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INDEX

A

aclarubicin, 47
activation of influenza virus, 21
activation of iNOS, 35
activation of kallikrein-kinin cascade, 21
Akaike, Takaaki, 21,57
albumin, 13,20,21,30, 31, 46
albumin-binding properties, 13
amino acid sequence, 8, 52
angina pectoris, 45
angiotensin II (AT), 2, 31, 37, 40, 41, 42
angiotensin II (AT) induced high blood pressure, 41,42
antigenicity, 13
antioxidant activity, 27
antitumor effect of NCS, 11
antitumor protein, 5
ARCO, 10
Asakawa Award, 22
AT-II, 31, 40, 41
AT-II-induced hypertension, 31
AUC (area under the concentration-time curve), 33, 51
augment the EPR, 53
augmentation of the EPR, 41
augmentation of EPR effect, 46

B

bacterial proteases, 1, 19, 21, 22
Bharate, G., 49
bilirubin, 47, 48
biliverdin, 47
bradykinin, 1, 20, 21, 29, 35, 36
bradykinin generation, 21

C

cancer, 2, 18, 26, 39, 42, 43, 46, 47
cancer chemotherapy, 46, 47
cancer treatment, 14
canolol, 27
carbon monoxide (CO), 36, 47
carcinogenesis, 1, 26, 27
CCRF, 7, 8
Chemical and Engineering News, 10, 52
chemical modification, 3, 9, 23, 29
chemical structure of SMANCS, 11
Children's Cancer Research Foundation (CCRF), 7
Children's Hospital Boston, 7, 34
Christophi, C., 35,57
chronic myelogenous leukemia cells, 49

cisplatin, 48
 citation frequency, 37
¹⁴C-labeled Lipiodol, 16, 17
 cleavage of hemagglutinin, 21
 clinical development of NCS, 11
 clinical effects, 52
 CO (carbon monoxide), 36,48
 collagenase (MMPs), 36
 Commemorative Gold Medal Award, 22
 compartment models, 12, 65
 computed tomography (CT), 15
 Controlled Release Society, 38
 CT images, 16
 CT scan images, 31, 41
 cytochrome-P450 reductase, 24

D

Dana-Farber Cancer Institute, 7
 Daruwalla, J., 34, 57
 Davis, California, 3, 30
 degradation of DNA, 11
 Department of Surgery, 13, 15, 37
 details of the EPR Effect, 29
 difficult-to-treat cases, 41
 discovery of the EPR, 2, 13, 29, 32, 43
 disintegration, 34, 49
 DIVEMA (divinyl ether and maleic
 anhydride copolymer), 23, 32
 DNA synthesis, 11
 doxorubicin, 47
 drawbacks of NCS, 13
 Duncan, Ruth, 10, 32,33,57
 Dvorak, H., 36

E

E. K. Frey-E. Werle Foundation, 22
 effect of SOD, 25
 elevating blood pressure, 40
 encapsulated drugs, 49
 endocytotic intracellular uptake, 49
 endogenous free, 1,22, 23, 55

endogenous oxidants, 48
 endyene chromophore, 52
 enhanced permeability and retention
 (EPR) effect, 12,30
 enhanced vascular permeability, 29
 enhancement of EPR effect, 39,46
 EPR effect, 2, 12, 13, 14, 29, 30, 31, 32,
 33, 35, 36, 37, 39, 40, 41, 43, 45, 46,
 53
 EPR effect and molecular weight, 33
 EPR effect, augmentation of, 41, 46
 EPR effect-based drugs, 53
 EPR effect citation, 37
 EPR effect, enhancement of, 40, 39
 Evans blue, 20, 21, 29, 31
 Evans blue-albumin, 21, 31, 46
 extravasation, 20, 21, 29, 30, 31, 35, 36

F

Factor XII, 20
 factors facilitating the EPR effect, 35
 Fang, Jun, 36, 45, 47, 48, 57
 Farber, Sidney, 7, 8
 Feeney, E. Robert, 3,5,51
 femoral artery, 14, 15
 fluorescein isothiocyanate (FITC), 6
 Folkman, Judah, 34
 free radicals, 1, 22, 23, 53, 57
 Fritz, Hans, 22, 57
 Fulbright, 3

G

gallbladder cancer, 41, 42
 Gandy, B. Judith, 57
 genetic divergence, 53
 Glaser, Charles, 8
 Greish, Khaled, 40, 47, 48, 57

H

Hageman factor, 20

Hakuaikai hospital, 40
Harvard Medical School, 7, 34, 40
heat shock protein, 36, 47
Helicobacter pylori, 27
hemagglutinin of influenza virus, 21
heme oxygenase-1 (HO-1), 47
hepatic artery, 14, 16, 17, 31, 42
hepatocellular carcinoma (HCC), 16, 39, 42, 52
hepatoma, 15, 16, 31, 32, 52
heterogeneity of EPR effect, 39, 45
Hinuma, Yorio, 8
Hirano, Takashi, 23
HO-1, 36, 47, 49
HO-1 inhibitor, 36, 49
honorary citizen, 32
honorary mayor, 32
HPMA (hydroxypropyl methacrylate copolymer), 32
HPMA-copolymer, 33
Hsp-32, 38
hydrophobic, 10, 13
hypertensive state, 40, 41
hypovascular tumors, 39
hypoxia-inducible factor (HIF-1 α), 39, 40, 46

I

immunogenicity, 13, 51
immunoglobulin, 30
immunosuppression, 13
inactivation, 51, 52
inducible form of NOS, 35
inflammation, 1, 19, 26, 27, 35, 36, 53
influenza virus, 1, 21, 22, 23
influenza virus infection, 1, 21, 22, 23, 25, 27
iNOS, 26, 35
Institute of Macromolecular Chemistry, 32
intracellular uptake, 9, 49
involvement of proteases, 22
ISDN; isosorbitol dinitrate, 46

Ishida, Nakao, 5, 7, 11, 52
Iwai, Ken, 17
Iyer, A. K., 48

J

Japan NO Meeting, 55
Japan Society of Drug Delivery System, 38, 55, 59
Japanese Society for Bacteriology, 22, 55
Journal of Drug Targeting, 43, 55
Journal of Medicinal Chemistry, 10

K

kallikrein-kinin cascade, 1, 20, 21, 22, 35
Kamata, Ryuji, 19
Kanamaru, Ryunosuke, 11, 57
Kawauchi, Hiroshi, 6
Kimura, Masami, 35, 57
kinin, 1, 20, 21, 22, 29, 35
kinin generation, 22, 29
Kobe University, 55
Koch, Robert, postulate of, 1, 23
Konno, Toshimitsu, 13, 14, 15, 16, 17, 32, 57
Kumagai, Katsuo, 6, 11
Kumamoto, 8, 9, 32, 40, 52, 55, 57
Kumamoto University, 9, 55
Kumamoto University Hospital, 13
Kumamoto University Medical School, 8, 9, 21
Kuraray Company, 10
Kuromizu, Kenji, 8
Kuwahara, Hideo, 27

L

laparotomy, 14, 15
Li, Chang, 40
Li, Chao Hao, 8
Linus Pauling, 23

Lipiodol, 14, 15, 16, 17, 52
 liquid ammonia, 8
 low vascular density, 39
 low vascular density tumor, 40
 lung cancer, 46
 lymphatic clearance, 17, 37
 lymphatic metastasis, 9
 lymphotropic drug, 9

M

macromolecules, 2, 9, 17, 30, 37, 40, 46
 macrophages, 13
 Maki, Shojiro, 32, 57
 Maruo, Keishi, 21, 57
 massive metastatic liver cancer, 43
 massive renal cell carcinoma, 42
 Matsumoto, Koki, 19, 20, 57
 Matsumura, Yasuhiro, 29, 30, 31, 35, 57
 Meares, Claude F., 30
 mechanism of mutation, 27
 metastatic liver cancers, 39, 42, 43
 micelle formation, 47
 micronodules, 34
 minimum inhibitory concentration, 11
 molecular target drugs, 52, 53
 molecular weight and AUC, 33
 Molla, Akhteruzzaman, 20, 57
 Moncada, Salvador, 55, 57
Mongolian gerbil, 27
 Müller-Esterl, Werner, 22
 mutant virus, 26
 mutants of virus and bacteria, 24
 mutation, 26, 27, 53
 myocardial infarction, 45

N

Nagai Award, 38, 59
 Nagai Innovation Award for Outstanding Achievement, 38
 Nagamitsu, Akinori, 40
 Nakamura, Hideaki, 49

National Cancer Center Hospital East, 29
 National Cancer Institute, 5
 National Institutes of Health (NIH), 6
 natural killer (NK) cells, 13
 NCS, 1, 5, 6, 8, 9, 10, 11, 12, 13, 23, 30
 Neocarzinostatin (NCS), 1, 5, 52
 nitration of G, 24
 nitric oxide, 2, 23, 36, 55
 nitric oxide synthase, 23
 nitrite ion (NO₂⁻), 45
 nitroglycerin, 2, 45, 46
 NO, 23, 24, 26, 47, 48
 NO releasing agents, 47
 NOS, 24, 26

O

O'Brien, Paul, 34
 Oda, Tatsuya, 23
 Okamura, Ryoichi, 19
 oncogene *bcl/abl*, 49
 one-compartment model, 12,
 Ono, Yasushi, 11
 ONOO⁻, 24, 26, 36
 ophthalmology, 19
 Osaka University, 55
 ovalbumin, 30
 ovarian cancer, 44
 ovomucoid, 3, 30

P

pancreatic cancer, 42, 43, 44
 pegylated proteins, 14, 52
 PEGylated ZnPP, 47
 PEG-ZnPP, 47, 48
 peroxy nitrite, 24, 26, 36
 pharmacokinetics, 9, 11, 12, 32, 48, 51
 pharmacokinetics of NCS, 11, 12
 pin point delivery, 34
 pinpoint targeting, 2
 pirarubicin, 34, 47, 48
 plasma concentration, 51

pO₂, 45, 46
 poly(styrene-co-maleic anhydride)
 (SMA), 10
 polymer leakage, 34
 polymer-conjugated superoxide
 dismutase (SOD), 22
 Postulates of Robert Koch, 1, 23
 protease, 1, 3, 19, 21, 22, 29, 51, 55
 protein drugs, 51, 52, 53
Pseudomonas aeruginosa, 19
 pyran copolymer, 23
 pyran-conjugated SOD, 23, 25

R

Raeder, Beate, 49
 reactive nitrogen species (RNS), 1, 19
 reactive oxygen species (ROS), 1, 19, 48,
 52
 Regelson, William, 32
 renal cell carcinoma, 39, 42, 44
 renal excretion, 12
 Ringsdorf, Helmut, 32, 38, 43, 57
 ROS, 1, 19, 23, 26, 27, 48
 ROS and RNS in infection, 26
 Royal Pharmaceutical Society, 43

S

Sahoo, S. K., 49
Salmonella, 27
 San Antonio, 32
 scanning electron micrographs of
 vascular casts, 34
 scavenger of NO, 35
 Seki, Takahiro, 45
 Seldinger's method, 15
 Sendai virus, 5, 26
Serratia marcescens, 19
 serratial 56K protease, 21
 Seymour, Len, 32, 57
 SMA, 1, 10, 13, 30, 34, 47, 48, 49, 51
 SMA micelles, 47, 48, 49

SMANCS, 1, 2, 10, 13, 16, 30, 31, 32,
 40, 41, 43, 44, 46, 51, 52,
 SMANCS application, 16
 SMANCS/Lipiodol, 14, 15, 16, 17, 31,
 40, 46
 SMANCS/Lipiodol infusion, 46
 SMANCS/Lipiodol injection, 31
 SMANCS, structure of, 11
 SMANCS synthesis, 10, 37
 SMA-pirarubicin micelles, 34, 50, 70
 SMA-THP (pirarubicin), 49
 SMA-ZnPP, 47, 49
 Society of Cancer Prevention of Japan,
 55
 SOD, 1, 22, 23, 25
 solid tumor tissues, 30
 solid tumors, 2, 20, 30, 32, 35, 37, 39, 53
 State of Oklahoma, 32
 stomach cancer, 42, 43
 structure-activity relationships, 9
 super oxide, 1, 22, 23, 25
 super oxide dismutase [SOD], 1, 22, 23
 Suzuki, Maro, 40

T

Takaki, Asami, 57
 Takeshita, Jiro, 10
 Taniguchi, Naoyuki, 55
 Tatematsu, Shoen, 27
 taxol, 47
 the B-type staining (peripheral ring
 shape), 43
 therapeutic effect of SMANCS
 (SX)/Lipiodol (LP), 42
 THP, 47, 48, 49
 time dependent increase of tumor uptake,
 33
 tissue distribution, 9, 51
 tissue oxygen tension (pO₂), 45, 46
 Toda, Noboru, 57
 Tohoku University, 3, 5, 11
 Tohoku University Medical School, 5,
 11

transferrin, 30
 tumor necrosis factor (TNF)- α , 36
 tumor nodules, 34
 tumor uptake of macromolecules, 30
 tumor-selective drug delivery, 2, 16, 34
 two-compartment model, 12

vesicorenal recirculation, 12
 viral infection, 1, 22, 23, 49
 virus infectivity, 21, 22
 vivo half-life, 23, 51
 VPF/VEGF, 36
 VX-2, 14, 16

U

ubiquitous characteristics, 53
 Ulbrich, Karel, 32
 University of California, 3, 8, 30
 University of Melbourne, 34
 University of Vienna, 49
 urinary bladder, 12
 urinary excretion, 12, 51, 52

V

Valent, Peter, 59
 vascular density, 37, 39, 40
 vascular endothelial cell growth factor
 (VEGF), 36
 vascular extravasation, 20
 VEGF, 36, 40, 46

W

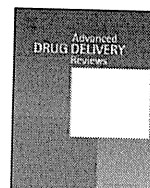
Walker 256 tumor, 6

Y

Yamanouchi Pharmaceutical Company,
 11, 52
 Yokoyama, Ikuzo, 15, 16
 Yokoyama, Mitsuhiro, 55

Z

zinc protoporphyrin (ZnPP), 50, 71
 ZnPP, 47, 48, 49



Preface

EPR effect based drug design and clinical outlook for enhanced cancer chemotherapy[☆]

Twenty-five years have already passed since our discovery of the enhanced permeability and retention (EPR) effect [1]. The concept of the EPR effect has prevailed in a wide range of applications including antibody delivery, gene delivery, and other nanomedicine-based delivery systems such as micellar, liposomal and polymer conjugates. After a rather quiet initial two decades, its citations now reached more than 6000 and have been increasing logarithmically, as shown by J. Fang et al. [2] in this issue. It is an ideal time to assess the past and present state in terms of limitations and further development, because the EPR effect is a more general principle for tumor-selective drug delivery compared to “molecular target” drugs. In this connection, the limitations of macromolecular target drugs are discussed by Fang et al. [2] and the impact of the EPR effect in drug delivery is well documented by Torchilin in the Commentary [3].

This issue provides some historical background and covers a number of topics ranging from basic principles to clinical outlook, to advantages and limitations, to key factors involved and nanomedicines under clinical development. Based on the concept of the EPR effect, a more sophisticated drug design is presented by Harashima et al. and Murayama et al., and the circumvention of barriers in drug targeting is also discussed by Fang et al. in this issue [2].

One problem that has caused some concern is the heterogeneity of the EPR effect. When the tumor nodule is very small or at an early stage of cancer development, there is no heterogeneity. However, in larger or later-stage tumors, the EPR effect becomes heterogeneous. In the case of a mouse tumor nodule greater than 500 mg (>1.7 mg in rats), we found less production of nitric oxide, which is one of the major factors for EPR effect (see Fang et al. in this issue [2]). This would incidentally lower the extravasation of macromolecules into the interstitial tissue space. This concept may be applicable to the tumor implanted at a non-orthotropic site, which may exhibit a heterogeneous EPR effect of lower vascular density such as metastatic tumors in the liver, as clinically observed in CT scan images of primary vs. metastatic human liver cancer after intra-arterial injection of SMANCS/Lipiodol. The former was more uniform and exhibited denser vasculature, and thus higher EPR effect, while the latter exhibited a hypovasculature pattern in the central part and thus lower EPR effect (heterogeneity). We (H.M.) recently published basic findings and clinical demonstrations to augment the EPR effect, and circumvention of this heterogeneity is discussed elsewhere [2,4–7].

Whatever minor issues might remain, nanomedicine drug development has been increasing during the past 10 years (for instance, see Ref. [8]). Along this line, the reviews by Sahoo et al., Maruyama et al., and Matsumura et al. give us the present situation of nanomedicine development and future prospects. Recent trends in this area of

polymeric drugs are reported by many authors more than ever, yet await for clinical breakthrough (see for instance ref.[9]).

Molecular targeting agents showed promise in the case of imatinib (Gleevec®). However, other cases appear disappointing, including antibody conjugates; some have unremarkable therapeutic effects and also occasionally exhibit serious side effects. The simple reason for this is that we have not yet found cancer-specific molecules that are universally effective for all or specific classes of cancer. Acquisition of information on the molecular biology of cancer is an ongoing process and molecular targeting agents are developed accordingly; however, it is still insufficient for cancer eradication. Consequently, there is an obvious need to clinically introduce the concept of the EPR effect as well as to improve conventional anticancer agents on this basis.

Under these circumstances, clinical application of nanomedicine based on the EPR effect would definitely benefit the patients, as discussed by Matsumura et al. in this issue. Furthermore, development of a method for augmenting the EPR effect, for instance, by using nitroglycerin, a nontoxic nitric oxide generator with proven safety if not overdosed, warrants future investigation and extension to the bedside.

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The EPR effect: Unique features of tumor blood vessels for drug delivery, factors involved, and limitations and augmentation of the effect[☆]

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ABSTRACT

The enhanced permeability and retention (EPR) effect is a unique phenomenon of solid tumors related to their anatomical and pathophysiological differences from normal tissues. For example, angiogenesis leads to high vascular density in solid tumors, large gaps exist between endothelial cells in tumor blood vessels, and tumor tissues show selective extravasation and retention of macromolecular drugs. This EPR effect served as a basis for development of macromolecular anticancer therapy. We demonstrated methods to enhance this effect artificially in clinical settings. Of great importance was increasing systolic blood pressure via slow angiotensin II infusion. Another strategy involved utilization of NO-releasing agents such as topical nitroglycerin, which releases nitrite. Nitrite is converted to NO more selectively in the tumor tissues, which leads to a significantly increased EPR effect and enhanced antitumor drug effects as well. This review discusses molecular mechanisms of factors related to the EPR effect, the unique anatomy of tumor vessels, limitations and techniques to avoid such limitations, augmenting tumor drug delivery, and experimental and clinical findings.

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Contents

1. Introduction	137
1.1. General problems in development of cancer treatment even after 50 years of endeavor	137
1.2. The EPR effect: the cutting edge	137
1.3. Problems related to the EPR effect and their solutions	137
2. The EPR effect: history and principle.	138
2.1. The EPR effect: a molecular size-based phenomenon	138
2.2. Problems and warnings during macromolecular drug development based on the EPR effect	139
2.3. Problems unrelated to EPR effect: various barriers to drug delivery to target tumor tissues.	140
3. Unique features of blood vessels in tumors: angiogenesis, hypervascularity, irregularity of blood flow, extensive vascular permeability, and abnormal lymphatic drainage	141
3.1. Abnormality of tumor blood vasculature: morphology	141
3.2. Lymphatic clearance of tumor tissue and lymphatic metastasis	141
4. Factors involved in the EPR effect	141
4.1. Bradykinin (kinin)	141
4.2. NO and its derivatives, and collagenase (matrix metalloproteinase)	142
4.3. Prostaglandins	144
4.4. Angiotensin-converting enzyme (ACE) inhibitors	144
4.5. Vascular endothelial growth factor	145

Abbreviations: NO, nitric oxide; SMA, styrene maleic acid copolymer; NCS, neocarzinostatin; CT, computed tomography; AUC, area under the concentration–time curve; IgG, immunoglobulin G; HPMA, *N*-(2-hydroxypropyl)methacrylamide; α_2 -M, α_2 -macroglobulin; XO, xanthine oxidase; RES, reticuloendothelial system; VEGF, vascular endothelial growth factor; SEM, scanning electron microscope; AT-II, angiotensin II; iNOS, inducible nitric oxide synthase; ONOO⁻, peroxynitrite; VPF, vascular permeability factor; PG, prostaglandin; SBTI, soybean trypsin inhibitor; cPTIO, carboxy-2-phenyl-4,4,5,5-tetramethylimidazole-1-oxyl-oxide; O₂⁻, superoxide anion radical; MMP, matrix metalloproteinase; NG, nitroglycerin; COX, cyclooxygenase; ACE, angiotensin-converting enzyme; HCC, hepatocellular carcinoma; ISDN, isosorbide dinitrate; pO₂, partial oxygen pressure.

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