

# Opportunities for the PhD in Biotech

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# Overview

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- Science at a Company vs. Academia
- Attributes for Success at a Company
- Biotech vs. Big Pharma
- Biotech : Innovation and Risk
- Drug Development 101
- Job Opportunities Outside of “Research”
- Getting Hired

# Science at a Company

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- Scientific endeavor on a project can be carried out at a scale that is very rare in a University setting
- Teams of competent people aligned toward a common goal can accomplish more than any individual scientist
- Discoveries can be translated into therapeutic opportunities with the potential to create new drugs and technologies
  - Understand molecular and cellular pathways defining a particular biology and how it goes wrong in disease
  - Create a drug to impact those pathways
  - Explore how that drug works in animals and humans
  - Design Clinical Program to prove that the drug is safe & effective
  - Register the drug with the FDA and Rest of World

# Differences Between Academia & Industry

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- *You will have access to far more resources, equipment, core facilities, and collaborative colleagues to advance your project*
- You will be required to work on projects of the company's choosing
- You may be asked to switch to (or add on) new projects
- Although you will report to one person, you will interact with many Scientists instead of a single PI
- Participate and present in cross-functional meetings where data is vetted and the future directions of a project are established by discussion and consensus
  - More heads are better than 1!
- You are likely to publish and attend scientific conferences

# Some Myths of Industry

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- You have failed if you don't pursue an academic position
  - *That's what some told me, but there are many, many incredibly competent people doing Science & Drug Discovery in Industry*
- The working day is 9-5
  - *Hard, effective work is expected and rewarded!*
- Compensation is dramatically better than academia
  - *Entry level scientist positions (3-5 year postdoc) are compensated similarly to Assistant Professors, but much better than post-docs, and there are stock options!*
  - *However, opportunity for advancement is more frequent and more rapid than Academia*
- You never get to publish
  - *I published more rapidly at Regeneron than anywhere else! Also, compensation is based on contributions beyond publishing*
- You can't move from Industry to Academia
  - *More and more, Universities value Industry experience and perspective, making a reverse move more likely*

# Attributes for Success at a Company

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- Team player who can collaborate effectively with others
- Ability to become interested in a wide variety of different scientific areas - learning is a continuous Life-long experience!
- Superb analytical, communication, and presentation skills
- All of us have particular skills that make us good Scientists, although my exact skill set may not be the same as yours
- Contribute *your* particular talent and expertise toward the common goal
- Success means that *your* project grows so that hundreds of people work on it!

# Biotech vs Big Pharma

Often more innovative, high-risk scientific approaches	Typically more traditional small molecule Drug Discovery, unless partnered with Biotech
More informal working environment, with a “we’re all in this together” spirit. A “do what it takes to get the job done” attitude that may provide more variety More likely to participate in decision-making process	Typically more hierarchical Employees can become pigeon-holed in a particular function. Larger organizations usually have more rules! Much larger experience base
More resources than Academia, but often partners with Pharma for expensive late stage clinical programs	Can bring huge resources to bear on a project, although there is always internal competition for resources
Can be acquired, have layoffs, or slowly go out of business	Can be acquired, or have periodic layoffs
More opportunities for advancement than Academia or Pharma if company grows Stock options can provide financial windfall if company successful	Base compensation often higher than Biotech, but usually doesn’t have as large a stock option upside Promotion may occur more slowly

# Career Opportunities Outside of "Research"

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- Preclinical Development
  - Immunoassays & Sample Analysis from Human Clinical Trials
  - Formulation Development
  - Pharmacology - Assessing Drugs in Animal Models
- Protein Sciences
  - Cell line generation to overexpress recombinant proteins
  - Protein characterization
  - New technology and assay development
  - Protein Manufacturing Process Development
- Program Coordination & Management
- Core Facilities
  - Methodology Oriented (DNA, in situ, FACS, Mass Spec, Biacore)
- Clinical
- Regulatory - understand FDA Guidance, liason for company to FDA, EU
- Scientific Writing
- Quality Control
- Business Development

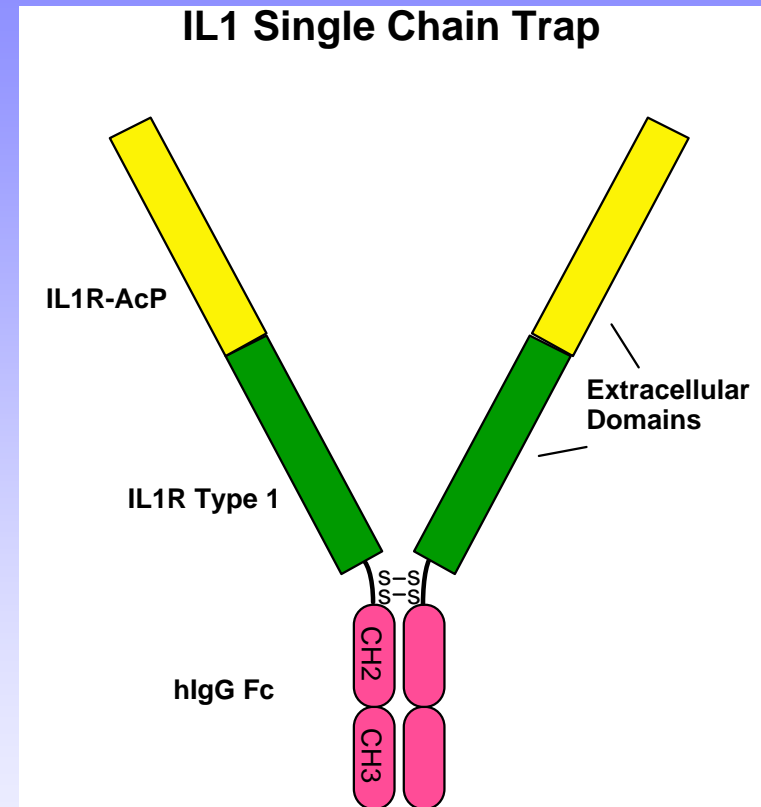
# PreClinical Development Checklist

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- BioMolecular Engineering
- Cell line Development - FASTR
- Process Development
- Formulation
- Assay Development
- Pharmacology
- Pharmacokinetics
- Toxicology
- Regulatory - IND = *Investigational New Drug Application*

# BioMolecular Engineering

- Create Trap candidates with different receptor order (eg:  $\alpha$ - $\beta$ -Fc,  $\beta$ - $\alpha$ -Fc,  $\alpha$ -Fc- $\beta$ ,  $\beta$ -Fc- $\alpha$ ), different fusion position in receptor sequence  $\pm$  linkers to increase flexibility
  - Evaluate for bioactivity, high expression level from CHO cells, clean folding
- $\Rightarrow$  *B- $\alpha$ -Fc with no extraneous linkers*

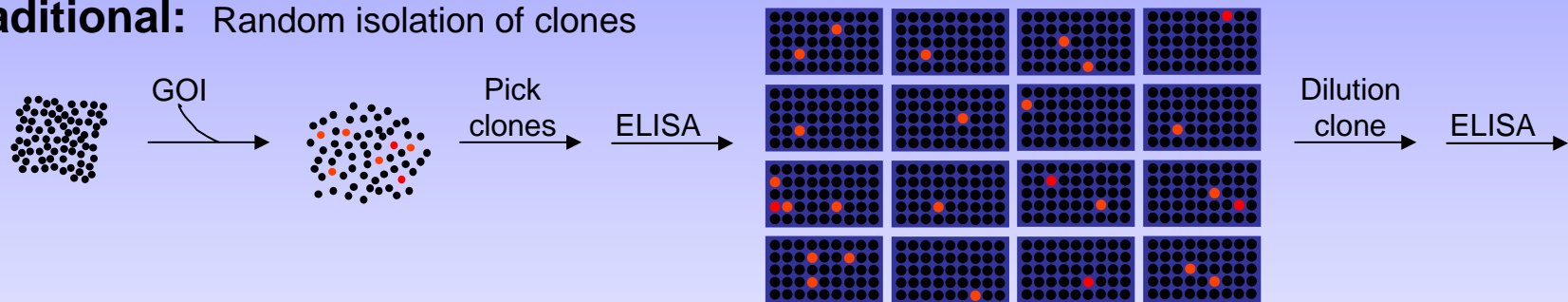


# Something Old, Something New

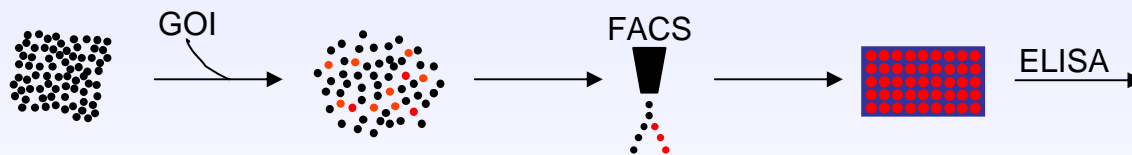
## Ways to Isolate Over-Expressing Cell Lines

How to isolate clones after transfection:

**Traditional:** Random isolation of clones



**FASTR:** Isolation based on expression / characteristic of secreted protein



# Process Development

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- Goal is to have protein secreted from CHO (Chinese Hamster Ovary cells) which have low viral burden and make human carbohydrate structures
- Batch-Fed Bioreactor Process - yield is 1-3 g/L after 10-12 days of culture
- Start at 2L scale, eventually to 10,000 L, which yields 10 kg at expression of 1 g/L
- 3 step purification process (Protein A, ion exchange, hydrophobic interaction chromatography) with up to 70% yield



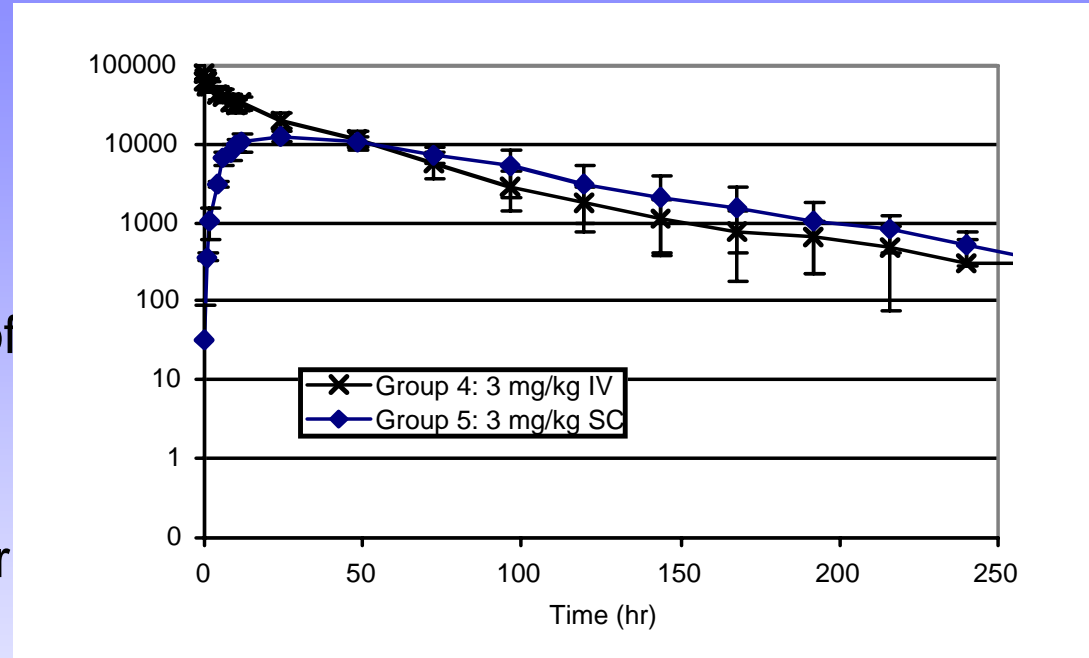
# Formulation

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- Desire high concentration with adequate stability to give  $\geq 2$  year shelf-life
- Add GRAS (*Generally Regarded as Safe*) excipients to stabilize protein from aggregation, deamidation, oxidation, fragmentation
  - Polysorbate, sucrose, amino acids, PEG
- IV formulations generally  $<10$  mg/ml
- Subcutaneous (SC) - 25-100 mg/ml
- IL1 Trap: liquid at 50 mg/ml or lyophilized at 80 mg/ml

# Assay Development/Pharmacokinetics

- Immunoassays to measure Trap and their complexes with target cytokines in plasma
- Assays to detect formation of antibodies against the Trap
- Use to measure PK - how the blood levels change over time, which often guides dosing frequency and active dose levels

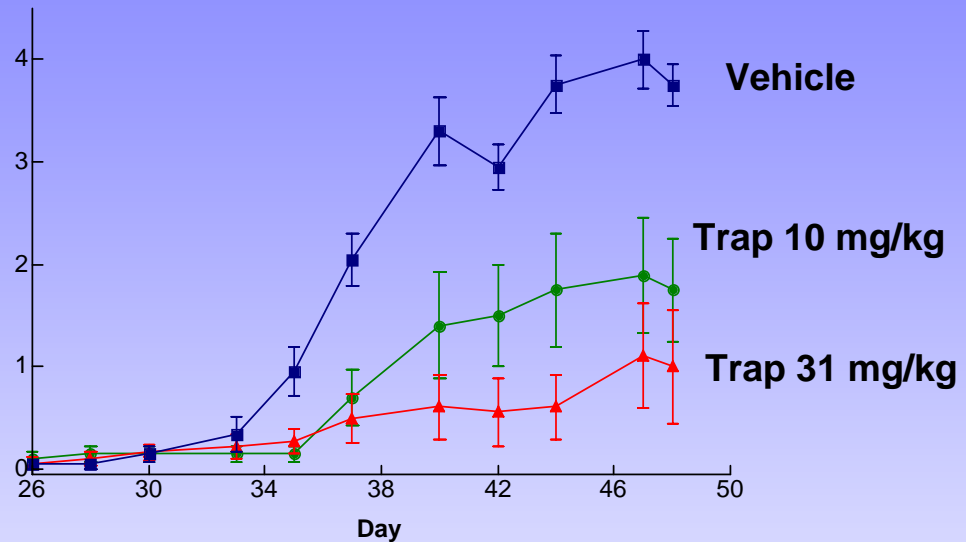


IV & SC pharmacokinetics in Monkeys

# Pharmacology: Murine Model of Collagen-Induced Arthritis

- CIA model in dba-1 mice is the most widely accepted model of rheumatoid arthritis
- Injection of bovine collagen II induces immune response that results in progressive autoimmune joint destruction
- Injection of zymosan IP at day 30 gives more robust and synchronous arthritis response
- Arthritis severity index grades inflammation, swelling, and deformity
- IL1 Trap blocks cartilage erosion, as well as joint swelling and deformity

Arthritis Severity Index



Vehicle



Trap



# Toxicology

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- Usually, new drugs are tested at high doses in 2 animal species to identify NOAEL (No Adverse Event Level) and MTD (Maximum Tolerated Dose)
- Test drugs at  $\geq 10x$  higher doses than expected human dose
- Many protein therapeutics have strict species specificity, and can only be tested in primates, but often KO data in animals is predictive of safety issues
- IL1RI KO shows no adverse phenotype except increased susceptibility to some types of bacterial infections
- Moreover, human proteins are often immunogenic in animals
- ⇒ *Immunogenicity in animals not predictive of Ab response in humans*
- IL1 Trap only binds primate IL1
- 6 week toxicology study in monkeys showed no evidence of toxicity, but an antibody response was observed after a few weeks that resulted in clearance of Trap from circulation
- No MTD observed, adequate safety to proceed to clinical trials!

# Regulatory

- FDA regulates testing of experimental drugs in people
- Must submit IND - Investigational New Drug Application
- Usually takes us ~1 year to complete, and may involve ~100 people
- Describes everything you know about the manufacturing and structure, PK, pharmacology, formulation, stability, toxicology, proposed clinical plan for Phase I trials
- FDA gets 30 days to respond, allowing you to go forward, or request more information, or to tweak your clinical trial design...



# Clinical Trial Overview

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## ***Phase I***

- Safety Dose Escalation in Volunteers or Patients

## ***Phase II***

- Dose Ranging Efficacy Studies to decide on dose and interval

## ***Phase III***

- Proof of Efficacy
- Treat larger number and broader range of patients to evaluate overall safety and look for less frequent adverse events (AEs)

⇒ As few as 4 clinical studies (each one a single “experiment”) could suffice to get a drug approved for use in humans!!

# Entry Level Positions in Biotech

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## *Research Post-Doctoral Scientist*

- Analogous to Academia, except more resources and mentoring available
- As in academic post-doc, a good publication record should allow return to Assistant Professor route

## *Pharmaceutical Post-Doctoral Scientist*

- Contribute to Clinical Development Projects or Core Technologies in ways that may not result in high profile publications
- Would lead to a career in Biotech/Pharma

## *Scientist*

- 2-5 years post-doctoral experience

## *Staff Scientist*

- 3 years experience following Post-Doc

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# Getting Hired

# Application & Hiring Process

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- Typically, job descriptions are posted, applications solicited
- Human Resource personnel (non-scientists) review applications, winnowing down to those that match job description, and pass on to Hiring Scientists
- Unsolicited applications to HR and Hiring Scientists can sometimes hit paydirt and find an opening before it's even listed

# CV & Cover Letter Essentials

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- Must communicate to multiple audiences
  - **Scientists** - trying to figure out if you have the raw materials that they can mold into a productive scientist and useful contributor
  - **Human Resources** - non-scientists checking for a match between your CV and a job description
- Usually your First & Only Chance to make a positive impression
- Should convey your
  - Intelligence & ability to communicate (Clear Writing = Clear Mind!)
  - Perspective of your field beyond your own project
  - Accomplishments - aimed at a non-expert and placed in context of the open questions in your field
  - Skill set - techniques that you *really* know as well as those for which you may have a passing knowledge and vocabulary
  - Enthusiasm!

# CV

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- Same CV can be used for all applications
- Need not be 1 page - can be 3-4 or longer
- Research summary
  - explain in 1 paragraph your projects and conclusions
  - aimed at someone who is not in your field
  - Can also briefly describe rotation & graduate research
- Clearly identify core skill sets
  - *Don't exaggerate - you'll get busted*
  - just because you have seen a mass spectrometer doesn't mean you should list it as a core competency!!!
- Presentations
- Awards/Grants
- Initiatives that you've undertaken outside your core requirements
- Publications - including submitted / in preparation
- Supervisory & Collaborative experiences

# Summary & Technical Skills

## **SUMMARY**

Ph.D. in Molecular Cell Biology

Expertise in the analysis of nuclear receptor signal transduction and transcriptional regulation. More than 12 years of scientific research experience in cell biology, virology, and immunology. Proven record of productivity (19 publications) as a result of strong technical skills.

## **TECHNICAL SKILLS**

Techniques in cell biology: *tissue culture, transfection and reporter gene assays, siRNA techniques, flow cytometry, cell cycle control and apoptosis assays.*

Techniques in molecular biology: *gene cloning, Southern blot, Northern blot, RT-PCR, real time PCR, DNA microarray.*

Techniques in biochemistry: *protein expression and purification, protein characterization, enzymatic assays, protein identification via mass spectrometry, affinity chromatography.*

Immunochemistry: *immunoprecipitation, immunofluorescence, immunohistochemical staining, immunoblotting, immunoelectron microscopy.*

Microscopy: *confocal microscopy, transmission electron microscopy of ultrathin section and negative staining samples*

Techniques studying nuclear receptor and extracellular receptor signal transduction pathways.

Techniques in virology: *virus multiplication maturation and release assays, vaccine*

# Cover Letter

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- Ideally should be customized for each application
- Should connect your skill set and experience to the job you are applying for so that it's easy for HR to understand and pass on to hiring scientist
- Should describe your project and findings in the broad context of your field - often the best way to convey to the Hiring Scientist that you were not just a skilled set of hands directed by your PI
- Rarely is an applicant “perfect” for the job - often we look for someone that appears to be smart, communicates well, and can grow into a job
- Therefore, it's usually a stretch to say that you can “make Regeneron a success...”
- More reasonable to emphasize your flexibility and ability to learn quickly...