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PROGRAMMABLE NANO-MACHINES

THE FUTURE OF CANCER THERAPEUTICS

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ABSTRACT:History of cancer therapeutics and its evolution in the last 80 years is bringing the limitations and toxicities associated with past and current cancer treatment modalities to our attention. Fundamental principles of cancer, namely CIN and ITH should get employed towards generation of future cancer therapeutics. Nano-technology could potentially enable us to tackle this problem in a fundamentally different way. By shuttling programmable nano-machine, into the tumor mass we could modify the genetic program and energetics of cancer cells. As such, we could slow down the speed of progress of cancer down the axis of time. This could potentially make cancer one of the many chronic diseases rather than a disease that kills the majority of patients within several years following diagnosis.

KEYWORDS: nano-machines for cancer treatment. tumor evolution. intratumor heterogeneity. future cancer therapeutics.

I. INTRODUCTION AND BASIC CONCEPTS

We have gone a long way in the last eighty years in the development of cancer therapeutics (DeVita & Chu, 2008). The centerpiece of drug discovery has been identification of more lethal agents while trying to minimize the associated toxicities (Sparreboom & Verweij, 2009).As we have become more knowledgeable about cellular pathways, cancer and cell biology, we have become more sophisticated cancer cell killers. Meanwhile, we have become aware of the associated limitations (Saltz, 2008).By the virtue of the two most fundamental pillars of cancer biology, namely, chromosomal or genetic instability and intra-tumor heterogeneity, tumor mass has become the beneficiary of past and current cancer therapeutics (Bakhoum & Landau, 2017).Cytotoxic agents and radiation therapy, for the most part promote evolution of tumor mass to a higher level of complexity through generation of new mutations.This has made achievement of cure a more formidable task (El-Deiry et al., 2017).Hormonal therapy, targeted therapeutic agents and the new generation of immunotherapy are far from a home run simply because they do not address the deep perturbances that have led to neoplastic transformation (Vogelstein et al., 2013).Thus, there is an urgent need for a shift in our thinking and strategy for development of future cancer therapeutics.

Based on evolutionary biology concepts, tumor mass acts as a sophisticated society armed with complex evolutionary means for survival (Venkatesan & Swanton, 2016).Each cancer cell in the tumor mass has acquired the identity of a society (Martin et al., 2013).In other words, it actively strives towards survival of other cells comprising the tumor mass, as much as it would defend and protect itself against threats to its survival originating from numerous sources including microenvironment (Alizadeh et al., 2015).As such, the best interest of one cancer cell, not only is its own best interest, but also is the best interest of other cells comprising the tumor mass population (Chigira, 1993).As one example, survival factors such as EGF residing in double minutes, would get released from the dying cancer cell to secure the survival of neighboring cancer cells (Henson & Gibson, 2006).Lack of incorporation of evolutionary cancer biology perspectives into the frame of our thinking has generated many false perceptions and definitions (Beerenwinkel et al., 2016).

One major example in this regard is the so called driver mutation that is used commonly in many publications and has become the target of many different drugs (Stratton et al., 2009).For the most part the majority of the developed drugs against driver mutations have had limited success (Nussinov et al., 2019).This is simply because down the path of evolution, tumor mass has adopted numerous drivers. Each driver drives only one step along this path (Iranzo et al., 2018).One step, however small it seems to be, indeed creates one future for the tumor mass. The future of tumor mass is generated one step at a time (Valastyan & Weinberg, 2011).During that short and however long step, that specific

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driver has to overcome the barriers preventing the forward move, during that step (McFarland et al., 2014).Following a forward move by one step, a new driver which is capable of handling the problems associated with the second step takes over (Brown et al., 2019).As Such, the tumor mass has many futures along its forward evolutionary move, and each future is guided and reached by a new driver (Greenman et al., 2007).That is why targeting one driver mutation can not prevent forward move of tumor mass and progression of cancer into metastatic stage (Sawyers, 2004).

The most fundamental law that has so far been ignored in development of cancer therapeutics, is the second law of thermodynamics and its fine interplay with living cell (Trevors & Saier, 2011).Living cell is the only machinery on the face of the known universe that has surpassed all other machineries, as far as minimizing the pace of rise in entropy is concerned (Davies et al., 2013).The hallmark of cancer cell is the breakdown of the fine interplay of this law with the living cell (West et al., 2012).This breakdown spreads to all cellular sub compartments, the way a wave spreads following the drop of a pebble in water (Henselmann & Welter, 2016).Chemotherapy and radiation therapy increase cellular or master regulator complex network entropy (Tarabichi et al., 2013).Neither hormonal therapy, nor targeted therapy and immunotherapy touch on this deep perturbation (Nijman, 2020). Chronic inflammation, which is the most immediate threat to the integrity of the living cell because of its pro-entropy effects, has already led to significant loading of cellular mutations in mid-life (Kiraly et al., 2015).This protective mechanism acts as a double edged sword, simply because as the cell gets older it flip flops in favor of neoplastic transformation (Aunan, 2017).Malfunction of telomeres and apoptotic machinery are among contributory factors to neoplastic transformation in an old cell (López-Otín et al., 2013).As such, we have the obligation to develop a new cancer therapeutic strategy that would decrease cellular network entropy.Hence, such a treatment strategy should be able to reverse the arrow of entropy by taking the malignant cell back in time (Luo et al., 2006).Cancer cells have numerous evolutionary paths and no two cancer cells have the obligation to go down the same path (Casás-Selves & Degregori, 2011).
Additionally, cancer cells can exercise their evolutionary freedom to change path.

II. METHODOLOGY

In figure 1, four major evolutionary pathways of malignant cells and their interchangeabilities and crossovers are depicted (Fittall & Van Loo, 2019).Our future cancer therapeutics strategy is going to be about changing the evolutionary path and game plan of tumor mass and not about destroying its game and path (Enriquez-Navas et al., 2015)Attempts at destruction of tumor mass have not withstood the test of time, witnessed by demise of metastatic and advanced stage cancer patients (Maeda & Khatami, 2018).We live at one of the most exciting times in the evolution of science and technology. Such advances, specifically in nano-technology could enable us to execute our future cancer treatment strategy (Gharpure et al., 2015).Along this line, programmable nano-machines are particularly attractive (Chen et al., 2013).

Figure 2 depicts different potential designs of these nano-machines.Such nano-machines could get delivered into the tumor mass either directly or systemically and they could get programmed to execute their task either physically or biologically (Haley et al., 2020)The first step is to do single cell sequencing of different zones of tumor mass (Saadatpour et al., 2015).For example, in case of glioblastoma-multiforme such single cell sequencing could be done in TMC/Tumor Mass Cell zone and STIC/Stem like Tumor Initiating Cell zone at the edge of tumor mass (Yi et al., 2016).In case of liquid cancers like leukemia, such single cell sequencing could be done on the stem cell compartment (Sachs et al., 2020).As such, one could determine the dominant evolutionary path of each cancer with its associated genetic and molecular details, including its master regulator complex entropy (Park et al., 2016)Consequently, programmable nano-machines could be designed and customized accordingly.Technologies such as Nuclear Magnetic Resonance spectroscopy could be used to measure the landscape energetics of receptors and molecules of interest (Sugiki et al., 2018).Delivery of electrostatic forces of interest, missing Micro-RNAs, or modification of genes of interest by CRISPR-Cas9 loaded on nano-machines are just a few different examples (Wei et al., 2020).

III. CONCLUSION

Programmable nano-machines are ready for prime time. We are armed with the technology that could enable us to do single cell sequencing of different cancer cells comprising the tumor mass, measure their molecular and genetic aberrancies, identify their master regulator complex network entropy (Liang et al., 2017) and decipher the landscape energetics of molecules and receptors of interest (Ma et al., 2019).We could employ nano-technology to deliver nano-machines into zones of interest in tumor mass or liquid cancers and make appropriate modifications.We need to

overcome our illusionary perception that sophisticated methodology of killing cancer cells is the way to cure cancer and embark on changing the evolutionary game plan of cancer (Pepper et al., 2009).

(FIGURE I)

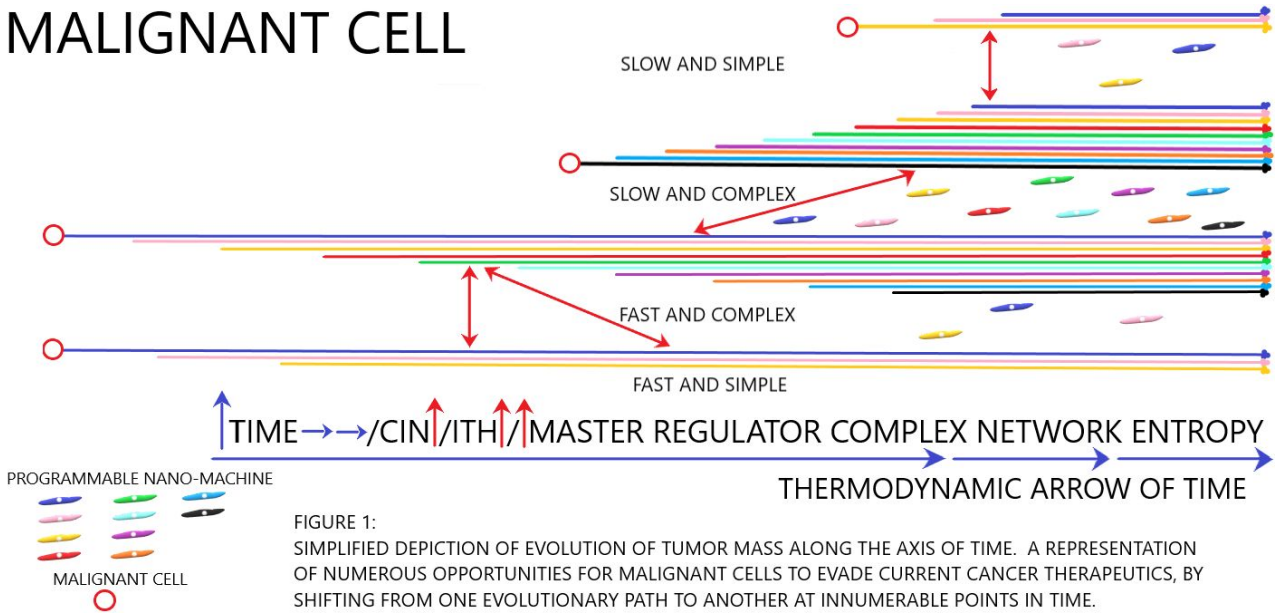

FIGURE 1:
SIMPLIFIED DEPICTION OF EVOLUTION OF TUMOR MASS ALONG THE AXIS OF TIME. A REPRESENTATION OF NUMEROUS OPPORTUNITIES FOR MALIGNANT CELLS TO EVADE CURRENT CANCER THERAPEUTICS, BY SHIFTING FROM ONE EVOLUTIONARY PATH TO ANOTHER AT INNUMERABLE POINTS IN TIME.

(FIGURE II)

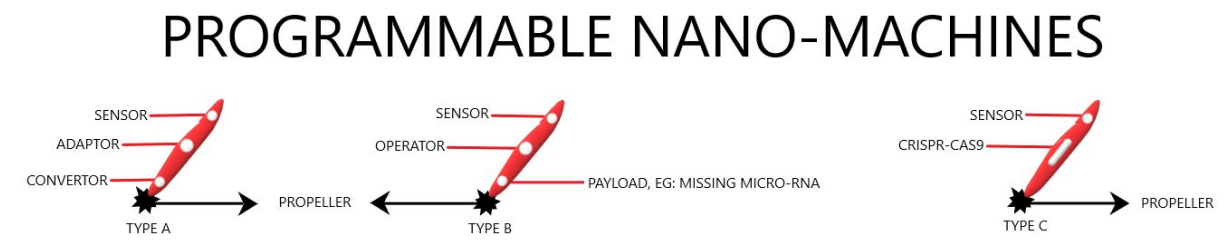

FIGURE 2

TYPE A: NANO-MACHINE COULD DELIVER THE ELECTROSTATIC FORCE OF INTEREST TO TAKE THAT VALUE TOWARDS NORMALCY. FOLLOWING IDENTIFICATION OF CANCER CELL OF INTEREST BY SENSOR.

TYPE B: NANO-MACHINE COULD DELIVER THE MISSING MICRO-RNA. FOLLOWING IDENTIFICATION OF CANCER CELL OF INTEREST BY SENSOR.

TYPE C: NANO-MACHINE COULD MODIFY THE GENETIC CODE OF INTEREST. FOLLOWING IDENTIFICATION OF CANCER CELL OF INTEREST BY SENSOR.

PROPELLER MOVES NANO-MACHINE AMONG TUMOR CELLS IN TUMOR MASS.

SENSOR IDENTIFIES CANCER CELL OF INTEREST, THROUGH NUMEROUS MECHANISMS INCLUDING A LIGAND SPECIFIC TO A RECEPTOR ON CANCER CELL OF INTEREST.

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