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From "undruggable" target to clinical potential: The journey of AOH1996

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When I first proposed targeting PCNA (proliferating cell nuclear antigen) as a therapeutic approach, the response I got was: "No one will ever make a drug against PCNA. It's undruggable." The protein lacks enzymatic activity, has a disordered region, and binds to over 200 other proteins within the cell. From a traditional drug development perspective, these characteristics made PCNA an impossible target.

Yet sometimes the most challenging problems yield the most rewarding solutions. What began as a seemingly impossible quest has evolved into AOH1996, a first-in-class PCNA inhibitor now advancing through clinical trials — a testament to what becomes possible when innovative science meets institutional commitment to translational research.

My fascination with DNA replication began during graduate studies, where I became captivated by a fundamental question: How do cells replicate three feet of DNA within a crowded nucleus in just eight hours? This led me to identify multiprotein complexes that carry out DNA replication, work that eventually revealed alterations in these complexes within cancer cells.

The discovery that our DNA replication complex was altered in breast cancer compared to normal cells opened new avenues of investigation. As we worked to identify which proteins within the complex were different, PCNA emerged as a key player.

Despite industry skepticism about its druggability, PCNA's central role in both DNA replication and repair, combined with its cancer-specific alterations, made it a compelling therapeutic target.

Impact of translational infrastructure

The transition from academic observation to clinical reality required more than scientific insight; it demanded institutional infrastructure capable of supporting the entire drug development pipeline. City of Hope provides this environment, with integrated capabilities spanning medicinal chemistry, pharmacology, regulatory affairs, and clinical trial management.

Working with David Horn, vice provost and deputy director of Beckman Research Institute of City of Hope, dean of faculty affairs and the Dr. & Mrs. Allen Y. Chao Chair in Developmental Cancer Therapeutics, we developed the first small molecules targeting PCNA. The collaboration with Jeff Perry, assistant professor in the Department of Molecular Diagnostics and Experimental Therapeutics, proved crucial.

After examining 10,000 crystals over two years, he successfully demonstrat-

ed that AOH1996 binds directly to PCNA's pocket, providing definitive proof of target engagement for FDA approval.

While we initially designed AOH1996 as a DNA replication inhibitor, subsequent research revealed a more complex and powerful mechanism. The drug acts as a molecular glue, capturing transcription-replication conflicts — instances when DNA replication and transcription complexes collide on the same DNA strand.

Specifically, AOH1996 causes PCNA to bind to the small subunit of RNA polymerase II, disrupting both replication and transcription complexes. This creates a "one-two punch" effect: the drug simultaneously increases DNA damage in cancer cells while inhibiting their repair mechanisms. The specificity for cancer cells over normal cells appears to stem from cancer-specific alterations in the PCNA complex itself.

Assessing clinical progress and combination potential

The therapy name, AOH1996, honors Anna Olivia Healy, an eight-year-old girl who lost her battle with neuroblastoma. Her family's $25,000 donation provided the initial funding that launched this research program, embodying the hope that drives our work toward better cancer treatments.

AOH1996 has demonstrated remarkable tolerability in phase I trials, with no significant toxicity observed, consistent with our preclinical animal studies. The drug is being evaluated both as monotherapy and in combination with standard-of-care treatments.

Early clinical data suggest AOH1996's most significant potential lies in combination therapy. Collaborations with institutions, including Karmanos Cancer Center, have demonstrated significant enhancement of standard-of-care efficacy when combined with AOH1996. Particularly compelling is the ability to reduce standard-of-care dosing by up to 50% while maintaining efficacy, potentially reducing patient toxicity burden.

The therapy is now advancing into additional indications, including demonstrating proof of concept in pancreatic cancer and a newly approved phase I trial in acute myeloid leukemia.

Expanding the therapeutic landscape

Beyond the current clinical program, ongoing research focuses on developing next-generation PCNA inhibitors and understanding the broader implications of PCNA modulation. Since PCNA interacts with approximately 200 cellular proteins, AOH1996 is likely to affect multiple pathways beyond DNA replication and transcription, thereby opening up options for additional therapeutic applications.

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Dr. Malkas is a pioneering researcher in cancer cell biology at City of Hope's Beckman Research Institute. Listen to her on City of Hope's new podcast, "On the Edge of Breakthrough: Voices of Cancer Research." Available on Spotify, Apple Podcasts and at cityofhope.org/edge-of-breakthrough.

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