

## REVIEW ARTICLE

# Current status and future outlook for patient-derived cancer models from a rare cancer research perspective

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## Abstract

Rare cancers are a group of approximately 200 malignancies with extremely low incidences and with a wide variety of genotypes and phenotypes. Collectively, they are more common than any single malignancy. However, given the small numbers of individuals diagnosed with rare cancers, it is difficult to design clinical trials with sufficient patient numbers. Therefore, few effective anticancer drugs have been developed, and evidence-based medicine is not always feasible for rare cancers. Consequently, their clinical outcomes are generally poorer. Cancer research requires adequate models that faithfully recapitulate molecular features and reproduce treatment responses of the original tumors. Such models allow us to focus on more efficacious drugs in the clinical studies. For rare cancers, patient-derived cancer models are particularly important because the enrollment of sufficient patients is rarely attainable within a reasonable period of time. However, extremely few models are available for rare cancers. For example, cell lines and xenografts are available for only a limited number of histological subtypes of sarcomas; therefore, most sarcoma research is performed without such models, and a lack of adequate cancer models causes a lag in therapeutic development. The establishment of novel rare cancer models will dramatically facilitate rare cancer research and treatment development in the near future. This review focuses on the status of patient-derived rare cancer models and discusses their pivotal problems and possibilities, using sarcomas as a representative rare cancer type. Multi-institutional collaboration will help address the scarcity of patient-derived rare cancer models.

## KEYWORDS

genomics, patient-derived cancer model, precision medicine, predictive biomarker, rare cancer

## 1 | INTRODUCTION

Approximately 200 different malignancies with incidences of <6 per 100 000 per year are defined as rare cancers.<sup>1,2</sup> While more common cancers are named for their original histology and organs of origin, rare cancers have different nomenclature. Rare cancers are actually far more common than their name implies; they account for 24% of

all malignancies in Europe,<sup>2</sup> 15% in Japan,<sup>3</sup> and 25% in the USA.<sup>4</sup> Thus, rare cancers combined are more common than any other single malignancy, and from this overall perspective, they are not rare. The fact that there are few patients with each type of rare cancer poses multiple problems in clinical practice. For example, a centralized expert review revealed considerable inconsistencies in diagnoses,<sup>5-7</sup> which interferes with the performance of evidence-based

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medicine.<sup>8</sup> For this reason, and others discussed later, the development of novel anticancer drugs for rare cancers lags behind that for other cancers. As a consequence, overall survival is shorter for rare cancers than for common cancers at all times after diagnosis.<sup>1</sup> In the last two decades, many innovative treatments have been generated, with an average of 24 oncology drugs approved annually by the US Food and Drug Administration (FDA) between 2014 and 2019.<sup>9</sup> However, for sarcomas as an example of rare cancers, only a total of 13 anticancer drugs have been shown to have sufficient efficacy to merit FDA approval.<sup>10</sup> This is a common situation for rare cancers; therefore, it is important to elucidate the factors underlying their poor clinical outcomes.

Patient-derived cancer models, including cell lines, organoids, and xenografts, are pivotal tools in cancer research. They allow the study of gene function, screening of the antitumor effects of novel agents, and validation of cancer biology and treatments. Recently, such models have increased in popularity, as shown by an increase in the number of papers using the PubMed search term “patient-derived” (Figure 1). This reflects the increase in the expectation, among researchers, that models derived from original tumors are required for modern cancer research, and global projects and consortia have been organized to reinforce the use of such models. For example, the effective drugs, drug-to-genetic background interactions, and biomarkers have been identified in the recent large-scale projects which implemented panels of several hundred patient-derived cancer cells of multiple cancer types.<sup>11–19</sup> To generate and share patient-derived xenografts (PDXs), an international network of partners in Europe and the USA has been established by the EurOPDX consortium.<sup>20</sup> This network has made freely available approximately 800 PDXs for six cancer types for transnational access. The US National Cancer

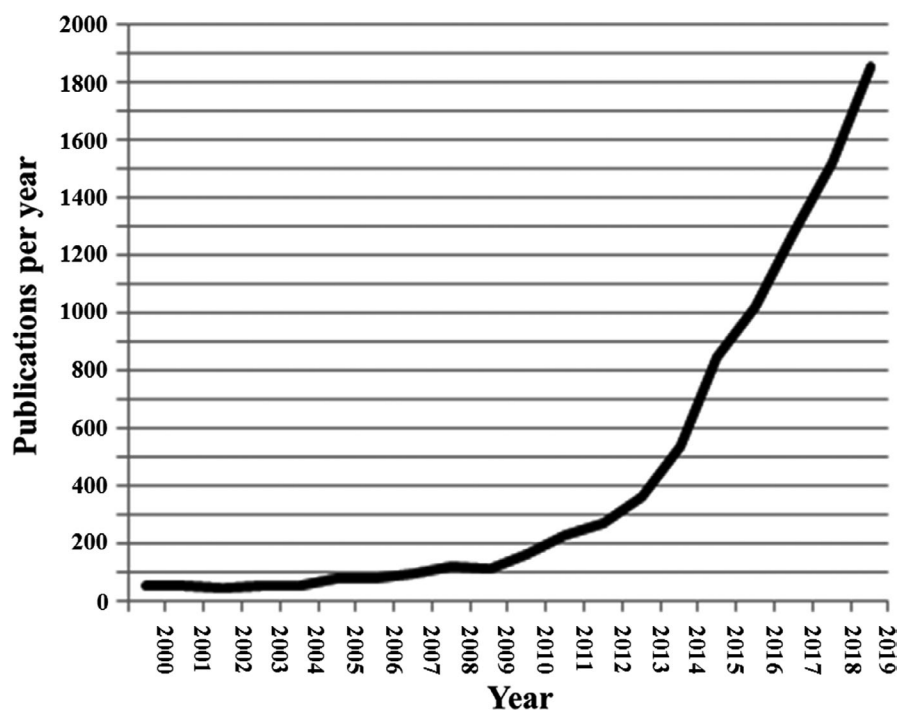
Institute Patient-Derived Models Repository (PDMR)<sup>21</sup> has established well-annotated PDX collections for provision to researchers presently in the USA. While patient-derived cancer models have multiple utilities, their use is now especially focused on improving the drug development process.<sup>22–24</sup>

Patient-derived cancer models are especially important for rare cancers, for which sufficient patient enrollment is more difficult to attain for clinical trials; therefore, high-quality preclinical studies are required to focus on the more promising anticancer drugs. However, the availability of such rare cancer models is highly limited, whether from public biobanks or for-profit companies. It is striking that this paucity of adequate models is a common issue for all rare cancers and is the root cause of the relative lack of effective and approved treatments.

In this article, the past and present status of patient-derived cancer models is reviewed, and critical problems in cancer models are highlighted. Using sarcomas as an example, concrete examples of the issues related to patient-derived rare cancer models are then summarized and discussed. This review will provide insights into how the future of rare cancer research can be improved via the generation of novel cancer models for rare cancers.

## 2 | WHY DO PATIENT-DERIVED CANCER MODELS CURRENTLY RECEIVE INTENSIVE RESEARCH FOCUS?

Recently, more than one thousand papers have been published annually on the development and/or use of patient-derived cancer models (Figure 1). This trend may evoke a sense of déjà vu for many oncologists and researchers because the clinical utility of

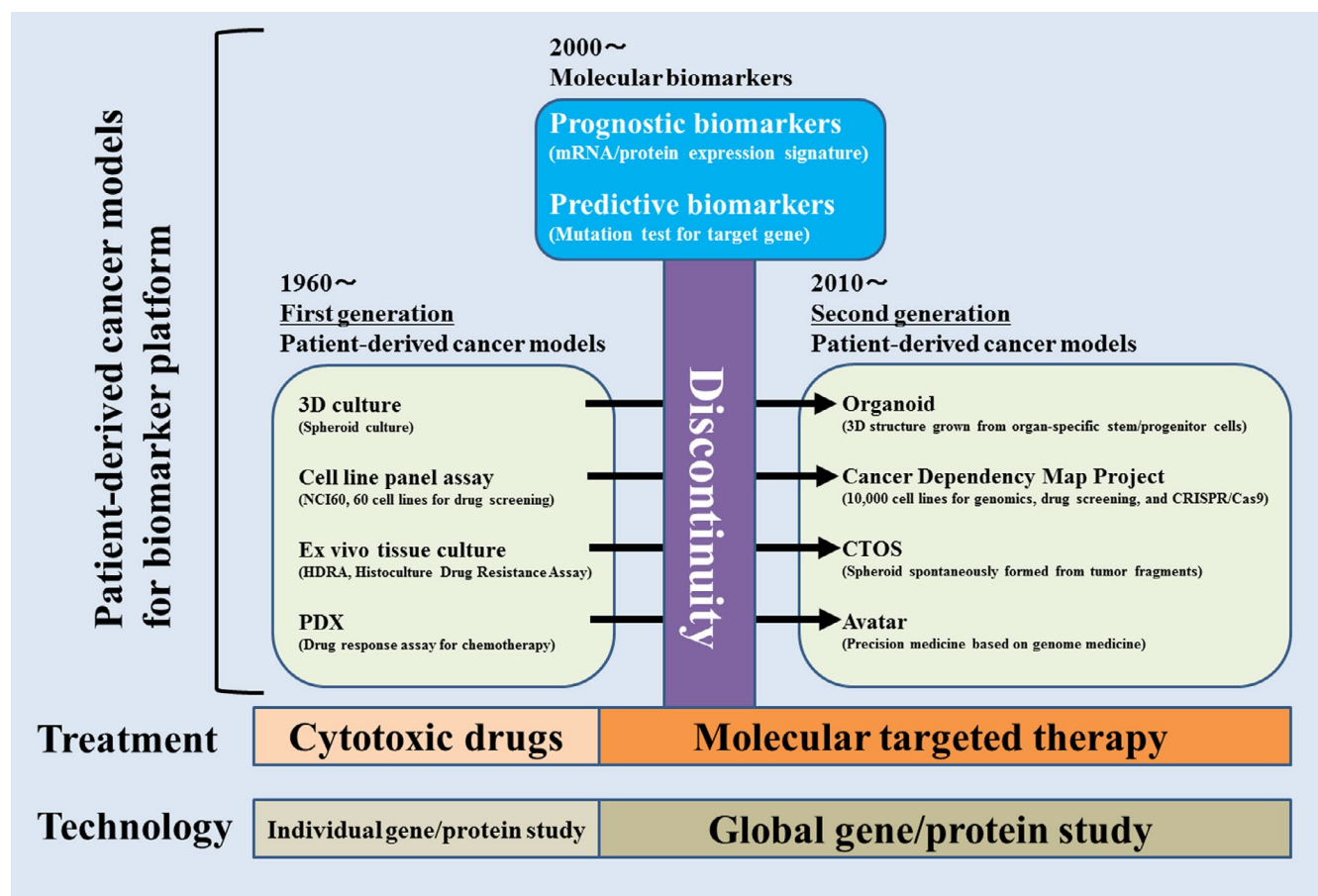


**FIGURE 1** Number of publications on patient-derived cancer models as a function of time based on the search results by PubMed. This graph demonstrates the increasing prevalence of the word “patient-derived” in academic articles, suggesting growing research interest in this field. Although many cell lines are derived from patients, investigators have tended not to focus on the sources of cell lines

patient-derived models such as cell lines, spheroids, and xenografts was extensively interrogated before the 2000s. The historical view of patient-derived cancer models is summarized in Figure 2 and Appendix S1 (Supplementary Information: Overview of traditional and current patient-derived cancer models). The history of patient-derived cancer models goes back to the 1950s and 1960s, when many *in vitro* and *in vivo* models were developed and applied to cancer research; the principles of all present cancer models were established at that time. For example, the establishment of cancer cell lines led to various types of cancer research, and short-term monolayer cultures (2D cultures) of biopsied tumor tissues enabled the identification of combination therapies for patients with acquired resistance.<sup>25</sup> It is noteworthy that,<sup>26</sup> in the 1970s, a panel of cell lines derived from multiple cancer types was systematically implemented in anticancer drug screening. The US National Cancer Institute (NCI)-60 Human Tumor Cell Line Screen was created to identify novel compounds that inhibit the growth of, or kill, 60 tumor cell lines.<sup>26</sup> By applying pattern recognition algorithms, NCI-60 allows the researcher to assign putative mechanisms of action to candidate compounds to better assess their similarity to known drugs. Recently, cell line panel screens have been conducted that include hundreds of cell lines and thousands of compounds, integrating data from

genomics and CRISPR-Cas9 screening; the Cancer Dependency Map contains examples of these screens.<sup>11–19</sup> Further, a pattern recognition approach has been developed to study the use of global mRNA expression data for speculating the activity of novel drugs in specific cancer types, leading to the production of a Connectivity Map.<sup>27</sup>

Spheroids, three-dimensional multicellular structures, were used as *in vitro* models of tumor tissues in the 1970s<sup>28</sup> and were later further developed as organoids, which are three-dimensional structures grown from organ-specific stem or progenitor cells. The potential of organoids for drug screening and personalized medicine has been suggested for many diseases, including malignancies.<sup>29</sup> Inoue et al reported a novel method, using cancer tissue-originated spheroids (CTOSs), in which cell-cell contacts are maintained throughout preparation and culture.<sup>30</sup> Its potential for drug development was demonstrated by the screening of 2427 drugs in the CTOS panel from 30 cases of colorectal cancer.<sup>31</sup> *Ex vivo* cultures, using tumor tissue obtained via surgery and biopsy, have been conducted since the 1950s<sup>32,33</sup> and have been used to evaluate responses to chemotherapeutic agents, demonstrating concordance with clinical observations.<sup>34</sup> The first PDXs were reported by Rygaard and Povlsen<sup>35</sup> in 1969, using tumor tissues from a patient with colorectal cancer. Fiebig et al<sup>36</sup> demonstrated that



**FIGURE 2** Contrasts between past and present patient-derived cancer models. The characteristics of each model are summarized in Appendix S1

the drug response of xenografts accurately predicted tumor sensitivity and resistance. Later, the patient-derived orthotopic xenograft (PDOX) model was reported to recapitulate the features of original tumors better than conventional subcutaneous transplantation models.<sup>37,38</sup> It is noteworthy that the implementation of PDXs in phase II clinical trials was challenged even in the 1990s.<sup>39</sup> Now, after 20 years of inattention, it is expected that PDXs will be ideal tools for drug development, drawing global attention from the research community.<sup>20,21</sup> They are expected to lead to rapid acceleration in drug development.<sup>19,40,41</sup>

The revived trend in the use of cancer models is attributable to an increased awareness of the limitations of molecular biomarkers. The idea that the clinical behavior of tumors could be associated with molecular biomarkers is very attractive and led to great excitement in our research community. Based on expectations arising from the development of omics techniques, the further development and application of cancer models stopped, or at least slowed in the 2000s (Figure 2). Thereafter, novel diagnostic and/or prognostic biomarkers were zealously developed using omics technologies, and were reported in thousands of papers, furthering our knowledge of cancer biology and demonstrating promise after extensive validation.<sup>42</sup> However, these biomarkers have not yet, overall, had the large expected impact on clinical practice. In parallel, drugs targeted to specific molecules have been introduced to clinical practice, with many reports that specific mutations in target genes are highly predictive of efficacy; examples include imatinib in chronic myeloid leukemia<sup>43</sup> and gastrointestinal stromal tumors,<sup>44</sup> as well as gefitinib in non-small cell lung cancer (NSCLC),<sup>45</sup> published in the early 2000s. Since then, many combinations of targeted drugs and mutation biomarkers have been published, making genomic medicine nearly synonymous with precision medicine; predictive molecular biomarkers were included in 39% of global oncology trials in 2018.<sup>46</sup> However, it appears that the utility of genome-based biomarkers is highly lineage-dependent. For example, although the oncogenic *BRAF*<sup>V600E</sup> mutation predicts the efficacy of vemurafenib treatment for melanoma,<sup>47</sup> hairy cell leukemia,<sup>48</sup> and NSCLC,<sup>49</sup> a phase II basket trial revealed that targeting *BRAF*<sup>V600E</sup> did not yield the expected results in colorectal cancers.<sup>50</sup> Similarly, while the overexpression of epidermal growth factor receptor has been associated with a favorable response to gefitinib in NSCLC, a phase II trial demonstrated that this was not the case for synovial sarcomas.<sup>51</sup> In addition, although the HER2-targeting therapeutic trastuzumab is of clinical benefit to patients with HER2-overexpressing breast cancers,<sup>52</sup> it did not show any clinical activity in patients with metastatic HER2-positive osteosarcomas in a phase II trial.<sup>53</sup> Such examples are too numerous to list in detail; overall, the same types of mutations are not always associated with favorable responses to corresponding therapies targeting those mutations. These observations are concordant with a lineage-dependency model in which cancer biology is linked to, and influenced by, the lineage and differentiation states of tumor precursor cells.<sup>54</sup> Equally importantly, because tumor tissues consist of multiple cell populations and

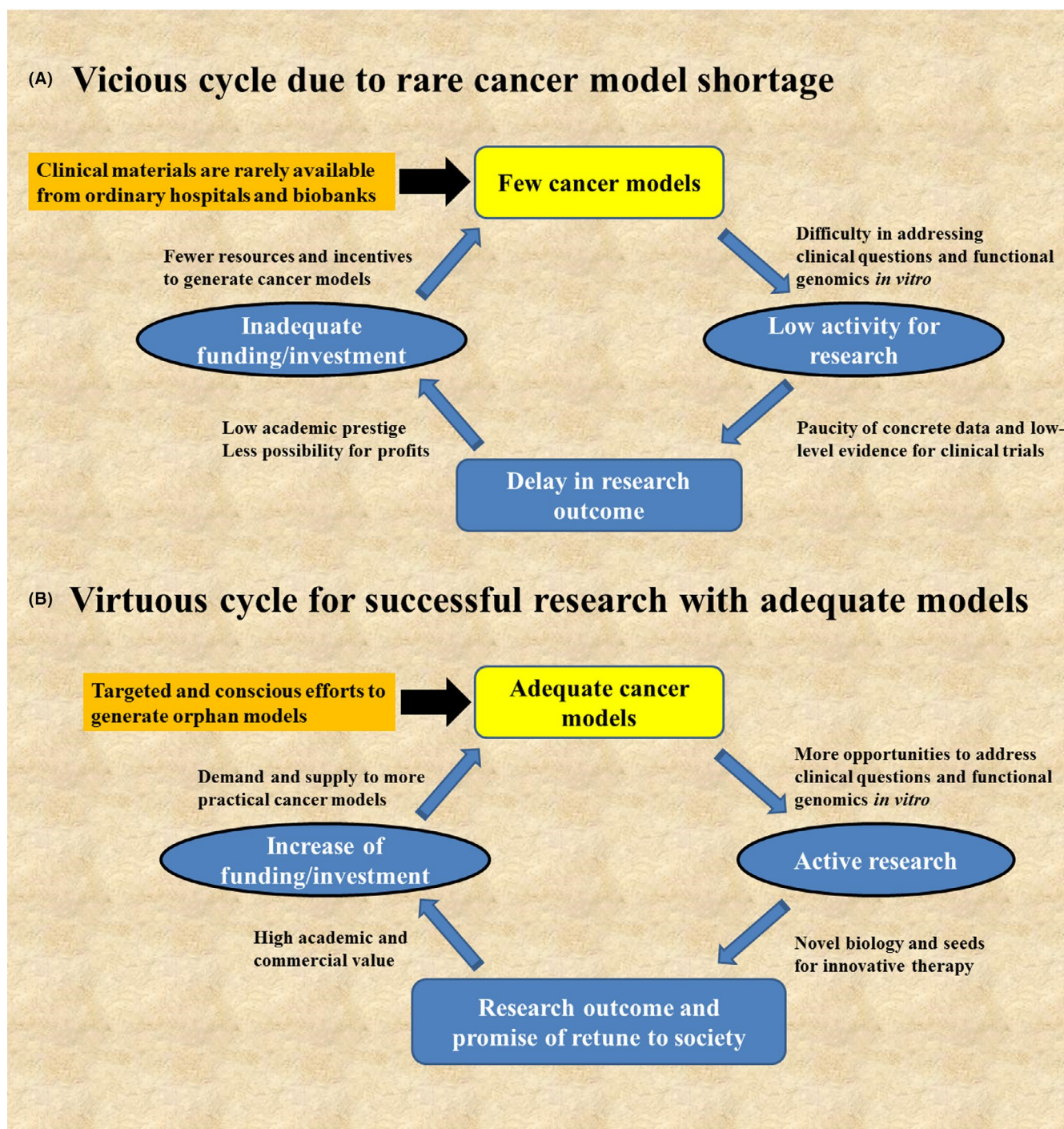
evolve in response to the selection imposed on them by treatment, genetic tests at particular time points have inherent limitations.<sup>55</sup> Overall, off-protocol use of unapproved targeted drugs based on mutation data did not outperform conventional therapies,<sup>56</sup> with genome-driven oncology benefiting only a small percentage of patients with advanced cancer.<sup>57</sup> Taken together, the predictive utility of genetic testing remains confined to a minority of patients, with the mutation-to-response relationship for a given cancer type only valid as an interim hypothesis until tested by rigorous clinical trials.

Given this notion, patient-derived cancer models were revived as a platform for predictive biomarkers, in the 2010s (Figure 2), representing a transition away from reductionism toward holism. The expectation, widely supported by the genetic and phenotypic data, was that patient-derived cancer models would faithfully capture the genetic and phenotypic features of tumor cells. However, the poor predictive value of preclinical cancer models has been made clear<sup>58–60</sup>; otherwise, the molecular biomarkers would not have been so enthusiastically welcomed in the early 2000s. It has been pointed out that the studies using cancer models had fundamental problems: protocols were not sufficiently detailed, reasonable sample criteria for inclusion and exclusion were not employed, only a small number of cases with specific cancer types were examined, they were not reproduced by other researchers, and the materials were not shared within the research community.<sup>61</sup> These issues date back to the earliest uses of patient-derived cancer models; there has long been a lack of prospective and randomized studies with sufficient numbers of patients for statistical evaluation, preventing the clinical utility of these models from being demonstrated. These old problems should be addressed using modern technology, insights obtained from biomarker studies, and community efforts.

### 3 | PATIENT-DERIVED RARE CANCER MODELS: SARCOMAS AS AN EXAMPLE

Despite their clinical importance and long history, patient-derived cancer models are not generally available for rare cancers. I will use sarcomas as an example of the current situation. Sarcomas are mesenchymal malignant neoplasms that account for less than 1% of total malignancies. There are more than 50 different histological sarcoma subtypes, with different clinical behaviors and responses to treatment.<sup>62</sup> Sarcoma classification is mainly based on histological similarities to normal mesenchymal tissues; the origins of many sarcomas remain to be elucidated. Sarcomas are grouped by their molecular profiles: some are characterized by typical chromosomal rearrangements, with some lacking typical chromosomal aberrations but with genetic instability and multiple mutations.<sup>63</sup> Although sarcomas are diverse and complex diseases, given the small number of sarcoma patients, they tend to be pooled together in clinical studies,<sup>64</sup> so the development of sarcoma therapeutics has lagged behind those addressing more common cancers.

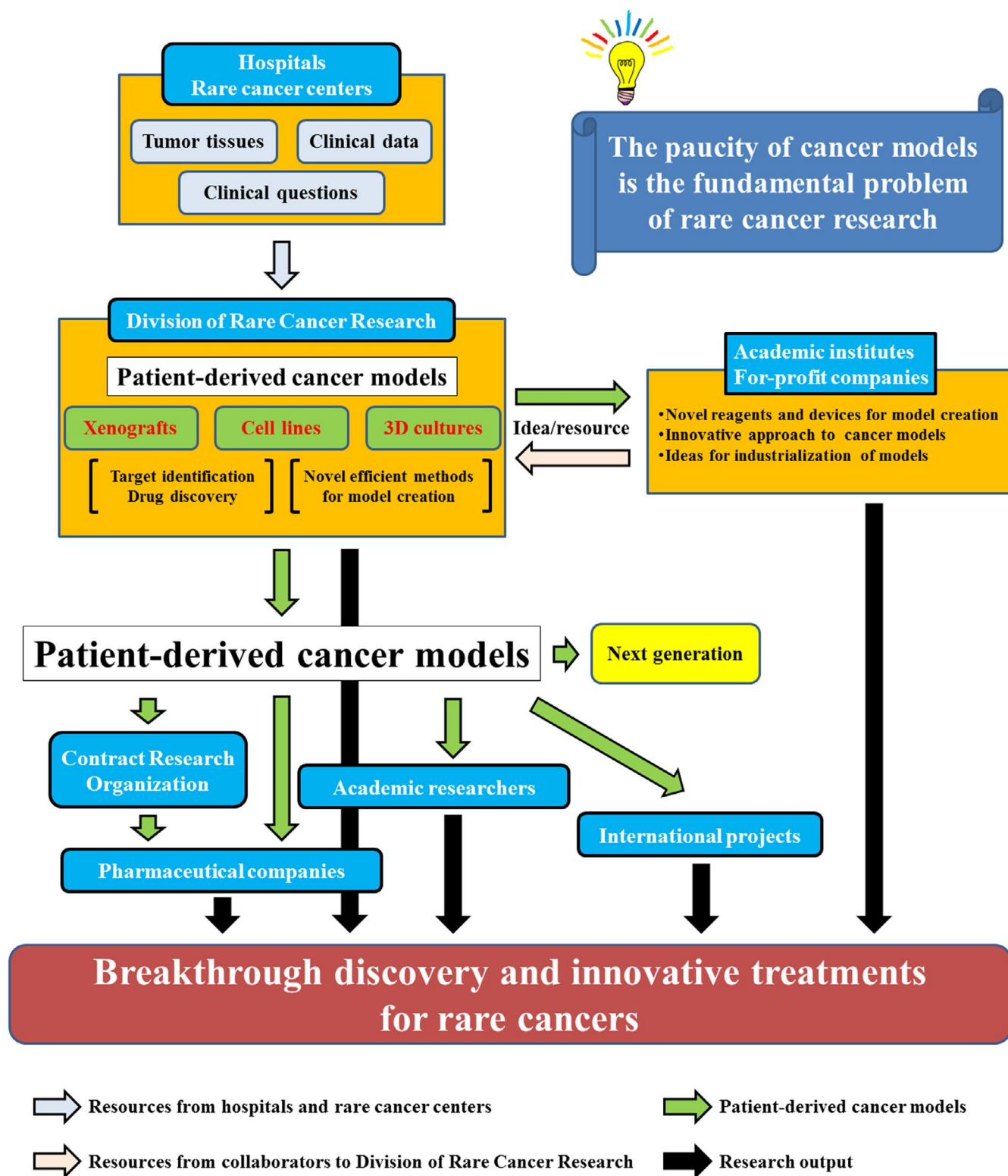




**FIGURE 3** Vicious and virtuous cycles between cancer models and research activity. A, The vicious cycle, based on the difficulty of accessing adequate cancer models in rare cancers. B, The virtuous cycle, based on the sufficient availability of cancer models in more common cancers

The difficulty of preclinical studies underlies the delay in therapy development, as sarcoma cancer models are rarely available from public biobanks. Hattori et al<sup>65</sup> assessed sarcoma cell lines cataloged in the world's largest cell-line database, Cellosaurus,<sup>66</sup> reporting that 674 had been reported and 139 were available from public cell banks. Among these cell lines, only 11 sarcomas accounted for 113 of the 139, whereas osteosarcoma, rhabdomyosarcoma, and Ewing's sarcoma combined accounted for 68 of the 139 lines.<sup>65</sup> PDXs have

similar drawbacks; a search of the PDXFinder database<sup>67</sup> revealed 104 sarcoma xenografts representing only 13 histological subtypes, with approximately 55 of these derived from only six sarcoma subtypes. Although organoid is a promising technology, it has not been available for sarcoma so far. The development of corresponding technology is an urgent issue. These observations suggest that most sarcoma research has to be done without publicly available cancer models. As a consequence, almost all sarcoma subtypes have been



**FIGURE 4** An example of multi-institutional collaborations for development and application of patient derived cancer models at the National Cancer Center. Patient-derived cancer models are established for rare cancers, and the developed models are delivered to the research community and industries

omitted from pan-cancer studies using large cell line panels.<sup>11-18</sup> This paucity of models stems from the lack of clinical materials for research, and it is not hard to see how the difficulty of using adequate cancer models may disturb research activity, discouraging adequate

funding and investment and reducing the numbers and efficacy of practical models (Figure 3A). We have to break this vicious cycle for rare cancers by emphasizing the generation and sharing of patient-derived cancer models (Figure 3B).



## 4 | FUTURE PERSPECTIVES FOR PATIENT-DERIVED RARE CANCER MODELS

The principles applied in current patient-derived cancer models were developed decades ago and have not evolved substantially since then. This situation is puzzling, because our knowledge of and treatment for many cancers have substantially progressed. For example, presently available tissue culture devices were designed to accommodate the size and shape of our forearms and fingers, so the volume of tissue culture medium they require is extraordinarily large relative to the volumes of body fluids in and around tumor tissues. Microfluidic devices such as organ chips<sup>68</sup> and bioprinting<sup>69</sup> may provide better-optimized tissue culture conditions for tumor cells. Although immunodeficient mice are available for xenograft experiments,<sup>70</sup> tumor cells may not faithfully exhibit their original characteristics in mouse models, in which microenvironments and the immune system are different from those of humans. Thus, the creation of animals bearing human microenvironmental components and immune systems,<sup>71</sup> as well as chimeric animals with human organs produced from human pluripotent stem cells,<sup>72</sup> will improve the accuracy and relevance of xenograft experiments. Other models, such as patient-derived chicken egg tumors<sup>73</sup> and zebrafish,<sup>74</sup> have shown promise with respect to novel biology and therapies. In addition to these examples, there exist more farsighted technologies that are likely to provide breakthroughs in serendipitous and unexpected ways.<sup>75</sup> Thus, it will require continuous effort to keep patient-derived cancer models up to date as new biology emerges.

For rare cancers, traditional cancer models should be generated, even using conventional methods, because the urgent need for rare cancer models has long been neglected. We need targeted and conscious efforts for generating "orphan models" to promote rare cancer research, as we currently have for orphan drugs. Such model creation should be conducted in a noncompetitive way. In one example, patient-derived rare cancer models are being generated at the National Cancer Center Research Institute, Tokyo, Japan, in global collaboration with multiple institutions. These models are then characterized and applied to translational research by our group and, in parallel, are delivered to multiple research groups (Figure 4, Table S1 Patient-derived sarcoma cell lines developed at the Division of Rare Cancer Research, National Cancer Center).

Establishing patient-derived rare cancer models requires multi-institutional collaboration. For example, we successfully established cell lines of CIC-DUX4 sarcomas from two out of all three patients we examined in the last 6 years at the National Cancer Center Hospital.<sup>76,77</sup> Therefore, it may not be technically difficult to establish cell lines of CIC-DUX4 sarcomas. We received the tumor tissues of CIC-DUX4 sarcomas only from a single institute, and developing a network of multi-institutional collaboration would enable us to establish a panel of cell lines of CIC-DUX4 sarcomas. In another example, we have obtained tumor tissues from more than 300 cases at the National Cancer Center Hospital since 2014 and established more than 50 cell lines for 25 histological subtypes. Even so, many of the subtypes were

not included. Given that more than 20 000 new sarcoma cases have occurred in Japan since 2014, we could establish sarcoma cell lines covering histological subtypes by collecting samples nationwide and concentrating them on the technically specialized laboratory.

The pursuit of model creation for common and rare cancers will be mutually beneficial. Cutting-edge model development technologies created for more common cancers will eventually spread to rare cancer research. Reciprocally, models developed for rare cancers with homogenous genetic backgrounds will drive innovation.<sup>78</sup>

## 5 | CONCLUSIONS

Available cancer models reflect our perspective on and understanding of cancer biology; conversely, at the same time, their features can restrict our imagination and research. Thus, we must challenge ourselves and others to produce more sophisticated cancer models that address the needs of understanding cancer biology and developing new cancer treatments.

It is essential to understand that paucity of cancer models is the fundamental problem in rare cancer research. It is necessary to intensively promote the development of rare cancer models, and to share them freely within the research community. It requires multi-institutional studies, as clinical samples are rare and the research that can be performed by single research groups is limited. Such efforts, and the models they produce, will enable future generations to better understand cancer biology and to develop novel biotechnologies and treatments, which will dramatically improve rare cancer outcomes. By creating novel patient-derived cancer models, we can change the future for rare cancer research.

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## DISCLOSURE

The author officially collaborates with Charles River Laboratories, Biospecimen Laboratories, and ZEON Corporation on research relevant to patient-derived cancer models.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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