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January 2017

# Histo Highlights

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## TransAtlantic Biomarker Laboratory Builds

In April, our non-laboratory personnel begin migrating 1 km away to our spacious and beautiful 4-story building. The laboratory teams begin their transition in May. We will send out updates and information. Our goal is to ensure continuous operations throughout this move. Each laboratory section is implementing a post-move platform qualification program and HistoGeneX is working closely with each vendor to ensure integrity of the instrumentation and reagents. Please do not hesitate to contact your Project Manager for further details.



Meanwhile in the US, we have hosted several client audits and have begun clinical testing, including a PMA IHC study. Our histotechnologists and pathologists have been trained and we have 3 onsite project managers. The laboratory is well-prepared to support companion diagnostic studies including reproducibility studies for 510k device or PMA trials. We have also begun implementing molecular extraction (DNA & RNA) and real-time PCR procedures.



We would love for you to visit. Please [contact us](#) to schedule for either location.

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## HistoGeneX Scientific Press

### Highs, Lows of Immune Checkpoint Inhibitors

Dr. Mark Kockx spoke at CAP16 in September regarding the level of inflammation in the tumor microenvironment and its role in



regulating immunosuppression. A portion of his talk is featured in the December 2016 issue of CAP Today. Please [click here](#) for a PDF version of the full article.



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NATURE MEDICINE | ARTICLE

日本語要約

## Vessel co-option mediates resistance to anti-angiogenic therapy in liver metastases

Sophia Frentzas, Eve Simoneau, Victoria L Bridgeman, Peter B Vermeulen, Shane Foo, Eleftherios Kostaras, Mark R Nathan, Andrew Wotherspoon, Zu-hua Gao, Yu Shi, Gert Van den Eynden, Frances Daley, Clare Peckitt, Xianming Tan, Ayat Salman, Anthoula Lazaris, Patrycja Gazinska, Tracy J Berg, Zak Eitahir, Laila Ritsma, Jacco van Rheenen, Alla Khashper, Gina Brown, Hanna Nyström, Malin Sund *et al.*

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Nature Medicine 22, 1294–1302 (2016) | doi:10.1038/nm.4197  
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## Vessel Co-Option: A Novel Therapeutic Target in Metastatic Colorectal Carcinoma

Our pathologist, Dr. Peter Vermeulen, recently described a non-angiogenic, vessel co-option phenomena in a Nature Medicine article, where tumors utilize existing vasculature of the normal organ instead of angiogenesis. This article provides examples with liver metastases of colorectal cancer and offers a histopathologic and mechanistic rationale why angiogenic inhibitors such as bevacizumab may not be effective in tumors where the co-option mechanism dominates. *The co-option pattern also appears to be associated with poor prognoses and correlates with the absence of infiltrating lymphocytes.*

The co-option mechanism can be detected with routine H&E and potentially offers significant hypothesis-driven investigative studies. We are able to provide this assessment for exploratory studies or in the clinical trial setting.

For more information, read the paper [here](#), download a PDF [here](#), or contact us at [info@histogenex.com](mailto:info@histogenex.com).



## Digital pathology in immuno-oncology – a roadmap for clinical development

Christopher Ung, Mark Kockx & Yannick Waumans

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HistoGeneX Global Laboratories announces its publication “Digital Pathology in Immuno-Oncology – A Roadmap for Clinical Development.” This timely manuscript describes validation methodologies that can be used for oncology clinical development, specifically immunotherapies. Digital pathology offers enticing features, not the least of which is an enhanced microscope platform for viewing, collaboration, and distribution. In addition, there are a broad milieu of downstream applications for analyzing the resultant high-resolution whole slide image. The combination is especially relevant given the renewed emphasis of assessing the tumor microenvironment (TME) when developing immune-oncology therapeutics. The paper discusses the varied pressures - such as cost, workflow, initial set up logistics, and regulatory factors - that constrain the use of a technology that seems so obviously suited for the anatomic pathology laboratory. The second part of the manuscript reviews the available validation guidelines from the FDA and CAP which primarily addresses manufacturers and clinical laboratories respectively but do not provide guidance for clinical developers. Both guidelines take on different approaches: the FDA unpacks the digital pathology system into components while CAP focuses on what emerges from the “black box.” A hybridized model – merging elements of both validation approaches – is presented to the clinical development reader. Finally, the manuscript reviews a series of analysis applications, in particular, the ones that extract valuable data from the TME, and introduces the concept of a laboratory developed digital application (LDDA) that leverages the familiarity of a LDT.

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## Spotlight on our Science

Interested in our scientific and laboratory research happenings? Download [Histo Notes](#) to read about our evaluations of novel platforms, affects of pre-analytical conditions on testing, or biomarker validations.

## Histo Notes: Leica Bond Rx System: Automating High Complexity ISH and Fluorescent Assays

Biomarkers such as DNA, RNA, and protein are powerful tools for understanding basic cellular functions, diagnosing clinical diseases, and identifying optimal therapies. Fluorescent in situ hybridization (FISH), immunofluorescence (IF), and RNA in situ hybridization are widely used imaging technologies that share the unique capacity to analyze a marker at the single cell level while preserving the morphology.

We recently acquired the Leica Bond RX system, an open automated staining system giving the freedom to choose dispense sequences, incubation times, and temperature settings to customized staining protocols. Fully automated single and duplex IF staining were tested and delivered a high level of precision and consistency.

HistoNote:  
January 2017

## Our first look at the Leica Bond Rx system

Automating High Complexity ISH and  
Fluorescent Assays

[Click here to view this and other Histo Notes.](#)

## Immuno-Oncology Biomarkers & More

Our assay development team actively validates new IHC biomarkers for clinical development use, especially those for immuno-oncology. Some recent ones include TIGIT, TIM3, and LAG3. Visit our [website](#) for an updated list or review our [IHC assay development process](#).

Have biomarker questions? Drop us a note if you have questions about biomarkers from our [validated menu](#) or our [biomarker pipeline](#).

## Biomarker portfolio @ HistoGeneX

validated
pipeline

ALK	Ang-2	AR	Aurora A	β7-H3	Bcl-2	Bcl-2:IGH	Bcl-6 <sup>new!</sup>	β-catenin	BRCA
BRAF	CA IX	cCK18	CD1a	CD3	CD3/FoxP3	CD4	CD7	CD8	CD8/Ki67
CD10 <sup>new!</sup>	CD16	CD20	CD31	CD34	CD38	CD45	CD45RO	CD56	CD68
CD79b	CD117	CD138	CD163	CEA	cMET	cMYC	COX IV	cPAP	cyclin D1
EBER	E-cadherin	EGFR	ER	FRCC1	FGFR1	FGFR2	FoxP3	GATA-3	Her2
Her3	HLA-DR	HPV	ICOS	IDO	IGF1R	IRF1	Ki67	KRAS	LAG-3 <sup>new!</sup>
Mdm-2	MGMT	MHC-I <sup>new!</sup>	MLH1 <sup>new!</sup>	MSI	Mum-1 <sup>new!</sup>	NRP-1	NRAS	OX40	p16
p21	p27	p4EBP1	p53	panCK	PD-1 <sup>new!</sup>	PD-L1 (SP142)	PD-L1 (E1L3N)	PD-L1 (22C3)	PD-L1 <sup>new!</sup> (28-8)
PGP9.5	Phospho-Akt	Phospho-EGFR	Phospho-ERK	Phospho-MEK	Phospho-mTOR	Phospho-p90RSK	Phospho-PRAS40	Phospho-S6	Phospho-STAT3
Phospho-Tau	PIK3CA	PMS2 <sup>new!</sup>	PR	PTEN	STING	Tim-3	TRAF1	TUNEL	UBE2C
UroVysion <sup>new!</sup>	VEGF-A	VEGF-R1	VEGF-R2	Vimentin	Vista				

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