JOURNAL OF CULTURE COLLECTIONS
Volume 4, 2004-2005, pp. 3-16

MCCOY AND MCCOY-PLOVDIV CELL LINES IN EXPERIMENTAL AND DIAGNOSTIC PRACTICE – PAST, PRESENT AND PERSPECTIVES

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Summary

The McCoy cell line has almost 50 years history. The cells are widely applied in the diagnostics and culture of various microorganisms with medical importance. The cell line is included in laboratory and diagnostic tests which are the basis for study of interactions between various pathogens and host cells leading to cytotoxic damage or cell death. With its importance in experimental and diagnostic laboratories, McCoy cell line is among the most popular cell cultures – HeLa, HEp-2, Vero, CaCo-2, 3T3, MDCK. An alternative for application of McCoy is the serum-free strain McCoy-Plovdiv. It is cultured in completely defined, serum-and protein-free medium. It keeps the properties of the parental line but also offers new opportunities.

Historical data

McCoy cell line is created in the Tissue Culture Laboratory, Department of Anatomy, the University of Texas Medical Branch, Galveston, Texas. In 1957 Pomerat et al. [116] published own investigations on radiation influence upon cells in tissue culture conditions. McCoy cells were among the available cell cultures and they were announced for the first time in research literature: "Synovial fluid - McC. A strain developed in this laboratory in October 1955 from cells in synovial fluid from the knee joint of a patient with a diagnosis of degenerative arthritis".

By chromosomal examination of eight cell strains Hsu et al. [63] found that even in more recently established cell lines such as McCoy, which chromosomes were analyzed approximately half a year after the primary cultures had been made, nearly all the cells showed heteroploid constitution.

In 1960 Defendi et al. [22] published data concerning identification of cell lines in culture on the basis of morphological, immunological and karyological criteria. As a result of these studies McCoy cell line, placed at disposal from two different laboratories (University of Texas, Houston and the Wistar Institute, Philadelphia), showed distinctions giving grounds to categorize the cell line as McCoy A (human cells) and McCoy B (mouse cells

possessing a marker chromosome, characteristic for L mouse fibroblasts). There are no data in literature whether any contamination of the original human cell line McCoy has emerged or when and under which circumstances an eventual contamination has lead to the peculiar karyotype and the presence of mouse antigens.

In American Type Culture Collection (ATCC) the cells have been left by the Center for Disease Control, Cell Culture Department, Atlanta, Georgia in March 1984 [2], where they have been registered with No CRL-1696. They were described as obtained from a mouse (*Mus musculus*), from unknown tissue, as adherent cells with fibroblast-like morphology. McCoy B subline is mainly distributed among the laboratories. This was confirmed also for McCoy, given us by National Bank of Industrial Microorganisms and Cell Cultures (NBIMCC) in Bulgaria [29].

Based on information in the ATCC Catalogue [1], Nogueira et al. [102] showed McCoy cell line as "a hybrid lineage with markers from human cells and mouse cells", confirming this with the fact that these cells express human CD4 receptors [101].

Culture medium

McCoy cell line can be cultured in various media – Minimum Essential Medium (MEM), Dulbecco's Modified Eagle's Medium (DMEM), Roswell Park Memorial Institute (RPMI) 1640, medium 199 and others (Table 1). The most commonly used medium is MEM, but it varies in the amount of serum and other supplements.

McCoy cells and microbial culture

McCoy cells are applied for culture of various microorganisms, which are dependent in their development on the eukaryotic host cell. During their interaction with pathogens the cells are subjected to various changes leading often to lethality of infected cells.

Chlamydia trachomatis. At the beginning of 60s of 20th century, the popularity of McCoy cells has increased considerably after the report of Gordon et al. [51] that cobalt-60 irradiated cultures of synovial fibroblasts strongly rise their susceptibility to infection with chlamydial strains. This has been confirmed in another publication of Gordon et al. [52] and allowed the introduction of McCoy cells as a method for diagnosis of genital and ocular infections caused by chlamydia [59]. Numerous investigations with various agents followed, aiming the increase of cell susceptibility to infection with chlamydial strains. Pretreatment of McCoy cells with diethylaminoethyl-dextran [20], cycloheximide [143, 15], cytohalasine B [137], 5-iodo-2-deoxyuridine [75], cycloheximide and centrifugation [151], polybrene [123], mitomicin C [152] fascilitates more successful infection of cell cultures. Inoculation and isolation of chlamydia in hen embryos has been replaced by cell cultures - commonly McCoy [142]. The attention was driven towards searching new cell lines which may be used for chlamydial culture with diagnostic purpose or study the life cycle of bacteria *in vitro*. Croy et al. [18] examined the susceptibility to infection with trachoma TW-3 (type C) and UW-5 (type E) of eleven cell lines - HeLa 229, HeLa M, HEp-2, FT, BHK-21, Vero, MK-2, MPK, L-WO5A2, McCoy and L-929; Rota [120] compared five cell lines - BHK-21, CHO, HeLa S3, McCoy, OWMK and two diploid strains, ST/BTL and WI-38, for their ability to be infected with trachoma strains B serotype; the monkey cell line BGM was studied for isolation of *C. trachomatis* by Krech et al. [74]. At present McCoy, HeLa 229 and BGMK are the most commonly used cells for maintenance of *C. trachomatis* growth [12].

C. trachomatis growth in McCoy cell cultu-

Table 1. Media for culture of McCoy cells.

Medium	Supplements	References
Gey' salt solution	45 % human ascitic fluid, 5 % chick embryonic extract	116, 63
Medium 199	1 % horse serum	22
MEM	10 % FCS	1, 2
MEM	5 % FCS, 2 mM L-glutamine, 100 μg/ml streptomycin	25
MEM	5 % FCS, 10 mmol/l L-glutamine, 200 U/ml penicillin, 200 μg/ml streptomycin	125
EMEM	10 % FCS, 10 mg/l gentamicin, 2 mM glutamin, 1 % non-essential aminoacids	126
Eagle's MEM with Hanks' salts	10 % FCS, 10 μg/ml gentamicin, 50 μg/ml vancomycin, 2 mM glutamin	10
EMEM	10 % FBS, 1 % L-glutamine w/v, 10 % (v/v) non-essential aminoacids and 1 % (w/v) of antibiotic/antibiotic mixture, containing penicillin, streptomycin and amphotericin B.	42
GMEM (Glasgow modification of Eagle's medium)	10 % new born calf serum, 25 mM glucose	91
RPMI 1640	10 % FCS, 30 mmol/l glucose, 10 μg/ml gentamicin, 2 mmol/l L-glutamin	82
RPMI 1640	10 % FCS	133
DMEM	4 % FCS	138
DMEM	10 % FCS	147
DMEM-H	584 mg/l L-glutamine, 4500 mg/l glucose, 10 mM HEPES, 10 % FCS	127
Liverpool-Waymouth medium	10 % FCS	70
SF-3		119

re, non-treated with cycloheximide, is deeply influenced by the lack of glucose and minimal changes in aminoacids in the environment and blood plasma. This is supported by the production of abnormal forms with lower infectivity [55]. McCoy cells show great capacity in terms of aminoacid concentration, which is important for the development of microorganisms [56].

The cell culture serves as a standard for comparative detection of *C. trachomatis* from genital specimens by Polimerase Chain Reaction (PCR), Ligase Chain Reaction (LCR) and cell culture [132, 99, 66, 80]. With the encroach of DNA amplification techniques in this field the cell cultures are applied less frequently, usually in specialized reference laboratories [12]. McCoy cells possess advantages which can not be duplicated by noncultural techniques, for example the culture may: i. preserve microorganisms and even allow them to multiply, ii. serve for examination of the interactions microorganisms-host cell which helps studying the bacterial biology and pathological effects as a result of bacterial metabolism, iii. allow testing for susceptibility to various antimicrobials.

The information elucidating complex chlamydia-host interactions has been

obtained mainly form investigations on cell cultures as an *in vitro* model of infectious process. Various cell lines (HeLa, HEp2, HeLa 229, CHO, VERO, BGMK) are applied now for culture of cells with chlamydia and studying the chlamydial pathogenesis. McCoy remains the leading cell line in these investigations.

The interaction between bacteria and host cells takes place in the following sequence: adhesion of microorganisms to the eukaryotic cell and entering it, intracellular development with bacterial amplification and releasing of new chlamydial bodies out of the cell.

Studying the kinetics of attachment and ingestion of *C. trachomatis* serotype L1 by monolayers of McCoy cells Söderlund et al. [135] proved that the accumulation of bacteria in cells needs 3 hours when the incubation is at 37 ^{o}C and cannot take place at 4 ^{o}C. They also established that chitobiose and chitotriose reduced association of *C. trachomatis* with McCoy cells. The precise mechanism through which the elementary bodies (EBs) attach to the cell and penetrate into it is not completely understood. Thermolabile proteins mediate adhesion of many *C. trachomatis* serotypes to a common receptor on McCoy and HeLa cells [148]. Hodinka et al. [61] performed ultrastructural studies upon endocytosis of *C. trachomatis* on McCoy cells. Following attachment to a non-well defined receptor on host cell surface, the bacterium internalizes in the cell. The internalization of *C. trachomatis* serotype L2 in McCoy cells may be realized through phagocytosis and pinocytosis [117]. In cytoplasm the EBs are membrane confined and their aggregation and fusion take place by means of cytosol anexins which participate selectively in the endosomal aggregation and escape the fusion with lysosomes during chlamydial infection [84]. In intracellular distribution and localization of chlamydia-containing vesicles actin and clathrin [83, 85], anexins together with the level of free intracellular calcium ions [84], and the host cell cytoskeleton [127] participate. It has been established that the way of accumulation and development of serotype L in HeLa cells is different from the one of serotype E in McCoy cells. These differences concern the cell types, respectively epithelial and fibroblast [127]. Entering the cell, bacteria begin multiplication. Van Ooij et al. [144] found that *C. trachomatis* serotype LGV L2 fusion does not take place at 32 ^{o}C in HeLa, McCoy and CHO-K1 cell lines and requires synthesis of bacterial proteins.

As a result of infection with *C. trachomatis*, McCoy cells produce interferon and nitric oxide in the absence of exogenous cytokines [25]. During chlamydial infection in eukaryotic cells, pro-apoptotic stimuli are induced, leading to apoptosis in non-infected adjacent cells [126]. The treatment with anti-oxidants reduces the degree of apoptosis. HeLa 229, HEp-2 and McCoy have been used by Shaw et al. [133] for characterization of proteases secreted by chlamydia.

Chlamydia psittaci. For *in vitro* isolation, culture, typing and studying the bacterium-host cell interaction and intracellular life of *C. psittaci* various fibroblast (McCoy, L-929, BHK-21) or epithelial (HeLa and BGM) cell cultures have been used [37]. The McCoy cell line is applied for characterization of *C. psittaci* isolates from horses [150] and pigeons [122]. Cultures facilitate studies on *C. psittaci* in ruminal and abomasal contents [3]. The ovine abortion isolate of *C. psittaci*, S26/3, may be cultured in McCoy cells which serve for investigation of biochemical properties of Major Outer Membrane Protein (MOMP) [153] and clarifying the antigenic organization of N-terminal part of the membrane proteins 90, 91A and 90B of *C. abortus* [149]. McCoy cells are the standard for development of new non-cultural methods for detection of chlamydia in bull semen fluid [28], introduction of PCR for diagnosis of enzootic abortion in ewes (EAE), [17] and/or development of new vaccines [48].

Chlamydia pneumonie. *C. pneumonie* can be hardly cultured *in vitro*. Cles et al. [14]

have established that this respiratory pathogen is better cultured in non-treated HL cells than in HeLa 229, McCoy, BHK-21. Roblin et al. [118] proved that HEp-2 was the most sensitive cell line (among HeLa 229, McCoy, HL, HEp-2, HTED) for infection with TW-183 strain and two clinical isolates. Although less frequently McCoy cells are applied for maintenance of some strains as *C. pneumonie* TW 183 strain [50].

Chlamydia pecorum. McCoy cell line is used for culture, identification and testing of *C. pecorum* [113, 114].

McCoy cells are applied for *in vitro* investigation of *C. trachomatis* [8, 9] and *C. pecorum* [113] persistence.

Helicobacter pylori. *H. pylori* participates in the pathogenesis of chronic superficial gastritis and ulcer [36]. Korych et al. [72], using in vitro cell models as VERO and McCoy cell lines, found that *H. pylori* strains caused cytotoxic effect on cells with changes in cell cytoplasm and morphology. The authors suggested that morphological changes in cell cultures support the idea for the pathogenic activity of bacterium on gastric mucosa. Similar association between cytotoxic strains and activity of gastritis was established by Hua-Xiang Xia et al. [64]. They also proved that McCoy cells are more sensitive than HeLa cells in detection of *H. pylori* cytotoxicity *in vitro*.

Gardnerella vaginalis. McCoy cells are applied as an *in vitro* cell model for testing the adhesion-receptor mechanism of interaction between *G. vaginalis* (a causative agent of bacterial vaginosis) and host cells as well as for various factors that inhibit pathogen adherence [129, 131]. The pathogen adhesion to vaginal epithelial cells, McCoy cells and red blood cells, was studied by electron microscopy [130].

Clostridium difficille. *C. difficile* causes a severe disease of the colon – pseudomembranous colitis. This bacterium produces two toxins - A and B, which are the main virulent factors [140]. They do not affect membrane permeability of intestinal cells and McCoy cells but inhibit protein synthesis of the latter [96]. *In vitro* toxins A and B cause cytotoxic effect which is manifested by change in morphology (shrinkage and roundness) of McCoy cells [5]. During cell intoxication, reorganization of cytoskeleton microfilaments occurs. The effects are mainly due to cytotoxin B – 1000 times more toxic than toxin A. Toxin A damages phosphorilation of intracellular proteins in contrast to cytotoxin L (released by *C. sordelli*, a pathogen capable of producing gas gangrene in humans). The latter acts through phosphorilation of pp80c on McCoy cells [128].

Various cell cultures have been used for detection of cytopathic effect of *C. difficile*. McCoy cells as suspension or monolayer may replace HeLa [86]. Comparative studies on several cell lines: african green monkey kidney (AGMK), MRC-5, primary rhesus monkey kidney (RMK) and Vero proved that only Vero could be used as equivalent to McCoy in detection of *C. difficile* toxin from stool filtrates [87].

The detection of cytotoxic effect on monolayers of McCoy culture cells is widely applied in the diagnostics of *C. difficile* infections [13]. This method is evaluated as a standard [23] and helps elucidation of etiology and pathogenesis of *C. difficile* - associated diarrhea [141].

McCoy cells are a comparative standard for various immunological and molecular methods (TCD Toxin A Enzyme Immunoassay (EIA), Toxins A/B Enzyme-linked Immunosorbent Assay (ELISA), PCR) for detection of *C. difficile* toxins [71, 88, 89, 90, 115].

***Bacillus cereus and other Bacillus* spp.** According to Jackson [65] McCoy cell line may be a rapid test for screening and detection of enterotoxin-producing *B. cereus* as a cause of toxin-mediated food-borne disease. Studying the cultural supernatants of 30 bacteria, the author established the cytotoxic effect of progressive damaging the McCoy cell monolayer.

This cell culture system is an excellent opportunity for testing the cytotoxicity of *Bacillus* isolates but also allows studying the mechanism of action of the cytotoxic components. Combining Methylthiazole-tetrazolium (MTT) cytotoxic test, Confocal scanning laser microscopy and Scaning electron microscopy, Lindsay et al. [79] showed that cytotoxic effects of *Bacillus* spp. isolates caused for three hours irreversible morphological changes leading to cell membrane damage, linkage of cell content and necrosis.

Trichomonas vaginalis. Clinical isolates and strains of *T. vaginalis* are successfully maintained in serum-free culture media [26] or as co-culture with eukaryotic McCoy cells [47, 15]. The results obtained are similar with those in conventional conditions of culture. The application of cell cultures in this field gives the chance to study the contact interaction with its intimate mechanism between this parasite and the eukaryotic cells. Thus the role of some soluble products of *T. vaginalis* was established. The example is the "cell detaching factor" (CDF), which causes monolayer damage of McCoy, HEp2, CHO cell cultures and human skin fibroblasts for 6 hours only [45]. The parasite develops in physical contact with McCoy cells and the cell death is a result of production of contact-dependent cytotoxicity [46]. In a co-culture of *T. vaginalis* (a highly vurulent strain) with McCoy Roussel et al. [121] proved that the cytopathic effect is specifically inhibited by monosaccharides, N-acetylglucosamine and manose. The researchers suggested that the cytopathic effect is mediated by a manose/N-acetyl-glucosamine-binding lectin. As it is known, there are molecules in serum, which may interact and bind directly to *T. vaginalis* [112]. Meysick et al. [93] examined the growth kinetics of *T. vaginalis* in McCoy cell culture in serum-free conditions. They obtained lower peak of *T. vaginalis* concentration and prolonged doubling time compared to the serum-containing system and the conventional culture of the parasite. It has been determined that serum proteins could interact with enzymes and directly with *T. vaginalis*.

Viruses. According to Consales et al., [16] rabies-infected McCoy cells may provide a useful assay system based on induction of cytopathic effect, high virus production and sensitivity to interferon. The authors proved cytopathic changes 24 to 72 hours after infection. The viral titre grew with the number of passages reaching maximum after the third one. This sensitivity was confirmed by Nogueira [100] in isolation of Rabies virus from central nervous system of a patient with rabies. A comparative study proved that McCoy cells are with higher sensitivity and specificity than N2A cells (a mouse neuroblastoma), which have been accepted as a reference culture [101]. This implies McCoy cells as an effective model for Rabies virus isolation.

There are data that HIV-1 is successfully replicated in McCoy cells [102] and the cell line is a suitable model for its isolation. It can be used for studying the dynamics of viral infection together with pharmacological testing of drugs as well as analysis of the immune response in vaccine therapies.

In contrast to Rabies virus, Measles virus does not induce cytopathic effect in McCoy cells but leads to the development of persistent infection which is maintained by an antiviral factor [125].

McCoy cell culture and antibacterial agents

A number of active substances with various origin are examined in the straggle against pathogens – plant extracts [145, 24], human defensin and porcine protegrin [156], microbial producers [62, 67], recombinant mouse interferon-gamma [25], semisynthetic [24], or synthetic ones [76, 155]. The ideal agent would be the one with no or minimal

cytotoxicity and high antibacterial activity. This implies the idea that in searching such drugs combined and parallel investigations for toxicity on eukaryotic cells on one hand and antimicrobial effect on the other should be performed. The minimal inhibitory concentration (MIC) of chloramphenicol for *C. trachomatis* in McCoy cell culture varies widely in terms of antibiotic preparation, duration of treatment and method of infection [60]. The considerable variations in accumulation of macrolides depend on the ability of the tested McCoy, HeLa 229F and HeLa 229W cells to accumulate the drug [73]. *In vitro* cultures allow to obtain the minimal inhibitory concentrations for normal (MICN) and abnormal inclusions (MICA) of *C. trachomais* when treated with various antimicrobials [62]. De la Maza et al. [21] found approximately 50 % inhibition of cell growth in McCoy cells, using 10 U/ml mouse recombinant interferon-gamma whereas at 1 U/ml over 95 % inhibition of chlamydial inclusions had been observed.

In vitro studies concerning inhibitory activity of various antibiotics against *C. trachomatis* in McCoy cells give satisfactory prelimenary information about the activity of the tested drugs which may be a basis for further clinical investigations. Lefevre et al. [78] showed that the lowest MIC values had been established for clarythromycin and sparfloxacin which were with the highest activity in clinical trials. Moulding *in vivo* the *in vitro* conditions of the cell culture test system McCoy, Lampe et al. [76] proved that chlorhexidine gluconate gel killed *C. trachomatis* serovar D and F at concentrations applicable in genital tract of women.

Electron microscopic studies on McCoy cells established a realtionship between the applied concentrations of doxycyclin, erythromycin and ofloxacin and the changes in cell cycle of *C. trachomatis* [19]. Studying the antichlamydial activity of doxycyclin, erythromycin, ofloxacin and trovafloxacin, Jones et al. [67] established that all 19 strains of *C. trachomatis* were sensitive to trovafloxacin. *In vitro* activity of a new fluoroquinalone - ABT-492, was examined on McCoy [54].

The sensitivity of chlamydia to β-lactam antibiotics is due to the presence of penicillin-binding proteins (PBPs). Using *C. trachomatis* 434 serotype L2, cultured in McCoy cell monolayer, the binding of seven β-lactams to chlamydial PBPs and their antichlamydial activity were examined *in vitro* [138].

Mast acids and monoglycerides inactivate *C. trachomatis in vitro*. The highly specific antichlamydial effect of monocaprin is combined with cytotoxic changes in McCoy cell monolayer at high concentration whereas at 50 μg/ml and lower, lysis has not been observed [11].

Sokyleszczyrska et al. [136] studied the effect of antibacterial and antitoxic serum against *C. difficile* by neutralization test on McCoy cell line. Martirosian et al. [88] moulded the influence of dioctahedral upon ten toxigenic strains of *C. difficile* and eight enterotoxigenic strains of *Bacteroides fragilis* using McCoy and HT 29/C1 cell lines.

There are microorganisms with ability to survive and multiply in eukaryotic cells. That is why it is important to know for the antimicrobial agent to have good penetration, accumulation and intracellular activity. Pascual et al. [105] examined in a series of experiments lomefloxacin and temafloxacin penetration in human neutrophils and peripheral macrophages, accumulation of fluconazole in human polymorphonuclear leucocytes [106], accumulation and intracellular activity of trovafloxacin, a new ketolide, HMR 3647, obtained by erythromycin A and linezolid in human phagocytes [107, 108, 109]. This allows elucidating the intracellular activity of antimicrobial agents and enriches the information about their intracellular pharmacology in macrophages and non-phagocytic cells as McCoy cells which are used in the studies as comparative cell culture. It has been proved that ofloxacin is carried by liposomes and its accumulation in McCoy cells is 2.6 fold higher than the one

of free drug [43].

Microbicides are strategy with great potential for prevention of sexually transmitted diseases (STD). An ideal topical microbicide should not only kill STD-causing pathogens and be potentially spermicidal, but also should not disrupt the normal flora of the vagina or rectum and cause cytotoxicity to the vaginal or rectal epithelium [6]. Two cecropin peptides D2A21 and D4E1 and gel formulations containing 0.1 to 2 % D2A21 act as effective topical microbicides against two urogenital strains of *C. trachomais* serovars (UW-3/Cx) and F (UW-6/Cx). This study was performed on McCoy cell test system combining preinoculation MCC-tests and postinoculation MIC-test [6].

Long treatment with given antimicrobials may evoke resistance of many microorganisms. *In vitro* serial passage of *C. trachomatis* and *C. pneumoniae* with McCoy cell monolayer established that increasing the number of passages developed resistance to the examined fluoroquinolones only in *C. trachomatis* [97]. Analysing quinolone resistance determinating regions of two quinolone-resistant *C. trachomatis* mutants, the authors proved the presence of a point mutation in the DNA-girase coding gene. They also assumed other, unknown mechanisms for the high level of resistance [97].

McCoy cell line - cytotoxicity and cell compatibility *in vitro* assessment

Cell cultures as method for *in vitro* study of the interaction between various substances and cells have already gone through a rapid development in the years. Numerous cell test models and methods for detection of cell response after the treatment have been created. McCoy cells are the suitable and widely applied *in vitro* cell test system for these investigations. McCoy cell culture has been used for investigation of the inhibitory effects of chloramphenicol [104] and cephalotin [103].

Using Neutral Red (NR) and MTT tests, Varanda et al. [145] studied the influence of a new isocoumarin (Paepalantine), isolated by them, with antimicrobial activity on McCoy cell line. Devienne et al. [24], applying the same culture test system, examined *in vitro* the cytotoxic effect of natural and semisynthetic isocoumarins of *Paepalanthus bromelioides* and the structural parameters influencing the cytotoxicity of isocoumarins, similar to paepalantine.

Vento et al. [146] studied the effect of dexamethazone on cell division and macromolecular synthesis in McCoy cell system. Fighetti at al. [41] established that various concentrations of cadmium caused cell damage, induced reduction of metaphase number and shortened the metaphasic chromosomes.

Microorganisms produce and secrete in the environment various substances, some of which cause cytotoxic or necrotic effect on eukaryotic cells. A rapid and easy way for detecting such virulent factors is the application of *in vitro* sensitive cell test systems from animal and human cell lines. Balaji et al. [4] reported a cytopathic effect in monolayers of McCoy, HEp-2, HeLa confluent cultures after treatment with *Burkholderia pseudomallei* supernatants.

Cytopathic effect was detected during treatment of McCoy cells with virulent factors, produced by *C. difficile* [86], *B. cereus* [65]; hemolysin, proteases and cytotoxin of *Aeromonas hydrophilia* and *A. sobria* [7, 81], phenol acids from *Scrophularia frutescens* [49].

Examining 48 chemicals on MEIC programme (The Multicenter Evaluation of *In Vitro* Cytotoxicity), Shrivastava et al. [134] used cell cultures of primary hepatocytes and McCoy and MDBK cell lines. They found significant correlation between *in vitro* and *in vivo* values.

Newly obtained silicone polymers, designed for contact eye lenses, have been

investigated on McCoy cells for cellular compatibility [95].

The interaction of cells with endoplasmic reticulum and the intercellular interactions are of great interest concerning the processes of cell differentiation and signal transduction. Latz et al. [77] studied the adhesion of McCoy and rabbit lens epithelial (LE) cells on modified acrylic polymers (EF35) and found different adhesive mechanism in substituted polymers, leading to an increased and sustained activation of integrin mediated kinases and changes in the cytoskeletons of McCoy and rabbit LE cells.

Other applications. Apoptosis may be induced by various physiological and pathological stimuli. Low-temperature shock causes DNA fragmentation in McCoy cells as well as morphological and biochemical changes, characteristic of apoptosis [111] as a result of activation of mechanisms with participation of Ca^{2+} and protein kinase C [110]. Investigations on apoptotic processes, induced by a new group of immune response modifiers, were carried out on McCoy cells and other cell cultures [92].

The culture medium, presence of serum and supplements influence the development of every cell culture. They affect cell growth, cell yield and production of specific cell products. Cell culture media contain glutamine as a permanent component which is the main energy source and biosynthetic precursor of cell growth. It is believed that adaptation of McCoy cells to a medium where glutamine is replaced by glutamate or 2-octaketoglutarate, would promote cell yield [57]. The effect of lactat and ammonium was studied on McCoy and other eight cell lines. It was confirmed that the cell yield is influenced by the accumulation of ammonium in the medium as a result of glutamine metabolism and its chemical degradation [58]. In biotechnological aspect the production of biological components can be limited by ammonium accumulation. McCoy and MDCK cell lines have been used as model cultures by McDermott et al. [91] for clarifying the metabolic changes concerning cell adaptation to glutamine-free medium and the role of glutamate-transport system.

Hanotte et al. [53] studied the development of McCoy cells and other animal cell cultures on microbeads “Cytodex 3”.

In several publications the metabolism of polyamines in McCoy cell culture was elucidated [38, 39, 40].

The McCoy-Plovdiv cell strain – a serum free and protein free culture

The serum-free cell culture McCoy-Plovdiv was derived from the McCoy cell line [31]. The cells are cultured solely in HD medium which is chemically defined, serum-free and does not contain additional proteins. The processes of freezing and thawing are completed in the same medium [34]. The morphological and karyological analysis confirmed the origin of McCoy-Plovdiv cell line [29]. The cell kinetics [33], the proliferative activity [44], the dynamics of cell monolayer and the postconfluent culture conditions [30] were studied. It was experimentally proved that McCoy-Plovdiv cells showed equivalent sensitivity and specificity as McCoy cells in detection of *C. trachomatis* from genital specimens of patients [98]. Cytotoxic studies established that McCoy-Plovdiv cells are more susceptible than McCoy to *in vitro* testing of chemicals [27]. The McCoy-Plovdiv cell test system for development of cytotoxic tests with vital dyes is in progress [94].

There are convincing data about advantages of McCoy-Plovdiv cell system in co-culture with *T. vaginalis* [32]. Hopeful results have been obtained for McCoy-Plovdiv cells as an appropriate substrate for antinuclear antibody detection [124] and a protocol for application of the serum-free cells in the screening of antinuclear antibodies has been proposed [35].

Additionally, McCoy-Plovdiv cells might

be an adequate cell line for serum-free culture of nanobacteria, a recently characterized group of extremely small bacteria, capable of precipitating calcium salts and implicated in the pathogenesis of human renal and gall stones and calcific atherosclerosis [68; 69]. Now nanobacteria are cultured by using cell culture media under mammalian cell culture conditions or 3T6 fibroblast monolayers. It has been established that the stone formation by nanobacteria is low in the presence of serum in the culture but extensive and rapid in serum-free conditions [69]. Thus McCoy-Plovdiv cell line may provide a good opportunity to study nanobacteria and their interactions with the cells.

Conclusion

McCoy cell line occupies an important place among the most popular cell cultures - HeLa, HEp-2, Vero, CaCo-2, 3T3, MDCK, with its application in experimental and diagnostic laboratories. As recent reports show the cells are actually important for culturing viruses, chlamydia, vaccine studies, development of models for *C. trachomatis* or cytotoxic activity [4, 48, 101, 102, 139, 154]. A new direction of McCoy application is the creation of McCoy-Plovdiv serum-free cell line.

Acknowledgments. This work was supported by Grant No 12/2002 from the "Scientific and Developmental Work", University of Plovdiv.

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КЛЕТЪЧНИ ЛИНИИ MCCOY И MCCOY - PLOVDIV В ЕКСПЕРИМЕНТАЛНАТА И ДИАГНОСТИЧНАТА ПРАКТИКА – МИНАЛО, НАСТОЯЩЕ И БЪДЕЩЕ

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Резюме

Клетъчната линия McCoy е с почти 50 годишна история. Клетките се прилагат широко за диагностика и култивиране на различни микроорганизми и вируси с важно медицинско значение. Клетъчната линия е включена в лабораторни и диагностични тестове, които са основа за изследване на взаимодействието между различни патогени и клетките-гостоприемник, чийто резултат е цитотоксично увреждане на клетките или тяхната смърт. Със своята значимост за изследователските и диагностични лаборатории клетъчната линия McCoy се нарежда сред най-популярните клетъчни култури – HeLa, HEp-2, Vero, CaCo-2, 3T3, MDCK. Нова алтернатива в използването на McCoy е разработеният безсерумен щам McCoy-Plovdiv, който се култивира в напълно дефинирана среда без серум и без протеини. Той съхранява качествата на изходната линия, а също така предлага и нови възможности.