



Alpha and Omega: from the Sagrada Familia to Placenta and Cancer

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The links between architecture and science are as old as these human achievements. But modern scientific thought and methods are much more recent than architecture. In 1660, Christopher Wren gave a lecture at one of the regular meetings of the natural philosophers who used to meet at Gresham College in the city of London, and there it was decided to form a society for the promotion of "Physical-Mathematical Experimental Learning". Two years later the Royal Society (now the National Academy of Sciences of the United Kingdom) was born. The Catalan architect Antoni Gaudí was more interested in geometry and God than in scientific research. His obsession with the Alpha and Omega is clearly visible in many of his works. Here we briefly review his impact on his masterpiece in Barcelona, and a certain symbolic conceptual parallelism with the hypothesis that some mechanisms of immunological escape from the placenta (which physiologically lead to Birth) may perhaps be redistributed by cancer cells to avoid immune surveillance (which pathologically leads to Death).

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Alpha and Omega: from the Sagrada Familia to Placenta and Cancer

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Abstract

The links between architecture and the sciences are as old as both of these human achievements. But modern scientific thought and methods are far more recent than architecture. On 30th November, 1660, Christopher Wren (the architect of Saint Paul's cathedral in London, among other endeavours) delivered a lecture at one of the regular meetings of the natural philosophers who used to meet at Gresham College in the City of London, and at that meeting it was decided to form a society for the promotion of 'Physico-Mathematical Experimental Learning'. Two years later, King Charles II granted the new body his personal imprimatur in the form of a charter, and so the Royal Society was born. Today the Royal Society is the United Kingdom's National Academy of Science, and it recently celebrated its 350th anniversary. The Catalan architect Antoni Gaudi was more interested in geometry and God than in scientific research, but he conceived a large part of his Sagrada Familia in 1911 when seriously ill with brucellosis (also known as Malta fever, or Mediterranean fever). His obsession with the Alpha and the Omega (the Beginning and the End) is patently visible in many of his works. Here we briefly review its impact on his masterpiece in Barcelona, and a certain symbolic conceptual parallelism with the hypothesis that some placental immune escape mechanisms (physiologically leading to Birth) may perhaps be redeployed by cancerous cells to avoid immune vigilance (pathologically leading to Death).

Keywords: Placental Immune Editing Switches, Foeto-Maternal Tolerance, Carcinogenesis, Immune Checkpoints, Antoni Gaudi



The 'Sagrada Familia'

Gaudi built the temple of La Sagrada Familia (meaning "the Holy Family") in Barcelona as a continuation of the effort to build the medieval cathedrals. An expression of faith through beauty, technique, and the will of the people, as were the cathedrals of Notre Dame, Cologne, and Santa Maria de Burgos, among many others.

Although not finished, it is already a symbol of Barcelona (Figure 1). It is not surprising that the most international guide to the city, that of Robert Hughes, states that "the Holy Family is the emblem of the city, as the Eiffel Tower is for Paris or the Harbour Bridge for Sydney."



Figure 1. An unfinished Sagrada Familia with the last five central spiralling towers symbolizing the Four Evangelists and Jesus Christ in his Glory, and the Virgin Mary tower.

The architect only almost finished part of the northern part of the temple, or "Birth" (meaning the birth of Jesus), with four original spiralling towers, reminiscent (for a Cambridge biochemist) of "protein cell membrane receptors", before he died at the age of seventy-four (in 1926, run over by a tram). We had to wait over fifty years before another less well-known artist (Subirachs) finished the four opposite (southern) lateral towers of "Passion" ("Death of Jesus").



The powerful symbolic message is the Alpha (in the north) and the Omega (in the south): the Beginning and the End (Miguel H. Bronchud, 2011). Birth and Death.

There is no authentic Gaudi model, or complete drawing of the culmination of the main tower of his work, the great central tower (or dome) of Jesus Christ. It has not reached us. It is assumed that it was lost or destroyed even if it existed at the time, perhaps only as a “blurred drawing or sketch” (Figure 2), since this piece of the Gaudian puzzle is undoubtedly the piece that culminates all his work, at a height of about 180 metres. There are indirect descriptions of students or collaborators, such as that of Rafols. In the latter, the young architect and assistant to the teacher clearly explains, a few years after the death of the genius, that the central tower, which was already beginning to rise from the Upper Room on the Transept — a spectacular room, about 40 metres high, inside what could be interpreted as an “upper temple” — would be completed by a cross that would dominate all of the great work. The exact shape and dimensions of this apical cross on top of this central tower remain a mystery, but builders and the Catholic Church are under logical public pressure to respect Gaudi’s favourite 3D “six arms cross”: four equal arms on the horizontal axis (representing the four cardinal points but also our four space and time dimensions) and two longer arms on the vertical axis representing the enigmatic Upper and Lower spiritual worlds. This would be a cross unlike the two other, more conventional, Christian shapes called the Greek Cross and the Latin Cross. The term Greek Cross designates a cross with arms of equal length, as in a plus sign, while the Latin Cross designates a cross with an elongated descending arm.

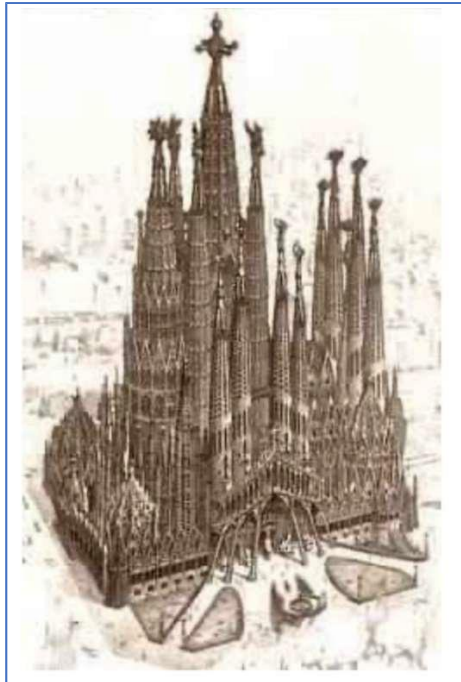


Figure 2. A deliberately “blurred drawing” of the Sagrada Família in Barcelona, left unfinished by the genius Antoni Gaudí. It can only be an approximate sketch, as the original final plans of the central spiralling towers were lost (some got burnt during the Spanish Civil War 1936-39, long after the master architect’s death).

The skyline of Barcelona is preparing for its new face. Less than ten years before the expected end of the impressive work of Antoni Gaudí, perhaps in 2026, the works that began over 136 years ago are facing the final stage: the construction of the six central towers. Of these, the tallest and most important one, that of Jesus Christ, was begun last October and will be exactly 172.5 metres tall. In addition to the impressive central tower of Jesus Christ, the four surrounding central towers of the Four Evangelists and the one dedicated to the Virgin Mary continue to rise. They will be lower than the most important central one, but will be larger than the current eight that preside over the Passion facades and the Birth (or “nativity”).

The final temple must have, according to Gaudí, 18 towers.

Hypotheses about Placental Immune Editing Switches (PIES).

Two studies published between 2016 and 2019 in *Oncotarget*, and their subsequent published reviews (Bronchud 2018, Bronchud et al. 2016, Bronchud, Tresserra & Zantop 2018, Hernández-Bronchud 2019), identified several dozen immune-regulating genes that we have found to be overexpressed in cancer cells, mimicking placental cells, and also identified



another long list of immunoregulatory genes that cancer cells manage to silence analogously to the placenta to prevent rejection. These studies start from the hypothesis that tumour development takes as an example of behaviour the growth of the foetus within the maternal body. To understand this analogy well, it is necessary to focus our attention on the similarity between the two processes: pregnancy is a cellular multiplication of a strange being, formed partly with biological material from another living being (including at times the two different living beings, father and mother, in cases of certain in-vitro and “maternal surrogacy” procedures). But far from rejecting this foreign or half-foreign body, the woman's body accepts it, and protects it throughout development because, during the growth of the foetus, the placenta serves as a barrier between the different immune systems to allow maternal and child tolerance.

The powerful symbolic message here is also the Alpha (placenta and birth), and the Omega (cancer and death): the Beginning and the End.

Thus the main contribution of PIES is simply the first clinical and molecular evidence for something which we were not taught at medical school: cancer cells can probably redeploy the immune regulatory mechanisms that foetal cells use to suppress rejection by the maternal immune system (Bronchud 2018, Bronchud et al. 2016, Bronchud, Tresserra & Zantop 2018, Hernández-Bronchud 2019). These “placental immune editing switches” have probably evolved over the past 10-150 million years to allow for different types of invasive uterine placentation models, in accordance with other models of “convergent evolution” or pleiotropy.

In order to verify this reasoning, a genomic study (Nanostring Technologies Pan Immune Panel, Seattle, USA) of six different biological tissues of the same pregnant patient, who developed breast cancer at the end of pregnancy, was carried out. The objective was to identify which immune-regulation genes were present in the patient's placenta to allow maternal-foetal tolerance. The study identified several dozen immune- regulating



genes that we have found to be overexpressed in cancer cells, mimicking placental cells, and another long list of immunoregulatory genes that cancer cells manage to silence analogously to the placenta to prevent rejection. Everyone during their life accumulates potentially carcinogenic mutations in their body, but not everyone develops cancer because the immune system may be able to detect and eliminate malignant or premalignant cells in time, except perhaps those which have already learned “to use old tricks of the placenta“ to avoid immune control, and which end up developing a cancer and its metastases.

In epigenetic terms (Bronchud, Tresserra & Zantop 2018) the methylation patterns of certain key regulatory DNAs (CpG islands with an influence on local chromatin structure and regulation of gene expression) in these same tissues of this unique clinical cancer patient were significantly more similar between placental and cancer tissues (cancer cells and tumour microenvironments in the breast and lymph nodes), than between these same cancer tissues and their normal counterparts (normal breasts and normal lymph nodes).

Some of these epigenetic regulatory patterns may have an influence on specific placental and embryonic transcription factors involved in blastula implantation and embryonic development, or on some of the several functions of trophoblasts (the first epithelium formed following conception), which we know are by nature heterogeneous and also immune regulatory, including the trophoblastic expression of immune checkpoints. In contrast to placental trophoblast, cells destined to become cancerous achieve an antigenically foreign phenotype as part of a multi-stage process. They generally accumulate somatic mutations over time, sometimes in remarkably high numbers, largely as a result of mismatch repair and replication errors (Hsieh & Yamane 2008). These mutations can increase their genetic diversity and provide a selective advantage to some cancer cells over others. Although a sub-set of these (driver mutations) may promote cancer, other (passenger) mutations may be irrelevant to oncogenesis but can be expressed on the cell surface as



“neoantigens” which, like paternal antigens on the trophoblast, are non-self as far as T-cells of the host immune system are concerned (Lee et al. 2018). So the further a cancer cell deviates from a normal cell, the more likely it is to be recognized as foreign by the immune system (Chen & Mellman 2017). The risk of immune recognition probably explains why most cancers are destroyed before they can become a threat and why metastatic cancer is largely a progressive disease mainly affecting older individuals. Although it was originally believed that successful neoplasms evaded T-cell recognition by losing immunogenicity, it is clear that aggressive cancers continue to display on their surface neoepitopes which, under the right circumstances, can become potential targets for therapeutic monoclonal antibodies and for autologous T-cells (Sahin & Türeci 2018), yet the presence of these alloantigens generally appears not to be a barrier that compromises the growth and spread of a successful cancer; nor, with few exceptions, do paternal antigens inhibit the progression of a pregnancy.

Conclusions

Dunn and colleagues (Dunn et al. 2002, Dunn, Old & Schreiber 2004, Dunn, Old & Schreiber 2004) proposed in 2002-2004 that during the often long process of carcinogenesis most cancers underwent some kind of clonal evolution to become independent (and as a matter of fact “enemies”) of their own body and organism (to the extent of actually “killing it”). As an important part of this self-destroying process, cancers undergo several kinds of “immunoediting” to become free from immunosurveillance, then go through a variable period of “equilibrium” between cancer and host, to end eventually in “tumour escape” from the control of the host’s immune system.

Hypotheses about placental immune editing switches (PIES) have proposed a broad and evolutionary framework for the molecular mechanisms of cancer-immune editing (particularly during the “escape phase”) by postulating that many (if not most) of such immunoediting mechanisms could be related to ancient epigenetic and genomic evolutionary mechanisms, in turn related to



foeto-maternal immune tolerance mechanisms in placental mammals.

Considerable experimental and clinical evidence has been published on cancer- immune editing (Dunn et al. 2002, Dunn, Old & Schreiber 2004, Dunn, Old & Schreiber 2004). It seems likely that during carcinogenesis and cancer progression there are T-cell- dependent, and T-cell-independent mechanisms of cancer immunoediting. Several immune cell types are involved in cancerous microenvironments — both "innate", like "decidual-like" NK cells, or antigen presenting cells like macrophages or dendritic cells, and "adaptive" immune cells like the B lymphocytes and particularly different types of T- cells — as well as several different types of stromal cells, like endothelial cells or fibroblasts.

The most aggressive epithelial cancers (like the adenocarcinomas or the commonest lethal ones in humans : lung, colon, breast, prostate, bladder, kidney, gastric, pancreas, etc.) — perhaps with the exception of some epithelial ovarian cancers, that are also relatively frequent in non-mammals (as in old egg-laying hens) because of unknown but probably hormonal and germ cell-related reasons — and their tumour microenvironments may use the placental immune regulatory pathways (among them, key immune checkpoints) already employed during pregnancy in placental mammals as part of the complex and multiple pathways of foeto-maternal tolerance. Not in a physiological context (such as pregnancy) but in a pathological and cancer-specific context, often secondary to abnormal PIES activation by mutated oncogenes or transcription factors as part of carcinogenesis itself. In other words, what an oncogene or mutated transcription factor might do in this carcinogenesis context is precisely to trigger the inappropriate or ectopic expression of batteries of immune regulatory genes underlying hidden immune tolerance and immune editing switches. We are so far just seeing the visible part of the iceberg and not the hidden or under-the-surface circuits that allow cancer cell clones to fool our immune systems. This research will continue, hopefully in different approaches.



On a personal and philosophical note, the “theory of creative destruction” (McCraw 2009) assumes that “long-standing arrangements and assumptions” must be destroyed to release resources and energy to be deployed for innovation. The term “creative destruction” was coined by the Austrian economist Joseph Schumpeter in 1942. It is used most frequently to describe innovations in manufacturing processes that increase productivity, but the term has been adopted for use in many other contexts (McCraw 2009). Schumpeter describes “creative destruction” as the “process of industrial mutation that incessantly revolutionizes the economic structure from within, incessantly destroying the old one, incessantly creating a new one.”

In the context of human evolution, the natural appearance, some 150 million years ago, of invasive placental anatomy and physiology can be envisaged as the end of the egg’s traditionally successful gestation mechanisms and the beginning of a new era in which the blastula is implanted into the uterine decidual microenvironments and grows like a parasite inside the mother’s womb, cheating its immune system. Clark et al. (Norfolk, Virginia, USA) mentioned in their classic 1997 paper (Clarke 1968) that the “human immunodeficiency virus (HIV) may be using the glycosylation system of the T-lymphocytes to acquire glycans for its glycoproteins that enable it to disrupt carbohydrate-dependent immune cell interactions, or induce aberrant immune reactions“. In a similar way as the human immunodeficiency virus (HIV) may be using the glycosylation system of the T-lymphocytes to acquire glycans for its glycoproteins (which enable it to disrupt carbohydrate-dependent immune cell interactions or induce aberrant immune reactions), so perhaps some placental immune editing switches (including the several ancient retroviral env genes exapted for a role in placentation) can confuse the immune system by altering its epitopic membrane glycoproteins or immune cell cellular receptors. Several authors have in fact suggested that the emergence of a primitive Eutherian placenta (Chuong 2018) may be related to the co-optation of a founding env gene with enough immunosuppressive capacity to allow for early foeto-maternal tolerance, and that several ancient human



endogenous retroviruses control many aspects of gene expression during placentation. In the same way as the trophoblast must continue to develop immune countermeasures with regard to the maternal immune system, for its own protection during gestation, so also must cancer cells, during cancer progression, continue to avoid immune rejection in spite of evolving antigenic landscapes, and the emergence of new ones.

Acknowledging the opportunities for human cancer research of much more powerful and specific research approaches to these placental immune foeto-maternal mechanisms is a priority (Chew et al. 2019, D'Souza & Wagner 2014).

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About the Author: Miguel Hernández-Bronchud was born in Barcelona but went to school at the Liceo Massimo d'Azeglio in Italy, Turin. He started research on cancer at the age of seventeen at the Chester Beatty Cancer Research Center in London and graduated BM, BCh (English equivalent to the American MD degree) from the University of Oxford, Wolfson College in 1983, and from the same university, Doctor of Medicine (DM degree) in 1990, following a BA, MA degree in Natural Sciences (Biochemistry Part II) at

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Arts. He has won several international awards in cancer medicine , and also a Cambridge literary price for translations of poems by Primo Levi from the original Italian into English . He has edited and published over twenty books in cancer medicine, including Principles of Molecular Oncology (Humana Press/Springer NY 2000, 2004 and 2008), and three non-fiction books in English: The Secret Castle (three editions: 2007, 2010 and 2019); From Stones to God (2011); In Search of a Missing God (2011). He now works as a clinician medical oncologist at GénesisCare Corachan (GCCC360) in Barcelona, Spain.

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