

Osteoarthritis

Clinical phenotypes, molecular endotypes and theratypes in OA therapeutic development

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Understanding the molecular endotypes that influence clinical phenotypes is a critical step for stratification of patients with osteoarthritis (OA) into therapeutic subtypes that

can help the development of targeted disease-modifying OA drugs (DMOADs) to provide genuine, long-term clinical benefit.

Main text

Osteoarthritis (OA) is the most common form of arthritis, affecting half a billion people globally. OA is a highly complex, slowly progressing, low-grade mechano-inflammatory disease that causes pain, disability, loss of joint function and considerable morbidity in the ageing population. Despite being recognized as a serious disease with an unmet medical need¹, drug development for OA is an extremely challenging, complex and arduous process², and numerous pharmaceutical companies have tried and failed to develop disease-modifying OA drugs (DMOADs)³. However, we have learned a lot from these failures, and the gradual transition of OA drug development from large-pharma-focused research and development to biotechnology companies is leading to the production of highly targeted biological, cell and gene therapies for OA.

One of the most exciting developments in OA research is the emergence of the concepts of clinical phenotypes and molecular endotypes⁴, which will pave the way for an understanding of the therapeutic subtypes (theratypes) of OA [\[Au: Cite Supplementary Box 1 here?\]](#), as has been proposed for other inflammatory diseases such as allergy and asthma⁵. The greatest weakness in the process of OA drug discovery and development has been the incorrect assumption that OA is a homogeneous 'wear and tear' disease. Rather, it is now clear that OA is a highly complex heterogeneous condition characterized by low-grade inflammation. Multiple risk factors including ageing, obesity and joint injury have long been recognized, and knowledge of the contribution of genetics is rapidly expanding, with the discovery of

over 100 gene variants associated with OA risk⁶. Furthermore, the existence of multiple clinical phenotypes and molecular endotypes of OA creates opportunities for a much more targeted drug-development approach, and poly-omics offers new platforms for deep phenotyping. The biggest challenge for OA drug discovery and development is the translation of pre-clinical discoveries to the clinical setting and demonstration of the efficacy of drugs that work effectively in pre-clinical animal models, but fail in translational studies and clinical trials.

The prevalence of OA continues to rise, and the global burden needs to be mitigated, especially the rising demand for joint-replacement surgery. To tackle this problem, better and more effective phenotype-directed and endotype-directed therapies need to be developed. This effort should be supported by gaining a better understanding of disease pathogenesis in the context of clinical phenotypes and molecular endotypes of OA and the framework of patient journeys, which will take several decades. The power of high-throughput omics technologies needs to be harnessed to enable an understanding of the molecular endotypes that promote OA disease pathogenesis⁴, and to provide the means for patient stratification in OA clinical trials⁷, so that clinical translation is facilitated.

OA is now recognized as a heterogeneous, multifactorial, multi-dimensional, multi-source, multi-origin, highly complex mechano-inflammatory disease affecting the entire joint. Drug development for OA needs to become much more patient-focused, to be aligned with the emerging phenotypes and endotypes, which presents several challenges. First, how do we introduce the concept of clinical phenotyping and molecular endotyping in trials designed to test the efficacy of new OA drugs? Second, can we use omics tools and artificial intelligence (AI) to develop novel stratification tools to enhance clinical trial design and outcomes? Third, how can emerging data-

driven and AI approaches inform and enhance OA drug discovery and development by stratification into phenotypes?

We need to categorize OA phenotypes and develop consensus definitions to progress the field (**Figure 1**). The term 'phenotype' has been widely applied in the published literature to define physical phenotypes, pain phenotypes, gait phenotypes, imaging phenotypes and phenotypes defined using biochemical markers in blood, urine, plasma and synovial fluid. However, from a purely clinical perspective, a phenotype is defined as any clinically observable characteristic or trait of a disease. In a primary health-care setting, a clinical phenotype is defined by externally observable morphological and behavioural characteristics [\[Au: Alternatively, Supplementary Box 1 could be cited here?\]](#). Clinical phenotypes and morphotypes can be defined from careful clinical examination and informed by detailed information from patients about the natural history of the condition and their clinical manifestations. The observable characteristics that define clinical phenotypes result from a combination of hereditary, environmental and morphological influences. Biochemical, physiological and molecular properties are not included in this purely clinical phenotypic context, implying that mechanistic and pathogenic aspects are distinct and are not part of a clinical phenotype, and should be categorized as molecular clusters or molecular phenotypes. A number of recent studies have focused on the identification and characterization of molecular endotypes of OA⁷. Molecular endotypes are distinct mechanistic pathways that underscore the variability of clinical phenotypes. They are measures and features derived from molecular, cellular, immunological, genetic, genomic and epigenomic analyses that provide insight into the underlying molecular mechanisms that promote disease pathogenesis and drive pathological progression. Currently, it is not possible to stratify patients with OA into therapeutic sub-groups and

there are no genetic or poly-omic tools that can enable us to do so. However, it is possible to make progress by harmonizing data collection from OA clinical studies and to enable true stratification by collecting a list of optional clinical data in all OA interventional and observational studies, providing a basis for the development and application of machine-learning algorithms to identify phenotypes and predictors of rapid progression, joint replacement and enhanced responses to specific interventions⁸⁻¹⁰.

Enabling future DMOAD-development programmes requires the establishment of robust OA classification criteria. OA drug development also needs to encompass earlier disease stages, where there will be less overlap between phenotypes. We should also move towards biological disease constructs and place greater research focus on OA risk and susceptibility, predictive and diagnostic biomarkers and biosensors with high specificity and sensitivity. Finally, understanding molecular endotypes that affect clinical phenotypes is a critical step for stratification of patients with OA into theratypes, thereby helping to develop targeted DMOADs that will provide genuine, long-term clinical benefit to a larger proportion of patients with OA⁴.

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Acknowledgements

A.M. acknowledges support from the European Cooperation in Science and Technology (COST) Association, Action CA21110-Building an open European Network on OsteoArthritis research (NetwOArk). R.L. recognizes support from NIH (grant P30 AR072580) and the Rheumatology Research Foundation. **[Au: Revised acknowledgements statement OK?]**

Competing interests

The authors declare no competing interests.

Supplementary information

Supplementary information is available for this paper at <https://doi.org/10.1038/s415XX-XXX-XXXX-X>

Figure 1 | Interactions that determine phenotypes and theratypes.

Phenotypes (the clinical presentation of a disease) are influenced by life events, ageing and interactions between genes and the exposome. Comorbidities also influence clinical phenotypes and can drive some pathogenic phenotypes. The observable characteristics that define clinical phenotypes result from a combination of hereditary and environmental influences, but do not include molecular and genetic aspects.

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