Inception
A Versant Discovery Engine

Engaging with development partners

NCI Drug Development Workshop
Entrepreneurship: Partnering and Advancing

Jeremy Caldwell, Ph.D
CEO, Inception Therapeutics
Venture Partner, Versant Ventures

November 19th, 2021

Versant focuses on de novo company building

Discovery engines are a significant source of newcos

Translate vision into important companies and medicines

LYCIA THERAPEUTICS · Therachon · akero · BlueRock · aprea therapeutics · OYSTER POINT · AUDENTES

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Inception Therapeutics:

A Versant Ventures Engine for Company Creation

A team of **visionary scientists, company creators, and venture capitalists** building and launching **transformative biotechnology companies**

- **Founded** in 2011
- **Data-driven drug developers:** deep expertise in chemistry, biology, biologics, DMPK across multiple therapeutic modalities
- **Experienced company builders:** proven track record in creating platform companies for drug discovery, development and translation
- **State-of-the-art wet labs**: molecular & cell biology, vivarium space, chemistry hoods, established relationships with CROs
- **Blue-chip healthcare investment capital** that champions innovation in biotech

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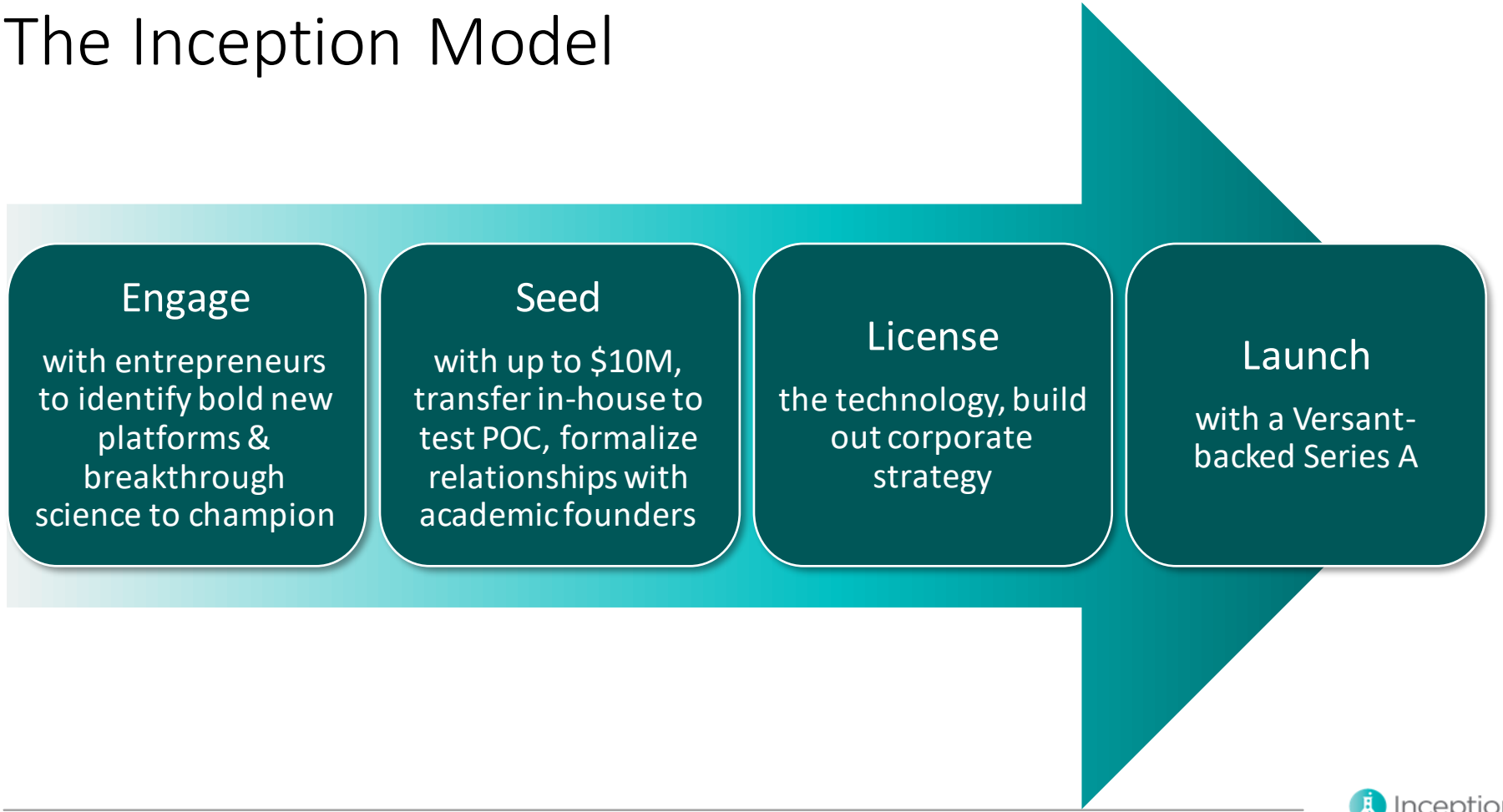
The Inception Model



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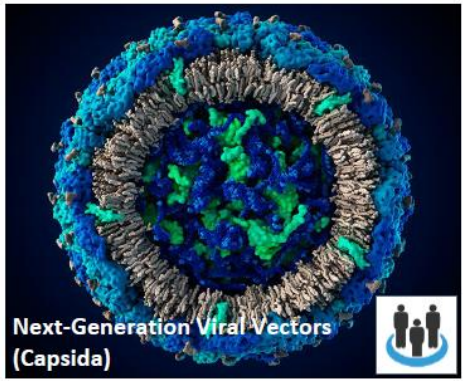
The Inception Value Proposition, Summarized

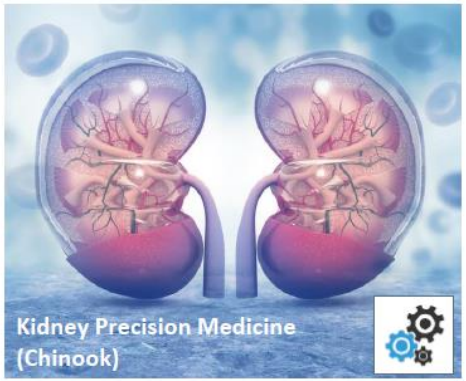
Champion innovation, position it for success

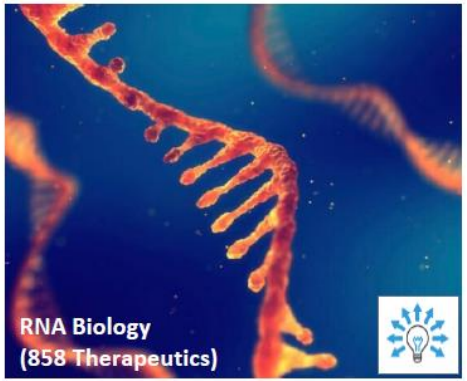
- ✓**Fast Validation and Development:** established wet lab capabilities
  - staffed with 30+ experienced drug developers: small molecule, protein, RNA, gene therapy, regenerative medicine
  - equipped with state-of-the-art technology
  - supported by an extensive network of CROs
- ✓**Shape the corporate strategy:** envision the opportunity, define the pipeline, identify the partners, drive the conversation
- ✓**Capitalize to succeed**

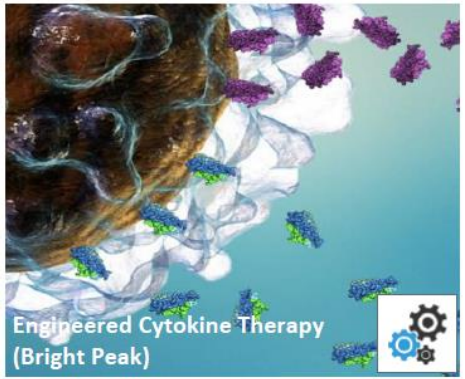
Innovative Companies

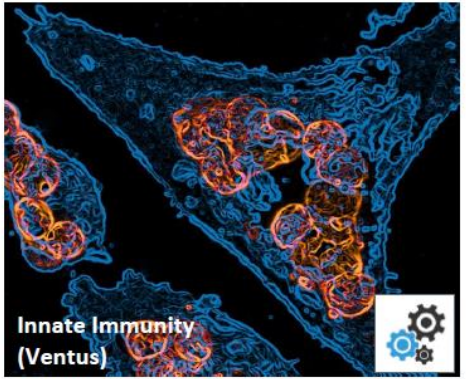
Inception/Discovery Engine launches (Lycia, Chinook, Ventus, Bright Peak)

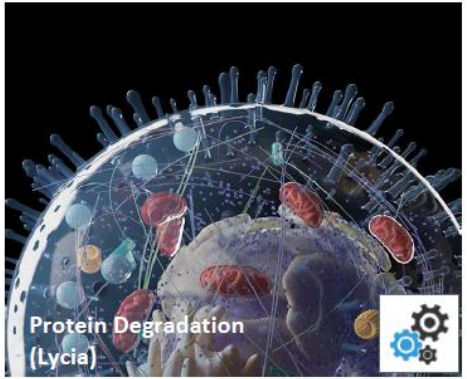












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Where do we find newco ideas?

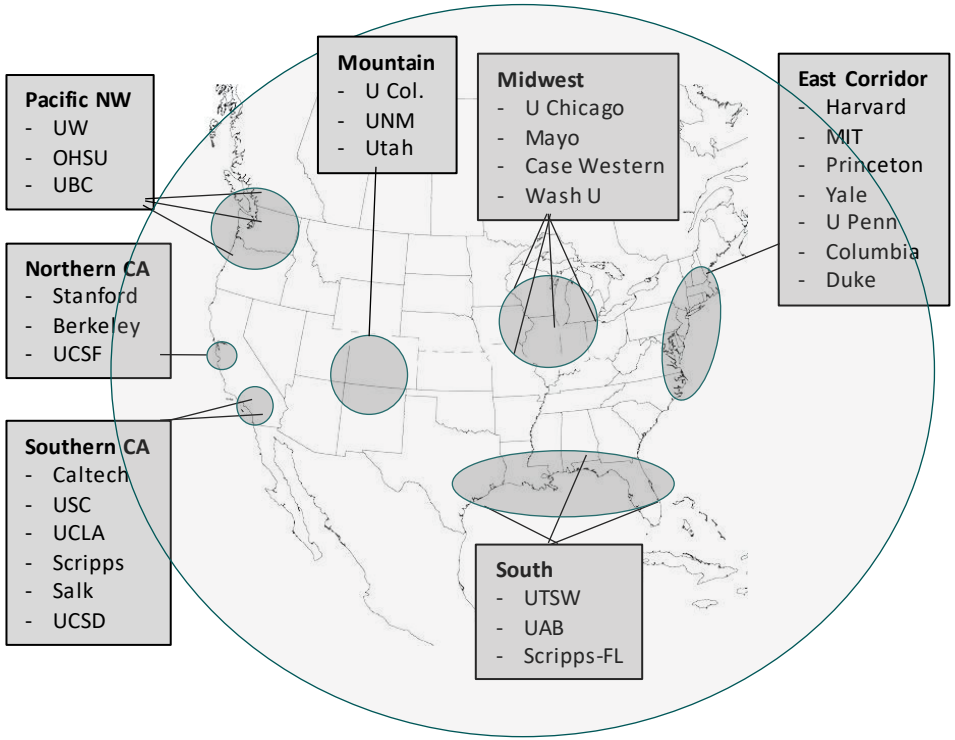
- **Hardwire sustainable pipeline of new ideas/opportunities through key relationships with KOLs, academics, entrepreneurs**
- **Continual mapping of "hot" idea space, waves, investment wants in collaboration with Versant, Pharma, futurists**
- **Add scientific leadership to contribute to idea generation**
- **Opportunities from multiple sources**

Academia/ Industry

- Geography Agnostic
- Relationships with universities established to identify ideas

Inception/ Versant Network

- Entrepreneurs, consultants, KOLs, connectors
- Inception/Versant Core
- Scientific Advisory Board



The Inception SAB:

World renowned chemists and biologists

Carolyn Bertozzi

- Stanford Professor
- MacArthur Fellow at 33
- Member, Nat'l Academy of Sciences
- Inventor of 'Bio-orthogonal Chemistry'
- Founder of 4 biotechs

Ben Cravatt

- Scripps Professor
- 15+ major academic awards
- Member, Nat'l Academy of Sciences
- Chemical proteomics pioneer
- Co-Founder: ActiveX, Abide, Vividion

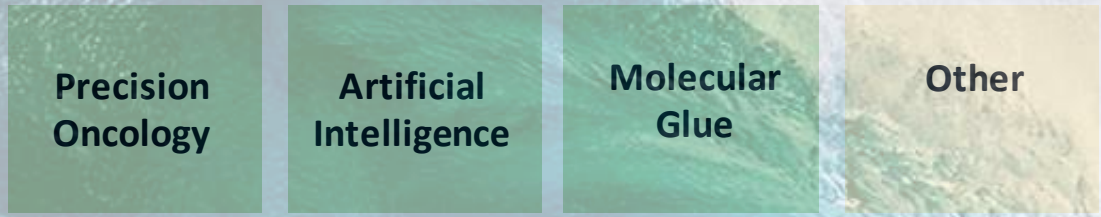
Nathanael Gray

- Harvard/DFCI Prof, moving to Sanford
- Co-Founder: C4, Syros, Soltego, Petra
- Responsible for 2 GNF drugs
- Eli Lilly Award in Biological Chemistry
- Nancy Lurie Marks endowed professorship

Jim Wells

- UCSF Professor
- Inventor of "Tethering"
- Founding scientist in Genentech's Protein Engineering Department
- Co-Founder: Sunesis, Soteria
- Member, Nat'l Academy of Sciences

Waves of innovation



- Would you rather jump on a wave that is just forming or cresting?
- How do we think about this?

What to look for in a new concept?

- Wave of innovation - is the field cresting or just forming? Are we late or too early?
- Compelling technology platform
  - Reduce biological risk
  - Take on technical risk
- Differentiation - what is the unfair advantage? Does it uniquely solve a problem in the field?
- Opportunities – are there many applications or is the risk binary?
- Reduction to practice – how ready is the technology for financing?
- Star Power – are there credible founders, proven company builders involved, the right team?
- Dual Liquidity -
  - IPO - is there a path to IPO?
  - M&A – is there pharma interest in the area?

Precision Oncology

	Diagnostics	Precision Oncology	"Precision" Oncology
Approaches	• Genome, ctDNA, exosome sequencing based approaches • Focus on enabling more sensitive, tissue sparing biopsies and integrating "multi-omics" datasets	• Targeting specific oncology-drivers based on mutation, lineage dependent fusions • Low biological risk	• Targeting specific oncogenic drivers – overexpression, linkage to cancer, tumor suppression • Delivering payloads to specific cells
Representative companies	GRAIL, FOUNDATION MEDICINE, freenome, EXACT SCIENCES	BLACK DIAMOND THERAPEUTICS, TYRA, blueprint MEDICINES, cogent BIOSCIENCES	CODIAK, KINNATE BIOPHARMA, BOUNDLESS BIO, REPARE THERAPEUTICS
Notes	• Highly crowded space • Identify patterns consistent with cancer • Diagnostic model a tough business – low margins	• Hot area/competitive • Challenging to be 1st to find target/prevalence • Selectivity over wild-type gene often key for TI	• Hot area with many competitors • Requires biological insights/delivery platforms insights over obvious mutations • Loose definition of "precision"

- What new avenues could be opened to create new entrants in this space?

Artificial Intelligence – Drug Discovery

	Screening	Small Molecule Discovery	Target Identification
Approaches	• Computation assisted methods to find novel starting points against targets	• Drug lead optimization using structure-guided methods	• Novel target identification using massive biological datasets
Representative companies	Atomwise SCHRÖDINGER	Genesis Therapeutics XtalPi Exscientia	Recursion insitro
Notes	• Vintage of AI approaches • Many partnerships harvested from these approaches • Is there still meat on the bone?	• Attractive area for investment but does it work? • What are opportunities and who are the experts?	• Higher biological risk • Drug repurposing (Recursion) not a very investable thesis

- Which of these areas has opportunity for most transformation?

Molecular Glue

	Hetero-bifunctional	Mono-valent	Screening
Approaches	• Ligase linked to target binder; branching out to DUBs and other enzyme functions	• Newest foray aimed at solving the challenge of large bifunctionals	• Systems developed to identify glue-able partners or small molecules that favor interactions
Representative companies	Monte Rosa Therapeutics, FRONTIER MEDICINES, stablix, nurix, C4 Therapeutics, ARVINAS	NEOMORPH, AMPHISTA THERAPEUTICS, DUNAD therapeutics	A-ALPHA BIO
Notes	• Many PROTAC companies • Typically large molecules with poor developability properties	• Amenable to more traditional small molecule optimization • Difficult to find – a few from nature	• Reliance on HT RNAseq; typically in vitro systems • Unclear value but well-funded

- Nature has not delivered many glues (Auxin, FK506, etc.) so is best bet to find/establish screening methodology?

Protein degradation is a compelling area

	Cytosolic proteins	Cell surface receptors	Secreted proteins
Approaches	• Ligase-targeting bispecific compounds (PROTACs, dTAGs, Trim-Away, SNIPERs, etc) *	• PROTACs (if cytosolic domain is large, *e.g.* RTKs) • mAbs that drive target internalization • Receptor cross-linking	• Targeting circulating IgG antibodies (FcRn binders, SELDEGs) • ENDTACs – ligand for internalizing GPCRs coupled to targeting ligand (from Arvinas founder's lab)
Representative companies	ARVINAS, VIVIDION, nurix, KYMERA, Cedilla, Frontier, C4 Therapeutics, Cullgen, Plexium		CHUGAI, argenx, ucb, ALEXION
Notes	• Multiple companies focused on developing orally available ligase-targeting bispecific molecules	• Relatively few companies	• Competition with antibodies, however opportunity exists

- What is the next wave of innovation in the protein degradation space?

Criteria for assessing platform opportunities

Science

- **Scientific de-risking:**
  - What are the scientific risks each concept faces, and how well have they been addressed?
- **Identifying the "killer app":**
  - Having a highly compelling lead program often helps to drive interest in a platform. Do we have visibility on a lead, and realistically, how soon do we think we can get a lead program into the clinic?
  - Line of sight to additional pipeline targets?
- **Differentiation:**
  - How unique and enabling is the approach relative to others in the space?
  - Would the company have an unfair advantage?

People, Business

- **Star power:**
  - How well known/strong are the scientists/entrepreneurs/potential C-suite?
- **Market opportunity:**
  - What is the breadth of the platform/opportunity?
  - Does it address or create numerous opportunities which will capture market interest?
- **Pharma interest:**
  - Are the opportunities in areas where pharma is showing strong interest?
  - How confident are we that we'll be able to raise non-dilutive capital for these?

Criteria for assessing asset/pipeline opportunities

Science

- **Scientific de-risking:**
  - Does the target(s) have strong evidence for therapeutic utility via human genetics, compelling human biology
  - How predictive are the translational models?
- **Time to the clinic; time to PoC:**
  - How soon do we think we can get a lead program into the clinic?
  - Is there a clear regulatory path for the indication/modality?
  - How soon can PoC be achieved in the clinic (Phase 1, 2; trial length)?
- **Differentiation/Competition:**
  - How unique and enabling is the approach relative to others to the target(s) in the space?
  - Is there FTO and a clear path to protectable IP
  - Would the company have an unfair advantage?

People, Business

- **Star power:**
  - How credible are the scientists/entrepreneurs/potential C-suite?
- **Market opportunity:**
  - Does the target(s) address or create numerous opportunities which will capture market interest?
  - Is there evidence for utility in multiple indications?
- **Pharma interest:**
  - Are the assets in areas of high interest to big pharma
  - How confident are we that we'll be able to raise non-dilutive capital for these?

Stage of newco concepts of interest

Academic – white space

- ❑ Investable theme
- ❑ No validation
- ❑ Unpublished
- ❑ No IP
- ❑ No VCs associated yet, possible relationships
- ❑ Unfunded, looking for backers or NIH
- ❑ No mgmt team
- ❑ Post docs starting
- ❑ High risk

Academic – PoC achieved

- ❑ Investable theme
- ❑ Some validation - 1 lab
- ❑ Pre-pub/early pub
- ❑ IP filed/being filed
- ❑ Other VCs involved? Tier 1 or 2
- ❑ Unfunded, looking for backers
- ❑ No mgmt team
- ❑ Ready post docs
- ❑ High risk

Proto/Seed Co - early

- ❑ Investable theme
- ❑ 1+ lab validation
- ❑ Pre-pub/early pubs
- ❑ IP filed
- ❑ Other VCs involved? Tier 1 or 2
- ❑ Modest funding, pre-value creation
- ❑ Partial mgmt team
- ❑ Small science team
- ❑ Med/high risk

Seed Co – later stage

- ❑ Investable theme
- ❑ Most PoC achieved
- ❑ Pre-pub/early pubs
- ❑ Multiple IP filed
- ❑ Other VCs involved, Tier 1 or 2
- ❑ Modest funding, early value created
- ❑ Partial mgmt team
- ❑ Med science team
- ❑ Medium risk

Series A

- ❑ Investable theme
- ❑ PoC achieved
- ❑ Early pubs
- ❑ Multiple IP filed
- ❑ Other VCs involved, Tier 1
- ❑ Modest funding, value created
- ❑ Mgmt team
- ❑ Science team
- ❑ Med/low risk

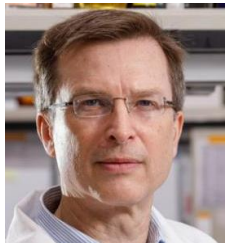

LYCIA
THERAPEUTICS

How did Lycia get it’s start?

Carolyn Bertozzi

ChemRxiv™

Pre-print journal



Craig Crews

twitter

Social media

VERSANT ventures

Venture Firm

iPhone

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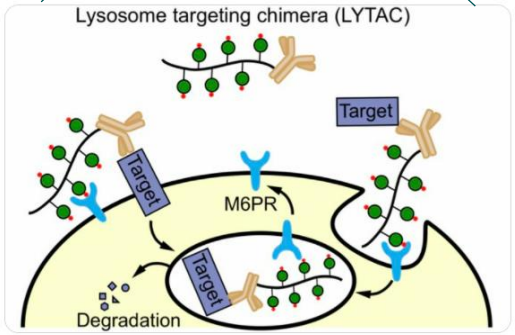
Discovery Engine



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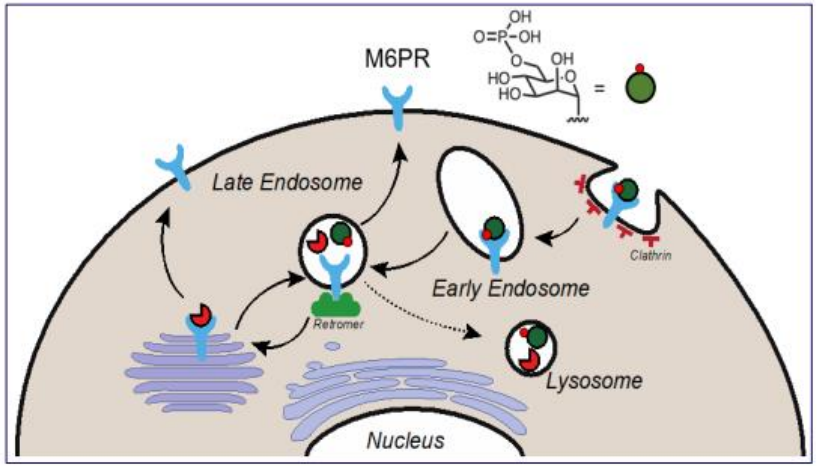
Is this a differentiated opportunity in a compelling space?

40% of proteome

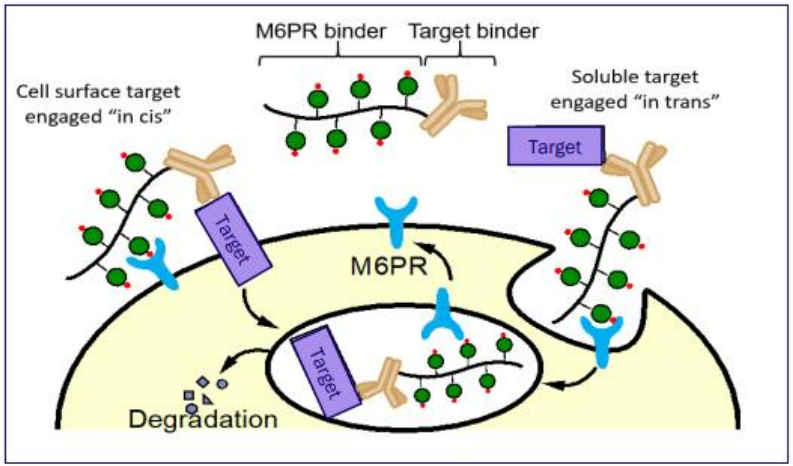
	Cytosolic proteins	Cell surface receptors	Secreted proteins
Approaches	• Ligase-targeting bispecific compounds (PROTACs, dTAGs, Trim-Away, SNIPERs, *etc.*)	• mAbs that drive target internalization • Receptor cross-linking	• Targeting circulating IgG antibodies (*e.g.*, FcRn binders), other soluble proteins
Representative companies	ARVINAS, VIVIDION, nurix, KYMERA, Cedilla, Frontier, C4 Therapeutics, Cullgen, Plexium		CHUGAI, argenx, ucb, ALEXION
Notes	Multiple companies focused on developing orally available ligase-targeting bispecific molecules	**LYTAC platform addresses these categories – limited competition focused primarily on lysosomal targeting of circulating autoantibodies *via* FcRn**	

How much technical and biological risk is involved?

- The mannose-6-phosphate receptor (M6PR) is a lysosomal trafficking shuttle
- M6PR ligands bind M6PR and are internalized through endosomes and shuttled into lysosomal degradation compartments
- M6PR ligands linked to target binders drag extracellular targets into lysosomes for degradation

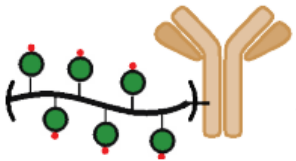


~Decades of work – well understood biology



Leveraging millions of years of evolution

Are there a broad set of applications or few?



1. **Degradation of challenging membrane targets**
   - e.g., Ligand-independent and TKI-resistant RTKs in oncology
2. **Clearing protein aggregates and immune complexes**
   - e.g., pathogenic Ig elimination
3. **Removal of circulating immunoglobulin**
   - e.g., deletion of auto Abs
4. **Tissue-specific target inhibition to improve therapeutic indexes**
   - e.g., tumor-targeted degradation

1 Degradation of Challenging Membrane Targets

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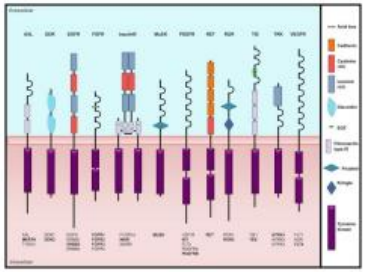
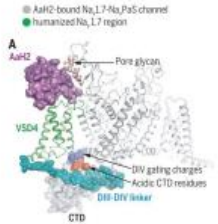
Ligand-independent and TKI-resistant RTKs

- Over-expression and activating mutations observed in many cancers (*e.g.*, EGFR, TRK, ROS, FGFR)



Ion channels

- Mutations in $Na_V1.7$ and other related sub-types can cause devastating disease
  - Potential to leverage epitope on NaV subunit that is recognized by toxin 'blockers' to drive degradation



LYTAC platform could provide:

- Ability to degrade otherwise undruggable targets
- Sustained suppression of target signaling
- Increased epitope space: ability to utilize a non-functional Ab with LYTAC to drive degradation
- Possibility to overcome primary resistance by degrading multiple mutant forms with a single drug

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❷ Clearing Protein Aggregates and Immune Complexes

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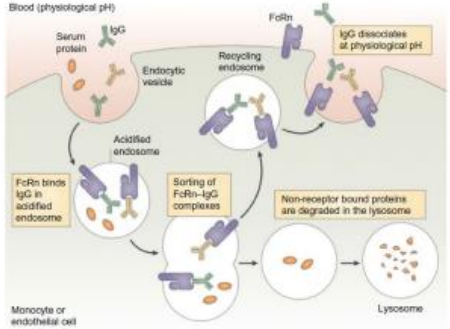
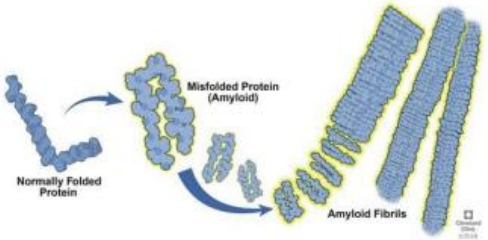
Pathogenic Immune Complexes (ICs) as LYTAC Targets

- Depletion of pathogenic ICs validated with FcRn inhibitors
- Model system of IgG2a established to demonstrate uptake of LYTACs and LYTAC-mediated clearance of ICs *in vitro*



Proteinopathies driven by protein misfolding and aggregation

- Amyloidoses (TTR, AL - light chain, beta2-microglobulin)
- Alzheimer's disease



LYTAC platform could provide:

- Selective removal of specific Ig complexes → improved safety and efficacy
- Degradation of large complexes inaccessible to other modalities

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❸ Removing of Circulating Immunoglobulin

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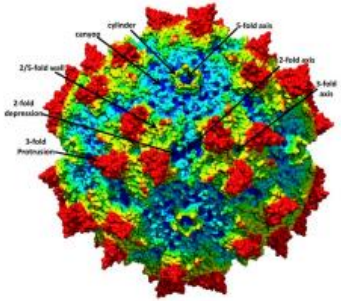
Selective depletion of Abs with antigen-LYTAC

- Autoantibodies to discrete antigens drive autoimmunity in *e.g.*, myasthenia gravis, pemphigus, Graves disease

Degradation of neutralizing antibodies to neoantigens, *e.g.*,

- **Adeno-associated virus (AAV)**: host immunity against AAV capsids represent major challenge to gene therapy, with cross-reactivity of NAbs across multiple AAV serotypes
- **Enzyme replacement therapies**: NAbs to ERTs significantly reduce efficacy, thereby enabling disease progression and potentially death (*e.g.*, Pompe's disease)
- **Clotting factors**



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4 Tissue-Specific Target Inhibition to Improve Therapeutic Indexes

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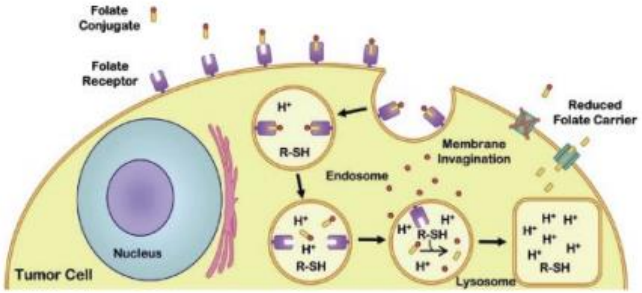
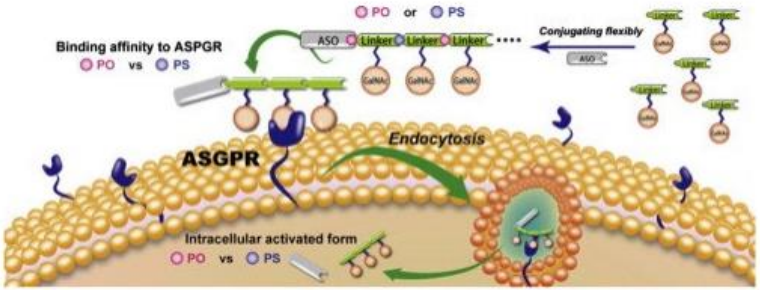
Candidate receptor systems provide opportunity to target specific tissues and avoid toxicity

Folate Receptor



- Folate receptor is overexpressed in certain tumors (ovarian, breast, lung), with low/restricted expression in normal tissues

ASGPR



- Liver-specific expression for tissue specific degradation

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Can it be reduced to practice beyond the founder's lab?
~cell surface receptors

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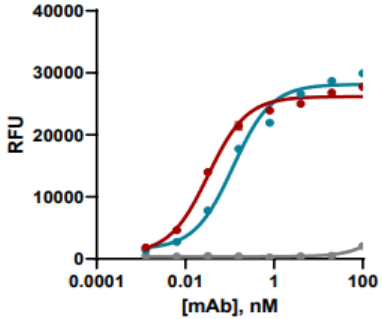
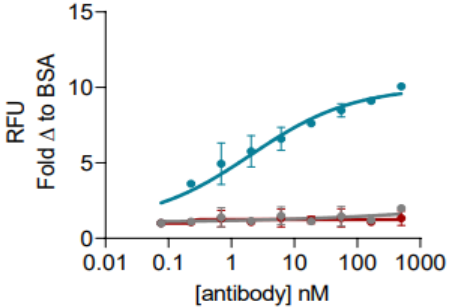
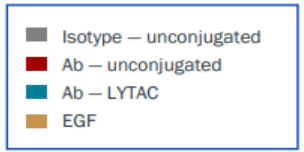
EGFR binding ELISA

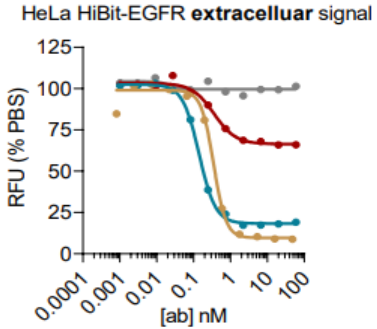


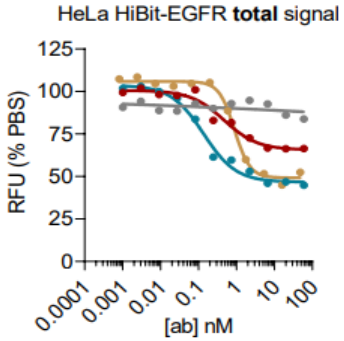
Cl-M6PR ELISA



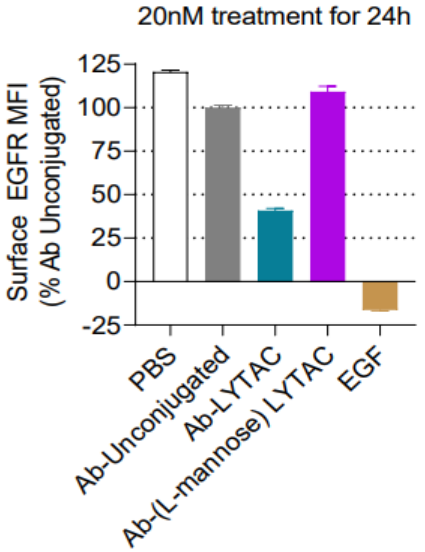


High throughput surface and total EGFR detection





Surface EGFR by flow cytometry



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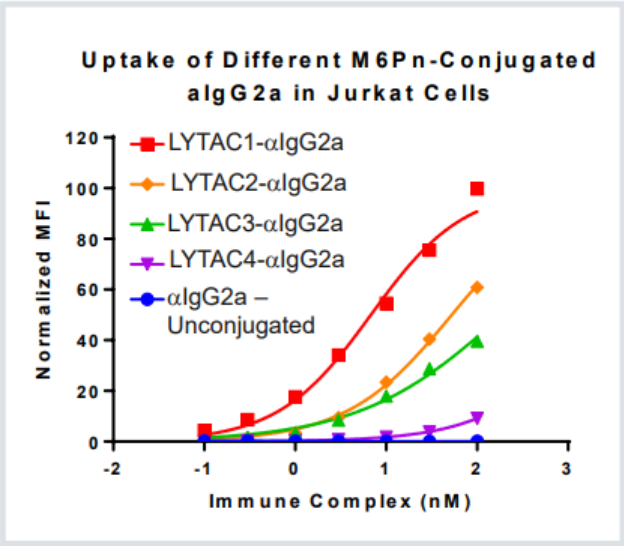
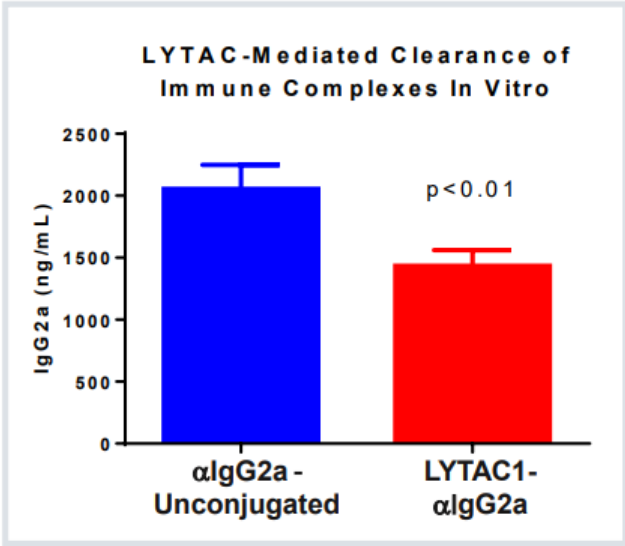
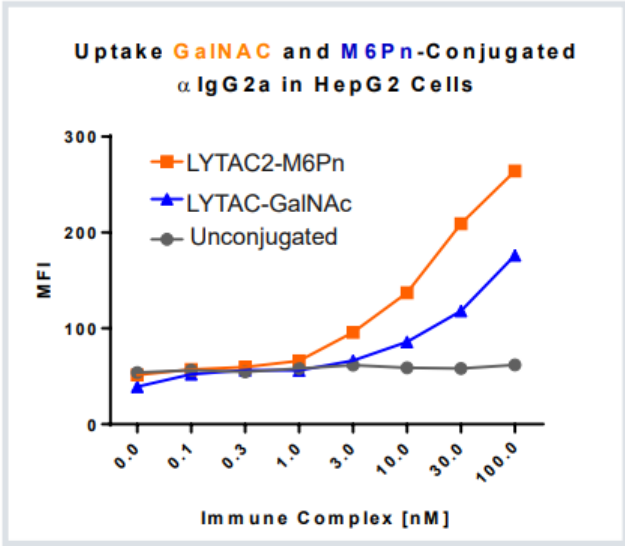
Can it be reduced to practice beyond the founder's lab?
~soluble proteins







LYTAC technology has the elements of an investable company

- ✓ Wave of innovation - is the field cresting or just forming? Are we late or too early?
- ✓ Compelling technology platform
  - ➢ Reduce biological risk
  - ➢ Take on technical risk
- ✓ Differentiation - what is the unfair advantage? Does it uniquely solve a problem in the field?
- ✓ Opportunities – are there many applications or is the risk binary?
- ✓ Reduction to practice – how ready is the technology for financing?
- ✓ Star Power – are there credible founders, proven company builders involved, the right team?
- ✓ Dual Liquidity -
  - ➢ IPO - is there a path to IPO?
  - ➢ M&A – is there pharma interest in the area?

So we established Lycia and began building company

- Currently > 20 FTEs progressing platform and pipeline programs
- Founder Carolyn Bertozzi intimately involved with company
- HQ to be established in San Francisco Bay Area

- Strong and growing intellectual property position
- Multiple programs to fuel a pipeline of LYTAC therapeutics

* Secured Lilly partnership and $70M Series B financing in 3Q2021

Lessons learned

Finding newcos, competing for the deal, engaging the founders and scientists

VERSANT ventures

Inception
A Versant Discovery Engine

Platform versus pipeline, striking the balance

People, culture, credibility

Aetna Wun Trombley, CEO

Science driven

Carolyn Bertozzi, Founder