Review

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Animal models of colorectal peritoneal metastasis

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Abstract: Colorectal cancer remains an important cause of mortality worldwide. The presence of peritoneal carcinomatosis (PC) causes significant symptoms and is notoriously difficult to treat. Therefore, informative preclinical research into the mechanisms and possible novel treatment options of colorectal PC is essential in order to improve the prognostic outlook in these patients. Several syngeneic and xenograft animal models of colorectal PC were established, studying a wide range of experimental procedures and substances. Regrettably, more sophisticated models such as those giving rise to spontaneous PC or involving genetically engineered mice are lacking. Here, we provide an overview of all reported colorectal PC animal models and briefly discuss their use, strengths, and limitations.

Keywords: metastasis, mouse model, PDX model, peritoneal.

Introduction

With an annual worldwide mortality rate of over half a million, colorectal cancer (CRC) remains a major cause of cancer related mortality [1]. Since malignant disease ultimately causes death by distant organ invasion, the unraveling of molecular mechanisms underlying hematogenous and lymphatic metastasis is a topic of intensive research activity [2]. In parallel, the introduction of targeted biological agents has met with considerable survival prolongation in patients with metastatic disease [3]. On the other hand, intraperitoneally located tumors may be at the origin of locoregional peritoneal spread. Although often coexisting with systemic disease, it is increasingly realised that colorectal tumor dissemination within the peritoneal cavity may represent a separate phenotypic and molecular entity. Established peritoneal carcinomatosis (PC) from CRC is much less responsive to systemic therapy and causes considerable morbidity in affected patients. Synchronous peritoneal metastases are found at the time of surgery with curative intent in about five to six percent of patients, and are more frequently observed in right sided cancers [4]. Peritoneal carcinomatosis is present in 25–30% of patients with recurrent or metastatic colorectal cancer; in approximately 3% isolated peritoneal disease without systemic spread is observed [5, 6]. Recognition of the causes and mechanisms of peritoneal metastasis may contribute to strategies to effectively prevent the development of PC in colorectal cancer. Moreover, in a small group of patients with low volume peritoneal disease, a locoregional treatment strategy combining surgery with intracavitary cytotoxic therapy has been shown to improve outcome [7]. The concept of intraperitoneal (IP) drug delivery in itself not entirely new. The earliest IP “drug therapy” was reported in 1744 by the English surgeon Christopher Warrick, who, apparently with great success, injected a mixture of ‘Bristol water’ and ‘claret’ (a Bordeaux wine) in the peritoneal cavity of a woman suffering from intractable ascites [8]. Intraperitoneal adjuvant chemotherapy has been extensively studied in stage III epithelial ovarian cancer, where it was found to be superior over intravenous (IV) chemotherapy alone in large randomized trials [9]. In patients with PC from appendiceal or colorectal origin, the combination of cytoreductive surgery (CRS) and intraoperative hyperthermic intraperitoneal chemoperfusion (HIPEC) has witnessed an impressive rise in clinical application over the past years [10]. In parallel, innovative pharmaceutical platforms such as targeted agents, nano-sized medicine and drug eluting beads have the potential to further increase the appeal of locoregional drug delivery.

Preclinical animal based research remains an essential tool in the unraveling of the pathophysiology of the metastatic cascade, and the therapeutic insights gained therefrom. Here, we provide a systematic overview of the animal models that have been used to study various aspects of peritoneal metastasis from colorectal origin.

Methods

A systematic search (completed 25/12/2015) was performed using Web of Science with the following keywords: [periton* and meta* and colo* and (animal or
mice or mouse or rat or rodent or rabbit). Eligible studies reported on animal experiments involving, in part or exclusively, the establishment of colorectal peritoneal carcinomatosis by IP introduction of a colorectal cancer cell line or tissue fragment. Only papers published as full text were eligible. The resulting abstracts were scrutinized and those deemed to fit the criteria were retrieved as full text papers. Additional studies were searched for in the reference lists of these papers, and in the citing studies.

Results

The selection process (Figure 1) resulted in a total of 164 included papers, the details of which are summarized in Table 1. The large majority of studies used syngeneic rodent cell lines (usually CT26, MC38, or CC531) injected in the peritoneal cavity of immunocompetent mice or rats. Human colon cancer cells were xenografted IP in athymic nude or BALB/c mice in 46 studies, and in athymic nude rats in two. Only a small minority of studies used SCID mice, patient derived xenografts, or transgene animals.

Research questions and topics

From the wide variety of reported research topics, only a small minority addressed fundamental mechanisms of the peritoneal metastatic cascade. Experimental designs and questions include:

– Mechanisms and prevention of port site metastasis after laparoscopy
– Activity of IP chemotherapy, heparin, anti-adhesive products, gene therapy, photodynamic therapy, immunotherapy, or radioimmunotherapy
– Evaluation of novel pharmaceutical formulations and carriers for IP delivery
– Evaluation of novel optical, fluorescence, or radioactivity based imaging techniques for diagnosis and staging of PC

Choice of cell line and animal model

Syngeneic models

Syngeneic or allograft models use cells or tissue derived from the same genetic background. The recipient
| Author                        | Year | Research question                                                                 | Cell line/tissue          | Animal       | IP dose          | Interval before endpoints | Quantification of PC                                                                 |
|-------------------------------|------|-------------------------------------------------------------------------------------|---------------------------|--------------|------------------|----------------------------|--------------------------------------------------------------------------------------|
| **Patient derived xenografts** |      |                                                                                     |                           |              |                  |                            |                                                                                      |
| Navarro-Alvarez [20]          | 2010 | Isolation of a CRC CD133− cancer stem cell line (NANK)                                | Tissue from CRC primary and ovarian metastasis | NOD-SCID     | 2 mm³ fragments | 6–8 w                     | Cell isolation                                                        |
| Flatmark [19]                 | 2010 | IHC study of human PMP and related animal models                                      | Tissue from mucinous CRC  | BALB/c nude  | 3 × 3 × 3 m fragments | 1–3 m                | IHC markers of differentiation, proliferation, and metastasis                  |
| Kotanagi [18]                 | 1998 | Characterization of patient derived metastatic cell lines                             | CRC patient derived cell line | SCID         | 1 × 10⁷          | 40 d                      | Number and weight of nodules, histology                                         |
| **Human cell lines, transgene mice** |    |                                                                                     |                           |              |                  |                            |                                                                                      |
| Abdul-Wahid [21]              | 2012 | Antitumor activity of CEA immunization                                               | MC38.CEA                 | CEA.Tg       | 2 × 10⁵          | 35 d                      | Number, volume                                                            |
| **Human cell lines, SCID mice** |    |                                                                                     |                           |              |                  |                            |                                                                                      |
| Mikula-Pietrasik [32]         | 2015 | Role of senescent Mesothelium in CRC metastasis                                     | SW480-luc                | SCID         | 2 × 10⁶          | 18 d                      | Bioluminiscence (IVIS)                                                        |
| Inoue [33]                    | 2011 | Antitumor activity of a multifunctional Treg cell line                               | WiDr-EGFP-9              | NOD-SCID     | 1 × 10⁷          | 5 w                       | Fluorescence stereomicroscopy; survival                                        |
| Navarro-Alvarez [20]          | 2010 | Isolation of a CRC CD133− cancer stem cell line (NANK)                                | CD133− NANK               | NOD-SCID     | 1 × 10⁶−1 × 10⁵ | 8–12 w                    | immunostaining                                                              |
| Lubbe [34]                    | 2009 | Role of receptor guanylyl cyclase C (GCC) in cancer cell MMP-9                       | T84 (wt or transduced with MMP-9) | Cr:NIH-bg-nu-Xid | 1 × 10⁷          | 2 w                       | Peritoneal biopsies for quantification of metastatic tumor burden by RT-PCR     |
| **Human cell lines, Immunodeficient mice** |    |                                                                                     |                           |              |                  |                            |                                                                                      |
| Harada [35]                   | 2001 | Antitumor activity of antisense CD44s                                               | CD44 transfected LS174T  | SCID         | 2 or 4 × 10⁶    | 4 w                       | Ascites volume, tumor weight                                                 |
| Sakamoto [36]                 | 2001 | Involvement of c-Src in carcinoma cell motility and metastasis                       | HCT15                     | SCID         | 2 × 10⁶         | 3 w                       | Number of nodules, histology                                                  |
| Watson [37]                   | 1996 | Antitumor activity of the MMP inhibitor batimastat                                   | C170HM₂                   | SCID         | 5 × 10⁶         | 28 d                      | Ascites volume and cell density, tumor weight                                   |
| Yasui [38]                    | 1997 | Tumor metastasis of human CRC cell lines in SCID mice                                 | 10 colorectal cell lines  | SCID         | 5 × 10⁶         | 3 w                       | Number of nodules                                                            |
| **Gremonprez et al.: Animal models of colorectal peritoneal metastasis** | |                                                                                     |                           |              |                  |                            |                                                                                      |
| Gremonprez [30]               | 2015 | Effect of pretreatment with VEG(R) inhibitors on IFP, Pt penetration, and tumor growth of isolated peritoneal tumors | HT29                      | Athymic nude | 1.5 × 10⁶ subperitoneal injection | 15 d | IFP, tissue oxygenation, Pt distribution, tumor growth                        |
| Wang [39]                     | 2015 | Role of Cullin1 in invasive properties of CRC                                        | HCT116 and SW480          | BALB/c nude  | 1 × 10⁶          | 22 d                      | Number, size nodules                                                         |
| Takemoto [40]                 | 2015 | Cytotoxic effects of lavage with hypotonic fluid in CRC                               | DLD1, HT29, and CACO2     | BALB/c nude  | 1 × 10⁶          | 4 weeks                    | Number, size, weight nodules                                                  |
| Author       | Year | Research question                                                                 | Cell line/tissue | Animal          | IP dose | Interval before endpoints | Quantification of PC endpoints | Characteristics |
|-------------|------|-----------------------------------------------------------------------------------|------------------|-----------------|---------|----------------------------|-------------------------------|-----------------|
| Shen [41]   | 2015 | Interplay between SOX9 and S100P in metastasis and invasion of CRC               | Transfected      | Nude mice       | $1 \times 10^7$ | 1 month                     | In Vivo F Imaging System (Kodak) | Number of nodules |
| Liu [42]    | 2015 | Role of microRNA-409-3p in invasiveness and metastasis                            | Transfected SW480 | BALB/c nude     | $2 \times 10^6$ | 8 weeks                     | Number of nodules             | |
| Lee [43]    | 2015 | Development of novel biodegradable hydrogel for delivery of bevacizumab          | HCT116           | BALB/c nude     | $4 \times 10^6$ | 62d                          | None (survival)               | Number, volume, size, number |
| Amini [44]  | 2014 | N-cadherin and laminin-α depletion with mesothelial and stromal cells            | HCT116           | BALB/c nude     | $5 \times 10^6$ | 28                           | Number, weight                | Size, number |
| Liu [45]    | 2014 | Hypoxia-mediated and hypoxia-induced angiogenesis                                | HCT116           | BALB/c nude     | $5 \times 10^6$ | 17d                          | Number, weight                | Size, number |
| Tang [46]   | 2014 | Effect of nuclear overexpression and nuclear accumulation                        | HCT116           | BALB/c nude     | $5 \times 10^6$ | 45d                          | Number, weight                | Size, number |
| Lee [47]    | 2014 | Antitumor activity of a nanoparticulate formulation of SN38, a metabolite of irinotecan | HT29             | Athymic nude    | $5 \times 10^6$ | 45d                          | Number, weight                | Size, number |
| Kondo [48]  | 2014 | Effect of nuclear overexpression and nuclear accumulation                        | HT29             | Athymic nude    | $5 \times 10^6$ | 45d                          | Number, weight                | Size, number |
| At-kassimopoulos [49] | 2014 | Photodynamic diagnosis using 5-aminolevulinic acid and intraperitoneal injection | HT29             | Athymic nude    | $5 \times 10^6$ | 45d                          | Number, weight                | Size, number |
| Derfler-Wallace [50] | 2013 | Antitumor activity of a nanoparticulate formulation of SN38, a metabolite of irinotecan | HT29             | Athymic nude    | $5 \times 10^6$ | 45d                          | Number, weight                | Size, number |
| Naya [51]   | 2013 | Antitumor activity of a nanoparticulate formulation of SN38, a metabolite of irinotecan | HT29             | Athymic nude    | $5 \times 10^6$ | 45d                          | Number, weight                | Size, number |
| Steri [52]  | 2012 | Antitumor activity of a nanoparticulate formulation of SN38, a metabolite of irinotecan | HT29             | Athymic nude    | $5 \times 10^6$ | 45d                          | Number, weight                | Size, number |
| Straza [53] | 2010 | Antitumor activity of a nanoparticulate formulation of SN38, a metabolite of irinotecan | HT29             | Athymic nude    | $5 \times 10^6$ | 45d                          | Number, weight                | Size, number |
| Ziauddin [54] | 2010 | Antitumor activity of a nanoparticulate formulation of SN38, a metabolite of irinotecan | HT29             | Athymic nude    | $5 \times 10^6$ | 45d                          | Number, weight                | Size, number |
| Wagner [55] | 2009 | Antitumor activity of rapamycin in CRC peritoneal metastasis                      | HT29             | Athymic nude    | $5 \times 10^6$ | 45d                          | Number, weight                | Size, number |
| Author         | Year | Research question                                                                 | Cell line/tissue          | Animal       | IP dose       | Interval before endpoints | Quantification of PC                                                                 |
|----------------|------|-------------------------------------------------------------------------------------|---------------------------|--------------|---------------|----------------------------|--------------------------------------------------------------------------------------|
| Kishimoto [60] | 2009 | In vivo tumor illumination by IP adenoviral GFP                                       | HCT-116 and HCT-116-RFP   | Athymic nude | $3 \times 10^6$ | 17d                        | Fluorescence Optical Imaging; histology                                               |
| Li [61]        | 2007 | Evaluation of hypoxia in PM                                                          | HT29 and HCT-8            | Athymic nude | $5 \times 10^6$ | 3–7 w                      | IHC and in vitro fluorescence imaging                                                |
| Kinuya [62]    | 2007 | Antitumor activity of RIT with a $^{131}$I labelled IP A7 antibody                   | LS180                     | BALB/c nude  | $1 \times 10^7$ | variable                   | Survival                                                                           |
| Jie [63]       | 2007 | Antitumor activity of recombinant adenovirus, rtAdCMV/NK                               | LS174T                    | BALB/c nude  | $1 \times 10^7$ | 15 d                       | Number, site, and weight of nodules                                                 |
| Sasaki [64]    | 2006 | Antitumor activity of IP linoleic acid (LA)                                          | Colo320                   | BALB/c nude  | $1 \times 10^7$ | 12 w                       | Number of metastatic foci                                                           |
| Kuniyasu [65]  | 2006 | Antitumor activity of IP conjugated linoleic acid (CLA) on PM                         | Colo320                   | BALB/c nude  | $1 \times 10^7$ | 4–16 w                     | Number of metastatic foci, survival                                                 |
| Koppe [66]     | 2006 | Antitumor activity of radioimmunotherapy combined with gencitabine                   | LS174T                    | BALB/c nude  | $1 \times 10^6$ | NA                         | Survival, tumor weight, IHC                                                        |
| Koppe [67]     | 2006 | Antitumor activity of radioimmunotherapy combined with parecoxib                      | LS174T                    | BALB/c nude  | $1 \times 10^6$ | NA                         | Survival, mPCI, tumor weight, tracer biodistribution                               |
| Pourgholami [68]| 2005 | Antitumor activity of IP albendazole                                                  | HT29                      | BALB/c nude  | $1 \times 10^6$ | 6w                         | Number of nodules                                                                  |
| Kinuya [69]    | 2005 | Locoregional $^{188}$Re-RIT versus $^{131}$I-RIT for experimental PC                 | LS180                     | BALB/c nude  | $1 \times 10^7$ | variable                   | Tissue radioactivity, number and weight of nodules, survival                        |
| Zeamari [70]   | 2004 | Identification of growth factors during peritoneal wounding in relation to tumor cell seeding | HT29                      | BALB/c nude  | $1 \times 10^6$ | 28 d                       | Tumor load (a. u.), PCR of granulation tissue                                         |
| Koppe [71]     | 2004 | Antitumor activity of $^{125}/^{33}$I, $^{188}$Re-, or $^{177}$Lu-Labeled Monoclonal Antibody MN-14 to CEA | LS174T                    | BALB/c nude  | $1 \times 10^6$ | NA                         | Survival, tumor weight, tracer biodistribution                                      |
| Favoulet [72]  | 2004 | Antitumor activity of IP pirarubicin                                                  | LS174T                    | Athymic nude | $1 \times 10^7$ | 21 d                       | Ascites volume, tumor size                                                        |
| Koppe [73]     | 2003 | Antitumor activity of IP radioimmunotherapy using $^{131}$I-labeled MN-14            | LS174T                    | BALB/c nude  | $1 \times 10^6$ | variable                   | Biodistribution, IHC                                                              |
| Kinuya [74]    | 2003 | Antitumor activity of IP versus IV radioimmunotherapy with $^{131}$I-A7              | LS180                     | BALB/c nude  | $1 \times 10^7$ | variable                   | Survival, biodistribution                                                         |
| Stoeltzing [75]| 2002 | Effect of angiopoietin-1 on PM tumour growth and angiogenesis                         | Ang1- or pcDNA transfected KM12L4 | Athymic nude | $1 \times 10^6$ | variable                   | Ascites volume, diameter of largest PM, number of nodules, IHC                     |
| Fan [76]       | 2002 | Effect of the angiogenesis inhibitor TNP-470 on peritoneal dissemination              | LoVo                      | BALB/c nude  | $5 \times 10^7$ | 10 d or 30 d              | Survival, number and size of nodules                                                |
| Hubbard [77]   | 2002 | Antitumor activity of hyaluronan-based membrane                                       | KM12-L4                   | BALB/c nude  | variable       | 28 d                       | Tumor weight, presence of ascites, histology                                        |
| Shaheen [78]   | 2001 | Antitumor activity of IP anti-VEGFR and anti-EGFR antibodies                          | KM12L4                    | Athymic nude | $1 \times 10^6$ | NA                         | Tumor size, ascites (semiquantitatively), IHC                                       |
| Author          | Year | Research question                                                                 | Cell line/tissue                  | Animal       | IP dose   | Interval before endpoints | Quantification of PC                                                                 |
|-----------------|------|------------------------------------------------------------------------------------|----------------------------------|--------------|-----------|---------------------------|--------------------------------------------------------------------------------------|
| Goto [79]       | 2001 | Antitumor activity of gene therapy using the Cre/loxP system                       | LoVo                             | Athymic nude | $1 \times 10^6$ | 35 d                      | Tumor weight, histology                                                              |
| Kondo [80]      | 2000 | Role of VEGF in peritoneal cancer growth                                            | VEGF transfected LoVo            | BALB/c nude  | $2 \times 10^6$ | variable                  | Metastatic pattern, number and size of nodules, ascites volume                      |
| Crosasso [81]   | 1997 | Antitumor activity of IP 5-FU produg formulated in liposomes or immunoliposomes    | HT-29                             | Athymic nude | $1.5 \times 10^7$ | variable                  | Histology, Residual tumor mass (RTM, % of tumor mass in treated vs control mice)     |
| Asao [82]       | 1995 | Role of Fucosyltransferases in cancer cell adhesion                                 | KM12C and KM12SM                 | BALB/c nude  | $1 \times 10^6$ | 4 w                       | Tumor weight                                                                        |
| Quadri [83]     | 1995 | Biodistribution of IP In-111-labeled IgM                                           | SW620                             | Athymic nude | $6 \times 10^6$ | variable                  | Biodistribution, whole body autoradiography                                           |
| **Human cell lines, Immunodeficient rats**                      |      |                                                                                    |                                  |              |                        |                                          |                                                                                      |
| Harlaar [84]    | 2010 | Validation of bioluminescence in PC animal models                                  | HT-29-luc-D6                      | Athymic nude | $2 \times 10^6$ | 8 w                       | Bioluminescence, PCI                                                                 |
| Mahteme [85]    | 2005 | Effect of vasoconstriction on IP 5FU tumor uptake                                   | LS 174T                           | Athymic nude | $1 \times 10^7$ | variable                  | Whole body autoradiography for biodistribution                                        |
| **Syngeneic cell lines, Immunocompetent mice**                |      |                                                                                    |                                  |              |                        |                                          |                                                                                      |
| Carpinteri [86] | 2015 | Effect of laparoscopy with humidified-warm CO2 on peritoneal inflammation and metastasis | (MSCV)-mCherry-CT26               | BALB/c       | $1 \times 10^6$ | 10 d                      | Number; Cherry-Red fluorescence (Maestro)                                            |
| Zhang [87]      | 2015 | Antitumor activity of IP curcumin in a thermosensitive hydrogel                    | CT26                              | BALB/c       | $2 \times 10^5$ | 22 d                      | Number of nodules, tumor weight, survival, IHC                                      |
| Ryan [88]       | 2015 | Antitumor activity of nuclear factor (NF)-κB inhibition                             | CT26/EV and CT26/λκB-α SR         | BALB/c       | variable               | variable                  | Tumor weight, histology, survival                                                   |
| Zhang [89]      | 2014 | Antitumor effects of placenta-derived mesenchymal stem cells expressing endostatin | Endostatin                       | CT26         | $3 \times 10^5$ | variable                  | Number, size of nodules                                                              |
| Fan [90]        | 2014 | Evaluation of docetaxel loaded microspheres for IP delivery                        | CT26                              | BALB/c       | $2 \times 10^5$ | 14 d                      | Number, size                                                                         |
| Sedlacek [91]   | 2013 | Effect of peritoneal immunization by IP injected irradiated cancer cells           | eGFP transfected MC38             | C57BL/6      | $1 \times 10^6$ | 3 or 7 d                  | GFP fluorescence of resected omenta                                                  |
| Liu [92]        | 2013 | Evaluation of camptothecine loaded polymeric microsphere in thermosensitive hydrogel for IP delivery | CT26                              | BALB/c       | $2 \times 10^5$ | 20 d                      | Number and weight                                                                    |
| Li [93]         | 2013 | Role of high-mobility group box 1 (HMGB1) in PM                                   | CT26                              | BALB/c       | $1 \times 10^5$ | 2 w                       | modified sPCI                                                                         |
| Yao [94]        | 2013 | Antitumor activity of a water-soluble BSA-SN38 conjugate                          | CT26                              | BALB/c       | $2 \times 10^5$ | 18 d                      | Tumor weight                                                                         |
| Author        | Year | Research question                                                                 | Cell line/tissue | Animal       | IP dose | Interval before endpoints | Quantification of PC                                     |
|--------------|------|-------------------------------------------------------------------------------------|------------------|--------------|---------|------------------------|---------------------------------------------------------|
| Yu [95]      | 2013 | Peritoneal immune response after IP vaccination with irradiated CT26 cells          | CT26             | BALB/c       | $5 \times 10^5$ | variable               | Peritoneal immune response                              |
| Lee [96]     | 2013 | Effect of surgery on matrix metalloproteinase-9 activity                             | MC38             | C57Bl/6J     | $1 \times 10^5$ | 2w                     | modified sPCI                                            |
| Wu [97]      | 2012 | Antitumor efficacy of Adeno-associated virus mediated human pigment epithelium-derived factor (PEDF) | CT26             | BALB/c       | $5 \times 10^5$ | 18d                    | Number, weight                                           |
| Lehmann [98] | 2012 | Synergism of HIPEC with the SOD inhibitor diethyldithiocarbamate (DDC)             | MC38             | C57Bl/6J     | $2 \times 10^6$ | 7d                     | Tumor mass                                              |
| Tsai [99]    | 2011 | Antitumor efficacy of $^{185}$Re-labeled nanoliposomes (IV)                        | CT26             | BALB/c       | $2 \times 10^5$ | 7–14d                  | Ascites weight, tumor weight, PET-CT                     |
| Puskas [100] | 2011 | Antitumor efficacy of an attenuated interleukin-2 fusion protein                  | MC38             | C57Bl/6J     | $5 \times 10^5$ | 7d                     | Flow cytometry and CRU on omental lysates               |
| Nishizaki [101]| 2011 | Inhibition of surgical trauma-enhanced PM by human catalase derivatives          | CT26-Luc         | BALB/c       | $1 \times 10^5$ | 3d                     | Luminoimetry on omentum and GI tract lysates             |
| Dai [102]    | 2011 | Antitumor activity of camptothecin-loaded microspheres                            | CT26             | BALB/c       | $2 \times 10^5$ | 14d                    | Size, number                                            |
| Ziauddin [54]| 2010 | Antitumor activity of vTRAIL-mediated oncolytic gene therapy                      | MC38             | C57Bl/6J     | $2 \times 10^5$ | NA                     | survival                                                |
| Wang [103]   | 2010 | Antitumor activity of 5-FU-loaded hydrogel system                                  | CT26             | BALB/c       | $2 \times 10^5$ | 20d                    | Size, number                                            |
| Tanaka [104] | 2010 | Antitumor activity of the Transforming growth factor ß signaling inhibitor, SB-431542 | CT26             | BALB/c       | NS        | 14d                    | Cytotoxic T cell (CT) activity against CT26             |
| Lan [57]     | 2010 | Antitumor activity of a cationic liposome coupled with the murine endostatin gene | CT26-luc         | BALB/c       | $3 \times 10^5$ | 3w                     | Bioluminiscence; gene expression; survival; tumor weight |
| Keese [105]  | 2010 | Fluorescence lifetime imaging of chemotherapy induced apoptosis by optically monitoring the caspase-3 sensor state | tHcred-DEVD-EGFP transfected CT26 | BALB/c | $1 \times 10^6$ | 10d                    | Fluorescence lifetime imaging microscopy (FLIM)         |
| Wagner [59]  | 2009 | Antitumor activity of rapamycin                                                  | CT26             | BALB/c       | $5 \times 10^5$ | NA                     | Ascites volume; tumor weight                            |
| Kulu [106]   | 2009 | Comparison of IV versus IP administration of oncolytic herpes simplex virus 1      | CT26             | BALB/c       | $1 \times 10^5$ | 20d                    | Tumor weight                                            |
| Keese [107]  | 2009 | Antitumor activity of doxorubicin and mitoxantrone drug eluting beads for PC     | EGFP-C26        | BALB/c       | $1 \times 10^6$ | 15d                    | In vivo fluorescence microscopy; mPCI, tumor volume, PCR for EGFP |
| Lan [108]    | 2007 | Antitumor activity of liposome coupled BikDD on PM                                | CT-26-Luc        | BALB/c       | $1 \times 10^5–1 \times 10^6$ | 21d            | Bioluminiscence; tumor weight                           |
| Hyoudou [109]| 2007 | Antitumor activity of cationized catalase-loaded hydrogel                         | CT-26-Luc        | BALB/c       | $1 \times 10^5$ | 21d                    | Bioluminiscence; Luminometry on organ lysates           |
| Author               | Year | Research question                                                                 | Cell line/tissue | Animal     | IP dose   | Interval before endpoints | Quantification of PC                                    |
|---------------------|------|------------------------------------------------------------------------------------|-----------------|------------|-----------|---------------------------|---------------------------------------------------------|
| Dvir-Ginzberg       | 2007 | Antitumor activity of IP scaffolds containing retroviral vector producing cells    | MC38             | C57bl/6    | $5 \times 10^5$ | NA                       | Survival, extent of PC (not quantified)                 |
| Hyoudou            | 2006 | IP PEG-catalase to inhibit peritoneal dissemination                                 | CT-26-Luc       | BALB/c     | $1 \times 10^5$ | variable                 | Bioluminescence, expression of adhesion molecules, MMP activity in ascites |
| Helguera           | 2006 | Antitumor activity of IL-12 and GM-CSF mono-AbFPs against HER2/neu expressing PC   | CT26-HER2/neu   | BALB/c     | $1 \times 10^6$ | NA                       | Survival                                                |
| Yu                  | 2005 | Antitumor activity of gene therapy using LK68 cDNA                                  | CT26-LK68-7     | BALB/c     | $5 \times 10^5$ | 14 d                     | Survival, number of nodules, ascites volume             |
| Yamaguchi          | 2001 | Effect of CO$_2$ pneumoperitoneum on hyaluronic acid production and PM              | CT26             | BALB/c     | $5 \times 10^6$ | 7 d                      | Number and weight of port site metastasis, histology    |
| Miyata             | 2001 | Antitumor activity of MIP-1 gene therapy                                           | CT26             | BALB/c     | $1.5 \times 10^5$ | NA                       | Survival, gene expression                              |
| Moreno             | 2000 | Effects of pneumoperitoneum on tumor cell biology                                   | 51BlM            | BALB/c     | $1 \times 10^5$ or $5 \times 10^3$ | 6 w                      | Survival, frequency of IP tumor growth                  |
| Maruyama           | 1999 | Intrapерitoneal versus intravenous CPT-11 for peritoneal seeding                    | CT26             | BALB/c     | $1.5 \times 10^6$ | 14 d                     | Number of nodules                                      |
| Guichard           | 1998 | Efficacy and pharmacokinetics of IP versus IV CPT-11                               | CT26             | BALB/c     | $2 \times 10^6$ | NA                       | Survival, pharmacokinetics                             |
| Kurihara           | 1997 | Antitumor activity of oral UFT plus IV cisplatin (UFT regimen)                      | Colon 26 PMF-15 | CDF1       | $1 \times 10^6$ | NA                       | Survival                                                |
| Gutman             | 1996 | Antitumor activity of PO thalidomide                                               | CT26             | BALB/c     | $1 \times 10^5$ | 21 d                     | Number of nodules                                      |
| Mayhew             | 1990 | Antitumor activity of free versus liposomal IP doxorubicin                          | CT26             | BALB/c     | $2 \times 10^5$ | NA                       | Survival, pharmacokinetics                             |
| **Syngeneic cell lines, Immunocompetent rats** | |                                                                 | | | | | |
| Imano               | 2013 | Establishment of a PC model of the peritoneal extension type (PET)                  | RCN-9            | Fischer 344| $1 \times 10^6$ | 1–21 d                  | Histology (tumor and submesothelial thickness)          |
| Eriksson           | 2012 | Antitumor efficacy of $^{177}$Lu-DOTA-BR96                                          | BN7005-H1D2     | Brown Norway (BN) | $3 \times 10^5$ (subperitoneal) | Up to 119 d                           | Tumor volume                                           |
| Moretto            | 2011 | Antitumor efficacy of new platinum(Ill) metallocintecator                           | PROb             | BD-IX      | $2 \times 10^6$ | 35 d                     | Semi-quantitative score of PC (0 to 3) and hemorrhagic ascites |
| Klaver             | 2011 | Antitumor activity of hyperthermia and IPC in PC                                    | CC531            | WAG/Rij    | NS         | 126 d                    | mPCI, survival                                          |
| Serafini           | 2011 | Antitumor activity of new IP bioconjugate of hyaluronic acid (HA) with SN-38         | DHD/K12/PROb    | BD-IX      | $1 \times 10^6$ | 28 d                     | Ascites volume, tumor volume (water immersion), mPCI    |
| Klaver             | 2010 | Antitumor activity of surgery and HIPEC versus surgery alone for PC                 | CC531            | WAG/Rij    | $2 \times 10^6$ | NA                      | Survival; mPCI                                         |
| van der Bij        | 2008 | Role of tumor infiltrating macrophages in colorectal PC                              | CC531s           | WAG/Rij    | $0.5 \times 10^6$ | 14 d                     | Number, diameter, IHC for ED2 + resident macrophages    |
| Author          | Year | Research question                                                                 | Cell line/tissue | Animal      | IP dose | Interval before endpoints | Quantification of PC                                                                 |
|-----------------|------|-------------------------------------------------------------------------------------|------------------|-------------|---------|--------------------------|--------------------------------------------------------------------------------------|
| Taguchi [129]   | 2008 | Antitumor activity of KRN951                                                        | RCN-9            | Fisher 344  | $1 \times 10^7$       | 16–21 d                                                              | Ascites volume, number of nodules, mesenteric vascularity                          |
| Oosterling [130]| 2008 | Role of 1 integrin-dependent tumor adhesion in PM                                    | CC531s and Dil-CC531s | WAG/Rij    | $2 \times 10^6$       | 21 d                                                                  | Tumor load (mm); fluorescence imaging                                           |
| Aarts [131]     | 2008 | Antitumor activity of whole-body hyperthermia or fibrinolytic therapy combined with RIT adjuvant to surgery in PC | CC531           | WAG/Rij    | NA                  | NA                                                                 | Survival, mPCI                                                              |
| Otto [132]      | 2007 | Antitumor activity of intraperitoneal application of phospholipids                  | DHD/K12/TRb     | BD-IX       | $2 \times 10^6$       | 30 d                                                                  | mPCI, tumor volume (water immersion), surface of PC (digitized)                    |
| Hribaschek [133]| 2007 | IV versus IP Taxol™ in experimental PC                                              | CC531           | WAG/Rij    | $5 \times 10^6$       | 30 d                                                                  | Tumor weight, number of nodes per zone (omentum and peritoneum), microscopic tumor growth |
| Bobrich [134]   | 2007 | Effect of IP administration of taurolidine/heparin on expression of adhesion molecules and PC extent | DHD/K12/TRb     | BD-IX       | $1 \times 10^6$       | 4w                                                                   | Tumor weight, IHC                                                            |
| Aarts [135]     | 2007 | Effect of timing of RIT as adjuvant therapy after CS                                 | CC531           | WAG/Rij    | $2 \times 10^6$       | NA                                                                   | Survival, mPCI                                                            |
| Aarts [136]     | 2007 | Radioimmunotherapy versus HIPEC after CS                                             | CC531           | WAG/Rij    | $2 \times 10^6$       | NA                                                                   | Survival, mPCI, ascites volume, microscopic tumor                                  |
| Pelz [137]      | 2006 | Antitumor activity of HIPEC after CS                                                | CC531           | WAG/Rij    | $2.5 \times 10^5$     | 20 d                                                                  | Dose-tumor load study, tumor score, fluorescence imaging                           |
| Oosterling [138]| 2006 | Role of omentum in prevention of tumor growth in MRD                                 | CC531           | WAG/Rij    | $2 \times 10^5$       | variable                                                              | Tumor weight, number of nodules, mPCI, tumor weight, IHC                         |
| Nestler [139]   | 2006 | Antitumor activity of intraperitoneal application of phospholipids                  | CC531           | WAG/Rij    | $5 \times 10^6$       | 21 d                                                                  | Survival, mPCI, tumor weight, IHC                                                |
| Koppe [140]     | 2006 | Radiomunotherapy as adjuvant therapy after CS for PC                                | CC531           | WAG/Rij    | $2\times 10^5$        | NA                                                                   | Tumor weight, number of nodes per zone (omentum and peritoneum), microscopic tumor growth, ascites volume |
| Hribaschek [141]| 2006 | IV versus IP CPT-11 for experimental PC                                             | CC531           | WAG/Rij    | $5 \times 10^6$       | 30 d                                                                  | Tumor weight, number of nodes per zone (omentum and peritoneum), microscopic tumor growth, ascites volume |
| van den Tol [142]| 2005 | Adhesion-preventing properties of IP icodextrin                                      | CC531s          | WAG/Rij    | $0.5 \times 10^6$     | 21 d                                                                  | mPCI, tumor adhesion                                                           |
| Oosterling [143]| 2005 | Role of macrophages on tumor histology and outcome                                   | CC531           | WAG/Rij    | $2 \times 10^6$       | variable                                                              | Survival, Omental weight, IHC                                                   |
| Alkhamesi [144] | 2005 | Role of ICAM-1 in mesothelial–tumour adhesion and effectiveness of therapeutic intervention | CC531s         | WAG/Rij    | $1 \times 10^5$       | 14 d                                                                  | mPCI, IHC                                                                 |
| Alkhamesi [145] | 2005 | Effect of novel nebulization technique on post laparoscopy tumor dissemination       | CC531           | WAG/Rij    | $1 \times 10^5$       | 14 d                                                                  | Number and size of lesions, histology                                             |
| Mahteme [146]   | 2004 | IV versus IP 5-FU administration with or without CS                                 | CC531           | Wistar rat | $1 \times 10^7$       | 3w                                                                   | Whole body autoradiography for biodistribution                                   |
| Author            | Year | Research question                                                                 | Cell line/tissue | Animal | IP dose | Interval before endpoints | Quantification of PC                                                                 |
|-------------------|------|------------------------------------------------------------------------------------|------------------|--------|---------|---------------------------|-------------------------------------------------------------------------------------|
| Favoulet [72]     | 2004 | Antitumor activity of IP pirarubicin                                                | DHD/K12/PROb     | BD-IX  | $1 \times 10^6$ | 30 d                      | Ascites volume, tumor size                                                          |
| Zayyan [147]      | 2003 | Effect of CO$_2$ flow rate during laparoscopy on cancer cell dispersal              | RCC2             | Fisher 344 | $7.5 \times 10^6$ | 4 w                      | Histology for presence of tumor                                                      |
| Optitz [148]      | 2003 | Effect of adhesion prophylactic substances and taurolidine/heparin on local recurrence and intraperitoneal tumor | DHD/K12/TRb     | BD-IX  | $1 \times 10^6$ | 4 w                      | Adhesion score, number and weight of nodules, histology                             |
| Hribaschek [149]  | 2002 | Antitumor activity of IP CPT-11 or oxaliplatin                                     | CC531            | WAG/Rij| $5 \times 10^6$ | 15 d or 30 d               | Tumor weight, number of nodes per zone (omentum and peritoneum), histology          |
| Gahlen [150]      | 2002 | Efficacy of 5-ALA-induced protoporphyrin IX accumulation and fluorescence in experimental PC | CC531            | WAG/Rij| $5 \times 10^5$ | 12 d                      | Fluorescence Laparoscopy, spectrometry, histology                                   |
| van den Tol [151] | 2001 | Effect of glove starch-induced peritoneal trauma on adhesions and PM                | CC531s           | WAG/Rij| $0.5 \times 10^6$ | 21 d                      | mPCI                                                                                |
| Tan [152]         | 2001 | Effect of hyaluronate on tumor cell metastatic potential                             | DHD/K12          | BD-IX  | $0.5 \times 10^5$ | 4 w                      | Nodule count                                                                        |
| Hoffstetter [153] | 2001 | Effect of topical povidone-iodine on port site metastasis                           | DHD/K12          | BD-IX  | $2 \times 10^5$ | 3 w                      | Number of port site metastases                                                     |
| Miyoshi [154]     | 2001 | Peritoneal angiogenesis and VEGF role in colorectal PC                              | RCN-9            | Fisher 344 | $1 \times 10^7$ | variable                  | Mesenteric angiogenesis (intravital microscopy), ascites VEGF concentration          |
| Cardozo [14]      | 2001 | Establishment of PC model based on the CC531 cell line                              | CC531s           | WAG/Rij| $2 \times 10^6$ | variable                  | Tumor distribution, IHC                                                             |
| McCourt [155]     | 2000 | Antitumor activity of IP Taurolidine                                               | DHD/K12/TRb      | BD-IX  | $0.25 \times 10^6$ | 24 d                      | Number of nodules                                                                  |
| Hofstetter [156]  | 2000 | Effect of CO$_2$ insufflation on hematogeneous cancer spread                        | DHD/K12          | BD-IX  | $2 \times 10^5$ | 3 w                      | Incidence of PM                                                                    |
| van Rossen [157]  | 1999 | Effect of RBC derived factors on tumor cell adhesion and PC                         | CC531            | WAG/Rij| $1 \times 10^6$ | 3 w                      | mPCI                                                                                |
| Onier [158]       | 1999 | Antitumor activity of OM 174                                                       | DHD/K12/PROb     | BD-IX  | $1 \times 10^6$ | variable                  | Survival, mPCI, ascites volume                                                      |
| Jacobi [159]      | 1999 | Effect of different insufflation gases and of taurolidine, heparin, or povidone-iodine on PC | DHD/K12/TRb     | BD-IX  | $1 \times 10^6$ | 4 w                      | Tumor weight, histology, incidence of port site metastasis                         |
| Jacobi [160]      | 1999 | Effects of taurolidine, heparin, and povidone-iodine on PC                          | DHD/K12/TRb      | BD-IX  | $1 \times 10^6$ | 4 w                      | Tumor weight, incidence of port site metastasis                                    |
| Gahlen [161]      | 1999 | δ-aminolevulinic acid (ALA) based fluorescence imaging for PC diagnosis and staging | CC531            | WAG/Rij| $5 \times 10^5$ | 12 d                      | Fluorescence imaging (ALA), nodule size, histology                                 |
| Gahlen [162]      | 1999 | δ-aminolevulinic acid (ALA) based fluorescence imaging for PC diagnosis             | CC531            | WAG/Rij| $1 \times 10^6$ | 12 d                      | Fluorescence imaging (ALA), histology                                              |
| Lundberg [163]    | 1998 | Effect of CO$_2$- and air-induced pneumoperitoneum on tumor growth                  | Colon adenoCA, NOS | Wistar Fu | $1 \times 10^5$ | 12 d                      | mPCI, histology                                                                     |
| Author          | Year | Research question                                                                 | Cell line/tissue | Animal    | IP dose | Interval before endpoints | Quantification of PC                                                                 |
|-----------------|------|------------------------------------------------------------------------------------|------------------|-----------|---------|--------------------------|-------------------------------------------------------------------------------------|
| Veenhuizen      | 1997 | Efficacy of mTHPC-mediated photodynamic therapy                                     | CC531            | WAG/Rij  | $1 \times 10^6$          | 10–14 d                                    | Drug biodistribution                                                               |
| Jacobi          | 1997 | Effect of IP taurolidine and heparin on growth of colon adenocarcinoma              | DHD/K12/PROb     | BD-IX    | $1 \times 10^6$          | 4 w                                      | Tumor weight, histology                                                            |
| Jacquet         | 1996 | Effect of IP doxorubicin and rT-PA postoperative tumor implants                    | DHD/K12/PROb     | BD-IX    | $6 \times 10^5$          | 20 d                                    | Incidence of tumor implantation, tumor volume                                       |
| Bouvy           | 1996 | Effect of CO$_2$ pneumoperitoneum, gasless laparoscopy, and laparotomy on PC      | CC531            | WAG/Rij  | $350$ mg fragment and $5 \times 10^5$ | 4 or 6 w | mPCI                                                                   |
| Onier           | 1993 | Antitumor efficacy of IP immunomodulator, OM163                                   | DHD/K12/PROb     | BD-IX    | $1 \times 10^6$          | 6 w                                      | mPCI, ascites volume, survival                                                    |
| **Human cell line, immunocompetent Hamster** |      |                                                                                   |                  |           |                      |                                         |                                                                                     |
| Wu              | 1998 | Effects of pneumoperitoneum on tumor implantation                                 | GW-39            | Syrian gold hamster | $1.6 \times 3.2 \times 10^6$ | 8 w                                      | Number of tumor nodules                                                          |
| Wu              | 1997 | Effect of pneumoperitoneum on the implantation of tumor at trocar sites            | GW-39            | Syrian gold hamster | $0.8 \times 10^6$         | 8 w                                      | Frequency of tumor implantation                                                  |
| **Large immunocompetent animal models**          |      |                                                                                   |                  |           |                      |                                         |                                                                                     |
| Turner          | 1998 | Establishment of a large animal model to evaluate RIT                             | LS174T           | Sheep (cyclosporin treated) | $1 \times 10^7$ (Matrigel injection in peritoneal wall) | 3–6 w                                    | Histology, tracer uptake                                                          |
| Hewett          | 1996 | Movement of cells throughout the peritoneal cavity during laparoscopy             | Lim1215          | Pig      | $10–15 \times 10^6$      | immediate                                | Presence of tumor cells in filters                                                |

PMP, pseudomyxoma peritonei; CRC, colorectal cancer; PM, peritoneal metastasis; PC, peritoneal carcinomatosis; RIT, radioimmunotherapy; PCI, peritoneal cancer index; mPCI, modified PCI; IP, intraperitoneal; IV, intravenous; SC, subcutaneous; PO, per os; 5FU, 5-fluorouracil; CS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemoperfusion.
animals have a normal immunity, and the resulting IP tumors therefore display a more representative microenvironment. On the other hand, these colon tumors are chemically induced and are not representative of the genetic and molecular heterogeneity of human cancers. Obviously, use of syngeneic models is the preferred approach for the study of cancer immunotherapy.

In immunocompetent mice, all published studies have used either the CT26 (colon tumor 26) or MC38 cell line, which are syngeneic to the BALB/c and C57BL/6 mouse, respectively. Both cell lines were developed in 1975 by exposing mice to repeated intrarectal applications of N-nitroso-N-methylurethane (NMU) or 1,2-dimethylhydrazine dihydrochloride (DMH) [11]. CT26 is a rapid-growing grade IV carcinoma that is easily implanted and readily metastasizes; it shares molecular features with aggressive, undifferentiated, refractory human colorectal carcinoma cells [12]. The MC-38 murine colon tumor is a grade III adenocarcinoma [11]. Both cell lines cause widespread PC two to three weeks after IP injection.

In immunocompetent rats, the most commonly cited model is the syngeneic CC531 cell line in the WAG (Wistar Albino Glaxo) or WAG/Rij rat. Tumor CC531 is a DMH-induced, transplantable adenocarcinoma exhibiting weak immunogenicity and which has been widely used in metastasis research [13]. Upon IP injection, the CC531 cell line causes widespread carcinomatosis and haemorrhagic ascites after three weeks [14]. In Fischer F344 rats, the spontaneously metastatic RCN-9 syngeneic cell line was established by subcutaneous administration of DMH [15]. Other syngeneic, chemically induced rat colon cancer models include the BN7005-H1D2 cell line in the Brown Norway rat, DHD/K12/TRb in the BD IX rat, and RCC2 in the Fischer F344 rat.

Xenograft models

Xenograft models involve the transplantation of human cancer cells or tissue to immunodeficient animals. Nude mice (athymic nude and BALB/c nude) and the athymic nude rat have a biallelic mutation of the FOXN1 gene (which in humans encodes the Forkhead box protein N1), leading to an athymic state and the hairless phenotype. These animals are unable to generate mature T lymphocytes and the related adaptive immune response. Severe combined immunodeficiency (SCID) mice carry a homozygous mutation of a gene coding for Prkdc, an enzyme involved in DNA repair, resulting in absent or atypical T and B lymphocytes. Non obese diabetic (NOD) SCID mice have, in addition, deficient natural killer (NK) cell function. The disadvantages of xenografted models are higher costs due to isolation requirements, the fact that the stromal component of the tumors is rodent, that the hosts are immunodeficient, and that most of the tumor lines were developed using early technology. Also, a striking feature of xenografted tumors is early and extensive necrosis, which may hamper efficacy and imaging studies. In addition, use of a “standard” cell line can result in a population that is not truly representative of the original tumor and may therefore respond differently to therapy compared to. In fact, the use xenograft models has been debated due to their low ability to predict clinical response [16]. The colon cancer cell lines that were used in xenografted PC models include HCT116, LS174T, and HT29.

Patient derived xenografts (PDX)

In order to overcome the most important drawback of xenograft models, i.e. the loss of genetic and morphological heterogeneity of the original tumor, patient derived xenografts (PDX) were developed [17]. These models consist of patient derived cancer cells or tissues transplanted in immunodeficient animals. PDX models have a long latency period and low engraftment rate, and are therefore very costly to maintain. They are ideally suited for testing novel and “personalized” cancer therapeutics. In the field of colorectal peritoneal metastasis, three studies reported the use of PDX. Kotanagi et al. obtained colorectal PM tissue fragments from a patient with stage IV right sided colon cancer [18]. Intraperitoneal injection of a single cell suspension resulted in poorly differentiated PC in four out of five SCID mice. Flatmark and coworkers implanted tumor fragments originating from mucinous colonic or appendiceal cancer in BALB/c nude mice [19]. Mice developed mucinous ascites and widespread mucinous implants; after several passages the ascites component became more prominent. The histological and molecular properties of the engrafted tumors closely resembled those of the originating clinical material. Tumor tissue fragments from an ovarian metastasis in a stage IV colon cancer patient was transplanted IP in NOD-SCID mice by Navarro-Alvarez et al. [20] The resulting xenografts were used to identify and characterize a novel tumor-initiating cell (NANK).
Genetically engineered mouse models

Genetically engineered mice (GEM) including transgenic, knock-out, knock-in, and their intercrosses have not been used in the study of colorectal peritoneal metastasis. Only one author describes the use of mice expressing human CEA as a transgene [21].

Large animal models

Larger animals are rarely used in PC research. Apart from the cost and handling issues, colorectal syngeneic or xenograft models are unavailable in large animals. In rabbits, a non-colorectal PC model based on the V×2 cell line is available. The V×2 cell line is derived from the Shope papilloma virus (family Papovaviridae), an onco-genic DNA virus, transmitted by biting arthropods and causing hyperkeratotic skin lesions resulting in malignant transformation in the rabbit [22]. A ‘gastric’ peritoneal carcinomatosis model based on the V×2 cell line was proposed by Tang et al. [23, 24]. The authors simulated gastric cancer with early stage PC in New Zealand white rabbits (Oryctolagus cuniculus) by transmural injection of V×2 cells in the stomach. Turner and coworkers succeeded in engrafting human colon cancer cells (LS174T) in cyclosporine treated sheep by subperitoneal injection [25]. Tumors grew at all sites within three weeks, and were used to study the biodistribution of a radiolabelled antibody. The use of a pig model was reported by Hewett, who studied the pneumoperitoneum induced movement of colon cancer cells immediately after IP instillation [26].

Establishment of experimental PC

An orthotopic PC model is easily established by IP injection of cancer cells, which results in widespread and progressive carcinomatosis, leading to cachexia, hemorrhagic ascites, and death of the animal. The efficacy (engraftment or take rate) and speed of this process depend on the number of cells injected, virulence of the cell line used, and immunocompetence of the host. Although this model is orthotopic, the metastatic process and its underlying biology are different from spontaneous PC arising from a primary colon cancer. Cespedes and coworkers established a primary colon cancer model by submucosal injection of HCT116 cells in the colon of nude mice, and observed the development of PC in 100% of the animals [27]. Using this model, the same group showed that use of a colon cancer cell line overexpressing Snail1, which decreases E-cadherin, completely blocked spontaneous PC [28]. Similarly, Puig et al. injected patient derived colon cancer cell lines into the cecal wall of NOD-SCID mice and observed spontaneous PC when cell lines were used originating from cancer with a mucinous differentiation [29]. The disadvantage of the IP injection and spontaneous PC models is that the resulting tumor load is difficult to quantify. Also, their very small size precludes detailed physiological or drug penetration study at the individual tumor level. We recently established a colorectal PC model consisting of two isolated peritoneal nodules, which develop upon subperitoneal injection of HT29 cells in Matrigel™ [30]. This model allowed assessment of tumor tissue interstitial fluid pressure, oxygenation, platinum penetration, and growth delay (Figure 2).

Experimental endpoints

Extent and distribution of PC

Most authors have quantified the extent of experimental PC by a scoring system based on the number and/or size of peritoneal implants, similar to the peritoneal cancer index (PCI) that is clinically used. Use of such a score is difficult when the tumor forms a confluent mass or film rather than isolated nodules. Others have used the total weight or volume (as determined by water displacement) of the tumor mass, ascites presence and volume, or the metastatic pattern as endpoints. Alternatively, the extent of microscopic disease has been studied on resected omental tissue, peritoneal biopsies, or omental lysate using (immune)histology or PCR. The above methods require invasive procedures. Several authors have quantified PC load at different time points using optical (fluorescence or bioluminescence) techniques based on cancer cell lines transfected with a green or red fluorophore, or with the firefly luciferase gene. Alternatively, cells may be labeled immediately before injection with quantum dots or other reporters [31]. These techniques are sensitive and fast, and allow reproducible quantification using a variety of image processing methods. Some authors have used bioluminescence of organ and tissue lysates in order to quantify tumor growth.
Survival

In studies investigating novel therapies of colorectal cancer, survival is an important endpoint. Since advanced PC causes considerable animal suffering, care should be taken to sacrifice the animals whenever a predefined humane endpoint is reached. Actuarial (rather than actual) survival is usually calculated, and comparisons made with the log rank test or the Cox model.

Other endpoints

Various other endpoints were reported. Some authors have analysed the pO$_2$, VEGF concentration, or immune response of tumor associated ascites. Others have imaged PC distribution using optical techniques (Figure 3), or have analysed the biodistribution of isotope labelled tracers in tissue or in the whole animal.

Conclusions and recommendations

Colorectal peritoneal metastasis remains little studied in preclinical models, when compared to ovarian cancer or liver metastasis research. Standardized, reproducible syngeneic and xenograft colorectal PC models are available in rodents. The choice of a specific model is dictated by the aim of the study. Technical models involving IP chemoperfusion or laparoscopy are easier in a rat model. Tumor physiology, pharmacokinetics, and growth delay are better studied in isolated peritoneal tumors established by peritoneal implantation of tissue fragments or subperitoneal injection. Very few genetically modified mouse models have been reported in PM research. With the advent of sophisticated genome editing tools such as CRISPR-Cas9 (clustered regularly interspaced short palindromic repeats associated nuclease 9), the use of genetically engineered models is expected to gain in importance in the near future.

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References

1. Herszenyi L, Tulassay Z. Epidemiology of gastrointestinal and liver tumors. Eur Rev Med Pharmacol Sci 2010;14(4):249–58.
2. Royston D, Jackson DG. Mechanisms of lymphatic metastasis in human colorectal adenocarcinoma. J Pathol 2009;217(5):608–19.
3. Cunningham D, Atkin W, Lenz HJ, Lynch HT, Minsky B, Nordlinger B, et al. Colorectal cancer. Lancet 2010;375(9719):1030–47.
4. Benedix F, Kube R, Meyer F, Schmidt U, Gastinger I, Lippert H. Comparison of 17,641 patients with right- and left-sided colon cancer: differences in epidemiology, perioperative course, histology, and survival. Dis Colon Rectum 2010;53(1):57–64.
5. Knorr C, Reingruber B, Meyer T, Hohenberger W, Stremmel C. Peritoneal carcinomatosis of colorectal cancer: incidence, prognosis, and treatment modalities. Int. J. Colorectal Dis 2004;19(3):181–7.
6. Koppe MJ, Boerman OC, Oyen WJG, Bleichrodt RP. Peritoneal carcinomatosis of colorectal origin – incidence and current treatment strategies. Ann Surg 2006;243(2):212–22.
7. Ceelen WP, Flessner MF. Intraperitoneal therapy for peritoneal tumors: biophysics and clinical evidence. Nat Rev Clin Oncol 2010;7(2):108–15.

Figure 3: Fluorescence imaging of red fluorescent HCT-116 colorectal peritoneal metastases using intraperitoneal injection of OBP-401, a telomerase-dependent, replication competent adenovirus expressing GFP (green fluorescent protein).

(A) HCT-116-RFP human colorectal cancer cells were inoculated into the abdominal cavity of nude mice. Various sized disseminated peritoneal nodules appeared within 12 days. (Scale bar, 10 mm.) (B) At higher magnification, peritoneally disseminated nodules of HCT-116-RFP were clearly visible using a specific filter for RFP (Left), and these nodules did not express GFP (Right). (Scale bar, 2 mm.) (C) Mice with HCT-116-RFP peritoneal disseminated nodules were i.p. injected with OBP-401 at a dose of 1 × 108 PFU. Five days after virus administration, HCT-116-RFP peritoneal-disseminated nodules were detected with their endogenous RFP fluorescence (Left). These disseminated nodules now expressed GFP fluorescence (Middle). With the long-pass filter, for simultaneous observation of both GFP and RFP, it can be seen that all of the RFP tumors were apparently labeled with GFP after OBP-401 injection (Right). (Scale bars: Upper, 10 mm; Lower, 500 μm.). Reprinted with permission from Kishimoto H, Zhao M, Hayashi K, Urata Y, Tanaka N, Fujiwara T, Penman S, Hoffman RM. In vivo internal tumor illumination by telomerase-dependent adenoviral GFP for precise surgical navigation. Proceedings of the National Academy of Sciences of the United States of America 2009;106(34): 14514–14517.
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8. Warrick C. An improvement on the Practice of tapping; whereby that operation, instead of a relief for symptoms, becomes an absolute cure for an ascites, exemplified in the case of Jane Roman; and recommended to the consideration of the royal society, by Christopher Warrick, of Truro, surgeon. Phil Tran 1753;43(672–677):12–19.

9. Armstrong DK, Bundy B, Wenzel L, Huang HQ, Baerger R, Lele S, et al. **Intrapерitoneal cisplatin and paclitaxel in ovarian cancer.** N Engl J Med 2006;354(3):34–43.

10. Chua TC, Moran BJ, Sugarbaker PH, Levine EA, Glehen O, Gilly FN, et al. **Early, and long-term outcome data of patients with pseudomyxoma peritoneum from appendiceal origin treated by a strategy of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy.** J Clin Oncol 2012;30(20):2449–56.

11. Corbett TH, Griswold Jr DP, Roberts BJ, Peckham JC, Schabel JR FM. Tumor induction relationships in development of transplantable cancers of the colon in mice for chemotherapy assays, with a note on carcinogen structure. Cancer Res 1975;35(9):2434–9.

12. Castle JC, Loewer M, Boegel S, de Graaf J, Bender C, Tadmor AD, et al. **Interferon treatment of a transplantable rat colon adenocarcinoma: importance of tumor site.** Int J Cancer 1984;33(5):689–92.

13. Marquet RL, Westbroek DL, Jeekel J. **Interferon treatment of a transplantable rat colon adenocarcinoma: importance of tumor site.** Int J Cancer 1984;33(5):689–92.

14. Cardozo A, Gupta A, Koppe MJ, Meijer S, van Leeuwen PAM, et al. Metastatic pattern of CC531 colon carcinoma in the abdominal cavity: an experimental model of peritoneal carcinomatosis in rats. Eur J Surg Oncol 2001;27(4):359–63.

15. Inoue Y, Kashima Y, Aizawa K, Hatakeyama K. A new rat colon cancer cell line metastasizes spontaneously; biologic characteristics and chemotherapeutic response. Jpn J Cancer Res 1991;82(1):90–7.

16. Sausville EA, Burger AM. Contributions of human tumor xenografts to anticancer drug development. Cancer Res 1996;56(9):2434–9.

17. Khaled WT, Liu P. **Cancer mouse models: past, present and future.** Semin Cell Dev Biol 2014;27:54–60.

18. Kotanagi H, Saito Y, Yoshioka T, Koyama K. Characteristics of two cancer cell lines derived from metastatic foci in liver and peritoneum of a patient with colon cancer. Journal of Gastroenterology 1998;33(6):842–9.

19. Flatmark K, Davidson B, Kristian A, Stavnes HT, Forsund M, Reed W. Exploring the peritoneal surface malignancy phenotype: a pilot immunohistochemical study of human pseudomyxoma peritonei and derived animal models. Hum Pathol 2010;41(8):1109–19.

20. Navarro-Alvarez N, Kondo E, Kawamoto H, Hassan W, Yuasa T, Kubota Y, et al. Propagation of a human CD133(+) colon tumor-derived cell line with tumorigenic and angiogenic properties. Cell Trans 2010;19(6–7):865–77.

21. Abdul-Wahid A, Huang EHB, Lu H, Flanagan J, Mallick AI, Gariepy J. A focused immune response targeting the homotypic binding domain of the carcinoembryonic antigen antibodies, the establishment of tumor foci in vivo. J Int Cancer 2012;33(12):2839–51.

22. Meredith AL. **Viral skin diseases of the rabbit.** Vet Clin North Am Exot Anim Pract 2013;16(3):705–14.

23. Tang L, Duan R, Zhong YJ, Firestone RA, Hong YP, Li JG, et al. Synthesis, identification and in vivo studies of tumor-targeting agent peptide doxorubicin (PDOX) to treat peritoneal carcinomatosis of gastric cancer with similar efficacy but reduced toxicity. Mol Cancer 2016;15(1):13–44.

24. Tang L, Mei L-J, Yang X-J, Huang C-Q, Zhou Y-F, Yonemura Y, et al. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy improves survival of gastric cancer with peritoneal carcinomatosis: evidence from an experimental study. J Trans Med 2011;9:53.

25. Turner JR, Rose AH, Glancy RJ, Penhale WJ. **Orthotopic xenografts of human melanoma and colonic and ovarian carcinoma in sheep to evaluate radiomunotherapy.** Br J Cancer 1998;78(4):486–94.

26. Hewett PJ, Thomas WM, King G, Eaton M. Intrapерitoneal cell movement during abdominal carbon dioxide insufflation and laparoscopy – an in vivo model. Dis Colon Rectum 1996;39(10):562–566.

27. Cespedes MV, Espina C, Garcia-Cabezaz MA, Trías M, Boluda A, Gomez del Pulgar MT, et al. Orthoptopic microinjection of human colon cancer cells in nude mice induces tumor foci in all clinically relevant metastatic sites. Am J Pathol 2007;170(3):1077–85.

28. Cespedes MV, Larribia MJ, Pavon MA, Alamo P, Casanova I, Parreno M, et al. Site-dependent E-cadherin cleavage and nuclear translocation in a metastatic colorectal cancer model. Am J Pathol 2010;177(4):2067–79.

29. Puig I, Chicote I, Tenbaum SP, Arques O, Herance JR, Gispert JD, et al. A personalized preclinical model to evaluate the metastatic potential of patient-derived colon cancer initiating cells. Clin Cancer Res 2013;19(24):6787–801.

30. Gremonprez F, Descamps B, Izmer A, Vanhove C, Vanhaecke F, De Wever O, et al. Pretreatment with VEGF(R)-inhibitors reduces interstitial fluid pressure, increases intraperitoneal chemotherapy drug penetration, and impedes tumor growth in a mouse colorectal carcinomatosis model. Oncotarget 2015;6(30):29889–900.

31. Chen C, Peng J, Sun SR, Peng CW, Li Y, Pang DW. **Tapping the potential of quantum dots for personalized oncology: current status and future perspectives.** Nanomedicine (Lond 2012;7(3):411–28.

32. Mikula-Pietrasik J, Sosinska P, Maksin K, Kucinska M, Piotrowska H, Murias M, et al. Colorectal cancer-promoting activity of the senescent peritoneal mesothelium. Oncotarget 2015;6(30):29178–95.

33. Inoue T, Tashiro Y, Takeuchi M, Otani T, Tsuji-Takayama K, Okochi A, et al. Potential anti-tumor killing activity of the multifunctional Treg cell line HOZOT against human tumors with diverse origins. Int J Oncol 2011;38(5):1299–306.

34. Lubbe WJ, Zuzga DS, Zhou Z, Fu W, Pelta-Heller J, Muschel RJ, et al. Guanylyl cyclase C prevents colon cancer metastasis by regulating tumor epithelial cell matrix metalloproteinase-9. Cancer Res 2009;69(8):3529–36.

35. Harada N, Mizoi T, Kinouchi M, Hoshi K, Ishii S, Shibira K, et al. Introduction of antisense CD44S cDNA down-regulates expression of overall CD44 isoforms and inhibits tumor growth in highly metastatic colon carcinoma cells. Int J Cancer 2001;91(1):67–75.

36. Sakamoto M, Takamura M, Itou Y, Miura A, Genda T, Hirohashi S. **Involvement of c-Src in carcinoma cell motility and metastasis.** Jpn J Cancer Res 2001;92(9):941–6.
37. Watson SA, Morris TM, Parsons SL, Steele RJ, Brown PD. Therapeutic effect of the matrix metalloproteinase inhibitor, batimastat, in a human colorectal cancer ascites model. Br J Cancer 1996;74(9):1354–8.

38. Yasui N, Sakamoto M, Ochiai A, Ino Y, Akimoto S, Orikasa A, et al. Tumor growth and metastasis of human colorectal cancer cell lines in SCID mice resemble clinical metastatic behaviors. Invasion Metastasis 1997;17(5):259–69.

39. Wang W, Chen Y, Deng J, Zhou J, Gu X, Tang Y, et al. Cullin1 is a novel prognostic marker and regulates the cell proliferation and metastasis in colorectal cancer. J Cancer Res Clin Oncol 2015;141(9):1603–12.

40. Takemoto K, Shiozaki A, Ichikawa D, Komatsu S, Konishi H, Tanaka K, Okugawa Y, Toiyama Y, Inoue Y, Saigusa S, Amini A, Masoumi-Moghaddam S, Ehteda A, Liauw W, Morris DL. Identification of the interplay between SOX9 and S100P in peritoneal carcinomatosis model. J Trans Med 2015;13:195.

41. Lee AL, Ng VW, Gao S, Hedrick JL, Yang YY. Injectable polycarbonates for the delivery of Avastin with enhanced biodegradable hydrogels from vitamin D-functionalized personalized medicine. J Trans Med 2015;13:195.

42. Liu M, Xu A, Yuan X, Zhang Q, Fang T, Wang W, et al. Downregulation of microRNA-409-3p promotes aggressiveness and metastasis in colorectal cancer: an indication for personalized medicine. J Trans Med 2015;13:195.

43. Rijpkema M, Oyen WJ, Bos D, Franssen GM, Goldenberg DM, Boerman OC. Combination therapy using gemcitabine and radioimmunotherapy in nude mice with small peritoneal metastases of colon cancer. Cancer Immunol Immunother 2010;59(4):632–8.

44. Li X-F, Ma Y, Sun X, Humm JL, Ling CC, O’Donoghue JA. High F-18-FDG uptake in microscopic peritoneal tumors requires physiologic hypoxia. J Nucl Med 2010;51(4):632–8.

45. Pan K-L, Fu Y, Ou Yang F, Sih-H L, Chan K-H. Cationic liposome coupled endostatin gene for treatment of peritoneal cancer. Clin Exp Metastasis 2010;27(5):307–18.

46. Hackl C, Lang SA, Moser C, Mori A, Fichtner-Feigl S, Hellerbrand C, et al. Activating transcription factor-3 (ATF3) functions as a tumor suppressor in colon cancer and is up-regulated upon heat-shock protein 90 (Hsp90) inhibition. BMC Cancer 2010;10:668.

47. Wagner M, Roh V, Streihlen M, Laemmle A, Stroka D, Egger B, et al. Effective treatment of advanced colorectal cancer by ramapycin and 5-FU/oxaliplatin monitored by TIMP-1. J Gastrointest Surg 2009;13(10):1781–90.

48. Kishimoto H, Zhao M, Hayashi K, Urata Y, Tanaka N, Fujiwara T, et al. In vivo internal tumor illumination by telomerase-dependent adenoviral GFP for precise surgical navigation. Proc Natl Acad Sci U S A 2009;106(34):14514–17.

49. Li X-F, Carlin S, Urano M, Russell J, Ling CC, O’Donoghue JA. Visualization of hypoxia in microscopic tumors by immunofluorescent microscopy. Cancer Res 2007;67(16):7646–53.

50. Kinuya S, Yokoyama K, Sasaki T, Sasahira T, Fujii K, Ohmori H, et al. Intraportal radioimmunotherapy to treat the early phase of peritoneal dissemination of human colon cancer cells in a murine model. Nucl Med Commun 2007;28(2):129–33.

51. Lie J-Z, Wang J-W, Qu J-G, Hung T. Suppression of human colon tumor growth by adenoviral vector-mediated NK4 expression in an athymic mouse model. World J Gastroenterol 2007;13(1):1938–46.

52. Shen Y, Hero R, Doxey BW, Xu C, Gray PD, Kuwada SK. Pharmacologic downregulation of c-FIPI, restores juxtacrine death receptor-mediated apoptosis in cancer cells in a peritoneal carcinomatosis model. Int J Cancer 2012;130(7):1494–503.

53. Nayak TK, Garmestani K, Milenic DE, Brechbiel MW. PET and MRI of metastatic peritoneal and pulmonary colorectal cancer in mice with human epidermal growth factor receptor 1-targeted Zr-89-labeled panitumumab. J Nucl Med 2012;53(1):113–20.

54. Ziauddin MF, Guo ZS, O’Malley ME, Austin F, Popovic P, Kavanagh MA, et al. TRAIL gene-armed oncolytic poxvirus and oxaliplatin can work synergistically against colorectal cancer. Gene Ther 2010;17(4):550–9.

55. Straza MW, Paliwal S, Kovi RC, Rajeshkumar B, Trenh P, Parker D, et al. Therapeutic targeting of C-terminal binding protein in human cancer. Cell Cycle 2010;9(18):3740–50.
cyclooxygenase-2 inhibitor Parecoxib and radioimmunotherapy in nude mice with small peritoneal metastases of colonic origin. Cancer Immunol Immunother 2006;55(1):47–55.
68. Pourgholami MH, Akhter J, Wang L, Lu Y, Morris DL. Antitumor activity of albendazole against the human colorectal cancer cell line HT-29: in vitro and in a xenograft model of peritoneal carcinomatosis. Cancer Chemother Pharmacol 2005;55(5):425–32.
69. Kinuya S, Yokoyama K, Izumo M, Sorita T, Obata T, Mori H, et al. Locoreginal radioimmunotherapy with Re-186-labeled monoclonal antibody in treating small peritoneal carcinomatosis of colon cancer in mice in comparison with I-131-counterpart. Cancer Lett 2005;219(1):41–8.
70. Zeamari S, Roos E, Stewart FA. Tumour seeding in peritoneal wound sites in relation to growth-factor expression in early granulation tissue. Eur J Cancer 2004;40(9):1431–40.
71. Koppe MJ, Bleichrodt RP, Soede AC, Verhofstad AA, Goldenberg DM, Oyen WJG, et al. Biodistribution and therapeutic efficacy of I-125/131-, Re-186-, Y-88/90- or Lu-177-labeled monoclonal antibody MN-14 to carcinoembryonic antigen in mice with small peritoneal metastases of colorectal origin. J Nucl Med 2004;45(7):1224–32.
72. Favoulet P, Benoit L, Osmak L, Polycarpe E, Esquis P, Duvillard C, et al. Prevention of peritoneal carcinomatosis from colon cancer cell seeding using a pirarubicin solution in rats and nude mice. World J Surg 2004;28(5):451–6.
73. Koppe E, Soede AC, Pels W, Oyen WJG, Goldenberg DM, Bleichrodt RP, et al. Experimental radioimmunotherapy of small peritoneal metastases of colorectal origin. Int J Cancer 2003;106(6):965–72.
74. Kinuya S, Li XF, Yokoyama K, Mori H, Shiba K, Watanabe N, et al. Intraperitoneal radioimmunotherapy in treating peritoneal carcinomatosis of colon cancer in mice compared with systemic radioimmunotherapy. Cancer Sci 2003;94(7):650–4.
75. Stoeltzing O, Ahmad SA, Liu W, McCarty MF, Parikh AA, Fan F, et al. Angiopoietin-1 inhibits tumor growth and ascites formation in a murine model of peritoneal carcinomatosis. Br J Cancer 2002;87(10):1182–7.
76. Fan YF, Huang ZH. Angiogenesis inhibitor TNP-470 suppresses growth of peritoneal disseminating foci of human colon cancer line Lovo. World J Gastroenterol 2002;8(5):853–6.
77. Hubbard SC, Burns JW. Effects of a hyaluronan-based membrane (Seprafilm (R)) on intraperitoneally disseminated human colon cancer cell growth in a nude mouse model. Dis Colon Rectum 2002;45(3):334–41.
78. Shaheen RM, Ahmad SA, Liu W, Reinmuth N, Jung YD, Tseng WW, et al. Inhibited growth of colon cancer carcinomatosis by antibodies to vascular endothelial and epidermal growth factor receptors, Br J Cancer 2001;85(4):584–9.
79. Goto H, Osaki T, Kijima T, Nishino K, Kumagai T, Funakoshi T, et al. Gene therapy utilizing the Cre/loxP system selectively suppresses tumor growth of disseminated carcinoembryonic antigen-producing cancer cells. Int J Cancer 2001;94(3):436–19.
80. Kondo Y, Arii S, Mori A, Furutani M, Chiba T, Imamura M. Enhancement of angiogenesis, tumor growth, and metastasis by transfection of vascular endothelial growth factor into LoVo human colon cancer cell line. Clin Cancer Res 2000;6(2):622–30.
81. Crosasso P, Brusa P, Dosio F, Arpicco S, Pacchioni D, Schuber F, et al. Antitumoral activity of liposomes and immunoliposomes containing 5-fluorouridine prodrugs. J Pharm Sci 1997;86(7):832–9.
82. Asao T, Nagamachi Y, Morinaga N, Shitara Y, Takenoshita S, Yazzawa S. Fucosyl-transferases of the peritoneum contributed to the adhesion of cancer-cells to the mesothelium. Cancer 1995;75(6):1539–44.
83. Quadri SM, Malik AB, Tang XZ, Patenia R, Freedman RS, Vriesendorp HM. Preclinical analysis of intraperitoneal administration of in-111-labeled human tumor reactive monoclonal IGM AC6C3-2812. Cancer Res 1995;55(23):55736–55742.
84. Harlaar NJ, Hesselink JW, de Jong JS, van Dam GM. Bioluminescence as Gold Standard for Validation of Optical Imaging Modalities in Peritoneal Carcinomatosis Animal Models. Eur Surg Res 2010;45(3–4):308–13.
85. Mahteme H, Sundin A, Larsson B, Khamis H, Arow K, Graf W. 5-FU uptake in peritoneal metastases after pretreatment with radioimmunotherapy or vasoconstriction: an autoradiographic study in the rat. Anticancer Res 2005;25(2A):917–22.
86. Carpentieri S, Sampurso N, Bernardi M-P, Germann M, Malaterre J, Heriot A, et al. Inflammation are ameliorated by humidified-warm carbon dioxide insufflation in the mouse. Ann Surg Oncol 2015;22:S1540–S1547.
87. Zhang W, Cui T, Liu L, Wu Q, Sun L, Li L, et al. Improving anti-tumor activity of curcumin by polymeric micelles in thermosensitive hydrogel system in colorectal peritoneal carcinomatosis model. J Biomed Nanotechnol 2015;11(7):1173–82.
88. Ryan AE, Colleran A, O’Gorman A, O’Flynn L, Pindjacova J, Lohan P, et al. Targeting colon cancer cell NF-kappa B promotes an anti-tumour M1-like macrophage phenotype and inhibits peritoneal metastasis. Oncogene 2015;34(12):1563–74.
89. Zhang D, Zheng L, Shi H, Chen X, Wan Y, Zhang H, et al. Suppression of peritoneal tumorigenesis by placenta-derived mesenchymal stem cells expressing endostatin on colorectal cancer. Int J Med Sci 2014;11(9):870–9.
90. Fan R, Wang Y, Han B, Luo Y, Zhou L, Peng X, et al. Docetaxel load biodegradable porous microspheres for the treatment of colorectal peritoneal carcinomatosis. Int J Biol Macromol 2014;69:100–7.
91. Sedlacek AL, Gerber SA, Randall TD, van Rooijen N, Frelinger JG, Lord EM. Generation of a dual-functioning antitumor immune response in the peritoneal cavity. Am J Pathol 2013;183(4):1318–28.
92. Liu L, Wu Q, Ma X, Xiong D, Gong C, Qian Z, et al. Camptothecin encapsulated composite drug delivery system for colorectal peritoneal carcinomatosis therapy: Biodegradable microsphere in thermosensitive hydrogel. Colloids Surf B Biointerfaces 2013;106:93–101.
93. Li W, Wu K, Zhao E, Shi L, Li R, Zhang P, et al. HMGB1 recruits myeloid derived suppressor cells to promote peritoneal dissemination of colon cancer after resection. Biochem Biophys Res Commun 2013;436(2):156–61.
94. Yao Y, Su X, Xie Y, Wang Y, Kang T, Gou L, Yi C, et al. Synthesis characterization, and antitumor evaluation of the albumin-SN38 conjugate. Anti-Cancer Drugs 2013;24(3):270–7.
model of peritoneal dissemination of colorectal cancer. J Surg Res 2013;180(2):252–9.

97. Wu QJ, Gong CY, Luo ST, Zhang DM, Zhang S, Shi HS, et al. AAV-mediated human PEDF inhibits tumor growth and metastasis in murine colorectal peritoneal carcinomatosis model. BMC Cancer 2012;12:129.

98. Lehmann K, Rickenbacher A, Jang J-H, Oberkofler CE, Vonlanthen R, von Boehmer L, et al. New insight into hyperthermic intraperitoneal chemotherapy induction of oxidative stress dramatically enhanced tumor killing in vitro and in vivo models. Ann Surg 2012;256(5):730–8.

99. Tsai C-C, Chang C-H, Chen L-C, Chang Y-J, Lan K-L, Wu QJ, et al. Preparation of retroviral vector producer cells in three-dimensional adipose tissue scaffolds for potential use in cancer gene therapy. J Biomed Mater Res Part B Appl Biomater 2007;80B(3):59–66.

100. Puskas J, Skrombolas D, Sedlacek A, Lord E, Sullivan M, Kulu Y, Dorfman JD, Kuruppu D, Fuchs BC, Goodwin JM, Fujii T, Tanaka H, Shinto O, Yashiro M, Yamazoe S, Iwauchi T, Dai M, Xu X, Song J, Fu S, Gou M, Luo F, et al. Preparation of camptothecin-loaded PCEC microspheres for the treatment of colorectal peritoneal carcinomatosis and tumor growth in mice. Cancer Lett 2011;312(2):189–96.

101. Puskaric A, Skrombolas D, Sedlacek A, Lord E, Sullivan M, Frelinger J. Development of an attenuated interleukin-2 fusion protein that can be activated by tumour-expressed proteases. Immunology 2011;133(2):206–20.

102. Dai M, Xu X, Song J, Fu S, Mao F, et al. Preparation of camptothecin-loaded PCEC microspheres for the treatment of colorectal peritoneal carcinomatosis and tumor growth in mice. Cancer Lett 2011;312(2):189–96.

103. Wang Y, Gong C, Yang L, Wu Q, Shi S, Shi H, et al. 5-FU-hydrogel inhibits colorectal peritoneal carcinomatosis and tumor growth in mice. BMC Cancer 2010;10:402.

104. Tanaka H, Shinto O, Yamazoe S, Iwauchi T, Muguruma K, et al. Transforming growth factor beta signaling inhibitor, SB-431542, induces maturation of dendritic cells and enhances anti-tumor activity. Oncol Rep 2010;24(6):1637–43.

105. Keese M, Yagublu V, Schwenke K, Post S, Bastiaens P. Fluorescence lifetime imaging microscopy of chemotherapy-induced apoptosis resistance in a syngeneic mouse tumor model. Int J Cancer 2010;126(1):104–13.

106. Kulu Y, Dorfman JD, Kuruppu D, Fuchs BC, Goodwin JM, Fuji T, et al. Comparison of intravenous versus intraperitoneal administration of oncolytic herpes simplex virus 1 for peritoneal carcinomatosis in mice. Cancer Gene Ther 2009;16(4):291–7.

107. Keese M, Gasimova L, Schwenke K, Yagublu V, Shang E, Faissner R, et al. Doxorubicin and mitoxantrone drug eluting beads for the treatment of experimental peritoneal carcinomatosis in colorectal cancer. Int J Cancer 2009;124(1):2710–8.

108. Lan K-L, Yen S-H, Liu R-S, Shih H-L, Tseng F-W, Lan K-H. Mutant Bik gene transferred by cationic liposome inhibits peritoneal disseminated murine colon cancer. Clin Exp Metastasis 2007;24(6):661–70.

109. Hyoudou K, Nishikawa M, Ikemura M, Kobayashi Y, Mendelsohn A, Miyazaki N, et al. Cationized catalase-loaded hydrogel for growth inhibition of peritoneally disseminated tumor cells. J Controlled Release 2007;122(2):151–8.

110. Divir-Ginzberg M, Konson A, Cohen S, Agbaria R. Entrapment of retroviral vector producer cells in three-dimensional alginate scaffolds for potential use in cancer gene therapy. J Biomed Mater Res Part B Appl Biomater 2007;80B(3):59–66.

111. Hyoudou K, Nishikawa M, Kobayashi Y, Kuramoto Y, Yamashita F, Hashida M. Inhibition of adhesion and proliferation of peritoneally disseminated tumor cells by pegylated catalase. Clin Exp Metastasis 2006;23(5–6):269–78.

112. Helguera G, Rodriguez JA, Penichet ML. Cytokines fused to antibodies and their combinations as therapeutic agents against different peritoneal HER2/neu expressing tumors. Mol Cancer Ther 2006;5(4):1029–40.

113. Yu HK, Ahn JM, Lee HJ, Lee SK, Hong SW, Yoon Y, et al. Expression of human apolipoprotein(a) kringles in colon cancer cells suppresses angiogenesis-dependent tumor growth and peritoneal dissemination. J Gene Med 2005;7(2):39–49.

114. Yamaguchi K, Hirabayashi Y, Suematsu T, Shiraiishi N, Adachi Y, Kitano S. Hyaluronic acid secretion during carbon dioxide pneumoperitoneum and its association with port-site metastasis in a murine model. Surg Endosc 2001;15(1):59–62.

115. Miyata T, Yamamoto S, Sakamoto K, Morishita R, Kanedo Y. Novel immunotherapy for peritoneal dissemination of murine colon cancer with macrophage inflammatory protein-1 beta mediated by a tumor-specific vector, HV cationic liposomes. Cancer Gene Ther 2001;8(11):852–60.

116. Moreno EF, Nelson H, Carugno F, Hodge D, Mozes G, Thompson GB. Effects of laparoscopy on tumor growth. Surg Laparosc Endosc Percutan Tech 2000;27(3):296–301.

117. Maruyama M, Nagahama T, Yuasa Y. Intraperitoneal versus intravenous CPT-11 for peritoneal seeding and liver metastasis. Anticancer Res 1999;19(SB):4187–91.

118. Guichard S, Chatelut E, Lochoin I, Bugat R, Mahjoubi M, Canal P. Comparison of the pharmacokinetics and efficacy of intravenous administration by the intravenous versus intraperitoneal route in mice. Cancer Chemother Pharmacol 1998;42(2):165–70.

119. Kurihara H, Uchida J, Fujioka A, Kato T, Ohshimo H, Abe M, et al. Effect of combination therapy with UFT plus cisplatin (UFTP) on the survival of mice in the experimental model for wide-spread metastasis in the peritoneal cavity of gastrointestinal cancer using colon 26 PMF-15 cells. Anticancer Res 1997;17(1C):2217–20.

120. Gutman M, Zsold A, Ravid A, Lazauskas T, Merimsky O, Klausner JM. Failure of thalidomide to inhibit tumor growth and angiogenesis in vivo. Anticancer Res 1996;16(6B):3673–7.

121. Mayhew E, Cimino M, Klemperer J, Lazo R, Wiernikowski J, Arbuck S. Free and liposomal doxorubicin treatment of intraperitoneal colon-26 tumor – therapeutic and pharmacological studies. Semin Cancer Biol 1996;6(4):193–209.

122. Imano M, Itoha T, Satou T, Kido A, Tsukami M, Yasaki A, et al. Establishment of a Novel Model of Peritoneal Carcinomatosis of the Peritoneal Extension Type. Anticancer Res 2013;33(4):1439–46.

123. Eriksson SE, Ohlsson T, Nilsson R, Repeated TJ. Establishment of a Novel Model of Peritoneal Carcinomatosis of the Peritoneal Extension Type. Anticancer Res 2013;33(4):1439–46.

124. Mayhew E, Cimino M, Klemperer J, Lazo R, Wiernikowski J, Arbuck S. Free and liposomal doxorubicin treatment of intraperitoneal colon-26 tumor – therapeutic and pharmacological studies. Semin Cancer Biol 1996;6(4):193–209.

125. Moretto J, Chauffert B, Ghiringhelli F, Aldrich-Wright JR, Bouyer F. Discrepancy between in vitro and in vivo antitumor effect of a new platinum(II) metallointercalator. Invest New Drugs 2011;29(6):1164–70.
the treatment of peritoneal carcinomatosis: an experimental study. Ann Surg 2011;254(1):125–30.

126. Serafino A, Zonfrillo M, Andreola F, Psaila R, Mercuri L, Moroni N, et al. CD44-Targeting for Antitumor Drug Delivery: A New SN-38-Hyaluronan Bioconjugate for Locoregional Treatment of Peritoneal Carcinomatosis. Curr Cancer Drug Targets 2011;11(5):572–85.

127. Klaver VL, Hendriks T, Lomme RM, Rutten HJ, Bleichrodt RP, de Hingh IH. Intraoperative hyperthermic intraperitoneal chemotherapy after cytoreductive surgery for peritoneal carcinomatosis in an experimental model. Br J Surg 2010;97(12):1874–80.

128. van der Bij GJ, Bogels M, Oosterling SJ, Kroon J, Schuckmann DTM, de Vries HE, et al. Tumor infiltrating macrophages reduce development of peritoneal colorectal carcinoma metastases. Cancer Lett 2008;262(1):77–86.

129. Taguchi E, Nakamura K, Miura T, Shibuya M, Isoe T. Anti-tumor activity and tumor vessel normalization by the vascular endothelial growth factor receptor tyrosine kinase inhibitor KRN951 in a rat peritoneal disseminated tumor model. Cancer Sci 2008;99(3):623–30.

130. Oosterling SJ, van der Bij GJ, Boegels M, ten Raa S, Post JA, Meijer GA, et al. Anti-beta 1 integrin antibody reduces surgery-induced adhesion of colon carcinoma cells to traumatized peritoneal surfaces. Ann Surg 2008;247(1):85–94.

131. Aarts F, Hendriks T, Boerman OC, Oyen WJG, Bleichrodt RP. Hyperthermia and fibrinolytic therapy do not improve the beneficial effect of radioimmunotherapy following cytoreductive surgery in rats with peritoneal carcinomatosis of colorectal origin. Cancer Biother Radiopharm 2008;23(3):301–9.

132. Otto J, Jansen PL, Lucas S, Schumpelick V, Jansen M. Reduction of peritoneal carcinomatosis by intraperitoneal administration of phospholipids in rats. BMC Cancer 2007;7:104.

133. Hribaschek A, Meyer F, Schneider-Stock R, Pross M, Ridwelski K, Lippert H. Comparison of intraperitoneal with intravenous administration of taxol in experimental peritoneal carcinomatosis. Chemotherapy 2007;53(6):410–17.

134. Bobrich E, Braumann C, Opitz I, Menenakos C, Kristiansen G, Jacobi CA. Influence of intraperitoneal application of taurolidine/heparin on expression of adhesion molecules and colon cancer in rats undergoing laparoscopy. J Surg Res 2007;137(1):75–82.

135. Aarts F, Koppe MJ, Hendriks T, vanEerd JEM, Oyen WJG, Boerman OC, Bleichrodt RP. Timing of adjuvant radioimmunotherapy after cytoreductive surgery in experimental peritoneal carcinomatosis of colorectal origin. Ann Surg Oncol 2007;14(2):533–40.

136. Aarts F, Hendriks T, Boerman OC, Koppe MJ, Oyen WJG, Bleichrodt RP. A comparison between radioimmunotherapy and hyperthermic intraperitoneal chemotherapy for the treatment of peritoneal carcinomatosis of colonic origin in rats. Ann Surg Oncol 2007;14(11):3274–82.

137. Pelz JOW, Doerfer J, Dimmler A, Hohenberger W, Meyer T. Histological response of peritoneal carcinomatosis after hyperthermic intraperitoneal chemoperfusion (HiPEC) in experimental investigations. BMC Cancer 2006;6:162.

138. Oosterling SJ, van der Bij GJ, Bogels M, van der Sijp JRM, Beelen RJH, Meijer S, et al. Insufficient ability of omental milky spots to prevent peritoneal tumor outgrowth supports omentectomy in minimal residual disease. Cancer Immunol Immunother 2006;55(9):1043–51.

139. Nestler G, Schulz HU, Tautenhahn J, Kuhn R, Kruger S, Lippert H, et al. Effects of the angiogenesis inhibitor angiostatin on the growth of CC531 colon carcinoma cells in vitro and in a laparoscopic animal model of peritoneal carcinomatosis. Int J Colorectal Dis 2006;21(4):314–20.

140. Koppe MJ, Hendriks T, Boerman OC, Oyen WJG, Bleichrodt RP. Radioimmunotherapy is an effective adjuvant treatment after cytoreductive surgery of experimental colonic peritoneal carcinomatosis. J Nucl Med 2006;47(11):1867–74.

141. Hribaschek A, Kuhn R, Pross M, Meyer F, Fahike J, Ridwelski K, et al. Intraperitoneal versus intravenous CPT-11 given intra- and postoperatively for peritoneal carcinomatosis in a rat model. Surg Today 2006;36(2):57–62.

142. van den Tol P, ten Raa S, van Grevenstein H, Marquet R, van Eijck C, Jeekel H. Hicodextrin reduces postoperative adhesion formation in rats without affecting peritoneal metastasis. Surgery 2005;137(3):348–54.

143. Oosterling SJ, van der Bij GJ, Meijer GA, Tuk CW, van Garderen E, van Rooijen N, et al. Macrophages direct tumor histology and clinical outcome in a colon cancer model. J Pathol 2005;207(2):147–55.

144. Alkhamesi NA, Ziprin P, Pfistermuller K, Peck DH, Darzi AWICAM-. 1 mediated peritoneal carcinomatosis, a target for therapeutic intervention. Clin Exp Metastasis 2005;22(6):449–59.

145. Alkhamesi NA, Ridgway PF, Ramwell A, McCullough PW, Peck DH, Darzi AW. Peritoneal nebulizer: A novel technique for delivering intraperitoneal therapeutics in laparoscopic surgery to prevent locoregional recurrence. Surg Endosc 2005;19(8):1142–6.

146. Mahteme H, Larsson B, Sundin A, Khamis H, Graf W. Uptake of 5-fluouracil (5-FU) in peritoneal metastases in relation to the route of drug administration and tumour debulking surgery: an autoradiographic study in the rat. Eur J Cancer 2004;40(1):142–7.

147. Zayyan KS, Christie-Brown JS, Van Noorden S, Yiu CY, Sellu DP, Mathie RT. Rapid flow carbon dioxide laparoscopy disperses cancer cells into the peritoneal cavity but not the port sites in a new rat model. Surg Endosc 2003;17(2):273–7.

148. Opitz I, van der Veen HC, Braumann C, Ablassmaier B, Fuhrer K, Jacobi CA. The influence of adhesion prophylactic substances and taurolidine/heparin on local recurrence and intraperitoneal tumor growth after laparoscopic-assisted bowel resection of colon carcinoma in a rat model. Surg Endosc 2003;17(7):1098–104.

149. Hribaschek A, Pross M, Kuhn R, Kruger S, Ridwelski K, Halangk W, et al. Prevention and treatment of peritoneal carcinomatosis in experimental investigations with CPT-11 and oxaliplatin. Anti-Cancer Drugs 2002;13(6):605–14.

150. Gahlen J, Prosslt RL, Pietschmann M, Haase T, Rheinwald M, Skopp G, et al. Laparoscopic fluorescence diagnosis for intraabdominal fluorescence targeting of peritoneal carcinosis experimental studies. Ann Surg 2002;235(2):252–60.

151. van den Tol MP, Haverlag R, van Rossen MEE, Bonthuis F, Marquet RL, Jeekel J. Glove powder promotes adhesion formation and facilitates tumour cell adhesion and growth. Br J Surg 2001;88(9):1259–63.

152. Ban T, Wang JH, Wu QD, Kirwan WO, Redmond HP. Sodium hyaluronate enhances colorectal tumour cell metastatic potential in vitro and in vivo. Br J Surg 2001;88(2):246–50.
153. Hoffstetter W, Ortega A, Chiang M, Paik P, Beart RW. Effects of topical tumoricidal agents on port-site recurrence of colon cancer: An experimental study in rats. J Laparoendosc Adv Surg Tech A 2001;11(1):9–12.

154. Miyoshi C, Ohshima N. Vascular endothelial growth factor (VEGF) expression regulates angiogenesis accompanying tumor growth in a peritoneal disseminated tumor model. In Vivo 2001;15(3):233–8.

155. McCourt M, Wang JH, Sookhai S, Redmond HP. Taurolidine inhibits tumor cell growth in vitro and in vivo. Ann Surg Oncol 2000;7(9):685–91.

156. Hofstetter W, Ortega A, Chiang M, Brown B, Paik P, Youn P, et al. Abdominal insufflation does not cause hematogenous spread of colon cancer. J Laparoendosc Adv Surg Tech A 2000;10(1):1–4.

157. van Rossen MEE, Stoop MPO, Hofland LJ, van Koetsveld PM, Bonthuis F, Jeekel J, et al. Red blood cells inhibit tumour cell adhesion to the peritoneum. Br J Surg 1999;86(4):509–13.

158. Onier N, Hilpert S, Arnould L, Saint-Giorgio V, Davies JG, Bauer J, et al. Cure of colon cancer metastasis in rats with the new lipid A OM 174. Apoptosis of tumor cells and immunization of rats. Clin Exp Metastasis 1999;17(4):299–306.

159. Jacobi CA, Wildbrett P, Volk T, Muller JM. Influence of different gases and intraperitoneal instillation of antiadherent or cytotoxic agents on peritoneal tumor cell growth and implantation with laparoscopic surgery in a rat model. Surg Endosc 1999;13(10):1021–5.

160. Jacobi CA, Peter FI, Wenger FA, Ordemann J, Muller JM. New therapeutic strategies to avoid intra- and extraperitoneal metastases during laparoscopy: Results of a tumor model in the rat. Dig Surg 1999;16(5):393–9.

161. Gahlen J, Laubach HH, Stern J, Pietschmann M, Herfarth C. Improving diagnostic staging laparoscopy using intraperitoneal lavage of delta-aminolevulinic acid (ALA) for laparoscopic fluorescence diagnosis. Surgery 1999;126(3):469–73.