Drug production in the region Constraints and Prospects

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Potential of Industry: Economic Growth

Public health: Ensuring access to quality medicines Readily regulated to attain and maintain high quality standards –Partner of MRA

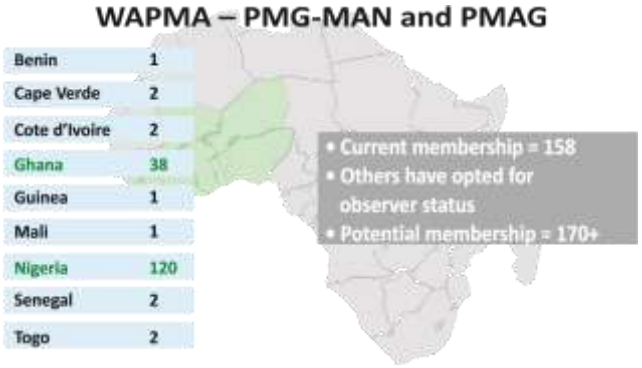
Patronage of locally manufactured medicines reduces influx of sub-standard medicines economic development: Importance in poverty reduction

Direct effect on healthcare: Health = Wealth

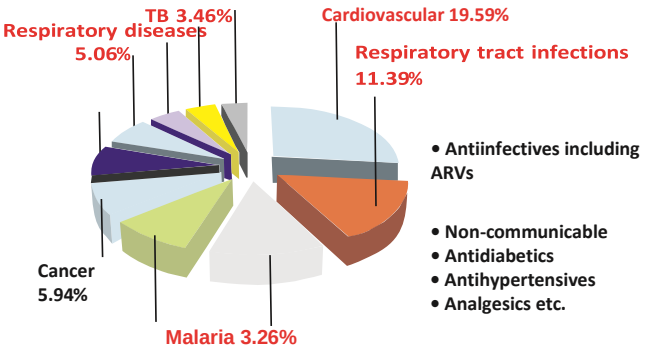
Innovation driven industry – improving standing on the competitiveness index

Demands & creates sophisticated labor – Highest levels of education

Better working conditions than most industries



Generic Medicines: Broad Range of Diseases

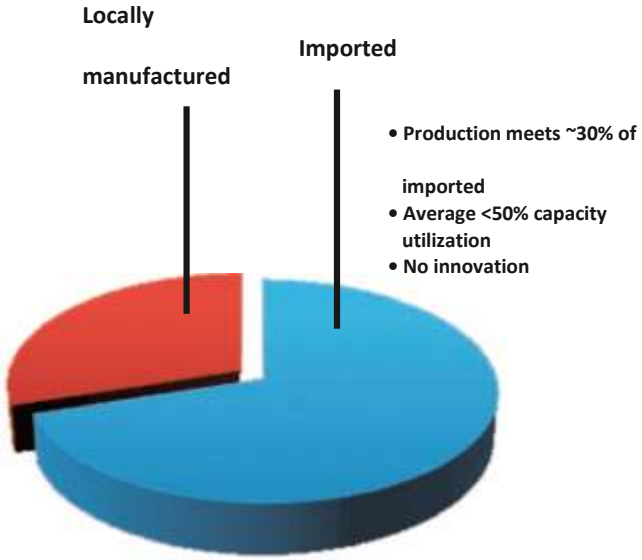


HIV/AIDS 5.75%

Diarrheal Perinatal causes diseases 9.13% 6.88%

WHO, Burden of disease Sub-Saharan Africa

Facts on the Ground – Local Industry



regional needs > 70%

Challenges and Issues

- Foreign competitive advantage
  – Export subsidies for Indian companies– Export incentives for Indian and Chinese manufacturers
  – Pricing disadvantage for the local manufacturer• Most raw material is imported:
  APIs, Excipients, Packaging
- Perception of locally manufactured drugs
  – Not the best
- Intra and inter-regional barriers to trade and growth
  – Lack of harmonization
  – Restricted movement of goods and services
- Ready availability of fake and sub-standard medicines
- Excessive reliance on donation of medicines

Success factors for the Industry (WAPMA)

Attainment of international standards of Good Manufacturing Practices: –

WHO prequalification of medicines to denote GMP compliance – West African Health Organization certification scheme • Self sufficiency in manufacturing
– Finished products
– Active pharmaceutical ingredients
• Innovation – Drug discovery and development

Reliance on donors – Unintended consequences

Participation in donor funded procurement requires WHO prequalification

• **Can stunt growth of the industry** - Local antimalarial production has stopped because of Affordable Medicines Facility malaria (AMFm)
- Minimal local production of antiretrovirals

• **Unsustainable solution:**
- Giving fish vs. Teaching to fish
- Maintaining the dependence culture

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Progress in Quality Standards

Facilities
• Built to ensure quality
• Equipped to maintain standards Personnel
• Have basic educational foundation
• Trained to establish processes
• Committed to maintaining quality

Emergence: World-Class Facilities

Zoning

- Control of activities Environment
- Control of air quality
- Control of temperature
- Control of humidity

Water Quality

- Control of physicochemical parameters
- Control of microbial contamination

Emergence: World-Class Facilities

Equipment

- State of the art
- Installation, operation stages qualified and documented
- Performance monitored to ensure reproducibility
- Maintained to ensure continued quality performance

Quality control instrumentation

Manufacturing

- DocumentationLaboratory Information Management Systems
- Validated
- Compliant with international standards

FT-Infra red spectrometer
Atomic absorption spectrometer
Polarimeter
Refractometer
Dissolution Tester
Disintegration Tester
Friability tester
Nephelometer
Spectrophotometers
Karl Fischer titrator
HPLCs
Gas chromatograph
IR Moisture Determination apparatus

Quality management systems

Needed to Attain and Sustain Quality: Facilities

Peer Regulation and Support – Minimum quality standards required for membership of trade organization: PMG-MAN – Self-

inspection and sanctions for not meeting standards • Regulatory Authority as Partner
– Closer association with organizations –
Mutually set milestones for meeting standards

Human capacity development

GMP training for personnel Support for personnel training from WAHO

Technical assistance from UNIDO, GTZ etc.
- Training at St Luke Kilimanjaro School of Pharmacy - Identification of gaps and development of national/regionaldevelopment plans - Direct assistance to 2 companies toward WHO prequalification

Sustaining Quality: Human Capacity

• Explore ways to promote interest in industry – Waning interest in first degree pharmacists
– Dearth of candidates with graduate training In pharmaceutics
– Traditional pharmacist roles in industry being taken over by others
• Strong theoretical background needed
– Modern concepts e.g. QbD
• Internships and practical training in industry
– Graduate research collaborations with industry Could be mutually beneficial

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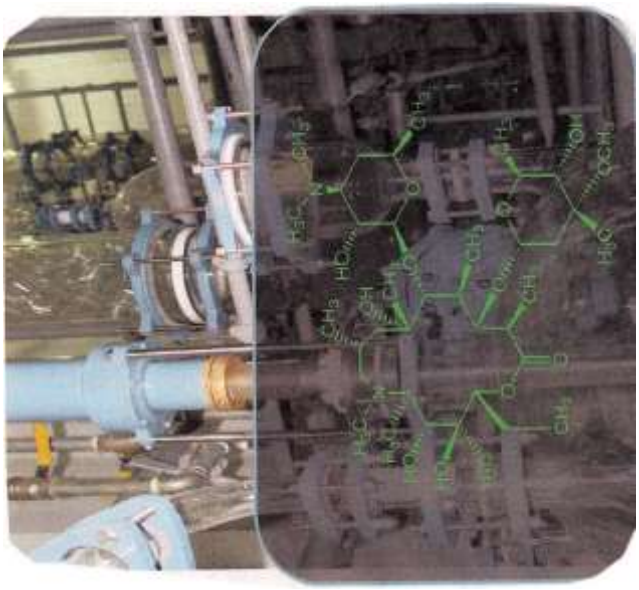
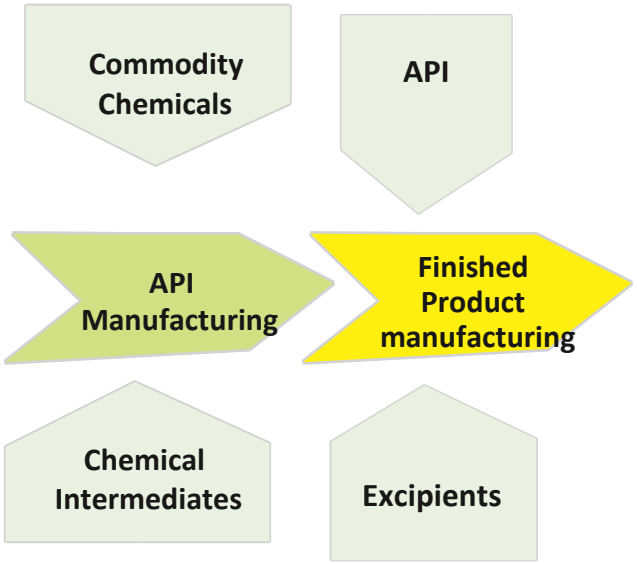
Technologies for Self Sufficiency



• Technology has existed since 1957 for dosage form manufacturing – Oral solids and liquids
– Topicals
– Parenterals

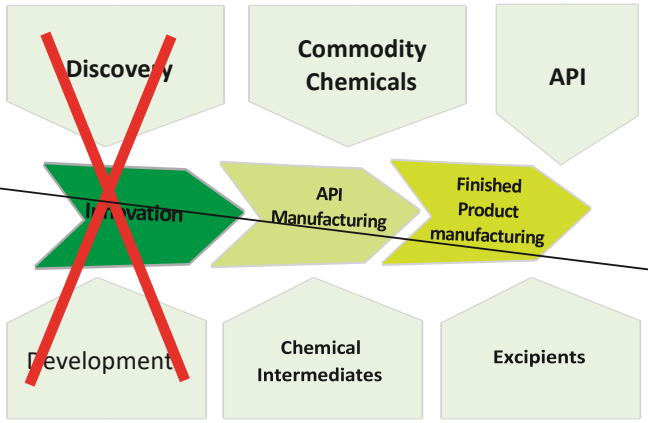
- Technology established for manufacture of APIs in West Africa
- Vertical integration – drug manufacturing from start to finish

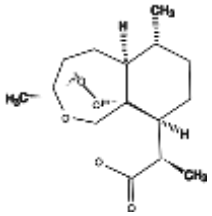
Most Raw Material Imported



• Need to build up capacity in API manufacturing
- Utilize existing capacity fully
- Grow the API industry
• All excipients still imported
- Expore feasibility of basic excipient manufacturing

Entire value chain Some ways to go





Artemisinin

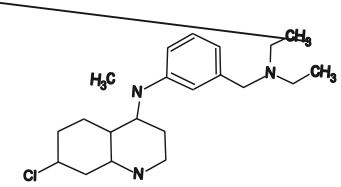
Artesunate

Artemether

Artelinate

Dihydroartemisinin

Endoperoxides

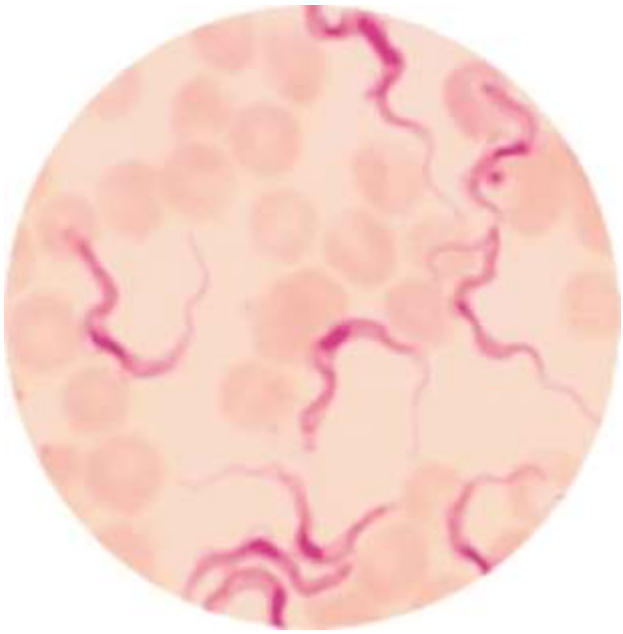


Chloroquine

4-aminoquinolines Amodiaquine

Resistance to Antimalarial Drugs

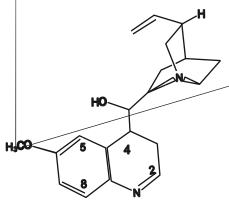
Chloroquine Resistance



Started in Thai-Cambodia border in the 1960s

- 1979 First confirmed report in East Africa
- C.C. Campbell et al., Lancet ii, 1151 (1979)
- 1985 – First report in Central Africa (Cameroon)
- P.J. Sensonetti et al., Lancet i, 1154 (1985)
- 1986 – First report in West Africa (Benin)
- J. Le Bras et al., Lancet ii, 1043 (1986)

Classes of antimalarial drugs used in ACTs



Quinine

Mefloquine

Halofantrin

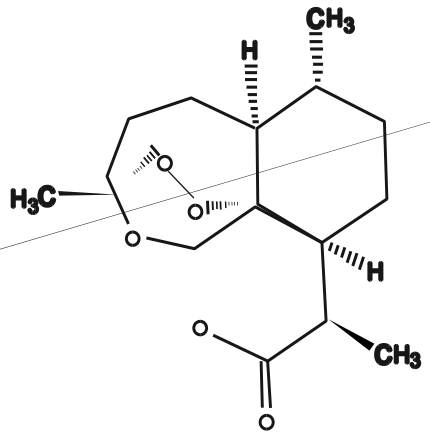
Arylmethanols Lumefantrine

- US pharma industry spending in R&D = USD 67.4 billion in 20101
- Pharmaceutical research has US government support:
  - Tax credit to industry
  - NIH/NSF support for basic research behind drug discovery.

Rationale

- Difficult for resistance selection to occur against two drugs simultaneously
- Good pharmacokinetic match
- Short acting drug in combination with longer acting drug
- Some additive or synergistic effects on the biological target

Recipe for disaster looming



- Monotherapy with artemisinins- Increased use of artemisinin derivatives as monotherapy

- Non adherence to dosage instructions
- Overuse – Only recommended first line
- Empiric use in all fevers

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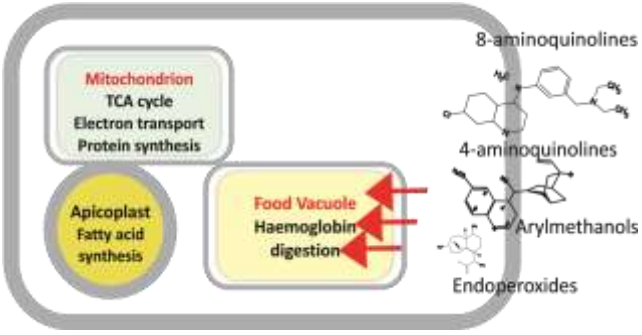
Endoperoxides

Artemisinin Artemether Artesunate Artelinate

Potential for Resistance development to the ACTs

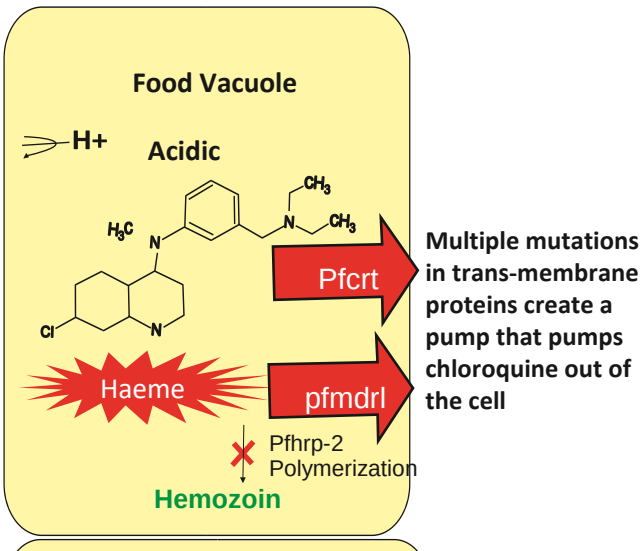


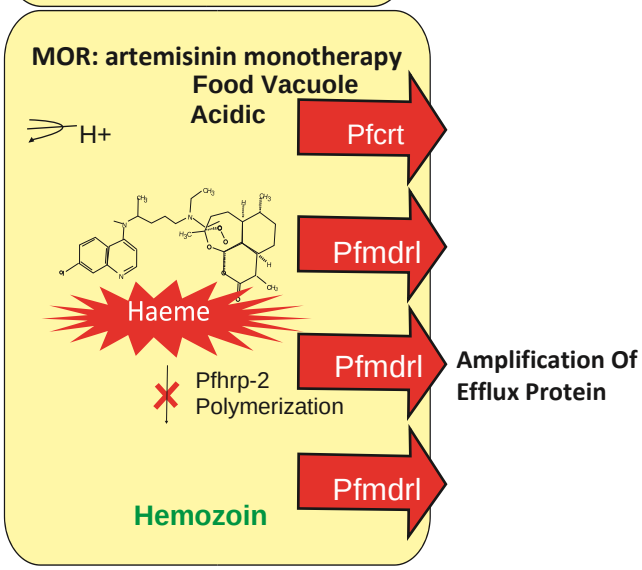
All classes in the combination have the same mechanism of action **What has happened**

Thai-Cambodia border

- First clear sign of resistance published in 2007 showed
- 10% to monotherapy
- 10% to ACT A.P. Alker, Am. J. Trop. Med. Hyg. 76, 641 (2007)
- Second study in 2009 - 30% to monotherapy
- Luckily still approx. 10% to ACT A.M. Dondorp, New Engl. J. Med. 361, 455 (2009)

MOR of Chloroquine





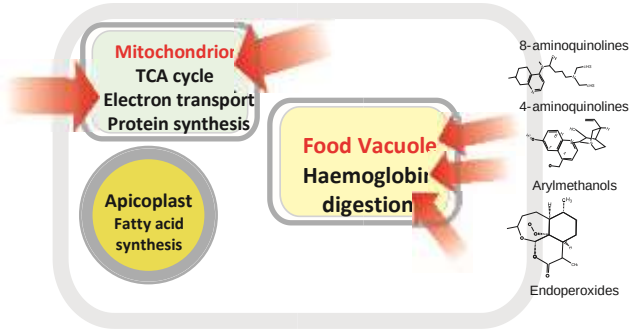
When resistance to the ACTs hit!

Where do we go next?

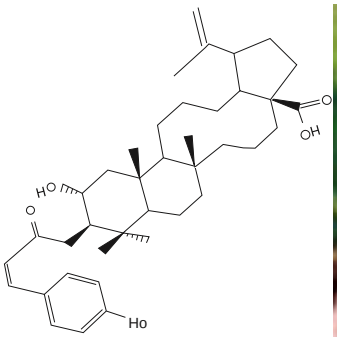
Drug production in the region

Maintain dependence?
– WHO to find next solution
– India and China to produce
– Global fund to supply

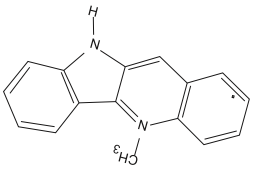
- Different mechanisms of action
- Synergism vs antagonism studies
- Pharmacokinetic matching
- Clinical studies



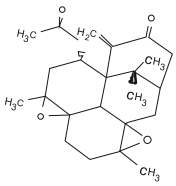
Exploration of Promising Indigenous Leads



Cochlospermum tinctorium Roots
Cumaroyl alphitolic acid 2.3 µM



Cryptolepis sanguinolenta Roots
Cryptolepine 0.27 µM



Hypoestes rosea Leaves

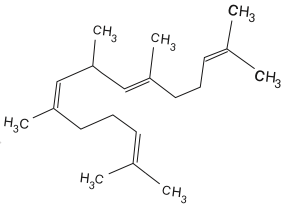
Hypoestoxide 10 µM

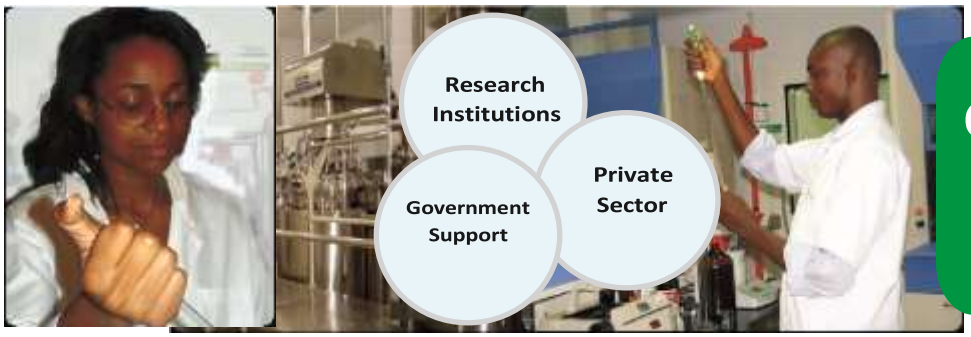
Croton lobatus Stems and leaves

Geranyl geraniol 1.07 µM

Potential for innovation

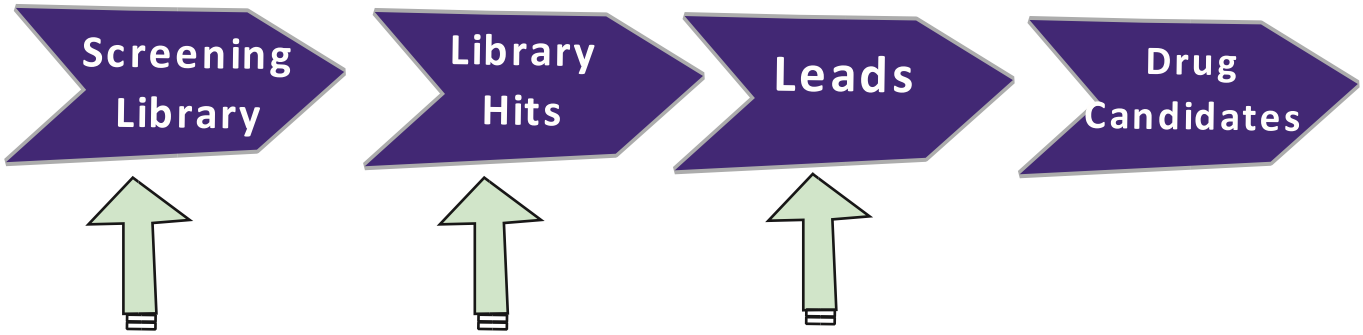
Traditional Medicines → Validated through Science → Developed through partnership





Commercialized by Private Sector

Primary Drug Discovery



Screening
- In vitro activity
- Small MW compounds

Hit to Lead
- In vitro activity
- In vitro toxicity

Lead Optimization
- In vivo evaluation
- Synthetic modifications

Collaborative Primary Drug Discovery Research

Novel Bioactive Compounds from Indigenous Wood Decay Fungus

Dr. Patrick K. Arthur
Department of Biochemistry and Molecular Biology
University of Ghana, Legon

Samuel Yaw Aboagye Student

Fungi as Source of Novel drugs

Antifungal griseofulvin from Penicillium griseofulvum Cholesterol lowering agent lovastatin from Aspergillus terreus Basidiomycetes and Ascomycetes

- Indigenous species have not been explored for novel bioactivity
- Readily harvested and distinguished from each other
- Drug candidates discovered may be novel

Scalable to

Commercial Process

Sample of mycelia

Fruiting body sample grown in media in by fermentation

grown

test-tubes

in culture flasks 10 – 21 days

Filtered

Mycelia isolated

- Mycelia stored and used – No need for reharvesting
- Fermentation can be scaled up to produce multigram gram to kilograms of material
- Conditions can be modified to improve yields
- Process can be transferred to commercial fermenters

Fermentation Beer

Concentration and drying

Hit Identification

Reconstitution (1 mg/mL)

Drug production in the region

Fermentation
Beer

Primary Library

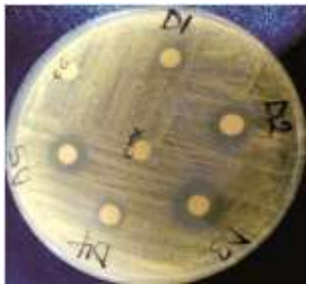
Extracted with EtOAc
Dried and reconstituted
Characteristics of Leads
1 mg/mL

Re-fermentation
Retesting

Hits

LH-20 size exclusion

Confirmed Hits



- Organic molecule
- Tractable molecular weight – not large protein
- Interesting potency

Tested for activity

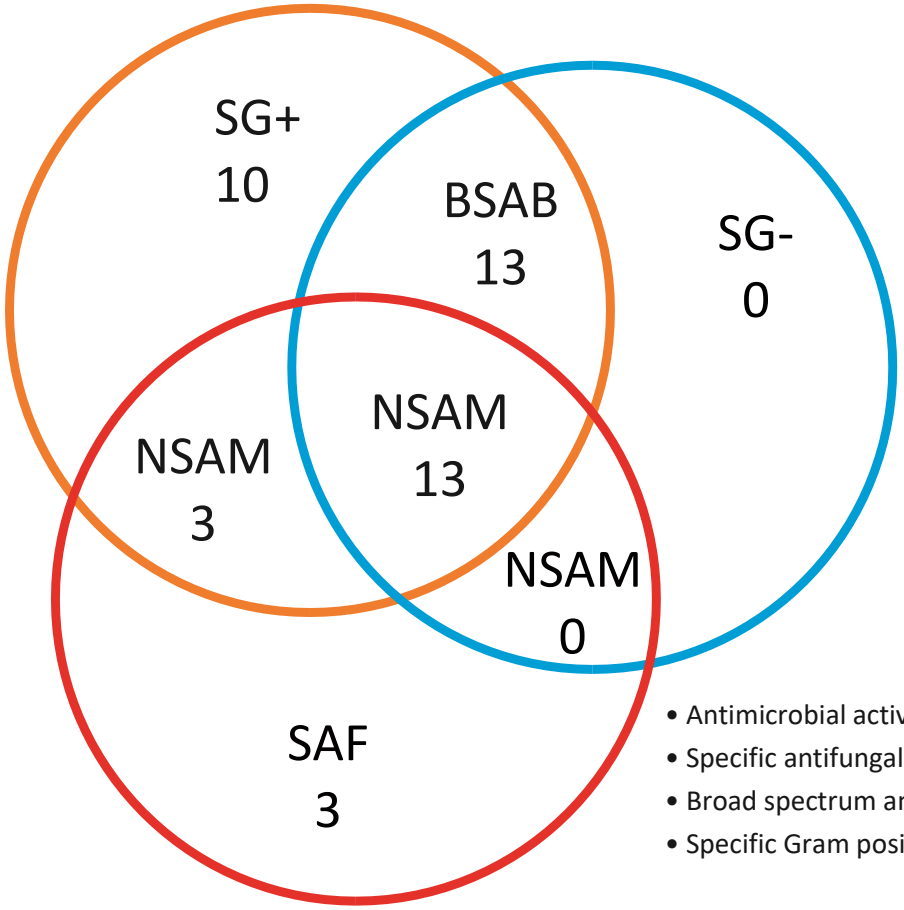
chromatography

Gram Positive Activity	Gram Negative Activity	Antifungal Activity
Staphylococcus aureus	Escherichia coli	Candida albicans

Target Profile

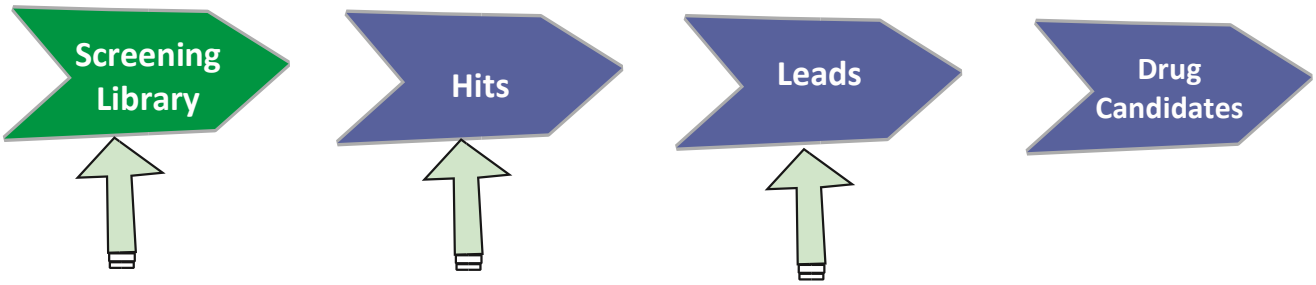
- Selective gram positive activity and activity vs. MRSA in secondary screening
- Selective gram-negative activity
- Broad spectrum antibacterial activity
- Selective antifungal activity

Results of Screening 60 Isolates



- Antimicrobial activity = 39
- Specific antifungal activity = 3
- Broad spectrum antibacterial activity = 13
- Specific Gram positive activity = 10

Primary Drug Discovery



Screening
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- Small MW compounds

Hit to Lead
- In vitro activity
- In vitro toxicity

Lead Optimization
- In vivo evaluation
- Synthetic modifications

Identified for Further Studies: B7

Reproducible selective gram positive activity

Staphylococcus aureus ATCC2
Staphylococcus aureus KBTH2
Staphylococcus epidermidis ATCC3 Streptococcus pyogenes NMIMR3

- Activity yield optimization
- Chromatographic purification of components for further characterization

Collaborative Primary Drug Discovery Research

Samuel Yaw Aboagye
MPhil, Biochemistry
Analysis of Low Molecular Weight
Compounds Produced by Wood Decay Fungi

March 2012

Need for special treatment of the industry

- Africa Union: Pharmaceutical Manufacturing Plan for Africa - 2007
  – Increase local production on the continent – commitment of member governments
  – Use TRIPS flexibilities

- World Health Assembly: Strategy and Plan of Action of Public Health, Innovation and Intellectual Property (GSPOA) - 2008
  – Encourage needs driven research
  – Encourage research in developing countries– Discover and develop drugs for diseases affecting developing countries

- Noordwijk Medicines Agenda-2007 and Yaounde Process - 2009
  – Increase research cooperation
  – Provide financial incentive for research
  – Support synergies in healthcare research in Africa

Recommendations

- Set target dates for harmonization of regulations

- Strengthen medicine regulatory authorities • Patronize local manufacturers - Profitability, sustainability and growth • Assist in improving competitiveness - Reduce tax burden • Improve access to financing for upgrading facilities and WHO prequalification

- **Encourage R&D with grants and tax incentives**

Thank You