Sugar transporters as potential drug targets biology essay

Science, Biology

Introduction and Background

Malaria is a vector borne disease caused by the protist microorganism of the genus group Plasmodium. It is carried by the female Anopheles mosquito therefore is a mosquito vectored disease. An infected mosquito will bring about Plasmodium once it has bitten its host. Plasmodium then enters the blood stream and circulates to the liver where it matures and reproduces. It affects the tropical and the sub tropical areas, in particular the Americas, Asia and Africa. There are approximately one million human deaths worldwide resulting in a global health threat in those particular areas [Slavic et al. 2011]. Majority of the deaths occur in Sub Saharan Africa amongst young children and ninety percent of the deaths caused by malaria also occur in this region. The reason why malaria is common in these areas is due to the warm climate with rainfall as this creates stagnant pools which provide a prime breeding ground for mosquito larvae. The disease affects both humans and animals. The most common species of malaria is Plasmodium falciparum this particular one causes the most deaths worldwide and is the most life threatening. Other species include P. vivax, P. malariae, and P. ovale these are not as life threatening but cause a mild version of malaria. The symptoms of malaria are fevers, chills, headaches and lethargy. In some cases sufferers become nauseous, they vomit, cough, and have diarrhoea and also jaundice. The fever and chills occur in cycles of every few days. The more severe complications are liver failure, central nervous system failure and comas. These are generally caused by P. falciparum species and there is a long list of symptoms and complications it causes. Malarial transmission is via the female anopheles mosquitoes. This has to be

infected prior to transmission; once it bites a host human it transmits the Plasmodium parasite into the blood stream which is shown below. Figure 1: Showing the transmission of malaria.[Ankur Chakravarthy, 2011] http://exploreable. files. wordpress. com/2011/04/malaria_lifecycle. jpgFigure 1 briefly shows the transmission of malaria. Once the parasite is in the body it rapidly goes to the liver were it starts reproducing and gets into the blood stream subsequently. This causes the bursting of red blood cells which depletes the oxygen capacity in the body causing symptoms like fevers anaemia and jaundice. Once another mosquito ingests the blood, the subsequent mosquito is infected with the parasite and the cycle starts again with this infected mosquito carrying it to its next host. Areas that have malaria generally have a high population of humans for mosquitoes to feed from. They will generally have a significant mosquito population density and transmission between the human hosts and mosquito vectors. Vector control is a method used to prevent malaria and its subsequent effects. The main aim of this is to prevent mosquito bites. Techniques like indoor residual spraying (IRS) uses the spraying of insecticides in the homes which subsequently kills mosquitoes and prevents further transmission. This has been quite an effective control measure especially in areas with endemic malaria and the World Health Organisation (WHO) recommends spraying of insecticides. A downside is that there is resistance to this technique as a result of evolution. Another control measure is the use of mosquito nets this prevents transmission by creating a barrier which prevents bites. They are often coated with insecticides. These also reduce cases of malaria although is not the best preventative measure. Treating stagnant pools or still water

with chemicals helps prevent a breeding ground for mosquitoes. There are chemical prophylaxes taken in drug form which are mainly used to prevent malaria. One of the first was quinine which is being used to treat the resistance malaria parasite and severe cases of malaria. But these days it is used less instead chloroquine, mefloquine, and other drugs are used. These are regarded as suppressive in the terms of a prophylaxis because they work at particular stages of the life cycle. These are Artemisinin based combination therapy (ACT) which is currently recommended by WHO as first line of treatment [Slavic et al. 2011]. This is generally used to treat P. falciparum malaria. The reason Artemisinins are combined with other drugs is because if Artemisinins are administered on their own the likelihood of resistance may increase. Therefore they are combined to make them more effective and reduce the likelihood of resistance. There are no vaccines that are currently available for malaria. There is now a need to look for new alternatives to ACT because there are cases of resistance in Eastern Asia. Therefore scientists are looking for new control measures and treatments as a result of this. One such concept is to target the sugar transporters in the Plasmodium parasite. As sugar transporters are the main routes for energy into Plasmodium the hope is that targeting these transporters will block or destroy the sugar transporters and therefore reduce or prevent the uptake of glucose. This in theory will work because it will destroy a glucose transport system which in theory will kill of the Plasmodium parasite. The targeting of sugar transporter is not only being looked at for malaria it is also being looked at in cancers. In cancers it would be theoretically harder because you would target tumour sugar transporters. Any new drugs used to target sugar

transporters will use different mechanism of action to the current drugs. The reason why sugar transporters have emerged as new potential targets is because they target the supply of sugars within the parasite. If targeting sugar transporters in the future is successful it could be used as a new treatment for malaria especially if there are cases of resistance in ACT. In this literature review I will be looking at sugar transporters as potential drug targets for malarial control. This will enable me to conclude the viability of sugar transporters as potential targets for malarial control.

Background on sugar transporters

Sugar transporters are part of a group of membrane bound proteins which are involved in the binding and the transport of molecules in all types of animals and plants. They come under a group called major facilitator super family (MFS). Sugar transporters exist in all phyla and are used to transport sugars such as glucose as this is a vital source of energy in all life forms. The most common glucose/sugar transporter in mammal is the GLUT/ SLC2A family. In humans glucose is taking up from the extracellular fluid into the cell. This is via membrane bound proteins and there are two types of structurally related glucose transporters. One of them as mentioned before is the GLUT/ SLC2A family GLUT is the protein symbol and SLC2A is the solute carrier. These come under the family of the facilitative glucose transporter family. These mediate bidirectional and energy independent processes of glucose transport in cells and tissues [Feng-Qi Zhao, 2011]. The other type is sodium-glucose co transporters with the solute carriers SLC5A and with a protein symbol of SGLT. These use sodium linked transport mechanism and

go against the electrochemical concentration gradient. Both types have a prime role in transporting sugars or carbohydrates across membranes in particular glucose, as this is the primary energy source in the human body. But they differ as one is sodium dependent and the other is sodium independent in the terms of function. As glucose is obtained in via the diet coming from the lumen of the small intestine and the need of glucose transporters is significant as they introduce an energy source into the cells. Sodium dependent glucose transporters transport primarily glucose and other sugars like galactose. This is done through as earlier describe an electrochemical gradient which is uses an active transport process to get molecules across the other side of the membrane along with the aid of the sodium potassium ion pump. They are mainly associated with small intestine and they transport glucose across luminal membrane of cells found ling the small intestine. Also they transport the glucose molecule across the proximal tubules of the kidneys. There are two commonly known types of this glucose transporter and they differ in affinity for glucose uptake. The first to be effectively cloned is SGLT1 this is a high affinity transporter this was done using a rabbits intestine as the source [Hediger 1987]. The human intestinal transporter was also cloned a few years later. SGLT1 is located in the small intestinal absorptive cells were in particular the membranes and also the renal proximal tubules in the kidneys. The other type Sodium dependent glucose transporters is the SGLT2 this is found on the convoluted tubules in particular the membranes. This transporter has a low affinity for glucose. The difference in affinity means greater efficiency in the uptake of glucose and less loss in the terms of being excreted. As SGLT2 is involved in moving

larger quantities of glucose and SGLT1 has a higher affinity to uptake any glucose which SGLT2 has not already picked up. Therefore this prevents loss down to the urinary tract which it therefore will be excreted and wasted. They also differ in capacity as one has to move large quantities of glucose and the other smaller quantities and more specific quantities. Facilitative glucose transporters are independent of the use of sodium. They mainly use diffusion as the primary mechanism of transport unlike the sodium dependent glucose transporters which use active transport which requires energy. These along with glucose transport other sugars also. Facilitative glucose transporters have the protein symbol GLUT. In humans there are thirteen known versions of this GLUT family and they are further divided into three different classes. The first to be successively discovered is GLUT 1. There have been debates by scientist on the in the naming of the structures but now it has been agreed that there are twelve GLUTs and one HMIT. There are three different types of classes respectively, the first is class one, the second class two and the third class three. These have been put in these classes on the basis of function, structure and tissue expression. There are others features like substrate specificity and transport kinetics and were they are expressed. Other species of organism including microorganisms and plants have sugar transporters. If we look at yeast for example at the species Saccharomyces cerevisiae this is the most common found yeast species in foodstuffs like bread and winemaking process. The main sugar transporters in this species belong to the Hxt family and a few other transporters. The glucose transport mechanism occurs mainly by facilitative diffusion there are thirteen known glucose transporters with their functions being known and

with their sugar uptake affinity being known also. Hxt 1 this is one of the transporters found in Saccharomyces cerevisiae this particular transporter is a low affinity glucose transporter. Induction of this transporter is when there are high levels of glucose. Hxt 2 transporter is the opposite type of transporter in the terms of role. Hxt 2 has a high or immediate level affinity for glucose and it is induced by low levels of glucose. Other transporters in this family are Hxt 1 to Hxt 9 and Hxt 11 with different levels of glucose affinities. Other transporters outside the Hxt family are Snf3, Rgt2 and Gal2. Snf3 and Rgt2 are glucose sensors and the Gal 2 is a galactose transporter. Recently the genome of bacteria Oenococcus oeni had been sequenced [Ok Bin Kim, 2011] which uses the hexose sugar which are six carbon sugars like glucose as part of it metabolism. This gram positive bacterium can be found in grapevine and ferment hexose sugars. The significance of sequencing the genome meant that any pre existing transporters within this bacterium can be identified. There have been forty different genes that code for transporters within the bacteria an example is COG0580 this is involved in glycerol and related permease uptake Ok Bin Kim, 2011]. Further study shows that there are two transporters for glucose uptake they vary on structure and function. Glucose is uptake in this particular species is by transporter proteins 1574 and 0819[Ok Bin Kim, 2011]. These are not considered to be major glucose transporters in this species, as bacteria generally use a phosphotransferase system to uptake sugars and the phosphoketolase pathway to degrade sugars. But this study does that transporters are used in the transport of glucose. The study shows that transporter 1574 is a secondary transporter with its structure being

accounted for. It is thought to be part of a MFS transporter group. Transporter 0819 is an also a secondary glucose transporter that is also induced by glucose. Although information on glucose transport is known sufficiently in bacteria as whole to identify their specific sugar transporter expression is very difficult and there is a genuine lack of information. This study shows that these two transporters are potential and not fully confirmed transporters but it shows that there is of evidence to prove in their favour as transporters. In plants the major energy yielding sugar is sucrose and is vital photosynthetic synthesis product. The initial process starts in the leaves and the sugar transport in plants occurs over long distances and sugar transporters have a highly invaluable role in transport and regulation. Sucrose transporters are apparent the source which are the leaves where they help transport sucrose to the sink which are organs and tissues in the plant. It has been found that sucrose transporters are regulated normally in the terms of transcription and translation but also after translation also. Sucrose transporters also belong to the MFS which is one of the largest membrane transporters group across the phyla. Looking at the Arabidopsis genus this has its sugar transporter fairly well documented. Studies have shown that there are approximately 69 sugar transporters and are further sub divided into 8 families [Katsuhiro, 2007]. These eight subdivisions of transporters have different roles there have been sucrose transporters, hexose transporters and glucose transporters as few as examples. The sucrose transporter is the SUC/SUT family overall there is three different divisions of this group also based structural differences. The first of the three is SUC2/SUT1, SUC3/SUT2 and SUC4. Within the sub families they are very

close structurally. There is indeed a difference between the three sucrose transporter families. Structurally the way all three of these structures differ is mainly location and size of the exons.

Sugar transporters in human systems

Sugar transporters in humans belong to the GLUT family as mentioned earlier and are separated into three classes e. g. class one, two and three. Class one facilitative transporters consists of four transporters GLUT 1 to 4. GLUT 1 is expression is highest in the red blood cells in humans. It is also expressed highly in the brain in particular the blood brain barrier in the endothelial cells. It is also expressed in lower levels in other areas like muscles and adipose tissue for respiration. This is the primary transporter for the erythrocytes which relies on glucose from the blood plasma for an ongoing supply. The average concentration of glucose in the blood stream is maintained at 5mM which provides a constant supply. This particular transporter increases its presence on the membrane when there is a lowered level of glucose and decreases its presence when there is a higher level of glucose present. GLUT 2 is also a transmembrane glucose transporter that passively allows the transport of glucose. The distribution of this particular transporter is primarily in the liver and in the pancreas in the beta cells and also found in kidney tubules and the small intestine. In the beta pancreatic cells it is known to play a role in glucose sensing where it is one of the high quantity and low glucose affinity transporters of glucose. In the liver it plays a role on the membrane of the hepatocytes. GLUT 3 is considered to be a high affinity transporter including in times of low glucose concentration and

that is partly due to the location it is commonly found. It is the primary supplier of energy to the brain in particular the neurons and other locations include the placenta. It supplies the brain along with the GLUT 1 transporter. GLUT 4 is different to the others in this class as the regulation is by the hormone insulin. It is found most commonly in the heart in the cardiac muscle, also a number of different locations in the skeletal muscle and found in adipose tissue. Both muscle and fat tissues are the major tissues that are sensitive to insulin. Once insulin is present it stimulates GLUT 4 to be in place on the membrane and to uptake more glucose. Class one transporters have been studied more compared to class two and three. Therefore there is more known on a structural and basis in class one compared to the others. This is evident with a number of class two transporters that have been uncharacterised in the term of a structural and functional basis. If we look closely at class two transporters in particular the first one GLUT 5. This transporter is a known fructose transporter. The next three transporters GLUT 7, GLUT 9 and GLUT 11 there is evidence of their functions which has been recently made clear but was uncategorised until recently. GLUT 7 has a role in glucose transport out of the endoplasmic reticulum. GLUT 9 has been known to be expressed in the kidneys and liver. It is thought to play a role transporting uric acid. GLUT 11 the information is scarce but is a known solute transporter. Class three transporters consist of five transporters. These transporters location have all been accounted but on a functional basis not all have been accounted. Determining the location of each and every transporter is difficult but determining the function takes a lot of research and time. In this case GLUT 12 function is unknown but the rest

have a known function. GLUT 6, GLUT 8 and GLUT 10 are known to be functional glucose transporters. The fifth transporter is a H+/myoinositol transporter is found in the human brain and used as a neuronal transporter. GLUTs are the main transport proteins for sugars in mammals as a whole. Overall the transporters have in some cases completely different role in different locations and they are also different affinities to their sugars. Individually they all differ functionally i. e. some are only found in the brain and prevent loss of glucose in the urine. The difference between each of the thirteen transporters is for the locations they are in; they all provide the respective sugars in these locations.

Sugar transporters in plasmodial systems

When plasmodium is within the blood glucose from the blood is transported via the sugar transporters in the humans and the plasmodium??? s plasma membrane. GLUT 1 is the glucose transporter that transports glucose from the blood plasma into the red blood cell. This transporter is vital to the life cycle of the plasmodium and is the most commonly found on the membrane of the red blood cell. The plasmodium sugar transporters are therefore reliant on the uptake of glucose into red blood cell by GLUT 1. The sugar transporter identified in plasmodium is the PfHT (plasmodium faciparum hexose transporter) [Slavic et al. 2011]. This is the primary supplier of hexose sugars which are six carbon sugars that includes glucose and fructose in the P. faciparum species. This PfHT transporter belongs the MFS and found in parasites as a hexose transporter. There have been more potential transporters been identified but not as typical sugar transporters.

Studies show that this transporter does not require the use of sodium and therefore is sodium independent. Another transporter that has been identified is the putative sugar transporter PFI0955w which also belongs to the MFS. Another sugar transporter to be identified is PFI0785c. on the basis of their substrate transport they have only been recognised to be sugar transporters. More focus has been on the PfHT 1 transporter as this has arisen as a potential drug target for malaria due to the fact that it is the main sugar transporter in the plasmodial system. Therefore more research has been focused on PfHT 1 and information is more readily available than these other mentioned transporters. Research shows that PfHT is undoubtedly essential for the development of the parasite in the red blood cell stage. There have been many other membrane bound proteins that have also been recognised like ion transporters in the P. falciparum species but the focus is sugar transporters. In other species of plasmodium other sugar transporters have been recognised but because P. falciparum causes the most fatalities the focus has been on that. Plasmodium berghei is another species of plasmodium mainly found to infect rodent, the sugar transporter the gene that encodes this particular transporter has been named as PBANKA 082040. Other species like Plasmodium vivax have also had their gene that encodes the sugar transporter indentified as PVX 099390. Many other species have their genes that encode the sugar transporter identified. The transporter for the rodent species has also been identified as PbHT in P. berghei. This species of plasmodium causes malaria rodents and the PbHT has been confirmed to have the same importance as PfHT does in P. falciparum. PbHT

has been confirmed as the main sugar transporter in in the rodent species of plasmodium.

Structural features of both human and plasmodial sugar transporters

Structure is important as it generally enables functional roles in proteins. If we look at the structure of both plasmodium and human sugar transporters we can it can indicate how the structure of the protein relates to the relative function of the protein. Looking at GLUT 1 this is commonly found in the erythrocytes and provides them a viable energy source in glucose. The glucose binds to the GLUT 1 protein on the plasma membrane of the erythrocyte. The GLUT 1 protein must be open to allow glucose to bind. Once bound to the GLUT 1 protein changes its conformational structure to allow the glucose to pass into intracellular environment. This is done by subsequently open the protein on the intracellular side of the protein transporter and closing the protein in the extracellular environment. This type of transport is facilitated diffusion as substrate had to bind and change the structure on conformational basis to allow diffusion. Figure 2: Showing the structure of GLUT 1, [Trista K, 2011]The human GLUT 1 molecule is hydrophobic but does have region being polar and charged. It is made up of 492 amino acids and more than half of these amino acids make it the hydrophobic in nature. Which is not uncommon of membrane bound proteins especially them that are subsequently part of the MFS. This means that on the hydrophobicity scales the amino acid residues are positive therefore hydrophobic. The GLUT 1 molecule consists of 12 membrane spanning alpha helices [Trista K, 2011] with cytoplasmic N and C termini. The N terminus is

NH2- and it found on the bottom left hand side shown in Figure 2 sticking out of the membrane bound structure. The C or COOH (carboxylic acid) terminus also shown in Figure 2 as the long molecule that loops at the end on the bottom right hand side of Figure 2. In the middle of Figure 2 is a long loop like structure connecting one transmembrane protein to another. This is called a cytoplasmic loop and is found in an intracellular environment. It also has another loop this is the glycosylated loop connecting the first two transmembrane proteins found on the top left hand side of figure 2. This loop is based within the extracellular environment. Figure 2 shows a predicted model of the GLUT 1 protein as a comprehensively detailed structure has not been drawn due it not being known. The GLUT 1 protein overall is amphipathic this is a result of hydrophobic regions and polar regions, these particular regions are the membrane helices. The glucose molecule passes through the polar region via a channel. The conformational change described early is not only for glucose also for other molecules like inhibitors. GLUT1 is a primary transport protein for vitamin C in particular in humans due to the fact humans cannot synthesize it so has an importance in that aspect also. The transmembrane proteins the twelve of theme sit side by side made up of their constituent amino acids. There are six of these transmembrane proteins thought to be adjoined together, and then there is a channel for the substrate to be transported through this is thought to be water filled and then on the other side of the channel there are the other six transmenbrane proteins which make up the 12 in total. Structurally it is a very basic integral membrane protein that only adheres to certain substrates and inhibitors unlike other transporter does not require sodium or other factors. The overall

structure is a fairly simple sugar transporter; this is shown by its relatively basic structural formation as described. The PfHT transporter is found in the parasites plasma membrane in P. falciparum. Unlike the human GLUT family it can facilitate the transport of both glucose and fructose, thus the name hexose transporter. This is important to the survival of the organism it is found in as when glucose supplies are low it can turn to fructose as the major energy sugar. As a result of the human body being more complex than the parasites there are many different sugar transporters, the fructose transporter in humans described early is GLUT 5. The GLUT family generally is singled out to be specific to on sugar. There are potentially other sugar transporters in the P. falciparum species but due to a research bias in PfHT being a new target for drugs to fight malaria the research and information has been focused of this transporter particularly. Like the GLUT 1 transporter it is also sodium independent therefore is not influenced by ions. Figure 3: PfHT predicted structureAsha Parbhu Patel et al, 2008http://ars. els-cdn. com/content/image/1-s2. 0-S1477893908000069-gr3. jpgThe two dimensional structure as predicted above is of the PfHT transporter. This shows by briefly looking at the GLUT 1 transporter and the PfHT transporter they are fairly similar in structure. This is documented in many research journals also. In fact the closet human equivalent is the GLUT 1 transporter. Ideally this would be the case because they both operate in similar function but most importantly the location i. e. when the parasite is in the erythrocyte having a similar structure to GLUT 1 is likely to show similar function, substrate specificity and also may be advantageous being very similarly matched in terms of structure to the host glucose transporter and maybe

crucial in survival. PfHT is made also from 12 transmembrane protein that appear to be arranged side by side judging from the two dimensional depiction. The bottom left hand side in the intracellular environment in the cytoplasm shows the N (amino) terminal which is very similar to the GLUT 1 structure. On the right hand side in the intracellular environment there is the C (carboxylic acid) terminal which also is similar to GLUT 1. But the C and N termini are found in similar locations but differ slightly in shape GLUT 1s N termini was a straight line of amino acids constituents and C termini was shaped like a long hook. Whereas the C and N termini both identical in the PfHT organism in a way they look like a test tube. Also in the in the intracellular environment in the middle there is also a long loop like structure connecting two adjacent transmembrane proteins, this is also apparent in GLUT 1. The extracellular structures are likely to be glycosylation sites and other residues but this not one hundred percent confirmed as the structures itself is a prediction also.

Homology and differences key of human and plasmodial sugar transporters

DNA analysis of the genome of P. falciparum has shown PfHT gene. It shows that PfHT transporter shows similar homology to the human GLUT family. The level of homology between the GLUT families is between fifty to sixty percent; this is with regards to sequence analysis of the PfHT. This shows that PfHT is fairly similar to the human family. It shows particular homology to the GLUT 1 transporter. The expression of the PfHT is studied on a frog germ line this has been crucial in studying the sequences of the genome of P. falciparum [Slavic et al. 2011]. As described before PfHT predicted

structure is very similar to the GLUT 1 structure. It shares 12 transmenbrane that have C and N terminal on either side of the transmembrame proteins in the intracellular environment which is also seen in the GLUT 1 one structure. The way it differs is GLUT 1 has a mechanism of up taking glucose in the cell as described before where it changes its conformational shape to allow glucose into the cell. It is not known whether PfHT has a mechanism but is has a different mechanism in place compared to GLUT 1. This can be crucial to know for choosing inhibitors to the stop substrates from being transported . What is known is that PfHT is a hexose transporter and GLUT 1 is a glucose transporter. PfHT specialise for two substrates glucose and fructose whereas GLUT 1 is only specific to single substrate glucose. PfHT has a far greater affinity to glucose in comparison to GLUT 1. They are both sodium independent transporters which looking at the sequence analysis has shown to be correct. On the basis of homology the two transporters are relatively similar but also differ. They are homologous in the sense they are facilitative sugar transporters they differ in substrate specificity i. e. PfHT is a facilitative hexose transporter and GLUT 1 is a faciltative glucose transporter. They both do not require the use of sodium but mechanistically they differ on uptake. On the basis of sequences GLUT 1 differs only by about forty to fifty percent and both show similar structure depicted by figure 2 and 3. They both have 12 transmembrane proteins but the terminals on the transmembrane proteins and other structures differ in structure but very slightly.

Identifying the specific sugar transporters to targets and the techniques/methods of targeting these sugar transporters in plasmodium.

PfHT is the major sugar transporter in the P. falciparum species and it is the key supply route for glucose into P. falciparum. As this is crucial for the life cycle of stage within the erythrocyte this has made it as a genuine target for potential drugs. Other transporters have been identified in P. falciparum but these are not key facilitative transporters so research has not really focused into them. Theoretically if you can prevent any hexose sugars from being used in the parasite this can kill of the organism as it will not have enough energy yielding ATP to survive. Also it is a very high affinity facilitative transporter and therefore is highly important to the parasite. There have been two method identified to exploit this PfHT one approach is a chemical approach and the other is a genetic approach. The chemical approach entails use of inhibitor molecules to inhibit the glucose uptake into the parasite. The genetic approach target the genes that encode the PfHT transporter which would in theory would disable this protein and lose function overall. If both or one of these techniques prove feasible they can work more effectively than current drugs as they will have an impact as soon as they are administered. This is because the current drugs take many hours whereas these maybe more effective time wise. The chemical technique requires an inhibitor that targets the parasites sugar transporters without attacking host proteins. It has to be specific to the parasites transporter as GLUT 1 is fairly similar in structure. The inhibitor should work in an artificial environment just as much as in the body. Theres two ways that the genetic method can work one is to

target the gene encoding the PfHT with the hope it will be unable to use the sugar transporter and render it useless. The other potential genetic method would entail the use of an inhibitor, by expressing the gene the encodes the PfHT in a way that its expressed more than usual and using the inhibitor to block all the expressed transporters. This could work as the PfHT will be over expressed and the drug inhibitor will render it useless and the parasite cannot express anymore transporters as it they have already over expressed. This method would not give the parasite a backup plan by expressing more PfHT and will limits its survival. Also the gene that encodes PfHT is thought to be a one off copy so this transporter cannot be expressed elsewhere in the genome. Like every drug in the form as an inhibitor it has to be developed on the basis of target specificity the effective concentration of the inhibitor. These along with being specific to target protein without attacking host proteins are important concerns to think about. Especially when GLUT 1 is very similar to PfHT. One study actually describes how to genetically target the pfht gene [Ksenija Slavic, 2010]. It is a potential technique to target this gene. This technique although sophisticated uses briefly primers to cut of the gene from the genome. Although I have briefly mentioned what it does and how it supposedly work there are complicated set of steps that would go to achieve this. This step would only work if a certain type of vector is retrieved this is when I would likely to be dangerous to the organism. Also the study also describes the second type of genetic approach to potentially targeting PfHT I mentioned. Using a genetically modified version of the parasite this over expressed PfHT transporter this made it easier to inhibit chemically and also has been documented in the

study to effectively be inhibited. This makes this genetically modified version essential to further research. These two genetic techniques have been carried out on genetically modified organisms rather than actual than actual parasite version. The chemical technique involved testing out a variety of different potential inhibitors. Only certain inhibitors would work due to the specificity of the PfHT transporter as those that have certain groups on the third carbon. These inhibitors will have to be glucose derived. Two potential inhibitors have been identified as compound 3361 which is a glucose derivative [Ksenija Slavic, Michael J. Delves Et al, 2011]. The other potential inhibitor is catechins which is not a glucose derivative yet a tea derivative [Ksenija Slavic, Elvira T. Derbyshire et al, 2009]. The first mentioned is probably the most effective compound 3361. This glucose derivative showed high levels of specifity the the PfHT transporter. This transporter does not have any effect on the GLUT transporters including GLUT 1. This inhibitor compound 3361 is effective in killing the parasite organism and fifty percent inhibitor concentration in a controlled artificial environment [Ksenija Slavic, Michael J. Delves Et al, 2011]. It was also tested against the rodent species of parasite within the rodent and also proved effective in killing plasmodium in the rodent. Compound 3361 has also been used against other species of plasmodium and has been effective in killing them also. This proves that compound 3361 is a potentially new inhibitor against the malaria parasite in human. The compound 3361 could be at the heart of new anti malarial drugs in the future with it not only being specific to humans but also animals. Also it can be used to fight variety of species plasmodium causing malaria. The reason this is because it target PfHT with a very high specificity but does not

interfere with the host sugar transporters like GLUT 1 which would highly present in the erythrocyte stage of the parasites life cycle. It only targets the specific sugar transporters which supply the parasite with energy. The other potential inhibitors uncovered were the catechins. These were in fact discovered earlier than the compound 3361. This is a type of phenol molecule which differs in structure compared to compound 3361. Like compound 3361 catechins have the ability to inhibit sugar transporters. These in fact do inhibit the PfHT [Ksenija Slavic et al, 2009]. One type of catechins inhibited PfHT whereas another type was not effective in inhibition. The type that did inhibit PfHT also inhibited GLUT 1 and 5 the glucose and fructose transporters in humans. The key inhibitory property of the specific catechins is down to the structure which is also the case for compound 3361. These also show that they have anti malarial potential as sugar inhibitors. But saying this they do in fact inhibit GLUT 1 and 5 which would be potential dangerous as it would block key sugars transport to the host cells. This is not what we would expect to achieve as a key feature for the inhibitor was to not affect host transporters. If they can be modified in way that they can only target the PfHT without inhibiting the GLUT 1 and 5 transporters in humans they can potentially be used as anti malarial drugs. Also they have the advantage of being naturally available because it is found in green tea. Catechins prove to potential targets but as people who first investigated it and published a study of it in 2009 they found that it had it limitation. This why the in 2011 compound 3361 was identified as a better alternative as it did in fact only target the parasites key sugar transporter. Although being broader in the terms of specificity catechins can be used to target other

sugar transporters for other uses. Compound 3361 appear to be the best hope as a potential inhibitor.

Conclusion

The current state of knowledge I believe is promising. Research show far has found the so called Achilles heel in the most deadly malaria parasite Plasmodium falciparum. This is the key sugar transporter PfHT in this particular species. The current research has proved that this is the key supply of sugars to the parasite once in the erythrocyte stage and cutting of the supply of sugars via the PfHT sugar transporter proves that the organism cannot look to any other transporters or mechanism to bring glucose into parasites cells. This reduces the ATP levels subsequently the organism runs out of energy and dies. The key to developing drugs is that once the parasites PfHT sugar transporter has been targeted the organism cannot in its genome activate the PfHT to be present on the membrane, prevent inhibition of inhibitor molecule or turn another sugar transporter. In the fact parasite dependence on the PfHT is very high and once the the primary sugar glucose is in short supply the transporter can use fructose sugar as a energy source. In the terms of survival the parasite can only switch sugar source to a hexose sugar. This proves that PfHT is vital for the parasite an in terms of survival it can only sugar sources to survive rather than bring in energy via another transporter or another mechanism. This proves that PfHt is genuine target for the next generation of anti malarial drugs. In terms of a targeting approach of the PfHT transporter I believe in this current time the chemical approach looks very promising. I would say this because the

genetic approach has not been well documented and is only a proposal currently. Whereas the chemical approach in terms of compound 3361 has shown to work in vitro and also in vivo within a rodent. Within the rodent it targeted its species of plasmodium which is P. berghei and is also effective in killing other species of Plasmodium. The genetic approach was documented but not significantly to have a valued opinion on it. So at the moment I would say this approach is not viable at the moment. But good progress has been made in the terms of the chemical approach as an inhibitor has been identified and tested within an in vivo and in vitro environment. This has shown to kill the specific plasmodium species and other species of plasmodium. This inhibitor has yet to be tested in humans. Although research proves it can work as an anti malarial potential drug, no drugs have been made with compound 3361 at the heart of them. I believe this is because it is passed the discovery stage and now in the testing and publishing scientific journal on the compound and it??? s potential. There has not been too much emphasis on it being developed into a drug just suggestion that it is in inhibitor that can be used in the future for drugs. Also another consideration for this is mechanism of action of any inhibitor needs to be known. This would be beneficial for researchers for research and drug development purposes to know but the PfHT mechanism of transport of sugars is not known either. I believe that the current situation for compound 3361 is at a stage where they have tested it and confirmed that it can inhibit sugar transporters in a range of malarial species. But I believe that any further progress in the terms of developing drug based around compound 3361 has not been made yet and is not really at that stage yet. Overall the

viability of targeting sugar transporters has proven effective as they are the main energy mediums for sugars into the parasite organism. Once they are targeted they kill off the organism which has been proven. The aim of this is to kill the parasite that causes malaria. The success of identifying an inhibitor has made targeting sugar transporters even more viable. With reports of resistance to the current range of anti malarial drugs this is good news. The importance in being able to target sugar transporters in P. falciparum has been emphasized by resistance to current drugs and the lack of any alternatives. This is why I would say it is good news because a possible new inhibitor has been identified and in the future it could be used in drugs. With the significance of malaria as a worldwide disease that kills millions of people each year this could be the new way to fight malaria worldwide. Currently there are other anti malarial drugs that are undergoing clinical trials and are expected to be used as early as 2020.