Cellosaurus micro-review 1: cellonauts, spacefaring cell lines

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Abstract: This micro-review is intended to provide an up to date list of the cell lines that have flown in space, starting with HeLa in 1960. We coin a new term, *cellonaut* for cell lines that have been sent in earth orbit. As of June 2019, we were able to identify 52 different cellonauts. Cell lines that are cellonauts are annotated as such in the Cellosaurus.

Introduction: the HeLa space saga

In the book that Rebecca Skloot wrote [[Skloot, 2010](#)] on the HeLa cell line ([CVCL_0030](#)) and the woman from who it was established, Henrietta Lacks, it is stated that “*Henrietta’s cells went up in the second satellite ever in orbit, which was launched by the Russian space program in 1960, and almost immediately afterward, NASA shot several vials of HeLa into space in the Discoverer XVII*”.

While it is true that HeLa was the first cell line to go to space, the book takes some liberty with the true space exploration career of HeLa which we tried to reconstruct. HeLa was flown in the 1960s on at least 7 different Soviet space missions [[Dickson, 1991](#)]. The first one took place on the 19th to 20th of August 1960, HeLa, along with some bacterial and phage cultures, plant seeds and rabbit and human skin samples shared passenger space with two dogs, Belka and Strelka on the Korabl-Sputnik-2 [[W01](#)] spacecraft (also known as Sputnik-5). Skloot most probably confused Korabl-Sputnik-2 with Sputnik-2 [[W02](#)], which was the second man-made satellite to make it to earth orbit. It was launched on November 3, 1957 and did carry a passenger, but it was not HeLa, but Laika, a dog that died a few days later. From table 3 in [[Rees and King-Hele, 1963](#)] we estimate that Korabl-Sputnik-2 was the 30th artificial satellite. Thus HeLa started its space career quite early in the history of space exploration but not as early as stated by Skloot.

The following year HeLa flew with Yuri Gagarin on Vostok-1, the first manned spaceflight. This was followed by four other manned missions: Vostok-4 in 1962, Vostok-5 and Vostok-6 in 1963 and Voskhod-1 in 1964. HeLa also travelled along with some tortoises [[W03](#)] on Zond-5 in 1968, an unmanned mission that was the first one that achieved a flyby of the moon followed by a successful return to earth.

HeLa flew on the American satellite Discoverer XVIII [\[W04\]](#) which was launched on December 7, 1960. Three days later it ejected a capsule that was recovered in mid-air near Hawaii by a military transport plane. While the capsule was carrying a scientific experiment package, its real aim was to bring back film packs. Discoverer XVIII was part of a then classified CIA photographic surveillance system, the Corona program [\[W05\]](#). The biological samples on Discoverer XVIII [\[Katzberg, 1962\]](#) were sealed in individual glass ampules. The paper states that “*Seven human cell lines were employed. Five of these were normal, definitive representatives of the three embryonic germ layers, and two were of neoplastic origin.*” The “cell lines” are listed as: “*Ectodermal: Amnion, Conjunctiva, Sternal marrow, Synovia; Mesodermal (neoplastic cell lines): Monocytic leukemia, Hela; Endodermal: Embryonic lung*”. It is most probable that the terminology “cell line” for the six non-HeLa samples is incorrect and most probably refers to primary cells.

Skloot book does not cover the second part of HeLa career in space which we tried to reconstruct. After a long hiatus, HeLa returned to space, sent by a Japanese research group [\[Ohnishi et al, 2002\]](#) on two missions, one on the Russian Mir space station for 41 days in 1997 and the other on the American Shuttle flight STS-89 in 1998 for 9 days, both to study the effect of space radiation on DNA damage. Finally it also went to the International Space Station (ISS) in 2006 but under an “alias” as the experimenters [\[Meloni et al, 2011\]](#) thought that they were studying a leukemia cell line but were in fact using a HeLa contaminated culture (see the results section).

Methodology, scope and terminology

While the space story of HeLa is interesting, it is by far not the only cell line to have made it to space and we wanted, in this micro-review to establish an up to date list of spacefaring cell lines. To establish this list we first started with two useful reviews published in the 1990s [\[Dickson, 1991; Moore & Cogoli, 1996\]](#). But it was necessary to dig a bit deeper, on one hand to find out which cell lines have been to space in the more than 20 years that elapsed since the second review was published but also to uncover the exact identity of the cell lines that are mentioned in these two reviews. To complete the list we carried out a large panel of searches on Google Scholar, PubMed and Europe PMC, the various European Space Agency (ESA), NASA and China National Space Science Center servers, the GeneLab Data System [\[Ray et al, 2019\]](#), a database of omics data generated during space flights and the Erasmus Experiment Archive [\[Isakeit et al, 2004\]](#), a database of ESA funded and co-funded experiments.

It is important to state that this micro-review only concerns itself with cell lines that have at least orbited earth once thus excluding cell lines that have flown on airplane parabolic flights, sounding rockets or stratospheric balloons. We have decided to coin a new term, ‘*cellonaut*’, for such space-faring cell lines.

While digging deeply in publication relevant to cellonauts we encountered cell lines that were not yet in the Cellosaurus [Bairoch, 2018], we created new Cellosaurus entries for these entities. We also implemented a new “Group” comment “*Space-flown cell line (cellonaut)*” that was retrofitted to all the cell lines described in this review. Thanks to these developments you can, on the ExPASy server, obtain the list of all cellonauts in the Cellosaurus using the following query: <https://web.expasy.org/cgi-bin/cellosaurus/search?input=cellonaut>

Results

Overall we could identify [Table 1] 52 different cellonauts that have flown on American, Chinese and Russian spaceflights as well as on the International Space Station (ISS). The identified cellonauts include 27 different human cell lines, 12 from mouse, 6 from rat, 4 from hamster and one each from pig (PICM-19; [CVCL V146](#)), macaque (JTC-12; [CVCL 3631](#)) and the insect *Spodoptera frugiperda* (Sf9; [CVCL 0549](#)). We have not been able to find any bird, reptile, amphibian or fish cellonaut.

In two cases we had difficulties to identify the exact cell line that was used on a space mission. The first case is what is reported by [Dickson, 1991] to be “Chinese hamster L cell culture” and which was used in experiments carried by the Soviet Cosmos-782 satellite. But going back to the original report [Sushkov et al, 1977], we believe that this is what is often known as the mouse “L cells” (recommended name NCTC clone 929; [CVCL 0462](#)) which, in addition to being a very popular cell line is also famous for being the first ever established continuous cell line [Sanford et al, 1948].

The second case is quite puzzling and concerns an experiment, called CoCulture which flew on Shuttle STS-89 in January 1998, was transferred on the Russian Mir space station and was brought back on earth on STS-91 in June 1998. In a number of NASA documents including [W11] it is stated that “*During the Biotechnology Coculture experiment conducted aboard Mir in the spring of 1998, breast carcinoma cells and endothelial cells were grown together in the Bioreactor Demonstration Unit. Principal investigators (PIs) Elliot Levine, of Wistar Institute, and Thomas Goodwin, of JSC, wanted to produce tumor tissue with blood vessel precursors*”. However we could not find in any publication or technical document any mention of the name of the two cell lines nor of the outcome of the experiment. By serendipity we could assign and identity to the “*endothelial cells*”: in the 1970-90s Elliot Levine established a number of finite life human adult vascular endothelial cell lines. Some of them are still distributed by the Coriell Institute and one of them; HIVE-86 (also known under its Coriell assigned name: AG10773) contains the following sentence in a “Remarks” field [W13] “*Microgravity experiment in space (Mission STS-89/Mir)*”. Thus most probably HIVE-86 is the “endothelial” cellonaut, but we were unable to pinpoint the identity of the breast carcinoma cell line.

Many different types of cell lines have become cellonauts and the current roster includes 21 cancer cell lines, 16 spontaneously immortalized cell lines, 5 finite cell lines (2 fibroblasts, 2 fetal cell lines - including the famous WI-38 ([CVCL_0579](#)) used for vaccine production and 1 endothelial cell line), 4 hybridomas, 2 EBV-transformed cell lines, 2 SV-40 immortalized cell lines, one conditionally SV40 immortalized cell line (hFOB 1.19; [CVCL_3708](#)), and one hybrid cell line (EA.hy 926; [CVCL_3901](#)). Embryonic stem cell lines do not yet seem to have made it to space. While the same seems true of induced pluripotent stem cells (iPSC), we found a publication [[Li et al, 2019](#)] reporting the study of embryoid bodies derived from two different mouse iPSCs in space during the Chinese Tianzhou-1 space mission.

In three instances contaminated cellonauts were flown in space without the knowledge of such contamination by the experimenters. The first instance is on the Zond-5 spacecraft in 1968. Along with HeLa, two other cell lines were flown on this mission [[Zhukov-Verezhnikov et al, 1971](#)]: CaVe ([CVCL_8444](#)) and a variant, CaVe K-10V ([CVCL_WN72](#)). CaVe was originally thought to be a gastric cancer cell line but is in fact contaminated by HeLa. So unknowingly Zond-5 was carrying three different samples of HeLa! The second instance is much more recent and concerns J-111 ([CVCL_2965](#)), also a HeLa contaminated cell line. J-111 was flown on the ISS in 2006 [[Meloni et al, 2011](#)]. While J-111 is known to be contaminated since 1968, the group that carried out this space experiment were still describing it as "*a monocyte/macrophage cell line derived from human acute monocytic leukemia*" in their 2011 publication. Finally, the third instance concerns MIP-101 ([CVCL_H689](#)) which has flown on two Shuttle flights and on the ISS and which has very recently been shown to be a DLD-1 ([CVCL_0248](#)) derivative.

We encountered one instance where a new variant of an existing cell line (rat L8; [CVCL_4236](#)) emerged during the space flight. It was called L8SF - for L8 Space Flown - ([CVCL_WN49](#)) [[Kulesh et al, 1994](#)]. There is also a publication reporting the sub-cloning of Ca Ski ([CVCL_1100](#)) after a flight on Shenzou-8 [[Yang et al, 2007](#)] and reporting the characterization of 4 such sub-clones. While these two reports seem to be so far the only ones describing space "born" cellonauts, they are maybe other unreported births. For example, in the list of experiments that were planned to be carried out inside the German Spacelab module on the American shuttle flight STS-55 in 1993, the one untitled "*Enhanced hybridoma production under microgravity*" [[W06](#)] which was expected to produce new hybridomas using electrofusion. However we could not find any publication reporting the results of this experiment. Thus whether or not new hybridomas were generated on this space mission remains a mystery.

As it is apparent from the publication list in our table of cellonauts, many of the experiments that were carried out in space using cell lines produced publishable results on the effect of microgravity on quite a lot of biological processes such as cellular growth, protein secretion, DNA damage, cytoskeleton, apoptosis, etc. But in some cases technical problems precluded a successful outcome. One example are

the experiments carried out on the ISS in 2001 on PC12 ([CVCL_0481](#)) and EMS-3 ([CVCL_WN68](#)) as described in a NASA technical document [[Robinson et al, 2006](#)]: *"There were problems in the growth and preservation of all of the cell lines grown on Expeditions 3 and 4. The PC12 and erythroleukemia cells did not survive well in long term culture, so no scientific results are expected from these experiments."* We found another example, concerning mouse C3H/10T1/2 clone 8 ([CVCL_0190](#)) as described from an ESA document [[W17](#)] *"No results in microgravity were obtained due to a combination of malfunctioning hardware and unfulfilled temperature requirements."*

Cellonauts did not always return safely on earth: a co-culture of LNCaP ([CVCL_0395](#)) and MG-63 ([CVCL_0426](#)) was one of the experiments on board of shuttle flight STS-107 [[Wang et al, 2005](#)]. The STS-107 mission flown on shuttle Columbia came to a tragic end on February 1, 2003 due to an in-flight break up during reentry into the atmosphere killing all 7 astronauts on board [[W07](#)].

The researchers preparing space flown biological experiments can also put themselves in danger. This was the case of two students, Georg Keller and Vlada Stamenkovic from the Zurich Space Biology Group at the Swiss Federal Institute of Technology [[W18](#)]. They had prepared an experiment to send pig chondrocytes (technically not cellonauts as these were primary cells) in space on the Russian Foton-M-1 unmanned space mission. On the 15th of October 2002, they were present at the Plesetsk launch complex when the rocket exploded 29 seconds after blastoff showering flaming debris over the launch area, killing one person and injuring 8 others [[W19](#)]. Fortunately the two students were not hurt, but they were quite shocked by this tragic event.

If you are interested in the backstage work implicated in the preparation of a cellonaut for a space flight, we encourage you to read the blog on Grimm's group website [[W08](#)] at the Otto-von-Guericke University Magdeburg in Germany. It describes the days that precede the launch on a Falcon-9 rocket of the Dragon resupply capsule that brought the CellBox-2 experiment to the ISS. CellBox-2 was designed to study the effect of microgravity on the transcriptome and proteome of the thyroid carcinoma cell line FTC-133 ([CVCL_1219](#)).

Conclusion

Next year will mark the 60th anniversary of the first space flight of a cell line. While HeLa has been joined by 50 other cellonauts, we were surprised by their relative low number. One reason may be that, in addition to sounding rockets and parabolic flights there are a number of ground-based alternatives to space flight to study cells response to microgravity. Clinostats, rotating wall vessels (RWV) or random positioning machines (RPM) are devices that were developed to simulate the effect of microgravity [[Anken, 2013](#); [Herranz et al, 2013](#); [Wuest et al, 2015](#); [W09](#)]. These devices are quite efficient while, as stated by Wuest et al *"due to the extensive preparation effort, safety constraints and rare flight opportunities, however, access to space experiments is limited"*.

As we are not expert in the field of microgravity research we probably have overlooked some Cellonauts and/or missed missions in which those listed in [\[Table 1\]](#) have participated. We therefore encourage reader to [write to us](#) so that we can correct and complete this mini-review.

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Table 1: List of known cellonauts and the space missions on which they were flown

Cell line name	Cellosaurus ID	Species	Space flight(s)	Reference(s)
3G10G5	CVCL WN00	Mouse	Shuttle STS-77	Smiley et al, 1997
7E3-N	CVCL WN48	Mouse	Shuttle STS-42 (Spacelab IML-1)	Bechler et al, 1993
AG01522	CVCL H759	Human	ISS Expedition 39	Lu et al, 2017
AM2	CVCL WN52	Mouse	Shuttle STS-61A (Spacelab D-1)	Beaure d'Augeres et al, 1986
B11d-ii-FAF 28 clone 237	CVCL WN69	Hamster	Cosmos-782	Sushkov et al, 1977
B6MP102	CVCL WN53	Mouse	Shuttle STS-37, STS-43, STS-50	Chapes et al, 1992 ; Chapes et al, 1994
BHK-21	CVCL 1914	Hamster	Cosmos-368	Sushkov et al, 1976
C3H/10T1/2 clone 8	CVCL 0190	Mouse	Soyuz-TM-4/ISS Expedition 9/Soyuz-TM-3	W17
Ca Ski	CVCL 1100	Human	Shenzhou-4	Yang et al, 2007
CaVe	CVCL 8444	Human	Zond-5	Zhukov-Verezhnikov et al, 1971
CaVe K-10V	CVCL WN72	Human	Zond-5	Zhukov-Verezhnikov et al, 1971
EA.hy 926	CVCL 3901	Human	Shijian-10, CRS-8/ISS Expedition 47	Pietsch et al, 2017 ; Li et al, 2018 ; Kruger et al, 2019
EMS-3	CVCL WN68	Mouse	ISS Expedition 4	Robinson et al, 2006
FLC-707-02	CVCL WN47	Mouse	Shuttle STS-42 (Spacelab IML-1)	Bechler et al, 1993
FTC-133	CVCL 1219	Human	Shenzhou-8, CRS-3/ISS Expedition 39, CRS-13/ISS Expedition 54	Pietsch et al, 2013 ; Ma et al, 2014 ; Riwaladt et al, 2015 ; Melnik et al, 2019
HaK	CVCL 3315	Hamster	Shuttle STS-42 (Spacelab IML-1)	Lorenzi et al, 1993
HeLa	CVCL 0030	Human	Korabl-Sputnik-2, Vostok-1, Vostok-4, Vostok-5, Vostok-6, Voskhod-1, Zond-5, Discoverer XVIII, Progress M-35/Mir/Soyuz-TM-25, Shuttle STS-89/Mir	Dickson, 1991 ; Katzberg, 1962 ; Ohnishi et al, 2002
hFOB 1.19	CVCL 3708	Human	Shuttle STS-80	Harris et al, 2000
HIVE-86	CVCL 0E19	Human	Shuttle STS-89/Mir/STS-91	W11 ; W12 ; W13
HL-60	CVCL 0002	Human	Shuttle STS-67, STS-86/Mir, STS-90	Piepmeier et al, 1997 ; W10
HL-60/AR	CVCL WR44	Human	Shuttle STS-67	Piepmeier et al, 1997
J-111	CVCL 2965	Human	ISS Expedition 13	Meloni et al, 2011
JC-1	CVCL WN03	Human	Shuttle STS-47 (Spacelab-J)	Suganuma et al, 2001
JTC-12	CVCL 3631	Macaque	Shuttle STS-47 (Spacelab-J)	Sato, 1993 ; Sato et al, 2001
Jurkat	CVCL 0065	Human	Cosmos-2044	Limouse et al, 1991
Jurkat E6.1	CVCL 0367	Human	Shuttle STS-76, STS-80, STS-95	Lewis et al, 1998 ; Cubano et al, 2000 ; Lewis et al, 2001 ; Schatten et al, 2001
L-M	CVCL 4535	Mouse	Shuttle STS-50 (USML-1), STS-54, STS-57 (Spacehab-1)	Woods & Chapes, 1994

L8	CVCL 4236	Rat	Shuttle STS-45, STS-63	Kulesh et al, 1994 ; W14
L8SF	CVCL WN49	Rat	Shuttle STS-45	Kulesh et al, 1994
LN1	CVCL 9U28	Human	ISS Expedition 3	Hammond et al, 2005
LNCaP	CVCL 0395	Human	Shuttle STS-107	Wang et al, 2005
MC3T3-E1	CVCL 0409	Mouse	Shuttle STS-56, STS-76, STS-81, STS-84	Hughes-Fulford & Lewis, 1996 ; Hughes-Fulford, 2001
MCF-7	CVCL 0031	Human	Foton-12	Vassy et al, 2001 ; Vassy et al, 2003
MG-63	CVCL 0426	Human	Shuttle STS-107, Foton-10, Foton-M3, ISS Expeditions 47-50	Carmeliet et al, 1997 ; Carmeliet et al, 1998 ; Wang et al, 2005 ; Guignandon et al, 2014 ; W15
MIP-101	CVCL H689	Human	Shuttle STS-70, STS-85, ISS Expedition 3	Jessup et al, 2000 ; Robinson et al, 2006
MLO-Y4	CVCL M098	Mouse	Tianzhou-1	Gao et al, 2018
MN7	CVCL WS46	Mouse	Cosmos-2229 (Bion-10)	Bierkens et al, 1994 ; Berezovskaia et al, 1998
NCTC clone 929 (L cells)	CVCL 0462	Mouse	Cosmos-782	Sushkov et al, 1977
NHF-23	CVCL WN76	Human	Shuttle STS-65 (Spacelab IML-2)	Horneck et al, 1997
NR8383	CVCL 4396	Rat	CRS-6/ISS Expedition 43	Thiel et al, 2017
PC12	CVCL 0481	Rat	Shuttle STS-86/Mir, ISS Expedition 3	Unsworth et al, 1998 ; Robinson et al, 2006
PICM-19	CVCL V146	Pig	Shuttle STS-126	Talbot et al, 2010
ROS 17/2.8	CVCL 0508	Rat	Cosmos-2229 (Bion-10), Foton-11, Foton-12	Guignandon et al, 1997 ; Guignandon et al, 2001
Sf9	CVCL 0549	Fall armyworm	Shuttle STS-50 (USML-1), STS-54, STS-57 (Spacehab-1)	Moos et al, 1994
THP-1	CVCL 0006	Human	Cosmos-2044	Limouse et al, 1991
TSCE5	CVCL WN50	Human	STS-126/ISS Expedition 18/STS-119	Takahashi et al, 2010 ; Yatagai et al, 2011
U-937	CVCL 0007	Human	Shuttle STS-76, Shenzhou-8	Hatton et al, 1999 ; Paulsen et al, 2013
V79-4	CVCL 2796	Hamster	Salyut-6/Soyuz-31	Dickson, 1991 ; W16
WB-F344	CVCL 9806	Rat	Tianzhou-1	Gao et al, 2018
WI-26	CVCL V826	Human	ISS Expeditions 47-50	W15
WI-38	CVCL 0579	Human	Skylab-3	Montgomery et al, 1978
WTK-1	CVCL 6742	Human	STS-126/ISS Expedition 18/STS-119	Takahashi et al, 2010

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