What is Molecular Pathology?

The discipline involved in diagnostic, prognostic and predictive testing on samples (usually tumor) derived from patient in the course of investigation and treatment of disease.
What Happens in a Cell?

> 20,000 genes

~37 trillion cells

~50-70 billion cell division/day

10,000’s mistakes in the DNA per day
How Tumor Comes to Stand?

What a Molecular Pathologist Studies?

How to Use It for Diagnosis?

Chordoma is rare tumour
Histology might be difficult to
differentiate from chondrosarcoma
Tumor specific markers might be helpful
Genes expressed only in one entity and
not in the other(s)
• (checking all genes if they were turned
on or not)
Brachyury (T) and Cytokeratin 19
extension was found to be specific to
chordoma
What Happens with the Genes in Chordoma?

Targeted research explaining the activity of Brachyury (T) was done:
- T was not mutated
- T was not translocated
- T was often duplicated (in more copies)
- A common SNP in the gene could make it more active

Several studies looked for recurrent mutation, translocation that can be responsible:
- No other pathognomonic mutation was found (a mutation that is in almost all the cases)
- No translocation was found
- Few recurrent mutation, deletions were associated with progression of the disease (p16)

Loss of Brachyury (T) and CK19 expression in dedifferentiated chordoma

How all Genes in Chordoma Function?

An integrated functional genomics approach identifies the regulatory network directed by brachyury (T) in chordomas

How To Use It for New Treatment?

- Switching off Brachyury (T) stops tumour cells
- Inactivation of non-key players have no effect
- Inactivation of too many players is too toxic
- For many players no tool for inactivation is existing

Cell lines are needed for research. Initiative from Chordoma Foundation
How to Use It for New Treatment?

- EGFR inhibitors identified as a potential treatment for chordoma in a focused compound screen.
  Scheipl et al (Flanagan group), J Pathology, 2016
  In 4 out of 7 cell lines reacted, no explanation for non-response in others

What Molecular Pathology Can Add?

- We have marker to help the diagnosis
  - Brachyury and CK19
- We know that Brachyury is often involved in chordoma
- We identified several pathways involved in chordoma
- We could identify new targets for treatment
- We need to establish more cell lines and newer drugs to test
- Immune therapy against Brachyury (T)