

## GRANULOCYTE COLONY-STIMULATING FACTOR (G-CSF): A NOVEL ANTICANCER THERAPY BASED ON THE “UNIVERSAL DYNAMICS OF TUMOR GROWTH”?

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It has recently been proposed that all solid tumors exhibit the same growth dynamics. This hypothesis, developed by Bru and coworkers and called the universal dynamics of tumor growth, says that the main mechanism responsible for tumor progression is cell diffusion on the tumor border. The authors of this hypothesis claim that, by inducing strong neutrophilia around the tumor, this dynamic can be changed; neutrophils would locate themselves to eliminate cell diffusion on the tumor border therefore inhibiting tumor growth. The authors suggest that this approach may be exploited to develop effective anticancer strategies, and they have recently reported the possible cure of a 56-year-old patient with advanced hepatocarcinoma treated with granulocyte colony-stimulating factor (G-CSF), a key regulator of neutrophil production. The present report shows evidence that suggests that it is very unlikely that neutrophil-induced cancer cell death is mediated by a mechanical impediment at the tumor border. Furthermore, it is shown that the induction of neutrophilia is not a new anticancer strategy based on the “universal dynamics of tumor growth”, but a known approach that has been widely explored along the years. The merits of G-CSF for being tested in clinical trials with cancer patients are finally evaluated.

**Key Words:** tumor growth, cell diffusion, granulocyte colony-stimulating factor, neutrophilia.

In 1998, the group led by the physicist Antonio Brú published a report describing in mathematical terms the contours of a brain tumor growing *in vitro*. They showed that its dynamics was mainly due to contour cells and that the tendency of an interface cell to duplicate was a function of the local curvature [1–3]. Several years later, in an article entitled “The universal dynamics of tumor growth”, they reported experiments that supported that this dynamics was shared by all solid tumors. Based on these findings, they suggested that tumor growth should be conceived as a competition for space between the tumor and the host, and not for nutrients or other factors, and that we might need to revise our current radiotherapy and chemotherapy strategies [4]. In 2004, they reported anticancer effects in mice implanted with Ehrlich tumors and subsequently treated with granulocyte-macrophage colony stimulating factor (GM-CSF), a factor that induces neutrophilia. They proposed that neutrophils would locate themselves around the tumor to hinder cell surface diffusion. Since the cells at the border would no longer find sufficient space, they would no longer proliferate, and those inside the tumor would eventually become necrotic [5]. One year later, Bru and coworkers reported the possible cure of a 56-year-old patient with advanced hepatocarcinoma treated with granulocyte colony-stimulating factor (G-CSF) [6]. G-CSF is a key regulator of neutrophil production that is commonly used in the clinic to increase the production of neutrophils in patients with chemotherapy-induced neutropenia [7].

The investigation carried out by Bru and coworkers has received important media attention and many people with terminal cancers are currently seeking treatment with G-CSF. Oncologists are reluctant to administrate this drug because there are no clinical trials that support its effectiveness in the treatment of cancer. While many oncologists consider that the investigation carried out by Bru and coworkers is not sound enough to deserve clinical evaluation, many people believe that Bru’s team has developed a new theory that may be used to treat all solid tumors, and they do not understand why this strategy is not being evaluated further. In the present report, I briefly discuss that there is no scientific evidence that relates the theory of universal tumor dynamics with the anticancer effects produced by neutrophils. On the contrary, there are many published data that strongly suggest that neutrophil-induced cancer cell death is mediated by other mechanisms. However, there is evidence that suggests that the induction of neutrophilia might be a valid anticancer strategy in specific situations; this evidence mainly consists of several reports (most of them published prior to the works by Bru et al.) that have shown that G-CSF produces anticancer effects in patients with cancer.

### THE THEORY OF THE UNIVERSAL DYNAMICS OF TUMOR GROWTH DOES NOT EXPLAIN THE ANTITUMOR EFFECTS OF NEUTROPHILS

According to Bru et al. (2005), the neutrophilia achieved by administering G-CSF is an experimental treatment based on their theory of the universal dynamics of tumor growth [6]. Although their theory of the universal tumor dynamics is a sound hypothesis based on experimental evidence, the authors do not provide experimental data that demonstrate that neutrophil-induced cancer cell death is produced by

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**Abbreviations used:** G-CSF – granulocyte colony-stimulating factor; GM-CSF – granulocyte-macrophage colony stimulating factor; H<sub>2</sub>O<sub>2</sub> – hydrogen peroxide; ROS – reactive oxygen species.

a mechanical effect [4]. On the contrary, there are many published data that strongly suggests that the antitumor effect of neutrophils is mediated by other mechanisms. It is well known that neutrophils produce several mediators that induce cell death. These cytotoxic mediators include reactive oxygen species (ROS), proteases, membrane-perforating agents, and soluble mediators of cell killing, such as TNF- $\alpha$ , IL-1 $\beta$  or IFNs [8–10]. For instance, it has been demonstrated that ROS such as hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) are crucial in the anticancer effects of neutrophils [10–12].

As mentioned before, Bru et al. propose that neutrophils produce cancer cell death because they locate themselves around the tumor to hinder cell surface diffusion; cells would not find sufficient space to proliferate and they would eventually die [5]. If this were the case, neutrophilia induction by G-CSF would have no anticancer effect in patients with leukemia, as these types of cancer grow in suspension and do not follow the universal dynamics of tumor growth proposed by Bru and coworkers [4]. However, Picalluga et al. [13] showed that there are more than 20 reports (published between 1991 and 2001) that describe that the administration of G-CSF in patients with different types of leukemia resulted in complete remissions of these cancers. These data make it difficult to accept that neutrophil-induced cancer cell death is mediated by a mechanical effect.

### SHOULD G-CSF BE TESTED IN CLINICAL TRIALS WITH CANCER PATIENTS?

There is substantial evidence that suggests that G-CSF might be useful in the treatment of cancer. Firstly, it is well-known that G-CSF administration increases the production of neutrophils [13] and that neutrophils produce cytotoxic mediators that can kill cancer cells [8–12]. In addition, there are many human studies that have shown that the administration of G-CSF, alone or in combination with chemotherapy, produces anticancer effects [6, 13–17].

On the other hand, it is important to mention that the use of G-CSF has been associated with toxicity. Thus, fatal outcomes following G-CSF administration have been described in the literature [18–20]. It has also been reported that G-CSF can favor tumor progression [21–23]. This is understandable because neutrophils are well-known to generate H<sub>2</sub>O<sub>2</sub>, and H<sub>2</sub>O<sub>2</sub> is an oxidant highly involved in cancer development [24, 25]. For instance, it is now accepted that H<sub>2</sub>O<sub>2</sub> is a key activator of hypoxia-inducible factor 1, a transcription factor whose activation is observed in most human cancers and has been associated with increased patient mortality [26].

The scientific literature shows that G-CSF might be effective in the treatment of cancer but can also produce severe toxicity. So, should G-CSF be tested in clinical trials with cancer patients? The key parameter to consider here is the efficiency of our current anticancer strategies and the possible benefit/risk of using G-CSF in cancer patients. The current cancer

chemotherapeutic strategies are very useful in specific cancer types at specific stages of disease. In these situations, it is not easy to deprive cancer patients of these therapies in order to try a drug that may not be effective and may be toxic. However, we have to accept that our current strategies have very little efficiency in the treatment of several common metastatic cancers [27]. In situations in which the possibilities of success are extremely low, new anticancer strategies should be explored. It is the author opinion that patients with terminal cancers who insist on being treated with G-CSF should be offered the possibility of participating in a clinical trial with this drug, as there are preclinical and clinical data that support that G-CSF may have anticancer effects. However, these patients should be informed that G-CSF is not a “miraculous” anticancer treatment discovered by Bru and coworkers, but a known drug that may be completely ineffective and may produce severe toxicity.

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## ГРАНУЛОЦИТАРНЫЙ КОЛОНИЕСТИМУЛИРУЮЩИЙ ФАКТОР (Г-КСФ): НОВЕЙШАЯ ПРОТИВООПУХОЛЕВАЯ ТЕРАПИЯ, ОСНОВАННАЯ НА ПРИНЦИПАХ ТЕОРИИ ОБ “УНИВЕРСАЛЬНОЙ ДИНАМИКЕ ОПУХОЛЕВОГО РОСТА”?

Не так давно была предложена гипотеза о том, что всем солидным опухолям присуща некая общая динамика роста. Она была выдвинута Вги и соавторами и названа теорией универсальной динамики опухолевого роста. Она указывает на основной механизм, отвечающий за развитие опухоли, которым, по мнению авторов, является клеточная диффузия на границе опухоли. Утверждается, что при индукции выраженной нейтрофилии вокруг опухоли, эта динамика может быть изменена. Нейтрофилы устремляются на границу опухоли для элиминации клеточной диффузии и вследствие этого подавляется рост клеток опухоли. Исследователи считают, что этот подход может быть использован для разработки эффективной противоопухолевой стратегии. Недавно они сообщили об успешных результатах лечения больного в возрасте 56 лет с прогрессирующей гепатокарциномой при помощи гранулоцитарного колониестимулирующего фактора (Г-КСФ), ключевого регулятора выработки нейтрофилов. Приведенные данные указывают на малую вероятность того, что нейтрофилы, стимулирующие гибель раковых клеток, в свою очередь активируются при помощи механического препятствия на границе опухоли. Показано также, что стимуляция нейтрофилии не является новой стратегией, основанной на теории “универсальной динамики роста опухоли”. Она основывается на подходах, широко исследованных и известных на протяжении ряда лет. Качественные характеристики Г-КСФ, изученные во время клинических испытаний, наконец-то получили полную оценку.

**Ключевые слова:** опухолевый рост, клеточная диффузия, фактор стимуляции роста колоний гранулоцитов, нейтрофилия.