African Pharmacological Science Gateway: demonstrator of an e-infrastructure community

Suggested host and collaborators: AIBST (African Institute of Biomedical Science & Technology www.aibst.com, Zimbabwe) collaborating with Muhimbili University (Tanzania), Makerere University (Uganda), Addis Ababa University (Ethiopia), University of Nairobi (Kenya), University of Ibadan (Nigeria), University of Cape Town (South Africa), and Obafemi Awolowo University (Nigeria).

Support institutions/actions: EU-project eI4Africa (www.ei4africa.eu), Karolinska Institutet (Sweden), Royal Institute of Technology (Sweden), Catania University (Italy), Brunel University (United Kingdom) and optionally IUPHAR (International Union of Pharmacology & Clinical Pharmacology).

Aims: Design, develop, test, implement and evaluate a concept for cost-effective virtual e-infrastructure for African medical science collaboration (e-science) focusing on biomedical and pharmacological sciences and clinical trials for improving African healthcare.

We will focus on the following areas of importance for Drug Discovery & Development and Rational Use of Medicines:

1. Genomics and bioinformatics
2. Bioanalysis, drug analysis and metabolism
3. Pharmacokinetics/pharmacometrics
4. Clinical trial sciences
5. Electronic library webpage
6. e-learning environment

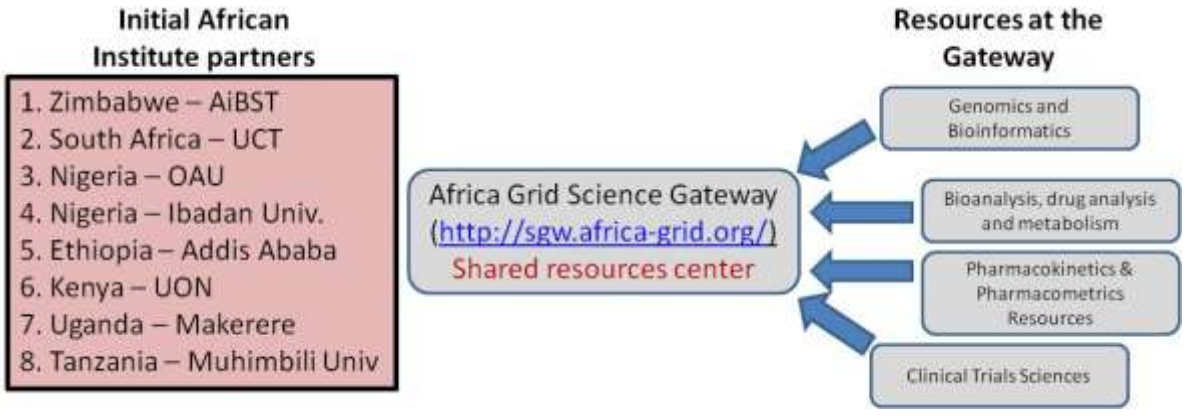
Rationale

Over the years, under the North-South (N-S) Scientific and Technology transfer drive, many African scientists went for postgraduate training in developed countries such as Sweden, UK, USA, and France. This N-S initiative however did not achieve the technology transfer aspect resulting in the trained African scientists failing to continue with their work on returning to their home institutions. Some invariably return to laboratories and institutions of developed countries making the N-S initiative a conduit of brain drain from Africa. Those who remain on the continent are not fully functional scientifically and contribute minimally to maintain strong research institutions. A few groups in Africa have managed to benefit from the N-S initiative and set up competence in some key research areas important for Drug Discovery, Development and Rational Use of Medicines. These groups are often scientifically isolated with few opportunities or possibilities for South-South (S-S) interaction to realize and build on the synergies of the knowledge and technical skills they have individually established.

The proposed Pharmacological Science Gateway will significantly contribute towards S-S collaboration and strengthening both capacity and capability for drug development and Rational Use of Medicines in Africa. This will be achieved by ensuring that graduate students continue laboratory based pharmacological research in Africa by having access to tools for generating, analyzing and calculating data as well as expertise in these areas. This will contribute towards the reduction of the migration of African scientists to US/Europe or reduce costly visits to US/Europe which weaken the local research environments. In general, the e-infrastructure addresses a long standing challenge of scientific and technical strengthening of Africa where the older and current approach of courses and workshops has generally either been slow or not sustainable once participants and experts disperse. This initiative will ensure continued contacts, mentorship and access to necessary tools and establish strong capacity to maintain collaborations between African laboratory-based pharmacological scientists. This will contribute to enrichment of basic and clinical pharmacological sciences in Africa.

Properties of shared tools: Easily and openly available tools simplifying collaboration across institutions within and outside Africa for basic and clinical drug research for African scientists in the four focus areas. The virtual collaborative community should build on easily accessible tools that either interested partners or the eI4Africa project can gain access to. To make things affordable and sustainable open access tools and solutions are to be preferably used including establishment of technical competence for maintenance and development. It is the intention that a successful demonstrator/virtual community in the pharmacological field should be maintained as specific research infrastructures in Africa provided by Ubuntunet, WACRAN (research e-infastrcutures organizations) and others maintaining links to the global research infrastructures. The required tools and collaborative platforms for knowledge sharing should be linked to a pharmacological site at the African Grid Science Gateway (http://sgw.africa-grid.org/).

Figure 1: Conceptual overview of the structure of African Community and Contents of the Science Gateway:



Genomics and Bioinformatics

Genomics is one of the most rapidly advancing fields of medical research. There will be continuous development of new software and tools but these should be validated against existing tools linked to the Pharmacological Science Gateway. Validated biostatistical tools are

also required. To support the high throughput genetic data generated in genomics research, the subdiscipline bioinformatics has also developed in parallel. Bioinformatics has the added advantage for resource limited settings which cannot afford 'wet laboratory' activities as scientists can use the publicly available DNA and protein databases to conduct 'dry lab' bioinformatics research.

Some open source software useful in bioinformatics and genomics research include:

i. *ClustalW* (*www.**ebi**.ac.uk/Tools/phylogeny/**clustalw**2_phylogeny/*)
ii. *G-HMMER* (*sgw.**africa**-grid.org/**g-hmmer***)
iii. *GROMACS* (*sgw.**africa**-grid.org/**gromacs***)
iv. BLAST (***blast**.ncbi.nlm.nih.gov/*)
v. The Human Cytochrome P450 (*CYP*) Allele Nomenclature Database (www.cypalleles.ki.se/)
vi. NAT2 website (http://nat.mbg.duth.gr)
vii. haploview (http://www.broadinstitute.org/scientific-community/science/programs/medical-and-population-genetics/haploview/haploview)
viii. The Pharmacogenomics Knowledgebase (http://www.pharmgkb.org/)
ix. The drug transporter database supported by NIH at http://pharmacogenetics.ucsf.edu/
x. H3Africa (Human Heredity and Health in Africa; www.h3africa.org

This website (x) brings together consortium that is being funded through the joint Wellcome Trust-NIH venture to support genomics research in Africa. It is hoped that some of the data will be made freely available and this would be a huge catalyst for pharmacogenetics/ pharmacogenomics research in different African countries. This will assist researchers in different parts of Africa to pursue informed questions based on findings or ongoing H3Africa projects. These H3Africa projects aim to build capacity to carry out research, thus, can be used as possible referral centres for researchers to seek expert advice.

Bioanalysis, drug analysis and metabolism:

For drug analysis members could share information on available HPLC and LCMS/MS platforms on the continent where participants can either go to analyze their samples or send them for analysis. For the users, they can share chromatograms with a view to trouble shoot methods which are being transferred between laboratory groups. The AiBST Institute has presently two LCMS/MS machines and the group headed by Dr Muhammad Ntale (muhntale@yahoo.co.uk) plan to establish LCMS/MS resources at Makerere University with support from the drug analytical and metabolomics group at Karolinska Institutet Stockholm Sweden (Professor Olof Beck at Clinical Pharmacology). Dr. O Minzi at Muhibili University of Health and Allied Sciences has an Interlaboratory analytical platform for some anti-malarial drugs in collaboration with a lab in Germany (Analytical Clinical Concept). Members of the African community have HPLC-methods for drug analysis established and LC-MS/MS methods as part of this Quality Assurance Proficiency Testing scheme. In future it should be

feasible to share required software openly to decrease maintenance and running costs by using the e-platform for collaboration.

Pharmacokinetic/pharmacometric resources

AiBST is piloting an e-platform to share knowledge and technical expertise in this field.This involves accessing important softwares for pharmacokinetic data analysis (some of which are free, sharing data to either train on how to use these tools or to strengthen scientific research). The field of pharmacometrics has proved to be complex and requiring multidisciplinary expertise which is not usually located at one institute, in the proposed virtual network, links to leading groups such as the Pharmacometrics group at Uppsala University and at Manchester University will provide useful support to the current efforts to establish expertise in pharmacometrics. Through the support of Novartis Pharmaceutical Company, there is now an active Pharmacometrics working group which is organizing annual courses for African scientists. The first one was in Cape Town, the second in Harare, and now the third one was in Tanzania and next year in Ethiopia.

Software of interest to be accessed through the gateway include initially

i. http://www.uppsala-pharmacometrics.com/software.html incl
ii. NONMEM for sparse pharmacokinetic/dynamic analyses available at http://psn.sourceforge.net/
i. Xpose application for Nonmem at http://xpose.sourceforge.net
ii. *Population Experimantal Design at http://poped.sourceforge.net/*
iii. monolix, software for pharmacometric work: www.lixoft.com
iv. http://www.summitpk.com/tools/tools.htm

Clinical Trial Sciences:

There is an increasing drive to conduct Phase 1 and phase 2 clinical studies in Africa. To achieve this, there is need to train more Clinical Trial Scientists. A number of companies are showing interest for the testing of drugs whose patient target population is mainly in Africa. There is also an interest for clinical trials for drugs to treat non-communicable diseases given that African countries are going through a transition where there is an increased number of such patients. Online training in Clinical Trials Sciences is well established. The proposed network would work together in clinical trial protocol development, conduct multicentre clinical trials etc. The group will have a combination of clinicians, laboratory scientists, epidemiologists and biostatisticians.

There are several helpful tools with critical information and also help outlining standard protocols:

a. The website www.clinicaltrials.gov (US governmental website over registered clinical trials)
b. The toolkit for writing clinical trial protocol www.ct-toolkit.ac.uk/rotuempa/protocol-development

SPIRIT 2013- Standard Protocol Items (presented at annals.org/ article.aspx?articleid= 1556168 and explained at www.bmj.com/content/346/bmj.e7586.pdf%2Bhtml

In resource limited settings epiinfo is a valuable tool for data collection, analysis and focusing on the needs in epidemiological research. Software available at http://wwwn.cdc.gov/epiinfo/

Electronic library of publications and basic software packages
There is limited access to publications published in high impact journals. This platform will ensure that all publications in areas of focus for this initiative are freely accessible by members in this initiative. A repository will be created such that open access and hinari supported publications will be accessible from the repository. The initiative will then subscribe to journals/publishers not supported by hinari to increase accessibility to publications.

There will be a repository for scripts (R scripts, NONMEM/MONOLIX control streams) and packages for use in different software made available through this platform.

Platform for multimedia contacts and e-learning tools: These tools are useful for all areas and they should support collaboration, help sharing technical expertise, scientific and medical expertise, simplify problem solving and be useful for distance learning/consultations. The platform will be used to also share laboratory data outputs especially towards finding solutions to problematic methods, e.g. a researcher failing to amplify a particular gene could post the PCR amplification picture and others could help trouble shoot the problem. A potential platform for communication and data sharing could be Moodle (https://moodle.org/) that is an open sourced e-tool which is also easy to link up with other software, e.g. Adobe Connect.

Time schedule: 1. A pilot demonstrator being realized and shown at ei4Africa Lagos meeting March 2014. A refined demonstrator with initial evaluation in early June at ei4Africa Tanzanian meeting in Dar-es-Salaam and a well-developed demonstrator shown and presented at World Congress in Basic & Clinical Pharmacology July 13-18th, Cape Town South Africa. 2. Sustainable management plan should be approved in autumn 2014 with ongoing activities for longterm support by involving IUPHAR and other scientific organizations.

Internet Connectivity Challenges
The discussion of the e-platform will include solutions for internet accessibility that is required for the efficient participation of the community partners.

Currently the institutions have the following connections:

AiBST:

1. ADSL – asynchronous digital subscriber line (from Telone company in Zimbabwe). It has a 2Mbs pipe high speed link (shared with others users such that it slows down speed. There is unlimited access. It costs 245 USD/month.

2. TELCO – A Fiber Optic 2Mbs pipe unlimited and UNSHARED access hence very fast and reliable but expensive at 450 USD/month.

UCT: Connected at about 540 Mbps international.

University of Nairobi: 600 Mb/s international bandwidth and 1 Gb/s capacity for local traffic.
Muhimbili University of Health and Allied Sciences: 30mbps uplink and downlink. During peak hours this bandwidth is maximally utilized
University of Makerere:68 Mb/s to be increased in near future.

OAU: Primary link on main 1= 200MB/s (duplex), secondary link on IPNX=45Mb/s (duplex) and an aggregate of 245Mb/s (duples)

University Of Ibadan: 90Mbps full duplex.

List of individuals involved in the proposed community.

	Institute	**Contacts**	**Country**	**Status**
1	African Institute of Biomedical Science and Technology (AiBST)	**Collen Masimirembwa** (collen.masimirembwa@aibst.com) Milcah Dhoro (milcah.dhoro@aibst.com) Roslyn Thelingwani (roslyn.thelingwani@aibst.com)	Zimbabwe	Suggested Host
2	Muhimbili University	Omary Minzi minziobejayesu@gmail.com Eliford Ngaimisi engaimisi@gmail.com	Tanzania	collaborator
3	Makerere University	Jackson Mukonzo mukojack@yahoo.co.uk Norah Mwebaza mwebno@yahoo.com KSarah Nanzigu snanzigu@yahoo.com Muhammad Ntale muhntale@yahoo.co.uk	Uganda	collaborator
4	Addis Ababa University ,	Eleni Aklillu eleni.aklillu@ki.se Abiy Eyakem abiyeyakem@gmail.com	Ethiopia	collaborator
5	University of Nairobi ,	Anastasia Guantai anguantai@yahoo.com Margaret Oluka olukamarga@yahoo.com	Kenya	collaborator
6	University of Ibadan	Chinedum Peace Babalola (peacebab2001@yahoo.com>;	Nigeria	collaborator
7	University of Cape Town,	Collet Dandara [collet.dandara@uct.ac.za] Simbasashe Zvada	South Africa	collaborator

		simba.zvada@gmail.com Emmanuel Chigutsa emmanuel.chigutsa@uct.ac.za		
8	Obafemi Awolow University	Oluseye Bolaji obolaji@oauife.edu.ng	NIgeria	collaborator

Contact persons: collen.masimirembwa@aibst.com (primary), collet.dandara@uct.ac.za (specific tasks) and lars-l.gustafsson@ki.se (support person)

Appendix A: Pharmacological Science Gateway Structure

The following diagrams are based on the African Science Gateway at https://sgw.africa-grid.org/ . Figure 1 shows the overall Pharmacological Science Gateway (PSG) structure. Note that "Level X" refers to submenus or webpages. As Figure 1 shows, Level 0 refers to the African Science Gateway home page. Level 1 refers to the drop down menus. Initially PSG would be accessed initially as a third drop down menu offering Level 2 categories. Selecting one of these (e.g. Genomics and Bioinformatics) would then lead to a Level 3 web page (as the drop down menus would too cumbersome to use at this point). This structure is outlined in Figure 1 with Figure 2 (Genomics and Bioinformatics, Bioanalysis, drug analysis and metabolism, Pharmacokinetics & pharmacometrics resources) and Figure 3 (Clinical trials sciences, electronic library, and multimedia contacts and e-Learning tools).

Issues

Figure 1: Pharmacological Science Gateway Outline

Raised issue: Is this design preferable? i.e. PSG drop down menu leading to menu choices leading to web pages. The answer is YES

TEXT

This e-Science platform SIMPLIFIES COLLABORATION AND SHARING OF RESEOURCES IN AFRICA. THEREFORE it serves to promote and implement African medical science collaboration focusing on biomedical and pharmacological sciences and clinical trials AND CLINICAL DRUG STUDIES for improving African healthcare. The platform makes accessible open sources software for study designs, biomedical data processing and facilities for sharing data and discussing scientific and technical topics of interest to network members. The platform also effectively enables north-south and south-south capacity and capability strengthening as African researchers and their international collaborators WILL GET AN EASY ACCESSIBLE ARENA of interaction.

It is supported by the EU-project eI4Africa (www.ei4africa.eu), Karolinska Institutet (Sweden), Royal Institute of Technology (Sweden), Catania University (Italy), Brunel University (United Kingdom) and optionally IUPHAR (International Union of Pharmacology & Clinical Pharmacology). It will be hosted by the African Institute of Biomedical Science and Technology (AiBST) IN HARARE which leads a network of African researchers. THIS NETWORK CURRENTLY includes AIBST (African Institute of Biomedical Science & Technology www.aibst.com , Zimbabwe) collaborating with Muhimbili University (Tanzania), Makerere University (Uganda), Addis Ababa University (Ethiopia), University of Nairobi (Kenya), University of Ibadan (Nigeria), University of Cape Town (South Africa), and Obafemi Awolowo University (Nigeria).

The power and value of this e-Infrastructure will depend on the input and suggestions and sharing between institutions and persons. This African Pharmacology Science Gateway supports open access of software and research resources.

Figure 2: Genomics & Bioinformatics, Bioanalysis, Drug Analysis and Metabolism, and Pharmacokinetics &Pharmocometrics Resources

Genomics and Bioinformatics (G&B) Web Page

1. BLAST (*blast.ncbi.nlm.nih.gov/*)

Link directly to web address? **Answer**: YES

TEXT

The US National Center for Biotechnology Information (NCBI) provides BLAST, a suite of programs for aligning query sequences against genomes selected from a database. Click the icon below to access the NCBI BLAST homepage at ***blast****.ncbi.nlm.nih.gov*. See ftp://ftp.ncbi.nlm.nih.gov/pub/factsheets/HowTo_BLASTGuide.pdf for a guide to the BLAST homepage and selected search pages.

Description of BLAST by *Johnson M et al. (2008). NCBI BLAST: a better web interface. Nucleic Acids Res;36(Web Server issue):W5-9.*

2. *ClustalW* (*www.ebi.ac.uk/Tools/phylogeny/clustalw2_phylogeny/*)

Implemented as a Grid service. Files are uploaded to Grid (output) and downloaded back to the user (input).

The following file types are possible
(.aln) ALN file is a **ClustalW2** Alignment Data. One will be submitting sequences they wish to align with other sequences fiund in databases.
Input/Output
This program accepts a wide range of input formats, including NBRF/PIR, FASTA, EMBL/Swiss-Prot, Clustal, GCC/MSF, GCG9 RSF, and GDE.
The output format can be one or many of the following: Clustal, NBRF/PIR, GCG/MSF, PHYLIP, GDE, or NEXUS.
Program available for for Windows, Mac OS, and Unix/Linux

TEXT

ClustalW2 is a widely used program for the multiple alignment of nucleic acid and protein sequences.

The program accepts a wide range on input formats including: NBRF/PIR, FASTA, EMBL/Swissprot, Clustal, GCC/MSF, GCG9 RSF, and GDE, and executes the following workflow:

Pairwise alignment

1. Creation of a phylogenetic tree (or use a user-defined tree)
2. Use of the phylogenetic tree to carry out a multiple alignment

Users can align the sequences using the default setting but occasionally it may be useful to customize one's own parameters. The main parameters are the gap opening penalty and the gap extension penalty.

For more information :

- http://www.clustal.org/clustal2/#Documentation
- *Larkin MA et al Clustal W and Clustal X version 2.0. Bioinformatics 2007; 23, 2947-8.*
- The MP4 file below is a video showing how to use the ClustalW program from this Science Gateway.

  Access the program by clicking the icon below.

Roberto – can you label the mp4 file with "ClustalW Tutorial"

3. Genetic Archives on Metabolism and Transporters

Merged database sites together.

TEXT

- The Human Cytochrome P450 (CYP) Allele Nomenclature Database (http://www.cypalleles.ki.se)

  Overseen by The Human Cytochrome P450 (CYP) Allele Nomenclature Committee, the main purpose of the Human Cytochrome P450 (CYP) Allele Nomenclature website is the management of an official and unified allele designation system, as well as the provision of a database of CYP alleles and their associated effects. Inclusion criteria are summarized at http://www.cypalleles.ki.se/criteria.htm.

  Additional information by *Sim SC, Ingelman-Sundberg M. Update on allele nomenclature for human cytochromes P450 and the Human Cytochrome P450 Allele (CYP-allele) NomenclatureDatabase. Methods Mol Biol 2013;987:251-9.*

- Pharmacogenetics of Membrane Transporters Database (http://www.pharmacogenetics.ucsf.edu/)

  Provided by the University of California, San Francisco Pharmacogenetics of Membrane Transporters (PMT) Project, this database provides provides information on genetic variants (including single nucleotide polymorphisms (SNPs) and insertions/deletions) in membrane transporter genes that have been discovered by the PMT project. Additional information by *Morrissey KM et al. The UCSF-FDA TransPortal: a public drug transporter database. Clin Pharmacol Ther. 2012;92:545-6.*

- Arylamine N-acetyltransferases (NATs) Databases (http://nat.mbg.duth.gr/background_2013.html#_The_NAT_websites)

  The database of Arylamine N-acetyltransferases (NATs) contains information relevant to the consensus nomenclature of human and non-human NATgenes and alleles in humans and other organisms. These databases are intended to be a useful resource to study the genetic, evolutionary and functional diversity of the NAT isoenzymes.

To suggest additions please contact the Science Gateway administrator at ADDRESS.

4. *G-HMMER* (*sgw.africa-grid.org/g-hmmer*)

Implemented as a Grid service. Files are uploaded to Grid (output) and downloaded back to the user (input).

Which file types? Submission information summarized below:

Software which models protein or nucleic acid sequences. Hmmer is a suite of programs which use profile hidden Markov models (profile HMMs) to model the primary structure consensus of a family of protein or nucleic acid sequences. HMMER is used for searching sequence databases for homologs of protein sequences, and for making protein sequence alignments. It implements methods using probabilistic models called **profile hidden Markov models** (profile HMMs).

You submit sequence in the following format: >2abl_A mol:protein length:163 ABL TYROSINE KINASE
MGPSENDPNLFVALYDFVASGDNTLSITKGEKLRVLGYNHNGEWCEAQTKNGQGW
VPSNYITPVNSLEKHSWYHGPVSRNAAEYLLSSGINGSFLVRESESSPGQRSISLRYEG
RVYHYRINTASDGKLYVSSESRFNTLAELVHHHSTVADGLITTLHYPAP

For more information see:

- *Finn RD, Clements J, Eddy DR. HMMER web server: interactive sequence milarity searching. Nucleic Acids Research. Web Server Issue 2011;39:W29-W37.*
- Search parameters guide at http://hmmer.janelia.org/help/search

Note to add user guide video.

5. *GROMACS* (*sgw.**africa**-grid.org/**gromacs***)

Implemented as a Grid service. Files are uploaded to Grid (output) and downloaded back to the user (input).

GROMACS (GROningen MAchine for Chemical Simulations) is a molecular dynamics package primarily designed for simulations of proteins, lipids and nucleic acids. A beginner's guide to GROMACS can be found at http://www.gromacs.org/Documentation/How-tos/Beginners

Which file types? Answer: eiwit.pdb. Submission information: protein sequences or DNA sequences.

6. Haploview

http://www.broadinstitute.org/scientific-community/science/programs/medical-and-population-genetics/haploview/haploview

Link directly to web address? **YES**

TEXT

Haploview is a software tool developed by the Broad Institute and aims to simplify and facilitate the process of haplotype analysis. The tool supports a wide range of functions including LD & haplotype block analysis, haplotype population frequency estimation, single SNP and haplotype association tests and permutation testing for association significance. See the HAPLOVIEW home page for a full description of functionality.

For more information see:

The tutorial at http://www.broadinstitute.org/scientific-community/science/programs/medical-and-population-genetics/haploview/tutorial

The user manual at http://www.broadinstitute.org/science/programs/medical-and-population-genetics/haploview/user-manual

The integration of this tool in the ASG is still under development.

7. Useful Links

Create a new section labelled "Useful Links" *and include:*

H3Africa (http://www.h3africa.org/)

The Human Heredity and Health in Africa (H3Africa) Initiative aims to facilitate a contemporary research approach to the study of genomics and environmental determinants of common diseases with the goal of improving the health of African populations. To accomplish this, the H3Africa Initiative aims to contribute to the development of the necessary expertise among African scientists, and to establish networks of African investigators.

The Pharmacogenomics Knowledgebase (http://www.pharmgkb.org/)

The **Pharmacogenomics Knowledgebase** (PharmGKB) supported by Standford University is a comprehensive resource that encompasses clinical information including dosing guidelines and drug labels, potentially clinically actionable gene-drug associations and genotype-phenotype relationships. PharmGKB collects, curates and disseminates knowledge about the impact of human genetic variation on drug responses.

To suggest additions please contact the Science Gateway administrator at ADDRESS.

Bioanalysis, drug analysis and metabolism Web Page

For the purposes of sharing knowledge and resources this page can include

1. Library of available bioanalysis protocols at different bioanalysis laboratories
2. A library of how to … e.g. how to make an acetonitrile/ammonium acetate buffer with ionic strength of 10
3. A forum for discussing real bio-analytical questions requiring solution at one of the participating labs
4. A library of bio analytical methods being developed or adopted by the participating labs

This refers to a chromatogram database that is to be implemented. How should this be implemented? Design? Storage technology? Capacity?

Comments. Chromatragrams can be submitted as pdf documents for shared discussion.

TEXT

This page will host a database of chromatograms and is currently under development.

Pharmacokinetic/pharmacometric Web Page

1. Monolix, software for pharmacometric work: www.lixoft.com

Link directly to web address? YES

TEXT

Monolix® is a platform for model-based drug development. It can be used for parameter estimation in non-linear mixed effect models, model diagnosis and assessment, and advanced graphical representation.

For other information see:

Tutorial information http://www.lixoft.eu/products/monolix/tutorial/
Documentation http://www.lixoft.eu/products/monolix/documentation/

The integration of this tool in to the Science Gateway is still under development.

2. *Population Experimantal Design at http://poped.sourceforge.net/*

Is this actually a Grid application?
PopED 2.x is a Optimal Experimental Design tool for Non-Linear Mixed Effect Models. PopED 2.x is based on Matlab scripts and, for Windows .NET users or Mono users, a Graphical User Interface (GUI) is available.
The PopED GUI is a Windows based program written in the language C# .NET 2.0 that will wrap around the script version of PopED (written in Matlab) that performs the calculations needed to get an optimal design.

TEXT

PopED 2.x is a Optimal Experimental Design tool for Non-Linear Mixed Effect Models.

The integration of this tool in the Science Gateway is currently under investigation.

3. Xpose application for Nonmem at http://xpose.sourceforge.net

Link directly to web address? **YES**

Complete?

TEXT

Xpose (http://xpose.sourceforge.net/)

Xpose has been developed by Uppsala University and is an R library for post-processing of NONMEM output (NONMEM (http://www.iconplc.com/nonmem) is a nonlinear mixed effects modelling tool used in population pharmacokinetic/pharmacodynamic analysis). Xpose takes one or more standard NONMEM table files as input and generates graphs or other analyses.

For more information see:

An overview of Xpose http://xpose.sourceforge.net/bestiarium_v1.0.pdf
Documentation http://xpose.sourceforge.net/docs.php
or the article *Keizer RJ, Karlsson MO, Hooker A. Modeling and Simulation Workbench for NONMEM: Tutorial on Pirana, PsN, and Xpose. CPT Pharmacometrics Syst Pharmacol. 2013:2:e50.*

4. Other Tools

General tools (?) link http://www.uppsala-pharmacometrics.com/software.html as well as NONMEM for sparse pharmacokinetic/dynamic analyses available at http://psn.sourceforge.net/

Link directly to web address? **YES**

TEXT

Perl-speaks-NONMEM (PsN)**from Uppsala University (http://www.uppsala-pharmacometrics.com/software.html)** is a collection of Perl modules and programs aiding in the development of non-linear mixed effect models using NONMEM. The functionality ranges from simpler tasks such as parameter estimate extraction from output files, data file sub setting and resampling, to advanced computer-intensive statistical methods. PsN includes both stand-alone tools as well as development libraries for method developers. PsN is freely available at psn.sf.net.

5. http://www.summitpk.com/tools/tools.htm

Link directly to web address? **YES**

Figure 3: Clinical Trial Services, Electronic Library and eLearning

Clinical Trial Sciences Web Page:

1. The website www.clinicaltrials.gov (US governmental website over registered clinical trials)

ClinicalTrials.gov is service of the U.S. National Institutes of Health and is a searchable registry and results database of publicly and privately supported clinical studies of human participants conducted around the world.

Link directly to web address? **YES**

2. The toolkit for writing clinical trial protocol www.ct-toolkit.ac.uk/rotuempa/protocol-development

   NOTE NEW WEB ADDRESS http://www.ct-toolkit.ac.uk/

The Clinical Trials Toolkit provided by the National Institute for Health Research (NIHR) provides practical advice to researchers in designing and conducting publicly funded clinical trials in the UK. Through the use of an interactive routemap, this site provides information on best practice and outlines the current legal and practical requirements for conducting clinical trials. The Toolkit is primarily focused on Clinical Trials of Investigational Medicinal Products (CTIMPs) and the regulatory environment and requirements associated with these. However researchers and R&D staff working on trials in other areas will also find useful information and guidance of relevance to the wider trials environment.

Link directly to web address? **YES**

3. In resource limited settings epiinfo is a valuable tool for data collection, analysis and focusing on the needs in epidemiological research. Software available at http://wwwn.cdc.gov/epiinfo/

Is this actually a Grid application? You can down load this software on your computer and do not have to be online to use it.

Physicians, nurses, epidemiologists, and other public health workers lacking a background in information technology often have a need for simple tools that allow the rapid creation of data collection instruments and data analysis, visualization, and reporting using epidemiologic methods. Epi Info™, a suite of lightweight software tools, delivers core ad-hoc epidemiologic functionality without the complexity or expense of large, enterprise applications.

Visit the Epi Info website to download the tools.

Comments

4. SPIRIT 2013- Standard Protocol Items (presented at annals.org/ article.aspx?articleid= 1556168 and explained at www.bmj.com/content/346/bmj.e7586.pdf%2Bhtml

Replace with home page - http://www.spirit-statement.org/

The protocol of a clinical trial is essential for study conduct, review, reporting, and interpretation. SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) is an international initiative that aims to improve the quality of clinical trial protocols by defining an evidence-based set of items to address in a protocol.

Electronic Library Web Page

Text

This page under development

Link to Hinari resources or have a set of dedicated links for convenience? Seek Hinari username and password for this network.

e-Learning environment

Text

This page under development

This needs to be expanded significantly at a later stage. Suggested Moodle with the capability to support courses, learning resources, etc.

Appendix B: Text for PSG

1. PSG Home Page

This e-Science platform simplifies collaboration and sharing of resources in Africa. Therefore it serves to promote and implement African medical science collaboration focusing on biomedical and pharmacological sciences, clinical trials and clinical drug studies for improving African healthcare. The platform makes accessible open sources software for study designs, biomedical data processing tools and facilities for sharing data and discussing scientific and technical topics of interest to network members. The platform also effectively enables north-south and south-south capacity and capability strengthening as African researchers and their international collaborators will get an easily accessible arena of interaction.

The development and implemention of this African Pharmacology Science Gateway are supported by the EU-project eI4Africa (www.ei4africa.eu), Karolinska Institutet (Sweden), Royal Institute of Technology (Sweden), Catania University (Italy), Brunel University (United Kingdom) and optionally IUPHAR (International Union of Pharmacology & Clinical Pharmacology). It will be hosted by the African Institute of Biomedical Science and Technology (AiBST) in Harare which leads a network of African researchers. This network currently includes AIBST (African Institute of Biomedical Science & Technology www.aibst.com , Zimbabwe) collaborating with Muhimbili University (Tanzania), Makerere University (Uganda), Addis Ababa University (Ethiopia), University of Nairobi (Kenya), University of Ibadan (Nigeria), University of Cape Town (South Africa), and Obafemi Awolowo University (Nigeria).

The power and value of this e-Infrastructure will depend on the input and suggestions and sharing between institutions and persons. This African Pharmacology Science Gateway supports open access of software and research resources.

2. Genomics and Bioinformatics (G&B) Web Page

BLAST (blast.ncbi.nlm.nih,gov)

The US National Center for Biotechnology Information (NCBI) provides BLAST, a suite of programs for aligning query sequences against genomes selected from a database. Click the icon below to access the NCBI BLAST homepage at **blast**.*ncbi.nlm.nih.gov*. See ftp://ftp.ncbi.nlm.nih.gov/pub/factsheets/HowTo_BLASTGuide.pdf for a guide to the BLAST homepage and selected search pages.

Description of BLAST by *Johnson M et al. NCBI BLAST: a better web interface. Nucleic Acids Res 2008;36 (Web Server issue):W5-9.*

ClustalW (*www.ebi.ac.uk/Tools/phylogeny/clustalw2_phylogeny/*)

(.aln) ALN file is a **ClustalW2** Alignment Data. One will be submitting sequences they wish to align with other sequences found in databases.

Input/Output

This program accepts a wide range of input formats, including NBRF/PIR, FASTA, EMBL/Swiss-Prot, Clustal, GCC/MSF, GCG9 RSF, and GDE.
The output format can be one or many of the following: Clustal, NBRF/PIR, GCG/MSF, PHYLIP, GDE, or NEXUS.
Program available for for Windows, Mac OS, and Unix/Linux. (Added comment: In the Pharmacology Science Gateway we can only guarantee that the Linux based applications work.)

ClustalW2 is a widely used program for the multiple alignment of nucleic acid and protein sequences.

The program accepts a wide range on input formats including: NBRF/PIR, FASTA, EMBL/Swissprot, Clustal, GCC/MSF, GCG9 RSF, and GDE, and executes the following workflow:

Pairwise alignment

- Creation of a phylogenetic tree (or use a user-defined tree)
- Use of the phylogenetic tree to carry out a multiple alignment

Users can align the sequences using the default setting but occasionally it may be useful to customize one's own parameters. The main parameters are the gap opening penalty and the gap extension penalty.

For more information:

- http://www.clustal.org/clustal2/#Documentation
- *Larkin MA et al Clustal W and Clustal X version 2.0. Bioinformatics 2007; 23, 2947-48.*
- The MP4 file below is a video showing how to use the ClustalW program from this Science Gateway.

Access the program by clicking the icon below.

Genetic Archives on Metabolism and Transporters

- The Human Cytochrome P450 (CYP) Allele Nomenclature Database (http://www.cypalleles.ki.se)

  Overseen by The Human Cytochrome P450 (CYP) Allele Nomenclature Committee, the main purpose of the Human Cytochrome P450 (CYP) Allele Nomenclature website is the management of an official and unified allele designation system, as well as the provision of a database of CYP alleles and their associated effects. Inclusion criteria are summarized at http://www.cypalleles.ki.se/criteria.htm.

  Additional information at the publication *Sim SC, Ingelman-Sundberg M. Update on allele nomenclature for human cytochromes P450 and the Human Cytochrome P450 Allele (CYP-allele) NomenclatureDatabase. Methods Mol Biol 2013;987:251-9.*

- Pharmacogenetics of Membrane Transporters Database (http://www.pharmacogenetics.ucsf.edu)

Provided by the University of California, San Francisco Pharmacogenetics of Membrane Transporters (PMT) Project, this database provides provides information on genetic variants (including single nucleotide polymorphisms (SNPs) and insertions/deletions) in membrane transporter genes that have been discovered by the PMT project. Additional information by *Morrissey KM et al. The UCSF-FDA TransPortal: a public drug transporter database. Clin Pharmacol Ther. 2012;92:545-6.*

- Arylamine N-acetyltransferases (NATs) Databases (http://nat.mbg.duth.gr/background_2013.html#_The_NAT_websites)

  The database of Arylamine N-acetyltransferases (NATs) contains information relevant to the consensus nomenclature of human and non-human NATgenes and alleles in humans and other organisms. These databases are intended to be a useful resource to study the genetic, evolutionary and functional diversity of the NAT isoenzymes.

To suggest additions please contact the Science Gateway administrator at ADDRESS.

G-HMMER (*sgw.africa-grid.org/g-hmmer*)

Software which models protein or nucleic acid sequences. Hmmer is a suite of programs which use profile hidden Markov models (profile HMMs) to model the primary structure consensus of a family of protein or nucleic acid sequences. HMMER is used for searching sequence databases for homologs of protein sequences, and for making protein sequence alignments. It implements methods using probabilistic models called **profile hidden Markov models** (profile HMMs).

You submit sequence in the following format: >2abl_A mol:protein length:163 ABL TYROSINE KINASE
MGPSENDPNLFVALYDFVASGDNTLSITKGEKLRVLGYNHNGEWCEAQTKNGQGW
VPSNYITPVNSLEKHSWYHGPVSRNAAEYLLSSGINGSFLVRESESSPGQRSISLRYEG
RVYHYRINTASDGKLYVSSESRFNTLAELVHHHSTVADGLITTLHYPAP

For more information see:

- *Finn RD, Clements J. And Eddy DR. HMMER web server: interactive sequence milarity searching. Nucleic Acids Research. Web Server Issue 2011;39:W29-37.* Search parameters guide at http://hmmer.janelia.org/help/search

Note to add user guide video.

GROMACS (*sgw.**africa**-grid.org/**gromacs***)

GROMACS (GROningen MAchine for Chemical Simulations) is a molecular dynamics package primarily designed for simulations of proteins, lipids and nucleic acids.

The files are of type eiwit.pdb. They should be submitted as protein sequence or DNA sequences. A beginner's guide to GROMACS can be found at http://www.gromacs.org/Documentation/How-tos/Beginners

Haploview
http://www.broadinstitute.org/scientific-community/science/programs/medical-and-population-genetics/haploview/haploview

Haploview is a software tool developed by the Broad Institute and aims to simplify and facilitate the process of haplotype analysis. The tool supports a wide range of functions including LD & haplotype block analysis, haplotype population frequency estimation, single SNP and haplotype association tests and permutation testing for association significance. See the HAPLOVIEW home page for a full description of functionality.

For more information see:

The tutorial at http://www.broadinstitute.org/scientific-community/science/programs/medical-and-population-genetics/haploview/tutorial

The user manual at http://www.broadinstitute.org/science/programs/medical-and-population-genetics/haploview/user-manual

The integration of this tool in the ASG is still under development.

Useful Links

Create a new section labelled "Useful Links" *and include:*

H3Africa (http://www.h3africa.org/)

The Human Heredity and Health in Africa (H3Africa) Initiative aims to facilitate a contemporary research approach to the study of genomics and environmental determinants of common diseases with the goal of improving the health of African populations. To accomplish this, the H3Africa Initiative aims to contribute to the development of the necessary expertise among African scientists, and to establish networks of African investigators.

The Pharmacogenomics Knowledgebase (http://www.pharmgkb.org/)

The **Pharmacogenomics Knowledgebase** (PharmGKB) supported by Stanford University is a comprehensive resource that encompasses clinical information including dosing guidelines and drug labels, potentially clinically actionable gene-drug associations and genotype-phenotype relationships. PharmGKB collects, curates and disseminates knowledge about the impact of human genetic variation on drug responses. Further information is given *byThorn CF, Klein TE, Altman RB. PharmGKB: the Pharmacogenomics Knowledge Base. Methods Mol Biol 2013;1015:311-20.*

To suggest additions please contact the Science Gateway administrator at ADDRESS.

3.Bioanalysis, drug analysis and metabolism Web Page

For the purposes of sharing knowledge and resources this page can include

- Library of available bioanalysis protocols at different bioanalysis laboratories

- A library of how to … e.g. how to make an acetonitrile/ammonium acetate buffer with ionic strength of 10
- A forum for discussing real bio-analytical questions requiring solution at one of the participating labs
- A library of bio analytical methods being developed or adopted by the participating labs

This part is to be further developed. *To suggest additions please contact the Science Gateway administrator at ADDRESS.*

Chromatragrams can be submitted as pdf documents for shared discussion. This page will host a database of chromatograms and is currently under development.

4.Pharmacokinetic/pharmacometric Web Page

Monolix, software for pharmacometric work: www.lixoft.com

Monolix® is a platform for model-based drug development. It can be used for parameter estimation in non-linear mixed effect models, model diagnosis and assessment, and advanced graphical representation.

For further information see:

Tutorial information http://www.lixoft.eu/products/monolix/tutorial/
Documentation http://www.lixoft.eu/products/monolix/documentation/

The integration of this tool in to the Science Gateway is still under development.

Population Experimantal Design at http://poped.sourceforge.net/

PopED 2.x is a Optimal Experimental Design tool for Non-Linear Mixed Effect Models.
PopED 2.x is based on Matlab scripts and, for Windows .NET users or Mono users, a Graphical User Interface (GUI) is available.
The PopED GUI is a Windows based program written in the language C# .NET 2.0 that will wrap around the script version of PopED (written in Matlab) that performs the calculations needed to get an optimal design.

PopED 2.x is a Optimal Experimental Design tool for Non-Linear Mixed Effect Models.

The integration of this tool in the Science Gateway is currently under investigation.

Xpose application for Nonmem at http://xpose.sourceforge.net

Xpose has been developed by Uppsala University and is an R library for post-processing of NONMEM output (NONMEM (http://www.iconplc.com/nonmem) is a nonlinear mixed

effects modelling tool used in population pharmacokinetic/pharmacodynamic analysis). Xpose takes one or more standard NONMEM table files as input and generates graphs or other analyses.

For more information see:

An overview of Xpose http://xpose.sourceforge.net/bestiarium_v1.0.pdf. Documentation at http://xpose.sourceforge.net/docs.php or by *Keizer RJ, Karlsson MO, Hooker A. Modeling and Simulation Workbench for NONMEM: Tutorial on Pirana, PsN, and Xpose. CPT Pharmacometrics Syst Pharmacol 2013;2:e50.*

Other Tools

General tools (?) link http://www.uppsala-pharmacometrics.com/software.html as well as NONMEM for sparse pharmacokinetic/dynamic analyses available at http://psn.sourceforge.net/

Perl-speaks-NONMEM (PsN)**from Uppsala University (http://www.uppsala-pharmacometrics.com/software.html)** is a collection of Perl modules and programs aiding in the development of non-linear mixed effect models using NONMEM. The functionality ranges from simpler tasks such as parameter estimate extraction from output files, data file sub setting and resampling, to advanced computer-intensive statistical methods. PsN includes both stand-alone tools as well as development libraries for method developers. PsN is freely available at psn.sf.net.
Pharmacokinetic information is also available at http://www.summitpk.com/tools/tools.htm

5.Clinical Trial Sciences Web Page

The website www.clinicaltrials.gov (US governmental website over registered clinical trials)

ClinicalTrials.gov is service of the U.S. National Institutes of Health and is a searchable registry and results database of publicly and privately supported clinical studies of human participants conducted around the world.

The toolkit for writing clinical trial protocol www.ct-toolkit.ac.uk/rotuempa/protocol-development

The Clinical Trials Toolkit provided by the National Institute for Health Research (NIHR) provides practical advice to researchers in designing and conducting publicly funded clinical trials in the UK. Through the use of an interactive routemap, this site provides information on best practice and outlines the current legal and practical requirements for conducting clinical trials. The Toolkit is primarily focused on Clinical Trials of Investigational Medicinal Products (CTIMPs) and the regulatory environment and requirements associated with these.

However researchers and R&D staff working on trials in other areas will also find useful information and guidance of relevance to the wider trials environment.

EPIINFO

In resource limited settings epiinfo is a valuable tool for data collection, analysis and focusing on the needs in epidemiological research. Software available at http://wwwn.cdc.gov/epiinfo/ You can down load this software on your computer and do not have to be online to use it.

Physicians, nurses, epidemiologists, and other public health workers lacking a background in information technology often have a need for simple tools that allow the rapid creation of data collection instruments and data analysis, visualization, and reporting using epidemiologic methods. Epi Info™, a suite of lightweight software tools, delivers core ad-hoc epidemiologic functionality without the complexity or expense of large, enterprise applications.

Visit the Epi Info website to download the tools.

SPIRIT 2013 at http://www.spirit-statement.org/ and presented as standard Protocol Items (presented at annals.org/ article.aspx?articleid= 1556168 and explained at www.bmj.com/content/346/bmj.e7586.pdf%2Bhtml

The protocol of a clinical trial is essential for study conduct, review, reporting, and interpretation. SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) is an international initiative that aims to improve the quality of clinical trial protocols by defining an evidence-based set of items to address in a protocol.

6.Electronic Library Web Page

Text

This page under development

Link to Hinari resources or have a set of dedicated links for convenience? Seek Hinari username and password for this network.

7.e-learning environment

Text

This page under development

This needs to be expanded significantly at a later stage. Suggested Moodle with the capability to support courses, learning resources, etc.

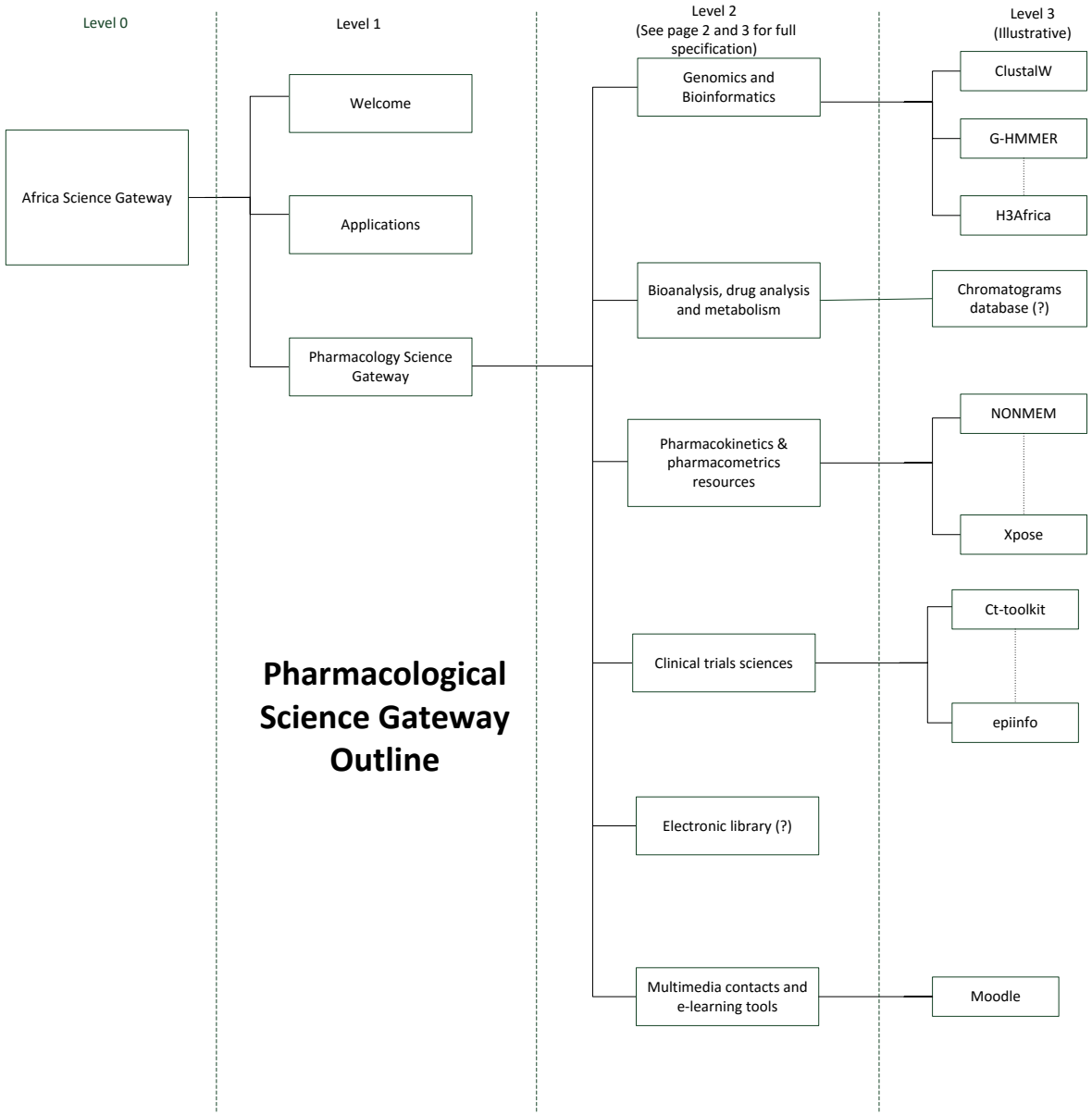


Figure 1: Pharmacological Science Gateway Outline

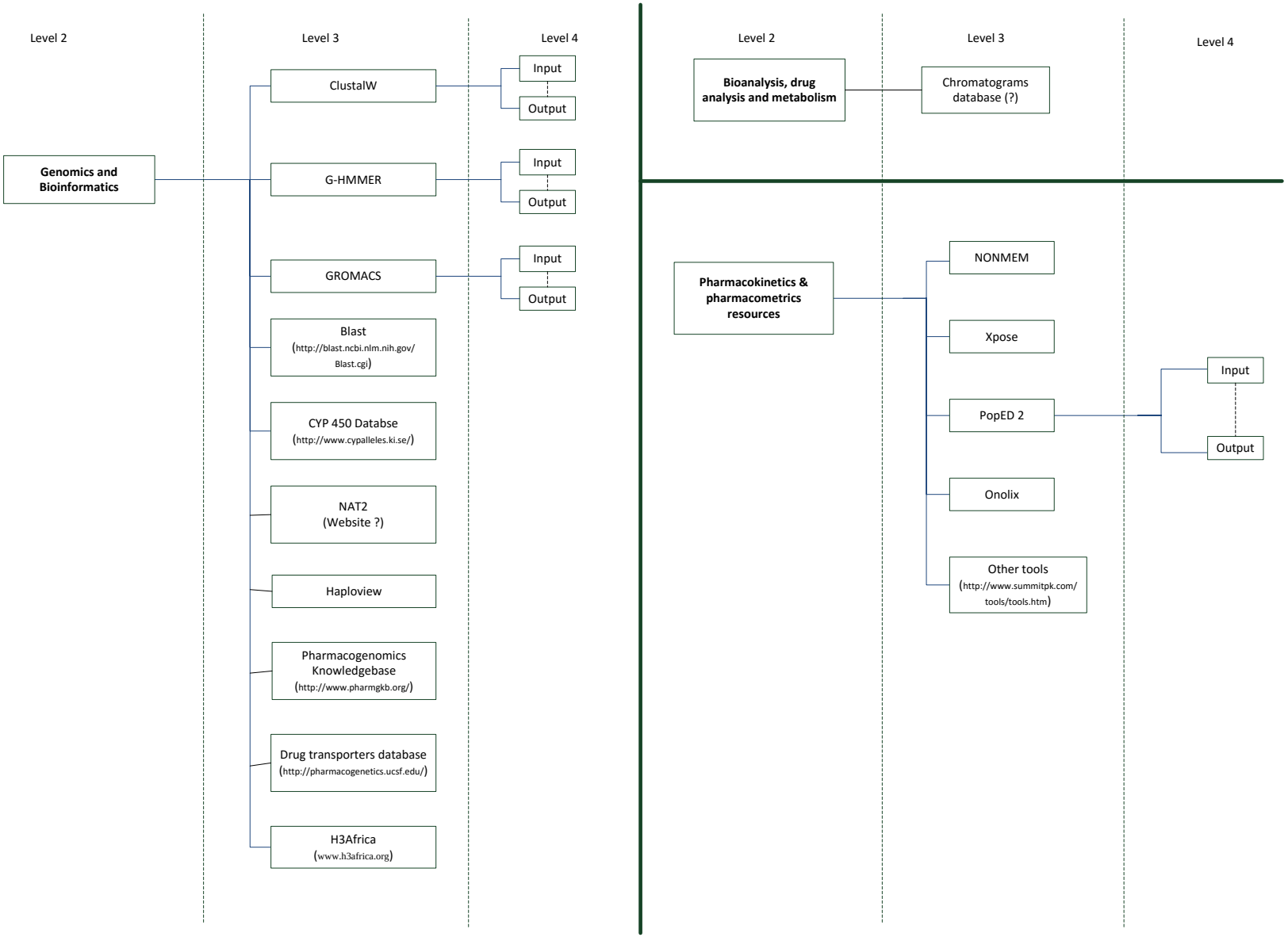


Figure 2: Pharmacological Science Gateway Outline (G&B, BDM and P&PR Levels 2-4)

Figure 3: Pharmacological Science Gateway Outline (Clinical Trial Services, Electronic Library and eLearning Levels 2-4)