Domain Therapeutics Presents Novel Data Addressing Key Challenges in Oncology at AACR 2025

- *Phase I clinical results of DT-9081, an EP4 receptor antagonist, allowed selection of recommended Phase II dose (RP2D) for further development in solid tumors*
- *Preclinical data of DT-7012 position this Treg depleting anti-CCR8 antibody as a highly differentiated candidate for clinical development*
- *Preclinical findings demonstrate high potential of the PAR2 biased negative allosteric modulator (NAM) program to potentiate anti-tumor immunity*

Strasbourg, France – Montreal, Canada – Boston, United States, April 30, 2025: Domain Therapeutics ("Domain" or "the Company"), the GPCR experts harnessing deep receptor biology to develop breakthrough treatments for patients, today announces new clinical and preclinical data for its key oncology programs DT-9081 and DT-7012, and preclinical insights on its PAR2 biased NAM program at the American Association for Cancer Research (AACR) in Chicago, USA.

The presentations underscore Domain's commitment to redefining cancer therapy and the potential of GPCRs to modulate the tumor microenvironment (TME) and enhance anti-tumor immunity. Details on the poster presentations are highlighted below:

Poster presentation #7450 titled *"Clinical PK, PD and safety analysis of a phase I clinical trial of DT-9081, an EP4R-antagonist, for RP2D determination in patients with advanced solid tumors",* details Phase I clinical trial results for DT-9081, a novel EP4 receptor antagonist. The findings outline DT-9081's promising potential to inhibit tumor growth and enhance immune response in patients with advanced solid tumors. Administered orally once daily, DT-9081 has demonstrated:

- Sustained EP4R target engagement as shown by cytokine release measurements and dose-proportional pharmacokinetics (PK) exposure with the best target coverage profile reported at the dose of 600 mg
- An acceptable safety profile with no dose-limiting toxicities (DLT) observed at the highest doses (400 mg and 600 mg). In addition, one-third of patients achieved stable disease after two cycles of treatment

The comprehensive evaluation of safety, tolerability, and PK/pharmacodynamics (PD) profile of DT-9081 allowed to select 600 mg as the RP2D for further clinical development in advanced solid tumors.

Poster presentation #7080 titled *"Comprehensive Characterization of DT-7012, a Differentiated CCR8-Depleting Antibody for the Treatment of Solid Tumors"*, details preclinical and benchmark data highlighting the sophisticated profile of DT-7012, a Treg depleting anti-CCR8 monoclonal antibody. The study highlighted that DT-7012:

- Demonstrates a broad pattern of CCR8 binding, high affinity to CCR8, and potent effector functions, enabling effective targeting and selective depletion of CCR8+ Tregs in patient samples
- Exhibits high specificity for CCR8, avoiding depletion of circulating immune cells and presenting a favorable safety profile
- Maintains functional efficacy, preserving antagonistic activities (ADCC/ADCP) even under high concentrations of the CCR8 ligand CCL1 and effectively blocking CCL1-induced receptor internalization

The highly differentiated and competitive properties of DT-7012 differentiate it from other clinical anti-CCR8 candidates, positioning it as a promising therapeutic solution to overcome

immune evasion mechanisms and enhance anti-tumor immune responses in solid tumors. These preclinical findings support the advancement of DT-7012 into Phase I/II trials, anticipated to start in 2025.

Poster presentation #6157, titled *"PAR2 inhibitors reduce resistance to immunotherapy against cancer"*, details the groundbreaking research in collaboration with Prof. John Stagg, demonstrating the promising potential of its PAR2 biased NAM in overcoming resistance to immune checkpoint blockade (ICB) and addressing T cell dysfunction in cancer. The preclinical findings revealed that PAR2 biased NAM:

- Synergizes with anti-PD1 therapy, turning macrophage phenotype and cytokine profile toward a pro-inflammatory TME
- Promotes antigen-presenting cells and T cells, facilitating robust antitumoral responses

This research provides critical insights into the mechanisms of PAR2 inhibition, positioning Domain's PAR2 biased NAM program as a transformative therapeutic approach to overcome tumor resistance to ICB and restore effective immune control.

Stephan Schann, Chief Scientific Officer of Domain Therapeutics, said: "The exciting data presented at AACR 2025 further validates our unique and differentiated drug discovery and development approach, built on our proprietary platform and deep expertise in GPCR biology. These findings underscore the transformative potential of our compounds to address significant unmet medical needs and illustrate our commitment to provide better treatments for patients, a goal that is profoundly important to us."

Prof. John Stagg, Principal Investigator at the Centre Hospitalier de l'Université de Montréal (CHUM), Canada and Member of Domain Therapeutics' Scientific Advisory Board, commented: "This collaboration with Domain Therapeutics, a unique GPCR company, highlights the importance of tackling challenging targets like PAR2. The comprehensive research presented at AACR 2025, which explores PAR2's role in the tumor microenvironment, demonstrates its potential to combat resistance mechanisms and improve treatment efficacy, paving the way for new advancements in immuno-oncology."

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About Domain Therapeutics
Domain Therapeutics is a clinical-stage biopharmaceutical company developing highly differentiated therapeutic strategies targeting G protein-coupled receptors (GPCRs), a crucial class of drug targets. Its robust regulatory and clinical pipeline aims to address significant unmet medical needs, offering novel solutions for patients, particularly in immuno-oncology and inflammation. Domain's key programs include a first-in-class biased antagonist of PAR2 and a best-in-class Treg-depleting anti-CCR8 antibody. These innovative therapies are driving value creation, positioning the company in a competitive and fast-expanding markets.

Domain leverages its proprietary drug discovery and development approach, founded on a unique platform and unmatched knowledge of GPCR receptor biology, to successfully unlock very challenging GPCR targets, including intractable and orphan receptors. The team's expertise, developed over two decades, is reflected in its solid track record of collaboration with major pharma, KOLs and physicians worldwide. By integrating detailed biological

understanding of GPCRs at each step of the drug discovery and development process, Domain creates highly effective and differentiated drugs that target specific pathways, thereby improving therapeutic efficacy. For more information, please visit https://www.domaintherapeutics.com/

About GPCRs

G Protein-Coupled Receptors (GPCRs) are at the top of complex signaling cascades and are responsible for translating extracellular messages into intracellular actions, making them critical for various biological processes and attractive for therapeutic intervention. Despite being the most validated drug target family, with 30-35% of all marketed drugs acting on them, they remain challenging to drug, with existing drugs targeting only 10% of the total potential GPCR targets. While most efforts in GPCR drug discovery and development have traditionally focused on central nervous system and cardio-metabolic disorders, Domain recognizes the untapped potential of GPCRs in immuno-oncology and inflammatory diseases, areas where GPCRs have not been as extensively explored.