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Enhancing DNA Repair by Combining only Dietary Supplement Ingredients that do not Metabolically Compete in Order to Achieve Synergism

Ronald W. Pero
Section of Immunology, BMC: D14 Lund University, Lund, Sweden

1. Introduction

Here this presentation embraces dietary supplement compositions containing resveratrol material, carotenoid material, nicotinamide material, DMAE material, zinc source material, and qjuinic acid-containing material , where no other known bioactive nutrient agents having competing modes of action to these specified agents are intentionally excluded from mixtures containing at least two of these DNA repair enhancing ingredients. The compositions may be embodied in formulations for oral administration, or alternatively, in formulations for peritoneal administration.

The combined composition may be selected from the group consisting of resveratrol (3, 5, 4'-trihydroxy-stilbene or an equivalent polyphenol in pure chemical form); the carotenoid material may be alpha carotene, beta carotene, canthaxanthin, lycopene and mixtures thereof; the nicotinamide material may be selected from the group consisting of nicotinamide, niacin, and mixtures thereof; the DMAE material selected from a group consisting of other choline analogs that pass the blood brain barrier; the zinc source material may be one or more zinc salts; and the quinic acid-containing material selected from a group consisting of quinic acid compounds that can enhance DNA repair by enhancing the uptake of tryptophan and nicotinamide ingredients (Pero et al 2009b; Pero and Lund 2011).

For human administration, the resveratrol material, carotenoid material, nicotinamide material, zinc source material, DMAE material, and quinic acid material may be present in proportions effective, in combination, to improve resistance to DNA damage, enhance DNA repair capacity, and stimulate immune function in a human subject to whom the composition is administered as a daily dosage (Pero et al 2009b; Pero and Lund 2011).

This formulation named Nutra-Reservatrol (Pero and Garret 2010) also contemplates the provision of a method of treating a human or other animal subject, consisting of administering resveratrol material, carotenoid material, nicotinamide material, DMAE material, zinc source material and quinic acid material to the subject to selectively supplement the subject's dietary intake thereof (i.e. without supplementing the dietary intake of any other active nutrient agents having competing modes of action) and repeating the administration on a substantially daily basis.

Thus, in a particular sense, this dietary supplement combination contemplates the provision of a method of treating a human subject consisting of selectively administering to the subject resveratrol material, carotenoid material, nicotinamide material, DMAE material, zinc source and quinic acid material in daily dosage amounts effective, in combination, to improve resistance to DNA damage, enhance DNA repair capacity, and stimulate immune function. In a specific example of currently preferred dosage range for humans, about 100-500 mg resveratol material, about 100 mg of carotenoid material, about 100 mg of nicotinamide material, about 100-200 mg DMAE material, about 10 mg of zinc source material and between 250-700 mg quinic acid source material are administered daily in this method (Pero and Garret 2010). So far as the author is aware, this particular combination of ingredients devoid of other bioactives has heretofore already been recognized as being synergistic or even effective (Pero 2000, Sheng et al 1998).

The discovery that natural products should not be combined into a natural medicine unless one tests whether each ingredient is additive to the overall desired biological effect, and that one way to accomplish this endpoint is to not combine natural products that have similar modes of action and thus competitive routes of absorption and excretion without first testing the combination for additive effects. That is to say, the present invention avoids inhibited uptake and absorption of natural products, thereby obtaining additive biological effects, by combining only natural products having well defined different, and thus potentially non-competitive modes of action which is, for example, the case with the exclusive combination of carotenoids + nicotinamide + zinc (Pero 2000, Sheng et al 1998).

Diet supplementation of humans or animals for example, by the oral, intraperitoneal, intravenous, subcutaneous or intramuscular routes of administration with the combination of carotenoids + nicotinamide/niacin + an appropriate zinc salt at a dose of this combination that exceeds a normal dietary levels was effective. This practice showed that dietary supplementation containing this combination together with simultaneous supplementation of other nutrients and/or natural products cannot enhance immune function (Payette, H. et al 1990; Zhang et al 1995), but when daily doses of carotenoids (as lycopene at 20 mg and Vitamin E 36 IU), niacin (120 mg) zinc salt (12 mg), reservatol (300 mg) and a quinic acid material (400 mg) were administered in the absence of other known DNA repair enhancers, and above dietary levels, the resistance to oxidative cellular DNA damage, and enhancement of DNA repair and immune function were observed in the clinic (Pero and Lund 2011). These data were taken as proof of concept for this dietary supplement to avoid metabolic competition and synergize DNA repair.

A clinical evaluation already published (Pero 2000, Sheng et al 1998) was also determined by comparing each individual's biological response before and after supplementation. In such a manner, each individual became his own control; e.g. the male subjects were given baseline measurements of resistance to cellular DNA damage, enhancement of DNA repair and stimulation of immune function once a week for 4 weeks, and then they were supplemented daily and the same measurements repeated once a week for the last 5 weeks of a 7 week intervention period. The before measurements (i.e. n = 4) were the baseline biological response parameters to be compared to the after measurements (i.e. n = 5). One individual was not supplemented to provide a control for the supplemented individuals. The data from this experimental design has taught that resistance to cellular DNA damage, enhancement of DNA repair and stimulation of immune function were all significantly modulated by a combination of carotenoids + nicotinamide + zinc when administered as an exclusive drug

combination above dietary levels, but not when co-administered together with other additional nutrient or natural product supplements.

The design of this previous study to prove the discovery was based on combining substances with known properties to prevent cancer and stimulate immune function, but with differing mechanisms of action; e.g. carotenoids = electrophilic scavenger of radicals produced endogenously by cells or exogenously by the environment, nicotinamide = amplified source of energy via increased production of NAD or ATP, and zinc = an essential cofactor to antioxidant, replicative and DNA repair enzymes in cells. The hypothesis was that since none of these substances have produced consistent effects in humans as a single administered agent, this shortcoming could be overcome when administered in combination because these substances might produce a consistently additive or synergistic chemo-preventive biological response because of non-competitive modes of action instead of, for example, an inhibited one.

2. Scientific history

In 2010 there was an extensive review article published entitled "Historic development of Uncaria preparations and their related bioactive components" (Pero 2010b). This overview has specific relevance to the current review because it was the first recognition of the concept that ingredients could in fact convey properties of enhancement of DNA repair. Before this time, there were no clear cut examples where the process of DNA repair could be shown to be stimulated to higher levels of activity by exogenous nutrients or supplements in our environment. Previously it was believed that DNA repair which regulated our genetic integrity could not afford to be anything less than perfect to satisfy the requirements of orderly evolutionary change. Now it is quite accepted that even genes need to have nutritive treatment, functionality repaired and developed to maturity during life.

Uncaria sp. is a well known herbal medicine used for generations by the Ashinka Indians native to the Amazon basin. There have been two sets of bioactive ingredients for which Uncaria extracts have been developed and standardized. The first are oxindole alkaloids, initially studied and described in 1967; the second are a set of molecules know as Carboxy Alkyl Esters (CAEs ™) first identified and described in 1997 as the bioactive ingredients in AC-11® (Reviewed in Pero 2010b). More recently in 2005 (Sheng et al 2005) it was shown that one of the acid moieties of CAEs is quinic acid, and it is now documented to be one of the more effective DNA repair ingredients found in Uncaria spp, or brightly-colored berry extracts that also contain quinic acid (Stoner et al 2008, Pero 2006), and in turn can enhance DNA repair. It is important to remember that quinic acid is a natural-occurring alpha hydroxy organic acid quite ubiquitous in berries, and also the metabolic source of all other aromatic compound production in plants via the shikimate pathway (Pero 2010a); e.g. the bioactive agents in berries such as hydroxy organic acids (hydroxy benzoic, hydroxy cinnamonic and caffeic acids), flavinoids, and ellagic acid (Stoner et al 2008).

The progression of events that established Cat's Claw extracts as the most consistent and potent DNA repair enhancer of anti-aging effects has become obvious, and signaled why some elements are built of the knowledge of the later events that have happened, to paint a more complete picture of how DNA repair regulates aging. A chronology of events that remain unbroken and additive of each other, that Pero and colleagues have in turn built and learned from are as follows:

1. Specifically Uncaria spp. are an important historical medicine having been used for centuries to treat inflammation and other age-related diseases.
2. When carefully studied, alkaloids were not the main class of bioactive agents, but rather the water soluble carboxy alkyl esters (CAEs) which were only found extracted by water, which explains why indigenous Indians found them useful.
3. Quinic acid containing analogs such as quinic acid esters (QAEs) were identified as the bioactive agents.
4. The mode of action of CAEs/QAEs is via stimulating uptake of tryptophan and nicotinamide (Pero et al 2009b, Pero and Lund 2011). There are no other DNA repair enhancing substances having this mode of action.
5. It became apparent that if a DNA repair enhancer had other non-competitive metabolic modes of action then they would be synergistic to each other.
6. Given that bioactive quinic acid analogs (e.g QAEs) were first discovered in Cat's Claw bark in the 1990's, the bulk of our knowledge that dietary supplements can enhance DNA repair and provide anti-aging properties comes from this plant species (Reviewed in Pero 2010b). There is little doubt that the most extensive documentation of a DNA repair enhancer leading to treatment of anti-aging effects comes from quinic acid analogs and extracts isolated from Uncaria spp. For example, there are voluminous data published establishing Uncaria products can induce (a) DNA repair and anti-aging effects, (b) immune function enhancement, (c) anti-oxidation and (d) neurological effects (Pero 2010b).
7. Based on this historical data, and combined with our background knowledge of the process of excision DNA repair involving at least 5 enzymes each having separate regulatory functional components, it has been fortunate to determine that there exists for many DNA repair enzymes a non-competitive metabolism allowing for a cooperative DNA repair effect that can be synergistic or at least additive. For example, when known DNA repair modulating ingredients were combined to synergize DNA repair, if competing metabolic events were eliminated from these mixtures then metabolic synergism was observed as evidenced by accounting for rehydration properties; i.e thirst quenching, (Pero and Garret 2010) as well as enhanced DNA repair (Pero 2000; Sheng et al 1998, Pero and Lund 2011).
8. After reviewing the Background and Historical Development Sections presented above, it is safe to conclude there have been many milestones achieved documenting the successful development of a dietary supplement that optimally can enhance DNA repair and reduce aging effects from chronic diseases. The learning curve is presented within these 8 points of development, ending up with a synergized combination of the dietary supplements including: resveratrol material, carotenoid material, nicotinamide material, zinc source material, and quinic acid material that is present in proportions effective, in combination, to improve resistance to DNA damage, enhance DNA repair capacity, and stimulate immune function in a human subject to whom the composition is administered as a daily dosage. Any product not encompassing these points of development is by definition an inferior product development.

Prevalence of DNA repair deficiencies in the general population. There are now more than 130 DNA repair - regulated genes identified that also can influence individual susceptibility to DNA damage, and as a consequence, the incidence of human diseases. The number has increased dramatically in the last 20 years, and no doubt will continue to

increase as the causative importance of this research area to human disease development becomes better known (Wood et al 2001). So far nearly all areas of DNA repair are represented by defective metabolism such as: base excision repair (BER) (glycosylases, endonucleases), PARP (poly ADP ribose polyemerase), direct reversal of damage, repair of DNA protiein crosslinks, mis- matched excision repair (MMR), nucleotide excision repair (NER), homologous recombination, non-homlogous end-joining, modulation of nucleotide pools, DNA polymerase, editing and processing nucleases, Rad 6 pathway, chromatin structure, and genes defective in disease that modulate DNA damage. The mere fact there are so many variant ways to become diseased by defective DNA repair mechanisms is a biologic testimony to the impotance of this pathway to human health.

3. A dietary supplement composition that induces rehydration and enhances DNA repair and anti-aging effects

3.1 The reservatrol material

The known molecular mechanisms of resveratrol are described herein. The main effects of resveratrol are to regulate cell cycle events that favor growth arrest allowing DNA repair enhancement before cells die from DNA damage blockage of cell replication (Valenzano et al 2006; Gatz et al 2008; Feng et al 2002; Whyte et al 2007). There are changes in both gene and protein expression, such as the up-regulation of p53 and p21 and the down-regulation of cyclin A, chk1, CDC27, and Eg5 (a mitotic motor protein). Resveratrol also alters the intracellular Smad signaling of the TGF-β pathway. Finally, dietary restriction, the best-studied life-extension treatment, causes overexpression of SIRT 1 (Cohen et al. Science 2004), and since these effects are not additive to resveratrol, they suggest that a similar molecular mechanism to dietary restriction.

3.2 The carotenoid material

The known molecular mechanisms of carotenoids are described herein. The exact mechanism of action of carotenoids such as beta carotene is not fully understood but it is commonly accepted scientifically that one primary mechanism is to directly scavenge oxygen derived free radicals produced either as by-products of metabolism or from exogenous environmental exposures (Lieber 1993; Bohm et al 1993; Regnault et al 1993; Riso 1999). As a free radical scavenger, carotenoids can be expected to reduce or protect against the chemical damage induced in DNA, RNA and protein of cells by toxic environmental exposures or endogenous cellular metabolic errors that ultimately can result in a disease state. On the other hand, nicotinamide and zinc salts do not possess this chemical property which results in an improved biological cellular function.

3.3 The nicotinamide material

The known molecular mechanisms of nicotinamide are described herein. Nicotinamide and its metabolic equivalent nicotinic acid (niacin, vitamin B) or even tryptophan which is the synthetic precursor to niacin is the main precursor for the formation and maintenance of the cellular pool of NAD (Bernofsky 1980; Olsson et al 1993). NAD is essential for cellular ATP production and maintenance of the cell's redox potential, and it is also the substrate for the DNA repair enzyme, poly ADP-ribosyl transferase (ADPRT). Niacin deprivation decreases the NAD pools significantly both in tissue culture cells (Jacobson, E et al 1992) and animal

systems (Zhang et al 1993) as well as humans (Fu et al 1989). The depleted cells have an increased sensitivity to DNA damage and the levels of poly (ADP-ribose) production in cultured cells (as cited by Jacobson, E L in Poirier and Moreau (eds) 1992) or in rat liver (Rawling et al 1994) were significantly lower after mild nicotinamide deficiency. On the other hand, when niacin was given as a supplement to ordinary nutrition (i.e. above known dietary levels) the NAD pool increased and the cells were less sensitive to oxygen radicals (Weitberg 1989). Therefore, it is obvious from this review of the prior art that the primary mechanism of action of nicotinamide/niacin differs from carotenoids and zinc in that the cell's potential for energy metabolism is increased by amplifying NAD and ATP pool supplies (i.e. these biochemicals are the energy sources of living organisms) which in turn is useful to cells, tissues and organs to reduce DNA damage, enhance DNA repair (i.e. poly ADP-ribosylation) and stimulate immune function where the relevance to the disease state is apparent (Pero et al 1995).

3.4 The zinc material

The known molecular mechanisms of zinc source are described herein. Zinc differs from the resveratrol, carotenoids and nicotinamide with regard to its mechanism of action in that it influences disease development and immune function by being an essential co-factor in several enzyme functions involving replication, DNA repair and antioxidant defense of cells. Zinc is required for cell replication and DNA polymerase activity (Williams, RO et al 1973). There are two zinc fingers in the DNA binding domain of the poly adenosine diphosphate ribosyl transferase (ADPRT) gene and other DNA repair proteins (Dawat, P. et al 1995; Matsuda, T. et al1 1995; Chiriccolo, M. et al 1993) which contain cysteine residues (i.e. an amino acid), and if these cysteine residues are oxidized at their thiol constituents, they would prevent DNA binding and participation in DNA repair (Mazen et al 1989; de Murcia, G. et al 1989; Pero 1995; Althaus et al 1994). Moreover, superoxide dismutase is an antioxidant enzyme protecting cells from the harmful superoxide anion because this radical is a substrate for the enzymatic reaction that also requires zinc as a cofactor (Brunori and Rotilio 1984).

3.5 The DMAE material

The known molecular mechanisms of DMAE material is described herein. Dimethylaminoethanol (DMAE) material, also known as deanol, is a naturally occurring substance that has been studied as a possible anti-ageing therapy that can also improve cognitive function, reduce neurological stress, improves immunity and DNA repair especially in skin. It is the precursor to choline and may increase acetylcholine levels (Grossman 2005). While choline is known to be the precursor of acetylcholine, a recognized neurotransmitter, DMAE may also prove to offer a more direct approach to this function by moving into the brain, being acted on by an enzyme (methylation), and thereby undergoing conversion into choline directly where it is needed. DMAE inhibits production of the age-related pigment lipofuscin, which accumulates in all aging tissues. This is significant because cells with increased lipofuscin cause lysosomes to perform poorly, which leads to increased accumulation of poorly functioning mitochondria and increased reactive oxygen species (ROS) production (Terman and Brunk 2006). Evidence also suggests that DMAE decreases the extent of crosslinking of proteins possibly by acting as a free-radical scavenger (Nagy and Nagy 1980).

3.6 The quinic acid material

A water extract of Cat's Claw (Uncaria species) called AC-11 or one of its active ingredients quinic acid are also DNA repair enhancers that do not metabolically compete with resveratrol material, carotenoid material, nicotinamide material, DMAE material or zinc material, and as such could be added to the DNA repair mixture without inducing metabolic competition and thus inhibiting DNA repair instead of being synergistic, because the mode of action of AC-11/quinic acid to increasing DNA repair is novel to inducing DNA repair by increasing uptake of urinary tryptophan and nicotinamide (Pero 2008, Pero et al 2009b, Pero and Lund 2009a , 2011). The quinic acid analog being selected for commericial development is from the group consisting of quinic acid salts, chelates, and Uncaria or other plant extracts containing quinic acid analogs (Pero 2001, 2002, 2005, 2006, 2009a, 2009b; Pero and Garret 2010a).

4. Discussion

The family of dietary supplements proposed herein; e.g. Nutra-Reservatrol, ReservaQuin, AIO, or carotenoids/nicotinamide/zinc combinations (Pero and Garret 2010, Pero and Lund 2011, Sheng et al 1998) are break through products embedded in the science of synergism, often hypothesized, rarely if ever accomplished. Listed below are 6 ingredients all known to be useful in enhancing DNA repair by independent molecular mechanisms, because their interaction with the DNA repair process results in non-competitive molecular metabolism; i.e. they regulate different pathways essential to mediate successful repair of genetic lesions. In order to achieve synergism of DNA repair, it is necessary to combine at least two of this family of dietary supplements to achieve a synergistic mixture development. This fact in turn provides a great diversity to product development by providing 6 ingredients to choose from and still achieve an increased blend of efficacy for any desired clinical indication. For example, nicotinamide supplies the energy source, zinc helps bind a repair enzyme to the damaged are in DNA, carotenoids help scavenger radicals that in turn damage the DNA in the first place, resveratrol modulates growth arrest and cell survival, DMAE (deanol, dimethylaminoethanol) dietary supplement reduces the harmful health effects of neurological stress, and by increasing critical nutrient uptake such as tryptophan and nicotinamide with quinic acid analogs. The scientific basis for further substantiation can be found in Sections 3.1 to 3.6 of this review.

Most anti-aging products have at least one of the following mechanisms of action that address: Inflammation, Immunity, DNA repair, Nutrition, or Oxidative stress. However, rarely do anti-aging products have most of these known modes of action present and shown to occur by simply avoiding metabolic competition the DNA repair ingredients. The logic in this case is that synergism is hypothesized to come from co-varying lifestyle factors all being simultaneously metabolically regulated by the same dehydration/rehydration properties being induced by non-competitive metabolism of a family of DNA repair enhancing dietary supplements (data in Pero 2000, Pero and Garret 2010, Pero and Lund 2011,). They are listed below together with optimal dose ranges:

1. NAD (NICOTINAMIDE) INGREDIENT
   (Energy source to Enhance Repair of Cellular Damage to DNA, RNA and protein) (100-200 mg/day)
2. ZINC INGREDIENT
   (Helps Recognize Harmful Lesions in Genetic Material)(10-20 mg/day

3. CAROTENOIDS (CANTAXATHIN) INGREDIENT
   (Powerful water soluble antioxidant carotenoid) (100-200 mg/day)
4. RESERVATROL INGREDIENT
   (Modulates Growth Arrest and Cell Survival and DNA repair) (70-2000 mg/day)
5. DMAE (Deanol) INGREDIENT
   (Reduces Neurological Stress) (100-200 mg/day)
6. QUINIC ACID ANALOG OR EXTRACT INGREDIENTS
   (Enhances DNA repair by increasing tryptophan uptakr, and also providing anti-infective properties (350-700 mg/day)
7. DO SUPRA-PHYSIOLOGIC LEVELS OF DIETARY SUPPLEMENTS AUGMENT DNA REPAIR CAPACITY. The ingredients identified above with the exception of Resveratrol were known to be effective in vivo at the indicated doses above, which were in turn above normal physiologi occurring levels . However, metabolic competition between some agents can seriously alter their bioavailability to the extent that when administered in combination they are no longer efficacious (Sheng et al 1998, Pero 2000). It was hypothesized that this could be the case with resveratrol and the other agents in Nutra-Reveratrol. Hence, they were pre-screened before formulation to avoid any metabolic competition originating from their DNA repair mechanism of action (Pero and Garret 2010).

Weight regulates essentially all aspects of a disease-free life via nutrition and metabolism balances/imbalances that can be estimated reproducibly by assessment of dehydration (Cheuvront et al 2010). Primary causes of everyday ill health from weight gain are bodily fluctuations in water balance (hydration) (Manz 2007). Moreover, it is a very large market since 27% of American adults have metabolic syndrome (i.e. disturbances in hydration), while 85% of overweight people do (Ford et al 2004, Grundy et al 2005). Your lifestyle demands you to react to your environment, and metabolic hydration is the gage of how successful you have managed health risk from exposure to these factors.

Lifestyle factors are key to generation of oxidative stress, aging, and dehydration in turn is the dominant cause behind weight generated ill health, because weight gain also co-varies with the lifestyle changes associated with the obese. Examples are narcotics (smoking, alcohol consumption, drugs, binge over-eating), diet (fats, proteins, carbohydrates, fiber, vitamins, minerals) exercise, weight gain, sleep (psychotropic stress). Hence, treating dehydration with re-hydration, and anti-DNA damaging agent metabolism also optimizes a first good line of defense against age-associated diseases in general.

There is another important link between essential amino acid metabolism and DNA repair capacity. It is based on the discovery of a previously unappreciated metabolic connection between naturally occurring hippuric acid and quinic acid. Hippuric acid is not found in plant material nor is it metabolized by higher plants (Reviewed in Pero 2010b). Hippuric acid is known to be catabolically synthesized from benzene-type aromatic compounds usually believed to be originating from environmental exposures, or from the cyclic sugar type-compound quinic acid. Quinic acid is ubiquitous especially in healthy foodstuffs which in turn can lead to aromatic plant biosynthesis *via* the microbial shikimate pathway existing in the human gastrointestinal tract. Consequently, Pero (2010a) reasoned that if the urinary level of hippuric acid co-varied and increased in proportion with urinary quinic acid levels as they in fact did, then it follows then that the primary levels of these metabolites (i.e hippuric and quinic acids) are coming from the diet and not environmental exposures. Hence, because the GI tract was primarily responsible for this metabolism and not the liver,

then there must also be produced large amounts of tryptophan and nicotinamide which becomes immediately available for human absorption and the benefits thereof. In fact this proved to be the case and a direct benefit to stimulation of human DNA repair was established (Pero et al 2009a; 2009b; Pero et al 2011).

Finally the common thread tying this particular dietary supplement development together is the common predominant role of life style factors. First there was the composition itself. Although the DNA repair enhancing ingredients have been studied many times before never in high dose combination with each other. When they were the included DNA repair ingredients they also possessed thirst quenching abilities, never before observed to be associated with DNA repair. This observation was accounted for by the fact that non-metabolic competition between the DNA repair enhancing ingredients could be observed because thirst quenching (i.e. rehydration) was observed whereas as single agents none was.

Second, lifestyle factors are key to generation of oxidative stress, aging, and dehydration in turn is the dominant cause behind weight generated ill health, because weight gain also co-varies with the lifestyle changes associated with the obese. Weight regulates essentially all aspects of a disease-free life via nutrition and metabolism balances/imbalances via dehydration/rehyration imbalances.

Thirdly, DNA repair enhancers have also been shown in human studies to be regulated by life style factors that are in turn associated to obesity and lifespan (Banne et al 2004, Pero et al 1985,Pero et al 2000,) and as cited therein for life syle fluctutions and DNA repair capacity) These facts have allowed the development of a proprietary "Wellness Test" that is sensitive to individual fluctuations in life style factors because it can estimate daily changes in urinary nicotinamide and trypotphan and compare them with serum thiol status (Pero 2008). Now success or failure of dietary supplements like Nutra-Reservatrol can be monitored by this functional test to deliver even more accurate health care monitoring.

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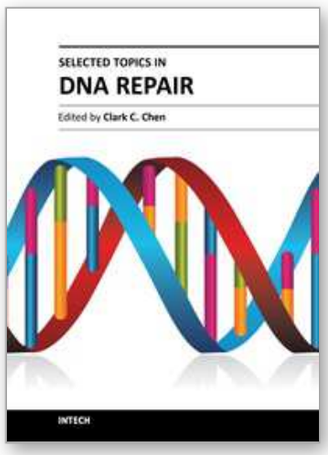

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This book is intended for students and scientists working in the field of DNA repair, focusing on a number of topics ranging from DNA damaging agents and mechanistic insights to methods in DNA repair and insights into therapeutic strategies. These topics demonstrate how scientific ideas are developed, tested, dialogued, and matured as it is meant to discuss key concepts in DNA repair. The book should serve as a supplementary text in courses and seminars as well as a general reference for biologists with an interest in DNA repair.

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中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
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