Precision Therapy in RAS Mutant Colorectal Cancer

Rat sarcoma virus (RAS) represents the most frequently mutated oncogene family across all malignancies and has therefore motivated decades of research aimed at understanding and targeting aberrant signaling elicited by oncogenic gain-of-function mutations. Of the 3 *RAS* genes (*KRAS*, *NRAS*, and *HRAS*), *KRAS* is most commonly mutated in pancreatic, colorectal, and lung adenocarcinomas, whereas *NRAS* and *HRAS* mutations are mostly found in selected hematologic malignancies, melanomas and thyroid cancers.[1] In colorectal cancer (CRC), activating missense mutations in *KRAS* and *NRAS* have been reported at frequencies of approximately 40% and 4%, respectively, with more than 95% of mutations occurring in 1 of 3 major hotspots (residues G12, G13, and Q61). Non-G12 *KRAS* mutations are enriched in tumors of the right side of the colon, in those with microsatellite instability (MSI) and high tumor mutational burden.[2] Interestingly, the overall frequency of *KRAS* mutations increases with age in microsatellite stable (MSS) CRC, particularly in males. In contrast, a reduced prevalence of *KRAS* mutations is observed in MSI/high mutational burden tumors in the elderly population.[2]

RAS family proteins act as molecular switches that function to govern a variety of intracellular signaling networks controlling cell proliferation, migration, differentiation, senescence, and apoptosis, among others.[1] Oncogenic *RAS* mutations result in a shift from the inactive guanosine diphosphatase-bound state toward active guanosine triphosphatase (GTP) via disruption of the normal RAS guanine nucleotide exchange factors and GTPase activating proteins. Wild-type KRAS dimerization with KRAS mutants seems to be critical for full oncogenic activity, particularly the KRAS G12D and/or G12V isoforms.[3] Furthermore, RAS proteins become active and engage with downstream effectors only when interacting with the plasma membrane, a process facilitated by farnesyltransferase and the chaperone protein phosphodiesterase-δ. RAS is a member of the mitogen-activated protein kinase (MAPK) signaling pathway (RAS/RAF/MEK/ERK), which is activated by ligand binding to a receptor tyrosine kinase such as epidermal growth factor receptor (EGFR) and ERBB2. Mutant RAS activates an array of other downstream cascades, including PI3K/AKT/mTOR, as illustrated in Figure 1.[1]

Patients whose colorectal tumors harbor *RAS* mutations frequently exhibit poorer clinical outcome than *RAS* wild-type counterparts, particularly in the metastatic setting.[4–6] Aberrant RAS pathway activation interrupts upstream signal regulation and confers resistance to receptor tyrosine kinases inhibitors, which limits targeted treatment options in *RAS*-mutant CRC.[7] Current treatment for *RAS*-mutant metastatic CRC is primarily based on combinations of 5-fluorouracil with oxaliplatin or irinotecan and antiangiogenic agents bevacizumab and aflibercept in the first- and second-line settings. Upon progression, which occurs within 2 years of diagnosis of metastases in more than 90% of cases, systemic therapies offer very limited benefit.[6] *RAS* mutations not only confer upfront resistance to EGFR blockade, but also arise de novo upon targeted treatment pressure. Indeed, subclonal *RAS* mutant populations have the potential to "contaminate" the broader tumor environment and confer a predominantly *RAS* mutant phenotype in response to anti-EGFR intervention.[7] The same phenomenon may help to explain the primary resistance of *RAS* mutant mCRC to double HER2 blockade in the setting of *ERBB2* amplifications.[8]

Failures and Promises of RAS Targeting in CRC

Initial strategies to down-regulate the MAPK pathway in *RAS* mutant cancers focused on agents targeting post-translational modifications of RAS, such as farnesyltransferase inhibitors or allosteric MEK inhibitors.[9] Different drugs were investigated in metastatic CRC, but none showed clinical efficacy in patients with *KRAS*-mutant tumors. Farnesyltransferase inhibitors decrease tumor growth in preclinical models of *HRAS*-driven cancers. Indeed, tipifarnib is in phase II clinical development in this genomic subset of squamous cell carcinomas and hematologic malignancies. MEK inhibitors have shown minor activity as monotherapies in *KRAS* mutant CRC, but their efficacy is limited by rapid development of resistance and dose-limiting toxicities.[9] Promising activity of MEK inhibitors has been seen in *KRAS* mutant low-grade serous ovarian cancers and histiocytic neoplasms.

In the last decade, knowledge gaps in RAS targeting have begun to be filled following new insights into the specific vulnerabilities of *RAS* mutant cancers and availability of agents targeting key downstream MAPK pathway effectors. Synthetic lethal screens have identified different cellular processes as potential sensitizers to MEK or ERK inhibition in *KRAS* mutant cancers, such as regulators of cell cycle and apoptosis, metabolism, receptor tyrosine kinase signaling, chromatin state, and transcription factors.[9] Some of these hits have already moved to clinical development, with negative results of early trials such as double EGFR/ERBB3 blockade plus MEK inhibition.[10] There are ongoing trials looking at alternative combinations with promising preclinical data, such as CDK4/6 inhibitors plus MEK or ERK inhibitor in *KRAS* mutant CRC (Table 1). In an anti-EGFR refractory setting, with acquired *KRAS* mutant subclones, vertical inhibition of EGFR and MEK pathway is also under investigation. In contrast, given known signaling cross-talks and adaptive feedback loops, horizontal dual inhibition of PI3K and MEK signaling pathways has been extensively studied. Disappointingly, different regimens showed no antitumor activity in *KRAS* mutant CRC patients, in part related to poor pharmacodynamic effects and high toxicity.[9]

The limited efficacy observed with these MAPK-targeting combination

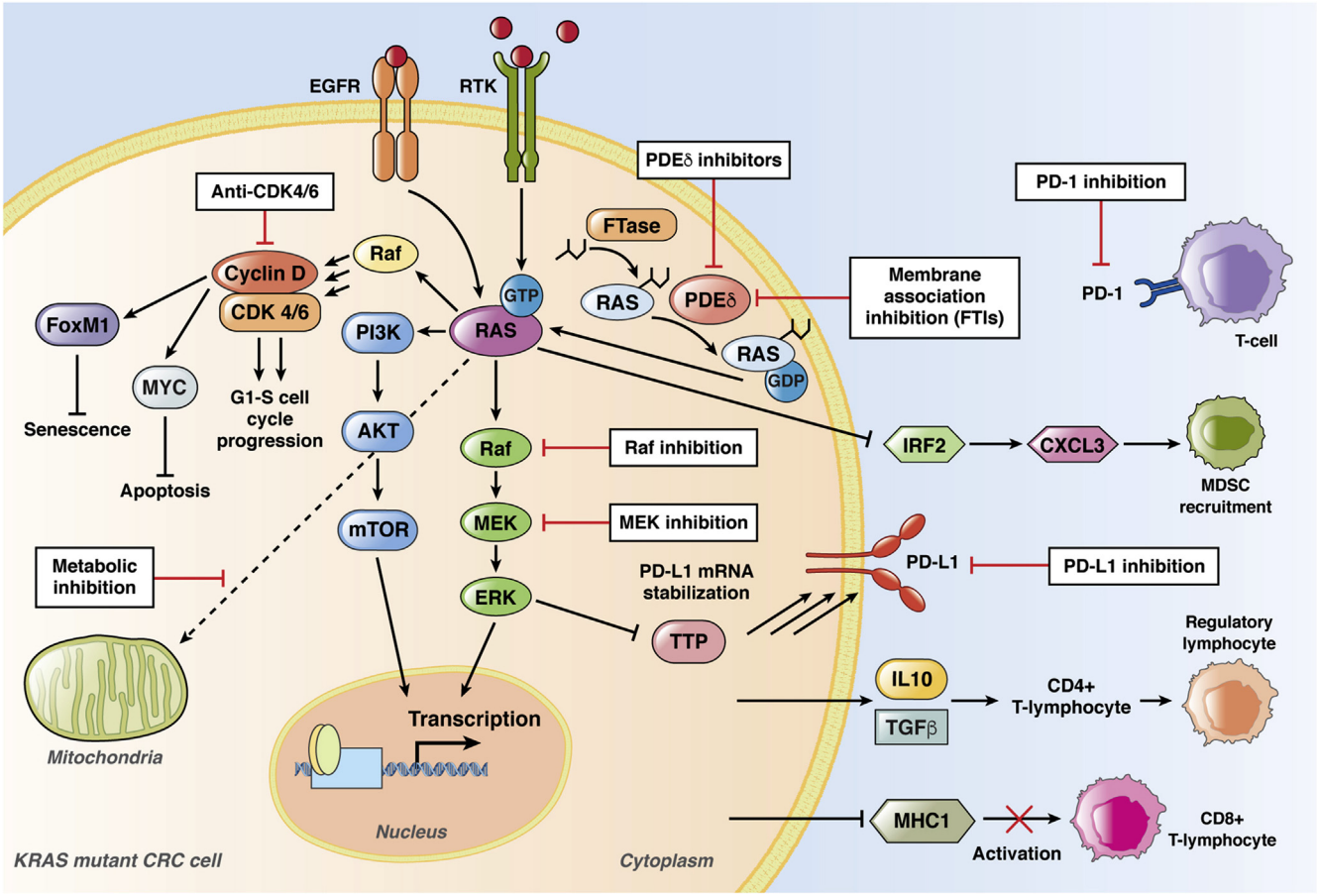

Figure 1. Rat sarcoma virus (RAS) signaling, impact within the tumor microenvironment (TME) and associated therapeutic approaches. Overview of aberrant intracellular RAS signaling and its effects within the TME. Oncogenic RAS mutations result in a constitutively activated state whereby RAS proteins are no longer self-inhibited by normal GTPase activity. Approaches to inhibit mutant RAS signaling include single or dual targeting of RAS itself, the RAS-RAF-MEK-ERK axis, the PI3K-AKT-mTOR axis, CDK4/6 signaling, RAS membrane binding capacity, phosphodiesterase activity, and anti-programmed death-1 and anti-programmed death ligand 1 approaches.

strategies are in line with preclinical data that support a cytostatic effect in most *RAS*-mutant cancer models, without induction of cell death[11] *RAS*-mutant models remain resistant to apoptosis and became largely arrested in proliferation. *KRAS* expression levels, the ratio of mutant to normal transcripts and copy number imbalance—arising from either the amplification of the mutant allele or loss of the wild-type allele—have been shown to modulate MAPK pathway dependence in CRC and may help to understand the lack of response to downstream inhibitors.[3,12] Of note, the pattern of allelic imbalance is linked to specific *KRAS* mutations in CRC. Although mutations in residue G12 are often copy number neutral, amplification of the mutant allele is enriched in rare codons, such as A146.[2] In addition, coexisting genomic alterations have been shown to affect response to MEK inhibitor combinations in preclinical models of CRC, including *TP53* and *PIK3CA* mutations. Apoptosis may be unleashed upon treatment with MEK and SRC inhibitors only in double *KRAS*/*PIK3CA*-mutant CRC, for example.[13]

Attempts to identify small molecules to antagonize GTP binding have failed owing to the picomolar affinity of RAS for GTP and high cellular concentrations of GTP. Also contributing to this failure is the lack of well-defined hydrophobic pockets on the surface of RAS proteins. Of late, there has been renewed interest in the field of RAS targeting, following the discovery of a plethora of small molecules directly interacting with mutant KRAS. The KRAS G12C mutant protein differs from other mutant variants as it can actively cycle between the guanosine diphosphatase-bound and the GTP-bound states. The thiol group in the cysteine residue is an attractive target for covalent inhibitors located next to the nucleotide-binding pocket and the switch I/II domains, which govern the interactions with both guanine nucleotide exchange factors and downstream effectors. This difference enables specific inhibition of the KRAS G12C protein, locking it in the inactive conformation.[9] In preclinical models, direct KRAS G12C inhibitors induce tumor shrinkage linked to increased apoptosis specifically of G12C-containing cancer cell lines.[14] In the clinic, the compound AMG-510 has shown remarkable single-agent activity in *KRAS* G12C mutant lung cancer, with 50% of the patients achieving partial

Table 1. Selected Ongoing Clinical Trials in Ras Mutated Metastatc Colorectal Cancer

Direct KRAS inhibitors			
AMG510	Direct KRAS G12C inhibitor	NCT03600883	Phase 1
JNJ-74699157	Direct KRAS G12C inhibitor	NCT04006301	Phase 1
MRTX849	Direct KRAS G12C inhibitor	NCT03785249	Phase 1
TNO155	Direct KRAS G12C inhibitor	NCT03114319	Phase 1
Apoptotic, cell cycle and DNA damage pathways			
ABBV-621 + FOLFIRI + bevcizumab	TRAIL receptor agonist + Chemotherapy + anti-VEGF therapy	NCT03082209	Phase 1/2
Onvansertib + FOLFIRI + bevcizumab	PLK1 inhibitor + Chemotherapy + anti-VEGF therapy	NCT03829410	Phase 1/2
AZD1775 + Irinotecan	Wee 1 inhibitor + Chemotherapy	NCT02906059	Phase 1
Palbociclib + Binimetinib	CDK4/6 inhibitor + MEK inhibitor	NCT03981614	Phase 2
HDM201 + Trametinib	MDM2 inhibitor + MEK inhibitor	NCT03714958[a]	Phase 1
Metabolic pathway			
TVB2640	FASN enzyme inhibitor	NCT02980029	Phase 1
Vitamin C + FOLFOX ± bevacizumab	GAPDH enzyme inhibitor + Chemotherapy ± anti-VEGF therapy	NCT02969681	Phase 3
Immunotherapy combinations			
Binimetinib + Nivolumab ± Ipilimumab	MEK inhibitor + anti-PD1 therapy ± anti-CTLA4 therapy	NCT03271047	Phase 1/2
Utolimumab + Cetuximab + Irinotecan	4-1BB/CD137 agonist + anti-EGFR therapy + Chemotherapy	NCT03290937	Phase 1/2
Hu5F9-G4 + Cetuximab	anti-CD47 therapy + anti-EGFR therapy	NCT02953782	Phase 1/2

[a]TP53 wild-type tumor is also mandatory

tumor response.[15] However, the efficacy of this compound is not so encouraging in CRC, with <5% of evaluable patients reaching major tumor shrinkage, and one-third having disease stabilization as best response. Moreover, given that *KRAS* G12C mutation is seen in only 4% of CRC, as compared with 13% in lung cancer, the use of these compounds will be limited to small populations, likely in combination regimens.[2]

Complexity of Molecular and Immune Subtypes of RAS Mutant CRC

Colorectal carcinogenesis develops as a result of genomic, transcriptomic, epigenomic and metabolomic alterations, which synchronize with tumor microenvironment (TME) components to result in the heterogeneity which defines this disease. The consensus molecular subtypes (CMS) of CRC solved major inconsistencies among previously reported transcriptomic subtyping frameworks of primary tumors.[16] The marked interconnectivity between independent gene expression classifiers gave rise to the 4 CMS groups, which not only reflect cancer cell phenotypes, but also microenvironment features present in bulk tumor tissue samples. CMS1 tumors (MSI immune, 14%) present as predominantly MSI, with high mutational burden, hypermethylated, and with strong cytotoxic immune activation; CMS2 (canonical, 37%) have epithelial markers and marked WNT and MYC signaling activation and EGFR expression; CMS3 (metabolic, 13%) exhibit epithelial features with prominent metabolic pathway dysregulation, are enriched for *RAS* mutations and sometimes present with hypermutated/hypermethylated phenotype; and finally CMS4 tumors (mesenchymal, 23%) are characterized by strong transforming growth factor-β activation, stromal invasion and angiogenesis.[16] Most CMS2 and CMS3 tumors exhibit low immune and inflammatory signatures, and lack tumor-infiltrating lymphocytes and immune-regulatory cytokines in the microenvironment.[17]

With regard to *RAS* mutations across CMS subtypes, despite enrichment in the CMS3 metabolic subtype (80%), mutations can additionally be found in up to 40% of tumors from other CMS groups. In another CRC classifier derived from patient-derived xenograft (PDX) gene expression data to distinguish between cancer cell–specific (human) versus stromal (mouse) transcripts, *KRAS* mutations were enriched in an MSI-like subtype also displaying secretory traits, glycolytic metabolism and an inflammatory phenotype.[18] A similar spread of *RAS* mutations has also recently been described across a chromosomal instability dependent CRC classification method predictive for bevacizumab response in the metastatic CRC.[19]

When exploring transcriptomic markers as predictors of drug response, it is important to highlight that pathway addictions defined by gene expression signals are not a simple on–off phenomenon, and there are no targetable alterations that represent hallmarks of a single CRC molecular subtype. Interestingly, data have now begun to emerge that demonstrate a role for transcriptomic differences in therapeutic response of *RAS* mutant CRC cell lines. The combination of a MEK inhibitor plus neratinib (EGFR/HER2 inhibitor) effectively reduced cell viability in nonmesenchymal subtypes, showing synergistic activity in a CMS1 xenograft model independent of *KRAS* status.[20] In contrast, an ERK inhibitor proved synergistic with neratinib in CMS4 cell lines. It is very unlikely that these

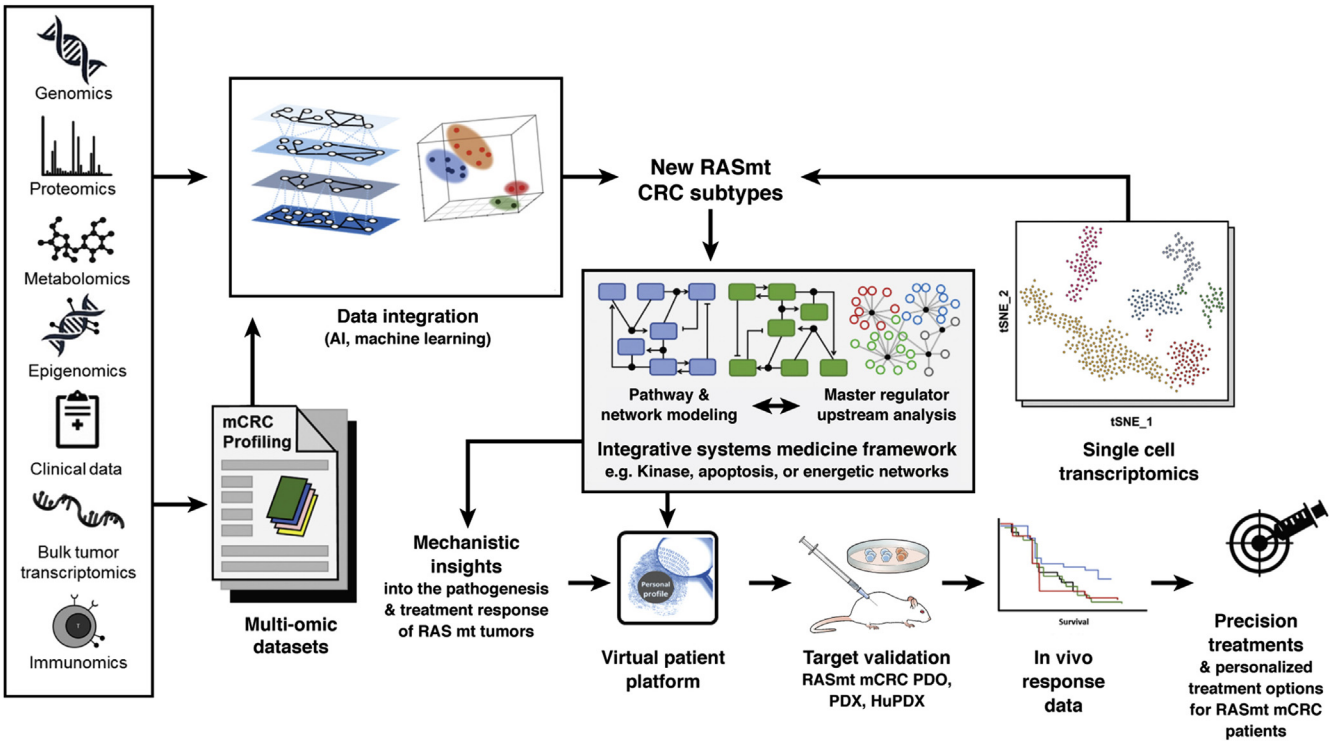

Figure 2. Integrative systems medicine framework for precision treatment in mutated rat sarcoma virus (RASmt) colorectal cancer (CRC). Omics data are collected from genomic, proteomic, metabolomic, epigenomic, immunomic and transcriptomic analyses. Machine learning and artificial intelligence (AI) methods support the clustering, classification and integration of 'omics and clinical data resulting in the generation of personal prediction profiles. This novel systems biomedicine framework will identify new actionable pathways, biomarkers, and therapeutic targets across CRC subtypes. Thus, within COLOSSUS new RASmt specific molecular subtypes with unique signaling dependences will be identified through a multi-omics approaches. Subsequently, a novel systems modelling and network analysis framework will be used to identify new actionable pathways, biomarkers, and therapeutic targets across subtypes. These therapeutic targets and novel combinatorial approaches will be interrogated in state-of-the-art patient derived organoid (PDO), patient-derived xenograft (PDX), and humanized PDX (HuPDX) models.

associations will be validated in prospective clinical trials.[20]

Information on the TME in *RAS* mutant CRC may guide new directions for the application of immunotherapy approaches in MSS tumors. Using the microenvironment cell populations counter computational tool to assess the TME cellular composition and functional orientation, *RAS* mutant and wild-type tumors have been shown not to differ significantly, excluding a trend toward lower neutrophil and endothelial cells in mutant tumors.[17] Nevertheless *KRAS* mutations are known to be at least partially responsible for the induction of an immunosuppressive TME through a series of complex adaptive mechanisms, including induced secretion of IL-10 and transforming growth factor-β, subsequent activation of suppressive regulatory T cells, immune checkpoint protein expression, and various cell-extrinsic mechanisms that prevent tumor recognition by the immune system.[21] *KRAS* mutations decrease the expression of the immune modulator IRF2, which normally functions to repress CXCL3 expression, thereby driving myeloid-derived suppressor cell infiltration into the TME via CXCR2 interaction.[22] Indeed, signatures reflecting interferon gamma pathway and Th1-centric coordinate immune response cluster are significantly reduced in *KRAS* mutant CRC as compared with wild type, particularly in CMS2 tumors. These data suggest that the immune status of *RAS* mutant CRC may vary according to transcriptional context.[23]

Targeting the MAPK signaling axis was expected to improve response to immune checkpoint inhibitors in CRC. Despite early signals of antitumor activity in a phase I clinical trial combining the MEK inhibitor cobimetinib plus the anti-programmed death ligand 1 agent atezolizumab in *KRAS* mutant metastatic CRC, a randomized phase III study comparing this targeted immunotherapeutic combination with standard regorafenib in unselected patients with refractory disease did not show survival differences between the regimens.[24]

Future of Precision Oncology in RAS Mutated CRC: A Research COLOSSUS

As described, because *RAS* mutations are present across subtypes that differ in cancer cell pathway dependencies and immune–stromal contextures, we propose an integrated discovery strategy incorporating multi-omics profiling and computational models to advance and extend upon recent learnings in the field (Figure 2). Single cell sequencing technologies will support an improved understanding of how mutant *RAS* may impact the cellular

landscape and how cancer cells and the TME reciprocally shape tumor progression and resistance to therapy.[25] This integration and combined biomarker identification using machine learning models is expected to improve the power of capturing different hierarchies of heterogeneity in *RAS*-mutant CRC and interactions between the genome, transcriptome, epigenome, metabolome, and immunome. These computational approaches serve 2 purposes: (1) classification and integration of large amounts of diverse datasets, and (2) mechanistic analysis using fine-grained models that simulate biochemical pathways and allow prediction of new drug targets and novel drug combinations.

To better exploit molecular subtypes for therapy selection and optimize the use of existing drugs, we should exit the paradigm of "one marker fits one targeted drug regimen." We are actively working to refine the molecular stratification of *RAS* mutant CRC from a functional perspective, applying a systems approach for identifying targetable contexts of vulnerabilities that will be validated in state-of-the-art preclinical models. In a fully integrated bench-to-beside-to-bench approach, the recently commenced European Commission–funded cross-sectoral research network "COLOSSUS" (www.colossusproject.eu) will (1) conduct in-depth biological interrogation and refinement of CRC subtypes in the MSS *RAS* mutant CRC setting and (2) search for a targetable set of driver alterations that will guide novel-novel drug combinations (Figure 2). Agents targeting rewired metabolic or apoptotic pathways in *RAS* mutant CRC are of highest interest.[26] In parallel, we will implement high-fidelity pharmacogenomic screens in a large series of human cancer specimens cultured ex vivo (patient-derived organoids) or directly transplanted into mice (PDXs), to assess treatment with targeted agents ("xenopatients") in molecularly defined study populations. The absence of many components of the immune system in PDX models, and loss of endogenous human immune cells upon propagation of the human tumor tissue over multiple passages, limit the usefulness of such models to explore the role of the TME in cancer progression.[27] Therefore an important added value of the COLOSSUS xenopatient platform is the availability of humanized mouse models with functional human immune system to test novel immune-oncology therapeutic regimens in MSS *RAS* mutant cohorts displaying signs of strong immune dependence.

Targeting *RAS*-driven CRC remains one of the most difficult challenges in oncology today owing to several obstacles, including the pervasiveness of *RAS*-mediated signal transduction feedback loops with compensatory significance, the difficulty in coping with pathway redundancy, the effects of tumor heterogeneity on the positive selection of drug-resistant subclones, and interactions with immunosuppressive microenvironment cells. It is thus essential to comprehensively understand the functional relationships and genetic interactions of the signaling circuits operational in *RAS*-mutant CRC to develop more effective therapies.

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References

1. Fernández-Medarde A, Santos E. Ras in cancer and developmental diseases. Genes Cancer 2011; 2:344–358.
2. Serebriiskii IG, Connelly C, Frampton G, et al. Comprehensive characterization of RAS mutations in colon and rectal cancers in old and young patients. Nat Commun 2019;10:3722.
3. Ambrogio C, Köhler J, Zhou ZW, et al. KRAS Dimerization impacts MEK inhibitor sensitivity and oncogenic activity of mutant KRAS. Cell 2018;172:857–868.
4. Roth AD, Tejpar S, Delorenzi M, et al. Prognostic role of KRAS and BRAF in stage II and III resected colon cancer: results of the Translational Study on the PETACC-3, EORTC 40993, SAKK 60-00 Trial. J Clin Oncol 2010;28:466–474.
5. Dienstmann R, Mason MJ, Sinicrope FA, et al. Prediction of overall survival in stage II and III colon cancer beyond TNM system: a retrospective, pooled biomarker study. Ann Oncol 2017; 28:1023–1031.
6. Stintzing S, Miller-Phillips L, Modest DP, et al. Impact of BRAF and RAS mutations on first-line efficacy of FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab: analysis of the FIRE-3 (AIO KRK-0306) study. Eur J Cancer 2017;79:50–60.
7. Dienstmann R, Tabernero J. Spectrum of gene mutations in colorectal cancer: implications for treatment. Cancer J 2016; 22:149–155.
8. **Siravegna G, Sartore-Bianchi A**, Nagy RJ, et al. Plasma HER2 (ERBB2) COPY NUMBER PREDICTS response to HER2-targeted therapy in metastatic colorectal cancer. Clin Cancer Res 2019; 25:3046–3053.
9. Ryan MB, Corcoran RB. Therapeutic strategies to target RAS-mutant cancers. Nat Rev Clin Oncol 2018;15:709–720.
10. Lieu CH, Hidalgo M, Berlin JD, et al. A phase Ib dose-escalation study of the safety, tolerability, and pharmacokinetics of cobimetinib and duligotuzumab in patients with previously treated locally advanced or metastatic cancers with mutant KRAS. Oncologist 2017;22:1024.
11. **Migliardi G, Sassi F, Torti D**, et al. Inhibition of MEK and PI3K/mTOR suppresses tumor growth but does not cause tumor regression in patient-derived xenografts of RAS-mutant colorectal carcinomas. Clin Cancer Res 2012;18:2515–2525.
12. Burgess MR, Hwang E, Mroue R, et al. KRAS allelic imbalance enhances fitness and modulates MAP kinase dependence in Cancer. Cell 2017;168:817–829.
13. Anderson GR, Winter PS, Lin KH, et al. A Landscape of therapeutic cooperativity in KRAS mutant cancers reveals principles for controlling tumor evolution. Cell Rep 2017;20:999–1015.

14. Janes MR, Zhang J, Li LS, et al. Targeting KRAS mutant cancers with a covalent G12C-specific inhibitor. Cell 2018;172:578–589.
15. Govindan R, Fakih MG, Price TJ, et al. Phase 1 study of AMG 510, a novel molecule targeting kras g12c mutant solid tumors. Ann Oncol 2019;30(Suppl):v159–v193.
16. **Guinney J, Dienstmann R**, Wang X, et al. The consensus molecular subtypes of colorectal cancer. Nat Med 2015;21:1350–1356.
17. Becht E, de Reyniès A, Giraldo NA, et al. Immune and stromal classification of colorectal cancer is associated with molecular subtypes and relevant for precision immunotherapy. Clin Cancer Res 2016;22:4057–4066.
18. Isella C, Brundu F, Bellomo SE, et al. Selective analysis of cancer-cell intrinsic transcriptional traits defines novel clinically relevant subtypes of colorectal cancer. Nat Commun 2017;8:15107.
19. **Smeets D, Miller IS, O'Connor DP**, et al. Copy number load predicts outcome of metastatic colorectal cancer patients receiving bevacizumab combination therapy. Nat Commun 2018;9:4112.
20. Pal R, Wei N, Song N, et al. Molecular subtypes of colorectal cancer in pre-clinical models show differential response to targeted therapies: treatment implications beyond KRAS mutations. PLoS One 2018;13:e0200836.
21. Zdanov S, Mandapathil M, Abu Eid R, et al. Mutant KRAS conversion of conventional T cells into regulatory T cells. Cancer Immunol Res 2016;4:354–365.
22. Liao W, Overman MJ, Boutin AT, et al. KRAS-IRF2 axis drives immune suppression and immune therapy resistance in colorectal cancer. Cancer Cell 2019;35:559–572.
23. **Lal N, White BS**, Goussous G, et al. KRAS mutation and consensus molecular subtypes 2 and 3 are independently associated with reduced immune infiltration and reactivity in colorectal cancer. Clin Cancer Res 2018;24:224–233.
24. Bendell J, Ciardiello F, Tabernero J, et al. Efficacy and safety results from IMblaze370, a randomised phase III study comparing atezolizumab+cobimetinib and atezolizumab monotherapy vs regorafenib in chemotherapy-refractory metastatic colorectal cancer. Ann Oncol 2018;29(Suppl):LBA4.
25. **Li H, Courtois ET**, Sengupta D, et al. Reference component analysis of single-cell transcriptomes elucidates cellular heterogeneity in human colorectal tumors. Nat Genet 2017;49:708–718.
26. Yau EH, Kummetha IR, Lichinchi G, et al. Genome-Wide CRISPR Screen for essential cell growth mediators in mutant KRAS colorectal cancers. Cancer Res 2017;77:6330–6339.
27. Byrne AT, Alférez DG, Amant F, et al. Interrogating open issues in cancer precision medicine with patient-derived xenografts. Nat Rev Cancer 2017;17:254–268.

Author names in bold designate shared co-first authorship.

Acknowledgments
RD and ATB contributed equally to this work.

Conflicts of interest
The authors disclose no conflicts.

Funding
ATB, WHF, DL, JT, AS, LT, JHMP, WK, and RD are funded by the COLOSSUS framework; A European Union Horizon 2020 research and innovation programme (Grant agreement No. 754923). ATB, JHMP, and WK are supported by Science Foundation Ireland under grants 13/CDA/2183, 14/IA/2582 and 14/IA/2395 respectively. ATB further receives funding from the Irish Health Research Board under grant ILP-POR-2019-066.

The COLOSSUS Consortium includes W.H. Fridman (Université Paris Descartes, Université Pierre et Marie Curie, Paris, France), D. Lambrechts (VIB Center for Cancer Biology, Laboratory for Translational Genetics, Leuven, Belgium), A. Sadanandam (Division of Molecular Pathology, Institute of Cancer Research, London, United Kingdom), L. Trusolino (Candiolo Cancer Institute, FPO-IRCCS, Candiolo and Department of Oncology, University of Torino, Torino, Italy), J.H.M. Prehn (Royal College of Surgeons in Ireland, Dept of Physiology and Medical Physics, RCSI Centre for Systems Medicine, Dublin 2,), J. Tabernero (Medical Oncology Department, Vall d'Hebron University Hospital, Barcelona, Spain), and W. Kolch (Systems Biology Ireland, University College Dublin, Dublin, Ireland).

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0016-5085/$36.00
https://doi.org/10.1053/j.gastro.2019.12.051