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The process of development of new drug against malaria

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Abstract:

In the malarial drug discovery the problem is presence of the resistance against the multi drug like chloroquine. Firstly problem was reported in South East Asia and South America. The synthesis of resistance was seldom but it was the high drug pressure that lead its wide propagation. African resistance was originate from Asian resistance. In case of Sp. PfCRT have the ability to show resistance against the chloroquine by complicated series of point mutation. Afracian and Asian resistance PfCRT at the same 7-8 point mutations. For the conformation of resistance the experiment have been done in vitro. If minor chemical change are shown to chloroquine indicate that resistance is persistence. PfCRT have the ability to change parasite effect against many malarial drug. Rumination is taking place on the synthesis of resistant drug for artemisinin. These are the partner drugs. In the first instance dihydro artemisinin have the ability to deactivate in ring stage parasite.

INTRODUCTION

Malaria is world widely distributed disease.300-500 million people have the risk of malaria disease and one million people annually die due to malarial disease .Malarial parasite Plasmodium *falciparum* have the ability to show the resistance against the multi drugs. So control of this disease is hampered. Synthetic antimalarial drugs and antimalarial vaccine are recently being developed but their effect against malaria lurch arduous clinical testing. From Artemisia annual Artemisinin, a sesquiterpene lactone endoperonide is extracted. It is highly effective against the multi drug resistance plasmodium spp. But it is much expensive for the malarial sufferers.The complete synthesis artemisinin is expensive and problematic.Semi synthesis of artemisinine from atremisinic acid could be cheap and no environmental damage.

Artemisinic acid producing yeast in three steps:

- Engineering the farnesyl pyrophosphate (FPP)
- By addition of amorphadiene synthase gene (ADS)
- Cloning a unique cytochrome P450

Cytochrome P450 that shows a three step oxidation of amorphadiene to artemisinic acid. In first reaction artemisinin biosynthesis is catalyzed by ADS ,it is used for the new producton of amorphadiene in E.Coli.To check for the betterments in FPP production ADS expressed under the control of GALI promoter located on PRS425 plasmid.

To increase FPP production in S.cerevisiae ,the gene which are responsible for FPP synthesis was up regulated and one gene that convert FPP to sterol was down regulated. All of these variations to the host strain were done by chromosomal completions to confirm the genetic stability of the host strain. Approximately five fold production of amorphadiene is improved by the over expression of soluble form of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase.

For the production of artemisinic acid from amorphadiene we create a strain. Separation of the genes whichpossess the enzyme that convert amorphadiene to artemisinic acid in A.annua. Artemisinin is a sesquiterpene lactone derivative which is widely distributed and have the qualities of secondary metabolites present in the Asteraceae. We supposed that plants belonging to Asteraceae have the common enzyme ancestor for the biosynthesis of sesquiterpene lactones.

Many coloning P450 fragments from an A.annua trichome. Enriched complementary DNA pool BLAST analyses of these P450 gene against sunflower and EsTs lettuce. Annua P450 gene fragment have the high sequence identity(At amino acid level 85-88% to EsTs of unknown function from both sunflower and lettuce. Identity of A.annua P450 fragments outside the Asteraceae family is ~50%. P450 gene was used for the conserved Asteraceae sesquiterpene lactone by synthetic enzyme. The full length P450 cDNA (Cyp71AVI). The close relationship with other P450.For example, Simple sugar into acetyl CoA with the help of ERG10 it is converted into acetyl CO enzyme A with the help of ERG13 it is converted into HMG –COA with the help of 2XtHMGR converted into mevalonate with the help of ERG12 converted into mevalonate with the help of ERG8 Converted intomevalonate-ppand it is converted into IPPthat is converted intoDMAPPand GPP . The GPP change into FPP by chemical reaction andthis product is converted into squalene .Squalene into Ergosterol . the erg9::met3-ERG9 convert FPP into amorpha -4,11-diene . It is converted into CYP71AV1\CPR and it is into Artemisinic acid and then into Artemisinin.

DRUG DEVELOPMENT

There are four methods for the drug development.

Chemical and Plant Material

Artemisinic acid is derived from the leaves of artemisinic annua.

Screening Methods of Blood Stage Parasite

The immediate demonstration to drug development of the active compound against the infective stage of P.Falciparum. The infection is due to the presence of normal range of in vitro screening and the animal models. For example, Plasmodium Falciparum: HTS screen for Plasmodium Falciparum using hypoxanthine, colorimetric or fluorescent assay have been widely used.

GC-MS Analysis of Amorphadiene

The synthesis of amorphadiene by different strain was analyzed by GC-MS with the help of dodecane layer. The amorphadiene free from impurities is synthesized with the help of fermentation by using E.Coli.

Important feature of screening assay for the unique compound active against many stages of malaria parasite life cycle that are

Robust; It is less expensive, effective for screening of abundant quality of chemo type and natural products.

Validated; Efficacy of the compound against the parasite.
Reproducible; Comparison of result obtained from different laboratories.
Representative of human malaria; Result indicate the dominant action of the compound when applied to the sufferer. Selection of the unique target; For the formation of new antimalarial drugs the basic need is the selection of unique chemical series along with the unique way of action. The recent fact is that high level of drug discovery is still focused on the historic target.
The Plasmodium Falciparum and Plasmodium Vivax genetic make up indicates high level of conservations by combining effort against malarial disease lead to elimination stage from control stage.
Selection of the unique drug classes; Mining of the malaria boxes which comprises of libraries of natural products. Selection in secondary screens comprises of molecular targets. Million of the chemicals have been recognized for the antimalarial activity.
Feature of the drug efficacy;
The compound have the ability to destroy the parasite in limited hours that is 48 hours by two way inhibition or interaction of compound with target.
The target chemically or genetically validated in in both in vivo and vitro.
Efficacy at low level of concentration.
Cellular effect.

NATURAL PRODUCTS

The wide range of the chemical extracted from natural product is fabulous. The sources of new drugs are natural products .A large numberof natural products have the capacity of anti plasmodial effects.The natural products are different from the synthetic compounds. Natural product are bio available and they are evolved to interact with biological molecules.The new anti malarial drugs have low cost,less toxicity, it include amodiaquine and chlorproguanildapsone.The replacement of these new drugs provide few year of efficacy.They must provide better efficacy and have the ability to reduce less addictive effect and provide synergistic activity.In vitro screening for active compound which consist of main component for anti malarial drug decovery.

Drug interaction studies

Invitro drug interaction the standard dose are use for interaction between two anti-malarial .
FIC DrugA= IC50A(B)/IC50A
Isobologram analysis depend upon the sum of FICS which indicate that the reaction is antagonistice additive or synergistic

In-vovo screening of atni malarial:Plasmodium species that cause human disease are not capable of causing disease in non primate.So expirment are typically done on the rodents for purpose many plasmodium species are used.Rodents models have the ability to recognize of several anti malarial.The example are mefloquine,halofantrine and more currently artemisinin derivitives.The most abundantly used initial test that uses P.berghei and less abundantly P.chabaudi which shows efficacy of four regular doses of compound.Its showed efficacy against the malarial diseases.Primate model have the much importance.Its play critical role in pre clinical development because it give the final confirmation.Plasmodium falciparum have the ability in both Aouts and Saimiri monkeys.

From anti malarial drug discovery

The main target for the drug discovery is the recoginization and formation of compound with characterstics that have the ability to protect the humanbeing.The ability of compound to be use by young children and pregnant women.It efficacy against un complicat P.Falciparum malaria compound.The identification of the lead can be both biology and chemistry or specifically by chemistry by changing of existence catagores of ant malarial to improved efficacy,protection or ease of synthesis . Example Formation of many quinolone and Artemisinin anti malarial was extracted.

CONCLUSION

The malarial elimination will only attained by the help of the new drug development mainly focus onboth control and elimination . Demonstration of the wide range of potency of drug targets. These may be shortcoming of the recent

range of antimalarial. A wide range that explains whole parasite,s life cycle. These drugs are less expensive and easily available ,less side effects and have the critical role in current challenges to reduces the malarial diseases.

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