Dr. Ramona Doyle is currently Vice President at the California Institute of Regenerative Medicine (CIRM) where she oversees teams working to advance cell-based therapies across multiple disease areas including hematology and oncology, neurodegenerative diseases, blinding eye diseases, as well as heart, lung and liver diseases. Dr. Doyle is also Clinical Professor of Medicine at UCSF where she volunteers her time as an attending physician in the Adult Pulmonary Hypertension Clinic. Prior to moving to CIRM in July 2015 Dr. Doyle was at Genentech for 6 years where she lead the Respiratory and Allergic Disease franchise in Product Development. At Genentech she built a highly regarded respiratory group, growing the group from 5 individuals based in the US to a team of 15 with members in the UK and China. At Genentech she successfully lead the filing and execution of global trials in asthma, COPD, IPF as well as championing other respiratory diseases, helping build the franchise from a single product and indication (Xolair for asthma) to multiple disease areas in respiratory and allergic disease. At Genentech she was the R and D lead for the $8 billion Roche acquisition of Intermune and its lead therapy for IPF, Esbriet.

Prior to moving to biotech Dr. Doyle was on the faculty at Stanford University for 12 years where she was the Medical Director of the Lung and Heart-Lung Transplantation Program and founded the PH program. She has served on the United Network for Organ Sharing (UNOS) Ethics Committee, and the Board of the American Lung Association, California Chapter. During her time at Stanford a generous donation from an anonymous family affected by PH led to the establishment of The Vera Moulton Wall Center for Pulmonary Vascular Disease, a center for research, education and clinical care of adults and children, which she Co-Directed. From 2007-2009 she was Medical Director at Gilead Sciences where she was responsible for programs in pulmonary hypertension and cystic fibrosis.

OBJECTIVES:
Participants should be better able to:

1. Understand the basics of the drug development process;
2. Understand the role of the private versus the public sector in drug development;
3. Understand the challenges of developing innovative drugs for patients with unmet need.
Drug Development: How It’s Done

Ramona L. Doyle, MD
Vice President, California Institute of Regenerative Medicine

NAMDRC Annual Meeting
March 3, 2016

Dr. Doyle has declared no conflicts of interest related to the content of her presentation.
Conflict of interest disclosures

- I am a Clinical Professor of Medicine at UCSF
- My spouse works at Genentech
From academics to biotech…my learning curve

Academic viewpoint (2006)

- Scientific research is the key to new treatments for patients
- My biggest impact on a patient’s health is in the clinic
- The most prescriptions for the most patients = the most profit for companies
- Drug development--how hard can that be?!
- Drug company profit margins are excessive!
From academics to biotech…my learning curve

Academic + industry viewpoint (2015)

- Scientific research is the key to new treatments for patients
- Drugs and policy make the biggest impact on patients’ health (The Affordable Care Act, HIV, PAH)
- High price drugs must deliver high value
- Development of innovative drugs is expensive and risky and often fails
- Drug company profit margins are “excessive”

Drug development – public and private sector contributions

- 70-90% of drug development is conducted by the private sector
- Scientific contributions from industry go beyond drug development and include basic and applied research
- Government funding plays an indirect role in drug development
- To replace industry funding with government funding the NIH budget would have to double
Drug development – public and private sector contributions

In industry scientific disciplines are practiced at a scale and level of competence and integration that far exceed the capabilities of academic institutions…

- Medicinal chemistry
- Process chemistry and formulation
- Drug metabolism and pharmacokinetics
- Safety science
- Technology innovations
- High throughput screening
- Structure based drug design
- Biomarker development and validation
- Biostatistics

Public versus private sector contributions in the 4 phases of R and D

<table>
<thead>
<tr>
<th>BASIC</th>
<th>DISCOVERY</th>
<th>CMC</th>
<th>Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>54% public</td>
<td>58% private</td>
<td>81% private</td>
<td>73% private</td>
</tr>
</tbody>
</table>

Discovery and CMC represent a series of complex and iterative processes called The Translational phase
Drug discovery and development is a lengthy and expensive process.

Costs ~ $1 billion per successful product

Likelihood of success varies by phase of development.

Figure 1 Phase success and LOA rates. (a) Phase success rates for lead and all indications. The rates represent the probability that a drug will successfully advance to the next phase. (b) LOA from phase 1 for lead and all indications. Rates denote the probability of FDA approval for drugs in phase 1 development.
Likelihood of success varies by disease area

Drug discovery and development is a lengthy and expensive process

SOURCE: PhRMA 2008, Stages of Drug Development Process and attrition rate of compounds as they travel through the drug development process over time.
Translation--the valley of death in drug development

DISCOVERY

(NIH $29 billion/year)

TRANSLATION = VALLEY OF DEATH

- Target validation
- Lead optimization
- Process chemistry
- Preclinical development
- Phase I clinical trial

PHASE II CLINICAL TRIAL

FDA APPLICATION AND APPROVAL

(Biotech/pharma $64 billion/yr)

Research Spending vs New Drugs Approved from 1997-2011

Source: InnoThink Center for Research in Biomedical Innovation; Thomson Reuters Fundamentals via FactSet Research Systems
Challenges in drug development

- It takes more than 10 years and over $1B to bring one drug to market
- Clinical investigation, premarket application, and postmarket safety monitoring and other obligations are heavily regulated?
- How sustainable is the current paradigm?
- How able, and willing, will society be to pay for novel therapies?
Challenges in drug development

- How to balance information needs of prescribers, public health officials, patients and payers... against a desire for speedy access to better therapies?

- How to keep the biomedical innovation sector alive with a viable business model... but also keep new innovations affordable for society

- How to translate the vast amount of new knowledge about human health and disease efficiently... rather than using the time-consuming, costly and inefficient methods currently in place

- Is there a more prominent role for the practicing physician and those in the academic biomedical sector?

Drug development in respiratory medicine—a tale of 2 diseases: HIV

1981 the CDC publishes a report from Los Angeles of five young gay men with fatal or *life-threatening PCP pneumonia*

2016: The life expectancy of Americans with HIV is higher than ever, almost reaching the life expectancy of the general population.

HOW DID WE GET FROM THERE TO HERE??
Drug development in respiratory medicine—a tale of 2 diseases: HIV

- **In 1983** NIH and Pasteur Institute researchers **find a virus** in the swollen lymph gland of an AIDS patient.

- **1987** New Yorkers form ACT UP to protest the $10,000 per year cost of AZT. It adopts the motto “SILENCE=DEATH.”

- **1988** Protests by ACT UP shut down the FDA. Within a week the FDA begins a **“fast-track” policy allowing public access to lifesaving drugs** still in clinical trials.

- **1991** AIDS becomes the leading cause of death in U.S. men aged 25-44.

- **1996** A treatment breakthrough: -- highly active anti-retroviral therapy or **HAART**

**Drug development in respiratory medicine—a tale of 2 diseases: HIV**

**WHY WE AREN’T THERE YET**

Of the 33 million people living with HIV, 3 million are getting treatment.

That's less than a third of those who need treatment right away.
Drug development in respiratory medicine—a tale of 2 diseases: severe asthma

Understanding of TH2-TH1 paradigm

Understanding/recognition of heterogeneity of asthma

Identification of patients who will respond to novel personalized therapies = a change for asthma classification and treatment

Table 1 | Summary of available data from trials of treatments directed at type 2 inflammation in asthma*

<table>
<thead>
<tr>
<th>Therapeutic antibody</th>
<th>Isotype</th>
<th>Targeted epitope</th>
<th>Relative affinity</th>
<th>Main effects in human asthma trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omalizumab</td>
<td>Humanized IgG1 IgE (CH2 and CH3 domains)</td>
<td>0.06 nM[^M]</td>
<td>Decrease in asthma exacerbation rates and reductions in maintenance doses of oral corticosteroids[^1, 2, 13]. Small effects on FEV1 and asthma symptoms.</td>
<td></td>
</tr>
<tr>
<td>Mepolizumab</td>
<td>Humanized IgG1 IL-5</td>
<td>NA</td>
<td>Decrease in asthma exacerbation rates when used to treat patients with asthma who have persistent eosinophilia despite corticosteroid treatment[^11, 13].</td>
<td></td>
</tr>
<tr>
<td>Benralizumab</td>
<td>Humanized IgG1 IL-5Ra</td>
<td>NA</td>
<td>Decrease in asthma exacerbation rates when used to treat patients with asthma who have persistent eosinophilia despite corticosteroid treatment[^11, 13].</td>
<td></td>
</tr>
<tr>
<td>Reslizumab</td>
<td>Humanized IgG4 IL-5</td>
<td>20 pM</td>
<td>Improvements in airway function and a trend towards greater asthma control when used to treat patients with asthma who have persistent eosinophilia despite corticosteroid treatment[^13].</td>
<td></td>
</tr>
<tr>
<td>Lebrikizumab</td>
<td>Human IgG4 IL-13 (IL-4Ra-binding epitope)</td>
<td>&lt;10 pM[^13]</td>
<td>No effect on FEV1 in steroid-naive individuals with asthma[^13]. Improvements in FEV1 and asthma exacerbations in steroid-treated patients with moderate and severe asthma[^13]. Greatest effects in patients with high serum periostatin levels.</td>
<td></td>
</tr>
<tr>
<td>CSK670586</td>
<td>Human IgG1 IL-13Ra1 and IL-13Ra2</td>
<td>300–400 pM[^13]</td>
<td>No improvement in FEV1 or exacerbations in patients with moderate to severe asthma.</td>
<td></td>
</tr>
<tr>
<td>Tralokinumab</td>
<td>Human IgG4 IL-13Ra1 and IL-13Ra2</td>
<td>185 pM[^13]</td>
<td>Limited effects on FEV1 but effective in reducing asthma exacerbations. Greatest effects in patients with high serum periostatin levels.</td>
<td></td>
</tr>
<tr>
<td>Dupilumab</td>
<td>Human IgG4 IL-4Ra</td>
<td>NA</td>
<td>Maintenance of asthma control and FEV1 when corticosteroid dose is tapered in patients with moderate to severe asthma[^3]. Effects are greatest in patients with high blood eosinophil levels.</td>
<td></td>
</tr>
</tbody>
</table>

*The table is restricted to data from Phase II trials or beyond. FEV1, forced expiratory volume in 1 second; IL, interleukin; IL-5Ra, a-chain of the IL-5 receptor; NA, not applicable.
Drug development in respiratory medicine—a tale of 2 diseases: severe asthma

Establishing a new treatment paradigm

- Classifying subpopulations on molecular mechanisms or treatment response—endotype
- Use of individual genomic, proteomic and metabolic profiles to predict diagnosis, treatment, response to treatment, prognosis
- Use of personal health data---from physiologic monitoring to genetic, metabolic, genomic signatures

Drug development in respiratory medicine—a tale of 2 diseases: severe asthma

- Establishing a new treatment paradigm allows for new definitions of success…beyond “control”
  - Improving lung function?
  - Minimizing damage to the lung, potentially modifying disease course?
  - Preventing disease?
  - All of the above?
Drug development in respiratory medicine—a tale of 2 diseases: severe asthma

- Biomarkers can positively impact on aspects of drug development

Lessons learned: why promising drugs fail

*Incomplete understanding of the pathophysiology of the disease*

Wrong target
- Hypothesis on criticality of target/pathway in disease is incorrect
- Safety issues associated with target

Wrong outcomes
- Clinical outcome measure not related to biology of target or not relevant in trial population
- Outcomes are not approvable by regulatory or health authorities or reimbursable by payors
- Trials cannot detect effect in appropriate patients
Lessons learned: why promising drugs fail

Wrong patients

• Patients too heterogeneous or cannot stratify by relevant molecular or clinical phenotypes

Wrong timing

• Internal portfolio risk/benefit not favorable
• External competition
• Regulatory risk tolerance
• Public interest/political environment

From biotech to government agency...my learning curve(ball) 2016

• Scientific research is the key to new treatments for patients
• Drugs and policy make the biggest impact on patients’ health (The Affordable Care Act, HIV, PAH)
• High price drugs must deliver high value
• Development of innovative drugs is expensive and risky and often fails
• Drug company profit margins are “excessive”
• New ways of developing therapies are needed, including innovative academic-public-private partnerships
California Institute of Regenerative Medicine

Specific Aims and Scope of Proposition

In authorizing these funds, Californians are expected to speed the delivery of stem cell therapies and cures to patients with unmet medical needs, including a priority for funding pluripotent and progenitor cell research that was not receiving timely or sufficient federal funding. Additional potential benefits to Californians include propelling California into a leadership position in regenerative medicine, establishing California as the premier international location to advance stem cell medicine, stimulating the economy, reducing healthcare costs by replacing chronic treatments with cures, and ensuring that the State has the opportunity to benefit from the potential receipt of royalty payments arising from CIRM-funded therapies or technologies.

About the Governing Board

CIRM is governed by a 29-member Governing Board, the Independent Citizens’ Oversight Committee (ICOC), which is composed of leaders in California from the patient advocate, biotechnology industry, and biomedical research sectors. In addition to its fiduciary responsibility to the people of California, the Board is charged with: (1) adopting scientific, medical, ethical, and intellectual property policies; (2) making final funding decisions on grant and loan awards; and (3) providing oversight of CIRM.

The CIRM Infrastructure Program builds real and virtual centers that provide the resources, expertise, and information necessary to more efficiently advance CIRM’s Programs and projects.

CIRM’s Education Programs support the development of a workforce qualified to drive achievement of the CIRM Mission, now and in the future.

(formerly referred to as Basic Biology): The Discovery Program supports the exploration of new, potentially groundbreaking stem cell-based therapies and technologies from their inception through translation.

The Translation Program supports the acceleration of early development activities necessary to prepare stem-cell-based therapeutic candidates, devices, or tools for clinical study.

The Clinical Program supports the acceleration high-quality clinical trials of stem cell-based therapies to address unmet medical needs.
CIRM's Development Portfolio
From academics to biotech to government…my learning curve

- Great science makes great drugs (and generally makes money)
- Question assumptions about what goes into getting effective and safe drugs to patients—it is harder than you think
- Do great science and communicate it
- If you care about patients contribute however you can to the effort of translating new scientific discoveries into therapies to patients who need them

“O.K., let’s slowly lower in the grant money.”
The future of drug development

- Bring down cost of developing new therapies using technology and more efficient conduct of clinical trials
- Better leverage public-private partnerships
- More understanding and better collaboration between everyone involved
  - Patients
  - Practicing clinicians
  - Academics
  - Industry
  - Public agencies

QUESTION 1

The majority of the cost of drug development is born by the government.

a. True

b. False
QUESTION 1

The majority of the cost of drug development is born by the government.

a. True
b. False

QUESTION 2

The translational phase of drug development includes which scientific disciplines?

a. Process chemistry
b. Drug metabolism and pharmacokinetics
c. Safety science
d. Biostatistics
e. All of the above
QUESTION 2

The translational phase of drug development includes which scientific disciplines?

a. Process chemistry
b. Drug metabolism and pharmacokinetics
c. Safety science
d. Biostatistics
e. All of the above

QUESTION 3

The average length of time from discovery to bringing a new drug to market is

a. 3 years
b. 5 years
c. 10 years
d. 15 years
QUESTION 3

The average length of time from discovery to bringing a new drug to market is

a. 3 years
b. 5 years
c. 10 years
d. 15 years

QUESTION 4

For every drug that comes to market how many fail during the course of development?

a. 3
b. 5
c. 10
d. 30
e. 100
QUESTION 4

For every drug that comes to market how many fail during the course of development?

a. 3
b. 5
c. 10
d. 30
e. 100

QUESTION 5

In the 1980s the largest share of new drug approvals has shifted from anti-infectives and cardiovascular drugs to anti-neoplastic drugs.

a. True
b. False
QUESTION 5

In the 1980s the largest share of new drug approvals has shifted from anti-infectives and cardiovascular drugs to anti-neoplastic drugs.

A. True  
B. False

QUESTION 6

Once a drug receives regulatory approval the development process is over.

a. True  
b. False
QUESTION 6

Once a drug receives regulatory approval the development process is over.

a. True
b. False