Cancer is one of the most deadly diseases worldwide. Colorectal cancer is the fourth most common cancer in men and the third most common cancer in women worldwide. Although distributed worldwide, the incidence is higher in industrialized and western countries (Parkin. DM. et al., 1999). Many Asian countries, including China, Japan, South Korea, and Singapore, have experienced an increase of 2-4 times in the incidence of colorectal cancer during the past few decades. The rising trend in incidence and mortality from colorectal cancer is more striking in affluent than in poorer societies and differs substantially among ethnic groups. Although changes in dietary habits and lifestyle are believed to be the reasons underlying the increase, the interaction between these factors and genetic characteristics of the Asian populations might also have a pivotal role (Sung. JJ. et al., 2005).

Breast cancer is the most common malignancy type diagnosed in women in developed countries and the second most common type diagnosed in developing countries. In India Breast cancer has been described as an alarmingly health problem (Yeole, et al., 2003). According to the reports, breast cancers have badly attacked women population in India. A survey carried out by Indian Council of Medical Research (ICMR) in the metropolitan cities viz. Delhi, Mumbai, Bangalore and Chennai; from 1982 to 2005; has shown that the incidences of breast cancer have doubled. Over the years, the incidences of breast cancer in India have steadily increased and as many as 100,000 new patients are being detected every year (Yip, et al., 2006 ; Michael, et al., 2003). A 12% increase has been registered by cancer registries from 1985 to 2001, which represented 57% rise of cancer burden in India (Yip. et al., 2006 ; Hadjiiski, et al., 2006).

Estimation of the population at risk of developing cancer was done by the exponential growth rate method, and using data from the Census of 1991 and 2001. Estimation of the death rate for cancer was done by using mortality data of the Chennai and Mumbai registries only, based on data quality. Estimation of prevalence was done by assuming the average duration of disease as 2.5 years. Estimation of the cancer incidence for the entire country in the year 2015 is done by assuming a constant rate without any change as done for the year 2004 (ICMR; 2006).
Based on the increasing trends of cancer patients during the last few decades, the numbers of cancer patients have been predicted by the end of 2015 and 2020 in India. These compiled data show that the number of male, female and the total cancer patients in 2004 were 390809, 428545 and 819354 respectively. The number of male and female cancer patients increased continuously up to 2009, with 454842, 507990 and 962832 cases for male, female and total cancer patients, respectively. Similarly, 462408 male cancer patients and 517378 female cancer patients were recorded, with a total number of 979786 patients in 2010. Thus, it is clear from this figure that the number of cancer cases has increased gradually with time. Moreover, a prediction of cancer patients in 2015 and 2020, respectively, has also been made (ICMR; 2009).

Although the incidence of colorectal cancer in Indian older age group subjects is currently very low when compared with Western population, the younger generation is experiencing an increase in incidence. In our institution CRC is more often seen in younger individuals than what is reported in PBCR in other parts of the country. All patients including those in younger age group presenting with rectal bleeding or other alarming signs and symptoms should be properly evaluated including endoscopy to rule out malignancy. A high index of suspicion among young adults is necessary (Sudarshan. V, et al., 2013).

Various factors responsible for cancer genesis have been discussed, which need to be controlled for their eradication. India is a growing country playing a crucial role in the development of the whole world, and, hence, needs special attention on this issue. We should create awareness among public about the cancer havoc and its prevention. The different programs should be started by Government and NGOs for creating awareness among Indian public. The diet and living style are important factors to control the spreading of cancers and, hence, Indians should be careful about these facts. Briefly, cancer is disturbing the growing economy of the country, which can be saved by proper handling of this disease. In view of these facts, it is very important to eradicate this havoc. Let us hope for the best future of this country, which is playing an essential role in the development of the whole world (Imran Ali, et al., 2011).
Bacterial proteins in cancer therapy: Future

Much focus has recently centered on the need for multi-targeting drugs, whether analgesics or anticancer drugs, because of the complexity of neuronal systems or the complex network of signaling and growth promoting pathways that regulate cancer growth (Ohlson. S. 2008). As pointed out previously (Avner. BS, Fialho. AM, Chakrabarty. AM 2012) single targeting, or drugs that target a few similar types of targets with strong inhibition, elicit quick response from the vulnerable cancer cells to resist such drug action. Another problem has been the process of drug development using the current rational or structure-based drug design where a drug competes selectively with a key molecule. For example, for tyrosine kinases, the target is the ATP-binding pocket where the intended drug competes with ATP for its binding to the pocket, thereby reducing ATP binding and the resultant kinase activity. Not only do the cancer cells change or switch over the target binding pocket, but the drug can compete with ATP in binding tyrosine kinases involved in normal cell function, thus creating toxicity problems (Avner. BS, Fialho. AM, Chakrabarty. AM, 2012).

It is thus interesting to note that within the limited number of weeks during which the clinical trials were conducted with p28, there was very little side effect seen while p28 allowed partial or sometimes complete regression of the drug-resistant tumors in 15 stage IV cancer patients. (Richards. JM, et al., 2011, Warso. AM et al., 2013). While selective entry in cancer cells is certainly one reason not to elicit toxic symptoms, the protein-protein complex formation seems to provide the specificity that is needed to reduce any toxic reaction. We will be able to know whether such mode of cancer growth inhibition at multiple points will prevent, or reduce, drug resistance development after long-term use of azurin, if and when approved.

As discussed above, azurin has other domains in addition to its p28 domain that can make it a much more effective drug if its efficacy, lack of toxicity and hopefully a lack of susceptibility to resistance development can be demonstrated in pre-clinical and human clinical trials. A drawback of a protein drug, as is often illustrated with insulin, is its mode of administration, mostly through intravenous injections. Given azurin’s propensity for both therapeutic and cancer preventive activity, it’s demonstrated that a weekly or bi-weekly injection of azurin in vulnerable people, for example women with family history
of breast or ovarian cancers and with diagnosed BRCA1/BRCA2 mutations, may be one way to prevent, or greatly reduce, the onset of cancer in such people (Fialho. AM, Chakrabarty. AM 2012).

There are, however, other approaches that are under development for making protein drugs amenable to oral administration. Attempts are being made to chemically modify insulin with small polymers in which a single amphiphilic oligomer, often polyethylene glycol (PEG), is covalently linked to specific amino acids in insulin that allows it to resist degradation by the acids or enzymes in the stomach and intestine for absorption to the blood stream(Shaji. J, Patole. V 2008). Indeed, limited clinical trials using such conjugated, orally-administered insulin, for example oral insulin capsules (ORMD-0801, 8 mg insulin) have shown their tolerability and efficacy in reducing glycemia in eight type I diabetes patients (Eldor. R, 2013). Since azurin (14 kDa) is also small, although somewhat larger than insulin (5.7 kDa), it should be possible to use such chemical modification to develop an oral variety of azurin (or p28 which is half the size of insulin) for treating and/or preventing the onset of cancer, once its lack of toxicity and anticancer efficacy is demonstrated after successful phase I/II clinical trials.

Another exciting possibility, also on the horizon, is the use of bio-encapsulated proteins for oral delivery using plant cell expression (Kohli. N. et al., 2014, Zimran. A. et al., 2011) Using such emerging technology, azurin can be expressed in certain plant cells for oral consumption that would then allow azurin to be protected from stomach acids and proteolytic enzymes to be acted on by the intestinal microflora for passage through the intestinal lumen to the blood stream to reach the tumors. It is also noteworthy that all the four bacterial proteins, azurin, Laz, MPT63 and arginine deiminase, have anti-viral activity, including anti-HIV-AIDS activity (Fialho. AM, Chakrabarty. AM, 2010b). Thus if a bacterial protein such as azurin can be shown to be non-toxic in humans, it can be tested in both cancer and AIDS patients for its potential efficacy. Indeed, the role of bacterial proteins has been fictionalized in a book *Bugging Cancer* (http://logos-press.com/books/bugging-cancer/) to draw attention to the role microorganisms can play in our efforts to combat cancer and other diseases, and was discussed in a
colloquium entitled Bugs as Drugs, organized by the American Academy of Microbiology in San Diego during April 9–11, 2014.

Finally, the development and marketing of an academic research-led potential anticancer protein drug such as azurin require not only hard work but a strong desire on the part of the university, and in fact the country, to translate university research to marketable commodities that help generate wealth both for the institution and the country. It’s thus no wonder that the University of Illinois applied for and owns more than 12 US patents and many international patents on azurin/p28 and issued an exclusive license to a start-up company CDG Therapeutics Inc. that in turn raised and invested more than 12 million dollars to conduct the research and phase I clinical trials with p28. Can similar efforts be reproduced in other universities in other countries? In a very meticulous, well-reasoned and thought-provoking article, Timmis et al (Timmis. K, et al., 2014) have argued for a strategy for the creation of pipelines for new chemicals, involving drugs and many other products, and encouraging national center network partnerships and stronger university-industry collaborations for wealth generation in cash-strapped Southern European countries. They also emphasize patent protection of new inventions, commercial assessment and stronger academic-industry partnership (Timmis. K, et al., 2014)

Although the emphasis of the article of Timmis et al. is to encourage new chemical development, mostly natural products, in Southern European countries to promote an innovation-based industrial culture and economic revival, there are interesting differences among European Union (EU) countries in the legal enforcement of patent rights and in the conceptual framework of patent protection. As we pointed out earlier (Fialho. AM, Chakrabarty AM. 2010), while “anything under the sun that is made by man” is patent eligible in the United States (US Supreme Court decision 447 US 303, 1980), inventions that are contrary to public order or morality, including for example patenting of human embryonic stem cells, are not patent eligible under article 53 and rule 23 (c, d, e) of the European Patent Convention (EPC). While many innovations outlined by Timmis et al. will involve microorganisms which would be patent eligible in the EU, many involving higher forms of life will not. This then raises a broader issue, not between Northern and Southern Europe, but between the EU and the US about economic
progress through patent protection of commercially valuable inventions, including for example, the evolving technology for using stem cells to generate human organs such as liver or lung for transplantation purposes.

There is a need and a lot of scope in India for the development of Therapeutic proteins to treat cancer due to increased population with Cancer. There is a need for frank and open discussions on how our society will benefit if we do not arbitrarily leave it to the industry or the governmental agencies to decide how our people, and our economy, can benefit from the academic innovations and a thoughtful strategy to bring such innovations to the bedside and the marketplace and finally reach the needy i.e., the patients who are really suffering.