The iKnife: Translational metabolic phenotyping for precision surgery

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Introduction: Overview

- Why do we need precision surgery? And what is it?
- Why can’t we sequence our way out of poor cancer outcomes?
- What is a phenome?
- What is ambient mass spectrometry?
- DESI imaging – Why is it relevant to surgery?
- REIMS – how does it work?
- Current overview of work:
  - Ovarian
  - Breast
  - Colorectal
  - Microbiology in chronic disease
- Future vision – Supersystem surgery
Surgical Oncology: History

The surgical oncologist
- Diagnosis and prognosis
- Staging (molecular staging)
- Cure: Local control, resection of LNs and isolated metastases
- Palliation and debulking
- Prevention
- Assess response to therapy
- Maintain function and quality of life

Evolution in minimally invasive oncological surgery

- The maintenance of form and function
- The preservation of quality of life
Not all units created equally: Systems failure

Advances in colorectal surgery
Mr. James Kinross
Clinical lecturer in Surgery: Imperial College London
j.kinross@imperial.ac.uk
@bowel surgeon

Radical resection or organ preservation?
Precision oncology: Genomics

Precision oncology: Molecular phenotyping

Stratified Surgery: Stratified therapy

“At present no robust markers of prediction of pCR have been identified and the topic remains an area for future research.”


Precision Medicine

“Coupling established clinical–pathological indexes with state-of-the-art molecular profiling to create diagnostic, prognostic, and therapeutic strategies precisely tailored to each patient's requirements”.
What is a Phenome?

Analytical

An integrated set of measurable physical and clinical features coupled to chemical, metabolic and physiological properties that define biological sub-classes

Philosophical

The direct product of gene-environment (exposome) interactions on an individual or group operating throughout development and life - a dynamic property
Precision = Systems Surgery

Precision Surgery: The patient journey

SCALABLE AND TRANSLATABLE MODELS:
CANCER CHEMOTHERAPY
CARDIOVASCULAR
NEUROENDOCRINE DISEASE
RARE DISEASES
GUT SURGERY, SURGICAL ONCOLOGY
CRITICAL CARE
LIVER DISEASES
RENAL TRANSPLANTATION
Ambient Mass Spectrometry: Theory

The concept of Ambient MS

- Generally makes sense for solid samples
- Ambient MS methods ≈ Atmospheric pressure desorption ionization methods

Ambient MS methods  Non-AMS methods
Desorption Electrospray Ionization (DESI)

Nitrogen nebulizing gas
Spray capillary
Primary charged droplets
Analyte on surface
Surface
Outer capillary
Secondary charged droplets
Excess liquid on surface
MS atmospheric inlet

Advantages of Ambient MS Profiling

- Low \( H_{\text{desorption}} \)
- Ionic character

Ambient MS

>95% lipidome
15% metabolome in a few seconds
Chemical interpretation is relatively simple

Integration of various methods at the level of well-defined chemical species
(e.g. DESI-REIMS-LC/MS)
Mass Spectrometric Imaging (MSI)

Analytical beam

Slide courtesy of Andreas Römpp, JLU, Gießen

Rapid DESI with new sprayer

Emrys Jones

Waters Xevo G2-XS Q-TOF OmniSpray source
30 scans per second
100µm x 100µm pixel

Total time 23 minutes
Analysis time 6 minutes

16 µm tissue section

Approx: 10 x 20 mm
DESI Imaging - Characteristics

- Resolution 20 – 500 μm
- Adjustable
- Non destructive analysis
- Multiple consecutive DESI analysis is possible
- Staining after imaging
- Good co-registration

Analysis: univariate
Ion intensity distributions

- Ion intensity distribution ~ Species concentration distribution
- 500 – 5000 species in a single experiment!

Example: Lipid metabolism of ovarian cancer

[Diagram showing lipid metabolism pathways with box plots for different lipid species in tumour, tumour associated stroma, and healthy stroma.]
Lipid metabolism in cancer

Analysis: Multivariate
Multivariate Analysis of Mass Spectrometry Imaging Datasets

Robust raw mass spec signal pre-processing

Co-registration of optical and MS images

Biomarker recovery via multivariate statistical analysis

Database
- Colorectal adenocarcinoma
- Colorectal muscle
- Colorectal mucosa

Extraction of tissue specific discriminating vectors

Tissue reconstructions via multivariate ion patterns

Biomarker recovery via multivariate statistical analysis

Co-registration of optical and MS images

Precise Image Co-registration

Non Aligned Optical Image

Total Ion MS Image
Identification of histology - Statistical analysis (PLS)

**cross validation: 98.2% accuracy**

<table>
<thead>
<tr>
<th>Target Class</th>
<th>Adipose Tissue</th>
<th>Connective Tissue</th>
<th>Glandular Tissue</th>
<th>Tumor Tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adipose Tissue</td>
<td>98.3%</td>
<td>0.0%</td>
<td>0.7%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Connective Tissue</td>
<td>1.6%</td>
<td>97.8%</td>
<td>0.4%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Glandular Tissue</td>
<td>1.7%</td>
<td>5.5%</td>
<td>94.8%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Tumor Tissue</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Highly accurate reconstruction of different tissue types based on molecular ion patterns extracted *via* supervised machine learning

Optical image of colorectal tissue types

RGB image of multivariate ion patterns of 3 tissue types

Multivariate ion patterns for adenocarcinoma

Adjacent mucosa

Muscle
1H NMR – Colorectal cancer

Virtual Immunohistochemistry

Anti-cytokeratin AE1/AE3 stain

In-silico Visualization of tumour tissue using DESI data
3D DESI-MS hyperspectral imaging: Tumor heterogeneity using statistical biomarker mapping

Statistical segmentation:
- tumor
- normal

51 biopsy slices in m/z range [600, 950] ppm
290,000 spectra and 2,500 metabolites
= 725 million metabolic parameters dispersed in 3D

Heterogeneity of liver tumour molecular phenotypes

8 metabolic phenotypic sub-classes (Veselkov et al.)
Heterogeneity of tumor molecular phenotypes

The iKnife: REIMS
Phosphatic acids (PA)

Phosphatidylethanolamines (PE)

Phosphatidylserines (PS)

Phosphatidylinositols (PI)

Phosphatidylglycerols (PG)

REIMS Tissue Data

Human healthy liver, in-vivo

Human liver metastatic tumor, in-vivo
Data Analysis – Scheme

I. Database building

1. Acquiring spectra

2. Histological validation

3. Histologically validated database

II. Creating PCA + LDA models in the database

III. Real-time classification

Systematic data collection
The Concept of Profiling - Practice

Method capable of the parallel determination of thousands of system parameters

- Highly reproducible

Construction of authentic database

- Identification of elements by accepted, alternative method
- Statistically relevant numbers

Identification of unknowns by similarity to database elements

- Similarity scores
- Multivariate statistical models

Initial Results

<table>
<thead>
<tr>
<th>Organ</th>
<th>Tumor type</th>
<th>Number of patients</th>
<th>Number classified</th>
<th>Correct classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric</td>
<td>Adenocarcinoma</td>
<td>37</td>
<td>37</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Mucinous</td>
<td>14</td>
<td>14</td>
<td>100%</td>
</tr>
<tr>
<td>Large intestine/colon</td>
<td>Adenocarcinoma</td>
<td>85</td>
<td>85</td>
<td>98.24%</td>
</tr>
<tr>
<td>Large intestine/rectum, border</td>
<td>Adenocarcinoma</td>
<td>72</td>
<td>72</td>
<td>100%</td>
</tr>
<tr>
<td>Liver</td>
<td>HCC</td>
<td>14</td>
<td>14</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Metastasis</td>
<td>38</td>
<td>38</td>
<td>100%</td>
</tr>
<tr>
<td>Lungs</td>
<td>Adenocarcinoma</td>
<td>52</td>
<td>52</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>SCC</td>
<td>16</td>
<td>16</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>9</td>
<td>6</td>
<td>76.67%</td>
</tr>
<tr>
<td>Breast</td>
<td>Lobular</td>
<td>23</td>
<td>18</td>
<td>100%</td>
</tr>
<tr>
<td>Brain</td>
<td>Mixed</td>
<td>43</td>
<td>23</td>
<td>100%</td>
</tr>
</tbody>
</table>

Overall 525 interventions, tumor was identified in 417 cases, 2 misclassifications (other type of cancer)
DESI and REIMS are complimentary

Ovarian
DESI-MSI: Identification of Different Ovarian Tissue Types

Histological Image

PCA analysis

MMC components

DESI - Histological classification of unknown samples

Predicted image

Cross Validation

Serous carcinoma
Serous carcinoma associated stroma
Normal stroma from ovary
background
DESI - Tumour classification

**PCA**

### Cross Validation

<table>
<thead>
<tr>
<th>Actual Class</th>
<th>Predicted Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serous</td>
<td>80.3%</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>15.1%</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>4.6%</td>
</tr>
<tr>
<td>Normal</td>
<td>0.0%</td>
</tr>
<tr>
<td>Borderline</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

n= 91

**REIMS (iKnife) – Ovarian raw data**

546 sampling points (cuts) – average 3.7 cuts per sample

Species within fatty acid, phospholipid and triglyceride range

Phospholipid (600-900 m/z) spectra yielded unique fingerprints

Spectra average of all serous adenocarcinoma

Spectra average of all normal ovary samples
REIMS (iKnife) – Ovarian cancer vs normal

Normal Ovary versus Ovarian Cancer
Principal component analysis (unsupervised)

Normal Ovary versus Ovarian Cancer
Linear discriminant analysis (supervised)

LOOCV multivariable analysis:
N=189, 100% specificity, 100% sensitivity

Ovarian cancer tumour content 100% in analysed samples

REIMS (iKnife) – Ovarian tissue types

Ovarian Cancer versus Normal Gynaecological Tissue
Linear discriminant analysis (supervised)

Ovarian Cancer versus Borderline tumours
Linear discriminant analysis (supervised)

Normal, Benign, Borderline tissue
Linear discriminant analysis (supervised)

LOOCV multivariable analysis:
N= 291, 100% specificity, 100% sensitivity
Correct tissue classification 92.7%
DESI: Depth of information in breast cancer

Tumour grade

<table>
<thead>
<tr>
<th>Component #1</th>
<th>Component #2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade II</td>
<td>Grade III</td>
</tr>
<tr>
<td>HER2 status</td>
<td>HER2 status</td>
</tr>
<tr>
<td>Grade II</td>
<td>Grade III</td>
</tr>
<tr>
<td>HER2 +</td>
<td>HER2 -</td>
</tr>
</tbody>
</table>

AUC=0.97

AUC=0.98

Tumour pixels only
DESI Diagnostic value in breast cancer

**Tumour grade**

- AUC = 0.97

**ER status**

- AUC = 0.97

**Tumour type**

- AUC = 0.82

---

**DESI Breast TISSUE Phenotyping status – HER2**

- **Adipose Tissue**
  - N = 216 from 10 patients
  - Total accuracy: 98.1%
  - Predicted class:
    - HER2 +: 97.0%, HER2 -: 3.0%
    - HER2 +: 1.3%, HER2 -: 98.7%

- **Connective Tissue**
  - N = 127 from 10 patients
  - Total accuracy: 99.2%
  - Predicted class:
    - HER2 +: 100.0%, HER2 -: 0.0%
    - HER2 +: 1.0%, HER2 -: 99.0%

- **Tumor Tissue**
  - N = 15 from 3 patients
  - Total accuracy: 100%
  - Predicted class:
    - HER2 +: 100.0%, HER2 -: 0.0%
    - HER2 +: 0.0%, HER2 -: 100.0%
DESI - Breast Cancer Tumour heterogeneity

1. Supervised segmentation
2. Unsupervised segmentation of the tumour

Clonal populations?

REIMS: Typical Breast Spectra (600-1000m/z)

PHOSPHOLIPIDS

TRIGLYCERIDES

Fibroadenoma

Invasive ductal carcinoma

Normal breast
REIMS Margin test – Normal through Tumour

There is no spectrum to recognize.

REIMS Intra-Operative Method
Phospholipids identified in both REIMS MS/MS and DESI-MS

Green = more abundant in Normal in DESI
Yellow = more abundant in Tumour in DESI

<table>
<thead>
<tr>
<th>671.47</th>
<th>673.48</th>
<th>699.5</th>
<th>713.51</th>
<th>714.51</th>
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</thead>
<tbody>
<tr>
<td>716.52</td>
<td>735.47</td>
<td>742.54</td>
<td>744.55</td>
<td>747.51</td>
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<tr>
<td>766.54</td>
<td>768.55</td>
<td>770.57</td>
<td>772.58</td>
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</tbody>
</table>

Summary

- MS optimised for rapid analysis of heterogeneous breast tissue
- High accuracy for identification of ex-vivo breast tissue
- Intra-operative spectra obtained throughout entire operation

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frozen Section</td>
<td>65-78%</td>
<td>98-100%</td>
</tr>
<tr>
<td>Touch imprint cytology</td>
<td>70-80%</td>
<td>85-100%</td>
</tr>
<tr>
<td>Digital Specimen X-ray</td>
<td>54%</td>
<td>87%</td>
</tr>
<tr>
<td>iKnife (REIMS)</td>
<td>92%</td>
<td>96%</td>
</tr>
</tbody>
</table>
Results: DESI-MSI shows cancer harbors topographically discrete regions of lipids that are diagnostic of CRC
REIMS: Diagnostic accuracy

Linear Discriminant (LDA) scores plot

Results: Lipid Chemistry

<table>
<thead>
<tr>
<th>m/z</th>
<th>Putative Molecular structure</th>
<th>P value</th>
<th>Cancer</th>
<th>Adenoma</th>
<th>Normal</th>
</tr>
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<tbody>
<tr>
<td>633.465PA(31:0)</td>
<td>0.0001</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>886.565PS (44:6)</td>
<td>1.11E-16</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>886.565PS(44:6)</td>
<td>1.11E-16</td>
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<tr>
<td>886.75PS(41:0)</td>
<td>1.38E-12</td>
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<td></td>
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<td></td>
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<tr>
<td>702.625Cer(D18:0/H24:0)</td>
<td>2.28E-11</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>775.545PG(36:1)</td>
<td>0.0001</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>673.485PA(34:0)</td>
<td>3.33E-16</td>
<td></td>
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<tr>
<td>642.495GlcCer(30:1)</td>
<td>2.47E-12</td>
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<tr>
<td>880.665PS (43:4)</td>
<td>1.86E-07</td>
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<tr>
<td>699.505PA</td>
<td>1.12E-07</td>
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<tr>
<td>710.485PE(34:4)</td>
<td>6.73E-08</td>
<td></td>
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<td></td>
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<tr>
<td>718.615Cer(T18:0/24:0(2OH))</td>
<td>9.30E-10</td>
<td></td>
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<tr>
<td>653.4951,2-DG(36:3)</td>
<td>0.0002</td>
<td></td>
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<tr>
<td>797.535PG(38:4)</td>
<td>0.04</td>
<td></td>
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<tr>
<td>864.675Plasmalogen</td>
<td>0.0004</td>
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<tr>
<td>891.725TG (54:0)</td>
<td>1.63E-08</td>
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</table>

Metabolites were over expressed (red) or under expressed (green) in specific histological states of cancer, adenoma or normal associated mucosa.
### Results: Rectal Cancer Lipidomic Phenotypes

![Images of lipidomic analysis graphs](image)

### Results: Summary accuracy

<table>
<thead>
<tr>
<th>Diagnostic markers</th>
<th>Spectra n</th>
<th>Accuracy</th>
<th>True Positive</th>
<th>True Negative</th>
<th>False Positive</th>
<th>False Negative</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>220</td>
<td>90.5%</td>
<td>86.7%</td>
<td>92.4%</td>
<td>13.3%</td>
<td>7.6%</td>
<td>0.96</td>
</tr>
<tr>
<td>Cancer vs. NAM</td>
<td>89</td>
<td>94.4%</td>
<td>78.6%</td>
<td>97.3%</td>
<td>2.7%</td>
<td>21.4%</td>
<td>0.99</td>
</tr>
<tr>
<td>Cancer vs. Adenoma</td>
<td>159</td>
<td>97.0%</td>
<td>85.7%</td>
<td>98.6%</td>
<td>1.4%</td>
<td>88.6%</td>
<td>0.99</td>
</tr>
<tr>
<td>Histological subtype (Mucinous vs. Adenocarcinoma)</td>
<td>75</td>
<td>90%</td>
<td>94.2%</td>
<td>83.3%</td>
<td>16.7%</td>
<td>5.8%</td>
<td>0.96</td>
</tr>
<tr>
<td>Prognostic performance – whole model</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumour differentiation (Mod vs. poor)</td>
<td>163</td>
<td>83.1%</td>
<td>66.3%</td>
<td>87.3%</td>
<td>12.7%</td>
<td>31.7%</td>
<td>0.88</td>
</tr>
<tr>
<td>Tumour budding</td>
<td>234</td>
<td>78.2%</td>
<td>80.6%</td>
<td>74.4%</td>
<td>35.6%</td>
<td>19.4%</td>
<td>0.87</td>
</tr>
<tr>
<td>LVI</td>
<td>234</td>
<td>73.9%</td>
<td>71.6%</td>
<td>75.3%</td>
<td>24.7%</td>
<td>28.4%</td>
<td>0.83</td>
</tr>
<tr>
<td>EMVI</td>
<td>234</td>
<td>73.5%</td>
<td>68.3%</td>
<td>72.7%</td>
<td>22.8%</td>
<td>34.7%</td>
<td>0.81</td>
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<tr>
<td>+ve Nodes</td>
<td>234</td>
<td>77.4%</td>
<td>69.0%</td>
<td>81.0%</td>
<td>19.0%</td>
<td>31.0%</td>
<td>0.81</td>
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<tr>
<td>Rectal cancer prognostic factors</td>
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<td></td>
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<tr>
<td>Differentiation (Mod vs. poor)</td>
<td>84</td>
<td>94.4%</td>
<td>78.6%</td>
<td>98.2%</td>
<td>1.8%</td>
<td>21.4%</td>
<td>0.99</td>
</tr>
<tr>
<td>Tumour Budding</td>
<td>84</td>
<td>84.0%</td>
<td>88.1%</td>
<td>70.6%</td>
<td>29.4%</td>
<td>11.9%</td>
<td>0.82</td>
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<tr>
<td>LVI</td>
<td>84</td>
<td>71.4%</td>
<td>72.4%</td>
<td>30.8%</td>
<td>69.2%</td>
<td>27.6%</td>
<td>0.75</td>
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<tr>
<td>EMVI</td>
<td>84</td>
<td>96.4%</td>
<td>85.7%</td>
<td>98.6%</td>
<td>14.3%</td>
<td>1.4%</td>
<td>0.88</td>
</tr>
<tr>
<td>+ve Nodes</td>
<td>84</td>
<td>92.9%</td>
<td>83.3%</td>
<td>94.4%</td>
<td>5.6%</td>
<td>16.7%</td>
<td>0.92</td>
</tr>
<tr>
<td>LCRT vs. None</td>
<td>75</td>
<td>96%</td>
<td>96.7%</td>
<td>96.2%</td>
<td>3.8%</td>
<td>4.3%</td>
<td>0.99</td>
</tr>
<tr>
<td>dPR vs. NAM</td>
<td>52</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>0%</td>
<td>0%</td>
<td>1</td>
</tr>
</tbody>
</table>
iEndoscope: Chemically enhanced endoscopy

Real-time MS during endoscopic resection
iEndoscope (REIMS) Safety signal – submucosal cutting

- Incidence of bowel perforation is ~ 1-3% in electrosurgical polypectomy  – major complication
- On-line REIMS monitoring can give warning signal when smooth muscle layer is dissected

In-vivo REIMS endoscopy
Identification of Bacteria using Rapid Evaporative Ionisation Mass Spectrometry (REIMS)

1. Sampling
2. Ionisation
3. Analysis
Identification of Bacteria using Rapid Evaporative Ionisation Mass Spectrometry (REIMS)

Real time functional analysis of microbial signalling

REIMS spectrum indicating five QSM: Heptylquinoline-4(1H)-one, Heptyl-3-hydroxy-4(1H)-quinolone (PQS), Hydroxynonylquinoline, Hydroxynonynonylquinoline and Hydroxyundecenylquinoline identified from P. aeruginosa isolates.
Automated REIMS microbiology

REIMS-DESI-MSI integration

- Compiling large-scale database of bacterial spectral patterns
  - Dataset comprising 1264 bacterial strains (228 used in DESI-microscopy), cultured under various conditions.

- Extracting taxon-specific markers
  - ANOVA test followed by Tukey’s HSD test performed on different bacterial strains. Identification of markers with specificity on taxon level.

- Histologically assigned DESI imaging dataset
  - Dataset consisting of 60 human colorectal tissue samples (20 nonmalign, 30 healing from 10 different patients. Results of sequencing-based community analysis available.

- Generating single ion images for markers determined to be of bacterial origin
  - Generation of single ion images including predicted tissue outlines. Bacterial distribution to be non-identical with tissue distribution.
LCFAs coalesce with markers of Proteobacteria in the discrete regions of tumour

Clinical applications? iENDOSCOPE!!

- 3s response time
- 98.3% agreement with H. pylori urease test
- 94.6% agreement with histology

- 600-900 m/z negative ion mode
- 0.1 bin
- Linear discriminant analysis
Summary: Chemically augmented precision surgery

- Ambient spectroscopy flexible and highly amenable to challenging clinical environments.
- Precision ‘surgery’ means the right operation at the right time in the right person with the BEST outcome.
- REIMS and DESI are highly complimentary
- REIMS optimised for rapid analysis of heterogenous tissue
- Lipidome analysis robust and repeatable – NOT A BLACK BOX
- REIMS also provides phenotypic data on tumours.
- REIMS can AUGMENT current and future surgical and imaging technologies
- Analytical tool for studying cancer lipidome

REIMS: Multiple clinical functions

Adjuvant treatment

96%

cPR
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