BioProcess™ INTERNATIONAL
CONFERENCE & EXHIBITION

Delivering Innovation in Biotherapeutic Manufacturing

Ralph Lambalot, PhD
Vice President
AbbVie Biologics Development & Mfg Launch

ibc Life Sciences
an informa business
www.IBCLifeSciences.com/BPI

Delivering Innovation in Biotherapeutic Manufacturing

Ralph Lambalot, PhD
Vice President
Biologics Development & Mfg Launch

AbbVie BioResearch Center
Worcester, MA

BioProcess International Conference
Boston, MA
October 22, 2014

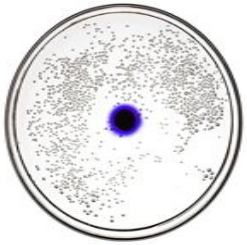
abbvie

AbbVie is a Leading Research-based Biopharmaceutical Company

We Aspire to Impact Patient Care in…

Liver Disease:
- HCV
- Fibrosis

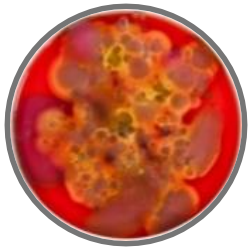
Immunology:
- Rheumatoid Arthritis
- Psoriasis
- Osteoarthritis
- Crohn's Disease
- Lupus
- Celiac Disease



Neuroscience:
- Alzheimer's Disease
- Multiple Sclerosis
- Parkinson's Disease

Oncology:
- Solid Tumors
- Hematologic Malignancies

Kidney Disease:
- Acute Kidney Injury
- Chronic Kidney Disease
- Fibrosis
- Diabetic Nephropathy



Other:
- Cystic Fibrosis
- Women's Health
- Ophthalmology

AbbVie's Biologics Discovery & Development Network

Spanning R&D, Operations, Regulatory Affairs and Legal

AbbVie Park, IL

Worcester, MA

Ludwigshafen, DE

Redwood City, CA

Barceloneta, PR

Tuas, Singapore

HQ
AbbVie Park, IL

Discovery
AbbVie Park, IL
Worcester, MA
Redwood City, CA
Ludwigshafen, DE

Process Development
Worcester, MA
Redwood City, CA
Barceloneta, PR
Singapore

API Manufacturing
Worcester, MA
Barceloneta, PR

ADC Conjugation
North Chicago, IL

Formulation, Fill/Finish
Ludwigshafen, DE
Barceloneta, PR

Pen Assembly, Packaging
AbbVie Park, IL

Manufacturing network further augmented by external CMO support worldwide

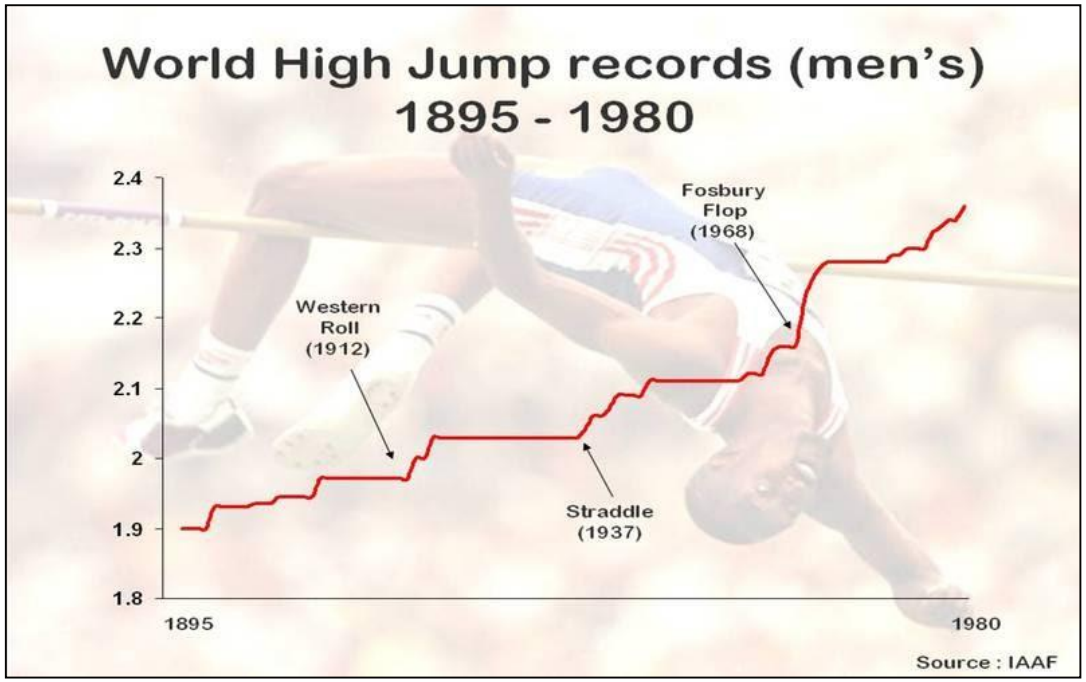
AGENDA

1. Innovation
2. Enablers
3. Barriers
4. Trends
5. Prospects

World High Jump records (men's) 1895 - 1980

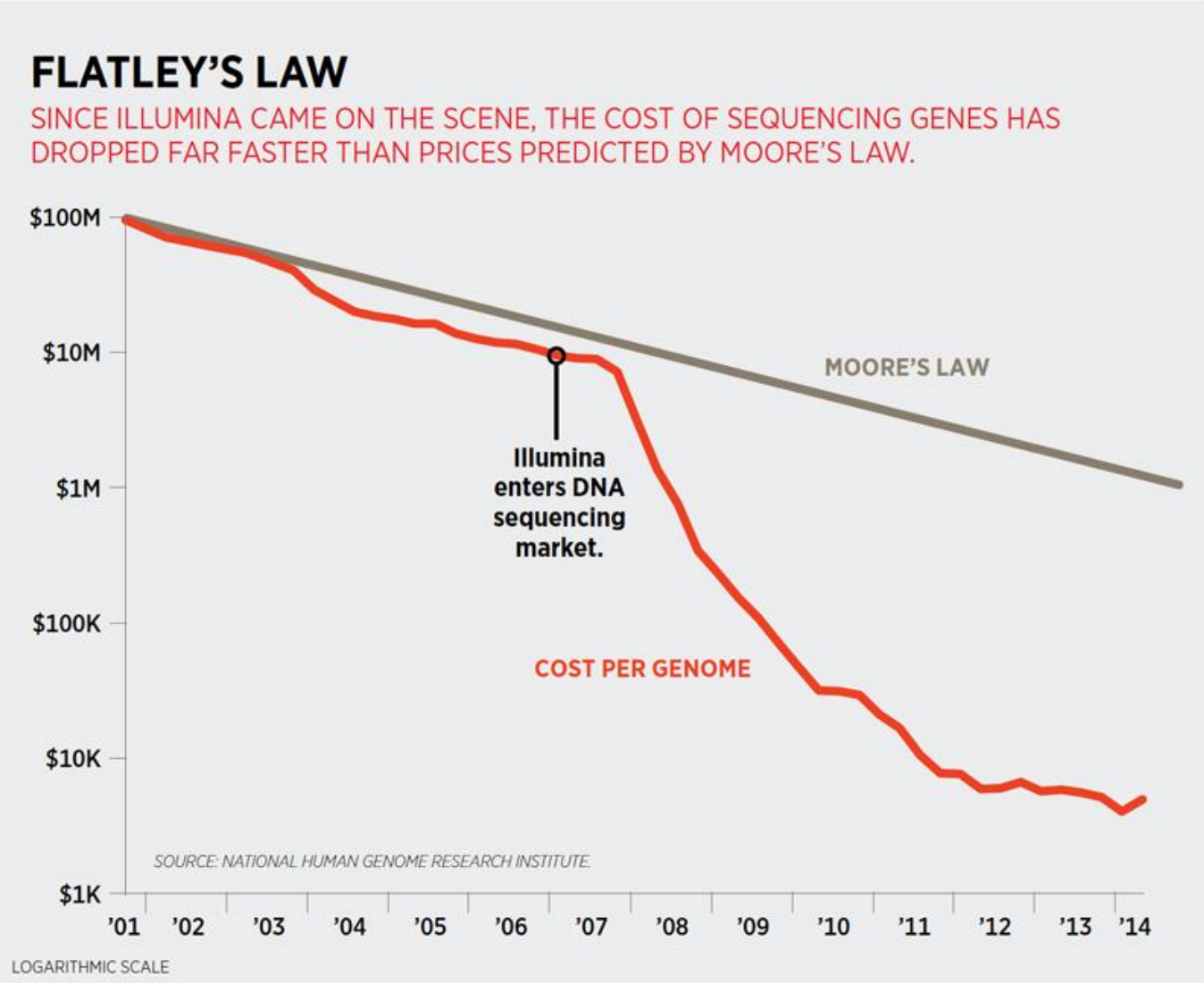
Disruption and Adoption

The Fosbury Flop: Floppers vs Straddlers



Olympic Year	Floppers	Straddlers
1968 – All competitors	1	Everyone else
1972 – All competitors	28	12
1980 – Finalists	13	3
1984 – Finalists	Everyone	0

Disruptive Innovation
Next Generation DNA Sequencing



FORBES 8/20/2014

INNOVATION

"If your business is not changing, it's not growing."
"If your business is not growing, it's dying."
unknown

What is it?

- A **change** made to something already established
- The introduction of **a new method, idea, product,** etc.

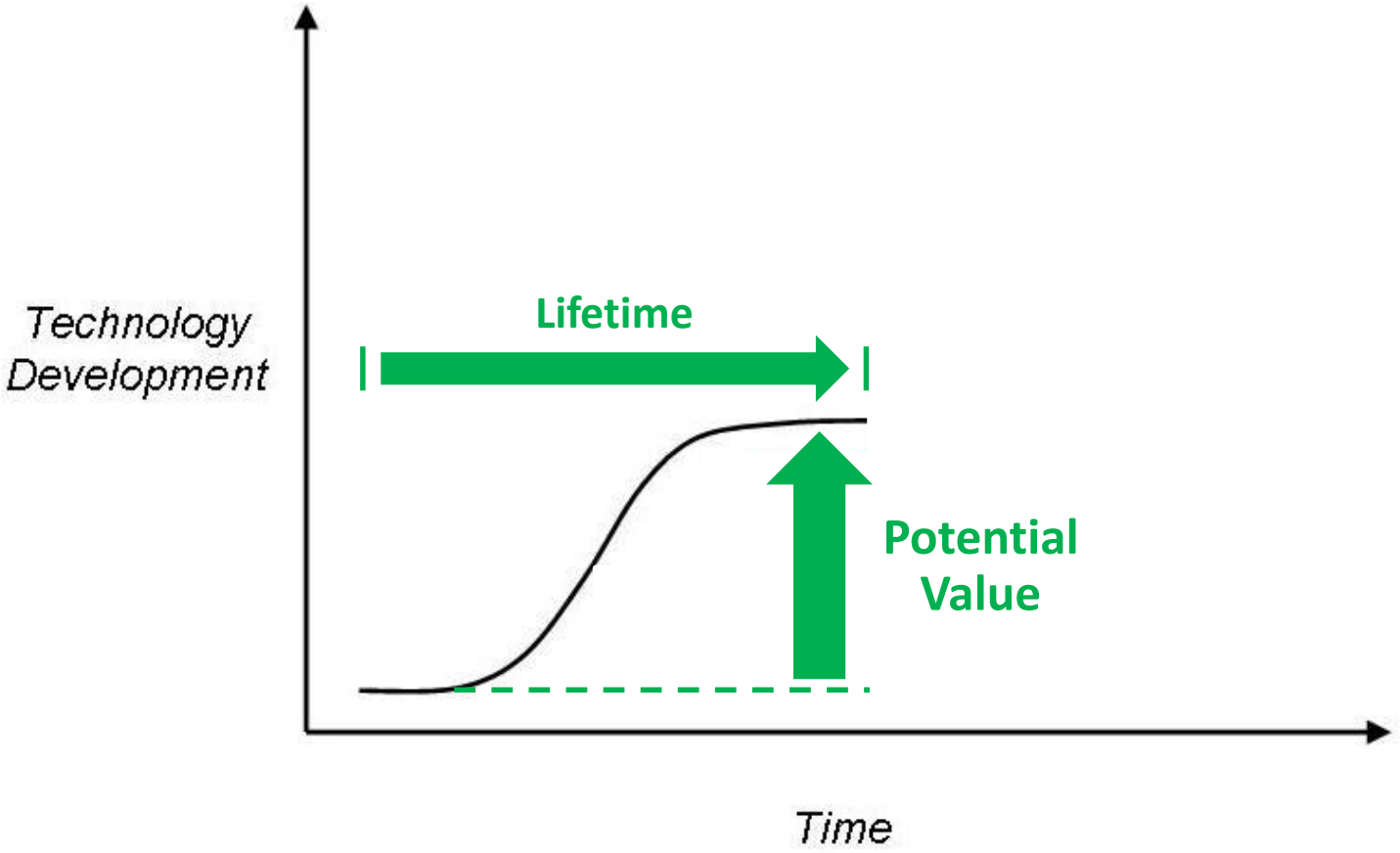
What do we expect from it?

- Favorable **differentiation** from our peers and competitors
- Increased **value**, efficiency, effectiveness, etc.
- Improved **performance**

Why do it?

- To **remain relevant** at a minimum
- To **secure an advantage** in the marketplace ideally

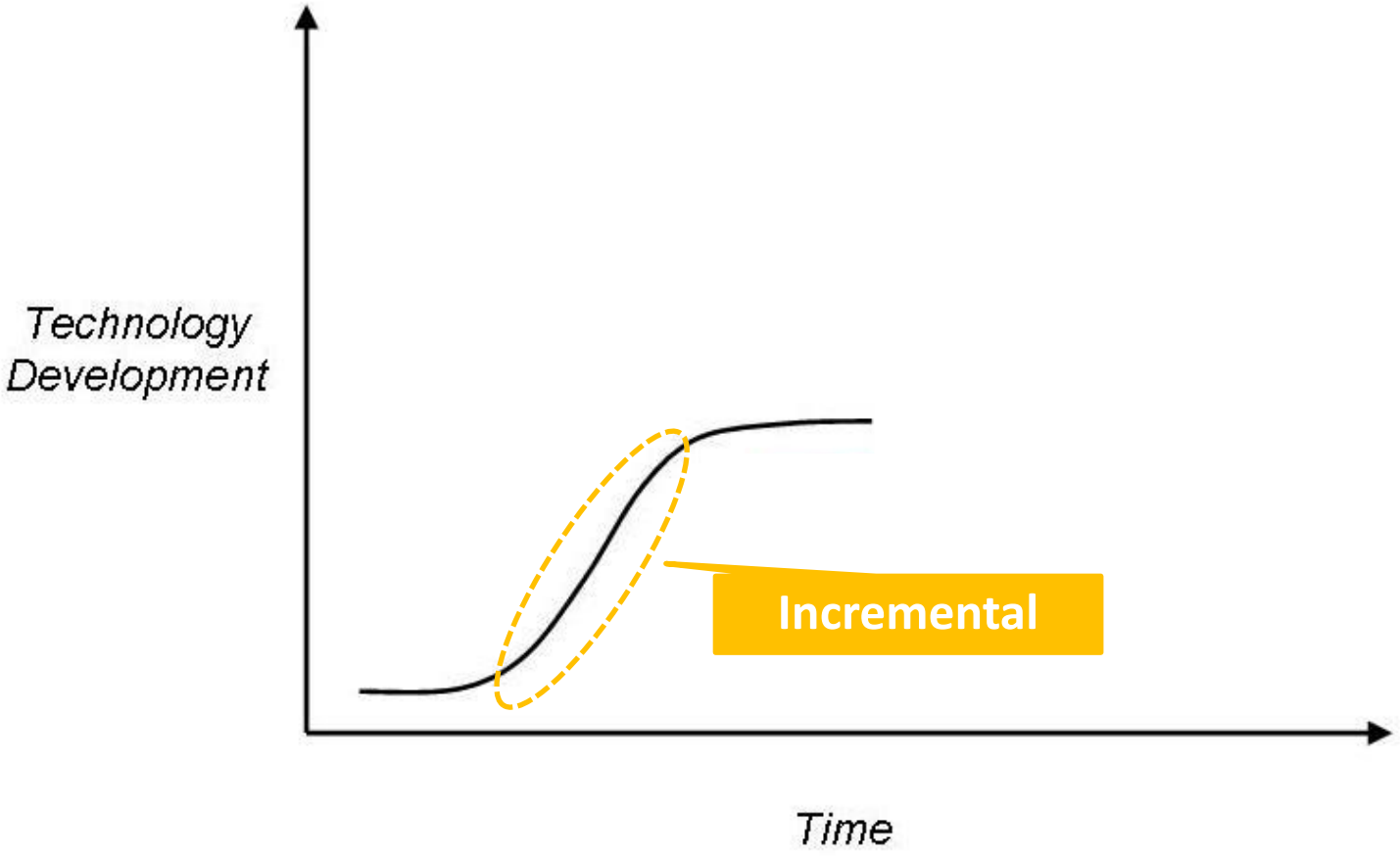
Innovation S Curve



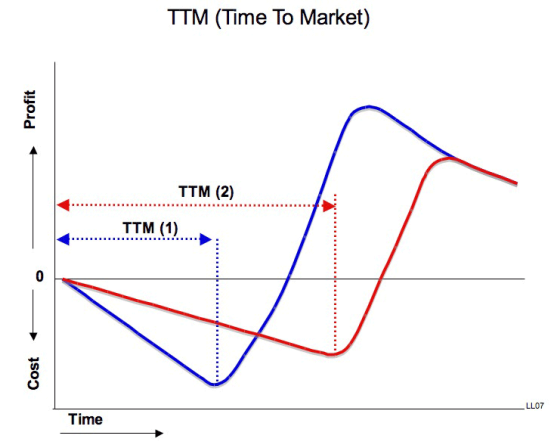
Types of Innovation

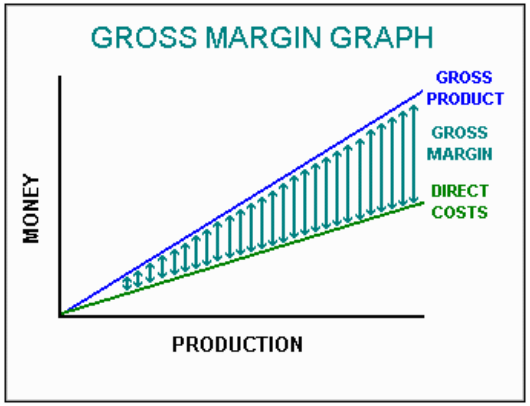
Incremental

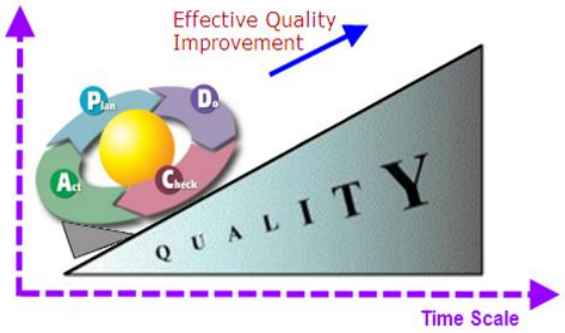
– Routine continuous improvement



Continuous Incremental Improvement







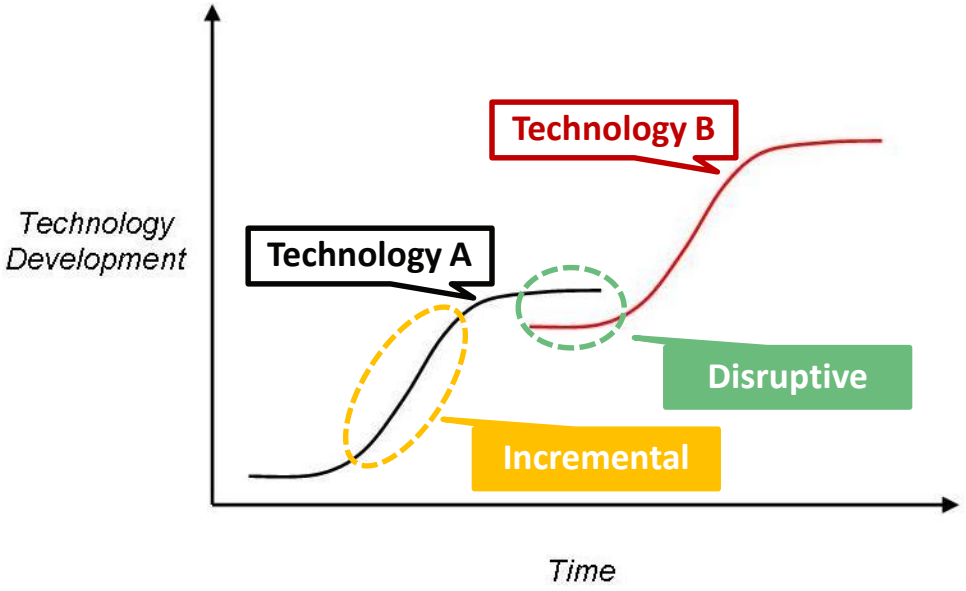
Types of Innovation

Incremental

- Routine continuous improvement

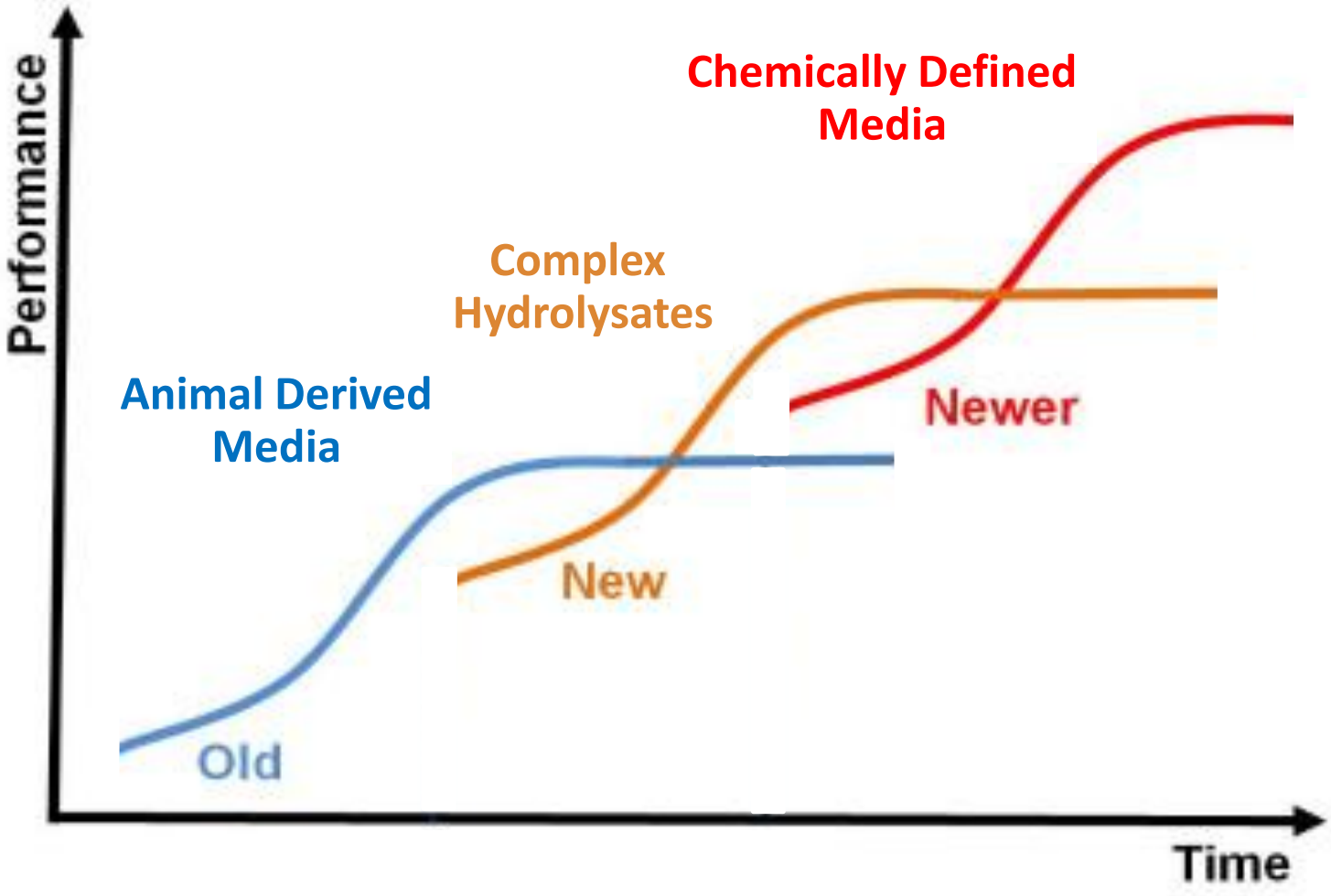
Disruptive

- Breakthrough therapeutic modalities
- Transformative manufacturing platforms



Innovation S Curve

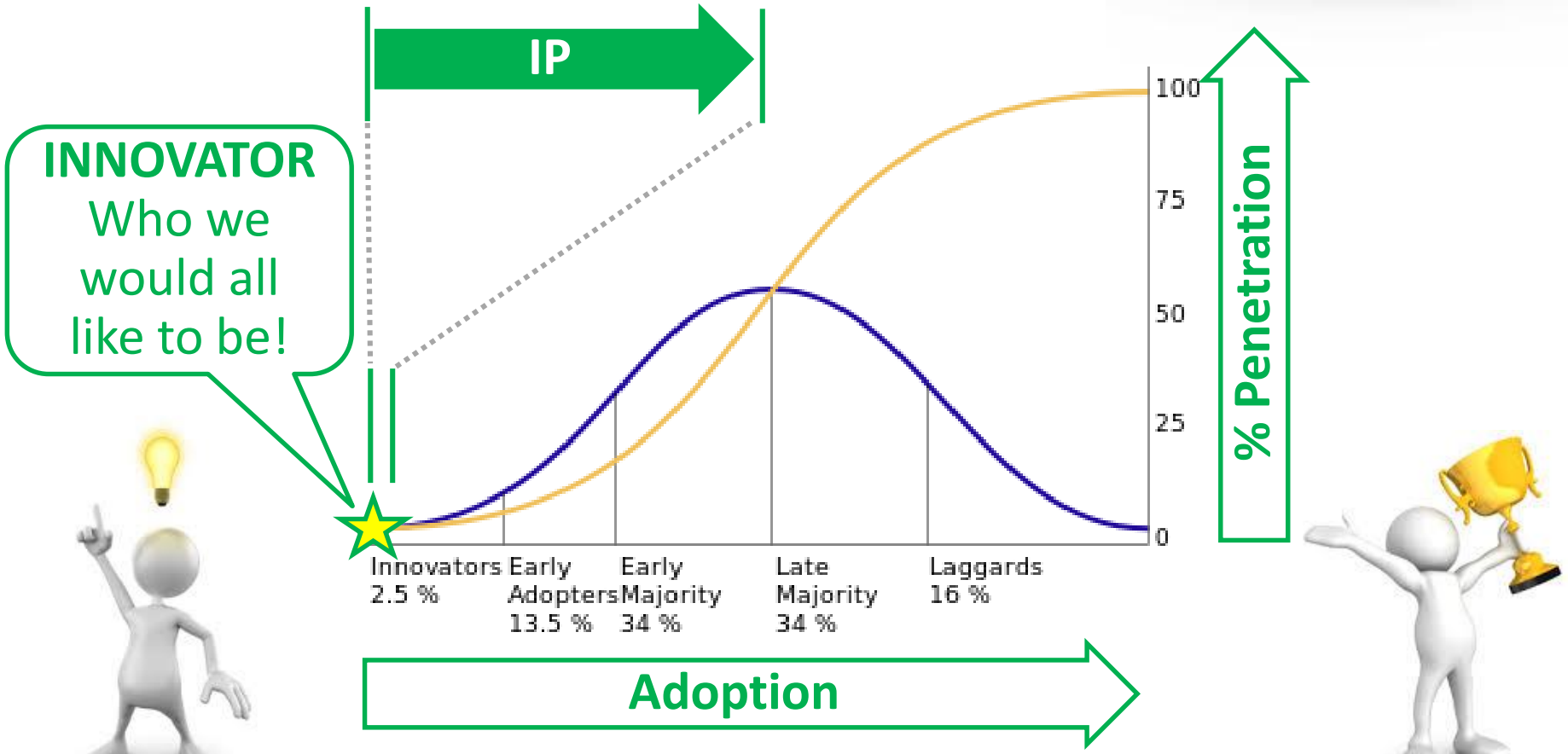
Waves of Successive Innovations



Innovation S Curve (2)

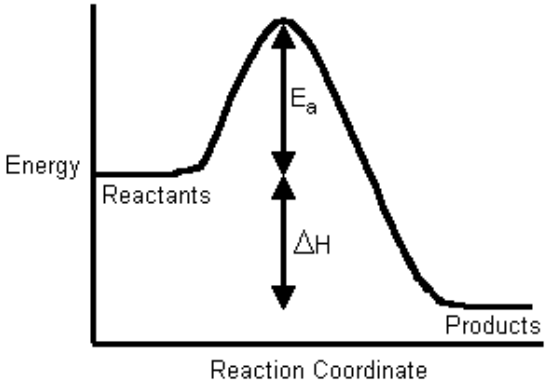
"Diffusion of Innovation" by Everett Rogers

Exclusivity = Advantage

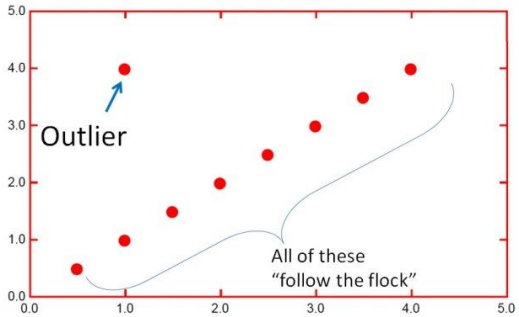


Enablers of Disruptive Innovation

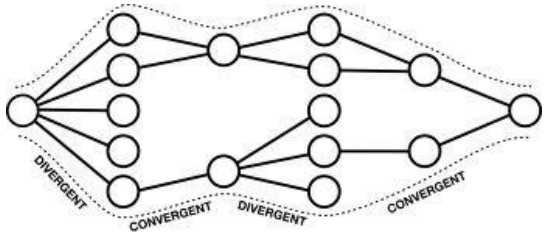
Initiative



Non-Conformity



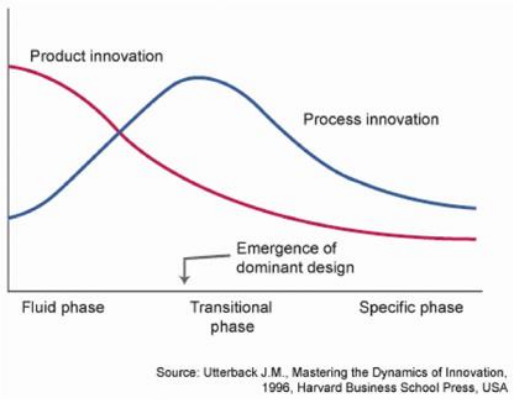
Collective Intelligence



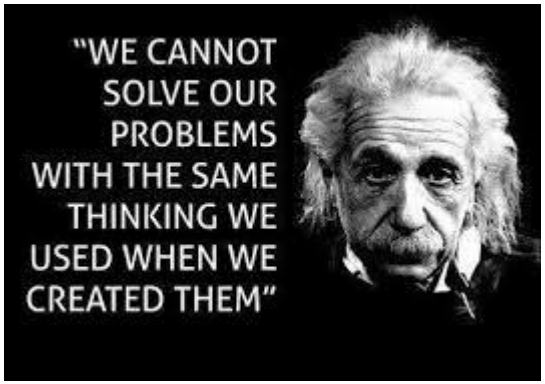
Marnix Assink, (2006) "Inhibitors of disruptive innovation capability: a conceptual model", European Journal of Innovation Management, Vol. 9 Iss: 2, pp.215 - 233

Barriers to Disruptive Innovation

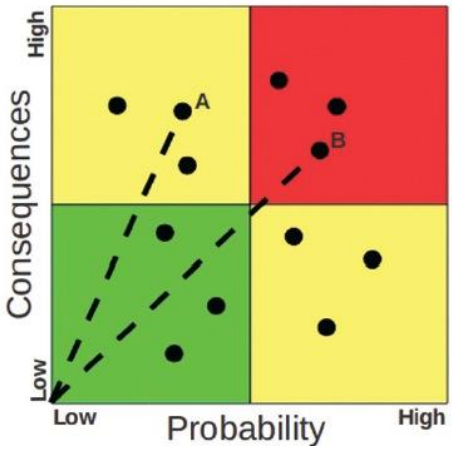
Successful Dominant Design



Obsolete Mental Models



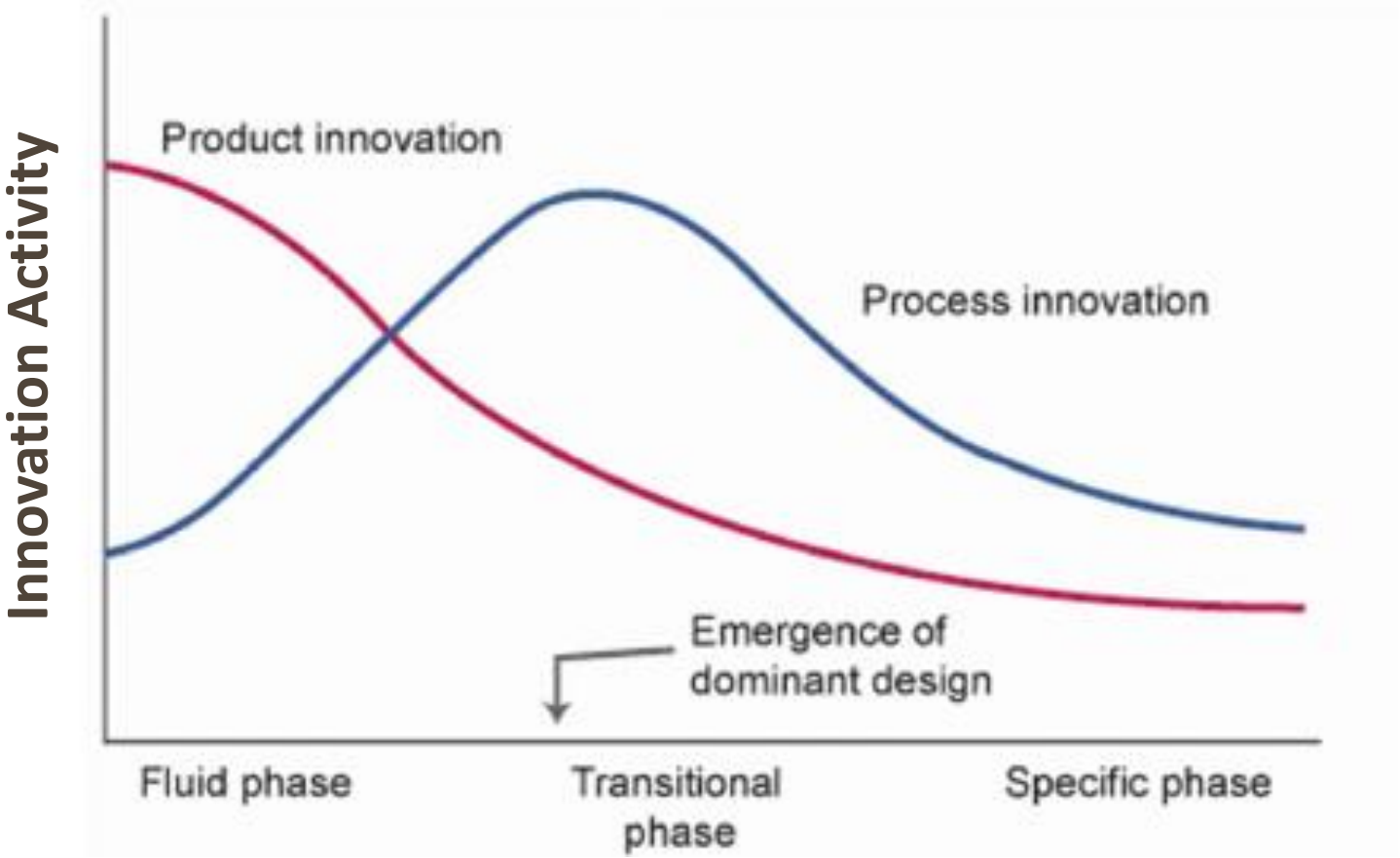
Risk-Averse Culture



Successful Dominant Design

Product and Process Life Cycle Management

Source: Utterback J.M., Mastering the Dynamics of Innovation, 1996, Harvard Business School Press, USA



Early Clinical **Late Clinical** **Launch**

Barriers to Innovation in BioProcess Manufacturing

Questions to ask ourselves:

- What successful **dominant designs** may be impeding our progress?
- What **established paradigms** may be on their way to obsolescence?
- What are the sources of **risk aversion** in our industry?

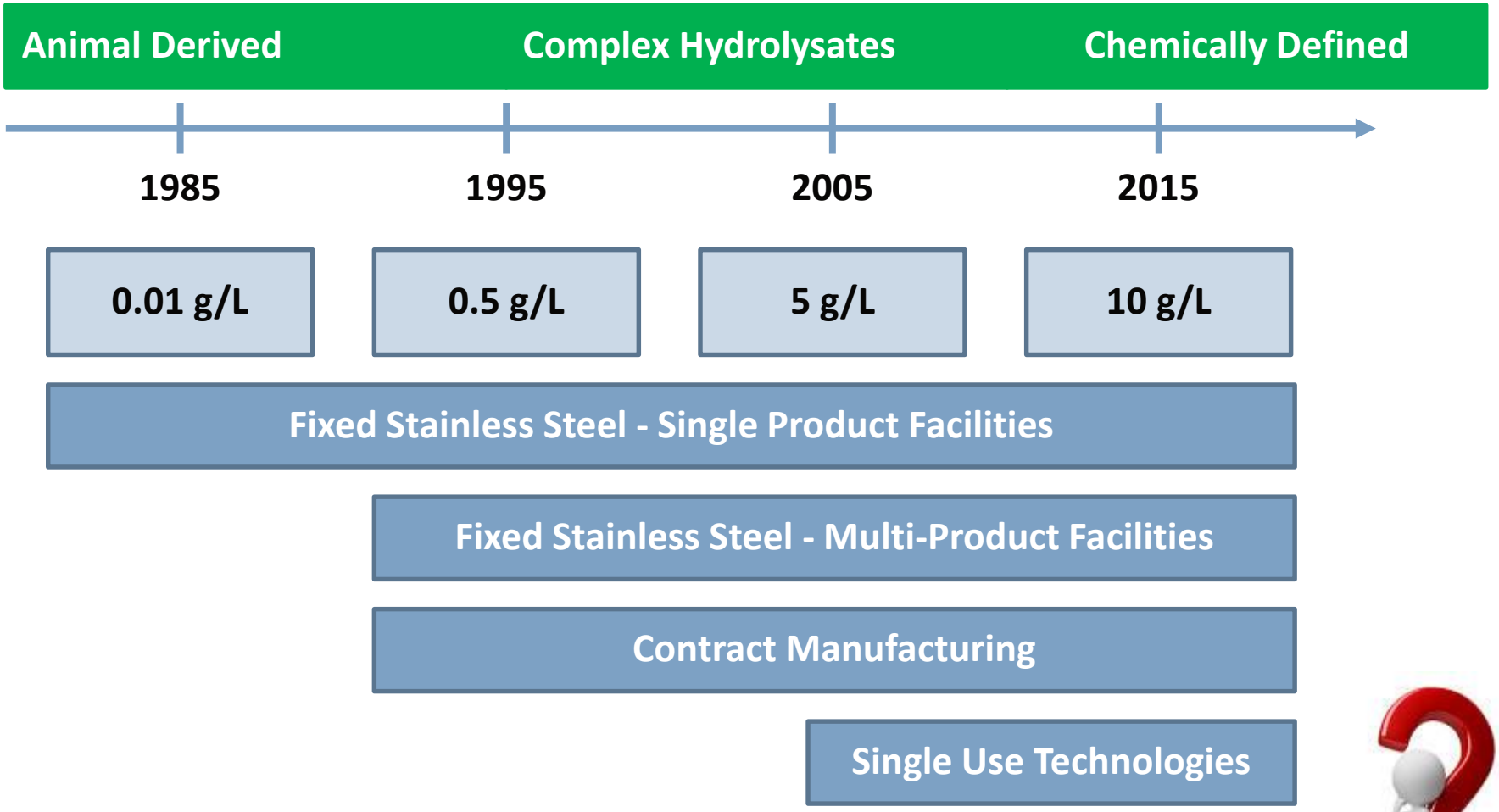
Trends

1. Manufacturing Technologies
2. Multi-Specifics
3. Antibody Drug Conjugates
4. New Modalities

Trends
Manufacturing Technologies

Trends

The Co-Evolution of Culture Media, Expression Titer, COGS and Facilities



Adapted from Odem, www.ispe.org/new-jersey/12-sep-2013-future-biologics-manufacturing.pdf

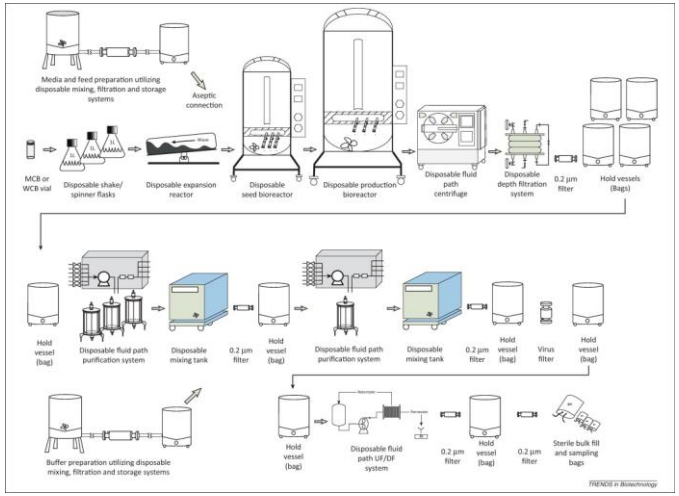
Current Trends

Single-Use Technologies

Filters

Bags

Bioreactors



Single-Use Process Trains

Columns

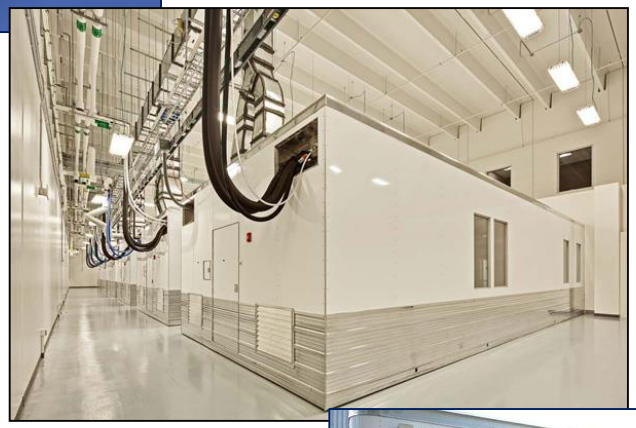
Today's Outlier could be Tomorrow's Norm

The Modularization of Facilities

Cabinets

Future Prospects:

- Distributed mfg networks
- In region mfg
- Scale-out vs scale-up
- Deferred CAPEX
- Platform validation



Indoor Modules
Box-in-Box

Mobile
Modules

MIT team receives $10.4 million grant from DARPA

With the grant, MIT's Biomanufacturing Research Program aims to develop new technologies that can rapidly manufacture biologic drugs on the battlefield.

"This DARPA program aims to manufacture biologic drugs on demand in a forward-operations setting, where resources are often limited. Making drugs available within 24 hours could save lives," says J. Christopher Love, an associate professor of chemical engineering, a member of MIT's Koch Institute for Integrative Cancer Research and lead investigator on the program.

This timing is unheard of, as such drugs now take six to 12 months to manufacture," he adds. ***"To make and release such medications on fast timescales will require orders-of-magnitude improvements on today's manufacturing practices. The goal for BioMAN is to transform biologic drug manufacturing from a time-consuming, stepwise process to a tightly integrated one for small-scale production."***

Barriers to Innovation in BioProcess Manufacturing

Mobile Modular Single-Use Facilities

Questions to ask ourselves:

- What successful **dominant designs** may be impeding our progress?
  - Batch processing continues to be very successful
  - What about continuous biomanufacturing?

- What **established paradigms** may be on their way to obsolescence?
  - Fixed Stainless Steel is established, but far from obsolete
  - Single-use, modular and mobile expands our tool box

- What are the sources of **risk aversion** in our industry?
  - Do bricks and mortar provide a greater sense of security?

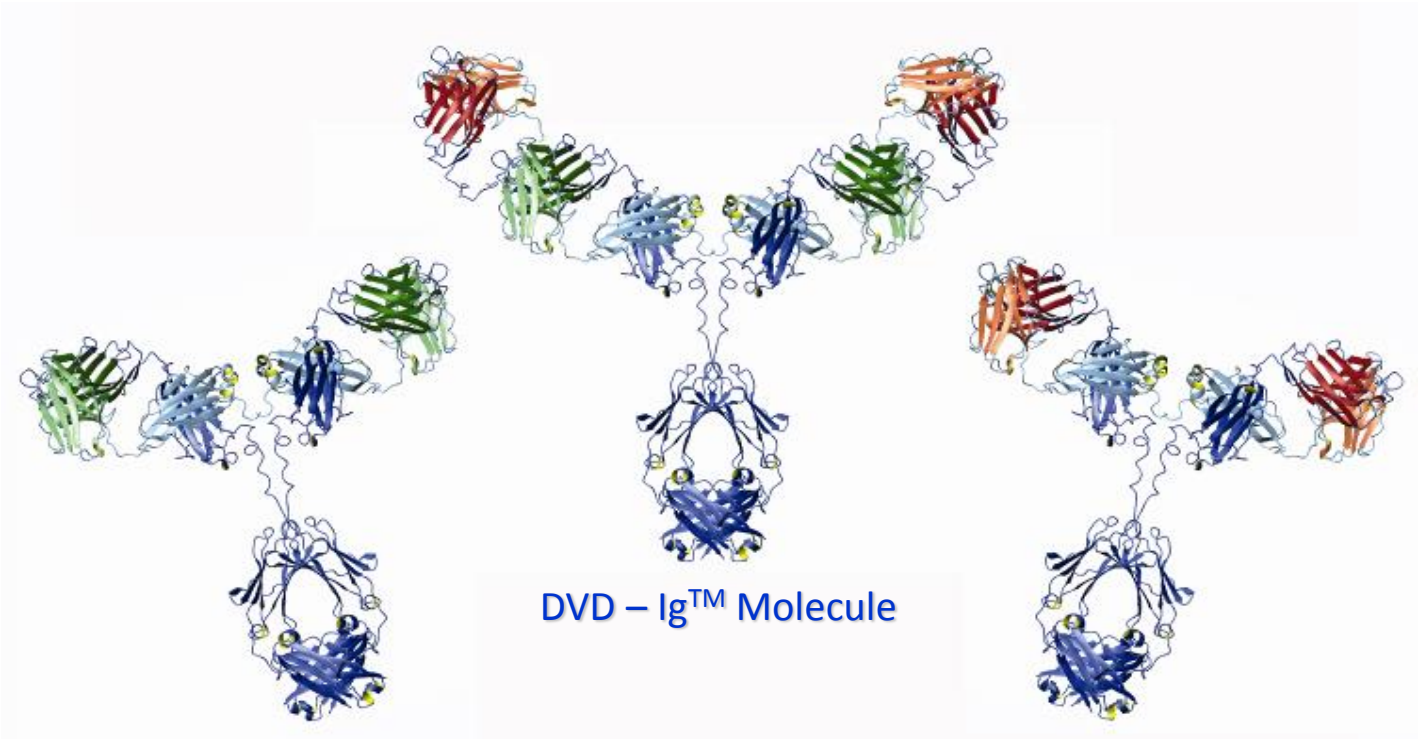
Trends

Multi-Specifics

Current Trends

Nature Biotechnology 25, 1290 - 1297 (2007)

Multi-Specifics: Dual Variable Domain-Ig (DVD)

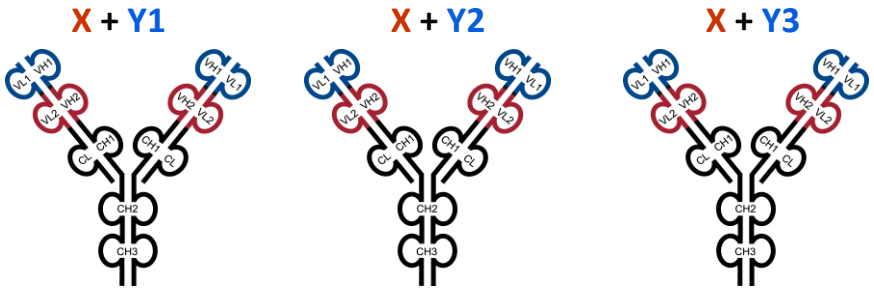


- Maintains symmetry of the mAb
- Constructed of native sequences
- Modular design
- Amenable to "***rapid iterative prototyping***"

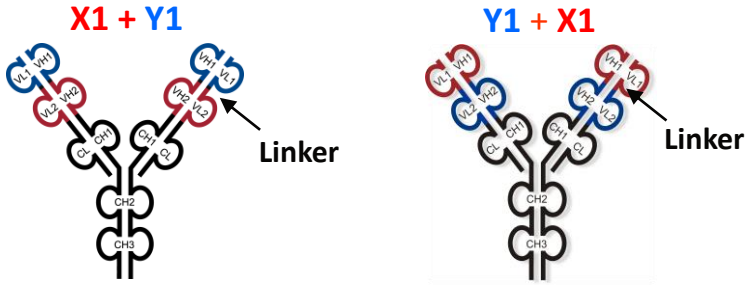
Current Trends

Multi-Specifics: Dual Variable Domain-Ig (DVD)

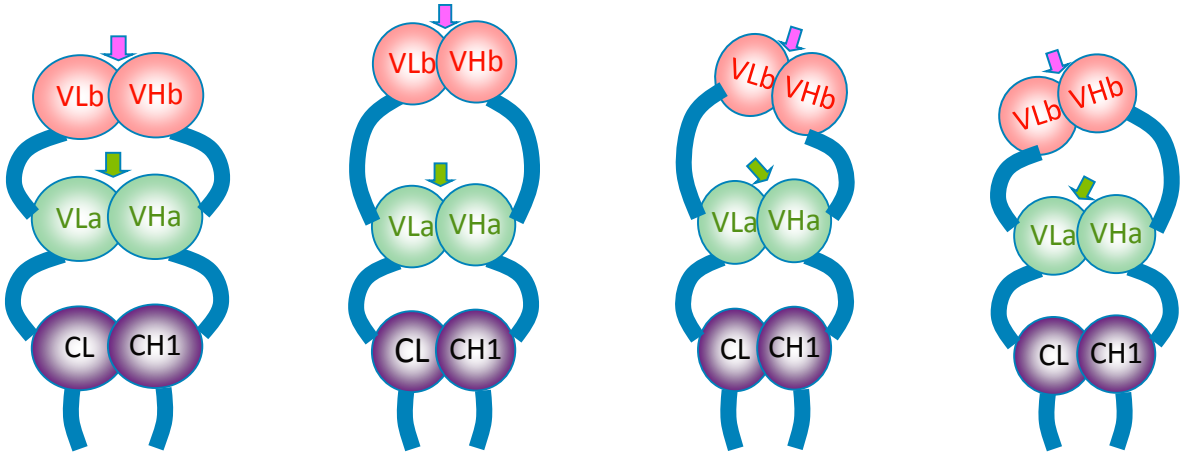
1. Domain Combinations (add new functionality)



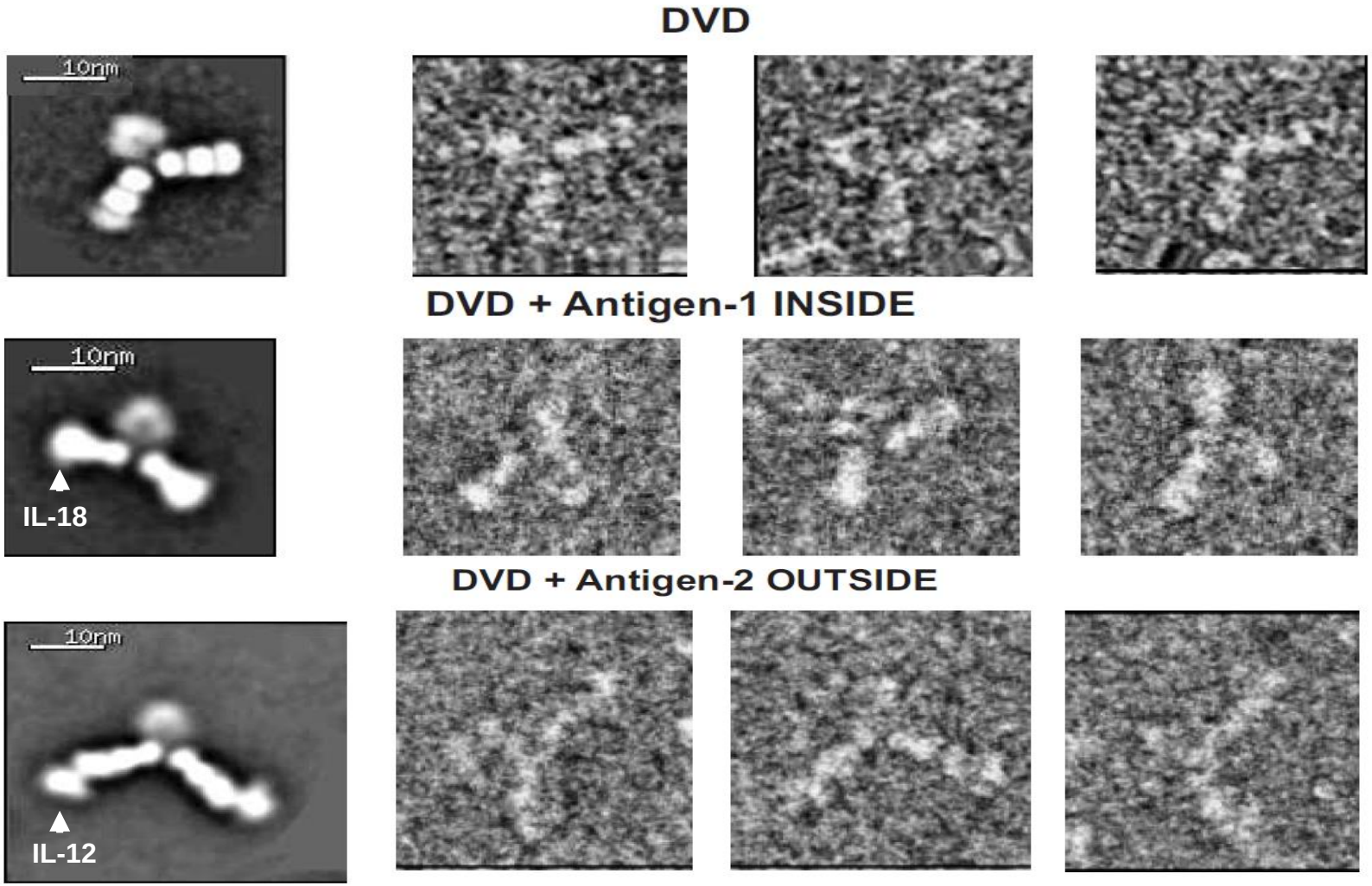
2. Domain Orientations (reveal new functionality)



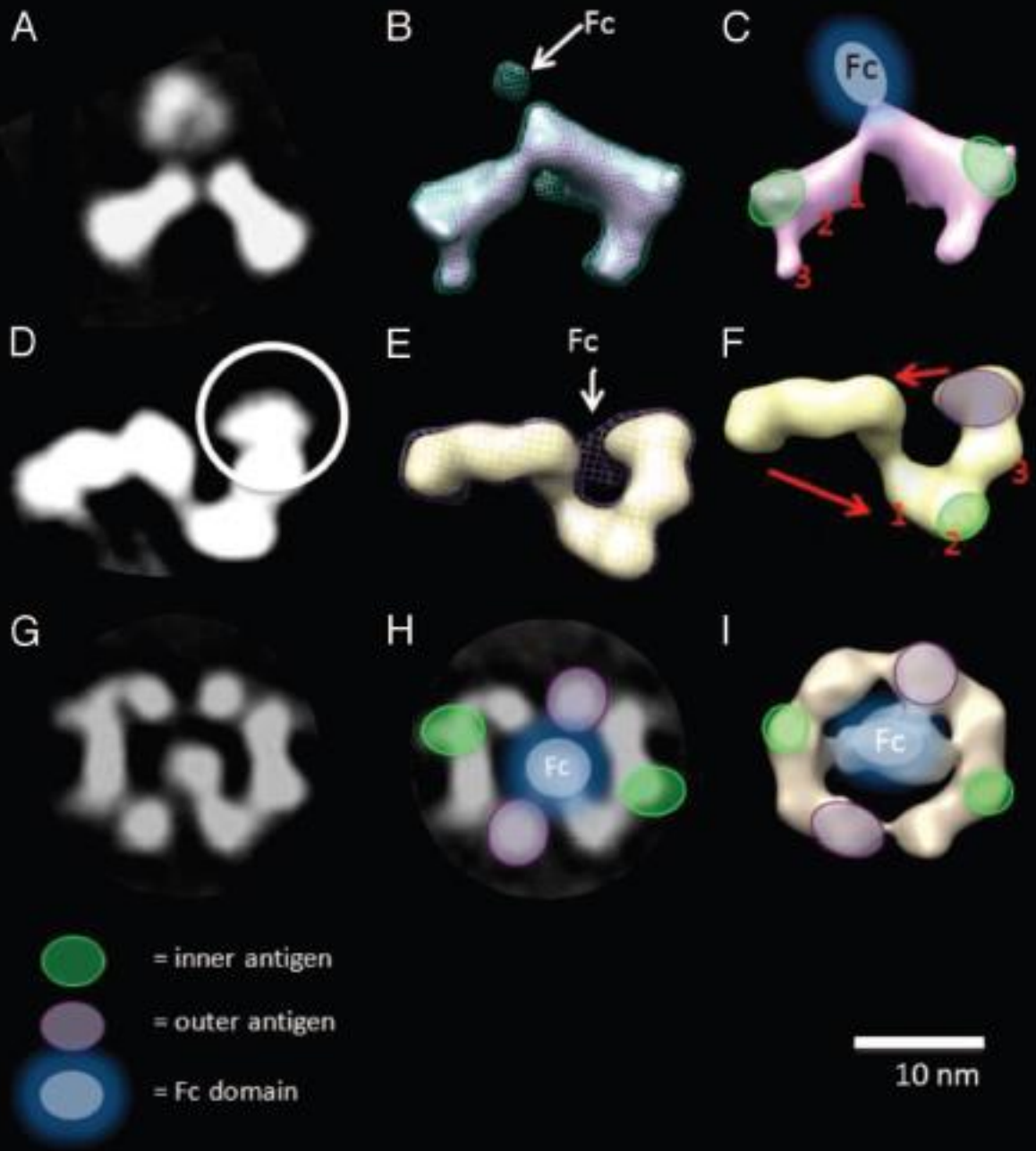
3. Linker Combinations (optimize functionality)



NanoImaging (Transmission Electron Microscopy, TEM)
Visualizing DVD-Ig flexibility

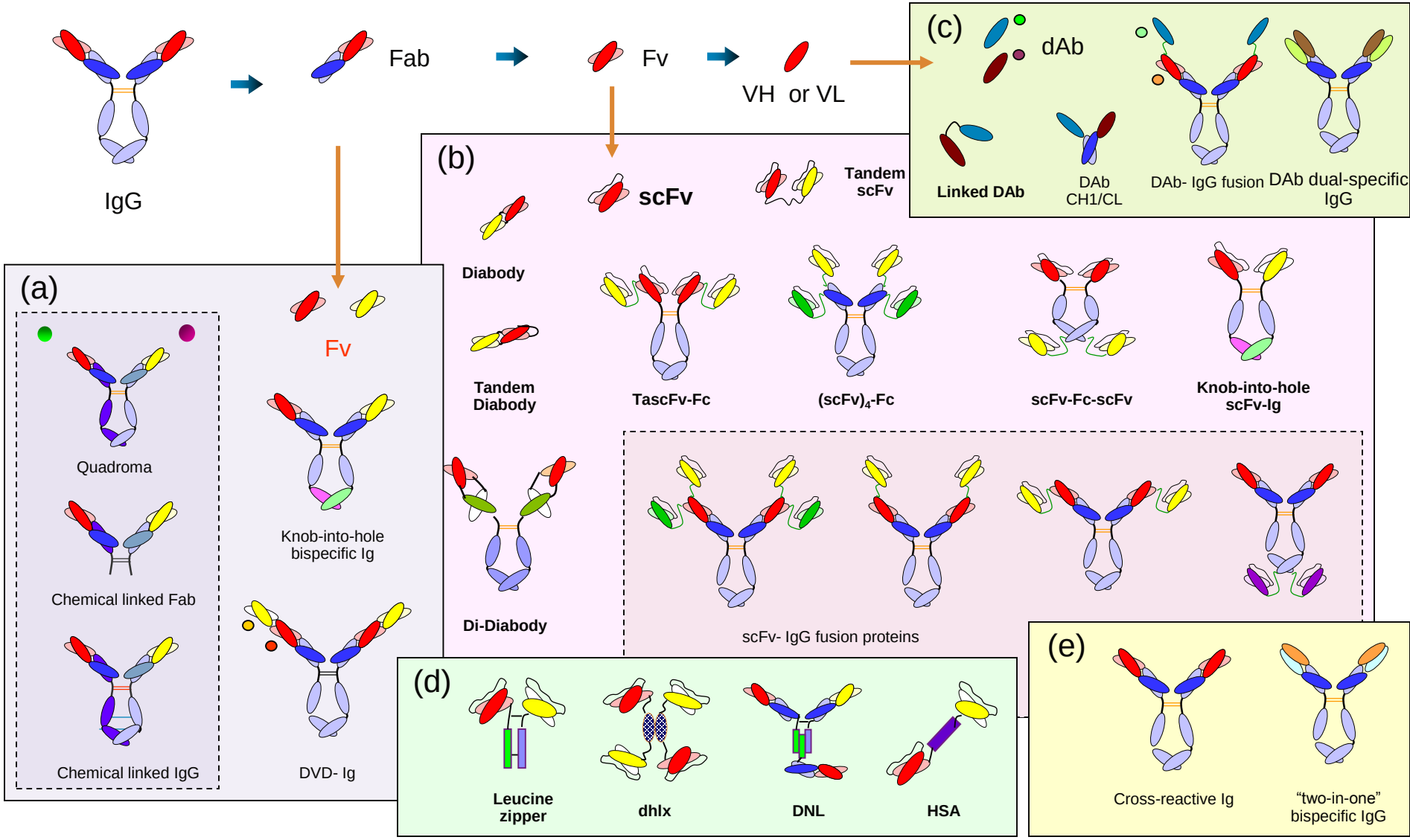


mAbs 5:3, 364–372; May/June 2013



mAbs 5:3, 364–372; May/June 2013

Current Trends
Multi-Specifics

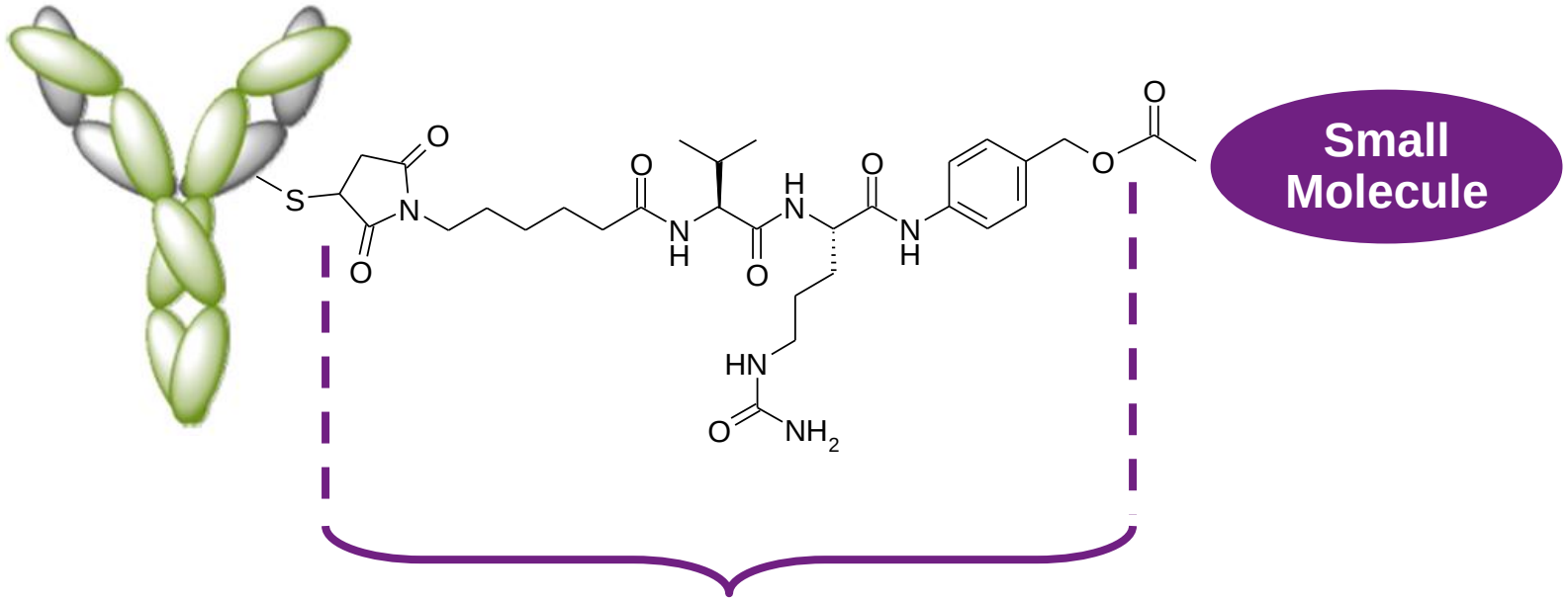


Trends

ADCs

Current Trends

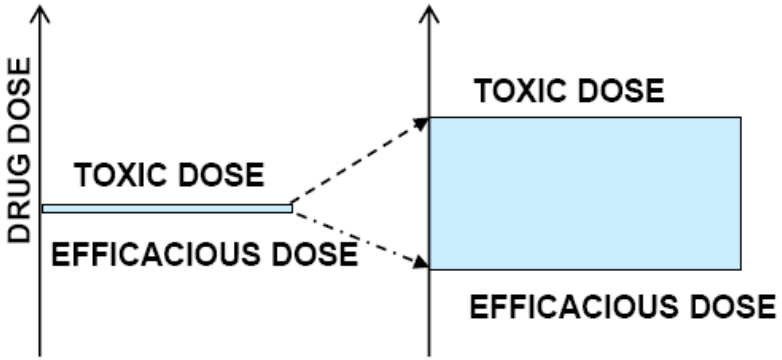
Antibody Drug Conjugates (ADCs)

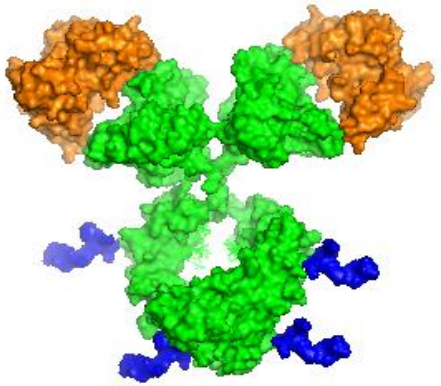


Current Trends

Antibody Drug Conjugates (ADCs)

Small Molecule



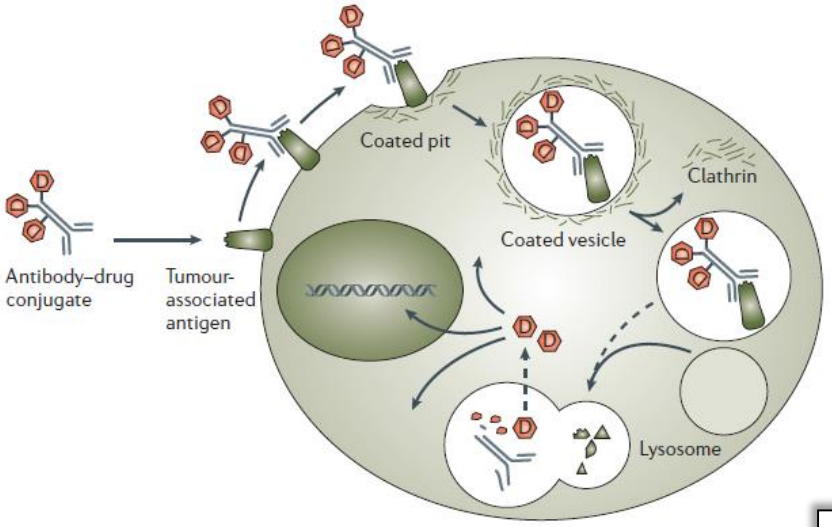


ADC

Wider Therapeutic Index

Targeted delivery of a potent small molecule producing activity with reduced systemic toxicity

Optimizing ADCs as Drugs: Biology ⇔ Technology



Target Cell

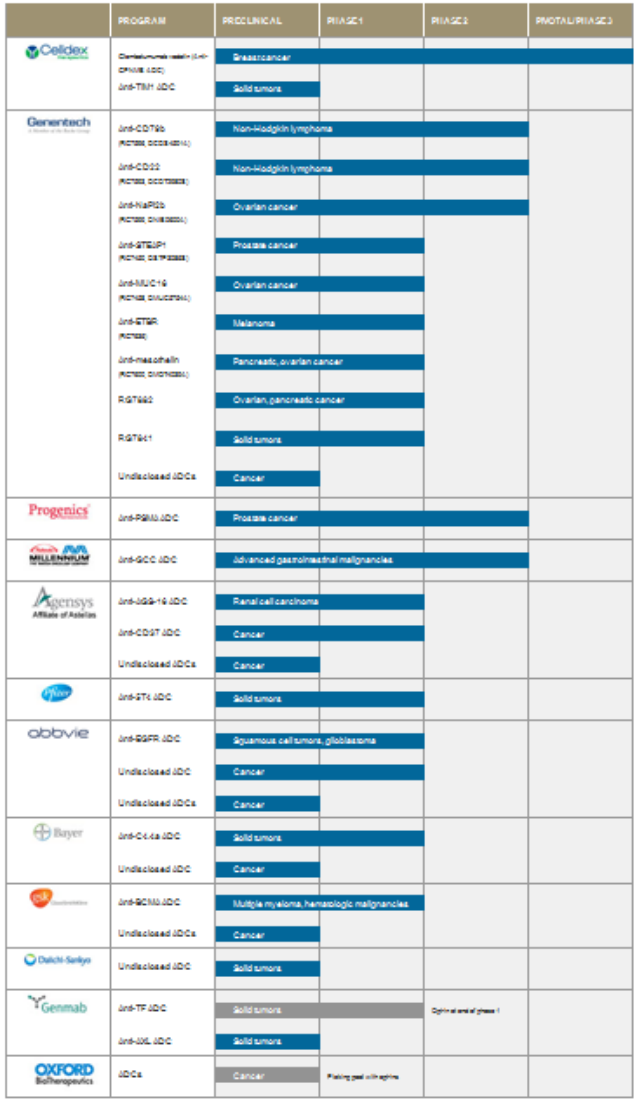
- Antibody directs drug to cellular site of action
- Active drug released upon internalization of complex

ADC Optimization Attributes:

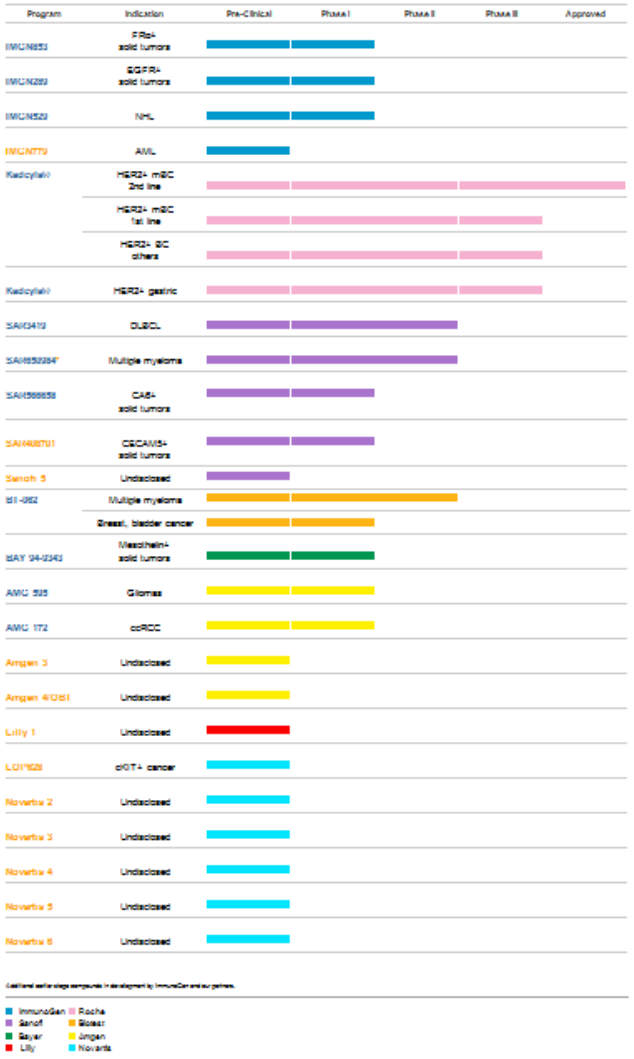
1. **Target**
2. **Antibody**
3. **Payload**
4. **Linker**
5. **Drug Antibody Ratio (DAR)**

Diffusion of a Disruptive Innovation

ADC Development Collaborations 2014



http://www.seattlegenetics.com/adc_collaborations

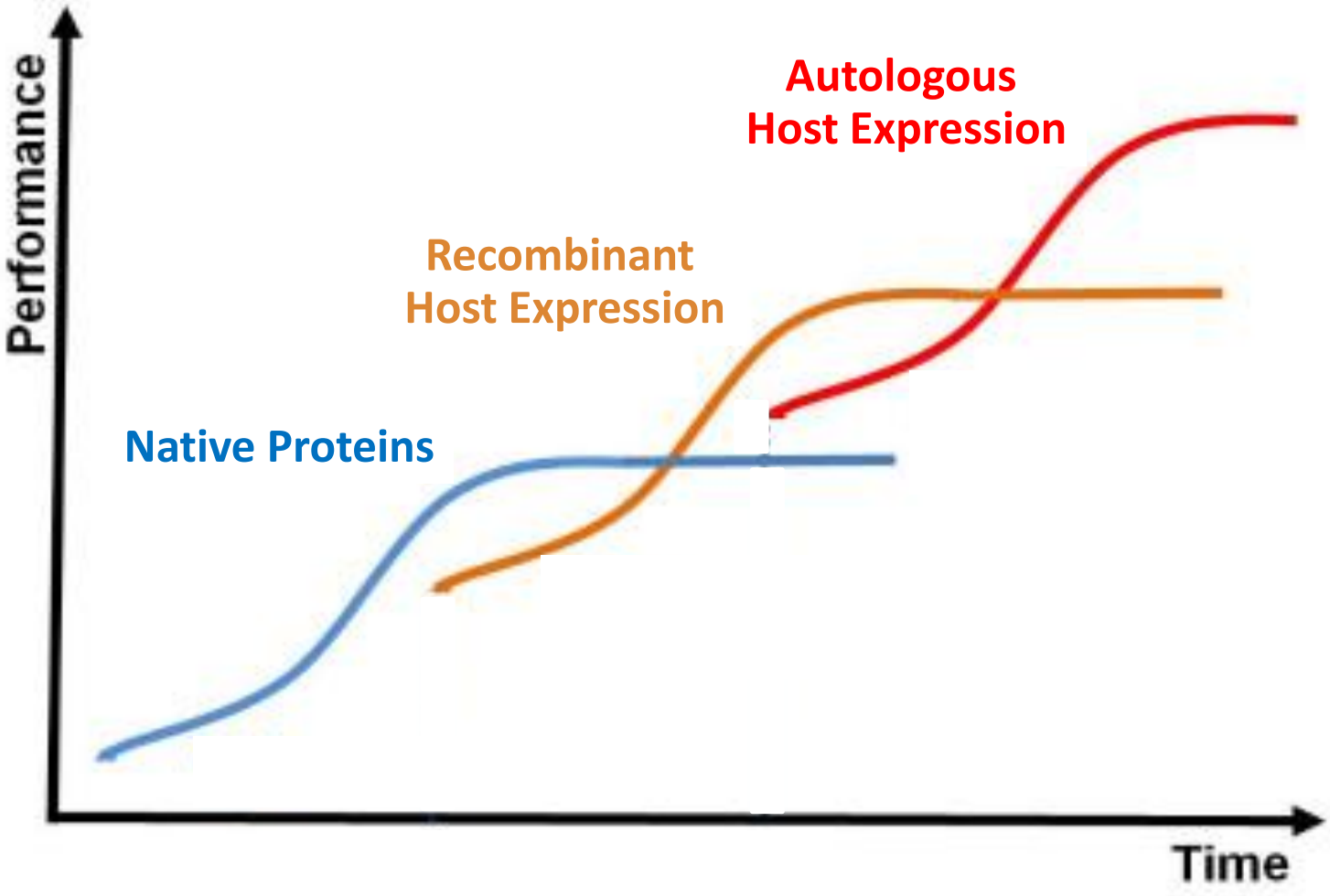


http://www.immunogen.com/pipeline/

Trends

New Modalities

The Next Wave
Novel Therapeutic Modalities



Barriers to Innovation in BioProcess Manufacturing

Novel Therapeutic Modalities

Questions to ask ourselves:

- What successful **dominant designs** may be impeding our progress?
  - Are mAbs, or are they just hitting their stride?
  - Are mAbs now a platform for launching future innovations?

- What **established paradigms** may be on their way to obsolescence?
  - Recombinant expression versus autologous expression?
  - Parenteral delivery versus *in situ* expression?

- What are the sources of **risk aversion** in our industry?
  - The past challenges of gene therapy?

Prospects

Convergence

Pathways

Roles

Platform Convergence

Chemically Defined Media

Single Use Technologies

Modular Manufacturing Plants

Continuous Processing

Process-Structure-Function Control

Multi-Specifics

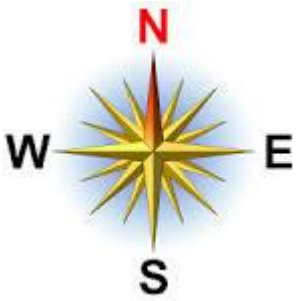
Antibody Drug Conjugates

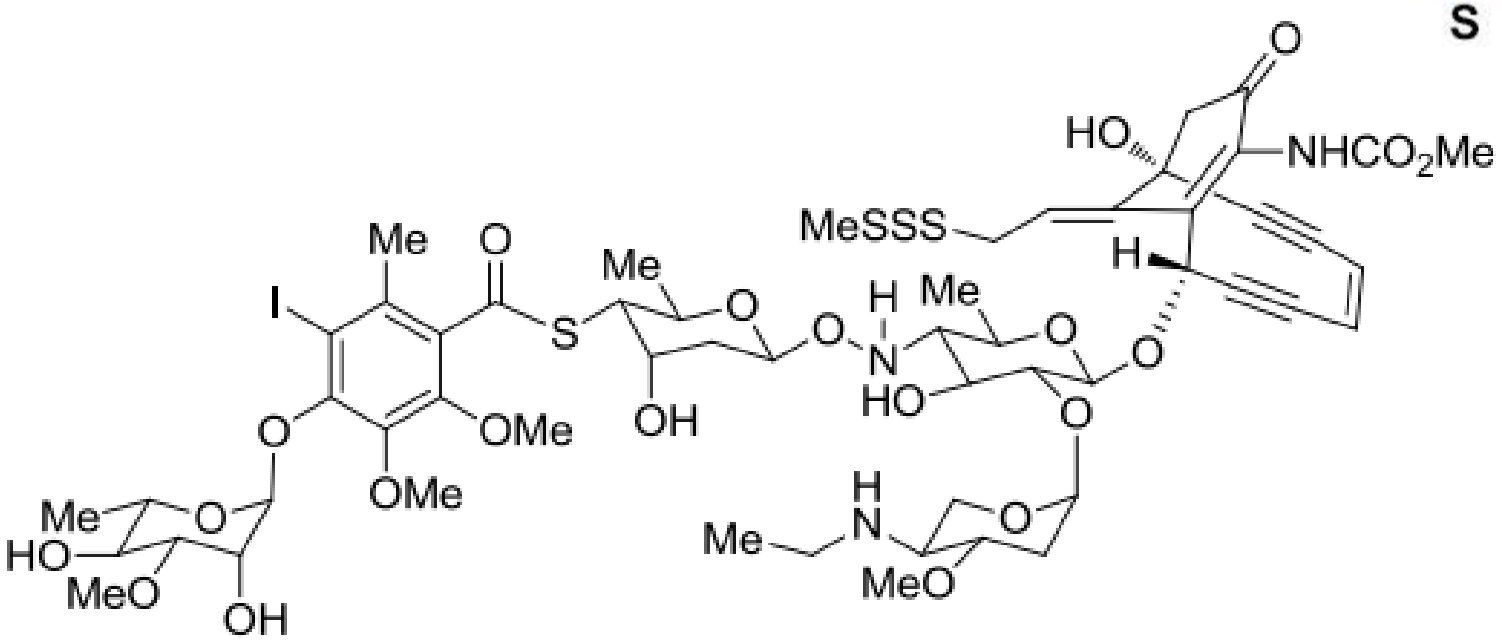
In Situ Delivery

Three Pathways to Innovation

Directed

- Guided, goal oriented, by design, retrosynthesis
- Example: Total Synthesis of Calicheamicin



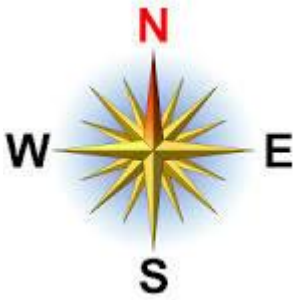


(-)-calicheamicin γ_1^I

Three Paths to Innovation

Directed

- Guided, goal oriented, by design, retrosynthesis
- Example: Total Synthesis of Calicheamicin



Iterative

- Evolutionary, closed feedback loop, prototyping
- Example: Drug Discovery Lead Optimization

Serendipitous

- Spontaneous, wild-card, eureka moment
- Example: Discovery of penicillin

These paths are not exclusive of one another,
They are dependent upon one another

Three Roles Critical to Sustainable Innovation

Broker

- Breaks down silos
- Shares information across functions

Role Model

- Understand the importance of risk
- Actively supports risk-taking

Risk Taker

- Resist the temptation of the status quo
- Continuously push organizations into new areas

http://www.forbes.com/sites/henrydoss/2013/07/25/three-critical-innovation-roles-broker-role-model-risk-taker/

Take Aways

Create a vision

Set a goal

Design a work-flow

Establish a platform to build from

Iterate rapidly with prototypes

Incorporate feedback

Allow for serendipity

Never be satisfied with the status quo

abbvie