

Targeted Immune Therapy as Example of Paul Ehrlich's "Magic Bullets" Developed More than 100 Years Ago

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In the article by Gerhard Zugmaier, Antibodies in hematology by the example of acute lymphoblastic leukemia, *Der Internist* 10 (2019) 1032–1035 [1], the application of antibodies in hematology was described by using the example of acute lymphoblastic leukemia. Antibodies have become an essential element of treatment for patients with hematological tumors. This concept was developed more than 100 years ago in a different context [2]. The German physician Paul Ehrlich (1854-1915) said, that for the defense against bacteria "antibodies" were be responsible [2,4]. In the antibodies Ehrlich saw therapeutic compounds, that like "magic bullets" would find their target and only destroy this target without affecting the organism. Paul Ehrlich became inspired by a scene in the German opera "Der Freischütz" ("The marksman") by the composer Carl Maria von Weber [3]. In this opera a certain kind of bullets, "free bullets", which were magic bullets, played a major role, because they always found their target. In 1878 Paul Ehrlich became resident and later attending physician at the Charité in Berlin. There, he worked closely together with Robert Koch, Emil von Behring, and Shibasaburo Kitasato. The chairman of the department, the famous internist Theodor von Frerichs, gave Paul Ehrlich enough space to conduct his experiments. Starting from 1882 Ehrlich investigated the acid resistance of the tuberculosis *mycobacterium* just discovered by Robert Koch and developed a method of dyeing the *mycobacterium*, thereby being able to detect it in the organism. Koch and Frerichs were important supporters of Ehrlich [4]. In 1890, Ehrlich was appointed by Koch to a position at the newly founded Institute for infectious Disease, the Robert Koch Institute. Ehrlich's groundbreaking research in immunology started at that time. Later, in 1899, Ehrlich was appointed as Chairman of the newly found Institute for Experimental Therapy in Frankfurt, the Georg Speyer Haus, in which until this day important research has been conducted. There he

continued his groundbreaking research in Immunology and Cancer Research. In 1908, Paul Ehrlich received the Nobel prize for Medicine [4]. Ehrlich's great ability for abstract concepts enabled the creation of terms such as 'receptor' [2]. In this context he also developed the concept of "magic bullets", which are drugs that move straight to their target. Targeted compounds attack pathogens that express the target and leave tissue alone that does not express the target [2]. It turned out later that the concept of magic bullets was not confined to bacterial infections and could be extrapolated from infectious disease to malignant tumors. Surface antigens on tumor cells could serve as target of these magic bullets.

The anti-clustered designation (CD) 20 antibody rituximab was one of the first antibodies, which have been successfully applied in hematologic malignant tumors. Rituximab was the front runner of the materialization of the concept of targeted treatment by Ehrlich's "magic bullets". His concept of a targeted therapy that is as tissue selective as possible has not changed and is equally actual now as it was more than 100 years ago. It has outlived all trends in science [1].

The concept of the "magic bullets" was recently expanded to antibodies linked to chemotherapy. The anti-CD22-antibody inotuzumab is conjugated to the chemotherapeutic compound calicheamicin [1].

One further step further involved the use of cells as "magic bullets". Blinatumomab belongs to BiTEs® ("Bi-Specific T-cell engagers"). BiTE® molecules are directed against CD19 on B-lymphocytes und CD3 on T-lymphocytes building an immunologic synapse between B lymphocytes and T lymphocytes. B lymphocytes are the targets, T lymphocytes the "magic bullet". The T lymphocytes cause the lysis of the B lymphocytes [1].

References

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