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Abstract: Despite significant advances in both our understanding and the treatment of cancer, the disease remains one of high mortality and morbidity in all species. Increase in survival times in human cancer have increased significantly in the past 25 years but most of these increases have been through small incremental changes. For some cancers, e.g. pancreatic cancer, survival times have not increased significantly in over 100 years. In veterinary oncology, we have seen major shifts in the management of cancer in companion animals. Increased availability of specialist centres, coupled with changing attitudes in owners and veterinarians, have meant that we have seen an improvements in veterinary cancer care borne from market pressures and increased awareness and understanding. In this review piece we will look at the changing face of cancer biology over the past 25 years, and consider the barriers to clinical progress in veterinary medicine. Finally, we will share an optimistic view of the future and the prospect for greater control over this devastating disease.

# 1 **Veterinary Oncology: Biology, Big Data and Precision Medicine**

2

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6

7

## 8 **Abstract**

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10 cancer, the disease remains one of high mortality and morbidity in all species.  
11 Increase in survival times in human cancer have increased significantly in the  
12 past 25 years but most of these increases have been through small incremental  
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14 increased significantly in over 100 years. In veterinary oncology, we have seen  
15 major shifts in the management of cancer in companion animals. Increased  
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20 biology over the past 25 years, and consider the barriers to clinical progress in  
21 veterinary medicine. Finally, we will share an optimistic view of the future and  
22 the prospect for greater control over this devastating disease.

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<sup>1</sup>Joint-winner of the Kennel Club Charitable Trust's International Award 2015

## 24 **Introduction**

25 According to data from Cancer research UK (CRUK), in 2012 there were 14.1  
26 million new human cancer diagnoses world-wide and 8.2 million deaths<sup>2</sup>.  
27 Reducing cancer mortality is clearly an international priority. However, despite  
28 incremental improvements in cancer therapies, the disease remains one of high  
29 morbidity and mortality in all species (Argyle and Blacking, 2008).  
30 Improvements in public health and the control of infectious disease have  
31 compounded the problem making cancer the world's leading cause of death in  
32 humans. In addition, cancer has a huge impact on the economy through loss of  
33 productivity, loss of years of life, and cost related to treatment. According to  
34 American Cancer Society the total economic impact of premature death and  
35 disability from cancer worldwide was \$895 billion in 2008<sup>3</sup>. This figure  
36 represents 1.5% of world's GDP and does not include direct cost of treating  
37 cancer. According to Murphy and Topel (2003), a 10% reduction in cancer  
38 deaths worldwide would be worth \$4.7 trillion in social value.

39

40 Cancer in veterinary species can have two broad consequences. Cancer in  
41 livestock species can have a major economical impact, especially an infectious  
42 cause of cancer, e.g. Marek's disease in poultry, or Bovine Leukosis in cattle,  
43 causing significant loss of production. In contrast, the major impact on  
44 companion animals relates to their long-term health and their relationship with  
45 their owners. Although true epidemiological data worldwide is lacking in

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<sup>2</sup> <http://www.cancerresearchuk.org/health-professional/worldwide-cancer-statistics>

<sup>3</sup> <http://www.cancer.org>

46 veterinary medicine, we estimate that the incidence of cancer in dogs is around 1  
47 in 3 (and 1 in 4 to 5 in cats) (Pang, et al., 2009). This is not dissimilar to man and  
48 with a similar pattern of improved control of infectious disease pushing cancer  
49 up the league table of significant causes of death. Cancer treatments and (and  
50 consequently cancer treatment centres) have increased significantly in the last  
51 20 years. Cancer treatments have become “accepted clinical practice” and  
52 owners now have much broader access to facilities such as external beam  
53 radiation. The control of cancer and cancer treatment-related side effects is  
54 much improved with the development of new drugs (e.g. NK-1 inhibitors for  
55 nausea) and we have seen the first targeted drugs for veterinary oncology being  
56 approved and launched (e.g. London et al., 2009). We have learnt a great deal  
57 about the biology of cancer in dogs and cats in the last two decades. This has  
58 been supported by the publications of species genomes which has also created,  
59 in small part, the tool box required to understand this disease at the genetic level  
60 and also investigate the clear breed predispositions for certain types of cancer  
61 (Ostrander and Kuglyak, 2000). However, as with human medicine, we still  
62 recognize cancer as the leading chronic disease and one of the biggest causes of  
63 death in companion animals (Argyle and Blacking, 2008).

64

## 65 **The hallmarks of cancer**

66 It is very difficult to define what a cancer is and to put that definition into a  
67 clinical context. If one considers that homeostasis is fundamental to health, then  
68 cancer can be considered in terms of a breakdown in the homeostatic  
69 mechanisms that control cell growth, cell division and cell death. Consequently,

70 we have to deal clinically with a group of cells, who have lost control of intrinsic  
71 cell growth and division, and can, under certain circumstances, spread  
72 (metastasize) to distant sites in the body. It is often this last critical step that can  
73 ultimately lead to the death of the patient.

74

75 Our traditional understanding of how a cancer develops comes from studies and  
76 mathematical modeling in diseases such as colon cancer in man (e.g. Little and  
77 Wright, 2003) and is built upon seminal work by Nordling (1953) and Knudson  
78 (1971). Colon cancer is one of the diseases that has allowed clinicians and  
79 scientists to model multistage carcinogenesis, demonstrating the changes from  
80 polyp formation to metastatic colon cancer. This model has been central to  
81 identifying key changes in cells that give rise to the malignant phenotype, from  
82 an initiation step (first fundamental genetic change to the DNA of the cell), and  
83 including the multiple stochastic genetic “hits” that the cell acquires to become a  
84 cancer cell (Figure 1). What is clear is that cancer is a disease that affects the  
85 fundamental genetic material (DNA) of a cell, the phenotype of which is passed to  
86 the daughter cell. The discovery of viruses that cause cancer laid the foundation  
87 for the discovery and description of oncogenes and tumour suppressor genes  
88 (Argyle and Blacking, 2008). These genes and their protein products are  
89 intimately involved with cell cycle regulation. Oncogenes are the cell’s  
90 “accelerator pedal” and drive cell growth and division. Tumour suppressors are  
91 the cells “brake pedal” and add a level of control to the cell cycle. Cancers often  
92 contain major changes in these genes, which cause a breakdown in homeostasis,  
93 making them significant targets for therapy.

94

95 The almost exponential advances in molecular biology over the past 25 years  
96 have facilitated the dissection of these pathways and the development of drugs  
97 to target them. For a disease for which clinical control has been centred on the  
98 crudest of treatments (cancer chemotherapy), the advent of these discoveries  
99 sparked a fiercely competitive search for drugs that could target specific  
100 pathways that are known to be dysregulated in cancer.

101

102 However, what has become apparent, are the myriad of “altered” pathways and  
103 genetic changes in cancer cells that present a picture of a far more complex  
104 syndrome at the cellular level. In 2000 and again in 2011, Hannah and Weinberg  
105 made a significant attempt to distil the cancer phenotype into the acquisition of  
106 fundamental characteristics. The initial six cancer traits defined in the 2000  
107 paper were added to in 2011, when the authors expanded the model to include  
108 evasion of the immune system and the acquisition of abnormal metabolic  
109 pathways (Figure 2). These traits are common across cancer phenotypes and  
110 offer the possibility of defining opportunities for biomarker discovery or  
111 therapeutic intervention. However, as we have developed the tools to define  
112 these pathways in detail, explore multiple genes in multiple cell types, define  
113 genetic and protein profiles, the complexity of the cancer cell seems to expand.  
114 As an added complication, both the cancer niche (microenvironment) and the  
115 epigenome have come to the foreground as being major players in cancer  
116 initiation and progression.

117

118 **Challenging the traditional model of cancer development**

119 In the last 10 years we have seen significant challenge to the traditional  
120 stochastic model of cancer development (described above). In many ways the  
121 simple model from initiation to metastatic cell (requiring the acquisition of  
122 multiple hits over time), did not fit well with our understanding of tissue and cell  
123 turnover in organ systems. An evolving model (cancer stem cell model) treats  
124 the cancer as an “organ system” where the bulk tumour population is driven by a  
125 small number of cancer stem cells (Blacking et al., 2007). This model has not  
126 been universally accepted (and may be different for different cancer types) but  
127 has gained significant ground in recent years. The clinical significance of this is  
128 immense as it gives the fundamental basis for tumour heterogeneity and  
129 suggests that a cancer is driven by cells that have striking resistance to  
130 conventional anti-cancer drugs. Cancer stem cells have been identified in cat and  
131 dog cancers that have significant resistance to conventional cancer drugs,  
132 radiation and have altered responses to DNA damage (Wilson et al., 2008; Pang  
133 et al., 2011, 2013 and 2015). The true classification of these cells is still  
134 controversial and there is still no universal cell marker for purification of these  
135 cells (Blacking et al., 2012). However, what is clear, is that cancers contain sub-  
136 populations of cells that are highly resistant to conventional therapies and  
137 contribute significantly to tumour heterogeneity and treatment failure (Figure  
138 3).

139

### 140 **Genes, dreams and cancer signatures**

141 From a position over 20 years ago, when we could only look at single pathways  
142 or genetic changes in cancer cells in a stepwise fashion, we have moved to a  
143 position when we can examine thousands of genes in a cancer sample using gene



144 array “chips”. Initially, these were expensive technologies but the cost has  
145 plummeted in recent years, accompanied by newer technologies such as high  
146 throughput sequencing and RNA sequencing (RNA-seq). RNA-seq uses Next  
147 Generation Sequencing (NGS) to rapidly analyze the changing transcriptome in a  
148 cancer cell. This has been coupled with cost-effective and rapid ways of  
149 examining the cancer protein profile, its secretome, the metabolome and many of  
150 the epigenetic mechanisms operating at the cellular level. These technologies in  
151 cancer discovery have been used to:

- 152 1. Identify common cancer signatures across phenotypes
- 153 2. Identify potential targets for drug development
- 154 3. Identify “driver” and “passenger” mutations to assist drug discovery
- 155 4. Identify biomarkers of cancer for early detection
- 156 5. Identify specific pathways that may be druggable.

157 These technologies have also become affordable enough to be used to study  
158 companion animal tumours, both in their own right and as models for human  
159 disease (e.g. Mudaliar, et al., 2013; Pang et al., 2014). There is little doubt that  
160 the information obtained from these studies is proving incredibly useful.

161 However, the challenge is still to be able to translate discovery into practical  
162 solutions for patients.

163

## 164 **Why no cure?**

165 We have experienced an exponential growth in understanding of cancer biology  
166 in the past 25 years. However, although we have seen some shift in survival  
167 times and improved mortality in humans, we have not seen the paradigm shift  
168 that the new cancer technologies promised. Pragmatically, this should not be a

169 surprise considering the complexity of the disease, but it is worth considering a  
170 number of issues that have arisen and how these may be overcome:

171

172 **Data, data and more data:** Our ability to dissect the cancer genome, proteome  
173 and metabolome has become incredibly refined and affordable. However, our  
174 ability to analyze the sheer volume of data (bioinformatics) has not kept pace  
175 with our ability to derive it. Much effort is now underway to expand our  
176 bioinformatics capability to keep pace with the information being gathered and  
177 to be able to use that information in a clinically relevant way. It is absolutely  
178 essential that cancer researchers and oncologists do not work in isolation but  
179 work across disciplines with bioinformaticians, mathematicians, engineers, and  
180 computer scientists, so we can both effectively mine and put some context to the  
181 enormity of the biological and clinical data that can now be generated.

182

183 Human colorectal cancer in man exemplifies the challenges that we face as  
184 cancer researchers and oncologists. Although colorectal cancer (CRC) was  
185 among the first solid tumors to undergo molecular profiling, the clinical  
186 translation of this knowledge into effective therapies has been impeded by the  
187 startling level of complexity and heterogeneity revealed among these tumours.  
188 Despite approval of several new drugs in recent years, the success of these and  
189 other agents in development has been stifled by the complex nature of CRC. It  
190 has become clear that the only way forward requires a paradigm shift toward  
191 integrative analyses that encompass multiple classes of genomic aberrations and  
192 consensus classification of CRC based on genomic data to facilitate more effective  
193 management of this disease.

194

195 **Darwinian evolution:** What has become very clear is that any “omic signature”  
196 gained for a specific cancer or biological sample reflects a simple snapshot in  
197 time for that sample. Expression of genes and proteins can rapidly change in a  
198 rapidly evolving tumour system and can be a reflection of inherent changes in  
199 the cell or as a result of changes in the cancer microenvironment (e.g. Greaves  
200 and Maley, 2012). This is hugely challenging as we may be identifying drug  
201 targets that are only transitory in nature or are subject to intense selection  
202 pressures. In addition to selection, there is also increasing evidence of  
203 significant cell plasticity in tumours (adaptation) that may also change the  
204 potential of druggable targets (Faurobert et al., 2015). It is clear that  
205 heterogeneity within tumours contributes significantly to treatment failure, but  
206 this heterogeneity is itself very dynamic and difficult to document in real-time  
207 (Brooks et al., 2015).

208

209 One of the major reasons for treatment failure in human and veterinary patients  
210 is the development of drug resistance. Drug resistance developing during  
211 treatment with conventional chemotherapy drugs is well documented in human  
212 and veterinary medicine and has been a subject of significant research  
213 investment. The development of targeted drugs which “hit” a specific pathway  
214 or “driver mutation” has been seen as a major breakthrough in cancer drug  
215 development, exemplified by the plethora of small molecules that have been  
216 developed to target the cancer kinome. Tyrosine kinases have been a hotly  
217 researched area of drug development as changes (e.g. mutations) in kinase  
218 pathways represent major drivers of malignancy (Bavcar and Argyle, 2012).

219 Imatinib (Gleevec) is a small molecule inhibitor that targets Receptor Tyrosine  
220 Kinases (RTK) and was one of the fastest cancer drugs to reach the market (from  
221 initial discovery to clinical licensing), being used extensively in human  
222 leukaemia. However, as with conventional drugs, the selection pressure created  
223 by using one single drug supports the development of drug resistance in certain  
224 groups of patients (Bixby and Talpaz, 2011). The development of Imatinib has  
225 been followed by the development of second and third generation RTK inhibitors  
226 to overcome the inevitable acquisition of resistance. However, as we have  
227 described above, cancer is far more complex and just targeting one driver  
228 mutation in a tumour is probably insufficient. It is likely that the greatest  
229 success in cancer control is going to be achieved through targeting multiple  
230 pathways in cancer and also paying close attention to tumour  
231 microenvironment and the role of epigenetic drivers in cancer.

232

233 The concept of tumour evolution also applies to how the body's immune system  
234 responds to cancer and how successful immunotherapy is in cancer patients  
235 (Figure 4). As with targeted drug therapy, advances in immunotherapy have  
236 resulted in remarkable clinical responses in some human patients (Raposo, et al.,  
237 2015). However, one of the biggest challenges in cancer therapeutics is the  
238 development of resistant disease and disease progression on or after therapy.  
239 For patients with metastatic cancer, conventional chemotherapy (plus or minus  
240 targeted therapies) has not proven curative. However, there is significant  
241 clinical trial data in human patients to suggest that immunotherapy has the  
242 potential to achieve long lasting remissions in patients with metastatic disease.  
243 However, as with some of the targeted therapies, immune-selective pressure for

244 resistant tumour cells clearly exists (Restifo et al., 2016). It is likely that this  
245 resistance derives from the type of Darwinian evolution described above (e.g.  
246 selection pressure on the tumour giving rise to selective loss of components of  
247 MHC). In addition, tumour cells may acquire resistance through adaptation in  
248 response to interactions with immune cells. One mechanism that has gained  
249 prominence recently has been the tumour cell expression of programmed cell  
250 death protein (PD1) and its ligand (PDL1), which serve to down regulate the  
251 anti-tumour immune response (Mamalis, et al., 2014). Drugs and monoclonal  
252 antibodies targeting this “immune checkpoint” are the subject of intense  
253 research and human clinical trials.

254

255 **“Big bang theory” and tumour heterogeneity:** Recent studies of colon cancer  
256 utilizing genomic data and mathematical modeling, suggest that the majority of  
257 genetics changes and intratumoural heterogeneity (ITH) actually occurs very  
258 early on in tumour evolution once the malignant phenotype of the cell has been  
259 achieved (Sottoriva et al., 2016). This also suggests that a tumour’s ability to  
260 invade and metastasize are programmed early in development rather than  
261 acquired by selective forces. This has major implications for drug and biomarker  
262 discovery as it suggests that the formation of new driver mutations during  
263 tumour evolution are not as common as once considered. It also means that  
264 some tumours are just “born bad” whatever we do to them

265

266 **The lack of good model systems:** Rodent xenograft models have been the  
267 traditional test bed for new anti-cancer therapies. However treatment responses  
268 in rodents frequently do not translate into benefit in patients (Pang and Argyle,

269 2009). This mismatch is multifactorial but broadly reflects major differences in  
270 tumour biology and pathophysiology and lack of tools to measure critical  
271 changes in the tumour microenvironment that drive tumour growth and  
272 response to treatment. Basic cancer research, combined with xenograft models  
273 have made great progress in our understanding of the mechanisms that underlie  
274 the development of human cancer and in cancer detection but the current pre-  
275 clinical models are too slow, too costly and lack predictability for the efficient  
276 translation into new cancer treatments. Similarly, small animals are insufficient  
277 for the development of new technology for detecting early cancers. Mouse  
278 models have played an important role in identifying the molecular pathways of  
279 cancer but the uncertainty of artificial tumours in mice to foresee the clinical  
280 outcome of new treatments and their insufficiency for testing new imaging  
281 technology have become ever tighter bottlenecks for bringing new treatments  
282 and technology to the benefit of the patients. Hence, new pre-clinical models to  
283 more rapidly translate advances in basic cancer research, diagnostics and  
284 treatment into the clinic are of most urgent need.

285

### 286 **A cause for optimism?**

287 Our ability to dissect the cancer genome and all of its components has far  
288 exceeded our ability to analyze and understand the data. We can therefore  
289 conclude that the complexity of the cancer cell is currently impeding our ability  
290 to define and produce better treatments and better outcomes for patients. As a  
291 community involved in cancer research, clinical oncology or both, what can we  
292 do to drive progress and is there cause for optimism? The simple answer to this  
293 is that there is great deal we can do and there is definitely cause for optimism in

294 both human and veterinary oncology. We are seeing a renaissance and  
295 rejuvenated interest in conventional treatments such as radiotherapy, we are  
296 developing new and innovative ways to study cancer, and more than ever before  
297 we are exploring cancer without any species boundaries. Below is not an  
298 exhaustive list, but offers an optimistic view of veterinary and human oncology:

299

300 **Advances in conventional therapies:** Patient responses to conventional  
301 treatments in veterinary oncology have become more predictable as we gain  
302 greater experience in managing common cancer types. However, for diseases  
303 such as Lymphoma, we have probably reached a “watershed” in terms of our  
304 ability to significantly alter disease free interval and survival times with the  
305 drugs we have available (Comazzi, et al., 2015). This is also considering our  
306 appropriate need in veterinary oncology to maintain quality of life in our  
307 patients. New cancer chemotherapy drugs are few and far between and we rely  
308 on orphan drugs from human medicine to fill the significant pharmacy gap that  
309 we have in veterinary oncology. We have, however, seen a major renaissance in  
310 radiation oncology, especially in terms of availability. We have gone beyond  
311 course fractionated regimes and embraced radiotherapy plans and prescriptions  
312 with curative intent. This is only set to increase with advances in planning  
313 systems and increased use an availability of IMRT (Intensity Modulated  
314 Radiotherapy) and SBRT (Stereotactic Body Radiotherapy) (Feng, et al., 2015  
315 and 2016)

316

317 **Advances in imaging:** In recent years there has been a tremendous  
318 improvement in imaging technologies and access to these technologies. We have

319 been able to go beyond radiographic analysis and been able to take advantage of  
320 the imaging resolutions afforded by Computerized Axial Tomography (CT) and  
321 Magnetic Resonance Imaging (MRI). While these modalities are improving the  
322 imaging resolution in terms of anatomy, functional imaging (e.g. Positron  
323 Emission Tomography (PET)) is set to become more available and will be a  
324 major diagnostic modality, especially for cancer patients and for the  
325 identification of primary and metastatic lesions. The cost and availability of new  
326 modalities is coming down and we can expect that these will become a common  
327 part of the cancer staging process both in primary care and referral centres.

328

329 **Drug and device development:** New drug development for cancer in  
330 companion animals is hugely challenging, not least for even the biggest  
331 pharmaceutical companies. Since the launch of toceranib (Palladia) and  
332 masitinib (Masivet), there have been no new “second generation” drugs as seen  
333 in human oncology. The indications for both of these drugs (as dictated by the  
334 license arrangement) was somewhat limited and was not the panacea for cancer  
335 that some may have wanted or predicted. We are still (as a community) learning  
336 a lot about how to use these drugs either alone or in combination with  
337 conventional drugs, and it is possible that their use will become more  
338 widespread in these scenarios. Dogs do develop resistance and with few follow-  
339 on options (no second generation drugs), their use can become limited in some  
340 patients. However, for the veterinary pharmaceutical industry the financial  
341 margins on these drugs and the expense of getting them to market are a huge  
342 challenge, especially when you consider the size of the market. The veterinary  
343 oncology market is a mere fraction of the \$100 billion dollar human cancer drug



344 market. A secondary route to market could involve using drugs developed for  
345 human oncology, as long as pharma can tolerate the potential price differential  
346 between what they can charge for a human drug and what can be reasonably  
347 charged for a veterinary drug.

348

349 However, instead of human and veterinary oncology drug development  
350 operating in parallel, there is a model that transcends the species boundaries to  
351 allow combined drug development. Rodent xenograft models have been the  
352 traditional test bed for new anti-cancer therapies. However treatment responses  
353 in rodents frequently do not translate into benefit in patients. This mismatch is  
354 multifactorial but broadly reflects major differences in tumour biology and  
355 pathophysiology and lack of tools to measure critical changes in the tumour  
356 microenvironment that drive tumour growth and response to treatment. Basic  
357 cancer research, combined with xenograft models have made great progress in  
358 our understanding of the mechanisms that underlie the development of human  
359 cancer and in cancer detection but the current pre-clinical models are too slow,  
360 too costly and lack predictability for the efficient translation into new cancer  
361 treatments (Pang and Argyle, 2009). Similarly, small animals are insufficient for  
362 the development of new technology for detecting early cancers. Mice models  
363 have played an important role in identifying the molecular pathways of cancer  
364 but the uncertainty of artificial tumours in mice to foresee the clinical outcome of  
365 new treatments and their insufficiency for testing new imaging technology have  
366 become ever tighter bottlenecks for bringing new treatments and technology to  
367 the benefit of the patients. Hence, new pre-clinical models to more rapidly  
368 translate advances in basic cancer research, diagnostics and treatment into the

369 clinic are of most urgent need. Spontaneous or naturally occurring tumours in  
370 dogs and cats share important molecular, histopathological and therapeutic  
371 characteristics with corresponding human disease and, thus, provide cancer  
372 models that are closer to man than rodent models (Rowell et al., 2011; Shearin  
373 and Ostrander 2010; Khanna et al., 2006; Pang and Argyle, 2009). Clinical data  
374 derived from trials in spontaneous tumours in domestic animals could serve not  
375 only to improve animal health but serve as an important link between basic  
376 cancer research and human and veterinary clinical trials. While much emphasis  
377 has been placed recently on translation of biology into clinical practice, this kind  
378 of approach aims to create a platform of inderdisciplinarity that supports both  
379 translation, and transformation of clinical cancer practice, offering the greatest  
380 opportunity for Impact. This would include:

- 381 1. Reducing the time taken for a therapeutic targets to be translated into clinical  
382 benefit
- 383 2. Reducing the high costs of therapeutic development
- 384 3. Increasing the predictability of human pre-clinical models.

385 This concept can go beyond drug development and also be applied to other  
386 aspects of cancer research such as the development of medical devices. As an  
387 example, IMPACT (Implantable Microsystems for Personalized Anti-cancer  
388 Therapy)<sup>4</sup> is a collaboration between engineering, veterinary oncology, human  
389 oncology, chemistry, and social science, to develop implantable sensors that are  
390 able to detect changes in tumour microenvironment in real time. For example, if  
391 we can detect subtle changes in hypoxia in real-time during radiotherapy, then

---

<sup>4</sup> <http://www.impact.eng.ed.ac.uk>

392 treatment plans can be adjusted rapidly to compensate and improve clinical  
393 outcomes in patients. This project aims to develop a platform technology that  
394 could be applied to a wide range of cancers and perhaps ultimately being able to  
395 deliver anti-cancer drugs locally, and in a controlled way.

396 **Monoclonal antibodies for diagnosis and treatment:** The development of  
397 small molecules to target RTK pathways and driver mutations was considered to  
398 be one of the major breakthroughs in cancer research. However, monoclonal  
399 antibodies have now far exceeded small molecules in terms of the market share  
400 of biologics being used in cancer treatments. Some of the advantages of  
401 monoclonal antibody therapeutics over conventional drugs are high specificity,  
402 precise mode of action and long half-life, which favours infrequent dosing of the  
403 antibody. Monoclonal antibodies have been developed for a number of cancer  
404 targets including Anti-CD20 (B cell Lymphoma, Anti-EGFR (multiple targets  
405 including head and neck cancer) and anti-VEGFR (Multiple cancer types  
406 targeting angiogenesis) (reviewed by Xin et al., 2013). However, the use of  
407 “human” monoclonal antibodies in veterinary oncology is usually not feasible  
408 due to the development of an immune response to foreign protein. Recently new  
409 techniques have allowed the development of species-specific (e.g. caninized)  
410 monoclonal antibodies. A full description of this technology is outwith the scope  
411 of this review but can be found by Breiro et al., 2016). Caninized anti-CD20 is in  
412 clinical use and a pipeline of discovery through to clinical application is being  
413 developed by a number of companies in the veterinary arena (Jain et al., 2016).  
414 This is a truly exciting prospect, as it will deliver new and affordable reagents to  
415 the veterinary oncology community.

416 **A renaissance for immunotherapy:** Immunotherapy for cancer in all species  
417 has followed a continuous sine wave varying between optimism and pessimism.  
418 Immunotherapy has become one of oldest forms of cancer treatment, the aim  
419 being to harness the body's immune system to target a tumour with altered "self  
420 proteins". While immunotherapy has achieved considerable success in some  
421 patients, we still do not fully understand why some patients will mount a  
422 positive anti-tumour response, and others do not. This is also confounded by  
423 Darwinian selection pressures (described above) and the development of  
424 adaptive responses to immunotherapy. As with our understanding of the  
425 molecular events in cancer, our understanding of immunity is also exponentially  
426 increasing. There is particular cause for optimism currently around the  
427 dissection of the pathways involved in adaptive responses and a good example of  
428 this is the PD1/PD1L axis. Programmed death-1 (PD-1) is expressed on the  
429 surface of immune cells, and programmed death ligand-1 (PD-L1) is often  
430 expressed on cancer cells. When PD-1 and PD-L1 bind, this results in suppression  
431 of T cell activity and reduction of T cell-mediated cytotoxicity (Robert et al.  
432 2014). Thus, PD-1 and PD-L1 are immune down-regulators or immune  
433 checkpoint "off switches" (Mamalis et al., 2014), which allow cancer cells to  
434 evade immune destruction. Anti-PD1 and PD1L drugs and monoclonal antibody  
435 development have been intensely pursued by the pharmaceutical and academic  
436 communities as a mechanism for immune-modulating cancer patients (e.g. in  
437 malignant melanoma). Whereas previous immunotherapies have focused on  
438 promoting anti-tumour immunity, this approach tries to inhibit immune  
439 checkpoints that protect cancers from immune destruction. Alone, this therapy  
440 may be insufficient to offer complete cures, but combining it with other

441 modalities or immunotherapies may offer a significant advantage over current  
442 treatments.

443 **Big data and precision medicine:** The development of the appropriate  
444 reagents for mining veterinary genomes, proteomes and metabolomes is rapidly  
445 expanding. Coupled with this is the reduction in costs associated with  
446 sophisticated genomic and proteomic analysis. With this will come an increased  
447 ability to:

- 448 1. Mine veterinary cancer genomes and proteomes using multiple samples.
- 449 2. Potentially identify biomarkers for the early detection of cancer, prediction of  
450 treatment success or the early detection of treatment failure.

451 These technologies are already in use and proving useful for dissecting the  
452 complexity of cancer. However, with this we must embrace the importance of  
453 bioinformatics, statistics and mathematical modeling if we are going to take full  
454 advantage of the amount of data we are generating. This must also be linked  
455 with appropriate clinical data from the field so we can develop appropriate  
456 algorithms that will be useful clinically. This will require a paradigm shift in how  
457 we traditionally approach veterinary medicine:

- 458 1. We must improve how we record and collect clinical data. We suffer in  
459 veterinary medicine with low patient numbers compared to human medicine  
460 and this is challenging when we need large cohorts of patients for specific  
461 studies. With this, there will be a requirement for national and international  
462 collaboration, standardization of clinical recording, and significant  
463 investment in biobanking resources. Some of these are being addressed in  
464 some part, but this will require significant funding and organization. The

465 concept of “Big Data” is being embraced by human medicine and, as a  
466 profession, if we are going to retain a competitive edge we must also embrace  
467 this.

468 2. We must break down the discipline barriers and develop systems to handle  
469 large data sets. This will involve developing systems that will allow us to  
470 integrate clinical, biological and epidemiological data to provide the optimum  
471 clinical care for our patients (precision medicine). This may involve mapping  
472 a specific “comparative oncology ecosystem” that will provide the framework  
473 for interdisciplinarity and collaborative research.

474 3. In embracing new technologies, we must also consider how we train the next  
475 generation of veterinarians to ensure they know how to interpret the  
476 potentially large amounts of data they will be able to generate from an  
477 individual patient.

478 4. In the earlier years of the twentieth century, we relied up symptom  
479 recognition and application of knowledge. Today, we are more in tune with  
480 pattern recognition and application of the evidence base. Tomorrow, it is  
481 likely that we will embrace the acquisition of multiple levels of patient data  
482 (genome, to phenome) and apply that knowledge and information to  
483 treatment, but based up on specific algorithms derived from an evidence  
484 base. This will herald the dawn of precision veterinary medicine (Figure 5).

485 There is much cause for optimism in this arena as we are in the early stages of  
486 developing some of these systems to achieve this end goal. Our challenge will be  
487 to work collaboratively and to ensure these approaches are adequately funded.

488

489 **Concluding remarks**

490 At the start of this synopsis, I painted a rather challenging view of cancer  
491 research and clinical oncology where complexity of this disease will constantly  
492 hinder progress. However, I strongly believe that many of the hurdles that I have  
493 described can be overcome to the benefit of all species. As a community, we  
494 must think far beyond the translation of basic biology into clinical practice, and  
495 consider the defining research and application that will truly transform clinical  
496 practice to the benefit of patients. We have to remove the boundaries to  
497 research silos that are restricting progress and also the traditional species  
498 boundaries between human and veterinary oncology. As an example, data  
499 science and large data set analysis will be vital to understanding the complexity  
500 of cancer at the cell and population level. We will need to integrate clinical and  
501 biological data to improve treatment outcomes and design specific therapies.  
502 Precision medicine has been coined in human medicine as a model that proposes  
503 the customization of healthcare, with medical decisions, practices, and/or  
504 products being tailored to the individual patient. It is possible, with new  
505 technologies that veterinary medicine will have to move in a similar direction.  
506 However, we have to embrace new technology and work collaboratively across  
507 disciplines to achieve this.

508

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516 **Conflict of Interest**

517 The Authors have no conflict of interest

518

519

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655

656 **Figure Legends:**

657

658 **Figure 1:** The Stochastic and Traditional Model of Cancer Development: This  
659 supports that a cell within the body sustain an “initiation” event, which  
660 causes a damage and change to the cell’s DNA (loss of gain of function of  
661 oncogenes or tumour suppressor genes). In most cells receiving such  
662 damage, the cell would either die by programmed cell death or arrest so that  
663 the cell could repair it’s DNA. In cell’s where this fails, they can accumulate  
664 genetic “hits” ultimately leading to the development of a cell with a malignant  
665 phenotype and the ability to metastasize.

666

667 **Figure 2:** The Hallmarks of cancer as proposed by Hannah and Weinberg  
668 (adapted). The model suggests that all cancers can be defined by the  
669 acquisition of 6 fundamental characteristics. In 2011, altered metabolism  
670 and evasion of the immune system were also included as enabling  
671 characteristics of cancer cells.

672

673 **Figure 3:** The stem cell model of cancer is not universally accepted and may  
674 be different for different cancer types. In the model proposed in this  
675 diagram, an adult stem cell is the target cell, which receives the initial genetic  
676 “hit” or “hits” which allows “reprogramming of the cell” to a primitive  
677 phenotype (Tumour Initiating Cell or TIC). This has been likened to the  
678 development of induced pluripotency in somatic cells in culture. Once  
679 established the tumour resembles an organ structure in that the bulk of the  
680 tumour (Daughter Cancer Cells, DCCs) is driven by a very small population of

681 cancer stem cells (CSC) that are capable of self-renewal. There is also  
682 emerging evidence that there is considerable plasticity in these cells that  
683 contribute to supporting metastatic spread.

684

685 **Figure 4:** The tumour is subjected to intense Darwinian selection pressures,  
686 both in terms of selection of phenotypes resistant to drugs or cell death, but  
687 also refractory to immune surveillance. Within this model, evolving tumour  
688 heterogeneity is compounded by cellular adaptation. This results in a very  
689 complex problem for the development of treatments for cancer.

690

691 **Figure 5:** The Development of Precision Veterinary Medicine. In the earlier  
692 years of the twentieth century we relied upon symptom recognition and  
693 application of intuition. Today, we are more in tune with pattern recognition  
694 and application of the evidence base. Tomorrow, it is likely that we will  
695 embrace the acquisition of multiple levels of patient data (genome, to  
696 phenome) and apply that knowledge and information to treatment, but based  
697 up on specific algorithms derived from an evidence base.

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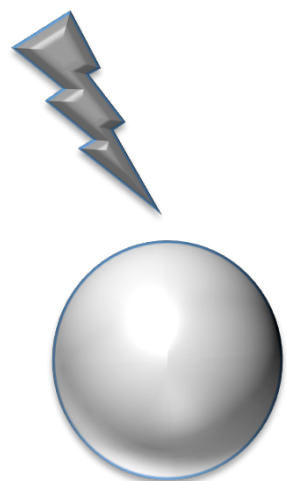
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Figure 1

Initiation event



Accumulation of secondary mutational events

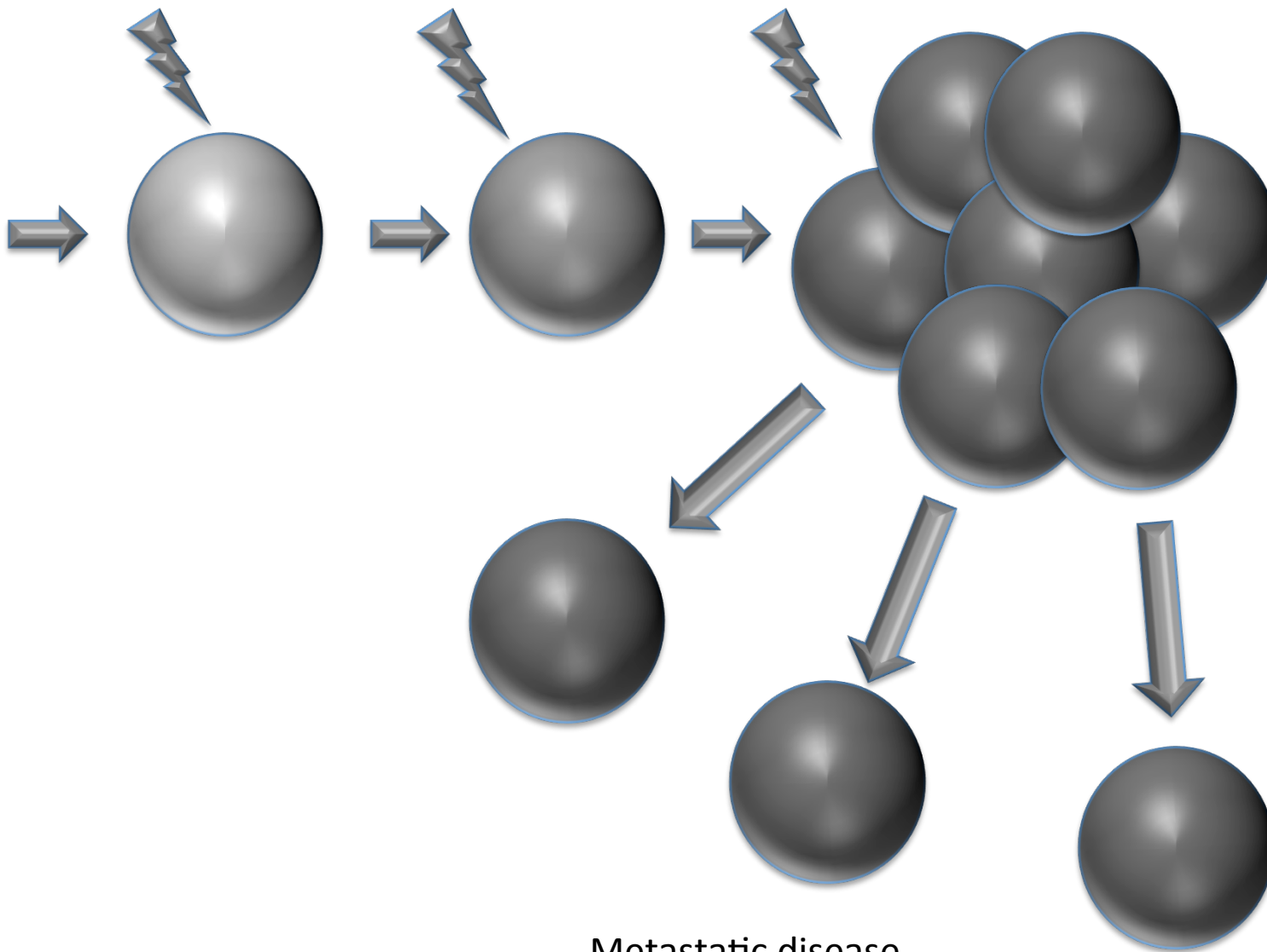


Figure 1

Metastatic disease

Figure 2

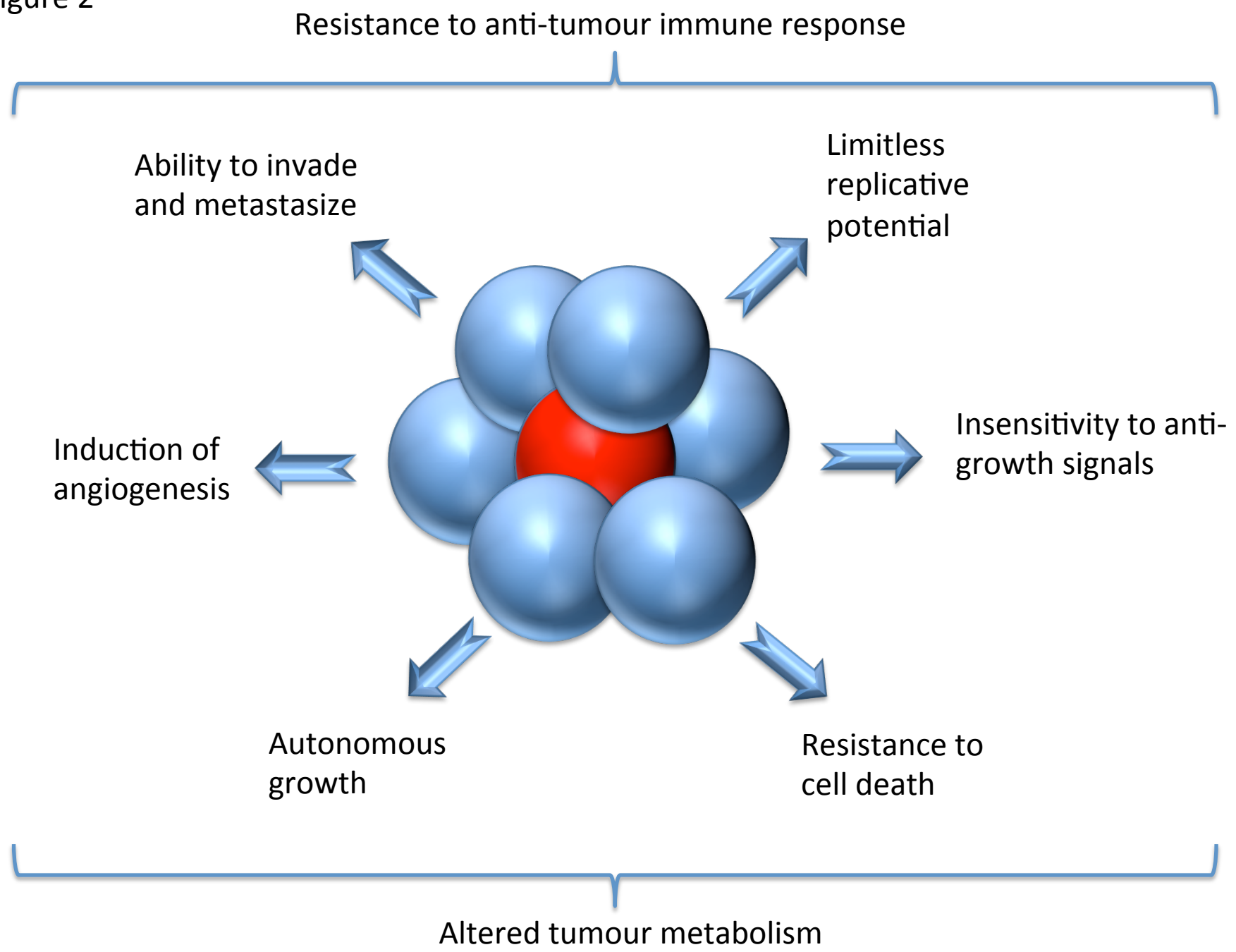


Figure 3

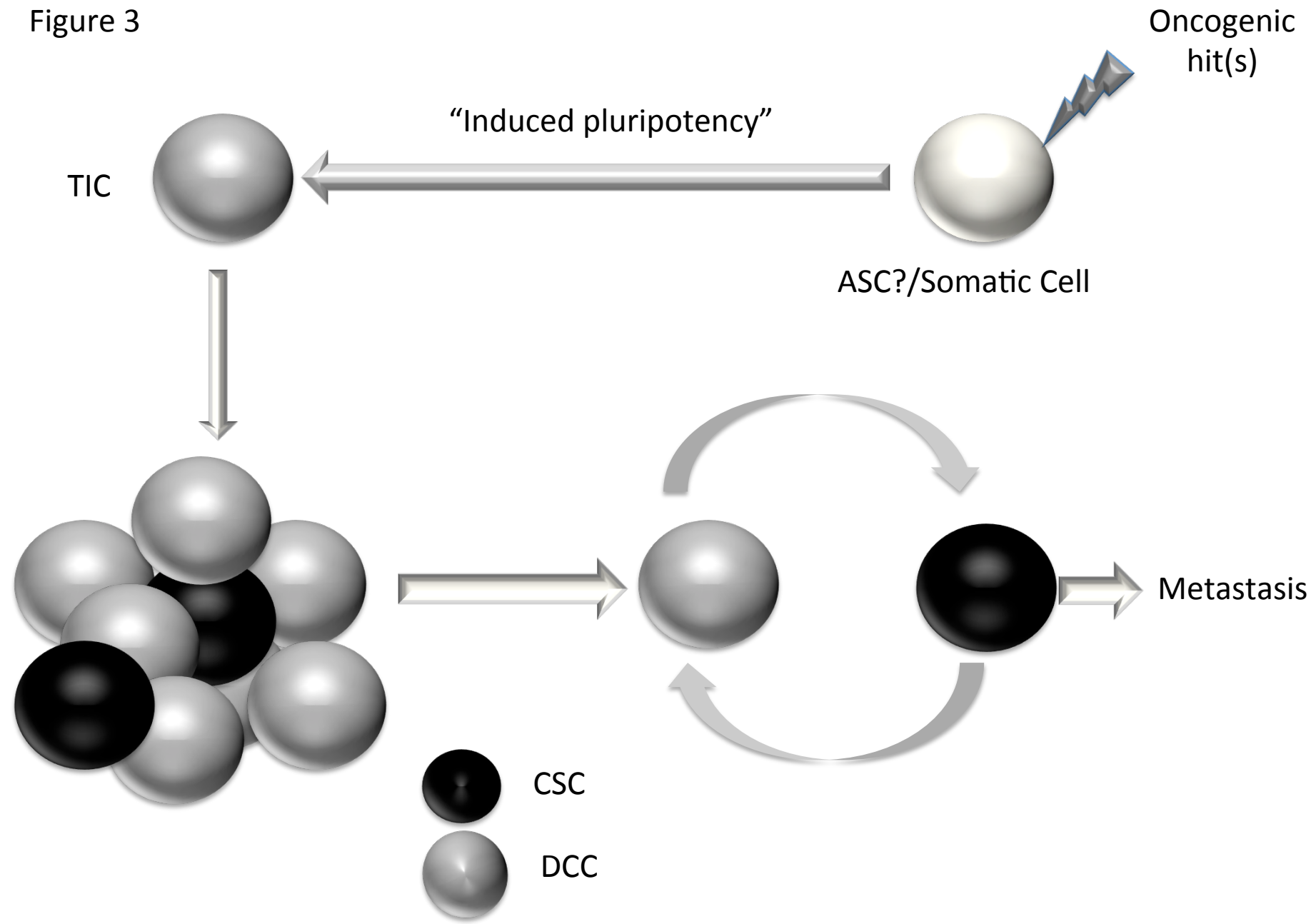


Figure 4

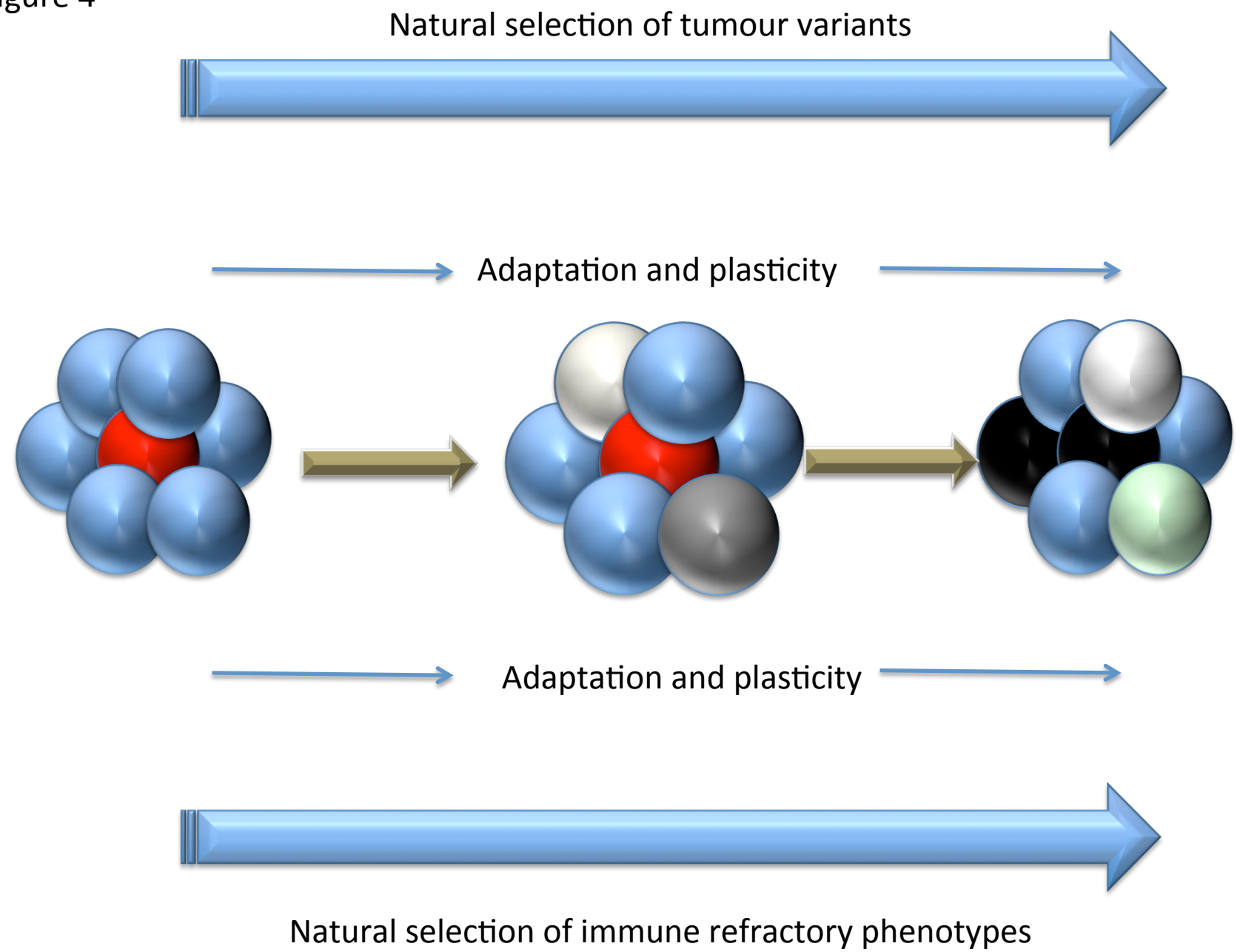


Figure 5

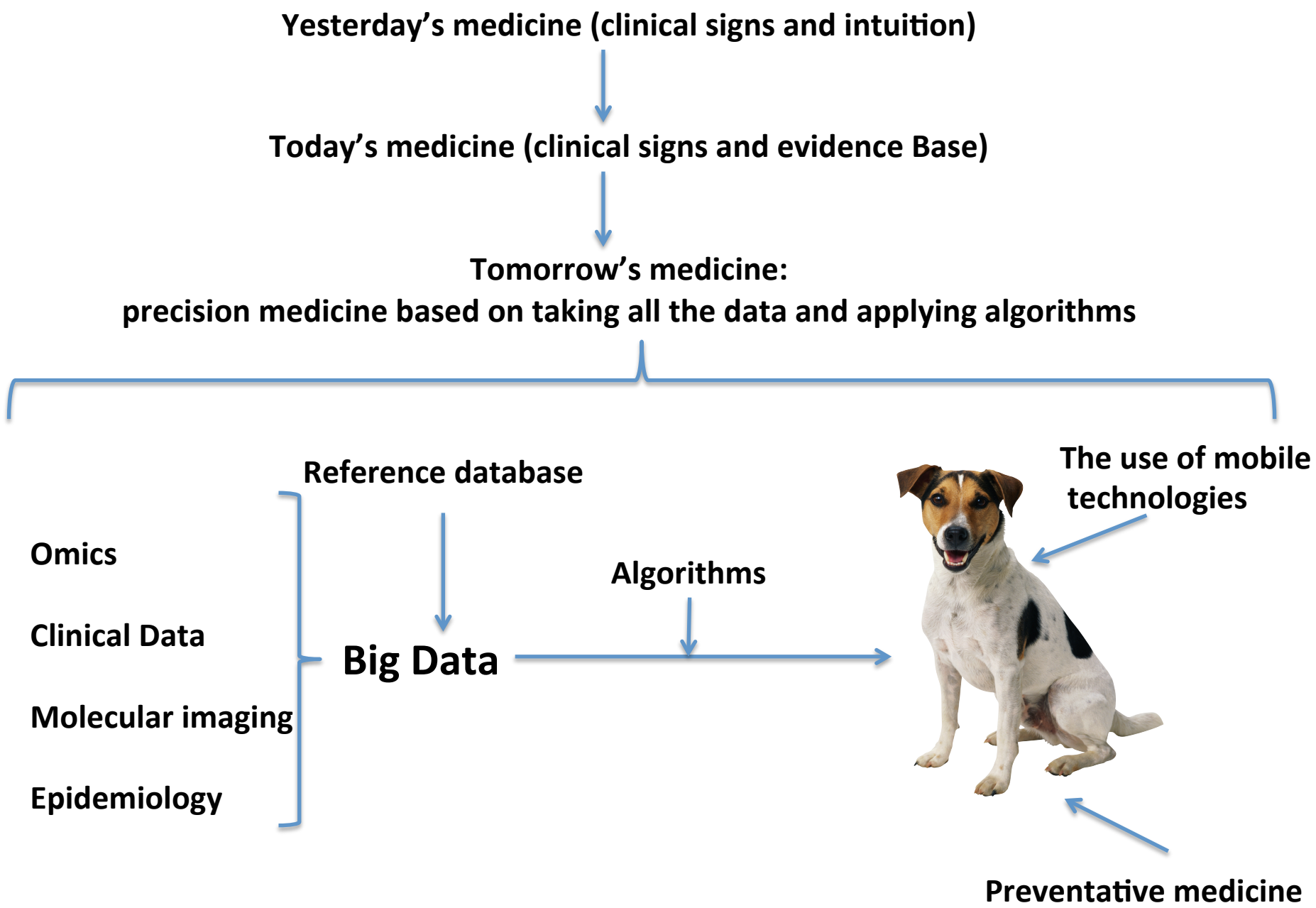


Figure 5

### **Highlights for Review**

- Our understanding of cancer has increased exponentially in the past 25 years
- Our treatment of cancers in domestic animals has greatly improved
- Our ability to generate data about cancer exceeds our capacity to analyse it
- Much effort is needed to bring disciplines together to understand large data sets in cancer as they are too complex to be considered in isolation
- As we move forward in veterinary medicine, we will become more reliant on ways to quickly assimilate data from multiple sources in order to make appropriate clinical judgements.