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Dedicated to Professor Claude Nicolau
on the occasion of his 80th anniversary

CLAUDE NICOLAU AND THE BIOTECHNOLOGY INDUSTRY

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I met Claude Nicolau in the nineties in the kitchen of our common friend Carl Alving in Bethesda, MD. We were discussing the development of the Biotech Industry in the USA as compared to Europe. Carl had been already involved in the founding of a Biotech Company in Rockville, MD and told us about the stages and mechanisms of such undertaking. We kept in contact, Claude Nicolau and I, since we had overlapping scientific interests and communicated with each other easily and pleasantly.

During a conversation with Professor Jean-Marie Lehn in 1999, Claude Nicolau discussed a recent invention that he had made and patented called Dynamic Combinatorial Chemistry (DCC). It appeared likely that it could contribute substantially to the rapid synthesis of a variety of drugs and be a technological platform worth developing and commercializing. Together with several friend and colleagues, it was decided to found a company called Therascope. Together with Dr. W. Stoiber, an expert in fund raising for very early biotechnology companies, they went on a "road show" and raised sufficient funds to start working. Nicolau wrote a grant application about the use of DCC and submitted it to the German Federal Ministry of Research and Technology. The grant was awarded and he and Lehn began to organize a company in Heidelberg, Germany. Nicolau was the first Chief Scientific Officer. He created the necessary laboratories, hired the scientific personnel and initiated scientific investigations. The Company developed well and a number of successful patent applications and publications in leading journals followed. A second round of financing was completed successfully in 2002. The company changed its profile somewhat and its name to Alantos. The headquarters were moved to Cambridge, MA, but laboratories were kept in Heidelberg. Seven years after the founding of the company, it was acquired by Amgen, a large American Biotechnology Company.

AC Immune

In his laboratory at the Center for Blood Research, an affiliate of Harvard Medical School in Boston, MA, Nicolau started working on breaking the immune tolerance of organisms towards some "self" proteins. The goal was an immunotherapy against Alzheimer's disease. His first published work in this field in 1995 dealt with the breaking of the immune tolerance to the P-glycoprotein in animals bearing tumors. The results were encouraging and he applied for a grant to extend this work towards the breaking of the immune tolerance to amyloid aggregates (plaques), especially to beta amyloid in beta-sheet conformation. The results indicated that the antibodies elicited by the "supramolecular antigen" solubilized the amyloid aggregates *in vitro* and reduced the plaque burden in animals transgenic for Alzheimer's disease (AD). These findings were published in 2002. After discussing them extensively with Jean-Marie Lehn, they concluded that it was justified to create a new company in order to develop and commercialize the following agents:

1. A vaccine against Alzheimer's disease for an active immunotherapy against the disease.
2. A monoclonal antibody against beta-amyloid that is conformation sensitive, capable of dissolving amyloid plaques *in vivo* and having a therapeutic effect on Alzheimer's disease.
3. Morfomers – a term coined by Jean-Marie Lehn to describe compounds able to interact specifically with beta-amyloid , in this case.

Discussions with colleagues and friends (Roscoe Brady, Fred van Leuven, Detlev Riesner, Ruth Greferath) helped refine the project. We needed a chief executive officer (CEO) for the new company. Dr. W. Stoiber, who Dr. Nicolau had asked to be the CEO of the new company, recommended Dr. Andrea Pfeifer, formerly at NESTLE for the position. She came to Strasbourg and presented her past activities and became acquainted with the Alzheimer's disease project and the Nicolau's first patent application filed on the subject. She was introduced to Jean-Marie Lehn who explained the morphomer approach. Jean-Marie Lehn and Claude Nicolau offered her the position of chief executive officer in the new company. She accepted and AC Immune was thus born. Nicolau was its first chief scientific officer who continued to direct the scientific work of the company and laid the basis of the future development of an anti-Alzheimer's disease therapy.

AC Immune developed well. Major steps forward were the agreements with Genetech (Roche Holdings) that led to the successful completion of a Phase I and a Phase II clinical trial of the company's monoclonal antibody, Crezenumab. Presently this monoclonal antibody is in a Phase III clinical trial on a large number of patients with Alzheimer's disease. The "Supramolecular Antigen" technology was extended to eliciting anti-tau antibodies that appears to open interesting therapeutic applications against Alzheimer's disease. The successful work in developing anti-Alzheimer's disease immunotherapy enabled AC Immune to conduct an Initial Public Offering (IPO) on the New York Stock Exchange (NASDAQ).

NormOxys

While Nicolau was working at the Max-Planck Institut für Strahlenchemie (Radiation Chemistry), Muelheim/Ruhr in Germany in 1977, he started studying with Klaus Gersonde, a colleague from the Rheinsch-Westphaellische Technische Hochschule in Aachen the possibility of the modulation of oxygen delivery by red blood cells (RBCs)using l allosteric effectors of hemoglobin that were more powerful than the human allosteric effector 2,3-bis phosphoglycerate. The first results published in 1979 indicated the possibility of such modulation. In France at the Centre de Biophysique Moleculaire du Centre National de la Recherche Scientifique where Nicolau worked between 1981 and 1986, he pursued this work and obtained very interesting results concerning the physiological effects of the reduction of hemoglobin's affinity for oxygen in a pig model. He continued this work at Harvard Medical School in the Center for Blood Research between 1991 and 2002. The results suggested the possibility of important therapeutic applications of this approach. However, there was a serious drawback. The allosteric effector of hemoglobin, inositol hexaphosphate (IP6) which he was using was a polyanion that could not cross the plasma membrane of red blood cells. He and his coworkers invented, patented and published a number of physical methods for the encapsulation of IP6 in red blood cells *ex vivo,* with good results. Unfortunately these methods were tedious, complex and difficult to use in a clinical setting. Nicolau contacted Jean-Marie Lehn and asked him whether it might be possible to synthesize an allosteric effector of hemoglobin having IP6 properties; *e.g.*, being more powerful than 2,3- bis phosphoglycerate and being water-soluble, capable to cross the plasma membrane of red blood cells and non-toxic up to high doses. Lehn said "We'll see". A few months later his laboratory came up with myo-inositol tris pyrophosphate (ITPP) that fulfilled all of these requirements. Together with their friend Conrad J. Bletzer,Jr, C.Nicolau and J-M Lehn, founded a third company called OxyPlus to develop and commercialize ITPP and its use. The name was later changed to NormOxys.

Knowing the important role of hypoxia in the growth of tumors, they used IPTT to treat early Morris hepatoma in rats. The tumors were completely eradicated five weeks after the beginning of administration of ITPP. Other experiments followed with Melanoma B16 in mice, pancreas adenocarcinoma in rats; colon cancer in mice; prostate cancer in rats all with very encouraging results. ITPP is currently in a Phase II Clinical Trial at the University Clinic in Zurich, Switzerland on patients with cancer of the biliary tract. ITPP appears to act in a two-fold manner. It increases the oxygen tension in tumors after being injected i.v. or intraperitoneally. It activates the phosphatase and tensin homolog (PTEN) leading to the normalization of the tumor vasculature.

Few people with whom I am acquainted have accomplished so many significant advances in medicine as Claude Nicolau. I am grateful for the opportunity to touch on his many accomplishments.