My own concept of the Synthetic Biology has evolved gradually between 1940 and 1970, starting at Politechnika Lwowska (Lvów Institute of Technology – the ‘Polish MIT’) in Lvów, Poland, when as a student I attended, in early 1940-thies, lectures by my professors: Edward Sucharda, on the first chemical synthesis in 1828 of a ‘natural’ organic compound, urea, from inorganic chemicals [these were the very beginnings of the era of SYNTHETIC ORGANIC CHEMISTRY], and Adolf Joszt, on the genetic engineering of microorganisms. Already then, I have decided that my future research endeavor would combine these two leads as to establish new field of bioengineering that I later named the SYNTHETIC BIOLOGY.

At that time, by a treacherous and callous consent between USA, UK and the arch villain, Joseph Stalin, my 600-years old Lvów, Politechnika Lwowska and a half of Poland were captured and ethnically cleansed by USSR, while the Polish Faculty and student body were deported, either to ‘wilderness’ of post-Nazi Western Poland or to various kinds of Soviet gulags, where most of them perished.

I found myself first in Gdansk, Poland, then miraculously in the Carlsberg Laboratory in Copenhagen, and ultimately as a staff member in the famous Cold Spring Harbor Laboratories in USA. My faith in DNA, which persisted since reading the 1944 paper of Avery et al., was now reinforced by my close association with Al Hershey, Marty Chase and their famous 1951 experiment, which proved that DNA, not protein, was transmitting the heredity of bacteriophages. Thus, it became clear to me that the essence of life depends on the chemistry of DNA, and that all what I learned about the synthetic organic chemistry from Professors Sucharda and Lesnianski in Lvów, Poland, pertains also to the double helix structure just discovered in 1953 by my friends Jim Watson and Francis Crick.

Although, it might be difficult for me to recall all the lectures and seminars where I have used my novel term of Synthetic Biology, some examples were preserved in various reviews and are also in Wikipedia, where under “Synthetic Biology” it says:

“In 1974, the Polish geneticist Waclaw Szybalski introduced the term "synthetic biology"...and wrote about "the new era of synthetic biology where not only existing genes are described and analyzed, but also new gene arrangements can be constructed and evaluated".
Control of eukaryotic gene expression: chromatin architecture and transcriptional memory

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Extraordinary progress has been made in the past twenty-five years toward understanding the structure of the eukaryotic genome and the mechanisms that underlie gene expression. Missing from the picture, though, is a fundamental understanding of the 3D organization of the genome and how higher order chromatin structure affects gene expression. Based on previously reported genetic and physical interactions between components of the transcription initiation and termination machineries in the yeast *Saccharomyces cerevisiae*, we have investigated the higher order structure of genes transcribed by RNA polymerase II (RNAP II). Using a powerful new technique, called “chromosome conformation capture” (3C), we have detected “gene loops” that specifically juxtapose promoter and terminator regions. Gene loops are formed following a pioneer round of transcription and are dependent upon components of both the initiation and pre-mRNA 3’-end processing machineries. We detect loops at every gene analyzed in our studies, suggesting that looping is a general phenomenon of RNAP II transcription. Analysis of the GAL10 gene demonstrated that looping persists for several hours through cell division following a cycle of galactose activation and glucose repression. GAL10 activation following initial exposure to galactose is relatively slow, requiring nearly two hours for full activation. However, GAL10 reactivation following a cycle of activation and repression is much faster, resulting in full activation in less than five minutes, a phenomenon defined as “transcriptional memory.” Remarkably, transcriptional memory is abolished in mutants that adversely affect looping. These results demonstrate that gene loops underlie transcriptional memory and define a physiological role for looping. We propose a model in which gene loops facilitate transcription reinitiation by translocation of RNAP II from the terminator to the promoter of the same gene. Gene loops have also been detected in mammalian cells, suggesting that looping might be a general feature of eukaryotic gene expression.

Design of clinical trials of therapeutic cancer vaccines

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Recent developments of advanced technologies for cancer treatment, including active immunotherapeutics, are not accompanied by proper clinical trials’ design modifications. Historically, rules designed for clinical testing of chemotherapy agents were automatically adopted for biological therapies which substantially differ in mode of action or profile and severity of toxicity. Various research groups have applied extremely different approaches especially for criteria for evaluation of clinical activity of therapeutic cancer vaccines. The need for uniform methodological criteria for clinical trials with new biologicals is driven by both industry and drug registration agencies but it is focused mainly on drugs interfering with signaling through growth factors’ receptors. Accordingly, we need to start discussion in the arena of cancer active immunotherapy.

Between 1995 and 2005 we have enrolled 445 advanced melanoma patients into phase I and II studies of various genes modified whole cell melanoma vaccines. 163 patients were in stage IIBC-IV with measurable metastases and 282 patients were in stage IIIB-IV with resected metastases. Four different vaccines based on two allogeneic melanoma cell lines were tested: (i) mixed autologous cells with allogeneic cell lines modified with IL-6 (interleukin-6) and soluble IL-6 receptor (sIL-6R) cDNAs — 24 patients; (ii) allogeneic vaccine modified with Hyper-IL-6 (fusion gene composed of linked IL-6 with sIL-6R) cDNA — 268 patients; (iii) allogeneic vaccine modified with Hyper-IL-6 and GM-CSF cDNAs — 96 patients; (iv) allogeneic non modified cells — 57 patients.

Conclusions of the above studies were: (i) It is useless to establish in Phase I the maximum tolerated dose (MTD) as these drugs exert maximal therapeutic effects far below the MTD. Phase I are needed as feasibility studies. An induction of an immune response (like induction of CTL activity) is no indication of anti-cancer activity; (ii) Optimal phase II endpoints should consider specific mode of action, time needed to elicit immune responses and potential to alter natural course of cancer; (iii) Conventional 3-stage clinical trial model is not an optimal methodological frame for therapeutic cancer vaccines. Traditional phase I and II could be combined in one-phase in order to assess feasibility, immunological and clinical activity and toxicity. In advanced cancer patients these early stage trial should even be a randomized study with control group and possibly survival as an primary end-point with less stringent statistical criteria for type I and type II errors.