In 1957, one of us (GK) participated in a 3-d meeting at The Burn in Scotland. The topic was "development, differentiation and cancer." The first day was devoted to a series of talks by embryologists. But each speaker was interrupted by Francis Crick in the beginning. He said: before you tell your story, explain why you work with embryos.

It was very embarrassing. Of course, embryologists work with embryos. Do they have to justify this?

Renato Dulbecco was in the chair. After Crick has repeated the same procedure for the sixth time he said "Francis, I am the chairman here, and I will not allow you to ask that question again. But before you shut up, please explain what you mean."

Crick answered:

Somebody says to you: I have discovered an enzyme that is a polysaccharide. Your immediate response is: I do not believe it. The fact that enzymes are proteins is therefore firmly established.

Another example in the days when it was still debated whether RNA viruses carry their hereditary information in nucleic acid or protein, one of the pioneers of the field, Fraenkel-Conrat was to give a seminar about Tobacco Mosaic Virus (TMV). Shortly before starting his lecture, he received a telegram from his laboratory: be very careful what you say. The last five experiments cannot exclude that TMV protein may be infectious.

Did Fraenkel-Conrat speak more cautiously? No. He immediately knew that this was a practical joke. It was already firmly established that the genetic information of RNA viruses is carried by their nucleic acid.

How many equally firm principles are there in biology?—Crick continued. Perhaps 10, not more. It is only worthwhile to work toward establishing firm principles. Therefore, you have to select your objects carefully. If you are interested in development and differentiation, take bacteria where billions can be induced to sporulate at the same time. Or take a single somatic cell from a carrot plant and allow it to generate a whole new plant. In systems like this you may find out something about the regulation of development. An embryo is a mess; you cannot learn anything from it.

I commented "Nothing is a model for anything else." Crick answered: "I could not disagree more profoundly."

This was in 1957. Crick was, of course completely wrong. It would not take long before transgenic and knock-out mice would provide precise experimental tools for the study of development.

Crick liked to throw out provocative statements. Fully aware of the distaste biologists would feel for the word "dogma," he formulated "the central dogma of molecular biology": "DNA makes RNA makes protein and it can never go backward." This dogma was challenged when reverse transcriptase (RT) was discovered in the RNA tumor viruses. In this case, the backward move was from RNA to DNA. But the central dogma was still valid for cells. Nevertheless, the dogma and the discussions it elicited led to better understanding of genetic regulation. The "reverse flow of information" and its tool the RT led to a search for it in human tumors, assuming that its presence would be a marker for RNA viruses that could contribute to tumorigenesis. We think of the 1970s that followed as the "panviral decade," a time of wrong concepts and awed experiments. For a long time, you could not speak of DNA tumor viruses or chemical or radiation carcinogenesis without someone asking whether latent RNA tumor viruses were not the real culprits.

We can illustrate this with a personal anecdote. In the early 1970s, we were at a meeting in Jerusalem, staying at the American Colony Hotel. Sol Spiegelman also stayed there. One evening, we had dinner in the beautiful garden restaurant. At one point, he suddenly looked at his watch and said that he must go to his room and call his lab in New York. He was gone for a full hour. He came back beaming: The cancer problem is solved.

Sol Spiegelman was one of the great pioneers of molecular biology. He invented molecular hybridization, the very basis of all nucleic acid work. His technique has later expanded in a
Deblocking may have a therapeutic effect. This argument is based on the normal program of the cell. If expressed in the proper window, they act by blocking the progression of the cell, allowing it to take an irreversible step toward differentiation. The tissue context and/or the normal development program of the cell thus plays an important role in determining the fate of the de-blocked cell.

Once it has entered the differentiation pathway it cannot turn back. Importantly, the production of infectious and transforming RSV was not influenced by the cell phenotype.

Basic experiments were performed on a chicken erythroblast system, driven by the temperature sensitive v-erbB oncogene and by Jain et al. on tamoxifen regulatable myc. The temperature sensitive v-erb B was switched off at the non-permissive temperature. Within half an hour or less the cells entered the irreversible pathway of terminal differentiation, as signaled by the appearance of DNase hypersensitive sites around the globin gene. The consequences of the myc switch-off depended on the cell type. The transformed osteo-blasts differentiated terminally into bone, and the thymus went to apoptosis. The tissue context and/or the normal development program of the cell thus plays an important role in determining the fate of the de-blocked cell.

Statement 1. Illegitimately activated or constitutively expressed oncoproteins may favor malignant transformation provided the cells are in a certain window of differentiation. If expressed in the proper window, they act by blocking the progression of the cell toward terminal differentiation or toward apoptosis, depending on the normal program of the cell. Deblocking may have a therapeutic effect. This argument is based on the early work of Holtzer and Boettiger. They showed that even temporary downregulation of the temperature sensitive Rous virus oncogene v-src in RSV-driven cells, allows the cell to take an irreversible step toward differentiation. The undifferentiated tumor cell differentiates to its original phenotype, melanocyte, osteocyte or chondrocyte.
have therapeutic implications toward tightening the surveillance of the patient.

Statement 5: Microenvironmental control is multicomponental and involves different players. This can be exemplified by the study of Partanen et al.19 The forward propelling force of the potential tumor cell—or its quiescence—is primarily determined by compounded changes at the cellular level. Oncogene activation initiates the drive. The induction of basal membrane function by Matrigel in 3D cultures of immortalized but non-neoplastic mammary epithelium leads to acinus formation. This may inhibit the forward propelling effect of the cellular changes. There is no such inhibition in 3D cultures in collagen where acini are not formed. Acinus formation may be blocked and Matrigel action prevented by knocking out the polarity gene LkB1.

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No potential conflicts of interest were disclosed.

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