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In Focus

The Need for Predictive, Prognostic, Objective and Complementary Blood-Based Biomarkers in Osteoarthritis (OA)

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Osteoarthritis (OA) has traditionally been viewed as a non-inflammatory arthropathy and has not been considered a 'serious disease'. However, this view has radically changed in recent years, due to the complexity and heterogeneity of the patient populations, spiralling socio-economical costs and long-term impact on the quality of life of affected individuals. There is an acute need for objective and non-invasive diagnostic biomarkers in OA, markers that can stratify patient subtypes and thereby direct therapeutic treatments at an earlier disease stage (read personal health care (PHC)) (Conaghan, 2013). Increased interest in the development of new diagnostic and prognostic tests for early forms of OA may incorporate the use of blood-based biomarkers; however, both research and regulated development and approval are still needed to reach a diagnostically important significant point where a given biomarker will benefit the clinical management of the patient.

1. The OA Biomarker Landscape Today

There are currently no disease-modifying osteoarthritis drugs (DMOAD) available for treatment of OA patients (Mobasheri, 2013; Qvist et al., 2008). This may be due to the heterogeneity of the OA population, where the origin and driver of disease progression is often poorly understood. The main treatment options for OA presently are pain relief, physical therapy and nutritional supplements (nutraceuticals). However, none of these can halt or reverse disease progression. In addition, diagnosis is often subjective, due to the lack of objective, precise and accurate diagnostic devices. Thus the limited clinical diagnosis and characterization of the individual patient will adversely influence healthcare management and the recruitment of the right patient cohorts for

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the testing of drugs in clinical trials. There is a medical need for objective, precise and accurate *in vitro* diagnostic devices for clinical trial enrichment (Kraus et al., 2015; Karsdal et al., 2013).

2. What Is the Medical Need for Biomarkers?

The lack of approved DMOADs in OA drags a long tail of failed clinical drug trials. Recently the US Food and Drug Administration (FDA), the European Medicines Agency (EMA) and other regulatory agencies have published guidelines on how biomarkers should be defined. Different groups and public-private partnerships have proposed different models for classifying OA biomarkers for clinical use (Bauer et al., 2006; Kraus et al., 2011; Bay-Jensen et al., 2016a,b). There is a general consensus on the medical need for biomarker development which may be summarized as seven key points:

1. Translational biomarkers, which allow better characterization of a drug in preclinical development, ensuring of selection of the most viable projects
2. Early identification of efficacy of intervention; Go/no-go decision-making already in phase 1b/2a studies, which normally do not include efficacy measures.
3. Phase II and Phase III trial enrichment; reduction in study size, and a particular OA phenotype tailored for a selective interventions, which will recuse length of the clinical study to allow more efficient and less costly trials
4. Identification of patients who are fast progressors and as such in greatest need of treatment.
5. Identification of super responders to a specific treatment; patients with high efficacy and low safety concerns
6. Biomarkers of disease activity; as OA is not a stabile disease, there is a need for devices for identification with high disease activity and potential progression
7. Easy accessible monitoring devices – point of care; post marketing patient care and personalized medicine

Although there are clear overlaps in the above, it is clear that no single biomarker will be the answer for all.

3. Message From the Regulators

The public attention to biomarkers is increasing, recently further emphasized by the "white house" initiate focusing on quantifiable tools for patient election and monitoring.[2] On the regulatory side, the FDA issued a position document describing the need and road ahead for personalized medicine "FDA: Paving the Way for Personalized Medicine",[3] which later resulted in new guidelines to faster biomarker tool development by the guidelines "Identifying Potential Biomarkers for Qualification and Describing Contexts of Use To Address Areas Important to Drug Development",[4] which are in addition to the standard guidelines for *in vitro* companion diagnostic device. This has led to the discussion on prospective-retrospective biomarker analysis for regulatory consideration, by the white paper from the industry pharmacogenomics working group (Patterson et al., 2011). This will greatly assist precision medicine and PHC by guiding the discussion on how to implement a "prospective-retrospective biomarker analysis". The prospective-retrospective biomarker analysis approach is developed to "rescue" failed phase III trials. Qualified biomarkers are to be measured in certified, high-quality laboratories and analyzed using predefined statistical analysis plans to test hypotheses related to retrospective analysis of technically and biologically validated biomarkers.

According to the FDA, a prognostic *in vitro* diagnostic biomarker would need a 510 K or *de novo* approval (class II device), whereas a predictive biomarker would need ldt pre-market approval (PMA, class III device). The main separating factor is that a prognostic biomarker provides you with an estimate for progression, whereas a predictive biomarker would be used to decide the exact treatment regimen for individual patients, and would therefore have a significant impact on the patient's life. A predictive biomarker will often become a companion diagnostic.[5] In addition, the recent "drug development tool (DDT) box" guidelines are also allowing for regulatory assessment of tools to assist in clinical drug development, such as the fibrinogen enrichment of patients in COPD clinical studies with a more severe outcome (fast progressors), which is now classified as a DDT.

No biomarkers have yet been qualified as biomarkers for OA, however several biomarkers have been developed targeting cartilage degradation and formation (*e.g.* CTX-II, ARGS, PIIANP), joint inflammation (*e.g.* C3M, Col2-NO2), bone remodelling (*e.g.* alpha CTX—I, osteocalcin) as well as inflammation and metabolic factors (Bay-Jensen et al., 2016a,b). The scientists and clinicians working in the biomarker field cannot expect a "one size fits all" solution for OA. Consequently it is important to

[2] The White house, 2015. Precision Medicine Initiative | The White House [WWW Document]. White house. URL https://www.whitehouse.gov/precision-medicine (accessed 2.5.16).

[3] FDA, 2013. Paving the Way for Personalized Medicine [WWW Document]. URL http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PersonalizedMedicine/UCM372421.pdf (accessed 2.5.16).

[4] FDA, 2015. Identifying Potential Biomarkers for Qualification and Describing Contexts of Use To Address Areas Important to Drug Development; Request for Comments [WWW Document]. FDA. URL https://www.federalregister.gov/articles/2015/02/13/2015-02976/identifying-potential-biomarkers-for-qualification-and-describing-contexts-of-use-to-address-areas (accessed 2.5.16)

[5] FDA, 2014. *In Vitro* Companion Diagnostic Devices. Guidance for Industry and Food and Drug Administration Staff.

test and validate a biomarker to a specific hypothesis. This can be done under the laboratory-developed test (LDT) (Sarata and Johnson, 2014), which is a type of *in vitro* diagnostic test that is designed, manufactured and used within a single laboratory.

4. How Do We Move Forward?

Different approaches, techniques and better-stratified patient samples are needed to move biomarker development towards qualification, which means that new partners need to come together and collaborate. For example development of a novel blood-based and cartilage-derived protein biomarker requires application of advanced analytical techniques such as proteomics and mass spectrometry, whereas development of the biomarker assay requires knowhow of biochemical and immunological assessment platforms. Furthermore, testing, validation and qualification requires access to high quality clinical samples from several independent retrospective or prospective cohorts. In the end a commercialisation plan needs to be established to push forwards and finance the qualification of biomarkers. Thus it is most likely that no single entity, public or private, will be able to complete these development steps alone. There is a need for i) Formation of public-private partnerships to develop, test, validate and qualify biomarkers for use in clinical trial and patient management, ii) Design of clinical studies that stratify patients and investigate trends and characteristics of specific OA cohorts and study populations, and iii) Collaboration between biotech and pharmaceutical companies to support the commercialization of biomarkers.

In summary, a great deal of collaborative work needs to be done in this area to develop more predictive, prognostic, objective and complementary biomarkers for OA management and DMOAD development.

Conflict of Interest Statement

The authors wrote this paper within the scope of their research positions. The authors declare no conflict of interests.

Competing Interests

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