

Comment on “The Role of β -Catenin in Embryonic Stem Cells and iPSCs

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ABSTRACT

Science is leaving the field of science since the new millennium. Nobody uses the scientific method in science. A systematic approach is widely missing to collect and interpret scientific data. The life-work of nearly all PhDs and postdocs is abolished. The example of β -catenin in stem cells reveals the entire challenge for academia and academic research in its details, from the scientist to the molecular level. Systems Biology, Open Science, Open Innovation, fairness and sustainability via hubs are the solution.

INTRODUCTION

After finishing my Ph.D. in Molecular Biology, Biochemistry and Stem Cell Biology at the University of Ulm, where I was researching embryonic stem cells, I went as a stipendiary of the Max-Planck-Society (MPS) to the Max-Planck Institute of immunology in Freiburg, where I wanted to continue my work. At that time, I realized that our reality is on repeat, everything had already happened before. It was not a Deja-vu, I was a complete repeat of my reality at the University of Ulm, where I initially discovered the role of β -catenin as a hub protein platform or docking station for many other proteins, not only TCFs and Lefs. It could also interact with Oct-3/4, Nanog, Sox2, Klf4 and others and thereby made stemness which allowed me to produce embryonic cells using these factors, however, I did not call them iPSC cells as Yamanaka did on the latest time frame of our reality. The conspiracy crime network, the one that usually destroys our life every day, decided to continue to steal everything they can from me, while they argued, if Roman Anton would be the star researcher, the crime network would still block him, but the researcher in Japan would get very much funding, institutes and jobs. This way they could convince the rest of the crime network that thought since decades they were stealing too much from me. Well, the truth of our reality is that they have always blockaded me, even and utmost the latest and most canonical version. Only rudiments of the previous timeframe were left over, a low paid job, robbery of my ideas which still had to be there to be stolen and blockage of all my success project.

To make a long story short, which is really better, as it would get really terrible now in the details, we live in a time in which a crime network destroys our life on the job market and career level. They steal all of your work, hinder us, blockade us and always want to pull us down. Do you think

the best scientist in the world will get one of these scarcely distributed faculty positions? There is only 1 in 150 and the situation looks even worse for male scientists, as they are more inhibited than female ones. Science of today lacks any systematic thinking; here they have forgotten intergenerational justice. My generation of male scientists and postdocs has been dramatically discriminated and disadvantaged.

All scientists of today get everything wrong, which is very bad for science, especially because it is nearly everything that they misunderstand. For example, when you read these words here in the introduction of this scientific publication, they already get it wrong, blinded by the stereotypes of publishing and might claim it is prose, metaphysical, personal view or not scientific enough to call it a scientific review. But this is wrong too, and as I said, it is nearly everything that they are getting wrong in every layer.

It is not possible for a single man to show the myriads of example when they are wrong, remember nearly all of the time, about probably everything. Just to illustrate it in this example, because we always need be able to back it up what we say, scientifically you need to have good arguments for that.

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Is it a personal view and topic or a scientific one? It is scientific, as the personal singular view is even more important than a statistic of many views. "Stop" is what the illegitimate faculty scientists would say here, and as I said, they are always wrong. Statistics give you a mean and deviation, which is artificial, not reality-based, and it takes away a lot of information on the data. If one personal view is right, correct, the truth, then there is no statistic that can be better, even with millions of data points. This doesn't mean you do not need statistics here and there; statistics is a helpful tool to use, but statistics can be fake, false, biased, artificial, a result of manipulation or way of acquisition and so on. And it does not stop here, nearly all statistics are interpreted in a wrong and false way, intentionally or not, what does that make a difference. The main strategic goal of a crime network is to hinder the scientific truth to be prevalent. My view is right and the truth: Science is controlled by a crime network that steals our success, publications, ideas, innovations, the truth in science and all opinion leadership.

And in the industry, it is even worse than this maximum of an organizational catastrophe. Coming back to the first point, we still need to further provide arguments for the points mentioned. Let me answer it with a question: Can science be conduction without a person? No, everyone knows. Do persons have opinions? Yes, everybody knows. So, science is person based that have opinions. Can you follow? Yes, good. In order to make good science in the details, it must be unbiased and according to the scientific method, which is the standards of all sciences, right? Most say yes but how can someone deny this? What must be the reason to deny this you must ask in such cases? The answer is a strategic network, a sort of conspiracy, has stolen science, all opportunities and wants to control opinion leadership. Moving on: Can the (I) scientific method and (II) unbiasedness be separated from the person, his opinion, a human with many wants and needs, who is dependent on his workplace and the network of crime that gave it to him? No, it can't. All scientific decisions are made by an employed and fully dependent scientist who must find solutions for his life and science at the same time. There is not one scientist independent in our faculty and grant money system of today, with all that peer-pressure, including biased peer-review and a forcedly biased impact point system, and very false hiring practices.

As a result, we have to scientifically conclude that science, which will always require (I) the scientific method, and (II) unbiasedness, must always include the person, the individual and its contexts and dependencies as the real basis for all scientific activity. "It is humans who do the science", hence they are part of the experiment too: The experimenter is part of the experiment and not excluded from it.

"THE EXPERIMENTER IS PART OF THE EXPERIMENT AND NOT EXCLUDED FROM IT"

However, the experimenter is in very urgent need of a job, a career, and has been discriminated for years, since he or she is in science, was oppressed, abused, hindered, blocked, inhibited, deprived, mislead, forced, misunderstood, biased, intimidated, pressured and should never ever do a good job.

(Those who group it into psychology are censors of the truth; psychology plays a biasing role here).

The entire job market for scientists is dominated by a crime network that wants to deprive all jobs of well-educated scientists, especially with a doctorate, while only a few of them have good chances.

Now, this is the real starting conditions of "the experiment", which, on top of all this, "must work".

Insane as it can get, everyone would say, but not everyone agrees. Some say it's an exaggerated view, but is it really only a percentage of this? The author thinks no, as the sum of all effect is already as strong as it can get. Even if all of this is only a percentage, let's say 30% instead of 100%, or 80% instead of 100%, as views and estimates might differ here from person to person. Remember we are all persons, with opinions, they can differ but should converge on the truth and reality, shouldn't they? Even if these are such number in a complex reality with thousands of such factors, what would happen? It is simple math: If thousands of such factors are in between 0.3 and 0.8 (30%, 80%) we would still end up with 0% truth in science. We would still have a 100% bias in all sciences. Everyone would still be dependent on something that influences his or her work too much. Even if it is 10%, it would not make a difference. It is not even crunching the numbers; it is as simple as $10\% \text{ to the power of } 1000 = 0\%$.

"WE HAVE 0% OF SCIENCE IN ALL SCIENTIFIC FIELDS BECAUSE OF A SIMPLE MATH PROBLEM"

This 0% looks very bold, it surely is a headline, but it does not fully correspond to what many scientists see in their daily work and published works. So why is this? It is still true due to the following reason: interesting new finding can still be published and true facts are still intermixed in recent publications. So how can it be 0% if there are also some correct findings? The answer is it is 0% over time. As the above formula has not included a time component, its solution is time-independent, which does not mean that time does not play a role here. It means that the Nash equilibrium is stable at 0% of science which forms over time and we are already very close to that state. In other words, even if there are still some true finding published today and this intermixing is also found in individual works. Look, how will someone in the future be able to tell you which of the fact is right and which is not? Even if there are the right things in it, it will be hard to tell, which are right and which

are not. Surely, there will be scientists and researchers who can tell you which are right and which are not, like me. But let's be honest, the job market is not functioning at all, HR (Human Resources) is not able to tell or discern which expert is an expert and which scientist and researcher can tell you what is right and what is not. Hence, they will not play relevance here. All applicants with real skills like this are disadvantaged the most; this has changed a lot since the last 20 years. Hiring wrong people is the reality of today like blockage of all able scientists. For the majority it is 0% science, for a tiny minority, it is maybe 4-8%.

“HIRING WRONG APPLICANTS IS THE REALITY OF TODAY LIKE BLOCKAGE OF ALL SCIENTISTS”

Coming back to the first two points we want to finally prove: (I) scientific method and (II) bias. We have already shown that the scientists are a key part of the experiment, not independent variable, but highly dependent on their work conditions and future expectations: thus, they are cheating all of the times.

95% of scientists see a reproducibility crisis and it is likely even more. This is what the scientists say about themselves, in fact, which is also a very positive and mild view in general if you judge yourself. Reproducibility crisis means the scientific system and the scientific method is not functioning. How can they all go on this way, if everything is so wrong? Well, the answer is: they need to earn money still, and there is a hell of a job market and a real “unemployment inferno” waiting for them otherwise.

Let's summarize, we have no scientific method but extreme bias and we need the opposite. No wonder, that science Nash equilibrium is 0% scientific in its output and workforce. Some remaining percent are saying we have not fully proven that the scientific method is not in place, it is still minimal reproducible, at least 5% believe and this would not be totally proving this point. Okay, no problem at all, we can go on to derive this remaining point with hard and undoubted facts for whoever may ask:

For this, we must briefly explain the scientific method, as outlined in the paper reviewed (1), which every scientist should know. The scientific method is a system of scientific procedure that must be met to be scientific, a more than 2000 years historic achievement of humanity in science that has been lost in science since a few decades: briefly, scientific hypotheses must be systematically organized, collected, verified or falsified, i.e., proven or disproven to build a tree of data, knowledge, facts, hypothesis, and correct models of the world. A hypothesis that is weakly proven is active; a hypothesis that is weakly disproven is inactive. All active hypotheses are proven until they are disproven and describe our world from the scientific angle.

Simply as yourself, if this system is somewhat in place today. Keep in mind; if science would function this way,

then we would have a realistic description of reality by science, from micro to macro cosmos. We do not have this; science does not cover all topics of our life and world in a somewhat suitable way. Also, keep in mind that both falsification and verification are equally important. Do we have this? No, clearly not at all, we publish only positive results or mainly and the latter does not much help us in the future. Also, censorship makes and directs the science of tomorrow and today.

“ALSO, CENSORSHIP MAKES AND DIRECTS THE SCIENCE OF TOMORROW AND TODAY”

The impact of today science is derived from biased positive results mainly and more and more also somewhat-fake story selling. Negative results are still unpublishable today, with a very few and maybe prominent exceptions maybe. But the big bulk of science is positive findings that are not reproducible. This is not a scientific method. The last remaining doubts are, one could still publish facts for a new theory, that is right, but does not help here quantitatively due to this: peer-review hinders falsification with new method if (a) expert-reviewers are the peers, which are mean competitors usually; or the alternative, if (b) non-specialist scientists are the peers, it will also be very detrimental for the house of scientific hypothesis, false will replace the true in both cases. Today we can see everywhere, the bad scientists replace good one everywhere. Good science has no chance at all against bad science.

Cutting this very long story short, we are forced to do science in a way it can never ever work. All have worsened since 2000. The steady-state of science is 0% in its consequence and output for the world. The remaining incremental findings are stolen if they can be instrumentalized for oppression or money.

“THE 0% SCIENCE EQUILIBRIUM WILL SOON BE ACHIEVED AND ALL REAL SCIENTISTS EXTINCT”

$$\text{Output} = p_1 * p_2 * p_3 * \dots * p_n \cong 0\%$$

p = How much percent of science is achieved in this factor in p (0 – 1.00)

n = How complex is your reality, described in number of factors n ?

Simplified formula to illustrate the simple math behind the modern-day's end of science:

Science of today = 0% due to p_n and our reality is complex with many n (>100)

Common Good of Science = ca. 0% due to p_n with $n > 100$ (all inclusive)

0%, because the science is not assured and not enough maintained in the individual factors

Hypothesis Formation (1%), Verification (1%), Falsification (1%), Implementation (=0%?), etc.

Every good, able, honest, truthful, genius or mastermind scientists are hindered the most, etc.

Still, 0% could be even misleading optimistic – we are going backward with minus 5% maybe. A 0% output is also

negative in effect, as false new findings add to cover previous true ones.

In summary, a conspiracy crime network sabotages the scientific system, leading it into a zero percent output Nash equilibrium scenario, with zero reliable output “at the multi-factor-level” (**Figure 1**).

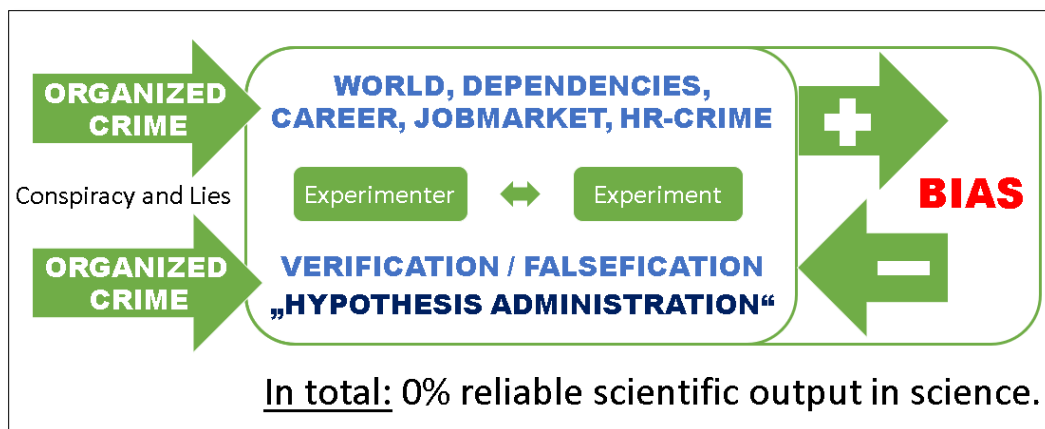


Figure 1. Organized crime has destroyed science. Bias dominates the scientist and all findings.

The solution to this problem has been presented in the recent paper (1) that is reviewed here.

CONTEXTUALIZATION OF THE PUBLICATION AT REVIEW

In light of this predicament and in view of this very tense situation of science and all scientists, the publication by Anton [1] proposes a solution for the future of science and all researchers and scientists. This publication describes the urgent need and possibility of “An International Systems Biology Approach of Open Science and Innovation” for basically all fields of science as the new way to go for all future scientists. We can no longer go the unscientific road in an outdated scientific system that has been modified in a way to hinder all postdocs and PhDs and in which only corruption and lies win and good scientific work and the best scientists are excluded the most. Instead, this publication reminds, in order to achieve a and b, i.e., the unbiased scientific method, we must also think of a way how to organize the vast amount of hypothesis and data and interpretation and models and so on and we may not forget about the scientist, the person, the life and career of the researcher and the job market, including all dependencies and pressures that there might be, as they are a fundamental part of the experiment, as we know today, looking back on decades of unreproducible results in all fields.

“...LOOKING BACK ON DECADES OF UNREPRODUCIBLE RESULTS IN ALL FIELDS”

What does it help to have a star paper here and there? Nothing much, if the whole field is drowning. Thus, we must

assure that the field and everyone is doing right, and the stars also have a big shot bias.

As indicated in **Figure 1**, biases are extremely high due to real-world dependencies of nearly all scientists, with the exception of rich and independent scientists, which are very few and they have a different problem. Furthermore, the verifications and falsifications are not functioning, leading to a multifactor level output of 0% at the Nash equilibrium level. Moreover, hypothesis administration does not function suitably since 2000 in many fields. The amount of scientific publications has exponentially increased, but at the same time, the efficiency and effectiveness of its administration have fallen at the same rate of even faster. For example, who can find the publications she or he is looking for? Despite the use of high-tech and artificial intelligence-driven search engines, most publications cannot be found. Thus, also the hypothesis and data administration has become very dysfunctional and not suitable for the scientific method, organizing sciences and also increases the biases very much.

This again shows the importance of scientific hubs, as mention in the paper (1), which achieve all of these shortcomings: (a) data storage, (b) hypothesis administration including the verification and falsifications, (c) materials and method storage to enable reproducibility, (d) suitable working conditions must always mean entire career path without job scarcity, (e) and independence for unbiased research the persons must have fair chance to perform a good work.

All of these preconditions are not met today. Also during my time as Ph.D. and Post Doc, we were facing brutal hostility against every free-thinking scientist, pressure, intimidation,

robbery of ideas, and so on, basically 80% of the scientific field in embryonic stem cell biology could be the robbery of my ideas, not only iPSCs, which was only one of the famous examples that have also received the noble price. Future, present and past have formed cheat loopholes due to a reality repeat time frame structure. These loopholes are used to steal all scientific ideas from me and others, bringing them back in the past, as you need to be first to steal them efficiently and effectively, to get a price, fame and “kudos”. This metaphysical finding is my hypothesis, which I can verify in 80% of the scientific literature about stem cells, which clearly corresponds to my ideas. Can you falsify a metaphysical hypothesis? No, as it requires linear causality in our current model of time. Hence, I must conclude, that time is not linear.

All scientific ideas of PhDs and Post Doc are stolen, projects and experiments are deprived, everything is under the control of a conspiracy network that hinders intelligent non-criminal scientists the most. Also, my ideas in the project “ β -catenin in embryonic stem cells maintenance” were deprived, as usual.

FROM MACROCOSM TO MICROCOSM OF SYSTEMS BIOLOGY CORES

In light of this predicament for all scientists, we must conclude that the macrocosm of the scientist directly influences the research focus and the analysis of the details in the microcosm at the molecular junction (**Figure 1**), as the experimenter is part of the experiment and not an independent variable.

Consequently, the independence of the scientists must be assured, like the scientific method, which also has an organizational component (**Figure 1**), e.g. administration of all active and inactive hypotheses, including the verification and falsification data that may be steadily renewed and must be accessible.

In other words, we need management of science and science of all fields that stems from scientists, not business people, as they have not learned the scientific skills. Scientists means good management must at least include them into the management; they often have additional top skills.

Systems Biology, Open Innovation and Open Science are the keywords that cover many of such topics (very many references can be easily found for these concepts using search engines on the internet and in the work at review and comment [1]. A second important concept is GSI, graded sustainable intrapreneurship, which assures that scientists must always get a fair chance in all required dimensions of their work [2]. Put simply, all fields of science need a scientific hub or center that manages the field in a normative managerial way, that assures reproducibility, progress, hypothesis administration and hypothesis, theory and results administration (**Figure 1**), unbiasedness, good working conditions for the scientists in the field, life-long career

opportunities for all PhDs, not only years or short-term contracts, access to all materials and methods, data storage and data banking, biobanking, model administration, bioinformatics, literature and reference systematics and much more [1].

Taking the stem cell and iPSC field as a key example (1), the iStemCore (**Figure 1** of [1]) is suggested as the first example in world history to achieve a better science for humanity. It should serve as an example for all scientific fields of today. iStemCore sets the normative procedures which assure the reproducibility, accessibility, organization of all scientific inputs and outputs without taking away the freedom and flexibility of research and scientists, which must go conventional and also very new ways.

But whatever the scientists are doing, iStemCore may ask for the materials, data, methods which must be provided in a complete form that makes the experiment fully reproducible. This is the only way to stop the reproducibility crisis in science and to suitably organize systems biology.

“ISTEMCORE MAY ASK FOR THE MATERIALS, DATA, METHODS WHICH MUST BE PROVIDED”

In exchange, iStemCore will deliver and provide and make accessible all materials, data and methods, as well as all information needed for future experiments and assures the independence of thought and workforce, who may not be under pressure and may not, be highly dependent on positive results.

From systems biology to the molecular junction

In the case of the iStemCore, the biology of stem cells and its molecular biology and more are the research objective of the field. By looking at the example of β -catenin we find myriads of publications, gene, transcript and protein interactions all with biological significance and relevance ([1] and references therein). The high number of publications (**Figure 2A**) reveals that a systematic way to order, assess, evaluate and systematize them is required to build the current models of our understanding. This is required, as complexity is very high at the molecular junction (**Figure 2B**) and the number of interactions, functions, forms, isotypes, modifications and more, is very high, as well as the layers of regulation, which govern cell fate, cell differentiation, cell specialization, cell physiology, metabolism, cellular health, cell communication, signaling, cell and tissue homeostasis, tissue formation and everything that is required for tissue engineering, stem cell engineering, regenerative medicine, iPSCs, assay development for R&D to find new cures and diagnostics for the many possible human disease, most of which have no cure and no good diagnostics until today (>50%, which is still unbelievable high – but truly a good estimate). Only scientific hubs, like the iStemCore, can deal with the complexity. Only scientific hubs, like the iStemCore, can assure reproducibility. Only scientific hubs, like the iStemCore, can assure unbiased

researchers and scientists by providing much more and better and more systematic jobs. Only scientific hubs, like the iSTEMCORE, can apply the scientific method. Hence, this paper is the solution for the 0% reliable long-term multifactor output of science. Only a fair and true, honest and integrative Open Science [2] can open the door for all sciences to become scientific. Even if some say, we are not at 0%, we surely will soon be. Systems biology that uses infrastructure hubs like the iStemCore [1] can prevent those

very good and precious findings of the past are lost or forgotten. They help the field to stay in touch with the latest state of the research, which nobody is aware anymore today. Today, they have to reinvent the wheel in all fields and are even selling it here and there or can't reproduce it. - These core hubs can provide the functioning wheels for all in future.

“These Core Hubs can provide the Functioning Wheels for all in Future”

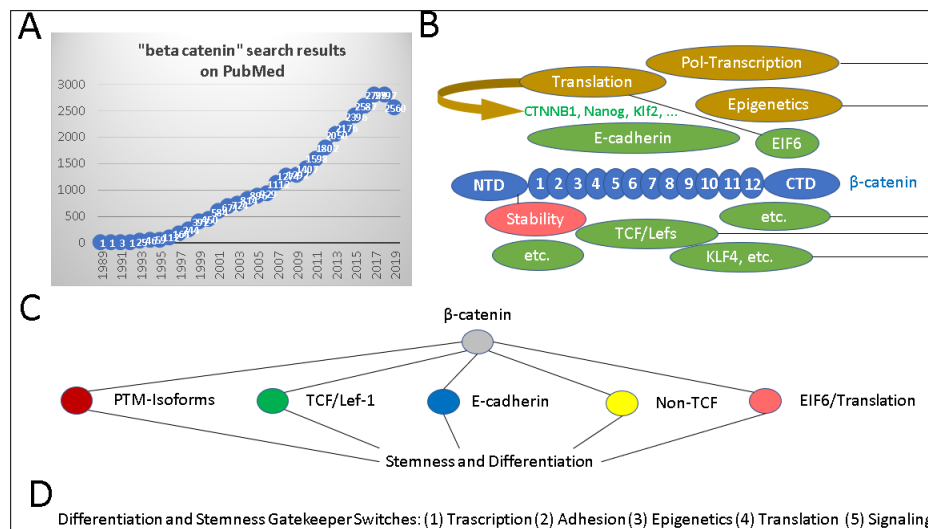


Figure 2. The complexity of molecular interactions requires systems biology at the molecular junction. (A) Number of publications found on PubMed using the search term “beta catenin”. (B) Protein-protein interactions of β -catenin with important but only very few of its binding partners reveals complexity on the domain level. The original publication (1) is a quick pilot proof of concept and proof of principle. The multiple functions of β -catenin in transcription, translation, epigenetics and histones, cell junction and adhesion, makes it a system biology project for only one gene and protein, but there are >40 K. (C) Systems biology must be flexible to integrate many views on the same topic to find the one truth. For example, promoter studies can be viewed on many levels as (1) shows, not only on the genomic DNA. (D) The paper offers open science based fair and transparent systems biology as a solution to provide a better order in the complexity, which finds a role of β -catenin in stemness and differentiation. Seeming contradictions, like a key role in stemness and differentiation can best be resolved this way, as the explanation is found in the next layer of complexity, e.g. molecular switches that can do both.

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