Laboratory of Medical and Molecular oncology

Jacques De Grève MD PhD
Jacques.degreve@uzbrussel.be

Erik Teugels PhD
Sylvia De Brakeleer PhD

Bart Neyns MD, PhD

Ilse Rooman PhD
irooman@vub.ac.be
Research topics

1. Pancreatic cancer pathogenesis

2. Genotype driven cancer therapies
   – Lung cancer targeted therapies

3. Genetic cancer
   – Breast cancer

4. Dendritic cell vaccination
   – In collaboration with LMCT
Pancreatic cancer
Ilse Rooman, PhD
Pancreatic tumour development & progression

Our previous work on loss of normal epithelial cell differentiation and metaplasia in pancreas

Rooman et al Am J Pathol 2006
Rodolosse et al Biochem J 2009
Martinez-Romero J Pathol 2009
Pinho et al Gut 2011
Pinho et al Cell Cycle 2011
Rooman et al Pancreatology 2013
Wauters et al Cancer Res 2013
Pinho et al Oncotarget 2016

Sirtuin 1/ Sox 9
Current projects

existing experimental mouse models

lack of experimental human models

Project: Study early tumor development in human

**Study pancreatic acinar cell dedifferentiation as a first event that predisposes for tumor development**
- Role of prioritized transcription factors from RNAseq analysis

**Replicate multi-step tumourigenesis using primary pancreatic cells from human cadavers**
- Introduce prevalent mutations by Crispr/Cas9 genome editing in human pancreatic acinar cells
- Analyse the neoplastic potential of human pancreatic acinar cells
Current projects

- Known genes (KRAS, TP53, SMAD4) and many novel genes/pathways

Current projects

Known genes (KRAS, TP53, SMAD4) and many novel genes/pathways

Project: define novel driver genes and mechanisms

Focus on Slit ligand-Robo receptor signalling

- Role in pancreatic epithelial cell proliferation and differentiation
- Role in pancreatic tumour development and progression
- Analyse the impact of specific genomic mutations on the above
Current projects

- **normal**
  - duct
  - acinar

- **pancreatitis**
  - Metaplasia
  - KRAS mutation
  - Dysplasia

- **preneoplastic**
  - Malignant transformation

- **tumour**

---

Recognition of subtypes in pancreatic cancer


---

International Cancer Genome Consortium

---

Oncologisch Centrum

Behandeling en Onderzoek van Kanker
Current projects

Project: develop a pragmatic molecular classifier

- Develop a subtype-specific biomarker panel
- Correlation of molecular signatures and histopathological characteristics
- Correlation of cancer subtypes to normal epithelial subtypes
Lung cancer: genomic drivers
Erlotinib

Recent highlights

• HER receptors: Fielt studie
  • Multicenter genomic study in lung cancer

• Actionability of HER2
  – De Grève J et al, Lung Cancer. 2015

• Actionability of HER 3
  – PhD’s I. Umelo & A Noeparast

• Now applied in national Precision study
  – Pl. L. Decoster
Actionability of HER2

HER2 exon 20 mutation

Afatinib

First-Line Erlotinib in Patients with Advanced Non-Small Cell Lung Cancer Carrying an Activating EGFR Mutation: A Multicentre Academic Phase II Study in Belgium*

• Tumor tissue from 229 phenotypically selected patients screened for mutations

• Mutations found in screened population:
  → EGFR in 24%
  → KRAS in 16%
  → BRAF in 5%
  → HER2 in 2%
  → HER3 in 0.4%

• All mutations were mutually exclusive

Validation of HER3 mutations as therapeutic target

Translational significance

Provide basis for clinical exploration of targeted therapies in mutant HER3 NSCLCs, and in other cancers (colorectal, gastric, breast) that more frequently carry HER3 mutations

Amir Noeparast, PhD

Ijeoma Adaku Umelo, PhD
National Precision trial

- Multicohort phase 2 study

- Afatinib in HER1,2 or 3 mutations *in any cancer type*

Dr. Lore Decoster, PI
Precision Flow

Precision 1

- No actionable mutation
- Existing clinical trial matched drug
- Approved drug indication
- Actionable, but non-matched drug given

Precision 2

- Phase II with drug matched for specific mutation
- Other mutation identification source

• Initiatief van de BSMO
• Zeven universiteiten

Samenwerking Kankercentrum
First-Line Erlotinib in Patients with Advanced Non-Small Cell Lung Cancer Carrying an Activating EGFR Mutation: A Multicentre Academic Phase II Study in Belgium*

• Tumor tissue from 229 phenotypically selected patients screened for mutations

• Mutations found in screened population:
  → EGFR in 24%
  → KRAS in 16%
  → BRAF in 5%
  → HER2 in 2%
  → HER3 in 0.4%

• All mutations were mutually exclusive

In NSCLC most BRAF mutations are non-V600

- V600E: 25.00%
- D594N: 25.00%
- G469A: 16.7%
- G466V: 8.33%
- D594E: 8.33%
- G596C: 8.33%
- G469V: 8.33%
- G469A: 16.7%
Non-V600 BRAF mutations

High-kinase
Activates MEK in-vitro, independent of CRAF (Acellular)

Impaired-kinase
No MEK activation in-vitro (Acellular)
But MEK/ERK activation via CRAF in cells

Amir Noeparast, PhD

Phase II precision proposal
Dabrafenib/trametinib in NSCLC
with any BRAF mutation

Lore Decoster, MD
Current genotype driven treatments can be very successful, but ultimately fail.

- Afatinib: median 13.7 months (95% CI 11.5–13.9)
- Gemcitabine and cisplatin: median 5.6 months (5.1–6.8)
- HR 0.26 (95% CI 0.19–0.36), p<0.0001
Acquired resistance to EGFR TKI

- No identification AR mechanism: ~15–20%
- T790M alone: ~40–55%
- T790M with EGFR amplification: ~10%
- SCLC with PI3K: ~4%
- SCLC alone: ~6%
- PIK3CA: ~1–2%
- MET amplification: ~5%
- HER2 amplification: ~8–13%
- EMT: ~1–2%
- Bypass tracks: ~20%
Discovery of co-drivers

<table>
<thead>
<tr>
<th>Sample</th>
<th>Cancer consensus genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>eeFLT034_T1</td>
<td>EGFR</td>
</tr>
<tr>
<td>eFLT005_T3</td>
<td>PRDM1, TP53</td>
</tr>
<tr>
<td>eFLT006_T3</td>
<td>ATM, EGFR, JAK3, SETBP1, PBRM1, XPC</td>
</tr>
<tr>
<td>eFLT020_T1b</td>
<td></td>
</tr>
<tr>
<td>eFLT028_T1b</td>
<td>FANCA</td>
</tr>
<tr>
<td>eFLT029_T1</td>
<td>KMT2D, TCEA1</td>
</tr>
<tr>
<td>eFLT040_T1</td>
<td>BAP1, NOTCH1</td>
</tr>
<tr>
<td>eFLT041_T1</td>
<td>CDH11, ERBB2</td>
</tr>
<tr>
<td>eFLT042_T1</td>
<td>CDKN2A</td>
</tr>
<tr>
<td>eFLT044_T1</td>
<td>TP53, EGFR</td>
</tr>
</tbody>
</table>

Diether Lambrechts

Rajendra Bahadur Shahi
Innate resistance

Lito et al, nature medicine, 2013
Innate resistance

**Team**
Dr Erik Teugels  
Prof. Dr. Jacques De Grève  
Head of Department  
Medical Oncology & LMMO

**Co-worker**
Philippe Giron  
PhD Candidate  
Laboratory for Medical and Molecular Oncology (LMMO)

**Collaborators**
Prof. Dr. Gustavo J. Gutierrez  
Laboratory of Pathophysiological Cell Signaling (VUB)

Prof. Dr. Pedro Aza-Blanc  
Facility Director: Functional Genomics  
Sanford-Burnham-Presby Medical Discovery Institute (La Jolla, California, USA)
Methods WP1

• siRNA ‘synthetic lethality’ screen
  – Ubiquitin & kinase libraries
  – Afatinib (most potent EGFR inhibitor)

Afatinib ↓  siRNA ↓  combination ↓↓↓

• NSCLC cell lines
  – Primary EGFR mutation (PC-9, HCC-827)
  – Various pheno/genotypes
Work Flow
Preliminary results: 11 strong candidate co-targets identified

Negative z-score indicate strong enhanced afatinib treatment
Preliminary results

Autophagy inhibition improves Afatinib treatment in EGFR mutant NSCLC
Autophagy inhibition improves Afatinib treatment in EGFR mutant NSCLC
Other topics

• Neoadjuvant platinum based chemotherapy in TNBC
  – Multicentrische BSMO studie
  – C. Fontaine PI

• Responders (pCR, 70%) vs non-responders
  – Who benefits from more toxic chemotherapy?

• Genome sequencing en nazich HRD genen als predictieve biomarker
  – Rajendra Bahadur Shahi
  – Sylvia De Brakeleer
  – Erik Teugels
  – Brightcore
Genetic breast cancer

• Search for additional breast cancer genes: BEXB study (exome study)
  – R Shahi, S. De Brakeleer, E Teugels
  – Brightcore
  – Familiale Kankerkliniek

• Olaparib in HRD deficiënt cancers
  – National Precision study
  – PI: S. Joris
New avenues: personalized therapies

• Mutanome vaccination
  – Collaboration with K Thielemans

• First patient (BC)
  – Tumor genome sequencing
  – Somatic mutations
  – Immunogenicity
  – Dendritic cells + trimix
  – Immunun checkpoint inhibitor
Jacques De Grève MD PhD  Ilse Rooman PhD  
Jacques.degreve@uzbrussel.be  irooman@vub.ac.be

Funding

- FWO
- Stichting tegen kanker
- Kom op tegen Kanker
- IWT
- WFWG
- VUB
- Farma
- Fonds Armand Everaerts
Laboratory of Medical and Molecular Oncology