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.
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
The Inception Model

Engage
with entrepreneurs to identify bold new platforms & breakthrough science to champion

Seed
with up to $10M, transfer in-house to test POC, formalize relationships with academic founders

License
the technology, build out corporate strategy

Launch
with a Versant-backed Series A
The Inception Value Proposition, Summarized

Champion innovation, position it for success

✓ **Fast Validation and Development**: established wet lab capabilities
  
  o staffed with **30+ experienced drug developers**: small molecule, protein, RNA, gene therapy, regenerative medicine
  
  o equipped with **state-of-the-art technology**
  
  o 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)
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
- Entrepreneurs, consultants, KOLs, connectors
- Inception/Versant Core
- Scientific Advisory Board

**Inception/Versant Network**

**Pacific NW**
- UW
- OHSU
- UBC

**Northern CA**
- Stanford
- Berkeley
- UCSF

**Southern CA**
- Caltech
- USC
- UCLA
- Scripps
- Salk
- UCSD

**Mountain**
- U Col.
- UNM
- Utah

**Midwest**
- U Chicago
- Mayo
- Case Western
- Wash U

**South**
- UTSW
- UAB
- Scripps-FL

**East Corridor**
- Harvard
- MIT
- Princeton
- Yale
- U Penn
- Columbia
- Duke

**Northern CA**
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- MIT
- Princeton
- Yale
- U Penn
- Columbia
- Duke
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

### Approaches

<table>
<thead>
<tr>
<th>Diagnostics</th>
<th>Precision Oncology</th>
<th>&quot;Precision&quot; Oncology</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Genome, ctDNA, exosome sequencing based approaches&lt;br&gt;- Focus on enabling more sensitive, tissue sparing biopsies and integrating “multi-omics” datasets</td>
<td>- Targeting specific oncology-drivers based on mutation, lineage dependent fusions&lt;br&gt;- Low biological risk</td>
<td>- Targeting specific oncogenic drivers – overexpression, linkage to cancer, tumor suppression&lt;br&gt;- Delivering payloads to specific cells</td>
</tr>
</tbody>
</table>

### Representative companies

**GRAIL**<br>**FOUNDATION MEDICINE**<br>**freenome**<br>**EXACT SCIENCES**

**BLACK DIAMOND THERAPEUTICS**<br>**TYRA**

**BLUEPRINT MEDICINES**<br>**COGENT BIOMEDICAL**

**CODIAK**<br>**KINNATE**

**BOUNDLESS BIO**<br>**REPARE THERAPEUTICS**

### Notes

- Highly crowded space<br>- Identify patterns consistent with cancer<br>- Diagnostic model a tough business – low margins

- Hot area/competitive<br>- Challenging to be 1st to find target/prevalence<br>- Selectivity over wild-type gene often key for TI

- Hot area with many competitors<br>- Requires biological insights/delivery platforms insights over obvious mutations<br>- Loose definition of "precision"

• What new avenues could be opened to create new entrants in this space?
## Artificial Intelligence – Drug Discovery

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

- Which of these areas has opportunity for most transformation?
# Molecular Glue

## Approaches

<table>
<thead>
<tr>
<th>Hetero-bifunctional</th>
<th>Mono-valent</th>
<th>Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ligase linked to target binder; branching out to DUBs and other enzyme functions</td>
<td>Newest foray aimed at solving the challenge of large bifunctionals</td>
<td>Systems developed to identify glue-able partners or small molecules that favor interactions</td>
</tr>
</tbody>
</table>

## Representative companies

- Monte Rosa Therapeutics
- Frontier Medicines
- stablix
- nurix
- C4 Therapeutics
- ARVINAS
- NEOMORPH
- AMPHISTA Therapeutics
- DUNND 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

<table>
<thead>
<tr>
<th>Approaches</th>
<th>Cytosolic proteins</th>
<th>Cell surface receptors</th>
<th>Secreted proteins</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>* Ligase-targeting bispecific compounds (PROTACs, dTAGs, Trim-Away, SNIPERs, etc)</td>
<td>• PROTACs (if cytosolic domain is large, e.g. RTKs) • mAbs that drive target internalization • Receptor cross-linking</td>
<td>• Targeting circulating IgG antibodies (FcRn binders, SELDEGs) • ENDTACs – ligand for internalizing GPCRs coupled to targeting ligand (from Arvinas founder’s lab)</td>
</tr>
</tbody>
</table>

Representative companies

<table>
<thead>
<tr>
<th>ARVINAS</th>
<th>VIVIDION</th>
<th>nLRnx</th>
<th>KYMERA</th>
<th>Cedilla</th>
<th>Frontier</th>
<th>Cellicon</th>
<th>Plexium</th>
</tr>
</thead>
</table>

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

<table>
<thead>
<tr>
<th>Science</th>
<th>People, Business</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scientific de-risking:</strong></td>
<td><strong>Star power:</strong></td>
</tr>
<tr>
<td>- What are the scientific risks each concept faces, and how well have they been addressed?</td>
<td>- How well known/strong are the scientists/entrepreneurs/potential C-suite?</td>
</tr>
<tr>
<td><strong>Identifying the “killer app”:</strong></td>
<td><strong>Market opportunity:</strong></td>
</tr>
<tr>
<td>- 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?</td>
<td>- What is the breadth of the platform/opportunity?</td>
</tr>
<tr>
<td>- Line of sight to additional pipeline targets?</td>
<td>- Does it address or create numerous opportunities which will capture market interest?</td>
</tr>
<tr>
<td><strong>Differentiation:</strong></td>
<td><strong>Pharma interest:</strong></td>
</tr>
<tr>
<td>- How unique and enabling is the approach relative to others in the space?</td>
<td>- Are the opportunities in areas where pharma is showing strong interest?</td>
</tr>
<tr>
<td>- Would the company have an unfair advantage?</td>
<td>- How confident are we that we’ll be able to raise non-dilutive capital for these?</td>
</tr>
</tbody>
</table>
## Criteria for assessing asset/pipeline opportunities

<table>
<thead>
<tr>
<th>Science</th>
<th>People, Business</th>
</tr>
</thead>
</table>
| **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? | **Star power:**  
- How credible are the scientists/entrepreneurs/potential C-suite? |
| **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)? | **Market opportunity:**  
- Does the target(s) address or create numerous opportunities which will capture market interest?  
- Is there evidence for utility in multiple indications? |
| **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? | **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

<table>
<thead>
<tr>
<th>Academic – white space</th>
<th>Academic – PoC achieved</th>
<th>Proto/Seed Co - early</th>
<th>Seed Co – later stage</th>
<th>Series A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investable theme</td>
<td>Investable theme</td>
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<td>Investable theme</td>
<td>Investable theme</td>
</tr>
<tr>
<td>No validation</td>
<td>Some validation - 1 lab</td>
<td>1+ lab validation</td>
<td>Most PoC achieved</td>
<td>PoC achieved</td>
</tr>
<tr>
<td>Unpublished</td>
<td>Pre-pub/early pub</td>
<td>Pre-pub/early pubs</td>
<td>Pre-pub/early pubs</td>
<td>Early pubs</td>
</tr>
<tr>
<td>No IP</td>
<td>IP filed/being filed</td>
<td>IP filed</td>
<td>Multiple IP filed</td>
<td>Multiple IP filed</td>
</tr>
<tr>
<td>No VCs associated yet, possible relationships</td>
<td>Other VCs involved? Tier 1 or 2</td>
<td>Other VCs involved? Tier 1 or 2</td>
<td>Other VCs involved, Tier 1</td>
<td>Other VCs involved, Tier 1</td>
</tr>
<tr>
<td>Unfunded, looking for backers or NIH</td>
<td>Unfunded, looking for backers</td>
<td>Modest funding, pre-value creation</td>
<td>Modest funding, early value created</td>
<td>Modest funding, value created</td>
</tr>
<tr>
<td>No mgmt team</td>
<td>No mgmt team</td>
<td>Partial mgmt team</td>
<td>Partial mgmt team</td>
<td>Mgmt team</td>
</tr>
<tr>
<td>Post docs starting</td>
<td>Ready post docs</td>
<td>Small science team</td>
<td>Med science team</td>
<td>Science team</td>
</tr>
<tr>
<td>High risk</td>
<td>High risk</td>
<td>Med/high risk</td>
<td>Medium risk</td>
<td>Med/low risk</td>
</tr>
</tbody>
</table>
How did Lycia get it’s start?

Carolyn Bertozzi

Craig Crews

Pre-print journal

Social media

Venture Firm

iPhone

Discovery Engine

Lysosome targeting chimera (LYTAC)

Target

Degradation

M6PR
Is this a differentiated opportunity in a compelling space?

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<th>40% of proteome</th>
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<td>compounds (PROTACs, dTAGs, Trim-Away, SNIPERs, etc.)</td>
<td>mAbs that drive target internalization</td>
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<td></td>
<td>Receptor cross-linking</td>
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<tr>
<td></td>
<td>Targeting circulating IgG antibodies (e.g., FcRn binders), other soluble proteins</td>
</tr>
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</table>

Representative companies

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
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 $\text{Na}_v 1.7$ 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
Clearing Protein Aggregates and Immune Complexes

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
3 Removing of Circulating Immunoglobulin

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
Tissue-Specific Target Inhibition to Improve Therapeutic Indexes

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

- Folate receptor is overexpressed in certain tumors (ovarian, breast, lung), with low/restricted expression in normal tissues
- Liver-specific expression for tissue specific degradation
Can it be reduced to practice beyond the founder’s lab?
~cell surface receptors
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

Platform versus pipeline, striking the balance

People, culture, credibility

Aetna Wun
Trombley, CEO

Carolyn Bertozzi,
Founder