



# Matters @ Heart

## *The endless river*

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As a child my parents took me to the source of the River Danube, a mere trickle of water destined to become a mighty river flowing past Vienna and Budapest to the Black Sea. I have chosen two examples, the discovery of p53, a tumor suppressor, and the discovery of insulin to show how great discoveries, like rivers, are insignificant and vulnerable at the beginning, but develop into mighty streams of science and medicine. There is as yet no end to these rivers of discovery, and their impact will be felt for years to come.

### p53

The earliest publications on p53 appeared in 1973. They described that after infection or transformation with a tumor virus, the simian virus SV40, an immunogenic protein could be precipitated. Further evidence showed that this protein is of cellular origin and is expressed in several murine

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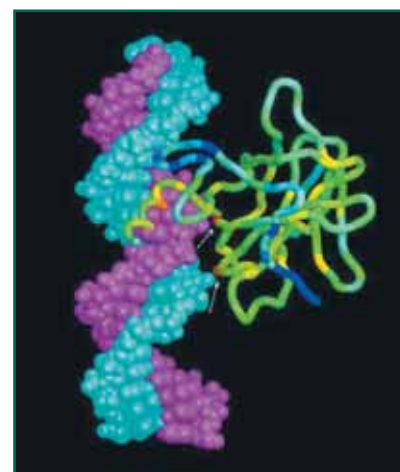
**FROM LITTLE TRICKLE...**  
One of the two contenders for the source of the Danube: the "Bregquelle" near Furtwangen, in the Black Forest, Germany. The square plate (in German) reads: "Source of the Danube. From here springs the main source of the Danube River, the Breg, at a height of 1078 m and a distance of 2888 km from its mouth. The source lies 100 m away from the watershed of the Danube and the Rhine, the Black Sea and the North Sea. © 2002, Haseluenne. All rights reserved.

carcinoma cell lines. The p53 protein is precipitated only by specific antibodies and is also found in tumors of nonviral etiology. At this point, like a meandering river, research on p53 took on a new course. It was the period in cancer research when oncogenes were the main and most fruitful topic. It was only natural to assume from these findings that p53 was an oncogene. Cloning of p53 furnished further evidence of its role in oncogenesis.

Now, the course of discovery changed again. It was found that the oncogenic effect of p53 was due to its mutations. Several mutants of p53 species were found, one containing a two-point mutation, the other a single different point mutation. It is the wild type of p53 which effectively interferes with the

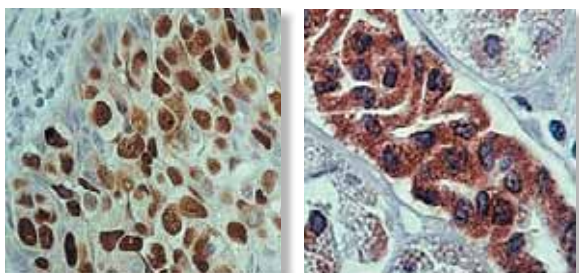
ability to elicit neoplastic transformation. Soon more evidence of the tumor inhibitory properties of p53 became available. Chromosomal changes in colon cancer had been known for a number of years, affecting primarily chromosome 17 where allelic deletions are expressed as mutations of the gene expressing p53. In colon cancer this deletion leads to tumor progression. Another evidence for the tumor inhibition by p53 was that mice lacking p53 are developmentally normal,

*p53 bound to DNA. The p53 molecule is colored according to the frequency of mutations (blue, very few; red many). Two of the most mutated residues are indicated with arrows. From: Cho Y, Gorina S, Jeffrey PD, Pavletich NP. Crystal structure of a p53 tumor suppressor-DNA complex: understanding tumorigenic mutations. Science. 1994;265:346-355. © American Association for the Advancement of Science.*



**INDIRECTED INACTIVATION OF p53**

**Nuclear exclusion of p53**



**Nuclear localization  
Mutant p53**

**Cytoplasmic localization  
Wt p53**

*Molecular and immuno-histochemical analyses demonstrate accumulation of wild-type p53 in the cytoplasm of tumor cells, leading to a functional inactivation of p53. After: Moll UM et al. Hum Pathol. 1992; 1995; 1996. © WB Saunders.*

but are very susceptible to spontaneous tumor formation. p53 accomplishes suppression of tumors by the triggering of apoptosis, programmed cell death. Apparently there are a multitude of mediators of p53-induced apoptosis, but in normal cells p53 is latent. A number of factors activate it, among them oncogenic activation, telomere attrition, nitric oxide and others. Like Moshe Oren writes in his Harvey Lecture, "all this extensive understanding will culminate in the development of new strategies to treat cancer". We only can hope that he is right.

practice was not lucrative and gave him time to think of advancing the cure of diseases, especially diabetes. One day he came across an article which described that ligation of the pancreatic duct leads to the digestion of the exocrine tissue while leaving the Islets

of Langerhans intact. This became Banting's idée fixe. Why not, he reasoned, tie the pancreatic duct in dogs and then extract the sugar-lowering substance from the remaining tissue? With this idea he went to Professor Macleod, the head of the department of Physiology at the University of Toronto. On his way to his native Scotland for vacation, Macleod gave Banting inadequate facilities in his department. He obviously expected little from a country surgeon. A young student, Charles Best, joined Banting during the summer and the two started to work on dogs by ligating their pancreatic ducts and extracting the remaining pancreatic tissue. The original idea of ligating the pancreatic duct was soon discarded in favor of using the whole pancreas. By the time Professor Macleod returned from Scotland,

**INSULIN**

The discovery of insulin occurred about 80 years before that of p53. At the time of the discovery of insulin, the nature of the gene and most of the biochemical processes were unknown. But the human drama of the discovery of insulin, with its small beginnings could have happened at any time in the history of science. The small brook of discovery was many times in danger of drying up.

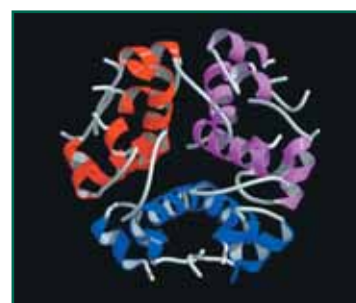
It started with Frederick Banting who practiced surgery in London, Ontario, at the beginning of the twentieth century. His



*From left to right: Charles Herbert Best (1899-1978). Frederick Grant Banting (1891-1941). John James Richard Macleod (1876-1935). © Wellcome-images.*



*The pancreas and the pancreatic duct. Engraving by Johann Georg Wirsung, 1644. © Wellcome-images.*



*Molecular model of insulin. Each dimer is shown in a different color. Insulin consists of two polypeptide chains (A and B) linked by disulfide bonds. © Wellcome-images.*



**The endless river - Bing**

Banting and Best were on the way to discovering insulin. When Macleod saw the progress, he tried to take over the project which he previously had considered with scorn.

I cannot help but speculate how Banting and Best's idea would play today. The animal rights committee would never have given the go-ahead for the use of dogs under these circumstances. As far as the granting agency is concerned, it would have written a scathing report, calling it a fishing expedition and the investigators unfit to undertake this task. On the other hand, they would have approved a sophisticated application submitted by Professor Macleod to study the effect of low carbohydrate diet on diabetes. Almost 100 years have passed between the discoveries of insulin and p53. As to be expected there are many differences, foremost in technique. The work on insulin was confined to tissue extraction with hydrochloric acid and alcohol. For p53 there was a long chain of techniques: cell cultures, transfection, transcription, immunoprecipitation, radiolabeling, hybridization,



...TO MIGHTY RIVER. The Danube in Budapest, with the Széchenyi Lánchíd (Chain Bridge) and Parliament. © Jon Hicks/CORBIS.

northern and southern blot, and others. Working with p53 needed thousands of dollars for equipment, running expenses, and salaries. In contrast, Banting and Best received no salary. In the case of insulin the idea came first, while the significance of p53 was recognized only later as a result of many

experimental findings. Banting was a country surgeon and Best was a student, while workers on p53 were highly trained scientists.

Banting and Best's discovery of insulin was the triumph of an idea; the discovery of p53 as a tumor inhibitor was the result of sophisticated techniques leading to significant experimental results. And yet, both discoveries had something in common: like the source of a river, the beginnings were modest, but then the river became a mighty stream, still coursing toward the distant sea. Both the discoveries of insulin and of p53 will influence the progress of medicine for years to come.

**FURTHER READING**

**Best HBM.**

*The personal story of Dr Charles Best: The co-discoverer of insulin.*  
Toronto, Canada: The Dundurn Group; 2003.

**Oren M.**

*The p53 saga: The good, the bad, and the dead.*  
*The Harvey Lectures.* 2001-2002;97:57.