CROI Community Cure Workshop, Sunday, February 2015 2015, Crowne Plaza

The "CROI community Cure Workshop" has become a tradition already: Three years ago it was held for the first time immediately before the actual conference. The program became more sophisticated every year. This year there were three top-notch presentations:

Javier Martinez Picardo: **Cord Blood Stem Cell Transplant Program and HIV Cure Research at the Institute IrsiCaixa**. In this lecture Javier briefly described the method of stem cell transplantation for the purpose of curing a malignant blood disease. However, it is still just a beneficial side effect that "along the way" an HIV infection may be cured (as in the "Berlin Patient" Timothy Brown), or additional insights can be gained. However, the number of bone marrow donors with the required Delta32 mutation in the gene for the CCR5 receptor is very small. Especially in the homozygous variant (i.e. both genes for CCR5 are non functional) less than 1% of donors are suitable. We urgently need alternatives to further explore this approach.

Cord blood stem cells are considered to be promising as they are less antigenic than adult cells, so a lower HLA matching is required (HLA are markers of the immune system that need to be matched for a transplant. Otherwise the graft will be rejected or, in this case, will attack the new host). Currently European cord blood banks are about to test their specimens for cells with the Delta32 mutation. It is hoped that until next year approximately 400-500 usable cell concentrates with homozygous Delta32 mutation will be found. These cells will then be reserved for transplantation of HIV-positive recipients. Unfortunately, so far the mortality after stem cell transplantation in HIV-positive patients seems to be higher than expected. It is not yet clear whether this is just a statistical phenomenon in the few cases seen so far (single digit numbers), or whether there are other reasons for it. Despite all the efforts, until today Timothy Brown remains the only living person cured from HIV infection.

Stephen Mason, BMS: **Anti-PD-L1 Antibody and HIV Cure Research**
Antibodies against PD1 receptor and its ligand PD-L1 are about to revolutionize the treatment of some forms of cancer. These drugs, also known as "Checkpoint-blockers" , can release a "brake" that prevents T-cells from recognizing and killing cancer cells or HIV-infected cells. These non-reactive T cells are referred to as "exhausted", but if you blocked PD1 or its ligand, these T cells may very well respond again and do their job. Until recently, the manufacturers of these antibodies were very reluctant to use these drugs in people with HIV in order not to jeopardize the approval process for the treatment of cancer. Meanwhile, some of these drugs are approved (PD1-inhibitor from Merck&Co.: Pembrolizumab, Keytruda™ and PD-L1-blocker from BMS: Nivolumab, Opdivo™, both approved for the treatment of malignant melanoma) and now the researchers turn to exploring these promising compounds in HIV.

The first trials in macaques showed a significant viral load reduction in about half of the animals. After the antibodies were cleared from the body, the viral load rebounded, but to a lower set-point than before. In the other animals the viral load reduction was less pronounced and the set-point was not lowered. One problem might be, that the active ingredients used in this experiment are *human* antibodies that can cause an reaction of the animals' immune system against the Fc portion (the "human part" of the antibody) and thus may make the drug less effective and reduce the desired effect. Apart from PD1,

there are also a number of other receptors that may affect the reactivity of T-cells (including LAG-3, CD244, CD160 and others). It is possible that for optimum effect once again a combination approach will be necessary.

A preliminary study with a PD-L1 blocker in humans with HIV infection has recently been halted because in experiments with mice at high doses and prolonged use "signals" showed up, i.e. side effects. It was not stated, which side effects were seen. Only when these problems are cleared, the study in human subjects will be continued. In a side note a problem with the use of HDAC inhibitors (eg, vorinostat, panobinostat, romidepsin) for the reactivation of latent HIV was noted: These drugs can activate latently infected cells and lead to stimulation and production of virus, but at the same time they also reduce the HLA-presentation required for identifying and ultimately killing these cells by the immune system. In other words, the proposed “shock & kill” approach doesn’t work as expected because, the "shock" occurs, but unfortunately, the “kill” doesn’t. Therefore, the researchers are now looking for other substances that can disrupt the latency of HIV. When HIV is forced out of it’s dormant state, the infected cells start to produce virus. T-cells that have been unleashed by a Checkpoint blocker then could potentially discover and destroy these virus-producing cells.

Afam Okoye: **B-cell Follicle Sanctuary Permits Persistent Productive SIV Infection in Elite Controllers: Implication for HIV Cure Research**.
Mainly CD8 effector cells are responsible for the discovery and killing of HIV-infected cells. Unfortunately, exactly these cells lack specific receptors (CXCR5, not to be confused with CCR5 and CXCR4!) that would grant them access to the so-called “B-cell follicles” (or "germinal centers”) in the lymph nodes where T-cells with particularly high viral density are abundant. This could turn out to be another major obstacle on the path to a cure.

Anna-Laura Ross (IAS): **IAS Towards a Cure initiative**: This project is intended to give any interested person a fundamental knowledge on the topics related to the cure of HIV. The material will be constantly expanded and updated and is now available on the website http://www.avac.org/cure-curriculum.

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