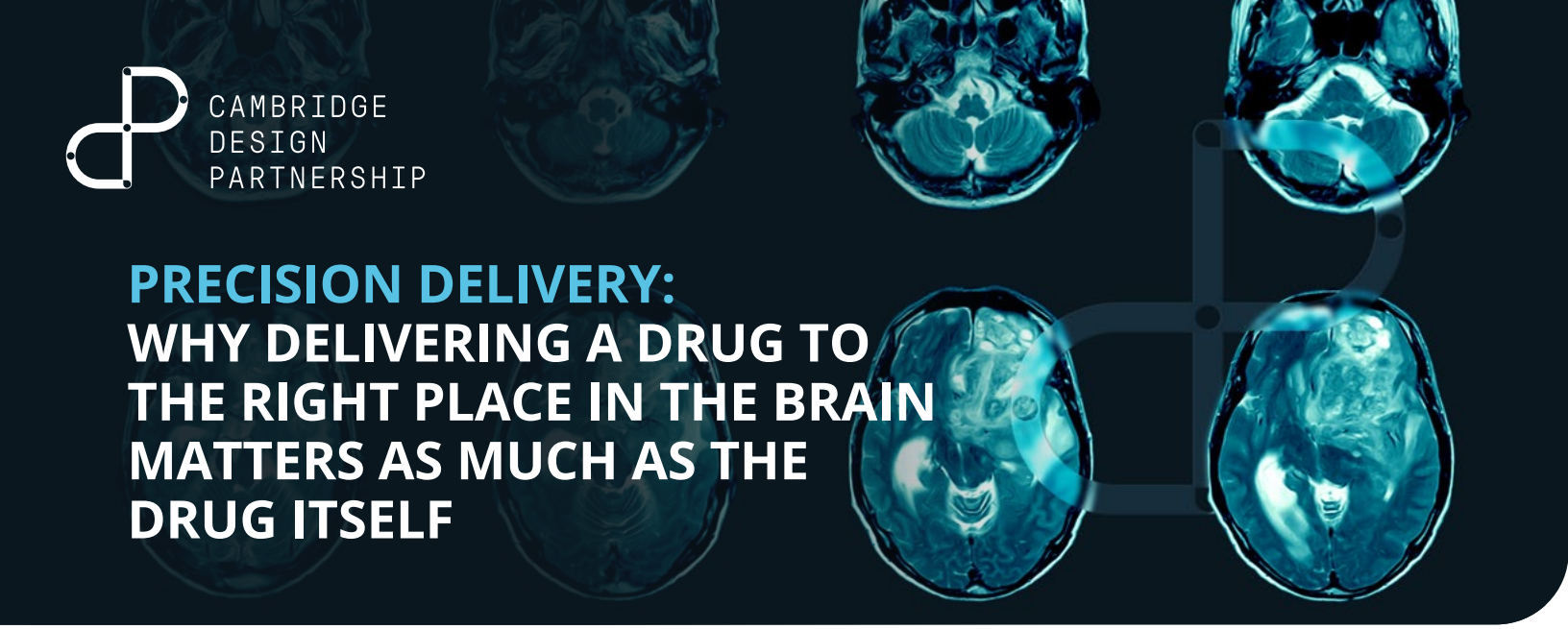
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PRECISION DELIVERY: WHY DELIVERING A DRUG TO THE RIGHT PLACE IN THE BRAIN MATTERS AS MUCH AS THE DRUG ITSELF



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Most of us in therapeutic technology development are focusing on key milestones, in a race to reach a clinical trial. Few programs get there. Fewer still succeed and get to patients, and when one fails, we don't often find out why. Was it the drug, the device, the training, the supporting technology? So, when I heard that PRECISE, a twenty-year-old glioblastoma clinical trial that had failed, had been looked at again, years later and at a deeper level of detail than before, I wanted to sit down with the people who were there then and are analyzing and learning from it today: Sandeep Kunwar and Stephan Mittermeyer of Precision NeuroMed.

In brief:

- As of November 2026, ClinicalTrials.gov lists nearly 600 active trials for glioblastoma, around 70% of them recruiting or about to start.[1] **Median survival after diagnosis (under two years) has barely moved in twenty years.**[2]
- Convection-enhanced delivery (CED) infuses therapeutics directly into brain tissue through a catheter, bypassing the blood-brain barrier (BBB) to enable higher payload with lower systemic toxicity than intravenous (IV) infusion.
- PRECISE, the only completed phase III CED trial in brain tumors,[3] tested CED-delivered drug against Gliadel wafers, the existing standard of care. Results published in 2010 showed the trial had missed its primary endpoint.[4] However, a retrospective analysis found that **only about half of the catheters were positioned as intended, and that on average only a fifth of the target tissue around the resection cavity was likely to have received the drug.**[5]
- Precision NeuroMed, co-founded by PRECISE's lead investigator, is one of several groups now rebuilding CED around confirmed, reproducible delivery: **delivery device, robotics, software and training treated as one system.**
- **A note on terms:** this article uses brain tumors, and PRECISE specifically, as its case study. The underlyingdelivery problem, and most of what follows, applies to central nervous system (CNS) delivery more broadly, anywhere a treatment mustreach a specific location inside the brain, not just brain tumors.

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HOW ONE PATIENT CHANGED THE STORY

The story that stuck with me during our conversation was that of Justin (not his real name).

In 2004 Justin was 56, when Sandeep operated on him to remove a glioblastoma tumor from the right side of his brain. Having enrolled Justin in the PRECISE trial, Sandeep then treated that side of the brain with the drug, cintredekin besudotox, a drug built to find tumor cells by their IL-13 receptors and kill them once it locks on.

PRECISE was designed to test whether delivering this drug directly to the tissue surrounding a resection cavity was more effective than the standard of care: implanting Gliadel wafers, carmustine-impregnated wafers, into resection sites.

This treatment worked far beyond expectations for Justin. He went more than fifteen years without symptoms: no further chemotherapy, no steroids.

But by then PRECISE had already been declared a failure, with results published in 2010 showing it had missed its primary endpoint.[4] Nobody, including Sandeep, knew what had happened to Justin, because nobody was tracking patients as the trial had ended.

Sandeep only found out at a social gathering, in 2023, when a colleague mentioned he'd just operated on one of Sandeep's old PRECISE patients for a recurring glioblastoma. Justin had had a seizure, his tumor was back, but only on the left side of his brain, the side that was never treated.

That single case sent Sandeep back into the trial's old imaging archives, re-analyzing scans with tools that didn't exist when PRECISE was conducted. What he found reframed the entire trial and his view of drug delivery to the brain.

WHY DOES ONE FAILED TRIAL MATTER?

Justin's case is one of many in a single trial, but the problem it exposed underscores the entire field. Nearly 600 trials globally are currently targeting glioblastoma, yet median survival after diagnosis of under two years has barely moved in twenty years.[2] Every one of those trials will eventually meet the question PRECISE asked twenty years ago: did the drug even reach its target?

> A brilliant drug that never reaches its target is, functionally, **no drug at all.**

This article uses brain tumors, and PRECISE specifically, as its case study. But the underlying problem isn't specific to neuro-oncology. Anywhere a treatment has to reach a defined location inside the brain, damaged tissue in Parkinson's, a misfiring circuit in epilepsy, runs into some version of the same challenge – getting across the BBB. What follows is really about brain-targeted delivery, and CNS delivery more widely. Brain tumors are an example, arguably one of the most intractable ones.

I sat down with Sandeep Kunwar, MD, principal investigator on PRECISE and now co-founder and CEO of Precision NeuroMed, and Stephan Mittermeyer, PhD, the company's Chief Technical Officer, to go through what happened in PRECISE, what's changed since, and what it means for anyone building a brain-targeted delivery program today.

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WHAT IS CONVECTION-ENHANCED DELIVERY AND ITS USE IN BRAIN TUMORS?

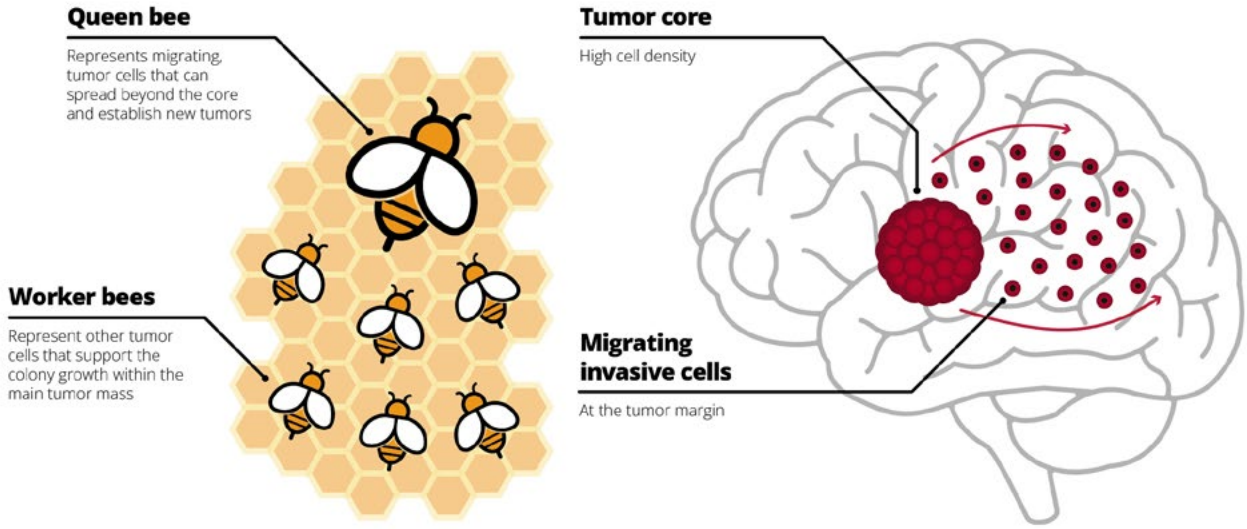
Convection-enhanced delivery, or CED, is a neurosurgical technique that infuses therapeutics directly into brain tissue through a catheter, using a steady pressure gradient to push the drug through the interstitial space within a target tissue. CED bypasses the blood-brain barrier (BBB), thus overcoming challenges of achieving sufficient drug payload in the brain via systemic delivery.

Brain tumors are difficult to reach and highly heterogeneous, which is why CED is an important delivery method for neuro-oncology. Sandeep likens it to a beehive. Picture thousands of worker bees in constant activity; that's the tumor you can see on a scan, the dense, contrast-enhancing mass a surgeon can find and cut out. Neurosurgeons do this routinely; Sandeep has done it for 25 years. And yet, Sandeep points out that removing the hive alone barely moves survival.

You can kill every worker bee in the colony, but if a single queen survives, the colony rebuilds. That's what drives recurrence, and it's also why where a drug goes matters just as much as what the drug is. CED gets the drug closer to the tumor site and can create a distribution that best covers the target region.

> **"The blood-brain barrier is 100 million years of evolution. It was designed to keep things out of the brain, and it's very efficient at doing that. CED bypasses that."**
>
> Sandeep Kunwar

> **"The reason why is because out in the periphery are all these queen bees, cells that are migrating out, invading tumor stem cells. Each one of those queen bees can make a new hive."**
>
> Sandeep Kunwar



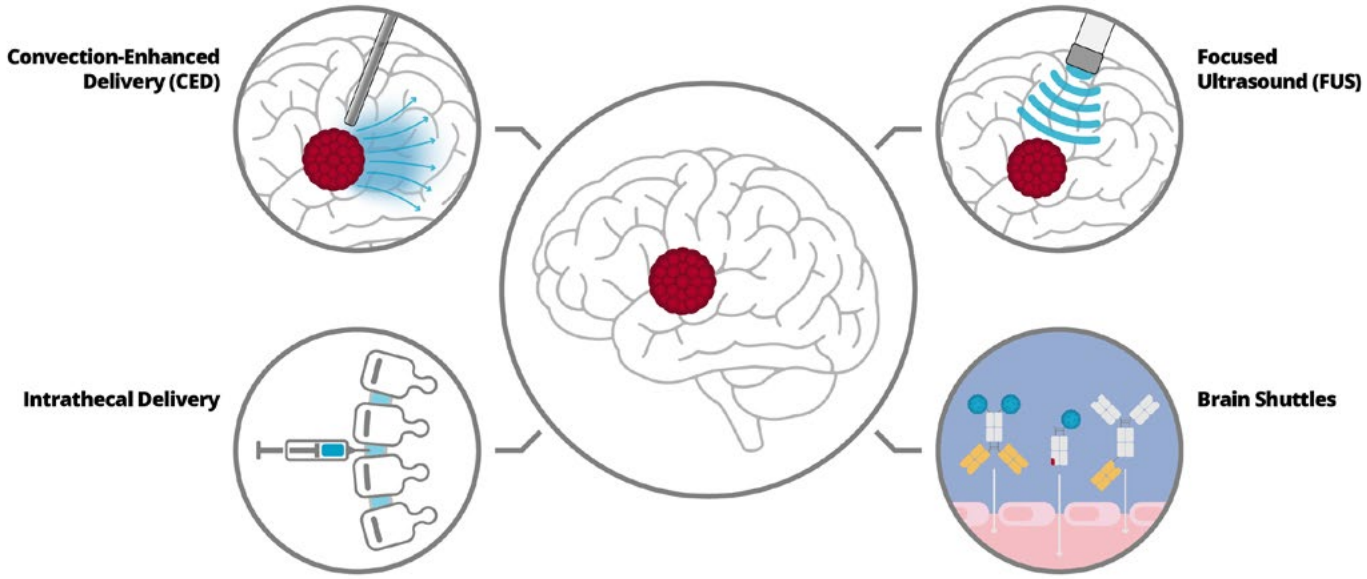
> The beehive analogy for brain tumors. The hive and its worker bees represent the visible tumor mass that surgery can remove. The queen bees represent invading tumor cells at the margin; if any survive treatment, each can found a new hive, seeding a recurrent tumor.

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> **"It's a local, regional treatment. People often ask why we don't just flood the whole brain with drug instead of targeting one site. It's less about the ability to do that and more about the fact you don't want to disrupt other brain regions unless you really have to. We know that most infiltrating cells can be found in a 2cm margin around the enhancing tumor. This is where we typically see recurrence, so we focus on what has the biggest potential impact."**
>
> Stephan Mittermeyer

The alternative, going in through the bloodstream, has its own ceiling, intravenous drugs have to cross the BBB, and for most CNS drugs this is a huge challenge. "You need to put in a lot systemically to get a little bit into the brain" Stephan says.

Whichever route you choose, brain shuttles, focused ultrasound, CED, intrathecal delivery, you're not really solving a pharmacology problem. You're solving a delivery problem: can this catheter tip, this ultrasound array, this infusion line, etc. put the dose at the same coordinate, at the same rate, without triggering backflow or shear damage to the payload, to the exact target location regardless of who's performing the procedure or which hospital they're in? Those are questions for mechanical engineering and human factors; brain tissue is poroelastic, it deforms, absorbs and redistributes fluid under pressure differently in gray matter than in white matter, and differently again inside a tumor than in the healthy tissue around it. A device built and tested for one part of the brain won't necessarily behave the same way three centimeters over.



> Methods for delivering drugs to the brain, and their current role in brain tumor treatment. Convection-enhanced delivery (CED) infuses drug through a catheter placed directly in brain tissue, bypassing the blood-brain barrier (BBB). Focused ultrasound (FUS) temporarily opens the BBB at a targeted site; the phase III SONOBIRD trial is testing this with carboplatin in recurrent glioblastoma. Intrathecal delivery injects drug into the cerebrospinal fluid and is used where tumors have spread into it, but penetrates poorly into solid tumor tissue. Brain shuttles carry drugs across the BBB from the bloodstream; none is yet approved for brain tumors, though ANG1005 reached phase II in recurrent high-grade glioma.

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Every potential route to get drug into the brain in the appropriate loading makes a version of the same trade-off.[6] Brain shuttles focus on getting large molecules across the BBB, but as Sandeep points out, they dilute the drug across five liters of blood, so even with a shuttle only a small percentage reaches brain tissue. Focused ultrasound offers a concentration boost but raises open questions about long-term safety if the treatment requires repeated disruption of the BBB. Intrathecal delivery covers the brain's surface well but tissue penetration tends to decline with depth i.e. towards the center of the brain tissue.

The challenge in CNS delivery is not a lack of engineering expertise, but that traditional pharma is not built to depend on it. Pharma has historically focused on the drug, with the device largely serving as a means of delivering it. CNS delivery is different: success can depend on positional accuracy as much as dose accuracy, making the device, procedure, user, and clinical environment integral to how the therapy performs. CED asks drug development teams to hand a meaningful share of their outcome to a surgical device and a surgical team they don't control. That's a new kind of collaboration in this space, and one I welcome.

CNS treatments are challenging traditional boundaries between drug, device, and clinical teams. Multidisciplinary expertise alone is not enough, **we must proactively work together to get to clinical success faster.**

WHAT WENT WRONG IN THE PRECISE TRIAL?

PRECISE remains the only completed phase III CED trial in brain tumors.[3] The phase I results that preceded it were extraordinary.[7] Sandeep recalls that the first patient treated lived six years disease-free after a single infusion, with early work spanning UCSF, Duke and Cleveland Clinic. Scaling that success was always going to be difficult. The trial expanded almost overnight, from three expert centers to dozens of hospitals across multiple countries, more sites than the field's training pipeline could keep pace with at the time.[8] The technology hadn't caught up either: CED was not as commonplace as it is now, catheters used in the trial were adapted CSF-drainage tubing run through anesthesia infusion pumps for delivery. Crucially, **no one had a way to confirm where the drug had actually gone.**

Re-analyzing imaging data from the trial, investigators found that only about half of the catheters met all positioning criteria, and estimated that on average only around 20% of the target region (the 2 cm margin around the resection cavity) was covered by the drug.[5] For patients whose drug didn't reach its target, the stakes are stark.

"GBM is a devastating disease, if you don't give any treatment to a brain tumor patient, the life expectancy after the initial tumor comes back is about 6 months."

Sandeep Kunwar

Where delivery was on target, results were exceptional, patients like Justin were disease-free for over a decade, until the tumor returned to the other side of the brain where the drug was not delivered. "Our data suggests that this wasn't a biology problem," Sandeep concludes. **"It was a delivery problem."**

The same delivery problem shows up anywhere a therapy depends on precise anatomical placement in the brain, not only in glioblastoma. Formulation efficacy, exact positional delivery, and whether a procedure can be done outside a handful of specialist centers are all part of one system. Treat them separately and you face the same challenges as PRECISE. Treat them as a unit and the next generation of trials looks different: imaging confirmation of every infusion, catheters engineered not to migrate after placement, and training standardized enough that a surgeon's tenth case is as accurate as an expert's hundredth.

> **"In the PRECISE trial, we didn't have a marker to see where the drug actually went. There was no way to find out if you had a non-responder because of the drug, or because of the delivery."**
>
> Stephan Mittermeyer

WHAT SOLUTIONS DO WE NEED FOR BETTER OUTCOMES?

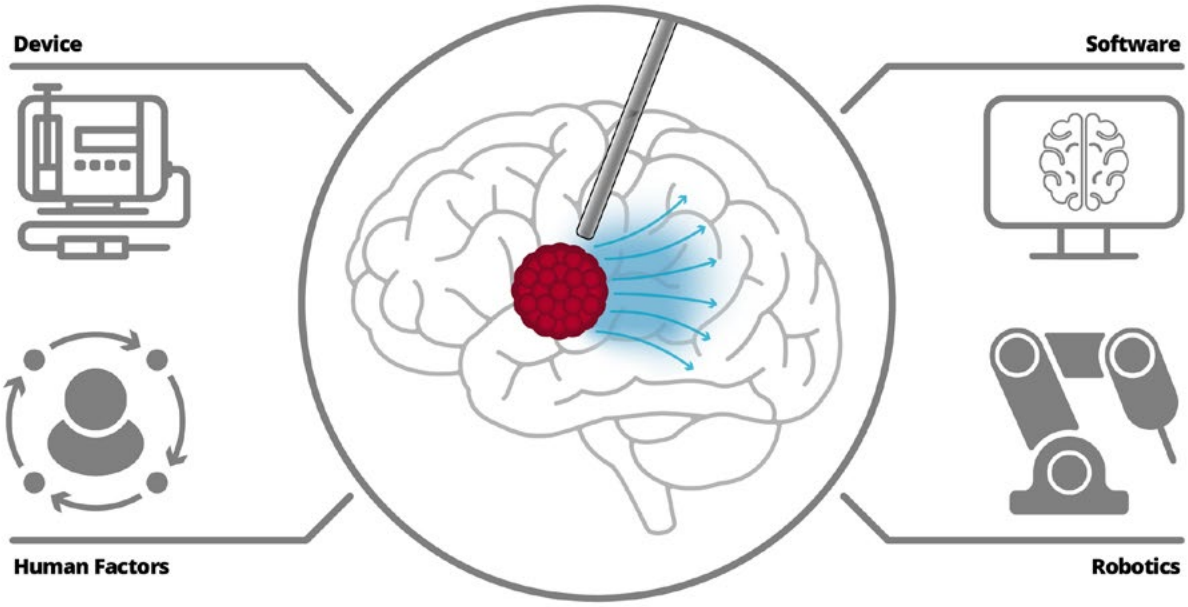
When I ask Sandeep and Stephan, where the struggle really lies, the answer is rarely the biology. It's coordination. Sandeep puts it down to a longstanding misalignment of goals: formulation teams have primarily focused on the drug itself, while device teams focus on the device. Risk-aversion and siloed development have traditionally kept the delivery device separate from the rest of the workflow until formulation efficacy shows promise, a legacy of how the industry is structured rather than any single company's choice.

The fix starts with hardware. Precisely engineered, rigidly fixed catheters have already replaced the adapted tubing of the PRECISE era, the single biggest lesson of that trial translated directly into the better devices of today. From there, the opportunity is in how that hardware gets used consistently, by every surgeon, in every hospital: planning software that borrows from radiotherapy's "inverse planning" model, so a surgeon defines the target and the system calculates the optimal trajectory rather than requiring every surgeon to reason through three-dimensional fluid dynamics by hand; training and procedure design that hold accuracy steady as a program scales; and robotic placement that removes variability at the point of execution. None of this replaces the device or the surgeon. It's what makes the device perform the same way every time, regardless of who's holding it or where.

> **"We want the patient who goes to a small-town hospital to have the same results as someone who goes to a big city specialist center."**
>
> Sandeep Kunwar

Precision NeuroMed's own recent collaboration with Brainlab,[9] a joint effort to build planning software, is one example of this kind of cross-industry pairing becoming more common across the field, not because anyone has fully solved the coordination problem, but because the cost of not solving it is now too visible to ignore.

> **"We're looking at the whole global supply chain: how do we make this scalable and effective for everybody."**
>
> Sandeep Kunwar



> Delivering a drug precisely to the brain as one integrated system. Accurate convection-enhanced delivery (CED) depends on four disciplines working together: the device (catheters engineered to stay where they are placed and achieve drug coverage of the target site), software (planning that calculates the optimal trajectory to the target and recalibrates following brain shift), robotics (removing variability resulting from manual placement and delivery) and human factors (training and procedure design that keeps results consistent across surgeons and hospitals).

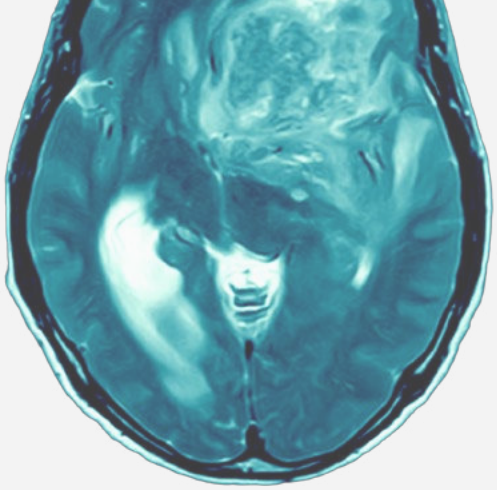
WHERE DOES CNS DELIVERY GO NEXT?

Asked to look ten years from now, Sandeep is optimistic. "I do see we're finally going to have a significant effect on modifying CNS diseases," he says. "I think glioblastoma will become a chronic disease. I think we'll be able to cure epilepsy. I think we'll be able to pause or stop the progression of Parkinson's. Alzheimer's may be a little more challenging, but I think we'll have an impact there. I think ALS will be able to slow down. Huntington's disease, we've got the ability to either halt its progression or perhaps even cure it."

He sees a new clinical field emerging: interventional neurology, following the path interventional cardiology carved out of cardiothoracic surgery. "There were cardiologists and cardiothoracic surgeons, and that was it for surgical treatment of heart disease. Now the biggest field is interventional cardiology." The same shift, he believes, can come to the brain, once delivery stops being the exception and becomes standard practice.

What strikes me most, listening back over this conversation, is how rarely the hardest part turns out to be the biology alone. Teams arrive with a promising molecule, and then spend years working through the problems that are, in the end, engineering and organizational: a catheter that drifts a millimeter out of position, a plan that doesn't survive contact with a real operating room, a procedure only its inventor can perform reliably. None of that is a failure of imagination. It's the ordinary, unglamorous work of taking something from possible to repeatable, the same design-test-refine loop that gets a bridge built or a spacecraft off the ground, just applied to three cubic centimeters of human tissue instead.

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At PODD 2026, I opened our panel on novel approaches to brain delivery with three questions I find worth asking before deciding how to approach any CNS delivery program:

Where is the target?

Is it deep in the brain or near the surface, a defined structure or a diffuse margin like the tissue around a resected tumor?

What is the modality?

Is it a small molecule, an antibody, a gene therapy or a cell therapy, and how does that shape the routes available and what the device must protect it from?

How often must you reach it?

Is it a single infusion, a repeated dose, or long-term treatment, and what does that mean for the procedure, the device and the patient?

We explore these questions with our partners from the very start.

For more on how CDP works with pharma, device and robotics companies on CNS delivery, get in touch with our CNS drug delivery team.

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About Cambridge Design Partnership

Cambridge Design Partnership (CDP) is a technology and product development consultancy. Our medical technology, robotics and human factors teams work alongside device, drug and robotics companies to build the kind of integrated delivery systems described here.

About the interviewer and interviewees

Karla Sanchez, PhD. Head of CNS Technology at Cambridge Design Partnership, where she works across the science, biology and device engineering of delivering therapies to the central nervous system, from the mechanism and behavior of the therapeutic through to the clinical realities of getting it to its target.

Sandeep Kunwar, MD. Kunwar is a neurosurgeon and was principal investigator on the PRECISE trial. He is now co-founder and Chief Executive Officer of Precision NeuroMed, which rebuilds convection-enhanced delivery around confirmed, reproducible drug delivery to brain tumors.

Stephan Mittermeyer, PhD. Mittermeyer is Precision NeuroMed's Chief Technical Officer and Head of Business Development, where he works with pharma, device and technology partners to help scale CED delivery platforms. He holds a PhD from Cranfield University and previously worked at Brainlab, Jan Medical and AskBio.

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