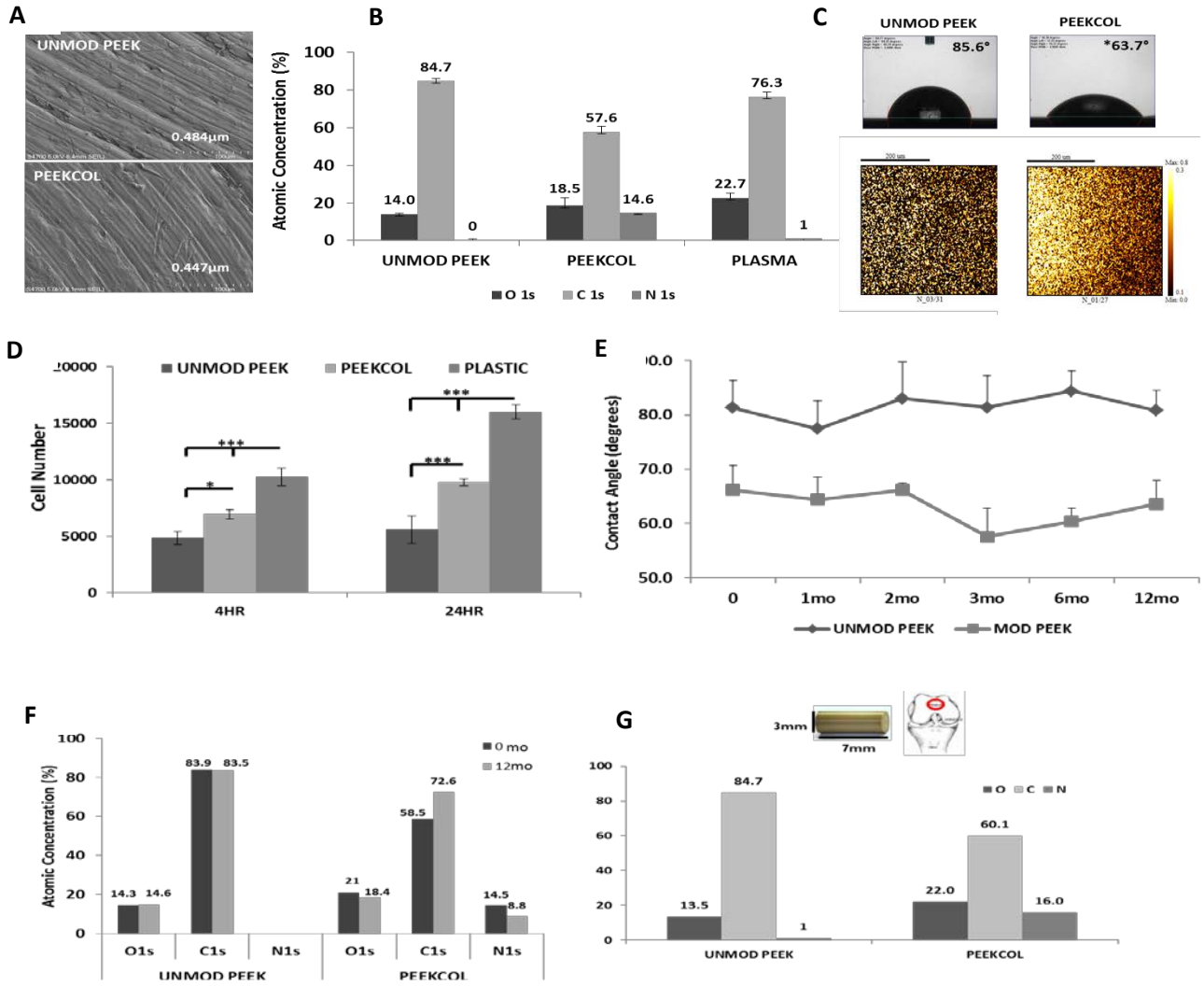
Background: Osteoarthritis (OA) is an incurable disease that has evaded pharmacological interference, biologic therapy or surgical intervention to prevent disease progression. Currently, OA is designated the 11th highest contributor (of 291 diseases) of global disability and affects approximately 400 million people globally. In the absence of effective treatment options, current standard of treatment of OA involves total joint replacement (TJR), which according to the Centre for Disease Control & Prevention, accounts for approximately 35% of arthritis-related procedures. One of the key aspects contributing to successful fixation is the rapid and complete integration of the device with bone. Without this biological reaction, stability is compromised. This results in pain and loss of motion and generally requires revision surgery. For OA patients the quality of bone is compromised, therefore, the potential for adequate implant stabilisation is substantially reduced. Given that the need for revision surgery for THR and TKR revision procedures are estimated to increase by 137% and 600%, respectively by 2030, the importance for rapid osseointegration (biological integration of the device to bone) in the prevention of implant failure is clear. The aim of this project was to develop biologically active metal implants for improved outcomes of osseointegration in joint athroplasty procedures.

Approach: Surface properties such as chemistry and micro-topography are well established determinants of osseointegration. Conventional coatings, such as hydroxyapatite, have demonstrated promise but a major stumbling block for reliable application of coating technologies is that they commonly fail during long-term implantation and may result in osteolysis, a major clinical problem relating to joint replacement procedures. In this study we use a non-thermal plasma device to deliver collagen onto the surface of the clinical polymer poly-(ether-ether)-ketone (PEEK), a material that has had significant clinical success in spinal and craniomaxillofacial application but more recently, is investigated for its application in load bearing orthopaedics. A limitation of PEEK, however, is that it is bio-inert, and therefore, does not readily support bone apposition. In brief, we aim to produce a clinically viable long-term, stable modification of PEEK that improves outcomes of osseointegration.

Main Results: Modification of PEEK with collagen (PEEKCOL) did not induce any marked micro topographical changes to the surface compared to unmodified controls (UNMOD PEEK) as demonstrated with SEM (A) and white light interferometry (A, inset). Surface chemical analysis using X-Ray photoelectron spectroscopy (XPS) demonstrated the presence of Nitrogen (N 1s) subsequent to collagen treatment, indicative of the amide/amine groups of the protein within the surface. Treatment with plasma alone (without collagen) failed to induce comparable changes in the N signal. This is further advocated by the fact that samples, plasma-treated in the absence of collagen (Plasma), did not present similar changes in N atomic concentration (B). Successful functionalization is further advocated by the significant reduction ($p=0.03$) in water contact angle observed (C). Tracking the N signal using imaging XPS showed that the incorporation of protein across the PEEK surface appeared well-distributed (D) and conventional XPS suggests that the modification was homogenous (E). Using this approach we demonstrated that collagen modification (PEEKCOL) can significantly increase (*$p<0.05$; ***$p<0.001$) initial human mesenchymal stem cell (hMSC) attachment compared to unmodified controls (UNMOD PEEK). Neither proliferation nor metabolic activity of hMSC's was negatively influenced by collagen modification (not shown). An increase in osteogenic differentiation was observed; however, this was not found to be significant (not shown). Assessment of the modification over the course of 1 year demonstrated a stable modification and establishes the clinical feasibility of this approach (F, G) as demonstrated by contact angle and XPS. The approach was further validated in an *in vivo* preclinical rabbit model (3x7mm PEEK cylinder implants implanted into the inter-condylar notch of the distal femur), however, issues with sufficient protein incorporation within a 3D implant were encountered and consequently, no significant outcome in osseointegration was observed. However, further optimisation of the modification approach has rectified this issue (H) and *in vivo* validation of the optimized implants is

underway with outcome parameters to include mechanical testing, histomorphometric analyses and micro-computed tomography to assess bone volume at the implant interface.



Potential clinical & socio-economic Impact: Ireland accommodates 8 of the top 10 medical technology companies. Therefore the national Research Prioritisation Steering Group has identified innovation and convergence between medical devices as a major factor in growth of the sector. Currently, the main focus of the Irish market in Europe involves late stage production of the devices; however, this project has greatly contributed to shift this focus towards innovation. This project has contributed to this aim through its novelty and successful completion of key performance indicators.

This project was aimed at tackling an unmet clinical problem that is considered a global challenge both socially and economically. We have successfully achieved our aim of producing a clinically viable long-term, stable modification of PEEK that has potential for improving the outcome of osseointegration in OA patients. This methodology provides an attractive, cost-effective, stable clinically relevant alternative for addressing current limitations relating to coating/modification technologies. Moreover, the plasma device is a bench-top, simple, quick, user-friendly device that could be easily housed in hospitals for on-site fabrication if required. Subsequent work arising from this proposal is investigating antibody modification of implant materials as well as osteoinductive modifications for further improving outcomes of osseointegration.