Track Title: Emerging Technologies and Patient Centricity in Early Drug Development

Session Title: Designing for Delivery: Drug Discovery and the Early Development Interface

Discovering and Developing Non-Traditional Drug Modality Molecules with Optimal Pharmaceutical Properties

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9 April 2019

Outline of Topics
- Developability of Nontraditional Molecules -

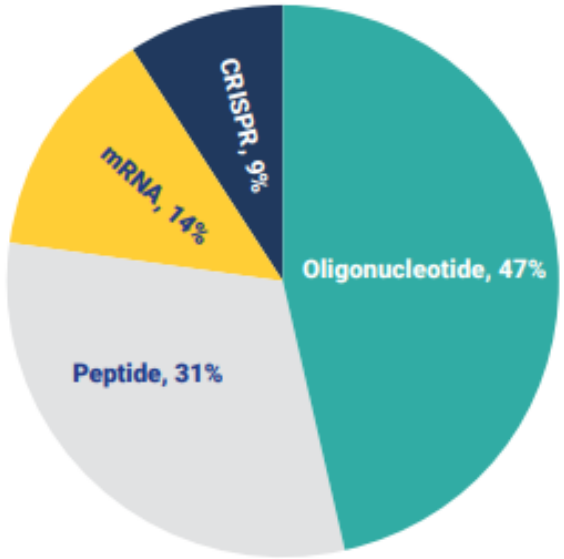
- **Increased Importance of New Modalities (TIDES)**
- **New Modalities and the ever Evolving Chemical Space**
  - Physiochemical Landscape and Drug Modality
  - Chemical Diversity and Drug Delivery
- **Defining a Preliminary Target Product Profile**
- **Physical Pharmacy & Drug Delivery**
  - Surrogates – Translation – Line-of-Sight
  - Drug Design with Delivery in Mind - A Marriage made in Discovery
  - The white elephant in the room -- TIDE Permeability
- **Discovery Mindset and Culture**
- **Acknowledgements**
  - Roy Haskell, Greg Amidon, Tom Raub
  - Arnold Repta, Takeru Higuchi, Val Stella, Ron Borchardt, Shri Valvani, Tony Sinkula, Walt Morozowich, Ev Hiestand, Chris Sinko, Steve Nail, Bob White, George Zografi, Ping Gao, Brian Rohrs, Randy Wald, Jim Freeman, John Skoug, Scott Grossman, Olafur Gudmundsson, Bruce Car, Ajit Narang, Rao Mantri
  - Many other colleagues in hallway discussions, coffee breaks, lunches and “Science at the Tavern”

What TIDE Area has the Most Opportunity for Commercial Success and Growth?

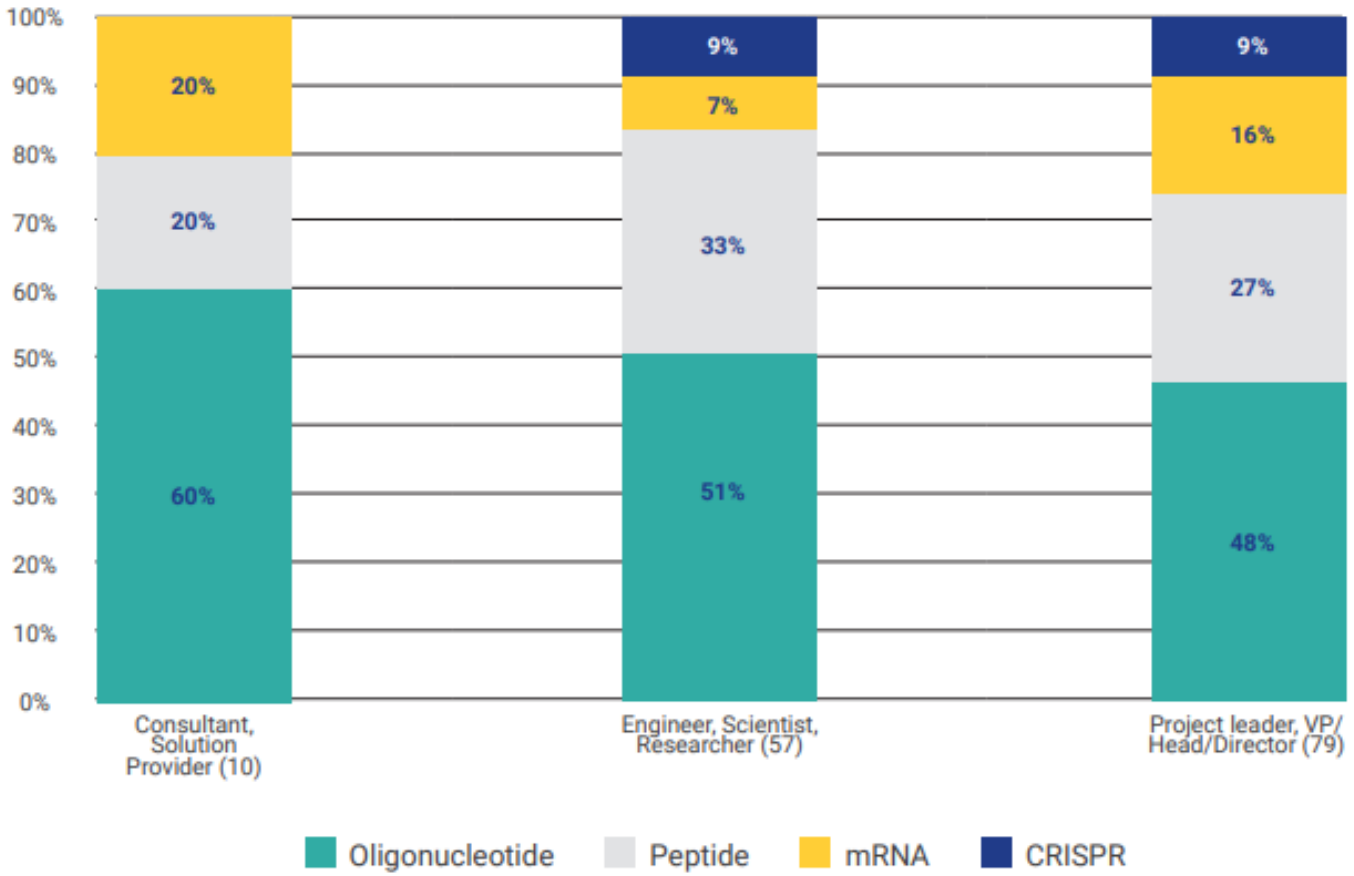
TIDES:
Oligonucleotide and
Peptide Therapeutics

OLIGO AND PEPTIDE THERAPEUTICS 2018: STATE OF THE INDUSTRY REPORT

Overall



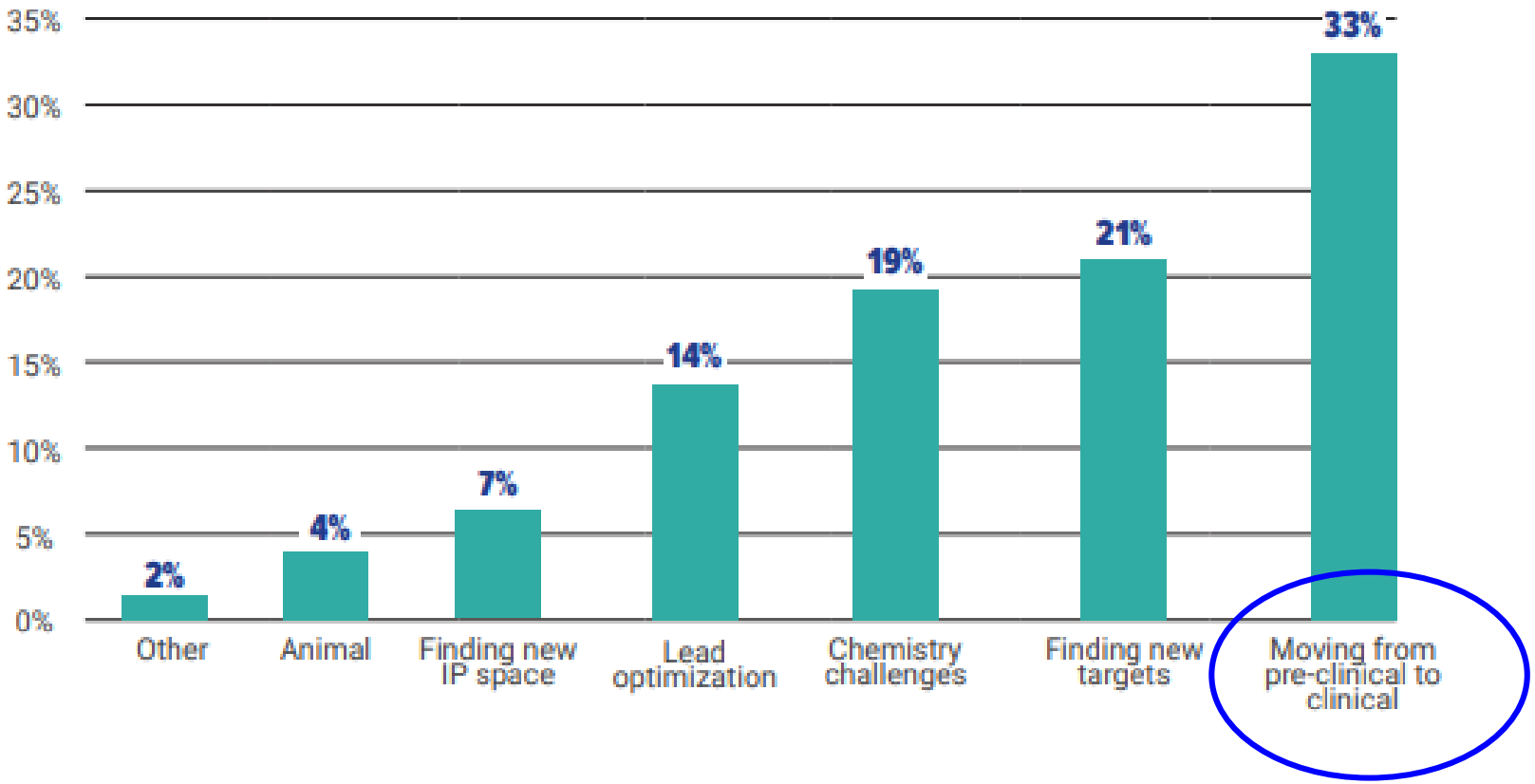
By Job Function



What is your biggest challenge in the discovery / pre-clinical space for TIDEs?

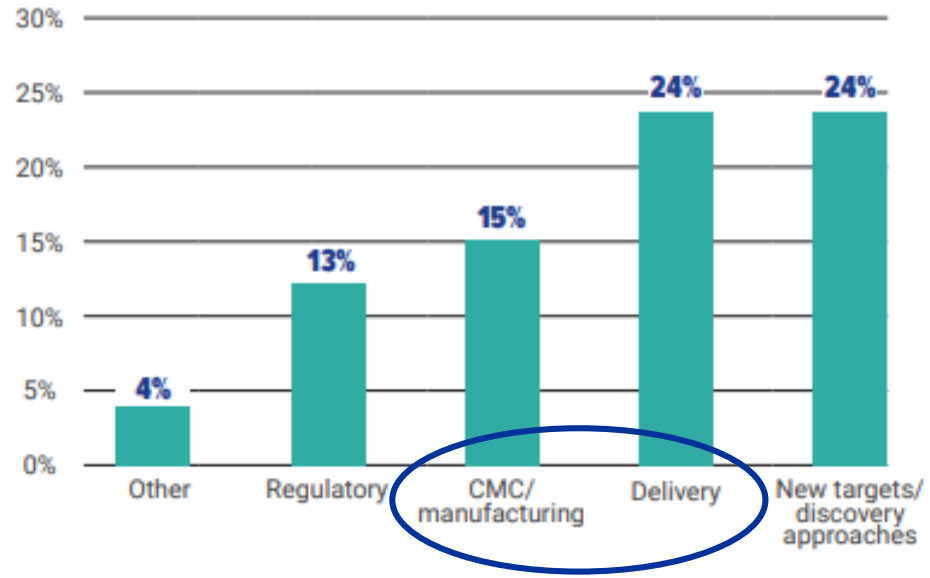
TIDES: Oligonucleotide and Peptide Therapeutics

OLIGO AND PEPTIDE THERAPEUTICS 2018: STATE OF THE INDUSTRY REPORT



Recognized Stumbling Block

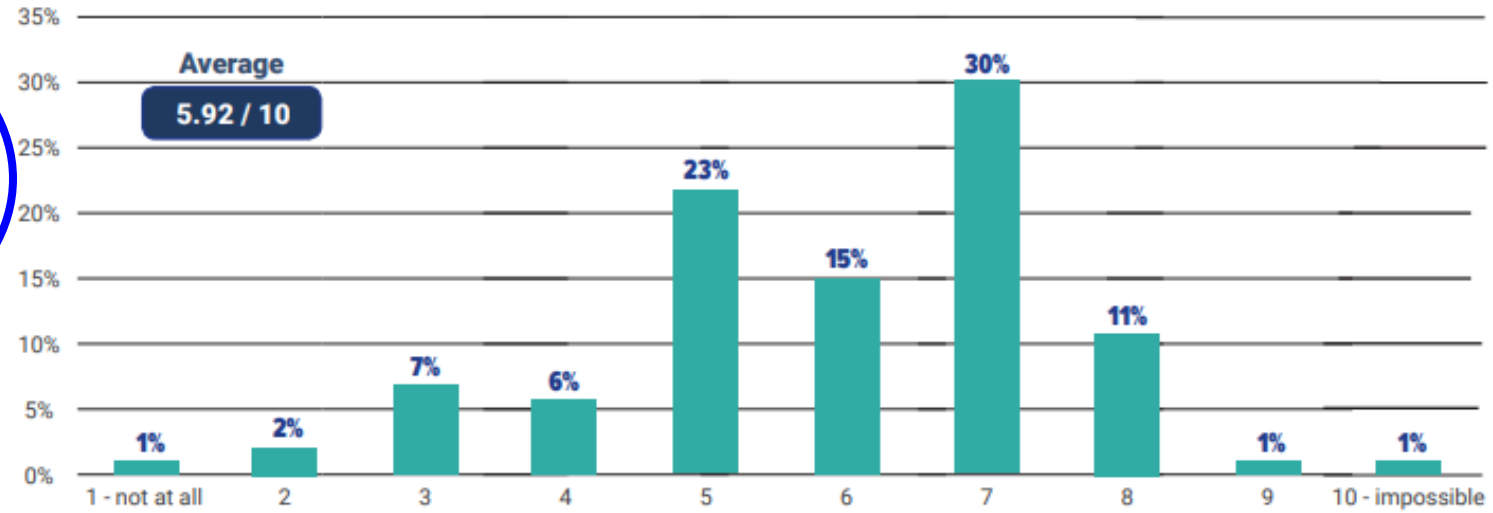
What is the biggest challenge that you are currently Facing with Novel Therapeutics?



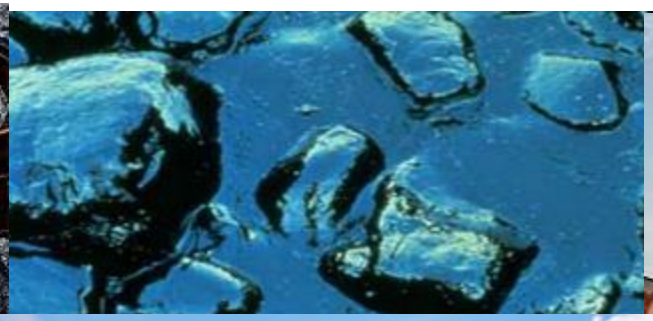
TIDES: Oligonucleotide and Peptide Therapeutics

OLIGO AND PEPTIDE THERAPEUTICS 2018: STATE OF THE INDUSTRY REPORT

How difficult will the delivery challenge for novel therapeutics be to overcome?



Underlying Premise for Small Molecule NCEs
- Not all Molecules Come from a Haystack -

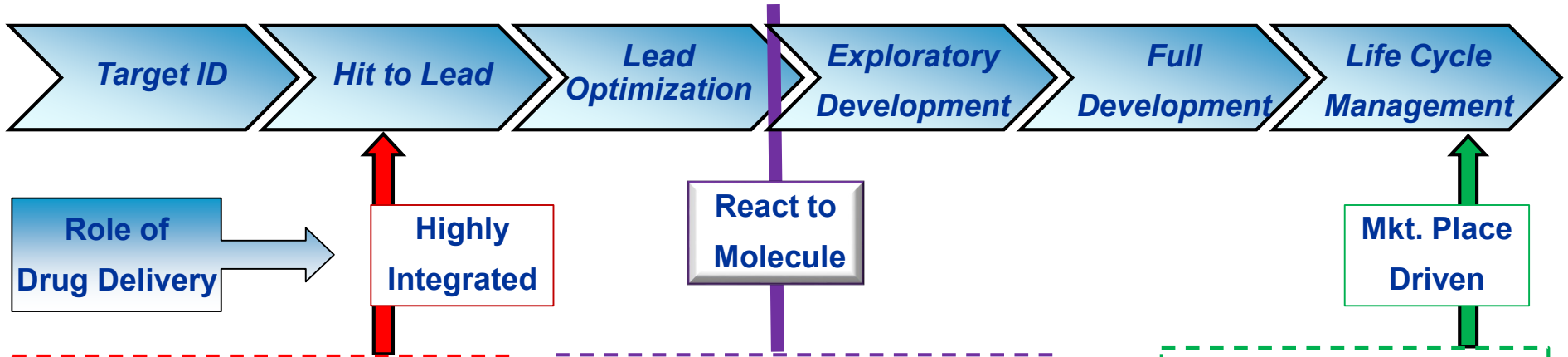





Evolving Modalities Underlying Premise

- Not all Molecules Come from a Haystack -

Increased Chemical Diversity Requires More Integrated Role of Drug Delivery During Lead Optimization



- Iterative Screening Funnel - Evolution
- Molecule not yet picked
- Opportunity to marry molecule with delivery
- Range of preclinical models used
- Limited API available; rapid iteration
- Focus on Progression Risk and Line-of-Sight for Technology

- Molecule selected
- Stage gate focused
- Seek viable technology
- Limited range of preclinical models
- API available but very timeline driven
- Preformulation Characterization
- Developability Assessment

- More clinical and pharmaceutics experience
- TPP well defined
- Substantially more resources
- Unlimited API

Commonly Applied Rules for "Drug-Like"

Lipinski rule of 5

- Poor absorption and permeation are likely when
  - H-bond donors > 5 MW > 500
  - logP > 5 H-bond Acceptors > 10

Veber Rules

- Good oral bioavailability in rats when
  - Rotatable bonds ≤ 10
  - Polar Surface Area(PSA) ≤ 140 Å^2 ; or ≤ 12 H-bonds (acceptors+donors)

Pardridge Rules

- Good probability of penetrating the blood-brain barrier(BBB) when
  - H-bonds (acceptors+donors) ≤8-10
  - MW < 400-500 and not acidic

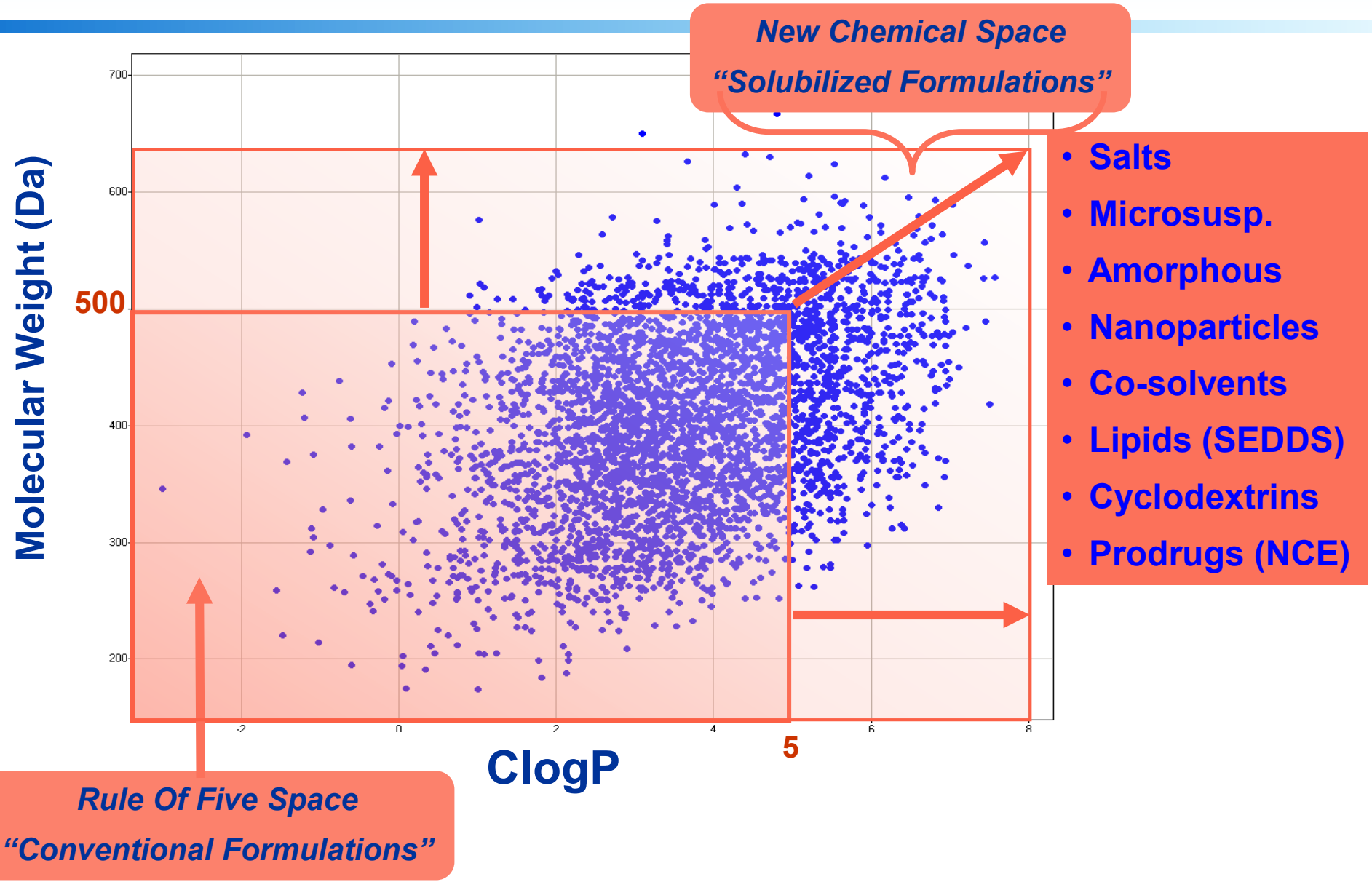
Spraklin

- Further states that of 8 total H-bonds for BBB permeation
  - H-bond donors < 2 and H-bond acceptors < 6

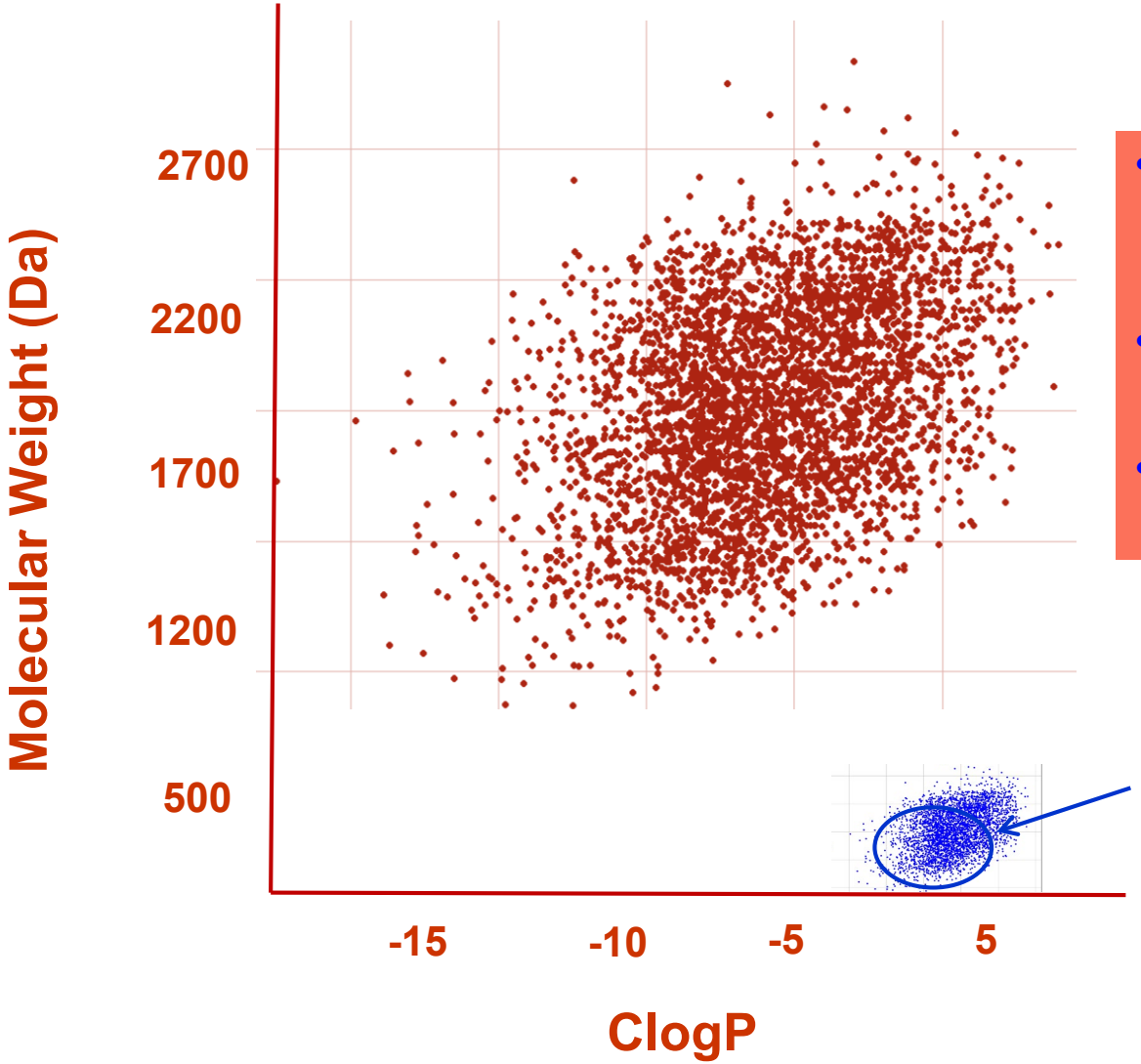
Clark & Lobell

- For good BBB barrier permeability
  - MW < 450 logD = 1-3
  - #N + #O < 6 clogP – (#N-#O) > 0
  - Polar Surface Area (PSA) < 60-70 Å^2

Contrasting to our Typical Use of Formulation to Expand Accessible Small Molecule Chemistry Space For Oral Delivery



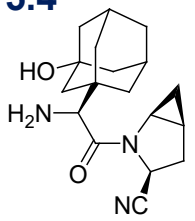
Moving Into Nontraditional Chemical Space – Alternative Delivery Strategies are Required



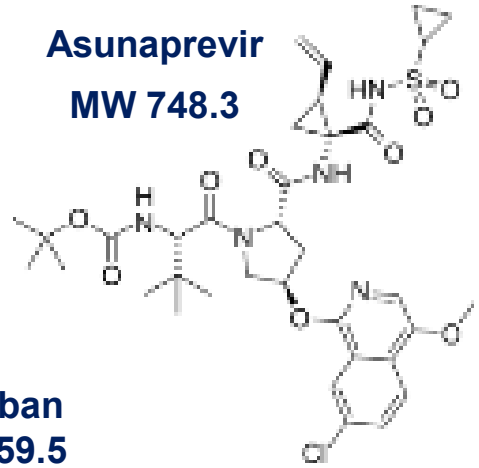
- Alternative Routes of Administration
- cLogP even valid / of value?
- Net charge important?

Evolving Chemical Space >>>> New Ball Game

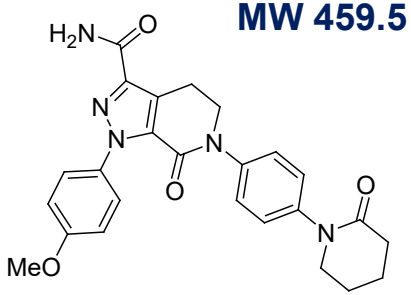
Saxagliptin
315.4



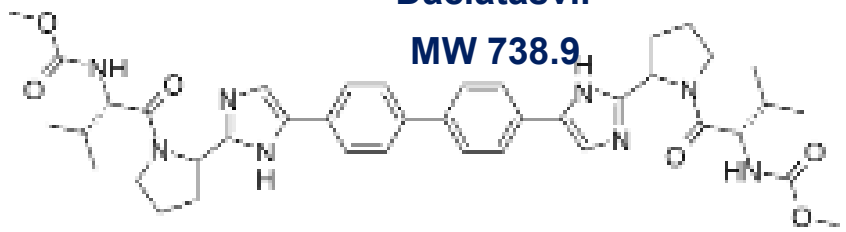
Asunaprevir
MW 748.3

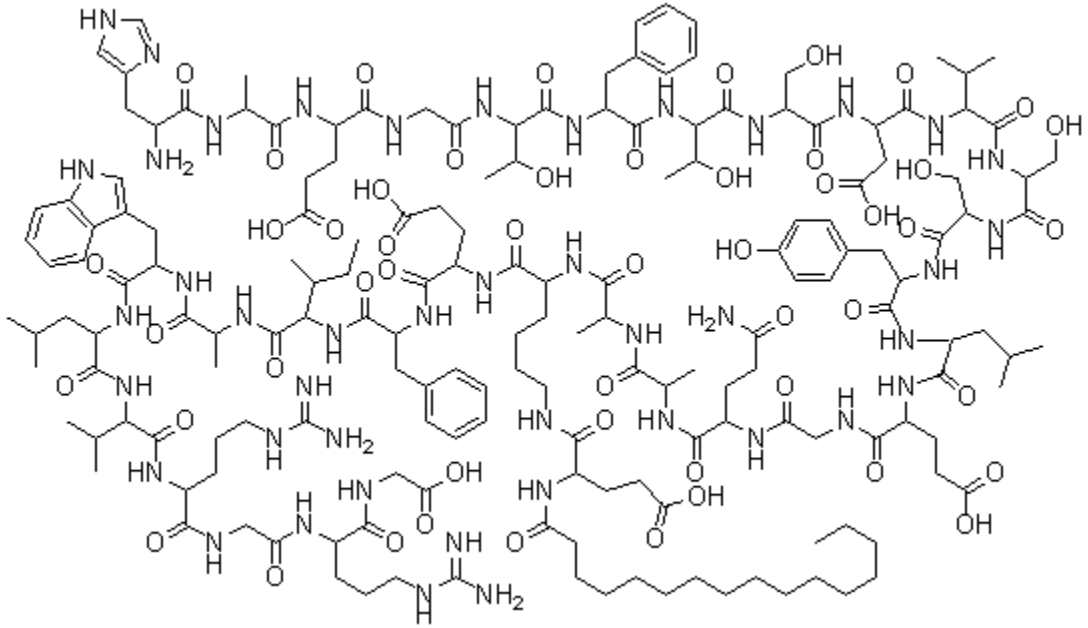


Apixaban
MW 459.5



Daclatasvir
MW 738.9

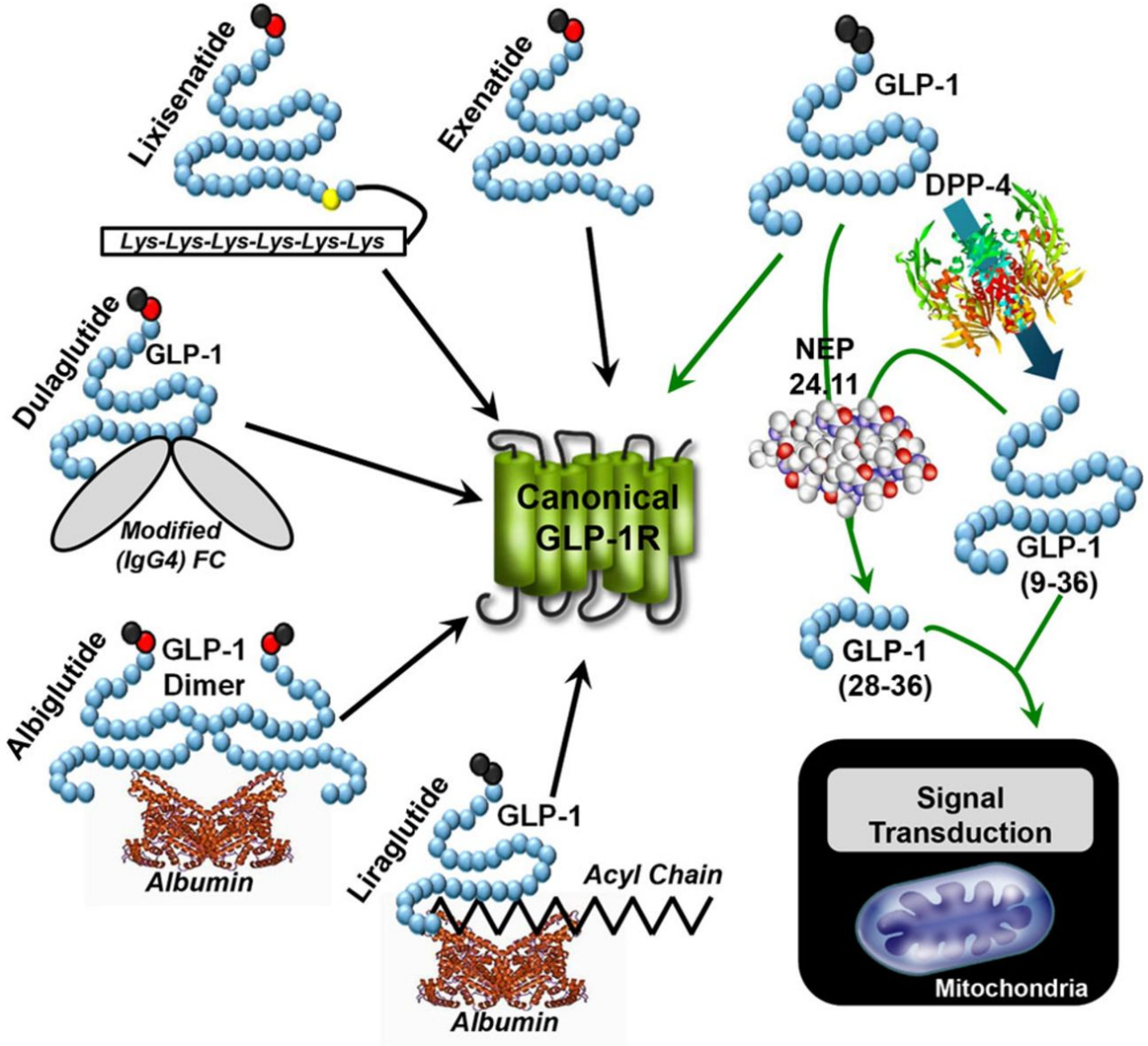




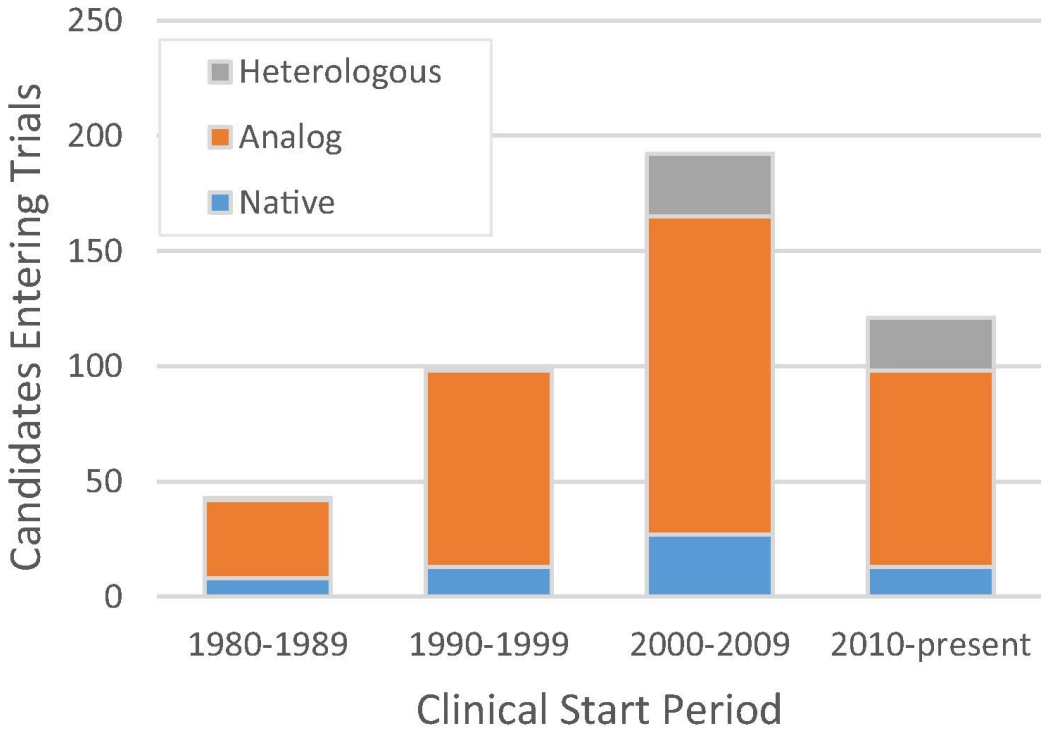
GLP1 Analogs
Liraglutide
MW 3751

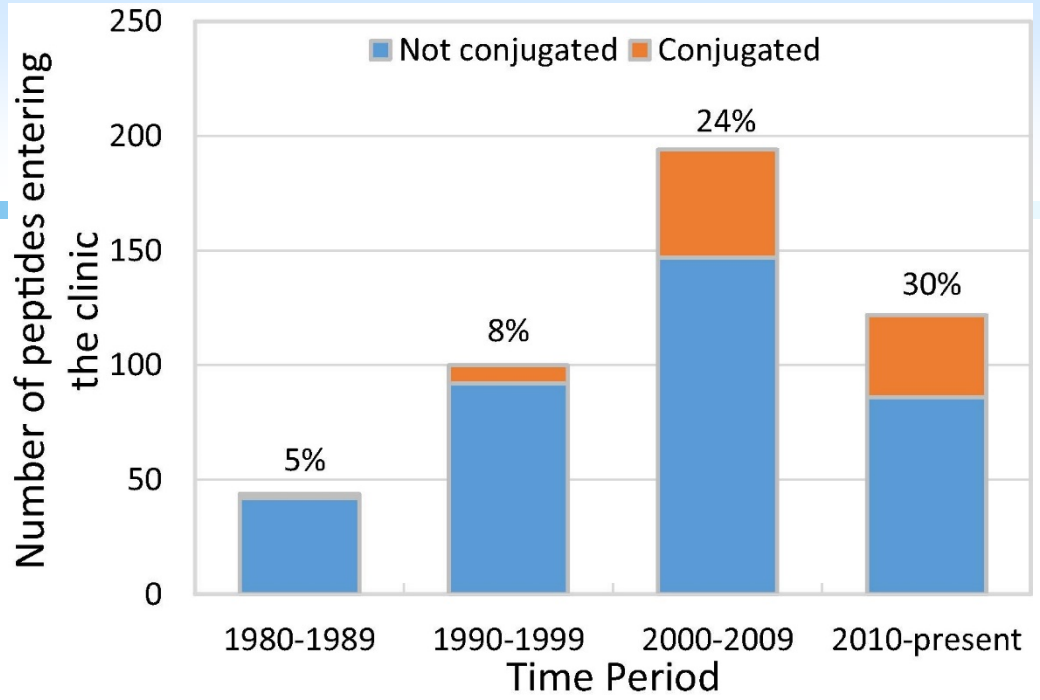
What are the physicochemical and formulation requirements of a molecule for delivery?

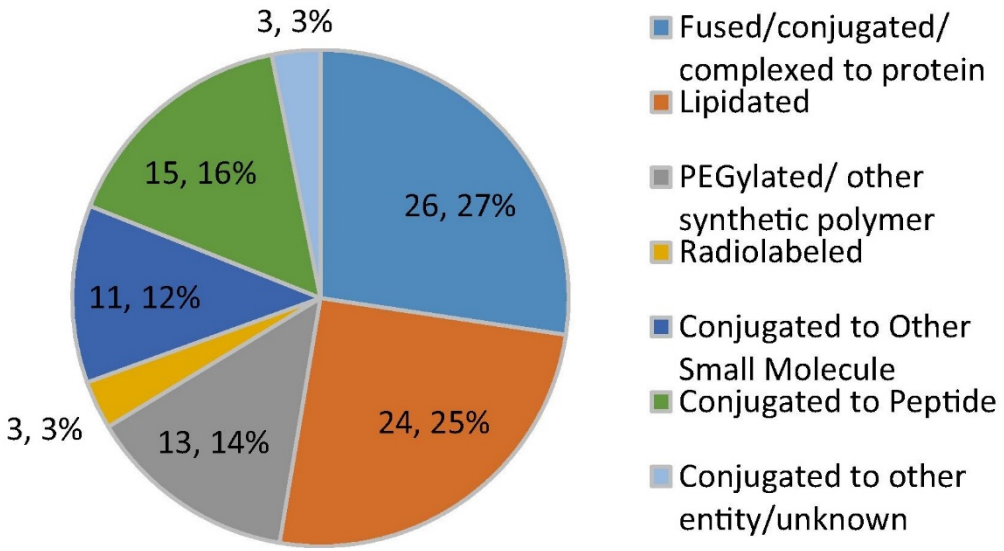
Structural Variety in Marketed GLP-1 Analogs



Incidence of Conjugated Peptides in the Clinic







Jolene L. Lau, Michael K. Dunn
Bioorganic & Medicinal Chemistry
Volume 26, Issue 10,
1 June 2018, Pages 2700-2707

Generate a Preliminary Target Product Profile (PTPP) Early in the Process

- **Provides basis on which developability hinges**
- **Initiated with target identification & based on business needs**

Element	***Commercial Design Target***
Therapeutic Indication	*Alz, CHF, RA, UC, Crohn's Disease, I-O, etc.*
Route of administration	*Oral, Subcutaneous Injection, IV injection, other?*
Projected Efficacious Dose	*X mg per dose (this will be refined with time, early on need to know are we at 1, 10, 100 or 1000 mg)*
Product	*Ready to use solution, lyophilize for reconstitution,*
Delivery system/Device	*Immediate release, Pre-filled syringe, small volume parenteral (<100ml), large volume parenteral, autoinjector pens, pump systems*
Dosing frequency	*Once a month, once a week, daily (may be coupled with device)*
Stability	*E.g. ≥24-month shelf life at 2-8°C with protection from light or do you require room temperature storage*

Discovery Enablement vs Candidate Enablement

Developability: The potential ability to carry an asset through its timeline with known risks and predictable, "reasonable", resource consumption.

Discovery Enablement and Tools

- Permits studies using suboptimal compounds
  - Must not compromise outcome of intended (bio)assays
- Really has no bearing on candidate enablement per se
  - Requirements are completely different
- Surrogate assays must be linked to
  - the desired molecular and product attributes
  - a "Line-of-sight" to Clinical, preferably Development

Candidate Enablement

- Verifies progression plausibility of approach(es) at point of selection
  - Avoids subsequent "no-go" decisions
- Estimate levels of risk/resource consumption likely with progression
- Different from life-cycle management

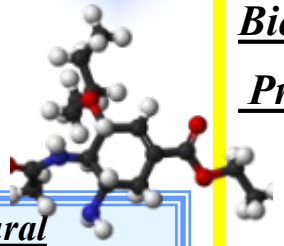
Goals:

Lead Optimization: Develop in vivo models, formulations, & tools; assess compatibility with program compounds

Candidate Selection: Explore behavior with candidate; assess specific clinical options; understand risk of progression

Translation of Molecular Properties Into Preclinical and Clinical Attributes

Molecular Properties → Physicochem Properties → Biochemical Properties → ADME → Pharmacology & Toxicology



Molecular / Structural Properties

- Polarizability
- Electronic Factors
  - resonance, dipole
  - charge transfer
  - ionization constants (pKa)
- Topological / Steric
  - surface areas
  - volume
  - connectivity
- Molecular Weight
- Hydrophobicity
- Hydrogen Bonding
- Reactivity

Biochemical Properties

- Target Binding
- Nontarget Binding
- Protein Binding
- Tissue Partitioning
- Membrane Partitioning
- Enzyme Binding
- Transporter Binding

Physicochemical Properties

- Solubility
- Permeability
- Diffusion Coefficient
- Chemical Stability
- Partition Coefficients
- Cohesive Energy
- Density

ADME Properties

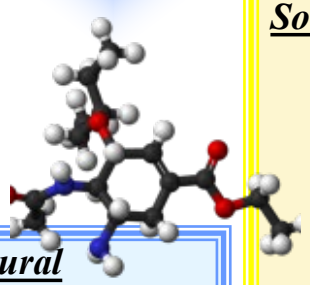
- Clearance
  - ~~hepatic, renal, gut~~
- Fraction Absorbed (%F)
- Rate of Absorption (k_a)
- ~~Drug-Drug Interactions~~
- Volume of Distribution
  - organ & tissue distribution
- Metabolism
  - phase 1 & 2
- Transporters
  - efflux & uptake

Pharmacol. & Tox. Properties

- On-Target Binding
  - IC50, IC90, ED50
- Off-Target Binding
  - hERG Binding
- Toxicity
  - LD50
  - acute, chronic

Translation of Molecular Properties Toward Pharmaceutical Developability Properties

Molecular Properties → Physicochem Properties → Solid Form Properties → API & Formul. Manufacturing Properties → Shelf-Life Properties



Molecular / Structural Properties

- Polarizability
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  - resonance, dipole
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- Topological / Steric
  - surface areas
  - volume
  - connectivity
- Molecular Weight
- Hydrophobicity
- Hydrogen Bonding
- Reactivity

Solid Form Properties

- Hygroscopicity
- Polymorphs / Solvates
- Salts, Co-crystals
- Crystallinity (Tm)
- Amorphous (Tg)
- Particle Size / Shape
- Dissolution
- Physical Stability
- Physicomechanical

Physicochemical Properties

- Solubility
- Permeability
- Diffusion Coefficient
- Chemical Stability
- Partition Coefficients
- Cohesive Energy
- Density

Formulation / Manufacturing Properties

- Filter, Isolate, Size
- Impurities control
- Particle size reduction
- Powder flow, compactable
- Device Compatibility
- Excipient Compatibility
- Process Stability
  - chemical & physical
- Formulation Strategy
  - salt, free base/acid, amorphous, crystalline
  - liquid fill, semi-solid
  - solubilizers
  - solid dispersion

Shelf-life Properties

- Chemical Stability
- Physical Stability
- Maintain Bioperformance
- Packagable
- Marketable

“Surrogate Measure” is Really Fit for Purposes and Translation Makes it of Value

Choice of Surrogate Measure Depends on the Decisions Desired and Confidence in the Inter-Relationship of Data for the Desired Attribute

“Surrogate Measure”
(can/should include computational)

Kinetic

or

Thermodynamic

In Vivo Behavior,
Bioavailability, Variability,
ADME, Safety / Tox,
5 yr API Storage Stability,
3 yr DP Storage Stability,
Device Compatability,
Interfacial interactions,
Underwrite Screening,
Underwrite GLP & POC studies,
Processability,
Manufacturability,
Formulation Strategy,
Analytical Strategy

“We tend to overvalue the things we can measure and undervalue the things we cannot.”
— John Hayes

The Problems of Peptide Oral Absorption

Enzymatic/Chemical stability

- Enteric coating/inhibitors
- Drives modified animal models

Solubility

Permeability

- Transient tight junction modulators
  - Specific vs nonspecific
- Membrane fluidizers (transcellular)
- Coordinated exposure (paracellular)

Multifunctional Excipients

- Fatty acids, EDTA, citric acid acyl carnitines, bile salts

Specific modulators

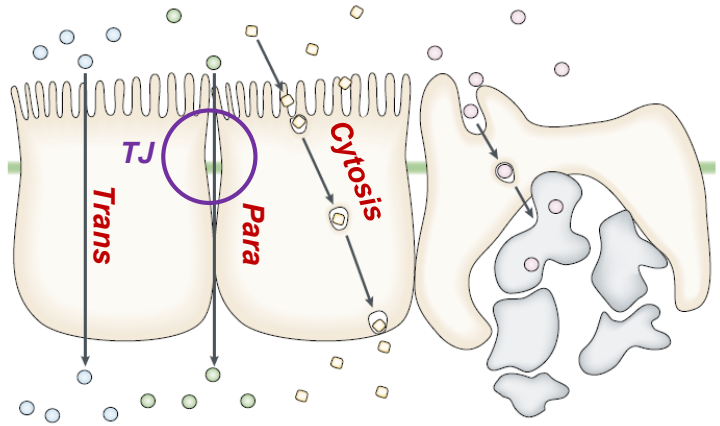
- Cadherin inhibitors

Stomach

- *Enzymatic & pH degradation*

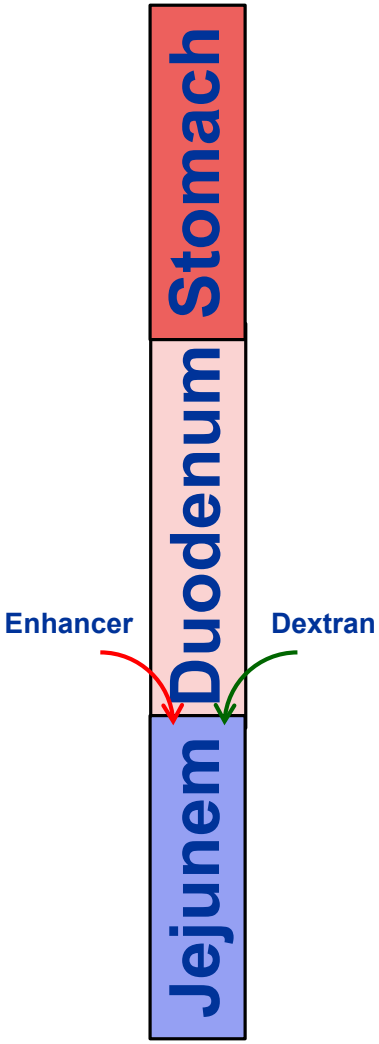
Intestine

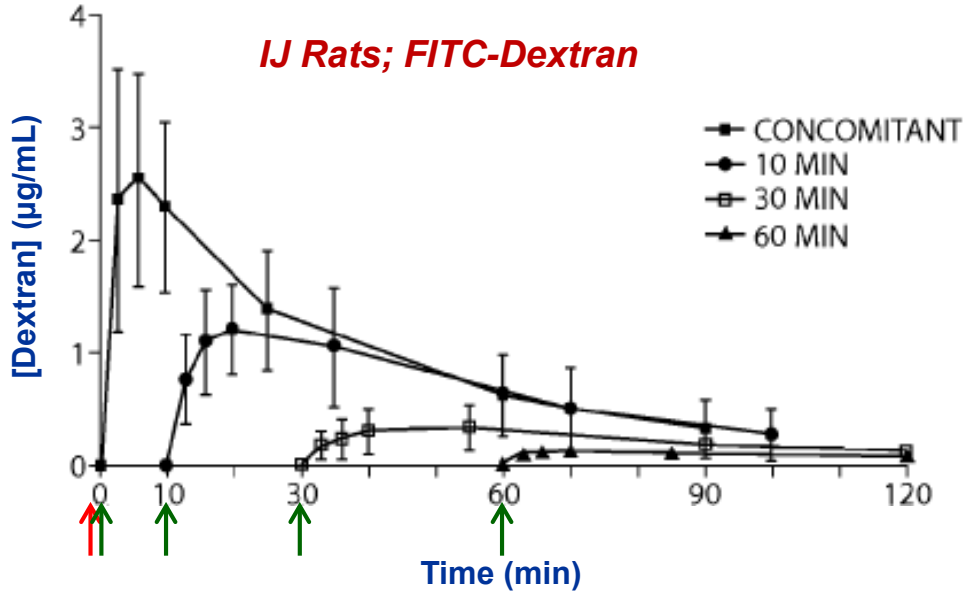
- *Enzymatic degradation*
- *Solubility*
- *Permeability*



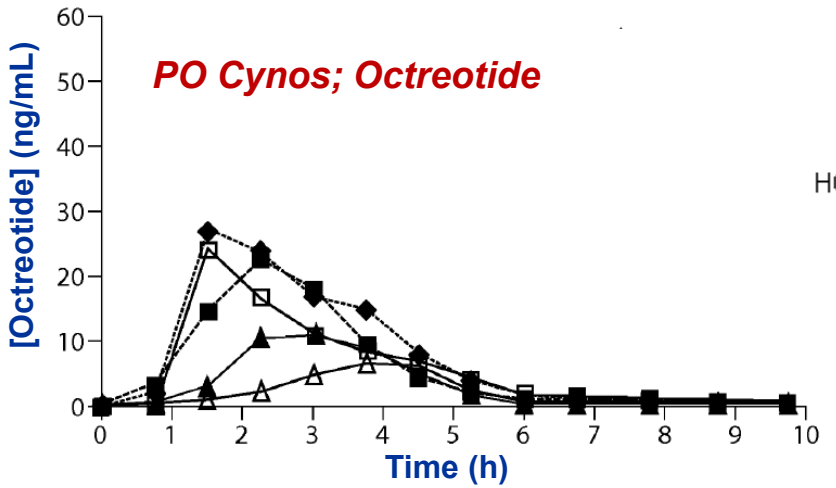
Measuring Permeation Enhancement

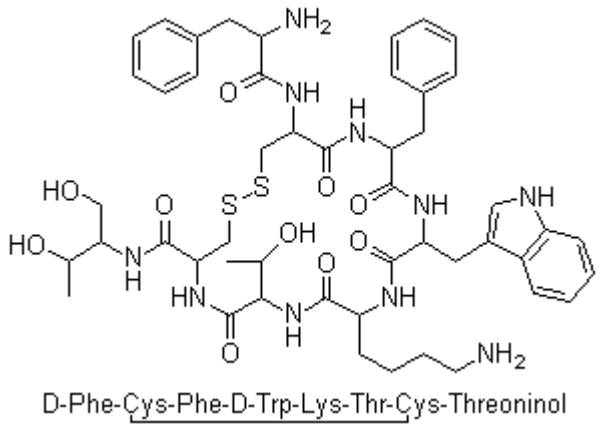
Pharm Res (2014) 31:2010–2021





- **Maximizes interpretability of results**
- **Avoid proteolysis**
- **Avoid hydrolysis**
- **High concentration**
- **Temporal control**



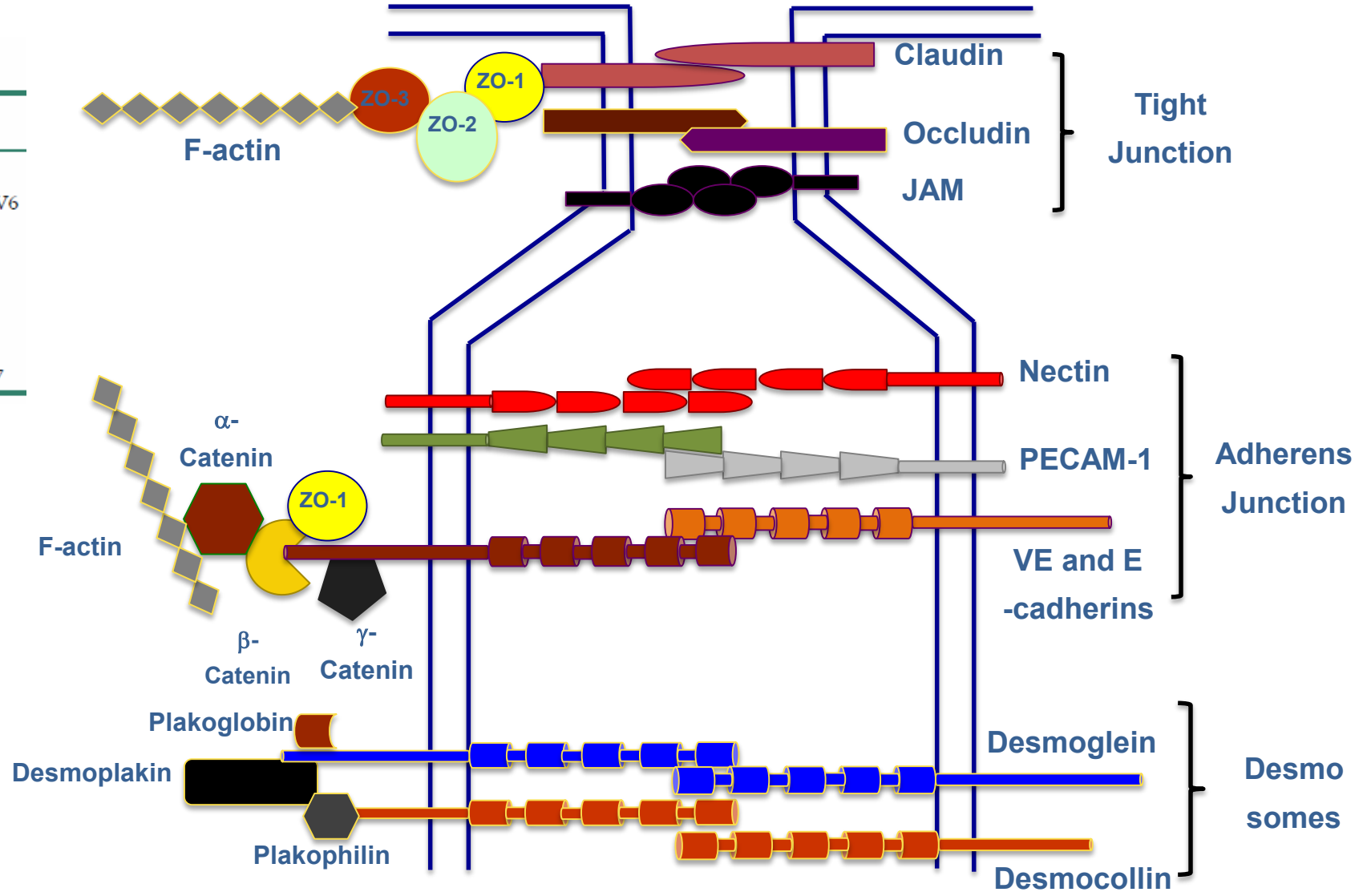


US 2010/0105627A1

Structure of Intercellular Junctions

Table 1. Peptide Names and Peptide Sequences

Peptide Name	Sequence	Peptide Origin
HAV6	Ac-SHAVSS-NH_2	EC1 of E-cadherin
HAV4	Ac-SHAVAS-NH_2	Ala5 mutant of HAV6
cHAVc3	Cyclo(1,6)Ac-CSHAVC-NH_2	EC1 of E-cadherin
ADTC5	Cyclo(1,7)Ac-CDTPPVC-NH_2	EC1 of E-cadherin
cLABL	Cyclo(1,12)PenITDGEATDSGC	I-domain of LFA-1
cIBR7	Cyclo(1,8)CPRGGSVC	D1 of ICAM-1
IS	Cyclo(1,8)CPRGGSIC	Ile7 mutant of cIBR7



Dr. Teruna J. Siahaan

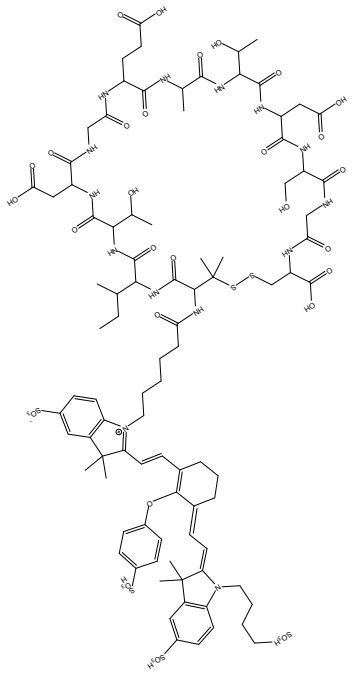
Aya & Takeru Higuchi Distinguished Professor

Department of Pharmaceutical Chemistry, The University of Kansas, Lawrence, Kansas 66047, USA.

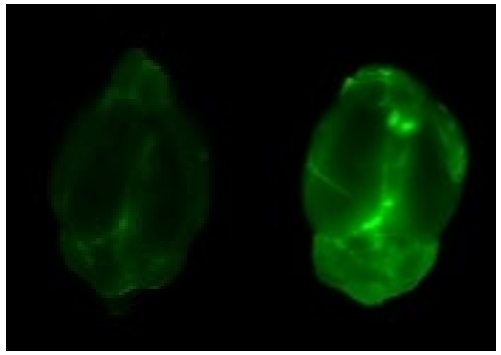
Email: siahaan@ku.edu

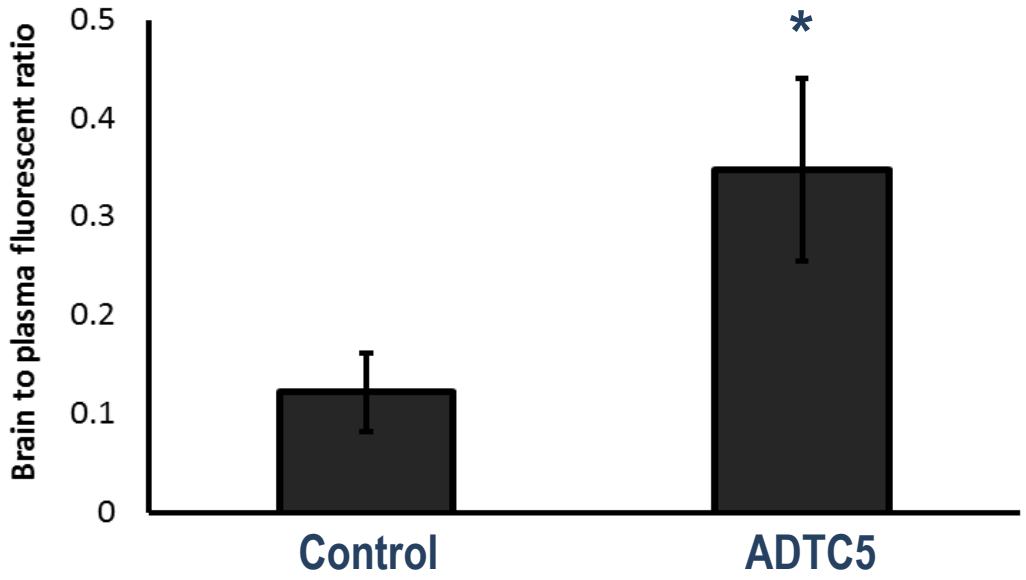
Peptide Brain Delivery: IRdye800-cLABL

Translating Blood Brain Barrier Knowledge to Oral Absorption Barrier?



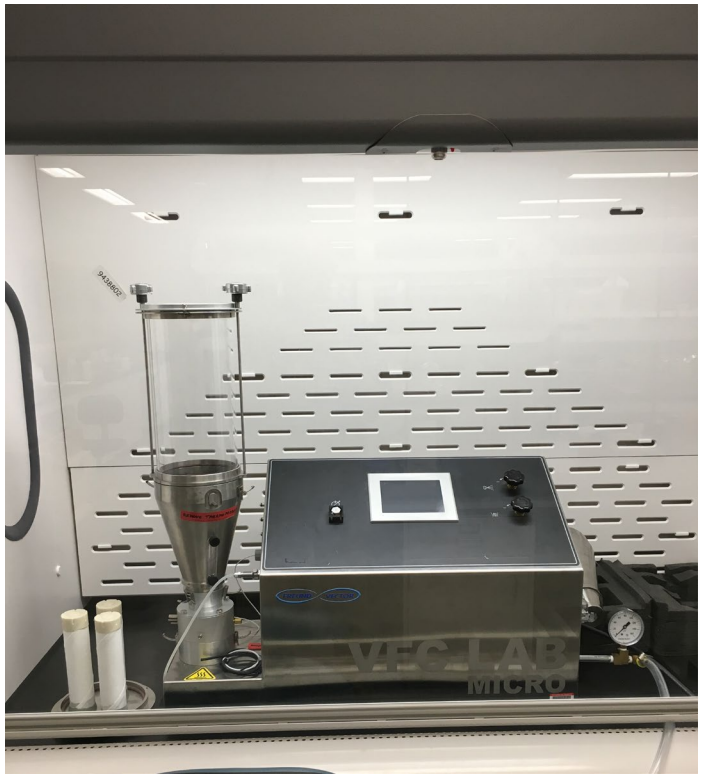
IRdye800-cLABL





Compliments - Teruna J. Siahaan

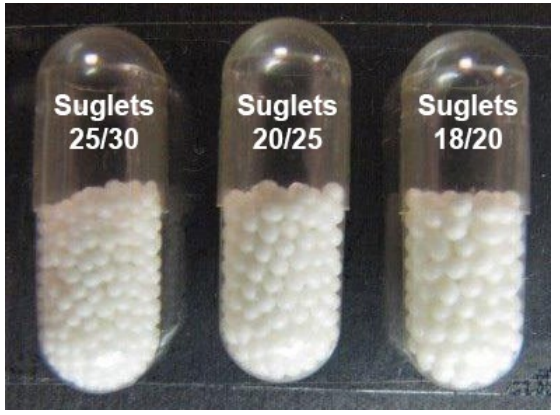
Co-Delivery of Enhancers and Peptides via Multiparticulates and Spray-Coating (200-1200 uM Multiparticulates)



Regional GI Targeting Layer
(enteric, biodeg polymer)

Peptide Stabilizing
Dispersion with Enhancer

Bead Substrate

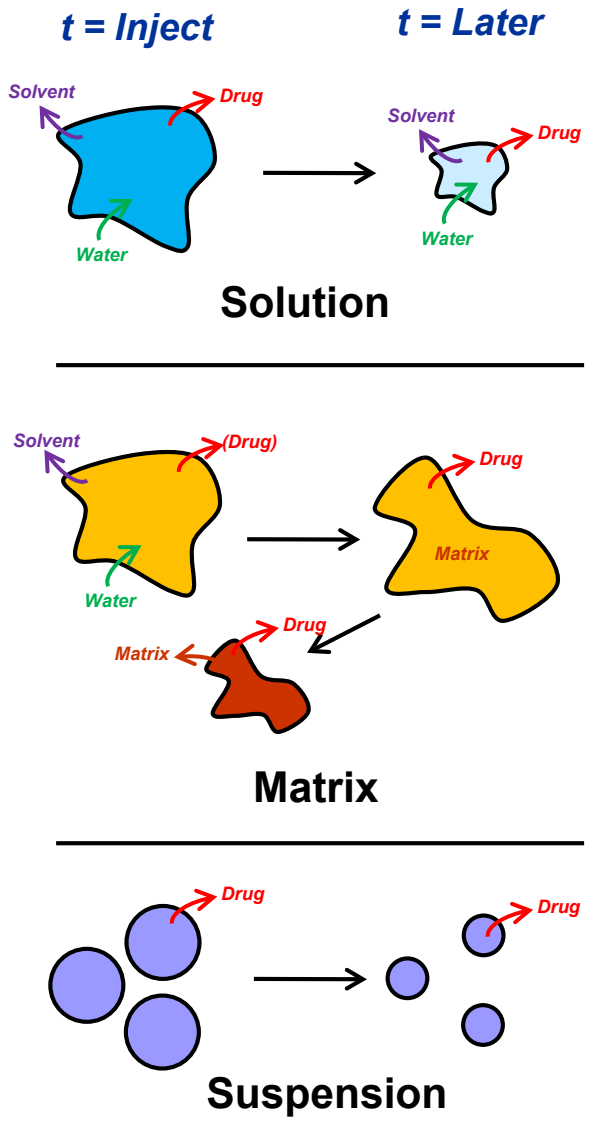


Suglets Range of Particle Sizes

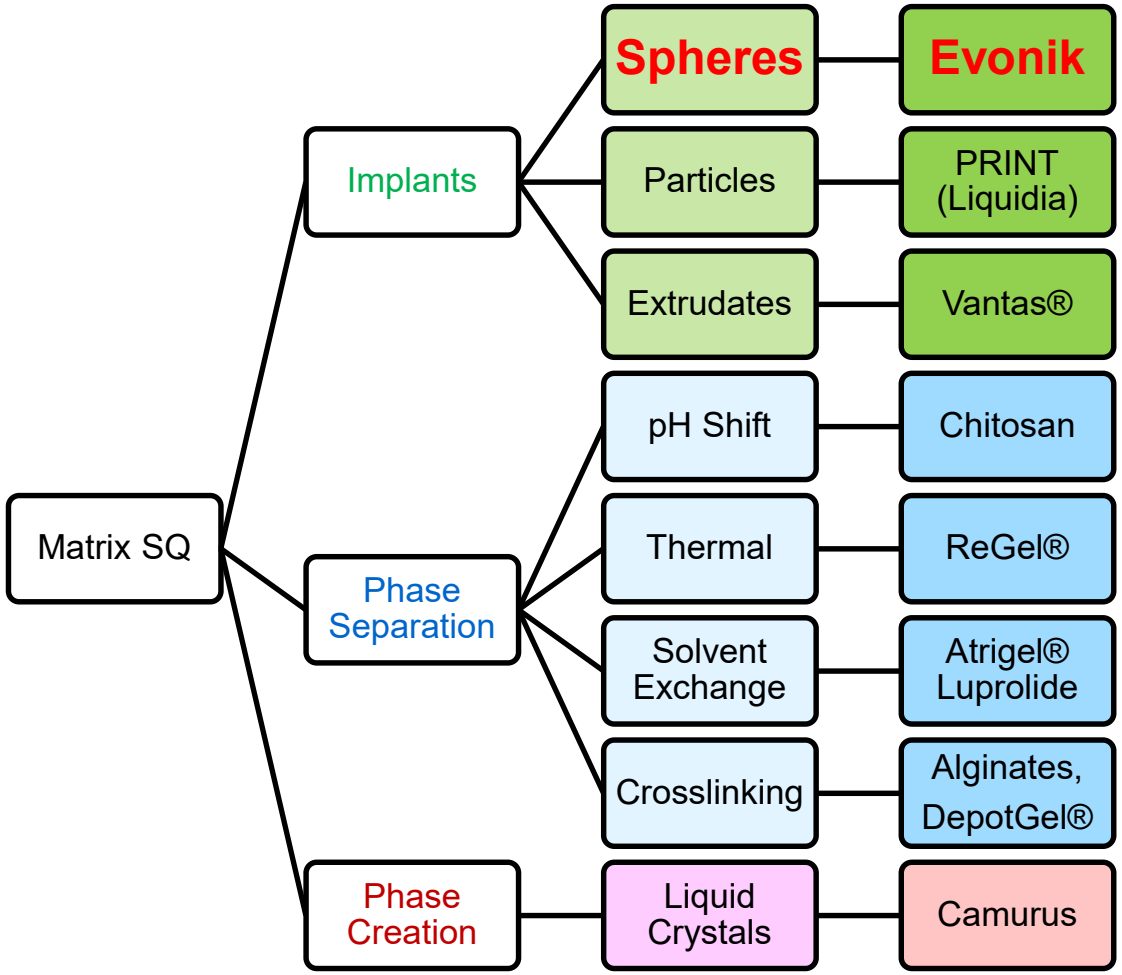
Mesh	Size (µm)
12/14	1400-1700
14/18	1000-1400
16/18	1000-1180
16/20	850-1180
18/20	850-1000
20/25	710-850
25/30	600-710
30/35	500-600
45/60	250-355
60/80	180-250

** other sizes available on request*

"Line-of-Sight" to Available Technologies



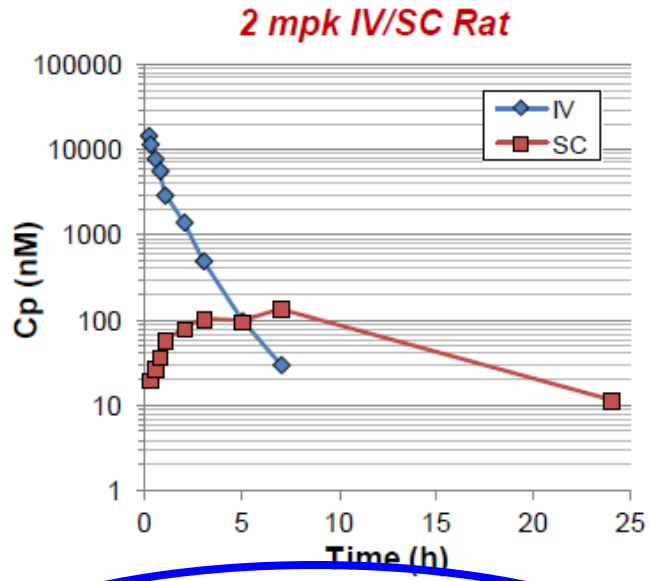
Subcutaneous: Lots of Options



Courtesy of Roy Haskell

Desirable Characteristics of SC Formulation

- Extended release: 1 week
- Low initial ("burst") release
  - Depends on TI
- Consistent exposure: Low C_{max}/C_{24h}
  - Preserve exposure for later
- Non-irritating
- Chemically stable
  - In formulation & in vivo
- Zero-order release: Constant rate
  - Implies not simple diffusion
- Volume less than 1-1.5 mL



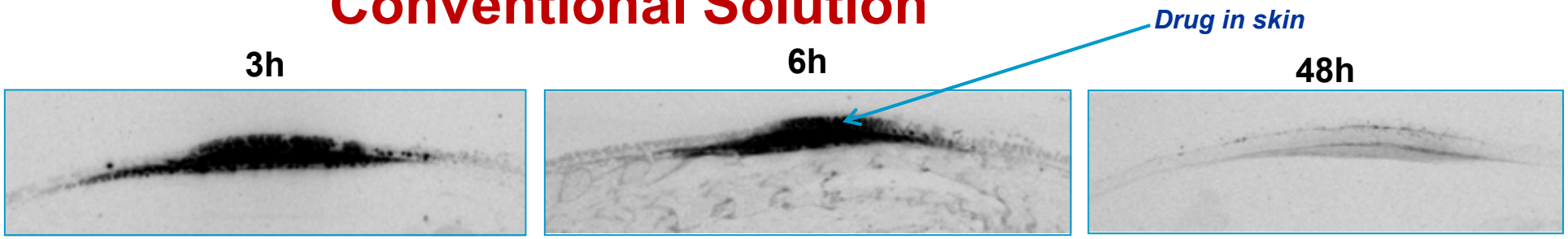
Species	Dose (mpk)	Total Volume (mL)	Dosing Volume (mL/kg)	Conc. (mg/mL)
Rat	2	0.8	2	1
Human	2	1.0	0.014	140

Translation Issue

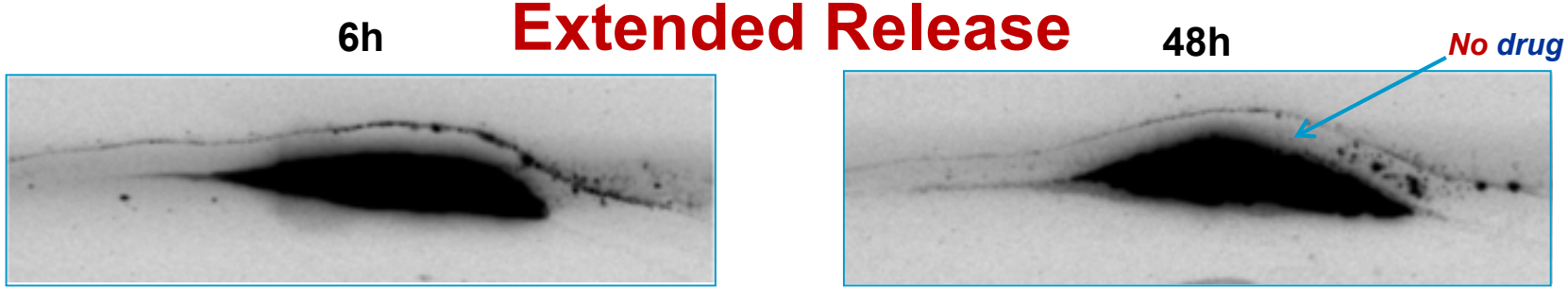
Courtesy of Roy Haskell

Diagnostic Measurements: Quantitative Whole-Body Autoradiography

Conventional Solution



Extended Release



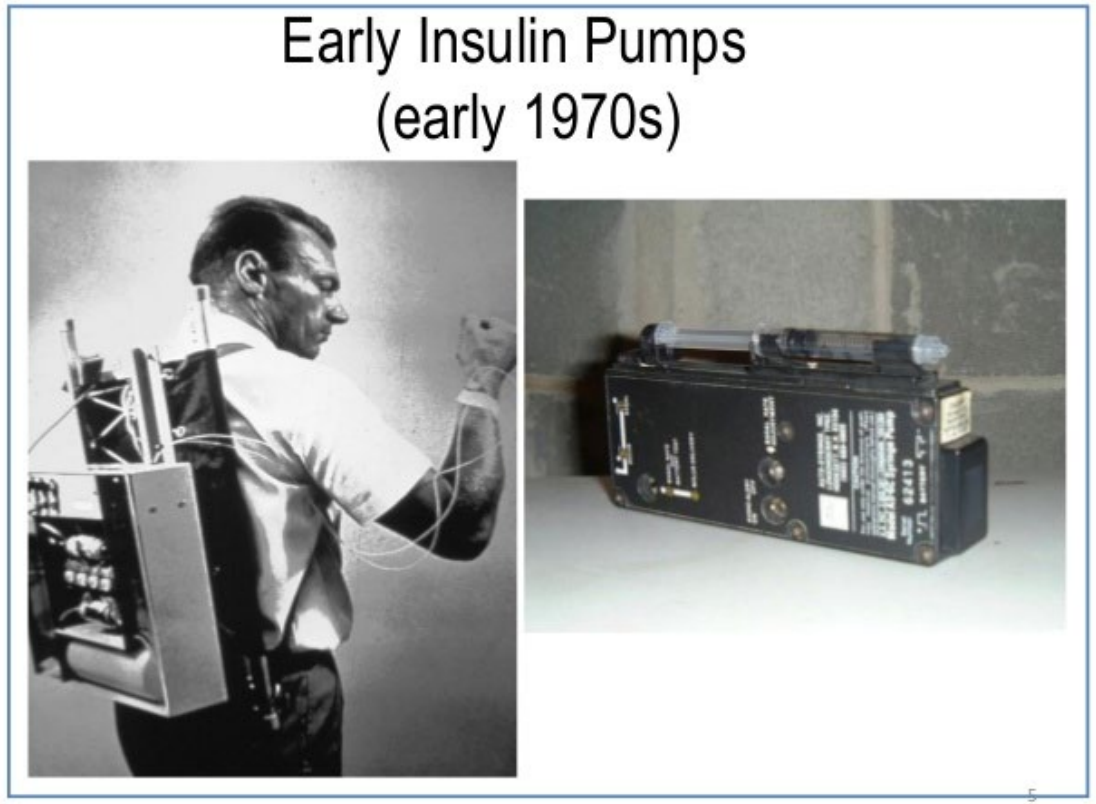
- ^{14}C radio-labeled compound
- Extra legs in biodistribution study
  - Two formulations; multiple time points
- Frozen tissue sectioned for 2D imaging
- Decomposition of compound within site of injection
- Presumed to be driven by formulation depot

Courtesy of Roy Haskell

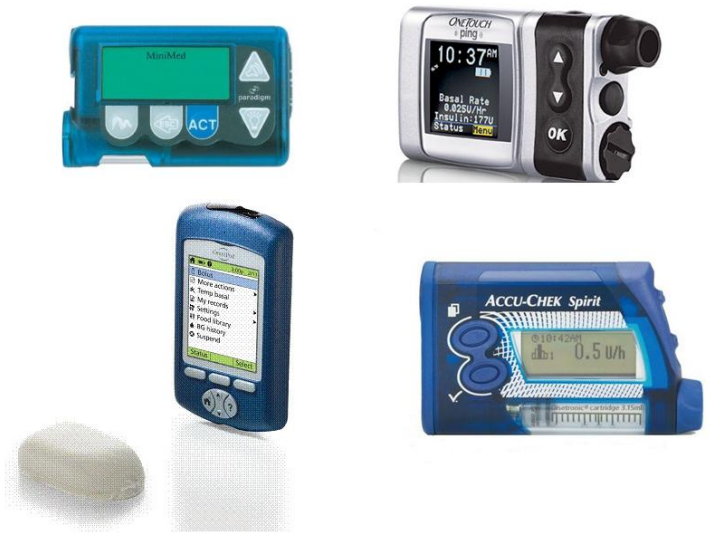
Large Expansion of Injector Pen Devices to Manage The Growth in Specialty Product Portfolios

What are the physicochemical and formulation requirements of a molecule for such systems?

The Ever Changing Device Market Driven by Needs -- Or -- By Technology Availability?



Today's Insulin Pumps



The need was there, but the solution tends to be limited by the technology and the culture it must penetrate.

Large Dose Volume Bolus Injection Systems

A flexible, scalable platform of wearable, disposable devices for the subcutaneous delivery of large-dose volume therapies with optimal patient comfort and convenience

UNILIFE

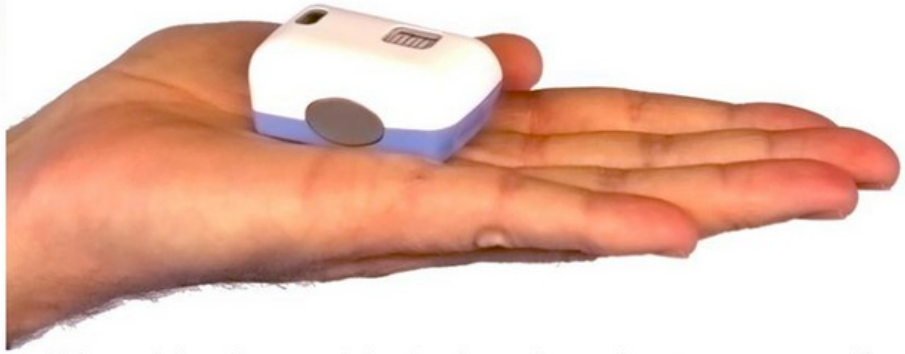
From 1mL - 30mL dose volumes

Bolus or Rate-Based Therapies

Standard Handling and Materials in Fluid Path

November 8, 2012

AutoInfusors

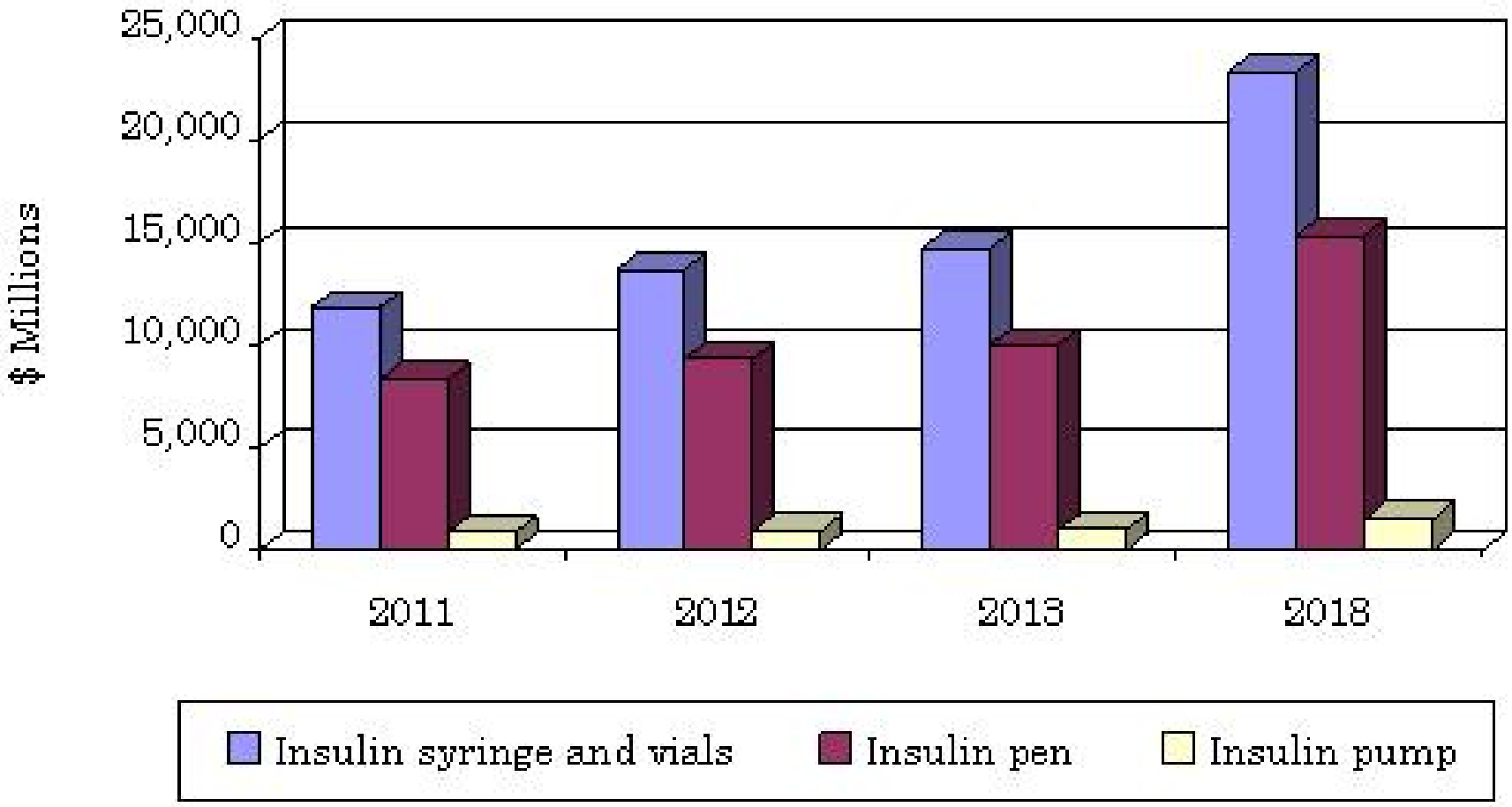


- Wearable, disposable devices for subcutaneous self-administration of large volume doses (i.e. 2mL to 15mL)
- Platform expanding rapidly in response to customer demands
  - Supplied to multiple parties for evaluations and user studies
  - Expect to enter commercial partnerships for human clinical drug trials

April 26, 2012 7

What are the physicochemical and formulation requirements of a molecule for such systems?

Don’t Forget the Simpler Technologies Though



57% **38%** **5%**

Joe Jancsurak, Sep 19, 2013 Medical Design

Preclinical Molecular Optimization

Challenges of Designing a Better Train While it is Moving

Discovery Culture will be integral to establish a way of thinking, a way of action, which can manage the dynamic tensions of speed and quality

Progressability & Developability

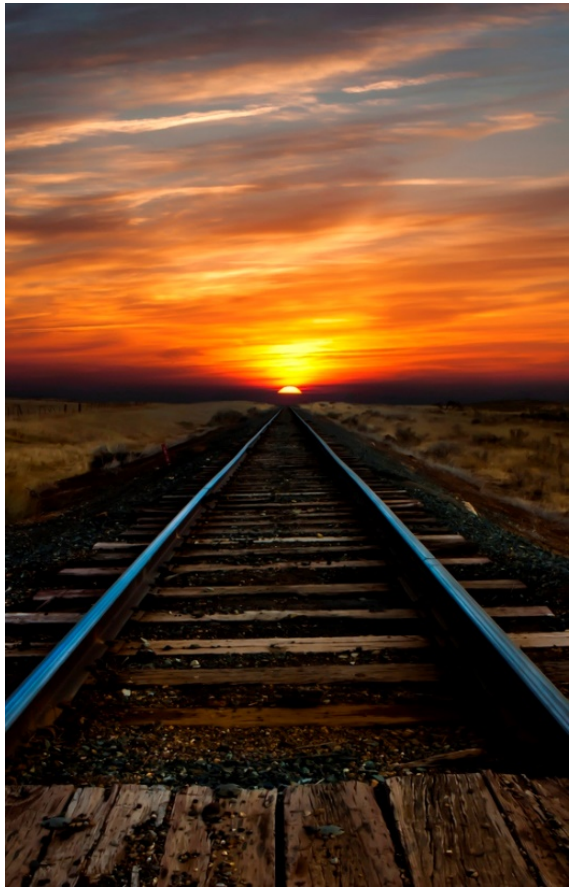
Measurable risk is preferred over unmeasurable uncertainty.

Now that we have a High Speed Train … A Highly Evolved Modality

Can we Keep it on the Tracks?

"Good"

"Better"



"Best"

Building a High Speed Trains is Fine But ….

The Infrastructure Supporting the System Will Often Dictate the Pathways and the Probabilities of Success

Take Away Messages in Today's Presentation

- **Complexity of new modalities (TIDES) will require us to go Beyond a Stage-Gate Mentality for Transition into Development**
  - Influence Molecular Structure Design and Selection
  - Obtain appropriate marriage of delivery technology and molecular entity selected
- **Ability to Produce Material and Data when Eliminative or Selective Decisions are being made is Paramount to Successful Integration**
- **Pharmaceutics has to be an Enabling Function for the Discovery Process Intended to Discover New Treatment Options as Opposed to Presenting a Gauntlet for Molecular Selection**
- **Surrogate Measurements & Technologies are Necessary to Derisk Progression**
  - Require implementation consistent with timelines and API availability within Discovery
  - We need better predictive models based on structure
- **Drug Delivery and Line-of-Sight Strategies or Technology Options are Critical to De-risk Progressability and Developability**
- **The culture and work process has to evolve with the evolving modalities**