

New Studies Presented at DDW Demonstrate Clinical Utility of Cellvizio® GI in Diagnosing Colorectal Cancer and Barrett's Esophagus

- Cellvizio GI Enables Immediate Diagnosis Of Colorectal Lesions with Malignant Potential and Distinguishes Them from Nonneoplastic Polyps with High Accuracy Level -

SAN DIEGO – May 19, 2008 – Mauna Kea Technologies, a leader in *in vivo* cellular imaging, today announced that leading international gastroenterologists presented data from four clinical studies on Cellvizio® GI at the Digestive Disease Week® (DDW) 2008 conference in San Diego. The reported data demonstrate Cellvizio GI's value in diagnosing colorectal cancer as well as other gastrointestinal diseases. A fundamentally new endoscopic imaging approach, Cellvizio could improve patient care by eliminating unnecessary biopsies and could further improve diagnostic rates across a broad range of diseases.

"This new evidence should lead to broader use of Cellvizio GI in the clinic as an essential tool for improving the diagnosis of a broad range of gastrointestinal diseases," said Sacha Loiseau, Ph.D., president and CEO of Mauna Kea Technologies. "The studies also highlight the technology's compatibility with other gastrointestinal diagnostic tools and its potential for improving the detection rate of gastrointestinal cancers."

Cellvizio and Colorectal Cancer

In a late-breaking oral presentation, Anna Buchner, M.D., Mayo Clinic, Jacksonville, FL, U.S.A., discussed the results of a 26-patient study assessing Cellvizio GI's applicability for diagnosing benign and malignant lesions in colorectal polyps during colonoscopy screening. The trial found that the technology predicted the presence of premalignant, advanced colorectal lesions and malignant lesions with a high accuracy of 86.5% (CI 75.5-97.5%), sensitivity of 82.6% (CI 68.9-86.7%), and specificity of 92.9% (CI 70.3-99.6%).

Cellvizio and Ulcerative Colitis

A poster presentation (S1169) on an ongoing study of ulcerative colitis patients by Pr. Frank J van den Broek, Academic Medical Center; Amsterdam, Netherlands, concluded that Cellvizio makes it feasible to recognize histological features *in vivo* and may eliminate the need for random biopsies and unnecessary biopsies from lesions without tumors. Nine patients and a total of 57 colonic areas have so far been examined. After inspection with the Cellvizio GI, normal colonic tissue was found in 33 specimens; inflammation in 11 specimens; hyperplasia changes in 9; and intraepithelial tumors in 4.

Cellvizio and Barrett's Esophagus

A poster presentation (S1392) on a study by Heiko Pohl, M.D., VA Medical Center, White River Junction, VT, U.S.A, concluded that Cellvizio GI is highly effective at identifying which Barrett's esophagus patients do not have advanced growth of precancerous cells in their esophagus. The 38-patient study compared Cellvizio GI's ability to accurately diagnose the degree of pre-cancerous tissue in patients with Barrett's esophagus compared to histology results of biopsies taken from the same areas. Cellvizio evaluation by two independent examiners to detect advanced neoplasia was accurate in 88% to 93%, and showed a sensitivity and specificity between 75% and 80%, and 89% and 94%, respectively, translating at best into a low positive predictive value of 44.4% and a high negative predictive value of 98.8%.

A poster presentation (M1316) by Rami J. Badreddine, Mayo Clinic, U.S.A., described the results of a study of 62 patients with a history of Barrett's esophagus with high-grade dysplasia or early adenocarcinoma. Results showed that in patients with flat normal appearing mucosa, Cellvizio GI guided EMR detected high-grade in a significantly higher number of patients compared to just surveillance biopsies (55% vs. 23%, $p < 0.03$). The detection rate of high-grade dysplasia or cancer Cellvizio GI targeted EMR in flat normal appearing mucosa was similar to that found in nodular mucosa (55% vs. 61%, $p < 0.75$).



Cellvizio is the first and only confocal microscopy system that is compatible with most endoscopes and allows physicians to view live tissue inside the body at the cellular level in dynamic, real-time images at 12 frames per second. Over 1,000 Cellvizio procedures have been completed to date. It has 510(k) clearance from the Food & Drug Administration and the European CE-Mark for use in the gastrointestinal and pulmonary tracts.

About Digestive Disease Week 2008

DDW is the largest international gathering of physicians, researchers and academics in the fields of gastroenterology, hepatology, endoscopy and gastrointestinal surgery. Jointly sponsored by the American Association for the Study of Liver Diseases, the American Gastroenterological Association (AGA) Institute, the American Society for Gastrointestinal Endoscopy and the Society for Surgery of the Alimentary Tract, DDW takes place May 17-22, 2008, at the San Diego Convention Center, San Diego, CA. The meeting showcases approximately 5,000 abstracts and hundreds of lectures on the latest advances in GI research, medicine and technology. For more information, visit www.ddw.org.

About Mauna Kea Technologies:

Mauna Kea Technologies leads the growing in vivo cellular imaging market enabling physicians to visualize, diagnose and treat pathologies that can not be seen using other imaging techniques. Mauna Kea Technologies' flagship Cellvizio system provides microscopic visualization of mucosal tissue and promises to improve clinical outcomes by increasing the diagnostic yield of existing endoscopic procedures. With over 1,000 Cellvizio procedures completed to date, Mauna Kea Technologies is currently focused on the gastroenterology and pulmonology markets. The company plans to expand into other markets in the future. The company also has a distribution agreement with Leica Microsystems to sell products for the Small Animal Imaging market in Europe, the U.S. and Japan. For more information about Mauna Kea Technologies: www.maunakeatech.com

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ABSTRACTS

(Embargo lifts during the time of the presentation)

Late Breaking Abstract

Title: "High Resolution Confocal Endomicroscopy Probe System (CFM) for in vivo Diagnosis of Colorectal Neoplasia: a Prospective Study"

Authors: Anna M. Buchner, Marwan Ghabril, Murlu Krishna, Herbert Wolfsen, Michael Wallace

Background:

The recently developed high resolution miniprobe-based confocal endomicroscopy system (CFM) may allow immediate diagnosis of gastrointestinal premalignant and malignant lesions based on imaging of surface

colonic epithelium *in vivo* during endoscopy. This CFM system's innovation includes compatibility of the miniprobe with any commercial endoscope and allows as-needed use.

Aims:

To assess the clinical applicability of the new CFM system and to develop and validate the *in vivo* CFM grading system for diagnosing neoplasia in colorectal polyps found during routine screening/surveillance colonoscopy.

Methods:

- Twenty-six patients underwent routine colonoscopy exam at Mayo Clinic, Jacksonville with the use of the Fujinon Intelligent Color Enhancement (FICE) system for evaluation of colorectal lesions. Kudo pit pattern of all these lesions was determined using virtual chromoendoscopy with the FICE system. Once the polyp was identified, the high definition confocal endomicroscopy (Minio probe, Mauna Kea Technologies, Paris, France) probe was passed through the accessory channel of the scope with intravenous administration of 4-5ml of fluorescein sodium. The confocal images were recorded before proceeding to the removal of the lesions.
- The set of confocal images of all identified polyps was divided into a testing set and validation set. The testing set included images of 10 hyperplastic and 10 adenomatous lesions from six patients. These were score by two endoscopists (AMB, MBW) unblinded to the histological results. The images were graded according to their pit pattern architecture (using the Kudo classification) and nuclear characteristics. The validation set included confocal images of 37 colorectal lesions from 25 patients that were evaluated in a blinded fashion without knowledge of their gold standard histologic diagnosis or the endoscopic appearance. Each polyp was classified as normal or neoplastic based on the combined confocal imaging grades.
- The sensitivity, specificity and accuracy of the overall CFM classification and individual histologic criteria for diagnosing neoplasia were calculated, with the respective 95% confidence intervals.

Results:

The presence of neoplastic changes (pre-malignant, advanced colorectal lesions and malignant lesions) was predicted by confocal endomicroscopy probe system (CFM) with a high accuracy of 86.5% (CI 75.5-97.5%), sensitivity of 82.6% (CI 68.9-86.7%), and specificity of 92.9% (CI 70.3-99.6%).

Table 1 lists specific graded characteristics with their corresponding estimates of sensitivities, specificities and accuracy in distinguishing between malignant and nonmalignant lesions *in vivo*.

<u>Characteristics</u>	<i>Sensitivity estimates with CI</i>	<i>Specificity estimates with CI</i>	<i>Accuracy estimates with CI</i>
Confocal pit pattern: round and stellate vs. villiform	87.0 % (73.5-91.1%)	92.8% (70.7-99.6%)	89.2% (79.2-99.2%)
Confocal Nuclear number: normal vs. increased	73.9% (60.1-86.2%)	50% (27.4-70.2%)	64.9% (49.5-80.3%)
Confocal Nuclear Morphology round vs. oval and	69.6% (55.1-76.7%)	85.7% (61.9-97.4%)	75.7% (61.9-89.5%)

irregular			
Endoscopic pit pattern (FICE) Round/ stellate vs.villiform and irregular	73.9% (59.3-83%)	78.6% (54.5-93.6%)	75.7% (61.9-89.5%)

Conclusion:

The high resolution miniprobe-based confocal endomicroscopy system (CFM) allows high quality epithelial imaging of colorectal lesions during standard colonoscopies, enabling immediate diagnosis of colorectal lesions with malignant potential and distinguishing it from nonneoplastic (hyperplastic) polyps with a high level of accuracy. Use of this method has the potential to avoid polypectomy of non-neoplastic polyps.

Research support was provided by the ASGE Foundation. No equipment or financial support was provide by the manufacturer.

Poster: S1169

EMBARGOED UNTIL SUNDAY, MAY 18, 2008 / 8:00 A.M. PACIFIC TIME

Title: Miniprobe Based Confocal Fluorescence Microscopy Is Feasible for Recognition of Histological Features in-Vivo for the Prediction of Final Histopathology in Patients with Longstanding Ulcerative Colitis

Authors: Frank J van den Broek¹, Susanne van Eeden², Paul Fockens¹, Evelien Dekker¹ 1. Department of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, Netherlands, 2. Department of Pathology, Academic Medical Center, Amsterdam, Netherlands

Background: Neoplasia in longstanding ulcerative colitis (UC) is difficult to visualize during colonoscopy, forcing the endoscopist to take random biopsies. Furthermore, a variety of non-neoplastic abnormalities may be found in UC, leading to unnecessary additional targeted, biopsies. Confocal fluorescence microscopy (CFM) provides in-vivo histology for differentiation of neoplastic and non-neoplastic tissue; and might therefore eliminate the need for random biopsies and reduce the number of unnecessary biopsies as well. **Aim:** To assess the feasibility of a newly developed probe-based CFM system (Cellvizio®-GI, MiniO-probe, Mauna Kea Techn., Paris, France) for surveillance of patients with UC; and to assess histological features of neoplasia and non-neoplastic mucosa in-vivo. **Methods:** In this ongoing study, consecutive patients with UC undergo colonoscopy, during which detected abnormalities and additional random areas are inspected by CFM. Intravenous fluorescein is administered for tissue contrast. CFM-videos are evaluated afterwards to describe histological features in-vivo which are compared to final histopathology. **Results:** So far, 9 patients with UC have been examined. A total of 57 colonic areas were inspected by CFM; corresponding histopathology revealed normal colonic tissue in 33, inflammation in 11, hyperplastic changes in 9 and intraepithelial neoplasia in 4. In normal colonic tissue, CFM demonstrated a regular distribution of round crypts surrounded by radiate lined dark goblet cells and grey enterocytes. The lamina propria with associated blood vessels was enlightened by fluorescein. Inflammation caused tubular change and irregular distribution of crypts, although goblet cells and enterocytes were still easily distinguished; the lamina propria contained numerous blood vessels and round inflammatory cells. Hyperplastic changes were represented by stellate or tubular shaped crypts with rather regular distribution; the epithelium became relatively crowded but goblet cells were readily recognized. Neoplastic mucosa was associated with heavily crowded dark epithelium lacking discrimination of goblet cells and enterocytes; furthermore, the lamina propria with associated blood vessels collapsed. **Conclusion:** In this ongoing study of patients with UC, we

demonstrated that probe based CFM is feasible for recognition of histological features in-vivo. These CFM features will prospectively be evaluated for prediction of final histopathology. In future, the use of CFM might therefore eliminate the need for random biopsies and unnecessary biopsies from non-neoplastic lesions.

Poster: S1392

EMBARGOED UNTIL SUNDAY, MAY 18, 2008 / 8:00 A.M. PACIFIC TIME

Title: Accuracy of Miniprobe Confocal Laser Microscopy for the Detection of Barrett Neoplasia

Authors: Heiko Pohl^{1,2}, Thomas Roesch², Michael Vieth⁵, Martin Koch³, Valentin Becker⁴, Ahmed C Khalifa², Alexander Meining⁴ 1. Gastroenterology, VAMC White River Junction, White River Junction, VT, USA, 2. Gastroenterology, Charite University Hospitals, Virchow, Berlin, Germany, 3. Pathology, Charite University Hospitals, Mitte, Berlin, Germany, 4. Gastroenterology, Klinikum rechts der Isar, Munich, Germany, 5. Pathology, Klinikum Bayreuth, Bayreuth, Germany

Background: Improvement of surveillance examinations of Barrett's esophagus may include improved detection of high-grade intraepithelial neoplasia (HGIN) or early carcinoma in macroscopically normal appearing mucosa. Miniprobe confocal laser microscopy (CLM) may have the potential to perform in-vivo microscopy and to aid in the detection of advanced Barrett neoplasia. Objective: To define miniprobe CLM criteria for HGIN and early esophageal adenocarcinoma and applying these criteria to evaluate the diagnostic yield of in vivo microscopic detection of HGIN or carcinoma Barrett patients. Method: We enrolled consecutive Barrett patients seen at two medical centers. 30 seconds CLM videos were recorded from pre-marked areas using Argon beamer coagulation spots after intravenous application of 5-10 ml 1% fluorescein. Biopsies were taken from the same area to allow precise comparison with histology. Recordings from the first 15 examined patients (95 areas) were obtained to define miniprobe CLM criteria of HGIN or carcinoma and used for training purposes. All CLM recordings of all subsequent patients were randomized and blindly evaluated by two gastroenterologists. Primary endpoints were accuracy, sensitivity, specificity in the detection of HGIN or carcinoma, and interobserver agreement. Results: We evaluated 296 biopsy sites from 38 patients (mean age 62.1 years, 89.5% men). The median Barrett length was 3cm. Carcinoma or HGIN was detected in 6.4% of biopsies. At blinded randomized evaluation, all initially defined miniprobe CLM criteria were detected significantly more frequently in advanced Barrett neoplasia as compared to no or low grade neoplasia. CLM evaluation by two independent examiners to detect advanced neoplasia was accurate in 88% to 93%, and showed a sensitivity and specificity between 75% and 80%, and 89% and 94%, respectively, translating at best into a low positive predictive value of 44.4% and a high negative predictive value of 98.8%. There was good interobserver agreement (kappa 0.6). **Conclusion:** In this pilot trial investigator-blinded evaluation of miniprobe CLM shows a high specificity and negative predictive value for the detection of advanced neoplasia in a representative cohort of Barrett patients.

Poster: M1316

EMBARGOED UNTIL MONDAY, MAY 19, 2008 / 8:00 A.M. PACIFIC TIME

Title: Confocal Laser Microscopy (Clm) Guided Endoscopic Mucosal Resection in Barrett's Esophagus with High Grade Dysplasia

Authors: Rami J Badreddine, Kenneth K Wang, Ganapathy A Prasad, Louis-Michel Wong Kee Song, Wytke Westra, Navtej Buttar, Lynn S Borkenhagen, Kelly T Dunagan, Lori S Lutzke Barrett's Esophagus Unit, Mayo Clinic, Rochester, MN, USA

Aims: EMR is an excellent diagnostic and therapeutic tool for high grade dysplasia in Barrett's esophagus. Unfortunately, dysplasia is often endoscopically occult and finding the correct area for EMR can be difficult. CLM of flat mucosa allows rapid identification of dysplastic tissue.

Our aim was to study a miniprobe CLM targeted EMR in the detection dysplasia in patients with BE undergoing surveillance. Methods: A prospective cohort of 62 patients with a history of Barrett's esophagus and either high grade dysplasia or early adenocarcinoma was studied. All patients underwent a standard protocol assessment with EGD and 4 quadrant biopsies every centimeter. Patients had CLM using an S-type miniprobe placed through the working channel of the endoscope (MaunaKea Technology, Paris, France). The probe operated at a wavelength of 488 nm, a maximal field of view of 600x500 μm , a depth of 50 μm and a frame rate of 12 frames/s. 2.5-5 ml solution of 10% Fluorescein was intravenously administered 3-5 minutes prior to taking confocal images. Imaging of the Barrett's segment was performed and assessed for dysplasia during endoscopy by an experienced endoscopist familiar with the technique (KKW). EMR was performed on all visible mucosal lesions and on flat mucosa in areas of dysplasia identified by CLM. Dysplasia was characterized by irregular appearing glands on CLM. Results: 62 patients were studied. 56 were males (90%). Median age was 70 (41-86), median BE segment length was 3 cm (0.5-14). 40 patients had EMR: 18 based on endoscopically visible abnormal mucosal lesions and 22 based on dysplasia in flat mucosa by CLM. In flat mucosa, CLM guided EMR vs surveillance biopsies respectively showed: LGD in 6 vs 12 patients (27% vs 54%, $p < 0.12$), HGD in 12 vs 5 patients (55% vs 23%, $p < 0.03$) and no dysplasia in 4 vs 5 patients (18% vs 23%, $p < 0.70$). One patient had cancer in the irregular mucosa group. In patients with flat normal appearing mucosa CLM guided EMR detected HGD in a significantly higher number of patients compared to just surveillance biopsies (55% vs 23%, $p < 0.03$). The sensitivity for CLM for dysplasia was 94% with a specificity of 50% based on EMR. The detection rate of HGD/CA by CLM targeted EMR in flat normal appearing mucosa was similar to that found in nodular mucosa (55% vs 61%, $p < 0.75$).

Conclusion: Miniprobe CLM targeted EMR significantly increases the detection rate of dysplasia in high risk BE patients in a surveillance program. CLM appears to be a useful tool especially in identifying areas of dysplasia in flat Barrett's mucosa.