PLAQUETEC
Revolutionary Coronary *Liquid Biopsy System™*

PERSPECTIVE PAPER

Next Steps in Exploring the Potential for Personalised Medicine in Coronary Artery Disease

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Despite major advances in diagnosis and treatment, coronary artery disease (CAD) remains the leading cause of death worldwide. Although coronary angioplasty and lipid-lowering statin therapy have improved outcomes, approximately 15-20% of patients still experience recurrent myocardial infarction (MI, heart attack) or stroke, often leading to death. Moreover, up to half of all such events appear to occur in apparently healthy individuals with few traditional risk factors, including dyslipidaemia.

The nagging problem of recurrent events has led many experts to question the rationale for current treatment approaches in CAD, sparking fresh interest in the concept of personalised medicine – providing the right therapy to the right patient at the right time. The phenomenon of recurrent events also underpins the hypothesis that inflammation plays a key role in the pathogenesis of CAD. Although inflammation has long been thought to contribute to the destabilisation and rupture of atherosclerotic plaques, leading to MI, the inflammation hypothesis is still a matter of some debate in the cardiology community. Although several investigations have elucidated the role of C-reactive protein (CRP) as an inflammatory biomarker in CAD, the lack of confirmatory evidence for the inflammation hypothesis effectively constrained research initiatives in this area for many years. As a result, the viability of relying solely on anti-inflammatory strategies to reduce atherosclerotic risk remained an unanswered question.

The recently published CANTOS study provided the first solid evidence to support the inflammation hypothesis: in this study, canakinumab, a human monoclonal antibody that inhibits the pro-inflammatory cytokine interleukin-1β (IL-1β), reduced the rate of recurrent MI, stroke, and cardiovascular death in patients with prior MI who were at high risk due to persistently elevated CRP. Additionally, the PROSPECT study and the Cambridge-run VIVA study, both published in 2011, effectively shifted the interventional focus away from “vulnerable plaque” towards the “vulnerable patient.” Although both studies identified predictors for non-culprit lesion events and showed frequency of high-risk “vulnerable” lesions, the frequency of such events was disappointingly low at 3-4 year follow-ups. However, identifying the at-risk “vulnerable” patients remains controversial due to the complex interaction between patients’

demographics/risk factors, peripheral inflammation, coronary inflammation, and coronary plaque phenotype, all of which have been implicated in future risk of adverse events.

Further complicating the challenge of risk assessment is the difficulty of detecting various cytokines, growth factors, and other bioactive molecules released from coronary plaques. Many of these biomolecules are most concentrated in the "boundary layer" of the vasculature, a slower-moving stratum of blood adjacent to the endothelial surface that does not mix with the general bulk flow. Such difficulty led PlaqueTec to develop the Liquid Biopsy System™ (LBS), which is designed specifically to sample from the boundary layer at four sites simultaneously. The LBS therefore enables detection of small gradients of released biomolecules by simultaneously collecting blood both upstream and downstream of individual plaques.

Data from the first-in-human and feasibility study (n = 10) and the first human proof-of-concept evaluation (n = 28) of the LBS were recently published in *JACC: Basic to Translational Science*. In these studies, investigators detected gradients of biomolecules across coronary plaques *in vivo*, with differential expression of these molecules in unobstructed vessels, in stable obstructive plaques, and after iatrogenic balloon injury (before stenting). The plaque-level individual patient data derived from these experiments may facilitate patient risk stratification, re-targeting of existing anti-inflammatory biologic agents, identification of novel inflammatory targets not detectable in peripheral blood, and de-risking of early-stage studies of novel pharmaceutical agents.

The advent of the LBS has opened up promising avenues for future research, including determining the relationship between indices of systemic inflammation and local/coronary inflammation, characterizing the morphology of coronary plaque, and examining other aspects of the atherosclerotic process. The LBS technology may also enable examination of different patient subgroups to identify key differences that may facilitate tailoring of therapies based on an individual patient's risk level and prognosis.

To explore these avenues, PlaqueTec needs partners who share our vision for further elucidating the mechanisms of CAD, and for improving outcomes for patients affected by this deadly disease. The need is urgent, and the rewards are potentially great. At the very least, it will be interesting to see where the science leads us, and we hope you will join us in this exploration.