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Mid-sized molecules: The new frontier for biopharma and CDMOs


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The rise of mid-sized molecules is visible in both approvals and the pipeline. We define "mid-sized" molecules as synthetic therapeutics that are larger and more complex than conventional small molecules: macrocyclic peptides, protein degraders and other complex molecules. Why care now? After decades of R&D, **the science is getting clinical validation.** Vepdegestrant became the first FDA-approved PROTAC in 2026, while icotrokinra became the first targeted oral IL-23R peptide. The pipeline is growing with close to **2000 programs globally with over $200 Bn TAM**.

Mid-sized molecules could expand what is druggable. Conventional small molecules penetrate cells well but generally need a defined binding pocket. Antibodies can engage much larger protein surfaces, but largely remain extracellular. Mid-sized molecules can potentially bridge this gap: large enough to disrupt protein-protein interactions, yet in some cases small and permeable enough to reach intracellular targets or be taken orally.

Macrocyclic peptides - the needle-to-pill opportunity and more: J&J's icotrokinra (covered by Hambright)**,** an oral IL-23R peptide for psoriasis, delivered ~70% IGA 0/1 and ~55% PASI 90 at Week 16 in Phase III studies. It was FDA approved in March 2026. **Hansoh's HS-20118** targets the same pathway but has a 6-7 day half-life, offering the potential for once-weekly oral dosing. Hansoh licensed ex-China rights for $120mn upfront and up to $2.18bn in milestones. But oral convenience is only part of the opportunity. **Chugai** has built a library of ~10^12 cyclic peptides designed to enter cells and reach intracellular targets. Two, AUBE00 and AQUA07, are in Phase I.

Protein degradation has finally reached clinical validation. Twenty-five years after PROTACs were first demonstrated, vepdegestrant became the first FDA-approved PROTAC in May 2026. BTK is emerging as an important next test. **BeOne's BGB-16673** degrades wild-type BTK and key resistance mutants and has shown encouraging activity in heavily pretreated CLL/SLL; BeOne is also taking CDACs into CDK2 and IRAK4. **Roche** is also in with Nurix's (covered by Walch) bexobrutideg, which showed an 83% ORR and 22.1-month median PFS in Phase I R/R CLL. Targeted degradation could also offer a way to **overcome drug resistance by eliminating the protein altogether**, rather than relying on sustained occupancy of a specific binding site. This is particularly relevant for BTK, where degraders such as BGB-16673 are designed to remove both wild-type BTK and resistance mutants that can emerge after covalent or non-covalent BTK inhibitors.

Besides biopharma, this trend would also benefit CRO/CDMOs. Discovery requires more specialized libraries, screening technologies and chemistry. Manufacturing adds more steps, stereochemical complexity, lower yields and harder purification. For cyclic peptides, SPPS, cyclization and purification are the core opportunity today; more advanced approaches such as Merck's biocatalytic enlicitide process offer another layer of value-add as these drugs scale.

See the Disclosure Appendix of this report for required disclosures, analyst certifications and other important information. Alternatively, visit our Global Research Disclosure Website.

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BERNSTEIN TICKER TABLE

			8 Oct 2026		TTM		Reported EPS			Reported P/E (x)		
Ticker	Rating	Cur	Closing Price	Price Target	Rel. Perf.	Cur	2025A	2026E	2027E	2025A	2026E	2027E
9926.HK (Akeso)	M	HKD	105.70	104.00	(47.0)%	CNY	(1.23)	(0.98)	(0.49)	(73.2)	(92.1)	(184.9)
ONC (BeOne)	O	USD	364.02	412.00	(12.5)%	USD	2.63	5.65	8.93	138.4	64.4	40.8
1093.HK (CSPC)	M	HKD	9.29	10.70	(27.0)%	HKD	0.34	0.75	0.62	23.4	10.6	12.8
3692.HK (Hansoh)	O	HKD	32.18	44.00	(40.3)%	CNY	0.93	0.97	0.88	29.6	28.4	31.3
1801.HK (Innovent)	O	HKD	92.60	128.00	(33.1)%	HKD	0.48	1.25	1.97	190.9	73.9	47.1
600276.CH (Hengrui)	O	CNY	47.01	65.00	(55.9)%	CNY	1.18	1.42	1.78	39.8	33.2	26.4
6990.HK (Kelun-Biotech)	O	HKD	445.80	526.00	(44.4)%	CNY	(1.66)	(2.75)	0.85	37.2	37.8	23.3
1177.HK (Sino BioPh)	M	HKD	5.49	6.20	(57.3)%	CNY	0.13	0.27	0.22	36.0	17.2	21.6
9688.HK (Zai Lab)	M	HKD	19.19	15.00	(48.0)%	USD	(0.16)	(0.15)	(0.09)	0.7	0.6	0.5
603259.CH (WuXi AppTec)	O	CNY	162.00	205.00	23.0%	CNY	6.72	7.88	9.57	24.1	20.6	16.9
2359.HK (WuXi AppTec)	O	HKD	209.00	247.00	52.3%	CNY	6.72	7.88	9.57	26.6	22.7	18.7
2269.HK (WuXi Biologics)	M	HKD	54.10	42.00	7.2%	CNY	1.22	1.54	1.85	44.3	35.2	29.2
002821.CH (Asymchem)	O	CNY	180.68	198.00	37.3%	CNY	3.16	4.04	6.07	57.2	44.8	29.8
6821.HK (Asymchem)	O	HKD	163.00	157.00	43.9%	CNY	3.16	4.04	6.07	44.1	34.5	23.0
4519.JP (Chugai)	O	JPY	6,107.00	9,700.00	(43.9)%	JPY	263.73	317.24	370.07	23.2	19.3	16.5
ROP.SW (Roche)	O	CHF	360.00	434.50	12.3%	CHF	19.46	20.44	23.50	18.5	17.6	15.3
ABBV (AbbVie)	M	USD	271.36	230.00	1.2%	USD	9.98	14.22	16.02	27.2	19.1	16.9
MRK (Merck)	M	USD	142.79	105.00	49.1%	USD	8.97	2.75	9.11	15.9	52.0	15.7
AMGN (Amgen)	M	USD	413.08	345.00	24.0%	USD	21.85	22.59	23.16	18.9	18.3	17.8
BMY (Bristol-Myers Squibb)	M	USD	59.70	61.00	17.8%	USD	6.15	7.05	6.53	9.7	8.5	9.1
LLY (Eli Lilly)	O	USD	1,188.72	1,385.00	24.4%	USD	24.20	36.64	48.92	49.1	32.4	24.3
GILD (Gilead)	O	USD	146.85	160.00	8.0%	USD	8.15	(0.56)	10.04	18.0	(263.7)	14.6
PFE (Pfizer)	M	USD	28.00	29.00	(7.2)%	USD	3.23	2.99	2.83	8.7	9.4	9.9
ASIAX			1,955.93									
SPX			7,801.77									
JPL			2,709.51									
EDME			1,564.23									

O - Outperform, M - Market-Perform, U - Underperform, NR - Not Rated, CS - Coverage Suspended

ROP.SW, ABBV, MRK, AMGN, BMY, LLY, GILD, PFE estimate is Adjusted EPS; 6990.HK, 9688.HK valuation is EV/Sales (x); ROP.SW, ABBV, MRK, AMGN, BMY, LLY, GILD, PFE valuation is Adjusted P/E (x);

Source: Bloomberg, Bernstein estimates and analysis.

DETAILS

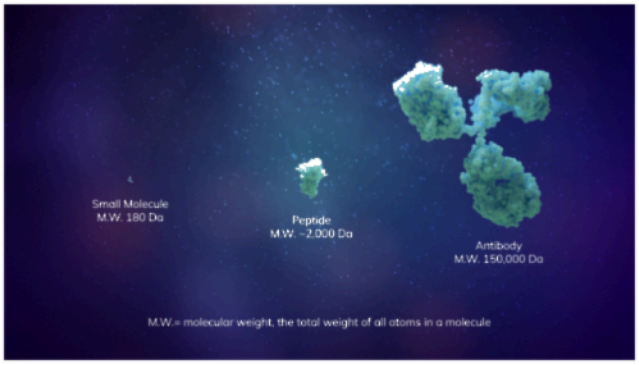
THE RISE OF MID-SIZED MOLECULES

We use "mid-sized molecules" as an umbrella term for synthetically manufactured therapeutics that go beyond conventional small-molecule space, including peptides, macrocyclic peptides, protein degraders, and other complex synthetic molecules (Exhibit 1).

Larger and more complex than traditional small molecules, these modalities combine some of the advantages of both worlds: the selectivity and larger binding interface associated with biologics, while retaining the potential for **intracellular access, oral delivery and scalable chemical synthesis.** This matters because conventional small molecules are best suited to proteins with well-defined binding pockets, while antibodies are largely confined to extracellular targets; mid-sized molecules can engage larger or flatter protein surfaces and protein-protein interactions that historically sat between the two (Exhibit 2, Exhibit 3).

Why should you be excited about these molecules now? Recently FDA-approved blockbusters (and potential blockbusters) shows a growing presence of synthetically manufactured drugs, with 2026 milestones including the first approved targeted oral IL-23R peptide, icotrokinra, and the first approved heterobifunctional PROTAC, vepdegestrant (Exhibit 4). After decades of basic research and R&D, **we now have clinical validation and a booming pipeline.** We believe mid-size molecules will create new incremental opportunities for biopharma and CRO/CDMOs, as detailed in the next sections.

EXHIBIT 1: **Size differences between small molecule, peptide and antibody**



Source: https://www.merck.com/stories/macrocyclic-peptides/

EXHIBIT 2: **"Mid-sized" molecules occupy the biochemical space between small molecules and antibodies, and may expand the range of targets reachable**

	Small molecule	Mid-size molecule	Antibody
Molecular weight	MW<500	700 < MW <1600	MW 150000
Oral administration	Available	Available	Not available
Effects on Intracellular targets	Available	Available	Difficult
Inhibition of protein-protein interaction	Difficult	Available	Available
Specificity	Low	Mid - High	High
Dosage interval	Short (Daily)	Short (Daily)	Long (Every 2-4 weeks)

Source: Chugai

EXHIBIT 3: **Expanding the druggable universe - new modalities access new targets**

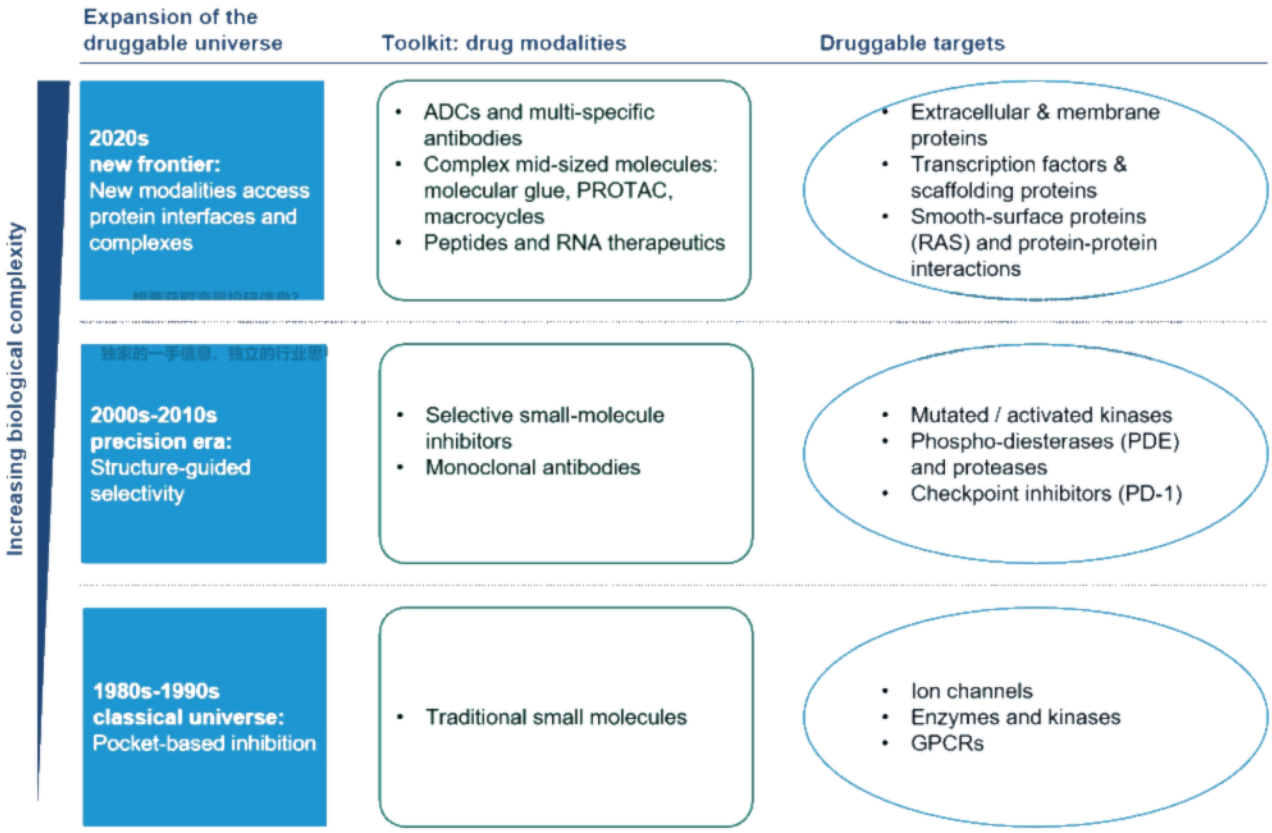
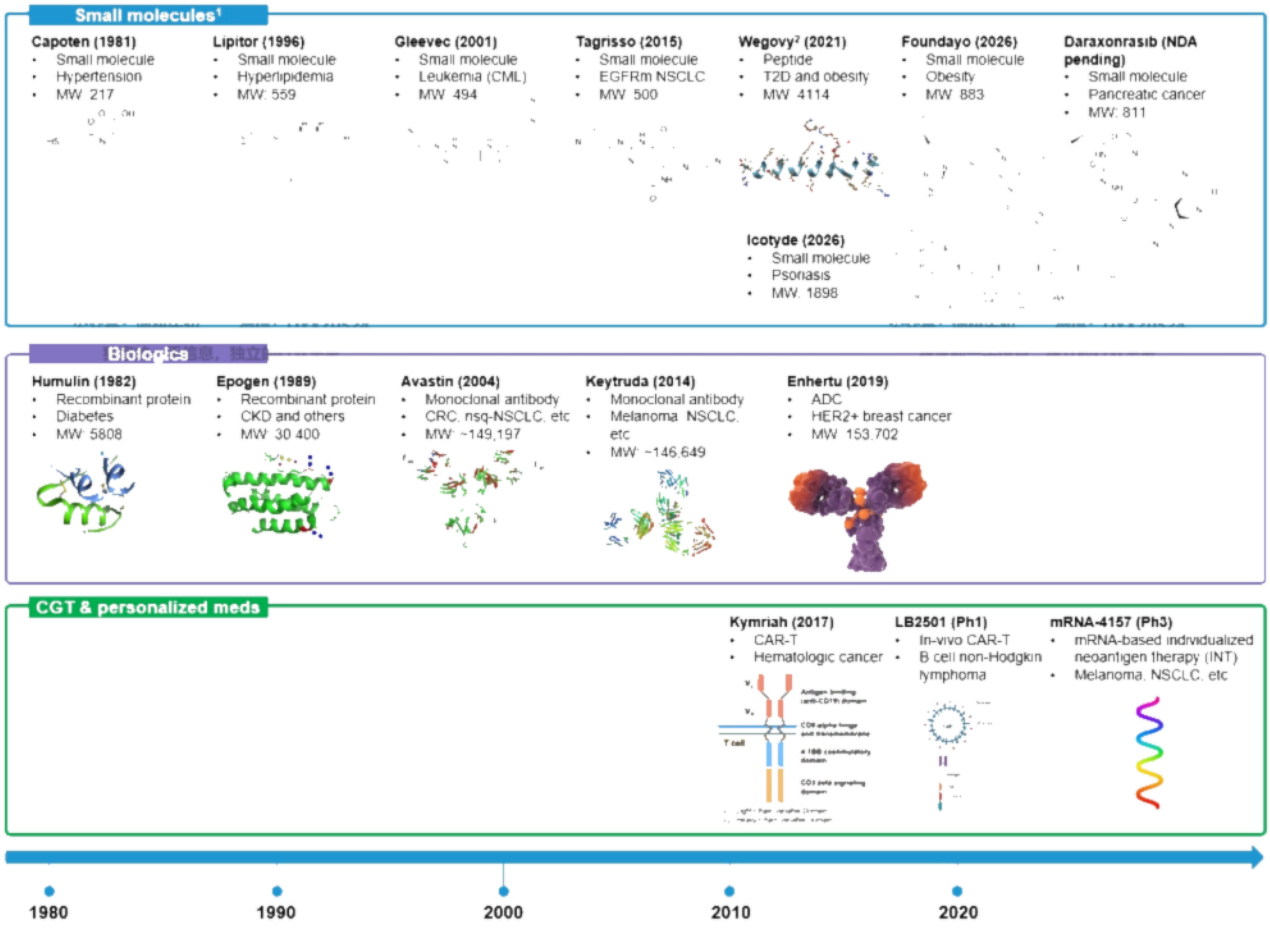


EXHIBIT 4: **Blockbusters over the decades: small molecules have gotten more complex and diverse in recent years**



1. This category also includes larger molecules, e.g. peptides, macrocyclics, etc. that are made synthetically

2. Branded Wegovy is manufactured through recombinant production. However, most peptide drugs, including semaglutide biosimilars, are made synthetically
Source: Bernstein analysis

MAJOR CLASSES, PIPELINE SIZE, AND COMMERCIAL OPPORTUNITIES

Major emerging classes span molecular glues, PROTACs (protein degraders), macrocyclic peptides and reversible covalent inhibitors (Exhibit 5). These modalities address targets across oncology, autoimmune disease, cardiovascular disease and other large therapeutic markets. **We estimate the combined end-market TAM represented by the selected opportunities at >$200bn**, with several emerging multi-billion blockbusters like daraxonrasib (RAS) and icotrokinra (IL-23). Moreover, we do not view the opportunity as simply displacing existing drugs: mid-sized modalities can open new markets by reaching targets previously regarded as undruggable or by bringing biologic-like specificity and efficacy into oral medicines.

EXHIBIT 5: **New "mid-sized" molecules unlock options spanning oncology, autoimmune, and rare diseases with > $200 Bn end-market TAM**

Category	Global pipeline size	Example targets	Example candidates	Main indications	Est. addressable patient pool	Est. end-market TAM
Molecular glue	~60	RAS	Daraxonrasib	RAS-mutant solid tumors; in particular PDAC, CRC, and NSCLC (estimated at 20% of all cancers)	3 - 4 Mn	$20-50bn+
		Raf kinase	NST-628	Solid tumors harboring MAPK pathway alterations	1 - 2 Mn	$10-15bn
PROTAC	~1100	Estrogen receptor / androgen receptor	ARV-471	ER+/HER2- metastatic breast cancer, prostate cancer	2 Mn	$15-30bn
		BTK	Tacabrutideg , bexobrutideg	B-cell malignancies (CLL / SLL, MCL, MZL)	1 Mn	$10-15bn
Macrocycles / cyclic peptide	~500	IRAK4	BGB-45035, KT-474	Atopic dermatitis, rheumatoid arthritis,	30 - 40 Mn	$20-30bn
		IL-23 / IL-17	icotrokinra / JNJ-2113	Plaque psoriasis, psoriatic arthritis, IBD	10 Mn	$20-50bn across IL-23 / IL-17 / advanced immunology markets
		β-catenin:TCF, Wnt pathway;	zolucatetide / FOG-001	Colorectal cancer and other Wnt-driven tumors	2 Mn	$10-25bn
Reversible covalent inhibitors	~200	BTK	rilzabrutinib	Immune thrombocytopenia, pemphigus, multiple sclerosis, rheumatoid arthritis & other B-cell / myeloid-mediated autoimmune diseases	10 Mn	$10-20bn

Source: Drughunter "Molecules of the Year 2025", company disclosures, Bernstein analysis and estimates

MACROCYCLIC PEPTIDES

Injectable-to-pill opportunity: examples in chronic diseases

Can a pill deliver biologic-like efficacy? Chronic diseases are particularly attractive for mid-sized molecules because oral administration could combine the target specificity of biologics with greater convenience and patient penetration / adherence.

In psoriasis, injectable IL-23/IL-17 biologics including Skyrizi, Stelara and Cosentyx have established large markets, but icotrokinra shows that the extracellular IL-23 pathway can also be targeted with an oral peptide. An IL-23R antagonist, icotrokinra became the first FDA-approved targeted oral peptide in March 2026; in two Phase III head-to-head studies, approximately 70% of patients achieved IGA 0/1 and ~55% achieved PASI 90 at Week 16, with efficacy superior to oral TYK2 inhibitor deucravacitinib and a favorable safety profile (Exhibit 8-Exhibit 10). Hansoh's HS-20118 provides another China-origin example: the oral IL-23R cyclic peptide has a 6-7 day terminal half-life supporting **once-weekly oral dosing**, and early Phase I psoriasis data showed PASI improvements continuing after treatment cessation, including -54.5% at Week 4 and -90.5% at Week 10 with 25mg QD dosing; Hansoh subsequently licensed ex-China rights for $120mn upfront plus up to $2.18bn in

milestones (Exhibit 11).

PCSK9 could provide an even larger test case. PCSK9 has historically been addressed by injectable antibodies such as Repatha/Praluent or siRNA Leqvio, but Merck's macrocyclic peptide enlicitide is designed to deliver similar pathway inhibition through a once-daily pill. In Phase III CORALreef Lipids, enlicitide reduced LDL-C by 55.8% versus placebo at Week 24, while CORALreef HeFH produced a 59.4% reduction, broadly comparable in magnitude to the LDL-C reductions achieved by leading injectable PCSK9 therapies in cross-trial comparison (Exhibit 7,Exhibit 12).

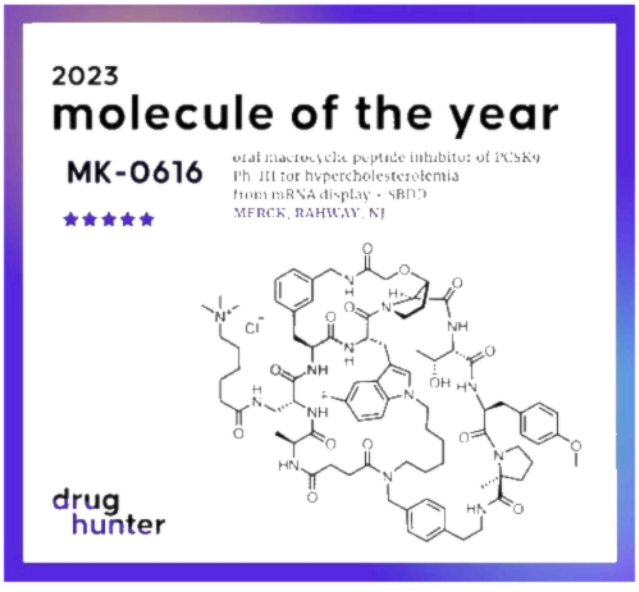
One question we pose - does a daily pill deliver equivalent outcomes in the real world? Daily dosing raises the barrier to adherence (despite oral convenience), so while these molecules are incredibly elegant - the market split between longer acting injectables & daily dosed orals, as well as achievement of clinical endpoints in the real world remains an outstanding question for these chronically used cyclic peptides.

EXHIBIT 6: **Injectable blockbusters in PsO and hypercholesterolemia could potentially lead to double-digit billion of peak sales**

Indication	Brand	Molecule name	Target	Dosing	2025 annual sales ($ Bn)	Peak sales est (BBG, $ Bn)
Psoriasis	Skyrizi	Risankizumab	IL-23	150mg Q12W SC	17.6	33.9 (2032E)
	Stelara	Ustekinumab	IL-12 / IL-23	45mg Q12W SC	6.1	10.9 (2023A)
	Cosentyx	Secukinumab	IL-17	300mg Q4W SC	6.7	7.6 (2028E)
Hypercholesterolemia	Repatha	Evolocumab	PCSK9	140mg Q2W/ 420mg Q1M SC	3.0	5.6 (2029E)
	Leqvio	Inclisiran	PCSK9	284mg Q6M SC	1.2	4.7 (2033E)
	Praluent	Alirocumab	PCSK9	75mg Q2W/ 300mg Q4W SC	~1.5	~1.8 (~2029E)

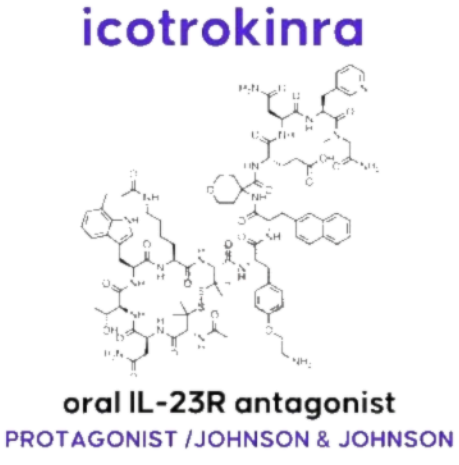
Source: Bloomberg, Bernstein analysis

EXHIBIT 7: **Structure of enlicitide (MK-0616)**



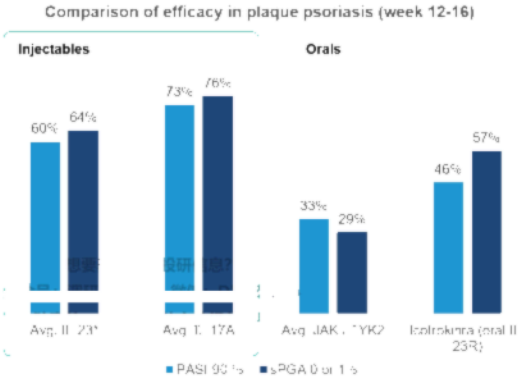
Source: Drug Hunter

EXHIBIT 8: **Structure of icotrokinra**



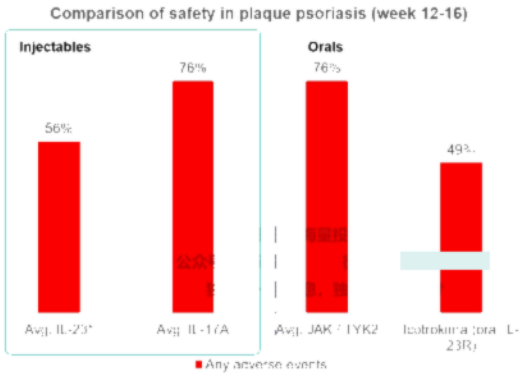
Source: Drug Hunter

EXHIBIT 9: **Icotrokinra has shown better efficacy than existing oral therapeutics for psoriasis**



*IL-23 includes IL-23(p19) and IL-23/IL-12p(40)
Source: Company disclosures, EADV, AAD, PubMed, Pharmcube, Bernstein analysis

EXHIBIT 10: **Icotrokinra has a relatively lower rate of adverse events compared to both existing injectables and orals**



*IL-23 includes IL-23(p19) and IL-23/IL-12p(40)
Source: Company disclosures, EADV, AAD, PubMed, Pharmcube, Bernstein analysis

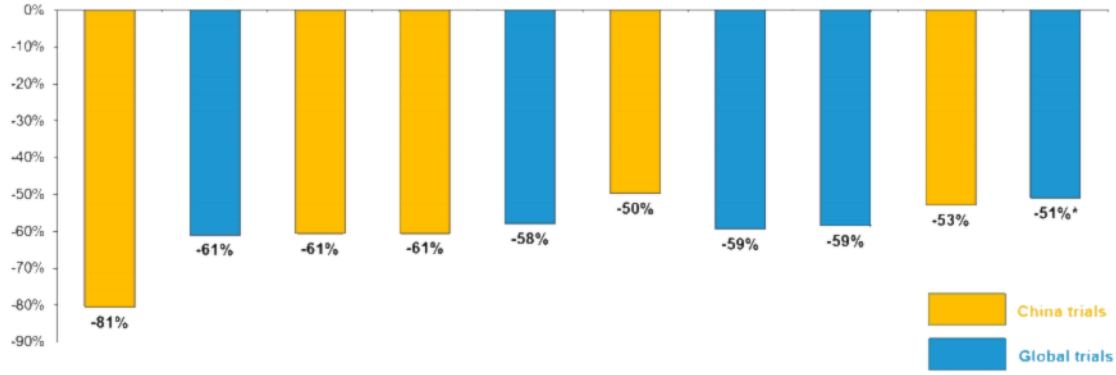
EXHIBIT 11: **HS-20118 has shown encouraging efficacy at week 4 and may offer a weekly dosing option**

Drug	Trial	Phase (data readout)	NO. of pts enrolled	Arm, n	Dosage&Admin (Maintenance stage)	Near-term efficacy		
						Duration (week)	PASI 90 %	sPGA 0 or 1 %
Icotrokinra	Meta-analysis of 4 trials	Ph II / III	1640	Icotrokinra, n= 1131	200mg QD	Week 4	15%	
				Placebo, n= 509	Matched dose	Week 4	2%	
Icotrokinra	NCT06095115	Ph III	684	Icotrokinra, n=456	200mg QD	Week 16	50%	65%
				Placebo, n=228	Matched dose	Week 16	4%	8%
HS-20118	NCT07033234 NCT06846710	Ph I	97	HS-20118	100mg QW	Week 4	PASI score improvement: 39.1%	
				HS-20118	50mg QD x 7days + 25mg QD x 21days	Week 4	PASI score improvement: 54.5%	
				Placebo	Matched dose	Week 4	PASI score improvement: 6.4%	

Week 4 data of icotrokinra are PASI 75 response rates; week 4 data of HS-20118 are PASI improvement % (not specified).
Source: Hansoh, International Journal of Dermatology, Bernstein analysis

EXHIBIT 12: **Enlicitide, the first oral against PCSK9, offers similar efficacy in LDL-C reduction as leading mAb / siRNA injectables (cross-trial comparison)**

	mAb						Peptide	FuSp	siRNA	
Drug name	Ongericimab	Evolocumab	Tafolecimab	Ebronucimab	Alirocumab	Recaticimab	Enlicitide	Lerodalcibep	SYH2053	Inclisiran
Company	Junshi	Amgen / Astellas	Innovent	Akeso	Sanofi / Regeneron	Hengrui	Merck	Lib Therap.	CSPC	Novartis
Approval status	NMPA approved	FDA & NMPA approved	NMPA approved	NMPA approved	FDA & NMPA approved	NMPA approved	FDA approved	FDA approved	Not yet approved	FDA & NMPA approved
Trial	NCT05325203	RUTHERFORD-2	CREDIT-2	Pooled study	ODYSSEY FH I & FH II	REMAIN-3	CORALreef	LIBerate-HeFH	NCT07421232	ORION-9
Phase[1]	Ph3	Ph3	Ph3	N/a	Ph3	Ph3	Ph3	Ph3	Ph2	Ph3
Dose & Admin	450 mg Q4W subQ	140 mg Q2W subQ	450 mg Q4W subQ	150 mg Q2W subQ	75 mg Q2W subQ	150 mg Q4W subQ	120 mg QD oral	300 mg Q4W subQ	300 mg subQ	300 mg twice / year subQ
Efficacy assessment week	wk.24	wk.12	wk.12	wk.12	wk.24	wk.12	wk.24	wk.24	wk.24	wk.24



Note: 1. Efficacy readout phase; * Visual estimates, c.±1-2% points
Source: Company disclosures, NEJM, FDA, ClinicalTrials.gov, Pubmed, NIH, Pharmcube, Bernstein analysis

Drugging the undruggable (1): WNT pathway

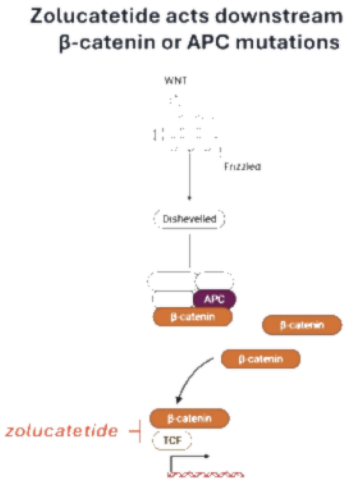
Stapled helical peptides offer another route into historically undruggable intracellular biology. Parabilis Medicines' Helicon platform engineers alpha-helical peptides using backbone crosslinking to stabilize their three-dimensional shape and noncanonical amino acids to expand chemical and functional diversity. The goal is to create cell-permeable molecules that could disrupt intracellular protein-protein interactions that conventional small molecules and antibodies struggle to reach (Exhibit 13). Lead asset zolucatetide, formerly FOG-001, is an example: it is cell permeable and disrupts the β-catenin/TCF interaction at the most downstream node of the WNT pathway. This is a target long considered difficult to drug despite being implicated across colorectal cancer, hepatocellular carcinoma, desmoid tumors and other cancers. Zolucatetide is now in clinical development across several WNT-driven tumors (Exhibit 14-Exhibit 15).

EXHIBIT 13: **Parabilis' Helicon platform: peptides with backbone crosslink to maintain alpha-helical shape and incorporation of non-canonical amino acids for functional diversity**



Source: Parabilis Medicines

EXHIBIT 14: **Cell-permeable zolucatetide acts downstream of the WNT pathway, blocking the b-catenin / TCF interaction**



Source: Parabilis Medicines

EXHIBIT 15: **Clinical development of zolucatetide: HCC and CRC represent the largest opportunities**



Source: Parabilis Medicines

Drugging the undruggable (2): Chugai's mid-size molecules are reaching intracellular targets

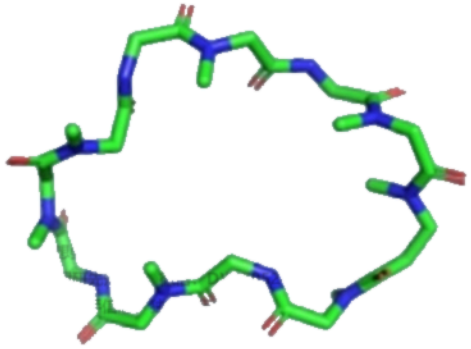
Chugai has built a large midsize molecule library of cyclic peptides coined as SnipeTide. These molecules consist of 11 amino acids with three key features (Exhibit 16): 1) **cell permeable to reach intracellular targets**; 2) **versatility**; and 3) **convenience of oral administration**. They now have two clinical assets in Ph1 for solid tumor.

1. **Cell permeable to reach intracellular targets**: Mid-size molecules were developed with a clear goal of "making undruggables druggable" by overcoming challenges of small molecules and antibodies to target disease-related proteins in the cells (Exhibit 2). Small molecules can penetrate through the cell membrane but target only proteins with a clear pocket for the small molecules to bind, which is present in only about 20% of all proteins. Small molecules cannot inhibit those involved in protein–protein interactions which, in many diseases, are the target you want drugs to interfere with. This is because the protein-protein interactions usually involves large surface of proteins thus small molecules are too small to influence them. Conversely, while much larger antibodies are able to inhibit these tough targets, they are too large to go inside the cells thus can only target proteins outside the cells and on their surface, again representing roughly 20% of all proteins. Thus Chugai's midsize molecules have been developed to circumvent these limitations by being small enough to enter the cells and large enough to interfere with protein-protein interactions, offering a way to address intracellular tough targets currently considered undruggable by small molecules and antibodies. Our research and Chugai's comment suggest that no other peptide platforms by other pharma/ biotech players have cell membrane-permeable peptides to date.

2. **Versatility**: Chugai's midsize molecules consists of 11 linearly linked amino acids, and they built a library of staggering 10^{12} molecules by changing the amino acids. This versatility is a very attractive feature of the midsize molecules as this large library can be screened for different disease-related target proteins. Chugai now has a semi-automated high-throughput screening platform for the midsize molecule for "undruggable" targets such as G protein-coupled receptors, ion channels, signaling molecules, and transcriptional factors that are found inside the cells (Exhibit 17).

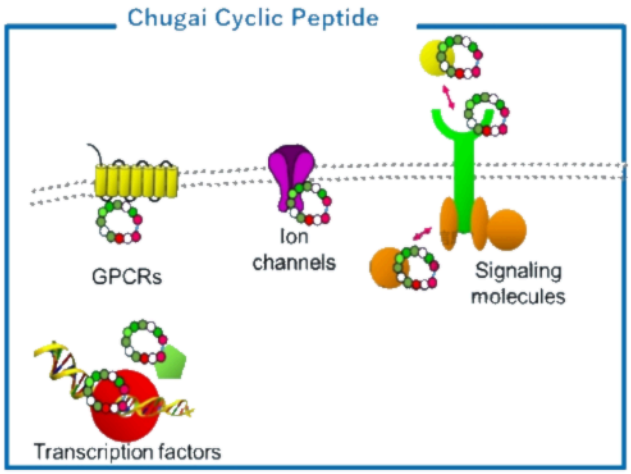
3. **Convenience of oral administration**: The mid-size molecules are small enough and rather simple in structure, it can be taken as an oral medication, which is always more convenient option for patients and healthcare providers.

EXHIBIT 16: **Chugai's mid-size molecules are cyclic polypeptides consisting of 11 linearly linked amino acids**



Source: Company reports

EXHIBIT 17: **Chugai has built a semi-automated high throughput screening platform for mid-sized molecules for "undruggable" targets inside the cells**



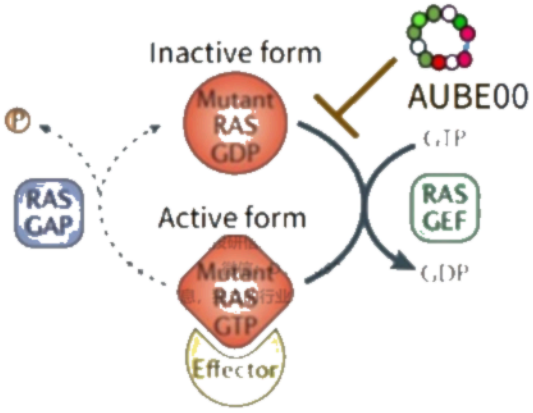
Source: Company reports

Chugai's two midsize molecules are currently in Ph1: AUBE00 and AQUA07

AUBE00 is the second clinical-stage midsize molecule and a pan-KRAS inhibitor targeting inactive form of GDP-bound RAS (Exhibit 18). This asset is currently in Ph1 for solid tumors. Strong efficacy demonstrated by recently approved Revolution Medicine's (covered by Walch) RASONQUE has set the bar for other drugs to target KRAS-mut cancers very high. So we have to see compelling data from AUBE's Ph1 in order to be excited about the drug.

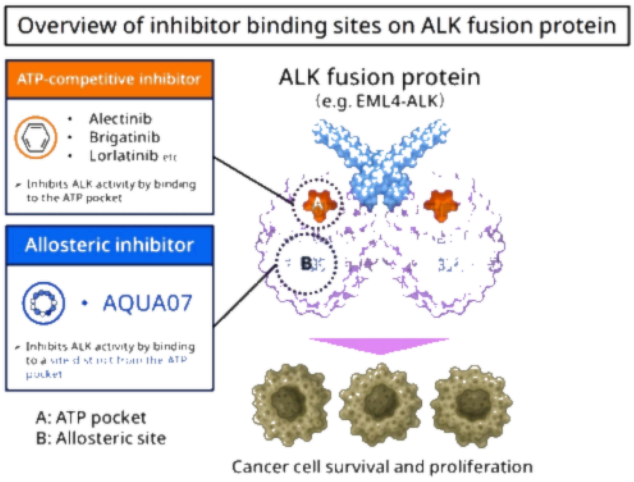
AQUA07 is an allosteric ALK inhibitor and in Ph1 for ALK-positive non-small cell lung cancer (NSCLC). Chugai/Roche's (Chugai's parent company) Alecensa, discovered by Chugai, is a successful 2nd-gen ALK inhibitor for ALK+ NSCLC and sold USD1.9Bn in 2025. While Alecensa is a ATP-competitive inhibitor by binding the ATP pocket, AQUA07 inhibits ALK activity by binding to a site distinct from the ATP pocket (Exhibit 19). Due to its distinct MoA, AQUA07 is expected to demonstrate efficacy in patients with acquired resistance to existing ALK inhibitors, as well as to enhance therapeutic effects in combination with existing 1st line treatments. While ALK+ NSCLC patients are limited to 3–5% of NSCLC, current ALK inhibitors' treatment durations are long which make them blockbusters. Thus if combination of AQUA07 and these ALK inhibitors can make the treatment of duration even longer, the drug can have an attractive commercial prospect.

EXHIBIT 18: **AUBE00 is the second clinical-stage midsize molecule and a pan-KRAS inhibitor targeting inactive form of GDP-bound RAS**



Source: Company reports

EXHIBIT 19: **While Alecensa is a ATP-competitive inhibitor by binding the ATP pocket, AQUA07 inhibits ALK activity by binding to a site distinct from the ATP pocket**



Source: Company reports

PROTEIN DEGRADERS

PROTACs crossed an important validation milestone in 2026

PROTACs were first demonstrated in 2001 but required nearly two decades to overcome the permeability, PK and oral-bioavailability challenges associated with large bifunctional molecules. Vepdegestrant entered the clinic in 2019 and became the first FDA-approved heterobifunctional PROTAC in May 2026. Its approval validates the therapeutic and manufacturing feasibility of large, beyond-Rule-of-Five molecules.

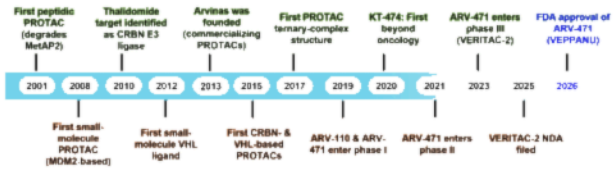
BTK degrader pipline grows

Degrader MoA is attractive in disease areas where earlier lines of treatment lead to resistance, and eliminating the target altogether could provide a last line of defense. This is true in chronic lymphocytic leukaemia (CLL), where sequential use of covalent and non-covalent BTK inhibitors (eg Calquence (AstraZeneca (O); Smith) and Jaypirca (Lilly; O; Courtney Breen) respectively) can select for different resistance mutations which creates unmet need.

BeOne's CDAC platform and BGB-16673

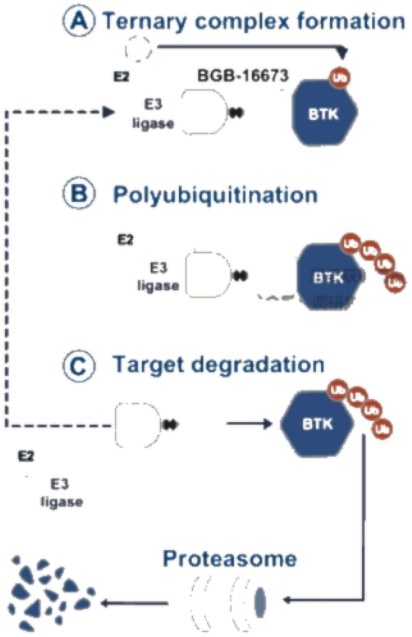
BeOne is building a broader degrader portfolio around its CDAC platform. BGB-16673 is an orally available BTK-targeted Chimeric Degradation Activation Compound (CDAC) that binds BTK and an E3 ligase to trigger ubiquitination and proteasomal degradation, thus removing the protein rather than turning off its enzymatic activity (Exhibit 21). This distinction could be particularly relevant after BTK inhibitors: BGB-16673 is designed to degrade both wild-type BTK and resistance-associated mutants including C481S and L528W, and has generated encouraging responses in heavily pretreated B-cell malignancies. Preliminary R/R CLL/SLL data compare favorably with historical non-covalent BTK inhibitor results on response and show an encouraging PFS trend (Exhibit 22). BTK is not a one-off application of the platform: BeOne has expanded CDAC into **BG-75098, a CDK2 degrader** in solid tumors, and **BGB-45035, an IRAK4 degrader** in autoimmune.

EXHIBIT 20: **25 years since the inception of the PROTAC concept, we now have the first FDA approved PROTAC drug**



Source: https://doi.org/10.1021/acs.jmedchem.6c02076

EXHIBIT 21: **Mechanism of BeOne's BTK degrader BGB-16673**



Source: BeOne

EXHIBIT 22: **Preliminary data of BGB-16673 in R/R CLL/SLL showed favorable response rates and PFS trend**

	CaDAnCe-101 (BGB-16673)	**BRUIN CLL-321** (pirtobrutinib)
Median prior lines of therapies	4	3
BTKi+BCL2i exposed	82%	50%
Prior BTKi discontinuation due to PD	89%	71%
ORR	85%	69%
PFS	12 months - 73.5%, 18 months – 65.9%	Median-14 months

Source: BeOne

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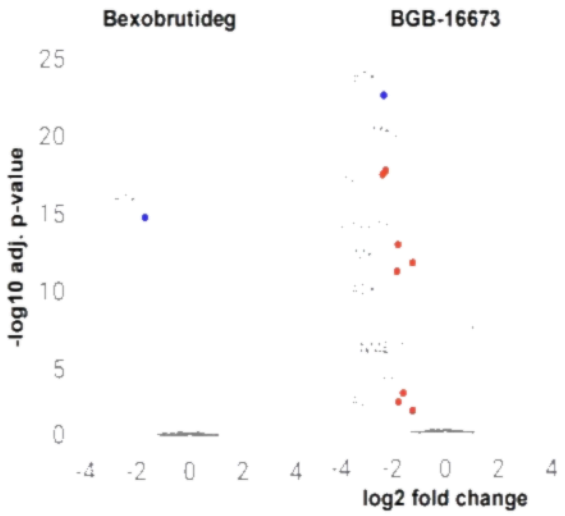
BEXOBRUTIDEG

In our view, Roche's decision to advance bexobrutideg ('bex-deg') into Phase III in blood cancer provides another important validation of targeted protein degradation. Bexobrutideg is an oral, heterobifunctional BTK degrader which Roche gained through its 2026 collaboration with Nurix.

Rather than occupying the kinase-binding site and temporarily inhibiting catalytic activity, bexobrutideg recruits an E3 ligase to ubiquitinate and remove the entire BTK protein, including its non-kinase scaffolding function.

By degrading, rather than inhibiting BTK, bexobrutideg could preserve pathway suppression across wild-type BTK and clinically relevant C481 and L528 variants. Meanwhile, repeated catalytic degradation means that one molecule can, in principle, eliminate the need to administer both covalent and non-covalent BTK inhibitors to CLL patients post relapse.

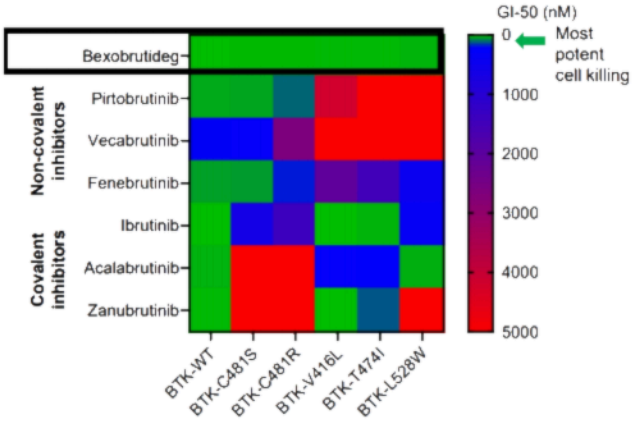
EXHIBIT 23: **Bexobrutideg phase I selectivity data**



BGB-16673 = Investigational CDAC/PROTAC type standard degrader
Source: Roche

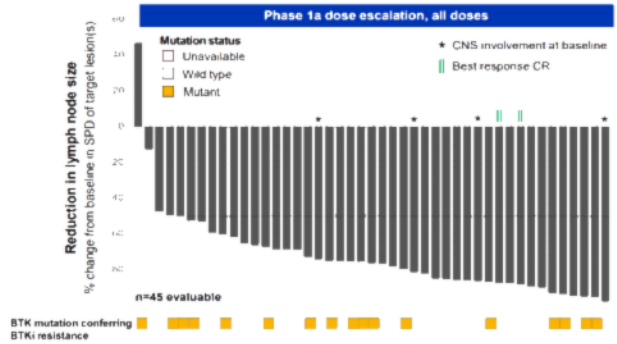
Roche also highlights improved selectivity of 'bex-deg' versus other BTK degraders and exceptional CNS penetration (Exhibit 23). The approved BTK inhibitors are not as effective at crossing the blood brain barrier. Together, broader mutation coverage (Exhibit 24), removal of scaffolding activity and potential activity in sanctuary sites provide a credible basis for differentiation beyond simply becoming another post-BTK inhibitor option. (The cancer killing ability of the BTK inhibitors is comprised as they don't remove the scaffolding in the cancer cells).

EXHIBIT 24: **Mutation coverage - bexobrutideg vs BTK inhibitors**



Pirtobrutinib (Jaypirca; Eli Lilly) = CLL, Vecabrutinib (Sunesis) = CLL, Fenebrutinib (Roche) = MS, Ibrutinib (Imbruvica; Abbvie) = CLL, Acalabrutinib (Calquence; AstraZeneca) = CLL/MCL, Zanubrutinib (Brukinsa; BeOne) = CLL
Source: Roche

EXHIBIT 25: **Bexobrutideg - phase I efficacy in relapsing/ remitting CLL**



Source: Roche

Roche believes that the early clinical profile supports Roche's potential best-in-class ambition for 'bex-deg'. But in our view this needs to be validated with phase 3 data. In phase I relapsed/refractory CLL patients, bexobrutideg generated an 83% overall response rate and median progression-free survival of 22.1 months in a heavily pretreated population, with responses observed across BTK mutations, high-risk molecular features and CNS disease (Exhibit 25).

We believe that the breadth of activity of 'bex-deg' is at least as important as the headline response rate. This is because 'bex deg's' activity after prior BTK-directed therapy across multiple resistance genotypes would support the mechanistic argument

that removal of the whole protein can recapture control of the cancer after conventional BTK inhibition fails.

Based on published data, safety also appears manageable for 'bex deg' with limited serious adverse events and only c.5% of patients discontinuing treatment. This is important in CLL, where tolerability and the ability to maintain chronic therapy can be as commercially relevant as initial response depth.

Cross-trial comparisons (between BTK inhibitors and 'bex-deg') remain imperfect and the phase I dataset for Roche's drug is necessarily small and selected. Durability, safety at scale and performance against active standards therefore remain open questions which should be addressed in a phase 3 trial. Nevertheless, in our view, the combination of broad mutation coverage, deep BTK degradation, CNS penetration and a potentially cleaner selectivity profile provides a highly credible rationale for moving 'bex deg' into registrational development.

Phase III trial will test whether BTK degradation can establish a new standard of care after BTK inhibition and whether degraders can expand beyond a small number of validated targets. Roche initiated the DAYBreak-CLL 306 phase III trial in second-line or later CLL in 3Q26 which compares 'bex-deg' to Jaypirca (Lilly; O; Courtney Breen) and is due to report results in 2029. (The consensus peak sales for Jaypirca are $3.4bn).

Roche has also started a phase I/II study combining bexobrutideg with Venclexta (AbbVie (M; Courtney Breen; 2025 sales $2.8bn), with or without an anti-CD20 (rituximab or Gazyva (Roche; O; 2025 sales $1.3bn). Roche's broader development plan for 'bex-deg' spans first-line and relapsed/refractory CLL, with expansion into mantle cell lymphoma and Waldenström's macroglobulinemia (but these latter two are very small indications).

Roche's strategy therefore extends beyond a single salvage setting. Monotherapy 'bex-deg' can test whether degradation overcomes acquired BTK resistance, while combinations and earlier-line development could determine whether deeper pathway removal improves the efficacy or duration vs standard of care BTK inhibitors. The success of 'bex-deg' would provide clinical validation for protein degradation, broaden the modality's commercial relevance across haematological malignancies and strengthen the case for applying the same design principles to other intracellular targets which remain difficult to address with conventional inhibitors (eg autoimmune diseases). The control arm of Jaypirca by Eli Lilly (Breen; O) is a non-covalent BTK target standard of care. Compared to the phase III trial that led to Jaypirca approval, the DAYbreak trial has twice the number of patients (~600 to ~250), and has both PFS and OS as primary endpoints. (We also note that 'bex-deg' is administered as a once daily tablet whereas the BTK inhibitors have to be swallowed twice daily).

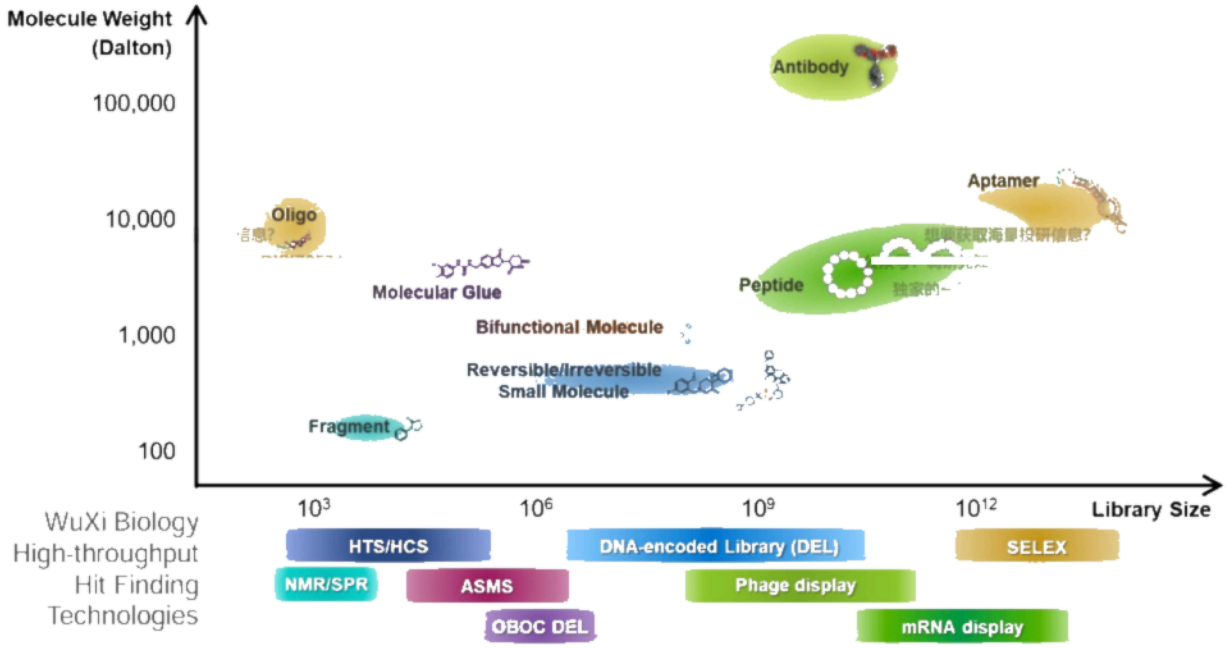
CRO AND CDMO OPPORTUNITIES

DEMAND FOR COMPLEX CRO SERVICE

A growing mid-sized pipeline needs specialized discovery tool kit from CROs. Cyclic peptides, PROTACs and other complex molecules require more specialized discovery tools than traditional small molecules. These include peptide and macrocycle libraries, affinity-based screening (like phage display), and assays for protein-protein interactions and ternary complexes.

WuXi AppTec already offers a broad toolkit spanning conventional high-throughput screening, DEL and peptide-based platforms(Exhibit 26). As the R&D pipeline of these modalities grows, we expect **CRO demand to shift not only in volume but also toward higher-complexity chemistry and screening services**, and providers of end-to-end support from hit discovery through optimization, development, and commercialization would benefit.

EXHIBIT 26: **Wuxi Apptec's CRO services cover a variety of screening platforms for drug discovery in mid-sized molecules: peptides, bifunctionals (molecular glue and PROTAC), etc.**



Source: Wuxi Apptec Investory Day 2025

MANUFACTURING OF MID-SIZED MOLECULES

More complexity = more demand for CDMO manufacturing. Mid-sized molecules are not just bigger. They involve more synthesis steps, greater stereochemical complexity, lower yields and harder purification than conventional small molecules (Exhibit 27, Exhibit 28). Macrocyclic peptides are a good example. The standard route uses SPPS to assemble a linear peptide, followed by chemical cyclization and purification (Exhibit 29). Longer sequences add impurities and reduce overall yields, while ring closing adds another challenging step.

Process innovation brings another layer of opportunity. Merck's enlicitide shows what more advanced manufacturing could look like. Its process uses biocatalysis for peptide assembly and macrocyclization, together with crystallization-based purification (Exhibit 30). For most cyclic peptides, **SPPS + cyclization + purification remains the core CDMO opportunity**. But as programs scale, better process chemistry, biocatalysis and route redesign could create incremental demand for CDMOs with specialized technical focus. For example, Asymchem has built an enzyme library of ~2400 enzymes for biocatalysis service.

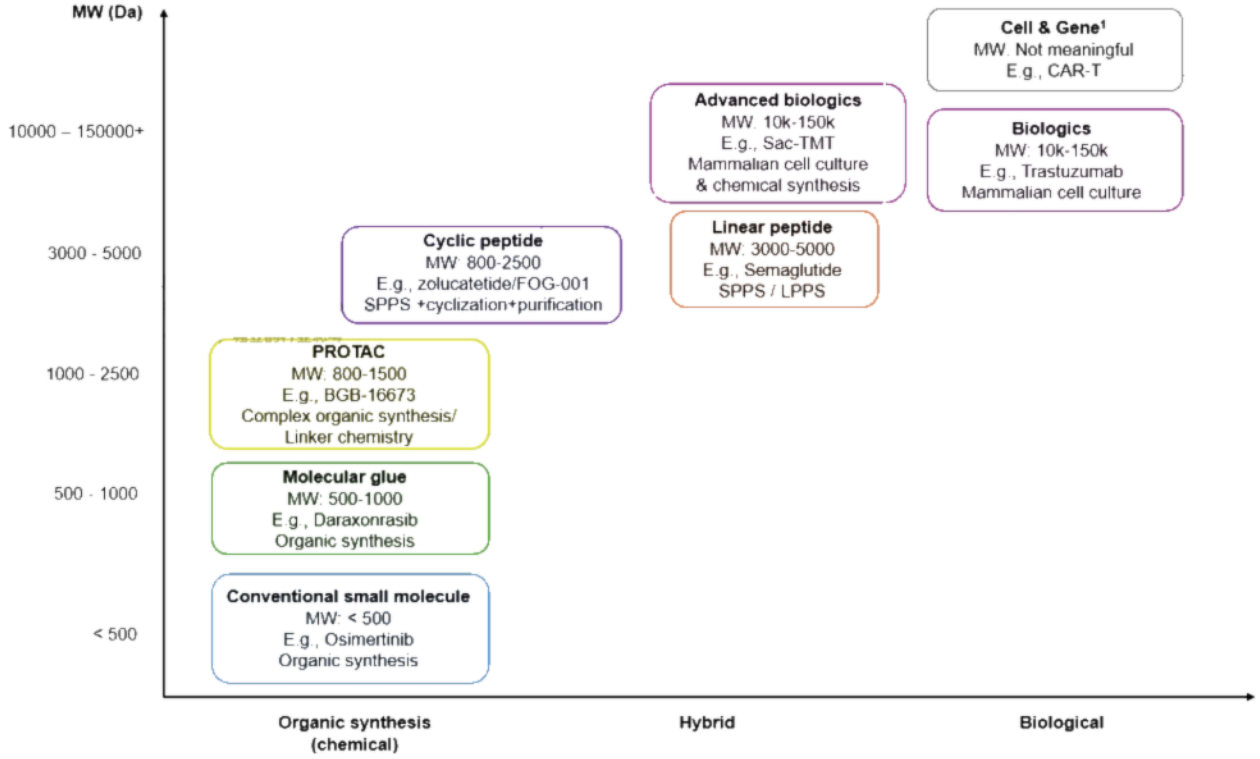
Leading CDMOs are also excited about potential (and barriers) of degraders. Protein degraders combine two binding elements through a linker and generally occupy a more complex chemical space than conventional small molecules, increasing the importance of route design, analytical control, purification and scalable synthesis. The excitement about these products is corroborated by the CEO of Siegfried (O), a leading small-molecule CDMO, who described these drugs as a **"A game changer….I'm sure in three years, we will talk more about these protein degraders"**.

EXHIBIT 27: **Peptides and mid-sized molecules introduce new challenges for commercial API manufacturing and more ways to differentiate for CDMO players**

Challenges in API manufacturing	Small molecules	Peptides	Complex mid-sized molecules
Synthetic approach	Classic organic synthesis	SPPS / LPPS / Hybrid	Advanced organic synthesis
Challenges	Chirality Pyrrole formation	Linear peptide length Peptide fragment assembly Low yield	Lengthy step counts Heterocycle construction Ternary complex Stereochemistry & impurity control
Chirality	0-2 simple stereocenters	30+ chiral centers	Multiple rigid or flexible stereocenters/axes
Linear steps	<10 steps	15-30+ steps for each peptide fragment + assembly	15-30+ steps
Purification	Routine precipitation / crystallization	chromatography and flow chemistry	chromatography and flow chemistry
Yield	30-60%	10-30%	10-30%
CDMO value add	**Simple cost & scale**	**Capacity and technology**	**Process optimization** (e.g. orforglipron synthesis had been optimized from the original 28-step route in the patent to an under 10-step process

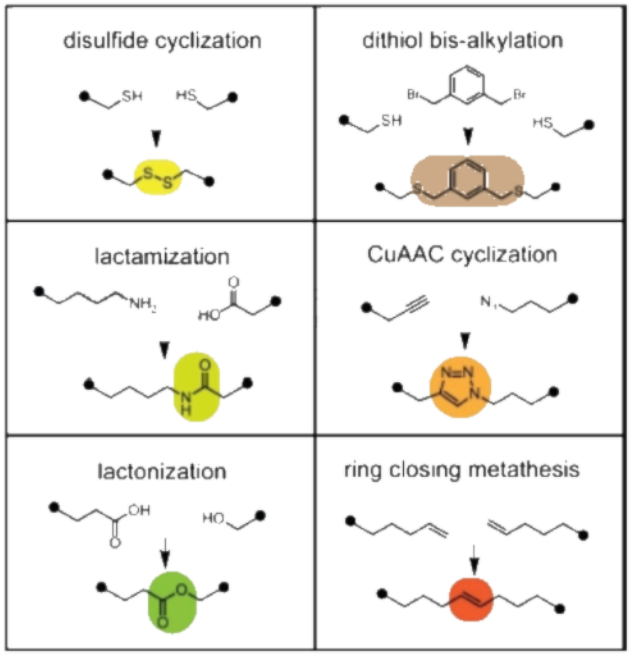
Source: company disclosures, USPTO, Bernstein analysis

EXHIBIT 28: **Manufacturing routes - chemical vs. biological vs. hybrid - for different modalities**



1: Cell: Autologous/allogeneic cell manufacturing; Gene: Cell culture + vector production
Source: Bernstein analysis and estimates

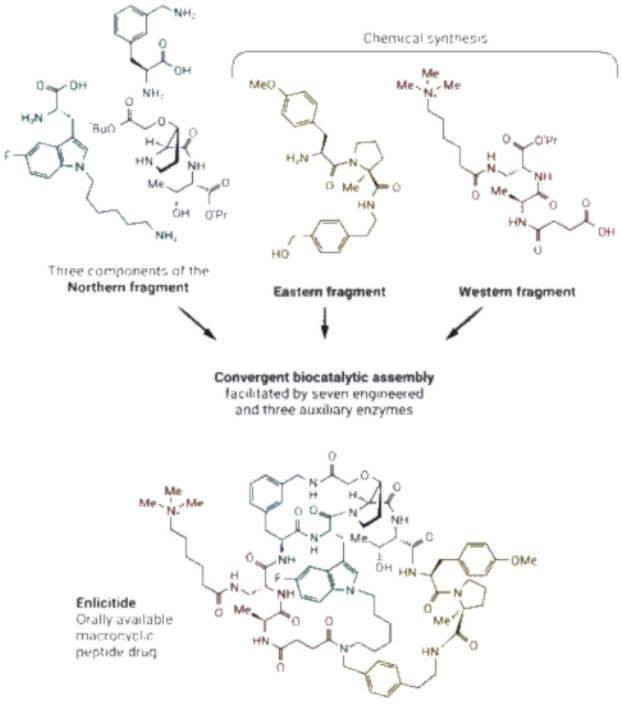
EXHIBIT 29: **Typical chemical cyclization of linear peptides**



Source: Angew. Chem. Int. Ed. 2024, 63, e202308251

doi.org/10.1002/anie.202308251

EXHIBIT 30: **Biocatalytic cyclization of enlicitide from three fragments**



Source: Science 2026, DOI: 10.1126/science.aed8713