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Review article

Hubrecht Institute Centennial – From embryos to stem cells

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A B S T R A C T

During the last 100 years, the Hubrecht Institute evolved from a small laboratory aimed at providing research material to the scientific community to a modern, fully equipped research institute with state-of-the-art infrastructure, performing research at the highest standard. The past 100 years have been eventful for the Hubrecht Institute with many glorious moments, but also threats to be shut down on several occasions. Here, we will briefly review the rich history of the Hubrecht Institute.

1. Founding of the Hubrecht Laboratory

Ambrosius Arnold Willem Hubrecht died in 1915, leaving behind his official residence in the center of Utrecht, the Netherlands (Fig. 1A) and a collection of embryological specimens. None of his relatives had the ambition or the capacity to follow in his footsteps. Instead, his wealthy and proud family set up the Hubrecht Foundation to salvage his scientific heritage. Thus, the Hubrecht Laboratory was founded in 1916. The following year, the house and collection were bequeathed to the Royal Netherlands Academy of Arts and Sciences.

Ambrosius Hubrecht was born in 1853. He was an intelligent child and at 16 years of age, he started as a student at the technical university of Delft with a great interest in marine research. Fortunately for all of us at the Hubrecht Institute, already after one year he switched to zoology in Utrecht. At the age of 31, he successfully defended his Ph.D. thesis on the anatomy and development of certain worms at Utrecht University. Ambrosius Hubrecht was an original, visionary, internationally oriented person and scientist, and contemporary of Charles Darwin. He was a firm protagonist of Darwin's theory and is considered to be the first Darwinist in the Netherlands. Hubrecht and Darwin never met in person, despite Hubrecht's attempts to arrange a visit to Darwin. However, Hubrecht did correspond with Darwin. A letter from Darwin to Hubrecht is preserved from which it is evident that Darwin did not always agree with Hubrecht's theories, which may have had a role in Darwin's evasion of Hubrecht's attempts to visit him. Nevertheless, Hubrecht believed that phylogenetic relationships were reflected in conservation of embryonic development, which prompted Hubrecht to collect and study embryos of early mammals.

Comparative embryology was not Hubrecht's only interest. He retained an interest in marine research, even though he switched to zoology early in his academic career, and he was a co-founder of the Royal Netherlands Institute for Sea Research. In addition, he was a co-founder of the Zoological Station in Naples and he was on the board of several other national and international scientific foundations. Importantly, Hubrecht was co-founder of the Institut International d'Embryologie (IIE) in 1911 in Paris. The IIE (which was renamed to International Society for Developmental Biology, ISDB) aimed to become an international platform to discuss aspects of comparative embryology. All co-founders returned to their home-countries to stimulate the founding of international research institutes in their respective countries. We now know that only Hubrecht succeeded in this mission, or actually his family, who founded the Hubrecht Laboratory in the name of their famous scion, Ambrosius Hubrecht.

Daniel de Lange became the first director of the Hubrecht Laboratory or International Embryological Institute. The bylaws stipulated the relationship between the IIE and the Hubrecht Laboratory and indicated that the IIE would legally be located at the premises of the Hubrecht Laboratory. In addition, the Hubrecht Laboratory was to take care of embryological collections in need, which resulted in the temporary housing of the famous research material of Spemann during World War One. Moreover, the Hubrecht Laboratory facilitated access to its embryological collections, in line with the spirit of Ambrosius Hubrecht, to provide services to the community of comparative embryologists. The Hubrecht collection and several other embryological collections were housed on Hubrecht premises well into the 21st century, when they were moved to the Natural History Museum in Berlin, where they are still accessible for scientists with an interest in comparative embryology.

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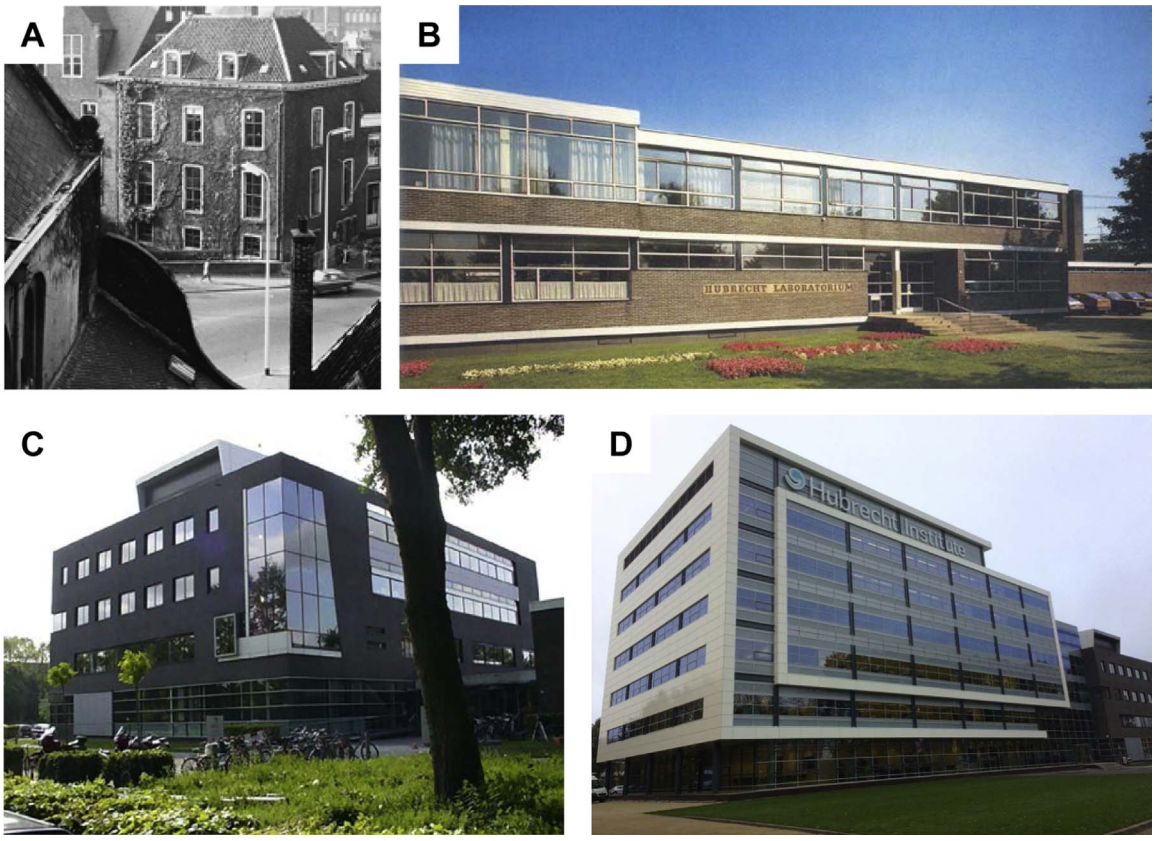

Fig. 1. The Hubrecht Institute building over the years. (A) 1916 – 1964, Janskerkhof, Utrecht. (B) 1964 – 2000, Uppsalalaan 8, the first building on Utrecht University Campus, the "Uithof". (C) 2000 – present, on the same premises at Uppsalalaan, a new building was built, connected to the former Hubrecht Laboratory. (D) 2015 – present, an extension was completed to house more Hubrecht research groups as well as research groups from University Medical Center Utrecht on the top two floors.

2. From comparative embryology to developmental biology and stem cell research

Scientifically, the Hubrecht Laboratory evolved from an institute that provided services for the comparative embryology community to a modern research institute that performs cutting edge science, focusing on developmental biology and stem cell research in the broadest sense. The history of science at the Hubrecht Laboratory in the 20th century has been reviewed by Faasse et al. (1999). Briefly, the science evolved from descriptive comparative embryology, initiated by Ambrosius Hubrecht himself, via experimental embryology in the Nieuwkoop years to molecular biology and (adult) stem cell research in the present day.

In line with Hubrecht's vision, initially the Hubrecht Laboratory, headed by Daniel de Lange, provided services to the community, in that the collection of Hubrecht and other embryological collections that were housed on Hubrecht premises in the center of Utrecht were made available to the embryological community. During World War II, all embryological institutes in the world, including the Hubrecht Laboratory were disconnected due to intellectual isolation, and the Hubrecht was almost closed down. In 1947, Chris Raven, professor of zoology and embryology at Utrecht University and associated with Hubrecht history at several critical moments (see below), became director of the Hubrecht Laboratory. In 1953, he stepped down as director, only to hand over to his pupil, Pieter Nieuwkoop. Raven became head of the board of the Embryological collection, the Hubrecht Foundation Fund, a powerful position, because all decisions had to be approved by him. Pieter Nieuwkoop focused on experimental embryology, rather than comparative embryology. Yet, Nieuwkoop still believed that providing information to the community was a key activity of the Hubrecht Laboratory. Due to the changes in the type of research that was done at the Hubrecht, it became apparent that the former official residence of Ambrosius Hubrecht was no longer able to accommodate the growing Hubrecht Laboratory. At the end of the 1950's, Chris Raven and Pieter Nieuwkoop managed to convince the minister of Education and Science that a new building was required for the Hubrecht Laboratory. To substantiate the claim that the Hubrecht Laboratory was of critical international importance, they brought a box full of stamps that were taken from letters and correspondence, diligently collected over the years, as evidence that the Hubrecht Laboratory had a central role in the international embryological community of that time. As a result, the Hubrecht Laboratory received funds for a new building on Utrecht University campus, "de Uithof" (Fig. 1B). Collecting stamps from all correspondence that was received by the Hubrecht Laboratory continued until well into the 1980's, despite the dislike of some that all their mail was mutilated by removal of the stamps. One never knows when these might come in handy. After all, the Hubrecht stamp collection had already resulted in a new laboratory building!.

Pieter Nieuwkoop stayed on as director of the Hubrecht until his retirement in 1980. As a scientist, Nieuwkoop did not retire at all and he continued to do experiments until a couple of weeks before he died in 1996. Nieuwkoop is world-renowned among developmental biologists because of his ground-breaking experiments using *Xenopus* embryos. The Nieuwkoop Center was named after him and is a group of cells in the dorsal- and vegetal-most region of the early blastula, which induces the Spemann organizer. The importance of the Nieuwkoop Center and Spemann organizer is underlined by the notion that axial organization is defective in embryos having smaller or larger organizers due to experimental intervention and that without an organizer the embryo develops no body axis (Gerhart, 2001). Nieuwkoop is also well-known for the Normal Table of *Xenopus laevis*, a series of 66 developmental stages and their structural descriptions of this amphibian model that was first published in 1967. An update was

published decades later (Nieuwkoop and Faber, 1994), and is widely used by developmental biologists to date.

Whereas important insights into embryonic development were gained from experiments of Nieuwkoop and others at the Hubrecht Laboratory, the scientific landscape was shifting. Ever since the discovery of the structure of DNA in 1953, researchers were getting more and more interested in the molecular genetics and the molecular biology of biological processes, including developmental biology. At the end of the 1970s, the Hubrecht Laboratory still focused primarily on experimental embryology. Marc Kirschner, a visiting scientist on a 7 month sabbatical in 1978, and John Gerhart, whose stay at the Hubrecht Laboratory overlapped, agreed that "compared to most laboratories, the Hubrecht was unusually focused in descriptive morphology and lacked the modern core of molecular biology and biochemistry" (Kirschner, 1999). Nieuwkoop was not about to change this. In fact, Nieuwkoop's opinion about molecular biology was documented in a publication years later (Nieuwkoop and Koster, 1995): "In this study the authors did not use molecular markers, because the first author, having more than 50 years of experience in normal and atypical histology, is perfectly sure of the correct identification of all the definitive larval structures. The reliance on molecular markers has actually given rise to misinterpretations in several recent articles, since the majority of molecular markers are expressed at rather early stages of development at which identification of structures is still uncertain."

At the end of the 1970s, there were intense debates at the Hubrecht Laboratory about the direction of the research. Particularly Paul van der Saag and Siegfried de Laat were strong proponents to start using stem cells as model system and to introduce molecular genetics and molecular biology into the Hubrecht Laboratory. Years of discussions within the Hubrecht Laboratory and with committees of the Royal Academy of Arts and Sciences followed. In the meantime, van der Saag and de Laat introduced neuroblastoma cells as a model for neuronal differentiation against Nieuwkoop's will. Finally, the crisis was resolved by emeritus and patriarch of the Hubrecht, Chris Raven. He decided the rebels should have their way and continue. As a result, Nieuwkoop stepped down as director in 1980 and the Royal Academy of Arts and Sciences went looking for a successor. Years went by, searching for a new director, to no avail. In 1983, Siegfried de Laat was summoned to appear at the Board of the Royal Academy of Arts and Sciences. Expecting that he would be fired because of revolutionary activities, de Laat got two options: (1) the Hubrecht would be shut down, or (2) de Laat was to become director under the condition that the turmoil would be put to rest. De Laat asked for a grace period of one week and he figured that closing down the Hubrecht would have been a great waste and therefore he accepted the position of director.

Stem cells and molecular biology entered the Hubrecht and the institute flourished. More and more PhD students were appointed and graduated from the Hubrecht. The Hubrecht had a central role in founding the graduate school for developmental biology in 1992, together with Utrecht University and University Medical Center Utrecht. To date, the Hubrecht is at the heart of this graduate school. De Laat retired as director of the Hubrecht Laboratory prematurely in 2000, for health reasons caused by a car accident in 1992. During the intervening 8 years, however, de Laat worked hard to improve laboratory conditions that had become dated in the building now 30 years old. This was a great achievement and de Laat's retirement coincided with moving to a new building in the backyard of the existing building (Fig. 1C). Ronald Plasterk was appointed to replace de Laat as director of the Hubrecht in 2000. Plasterk brought more hardcore molecular biology to the Hubrecht and at the same time, he broke with traditional comparative embryology. Under Plasterk's guidance - to the dismay of some – a new accommodation was found for the Hubrecht collection and several other collections that were housed in a vault in the basement of the Hubrecht at the time. To ensure continued accessibility to the collections for scientists and to have the opportunity to put items on display for the general public to see and enjoy, Plasterk argued that the Hubrecht collection would be better off in a museum. University museum Utrecht did not have the capacity to hold the Hubrecht collection. Fortunately, the natural history museum in Berlin, Germany, was willing and able to curate the Hubrecht collection and they have the Hubrecht collection on permanent loan now, while the Royal Academy of Arts and Sciences still owns the collection.

Plasterk also introduced a co-director into the Hubrecht, Hans Clevers. With Clevers, stem cell research at the Hubrecht was affirmed and research on adult stem cell was introduced. In 2007, instigated by Plasterk, the name of the Hubrecht Laboratory was changed to Hubrecht Institute to reflect that the institute comprised multiple laboratories. Plasterk suddenly stepped down as director in February 2007 to pursue a career in national politics, first as minister of Education, Culture and Science in the Netherlands. Clevers forged an affiliation with University Medical Center Utrecht in 2008, which entailed a significant financial injection, rendering the building too small before too long. He convinced the Royal Academy of Arts and Sciences to invest in a sizeable extension of the building, which was completed in 2015 (Fig. 1D). Clevers searched for a co-director for some time, until he recruited Alexander van Oudenaarden in 2012, a physicist by training with a keen interest in quantitative biology, who became acquainted with the Hubrecht during a 6 month sabbatical at the Hubrecht in 2009. Already before van Oudenaarden arrived to take his post as co-director, Clevers left his position as director of the Hubrecht to become president of the Royal Academy of Arts and Sciences, leaving van Oudenaarden as the sole director of the institute.

The Hubrecht Institute continues to flourish. Experimental model systems that are being used include (stem) cells, organoids, *Drosophila*, *Caenorhabditis elegans*, zebrafish, mice and rats as well as *Xenopus laevis*, which were re-introduced into the Hubrecht after an absence of some 10 years. Research topics vary greatly between the research groups (see www.hubrecht.eu), although all fall within developmental biology and stem cell research in the broadest sense. Multidisciplinary research, resulting from collaborations between research groups within the Hubrecht have been recognized to generate important breakthroughs in recent years. Given the rich history of the Hubrecht of the past 100 years and the tremendous change in research direction and research opportunities over the past century, it is impossible to predict what the next century or even the next decade will bring. With the current accommodations and research infrastructure, the circumstances are ideal for the Hubrecht Institute to thrive in many years to come.

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