Advanced tissue imaging & AI data analysis: the opportunities and challenge for application in supporting drug discovery

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Agenda

1. Challenges in developing new medicines
2. Advanced imaging technologies for efficacy and safety assessment
3. Image data analysis: challenges and opportunities
Expanding our drug modalities
Expanding our drug modalities

- Small Molecule
- PROTAC
- Antisense oligonucleotide
- Modified RNA
- Immunostimulatory oligonucleotide
- Oligonucleotide conjugate
- Bicyclic peptide
- Anticalin® protein
- Therapeutic protein
- Cell therapy
- CRISPR
Focus on quality not quantity
Emerging sample sources
Patient derived models (PDX, CDX, Organoids)

Emerging data themes
Multi-omics
Microbiome
Spatial transcriptomics

Asking more from every sample

Understanding biological complexity and complex safety endpoints
Convergence

Imaging is context that changes information into knowledge
Convergence

Molecular imaging

Medical imaging

Big data and AI
Convergence

Molecular imaging

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Molecular imaging

Medical imaging

Big data and AI

Artificial Intelligence
A computerized system that exhibits behavior that is commonly thought of as requiring HUMAN intelligence

Machine Learning
Development of statistically based programs that tries to derive rules or procedures with a given dataset that explains the data or can predict future data. Manual feature extraction

Deep Learning "The NEW AI"
A newer subfield of ML which uses Neural Networks and complex datasets and networks with automated feature extraction

- Random forest
- Support vector machines
- Neural networks

- Big data
- GPU / cloud computing
- Open source code

Adapted from NVIDIA
Molecular imaging and integrated data analysis

Spatial imaging

Multiplexed imaging

Multimodal analysis

Holistic understanding of drug delivery
Advanced imaging already impacting projects

In vivo imaging
- MRI
- PET

Multiplexed subcellular phenotyping
Whole section molecular imaging
Whole slide imaging and digital pathology
H&E, mIF RNAscope

Advanced imagine science
- Delivering more from every sample
- Greater understanding every patient and recapitulation and translation with preclinical models
- Project impact from early discovery to clinical

AI-empowered imaging delivering a holistic from in vivo to subcellular resolution

Supporting safety & efficacy in unprecedented detail
Advanced imaging technologies for efficacy and safety assessment
Advanced Imaging and analysis pipeline

Acquisition | Digitization & Integration | Analysis | Exploration

Stages need to build our digital future
Mass Spec Imaging (MSI)

Set of *ex-vivo* imaging techniques providing spatial distribution of *molecular species* within *biological tissue*.

Mass spectrum generated at each position (X&Y)

Ion density maps

Fresh frozen tissue section

Ionization source
Expanded biomarker landscape

**MSI**

Label-free

Imaging Mass Cytometry (IMC)

Label-based

- $m/z$ 100,000
- $m/z$ 150,000

**Ab:**
- Ly-6G/C
- Vimentin
- B220
- CD4
- NKP46
- CD11b
- CD68
- HIF1a
- Ly6G
- MCT8
Spatial omics analysis is delivering data for understanding of disease progression, compound optimisation and for improved patient stratification and diagnosis in the clinic.

**Mapping tissue microenvironment**

- **Lipids:**
  - Fatty Acids: SFA, MUFA, PUFA
  - Phospholipids: PC, PE, PA, PI…
  - SM, Cer, GL, Sulf, CL,…
  - DAG & TAG

- **Small metabolites:**
  - Glycolysis: Pyr, Lac, Glucose
  - TCA Cycle: Cit, Mal, Asp
  - AA: Gln, Ala, Leu,…
  - Ribonucleotides: AMP, ADP, ATP
  - Bile acids: TCA, TDCA,…

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**Metabolic pathways**

- ![Metabolic pathways diagram](image)

**Cell metabolism**

- ![Cell metabolism diagram](image)

**Tissue features**

- ![Tissue features diagram](image)
**Challenge:** Complexity of molecular events in tissues goes beyond morphology and can’t be seen

**Solution:** New molecular imaging technologies add multiple dimensions to the images (mass spectrometry imaging and CyTOF)

**Impact:** We can “see” drugs, biomarkers and tissue microenvironment simultaneously.

Advanced imaging is changing the way we can understand disease and evaluate drug safety

*Greg Hamm et al*
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**A complete cartography of cancer**

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Greg Hamm et al
A complete cartography of cancer

3D MS imaging

ex & in vivo translation

CT/PET imaging*

Greg Hamm et al

*David Lewis, Beatson institute Glasgow
Understanding: Drug disposition in lung

Highly complex tissue:
1. Alveolus
2. Bronchus/bronchioles
3. Bronchioles
4. Blood vessels
5. Bronchial epithelial cells layer (BECL)
6. Mucosa and Submucosa layer (MSL)
7. Lipids droplets (LD)

Challenge of lung analysis:
- Loss of spatial information using homogenates
Understanding: Drug disposition in lung by MSI

MSI Toolbox
- Spatial Distribution
- Multiplexing Analysis
- Quantitation

To Evaluate
- Administration Route
- Chemotypes
- Formulation

Inhaled Salmeterol
PC (36:4) = Bronchiolar marker
PC (32:0) = Alveolar marker

Greg Hamm et al
@35 μm
**Biodistribution of chemotypes**

**Inhalation v IV**

Understand the impact of molecule design & properties on its regional delivery and retention in lung.

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**Table: Biodistribution Comparison**

<table>
<thead>
<tr>
<th></th>
<th>Salmeterol</th>
<th>Salbutamol</th>
<th>Fluticasone Propionate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lung Deposited Dose</strong></td>
<td>~700µg/kg</td>
<td>~500µg/kg</td>
<td>~400µg/kg</td>
</tr>
<tr>
<td><strong>Time-points</strong></td>
<td>2 &amp; 30min</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>Inhalation &amp; IV (labelled version)</td>
<td></td>
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</tbody>
</table>

Salmeterol, a LABA, and salbutamol, a SABA, for the treatment of asthma.

FP is a corticosteroid binding to glucocorticoid receptor.

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*Revealing the Regional Localization and Differential Lung Retention of Inhaled Compounds by Mass Spectrometry Imaging, J Aerosol Med Pulm Drug Deliv 2020*
Biodistribution of chemotypes Inhalation v IV

Chemotypes retention in histological regions of lung

- Salmeterol and salbutamol highlight a high bronchial affinity whereas inhaled FP shows a strong alveolar retention

These data provide important information to design optimal molecules targeting the relevant structures of the lung

CNS Biodistribution in 3D

Simultaneous visualization of cassette dosed drugs in brain

Preclinical Comparison of the Blood-brain barrier Permeability of Osimertinib with Other EGFR TKIs Clin Cancer Res. 2021

Nicole Strittmatter
Image data analysis: challenges and opportunities
Advanced Imaging and analysis pipeline

Stages need to build our digital future
Advanced Imaging and analysis pipeline

Deep Learning-Based Annotation Transfer between Molecular Imaging Modalities: An Automated Workflow for Multimodal Data Integration Analytical Chemistry 2021
Advanced Imaging and analysis pipeline

Maximizing the impact from the data we collect

Digital pathology
AI outperforms human pathologists in diagnosing metastatic cancer

<table>
<thead>
<tr>
<th></th>
<th>Error rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathologists in competition</td>
<td>3.5%</td>
</tr>
<tr>
<td>Pathologists in clinical practice</td>
<td>13 - 26%</td>
</tr>
<tr>
<td>Pathologists on micro-metastasis</td>
<td>23 - 42%</td>
</tr>
<tr>
<td>AI deep learning model</td>
<td>0.65%</td>
</tr>
</tbody>
</table>
Can AI assist clinicians to find the right patients for the right drug?

Digital pathology

Tissue biomarkers

PD-L1 IHC, urothelial carcinoma
Can AI assist clinicians to find the right patients for the right drug?

Human assessment

- Complexity: +++
- Training: years
- Time: 20min
- Error rate: 10-20%

AI-based assessment

- Complexity: +++
- Training: days
- Time: seconds
- Error rate: 0.65%
Advanced Imaging and analysis pipeline

Stages need to build our digital future
Data volume & dimensionality challenge and opportunity

Hidden data in very tissue

Pixels: 404 x 409 (165,236)
Mass channels m/z 50-1000;
Data size 87 GB
30um
MS Image

Transverse Mouse Brain
AI delivering: Data reduction, segmentation, registration, classification and fusion
AI delivering: Data reduction, segmentation, registration, classification and fusion

A complete cartography of cancer
Multiscale integration for a molecular “Rosetta Stone”

Advanced imaging offering a complete view of molecular and cellular events in any tissue
Conclusion: Advanced integrated imaging can be a molecular “Rosetta Stone” for drug discovery

**Opportunity:** New imaging methods need deep learning AI to mine the large datasets to allows us to identify the molecules driving the tissue differences

**Impact:** True phenotypic classification using our advanced imaging platforms only achieved using deep learning
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