Targeted Protein Degradation by Proteasomal, Lysosomal & Autophagy Pathways:

An industry landscape analysis of stakeholders, technologies, pipeline, partnering and financing

released by
La Merie Publishing
on March 6, 2022

La Merie Publishing
Carrer Núria, 10, 3, 2a
E-17500 Ripoll
info@lamerie.com

Table 15: Overview of Remainder of TPD Discovery Technologies

Company	Drug Class	DegrPath	TPD Modal	Discovery Technologies
Origami Tx	SM	Protea	nd	AI & machine-learning, computational chemistry, patient derived 2D cells: ORICISION
Vividion Tx	SM	Protea	nd	Chemoproteomics screening platform with covalent chemistry-based library; novel E3 ligase binders
VectorY	Ab	?	?	Antibody-based TPD – no details
Prelude Th	SM	Protea	nd	Structure-based drug design with iterative cycles of synthesis and testing
Prazer Tx	SM	?	?	SPiDEM: Selective Protein Degradation Enabling Moiety – no details
Trilo Tx	PM	?	?	DNA-encoded library of constrained peptidomimetic compouds to target PoI
HB Tx	SM	Protea	MG	Cancer-cell based sumoylation screening
Isoprene Ph	SM	Protea	?	Mnk1/2 degrader

SM, small molecule, PM, peptidomimetic; MG, molecular glue; Pept, peptide; Ab, antibody; Bifunct, bifunctional; Autop, autophagy; Protea, proteasomal; Lyso, lysosomal; mono, monovalent (degrader); nd, not disclosed

Vividion's proprietary chemoproteomics discovery platform comprises three integrated, synergistic components (Vividion SEC Registration Statement S-1 June 25, 2021):

1. A proprietary covalent chemistry-based library of small molecules designed to selectively bind protein pockets, including cryptic and shallow pockets;
2. A novel chemoproteomic screening technology that Vividion designed to sensitively and precisely detect small molecule interactions with any class of protein in their native cellular context at scale; and
3. An integrated data portal that combines their proprietary chemoproteomic data with public databases to generate new insights into protein structure and locations of novel pockets on previously undruggable therapeutic targets.

The proprietary covalent chemistry-based library of small molecules is designed to selectively bind cryptic pockets. Through iterative cycles of design and proteome-wide testing, they have built and continue to refine a library of cysteine-reactive small molecules specifically designed to enter and form covalent bonds with accessible cysteine residues located in shallow binding pockets in proteins in their native conformations. Vividion's growing covalent chemistry-based library consists of over 15,000 highly diverse CRG-bearing small molecules that thoroughly exploit three-dimensional space.

The novel chemoproteomic screening technology represents industrialized methods to enable the parallel screening of thousands of surface cysteine residues across the entire human proteome. This technology uses high resolution mass spectrometry and chemical "probes" to detect the interactions between small molecules and any protein regardless of functional class. Vividion's approach allows to efficiently mine the proteome to find cryptic functional pockets that were

Arvinas with Pfizer. Without this deal, average revenues from collaboration agreements were US$ 133 mln per company.

Table 26 lists all investors of the pure play TPD technology companies listed in Table 25. Investors include private and public entities, such as CPRIT (Cancer Prevention & Research Institute of Texas); ALSF (Alex's Lemonade Stand Foundation – pediatric cancer); Michael J. Fox Foundation for Parkinson's Research; governmental investment funds; European Union funds and others.

Major pharma companies also have invested directly or indirectly via the venture capital vehicles. Among them are

- Novartis: Amphista; C4 Therapeutics, Dunad Therapeutics
- Eli Lilly: Amphista; Kymera Therapeutics; Lycia Therapeutics; Seed Therapeutics
- Bayer: Arvinas
- Pfizer: Arvinas; Kymera Therapeutics
- Roche: C4 Therapeutics
- AbbVie: Caraway Therapeutics;
- Amgen: Caraway Therapeutics; Kymera Therapeutics;
- Takeda Pharmaceutical Co: FIMECS
- Sanofi: Kymera Therapeutics
- Bristol Myers Squibb (via Celgene): Nurix Therapeutics
- Merck KGaA (EMD Serono): Plexium
- SK Holdings: Proteovant Therapeutics
- Vertex Pharmaceuticals: Kymera Therapeutics

Major pharma companies with more than one investment into a TPD company are Novartis, Eli Lilly, Pfizer and Amgen. According to the territory of the headquarters of a TPD company, investors usually are from the same territory, e.g. South Korea, China , UK.

Table 26a: Investors of TPD Technology Companies

Investor	Grant	Seed	Series A-C	Equity	Company	Territory
Scotish Investment Bank		X	X		Amphista	UK
Advent Life Sciences			X		Amphista	UK
European Investment Bank			X		Amphista	UK
BioMotiv			X		Amphista	UK
Forbion			X		Amphista	UK
Gilde Healthcare			X		Amphista	UK
Novartis Venture Fund			X		Amphista	UK
Eli Lilly and Company			X		Amphista	UK
Canaan Partners			X		Arvinas	US
5AMV Ventires			X		Arvinas	US
Elm Street Ventures			X		Arvinas	US
Connecticut Innovations			X		Arvinas	US

7.2.9 Ubix Therapeutics

Korean biotechnology company Ubix Therapeutics was founded in 2018 with the purpose to further develop and commercialize "Degraducer Technology". This Proteolysis Targeting Chimera (PROTAC) technology was developed by the Korea Research Institute of Chemical Technology and the Korea Research Institute of Bioscience and Biotechnology through a Creative Convergence Research Project supported by the National Research Council of Science & Technology. The company is focused on the development of new drugs targeting epigenetics and new immune-oncology proteins.

Financial background

On May 8, 2020, Ubix Therapeutics raised US$ 12.2 mln in a series B financing round from Atinum Investment, Korea Development Bank, Partners Investment, Premier Partners, and UTC Investment (source). In previous rounds, Ubix had secured US$ 3.6 mln.

Degraducer Technology

Degraducer is a technology that utilizes the ubiquitin-proteasome system (UPS), an intracellular degradation system. Degraducer is a bifunctional small molecule comprised of a "ligand", which binds to a target protein, and a "binder", which binds to E3 ubiquitin ligase. Thus, Degraducer is a powerful technology that enables target protein degradation and consequent therapeutic effects by placing a disease-related target protein nearby E3 ligase, which can then initiate the protein degradation system.

Partnering

In March 2020, Ubix Therapeutics entered into an exclusive license agreement with NeoImmuneTech to develop up to three drug candidates utilizing Ubix' Degraducer platform technology which enables target protein degradation (Press Release Mar 23, 2020). NeoImmuneTech (NIT) acquired the exclusive worldwide rights to research, develop, and commercialize drug candidates, in exchange for development and sales milestones, as well as royalties. NeoImmuneTech intends to broaden the company's T cell-focused portfolio to include novel **T cell suppressor blockades** in addition to their clinically advanced T cell amplifier, NT-I7 (long-acting human interleukin-7).

In June 2021, Debiopharm, a Swiss-based global biopharmaceutical company and Ubix Therapeutics announced their co-research agreement combining two novel proprietary technologies to specifically target cancer cells (Press Release June 16, 2021). The two companies are aiming to develop a new drug modality known as **Antibody Degraducer Conjugates** (ADeC), by combining one of Ubix's Degraducer molecules, with Debiopharm's antibody drug conjugate linker Multilink. Degraducer linked to therapeutic antibodies via Multilink will improve drug targeting and could have a synergistic effect on tumor cells, thereby resulting in improved efficacy and safety of cancer therapies.

C4 Therapeutics addresses toxicity driven by degradation of proteins other than the intended target, or off-target toxicity, by developing degraders with high selectivity. they confirm selectivity by global protein expression studies and validate the results through standard good laboratory practice, or GLP, toxicity studies. They also minimize the risk of toxicity driven by the chemical matter making up their MonoDAC and BiDAC molecules that is independent of the specific toxicities described above, or molecule-related toxicity, with high quality chemical matter optimized to minimize known chemical and metabolic liabilities.

8.2 Profiles of Heterobifunctional Proteasomal TPD Technologies

8.2.1 ACCU-Degron Technology Platform - Accutar

Accutar Biotechnology employs artificial intelligence (AI) for drug discovery. With capabilities in side chain flexible mode ligand docking, virtual screening, and drug ADME property prediction, Accutar's platform beats the industry standard in computation-aided drug design. The company's hybrid based approach, which uses computational drug design followed by wet lab validation, greatly reduces the time and cost necessary for traditional drug discovery efforts.

Accutar Biotech's AI is made up of several components: Accutar Virtual Screen, Docking, Intelligent-SAR, and Chemi-Net. These integrated components are used to design novel drug compounds and are intended to be used during the drug development and preclinical trial phases. The virtual representation of protein-ligand bindings is conducted through Accular Virtual Screen and Docking. Intelligent-SAR generates novel compounds which are then validated through co-crystallization and binding assays. Its Chemi-Net platform uses a deep neural network to predict absorption, distribution, metabolism, and excretion (ADME) of these compounds.

Orbital Drug Design is a deep neural network based docking platform. The prediction accuracy of protein-ligand complex (holo) from ligand free state (apo) structure is significantly higher than current standards. Simply provide the ligand in simplified molecular-input line-entry system (SMILES) format and the target protein, and docking becomes as easy as "one click". The typical ligand preparation and target grid definition, hydration, and other parameter-setting steps are no longer needed, because the traditional force field-based energy equations method was abandoned in this approach. Instead, a dynamic deep neural network framework performs the docking task with unprecedented accuracy and speed. The average running time for a drug docking case using "dock all" mode scanning for all potential binding pockets of a target protein is under 1 minute on a standard laptop.

Accutar is able to perform fast and accurate virtual screening of over 10 million compounds. The company also has an automatic and intelligent lead optimization platform based on structure-activity relationship (SAR).

Chemi-Net is a completely data-driven, domain knowledge-free, deep learning method for absorption, distribution, metabolism, and excretion (ADME) property prediction. It is a

monocytic origin. All four kinases have a similar domain structure, which include an N-terminal death domain (where dimerization and MyD88 interaction occurs), a proline/serine/threonine-rich (ProST) domain, a kinase/pseudokinase domain, and a C-terminal domain except for IRAK4. IRAK4 and IRAK1 have intrinsic kinase activities, whereas IRAK2 and IRAK-M are apparently pseudokinases.

Since IRAK-M is a pseudokinase which lacks kinase activity, it is considered 'undruggable' that could not be targeted pharmacologically by conventional small molecules. Therefore, FIMECS has developed heterobifunctional degrader molecules comprising an IRAK-M-binding moiety linked to proprietary XIAP E3 binders to eliminate the IRAK-M protein via the ubiquitin-proteasome system (UPS) (Gamo, 2019a). Optimization of IRAK-M degraders was conducted by applying the company'S RaPPIDS technology which is a proprietary divergent degrader synthetic platform, and FIMECS's scientists identified multiple preclinical candidates (Gamo. 2019b).

Gamo et al. (2019b) demonstrated dose- and time-dependent degradation of IRAK-M protein in THP1 human monocytic leukemia cells with degrader treatment in a proteasome-dependent manner. Myeloid-derived suppressor cell (MDSC) suppression assays revealed that the IRAK-M degrader could release the suppressive function of MDSC on both IFNγ production by CD8+ T cells as well as T cell proliferation. When examined in mouse models, the IRAK-M degrader showed significant anti-tumor activity in several syngeneic models at tolerated doses and schedules. In the 4T1-HA model, they found an increase of LPS-induced TNFα production in white blood cells from compound-injected mice associated with degradation of the IRAK-M protein as pharmacodynamic effect. FACS analysis showed that IRAK-M degradation translated into increased infiltration of M1-like activated macrophage into tumors and spleen. Advanced profiling of the drug candidate is ongoing in IND-enabling studies.

9.2.19 GT19506

One drugging modality in Kintor Pharmaceutical's technology toolbox are heterobifunctional PROTACs. GT19506 is Kintor's c-Myc targeted PROTAC currently in the lead optimization phase.

c-Myc is an oncogenic transcriptional factor, which forms a dimer with Max to activate its transcription activity, driving tumor initiation, progression and poor prognosis in 80% of all tumor types. IGH/Myc genomic translocations have been identified in B-cell lymphoma (15-100%). The amplification of Myc family members, MYC, MYCN, or MYCL has been revealed in 20% patients with small cell lung cancers (SCLC). Therefore, it is highly warranted to discover and develop novel c-Myc targeted compounds for treatment of c-Myc dependent tumors (Lymphoma and SCLC) with an acceptable therapeutic index.

Ma et al. (2021) described the discovery of GT19506, a c-Myc PROTAC, for targeting Myc-dependent tumors. GT19506 effectively degraded c-Myc protein in HL-60 cells with an IC50 of 0.10 μM. The selectivity against the physiologic function of c-Myc was determined in growth

lysosomal biogenesis
Sci Adv. 2021 Oct;7(40):eabj2485. doi: 10.1126/sciadv.abj2485. Epub 2021 Oct 1. (online access)

Gough SM, Sherman D, DeCarr L et al.
Potent and Orally Bioavailable BCL6 PROTAC TM Degraders Demonstrate Efficacy in Pre-Clinical Models of Diffuse Large B-Cell Lymphoma (DLBCL)
Blood 2021; 138 (suppl 1): abstract 2272 (online access to abstract)

Hagner PR, Man HW, Fontanillo C et al.
CC-122, a pleiotropic pathway modifier, mimics an interferon response and has antitumor activity in DLBCL
Blood 2015; 126: 779-789 (online access to paper)

Han X, Wang C, Qin C et al.
Discovery of ARD-69 as a Highly Potent Proteolysis Targeting Chimera (PROTAC) Degrader of Androgen Receptor (AR) for the Treatment of Prostate Cancer
J Med Chem 2019; 62: 941-964

Hansen JD, Correa M, Alexander M et al.
CC-90009: A Cereblon E3 Ligase Modulating Drug That Promotes Selective Degradation of GSPT1 for the Treatment of Acute Myeloid Leukemia
J Med Chem 2021; 64: 1835-1843

Hansen JD, Correa M, Nagy MA et al.
Discovery of CRBN E3 Ligase Modulator CC-92480 for the Treatment of Relapsed and Refractory Multiple Myeloma
J Med Chem 2020; 63: 6648-6676

He W, Zhang H, Perkins L et al.
Novel chimeric small molecule AC682 potently degrades estrogen receptor with oral anti-tumor efficacy superior to fulvestrant
Cancer Res 2021; 81 (4 suppl): abstract nr PS18-09 (online access)

Henderson JA, Kirby RJ, Perino S et al.
CFT7455: A novel, IKZF1/3 degrader that demonstrates potent tumor regression in IMiD-resistant multiple myeloma (MM) xenograft models
Cancer Res 2021; 81 (13 suppl): abstract nr LB007 (online access to abstract and Presentation)

He Y, Koch R, Budamagunta V et al.
DT2216—a Bcl-xL-specific degrader is highly active against Bcl-xL-dependent T cell lymphomas
J Hematol Oncol 2020; 13: 95 (online access)

Heterobifunctional Proteasomal Targeted Protein Degradation – 33 / 50

ID No.	Product Name	Target / Mechanism of Action	Class of Compound	Company	Product Category	Indication	R&D Stage	Message
31207	ORI-113	Degradation of mutant Huntingtin (mHTT): mHTT targeting and engagement of intra-cellu-lar E3 ligase complex	Small molecule PROTAC (PROteolysis TArgeting Chimera)	Origami Therapeutics	Small molecule (NCE)	Huntington's disease	Res	Origami Therapeutics Homepage Oct 14, 2021 - Origami's degrader molecules harness the body's natural protein degradation system to selectively degrade disease-causing proteins with the goal of completely removing them from the body.
30920	ORM-5029	Tumor targeting and degradation of intracellular target proteins within cancer cells via the E3 ubiquitin ligase pathway	Antibody neoDegrader Conjugate (AnDC): antibody conjugated to protein degrader payload	Orum Therapeutics	Antibody	Solid tumor	0	Orum PR June 23, 2021 - Orum closed a $84 million Series B financing. Orum plans to use the proceeds to advance the Company's lead therapeutic candidates into clinical trials, explore additional payload chemistries to develop additional payloads that modulate the ubiquitin pathway, and other general corporate purposes. The lead therapeutic programs from Orum's AnDC platform include ORM-5029 for the treatment of solid tumors. The company plans to file IND application for ORM-5029 in 2022. Based on MoA, degrader must be of molecular glue type