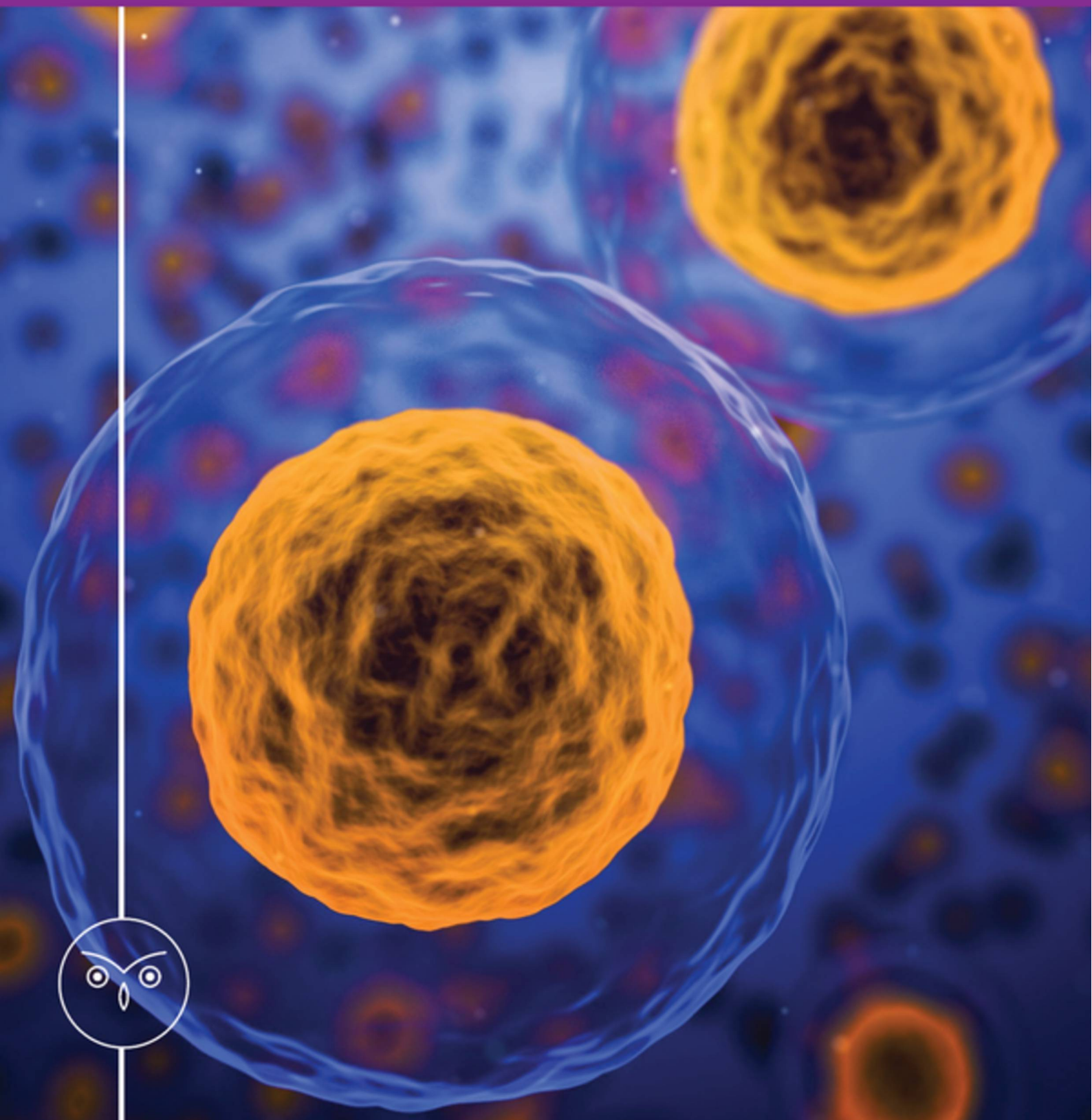
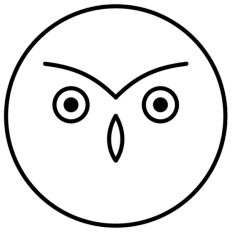
# The Cuban Scientist

Year 2020

Volume 1 | Issue 2





# The Cuban Scientist

**Volume 1, Issue 2**

January 15, 2021

With this issue, we close the first volume of The Cuban Scientist (TCS) in 2020 covering subjects in the fields of natural sciences (2 reports), medical and health science (2 reports), and social sciences (1 report) contributed by a multidisciplinary group of scientists abroad (Spain, Germany, and Belgium) and specifically in Cuba (Havana and Las Tunas). Although we expected to have more articles in this second issue, we are pleased to be publishing articles from diverse geographic settings of researchers.

We would like to share with the scientists already publishing in TCS, the enthusiasm to reach more colleagues interested in strengthening the ties among Cuban scientists wherever they work. We believe that by publishing in TCS the Cuban scientists will open their field of research to more opportunities for collaboration, as well as increasing the visibility of their work.

The launch of the journal TCS in 2020 coincided with the year when the COVID-19 pandemic began and whose devastating course still continues in 2021. Dealing with such threat in public health has revealed the strength of harnessing the full potential of the science, technology, and innovation in each country through efficient coordination between government, academy, and industry (and service). It is in this frame that TCS aims to become a reliable and systematic bridge making accessible the Cuban scientific contributions to all the actors facing domestic and global challenges.

Once again, we thank all researchers submitting articles to TCS, especially in this year dealing with new challenges (demands?) due to the pandemic. We are also open and grateful to any suggestion that can improve the mission of TCS.

In this issue:

# Unravelling the meaning of negative values of Intensity Modulated Photocurrent Spectroscopy in solar energy conversion devices

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*The meaning of negative IMPS transfer function values was experimentally demonstrated, providing a powerful opto-electronic method toward specific operational mechanisms insights in photoelectrochemical systems.*[b]

The detailed understanding of the optoelectronic properties of semiconductor materials used in photoelectrochemical (PEC) systems for solar-assisted fuel production, is key to further establish adequate strategies to overcome its limitations. Usually, this is a complex task, which involves the use of characterization methods delivering a set of results, which must be interpreted based on theoretical models. Small perturbation techniques are particularly useful to disentangle carrier dynamics in complex systems. Nevertheless, the interpretation of the obtained results can be challenging, and many controls and iterative validations are needed for a sound mechanistic description. In addition, the presence of "atypical" spectroscopic features makes interpretation even more complex. However, these anomalous features constitute a valuable source of information, which remains ignored in many occasions.

The Incident Modulated Photocurrent Spectroscopy (IMPS) technique has an important advantage for the study of PEC devices, by providing a small modulation of the minority carrier —playing the dominant role in the PEC performance—, with a modulated incident photon flux. An anomalous feature has been observed during IMPS measurements in $BiVO_4$ photoelectrodes, by a change of quadrant from positive to the negative real part of the complex plane representation at low frequency, usually at the region closer to the open circuit potential (OCP) (See Figure 1). In previous reports, this feature has been assigned to the switch of the photocurrent sign at this region. [1]. However, we have experimentally demonstrated that this feature is not related to the photocurrent sign, but it is directly connected to the variation of the steady-state extracted photocurrent $j_e$ with the incident illumination intensity $j_\phi$, *i.e.* the differential external quantum efficiency ($EQE_{\text{diff}}$) [2].

Note that, the connection between the $EQE_{\text{diff}}$ and the low frequency value of IMPS ($Q(0)$) has been previously described in perovskite solar cells [3], finding that both values are directly linked to the dc component of the slope of $\overline{j_e}$ with $\overline{j_\phi}$, as depicted in Eq. 1. The bar over the symbols denotes the steady-state condition.

$$Q(0) = \frac{\widehat{j_e}(0)}{\widehat{j_\phi}(0)} = \frac{\partial \overline{j_e}}{\partial \overline{j_\phi}} = EQE_{\text{diff}} \qquad (1)$$

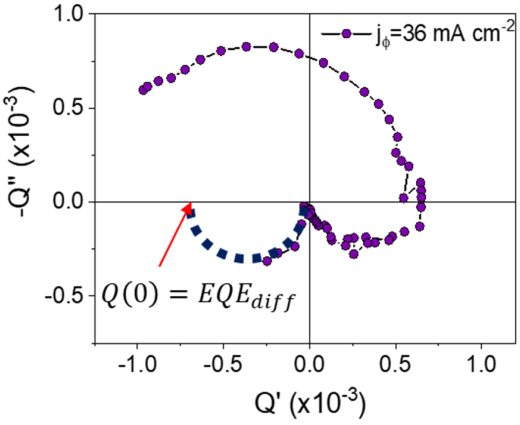


Figure 1: Complex representation of the IMPS transfer function on $BiVO_4$ photoanodes, measured at $-0.05\,V_{\text{RHE}}$, showing the low frequency value, $Q(0)$. Figure adapted with permission from the American Chemical Society [2].

However, such a connection had not been established to explain the change of sign of the low-frequency IMPS value observed in photoelectrodes used for PEC water splitting. Usually, the treatment of IMPS measurements in PEC systems is carried out by using a rate constants model, which focuses on the evaluation of the competition of charge transfer and recombination process at the electrode surface [4, 5]. However, the analysis of kinetic constants, which corresponds to the maximum $\omega$ of each arc observed in the $Q$ complex plane, usually neglects the analysis of the value of the real part of $Q$. In order to clearly show this relation, the $j_e - j_\phi$ steady-state curve of the $BiVO_4$ photoanode at an applied potential near to the OCP was recorded. Each point was measured during a sufficiently long time to reliably capture the steady-state condition of $j_e - j_\phi$, and to be compatible with the low-frequency domain of the IMPS measurements (100 s). As shown in Figure 2, at lower $j_\phi$ values there is a region where the extracted photocurrent is positive and its value decreases when increasing the light intensity, leading to a negative slope and, consequently to a negative $EQE_{\text{diff}}$. This observation was in good agreement with the measured negative $Q$ transfer function at low frequency. Analogously, at higher $j_\phi$, the negative $EQE_{\text{diff}}$ is related to the decreasing $j_e - j_\phi$ slope, independently of the negative sign of the photocurrent.

This experimental proof of a particular operational

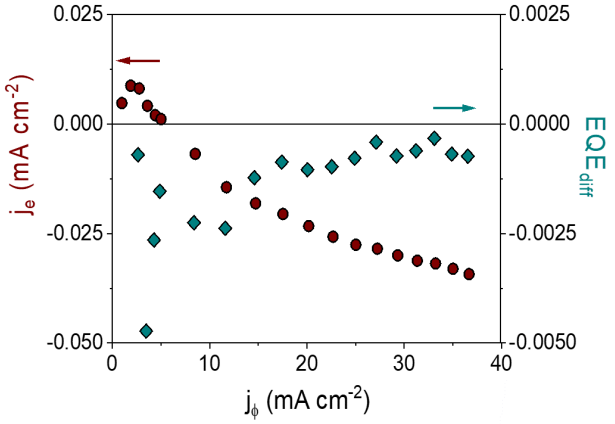


Figure 2: $j_e - j_\phi$ steady-state curve recorded for a $BiVO_4$ photoanode, and the calculated $EQE_{\text{diff}}$ from its slope. Figure adapted with permission from the American Chemical Society [2].

point, where both the IMPS response and the $EQE_{\text{diff}}$ are negative, while the photocurrent remains positive was critical for demonstrating that the negative value of the real part of the Q transfer function is associated with the derivative of the photocurrent with the light intensity, independently of the sign of the photocurrent. Moreover, this interpretation further establishes the measurement of the $j_e - j_\phi$ curves as a powerful optoelectronic method containing valuable information on specific recombination and trapping mechanisms during the operation of photoelectrodes.

In $BiVO_4$ photoanodes, $EQE_{\text{diff}} = 0$ at voltages close to OCP indicates an invariant value of $\overline{j_e}$ with $\overline{j_\phi}$, indicating that $j - V$ plots at different light intensities will converge to the same OCP value. This can be indicative of Fermi level pinning on $BiVO_4$. On the other hand, the observations of a negative $EQE_{\text{diff}}$ at voltages close to or beyond the OCP, suggest that incident light intensity promotes the filling of a local density of shallow traps around the electron Fermi level, promoting the recombination of photogenerated holes with the trapped electrons. This leads to a decrease in $j_e$. At larger applied anodic bias, the shallow traps are filled with holes, allowing the photogenerated holes to be efficiently extracted and causing an increase of photocurrent with light intensity, and hence, a positive $EQE_{\text{diff}}$, as usually observed in water oxidation conditions.

## Summary

It was demonstrated that the negative values of the real part of $Q$ is not related to the photocurrent sign, but it is directly connected to the variation of the steady state extracted photocurrent with the incident light intensity. Moreover, it was shown that the real part of Q contains significant physical information, allowing further understanding of operational mechanisms of photoelectrodes and hence, paving the way in searching for successful strategies to improve the current efficiencies of PEC systems for solar-assisted fuel production.

## Notes

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b. Original version of this article is Ref. [2]

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# SU(2)-Structure & Heterotic String Compactification

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*We briefly discuss SU(2)-structure 6-manifolds, their role in the compactification of the heterotic string and the resulting gauged supergravity at low energies [1].*

ΑΓΕΩΜΕΤΡΗΤΟΣ·ΜΗΔΕΙΣ·ΕΙΣΙΤΩ

String Theory replaces the idea of point-like elementary particles with that of tiny one-dimensional objects, a.k.a. strings (duh!), and attempts to describe their propagation and interaction by consistently applying relativistic and quantum principles. The resulting spin-2 vibrational state is readily identified as the graviton, and therefore String Theory is a natural candidate for a theory of quantum gravity.

Unfortunately, consistency of the theory requires a number of extra spatial dimensions. The supersymmetric string, for example, requires a ten-dimensional space-time. One solution to the discrepancy with the perceived four-dimensional world is to consider the extra six dimensions to be *compactified*, i.e. forming a very small, compact 'internal' manifold $Y$ over every four-dimensional point.

The effective action of the superstring in four dimensions at low energies[a], obtained by integrating out the six extra dimensions, depends of course on the mathematical properties of $Y$. Since supersymmetry seems to solve a number of issues also at low energies, it is desirable for at least part of the 10-dimensional supersymmetry to be preserved by the compactification process. This is achieved by requiring the existence of one or more globally-defined spinors on $Y$, which in turn implies the reduction of the structure group of $Y$ to a proper subgroup $G$ of SO(6).[b]

The existence of *two* globally defined, linearly independent spinors $\eta_1$ and $\eta_2$ on $Y$ implies SU(2)-structure and, for the heterotic string, leads to $N = 2$ supergravity in 4 dimensions. If, moreover, these spinors are covariantly constant with respect to the Levi-Civita connection, then $Y$ has SU(2)-holonomy and therefore $Y = \mathrm{K3} \times T^2$, i.e. a product of a complex K3 surface and a torus.

## SU(2)-holonomy case

The existence of such a pair of spinors, which can be chosen to satisfy the orthonormality condition $\bar{\eta}_i \eta_j = \delta_{ij}$, is equivalent to the existence of a triplet of self-dual two-forms $J^x = J^x_{ab} \mathrm{d}y^a \wedge \mathrm{d}y^b$ and a pair of real one-forms $v^i = v^i_a \mathrm{d}y^a$ on $Y$, as can be seen from the following relations,

$$\begin{aligned} J^1_{ab} + \mathrm{i} J^2_{ab} &= \mathrm{i}\bar{\eta}_2 \gamma_{ab} \eta_1, \\ J^3_{ab} &= -\tfrac{\mathrm{i}}{2}(\bar{\eta}_1 \gamma_{ab} \eta_1 + \bar{\eta}_2 \gamma_{ab} \eta_2), \\ v^1_a + \mathrm{i} v^2_a &= \bar{\eta}^{\mathrm{c}}_2 \gamma_a \eta_1, \end{aligned} \tag{1}$$

where $\gamma_a$ are the six SO(6) gamma-matrices and $\gamma_{ab}$ is the antisymmetrised product $\frac{1}{2}(\gamma_a \gamma_b - \gamma_b \gamma_a)$.

For $\mathrm{K3} \times T^2$, the fact that the spinors $\eta_i$ are covariantly constant with respect to the Levi-Civita connection implies that $J^x$ and $v^i$ as defined in Eq. (1) are closed: $\mathrm{d}J^x = \mathrm{d}v^i = 0$. In this case, $J^x$ are the three self-dual closed forms defining the hyperkähler structure on K3, and $v^i = \mathrm{d}z^i$, with $z^i$ the coordinates of $T^2 = S^1 \times S^1$.

The bosonic sector of the heterotic string consists of the ten-dimensional metric, the Neveu–Schwarz two-form $B_2$ and the $E_8 \times E_8$ Yang-Mills field $A_1$. An Ansatz for the Kaluza-Klein reduction on $\mathrm{K3} \times T^2$ to four dimensions $x^\mu$ can be written as follows,

$$\begin{aligned} \mathrm{d}s^2 &= g_{\mu\nu} \mathrm{d}x^\mu \mathrm{d}x^\nu + g_{mn} \mathrm{d}y^m \mathrm{d}y^n + g_{ij} \mathcal{E}^i \mathcal{E}^j, \\ B_2 &= \tfrac{1}{2} B_{\mu\nu} \mathrm{d}x^\mu \wedge \mathrm{d}x^\nu + B_{i\mu} \mathcal{E}^i \wedge \mathrm{d}x^\mu + \\ &\qquad + \tfrac{1}{2} B_{ij} \mathcal{E}^i \wedge \mathcal{E}^j + b_A \omega^A, \\ A^I_1 &= A^I_\mu \mathrm{d}x^\mu + A^I_i \mathcal{E}^i, \end{aligned} \tag{2}$$

where $\mathcal{E}^i = \mathrm{d}z^i - V^i_\mu \mathrm{d}x^\mu$, $y^m$ and $g_{mn}$ are the coordinates and metric on K3, and $\omega^A$ are the 22 harmonic two-forms on K3. The original $E_8 \times E_8$ gauge symmetry will be generically broken to an Abelian subgroup $\mathrm{U}(1)^{n_\mathrm{g}}$ for some $n_\mathrm{g}$, so $I = 1, \ldots, n_\mathrm{g}$.

Carrying out the Kaluza-Klein reduction with this Ansatz leads to $N = 2$ supergravity with fields organized in one gravity multiplet, $n_\mathrm{v} = 3 + n_\mathrm{g}$ vector multiplets and 20 hypermultiplets.[c] The bosonic content is distributed as follows: the metric $g_{\mu\nu}$ sits of course in the gravity multiplet; the $4 + n_\mathrm{g}$ vectors $V^i_\mu$, $B_{i\mu}$ and $A^I_\mu$ become the vectors in the $n_\mathrm{v}$ vector multiplets, plus the graviphoton in the gravity multiplet; the three scalars in the symmetric $g_{ij}$, plus the one scalar in the antisymmetric $B_{ij}$, plus the dilaton $\phi$, plus the scalar dual to the two-form $B_{\mu\nu}$ (the so-called axion $a$), plus the $2n_\mathrm{g}$ scalars $A^I_i$, become the $n_\mathrm{v}$ complex scalars in the vector multiplets; and finally, 58 scalars from the deformations of the K3 metric $g_{mn}$, plus the 22 scalars $b^A$, become the 80 real scalars sitting in the 20 hypermultiplets.

The hypermultiplet scalars can be organized in a $\mathrm{SO}(4, 20)$ matrix $\mathcal{M}$, and after tedious calculations the Lagrangian for these fields can be shown to take the following form,

$$\mathcal{L} = \tfrac{1}{8} \mathrm{tr}(\partial_\mu \mathcal{M} \partial^\mu \mathcal{M}). \tag{3}$$

In particular, no potential is generated for these or any of the scalar fields, which is seen as a problem and part of the motivation for considering a more general type of background.

### General SU(2)-structure backgrounds

For a generic SU(2)-structure manifold $Y$, the spinors $\eta_i$ are covariantly constant with respect to a connection with non-vanishing *torsion*. In this case, the forms $J^x$ and $v^i$ as defined in Eq. (1) fail to be closed.

The manifold $Y$ cannot be written as a Cartesian product in this general case; however, the existence of the pair of one-forms $v^i$ still allows for the definition of an *almost product structure* $\Pi_a{}^b = 2g^{bc}v^i_a v^i_c - \delta^b_a$ on $Y$ satisfying $\Pi_a{}^b\Pi_b{}^c = \delta^c_a$. This structure splits the tangent space over every point $y$ of $Y$ into two- and four-dimensional subspaces, $T_yY = V_2 \oplus W_4$. The subspace $V_2$ is spanned by the vectors dual to the one-forms $v^i$, and the orthonormality of the spinors implies $\iota_{v^i}J^x$, i.e. the two-forms $J^x$ must have legs only along $W_4$.

Due to this result, the most general departure from closure for the two- and one-forms on $Y$ can be parametrized in the following way,[d]

$$\mathrm{d}v^i = \theta^i v^1 \wedge v^2, \quad \mathrm{d}\omega^A = T^A_{iB} v^i \wedge \omega^B, \tag{4}$$

where the number of two-forms $\omega^A$ is generically $n$. Vanishing torsion means $\theta^i = T^A_{iB} = 0$, $Y = \mathrm{K3} \times T^2$ and $n = 22$.

Nilpotency of the d-operator, together with Stokes' theorem $\int_Y \mathrm{d}(v^i \wedge \omega^A \wedge \omega^B) = 0$, leads to the following constraints on the values of $\theta^i$ and $T^A_{iB}$,

$$T^A_{iB} = \theta_i \delta^A_B + \Theta^A_{iB}, \quad [\Theta_1, \Theta_2] = \theta^i \Theta_i, \tag{5}$$

where $\theta_i \equiv -\frac{1}{2}\epsilon_{ij}\theta^j$, with $\epsilon_{ij} = -\epsilon_{ji}$ and $\epsilon_{12} = 1$. Also, the two matrices $(\Theta_i)^A{}_B \equiv \Theta^A_{iB}$ are in $\mathfrak{so}(3, n-3)$, the algebra of $\mathrm{SO}(3, n-3)$, as there must be three self-dual and $n-3$ anti-self-dual two-forms.

### K3 fibration over a torus

A case with $\theta^i = 0$ can be constructed as a fiber bundle with fiber K3 over a torus $T^2$. The matrices $\Theta_i$ can be any two mutually commuting matrices in $\mathfrak{so}(3, 19)$. The one-forms are $v^i = \mathrm{d}z^i$, as in the SU(2)-holonomy case, and the $n = 22$ two-forms $\omega^A$ are closed on every K3 fiber, but depend on $z^i$ in the following way,

$$\omega^A(z) = (\exp z^i \Theta_i)^A{}_B \omega^B(0). \tag{6}$$

Going once around each torus coordinate ($z^i \sim z^i + 1$), the set of two-forms $\omega^A$ needs to come back to itself up to some discrete monodromy $\exp T^i$ in $\mathrm{SO}(3, 19, \mathbb{Z})$, which is indeed a symmetry of the string theory.

Performing the dimensional reduction on this background with the Ansatz in Eq. (2) produces a *gauged* $N = 2$ supergravity with the same field content. The hypermultiplet scalars become charged with respect to the Kaluza-Klein vectors $V^i_\mu$, and the Lagrangian in Eq. (3) becomes

$$\mathcal{L} = \tfrac{1}{8}\mathrm{tr}(D_\mu \mathcal{M} D^\mu \mathcal{M}) - \tfrac{1}{8}\mathrm{e}^\phi g^{ij}\mathrm{tr}([\mathcal{M}, \mathcal{T}_i][\mathcal{M}, \mathcal{T}_j]) \tag{7}$$

with covariant derivatives

$$D_\mu \mathcal{M} = \partial_\mu \mathcal{M} - V^i_\mu [\mathcal{M}, \mathcal{T}_i], \tag{8}$$

and the $24 \times 24$ matrix $\mathcal{T}_i$ defined as

$$\mathcal{T}_i = \mathrm{diag}(0, 0, \Theta_i) \in \mathfrak{so}(4, 20). \tag{9}$$

As can be seen from Eq. (7), a potential is generated for the hypermultiplet scalars. The scalars in vector multiplets remain neutral.

### K3 fibration over a 'twisted torus'

The case with $\theta^i \neq 0$ can be thought of as a K3 fibration over a 'twisted torus'. Though in all rigor a 'twisted torus' does not exist as a global manifold, the construction makes sense if we consider it in two steps: a reduction to 5 dimensions on $\mathrm{K3} \times S^1$ plus a further, Scherk-Schwarz-type compactification on another circle $S^1$.

The embedding into string theory remains problematic in this case, as the twist after going once around the circle is not in the U-duality group. Still, as far as the effective field theory is concerned, the result is consistent with a *gauged* $N = 2$ supergravity.

Eqs. (7) and (8) for the hypermultiplet sector still apply in this case, with

$$\mathcal{T}_i = \mathrm{diag}(\theta_i, -\theta_i, \Theta_i) \in \mathfrak{so}(4, 20). \tag{10}$$

The biggest difference is that the scalars in the vector multiplet sector become charged as well with respect to some linear combinations of the vectors $V^i_\mu$ and $B_{i\mu}$, and a potential is also generated in this sector.

The full equations for the bosonic part of the effective action are too big to fit here, but can be found in [1], together with all the necessary references.

### Notes

a. 'Low' with respect to the Planck energy $\sqrt{\hbar c^5/G}$, but still quite high with respect to energies accessible to modern particle accelerators.

b. This means that one can choose orthonormal bases on an open cover of $Y$ such that all transition functions take values in $G$ instead of the generic SO(6) rotation.

c. There are additional hypermultiplets whose number and structure depend on the details of the breaking of the $E_8 \times E_8$ gauge symmetry, but these will be ignored here.

d. There are no other one- or three-forms if one rules out massive gravitino multiplets.

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# Anti-angiogenic effects of Mangiferin in metastatic melanoma. A fair tale of two worlds.

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*We described here how international collaboration can validate the preclinical research of a new use for a given molecule produced in Cuba while strengthening the scientific capacity of the country.*[b]

Mangiferin is a bioactive xanthonoid $C_{19}H_{18}O_{11}$, 1,3,6,7-tetrahydroxyxanthone-C2-β-D-glucoside present in the mango tree (*Magnifera indica L.*) widely grown in tropical and some sub-tropical countries. Although many medicinal properties of the plant have been known for a long time among the rural populations where mango trees grow, it is only in the last 20 years that the research into the molecular mechanisms of its active component Mangiferin (Mg) has been revealed [1]. Interestingly, those molecular mechanism of actions are also involved in diseases of the developed world, such as cancer and degenerative diseases [2]. In this respect, we report to the TCS journal some novel insights of this particular research elucidating the anticancer mechanism of action of Mg against metastatic melanoma to show that the cooperation between the North and South can generate frontline science while strengthening the scientific capacity of the developing partner.

The Cuban Centre of Pharmaceutical Chemistry and other institutions in the scientific pole of Havana has been investigating for more than 20 years this natural bioactive glucosylxanthone as a potential molecule (either monoceutical or natureceutical) with new well-defined pharmacological properties. Previous research in Cuba demonstrated that Mg has antioxidant, anti-proliferative, anti-tumor, and anti-angiogenic properties in different ***in vitro*** and ***in vivo*** models [2]. On the other hand, Cuban researchers have been advancing the collaboration with Flemish researchers in Belgium through one of the VLIR-UOS projects [c]. One of the aims in VLIR-UOS is to offer partnership that can continue advancing in the developing country [d]. Indeed, the research published in the high-impact journal Melanoma Research [3] was the result of the long-term partnership between the University of Havana, and the University of Antwerp [4], in a network with other institutions of both countries: Cuba and Belgium. A Cuban Belgium researcher was also part of the team working at the University of Antwerp. The Belgium-Cuba research partnership owed its success to the leadership of Professor Gay Haegeman from the University of Gent who sadly passed away last year, and to Professor Wim Vanden Berghe from the University of Antwerp currently leading the project. Through this project, the Cuban partner institution received the expensive equipment used during training in Belgium.

Malignant melanoma continues being one of the most aggressive and deadly skin cancers. Despite the availability of novel therapies, there is still poor improvement of patient survival. Previous studies suggested that Mg might reduce aggressiveness of this tumor by interfering with vascular angiogenesis, a pivotal feature of the metastatic melanoma.

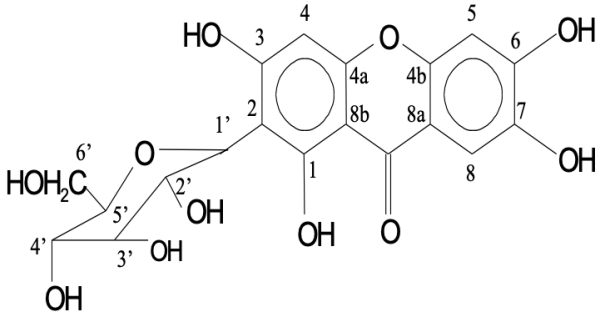


Figure 1: $C_{19}H_{18}O_{11}$, 1,3,6,7-tetrahydroxyxanthone-C2-β-D-glucoside

For this study, the glycosylated xanthone mangiferin was purified in Cuba as a mayor bioactive component (Figure 1) of extracts obtained from leaves and the stem bark of specific varieties of the mango tree *Mangifera indica L.*

Accordingly, a set of ***in vitro*** assays was carried out including cell scratch migration assay, human placenta blood vessel explant assay, capillary tube formation by endothelial cells, and the chorioallantoic mem-

brane (CAM) angiogenesis assay in order to find and validate markers of vascular angiogenesis.

In this paper [3] we demonstrate that Mg has the ability to inhibit the formation of new vessels from pre-existing vessels (angiogenesis) ***in vitro*** and ***in vivo***. These results support the hypothesis that its antiangiogenic activity is essential to explain its antitumor effect. Aggressive and metastatic tumors create their own vascular bed providing oxygen and nutrients to fast proliferating cancer cells. Finding signal transductions activated in this microenvironment is part of current strategies for the development of new antitumor products.

Mangiferin inhibits the gene expression of key signal molecules associated with processes of migration, proliferation, survival and vasculogenesis in metastatic B16 melanoma cells (B16F10 cell line). Using the Ingenuity Pathway Analysis (IPA, Ingenuity System) for functional enrichment and detection of significant pathways, our experiments illustrate that Mg selectively inhibits the up-regulation of the expression of genes such as IL6, TNF, IFNG, VEGFR2, PLAU, FGF1, MMP19, CCL2 and PGF, typical inflammatory and angiogenic mediators. Moreover, by showing dose-dependent Mg specific inhibition of phosphorylation of NF-$\kappa$B, a key mediator up-stream of the inflammatory response, we further demonstrate significant immunosuppressive effects of Mg treatment in metastatic melanoma cells.

Finally, our study demonstrated that Mg is also capable to inhibit TNF$\alpha$ induction of angiogenesis ***in vivo*** in a dose-response manner. The antiangiogenic activity was carried out in melanoma syngeneic studies ***in vivo*** (Figure 2), in models of tumor angiogenesis induced by TNF$\alpha$ and by the highly metastatic melanoma cells (B16F10).

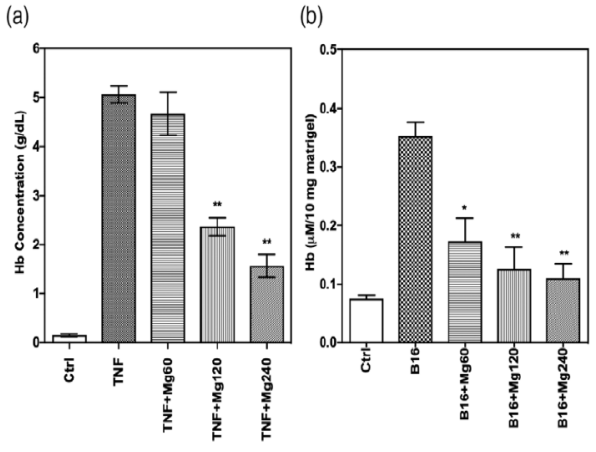


Figure 2: Mangiferin (Mg) (60-240 $\mu$M) inhibits neovascularization ***in vivo*** on (a) TNF alpha (10 ng/mL) and (b) B16F10 $10^5$ cells-induced angiogenesis in mouse abdominal subcutaneous connective tissue.

In conclusion, in this study we demonstrate that Mg holds promise for a novel pharmacophore candidate for cancer treatment. Although Mg showed a potent anti-angiogenic and anti-metastatic effects, highly tolerated, widely available and attractive due to its cost-effective production, these results require the development of pharmaceutical and clinical studies that validate the preclinical findings that are presented in this investigation.

The authors would like to dedicate this work to the memories of Janet Rodriguez Morales (Cuba) and Professors Sandra Apers and Guy Haegeman (Belgium).

## Notes

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b. Original version of this article is Ref. [3]

c. ZEIN2011PR383 and ZEIN2016PR418. Capacity building-Cuban bioactive compounds. `https://www.vliruos.be/en/projects/project/22?pid=3947`

d. VLIR-UOS supports partnerships between universities `https://www.vliruos.be/en/about_vlir_uos/2#annual-reports`

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# Inducible Nitric Oxide Synthase activity in human lung after cardiopulmonary bypass

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*The identification of the enzyme iNOS in human lungs after cardiopulmonary bypass was the result of the experimental and clinical cooperation of two teams aiming to identify new pathways in the pathophysiology of postoperative cardiac surgery.*[b]

The authors signing this paper were from two institutions: pharmacologists from the Centre of Pharmaceutical Chemistry and cardio-surgeons from the Hospital Hermanos Amejeiras in Havana. The aim of the study was to explore the inducible Nitric Oxide Synthase (iNOS) after cardiopulmonary bypass (CPB) in patients undergoing open heart operations [1]. Cardiopulmonary bypass refers to the extracorporeal circulation of the blood through a machine that takes the function of the heart and the lung during the open heart operations. Once the blood circulation in the heart and lung is restored, the ischemia and reperfusion trigger a cascade of inflammatory pathways affecting the postoperative outcome [2].

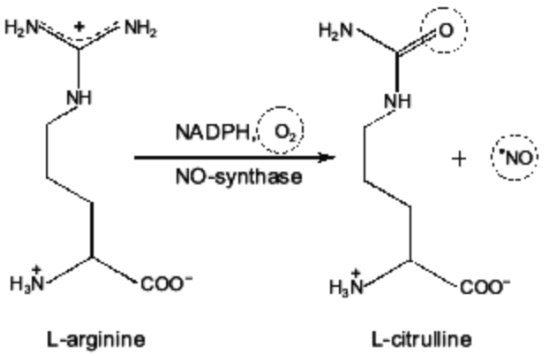


Figure 1: Reaction catalysed by the NOS

The Nitric Oxide Synthase catalyses the conversion of L-arginine into Nitric Oxide (NO) and L-citrulline (See Figure 1). There are three isoforms of the Nitric Oxide Synthase (NOS). Two are constitutive and calcium dependent: the endothelial (eNOS or NOS3) and the neuronal (nNOS or NOS1). The pulses of NO generated by these two isoforms are part of the signal transduction in the physiology of the vascular relaxation (eNOS) and in the neurotransmission (nNOS) mediated by the activation of the guanylate cyclase. The inducible isoform (iNOS, NOS2), however is involved in pathophysiology, expressed under inflammatory/infection settings, producing high output of harmful NO and it is calcium independent. The tissue damages reported after CPB [2] resemble those seen during experimental endotoxaemia [3] which, at least in part, are due to the detrimental excess of high output of NO on the vasculature.

## Materials and Methods

All patients gave their informed consent to be part of the study, which had the approval of the Hermanos Amejeiras Hospital Ethics Committee, according to the National Medical Ethics Regulations. None of the patients had previous pulmonary diseases and there were no evidences of haematological or biochemical disorders previous to the operation. Tissue samples from middle lobe of the lung were taken before ($n = 3$) and after ($n = 7$) cardiopulmonary bypass from patients undergoing open heart operations to repair mitral or aortic valve dysfunction. The mean duration of the cardiopulmonary bypass was $122 \pm 30$ minutes. After the CPB a significant reduction in haemoglobin was detected in all patients, as well as altered blood clotting parameters. Tissue samples were immediately frozen on dry ice and kept at $-70°$C until processing them for the enzymatic activity of NOS. Chemical reagents were obtained from Sigma (St. Louis, MO) and radiochemicals from Amersham International (Aylesbury, GB) through the scientific collaboration with The Wellcome Research Laboratories, Kent. Tissue samples were washed in ice-cold sucrose buffer solution before homogenising them in an enzyme-preserving buffer as described before [4]. The homogenates were then centrifuged at $100,000\,g$ for 20 minutes at 4°C. The NOS activity was measured in the cytosolic fractions by the conversion of radio labelled $^{14}$C-L-arginine to $^{14}$C-L-citrulline. Triplicate aliquots of 0.018 ml of the same cytosolic fractions were added to 0.1 ml the enzymatic reaction buffer [5] containing cofactors and the proportion of cold-hot substrate of 0.024 mM L-arginine and $^{14}$C-L-arginine (1.85 MBq/ml). Three tubes per sample were incubated for 20 minutes at 37°C having either water, or 1 mM L-NMMA ($N^G$-monomethyl-L-arginine, the NOS inhibitor), or 1 mM EGTA ($Ca^{2+}$ chelator). Reaction was terminated by adding 1.5 ml of $Na^+$-form dowex-50 resin in order to chelate hot and cold L-arginine [5]. The $Ca^{2+}$-independent NOS activity (iNOS) in the cytosolic fraction was determined by the differential production of $^{14}$C-L-citrulline formed in the presence and absence of the L-NMMA and EGTA,

expressed in pmol/min/mg protein.

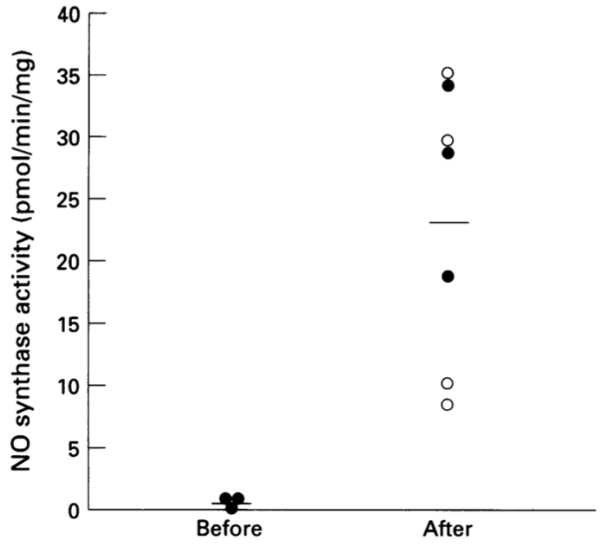


Figure 2: $Ca^{2+}$-independent NOS activity in cytosolic fractions of lung biopsies before and after CPB. Originally published in Thorax [1]

## Findings, discussion and conclusion

Lung tissue samples exhibited significant higher activity of $Ca^{2+}$-independent NOS (23.6 pmol/min/mg) after CPB compared with that found before the initiation of the extracorporeal circulation ($1.5 \pm 0.5$ pmol/min/mg), $p < 0.05$ (Figure 2). Although the cellular origin of the iNOS can not be precised in the current experimental setting, it is plausible to suggest that such difference before and after CPB in $Ca^{2+}$-independent NOS activity came from polymorphonuclear (PMN) cells within the alveolar vasculature, for two reasons: the neutrophils sequestration in alveolar circulation due to reduced flow when starting CPB [6] and their basal activity that has been found in human peripheral PMN cells [7]. Sair and Evans [8] discussing our results in the editorial section of this journal, have also referred the inflammatory role of neutrophils in the lungs after experimental CPB [9], addressing the time related cascade of inflammatory mediators. Indeed, our results can not differentiate if the increase of iNOS activity was due to more infiltrated PMN with basal and beneficial $Ca^{2+}$-independent NOS activity, or a pathological higher expression of iNOS in other lung tissues due to inflammatory mediators. Nevertheless, this findings may contribute to the understanding of the pathogenesis around the acute phase response observed after cardio-thoracic surgery.

The author acknowledge the contribution from Rene Delgado (IFAL, University of Havana) to this work and his subsequent input developing the research in Immunopharmacology in Cuba, and the posthumous recognition to Professor Noel Gonzalez, an outstanding researcher and the pioneer of Heart Transplant in Cuba [10] (`http://www.sld.cu/obituario/2016/01/17/profesor-julio-noel-gonzalez-jimenez`)

### Notes

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# Investigative approach and its influence on the level of development of the self-evaluation in pre-university students

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*This paper exposes some results obtained in my PhD thesis (Peña Acosta, 2005). Its scientific novelty lays in the determination of a relationship between the implementation of the investigative approach in the developer teaching-learning process and the self-evaluation of the students about their school performance.*

The investigative approach in the developer teaching-learning process (IA-DTLP) has been defined as a way to explain the process by relating it to the standard elements of an investigation. This includes all its components and links them to the search of knowledge on the part of the student, in constant interaction with the group and guided by the teacher. This approach is reflected in the goals, in the problematization of the contents, in the way of doing the evaluations and building the learning means, based on the design of the academic subject. In this way the teaching-learning scenario is transformed into one that trains the learners in the discover and develop of their own potentials.

The Vigotskyan concept of zone of proximal development is central in this context and is not restricted to intellectual development, but it is also applicable to the development of the personality and, within it, to the development of self-evaluation (Peña Acosta, 2004a; 2004b). So, the didactic alternative carried out in this study is built as a process of mediation with both psychological and pedagogical tools. At the same time, the so called developer teaching-learning process (DTLP) has been systematized as the result of the interaction of three dimensions: activation-regulation, significancy and motivation to learn (Addine Fernández, 2004). It additionally includes several sub-dimensions as can be seen in the first two columns of Table 1.

With these theoretical tools we hypothesized that the level of development of the self-assessment regarding school performance can be boosted within the pre-university education by a didactic alternative that connects the research approach with the DTLP through dimensions of self-knowledge, harmony and regulation of self-assessment. The specific tasks designed are listed below:

1. Critically evaluate the main tendencies of the process of integral formation of the personality as a goal of the pre-university education.
2. Characterize the self-evaluation of the students regarding their school performance from the psychological, sociological, pedagogical and didactic basis of self-assessment.
3. Diagnose the current state of students self-evaluation regrading their school performance, contributing to the integral formation of the personality.
4. Design a didactic conception of the relation between the IA-DTLP and the self-evaluation dimensions of the school performance.
5. Build a didactic alternative for the pre-university education as a practical implementation of the designed didactic conception.
6. Explore the feasibility of the implementation of the didactic alternative using the criteria of experts.
7. Determine the transforming potentials of the didactic alternative through the execution of a pre-experiment.

In the critical analysis of the practical experience for the application of this approach to pre-university education we established fifteen requirements to be included, in order to effectively improve the integral formation of the students. These requirements of the investigative approach can be observed in the third column of Table 1. This table also shows the correspondence between these requirements and the dimensions and sub-dimensions of the DTLP introduced before.

The results of this study found relationships demonstrating that the IA-DTLP have potential to improve the DTLP while stimulating the development of self-evaluation as a psychological constructor of the personality. This didactic conception was used as a curricular decision-making basis for the design of the didactic alternative that involved all the components of the DTLP of pre-university education, with active participation of the student, the group and the teacher. The didactic alternative was designed to improve the process of integral formation of the pre-university student, but with the particularity that it was also consistent with the goal of enhancing the level of development of the self-evaluation of the pre-university student about her school performance.

The proposed didactic alternative was framed in the perspective of the four fundamentals pillars of education proposed by the UNESCO International Commission for the present century: Learning to value oneself properly, that requires learning to know and to know

| Dimension | Sub-Dimension | Requirements of the Investigative Approach |
|---|---|---|
| Activation-Regulation | Productive-creative intellectual activity | Consider the age and previous formation of the student in research activities via an integral diagnostic including study techniques, study style and research abilities. |
| | | Build indicators to evaluate the develop of the personality, measuring processes and not only results. |
| | Metacognition | Promote the self-evaluation and self-reflection on the learning. |
| | | Actively involve the student in the determination of the goals and indicators of the evaluation. |
| Significancy | Establishment of significant relations | Orient research activities where the relation known-unknown is connected with daily life examples as well as interests and needs of the students that reveals the main idea of the matter under study. |
| | Implication in the formation of feelings, attitudes and values | Establish the dynamics of the students' role; exposing their results, acting as opponents or evaluators, leader of the team or any other. |
| | | Make space for the collective reflection on the activity, the debate and the constructive criticisms. |
| | | Include among the tasks the research about the life and contributions of scientists and outstanding figures in the topic under study. |
| | | Establish the necessary sessions of exchange, collective or individually, with the teachers in charge of the research. |
| | | Promote the team-work as a formation for social work and life. |
| Motivation to learn | Intrinsic motivation towards learning | Ensure that the accountability make students take reasonable decisions regarding how to better perform the research, avoiding rigid frames that hinder creativity. |
| | | Give opportunities to choice the particular content to study in depth. |
| | | Plan objective tasks in correspondence with the potential and abilities of the student. |
| | System of self-evaluations and positive expectations regarding learning. | Treat errors properly as sources of learning. |
| | | Stimulate individual and not only global achievements of the activity. |

Table 1: Correspondence between the dimensions and sub-dimensions of the DTLP and the requirements of the IA-DTLP.

oneself; learning to live together, that is best achieved when there is harmony in criteria, self-evaluations and valuation of the more significant people in the environment of the subject; learning to make, that implies the development of abilities to value others and value oneself; and learning to be, that needs a high regulatory potential of self-evaluation.

## Notes

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