Review Article/บทฟื้นฟูวิชาการ

# An Overview of CyberKnife Robotic Radiosurgery

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## Abstract

Stereotactic radiosurgery is a non-invasive procedure that utilizes precisely targeted radiation as an ablative surgical tool. Conventional radiosurgery devices, such as the Gamma Knife and X-Knife rely upon skeletally attached stereotactic frames to immobilize the patient and precisely determine the 3D spatial position of a tumor. A relatively new instrument, the CyberKnife (Accuray, Inc., Sunnyvale, CA), makes it possible to administer radiosurgery without a frame. The CyberKnife localizes clinical targets using a very accurate image-to-image correlation algorithm, and precisely cross-fires high-energy radiation from a lightweight linear accelerator by means of a highly manipulable robotic arm. CyberKnife radiosurgery is an effective alternative to conventional surgery or radiation therapy for a range of tumors and some non-neoplastic disorders. This report will describe CyberKnife technology and oncologic applications in neurosurgery and throughout the body.

**Key Words:** Radiosurgery, CyberKnife, Imaged-guided, Tumor Ablation, Stereotactic.

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## Introduction to the CyberKnife

The CyberKnife system (figure 1) is an image-guided targeting radiosurgery system composed of a lightweight (120 kg) and compact 6-MV LINAC mounted on a robotic manipulator that can position and point the LINAC with 6 degrees of freedom and 0.3 mm precision. The critical targeting innovation is real-time image guidance. This fully automated targeting process determines the location of a lesion with respect to adjacent skeletal anatomy all within the coordinate system of the robot and LINAC. Changes in target position are detected and beam pointing is corrected throughout treatment.[1,2] With thin-slice planning CT scans, overall error can be less than 1 mm.[3,4] The key features of the CyberKnife system is shown in TABLE 1.

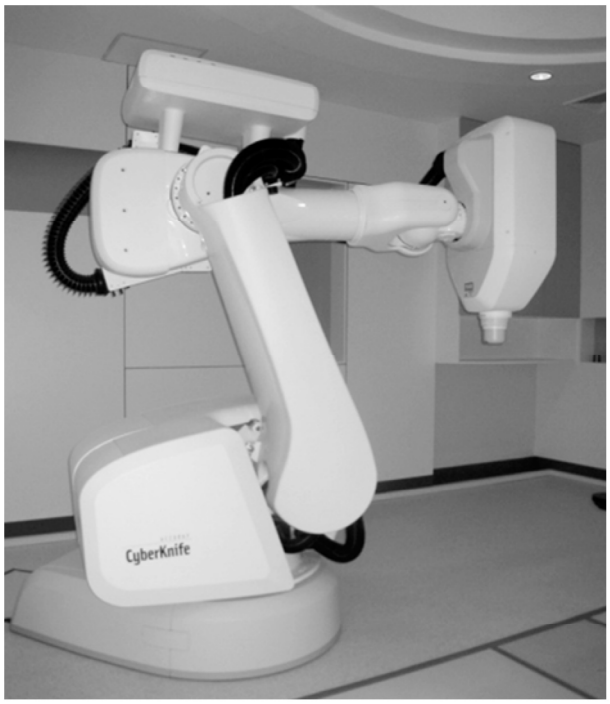


*Figure 1. The CyberKnife Radiosurgery System.*

## Clinical Experience

## Intracranial radiosugery

### Metastatic Brain Tumors

Chang et al.[5] published the early Stanford CyberKnife experience with brain metastases. Seventy-two patients with 84 lesions were treated, all with a single 10 to 36 Gy dose. Comparable to other types of radiosurgery, the tumor control rate was 95% and a 4% incidence of radiation injury was observed. Shimamoto et al.[6] reported the Osaka CyberKnife experience with ablating 66 metastatic lesions in 41 patients using doses of 9 to 30 Gy. The six-month overall survival rate of patients with a performance status (PS) of 0 or 1 was 83%, in patients with a PS of 2 or more, survival was only 13%. Prolonged peritumoral edema persisted in some patients but no severe complications were reported.

**Table 1** Key features of the CyberKnife

| Key feature | Benefits |
|---|---|
| Frameless system | Noninvasive immobilization with thermoplastic head mask and image guidance allows stereotactic precision without a rigid head frame<br>Flexible to perform single or multiple fractions |
| Accuracy | Accuracy (<1 mm.) is comparable to rigid, frame-based systems<br>Able to treat both intra- and extracranial sites |
| Respiratory tracking system | Movement of tumors during respiration such as in the lung, liver is automatically tracked and compensated Allowing high dose radiation to target with decreased treatment toxicity |
| Multimodality image fusion | Including CT, 4D CT, MRI and PET scans |
| Linear accelerator-based treatment | No need to dispose of radioactivity |

Young et al.[7] reported their experience with radiosurgical ablation of selected non-small cell lung cancer brain metastases using both the Gamma Knife and CyberKnife. In the Gamma Knife arm of this study the single-fraction dose was 14-20 Gy. In contrast, the CyberKnife dose, within a cohort of slightly larger brain metastases all treated in 1-3 sessions, was 14-30 Gy. This comparative study reported an overall tumor control rate with the Gamma Knife of 97.8%, and for the group of larger lesions treated with the CyberKnife, 96.7%.

### Acoustic Neuroma

A large literature now supports both the safety and efficacy of radiosurgical ablation of acoustic neuromas.[8-18] Chang et al[8] reported 61 patients with unilateral acoustic neuromas were treated at Stanford using three fractions of CyberKnife. The mean pretreatment tumor diameter was 18.5 mm (range, 5-32 mm). The tumor control rate was 98%. Importantly, after a mean follow-up of 4 years, 74% of patients maintained serviceable hearing, and no patient with at least some hearing before treatment lost hearing on the treated side. Two patients experienced transient facial twitching that resolved in 3 to 5 months.

Ishihara et al.[19] utilized the CyberKnife to treat 14 acoustic neuroma patients with Gardner Robertson class I or II hearing (serviceable hearing) and 24 with Gardner Robertson class III or IV hearing (non-serviceable hearing). The tumor control rate was 94%, hearing preservation occurred in 93% of cases with serviceable hearing. The authors concluded that improved tumor dose homogeneity and fractionated treatment may improve hearing preservation in patients with acoustic neuroma.

### Perioptic Lesions

A number of tumors arise in close proximity to the anterior visual pathways and are largely unresectable using conventional surgical techniques. Such lesions include many pituitary adenomas, meningiomas, craniopharyngiomas, and malignant skull-base tumors.

Mehta et al.[20] were the first to report on treatment of lesions involving anterior visual pathways with multi-session CyberKnife radiosurgery. After a median follow-up of 18 months (range 12 to 54), four patients experienced an improvement in either or both visual acuity and visual fields. No visual deterioration or tumor progression was observed.

Pham et al.[21] used CyberKnife radiosurgery to treat patients with meningiomas or pituitary adenomas within 2 mm of the optic apparatus. Radiosurgery was delivered in two to five sessions using a mean total dose of 20.0 Gy (range, 15.0-30.0 Gy), as defined at an average 71% isodose line (range, 67-95%). After a mean follow-up period of 29 months (range, 15-62), 94% of the patients experienced either a decrease or stabilization in tumor size. Although there was no change in visual field or acuity in 20 patients, improvement in vision was documented in 10 cases. Three patients experienced visual loss; massive tumor progression was the cause in two patients with atypical meningioma. Meanwhile, a prior course of radiotherapy and multiple radiosurgical treatments proved permanently injurious to vision in one patient with multiply recurrent Cushings disease. Most importantly, the vision in 91% of the patients in this series was preserved at pre-treatment levels despite the immediate proximity or even displacement of the optic apparatus. The authors concluded that fractionated CyberKnife radiosurgical ablation can effectively treat many small parasellar lesions while preserving visual function in nearly all cases.

In the largest study of multi-session CyberKnife ablation for peri-optic lesions, Adler and colleagues[22] retrospectively analyzed 49 patients with meningioma[27], pituitary adenoma[19], craniopharyngioma[2] or a mixed germ cell tumor[1] situated within 2 mm of the

optic apparatus. Once again CyberKnife radiosurgery was administered in 2 to 5 sessions. A cumulative marginal dose of 20.3 Gy was delivered to a mean tumor volume of 7.7 $cm^3$. After an average follow-up of 49 months, the visual field was unchanged in 38 patients, improved in eight (16%), and worse in three (6%). Forty-six patients (94%) experienced either a decrease of more than 20% or stabilization (15 cases) in tumor volume throughout follow-up. Only one previously irradiated patient in this series suffered visual loss that was attributed to radiosurgery. This investigation confirmed that multi-session radiosurgery is generally safe and effective for parasellar lesions in close proximity to a short segment of the anterior visual pathways.

## Head and Neck

### Nasopharyngeal Carcinoma (NPC)

Le et al.[23] reported universal local control when stereotactic radiosurgical boost was included in the treatment regimen of patients with NPC. In this reported, 45 patients with stage II-IV NPC received 66 Gy of conventional external beam radiotherapy (EBRT). Four to 6 weeks after EBRT CyberKnife radiosurgery was delivered in a single 7-15 Gy session to the primary site. The 3-year local control rate was 100% and the overall survival 75%. In addition, the rate of freedom from distant metastasis was 69% while progression-free survival was 71%. Late toxicity included transient cranial nerve weakness in 4 patients, radiation-related retinopathy in one, and asymptomatic temporal lobe necrosis in 3 patients, all of the latter originally having had intracranial tumor extension.

### Glomus Jugulare Tumors

Glomus jugulare tumors are highly vascularized lesions arising from chemoreceptor glomus cells within the adventitial dome of the jugular bulb's paraganglia. Because surgical extirpation frequently causes injury to adjacent cranial nerves, there has been considerable interest in radiosurgical ablation as an alternative. Lim et al.[24] described the outcomes after CyberKnife radiosurgery in 13 patients with 16 glomus tumors. Using a prescribed dose of 14-27 Gy, they reported a 100% rate of tumor control with no permanent morbidity.

## Spinal Radiosurgery

### Spinal Tumors

Ryu et al.[25] first reported the feasibility of treating spinal lesions with the CyberKnife. In this retrospective analysis, 16 patients with spinal hemangioblastomas, vascular malformations, metastatic carcinomas, schwannomas, a meningioma, and a chordoma were treated with doses of 11 to 25 Gy in one to five fractions. Among patients followed for at least 6 months there was no evidence of tumor progression or treatment-related complications.

Gerszten et al.[26,27] (who at the University of Pittsburgh have now treated over 700 spinal tumors with the CyberKnife) reported their experience in 125 patients with paraspinal lesions, treated exclusively with a single-fraction technique. This initial series was composed of 17 benign tumors and 108 metastatic lesions. 12-20 Gy (mean, 14 Gy) was prescribed to the 80% isodose line. No acute radiation toxicity or new neurological deficits occurred during the follow-up period (range, 9-30 months; median, 18 months). Axial and radicular pain improved in 74 of 79 patients.

Recently, Gerszten et al. combined spinal radiosurgery with kyphoplasty, a minimally invasive means for stabilizing vertebral bodies after pathological fractures.[28] Twenty-six patients underwent kyphoplasty followed by single-fraction CyberKnife radiosurgery (mean time after kyphoplasty 12 days). The tumor dose ranged from 16 to 20 Gy (mean 18 Gy) to the 80% isodose line. No acute radiation toxicity or new neurological deficits occurred during the follow-up period (range: 11-24 months), and axial

pain improved in 92% patients.

Degen et al.[29] at Georgetown University reported the results of a prospective study that measured safety, pain and quality of life outcomes among a group of patients with spinal tumors treated by the CyberKnife. Between March 2002 and March 2003, 51 patients with 72 lesions were treated with a mean dose of 21 Gy at an average 70% isodose line in 1-5 fractions. Many of the patients had received prior radiation therapy. Despite this fact, pain was improved across the board; at 4 weeks the mean VAS score decreased from 51.5 to 21.3. Meanwhile, physical and mental quality of life measures were maintained throughout a study period that averaged one year. No serious side effects were reported.

Dodd et al.[30] published their experience treating 55 benign spinal tumors with CyberKnife radiosurgery. This lesions were treated with 16-30 Gy to an average 80% isodose line delivered in 1-5 fractions (mean 2 sessions). Pain was reduced in 25-50% of patients 12 months after CyberKnife radiosurgery. At last follow-up, all lesions were either stable (61%) or smaller (39%). An incomplete radiation-induced myelopathy occurred 8 months after radiosurgery in one patient.

### Intramedullary spinal cord AVMs

Adler et al[31] reported 21 patients with intramedullary spinal cord AVMs treated with CyberKnife radiosurgery. In this series, radiosurgery was delivered in 1-5 sessions to an average lesion volume of 1.8 $cm^3$ (range: 0.14-4.94 $cm^3$); the average marginal dose was 19.5 Gy (range: 15.0-21.1 Gy). Patients received clinical and MRI follow-up at 6-month intervals and spinal angiography at three years. Clinical outcome was improved or stable in all patients. After a mean clinical follow-up of 29 months (range, 3-93 months), seven patients have been studied with post-treatment angiography; AVM obliteration was partial in 4 and complete in three patients. Significant AVM obliteration has been observed in nearly all cases who were more than 1 year from radiosurgery. No patient experienced a post-radiosurgical hemorrhage.

## Intra-thoracic and Intra-abdominal Tumors

### Lung Tumors

A pilot study of CyberKnife radiosurgical ablation for primary lung tumors was initially conducted at Stanford and Cleveland Clinic. Whyte et al.[32] reported the clinical results of the first dose increment, 15 Gy. Twenty-three patients received 15 Gy of radiation in a single session. At 1-3 months of follow-up, the radiologic response was deemed complete in 2 patients, partial in 15 and stable in 4; the imaging in two cases demonstrated progressive disease. Although this study demonstrated the feasibility of using CyberKnife radiosurgery to ablate lung lesions, the high recurrence rate showed the need for more aggressive dosing.

In a subsequent paper, Le et al.[33] reported the final experience from the above dose escalation study. Enrolled patients had stage I non-small cell lung cancer (NSCLC) or a solitary metastasis and were judged not to be surgical candidates. Among patients with NSCLC the 1-year freedom from local progression was 91% for doses > 20 Gy but 54% for doses ≤ 20 Gy. Patients with primary NSCLC had significantly higher freedom from relapse (FFR) and a trend towards better overall survival than patients with metastatic tumors. One-year FFR was 67% for NSCLC versus 25% for metastatic patients. One-year overall survival was 85% for NSCLC versus 56% for metastatic patients. Radiation-related complications, including four cases of grade 2-3 pneumonitis and one pleural effusion, were noted at doses ≥ 25 Gy; there were three possibly treatment-related deaths in patients with a history of prior thoracic radiation therapy. The authors concluded that single-session radiosurgery is feasible for ablating lung lesions and

that doses in the range of 25 Gy were both efficacious and well tolerated in previously unirradiated patients. However, this dose level appeared too toxic in a setting of previous thoracic radiation, especially when the lesion was centrally located. This conclusion led to the hypofractionated lung radiosurgery regimen that was subsequently adopted at Stanford.

### Hepatocellular Carcinoma (HCC) and Liver Metastases

Choi et al.[34] were the first to report their experience with CyberKnife ablation in cases of small inoperable or advanced HCC. 31 patients were treated with CyberKnife 30-39 Gy in 3 fractions. The overall response rate was 77.9% without serious toxicity. The median survival for small and advance HCC was 12 and 8 months respectively.

### Pancreatic Cancer

Koong et al.[35] conducted a phase I dose escalation trial in which 15 patients with locally advanced pancreatic cancer were treated in a single CyberKnife session with 15-25 Gy. Twelve patients experienced clinical benefit with significantly decreased pain and increased weight gain. Among the patients treated with 25 Gy, follow-up CT imaging demonstrated 100% local control of the primary pancreatic tumor. For the entire series, the median overall survival was 11 months. No grade 3 or higher toxicities were noted. The authors concluded that 25 Gy was the optimal dose to achieve local control of the primary lesion without inducing significant gastrointestinal toxicity.

A phase II investigation that studied boost radiation delivered to the pancreas by CyberKnife was conducted by Koong et al.[36] Treatment for this cohort of patients with locally advanced pancreatic cancer consisted of 45 Gy intensity-modulated radiotherapy (IMRT) and concurrent 5-FU, followed by a 25 Gy CyberKnife boost to the primary tumor. Sixteen patients completed the trial. Two experienced Grade 3 toxicity. Fifteen patients were free from local progression until death. Median overall survival was 33 weeks. The authors concluded that the addition of IMRT resulted in a higher rate of complications without any survival or palliative benefit. Because of these findings, IMRT is no longer part of the treatment regimen at Stanford for patients with locally advanced pancreatic cancer.

### Prostate Cancer

King et al.[37] reported 41 low risk prostate cancer patients treated with CyberKnife. The prescribed dose was 36.25 Gy in 5 fractions. No patients developed PSA failure in this preliminary result.

## Conclusions

The CyberKnife combines image-guidance technology and computer-controlled robotics to enable state-of-the-art frameless radiosurgery virtually anywhere in the body. In addition to being highly accurate, this procedure makes possible homogeneous irradiation of tumors with complex shapes and the delivery of fractionated “multi-session” treatments. There is now extensive clinical experience that documents the application of CyberKnife radiosurgery to lesions throughout the body. CyberKnife ablation is likely to become an important tool for managing nearly all cancers.

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Special Article/บทความพิเศษ

# Specificity VS Selectivity of Drug Action

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All drugs and poisons are chemicals, and the main difference between them is dose as proclaimed by Paracelsus (1493-1541) in his famous statement: “All substances are poisons; there is none that is not a poison. The right dose differentiates a poison and a remedy”.

A chemical compound that has no specificity is harmless, because it has no target of action, i.e., no receptor. In contrast, a substance that has some degree of specificity but without selectivity is a poison.

A clean distinction between specificity and selectivity is illustrated by the actions of atropine and cyanide as follow:

1. Atropine has specificity because it acts only at the muscarinic site, but it has no selectivity because all muscarinic receptors throughout the body are blocked.

2. Cyanide is specific for the iron of cytochrome a3 , but it is not selective since this cytochrome in the mitochondria of all cells are affected giving rise to cyanide poisoning.

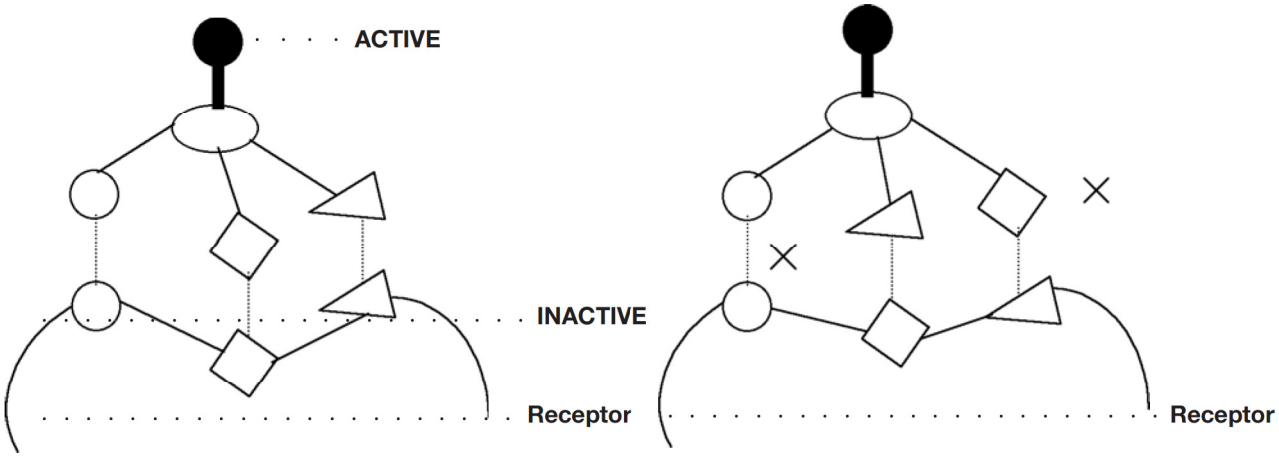


***Figure 1.*** *Molecular basis of specificity of a substance. Note that 3-point attachment between the substance (isomer) and its receptor is required for a proper interaction.*

The molecular basis for specificity of a substance is its 3-point attachment with its complementary sites on the receptor (Fig.1). An active substance (isomer) has at least 3 residues on its molecule to fit and react nicely with their counterparts (also 3 residues) on its receptor. In contrast, an inactive isomer does not possess this properties; it may have only one or two interacting residues. In another word, one may say that only an active isomer (drug) has the right configuration or conformation for its receptor. This concept helps explain why a drug like acetylcholine can act at more than one site or receptor; cis-ACH acts only on the nicotirnic receptor, whereas trans-ACH acts on the muscarinic receptor.

Adrien Albert (1907-1989), a famous Australian medicinal chemist, formulated the important concept of selective toxicity in the early 1960, and it still remains unchallenged even nowadays: "Useful drug actions are instances of selective toxicity while nonselective toxicity gives rise to what we call poisoning".

## Bases of Drug Selectivity

1. Selectivity related to drug distribution

A. Topical applications, e.g., topical steroid works mainly at the inflammatory site on the skin.

B. Selectivity by ionization,e.g., 2-PAM, an ionized quarternary compound, cannot cross the blood-brain barrier, and hence does not have any effect in the central nervous system.

C. Differential bloodflow, e.g., halothane acts as a general anesthetic because of its high blood

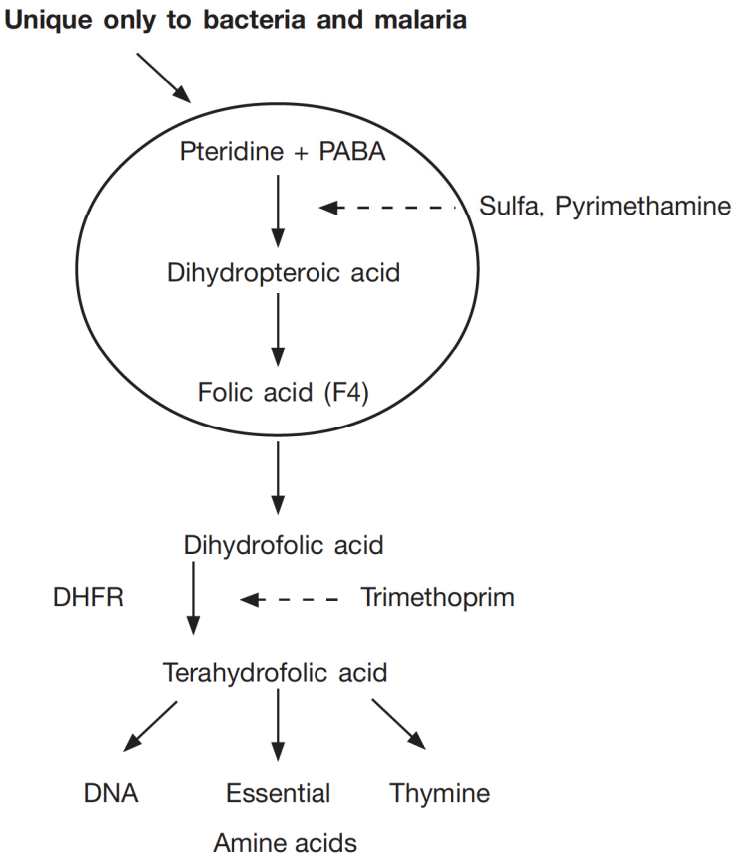


***Figure 2.*** *Steps in folate metabolism blocked by sulfa drugs, pyrimethamine and trimethopsim. The overall pathway is present in both bacteria (and malaria) and human host. Folic acid is synthesized by both bacteria and malarial parasites, but human cells cannot do so and hence must be supplied exogenously.*

solubility and the relatively greater bloodflow to the brain.

D. Selection concentration by excretion, e.g., nitrofurantoin is excreted unchanged in the urine and hence can act as a urinary antiseptic.

2. Selectivity related to tissue metabolic differences, e.g., a sulfa drug is toxic only to bacteria and not mammalian cells, because it inhibits the de novo biosynthesis of folic acid required for DNA synthesis and cell division, whereas manamalian cells have to acquire folic acid from an exogeneous source (Fig.2)

Selectivity may be trivial or subtle. For example, penicillins kill gram-positive bacteria by inhibiting their cell wall biosynthesis but host cells are devoid of the cell wall. In contrast, amphotericin B is toxic to both fungi and humans because it acts by causing leakage of cell membrane of all types of cells.

Trimethoprim has a higher binding affinity to bacterial dihydrofolate reductase (DHFR) than pyrimethamine (Table1), and thus is used as an antibiotic (Bactrin) while pyrimethanuine, which has a higher binding affinity for DHFR from P.falciprum, is used in the prophylaxis of malarial infection (Fansidar®).

**Table 1** $IC_{50}$ values for three DHFR inhibitors

| Inhibitor | DHFR isoform | | |
|---|---|---|---|
| | E. coli | Malaria | Mammal (rat) |
| Trimethoprim | 7 | 1,800 | 350,000 |
| Pyrimethamine | 2,500 | 0.5 | 1,800 |
| Methotrexate | 0.1 | 0.7 | 0.2 |

All values are in nM units.

(From: G.L. Mandell et al (eds). Principles and Practice of Infectious Disease, 6th ed., Philadelphia, Churchill Livingstone, 2004)

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