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Predictive Epigenetics: Fusing Theory and Experiment

Oxford Biodynamics Plc

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Oxford Biodynamics Plc (OBD), founded in 2007 as spin-off of the University of Oxford, is related through its Chief Scientific Officer Dr. Alexandre Akoulitchev to the PEP-NET Marie Curie network and the formation of the next generation of epigenetics researchers. Oxford Biodynamics grew from a labdesk at the University of Oxford to a global company with a headquarter in Oxford and an offshore lab in Penang, Malaysia. The company vision is to develop and commercialize the biomarker platform EpiSwitch® for early disease detection, prognostic testing, and drug response studies. The healthcare and pharmaceutical industry is going through a major shift with more and more affordable sequencing methods and the access to individual data enabling custom made and personalized medical care, which will help health care systems to deal with an ageing society, inefficiencies and capacity problems, and the related cost of autoimmune disease and cancer. Especially, the COVID-19 pandemic showed us clearly the challenges health care system face in the future.

The EpiSwitch® medical analysis platform is based on chromosomal conformation signatures (CCS) which are the combinations of three-dimensional orientations of the DNA, and function as biological markers. Biomarkers are classified based on their possible applications: *predictive biomarkers* to understand an individual's responsiveness to a specific treatment; *prognostic biomarkers* to mark risk groups with a possible severe course of disease; and as *diagnostic biomarkers* for early diagnosis. EpiSwitch® offers a mix of experimental and computational approaches to facilitate the product development phase in the pharmaceutical industry. In the initial EpiSwitch® design stage, DNA target sites are specified with predictive algorithms. In a second step, various modern experimental tools such as microarrays, polymerase chain reaction analysis (PCR), and next-generation sequencing (NGS) are used to narrow down promising candidates to a small number of highly informative markers. In a last step PCR is used to validate the biomarker for a later use by the industrial partner.

Oxford Biodynamics demonstrated recently the effectiveness of the EpiSwitch® platform as a *prognostic biomarker* tool to differentiate between asymptomatic, mild or severe COVID-19 infections (EpiSwitch® COVID Severity Test). The prognostic biomarkers were used to elucidate biomolecular pathways associated with each state and identify new potential therapies.

To develop the test using the EpiSwitch® platform, blood samples from 80 patients, with an age range of 24 to 95 years from the UK, US, and Peru, were taken on admission to hospital with COVID-19 and classified according to the severity of the disease they subsequently developed. Chromatin with intact chromosome conformations was extracted using the EpiSwitch® Explorer Array Kit. Bayesian methods and custom-made micro arrays were used

to annotate the human genome across several sites to develop a molecular classifier for the severity of disease.

The test identified a subset of prognostic markers based on the 3D genomic conformations (CCS) at immune-relate loci and revealed association of CCS with certain loci depending on the severity of the infection: asymptomatic, mild or severe. These associations were subsequently validated in a blind trial and showed high predictive scores. This demonstrates that an individual's disease onset and pathological response is largely comprised of lifestyle and environmental factors that influence the epigenome and the conformation of their chromatin.

More detailed analysis of the loci associated with CCS uncovered the molecular basis of disease severity. The genomic regions dysregulated between patients with mild or severe disease were identified as the pathways for olfactory signaling, ACE2, immune system signaling, IL6 and JAK-STAT, calcium signaling, nitric oxide signaling, coagulation, complement, cytokine interferon gamma response, TGF beta signaling, TNF alpha signaling, apoptosis and the MSP-RON systematic inflammatory response (Figure 1). In addition, the lipid prostaglandin E2, calcium, the cytokine MIP alpha and RANTES signaling pathway were identified, consistent with the therapeutic use of drugs such as dexamethasone, mTOR inhibitors and other immunosuppressants to treat COVID19.

Finally, the study motivates the development of a prognostic testing kit based on the identified biomarkers in a MIQE-compliant qPCR format to predict the severity of the disease discourse for clinical use.

The application of the EpiSwitch® technology as a *prognostic biomarker* tool for COVID19 highlights the importance of educating the next generation of epigenetics researchers in cutting-edge molecular biology, high-throughput sequencing and machine learning to deal with societies biggest problems, such as infectious disease, autoimmune disease and cancer.

References:

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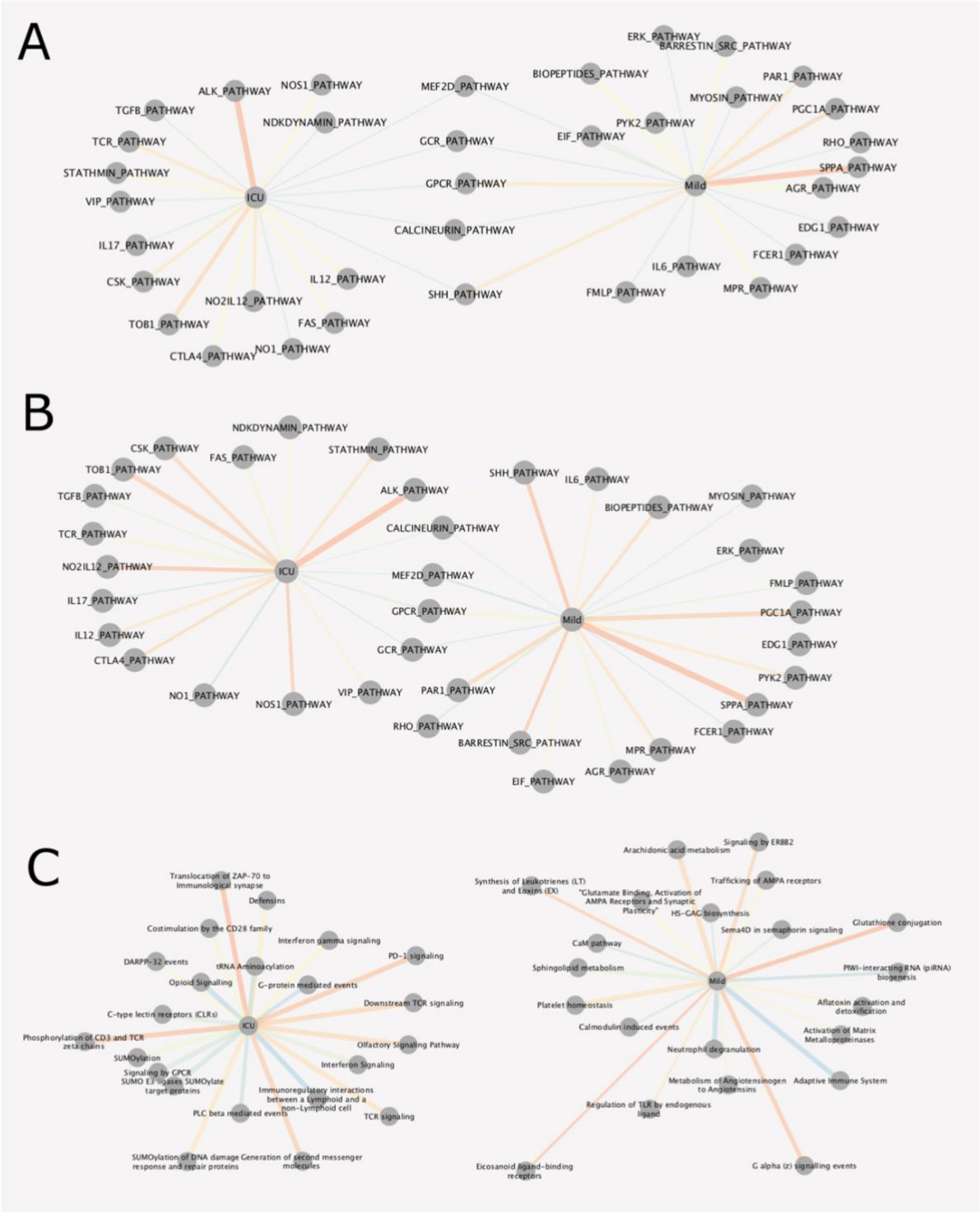

Figure 1. Mapping of top 3D genomic markers to the biological pathways (from Hunter et al. 2021).