drug giant Sanofi, that are aiming to identify nominal biosynthetic gene clusters related to potential antibiotic structures, working in this area?

The answer is definitely yes. One group that decided not to follow the whole genome route is led by Sean Brady at the Rockefeller University. In 2014, the Brady group published an article on metagenomic discovery methods in *Current Opinion in Microbiology* (Charlop-Powers et al. 2014). In this paper they described the then current methods for using metagenomic studies to obtain information without isolation. Then in 2016, they demonstrated that parks in New York City were a prolific source of natural product biosynthetic diversity (Charlop-Powers et al. 2016) and that they could find gene encoding in the biosynthesis of nonribosomal peptides and polyketides, which included a potentially novel calcium-dependent antibiotic (CDA).

This initial discovery of a CDA was followed up by the Brady group in a report in 2018, where they demonstrated the novel natural products, malacidin A (**52**) and B (**53**), following heterologous expression in *Streptomyces albus* (Hover et al. 2018). These are dissimilar in structure to the known CDA lipopeptide daptomycins and did not contain the Ca-binding motif, "Asp-X-Asp-Gly," but still required Ca^{2+} for activity against Gram-positive bacteria.

Using a different approach, this time using data from specific biosynthetic clusters and then using small peptide synthetic techniques, the same group reported in 2018 (Chu et al. 2018) further work from a discovery that they first reported in 2016 (Chu et al. 2016). In that initial report, they published a process (working from metagenomic data) that they named "syn-BNP". This acronym stands for "synthetic–bioinformatic natural products." Syn-BNPs are not intended to be exact copies of the isolated NPs but are analogues that structurally resemble the original agent; thus, using the lexicon of Newman and Cragg, these would be "NDs" (Newman and Cragg 2016). The base humimycin A structure (not shown) came from a study of the human microbiome and though not an antibiotic in its own right, it is in fact a "flippase" inhibitor that, when co-administered with a β-lactam such as carbenicillin (**54**), can overcome, to some extent, MRSA and *Enterococcus faecalis* (VRE-resistant) microbes. When the Brady group modified the *N*-acylated 7-mer linear peptide (humimycin A, 1S, **55**) by systematically changing the amino acid sequence and "adjusting the *N*-acyl group)," they developed humimycin 17S (**56**) that when co-administered with carbenicillin, inhibited the growth of highly resistant MRSA strains, including some that were also vancomycin resistant (Chu et al. 2018).

A second series of compounds that this time "descended" from studies from a bioinformatic analysis of nonribosomal peptide synthetase gene clusters led to the "syn-BNP-derived" paenimucillin A (**57**) and B (**58**) (Vila-Farres et al. 2018). Initially these were effectively only Gram-positive active, but by modification of the pair, paenimucillin C (**59**) was synthesized and using a rat open cutaneous wound model, infected with the ESKAPE pathogen *A. baumannii* showed no reinfection after twice daily treatment. It was recently