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5TH TRANSATLANTIC EXCHANGES IN ONCOLOGY

TrEx 2026 — Conference Report

Innovation in Cancer Drug Research

March 27, 2026 | Dana-Farber Cancer Institute, Boston

Introduction

The 5th Transatlantic Exchanges in Oncology (TrEx) was held on March 27, 2026, at the Dana-Farber Cancer Institute (DFCI) in Boston, Massachusetts, in a hybrid format uniting an in-person audience with over 600 virtual participants. The annual symposium, launched in 2021 during the COVID-19 pandemic under the name 'Dana-Farber Gustave Roussy Days in Oncology', has matured into one of the leading transatlantic forums dedicated to cancer drug research, fostering structured scientific exchange between two premier academic cancer centers—DFCI in Boston and Institut Gustave Roussy (GR) in Villejuif, France.

The 2026 edition marked several institutional milestones. For the first time, the symposium was hosted directly on the DFCI campus, in the Jimmy Fund Auditorium—a historically significant venue undergoing redevelopment the following week. This edition also integrated, for the first time, presentations from the second cohort of the DFCI–GR Research Fellowship Program, fellows whose research was funded in part by L'Institut Servier. Additionally, the proceedings from the 4th edition—dedicated to radioligand therapies—received formal acceptance for peer-reviewed publication in the weeks preceding the event.

The scientific theme for this edition was Innovation in Cancer Drug Research, spanning five sessions: drug repurposing and repositioning; cell therapies and the tumor microbiome; epigenetics in cancer; cellular reprogramming and engineered therapies; and translational research presented by the fellows. The program was co-chaired by Prof. Toni Choueiri (Director, Lank Center for Genitourinary Oncology, Harvard Medical School / DFCI) and Prof. Laurence Albiges (Chair, Medical Oncology Department, Institut Gustave Roussy).

L'Institut Servier—independent from the Servier pharmaceutical group—was acknowledged by multiple speakers as the foundational institutional partner enabling both the fellowship program and the symposium itself. Patrick Therasse, Managing Director of L'Institut Servier, addressed attendees directly, underscoring the organization's commitment to translational science and to creating structured pathways for the next generation of physician-scientists. Gérard Friedlander (Institut Servier) and Prof. Fabrice Barlesi (CEO, Institut Gustave Roussy) were also in attendance.

Keynote Address: Targeting RAS Oncogenes in Cancer

Prof. Alice Shaw, MD, PhD — Chief of Hematology/Oncology, Dana-Farber Cancer Institute | Harvard Medical School

Introduced jointly by Prof. Toni Choueiri and Prof. Fabrice Barlesi, Prof. Alice Shaw delivered the keynote on the rapidly evolving landscape of RAS-directed therapies—arguably the most consequential paradigm shift in solid tumor oncology over the past decade.

Molecular Background

RAS proteins constitute a family of small GTPases functioning as binary molecular switches that transduce mitogenic signals from membrane growth factor receptors to intracellular effectors controlling proliferation and survival. Under physiological conditions, the cycling of RAS between its GTP-bound (active) ON-state and GDP-bound (inactive) OFF-state is tightly regulated by guanine nucleotide exchange factors (GEFs) and GTPase-activating proteins (GAPs). Oncogenic missense mutations—predominantly at codons 12, 13, or 61—impair GAP-mediated hydrolysis, locking mutant RAS in a constitutively active conformation and driving aberrant downstream signaling through RAF-MEK-ERK and PI3K-AKT-mTOR pathways.

RAS mutations are present in approximately 19% of all human cancers, representing the most frequently mutated oncogene family. KRAS mutations predominate across pancreatic ductal adenocarcinoma (PDAC, ~90%), colorectal cancer (~40%), and lung adenocarcinoma (~30%), while NRAS mutations characterize a subset of melanomas and hematologic malignancies. The specific mutation G12D predominates in PDAC and colorectal cancer; G12C is the most common variant in lung adenocarcinoma and was historically the first to yield to targeted inhibition.

G12C OFF-State Inhibitors: From Discovery to Clinical Validation

The field was catalyzed by a landmark 2013 discovery by Kevan Shokat (UCSF) identifying a cryptic switch II pocket (S-IIP) in the GDP-bound, inactive form of KRAS G12C—enabling the design of covalent small molecules that trap G12C in its inactive conformation. The first clinical-stage compound derived from this strategy, AMG-510 (sotorasib), demonstrated proof-of-concept in KRAS G12C-mutant non-small cell lung cancer (NSCLC) in 2020 and received accelerated FDA approval. Adagrasib followed with a similar mechanism.

Despite their historical significance, phase III data for both sotorasib and adagrasib proved modest—sotorasib demonstrated only a five-week improvement in median progression-free survival versus docetaxel, with no overall survival benefit. Next-generation G12C inhibitors have sought to address these limitations through increased potency and selectivity. Divarasib (Genentech), optimized for higher affinity to the S-IIP, achieved a response rate exceeding 50% and median PFS over 13 months in previously treated G12C mutant NSCLC in early-phase data—results awaiting confirmation in an ongoing pivotal phase III head-to-head comparison against sotorasib or adagrasib. Elisrasib (D3S-001) has further differentiated through enhanced target engagement kinetics and CNS penetration, and received FDA Breakthrough Therapy Designation. In colorectal cancer, dual targeting of KRAS G12C and EGFR has emerged as the

standard paradigm, with combinations of divarasib and cetuximab demonstrating particularly striking response rate improvements.

G12D Inhibitors: Addressing the ON-State Challenge

KRAS G12D presents a fundamentally different pharmacological challenge compared to G12C, as it resides predominantly in the GTP-bound ON-state and undergoes minimal nucleotide cycling. The first-generation G12D inhibitor MRTX1133 demonstrated impressive preclinical activity but suffered from poor oral bioavailability, leading to early closure of its phase I trial. Improved second-generation molecules—including VS-7375 (Verastem)—have addressed this limitation through PK optimization while preserving potent dual ON/OFF-state inhibition. Phase I data in Chinese patients showed response rates of approximately 60–70% in previously treated G12D-mutant NSCLC and 41% in PDAC, with a manageable profile dominated by low-grade GI toxicity and myelosuppression.

Tri-Complex Inhibitors: A Mechanistically Distinct Platform

Revolution Medicines has pioneered a structurally unique class of RAS inhibitors exploiting a molecular glue mechanism. These tri-complex inhibitors first bind to the intracellular chaperone cyclophilin A, generating a neosurface with high affinity for GTP-bound RAS ON-state proteins. The resulting ternary complex sterically occludes interaction with downstream effectors such as RAF kinase. Daraxonrasib (RMC-6236), a Pan-RAS ON inhibitor with activity against both mutant and wild-type GTP-bound KRAS, NRAS, and HRAS, demonstrated 30% response rates and median overall survival of 13–15 months in second-line RAS-mutant PDAC—outcomes vastly exceeding historical second-line chemotherapy benchmarks. In RAS G12X-mutant NSCLC, similar efficacy was observed with median OS approaching 18 months. Tolerability was manageable, predominantly characterized by skin and GI toxicities attributable to MAP kinase pathway inhibition in normal tissues, with rash observed in most patients at the 300 mg standard dose.

Zoldonrasib (RMC-9805), a mutant-selective G12D tri-complex inhibitor forming a covalent bond with the aspartic acid at position 12, displayed an exceptional safety profile with near-absent rash and stomatitis. Phase I data in G12D-mutant NSCLC yielded response rates exceeding 60%. Both daraxonrasib and zoldonrasib have advanced to registrational trials in PDAC and RAS-mutant lung cancer.

Resistance Mechanisms: An Emerging Priority

As with all oncogene-targeted therapies, acquired resistance emerges universally under RAS inhibitor pressure. Approximately 50% of patients progressing on G12C inhibitors harbor acquired genetic alterations, predominantly activating mutations reengaging RAS-MAP kinase signaling—including secondary KRAS mutations, switch II pocket mutations disrupting drug binding, and RAF/MEK-activating alterations. Non-genetic mechanisms including epithelial-mesenchymal transition (EMT) and histologic transformation account for the remainder.

Resistance data for daraxonrasib has now emerged from PDAC and other RAS-mutant tumor types. Approximately 60% of progressing PDAC patients acquired genetic alterations in RAS signaling intermediates, with amplification of the mutant KRAS allele identified as a resistance driver. Novel resistance mechanisms specific to the tri-complex mechanism were also identified, including KRAS Y64 mutations that impair formation of the inhibitory tri-complex by reducing the affinity of the cyclophilin-daraxonrasib binary complex for GTP-bound RAS, and kinase-dead BRAF mutations that stabilize RAF-RAS dimers and sterically occlude the tri-complex.

Combination Strategies

Prof. Shaw outlined a taxonomy of combination approaches: vertical (or in-pathway) combinations targeting multiple RAS pathway nodes simultaneously, and orthogonal combinations pairing RAS inhibition with mechanistically distinct agents. The combination of the G12C ON-state inhibitor elironrasib (RevMed) and the Pan-RAS inhibitor daraxonrasib demonstrated response rates exceeding 60% in patients previously treated with G12C OFF-state inhibitors—a compelling clinical proof-of-concept for dual RAS targeting. Combinations with EGFR inhibitors remain the validated standard in colorectal cancer. However, vertical combinations with SHP2 or other pathway nodes have been limited by overlapping toxicities, with approximately 50% of patients experiencing grade ≥3 adverse events.

A particularly promising orthogonal strategy exploits the synthetic lethal relationship between homozygous MTAP deletion—present in 10–15% of lung cancers and 20–30% of PDAC—and inhibition of PRMT5, an epigenetic regulator selectively essential in MTAP-deleted cancers due to accumulation of its metabolic substrate MTA. MTA-cooperative PRMT5 inhibitors demonstrate responses in approximately 20–30% of MTAP-deleted solid tumors as single agents. DFCI, in collaboration with Tango Therapeutics, is currently evaluating combinations of their PRMT5 inhibitor TNG-462 with daraxonrasib and zoldonrasib in RAS-mutant MTAP-deleted cancers, with early emerging data suggesting favorable safety and preliminary efficacy. Gustave Roussy participates actively in this translational effort.

Prof. Shaw closed by identifying three strategic priorities: optimizing the RAS inhibitor anchor for maximal on-target activity; comprehensively mapping resistance mechanisms through tissue sampling at progression; and deploying rational orthogonal combinations in first-line settings to pre-emptively suppress the heterogeneous evolutionary landscape driving resistance.

Session 1: Drug Repurposing and Repositioning

Chairs: Prof. Eric Fischer, PhD (DFCI / Harvard Medical School) | Prof. Laurence Albiges, MD, PhD (Institut Gustave Roussy)

Prof. Eric Fischer opened Session 1 by reframing the concept of drug repurposing—preferring to characterize it as a biology-first, mechanism-informed process of repositioning clinical-stage or approved compounds to newly identified molecular dependencies, rather than the historically pejorative sense of phenotypic screening of compound libraries.

PI3Kγ Inhibition in Monocytic AML — Prof. Andrew Lane, MD, PhD (DFCI)

Prof. Andrew Lane presented translational work repositioning eganelisib—a selective class IB PI3Kγ inhibitor previously evaluated in solid tumor immuno-oncology settings—for the treatment of monocytic subtypes of acute myeloid leukemia (AML). Using a CRISPR interference screen at the Broad Institute in a panel of dendritic cell/monocytic AML overlapping subtypes, his laboratory identified PIK3CG (encoding the p110γ catalytic subunit) and PIK3R5 (encoding its obligate regulatory partner p101) as selective dependencies in myeloid and lymphoid leukemia cell lines—with no activity observed across hundreds of solid tumor lines.

Mechanistic investigation via proteomics and phosphoproteomics revealed that PI3Kγ inhibition in sensitive AML cells signals through PAK1 rather than through the canonical PI3K/AKT/mTOR axis. Gene expression stratification of AML patients by a 30-gene PI3Kγ/Immune Response Signature (IRS) demonstrated an independent prognostic impact on overall survival. Phenotypically, PI3Kγ dependency correlated with the FAB M4/M5 monocytic subtypes—historically resistant to BCL2-targeted therapy (venetoclax). In patient-derived xenograft (PDX) models, single-agent eganelisib prolonged survival in PIK3R5-high leukemias; combination with cytarabine showed additive and potentially synergistic effects, possibly mediated by upregulation of G protein-coupled receptor signaling in cytarabine-persistent minimal residual disease cells activating phospho-PAK1. A phase I/II trial of single-agent and combination eganelisib plus cytarabine is currently enrolling in relapsed/refractory AML and high-risk MDS, with biomarker-stratified expansion cohorts planned.

Rediscovery and Development of Drugs for Rare Cancers — Prof. George Demetri, MD (DFCI)

Prof. George Demetri delivered a historical and mechanistic account of drug repositioning in gastrointestinal stromal tumor (GIST), illustrating how structural biology insights drove successive therapeutic generations. The paradigm began with the structural observation that imatinib—developed by Brian Druker and Novartis for BCR-ABL in CML—occupied the ATP-binding pocket of cKIT with similar affinity to c-Abl, providing the molecular rationale for its pivotal efficacy in KIT-mutant GIST (first patient treated 2000; FDA approval 2002). The discovery that resistance arose through secondary KIT kinase domain mutations occupying the binding pocket prompted rational selection of sunitinib—a more compact KIT inhibitor originally designed as a VEGF receptor antagonist—capable of fitting within the sterically altered resistant pocket. The mechanism of hair depigmentation observed in sunitinib patients (attributed to wild-type KIT inhibition in melanocytes, elucidated by dermatologist-oncologist Prof. Caroline Robert) served as a pharmacodynamic biomarker of target engagement.

Subsequent generations of inhibitors—regorafenib, avapritinib (Blueprint Medicines/Sanofi), and velzatinib (IDRX42, now part of GSK)—were each developed through iterative structural biology, academic-industry collaboration, and biomarker-guided clinical development. Prof. Demetri highlighted that rare cancer models have served as biological laboratories enabling mechanistic insights broadly applicable across oncology. He noted emerging activity of FGF receptor inhibitors in SDH-deficient GIST (a non-kinase-driven subtype), with a manuscript demonstrating this activity in collaboration with Prof. Brad Bernstein accepted in Nature Medicine.

Hospital-Based Pharmaceutical Compounding as a Drug Development Platform — Dr. Maxime Annereau, PharmD, PhD (Institut Gustave Roussy)

Dr. Maxime Annereau presented a distinctive Gustave Roussy platform using hospital pharmaceutical compounding—authorized under French regulatory frameworks analogous to FDA 503A/503B categories—as a rapid, cost-effective drug development infrastructure. The approach enables adaptation of existing drugs to new formulations (pediatric dosing, novel routes of administration) and facilitates proof-of-concept clinical investigation on timelines of 6–18 months from concept to first patient treatment.

Illustrative examples included: pediatric temozolomide oral suspension development for glioma (progressed to spinoff and commercial pathway); an encapsulated formulation of a sarcoma agent to prevent mucositis (active program treating over 200 patients via compassionate use in collaboration with Institut Servier); oral arsenic trioxide with demonstrated bioequivalence from the parenteral route; and a bromodomain inhibitor program for a rare carcinoma indication with 4 out of 10 evaluable patients achieving partial responses after three months. Dr. Annereau underscored that emerging point-of-care manufacturing frameworks—particularly the MHRA's new regulation enabling small-batch advanced therapy manufacture—could reduce production costs by an order of magnitude, facilitating access for rare disease populations.

Session 2: Cell Therapies Beyond T Cells and the Role of the Microbiome

Chairs: Prof. Wendy Garrett, MD, PhD (Harvard T.H. Chan School of Public Health) | Patrick Therasse, MD, PhD (L'Institut Servier)

NK Cell Heterogeneity and Therapeutic Harnessing — Prof. Eric Vivier, PhD (Aix-Marseille University / Paris-Saclay Cancer Cluster / Institut Gustave Roussy / Innate Pharma)

Prof. Eric Vivier—who initiated his scientific career as a postdoctoral fellow at DFCI in 1989 studying NK cells—presented a comprehensive account of recent advances in NK cell biology and therapeutic exploitation. Single-cell and CITE-seq analyses of over 225,000 NK cells from more than 700 donors, performed in a 20-laboratory international consortium, resolved human peripheral blood NK cells into three major functional subsets: NK1 cells (cytotoxic effectors, ~90% of peripheral NK cells, expressing NKp46 and CD16); NK2 cells (non-cytotoxic, producing XCL1/XCL2 activating cDC1 dendritic cells); and NK3 cells (memory-like, expressing granzyme H and CCL5). This taxonomy is conserved between mouse and human, facilitating cross-species translational research.

On the therapeutic harnessing front, Prof. Vivier described two principal antibody-based strategies developed at Innate Pharma. First, monalizumab—an anti-NKG2A humanized antibody designed to release inhibitory signaling in both NK cells and CD8+ T cells via blockade of the NKG2A/HLA-E inhibitory axis. A phase II trial in consolidation-phase stage III NSCLC combining monalizumab with durvalumab (anti-PD-L1) demonstrated meaningful improvement in PFS compared to durvalumab monotherapy, prompting the launch of the phase III PACIFIC-9 trial (1,051 patients; global PI: Prof. Fabrice Barlesi). Results are expected by late 2026. Second, NKp46-targeting trispecific NK cell engagers designed to simultaneously activate NK cells via NKp46/CD16 agonism and redirect them to tumor antigens (CD123 in AML; BCMA in multiple myeloma). The CD123 trispecific achieved ~35% complete remission rates in relapsed/refractory AML and received FDA Fast Track Designation. Tetraspecific variants incorporating non-alpha IL-2 or interferon-alpha cytokine fusion domains have demonstrated the induction of cytokine-induced memory-like NK cells and enhanced antitumor activity in preclinical models, including resistance to IL-2-carrying variants.

Gut Microbiome as a Modulator of Cancer Immunity — Dr. Carolina Alves Costa Silva, PhD (Oncoclínicas / formerly Institut Gustave Roussy)

Dr. Carolina Alves Costa Silva summarized Gustave Roussy's pioneering contributions to understanding gut dysbiosis as a determinant of antitumor immunity and immunotherapy response. Key findings included: validation in a large lung cancer cohort (Nature Medicine 2022) that normal levels of Akkermansia muciniphila are independently associated with improved outcomes under anti-PD-1 therapy; the development of Species Interacting Groups (SIGs) as composite microbiome signatures predictive of overall survival; and the mechanistic demonstration that microbiota-centered interventions benefit patients primarily through loss of deleterious SIG1 bacteria rather than gain of beneficial ones—a distinction with important therapeutic implications for FMT design.

A mechanistically significant finding concerned MAdCAM-1, a high endothelial venule addressin controlling lymphocyte gut-to-systemic migration. In the context of antibiotic-induced gut dysbiosis, the loss of mucosal MAdCAM-1 barrier control was shown to facilitate migration of immunosuppressive cells from the gut to the tumor microenvironment, accelerating tumor progression. Soluble MAdCAM-1 levels in plasma correlated with gut microbiome composition and independently predicted outcomes in over 1,000 kidney cancer patients (validated in collaboration with DFCI). Crucially, recombinant MAdCAM-1 was shown to synergize with CTLA-4 and PD-1 blockade in murine models and to promote tertiary lymphoid structure (TLS) formation—establishing soluble MAdCAM-1 as both a biomarker of dysbiosis and a candidate therapeutic agent.

Diet, Microbiome, and Anti-tumor Immunity — Prof. Wendy Garrett, MD, PhD (Harvard T.H. Chan School of Public Health / DFCI)

Prof. Wendy Garrett presented two interconnected research programs linking dietary metabolites to anti-tumor immunity through microbiome-mediated mechanisms. The first program demonstrated that a high sulfur amino acid diet (methionine/cystine supplementation) selectively promoted the bloom of Mucispirillum schaedleri in the colonic mucus layer, leading to enhanced cDC1 dendritic cell activation—mediated by M. schaedleri lipid-derived XCL1/lymphotactin produced by NKT cells—and downstream CD8+ T cell anti-tumor activity. These effects were observed across mismatch repair-deficient and mismatch repair-proficient colorectal cancer models.

The second program elucidated how acetoacetate—a ketone body generated during ketogenic diet or fasting—enhances MAIT cell (mucosa-associated invariant T cell, MR1-restricted T cells) anti-tumor activity. Acetoacetate is shown to chemically condense with the microbiome-derived riboflavin precursor 5-ARU to generate 5-OP-RU, the canonical MR1 ligand, through a previously uncharacterized reaction producing methylglyoxal as an intermediate. This reaction was demonstrated both in cell-free systems and intracellularly in antigen-presenting cells, providing a biochemical mechanistic link between ketone metabolism, microbiome activity, and innate T cell activation. Ethyl acetoacetate (EAA)—an FDA-approved food flavoring—increased tumor-infiltrating MAIT cell frequency and effector function and reduced colonic tumor multiplicity across multiple mouse models. While not yet advocating clinical administration, Prof. Garrett emphasized the therapeutic tractability of this microbiota-ketone body axis.

Session 3: Epigenetics and Cancer

Chairs: Prof. Laurence Albiges, MD, PhD (Institut Gustave Roussy) | Prof. Kevin Haigis, PhD (DFCI)

Epigenetic Mechanisms in IDH-Mutant Glioma Initiation and Progression — Prof. Brad Bernstein, MD, PhD (DFCI / Harvard Medical School)

Prof. Brad Bernstein presented a mechanistic framework for IDH-mutant glioma biology built on three interconnected epigenetic phenomena. First, the hallmark global DNA hypermethylation—driven by 2-hydroxyglutarate (2HG)-mediated TET demethylase inhibition—silences tumor suppressors via promoter methylation (e.g., CDKN2A), activates oncogenes via insulator disruption (e.g., PDGFRA, through methylation-dependent loss of CTCF binding at a downstream insulator site, releasing an OPC-specific downstream enhancer to activate PDGFRA expression), and suppresses tumor-intrinsic interferon signaling.

Single-cell chromatin accessibility and transcriptomic profiling mapped the developmental state of glioma cells onto a normal brain cell reference atlas, demonstrating that low-grade (grade II) IDH-mutant gliomas are predominantly OPC-like, while progressive (grade III/IV) tumors acquire NPC-like transcriptomic profiles—consistent with de-differentiation driven by loss of hypermethylation through passive dilution during rapid proliferation. Critically, progressive tumors compensate for the loss of epigenetic oncogene activation and tumor suppressor silencing by acquiring focal genomic copy number variations (CNVs): amplification of PDGFRA, deletion of CDKN2A, and co-deletion of the interferon cluster (IFNA/IFNB) adjacent to CDKN2A.

This co-deletion of CDKN2A, the IFNA/IFNB cluster, and—critically—MTAP positions MTAP-deficient IDH-mutant grade III/IV gliomas as potential candidates for PRMT5 inhibitor therapy, a synthetic lethal strategy validated in other MTAP-deleted tumor types. Prof. Bernstein estimated that approximately one-third of patients progressing on vorasidenib (IDH inhibitor) may harbor MTAP deletion, suggesting a rational therapeutic sequence.

Menin Inhibitors in AML: From Target Discovery to Clinical Approval and Resistance — Prof. Scott Armstrong, MD, PhD (Chief Research Strategy Officer, DFCI)

Prof. Scott Armstrong chronicled the development of menin inhibitors for KMT2A-rearranged and NPM1-mutant AML—a trajectory spanning nearly two decades from fundamental biology to FDA-approved therapeutics. MLL1 (KMT2A) fusion oncoproteins drive leukemogenesis by maintaining a stem cell-associated HOX-A/MEIS1 transcriptional program in hematopoietic progenitors; disruption of the MLL-menin protein-protein interaction silences this program. The first potent small-molecule inhibitor of this interaction, VTP-50469 (modified to become revumenib/SNDX-5613), was validated in preclinical models demonstrating chromatin complex displacement and HOX-A/MEIS1 downregulation. The discovery that NPM1-mutant AMLs—representing ~30% of adult AML—share high HOX-A/MEIS1 expression and menin dependency significantly expanded the potential patient population, fueling industry investment.

Revumenib received FDA approval in November 2024 for KMT2A-rearranged leukemia in patients ≥1 year of age, and in 2025 both revumenib and ziftaminib (Cure Oncology) received approval for NPM1-mutant relapsed/refractory AML—together covering approximately 40% of adult and pediatric AML cases. Predictably, acquired resistance emerges through menin binding pocket mutations. CRISPR base-editing screens predicted these resistance mutations prospectively, and concordance with clinical resistance specimens validated menin as the functional therapeutic target. Dose-escalation PDX experiments demonstrated that higher drug concentrations delayed the emergence of resistance mutations. Additional mechanisms involving compensatory stabilizing mutations in KMT2A and LEGF (components of the same ternary complex) are being characterized. Synergistic combinations—including menin inhibitors with CAT6A (KAT6A) inhibitors in ER-positive breast cancer—are under active investigation.

Session 4: Cellular Reprogramming, Engineered Therapies, and Novel Modalities

Chairs: Prof. Eric Fischer, PhD (DFCI / Harvard Medical School) | Dr. Laurie Menger, PhD (Institut Gustave Roussy)

Genome-Wide CRISPR Screening to Enhance CAR T-cell Potency — Dr. Laurie Menger, PhD (Institut Gustave Roussy)

Dr. Laurie Menger described a genome-wide CRISPR loss-of-function screening platform deployed in immunosuppressive environments to identify non-redundant genetic targets enhancing T-cell fitness. Key findings included: (1) identification of SOCS1 (suppressor of cytokine signaling 1) as the primary brake on CD4+ memory T-cell expansion; SOCS1 knockout in CD19-BBZ CAR T cells enhanced CD4 persistence in the bone marrow and augmented CD8 polyfunctionality (granzyme B, TNF, IFNγ), yielding synergistic antitumor activity; (2) identification of FAS (rather than β-microglobulin) as the primary mediator of allogeneic NK and T-cell-mediated rejection, with FAS knockout offering superior persistence than B2M knockout for ‘off-the-shelf’ cellular products; (3) identification of an unnamed zinc-finger protein/epigenetic complex as a key regulator of T-cell stemness (TCF7, CCR7, CD27), whose knockout in TILs from ovarian cancer debulking specimens maintained progenitor phenotype, reduced exhaustion markers, expanded tumor-reactive clones (by TCR-seq), and enhanced antitumor control in lung cancer xenograft models. A Servier Therapeutics-funded collaboration with Massachusetts General Hospital is characterizing how IDH-mutant tumor-derived 2HG suppresses T-cell function in cholangiocarcinoma, with 2–3 gene candidates under validation.

TransTACs: Antibody-Based Targeted Membrane Protein Degradation — Dr. Xin Zhou, PhD (DFCI)

Dr. Xin Zhou presented TransTAC (transferrin receptor-targeting chimera) technology—a bifunctional antibody-based platform exploiting the high endocytic rate of TFR1 (transferrin receptor 1, ~100 molecules/second internalization) to degrade resistance-conferring cell surface proteins via lysosomal routing. TransTAC molecules are IgG-like constructs with TFR1-binding domains and pH-sensitive linkers engineered to decouple TFR1 from cargo in early endosomes, allowing TFR1 recycling while directing the target protein for lysosomal degradation.

The platform has demonstrated efficacy across structurally diverse targets: EGFR (including the C797S resistance variant resistant to osimertinib), PD-L1, CD20, CD19 (as a CAR on/off switch), and G protein-coupled receptors (CCR6, for which TransTAC achieved complete degradation as assessed by GFP signal loss). In EGFR-C797S xenograft models, EGFR TransTACs inhibited tumor growth in cells unresponsive to osimertinib. Dr. Zhou also presented a second program—phospho-specific protein binders combining engineered SH2 domains and nanobodies sandwiching phosphopeptides—enabling site-specific interrogation and rewiring of immune signaling. A synthetic PD-1 pathway construct redirecting phospho-PD-1 signaling to kinase activation (rather than the native SHIP-2 phosphatase cascade) was shown to gate IL-12 expression in a PD-L1-dependent fashion, significantly enhancing CAR T-cell activity in solid tumor models.

Engineered Monocytes as Phagocytic Cellular Therapy — Prof. Jean-Luc Perfettini, PhD (Institut Gustave Roussy)

Prof. Jean-Luc Perfettini presented a program developing p21-engineered monocytes as innate immune effectors for cancer therapy. Using a siRNA-based genetic screen in macrophages, p21 (CDKN1A) was identified as a transcriptional repressor of SIRPα—the inhibitory phagocytic checkpoint binding CD47 on cancer cells. Overexpression of p21 in monocytes (facilitated by a lentiviral transduction system exploiting Vpx-mediated SAMHD1 degradation enabling efficient myeloid cell transduction) suppressed SIRPα expression and markedly enhanced macrophage-mediated tumor phagocytosis. Phagocytic macrophages subsequently underwent pro-inflammatory reprogramming characterized by interferon-γ secretion, which in turn educated neighboring anti-inflammatory TAMs toward a pro-inflammatory phenotype—identifying a propagating immune reprogramming cascade.

Adoptive transfer of p21-engineered monocytes into leukemia-bearing mice induced significant disease regression and survival prolongation superior to anti-CD47 monoclonal antibody (magrolimab) therapy. Efficacy was reversed by depletion of the engineered monocyte-derived macrophage population or blockade of interferon-γ, confirming mechanistic specificity. The platform is being extended to solid tumors with plans to incorporate CAR constructs and myeloid cell-engager moieties. A spinout company has been established with an LNP-based in vivo monocyte engineering strategy as a central near-term objective.

Session 5: Gustave Roussy–Dana-Farber Research Fellowship Program

Chairs: Patrick Therasse, MD (L'Institut Servier) | Prof. Toni Choueiri, MD (DFCI / Harvard Medical School)

The fifth session showcased scientific presentations from three members of the second cohort of the Gustave Roussy–Dana-Farber Research Fellowship Program, funded through L'Institut Servier. Fellows were selected through a competitive process and have conducted research embedded within DFCI laboratories. This session was the first time fellows presented their work formally within the TrEx symposium framework—an integration described by Patrick Therasse as a significant evolution of the collaboration's scientific impact.

DNA-PK Inhibition and Lutetium-PSMA Radioligand Therapy in Prostate Cancer — Dr. Alice Bernard-Tessier, MD (Mentored by Prof. Himisha Beltran, DFCI)

Dr. Bernard-Tessier presented translational work exploring whether DNA-PK (DNA-dependent protein kinase) inhibition could potentiate lutetium-PSMA (177Lu-PSMA-617) radioligand therapy and modulate PSMA expression at the cell surface. DNA-PK, a critical mediator of non-homologous end joining (NHEJ), is overexpressed in metastatic castration-resistant prostate cancer (mCRPC) and is known to collaborate with the androgen receptor in DNA repair. In collaboration with Prof. Fay Nicolson's laboratory, DNA-PK inhibition with peposertib (Novartis) potentiated radiation-induced DNA damage (as measured by γ-H2AX foci) in mCRPC cell lines in a dose- and time-dependent fashion, and this sensitization extended to beta-irradiation from lutetium-labeled unlabeled PSMA targeting agents. Importantly, irradiation combined with DNA-PK inhibition was shown to upregulate PSMA cell surface expression—potentially expanding the addressable patient population for PSMA-targeted radioligand therapy. In vivo, DNA-PK inhibition alone produced a detectable increase in PSMA expression as assessed by gallium-68 PSMA-PET imaging, providing proof-of-concept for non-invasive pharmacodynamic monitoring. Dr. Bernard-Tessier will return to Gustave Roussy as Principal Investigator of a phase I trial combining peposertib with lutetium-PSMA.

Liquid Biopsy Epigenomic Profiling for Predictive Biomarker Discovery in Small Cell Lung Cancer — Dr. Damien Vasseur, MD (Mentored by Prof. Matthew Freedman, DFCI)

Dr. Damien Vasseur presented the application of cell-free chromatin immunoprecipitation followed by sequencing (cfChIP-seq) and the APEX (Associating Plasma Epigenomics with eXpression) machine learning framework to small

cell lung cancer (SCLC) patients receiving tarlatamab—a bispecific T-cell engager targeting DLL3, FDA-approved in May 2024. The APEX model, trained on matched tissue RNA-seq and cfChIP-seq data, predicts single-gene expression with a correlation coefficient of ~0.8, enabling non-invasive transcriptomic profiling of circulating tumor DNA.

In a cohort of 167 plasma samples from 46 patients, plasma-based epigenomic profiling enabled: (1) identification of the SCLC-A (ASCL1-driven) molecular subtype as the strongest predictor of clinical benefit from tarlatamab—with significantly longer progression-free survival compared to SCLC-N or SCLC-P subtypes; (2) detection of phenotypic subtype switching at progression—exemplified by a patient in whom baseline SCLC-A subtype markers (DLL3 high, ASCL1 high) at progression transitioned to a SCLC-N profile (gain of NEUROD1 and downstream targets, loss of DLL3), validated in a tarlatamab-sensitive mouse model with concordant Western blot and IHC findings; (3) identification of TROP2 upregulation at progression as a potential actionable ADC target—highlighting the utility of serial liquid biopsy epigenomic profiling for adaptive precision medicine. Dr. Vasseur will return to Gustave Roussy to advance programs in acquired resistance mechanisms.

Germline Predisposition to Immune-Related Adverse Events under Immune Checkpoint Blockade — Dr. François-Xavier Danlos, MD (Mentored by Prof. Catherine Wu and Prof. Alexander Gusev, DFCI)

Dr. François-Xavier Danlos presented a genome-wide association study (GWAS) for immune-related adverse events (irAEs) conducted through the institutional PREMIS cohort at Gustave Roussy—a prospective study enrolling 1,000 patients receiving anti-PD-1 or anti-PD-L1 monotherapy or combination regimens between 2018 and 2023. Applying a time-to-event GWAS framework (SPACox) adjusted for treatment type and disease, the study identified rs7164391—a low-frequency intronic variant in the first intron of RORα (encoding retinoic acid-related orphan receptor alpha, a transcription factor critical to immune cell polarization including ILC and CD4 T cell biology)—as significantly associated with irAE risk across all organ systems. Homozygous carriers demonstrated substantially elevated irAE risk independent of genetic ancestry, with allele frequency notably higher in individuals of African ancestry (~15–20%) compared to European populations (~0.2%).

Replication in the DFCI OncoPanel-linked clinical cohort and the Gustave Roussy STING study confirmed the association. Plasma cytokine profiling revealed on-treatment—but not at baseline—differences in IL-12p70 levels by genotype, suggesting the variant exerts a context-dependent (treatment-activated) biological effect. Single-cell RNA-seq of PBMCs stratified by genotype before and on treatment is ongoing to characterize the immune cell subtype responsible for the effect. If validated functionally, this variant could inform pre-treatment germline screening to stratify irAE risk and guide individualized immunotherapy management.

Closing Remarks and Conclusions

The 5th Transatlantic Exchanges in Oncology illustrated the depth and coherence of the scientific alliance between Dana-Farber Cancer Institute and Institut Gustave Roussy—an alliance that L'Institut Servier has enabled to grow from its inception during the COVID-19 pandemic to a scientifically rigorous, institutionally embedded bilateral exchange now in its fifth year.

Scientifically, the symposium reflected several cross-cutting themes. First, the translation velocity from biological insight to clinical trial has accelerated dramatically, with multiple presentations describing the arc from CRISPR screen or structural biology to first-in-human study within three to five years. Second, the pervasive challenge of acquired resistance—whether to RAS inhibitors, menin inhibitors, KRAS G12C-directed agents, or tarlatamab—is increasingly understood mechanistically, with tissue-based longitudinal sampling emerging as an indispensable tool that ctDNA alone cannot replace. Third, the tumor microenvironment, the microbiome, and innate immune compartments (NK cells, macrophages, MAIT cells, NKT cells) are no longer peripheral topics but central therapeutic frontiers with near-term clinical translation programs.

The fellowship program, showcased in Session 5, demonstrated that the scientific exchange between GR and DFCI generates genuinely original, publication-ready translational research within fellowship durations—a testament to the intellectual and organizational infrastructure that L'Institut Servier has helped build. The fellows' accounts of cultural and scientific alignment between Paris and Boston reinforce the sustainability and scalability of this transatlantic model.

Looking ahead, the 6th TrEx is anticipated in Paris before summer 2026 (exact date to be announced). The bidirectionalization of the fellowship program—with DFCI fellows now expected at Gustave Roussy—marks the maturation of this collaboration from an unidirectional to a genuinely symmetrical scientific exchange. The proceedings of TrEx 2026 are expected to be submitted for peer-reviewed publication, continuing the tradition established with the 4th edition.

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