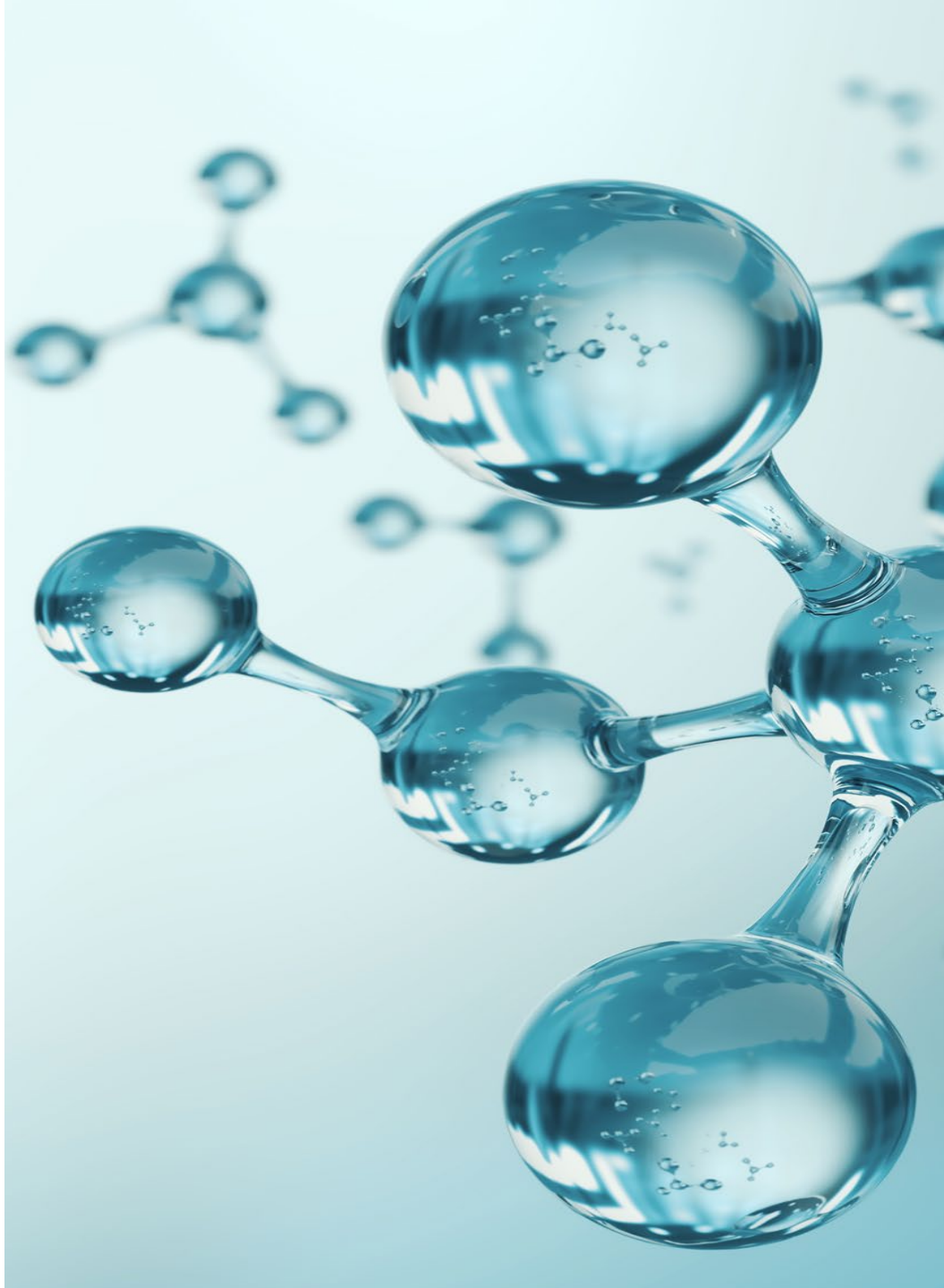
THERABENE

THE DEGRADERS COMPANY

Development of TB-003, a potent, selective CDK9 hetero-bifunctional degrader against Triple Negative Breast Cancer and other indications

Non-confidential Deck



Company Overview – Therabene LLC

- Founded in Feb 2020 and then incorporated as a Delaware company in Mar 2020
- The Therabene founding/operational team is comprised of experts in organic chemistry, translational medicine and clinical development
- Seed investments financed to-date by company founders for research and operations
- Lab and office spaces are leased through the BioIncubator in Mansfield MA USA (https://www.bioinc.org/)
- Therabene has been developing hetero-bifunctional small molecule degraders using proteolysis-targeting chimeras (PROTAC) technology

CDK9 dependency in transcriptionally addicted cancers

- Cyclin dependent kinase 9 (CDK9)-mediated phosphorylation of RNA polymerase II (RNAPII) at serine 2 (pSER2) and other transcriptional regulators is a necessary step to proceed from transcriptional initiation to elongation.

- MYC requires high rates of transcription and is therefore dependent on CDK9 for its expression and function as a cancer driver.

- Thus, inhibition of CDK9 has been shown to have anti-tumor effects in tumors that are addicted to high levels of MYC.

- ~30% of common cancer types have MYC amplification
  - NSCLC (30%), Ovarian (65%), Breast (30%), Pancreatic (28%) etc.

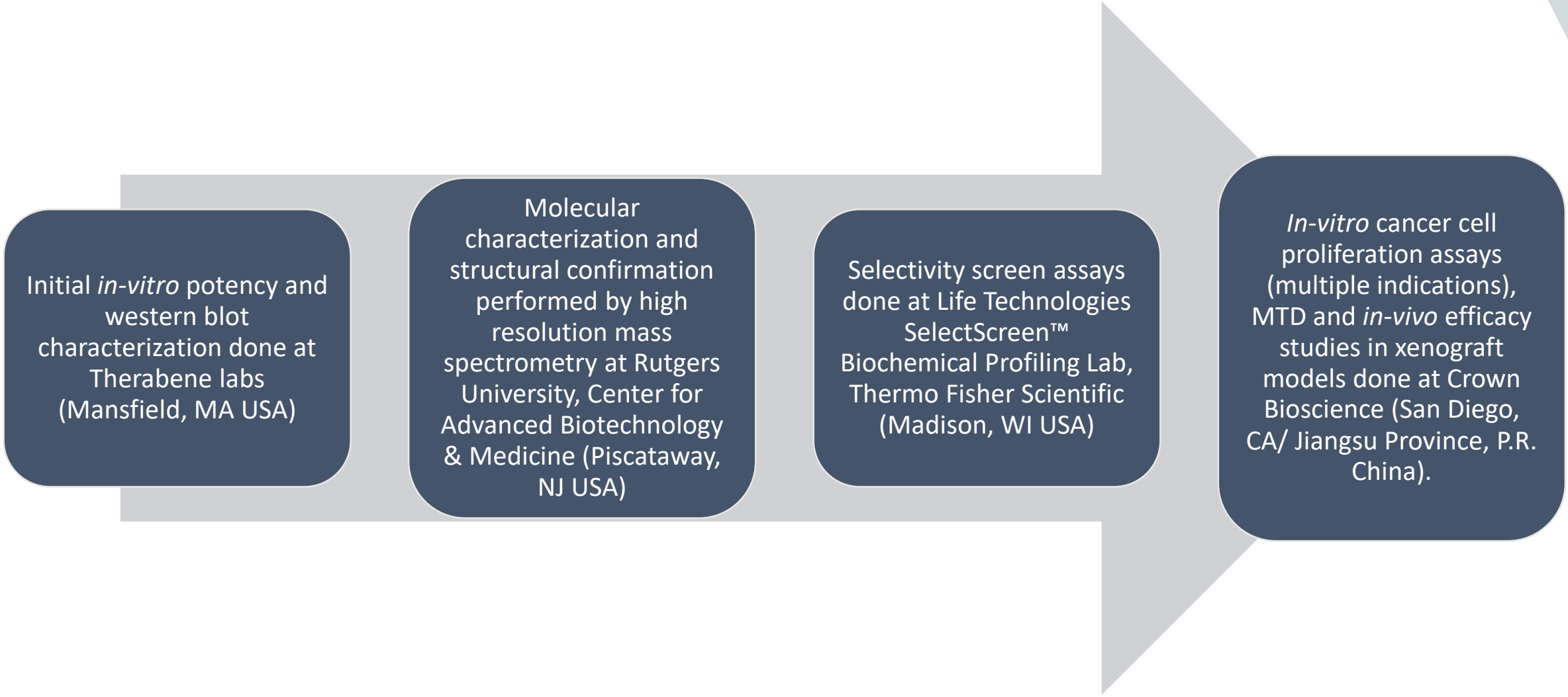
Competitive Landscape of CDK9 Inhibitor Therapeutics

- **Preclinical/Discovery**
  - PRT-2572 (Prelude Therapeutics)
  - VIP217 (Vincerx)
  - I-073 (Univ of South Australia)
  - JSH-150 (Chinese Academy of Sciences)
  - Research Program (Nankai Univ, breast cancer)
  - Research Program (Pharos, AML)
- **Phase I**
  - AZD4573 (AstraZeneca)
  - KB-0742 (Kronos Bio)
  - VIP152 (Vincerx)
  - GF-106 (GenFleet)
  - Sunaciclin (Aucentra)
- **Several pan-CDKs**
  - Fadraciclib (Cyclacel)
  - TP-1278 (Sumitomo Dainippon Pharma)
  - Voruciclib (MEI Pharma)

Currently NO competitor in CDK9 degrader space*

*Recently Wei et al. *J Med Chem* 2021 (publication date: Sep 20, 2021) from Chinese Academy of Sciences, Shanghai, China reported development of CDK9 degrader. However, no CDK9 degrader are under development from biotech/pharma companies to our knowledge.

Therabene's TB-003 CDK9 PROTAC – Chemistry and Biology



In-vitro Characterization of TB-003

- **Kinase screening**
  - CDK1, CDK2, CDK7 and CDK9 screening was conducted by the Life Technologies SelectScreen™ Biochemical Profiling Lab at Madison, WI
  - 10-point Titration: Thermo Fisher Scientific SelectScreen™ Kinase Profiling using either Adapta or Lantha assay methods
- **Protein degradation**
  - TB-003 treatment downregulated CDK9 by 2 hours. The loss in CDK9 protein was sustained at 24h and 48h time points. Performed in-house

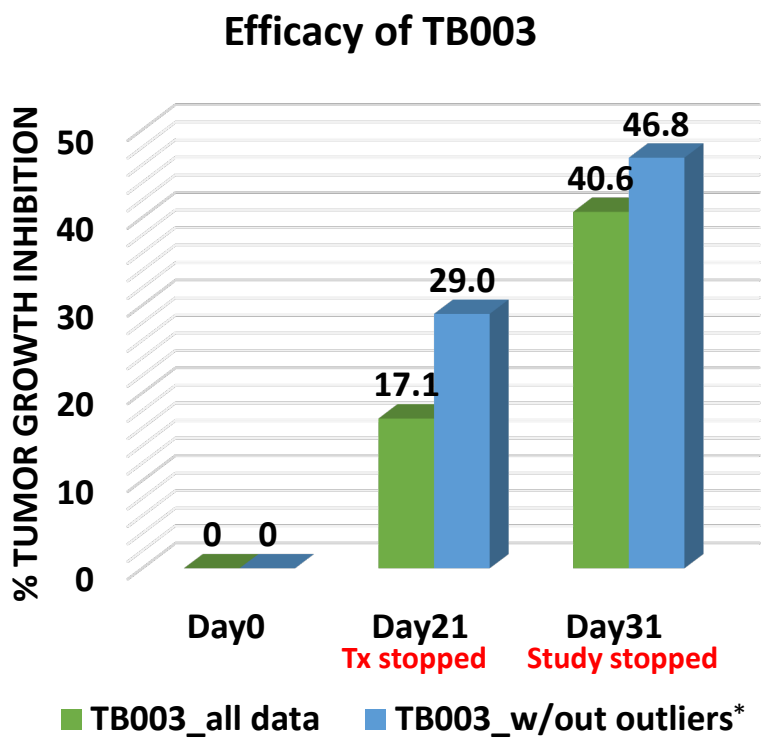
Compound		**TB-003**	**KB-130742**	**AZ4573**	**BAY1251152**
Modality		**CDK9 degrader**	**CDK9 inhibitor**	**CDK9 inhibitor**	**CDK9 inhibitor**
Potency (biochemical IC_{50})	**CDK9**	**5nM**	**15nM**	**3nM**	**3-4nM**
Fold selectivity CDK9 vs other selected CDK family members	**CDK7**	>200x	147x	18x	≥90x
	CDK2	>200x	447x	1x	730x
	CDK1	>200x	281x	2x	≥90x
Route of administration		**IP/Oral**	**Oral**	**IV**	**IV**

KB-130742, AZ4573 and BAY1251152 potency, fold selectivity data and route of administration information from public databases and/or corporate decks.

All confidential data available after CDA

In-vivo Characterization of TB-003

- TB-003 demonstrated excellent tolerability in MTD studies
- TB-003 treatment in HCC1187 triple negative breast cancer cell xenograft model (C57BL/6 female mice; 7 mice in each arm; dose - 10mg/kg i.p., Q2D x 3 weeks followed by 2 weeks of observation) showed nearly 50% decrease in tumor volume compared to control at Day 31
- TB-003 did not cause any body weight loss
- The observed response to TB003 treatment was bimodal, showing cytostatic followed by cytotoxic MOA.
- TB-003 has an excellent therapeutic window and we anticipate substantially stronger anti-tumor efficacy if dosage level and/or frequency/duration of treatment is (are) increased.



TB-003, 10 mg/kg, 10 µL/g, i.p., Q2D × 3 weeks followed by 10 days of observation

*1 outlier in each arm

All confidential data available after CDA

Summary

- Therabene is developing a series of degraders for treatment of cancer
- Of these, the lead candidate is TB-003, first-in-class, Cyclin Dependent Kinase 9 (CDK9) Degrader for the treatment of Triple Negative Breast Cancer (TNBC)
- TNBC accounts for >15% of all breast cancers and represents a substantial unmet medical need
- Currently, there are NO known CDK9 degraders in the clinical space
- TB-003 is highly specific for CDK9 with minimal or no interaction with other cyclin dependent kinases
- TB-003 causes a strong decrease in cell viability *in-vitro* and reduces tumor volume *in-vivo*
- TB-003 is well tolerated and has not shown any obvious toxicities
- Its mechanism of action is a unique bimodal anti-tumor activity, comprised of cytostatic and cytotoxic effects
- The founders of Therabene have privately financed the Seed Capital, covering operational and research expenditures to-date
- Therabene is looking to raise up to $5Million in capital to fund development activities to reach IND enabling stage within the next 18 months

Short-term milestones

- **File global patents for IP protection**
- **Complete the following studies within the next 6-12 months** (some of these studies will be run concurrently)
  - Oral formulation (2 strategies)
  - Pharmacokinetic studies
    - IP delivery
    - Oral delivery
    - TB-003 packaged in targeted nanoparticles
  - MTDs head-to-head with different delivery methods
  - Scale up production and produce GMP lot
  - Toxicity studies – mice, rat
  - *In vitro* characterizations in multiple MYC-amplified indications
  - *In vivo* characterizations – longer timepoints, intermittent dosing strategies
  - Preclinical combination approaches (SoC and novel-novel)
- **Expand on Therabene's CDK9 degrader pipeline**
  - Continue preclinical evaluation of TB-001-TB-004
- **Continue with AI-assisted molecular docking/chemical synthesis for discovery of novel degraders for new oncology targets**