LABEL-FREE DIGITAL PATHOLOGY

Learn how mid-infrared QCL microscopy is accelerating cancer research without the use of labels or stains.

DRS DAYLIGHT SOLUTIONS

VISUALIZE CHEMISTRY WITHOUT STAINS OR LABELS

The ability to classify cancer and other diseases without the use of stains is possible with a mid-infrared (MIR), laser-based microscope. The Spero® microscope, whose name originates from the Latin derivative of hope, is a breakthrough in label-free or stain-free chemical imaging. The new platform was conceived of and brought to practice with the purpose of making molecular-based cancer diagnoses automated, routine and non-subjective. Previous commercially available infrared imaging instruments could take days or weeks to analyze a single specimen. However, the Spero microscope is able to image a full slide in minutes by leveraging advanced optics in combination with a newly developed technology known as a quantum cascade laser (QCL). The Spero microscope has the potential to greatly increase productivity of the pathology work-flow while reducing the direct and indirect costs of, often toxic, chemical reagents. This new imaging technology allows pathologists and researchers to "see" disease in an entirely new way and discover biomarkers based on the sample's native chemistry. This type of automated chemical image analysis can support pathologists in their current work-flow by providing a fast, quantitative and objective second opinion for challenging, time-sensitive diagnostic situations.

Non-Destructive

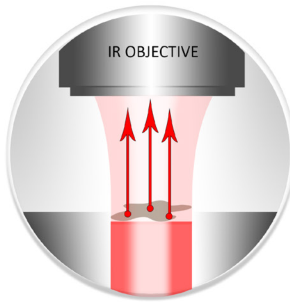
Simplified Workflow

Quantitative Data

HOW IT WORKS

MOLECULAR INFORMATION IS NOW AVAILABLE AT THE CLICK OF A BUTTON

Unstained, biopsied tissue is fixed to slide.



The tissue specimen is imaged using a tunable MIR quantum cascade laser.

An image of the tissue specimen is collected at as many as 450 different MIR wavelengths to produce a 3D hyperspectral data structure called an image cube.

The resulting image cube is then analyzed by a computer to produce a digitally stained image which can be easily evaluated by clinicians or researchers.

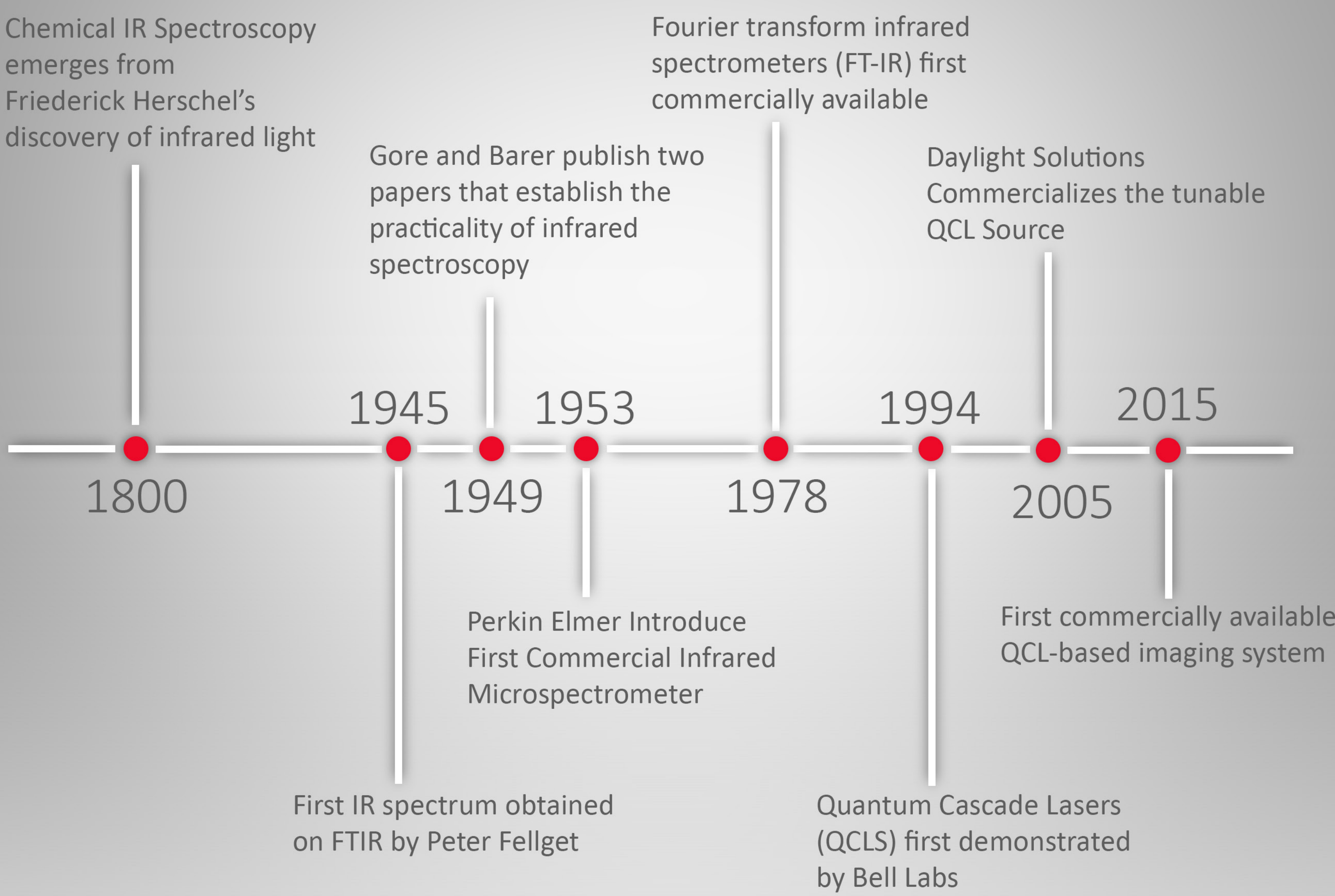
MIR digital imaging recently experienced a greater than 100-fold increase in throughput enabling single large-tissue specimens to be analyzed in minutes rather than days. This enhancement was made possible through the advent of new MIR quantum cascade laser (QCL) sources employed in a novel wide-field illumination mode.

The MIR spectral region, roughly spanning 3,000 to 12,000 nm, is rich in organic molecular information which can be analyzed to perform quantitative digital tissue classification, identify and track disease progression, and study the tumor microenvironment.

NEXT GENERATION TECHNOLOGY ROOTED IN DECADES OF RESEARCH

The Spero® IR imaging system is a next-generation approach to unbiased, high-speed tissue classification. While the system is novel, the technique benefits from a rich history of research in vibrational spectroscopy.

A BRIEF HISTORY OF IR SPECTROSCOPY



‘94

Quantum Cascade Lasers (QCLs) First Demonstrated

The Quantum Cascade Laser (QCL) serves as the engine to our spectroscopy instruments. The high-brightness of light enables our high-definition imaging at video rate speeds.

‘05

Daylight Solutions Commercializes the Tunable QCL Source

Since 2005, Daylight has specialized in manufacturing QCL sources to serve applications in defense, scurity, scientific research, and life sciences.

‘15

First commercially available QCL-based MIR imaging system

Since 2015, the Spero microscope has been used by researchers in over 10 countries to develop novel biomarkers in a wide range of tissues types including colon, lung, bladder, brain, liver, breast and prostate.

FROM THE EXPERTS

PIONEERS IN IR IMAGING

LEADING RESEARCHERS AND INDUSTRY EXPERTS
SHARE THE IMPORTANCE OF LABEL-FREE IMAGING IN THEIR LAB

THE RESEARCHER

PROF. KLAUS GERWERT
RUHR UNIVERSITY BOCHUM

Klaus Gerwert studied physics in Muenster and graduated in biophysical chemistry in Freiburg. After positions at the Max Planck Institute, Dortmund, and the Scripps Research Institute in La Jolla, USA, he became university professor and chair of the biophysics department at Ruhr-University-Bochum in 1993. He was Director at the Max-Planck-Partner Institute in Shanghai, China, from 2008 to 2013 and was Fellow of the Max-Planck Society till 2017. Gerwert actively promotes the development and application of vibrational spectroscopy in protein-research and diagnostics in over 200 publications. He also holds several patents and has been awarded several prizes.

In 2010, he founded the European "Protein Research Unit Ruhr within Europe" (PURE). In PURE, internationally renowned protein and clinical researchers pool their resources in the search of label-free techniques for the early detection of diseases such as cancer or Alzheimer's. Klaus Gerwert is the also founding director of ProDi, a federal/state-financed research center for molecular protein diagnostics.

THE CEO

CLAIRE WESTON, PHD
REVEAL BIO

Claire is an accomplished and dedicated scientific leader with a track record of success in cancer research. She was awarded a PhD from Cambridge University in the UK and has lead teams and projects focused on cancer biomarkers in both large pharma and start-up environments. Claire co-founded Reveal Biosciences in 2012 and has grown the company to bring quantitative pathology analysis to preclinical research, clinical trials, and diagnostics. She has authored numerous peer-reviewed publications in leading journals including Science and is a member of multiple professional organizations.

THE DATA SCIENTIST

CASEY LARIS

REVEAL BIO

Casey leads the machine learning development of AI-based diagnostics at Reveal. He is a world leader in high-throughput biological computer vision and has been at the forefront of analyzing big data sets from automated microscopy in pathology. Casey developed patented high-throughput microscopy technology at UCSD and productized it in a venture-backed start-up that was later acquired by Beckman-Coulter. There he was Global Product Manager for high content microscopy, reagents and software, leading both the world-wide roll-out and follow-on clinical ready instrumentation development. Casey helped further develop these computer vision tools at Sanford-Burnham Medical Research Institute with commercialization by Biovia. Casey leads the applications and engineering team at Vala Sciences to create several novel automated high throughput microscope based systems. Casey holds a BS from UC San Diego.

THE PATHOLOGY SCIENTIST

PROF. MICHAEL WALSH

UNIVERSITY OF ILLINOIS, CHICAGO

Michael started his PhD studies at Lancaster University in the UK in 2008, where his research was focused on developing infrared spectroscopic techniques towards identifying gastrointestinal stem cells, monitoring biochemical changes in cell lines, and identifying the premalignant grades of cervical cancer. After completing his PhD, he moved to the Bhargava lab at the University of Illinois at Urbana-Champaign, where he was the Carle-Foundation Hospital Beckman Institute fellow and where he shifted his research focus to high-definition infrared cancer tissue imaging. In 2013, he became an Assistant Professor at the University of Illinois at Chicago where he started his own research group, the Spectral Pathology Lab, which is focused on integrating novel infrared based technologies with pathology practice.

Michael's lab is focused on developing novel, label-free methodologies towards improving disease detection and predicting disease outcome. They are focused on identifying areas where current pathology techniques are limited and aim to give additional important information to the clinician and patient about their tissue biopsies.

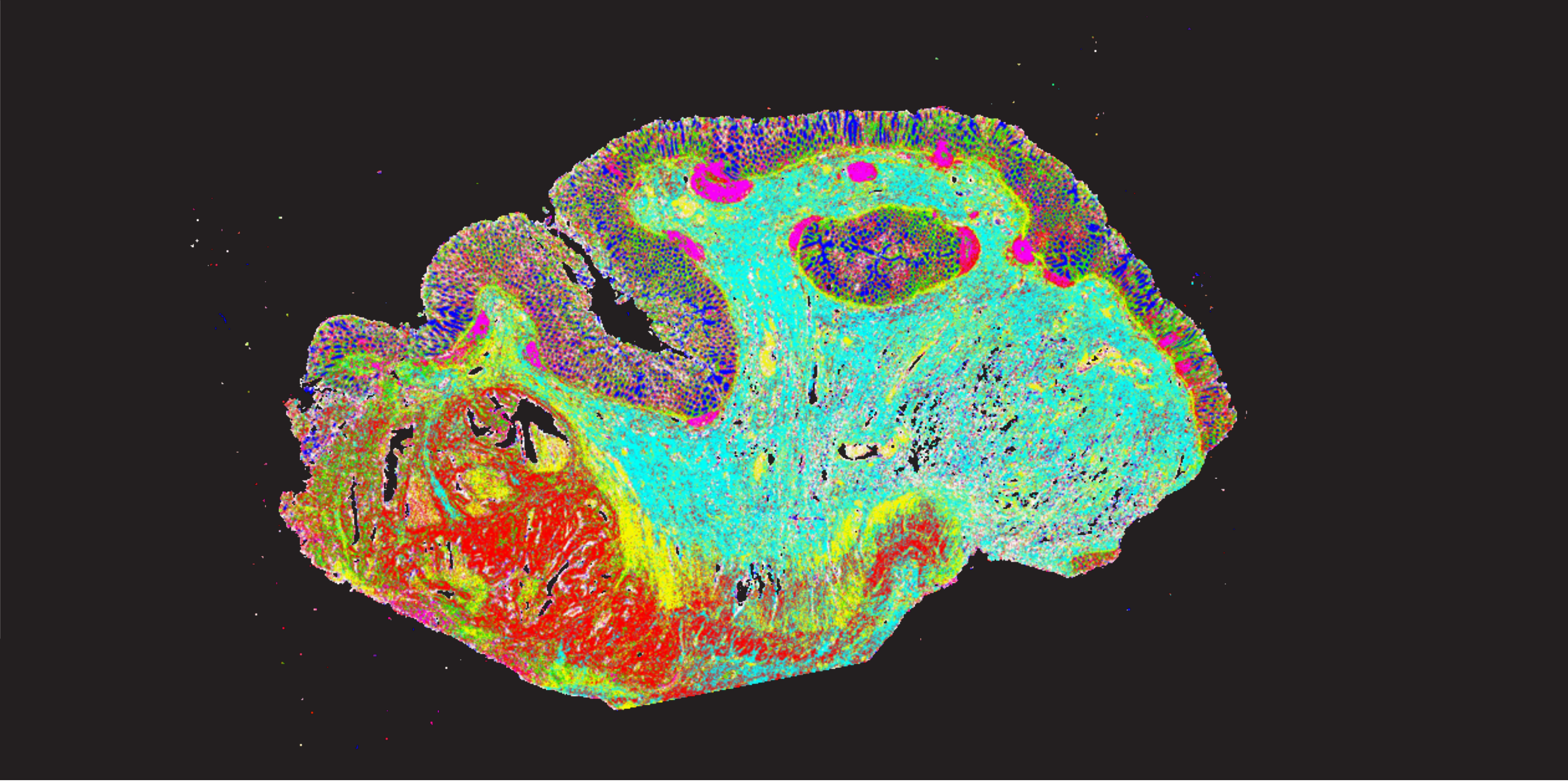
LABEL-FREE DIGITAL PATHOLOGY FOR DIAGNOSIS AND BIOMARKER RESEARCH

FREDERIK GROSSERÜSCHKAMP & KLAUS GERWERT
RUHR UNIVERSITY BOCHUM, BOCHUM GERMANY

LABEL-FREE DIGITAL PATHOLOGY BY IR IMAGING ALLOWS OBSERVER INDEPENDENT CLASSIFICATION OF TISSUE THIN SECTIONS

The gold standard today for cancer diagnosis in the clinic is the visual inspection of H&E labelled tissue thin sections by a pathologist. The presented "label-free digital pathology" approach uses spatially resolved measured infrared spectra as fingerprints for the biochemical status. The spectra are labelled automatically observer-independent by bioinformatics. In addition to H&E staining, immunohistochemical (IHC) stains are used in which specific molecules act as biomarkers for disease. Proper evaluation depends on reliable, reproducible staining and the pathologist's expertise. We established a technique that is both label-free and inter/intra-observer-independent approach for classification of tissue thin sections by infrared (IR) imaging. In this new approach, referred to as "label-free digital pathology," the unstained tissue is imaged with an infrared microscope and the "IR image" of the tissue is classified bioinformatically. The resulting index color images represent the tissue classification including cancer type, subtypes, all tissue types, inflammation status, and even the tumor grading. (Kallenbach-Thieltges et al. 2013; Kuepper et al. 2016) This can be resolved without labeling and without inter-/intra-observer variability. Exemplarily, we established a label-free classification of thoracic tumors and their subtypes with a sensitivity of 91% and a specificity of 97% compared to histological annotation. The differential diagnosis of the subtypes of adenocarcinoma of the lung was achieved with an accuracy of 96%.(Großerueschkamp et al. 2015)

The main hindrance for clinical use is the slowness and low usability of current IR imaging systems. In order to reduce the measuring time instead of a globar in FTIR imaging a quantum cascade laser (QCL) based IR microscope, Spero-QT® (DRS Daylight Solutions, San Diego, CA, USA) is used. In a pioneering study, we show for the first time that the QCL-based IR imaging classifies exemplarily colorectal cancer as reliably as the established FTIR imaging, but about 180 times faster. Colorectal cancer is one of the most common tumor diseases and has high survival



rates in early stages. We studied 100 samples with UICC Stage II and III colorectal cancer tissue and 20 tumor-free tissue samples of 110 randomly chosen patients older than 18 years. The developed workflow enabled the tissue classification for diagnosis in about 30 min for large thin sections, while smaller regions of interest can be analyzed within a few minutes only. Sensitivity of 96% and specificity of 100% as compared to classical histopathology validated the method. The tissue allows very precise tissue classification in a short time frame including the tumor environment, e.g. inflammatory cells. As control, the measurements were carried out using two Spero IR imaging systems, and several users performed the analyses; this did not affect the accuracy at all. In future studies, we intend to incorporate the method into clinical workflow. The automated image analysis should support a pathologist in the daily routine and provide a second opinion in challenging diagnostic situations. Furthermore, it could support surgeons in determining resection borders within the operation theater.

Besides its application in cancer diagnostics, the spectral data from the Spero-QT was combined with omics techniques to provide both spatial and molecular resolution. After label-free tissue classification, the spatially resolved tumor region can be cut out with laser microdissection and the sample can be subsequently analyzed by different omics techniques. We recently showed these exemplary for subtypes of diffuse malignant pleural mesotheliomas which were subsequently analyzed with proteomics. (Großerueschkamp et al. 2017) Mesothelioma tumors are mainly caused by asbestos. This combines label-free spatial resolution with a molecular resolving method. Thus, the differently expressed proteins in the two subtypes can be identified. A detailed bioinformatic analysis then selects the biomarker candidates from the larger number of identified proteins. In this approach, all biomarkers of clinical immunohistochemistry used today for mesotheliomas could already be identified on a small number of test persons. Thereby this approach is validated.

The newly developed approach, label-free digital pathology, will pave the way for precise diagnostics and more specific biomarkers that can be used in precision medicine.

AI MEETS IR

CASEY LARIS & CLAIRE WESTON

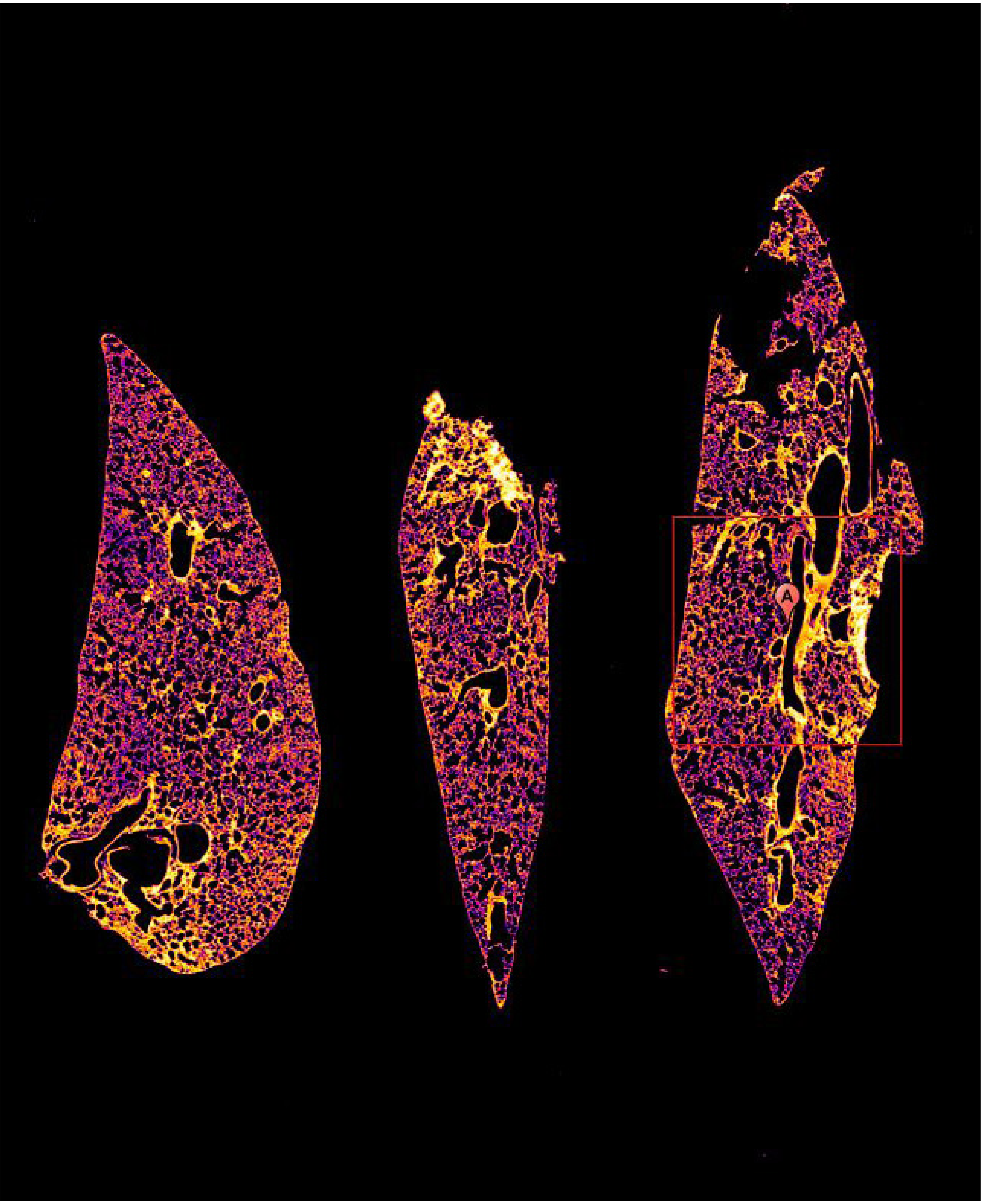
LABEL-FREE TISSUE ANALYSIS USING INFRARED MICROSCOPY IS ACCELERATED BY ARTIFICIAL INTELLIGENCE

A Novel Class of Label-free Tissue Diagnostics

Mid infrared (IR) microscopy is a well-established technique in spectroscopy and life sciences; however, until recently sample throughput and interpreting the large amount of data generated have been prohibitive in translating this technology into routine clinical use. New technological advancements in mid-IR microscopy help solve this problem by allowing high resolution whole slide images to be generated from unstained tissue sections in minutes. This technique does not require tissue stains, antibodies, or probes, allowing rapid data generation from formalin-fixed paraffin embedded (FFPE) or frozen tissue, ultimately changing the fundamental workflow of tissue analysis. A computational pathology company from San Diego, CA is leading the application of AI in tissue-based analysis by applying artificial intelligence (AI) to these large datasets to create a novel class of clinical diagnostics.

IR Joins the Big Data Revolution in Biology

Biology is facing a big data revolution. Recent advances in computer power and machine learning have enabled data processing that is several orders of magnitude faster than was possible only a few years ago. For example, a modern workstation leveraging the latest GPU hardware can calculate in one minute what would theoretically take 2 weeks on a similar best in class workstation of 2010. This sea change in computing power has huge future implications for many fields of healthcare including pathology. The hyperspectral tissue data generated from mid-IR microscopy combined with patient information is a perfect match for AI technology. Together, this approach has the potential to generate a novel class of label-free tissue diagnostics, ultimately accelerating the laboratory workflow and generating personalized data to benefit patients.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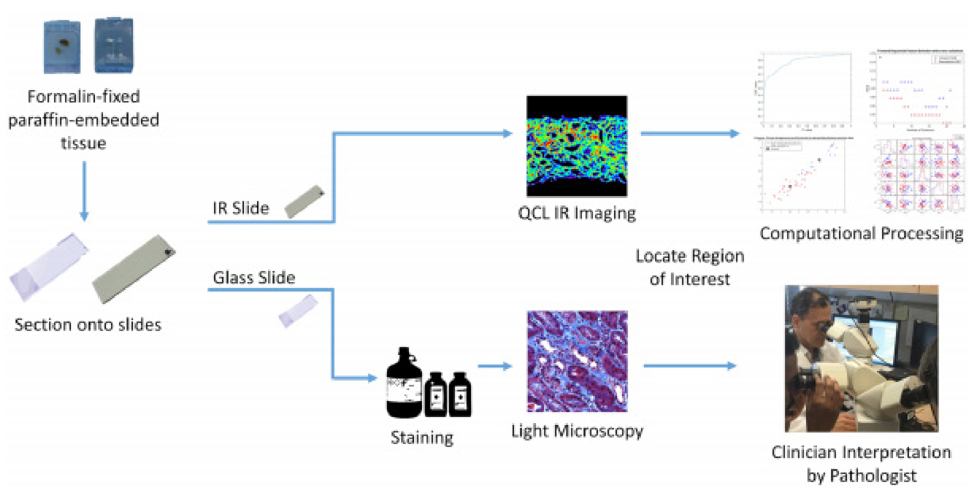
BIOMARKER IDENTIFICATION FOR TISSUE FIBROSIS

MICHAEL WALSH

QUANTITATIVE, LABEL-FREE IMAGING OF FIBROTIC TISSUE IS MADE EASY USING THE SPERO MICROSCOPE

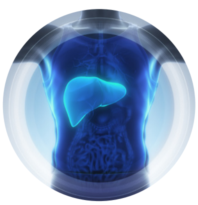
Infrared (IR) spectroscopic imaging allows for rapidly acquiring label-free biochemical information from tissue sections. IR imaging allows for mapping of multiple biochemical components such as proteins, lipids, DNA, carbohydrates and glycosylation across tissues. This derived biochemical information can be harnessed for automated cell-type, disease-type classification or to identify novel biomarkers predicting organ outcome. IR imaging is potentially very useful in examining tissues with fibrotic diseases. Fibrosis is a common pathological entity that can occur in a wide range of organs typically as a result of insult to the tissue. Traditional Fourier Transform Infrared (FT-IR)spectroscopic imaging is slow and creates large data sets which limits it's clinical feasibility. Recent advances in Quantum Cascade Lasers (QCL) implemented in an imaging microscope is potentially a key advance in making this technology feasible in a clinical setting. We applied wide-field QCL imaging to liver, lung, and kidney tissues to examine fibrosis. Here we will show that wide-field QCL-imaging can rapidly visualize the extent of fibrosis in multiple organs. In addition, using a mouse model of pulmonary fibrosis coupled with wide-field QCL-imaging can detect biochemical changes associated with both progression and remission of fibrosis. Finally, we have demonstrated that regions of fibrosis hold prognostic biochemical information that can predict whether a transplanted kidney will develop progressive fibrosis. IR imaging is a potentially powerful adjunct to current pathology practice, with the ability to visualize fibrosis in tissues and extract novel biomarkers that can predict the progression of fibrosis.



LOOKING FORWARD

MANY APPLICATIONS IN PATHOLOGY BENEFIT FROM LABEL-FREE INFRARED IMAGING

BIOMARKER DISCOVERY. The Spero microscope enables direct observation of the intrinsic biochemical information of the sample. This enables researchers to look for intrinsic markers in the tissue that can be indicative of type and stage of disease.



FIBROSIS & LIVER DISEASE. The Spero microscope is particularly well-suited for analyzing fibrotic tissue and can do so at video rates.

ROUTINE SCREENING. The work load continues to stretch the capacity of pathology labs around the world. The Spero microscope could be used to automate much of the routine cancer screening.

INTRA-OPERATIVE SURGICAL PATHOLOGY. Researchers have shown the ability to render accurate tumor margin analysis and cancer sub-typing of fresh frozen sections in minutes using the Spero microscope.

PRECLINICAL STUDIES. Spero has been used to quantitatively evaluate the effectiveness of candidate drugs on primary tumor sites while also assessing the impact of the candidate drug on vulnerable organs such as the liver.

ABOUT US

In 2005, three high-tech entrepreneurs founded DRS Daylight Solutions in San Diego, California, with the goal of developing breakthrough technologies and products around the company's core technology: mid-IR quantum cascade lasers (QCLs). Since then, the company has introduced groundbreaking instrumentation including the world's first MIR (mid-infrared), laser-based microscope, the Spero-QT®, for label-free chemical imaging. By coupling the quantitative data of the microscope with machine learning, automated tissue classification is finally possible without the use of stains or labels.

LET'S TALK

DRS Daylight Solutions is interested in partnering with other industry experts, digital pathology companies, and research institutions that share our vision in making meaningful breakthroughs in the biomedical sciences.

DRS Daylight Solutions
www.daylightsolutions.com
email: sci-sales@daylightsolutions.com | phone: 858.432.7500
16465 Via Esprillo | San Diego, CA 92127