#RESEARCHNEVERSTOPS

Land and Expand

Landing and expanding meaningful partnerships

Landmark develpments at the beginning of 2022

- **Land…**
  - ***Eli Lilly:*** Discovery of potential drug candidates for the treatment of diabetes and chronic kidney diseases from targets identified by Lilly or Evotec

- **Land again…**
  - ***Boehringer Ingelheim:*** iPSC-based disease modelling for ophthalmologic disorders, supported by **EVO***panOmics* platform, to identify small molecules able to modulate disease

- **…and Expand**
  - ***BMS:*** Massive extension and expansion of partnership with Bristol Myers Squibb in targeted protein degradation, originally signed in 2018

Delivering breakthrough therapies via targeted protein degradation

Drugging the undruggable via molecular glues

“Our breakthroughs in the understanding of the mechanism of action of CELMoDs® will enable the discovery of more drugs that can direct the degradation of proteins known to be causing disease.”

Rupert Vessey, BMS

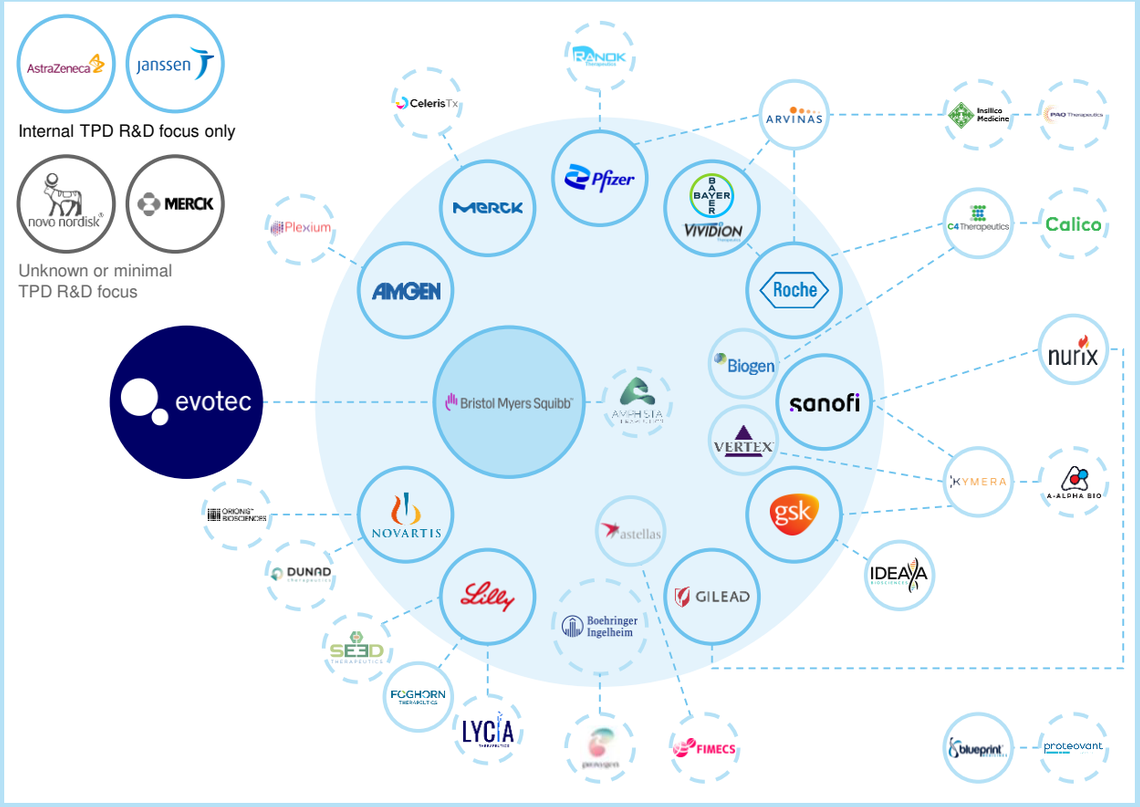
“Molecular glue degraders represent the most important innovation in small molecules in recent history. Industrialized omics combined with AI/ML will help garner the full potential.”

Cord Dohrmann, Evotec

Unique potential translates into a strong engagement industry

BMS & Evotec – Global Leadership in TPD

The expanding universe of Targeted Protein Degradation



- The targeted protein degradation enabling technologies market, anticipated to be **worth over $ 3.3 bn by 2030 (CAGR of around 27%)**
- Partnership activity has **grown significantly between 2014 and 2021 R&D agreements (25%) and research agreements (23%)** emerged as the most popular types of partnership models
- **> $ 5 bn** has been invested by private & public investors **since 2014**
- **>180 investors** have actively financed projects / initiatives in this domain

Public (> $ 25 bn mkt. cap) Public (< $ 25 bn mkt. cap) Private / subsidiary Strategic collaboration and/or license agreement

Sources: https://cen.acs.org/pharmaceuticals/drug-discovery/quest-drug-undruggable/96/i26; https://www.nature.com/articles/nrd892?proof=t
https://www.rootsanalysis.com/reports/view_document/protein-degradation-market/289.html

Moving from exploration to a long-term strategic partnership

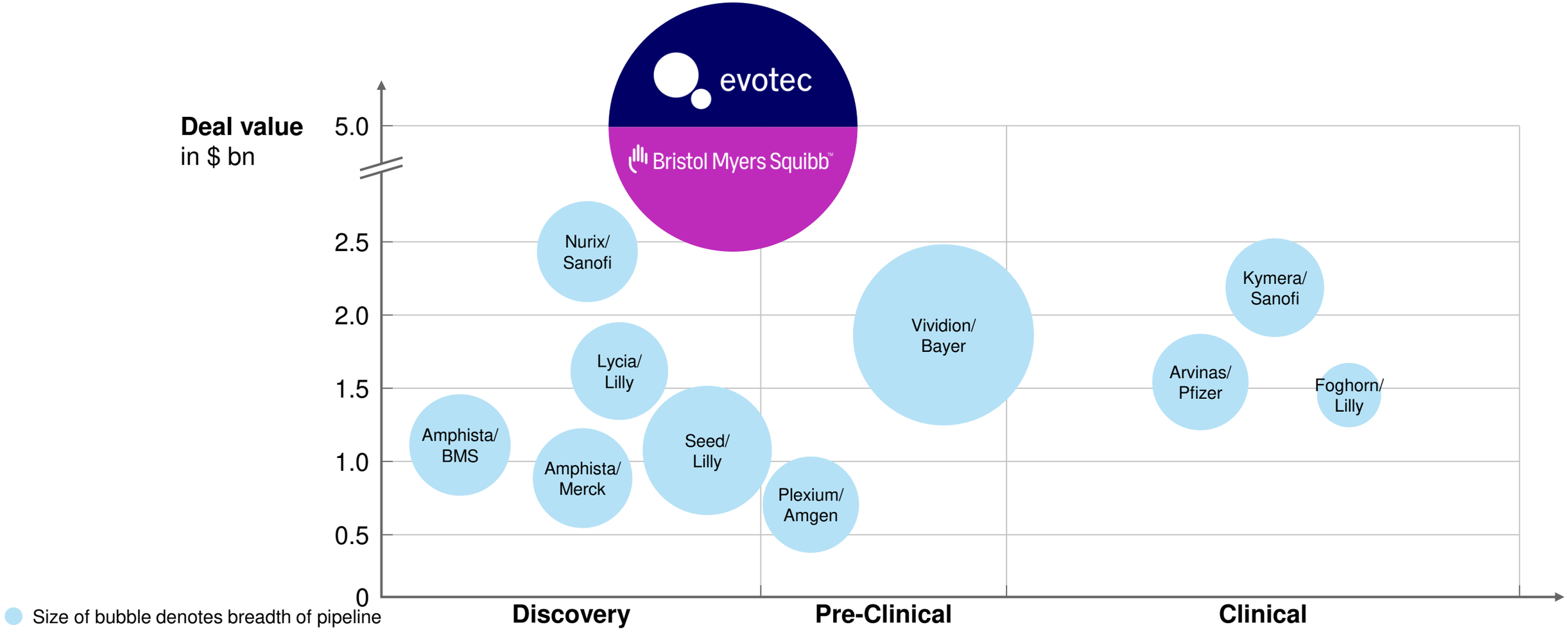
Strategic expansion of a successful partnership in targeted protein degradation

Developing a pipeline of breakthrough therapies based on molecular glue degraders

- 8-year extension and significant expansion of original agreement signed in 2018
- Collaboration leverages Evotec's **EVO***panOmics* and **EVO***panHunter* platforms including AI/ML capabilities
- Upfront payment of $ 200 m
- Deal potential of > $ 5 bn, milestone based payments
- Tiered royalties for each programme

Scope of deal places BMS & Evotec ahead of key players

Analysis of selected licensing deals – strong momentum in the last 2 years



Source: Company webpages, Evotec analyses

Targeted Protein Degradation opens a new path to fight disease

Mechanism of Action of targeted protein degraders

Compound mediated target interaction with E3 ligases

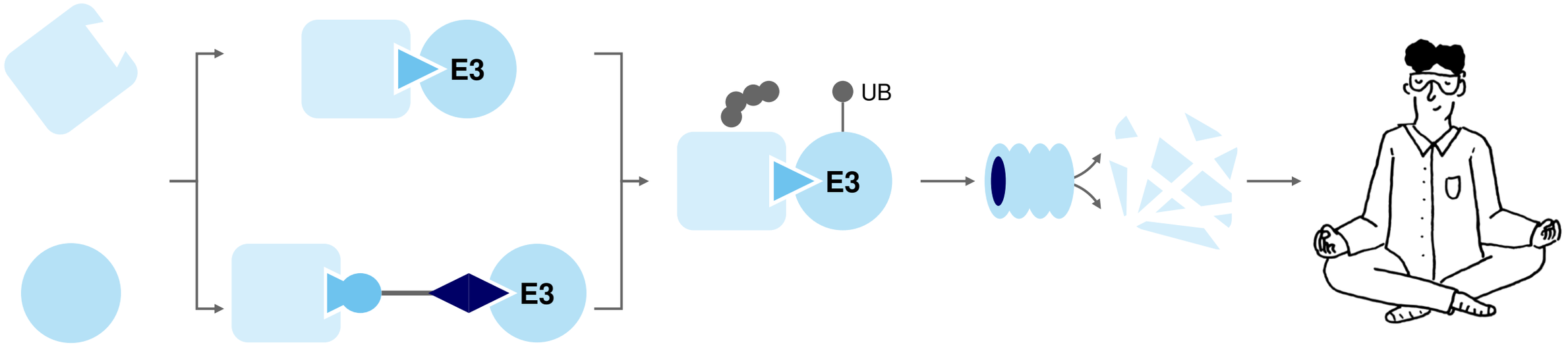
Target ubiquitination

Target degradation through proteasome

Therapeutic effect

Target protein

Molecular glues



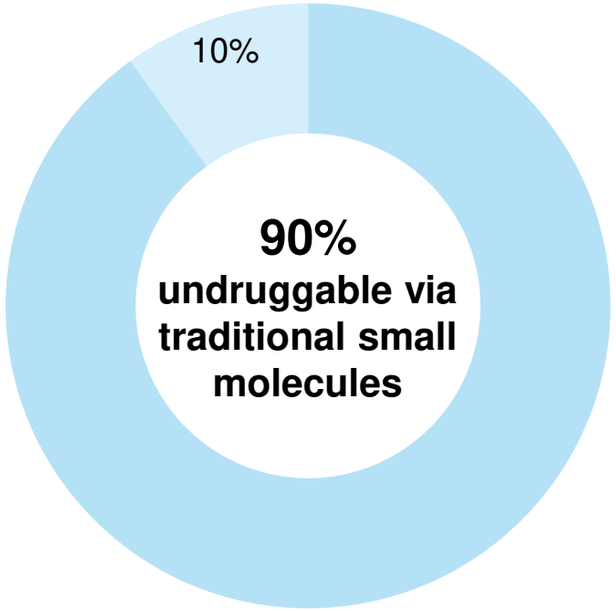
E3 ligase

PROTACs

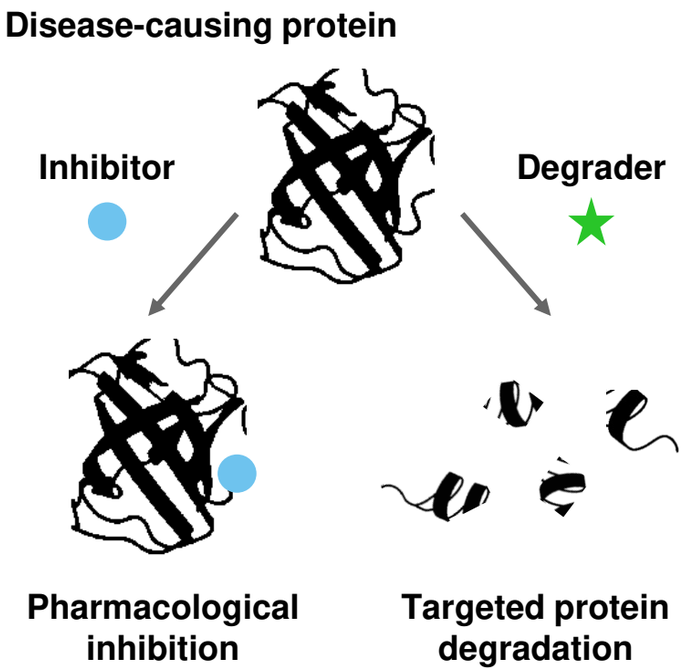
Drugging the undruggable harbours enormous potential

Vast majority of the proteome is currently not addressed by small molecules

Human proteome ~30,000



Degradation is a new paradigm



Major advantages of degraders

- Degrader compounds rely primarily on binding
  - Rather than binding and activity inhibition
- Catalytic, event driven, pharmacology
  - Enabling responses at lower exposures over longer intervals
- Degradation of target proteins
  - Less likely to lead to resistance

Undrugged opportunity Classically defined as “druggable” by small molecules / targeted by approved drugs

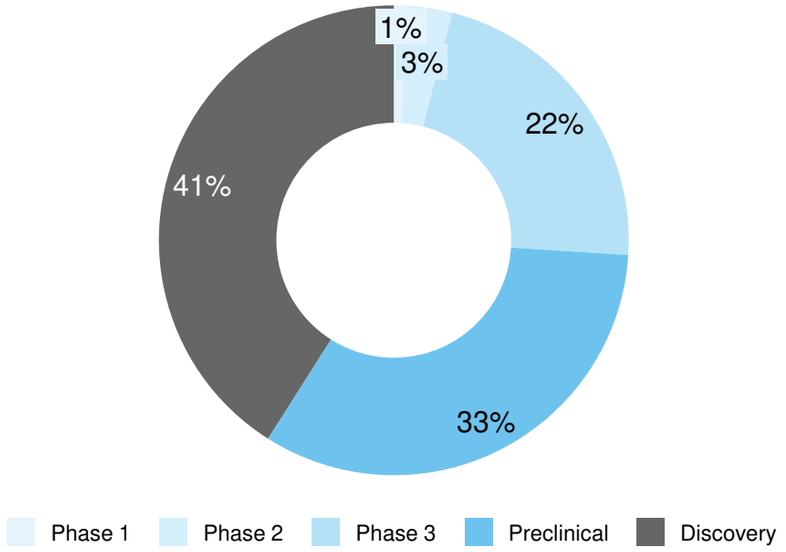
Sources: https://cen.acs.org/pharmaceuticals/drug-discovery/quest-drug-undruggable/96/i26; https://www.nature.com/articles/nrd892?proof=t https://www.rootsanalysis.com/reports/view_document/protein-degradation-market/289.html

Rapidly expanding therapeutic space reflects the potential of TPD

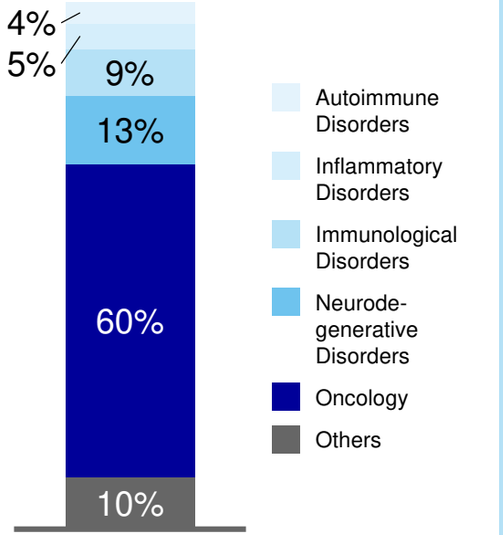
150 TPD projects currently in development

Targeted Protein Degradation Therapeutics

Distribution by Phase of Development

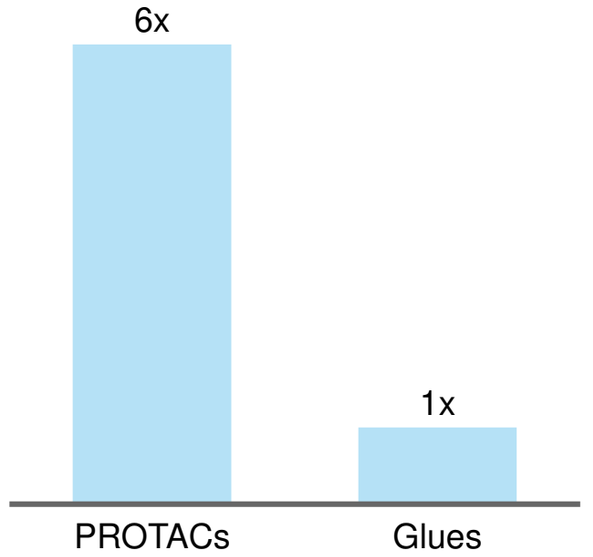


Distribution by Therapeutic Area



Current TPD pipeline is dominated by PROTAC development

Therapeutic projects within TPD space by modality



LLC Research & Roots analysis – Targeted Protein Degradation Market (2nd Edition), 2021-2030

Molecular glues are the more attractive degraders

Glues are currently under-represented in the TPD pipeline

	Molecular glues	PROTAC
Drug like-ness		
Pharmacological properties		
Synthetic tractability		
Discovery path	Challenging	Rational design

Nature Reviews Drug Discovery volume 21, pages181–200 (2022)

BMS is a leader in targeted protein degradation

Molecular glue targeted protein degraders on market and in clinical development

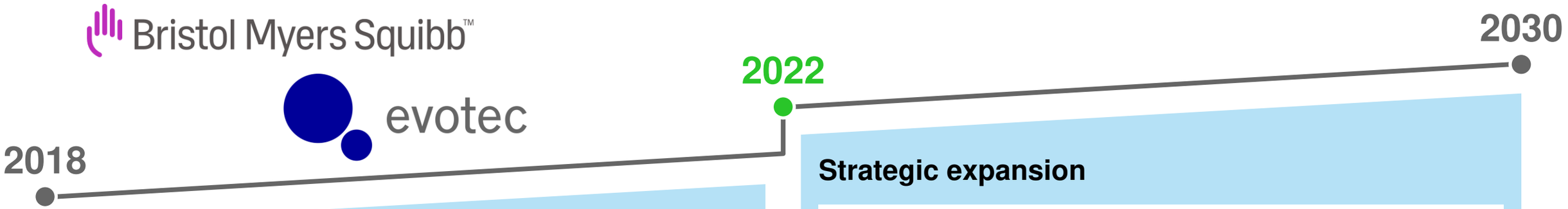
Company	Degrader	Target	Indications	E3 ligase	Highest phase
Bristol Myers Squibb™	CC-220 (Iberdomide)	IKZF1/3	Multiple Myeloma	CRBN	Phase II
Bristol Myers Squibb™	CC-92480	IKZF1/3	Multiple Myeloma	CRBN	Phase II
Bristol Myers Squibb™	CC-90009	GSPT1	AML	CRBN	Phase I
Bristol Myers Squibb™	CC-99282	IKZF1/3	Chronic myeloid leukaemia, non-Hodgkin lymphoma	CRBN	Phase I
Bristol Myers Squibb™	CC-91633	CK1a	AML	CRBN	Phase I
C4 Therapeutics	CFT7455	IKZF1/3	MM	CRBN	Phase I
biotheryx	BTX1188	IKZF1/3 GSPT1	HM, Solid tumours	CRBN	Phase I
NOVARTIS	DKY709	IKZF2	Solid tumours (NSCLC)	CRBN	Phase I

- **Strong sales**
  - Revlimid & Pomalyst together > $ 15 bn Sales in 2021
- **Strong pipeline**
  - 5 CELMoD®s and 1 PROTAC in clinical development
  - 2 PROTACs and 5 CELMoDs in full discovery

Nature Reviews Drug Discovery volume 21, pages181–200 (2022);
AML = Acute myeloid leukemia
MM = Multiple myeloma ; HM = Hematologic malignancies

Unbiased and systematic discovery of molecular glues

From exploratory to strategic partnership



Exploratory proteomics driven approach

2018

- Exploratory proteomics-driven approach to discover novel molecular glues
- Proved to be highly productive

Strategic expansion

May 2022

- Extend and expand unbiased and systematic approach to discover new molecular glues
- Driven by **EVO***panOmics* and **EVO***panHunter*
- Goal to build an extensive pipeline of breakthrough therapies based on molecular glues

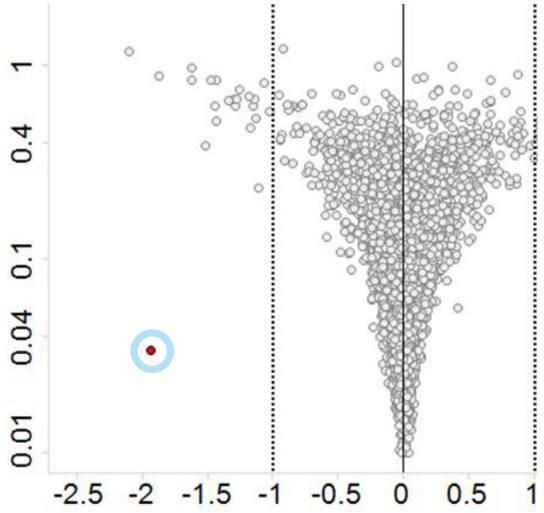
Selecting the most promising molecules via Omics profiling

EVO*panOmics* – High performance transcriptome and proteome analysis as the starting point

EVO*panOmics*

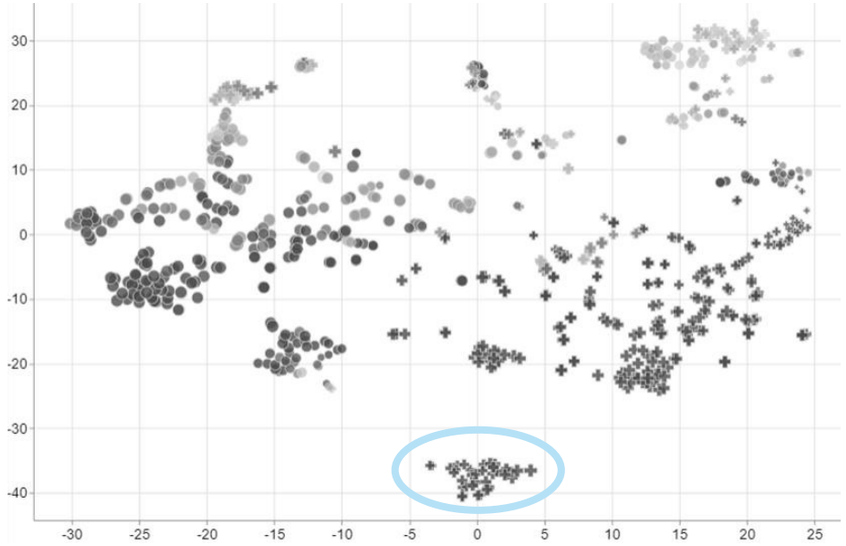
ScreenPep High performance proteomics

Unprecedented scale and protein coverage



ScreenSeq High performance transcriptomics

Unprecedented throughput and sequencing depth



Billions of datapoints require AI/ML-driven analytics

EVO*panOmics* & **EVO***panHunter*

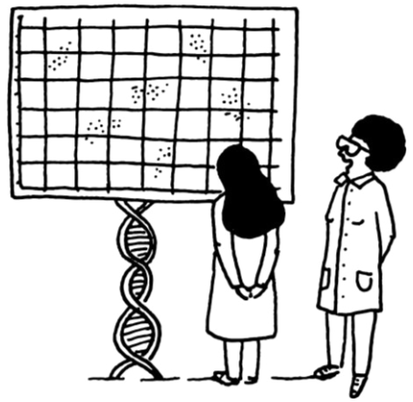
EVO*panOmics* **screening data**

Meta data

Chemical data

Clinical data

EVO*panHunter*



Data analysis & interpretation

Superior selection of molecular glues

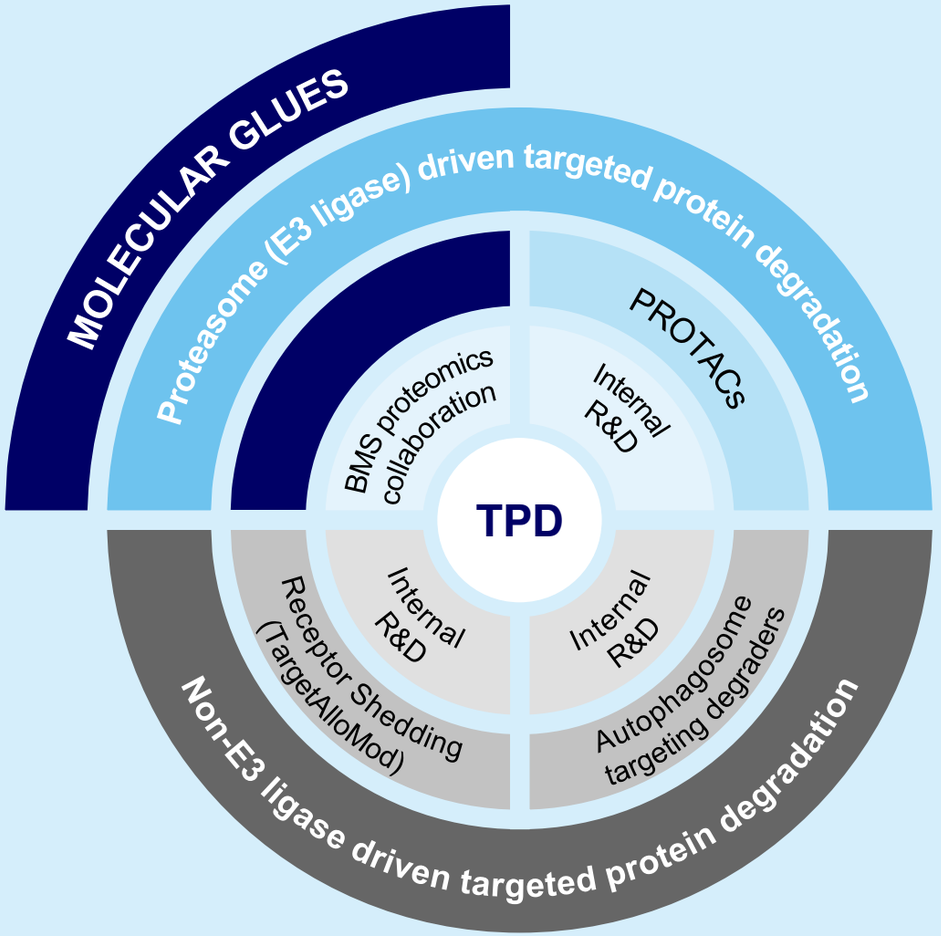
Improved efficacy and safety profiles

Accelerated LO to IND transition

Improved patient stratification

Systematic pursuit of TPD just at the beginning …

Harnessing various mechanisms of protein degradation



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