OMB No. 0925-0001 and 0925-0002 (Rev. 11/16 Approved Through 10/31/2018)

BIOGRAPHICAL SKETCH

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NAME: Brown, J. Martin

eRA COMMONS USER NAME (credential, e.g., agency login): MARTIN.BROWN

POSITION TITLE: Professor

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)

| INSTITUTION AND LOCATION | DEGREE(if applicable) | Completion DateMM/YYYY | FIELD OF STUDY |
| --- | --- | --- | --- |
| Birmingham University, UK | BS | 07/1963 | Physics |
| London University, UK | MS | 07/1965 | Radiation Physics & |
| Oxford University, UK | PHD | 07/1968 | Cancer Biology |
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**A. Personal Statement**

My lab has been actively involved in preclinical testing of strategies to enhance the efficacy of local tumor irradiation for the past 45 years, mostly focusing on overcoming or exploiting the low oxygen status (hypoxia) of tumors. Our entire focus has been on radiosensitizing tumors without sensitizing normal tissues and we have in the past developed a hypoxic cell radiosensitizer (etanidazole), and a hypoxic cell cytotoxin (tirapazamine), both of which have undergone phase III clinical testing. About 9 years ago we made an important discovery that fundamentally changed our direction with our novel finding that irradiation produced a large influx of monocytes/macrophages into the tumor. Further we showed that this influx could be inhibited by blocking the SDF-1/CXCR4 pathway, and that this produced a marked enhancement of the radiation response of the tumors. This led to a productive collaboration with Dr. Recht with his ENU induced brain cancer model in rats. In turn this developed to the clinical trial of blocking the SDF-1/CXCR4 pathway with GBM. I have developed considerable expertise in macrophage biology and have accumulated important reagents that will be important for the future development of this project. At the end of May 2016 I closed my own lab and joined that of Dr. Recht on a 25% appointment so as to continue our collaboration.

Relevant publications:

1. Kioi, M, Vogel, H, Schultz, G., Hoffman, RM., Harsh, GR., Brown, JM (2010) Inhibition of vasculogenesis, but not angiogenesis, prevents the recurrence of glioblastoma following irradiation in mice. J Clin Invest 120:694-705.
2. Ahn, GO Tseng, D, Liao, CH, Dorie, MJ. Czechowicz, A. Brown, JM (2010) Inhibition of Mac-1 (CD11b/CD18) enhances tumor response to radiation by reducing myeloid cell recruitment. PNAS 107(18):8363-8,
3. Liu,S-C., Alomran,R.,.Chernikova,SB., Lartey, F, Stafford,J., Jang,T., Merchant,M., Zboralski,D., Zöllner,S., Kruschinski, A., Klussmann,S., Recht, L., Brown, JM (2014): Blockade of SDF-1 after irradiation inhibits tumor recurrences of autochthonous brain tumors in rats, Neuro-Oncology;16(1):21-8.
4. Deng, L, Stafford, JH., Liu, S-C., Chernikova SB., Merchant, M., Recht, L., Brown, JM (2017) SDF-1 Blockade Enhances Anti-VEGF Therapy of Glioblastoma and Can Be Monitored by MRI. Neoplasia 19 (1) 1-7.

**B. Positions and Honors**

**Positions Held:** Stanford University, Dept. Radiation Oncology 1968–2016,

 Department of Neurology, 2016 - present

 Post-doctoral Fellow, l968–70
Research Associate, l970–7l
Assistant Professor, l97l–77
Associate Professor, l977–84
Professor, 1984–2016

 Emeritus Professor, 2016-present

 Director, Division of Radiation and Cancer Biology, 1984–2003
Director, Stanford University Interdepartmental Program in Cancer Biology, 1990–2002

**Honors and Awards:** Ninth Radiation Research Society Research Award, l980.
Henry S. Kaplan Memorial Teaching Award, 1989.
Radiation Study Section, 1992–96 (Chair, 1994–96)
AACR Bruce Cain Memorial Awardee, 1999.
ASTRO Gold Medal, 1999.
G.E. Adams Award: 1st International Conf. on Translational Research, 2000.
Failla Award, Radiation Res Society, 2000.
Weiss Medal, Association for Radiation Res, 2001
Honorary member of the European Society for Therapeutic Radiology & Oncology 2003

 Henry S. Kaplan Distinguished Scientist Award, International Association of Radiation Research, 2007

 Honorary Member Association for Radiation Research 2015

 Current Associate Editor of *Radiotherapy & Oncology, Neoplasia, Cancer Letters, Molecular Cancer Therapeutics* and *Cancer Biology & Therapy.*

**C. Contributions to Science**

1. **Identification of acute hypoxia and the importance of intermediate hypoxia in tumors**

Based on histological data it was postulated in 1955 by Thomlinson and Gray that human solid tumors would contain hypoxic cells due to the limited diffusion of oxygen through respiring tumor tissue and that these might limit the effectiveness of radiation therapy. This is the so-called model of chronic hypoxia. However, though these hypoxic cells certainly existed in tumors they did not explain certain phenomena such as the rapid “reoxygenation” of the surviving hypoxic cells after irradiation. In 1979 I published a paper showing that based on my own data of the pattern of killing of tumor cells by the drug misonidazole there must be a second type of hypoxic cells produced by the fluctuating blood flow in tumor blood vessels and which would also explain reoxygenation. These I called “acutely” hypoxic cells, a term used to this day. This novel concept has been validated by many investigators, is part of all textbooks dealing with tumor hypoxia and has fundamental implications for methods of overcoming tumor hypoxia.

 Over the years many investigators have modeled the influence of hypoxia on the effects of radiation on tumors and have concluded that if the dose is given in small (2Gy) doses over 6 or 7 weeks there is very little impact of tumor hypoxia. I realized however that all the models failed to take into account the fact that because there has to be a gradient of oxygen from the blood vessels to the most hypoxic tumor cells that there must be a large percentage of the tumor cells at intermediate hypoxia and intermediate radioresistance. Working with my post-doc Brad Wouters we showed using the diffusion equations for oxygen through tissue and the known radiosensitivity of cells at all oxygen levels that in fact these cells at intermediate hypoxia dominate the response with fractionated radiotherapy and therefore that fractionated by no means eliminates the hypoxia problem. We also showed that these cells could not be sensitized by current hypoxic cell radiosensitizers. Again this was a novel concept that has important implications for radiotherapy.

 1. Brown, JM. 1979. Evidence for acutely hypoxic cells in mouse tumours, and a possible mechanism of reoxygenation. British Journal of Radiology 52: 650-656.

 2. Wouters, B.G. and Brown, J.M. (1997) Cells at intermediate oxygen levels can be more important than the “hypoxic fraction” in determining tumor response to fractionated radiotherapy. Radiat. Res. 147: 541–550.

1. **Development of the hypoxic cell radiosensitizer etanidazole and its use in SBRT**

In the mid 1970’s work of Ged Adams and colleagues in the UK identified nitro aromatic compounds as able to radiosensitize hypoxic cells without changing the radiosensitivity of oxygenated cells. The lead compound, which showed excellent activity in mouse tumors was the 2-nitroimidazole misonidazole. This went into clinical trials but was soon shown to be too neurotoxic to be delivered at adequate doses with each radiation dose. Thus a less toxic but equally efficient drug was needed. My lab formed a collaboration with a chemistry group under Dr. Bill Lee to find such a drug based on rationally synthesizing and testing more polar analogs to exclude entry into neural tissues but still retaining penetration into tumors. This was achieved with the development of the 2-nitroimidazole SR2508, subsequently named etanidazole. Much clinical testing followed which validated that it was much less neurotoxic and it was eventually tested in a phase III randomized trial with head and neck cancer by the RTOG. However, the result was negative because the individual drug doses with each of the 30-fraction radiation doses were still too low for adequate radiosensitization as well as the issue intermediate hypoxic cells, which cannot easily be sensitized by these agents. We also showed that the efficacy of these agents could be enhanced by depletion of intracellular glutathione. Though this hypoxic radiosensitizer was not effective with fractionated irradiation we showed that it would be highly effective with the current use of stereotactic body radiotherapy (SBRT), and we are currently helping to get such a trial off the ground. This could markedly improve outcomes from SBRT.

1. Brown, J.M. and Workman, P. (l980) Partition coefficient as a guide to the development of radiosensitizers which are less toxic than misonidazole. Radiat. Res. 82: l7l–l90.
2. Brown, J.M., Yu, N.Y., Brown, D.M. and Lee, W.W. (l98l) SR-2508: A 2-nitroimidazole amide which should be superior to misonidazole as a radiosensitizer for clinical use. Int. J. Radiat. Oncol. Biol. Phys. 7: 695–703.
3. Bump, E.A., Yu, N.Y. and Brown, J.M. (1982) Radiosensitization of hypoxic tumor cells by depletion of intracellular glutathione. Science 217: 544–545.

4. [Brown JM](http://www.ncbi.nlm.nih.gov/pubmed?term=%22Brown%20JM%22%5BAuthor%5D), [Diehn M](http://www.ncbi.nlm.nih.gov/pubmed?term=%22Diehn%20M%22%5BAuthor%5D), [Loo BW Jr](http://www.ncbi.nlm.nih.gov/pubmed?term=%22Loo%20BW%20Jr%22%5BAuthor%5D). (2010) Stereotactic ablative radiotherapy should be combined with a hypoxic cell radiosensitizer. Int J Radiat Oncol Biol Phys. 2010 Oct 1;78(2):323-7.

1. **Development of the hypoxic cytotoxin tirapazamine**

With the realization that the available hypoxic cell radiosensitizers were unlikely to be successful with fractionated irradiation came the insight that if we could find a drug that killed hypoxic cells at very low concentrations this would be a perfect complement to irradiation. We thus embarked with the chemist Bill Lee to find such a drug based on the simple principle that such a drug would need to be electron-affinic and be a substrate for intracellular reductive enzymes. We found such a drug in the benzotriazine di-N-oxide SR4233, subsequently named tirapazamine. My lab spent years testing this drug, characterizing its action in various settings with radiation and chemotherapy and determining its mechanism of action. It was licensed to Sanofi and clinical testing was started. It proved very effective when combined with radiotherapy on head and neck tumors when the hypoxic tumors were selected. Unfortunately a multi-center phase III trial did not show a positive response but this was demonstrated to be the result of major protocol violations in some centers as well as lack of selection of hypoxic tumors. This negative result however, effectively killed the drug. The importance of this work is that it shows that tumor hypoxia can be turned from a disadvantage to an advantage in cancer therapy.

1. Zeman, E.M., Brown, J.M., Lemmon, M.J., Hirst, V.K. and Lee, W.W. (1986) SR 4233: A new bioreductive agent with high selective toxicity for hypoxic mammalian cells. Int. J. Radiat. Oncol. Biol. Phys. 12: 1239–1242.
2. Baker, M.A., Zeman, E.M., Hirst, V.K. and Brown, J.M. (1988) Metabolism of SR 4233 by Chinese hamster ovary cells: basis for selective hypoxic cytotoxicity. Cancer Res. 48: 5947–5952.
3. Brown, J.M. and Lemmon, M.J. (1991) SR 4233: A tumor specific radiosensitizer active in fractionated radiation regimes. Radiother. and Onc. 20: 151–156.
4. Brown, J.M. (1993) SR 4233 (Tirapazamine): a new anticancer drug exploiting hypoxia in solid tumours. Br. J. Cancer, 67: 1163–1170.
5. **Overcoming the mistaken dogma that apoptosis is the way that cells die from anticancer agents**

In the late 1990’s a widely held tenet of oncology was that tumor cells treated with anticancer agents die from apoptosis, and that cells resistant to apoptosis (such as with mutant p53) are resistant to cancer treatment. This and other short-term assays formed the basis for testing of chemotherapy agents (such as the NCI 60-cell panel). It also led to numerous grants on how to manipulate apoptosis and to many clinical studies to determine the status of apoptosis determining genes such as Bcl-2 and p53 in clinical samples. However, I knew from our own and others’ experience with irradiation that the cells of solid tumors died of a mitotically linked death and whether or not the cells eventually showed an apoptotic morphology (or had mutated Bcl-2, Bax or p53) did not affect their eventual level of cell death. We performed many experimental studies demonstrating that depending on their genetic makeup cells could have very different levels of short term death or apoptosis with no difference in overall cell kill determined by colony formation or tumor response. We summarized these in widely-cited Cancer Research and a Nature Reviews Cancer papers. These studies, reported not only in these papers but in two symposia at the AACR meetings, helped the oncology community realize that cells can die by several different ways and an assay such as colony formation has to be used to determine the overall level of cell kill or permanent cell arrest. The Cancer Research paper listed below was recently (Dec 1, 2016) highlighted in the Cancer Research 75th Anniversary Commentaries (Flores, ER Cancer Res December 1 2016 76 (23) 6763-6764)

1. Brown, J.M. (1997) Commentary: NCI’s Anticancer Drug Screening Program May Not Be Selecting for Clinically Active Compounds. Oncology Res. 9: 213–215.
2. Brown, J. M. and Wouters, B.G. (1999) Apoptosis, p53 and tumor cell sensitivity to anticancer agents. Cancer Res. 59: 1391–1399. (Highlighted in Dec 1, 2016 in Can. Res. 75th Anniversary Commentaries
3. Wouters, B.G., Denko, N.C., Giaccia, A.J., and Brown, J.M. (1999) A p53 and apoptotic independent role for p21waf1 in tumour response to radiation therapy. Oncogene 18: 6540–6545.
4. Brown, J.M. and Attardi, L.D. (2005) The role of apoptosis in cancer development and treatment response. Nat. Rev. Cancer 5(3): 231–237.
5. **Identification of the influx of macrophages into tumors after irradiation and the potentiation of the tumor response by inhibiting this influx.**

This work began with my realization that tumors recurring after very large doses of irradiation probably developed their vasculature from circulating blood vessel forming cells because the doses given would be sufficient to sterilize all the endothelial cells in the tumor and surrounding normal tissue that was also irradiated. My lab therefore set out to identify such cells using tumor-bearing chimeric mice with GFP bone marrow. What we found (and this was a novel discovery in the radiation field) was that there was a major influx after irradiation of bone marrow cells that became tumor associated macrophages (TAMs) and that these cells had to express MMP-9 for the blood vessels to be reconstituted. We then showed that induced hypoxia leading to increased HIF-1 levels and it’s downstream gene product SDF-1(CXCL12) was responsible for the influx. Importantly we demonstrated that this pathway could be blocked by pharmacological inhibitors of HIF-1, SDF-1 and its receptor CXCR4 and that this not only prevented the influx of TAMs but also produced a major delay or absence of tumor recurrences after irradiation. We have tested this strategy in several different models including subcutaneous head and neck xenografts and intracranial xenografts in mice and rats and chemically induced tumors in rats. In all cases we have shown a dramatic improvement in tumor response to irradiation. Since our first work others have demonstrated similar effects with some chemotherapeutic agents. Based on this preclinical work, we (L. Recht and myself) have launched a Phase I/II clinical trial that assesses the impact of administering the CXCR4 blocker, Plerixafor, in combination with standard treatment of GBM. This work establishes a new paradigm for how to sensitize tumors to cancer treatment, focusing entirely on the tumor microenvironment rather than the tumor cells. Early indication from this trial are positive.

1. Kioi, M, Vogel, H, Schultz, G., Hoffman, RM., Harsh, GR., Brown, JM (2010) Inhibition of vasculogenesis, but not angiogenesis, prevents the recurrence of glioblastoma following irradiation in mice. J Clin Invest 120:694-705.
2. Ahn, GO Tseng, D, Liao, CH, Dorie, MJ. Czechowicz, A. Brown, JM (2010) Inhibition of Mac-1 (CD11b/CD18) enhances tumor response to radiation by reducing myeloid cell recruitment. PNAS 107(18):8363-8,
3. Liu,S-C., Alomran,R.,.Chernikova,S.B., Lartey, F, Stafford,J., Jang,T., Merchant,M., Zboralski,D., Zöllner,S., Kruschinski, A., Klussmann,S., Recht, L., Brown, JM (2014): Blockade of SDF-1 after irradiation inhibits tumor recurrences of autochthonous brain tumors in rats, Neuro-Oncology;16(1):21-8
4. Brown, JM, Recht, L.,Strober, S. (2017): The Promise of Targeting Macrophages in Cancer Therapy**,** Clinical Cancer Res 23(13) 3241- 50

**List of publications (172 most recent from total of 312)**

https://www.ncbi.nlm.nih.gov/sites/myncbi/john.brown.1/bibliography/41156414/public/?sort=date&direction=descending

**D. Additional Information: Research Support and/or Scholastic Performance**

**Completed Research Support in past 3 years**

1R01 CA149318 Brown (PI) 08/01/11- 05/31/16

 No cost extension 06/31/17-05/31/17

 “Development of Clinical Strategies to Prevent GBM Recurrences After Radiotherapy”

The goal of this project is to test various strategies in preclinical models of inhibiting vasculogenesis to improve the cure rate of glioblastomas.

Role: PI

W81XWH-15-1-0031 DoD Breast Cancer Breakthrough Award 03/01/15 - 02/31/17

“Elimination of the Neurocognitive Defects following Whole Brain Irradiation for Breast Cancer Metastases”

Role: PI

The goal is to show that by blocking the SDF-1 pathway lower doses of whole brain irradiation can be delivered to achieve the same response of breast cancer brain metastases with lower cognitive defects.

2R44CA144817-STN001 (subaward of SBIR to NuvOx Pharma) 09/25/2014 – 05/31/2016

Role: PI

The goal is to determine the effect of the perfluorocarbon NVX108 on the oxygenation and response of the rat C6 GBM to irradiation.