New Insights Into Pancreatic Cancer: Notes from a Virtual Meeting

Elisabeth Hessmann,[1] and Günter Schneider,[2] on behalf of the 1st Virtual Göttingen-Munich-Marburg Pancreatic Cancer Meeting

[1]Department of Gastroenterology, Gastrointestinal Oncology and Endocrinology, University Medical Center Göttingen, Göttingen, Germany; and [2]Medical Clinic and Policlinic II, Klinikum rechts der Isar, Technische Universität München, Munich, Germany

Pancreatic ductal adenocarcinoma remains a major challenge in cancer medicine. Given the increase in incidence and mortality, interdisciplinary research is necessary to translate basic knowledge into therapeutic strategies improving the outcome of patients. On the 4th and 5th of February 2021, three German pancreatic cancer research centers, the Clinical Research Unit 5002 from Göttingen, the Collaborative Research Center 1321 from Munich, and Clinical Research Unit 325 from Marburg organized the 1st Virtual Göttingen-Munich-Marburg Pancreatic Cancer Meeting in order to foster scientific exchange. This report summarizes current research and proceedings presented during that meeting.

Keywords: Pancreatic Cancer; Microenvironment; Genome Dynamics; Emerging Therapies; Molecular Subtypes.

With more than 400,000 related annual deaths, a 5-year survival rate of 10%, and a rising incidence, pancreatic ductal adenocarcinoma (PDAC) remains a significant health burden. These characteristics illustrate the need to intensify research and to share concepts, expertise, and data. Therefore, 3 Deutsche Forschungsgemeinschaft–funded PDAC research consortia Clinical Research Unit (CRU) 5002, Collaborative Research Center 1321, and CRU325 organized the 1st Virtual Göttingen-Munich-Marburg Pancreatic Cancer Meeting. The meeting was balanced with respect to gender and career stage and, therefore, was also a forum for young scientists. Sixteen talks attracted more than 200 international participants and were separated into the following 4 sessions: genome dynamics, tumor microenvironment, cell-of-origin/differentiation/subtypes and emerging therapeutic concepts (Figure 1). This report summarizes important findings communicated during the meeting.

Genome Dynamics

Genome dynamics converges various aspects of biology, ranging from regulation of the transcriptome to the DNA damage response. The close entanglement of chromatin regulatory proteins and DNA replication were addressed by Gwen Lomberk. She reported on the tumorigenic histone methyltransferase G9a, which targets H3K9 for di-methylation, thus inducing transcriptional repression. Oncogenic KRAS induced the expression of G9a complex members. Inactivation of G9a in genetically engineered mouse models reduced H3K9me2 and abrogated the formation of precursor lesions, demonstrating a crucial role of G9a in tumorigenesis. Further, Gwen Lomberk introduced a role of G9a in regulating active replication forks. Her findings are of particular interest because the disturbed progression of replication forks triggers an intra–S-phase cell cycle checkpoint, activating the ataxia telangiectasia and Rad–related (ATR) CHK1 branch of DNA-damage signaling. She showed that combined G9a and CHK1 inhibition increased single-stranded DNA breaks, caused a collapse of the replication fork and induced cell death.[1]

Recent reports have documented the existence of a PDAC continuum ranging from classical to aggressive basal-like cancers.[2–4] Such subtypes differ in the response to therapies,[3] therefore, underpinning the idea of patient stratification. A prerequisite of this approach is the mechanistic understanding of the subtype biology. Shiv K. Singh offered a comprehensive overview on the dynamic interactions between classical or basal-like cancer cells and the inflammatory stromal components. He provided evidence that the proinflammatory cytokine tumor necrosis factor–α (TNFα) is enriched in basal-like tumors. His findings demonstrate that TNFα promotes transcriptional shifts from the classical to the basal-like subtype identity, provoking de-differentiation. Because US Food and Drug Administration–approved anti-TNF agents are available, inhibition of the TNFα-driven network might represent a strategy to reduce the aggressiveness.

Amplifications of the *MYC* oncogene are associated with worse survival. MYC has a great value as an integrator of KRAS signaling and therapies tackling MYC have been

Abbreviations used in this paper: **ATR, ataxia telangiectasia and Rad–related; CAF, cancer-associated fibroblast; CRU, Clinical Research Unit; DDR, DNA damage response; MEKi, MEK inhibitor; PDAC, pancreatic ductal adenocarcinoma; Prrx1, paired-related homeobox 1; TME, tumor microenvironment; TNFα, tumor necrosis factor–α.**

Most current article

0016-5085
https://doi.org/10.1053/j.gastro.2021.04.082

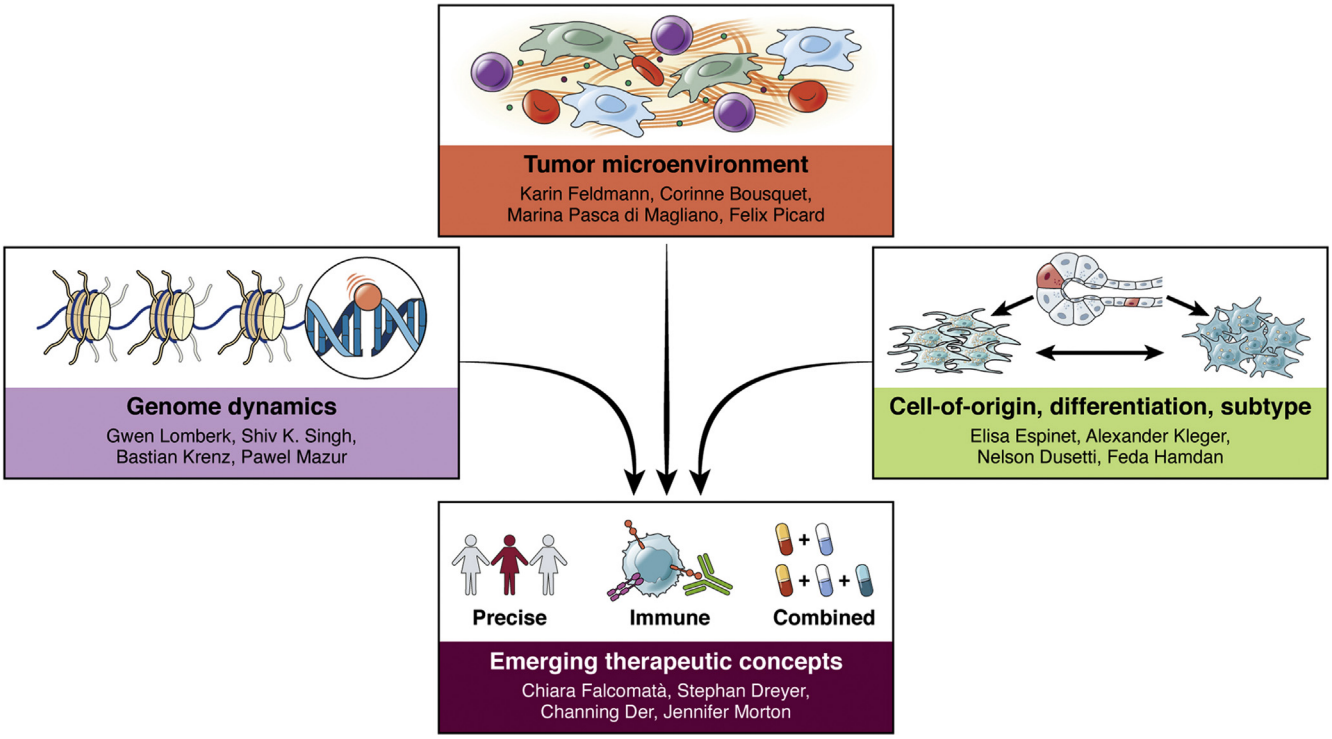

Figure 1. Drivers of PDAC biology and resistance. PDAC phenotypes are driven by highly entangled, unique features, which are characterized by alterations in genome dynamics and the TME, as well as the cell-of-origin that the tumor derives from and the predominant molecular subtype it represents. These hallmarks of PDAC determine the development of novel therapeutic strategies for personalized and improved PDAC treatment. The 1st virtual Göttingen-Munich-Marburg Pancreatic Cancer Meeting comprised scientific talks from all 4 fields of cutting-edge topics of PDAC research.

described. Recent work has emphasized a role of MYC in remodeling the tumor microenvironment (TME).[5,6] In order to further dissect this relationship, Bastian Krenz, Anneli Gebhardt, and Martin Eilers used a mouse model allowing inducible MYC inactivation to mimic therapeutic intervention. They showed that the tumor response on MYC inactivation is dependent on the immune system and illustrated novel molecular underpinnings of MYC's crosstalk with the TME.

PDAC is initiated, driven, and maintained by mutations in KRAS.[7,8] However, clinical inhibition of the canonical KRAS pathway has not yet been successful. Therefore, understanding redundancy, adaption, and resistance occurring in response to inhibition is pivotal for success. A cause of MEK inhibitor (MEKi) resistance was discussed by Pawel Mazur. By a genetic screen, the methyltransferase SETD5 was found to confer MEKi resistance.[9] Interference with SETD5 expression increased the sensitivity toward MEKi. The SETD5 complex contains the NCOR1-HDAC3 corepressor and the methyltransferases G9a and GLP. Mechanistically, the SETD5 complex removes the activating histone acetylation mark H3K9ac, allowing G9a to methylate this residue. Genes repressed by the SETD5 complex were connected to drug and glutathione metabolism, processes conferring drug resistance. Accordingly, a triple-therapy that combines MEKi with compounds targeting the enzymatic subunits HDAC3 and G9a/GLP is efficient in preclinical models.[9]

Microenvironment

Plasticity does not only apply to tumor cells, but also accounts for cells of the TME. Karin Feldmann from Max Reicherts laboratory characterized the role of paired-related homeobox 1 (Prrx1) transcription factor in the TME. Prrx1 is overexpressed in cancer-associated fibroblasts (CAFs), particularly in patients with basal-like cancers.[10] Using genetic models to inactivate the *Prrx1* gene in CAFs, she demonstrated that *Prrx1*-deficient CAFs were forced into the myofibroblastic CAF cellular state, increasing extracellular matrix deposition and restraining tumor progression. CAFs with high Prrx1 expression shaped an immune-suppressive microenvironment, promoted tumor cell epithelial-to-mesenchymal transition, and mediated gemcitabine resistance.[10] Karin Feldmann's data on plasticity of CAFs exemplified the promise of fibroblast reprogramming as a therapy.

The value of TME reprogramming was also demonstrated by Corinne Bousquet. Her talk focused on the implications of the somatostatin analog SOM230. Somatostatin acts via the G-protein–coupled receptors sst1-5. Previous work has already demonstrated that SOM230 acts on sst1, which is selectively expressed on CAFs.[11] Activation of sst1 by SOM230 blocked AKT-mTOR signaling–dependent protein synthesis. Subsequently, the production of interleukin-6, which acts in a paracrine fashion to drive tumor cell plasticity and chemoresistance,[11] was decreased.

Comprehensive secretome analysis of CAFs suggested that SOM230 caused reduced expression of the chemokine CSF-1 (macrophage colony-stimulating factor 1),[12] which contributes to the recruitment of monocytes and their polarization into macrophages. Hence, treatment with SOM230 reduced intra-tumoral M2-like polarized tumor-associated macrophages[12] and abrogated the pro-metastatic processes associated with these cells. Consistently, the combination of gemcitabine and SOM230 was sufficient to reduce tumor growth and metastasis.[12]

Cellular cross-talks in PDAC were also illustrated by Marina Pasca di Magliano. She introduced results from a multi-omics mapping approach of the TME. This multimodal analysis pointed to a substantial inter-tumoral heterogeneity of immune infiltration[13] and confirmed the highly immune-suppressive character of PDAC. $CD8^+$ T cell exhaustion was associated with abundant expression of the immune checkpoint T cell immunoglobulin and ITIM domain,[13] a key inhibitor of the immune anti-tumor responses. Intriguingly, T cell immunoglobulin and ITIM domain expression levels in patients with PDAC matched in tumor and blood, qualifying the immunoglobulin as a biomarker for patient stratification before immunotherapy, a strategy currently under evaluation (eg, ClinicalTrials.gov identifier NCT04294810). Furthermore, a role of ApoE, which was found to be overexpressed in tumor-associated macrophages, was discussed. In vivo experiments linked *ApoE* deficiency with reduced tumor growth and suggested a causative role of T cells mediating these effects. Treatment of PDAC cells with ApoE induced NFκB-dependent CXCL1 expression, further emphasizing the impact of the multidirectional tumor–stroma cell communication.

Felix Picard from Magdalena Huber's group presented data on the population of interleukin-17 producing noncanonical $CD8^+$ T cells (Tc17 cells) and illustrated their implications on the TME. Tc17 cell abundance was associated with advanced tumor stages and reduced survival. In murine models, Tc17 cells accelerated tumor growth in a paracrine manner. Culturing of quiescent pancreatic stellate cells with conditioned media from Tc17 cells directed their differentiation toward inflammatory CAFs, while co-culture of Tc17-induced inflammatory CAFs with PDAC cells enhanced their proliferation ex vivo and promoted tumor growth in vivo. Hence, Felix Picard demonstrated how the interplay of different cellular compartments of the TME can foster PDAC progression.

Cell of Origin, Differentiation, and Subtypes

Elisa Espinet from the laboratory of Andreas Trumpp showed that clustering based on DNA methylation revealed 2 groups with different methylation levels at genomic regions encoding repeat elements. $Methylation^{low}$ tumors showed higher expression of endogenous retroviral transcripts and strong engagement of the double-stranded RNA sensing machinery with subsequent activation of an interferon signature.[14] This resulted in pro-tumorigenic reprogramming of stromal cells and sensitized this subset of more aggressive tumors for JAK/STAT inhibition.[14] Interestingly, $methylation^{low}$/$IFNsign^{high}$ and $methylation^{high}$/$IFNsign^{low}$ PDAC cells revealed distinct lineage traits specific to ductal or acinar cells, respectively, at the methylation and transcriptional level, suggesting the existence of 2 distinct origins of PDAC.[14]

Alexander Kleger and his team have contributed protocols to differentiate human pluripotent stem cells toward the pancreatic lineage.[15] In his talk, he presented a protocol that promotes differentiation of human pluripotent stem cells into pancreatic duct–like organoids, which resemble human duct epithelium at various levels, including function.[16] Genetic engineering to induce $KRAS^{G12D}$ in *CDKN2A*-proficient and -deficient pancreatic duct–like organoids was used to demonstrate the value of such a model. The group not only used this novel platform to explore the impact of KRAS signaling on oncogene-induced senescence, but further explored processes operative in intraductal papillary mucinous neoplasms. This was exemplified by a *GNAS* R201C mutated mosaic culture of human bone marrow stromal cells from a patient with McCune-Albright syndrome. In accordance with the implication of *GNAS* mutations in driving intraductal papillary mucinous neoplasms, $GNAS^{WT/R201}$ mutated pancreatic duct–like organoids formed large proliferative cysts and grew as well-differentiated ducts resembling human intraductal papillary mucinous neoplasms in vivo. The power of the presented protocol to model human carcinogenesis and hereditary syndromes at early stages of plasticity and dysplasia was emphasized.

Nelson Dusetti presented the efforts of the PaCaOmics clinical trial to use patient-derived models, which conserve the intertumoral as well as the intratumoral heterogeneity of the disease[17,18] for translational research. In PDX models, a continuum of well-differentiated to undifferentiated PDACs was observed, which related to a gradient of transcriptional markers.[4] Only the extremes in the continuum express a pure classical or basal-like profile, while tumors with both subtype features and intermediate expression of markers exist. The models were used to establish predictive signatures for tumor progression and response toward therapies. Although a pancreatic adenocarcinoma molecular gradient is predictive for responsiveness toward the mFOLFIRINOX regimen,[4] a messenger RNA expression signature predictive of gemcitabine response (*GemPred*) identifies patients who benefit from adjuvant gemcitabine,[19] allowing selection of a less toxic therapy. In summary, Nelson Dusetti presented the relevance of preclinical patient-derived models to identify signatures predicting the clinical outcome.

Feda Hamdan from the groups of Steven Johnsen and Zeynab Najafova integrated gene expression and epigenome mapping data from PDX to identify subtype-specific enhancer programs. Complementary analysis of nascent transcription and chromatin topology identified a unique group of transcribed superenhancers that displayed frequent interactions, and were essential for basal-like target gene expression. She identified a basal-like A subtype-specific transcribed enhancer program

characterized by enhancer RNA production that is associated with higher-order chromatin interactions and gene activation. Notably, RNA in situ hybridization–based enhancer RNA detection represents a fast tool to identify patients with basal-like A subtypes. Feda Hamdańs findings provide a first proof-of-concept that subtype-specific epigenetic changes are relevant for tumor progression and can be detected at a single-cell level.

Emerging Therapeutic Concepts

A mesenchymal PDAC subtype overlapping basal-like cancers was described previously.[20] Mesenchymal PDACs showed increased *KRAS* messenger RNA expression,[20] which is consistent with copy number gains in murine mesenchymal[21] and human basal-like cancers.[3] Chiara Falcomatà from the Dieter Saur group observed a marked MEKi resistance of mesenchymal PDAC cells, which can be explained by higher signaling thresholds. To define options to break MEKi resistance, a combination drug screen was conducted. Here, a strong synergism between the MEKi trametinib and the multikinase inhibitor nintedanib was observed. Combined treatment induced apoptosis in vitro and disease regression in vivo. Using single-cell RNA sequencing and immunophenotyping, it was shown that these responses are paralleled by transformation of the TME. Indeed, the drug combination primes cytotoxic and effector T cells to infiltrate the tumors, thereby sensitizing mesenchymal cancers to PD-L1 inhibition. In summary, these data suggested that a combination of MEKi with nintedanib will prime for immune-checkpoint inhibitors.

Stephan Dreyer focused on the association between DNA damage response (DDR) and replication stress to develop precision treatments. By interrogating the transcriptome and genome of primary PDAC-derived cells, Dreyer tested a novel signature of homologous recombination deficiency that predicts responses toward platinum-based chemotherapy and PARP inhibition.[22] Independent of DDR deficiency, the basal-like subtype showed an enrichment of genes indicative for replication stress. Importantly, a transcriptomic signature of replication stress qualifies as a biomarker for responses toward ATR and WEE1 inhibitors.[22] Hence, replication stress and DDR deficiency can occur independently of each other and predict for different therapies.[22]

Channing Der illustrated the importance of targeting the canonical KRAS signaling. He showed that inhibition of KRAS signaling regulates metabolic processes fostering autophagic flux, thus rendering tumors dependent on autophagy. Consequently, inhibiting canonical KRAS signaling together with autophagy, achieved through hydroxychloroquine, represents a synergistic therapy that has been successfully explored in preclinical models[23] and is currently under clinical investigation (ClinicalTrials.gov identifiers NCT04386057 and NCT04132505). The second approach he presented was based on a forward genetic screen combined with a drug screen.[24] Analysis of KRAS-dependent PDAC cells showed that inhibition of all RAF isoforms—ARAF, BRAF, and CRAF—impairs growth. Therefore, a sublethal dose of a pan-RAF inhibitor was used for a combinatorial drug screen. Interestingly, MEK and ERK inhibitors synergized with the pan-RAF inhibitor. Mechanistically, ERK inhibition prevents the negative feedback reactivation of ERK previously observed on pharmacologic interference with canonical KRAS signaling. Consequently, the combination therapy disrupted transcription factor networks downstream of ERK, including MYC, E2F, and AP1, thus inducing apoptosis in in vivo models.[24] These findings support the development of novel therapeutic concepts of low-dose vertical inhibition of canonical KRAS signaling.

Jennifer Morton used genetic modeling of the disease in mice. She presented 3 important groups of genetic alterations: First, she showed data on the tumor suppressor *PTEN*, which signals upstream of the PI3K–AKT–mTOR pathway. Her findings associate *PTEN* loss with a rapid acceleration of pancreatic tumorigenesis and susceptibility toward mTOR inhibition.[25] Deletion of *Rictor* (rapamycin-insensitive companion of MTOR) or pharmacologic inhibition of mTORC2 could significantly extend survival of *KPC* mice.[26] Dual mTORC1/2 inhibitors effectively combine with MEKi, inducing tumor regression, significant metabolic rewiring and reprogramming of the TME. Second, she presented findings regarding the lysine demethylase *KDM6a*, which is mutated in basal-like cancers. *Kdm6a*-deficient genetically engineered mouse models showed a dramatic acceleration of tumorigenesis, and transcriptomic analyses link *KDM6a* to signatures associated with cell cycle control. Interestingly, down-regulation of $Kras^{G12D}$ expression was observed, suggesting that loss of *KDM6A* during tumor initiation may reduce the KRAS signaling threshold in precursor lesions, enabling them to circumvent senescence in favor of rapid progression. Third, she also presented models for DDR defective subtypes, based on *Atm*- and *Brca1*-deficiency. Treatment combining ATR and PARP inhibition was superior in extending mouse survival compared with single agents, demonstrating the therapeutic impact. Furthermore, *Brca1*-defcient and *Atm*-deficient models substantially differed in immune cell infiltration, underscoring the intertumoral heterogeneity and at the level of the immune phenotype.

Conclusions

The meeting consisted of presentations addressing a spectrum from basic through translational projects and provided insights into cutting edge technologies and innovative approaches, improving our overall understanding of PDAC. The need and options to target canonical KRAS signaling or downstream integrators were communicated. Possible drawbacks of toxicity associated with such strategies were discussed, but can probably be overcome by low-dose drug combinations. Combinatory regimens efficiently targeting the tumor cells will offer possibilities for immunotherapies. Considering the heterogeneity of immune infiltrates, there is also a need for personalizing such therapies. Monitoring of immune checkpoints, like T cell immunoglobulin and ITIM domain, may pave the way.

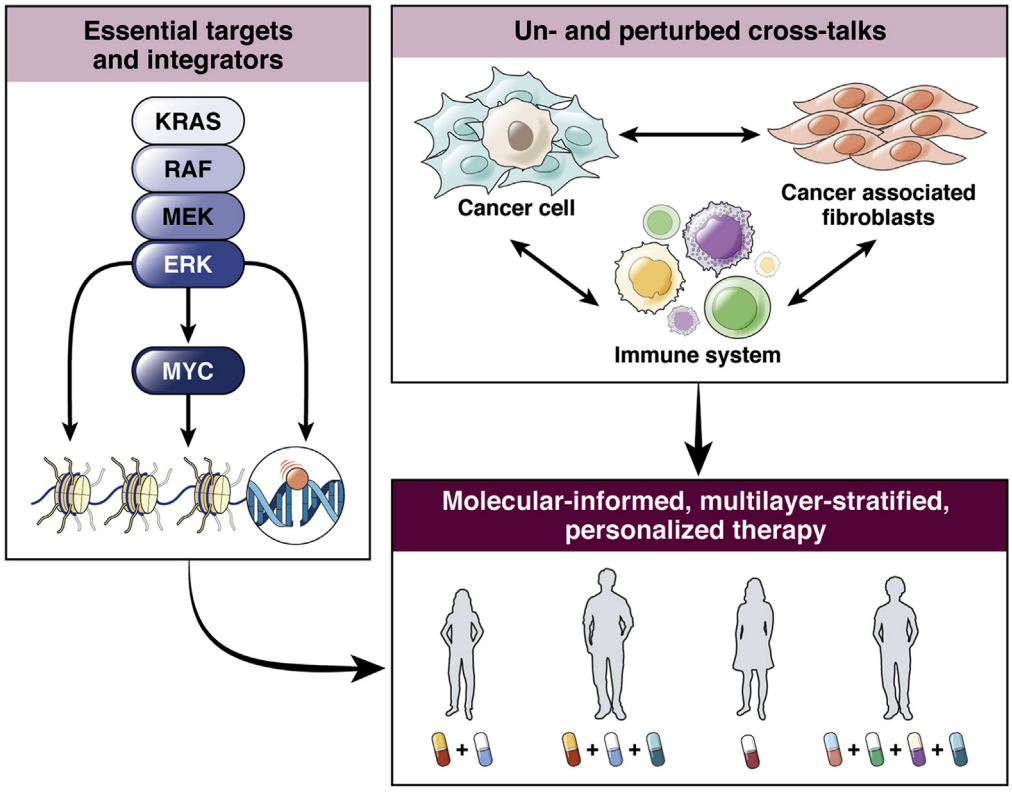

Figure 2. Challenges and emerging opportunities. The 1st virtual Göttingen-Munich-Marburg Pancreatic Cancer Meeting revealed several areas of progress in PDAC research. Based on these findings, novel scientific challenges and therapeutic opportunities evolve. Essential driver pathways and integrators can be targeted by rational combination therapies. The highly dynamic nature of cellular cross-talks, including their therapy-induced perturbance, needs to be analyzed and addressed therapeutically. Advances in these fields will lead to molecular-informed, multilayer-stratified, personalized treatments.

The meeting emphasized the necessity to model the various aspects of PDAC development, progression, and therapy response. The power of modeling combined with functional clinical platforms was exemplified by members of the Cancer Research Center of Marseille and the PRECISION PANC consortium. Such efforts will lead to implementation of precision oncology, which are emerging for chemotherapies or targeted therapies tackling DNA damage signaling.

The unique heterogeneity of PDAC was illustrated in all sessions. Multi-omics approaches resulted in the detection of signatures enabling subtype and therapy response prediction. Several talks highlighted the implication of multidirectional cross-signaling between different cellular compartments for progression, plasticity, and therapy. The therapeutic value of interfering with cellular and molecular crosstalk was highlighted. However, we are only at the beginning of efforts toward understanding the molecular interactions, especially under therapeutic perturbance.

Although not all current topics of PDAC research were presented, the forum documented the clear progress made in the last 5 years (Figure 2). Together, the meeting strongly encouraged us to increase our efforts in PDAC research in order to finally make an impact on patient outcomes.

References

1. Urrutia G, Salmonson A, Toro-Zapata J, et al. Combined targeting of G9a and checkpoint kinase 1 synergistically inhibits pancreatic cancer cell growth by replication fork collapse. Mol Cancer Res 2020;18:448–462.
2. Collisson EA, Bailey P, Chang DK, et al. Molecular subtypes of pancreatic cancer. Nat Rev Gastroenterol 2019; 16:207–220.
3. **Chan-Seng-Yue M, Kim JC**, Wilson GW, et al. Transcription phenotypes of pancreatic cancer are driven by genomic events during tumor evolution. Nature Genetics 2020;52:231–240.
4. Nicolle R, Blum Y, Duconseil P, et al. Establishment of a pancreatic adenocarcinoma molecular gradient (PAMG) that predicts the clinical outcome of pancreatic cancer. Ebiomedicine 2020;57:102858.
5. Sodir NM, Kortlever RM, Barthet VJA, et al. Myc instructs and maintains pancreatic adenocarcinoma phenotype. Cancer Discov 2020;10:588–607.
6. Muthalagu N, Monteverde T, Raffo-Iraolagoitia X, et al. Repression of the type I interferon pathway underlies MYC & KRAS-dependent evasion of NK & B cells in pancreatic ductal adenocarcinoma. Cancer Discov 2020; 10:872–887.
7. Collins MA, Bednar F, Zhang Y, et al. Oncogenic Kras is required for both the initiation and maintenance of pancreatic cancer in mice. J Clin Invest 2012; 122:639–653.
8. Ying H, Kimmelman AC, Lyssiotis CA, et al. Oncogenic Kras maintains pancreatic tumors through regulation of anabolic glucose metabolism. Cell 2012;149:656–670.
9. Wang Z, Hausmann S, Lyu R, et al. SETD5-coordinated chromatin reprogramming regulates adaptive resistance to targeted pancreatic cancer therapy. Cancer Cell 2020; 37:834–849.

10. Feldmann K, Maurer C, Peschke K, et al. Mesenchymal plasticity regulated by Prrx1 drives aggressive pancreatic cancer biology. Gastroenterology 2021;160:346–361.e24.
11. Duluc C, Moatassim-Billah S, Chalabi-Dchar M, et al. Pharmacological targeting of the protein synthesis mTOR/4E-BP1 pathway in cancer-associated fibroblasts abrogates pancreatic tumour chemoresistance. EMBO Mol Med 2015;7:735–753.
12. Samain R, Brunel A, Douché T, et al. Pharmacological normalization of pancreatic cancer-associated fibroblast secretome impairs pro-metastatic cross-talk with macrophages Stromal CSF-1 facilitates metastasis. Cell Mol Gastroenterol Hepatol 2021;11:1405–1436.
13. **Steele NG, Carpenter ES**, Kemp SB, et al. Multimodal mapping of the tumor and peripheral blood immune landscape in human pancreatic cancer. Nat Cancer 2020;1:1097–1112.
14. Espinet E, Gu Z, Imbusch CD, et al. Aggressive PDACs show hypomethylation of repetitive elements and the execution of an intrinsic IFN program linked to a ductal cell-of-origin. Cancer Discov 2021;11:638–659.
15. Hohwieler M, Illing A, Hermann PC, et al. Human pluripotent stem cell-derived acinar/ductal organoids generate human pancreas upon orthotopic transplantation and allow disease modelling. Gut 2017;66:473.
16. **Breunig M, Merkle J**, Wagner M, et al. Modeling plasticity and dysplasia of pancreatic ductal organoids derived from human pluripotent stem cells. Cell Stem Cell 2021;28:1105–1124.e19.
17. Juiz N, Elkaoutari A, Bigonnet M, et al. Basal-like and classical cells coexist in pancreatic cancer revealed by single-cell analysis on biopsy-derived pancreatic cancer organoids from the classical subtype. FASEB J 2020;34:12214–12228.
18. Nicolle R, Blum Y, Marisa L, et al. Pancreatic adenocarcinoma therapeutic targets revealed by tumor-stroma cross-talk analyses in patient-derived xenografts. Cell Rep 2017;21:2458–2470.
19. Nicolle R, Gayet O, Duconseil P, et al. A transcriptomic signature to predict adjuvant gemcitabine sensitivity in pancreatic adenocarcinoma. Ann Oncol 2020;32:250–260.
20. Dijk F, Veenstra VL, Soer EC, et al. Unsupervised class discovery in pancreatic ductal adenocarcinoma reveals cell-intrinsic mesenchymal features and high concordance between existing classification systems. Sci Rep 2020;10:337.
21. **Mueller S, Engleitner T, Maresch R**, et al. Evolutionary routes and KRAS dosage define pancreatic cancer phenotypes. Nature 2018;554:62–68.
22. Dreyer SB, Upstill-Goddard R, Paulus-Hock V, et al. Targeting DNA damage response and replication stress in pancreatic cancer. Gastroenterology 2021;160:362–377.e13.
23. Bryant KL, Stalnecker CA, Zeitouni D, et al. Combination of ERK and autophagy inhibition as a treatment approach for pancreatic cancer. Nat Med 2019;25:628–640.
24. Ozkan-Dagliyan I, Diehl JN, George SD, et al. Low-dose vertical inhibition of the RAF-MEK-ERK cascade causes apoptotic death of KRAS mutant cancers. Cell Rep 2020;31:107764.
25. Morran DC, Wu J, Jamieson NB, et al. Targeting mTOR dependency in pancreatic cancer. Gut 2014;63:1481.
26. Driscoll DR, Karim SA, Sano M, et al. mTORC2 signaling drives the development and progression of pancreatic cancer. Cancer Res 2016;76:6911–6923.

Author names in bold designate shared co-first authorship.

Received April 3, 2021. Accepted April 20, 2021.

Correspondence
Address correspondence to: Dr. Elisabeth Hessmann, Department of Gastroenterology, Gastrointestinal Oncology and Endocrinology, University Medical Center Göttingen, 37075 Göttingen, Germany. e-mail: elisabeth.hessmann@med.uni-goettingen.de; Dr. Günter Schneider, Klinikum rechts der Isar, Technische Universität München, 81675 Munich, Germany. e-mail: guenter.schneider@tum.de

Acknowledgments
The authors thank Anirban Maitra for help, advice, and discussion of the meeting report, as well as Alexander Müller for organizing the meeting. The authors thank the Deutsche Pankreas Club for announcing and supporting the meeting. Contributors of the 1st Virtual Göttingen-Munich-Marburg Pancreatic Cancer Meeting: Corinne Bousquet (INSERM UMR-1037, Cancer Research Center of Toulouse, Team Labellisée Ligue Contre le Cancer, Laboratoire d'Excellence Toulouse Cancer, Toulouse, France), Channing Der (Department of Pharmacology, Curriculum in Genetics and Molecular Biology, Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina and Charité Universitätsmedizin Berlin, Institute of Pathology, Laboratory of Molecular Tumor Pathology and Systems Biology, Berlin, Germany), Stephan Dreyer (Wolfson Wohl Cancer Research Centre, Institute of Cancer Sciences, University of Glasgow, Glasgow, Scotland, UK; West of Scotland Pancreatic Unit, Glasgow Royal Infirmary, Glasgow, United Kingdom), Nelson Dusetti (Cancer Research Center of Marseille, (CRCM), INSERM U1068, CNRS UMR 7258, Paoli-Calmettes Institut, Aix-Marseille University, Parc Scientifique et Technologique de Luminy, Marseille, France), Martin Eilers (Theodor Boveri Institute, Department of Biochemistry and Molecular Biology, Biocenter, University of Würzburg, Würzburg, Germany), Volker Ellenrieder (Department of Gastroenterology, Gastrointestinal Oncology and Endocrinology, University Medical Center Göttingen, Göttingen, Germany), Elisa Espinet (Heidelberg Institute for Stem Cell Technology and Experimental Medicine GmbH, Heidelberg, Germany; and Department of Stem Cells and Cancer, German Cancer Research Center, Heidelberg, Germany), Chiara Falcomatà (Division of Translational Cancer Research, German Cancer Research Center (DKFZ) and German Cancer Consortium (DKTK), Heidelberg, Germany; Chair of Translational Cancer Research and Institute for Experimental Cancer Therapy, Klinikum rechts der Isar, School of Medicine, Technische Universität München, München, Germany; Center for Translational Cancer Research (TranslaTUM), School of Medicine, Technical University of Munich, Munich, Germany), Karin Feldmann (Medical Clinic and Policlinic II, Klinikum rechts der Isar, Technical University Munich, Munich, Germany), Anneli Gebhardt (Theodor Boveri Institute, Department of Biochemistry and Molecular Biology, Biocenter, University of Würzburg, Würzburg, Germany), Thomas Gress (Department of Gastroenterology, Endocrinology, Metabolism and Infectiology, Center for Tumor and Immunology, Philipps University Marburg, Marburg, Germany), Feda Hamdan (Gene Regulatory Mechanisms and Molecular Epigenetics Lab, Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota), Magdalena Huber (Institute for Medical Microbiology and Hospital Hygiene, Philipps University Marburg, Marburg, Germany), Steven A. Johnsen (Gene Regulatory Mechanisms and Molecular Epigenetics Lab, Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota), Alexander Kleger (Department of Internal Medicine 1, Ulm University Hospital, Ulm, Germany), Bastian Krenz (Theodor Boveri Institute, Department of Biochemistry and Molecular Biology, Biocenter, University of Würzburg, Würzburg, Germany), Gwen Lomberk (Departments of Surgery and Pharmacology and Toxicology, LaBahn Pancreatic Cancer Program, and Genomic Sciences and Precision Medicine Center, Medical College of Wisconsin, Milwaukee, Wisconsin), Pawel Mazur (Department of Experimental Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas), Patrick Michl (Martin-Luther-Universität Halle/Wittenberg, Klinik und

Poliklinik für Innere Medizin I, Halle/Saale, Germany), Jennifer Morton (CRUK Beatson Institute and Institute of Cancer Sciences, University of Glasgow, Glasgow, UK), Marina Pasca di Magliano (Rogel Cancer Center and Department of Cell and Developmental Biology, University of Michigan, Ann Arbor, Michigan), Felix Picard (Institute for Medical Microbiology and Hospital Hygiene, Philipps University Marburg, Marburg, Germany), Maximilian Reichert (Medical Clinic and Policlinic II, Klinikum rechts der Isar, Technical University Munich, Munich, Germany), Dieter Saur (Division of Translational Cancer Research, German Cancer Research Center (DKFZ) and German Cancer Consortium (DKTK), Heidelberg, Germany; Chair of Translational Cancer Research and Institute for Experimental Cancer Therapy, Klinikum rechts der Isar, School of Medicine, Technische Universität München, München, Germany; Center for Translational Cancer Research (TranslaTUM), School of Medicine, Technical University of Munich, Munich, Germany), Roland Schmid (Medical Clinic and Policlinic II, Klinikum rechts der Isar, Technical University Munich, Munich, Germany), Susanne Sebens (Institute for Experimental Cancer Research, Kiel University and University Medical Center Schleswig-Holstein, Kiel, Germany), Shiv K. Singh (Department of Gastroenterology, Gastrointestinal Oncology and Endocrinology, University Medical Center Göttingen, Göttingen, Germany), Jens Siveke (Bridge Institute of Experimental Tumor Therapy, West German Cancer Center, University Medicine Essen, Essen, Germany; Division of Solid Tumor Translational Oncology, German Cancer Research Center and German Cancer Consortium, partner site Essen, Heidelberg, Germany), and Andreas Trumpp (Heidelberg Institute for Stem Cell Technology and Experimental Medicine GmbH, Heidelberg, Germany; and Department of Stem Cells and Cancer, German Cancer Research Center).

Conflicts of interest

This author discloses the following: Nelson Dusetti has a pending patent entitled “Simple Transcriptomic Signatures to Determine Chemosensitivity for Pancreatic Ductal Adenocarcinoma.” The remaining authors declare no conflicts.

Funding

The work was supported by Deutsche Forschungsgemeinschaft: CRU/KFO5002, CRC/SFB1321 (Project-ID 329628492), and CRU/KFO325.