FACULTY OF MEDICINE AND HEALTH SCIENCES

The evolving role of molecular techniques in surgical pathology:

focus on soft tissue and bone tumour diagnostics

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Curriculum vitae

Qualifications

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Main publications PhD

Cordier F, Creytens D. Unravelling the USP6 gene: an update. J Clin Pathol. 2023

Cordier F, Van Dorpe J, Sciot R, Flucke U, Van Gorp J, Debiec-Rychter M, Van Belle S, Loontiens S, Van der Meulen J, Van Gaever B, Ferdinande L, Dedeurwaerdere F, Creytens D. '*USP6*-associated neoplasms' (UANs) are characterized by a remarkable, but entityspecific, *USP6*-fusion partner diversity: a morphomolecular study of 175 cases. Submitted

Cordier F, Creytens D. RB1: governor of the cell cycle in health and disease: a primer for the practising pathologist. J Clin Pathol. 2024

Cordier F, Van Roy N, Matthys B, De Paepe P, Van de Vijver K, Van Dorpe J, Creytens D. Fibroepithelial Stromal Polyp of the Vulvovaginal Region as Part of the RB1 Family of Tumors: Friend or Foe? Int J Gynecol Pathol. 2023

Cordier F, Fadaei S, Ferdinande L, Dochy F, Vanwalleghem L, Van Den Bossche K, Loontiens S, Van der Meulen J, Van Roy N, Van Dorpe J, Creytens D. Revealing RB1 loss in an emerging entity: report of two cases of PRRX1-rearranged mesenchymal tumours. J Clin Pathol. 2023

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Summary

The implementation of (new) molecular techniques in the daily practice has transformed the role of pathologists, transitioning from a morphologic focus to a comprehensive morphomolecular perspective, encapsulated in the concept of 'integrated diagnostics'. Recent years have witnessed a rapid integration of advanced molecular techniques like next-generation sequencing (NGS) into routine pathology practices. This has significantly enhanced our comprehension of disease pathogenesis and led to the identification of novel tumour entities or subtypes. However, with this wealth of information comes the challenge of navigating through it.

Molecular findings challenge traditional taxonomies, urging us to reconsider the boundaries of diseases and the concept of distinct entities. Entering the realm of the 'splitters' and the 'lumpers', the 'splitters' advocate for finer distinctions based on molecular signatures, while the 'lumpers' argue for overarching categories that encompass shared characteristics. This debate surfaces in this thesis in which 2 projects were conducted.

1. '*USP6-associated neoplasms' (UANs):* Despite a common genetic pathway with *USP6* rearrangements leading to USP6 overexpression, morphological and clinical differences persist among entities like aneurysmal bone cyst (ABC) and nodular fasciitis (NF). In an exhaustive study of 175 cases using RNA NGS and fluorescence in situ hybridization (FISH) a significant entity- and location-specific *USP6* fusion partner diversity was revealed. We suggested that observed variations between members of the UAN are attributable to a distinct cell of origin. This suggests that these lesions can be classified as distinct entities within the UAN group.

2. '*RB1*-deleted soft tissue tumours': We identified the loss of *RB1*, using FISH, in fibroepithelial stromal polyps and in two cases of *PRRX*-rearranged mesenchymal tumours, suggesting an expansion of the group of '*RB1*-deleted soft tissue tumours'. However, controversies surrounding the FISH cut-off persist and warrants further exploration.

Furthermore, we elucidate that the use of molecular techniques not only uncovers new gene rearrangements and tumour entities but also proves invaluable in confirming diagnoses in uncommon locations. In some instances, making a diagnosis without these molecular techniques would be impossible. The discovery of new genetic alterations also leads to the development of surrogate immunohistochemical markers. However, the correlations between these markers and the underlying gene rearrangements are not always straightforward.

This thesis further discusses various aspects including epidemiology, clinical practice, and artificial intelligence. Yet, the fundamental question remains:

Should we split or lump?

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