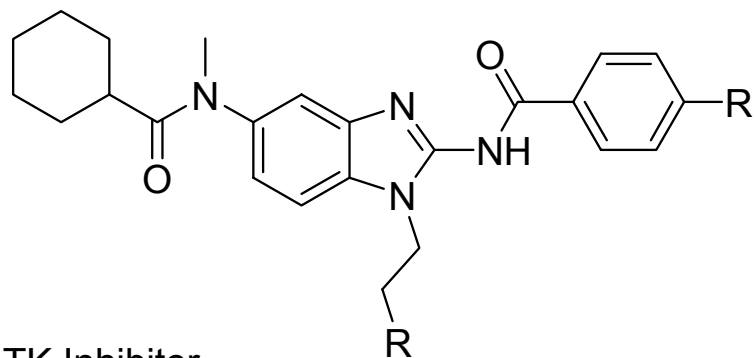
- Mg to Kg scale demonstrated
- Flow-through or batch operation
- Temperature control
- Atmospheric or pressurized reactions
- Single-mode reaction methods directly transferable for scale-up



Chemistry Highlights

Process Research → Combinatorial Chemistry → Medicinal Chemistry

Recognized the interface of chemistry and technology



ITK Inhibitor
sub nM activity achieved

US 2005/0176792

US 2005/0203158

US 6,825,219

Project Leadership: ITK, p38 backup, HTL

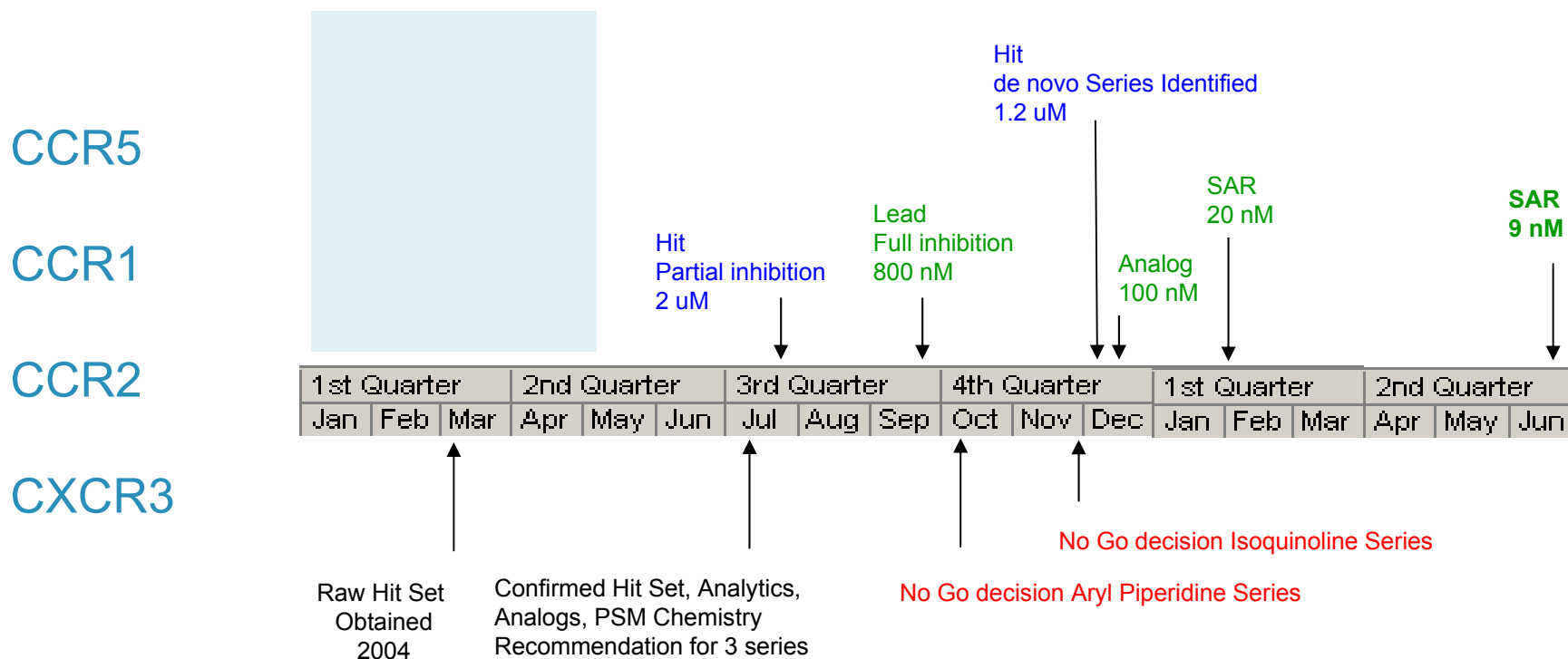


It was not just the chemistry. It was the overall problem to be solved !

Chemistry Highlights

Abbott Bioresearch Center

Focus was on establishing and leading GPCR platform development and lead identification for early programs. Biology intense exercise for a kinase-based organization!



Just because it's a high affinity ligand does not make it a drug !

Balancing Career and Personal Life

- Try not to bring work home, go to the office instead
- **Vacation is vacation**, leave work behind and recharge yourself
- Reserve school holidays for vacation days
- Establish family 'traditions' for business travel
- Have a hobby or two
- Have friends outside of chemistry/sciences
- Personal and professional life can mix nicely!

Time management and efficiency is important in industry

- You will be more effective
- You will get more done sooner
- Planning is essential
- Companies accommodate personal needs

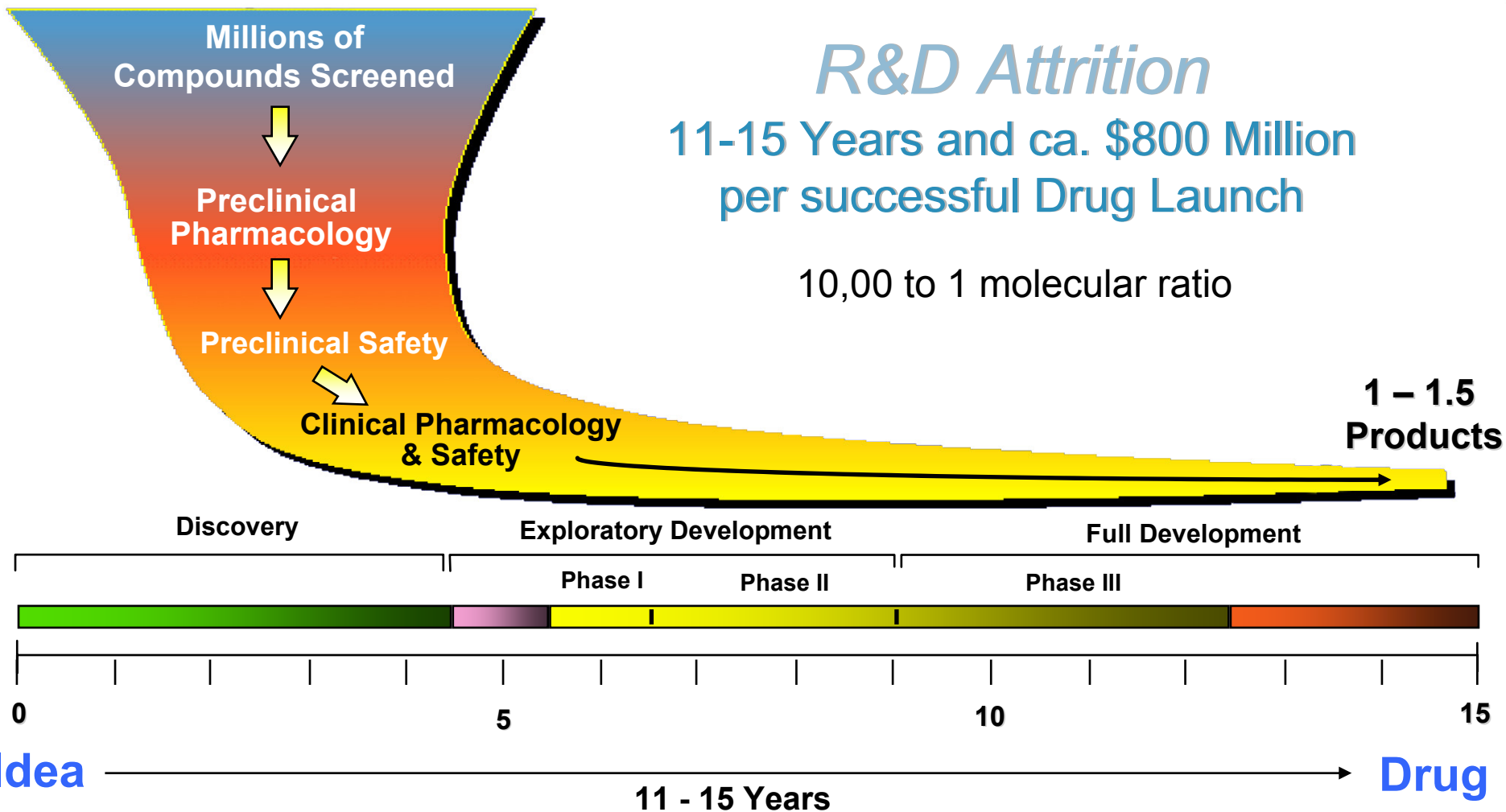


Looking at the Pharmaceutical Industry

- Pros and Cons of a Changing Industry
- General Attributes for a Chemist

Typical Drug Discovery Timelines

~100 Discovery Approaches



Criteria for Lead Selection

Compound Series

- **Reproducible activity**
 - **Dose responsive**
 - **Confirmed structural identity**
 - **Purity established**
 - **No evidence of class instability**
 - **Tractable synthetic route established**
 - **Favorable IP position and competitive assessment for class**
 - **Demonstrable exploitable SAR**
 - **Support for interaction with molecular target**
 - **Selectivity/Profile established**
 - **Assessment of 'drugability' (*in vivo* profile)**
 - **Secondary Assay Funnel Validated**
-
- The diagram uses blue curly braces on the right side to group the criteria into three categories:
- Chemical Attributes:** This group includes the first seven criteria: reproducible activity, dose responsive, confirmed structural identity, purity established, no evidence of class instability, tractable synthetic route established, and favorable IP position and competitive assessment for class.
 - Biochemical Attributes:** This group includes the next two criteria: support for interaction with molecular target and selectivity/profile established.
 - Pharmacology Attributes:** This group includes the final two criteria: assessment of 'drugability' (*in vivo* profile) and secondary assay funnel validated.

Development Candidates

- Good target potency and selectivity demonstrated
- Efficacious in animal models of disease
- Patentable (preferably novel structure and a patented novel use)
- Scalable, affordable synthesis (<8 steps preferred),
- Acceptable salt form, stable crystalline solid state, melting point <240°C
- Solubility and dissolution rate suitable for desired dosage form and route of administration
- Metabolically stable ($T_{1/2} > 40$ min vs. 2D6, 3A4; other p450 isoforms)
- Rapid absorption (blood levels) by intended route of administration, desired elimination half-life for dosing schedule
- No activity in predictors of toxicity (hERG channel interactions)

Industry-wide success rate: roughly 1 in 5 projects will deliver a development candidate within 5 years

Pharmaceutical Industry Today

Challenges

- Increasing cost of R&D
- Pressure on pricing
- Low output of new products
- Fierce competition
- Increased regulatory hurdles

Opportunities

- Innovation
 - Genomics
 - Proteinomics
 - Bioinformatics
 - Translational medicine
 - Collaborations
- Better understanding of mechanism for disease

Do you aspire to be 'Best in Class' or 'First in Class' with a new drug ?

Drug Discovery Caveats

Be Prepared: Discovery of a clinical candidate, let alone a marketed drug, is not easy !

Nature abhors a new chemical entity

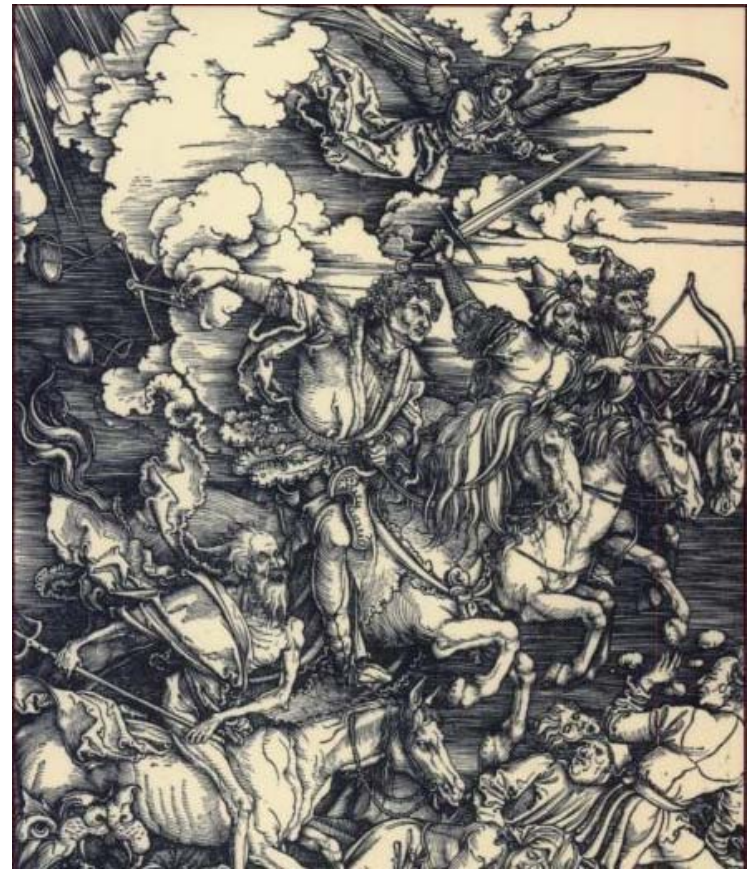
'Four Horsemen of the Apocalypse':

- Bioavailability
- Metabolism
- Toxicology
- Man

Events *in vivo* are not rational

Progress decreases as a function of time !

Be prepared to fail often and fast



Revelation 6

Successful Chemist Phenotype

Ideal Attributes

Team Player

'Warm' Interpersonal Skills

Focused, but Relaxed Attitude

Managing Upwards

Managing/Coaching Downwards

Well Developed Peer Relationships

Strong External Network

Typical Barriers to Success

Independent Researcher

Perceived as Arrogant

Too Intense

Fear and Comfort Level

Lack of Skill/Sensitivity

Too Competitive

Lack Self Confidence

These are skills that require continuous development and practice

Being a Good Chemist is Not Good Enough

Today's Medicinal Chemist must also have a fundamental mechanistic understanding of the following:

- Principles and practices of drug design: What to make ?
- Non-covalent binding interactions
- Structure-activity and property-activity relationships
- Compound patents and the patenting process
- Informatics
- Synthesis and HTS Technology
- Chemical genomics (RNAi)
- Molecular kinetics and thermodynamics
- The chemistry of drug metabolism and elimination (PK)
- Membrane partitioning and transport
- Principles of dissolution and solubility
- The chemistry of toxicity

Top 10 Med Chemist's Rules to Live By

- Start with 'good leads'
- Always seek the path of least resistance (prioritize)
- Every compound must ask (and answer) a question
- Get the data you need; Use the data you get; Believe the data
- Use every technology at your disposal and complain about those you can't access but need
- Be clear on the essential goals ("eyes on the prize"), remind yourself often
- Develop an emotional attachment to achieving organizational success
- Seek ideas from unobvious sources
- Know when to move on from a problem or project
- Also... Know your biology and pharmacology !

Career Recognition Growth

Professional Growth and Recognition develops in stages



Some General Advice

- Find a mentor (or 2)
- Ask for opportunities, don't wait to be asked
- Seek challenges for continuous growth
- Don't get emotionally attached to a problem or project
- Keep a even demeanor and high energy level
- Don't hang out with just chemists at the lunch table
- Pay attention to the 'soft' side of people/personalities
- Beat your ego into submission
- Stay current, jobs/companies are not secure
- Be prepared for change

Parting Thought

The most valuable things I've learned in the past 18 years...

An organization full of people who care about each other's success will be a successful organization

You must be committed to be part of an innovative team and not be afraid to try new approaches