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Bacterial pathogenesis, anticancer drug development and patent related issues

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It is now well-known that many pathogenic bacteria with long term residence in the human body as biofilms consider the human body as their habitat and try to protect it from outside invaders such as cancers, viruses and parasites through secretion of protein weapons. In one instance, Pseudomonas aeruginosa, an opportunistic pathogen secretes a protein azurin on contact with cancer cells. Upon release, azurin enters preferentially to cancer cells and interferes in cancer cell growth through multiple mechanisms involving complex formation with various cellular proteins in cancer cells that promote cancer cell growth. Such complex formation then leads to loss of function of such cancer growth promoting proteins. Thus azurin is known to induce apoptosis in cancer cells as well as interfere in rapid cancer cell growth, through stabilization of tumor suppressor protein p53. Azurin also forms complexes with vascular endothelial growth factor receptor (VEGFR) and cell surface associated receptor tyrosine kinases such as EphB2 to inhibit angiogenesis and cell signaling in cancer cells to inhibit their growth. A chemically-synthesized 28 amino acid fragment (Azurin 50-77), termed p28, has completed a phase-1 trial in 15 stage IV cancer patients with metastatic tumors that were resistant to all conventional drugs and these patients had a life expectancy of about 6 months. P28 not only showed very little toxicity but also significant beneficial effects including partial and complete regression of the tumors in four patients, significantly prolonging their lives. P28 has also shown similar lack of toxicity but good efficacy in several pediatric brain tumor patients. The University of Illinois at Chicago holds many patents on azurin/p28 as anticancer and anti-infective agents and the patent eligibility issues on such products of nature will be discussed.

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Rapid assessment of antimicrobial susceptibility profile directly from positive blood cultures by flow cytometry

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Positive blood cultures demand rapid initiation of antimicrobial therapy. However, a minimum of 48 hours are needed for susceptibility results. Early administration of appropriate antimicrobials increases patient survival and reduce hospitalization costs. Flow cytometric protocols for assessment of the most relevant antimicrobials versus common microorganisms isolated from biological specimens were developed by FASTinov and patented (WO2011138765A1). Such tests were applied to positive blood cultures (100 gram negative *Bacilli*, 50 gram positive *Cocci* and 20 yeasts) from Hospital S. João, Porto, Portugal, following ethics commission approval. After becoming positive, microscopic examination was performed and microbial cells were separated after centrifugation; 10^5 organisms per ml were incubated with antimicrobials, according to gram stain, during 1 hour; cells were afterwards stained with the adequate fluorescent probe and submitted to FC analysis. Susceptibility phenotype was defined according previously defined cut-off values; results were compared with routine susceptibility tests, VITEK-2 (BioMérieux, France). In case of discrepant results micro dilution was used as reference method. The impact of this early susceptibility results on therapeutic decision, direct and indirect costs were evaluated. A time to result of two hours after the blood culture bottle becoming flagged positive was possible, representing considerable time saving (up to 46 hours). Agreement between FC test and routine test was 99%; high clinical and economic impact was differences between 1-3 days of additional hospitalization days per patient. The use of flow cytometry for susceptibility profile analysis may represent a new paradigm in clinical microbiology and a step forward in targeted, cost-effective antimicrobial therapy.

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