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Five approaches to drug cancer's 'undruggable' β-catenin pathway

Clinical companies are targeting five different nodes to separate oncogenic signaling from Wnt's roles in healthy tissue

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A new generation of Wnt pathway inhibitors aims to avoid the toxicities that sank earlier attempts to disrupt β-catenin signaling. But rather than converge on a single solution, five clinical programs are pursuing five different points of intervention along the pathway.

Dewpoint Therapeutics Inc., Iterion Therapeutics Inc., Sapience Therapeutics Inc., Parabilis Medicines Inc. (NASDAQ:PBLS), and partners PRISM BioLab Co. Ltd. and Eisai Co. Ltd. (TSE:4523) all have molecules in the clinic, each inhibiting β-catenin signaling in a different way.

Data from Parabilis' program helped spur the largest NASDAQ IPO in history by a pure-play biopharma in June.

Developers of earlier-generation Wnt pathway inhibitors largely agreed on where to aim — upstream, at ligands and receptors — and mostly failed for the same reason: broad pathway inhibition could not separate oncogenic signaling in tumors from Wnt's essential roles in normal stem cell turnover.

The new generation of inhibitors is flipping that around; while the players are all seeking ways to avoid toxicity, they do not agree on where to aim.

The companies also differ in how they intend to prove their molecules are acting on-target and in the lead indications they have chosen to provide the first clinical proof of concept.

β-catenin-targeted therapies in the clinic

Company	Lead asset	MOA	Rationale	Lead indication	Modality	Clinical stage
Dewpoint	DPTX3186	Sequesters β-catenin in inactive nuclear condensates	Concentration dependent; only sequestered in high-β-catenin (cancer) cells	Gastric cancer	Small molecule (condensate modulator)	Ph I
Eisai/PRISM	E7386	Disrupts β-catenin:CBP interaction	β-catenin favors CBP over p300 in cancer; blocking CBP pushes cells toward differentiation	Endometrial cancer	Small molecule (PPI inhibitor)	Ph I/II
Iterion	Tegavivint	Disrupts β-catenin:TBL1 interaction	TBL1 shields nuclear β-catenin from degradation; disrupting it lets the cell destroy β-catenin itself	Hepatocellular carcinoma (HCC)	Small molecule (degrader)	Ph I/II
Parabilis	Zolucatetide	Disrupts β-catenin:TCF interaction	DepMap data shows this is the most important node in the pathway	Desmoid tumors	Peptide (cell-penetrating peptide macrocycle)	Ph I/II
Sapience	ST316	Disrupts β-catenin:BCL9 interaction	BCL9 is dispensible for normal physiology; BCL9 KO mice are viable	Colorectal cancer (CRC)	Peptide (cell-penetrating D-peptide)	Ph II

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Three takes on inhibiting a co-factor

Three of the five programs are built around denying β-catenin a nuclear co-factor it needs to drive transcription.

Iterion's tegavivint binds TBL1, a co-factor that shields nuclear β-catenin from proteasomal degradation and helps assemble the transcriptional "enhanceosome" complex on Wnt target genes.

Iterion CEO Rahul Aras told BioCentury that the molecule emerged from a target-agnostic phenotypic screen. The company has since solved an X-ray crystal structure of TBL1 showing the protein self-assembles into dimers that form the binding pocket tegavivint occupies.

Sapience's ST316 targets a different partnership, between β-catenin and BCL9 or its paralog, BCL9L. Rather than binding the co-factors, ST316 binds β-catenin at the armadillo repeat surface they use. Sapience CSO Jim Rotolo described BCL9's effect on β-catenin as "turning the β-catenin signal from a solid drip to a full flow of signaling and transcription."

The peptide binds β-catenin's ARM1 domain, which Rotolo said is used exclusively by BCL9 and BCL9L, while steering clear of the surfaces used by TCF/LEF and the destruction complex.

That distinction matters because β-catenin still needs to enter the nucleus for ordinary physiologic signaling — it just doesn't need to stay there. In healthy cells, β-catenin is transiently stabilized, recruited to the nucleus to drive transcription, and then degraded — a process Rotolo described as allowing it to "jump in, do its activity, and be gone."

In cancers with Wnt pathway mutations, by contrast, β-catenin remains stabilized and available. Sapience's model holds that BCL9 retains it in the nucleus, protects it from degradation and sustains the enhanceosome's output. Blocking that interaction should therefore allow β-catenin to enter the nucleus normally, but prevent it from remaining there long enough to sustain an oncogenic transcriptional program.

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BARRY KAPPEL, SAPIENCE

Founder, President, and CEO Barry Kappel frames that as Sapience's core differentiator from the broader field, not just its co-factor peers. Earlier attempts to drug Wnt signaling were "shutting down pathways," Kappel told BioCentury. "For us, it's shutting down aspects of pathways — the oncogenic aspect, the immunosuppressive aspect — versus physiologic aspects such as stem cell turnover."

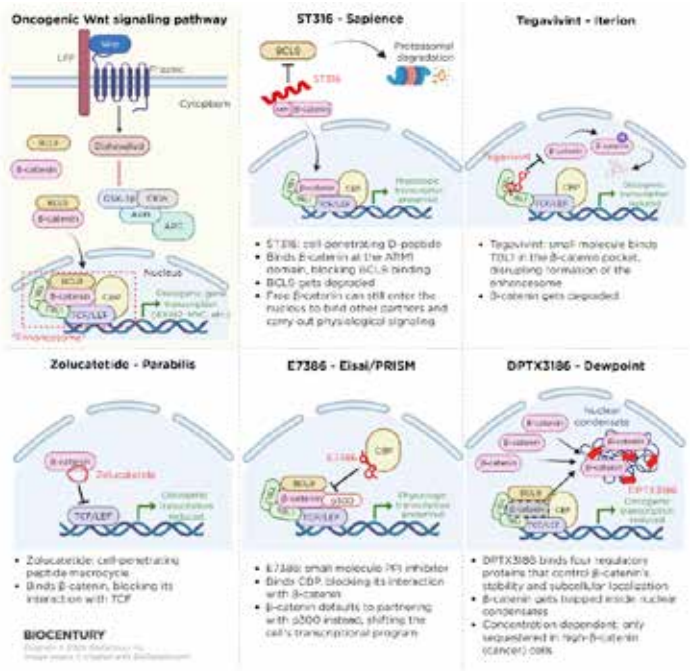
To make ST316, Sapience used enantiomeric peptide chemistry — building the peptide from D-amino acids, the mirror-image isomers of naturally occurring amino acids, to evade protease degradation — paired with a cell-penetrating domain that Kappel said skews this particular program toward the cytoplasm, with only slight nuclear activity.

Sapience argues that BCL9, unlike β-catenin, is dispensable for normal physiological signaling. As evidence, Kappel said mice with conditional BCL9 knockouts survive, whereas mice with knockouts of other Wnt pathway components do not.

PRISM BioLab Co. Ltd. and Eisai Co. Ltd. (TSE:4523) target a third co-factor with small molecule E7386, which blocks the interaction between β-catenin and CBP.

Eisai did not comment in time for publication, but published studies suggest that β-catenin can partner with either CBP or its close relative p300, with different consequences: CBP-driven transcription favors proliferation and stemness, the kind of activity cancer depends on, while p300-driven transcription favors differentiation.

By selectively blocking the CBP interaction, E7386 may push cancer cells toward differentiation rather than killing them outright, while leaving the p300 arm available for normal cell function.



Going straight for the transcriptional complex

Parabilis is targeting the interaction between β-catenin and the TCF family of transcription factors to disrupt DNA-binding — what Chairman, President, and CEO Mathai Mammen calls the pathway's "true chokepoint."

The rationale is backed by DepMap, the Broad Institute of MIT and Harvard's dependency-mapping dataset that uses CRISPR screens across more than 1,000 cancer cell lines to identify gene mutations that cancer cells depend on for survival. "If you look at DepMap for our pathway, the Wnt/β-catenin pathway, the interaction that lights up is β-catenin interacting with TCF — that node," Mammen told BioCentury.

It's a node Mammen and others tried and failed to drug earlier in their careers because the interface is flat, lacking the binding pocket conventional small molecules require.

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> MATHAI MAMMEN, PARABILIS

Parabilis produces cell-penetrating peptide macrocycles called Helicons, which the company likens to "intracellular antibodies" capable of engaging flat protein surfaces. Its Helicon zolucatetide binds β-catenin directly, sitting in the exact site where TCF would otherwise dock, functioning as a straightforward competitive inhibitor.

The company picked desmoid tumors, rare fibrous tumors typically driven by mutations in APC or CTNNB1, as its first indication. Parabilis is betting that a disease dominated by a single oncogenic pathway will provide a clean initial proof point before it enters genetically more complex cancers such as colorectal cancer.

Not everyone agrees that directly blocking the β-catenin–TCF interface will be safe. Sapience's Kappel argues that the approach is functionally similar to shutting down Wnt signaling at the cell surface because the β-catenin–TCF partnership drives physiological as well as oncogenic transcription.

Parabilis' early Phase I/II data suggest the approach may nevertheless have a therapeutic window, with no Grade 3 or higher GI, skin, or ovarian toxicities and no treatment discontinuations reported at the doses the company has identified as optimal.

Trapping β-catenin away from the genome

Dewpoint thinks the best method is functionally inactivating β-catenin – but only because it believes it can do so specifically in cancer cells. DPTX3186 targets four regulatory proteins that control β-catenin's stability and subcellular localization, trapping it inside nuclear condensates.

"Instead of asking only whether we can bind a protein and inhibit it, we can ask whether we can change where that protein resides," CSO Ann Boija told BioCentury.

The molecule sequesters β-catenin into what Boija calls "inactive depots," shutting down downstream transcription without engaging β-catenin directly.

"Condensates are concentration dependent, which means that in cancer cells, which have high levels of β-catenin in the nucleus, we can specifically sequester β-catenin off the genome into this inactive depot," said Boija. That leaves healthy cells with baseline levels of β-catenin unaffected.

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> ANN BOIJA, DEWPOINT

Because that trapping is irreversible, Isaac Klein, Dewpoint's Chief Development and Operating Officer, said DPTX3186 doesn't need to be dosed daily to keep working. The drug can be pulsed over a few days and then withdrawn, which the company says widens its therapeutic window compared with the constant dosing schedules that drive toxicity in most oncology drugs.

Klein said the approach has so far avoided the toxicities that sank earlier Wnt programs. The company dosed its first patient in January and is moving into its sixth dose-escalation level with no dose-limiting toxicities observed.

Dewpoint chose gastric cancer, an orphan-designated indication, as its lead program — a decision CEO Ameet Nathwani attributed to strong preclinical sensitivity to its drug and unmet need.

As an oral small molecule, Nathwani argued that DPTX3186 also carries a lower cost of goods than its peptide-based

competitors, a difference he believes could matter for combinability and global access.

Proving it's on-target, not just on-tumor

These β-catenin companies are gathering evidence to show that their molecules are working through their intended targets.

Parabilis's evidence forms a chain from structural data showing zolucatetide binding β-catenin where TCF would normally dock, through reduced expression of Wnt target genes including AXIN2 and MYC, to cell killing and tumor regression in PDX models. The company has also used paired pre- and post-treatment biopsies from patients in the Phase I portion of its Phase I/II trial to demonstrate pathway modulation in tumors.

Sapience is using a similar paired-biopsy strategy, but leans hardest on spatial transcriptomics, which Rotolo called "the real ironclad evidence" that ST316 is hitting the Wnt pathway "specifically in the tumor cells, but not in all the adjacent normal cells." In post-treatment biopsies, Kappel said nuclear β-catenin clears to "very low basal levels."

Iterion uses liquid biopsy: the company has reported circulating tumor DNA (ctDNA) reductions in its Phase I/II HCC trial that correlate with tumor shrinkage, alongside reduced tumor β-catenin protein in matched tissue samples.

Dewpoint's version of target-engagement proof runs through three liquid-biopsy biomarkers built specifically for this mechanism. The first, which Boija called the field's first condensate-specific assay, looks directly at the β-catenin depot inside circulating tumor cells.

A second uses exosomes to track downregulation of classic β-catenin target transcripts, and a third uses plasma proteomics to measure changes in Wnt-controlled proteins. Reducing β-catenin levels in cancer cells also desensitizes them to the drug in preclinical models, Boija said, evidence in her view that β-catenin concentration itself, not some off-target effect, drives the molecule's selectivity.

Patient selection, meanwhile, doesn't require testing β-catenin levels directly: Klein said any mutation in the Wnt pathway is a reliable surrogate for the high nuclear β-catenin state the drug is designed to sense, letting the company enroll patients based on standard genomic testing rather than a condensate-specific biomarker.

Dewpoint expects biomarker data from patients before year-end.

Early efficacy

Early clinical data suggest multiple routes to inhibiting β-catenin signaling can produce antitumor activity, although differences in tumor type, combination regimen, and patient selection make it too early to tell which approach has the greatest potential.

In second-line microsatellite stable colorectal cancer (MSS CRC), adding ST316 to FOLFIRI plus bevacizumab lifted the objective response rate to 47%, versus an 11% historical benchmark from the EAGLE trial, with a 93% disease control rate, according to data Sapience disclosed in April.

Median PFS had not been reached but exceeded 10 months at the data cutoff, Kappel said, in a population whose disease has historically progressed at 6-6.5 months.

The trial enrolled all comers, Kappel said, without selecting for an APC or β-catenin mutation. The company expected the vast majority of second-line MSS CRC patients to carry a relevant Wnt pathway mutation already, and found roughly 80% did. The benefit held regardless of KRAS/NRAS mutation status or prior bevacizumab exposure, Kappel said, and no gut wasting or bone thinning has emerged in preclinical or clinical testing.

The company is preparing familial adenomatous polyposis and desmoid monotherapy studies alongside a bigger randomized Phase IIb in CRC against standard of care.

Iterion's HCC trial had enrolled 40 patients as of the company's ASCO 2026 presentation, 73% of whom carry a Wnt-pathway mutation in AXIN1, APC, β-catenin, or CBP.

Among Wnt-mutated patients who received the recommended dose range of 3 to 6.5 mg/kg, tegavivint produced an 11% partial response rate and a 72% disease control rate, with median progression-free survival of six months — rising to eight months in patients with two or fewer prior lines of therapy, vs. four months in more heavily pretreated patients.

There were no responses among patients without a Wnt-pathway mutation, who had a 43% disease control rate, and just two months of median PFS.

Iterion reported an 80% objective response rate and no dose-limiting toxicities in its osimertinib combination for EGFR-mutated non-small cell lung cancer across 15 evaluable patients at ASCO 2026. Median progression-free survival reached 19.9 months and median overall survival reached 48.8 months, with responses occurring regardless of high-risk features such as TP53 mutation.

The company has also moved tegavivint into a Phase Ib combination with gemcitabine in relapsed osteosarcoma, and into colorectal cancer, dosing its first patient in a Phase I/II trial in February after preclinical data showed the drug induced apoptosis in patient-derived organoids.

For Parabilis, as of Feb. 16, 38 desmoid tumor patients had been enrolled and treated with zolucatetide; of the 25 with sufficient follow-up to be response-evaluable, all experienced tumor shrinkage and the disease control rate was 100%.

Among the 19 patients with at least two post-baseline scans, 74% (14 of 19) had an objective response per RECIST 1.1, including one complete response, with responses occurring in patients naive to gamma-secretase inhibitor therapy — the only FDA-approved desmoid drug — as well as those who had progressed on or discontinued it.

Zolucatetide has FDA fast track and orphan drug designations for desmoid tumors, and Parabilis, which went public in June, plans to begin a global registrational Phase III trial in the indication in the first half of 2027.

Eisai has reported efficacy data for E7386 from a global dose-expansion cohort of Study 102 in patients with advanced endometrial cancer who had progressed after platinum-based chemotherapy and anti-PD-(L)1 therapy.

Across 30 patients (data cutoff October 2024), E7386 plus lenvatinib produced an objective response rate of 30%, rising to 42.9% in the roughly half of patients who hadn't already been treated with lenvatinib — compared with a 14.3% ORR for lenvatinib alone in a similar post-chemotherapy population in an earlier Eisai trial.

A follow-on dose-optimization cohort within the same trial showed an even higher ORR of 43.8% in an initial 16 patients, according to a 2025 *International Journal of Gynecological Cancer* paper describing the study, though Eisai has not yet reported a complete dataset from that larger, randomized expansion.

On the preclinical development front, Captor Therapeutics S.A. (WSE:CPR) has disclosed work on a β-catenin-targeted degrader, and BioCentury's BCIQ database lists at least six other companies with preclinical candidates targeting β-catenin.

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