Building a Career in the Pharmaceutical Industry: Personal Reflections

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This Seminar is Really about YOU (not me)...

- Let’s talk about what it takes to build a successful career...
  - Process of looking for a job?
  - What’s it like to work in the pharma industry?
  - How is it different from academia?
  - Where (and when) do I start?
This Seminar is Really about YOU (not me)...

- But first, let’s take a brief survey of who is in the room:
  - Post-docs
  - Grad students
  - Undergrads
  - Technicians/scientists
  - Faculty
Another survey... (eyes closed)

- Academia or Industry?
- Post-doc or no post-doc? Or two post-docs?
- Lab career or other opportunities?
The topics for today’s talk include reflections from my own personal perspective
  • ...(and nothing to do with my company’s interests or policies)

I am not here as a company/industry recruiter

What works (i.e., is a good approach) for one person is not necessarily going to be the same (or even the right thing) for anyone else
Looking into the future: The healthcare environment is continually evolving

- The world’s population is aging. More healthcare treatments are needed, also prompting payors to aggressively manage costs.
- Poor nutritional habits and sedentary lifestyles are increasing the prevalence of chronic diseases.
- Economic growth of emerging countries is providing healthcare access to more people.
- New technological discoveries and trends are enabling the development of innovative medicines while increasing the cost of innovation.
Pharmaceutical Industry: 
*Characteristics of the innovative pharmaceutical industry*

- Long and **risky R&D process** which can take **more than 10 years**
- **High attrition rate** of development compounds: from every 10,000 compounds at the beginning of R&D only one new drug is brought to market
- The estimated costs of bringing a new chemical or biological entity to market is **>1 Billion USD**
- **Limited period of value creation** because of patent term and expiry
- Highly global business environment with significant **societal pressures**
Paradigm for Drugs in the 21st Century

Prescribe the right treatment...
For the right patient
At the right time
For the right reason
And with predictable outcome

Lessons along the way...

- Let’s use my personal career story as one example of many possible paths

- Think about the following:
  - Where do you start?
  - What are the most important factors in choosing a career?
  - How to make good career decisions?
  - How do you avoid making bad decisions that have a lasting impact?
LACK OF EVIDENCE FOR COVALENTLY-BOUND CARBOHYDRATES IN ENERGY-TRANSDUCING ATPases FROM MITOCHONDRIA, BACTERIA, AND CHLOROPLASTS

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1. Introduction

Recently Manz and co-workers proposed that the energy-transducing ATPases from Micrococcus luteus (Bf) and spinach chloroplasts (CF1) are glycoproteins [1,2]. Their evidence includes periodic acid-Schiff (PAS) staining of the enzymes' α and β subunits on sodium dodecyl sulfate polyacrylamide gels (SDS-PAGE gels), PAS staining of protein bands of the appropriate molecular weight on non-denaturing PAGE gels and sugar analysis of enzyme preparations. In addition, preliminary experiments indicate that the mitochondrial ATPase PAS staining none of the subunits of the individual ATPases give a positive reaction for sugar. In addition, the ATPases are not retained by Concanavalin A-Sepharose columns based on recovery of protein and enzymatic activity.

2. Experimental

2.1. Materials

Coupling factor, F1, from beef heart mitochondria [6] and CF1 from spinach chloroplasts [7] were prepared as described. BF1 from two strains of E. coli...
Adenine Nucleotide Binding Sites on Beef Heart F$_1$-ATPase

EVIDENCE FOR THREE EXCHANGEABLE SITES THAT ARE DISTINCT FROM THREE NONCATALYTIC SITES*

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(Received for publication, July 6, 1981)

5'-Adenylyl-$\beta$,y-imidodiphosphate (AMP-PNP), a nonhydrolyzable analog of ATP, has been used to probe the exchangeable nucleotide binding sites on beef heart mitochondrial F$_1$-ATPase. Equilibrium binding measurements at pH 8.0 in the presence of excess MgCl$_2$ reveal three AMP-PNP binding sites on native F$_1$, including one high affinity site, $K_d = 10$ nM, and two lower affinity sites, $K_d = 1.0$ nM. An inhibition constant of 14 nM is obtained for AMP-PNP inhibition of ATP hydrolysis.

Modification of essential amino acid residues of F$_1$ with pyridoxal 5'-phosphate or phenylglyoxal results in the loss of one AMP-PNP binding site, while modification of essential carboxyl residues or the binding of coupling factor, F$_0$, of the enzyme is composed of five different subunits, the stoichiometry of which is controversial (see Refs. 1-3). Although there appears to be general agreement that the two largest subunits, $\alpha$ and $\beta$, are present in equal amounts, both $\alpha_2\beta_2$ and $\alpha_3\beta_1$ have been strongly advocated for mitochondrial F$_1$. A stoichiometry of $\alpha_2\beta_1$ is favored for the chloroplast enzyme and $\alpha_3\beta_0$ for bacterial F$_1$.

The number of adenine nucleotide binding sites on F$_1$ is related to the stoichiometry of the $\alpha$ and $\beta$ subunits. Modification of F$_1$ by alkylation (4-6) or photofinity (7-13) analog of adenine nucleotides results in the labeling of $\alpha$ and $\beta$ but not the smaller subunits. Using purified subunits from bacterial F$_1$, nucleotide binding to $\alpha$ (14) and $\beta$ (15) has been
Adenine Nucleotide Binding Sites on Beef Heart F$_1$-ATPase

SPECIFICITY OF COOPERATIVE INTERACTIONS BETWEEN CATALYTIC SITES

(Received for publication, February 16, 1982)

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Cooperative interactions between nucleotide binding sites on beef heart mitochondrial F$_1$-ATPase have been studied by measuring substrate-promoted release of 5'-adenylyl-β,γ-imidodiphosphate (AMP-PNP) from a single high affinity site. The site is initially loaded by incubating F$_i$ with an equimolar amount of the nonhydrolyzable ATP analog. When unbound [PH]AMP-PNP is removed and the complex diluted to a concentration below the $K_d$, release of ligand shows an apparent absolute requirement for medium ADP. Release is biphasic with the extent of release during the initial rapid phase dependent on the concentration of medium ADP. Although phosphate alone has no effect, it enhances the rapid phase of ADP-promoted release over 2-fold with a half-maximal effect at 60 μM P. The binding of efrapeptin (A23871) to the F$_i$-AMP-PNP complex competes

nepsky, 1974; Philo and Selwyn, 1974). However, the β,γ-
imidodiphosphate bond cannot be cleaved to products which dissociate rapidly during normal catalysis. Hence, AMP-PNP forms a stable dead-end complex with the enzyme.

Inhibition of ATP hydrolysis by the analog is competitive with respect to ATP (Penefsky, 1974; Melnick et al., 1975) and is reversed under conditions for ATP synthesis (Penefsky, 1979, Chernyak and Kozlov, 1979). We have previously shown that, although F$_i$ contains three copies of the catalytic subunit, the binding of a single mol of AMP-PNP/mol of F$_i$ at a high affinity site ($K_d = 18 nM$) is sufficient for complete inhibition (Cross and Nalin, 1982).

In the current study, we have examined the possibility that soluble F$_i$ containing a single AMP-PNP bound at a catalytic site may serve as a useful model in assessing the cooperative
Selective Modification of Coupling Factor 1 in Spinach Chloroplast Thylakoids by a Fluorescent Maleimide*

Carlo M. Nalin, Richard Beliveau, and Richard E. McCarty

Role of a Disulfide Bond in the γ Subunit in Activation of the ATPase of Chloroplast Coupling Factor 1*

Carlo M. Nalin and Richard E. McCarty

Selective Modification of an α Subunit of Chloroplast Coupling Factor 1*

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Received October 23, 1984

Abstract: Lucifer yellow (I-amino-N-[1-(vinylsulfonyl)phenyl]jasphtalimide-3,6-disulfonate), a fluorescent probe that can react covalently with sulfhydryl or amino groups, has been used to modify chloroplast coupling factor 1 (CF1). Conditions are described whereby Lucifer yellow selectively labels the α subunit of CF1 to the extent of about 1 mol of probe per mole of CF1. An especially reactive amino group is apparently labeled, and modification has little effect on the ATPase activity of the enzyme. Lucifer yellow is a useful probe for fluorescence energy transfer measurements. The distances between this probe and fluorescent and absorbing molecules attached to seven specific sites on the β, γ, and α subunits were determined. Those distances converge to a single location. In addition to providing further information about the structure of CF1, these results suggest that the α subunits of CF1 are not structurally equivalent.

Chloroplast coupling factor 1 (CF1) catalyzes ATP synthesis by using the energy of the transmembrane proton gradient across the thylakoid membrane. The enzyme loses its ATPase activity if a latent ATP synthase activity is expressed after treating the enzyme with detergents (44), reducing CF1 (6), or after heating CF1 in the absence of Mg++. Distinct subunits (α, γ, and β) in a stoichiometry of about 1:1:2 are involved. The molecular weight has been determined by various techniques (8): the 100,000 and the 120,000 were obtained by proteolytic digestion.
Lucifer Yellow Modification of CF₁

![Diagram of Lucifer Yellow Modification of CF₁]

**Figure 6:** Model for CF₁ showing the distances between the Lucifer yellow site (LY) and other sites on CF₁. The positions of all other sites are based on the work of Snyder & Hammes (1984, 1985). L, D, and S–S stand for the cysteinylic residues of the γ subunit.

bound to CF₁ relative to that of the probe in aqueous solution indicates that the probe is in a hydrophobic environment. The high degree of polarization of bound Lucifer yellow fluorescence suggests that the probe has limited rotational freedom.

occurs when CF₁ is bound to F₀.

Asymmetry induced by organization of the subunits and ligand-induced asymmetry by substrates and products may play a role in maintaining CF₁ in its active conformations and its catalysis (Kohlbrenner & Boyer, 1983). Although the reaction of CF₁ with Lucifer yellow was influenced by nucleotides, turnover of the enzyme did not appear to enhance the reactivity of the α subunits to the probe (C. M. Nalin, unpublished results). Thus, at least with respect to the site on α, catalysis does not seem to affect the asymmetry of the enzyme.

Future experiments with the Lucifer yellow modified enzyme will focus on the role of the unique α subunit in energy coupling and on changes in this subunit that occur when CF₁ binds to F₀.

**Acknowledgments**

We thank Dr. Mark L. Richter for preparing CF₁ lacking the ε subunit, the ε subunit, and CF₁ containing DMSM-labeled ε subunit. These efforts, as well as his conceptual contributions, were most helpful.

**References**

Postdoc in Cell Biology at Roche Institute for Molecular Biology
**From Post-doc to Senior Scientist**

**HIV Research: Protein Chemistry for Roche**

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**Purification and characterization of recombinant Rev protein of human immunodeficiency virus type 1**

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**ABSTRACT**  Recombinant Rev protein of human immunodeficiency virus type 1 has been expressed in *Escherichia coli* and purified by ion-exchange and gel-filtration chromatography. Specific binding of the purified protein to the Rev-responsive element of the viral RNA is demonstrated. Physical characterization of the purified protein by circular dichroism and intrinsic fluorescence spectroscopy indicate that the protein preparation is suitable for structural analysis. Circular dichroism measurements show that the protein is approximately 40–45% α-helix. Trp tryptophan fluorescence measurements suggest that the single tryptophan residue is located near the surface of the protein. Gel-filtration chromatography of the product action with viral RNA will depend on having a suitable supply of functional and structurally uniform protein. Cochrane et al. (25) reported the purification under denaturing conditions of a recombinant HIV-1 Rev having an N-terminal extension containing six histidine residues. Although the renatured HIV-1 Rev protein prepared by this method was shown to be active in a qualitative cell-based assay, this material was not suitable for structural analysis due to aggregation of the protein that occurs during refolding. It is not known whether the histidine cluster contributes to protein aggregation. More recently, Daly et al. (20) have reported purification of recombinant HIV-1 Rev by using ion-exchange and gel-
Characterization of Recombinant HIV-1 Tat and Its Interaction with TAR RNA

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Abstract: Recombinant HIV-1 Tat (Tat 1–86) has been purified from the cytoplasmic fraction of *Escherichia coli* without the use of protein denaturants or chaotropic agents. Chloroquine-mediated uptake of the purified protein into cells resulted in transactivation of the HIV LTR promoter. Tat retains 1.64 mol of Zn²⁺/mol of protein by atomic absorption spectroscopy. Circular dichroism measurements indicated that the structure of recombinant Tat contains 15–20% α-helix. Filter binding assays showed that Tat binds to a 63-nucleotide target TAR RNA with a dissociation constant (Kₐ) of 10 nM at 25 °C, 0.05 M ionic strength, pH 7.5, in a 1:1 Tat–TAR RNA stoichiometry. Non-electrostatic interactions provide the principal source of free energy of association. While the pH optimum occurs over a wide H⁺ concentration, the salt dependence of Kₐ indicates formation of a single ionic pair. UV-induced protein–RNA cross-linking produced a labeled Tat–TAR RNA adduct, indicating that direct contact occurred between the Tat protein and TAR RNA.

The Tat protein of human immunodeficiency virus (HIV) is a virally encoded protein expressed in infected cells. The role of Tat in viral replication (Aquat et al., 1985) and protein interactions in RNA binding little information about...
True Drug Discovery
Apoptosis research enters the ICE age

Recent elucidation of the structure of interleukin-1β-converting enzyme (ICE), a protease with sequence homology to a nematode protein associated with programmed cell death, opens a new chapter in the study of how proteases may control cellular suicide.

Structure 15 February 1995, 3(3):143-145
Role for Bcl-xL as an inhibitor of cytosolic cytochrome C accumulation in DNA damage-induced apoptosis

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Communicated by Sidney Udenfriend, Roche Institute of Molecular Biology, Nutley, NJ, April 21, 1997 (received for review January 24, 1997)

ABSTRACT Cytochrome C is a mitochondrial protein that induces apoptosis when released into the cytosol or when added to cell-free extracts. Here we show that cells that overexpress the Bcl-2-related protein Bcl-xL fail to accumulate cytosolic cytochrome C or undergo apoptosis in response to apoptotic stress. Coimmunoprecipitation studies demonstrate related proteins may regulate apoptosis by controlling cytochrome C release into the cytosol.

The present studies demonstrate that the Bcl-xL protein blocks IR-induced release of cytochrome C. Similar results have been obtained with other genotoxic agents. The results also demonstrate that cytochrome C binds directly to Bcl-xL.
Expanding skill-set

Drug-Protein Interactions for Target Validation

Second-Site NMR Screening with a Spin-Labeled First Ligand

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How drugs can be developed: Imagine all the skills that are needed!

Adapted from USFDA Website: http://www.fda.gov/ForPatients/Approvals/Drugs/default.htm
Key Lessons from My Time in Project Management

- Search out and try to work with ‘real experts’ for any particular topic:
  - Clinical trial designs, standards of medical care
  - Statistics of clinical trials and population stats
  - Technical operations
  - Commercial operations
  - Marketing and Sales

- Learn what is important from experts
  - It’s really all about teamwork!

- Collaborate, Contribute, Communicate
So what made me ‘successful’ in my roles?

- Ability to do the following three things well:
  - Collaborate
  - Contribute
  - Communicate
So, you want to work in a Pharmaceutical Company:

WHY?
Reasons (some) people give for NOT wanting to work in Pharma

- You have to follow SOPs
- You prefer to explore uncharted science
- You want to publish lots of papers
- You don’t like to deal with bureaucracy
- You like to write grant proposals
- You want a lab full of students and post-docs
- You want to give presentations at scientific congresses
- You don’t work well under timelines/deadlines
- You want to be ‘in charge’
My TOP TEN
Reasons to work in the Pharma Sector

1. Transform lives
2. Help patients
3. Create innovative drugs / therapies
4. Diversity
5. Work in strong teams
6. Be a leader
7. Travel, travel, travel
8. Fast paced scientific advances
9. No grant writing necessary
10. Use cutting edge technologies
Building a Career Path

**Academic Version**

Grad Student

Postdoctoral training

Assistant Professor

Associate Professor

Full Professor

Chaired/Distinguished Professor

**Key Skills:**

- Teaching
- Research
- Communications
- Academic Administration

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Building a Research Career Path

Pharma Version in Research

Key Skills:
- Research
- Communications
- Business Administration

Grad Student

Postdoctoral training

Laboratory Head (Discovery)

Group Head (Discovery)

Management Executive

Drug Development
Scientific Opportunities in Pharma Sector

some examples

**Biology**

- Cutting edge application of scientific discoveries
  - Proof of concept studies
  - Biomarkers
  - Pharmacokinetics

**Chemistry**

- Cutting edge discovery or application of processes
  - New molecular entities (NMEs)
  - New process chemistries
  - Analytics
Building an Alternate Career Path
Pharma Version Outside Research

Grad Student → Postdoctoral training → Laboratory Head (Discovery) → Group Head (Discovery) → Management & Executive

→ Marketing & Sales

→ Business Operations

→ Clinical Development

→ Regulatory
Other Opportunities in Pharma Sector

*just a few examples*

**Business**

- Value generating **application** of scientific discoveries
  - Commercial roles (marketing, market access)

**Communications**

- Interactions with various stakeholders
  - Medical writing
  - Medical Scientific Liaison

**Regulatory Affairs**

- Registration liaison to Health Authorities
IT’S ALL ABOUT YOUR SKILLSET

**Basic Needs**
- Smart, good technical basis in your field
- Committed to moving into new areas (be flexible)
- Collaborative, good interpersonal skills
- Good (make that GREAT) communication skills
  - Writing
  - Presentations
  - Conversations (formal and informal)

**Special Skills (depending on your specific role)**
- What are you really good at doing?
- What makes you a unique contributor?
Networking: It’s all about...

- Whom do you know?
- Whom do they know?
- Is there anyone else who can connect you to others outside your immediate sphere?

- And don’t forget to follow-up!
Resources

Search for information online

- Company websites
- Harvard Business Review
- VersatilePhD
- Cheekyscientist.com
- Google

And there are probably many other sources...
More Networking Advice....

- Reach out to experts for advice/help in your search
  - Use social network sites to find contacts (LinkedIn, etc)
  - Ask your contacts to help you meet more people

- Don’t rely only on company job postings
  - Consider internships as a proving ground
  - Connect to potential employers through attendees at conferences (poster presenters, speakers, etc)

- Expand your search horizons and look beyond the traditional career paths
Internships

- Think of it as a ‘mini post-doc’
- It’s also a great networking opportunity....
- And use it to build interviewing skills, too.
Mentoring

- A good mentor can help you identify the important questions...

- ...and help you find your own answers

- You too can be a mentor to young scientists!
Some things to think about for career development experiences...

- **Learn about yourself**
  - Reflect – especially know what you do **not** want to do
  - Ask questions before you say ‘yes’ (or ‘no’)
  - Find people who are willing to give you candid, constructive feedback

- **Be honest with yourself**
  - Know your strengths
  - Know your limitations (opportunities for development?)
  - Know your personal needs / interests

- **Be creative**
  - You may find what you need in unexpected places:
    - projects, positions, or people
Keys to Success (IMHO)

- Keep an open mind
- Learn (continuously!)
- Adapt to changes
My (Humble) Career Advice (once you get ‘there’)

- Seek advice and feedback
- Learn the workplace culture early
- Find a mentor with experience in the company
- Read and apply new learnings to your work
- Set stretch goals and measurable objectives
- Learn how to prioritize
- Be willing to try new ideas... and let go of unproductive ones
- Stretch your comfort zone with new assignments or opportunities
- Follow your gut
- Remain passionate about what you do
A few words specifically for grad students...

- Should you do a post-doc?

- Should you consider consulting jobs?
Pick a good advisor
Stay focused: commit to your job search as much as your research project
Reach for the top
And don’t forget to keep in touch
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Thank you!