The Ecstasy of Gold – 
Starting your Academic Research 
and Turning it into a Biotech Startup

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Outline

I. Brief personal intro

II. Industry vs Academia as a Career

III. Developing and commercializing intellectual property within a university setting
Brief Personal
Introduction
1976-1980  B.A. Biochemistry/Molecular Biology UC Santa Barbara

ION CHROMATOGRAPHY OF ORGANIC ACIDS IN URINE

UNDERGRAD RESEARCH – CHROMATOGRAPHY OF DINOFLAGELATE PROTEINS

1980-1985 Research Assistant

PURIFICATION AND CHARACTERIZATION OF RECOMBINANT PLASMINOGEN ACTIVATORS

U.S. PATENT 5,219,569 PROTEASE RESISTANT UROKINASE (EXCLUSION UTILITY)

1985-1990 Ph.D. Biological Chemistry UC Irvine

CONSTRUCTED AND CHARACTERIZED CHIMERIC SERINE PROTEASES

1990-1994 Postdoc University of Oregon

PROTEIN CRYSTALLOGRAPHY, PROTEIN BIOPHYSICS

1994 FSU Department of Chemistry

2000 TENURED (COLLEGE OF ARTS & SCIENCES)

2005 College of Medicine

2007 Tenured (College of Medicine)
Intellectual property/commercialization efforts:

- 14 issued patents (US and European Union)

2008 – Co-founded Zign Therapeutics

2012 – Co-founded Trefoil Therapeutics
Industry vs Academia as a career
Imagine a job where everyone spontaneously cheers, high-fives and chants “USA!, USA!, USA!” when a goal is accomplished

• Genentech *was* like that…
• Currently, SpaceX is like that: jubilation with a vertical landing:
In a company, “Teamwork” is the operative word
• Corporate objectives and goals supersede any one individual’s career or advancement
• “There is no ‘I’ in Team”
Some aspects of a position in Industry to consider:

• Profit sharing/stock options are common (nice!)
• **Good benefits** (healthcare, retirement, occasionally others – childcare, long-term care, gym membership, reduced cost cafeteria, housing loans, relocation costs, continuing education support, etc.)
• Typical work hours are 9:00-5:00 (evenings and weekends are your own)
  • Consequently, working evenings and weekends can make you **stand out**
• **Competitive salaries and raises** (tied to local cost of living)
• The product of the company (a drug, a device, a service, etc.) can have a significant impact upon quality of life of the public (actually useful)
• All employee inventions are the **exclusive property of the company**
  • Employee **retains no rights** of ownership/licensing/royalty
• Legal protection of intellectual property takes precedence over public disclosure, **must get legal department approval for**:
  • All oral presentations and publications
  • And the legal department is **extremely conservative**
• Typical layoff notice is 2 weeks (or immediate with severance package)
  • Layoffs can come as a surprise – especially in small companies
For small companies, be aware of the business model/goals of the company founders/CEO/CFO!

- Many small companies have a business goal of being bought out
- Both the risks, and return on investment (ROI), are the greatest when the company is small
  - ROI of >100x for initial investors upon achieving a public offering
    - CEO, CFO, CSO are typically among the initial investors
  - ROI goes down as the company gets larger, more solid
- For a number of CEOs of small companies, this is not their first rodeo
  - They have a clear exit plan 3-5 years away (quit, start another company – maintain that large ROI)
  - Thus, in a small company the major management may depart in 3-5 years; where does that leave employees?
- Small companies feel a kindred spirit with employees that have a mature entrepreneurial spirit
  - Employees that have no anxiety about 5 years into the future, and recognize that things can turn south, and have their own exit plan
Larger companies are more likely to be structured for long-term employee satisfaction

• **Employee retention** is a major concern of large companies
  • Turn-over is expensive
  • Large companies are more likely to engage in long-term planning
    • Have income stream to support 5, 10-year business planning
    • May view market share as key aspect of business
  • Tend to develop a workforce comprising **specific individual expertise** rather than employee capability at diverse tasks
    • Can afford to retrain employees
  • Have a comparatively large human resource department devoted to employee relations
Academia

Academia is a business, but what exactly is their product?

- Universities strive to develop a reputation for scholastic excellence, and quality of:
  - Education
  - Graduates
  - Faculty
  - Programs and facilities
  - Intellectual property
    - Books, publications, compositions, film, art, etc.
- Academia is less a coherent whole, and more a collection of individuals of repute
- The university hires faculty based upon reputation, or potential to develop or expand upon the University’s reputation (in a specific island of excellence)
Some aspects of a position in Academia:

- **Salary:**
  - Initially nationally competitive; however, low annual raises typically result in *salary compression* quite quickly (a faculty position is effectively *non-movable*).
  - University business model provides for a *portion of salary*, with a *requirement for supplementation* by grants (10-90%).
- Benefits typically include options for healthcare, long-term care, life insurance, but as specific *pre-tax deductions from salary*.
  - You will have to *pay to park at your place of work* (geez!)
- Little (if any) recurring funds are provided for research support.
  - “Startup” package designed to last ~3 years.
  - Assumes that grant support will be obtained by then.
- **You decide what you will be working on** *perceived as the #1 benefit*.
  - Your lab is a *“Mom & Pop” store* (University provides space, lights, water, etc.) - can have a significant impact upon quality of life (*general paranoia*).
  - Your “team” is your lab group (students, postdocs, technicians, *spouse*).
  - Once trained and competent, **THEY LEAVE**! Also, you can’t fire students!
Some aspects of a position in Academia (cont.):

- Your goal is to get tenure
  - You cannot continue in a tenure-earning position past year 7
  - Tenure vote is typically in year 6
    - Must have national-level research grant
    - Must have record of publications
    - Evidence of successful teaching
    - Demonstrated service participation
    - Key part of tenure application is outside letters
- It’s critical to find out during the job interview what the expectations are for a successful tenure decision
  - It is also key during the job interview to present details of your anticipated first grant application
- If possible during your postdoc:
  - Collect significant preliminary data
  - Obtain funding that can move with you (this is a tough one, but often the basis for successful job offer)
Some aspects of a position in Academia (cont.):

• All employee inventions of are the **exclusive property of the university**
  • The university **pays all legal costs for patent filing**
  • Employee **DOES retain rights** to licensing/royalty
    • 85% of the first $10,000 in licensing/royalties **goes to the inventor(s)**
    • After the first $10,000 the university **recoups its legal fees**, and then subsequent royalty funds are divided:
      • 40% inventor(s)
      • 30% department (typically some kickback to inventor(s))
      • 30% university (typically some kickback to department)

• If you are going to invent something, **it is substantially more lucrative to do it at a university rather than at a company**
  • The **most lucrative situation** would be to invent, patent, and license a technology as a private citizen (but then, you have to pay all legal fees)
Bob Holton FSU Chemistry – Taxol semi-synthesis 1989
• ~$200 million in royalties; 40% ($80 million) to Bob Holton (minus legal)

• This is Bob
• He has reason to smile
Developing and commercializing intellectual property within a university setting
The process of intellectual property development:

• **Invent something** (here’s the criteria):
  1. Should be **patentable** (somethings are not patentable but might be copyrighted, e.g. software)
  2. **Novel**
  3. **Non-obvious**
  4. **Has utility**

• Ultimately, a patent examiner at the USPTO will judge the validity of each of these aspects of your patent application
The process of intellectual property development (cont.):

• Submit an invention disclosure to the university office of tech transfer
  • This describes the invention, the potential market, and the inventors

• If FSU is convinced of the utility of the disclosure, they will file a provisional patent application
  • Basically 1-2 page brief description
  • Submission sets the priority date of the application
  • The university has 1 year from the filing date of the provisional to convert to a full application (i.e. to file a full application)
The process of intellectual property development (cont.):

• FSU will hire a lawyer to draft a full patent application
  • Typically pursued ~30 days prior to deadline
  • Lawyer may have a STEM degree, but is unlikely to be familiar with the specific technology
  • It is critical to work with the lawyer to draft a strong application
    • Can take considerable time and effort, but the application will be weak otherwise
    • Costs for this (to FSU and deducted from future royalties) can be >$20,000
The process of intellectual property development (cont.):

- After full conversion submission, USPTO examiner may take **1-2 years** (or longer) to review
  - Patents are typically written quite broadly, and the patent examiner will often **disallow certain claims** in an “Office Action”
  - Disallowed claims are commonly due to being “**obvious**” (recall the “non-obvious” criteria for patent applications)
  - Also, there can be disallowed claims due to “**prior-art**” (recall the “novel” criteria for patent applications)
  - Broadly written claims are often considered to consist of **more than one claim** (and must be broken up)
From bench to bedside: My university research

Protein folding, evolution & design

• Did complex protein architecture evolve from simple peptide motifs?

• How is symmetry utilized in protein evolution & design?

• Fibroblast Growth Factor-1 (FGF-1) as the model system in investigating these questions
Over the course of this research hundreds of mutant forms of FGF-1 were constructed

- Typically their biophysical properties of folding and stability were characterized, but not functionality (i.e. in vivo properties)

- Upon learning (~2004) that FGF-1 had therapeutic potential, but that this was hampered by poor stability, we decided to also investigate the functional properties of some of our engineered FGF-1 proteins

  - eFGF-1A:
    - Increased thermostability
    - Elimination of reactive buried thiols (free cysteines)
Increase in functional half-life in cell culture media:

**Functional Half-life in Cell Culture Media**

- Half-life 1 hr
- Half-life 40 hr

Graph showing % T₀ Activity over Incubation Time (hours) for WT FGF-1 and eFGF-1A.
Resistance to proteolytic digestion in buffered saline:

Resistance to Trypsin Digestion
(1:100 mass ratio, PBS)

Fraction intact protein

WT FGF-1

eFGF-1A

Time (min)
FGF-1 causes many cell types to divide/grow

Potential therapeutic applications in regenerative medicine:

• Acceleration of dermal wound healing (diabetics, elderly)

• Angiogenic therapy in coronary occlusion

• Regeneration of cornea in Fuch’s corneal dystrophy

• Regeneration of damaged cornea due to mustard gas exposure (ISIS)

• Novel regulation of blood glucose levels in the diabetic

• However, FGF-1 biophysical properties make it a poor choice as a therapeutic agent (also non-patentable)

  • Stabilizing mutants may solve this problem, and are also protected intellectual property
From bench to bedside – Traversing the Valley of Death…

Your lab is here…

Investors prefer risk here…
Moving from *in vitro* to *in vivo* studies gets expensive quickly…
Enhanced Pharmacokinetic Properties:

Increased Pharmacokinetic Mean Residence Time

\[ C_p^* t \text{ (pg*min/ml)} \]

- WT FGF-1
- eFGF-1A

Time (hr)

0 4 8 12 16 20 24

0 \( \times 10^6 \) \( \times 10^6 \) \( \times 10^6 \)
40% enhanced rate of dermal healing in diabetic mice:

**Rate of Excisional Dermal Wound Repair in Diabetic NONcNZO10/LtJ Mice**

- PBX Buffer
- FGF-1 1.0μg/cm²
- FGF-1 1.0μg/cm² + HS
- eFGF-1A 1.0μg/cm²

Healing Rate (mm/day)
A brief history of corporate interest in FGF-1 mutants covered by FSU IP:

- CardioVascular BioTherapeutics (2005)
  - Treating coronary occlusion
  - Dermal wound healing
- Phage Pharma (2010)
  - Tympanic (ear drum) repair
- NovoCyte (2011)
  - Burns, autism
- VenaCava Therapeutics (2014)
  - Dermal wound healing
- InnovaTech (2015)
  - Novel bandage technology (dermal wound healing)
- MetaCrine (2015)
  - Blood glucose regulation
“Insanity is doing the same thing over and over again, and expecting a different result”

- Albert Einstein
Management Team

David Eveleth, PhD
Chief Executive Officer

Michael Blaber, PhD
Professor of Biomedical Sciences
College of Medicine
Florida State University
Co-Founder

Ralph Bradshaw, PhD
Chief Scientific Officer

Ken Thomas, PhD
Co-founder/Consultant
Trefoil Therapeutics – A startup biotech company

• Steps associated with commercialization of FGF-1:

  1. Signed 1 year exclusive option to IP (2012)

      • Prevents FSU from entering into a license agreement with another party for 1 year

      • A short duration option is much cheaper than full licensing

      • Provides the company with 1 year to raise the necessary seed capital for a full licensing agreement

      • Ties up IP for 1 year – after which, FSU can identify other interested parties if Trefoil fails

      • Necessary seed capital funding is “family & friends” (not “series A” as significant proof-of-concept data is needed for series A)
Trefoil Therapeutics – A startup biotech company cont.

• 2013-2014

  • Raised modest funds (<$100K)
  
  • Identified that investor interest was more significant in corneal dystrophy than dermal wound healing
  
  • Established scientific advisory board
  
  • Winner of Early Stage startup competition at 2014 SE BIO forum (mutant FGF-1 for corneal dystrophy)
  
  • Signed licensing agreement with FSU
Trefoil Therapeutics – A startup biotech company cont.

• FSU licensing agreement
  • Funds up front
  • Milestone payments:
    • Series A financing
    • First-in-human clinical trials
    • Drug approval
  • Equity (3-4% preferred stock)
  • Research support agreement (quarterly payments)
2015-2016: Adding value to the company

• Rented lab space in San Diego, California

• Awarded NIH R21 grant to study FGF-1 mutants to treat eye damage in soldiers due to mustard gas exposure (ISIS)

• Initiated pre-IND discussions with FDA for Fuchs’ dystrophy
  • Identified critical studies to enable human trials

• Initiated FDA discussions for Orphan drug status for Fuchs’ dystrophy

• Efficacy data generated in-house by Trefoil

• Next step: obtaining series A (first round) financing
QUESTIONS?