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History of the establishment of the Preterm Birth international collaborative (PREBIC)

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A B S T R A C T

Introduction: The primary aim of PREBIC is to assess the underlying mechanisms and developing strategies for preterm birth (PTB) prevention.
Materials and methods: We used concept mapping and logic models to track goals. This paper reviews our progress over 13 years using working group activities, research developments, guest speakers, and publications.
Results: Using interactions between genetics, environment, and behaviors we identified complex interactions between biological systems. PREBIC determined that epidemiology and biomarkers should be an initial focus. In 2005, we initiated presentations by young investigators, yearly satellite meetings, working groups including nutrition and inflammation, assessment of clinical trials, and accepted an invitation by the WHO to begin yearly meetings in Geneva.
Discussion: PREBIC used epidemiology to identify PTB factors and complex pathways. Candidate genes are associated with the environment, behavior (stress), obesity, inflammation and insulin resistance. Epigenetic changes and production of proteins can be used as biomarkers to define risk. Subsequently, we found risk factors for PTB that were also associated with the risk of cardiovascular disease (CVD) of the mother. Tanz et al. (2017) found that a history of PTB is independently predictive of CVD later in life and suggested that a modest proportion of PTB-CVD association was accounted by CVD risk factors, many of which have been identified in this paper.
Conclusion: Our findings support a relationship between genes, environment, behaviors and risk of CVD in women. The next several years must assess which factors are modifiable early in life and before pregnancy to prevent PTB.

1. Introduction

1.1. PREBIC: 13 year history

1.1.1. The establishment of PREBIC

In 2003, the March of Dimes (MOD), in collaboration with The National Institute of Child Health and Human Development (NICHD) and Centers for Disease Control (CDC) embarked on a global initiative to develop an organization that brought awareness to the issue of preterm birth (PTB). They selected a group of recognized investigators of various disciplines that focused on PTB research led by Claudia Holzman, DVM, MPH, PhD of Michigan State University and Paul Thorsen, MD, PhD of Denmark and the CDC. The first meeting entitled "Workshop on Biomarkers of Preterm Delivery" was held in East Lansing, Michigan in March of 2003.

Launched in 2004, PREBIC, the PREterm Birth International Collaborative, is a not-for-profit organization comprised of a multidisciplinary group of physicians and scientists who began to define solutions that deliver superior outcomes toward the prevention of PTB. The primary aim of PREBIC is to find ways of identifying women who have an increased risk of delivering too early, understanding the underlying mechanisms and developing ways to reduce the risk of PTB. This collaboration has been very successful in promoting awareness of PTB and foregoes efforts in managing research and developments toward PTB prevention globally.

The first three years of meetings (2003–2005) provided an

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opportunity to carefully develop a commitment to an intellectually bound course of action. The strategy established a group of investigators with the same vision who would be willing to invest the time and energy to engage others to participate and collaborate in the quest to identify the cause(s) of PTB.

Collaboration involves working with multiple disciplines with different approaches to the problem of PTB—a team effort. Collaboration leads to the formation of an international community who share a common value for improving the health of women to reduce the risk of PTB and improve the health of children worldwide. Collaboration at multiple levels leads to innovation. The overall goal of PREBIC has been to address PTB socially (behavioral) and environmentally, with genetics being a driving force by common genes and epigenetics. The focus of this paper will be to track the progress of PREBIC over a period of 13 years by navigating though concept maps to focus on key areas of research methodology and logic models set short- and long-term objectives while tracing the fruition of outcomes such as research developments and the publication of manuscripts related to PTB.

2. Materials and methods

The efficiency and success of PREBIC is due in part by its internal structure and workflow. Due to the multivariate nature of PTB, the executive board of PREBIC implemented a “systems thinking” method, which allowed experts carrying the same ideas, but often with different views and opinions, to collaborate [1,2]. This was accomplished by the use of organizational tools known as concept mapping and logic models. These processes helped frame the formation of PREBIC by allowing efficient engagement, collaboration and leadership.

2.1. Concept mapping

Principles of concept mapping were used to improve our understanding of the etiology of PTB. Concept mapping is a tool that allowed for “structured conceptualization” of goals [1,2]. It is a very practical exercise to organize and manage thoughts for a team of investigators. In addition, it also became a great participatory research method [4,5]. The process involves brainstorming ideas about an organization's function and purpose, gathering participant-generated input and feedback, sorting common ideas into overlying “themes” and finally “mapping” the themes to generate a figure which would display a proposed conceptual skeleton [4].

2.2. Preparation and planning

The initial “concept mapping” process was facilitated by Michael Katz, MD, from the MOD and supported by the NIH and CDC. The entire planning process took three years and three international meetings.

The **first international workshop** on PTB prevention was centered on identifying and testing key biomarkers. Six focus groups and 3 focal points (Fig. 1) were generated during this first meeting in Michigan. At the **second international workshop** in Denmark, members reviewed the focus groups and focal points from the first workshop, consolidated ideas and replaced five of the existing focus groups with new ones (Fig. 2). The concept of forming the PTB international collaborative (PREBIC) was suggested by Paul Thorsen, MD, PhD the host of the second meeting in Denmark in 2004.

2.3. Generation

The **third international workshop** consolidated ideas further and replaced three of the existing focus groups with new ones (Fig. 3). This was also the meeting where a call for an international collaborative was made, which led to the formation of PREBIC, The PREterm Birth International Collaborative. The organizational structure included the development of an executive, multi-disciplinary governing board and several working groups. The first official PREBIC meeting was held in 2006 at the WHO headquarters in Geneva, Switzerland. Board members used the most current concept map to generate a charter (Fig. 4), which helped focus activities for several years.

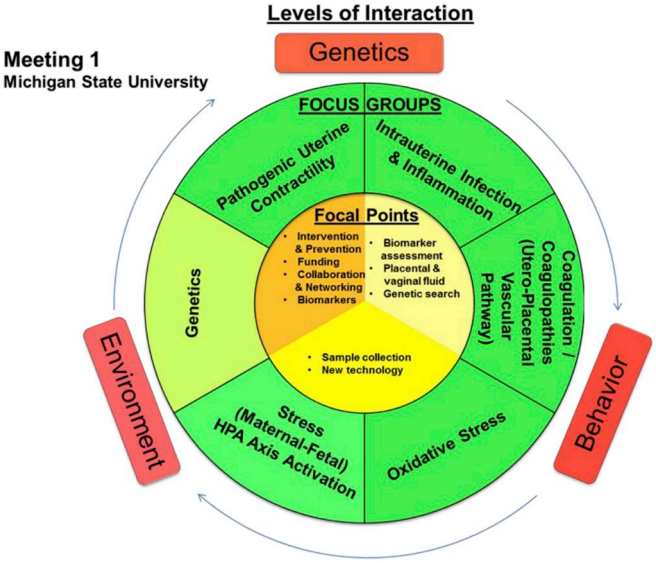

Fig. 1. At the 2003 meeting in Michigan, it was determined that genetics and pathways would be important topics across all areas of investigation for future meetings and would be driven by biomarkers that are associated with five pathways listed in dark green.

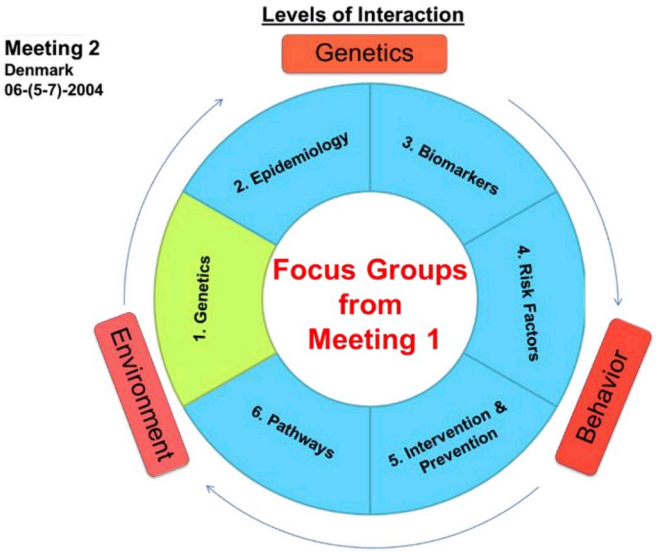

Fig. 2. The goal for 2004, five new focus groups were identified (new focus groups in blue).

2.4. Logic model

The Executive Board organized a plan of action for each goal displayed on the concept map by constructing a logic model for PREBIC (Appendix I). It sets a game plan for the working groups, and allows members to create a logical map toward reaching their goals [5]. The logic model for PREBIC was developed with the following underlying question in mind: How can a process of translational medicine improve collaborative efforts through our collective understanding of the cause of PTB?

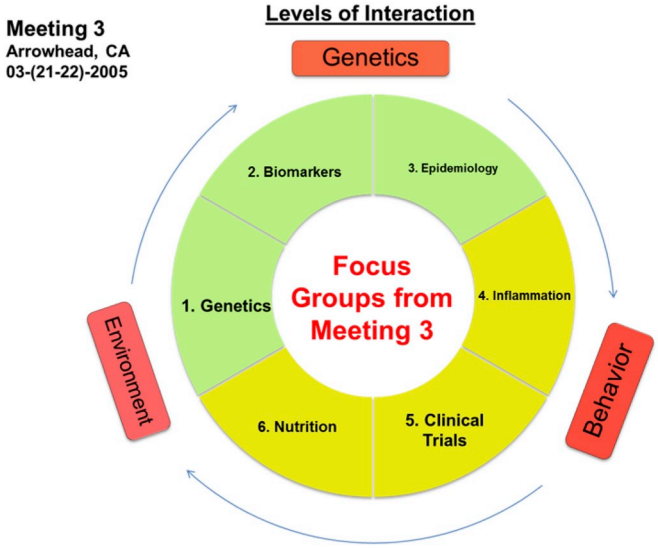

Fig. 3. At the 2005 meeting, genetics remained as the top priority, followed by biomarkers and epidemiology. In addition, three new focus groups came forth: inflammation, clinical trials and nutrition.

2.5. Working groups

The process of concept mapping identified "novel ideas" by using "working groups" as a process for developing focused areas determined by interactions and decisions via experienced and junior investigators through a process of collaboration. Each working group focuses on a particular aspect of PTB research, prevention, and awareness efforts in order to address the matter on all levels: socially, environmentally and behavioral, with a search for genetic associations. Teams were encouraged to create a concept-specific logic model in order to visualize the overall goals [4,6]. Professionals from various fields including genetics, systems biology, and nutrition were teamed together into working groups. Each working group has a representative in the executive board who reports the group's progress to the entire PREBIC team. We have had dynamic working groups that changed based on our evolution of objectives over the years, such as the addition of epidemiology, animal models and a focus on genetics.

3. Results

3.1. A thirteen year review

3.1.1. Meeting 1: 2003 | International PTB meeting | Michigan State University

The goal of the 1st International PTB Meeting was to identify the most promising biomarkers to characterize the risk of PTB delivery and to elucidate a strategy for primary and secondary intervention. Fig. 1 shows the overall structure of the first meeting.

From the beginning, the planning group recognized that there were three levels of interaction (genetics, environment and behaviors) with genetics being a focus (light green Fig. 1) to assess the interaction between genes, the environment and behaviors. The meeting started with a keynote speech by Xiaobin Wang on gene polymorphisms and PTB-family aggregation, genetic susceptibility and gene-environment interaction [8,9]. An update on the Human Genome Project (HGP) (1990–2003) was also provided which marked the beginning of the new millennium, when a vast majority of the human genome had been sequenced [8]. Subsequent presentations from the 6 "Focus Groups" included: genetics & pathological uterine contractility [10,11,12]; new Insights into molecular endocrinology [11,12]; vascular pathways [13]; infection and inflammation [14]; oxidative stress [15]; and maternal stress [16–18]. These presentations led to potential changes in Fig. 1, namely three "focal points" that needed to be addressed in future meetings, a process consistent with concept mapping as proposed by Burke and O'Campo [3]. The six focus groups of the first meeting accomplished the following focal points:

1. Identification of associations between vaginal infections, inflammation, oxidative stress, coagulopathies and stress;
2. Identification of issues on sample collection strategies, new technology on placental sampling for genetic studies, vaginal sample collection and storage and the establishment of a core set of biomarkers.

3. Initiation of a process of collaboration, networking and financial support to begin testing biomarkers to identify the risk of PTB and considering interventions to reduce the risk of PTB.

The major accomplishment of the first meeting was that genetics and pathways would be important topics across all areas of investigation for future meetings and would be driven by biomarkers that are associated with five pathways listed in dark green in Fig. 1.

3.1.2. Meeting 2: 2004 | International PTB meeting | Denmark

Soon after the first collaborative meeting, the co-host for the first meeting, Paul Thorsen, in collaboration with his associate Ida Vogel, began planning the second international workshop for 2004. The goal was to identify key members from the six focus groups listed in Fig. 1 to consolidate ideas. By implementing concept mapping, five new focus groups were identified: **Epidemiology**, **Biomarkers**, and **Pathways (Stress, Vascular, Infection/inflammation), Risk Factors and Interventions/Prevention**. The next step would be to use the literature to identify associations from epidemiological studies to link risk factors to biomarkers, biomarkers to genetic modifications, and characterize pathways.

The goal for 2004 was to identify key working groups with expertise to establish international protocols for PTB Collaborative Research. Five new focus groups (Fig. 2) were identified (new focus groups in blue). Most of the time spent in Denmark was for each working group to work on protocols to be reviewed and presented at the third international workshop. There were three major accomplishments during the 2004 meeting:

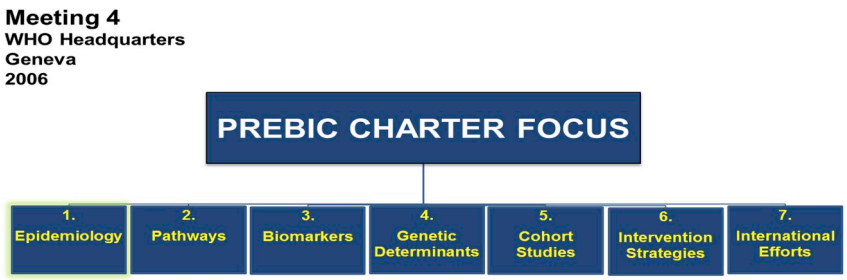

Fig. 4. "PREBIC Charter": a 7-point guide designed to focus PREBIC activities for the next several years.

Table 1
Protocol DevelopmentWorking groups (collaborative efforts).

Protocol Number	Developed by	Comments	Key References of Presentations
Protocol 1 and 2	Mario Merialdi at WHO & Nancy Green at MOD	Genetics (PREGENIA & WHO) and an update on the epidemiology of PTB carried out by WHO. Nutrition made the Focus Group list in 2005.	[19,20]
Protocol 3	John Newnham of Australia	Vascular Working Group	[21–23]
Protocol 4	Sabina Cauci, PHD from Italy	Infection/Immune-Inflammatory Processes	[24]
Protocol 5	Ramkumar Menon, PhD	Biomarkers and Ethnic Disparity in Prematurity	[25–27]
Protocol 6	Claudia Holzman, DVM, DPH, PhD.	Placental histopathology Summary Checkbox from the POUCH study in Michigan.	[28–30]

1. The Denmark hosts recommended that an international collaborative be established and suggested it be named PREBIC (Preterm Birth International Collaborative).
2. Denmark co-host Ida Vogel would develop the first PREBIC website (established June 2004).
3. A group of geneticists met and formed the Preterm Birth Genome Investigators Alliance (PREGENIA) group led by Ramkumar Menon and Paul Thorsen.

At the end of the 2004 meeting, Calvin Hobel would plan the next international meeting prior to the Society for Gynecological Investigation (SGI) meeting in Los Angeles in March 2005.

Through a process of concept mapping, five of the focus groups changed after the 2004 meeting with genetics remaining as the primary focus. Thus, the focal points for the next meeting had to be changed:

1. It was recognized that a focus on epidemiology was required to continue the quest to identify new risk conditions associated with PTB;
2. Research studies were required to identify potential biomarkers related to potential pathways associated mechanisms leading to PTB;
3. The identification of the most important risk factors associated with PTB became a high priority.
4. The concept of interventions to prevent PTB would require the identification of pathways.

3.1.3. Meeting 3: 2005 | International PTB meeting | Lake Arrowhead, CA

The third international meeting and was held at the UCLA Conference Center in Lake Arrowhead, CA just before the SGI Meeting in Los Angeles in 2005. The overall goal was to take what we learned through a process of concept mapping after the Michigan and Denmark meetings to expand the PREBIC vision for a more focused collaborative research agenda—to identify the cause(s) of PTB and eventually reduce the risk of this most serious complication of pregnancy. The meeting began with presentations of protocols developed by leaders of each working group.

Following these presentations, the organizing committee identified Professor Roger Smith of Australia to lead the initial discussion for the identification of the most promising areas of PTB research (see Table 1). After lengthy discussion, a prioritizing and voting process followed. Table 2 lists the top five and bottom five areas in order of importance formulated by a process of concept mapping. For the next two days, the focus was on all ten working groups because each of those listed were considered important.

The process of concept mapping in Fig. 3 continues to list genetics as the top priority but is now followed by biomarkers and epidemiology, remaining as a continuing process of searching large databases for associations to link the outcome of PTB with risk factors that can be linked to the identification of genes and biomarkers associated with PTB. In addition, three new focus groups came forth: inflammation, clinical trials and nutrition. This is the first year that nutrition became a working group. During the 2005 meeting, Mario Merialdi mentioned the paper by Jose Villar on the characteristics of randomized control trials and poor pregnancy outcomes [20]. In 2009, Maria Torloni published the fourth PREBIC paper on nutrition in reference to BMI and the risk of PTB [PP4].

This third meeting also marked the first time that PREBIC decided to take a new direction and begin the meeting by having grantees such as those supported by MOD Grants present their research to update the status of basic research. This activity was a highlight. (Table 3).

This meeting also focused on literature reviews and PREBIC publications. Members who attended the two prior biomarker meetings began identifying several key papers in preparation on for the PREBIC Genetics Working Group:

1. Genetic epidemiologic studies on PTB [PP1];
2. The Preterm Birth Genome Project (PGP), a call for an international consortium on genetics and PTB [PP2];
3. The Worldwide Incidence of PTB [PP3];
4. Maternal BMI and PTB [PP4]:
5. The PTB genetics knowledge base [PP5];
6. Guidelines for research by the PREBIC “Omics Research Group” [PP6]; and
7. Biomarkers of Spontaneous PTB: Overview of the literature on biomarkers of spontaneous PTB [PP7];

All of these manuscripts were published within the next 4–5 years by members of PREBIC to demonstrate progress being made in the area of PTB research.

The results of each of the 10 workshop presentations (noted above) by key investigators presented by the MOD Grantees as well as publications in press would be used in planning the structure of the 4th International Collaborative Meeting in April 2006 to be hosted by Mario Merialdi at the WHO in Geneva, Switzerland titled “Global Initiatives on Maternal and Child Health Development”.

3.1.4. Meeting 4: 2006 | International PTB meeting | World Health Organization | Geneva, Switzerland

This was the first meeting of PREBIC to be held at the World Health Organization (WHO). This meeting started a yearly connection with an organization that has the skills and infrastructure to help PREBIC establish itself as a worldwide leader in PTB research. In collaboration between the PREBIC Board of Directors and Mario Merialdi, this meeting had to establish a PREBIC framework to expand our worldwide effort on PTB research and develop a **mission statement:** “PREBIC

Table 2
Assessment of the top five working groups selected by concept mapping.
The result was the selection of both the top five and bottom five areas for group workshop activities.

Top Five	*Bottom Five*
Genetics	Stress
Biomarkers	Animal Models for research
Inflammation	Vascular markers
Clinical Trials	Role of the fetus
Nutrition	Myometrial Activation

Table 3
MOD young investigator grantees research report.

Presenter Name	Presentation	Key References
Steve Lye	Assessing genetic signatures of PTB. 101 genes identified of which 11 genes predicted time of delivery.	[31,32]
Carol Mendelson	Fetal determination of PTL. Proposed signal from fetal lung maturation. Surfactant protein A (SP-A) in mouse model induces PTL.	[12,33,34]
Sarah England	Can potassium channels alter the timing of labor? Disruption of labor in SK3 overexpressed mice may result in loss of synchronized lack of signal for oxytocin release. Studies on transgenic insertion in a disrupted mouse gene is required for parturition.	[35]
Louis Muglia	Genetic analysis of human PTB. Focus is a new initiative interested in biological clocks to identify the timing of birth. Who controls the clock, for parturition? Fetal or Maternal (*maybe the placenta?*)	[36,37]

Table 4
Eight key current activities.

Focal Points	Relevant Papers
Focal Point 1	Systematic Review of National, Regional & Global PTB Rates. (Currently being performed in collaboration between the MOD and WHO.) [PP3]
Focal Point 2	Systematic Review of Genetics and PTB to be carried out by Siobhan Dolan, MD, MPH, via Human Genome Epidemiology Network (HuGE.net) [PP5].
Focal Point 3	Systematic Review of Management of PTB from definitions to actual management. Currently being performed by members of several integrated PREBIC workshops.
Focal Point 4	Preterm Birth Genome Project (Genome Wide Association Study) by PREBIC/PGP Consortium [PP2].
Focal Point 5	PREBIC to foster Translational Research.
Focal Point 6	PREBIC to lead the Development of clinical Research Networks via Community Research.
Focal Point 7	PREBIC to Develop Public Private Partnerships to Develop Collaborative Research Teams.
Focal Point 8	Integration of data using bioinformatics from static Genetic Markers to Dynamic Biomarkers [PP8].

aims to improve pregnancy and birth outcomes and optimize infant health and long term development to assure optimal adult health of women and children." In addition, the Board of Directors of PREBIC established a "PREBIC Charter": a 7-point guide designed to focus our work activities for the next several years (Fig. 4).

The major development in formatting a strategy for PREBIC was the third meeting in California, where it was recognized that genetics would form the basic structure to identifying the cause of PTB. Biomarkers for facilitating the diagnosis of the risk of PTB was an exciting step forward because it was part of the search for a mechanism of PTB, recognizing that multiple pathways were most likely involved in its etiology. However, the epidemiologist in the group of investigators made it very clear that epidemiology would play an important role in the identification of risk factors associated with PTB. Epidemiology was listed first in the charter, followed by pathways and biomarkers. One of the first concepts identified was the importance of classifying the phenotype of different forms of PTB and that genetics and biomarkers would identify pathways.[PP1] Based upon the first PREBIC meeting, the relationship between risk factors and genetic determinants of PTB should focus on inflammation, stress and racial/ethnic disparities. Thus, the "Cohort Study" (Fig. 4) was thought to help identify intervention strategies for future international efforts for reducing the risk of PTB. During the 4th international meeting, it was recognized that the collaboration between the MOD and WHO, would begin a process to study the differences in the incidence of PTB worldwide [PP3].

Defined Activities in 2006 in preparation for 2007:

1) Formulate an "Epidemiology of PTB Group": an international perspective with standard definitions.
2) Begin a study of worldwide PTB rates to be initiated by WHO and MOD.
3) Begin a genetic association study of PTB (initiated by Siobhan Dolan)
4) Begin the PGP to establish a network of researchers involved in genetic association studies such as developing a data base, protocols and repository to be led by Ram Menon.

3.1.5. Meeting 5: 2007 | International PTB meeting | World Health Organization | Geneva, Switzerland

The 4th meeting at WHO in Geneva was an important turning point for PREBIC because the PREBIC Charter helped the members focus on the complexities of a strategy to pursue a search for a cause of PTB. Activities with a focus on epidemiology brought together a more unified collaborative of transdisciplinary investigators. In addition, knowledge of the international PTB rates would establish a global perspective and possibly provide new ideas about the complexity of PTB. Initiating a focused approach to the study of what is currently known about the genetic associations with PTB would be important and finalize a strategy for PREBIC to formally establish the PGP with funding from WHO and the MOD. The next step would be to find an association between genes and the risk of PTB. Thus, the PREBIC board of directors decided that to more rapidly progress in our quest to resolve the problem of PTB we decided to follow up the 5th PREBIC meeting with three planning meetings in the United States prior to the 6th international meeting.

The first planning meeting was a grand rounds presentation held at Albert Einstein College of Medicine in New York City on October 2, 2007 by members of the MOD, WHO, PREBIC members and guests from the Johnson & Johnson Pediatric Institute, which summarized activities of the 2007 meeting and begin a process of addressing PREBIC's global priorities and formalizing a 5-year plan. Eight key current activities (Focal Points) were identified (Table 4).

The second planning meeting was held at Johnson & Johnson Pediatric Institute in New Brunswick, New Jersey on October 8, 2007. The purpose of the meeting was to share important work and to address the challenges of PTB research. Recommendations were to develop a logic model to facilitate the PREBIC mission of improving pregnancy outcomes. The plan was to have a follow-up meeting in December with both the Johnson & Johnson Pediatric Institute members and the MOD in New York City.

The third planning meeting was held at the MOD in White Plains, New York on December 19–20, 2007. Goals of this meeting included developing a relationship with the Society for Gynecologic Investigation (SGI) to establish a yearly pre-SGI Satellite Meeting (SM) to present PREBIC's research progress and to encourage other investigators to join the PREBIC mission. The first pre-SGI meeting was set for March 26, 2008 in San Diego, CA. Another goal was to develop a five-year plan to expand and monitor PREBIC's research progress using the logic model, which was developed with the expertise of the Johnson & Johnson Pediatric Institute in December of 2007 **(See** Appendix I **Logic Model).**

3.1.6. Meeting 6: 2008 International PTB meeting, Geneva Switzerland

Prior to meeting 6, we had our first (official) PREBIC SM with the

Society for Gynecologic Investigation (SGI) in San Diego California on March 26, 2008. The title of the first workshop was “The Epidemiology of Preterm Birth” [38]. The purpose of participating in the SGI workshops was to increase the awareness of PREBIC by providing international leadership in addressing the problem of PTB. PREBIC provided eight lectures focusing on the following topics:

1) The title of the first SM was “The importance of epidemiology in the study of PTB: How epidemiology can stimulate the search for associated factors and the cause of PTB.”
2) Genetics was a major topic. Siobhan Dolan outlined her study on the “Human Genome Epidemiology (HuGE)” study. Using a large CDC database, she was beginning the search for genes associated with PTB [PP5].
3) Racial disparities and environmental factors were presented by Ram Menon [25,26].
4) The physiology pathophysiology of stress as it is related to PTB was presented by Pathik D Wadhwa and Calvin Hobel [16–18,39–41].

For the 6th PREBIC meeting we selected 5 of the focus groups listed in the Charter Focus; however, after 3 days of discussions we recognized that two new areas of focused investigations needed to be addressed. First, data from the literature and presentations at the meetings suggested that PREBIC needed to focus on animal models for research of a cause of PTL and placental biology for the assessment of the interaction between the mother and her placenta and her fetus and her environment. Fig. 5 shows the working groups selected for the 2008 meeting from the seven charter working groups established in 2005 plus continued use of concept mapping for the identification of new working groups.

3.1.7. Meeting 7: 2009 | International PTB meeting | Geneva, Switzerland

Prior to the 2009 meeting, PREBIC held its Second SGI SM in Glasgow, Scotland on March 18, 2009. The tile of the meeting was “Global issues for Preterm Birth”: Epidemiology, Genetics and Pathophysiology [42].

1) The guest speaker, George Davey Smith from the University of Glasgow gave a lecture titled “What can Genetic Epidemiology tell us about environmental causes of adverse birth outcomes”. His lectured covered data on the genome-wide metabolic analysis provides genetic associations with adiposity and fat distribution and how off springs' BMI can be used as an indicator of future mortality secondary to cardiovascular disease (CVD) [43–45]; This is the first time that environment, behavior and genetics was linked with the future risk of mortality secondary to CVD. Few investigators had not yet considered these factors which were being expressed as a result of the dramatic challenges in the cardiovascular and immune systems during pregnancy.
2) The above lecture was followed up with Craig Pennell who gave an update on the criteria adapted by the PREBIC PGP consortium that would be used to perform the PREBIC GWAS study [PP11]
3) Mario Merialdi presented the WHO's plans to carry out a worldwide assessment of the incidence of PTB [PP3] [46].
4) Connecting the epidemiology and environmental determinants of the risk of PTB, Michael Gravett gave a presentation of how studies in the primate model have led to the importance of transcriptomics and proteomics in understanding the pathophysiology leading to PTB with a focus on infection as a cause of PTB [47].
5) The PREBIC planning group decided to invite a special guest to introduce and discuss what preterm newborn issues needed to be addressed by the group. Physicians worldwide began to question what events during pregnancy, labor and delivery influence neonatal brain development, so the PREBIC planning group invited Giulio Bevilacqua from Italy to begin a discussion of what issues needed to be addressed [48,49].

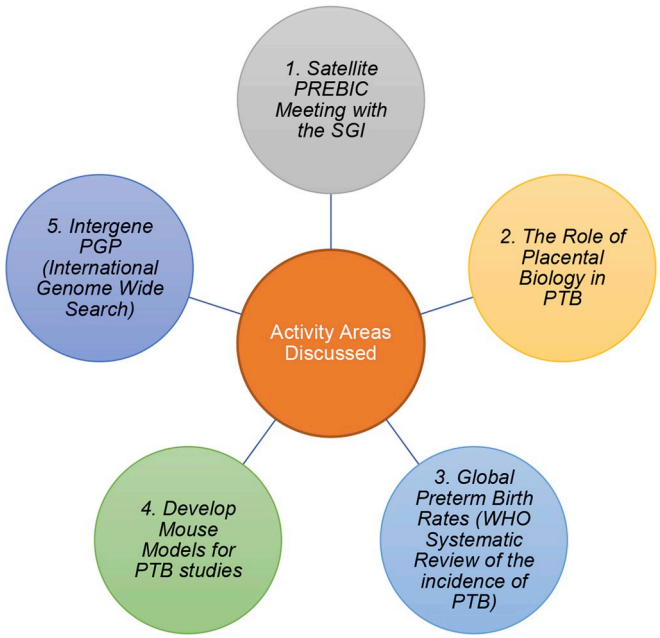

Fig. 5. Activity areas discussed during 2008 meeting.

The purpose of the 2009 meeting was to brainstorm interventions for preterm labor prevention using new information developed in the areas of genetics, biomarkers and epidemiology. First, two papers published by PREBIC members were reviewed.

The first paper was published in 2007 and was a product discussion initiated by the authors at the Third International Workshop on Biomarkers and Preterm Birth held near Los Angles, California is 2005. The title was “Genetic epidemiologic studies of PTB: guidelines for research”. Four areas are addressed: (1)Phenotypic criteria to define the types of PTB, (2)Study design, (3)The selection of control populations, and candidate gene selection [PP1].

The second paper was published a year later titled “A call for an international consortium on the genetics of PTB.” The consortium was established during the fourth PREBIC meeting in 2007 after two years of discussions and concept mapping which were used to facilitate the formation of focused groups, and established a hypothesis based upon pathways and genes [PP2]. With a consensus on the definition of PTB and three phenotypes (spontaneous PTB, premature rupture of the membranes and indicated preterm labor), the PGP was making progress.

Second, Juan Nardin from Argentina who had extensive experience working with WHO led three workshop groups: “Community Based Interventions”, “The status of Tocolytic Trials”, and an “Overview of Interventions for Preterm Labor.” [50–52] In addition, new information available in the literature began to indicate that early delivery secondary to prematurity, the infants experience insults to the developing brain because they lose the intra-uterine period for further brain development which does not continue during the neonatal period. Thus, we decided on “initiation of a systematic review of brain development as it relates to preterm delivery.”

3.1.8. Meeting 8: 2010 | International PTB meeting | Geneva, Switzerland

Prior to the 2010 meeting, PREBIC held its Third PREBIC SGI SM in Orlando Florida**:** Global Issues for Preterm Birth Epidemiology, Genetics and Pathophysiology, March 24, 2010 [53]. This SM was unique because it began to direct attention toward how complex PTB really is and the need for further research.

The first speaker, one of North America's best epidemiologists, Michael Kramer from Montreal, gave a very interesting presentation

where he discussed why the socio-economic disadvantaged have an increased incidence of PTB [54]. He used two of his studies to point out how his group has tried to link genetics and PTB in two areas, stress pathway and the vascular pathway. The reader can refer to two of his papers, which describe these two studies [55,56].

The second speaker was one of the United States' best geneticists, Ken Ward, who presented data from Utah on the link between families and the risk of PTL as studied by GWAS and how common genetic polymorphism by GWAS studies points to several novel genes related to the risk of PTB and preeclampsia [44,57,58].

The third speaker, Michal Elovitz, presented a superb study using host immunity in an animal model. Her research was a message to the PREBIC directors to begin to consider the use of animal models to study PTB [59,60].

The fourth speaker, Louis Muglia, gave an exciting talk on how evolution has played a role in understanding what genes have been conserved to prevent PTB [37].

Finally, the fifth speaker, Sam Mesiano, gave an update on how progesterone and estrogens and other hormones control the inhibition or stimulation of the onset of labor. There is a tremendous amount of literature on the role of progesterone for the prevention of PTB and a clearer understanding of the relationships between various hormones and their importance in improving our understanding of the endocrinology of normal and preterm labor [61,62].

There were three major accomplishments during 2010:

1) First was the establishment of a PREBIC "Animal Models" working group led by Elizabeth A. Bonney. The group began with 8 investigators who met at a PREBIC funded a SM in Atlanta, Georgia on March 28–29, 2010. The team developed a strategic plan to form a PREBIC working group for the April 2010 meeting in Geneva. An 8-page report was submitted to the president of PREBIC (Dr. Calvin Hobel) outlining a strategic plan for the utilization of animal models for PTB research with the goal of writing and publishing a comprehensive review of the literature.
2) The second accomplishment was the formulation of an Epidemiology Working Group led by Karla Damus and Juan Nardin. This group developed the following three objectives: To evaluate the different strategies (management) currently used in each country and region in order to develop studies of interventions (tocolytics, community-based interventions); To assess the relationships and effects of different interventions for the prevention of threatened PTB on maternal, fetal and neonatal outcomes (based on the previous systematic review of interventions for the treatment of preterm labor); to develop new systematic reviews; and to further develop PREBIC/WHO clinical guidelines for the diagnosis, prevention, and treatment of PTB.
3) The third key event in 2010 was a presentation of The MOD Global and Regional Toll of Preterm Birth by Christopher Howson titled, "The Next Steps" [PP10].

Several PREBIC members provided research updates at the 2010 meeting. Craig Pennell provided an update on the progress of the PGP [PP11]. Ramkumar Menon provided a lecture titled, "Are biomarkers reliable for assessing risk of PTB?" [63][PP7]. The lessons learned from Dr. Menon's focus on biomarkers made it clear to many investigators that biomarkers may be an important link between genetics and the risk of PTB. Lastly, Maria Regina Torloni provided an update on nutrition as it relates to PTB titled "BMI as a risk factor for PTB."[PP4]

3.1.9. Meeting 9: 2011 | International PTB meeting | Geneva, Switzerland

Prior to the 2011 meeting at WHO, we had the fourth SGI PREBIC SM in Miami Beach, Florida on March 16th, 2011 [64]. We decided to be futuristic and invite an international group of successful investigators to challenge PREBIC leadership to consider novel approaches to future research in PTB.

1) First, we invited Vinod Paul, a neonatologist from the India Institute of Medical Sciences in New Delhi, India to assess the value of an epidemiological approach to link PTB to neonatal outcomes. He discussed the importance of nutrition on reproductive health and how it influences growth and neurosecretory outcomes of very low birth weight infants [65–67].
2) We asked Jeff Murray, a neonatologist and geneticist in the United States to provide an update on what genes have been identified to help us understand PTB. Unfortunately, few genes have been identified and those identified need to be confirmed by replicating the findings using samples from other studies [46,68].
3) In addition, we asked the Chief of the NICHD Perinatology Research Branch, Roberto Romero, to review "novel" mechanisms associated with the PTB syndrome. It remains a complex interrelated constellation of pathways with overlap between phenotypes [69].
4) We also chose to include Derek Wildman from Wayne State University to provide new insights into the role of evolutionary genomics during normal pregnancy (what has been conserved to assure a successful pregnancy and what changes have occurred in the mother's genome and placenta to result in early delivery) [70]. There was a discussion of what maternal factors may influence placental function and the following paper by Sutton-Tyrell et al. addressed the role of low levels of sex hormone-binding globulin and high levels of the free androgen index levels and the risk of CVD in women. This paper was the first that discussed the connection between high risk women during pregnancy and the risk of CVD [71,72].
5) We were especially pleased to have David Barker, Professor of Clinical Epidemiology at the University of South Hampton, UK, who initiated interest in "fetal programming". His overview of fetal programming during pregnancy at different timepoints discussed how changes result in fetal alterations that affect all biological control systems resulting in later onset of diseases such as diabetes, hypertension, cancer, stroke (CVD) [73,74]. The presentation by Dr. Barker supported the connection between poor nutrition and poverty and the risk of CVD.
6) Taking all factors into account, we had Vincenzo Berghella from Thomas Jefferson provide an overview of evidenced based interventions currently thought to decrease the risk of PTB. Unfortunately, there were very few new approaches that have been successful [75–77].

It should be mentioned that the PREBIC leaders believe there are no single interventions to prevent PTB because the PTB Syndrome is a "complex disease" whereby multiple pathways may be involved. The future will require multiple interventions that are evidence based to address the problem of PTB during early in pregnancy and probably the risk beginning during the preconception period. See current opinion by John Newnham of the University of Western Australia [78].

At the 2011 PREBIC meeting at WHO, Karla Damus presented a key note presentation titled, "The impact of late PTB on the epidemiology of PTB in the United States." The MOD Study in Kentucky using a collaborative approach between physicians, nurses and hospitals demonstrated that avoiding unnecessary (not indicated) late PTB could have a significant impact on PTB in the United States [79]. The second issue that Dr. Damus addressed was the need to reach out to women to initiate preconception counselling to prepare women for successful pregnancies. Specifically, she presented the virtual patient advocate system called the Gabby Preconception Care System and preliminary data supporting it effectiveness [80].

In 2011 PREBIC developed partnerships with two other global groups that would support future benefits for networking and collaborations to begin PTB prevention programs worldwide. PREBIC member Michael Gravett presented a concept of "bridging the gaps in PTB prevention" and suggested that PREBIC should collaborate with The Global Alliance for Prevention of PTB and Still Birth (GAPPS) lead

by Executive Director Graig Rubens [47]. In addition, Ben WJ Mol, PREBIC member and the new Director of the GoNet Initiative launched by NICHD to facilitate the development of international studies on issues related to PTB, suggested that PREBIC should also work with GoNet to identify funding for designing evidence-based studies to prevent PTB worldwide [81–83].

Several updates on the progress of research in PTB were made in 2011. Craig Pennell presented new information from the PGP on the identification of and genetic variants in spontaneous PTB. Ramkumar Menon gave an update on the Biomarker Working Group's (PBP) progress on initiation of a new global consortium for the selection of a biomarker panel for 3 trimesters of pregnancy, study design and selection of samples for biomarker trials and an alliance between PREBIC and Perkin Elmer Corporation in biomarker trials. A major publication for 2011 was contributed by Ramkumar Menon et al. on "Biomarkers of Spontaneous PTD: An Overview of the Literature in the Last Four Decades" [PP7]. The logic model, which had been used to track changes over time between meetings and based on the charts presented by each working group, new teams were developed which included Biomarkers, Systems Biology, International/Global and Epidemiology.

In 2011, PREBIC had its first European SM in Lodz, Poland on May 26–27 in conjunction with the Fourth Symposium on Advances in Obstetrics & Gynecology. This meeting was set up with the help of Professor Jaroslaw Kalinka. The key presentations focused on global health issues, complex PTB phenotypes, the genetic determinants of PTB, the global burden of PTB, the epidemiology of PTB and the issue of whether or not antibiotics prevent PTB. This meeting was the first of several other European meetings planned by Ram Menon.

3.1.10. Meeting 10: 2012 | International PTB meeting | Geneva, Switzerland

Before the meeting at WHO in Geneva in 2012, we had our fifth SGI SM in San Diego, California on March 21, 2012 [84]. The title of the PREBIC SM was "Back to the Basics" and asked for national experts to share new advances in epidemiology, genetics, inflammation and oxidative stress to improve our understanding of mechanisms leading to PTB.

1) First, we had a superb presentation by Michelle Williams to take us back to basic epidemiology and relook at associations between recently published studies and new thoughts on the mechanisms leading to PTB [85].
2) Second, we had two presentations for an update on genetic studies. The first was a presentation by John Llekis from the NIH on the NICHD Proteomic Network (GPN) Study [86,87]. The second lecture was by Craig Pennell on the PREBIC PGP [PP11]. Both presentations demonstrated that there is very little new information on associations between specific genes and PTB and the identification of pathways leading to PTB.
3) Next, Irina Buhimschi from Yale University presented new data on how "Systems Biology" was being used to identify pathways leading to PT. It was clear that biomarkers associated with the risk of delivering preterm were related to specific genes. She mentioned that clinical use of this data for intervention studies would require prospective studies to verify associations and then replicate the findings [88].
4) Next, we had two presentations that highlighted the complexities of using genetic studies to identify pathways. The first presentation was by Elizabeth Bonney, who provided insight as to what comes first: will changes in genes or biomarkers lead to discovery? She summarized by stating: "are biomarkers of inflammation and oxidative stress the "*chicken* or the *egg.*" [89] The second presentation was by Kent Thornburg from Oregon that suggested **gender** needs to be taken into consideration by studying the effect of nutrition on one's health later in life. He showed how changes in nutrition flow to the fetus have different effects on the fetus depending upon its **gender** [73,90]. This presentation by Thornburg makes it very clear we need to understand the functional changes in the placenta during pregnancy that are driven by maternal behaviors and the environment and gender of the fetus. Prevention of chronic disease require improvements in the nutrition of girls and young women before pregnancy.
5) Finally, Catherine Spong from NICHD provided an update on how important collaborations between the Global Obstetric Network (GONet) and PREBIC was for progress to be made in PTB prevention worldwide. Linking basic science to clinical studies would help identify how to design prospective studies to provide new information. Dr. Spong discussed the results of several Maternal Fetal Medicine Network Studies that provided valuable information for planning future studies. The importance of the timing of indicated (late-PTBs); maternal vitamin D and PTB in twins; excessive early gestational weight gain and risk of gestational diabetes in nulliparous women and the use of 17-P to prevent PTB in nulliparous women with cervical measurements less the 30 mm should be carefully considered [91–94].

In 2012, several changes in leadership occurred. Dr. Calvin Hobel, President of PREBIC since 2005, stepped down and Dr. Ramkumar Menon gave the PREBIC Presidential Address for 2012. Joe Leigh Simpson became the Senior Vice President for Research and Global Programs for the MOD and presented the MOD "new initiatives for PTB prevention". Christopher Howson, Vice President for Global Programs for the MOD gave an update on "Born Too Soon" [PP10].

Several PREBIC members provided research updates. Felipe Vadillo-Ortega gave an update on his randomized trial on the prevention of preeclampsia with arginine and antioxidants supplements in a nutrition bar [95]. Elizabeth Bonney gave an update on the SM of several selected scientists involved in animal research to study PTB. Her group was commissioned to publish a paper on a review of animal studies for PTB [89]. Bo Jacobsson discussed his recent publication on Authorship Guidelines and Leslie Myatt et al. discussed a recent paper on "A standardized template for clinical studies in PTB" which was a major accomplishment in 2012 [PP8].

Beginning in the 2012 year we initiated a young scientist forum to encourage young investigators to present their research. The presenters and their lecture titles are in Table 5.

Fundraising efforts were also made in 2012. Julian Jenkins from Ferring International in Switzerland provided a presentation at PREBIC titled "Why health care professionals and pharma must work together." Ritra Gustafsson proposed potential collaborations via a presentation

Table 5
Young scientist forum 2012.

Investigator Name	Lecture Title
Joshua Vogel	Presented the WHO Global survey on maternal and neonatal health [98,99].
Uzdenova Stella, MD	The use of Liopsome Encapsulation for the placental transfer of drugs [96,97].
Inge Christinens, MD, PhD	Chronic Maternal Stress & metabolic dysregulation and Spontaneous PTB
Emma Fransson, PhD	Stressful Life Events during Pregnancy Modulate Local Inflammation during Pregnancy [98].
Teresa Cobo, MD	Main Determinants of Intra amniotic Inflammatory Response in Women with PROM [99,100].
Jossimara, Polettini, PhD	Interleukin 18 messenger RNA and pro IL-18 protein expression in Chorioamniotic Membranes.

Table 6
Young scientist forum 2013.

Investigator Name	Affiliation	Lecture Title
Joshua Vogel, MD, PhD	Doctoral Candidate University of Western Australia	"Trends in preterm survival in low- and middle-income countries" [117,118]
Sasha Parets BS	Doctoral Student Emory University	Fetal DNA methylation Associates with Spontaneous PTB and Gestational Age" [119,120]
Christina Vinter, MD, PhD	Junior Faculty, Odense University Denmark	"The Lifestyle in Pregnancy (LiP) Study- Intervention among obese pregnant women" [121,122]
Myrthe Peelen, MD, PhD	Junior faculty, Academic Medical Center, Amsterdam, Netherlands	"Impact of fetal Gender on the Chance of PTB" [123,124]
Jossimara Polettini PhD	Post-Doctoral Fellow, University of Texas medical Branch, Galveston, Texas	"In vitro Assessment of Fetal Membrane Oxidative Stress Risk Factors of Preterm Birth"

titled, "PREBIC-Perkin Elmer Partnership on Biomarker Panel Development".

3.1.11. Meeting 11: 2013 | International PTB meeting | Geneva, Switzerland

Prior to the 11th PREBIC meeting at WHO, the sixth PREBIC SM was held in Orlando, Florida on March 20th, 2013 [101]. The analysis of the 10th PREBIC meeting and the follow-up meeting at WHO suggested that epigenetics was becoming a more focused approach to the problem of PTB. Information was beginning to indicate that environmental factors (nutrition availability, climate changes) and behaviors such as psychosocial stress may be causing epigenetic changes leading to PTB. Thus, the first three lectures were based upon **epigenetics**.

1) The first lecture was by Craig Pennell, the president of PREBIC. Craig provided the background protocol for the global quality control analyses to assess the usability of DNA collected from four different sources using different DNA extraction techniques [PP11].
2) Next, Susan Murphy from Duke University presented the progress being made in the use of epigenetics to study imprinting changes within the placenta and fetus that may be associated with PTL [102,103].
3) The above presentation was followed by Amy Murtha who discussed the clinical relevance of epigenetics [104,105]. To counter the issue of PTB, we had Sarah England provided a lecture on how to maintain a pregnancy to full-term. She discussed how the maintenance of Na & Ca channels is conserved to assure uterine quiescence [106,107].
4) In keeping with the prior two years on the role of the gut and placental biome, we had Bo Jacobsson, a regular member of PREBIC, present his prior work on how the use of probiotics during pregnancy appear to reduce the incidence of both spontaneous preterm labor and preeclampsia [108,109]. It appears that the proper gut microbiome plays an important role in systems biology/regulation to improve the health of women.
5) In the search of mechanisms which control systems biology/regulation we asked Kjersti Aagaard from Baylor College of Medicine to present her studies on how the gut, vaginal and oral biomes play a role in modulating homeostasis during pregnancy. The basis of her hypothesis is that chromatin structure is epigenetically altered via covalent modifications of histones to allow for heritable gene regulation without altering the nucleotide sequence [110,111].
6) Finally, to complete our life course perspective, recognizing we have not been overly successful in the prevention of PTB, we asked Roberto Romero, Program Director for Perinatal Research at NICHD to provide an update on the success of multiple interventions to reduce PTB by using a combination of vaginal progesterone, cerclage and cervical pessary in prolonging the duration of pregnancy. Individually each of these interventions appear to have a short term effect of prolonging gestation [112].

The 2013 annual meeting in Geneva began with a presentation by the President of PREBIC, Ramkumar Menon and Senior Vice President of the MOD, Joe Leigh Simpson.

Two important and timely presentations set the stage for this meeting. First, Michelle Williams, Professor and Chair of Epidemiology at the Harvard School of Public Health, presented a very provocative view of the value of recent trends and overview of the etiological questions about PTB. It is very clear that epidemiological studies show associations and it us up the investigators to take associations and translate them into potential causality pathways. Translational science from association to causality is exciting. Her presentation reminds us of the extreme value of epidemiology in the study of PTB [113–115].

Second, in keeping with the 2012 presentation, Christopher Howson of the MOD presented on the release of a "Report on Preterm Birth" [PP1]. PREBIC also invited Jessica Nsungwa-Sabiiti, the Assistant Minister of Health in Uganda who gave us insight into Uganda's framework for rolling out the "Born Too Soon" interventions. It became clear that the publication by the MOD led by Christopher Howson was beginning to be addressed in Africa. Participants of the meeting began to discuss how PREBIC could support a program to include visitors from Africa with an update on the progress being made in programs to support maternal child health.

At the 2013 meeting, PREBIC continued to focus on the five working groups. Dr. Calvin Hobel included these five working groups into a logic model to help track of the current progress as of 2013 **(See** Appendix II **3D Logic Model with publications from each working group).**

3.2. Young scientist forum

After the success of 2012's Young Scientist Forum, we engaged young investigators to present their research to senior members of PREBIC (Table 6). We began with a repeat presentation by Joshua Vogel, a doctoral candidate from Australia who was continuing his work at WHO, and now working on the study of the outcome of PTB deliveries [116]. In concert with PREBIC's interest in the genetics of PTB, a student, Sasha Parets, presented a study on methylation changes and the risk of PTB [117,118]. In concert with the increased awareness of obesity a young scientist Denmark, Christina Vinter presented a paper on an intervention study among obese pregnant women [119,120]. Next Myrthe Peelen from Amsterdam presented a paper of the effect of **fetal gender** and the risk of PTB [121,122]. The most interesting finding was that fetal gender has become an important variable to include in studies on PTB. Finally, Jossimara Polettini from Texas presented a paper on the role of oxidative stress and the risk of PTB [123,124].

There were two major PREBIC publications between 2012 and 2013. The first was by Craig Pennell et al. on the PGP consortium, tilted "Validation of resources for PTB genome-wide studies" [PP11]. The second paper was by Marian Kacerovsky and the PREBIC Biomarker Working Group on a systematic Review of the literature [PP12].

3.2.1. Meeting 12: 2014 | International PTB meeting | Geneva

Prior to the twelfth PREBIC meeting in Geneva Switzerland we had the seventh SGI/SRI Meeting in Florence, Italy, where satellite groups were combined to improve translational interactions between disciplines [125].

1) The first lecture was presented by Mark Johnson from Imperial College London, UK on an overview of the onset of Labor: A "Progress" View. The talk reviewed "the importance of progesterone and the repression of myometrial inflammation" as well as the role of MKP-1 and AP-1 Systems [126].
2) The second lecture was by Nanbert Zhong, a member of the PREBIC board on his studies on epigenetic pathways associating premature rupture of the membranes [127–129].
3) The next two lectures focused on recent studies carried out to identify biochemical and biophysical changes in the cervix prior to the onset of labor. The first lecture was by Gullermina Girardi from King's College in London on the role of complement activation in cervical remodeling and myometrial contractility in PTL [112,130].
4) In concert with the trend over the past 15 years of attempts to link infection as a major cause of PTB, we selected Gil Mor from Yale University to update us on preterm labor as a polymicrobial disease. If all the microbiome studies on the oral cavity, vagina and the intrauterine cavity (including the placenta) show the presence of microorganisms, is their presence a cause or only an association? His subsequent publications suggest that bacteria in the human body play an important role in controlling homeostasis of multiple systems maintaining the health of women and children [131–133].
5) The next lecture followed the above theme but focused on changes in fetal membranes secondary to matrix inflammation and hemorrhage (vascular changes). This review was provided by R. Ann Word from the University of Texas, Dallas [134].
6) In keeping with the goal of allowing young scientists to present their research, we had two superb presentations. The first was by Joshua Vogel, a three-time presenter who continues his PhD work at WHO. He gave an update on the WHO assessment of PTB in low and middle-income countries. Some of the data from this study has been published [135,136]. The second young scientist paper was presented by Christina Vinter from Odense University, Denmark on "Maternal Obesity and Preterm Birth". Her focus was on the study of lifestyles as a cause of obesity and how specific intervention can reduce this risk [119,120].

The SM ended with a presentation by PREBIC member Ben WJ Mol for the study of interventions to reduce the risk of PTB. His study investigators presentations were an update of the "Novel use of Pessaries" and their value for prevent PTB in twin gestations [81–83]. In addition they discussed a new study using Nifedipine in the treatment of preterm labor in singleton pregnancies. They found a reduction in poor pregnancy outcome but it was not statistically significant [137].

3.3. PREBIC meeting in Geneva (March 31st to April 2nd)

The members of the PREBIC Board were very disappointed by the news that Mario Merialdi would be leaving his position at WHO to accept a position in industry. Mario Merialdi played a very important role in helping launch PREBIC during our 3rd International PTB Meeting when he recommended that PREBIC meet in subsequent years at WHO in Geneva to improve our opportunities in collaboration with the MOD by becoming an Important Leader in the global issues of PTB research.

In this transition period we asked PREBIC board member Silke Mader, the Chairwomen of the Executive Board of the European Foundation for the care of Newborn Infants, to give our key note address [138]. In addition, Marleen Jemmerman, WHO's Director of Reproductive Health Research, also gave an address titled "The Global Burden of Preterm Birth." In her talk, she suggested that during the period of Mario Merialdi's transition, she hoped that the WHO could continue to work with the MOD and PREBIC to continue work on the Global PTB issue.

To provide the Director of Reproductive Health at WHO an update on the progress of PREBIC, three special lectures were given by the leadership of PREBIC during this meeting. The first, by Hanns Helmer on the status of interventions for patients with imminent preterm labor. The second, was by Craig Pennell, an update on the PTB Genome Project supported by WHO and the MOD. The third presentation was by Calvin Hobel, on the use of logic models to track the progress of PREBIC.

Several major research advances were reported in 2015. The epidemiology group, under the leadership of Siobhan Doan and Michael Kramer updated us on how epidemiology can provide new insights into the causes of PTB [139–143].

1) The Biomarker group presented the importance of the Preterm Birth Microbiome Project.
2) The Global Initiatives group, under the leadership of David Olson, devised a new program, OPERA (Optimal Pregnancy Environment Risk Assessment) with plans to have a 2-day operations meeting prior to the 2015 SRI meeting in San Francisco, California.
3) The Nutrition group, under the leadership of Regina Torloni announced their participation in an international nutrition meeting in Modena, Italy in 2015 prior to the PREBIC meeting in Florence.
4) Geneticist Nanbert Zhong, an active member of the PREBIC, presented his work on the Lnc-RNA pathway involved in the premature rupture of membranes, an epigenetic approach to the study of the pathogenesis of reproductive disorders [128].
5) Finally, combining the Systems Biology group with the Animal Model group led to several future new animal studies by PREBIC investigators led by Elizabeth Bonney [89].

The Young Scientist Form was again a high light of the 2004 meeting (Table 7).

3.3.1. Meeting 13: 2015 | International PTB meeting | Florence, Italy

3.3.1.1. First SM. The first SM was a two-day meeting on March 24 and 25 organized by David Olson, who initiated an expanded global program during the 2014 PREBIC meeting at WHO referred to as OPERA(Table 8). **O**ptimal **P**regnancy **E**nvironment **R**isk **A**ssessment is an international, interdisciplinary program of women's health researchers, care providers, foundations and international agencies

Table 7
Young scientist forum 2014.

Investigator Name	Affiliation	Lecture Title
Sangmi Lee, PhD [144]	(Junior Faculty, mleukocytes ember of the Ewha University, Korea)	Feeding restriction and lactation induces programed changes in rat offspring
Jun Takeda MD, PhD [145]	(Junior Faculty, University of Alberta, Canada)	Pregnant peripheral leukocyte migration during late pregnancy
Frederik Hermans, PhD [146]	(Junior Faculty, Academic Medical Center, Amsterdam, Netherlands)	Risk stratification with cervical length and fetal fibronectin in women with threatened PTL
Jane Ng, PhD [147]	(Junior Faculty, University of Alberta, Canada.)	The utility of human DNA methylation for profiling mouse genomic DNA

Table 8
Topics discussed at OPERA pre-SRI SM.

Topic 1	The value of risk assessment & interventions
Topic 2	The outcome of victims of national disasters, violence and marginalized populations
Topic 3	Stress and allostatic load [148,149].
Topic 4	Inflammation and infectious diseases; genetic mediators and environmental exposures
Topic 5	Screening for pre-eclampsia
Topic 6	Gestational diabetes and preterm delivery in Zambia; report on a Brazilian multicenter study on PTB; Korean cohorts on adverse pregnancy outcomes; megacities and urban development
Topic 7	Achieving participation by women at risk; nutritional interventions; tobacco-free environment for healthier outcomes

Table 9
Topics discussed at PREBIC pre-SRI SM.

Topic 1	Can PTB be prevented? [77,158,159]
Topic 2	The use of probiotics for the prevention of PTB [161].
Topic 3	Dysregulation between decidual cell progesterone receptor activity in PTB.
Topic 4	Association between risk indicators and PTB: A structural approach.
Topic 5	Stress and Allostatic load [15,162].
Topic 6	The uterine unfolded protein response regulates gestational length.
Topic 7	Diagnostic and prognostic value of biomarkers of infection and inflammation in PTB.
Topic 8	Preterm labor: Improving clinical outcomes now and in the future.

dedicated to discovering and disseminating inexpensive and accessible tools to diagnose women at risk of (PTB) or other adverse pregnancy outcomes as early as possible in pregnancy [148]. Over a period of two days, 37 invited guests presented 20 lectures in seven sessions and six round-table discussions [112]. The table below depicts the topics covered:

3.3.1.2. Second SM. The second SM in San Francisco followed the above meeting and was the eighth PREBIC SRI SM prior to the SRI meeting on March 25th [150]. This SM consisted of a series of 8 lectures by invited guests prior to the 3-day SRI meeting (Table 10).

1) The first lecture was to be given by John Newnham of the University of Western Australia who initiated a prospective study on PTB prevention composed of a composite of 6 evidence-based interventions shown to reduce the risk of PTB [78]. This is the first study to systematically assess a combination of factors. Unfortunately, Professor Newnham could not attend the meeting and in his place, Craig Pennell a collaborator in this study, gave the presentation.
2) Next was a provocative presentation by Ronald Lamont from the University College of London UK on the use of Microbicides in the prevention of PTB "Lost in Transition" [151]. As the readers of this paper fully acknowledge that infection has been shown to be significantly associated with PTB; however, as epidemiologic studies have shown the association does not mean causation. The multiple studies on the use of antibiotics to treat/prevent PTB have been mixed [152,153].
3) Following the above lecture on infection, Ram Menon presented a paper on genital mycoplasmas as a modifier of PTB risk. Based on in vitro evidence, he suggested that genital mycoplasma providers of probiotic environment where they produce a substantial amount of anti-inflammatory cytokines. Potential cause of PTB during infectious setting is over growth of pathogenic bacteria such as E. coli, GBS and Gardnerella that can diminish anti-inflammatory mycoplasmas [154].
4) Over the past 3 years there has been a considerable interest by the Reproductive Endocrinologists in how the deciduae of the uterine wall controls implantation. Dysregulation could be secondary to progesterone deficiency as a regulator of successful implantation. Therefore, we asked Charles Lockwood of USF Health to provide an update as to how and why progesterone plays a role in decidual cell function [62,88,155].
5) We next had a series of five lectures to explore the components of an International effort to prevent PTB. First, Frederk Hermans from Amsterdam started with a discussion of the associations between risk indicators of PTB to identify women at risk for PTB [81,146]. Second, Gerlinde A Metz of the University of Lethbridge in Alberta, Canada, presented a "Novel" approach using an animal model to study how stress can cause PTB using allostatic load as a marker of risk [148,149]. Third, Jennifer Condon from Wayne State and the NICHD Perinatal Research Branch presented an interesting way using how and unfolded protein in uterine tissues can play a role in regulating gestation length which is an example of how dysregulation of uterine function can be assess by a protein biomarker [34]. Fourth, a long time member of PREBIC, Marian Kacerovsky, gave a very complete discussion of using a composite of biomarkers to assess the risk of inflammation & infection and PTB [156,157]. The fifth lecture was a summary by Jane Norman from the University of Edinburgh, UK. She assessed the current status of clinical outcomes using the state of the art approach to PTB birth by first discussing moving beyond silos and how to provide distributed personalized medicine [158]. In addition, she considered the future to characterize how the international community can reduce to incidence of PTB and reduce both maternal and infant poor outcome by summarizing the NICE UK guidelines from the National Institute for Health and care excellence [159,160].

The outcome of these two SMs provided up-to-date information about the epidemiology, mechanisms, behavioral and environmental issues about the cause, management and prevention of PTB. Over 200 investigators and clinicians chose to attend these two meetings for an update on the problem of PTB.

Table 10
Lectures given by PREBIC members at SM in Modena, Italy.

Lecture 1	PTB a global crisis
Lecture 2	Current interventions to prevent PTB
Lecture 3	PTB Prevention: A deep look into Progestogens
Lecture 4	Why does antioxidant supplementation fail to prevent PTB?
Lecture 5	The Microbiome and PTB [162,163].
Lecture 6	Probiotics and PTB prevention [108,109]
Lecture 7	Vitamin D and PTB [164]
Lecture 8	Alpha lipoic acid as an effective anti-Inflammatory agent

3.3.1.3. Third SM. The third PREBIC SM was held in Modena, Italy before the annual pre-PREBIC Meeting in Florence, Italy. PREBIC decided to have its 13th International meeting in Florence, Italy to take advantage of an invitation by the Society of Italian Perinatal Medicine to participate in their annual meeting on nutrition and PTB in Modena, seven PREBIC investigators gave lectures and two Italian investigators each gave a lecture. This meeting was attended by 225 Italian investigators. The PREBIC lectures are listed in Table 10:

3.4. PREBIC annual PTB Meeting in Florence, Italy, May 8–10, 2015

The meeting in Florence was hosted by Gian Carlo Di Renzo and held at the PREIS School Headquarters "The Institute Digli Innocentl". The meeting was started by a lecture from the president of PREBIC, Craig Pennell, on the future directions of PREBIC. The meeting for this year was broken down into two "state-of-the-art" lectures for the first day plus an update on the progress of OPERA and a review by each of the 6 established working groups.

3.5. Day 1 session 1: PREBIC: past, present and future

State of the art lecture 1: Why antioxidant supplementation fails in PTB prevention was given by Ram Menon with a fascinating lecture on the senescence signals generated by OS damage, a mechanistic perspective state of the art lecture [15].

State of the art lecture 2: The placental microbiome: "friend or foe" was discussed by Bo Jacobsson who reported on the young scientist group led by Indira Mysorekar [163].

These two lectures were followed up by a report on the progress and future of OPERA by David Olson. Next, the leader of each working group gave a report on the progress to date of each group. It should be noted that PREBIC continued to recognize the need to change the working group based upon an ongoing process of concept mapping. The PREBIC working groups are listed below in Table 11. During the previous two years it was recognized that presentations by young investigators became an important transition for PREBIC because the board of directors recognized the importance of talented young investigators contributing to the process of understanding the causes of PTB.

3.6. Day 1 session 2: PTB prevention in low and middle-income countries

Three issues were discussed:

1) A Global view of interventions to prevent PTB was presented by Gian Carlo Di Renzo with Practical considerations for PTB Prevention [165,166].
2) A report by Joe Leigh Simpson, the Senior VP of the MOD on the coordination of international PTB research.
3) The formulations for PREBIC guidelines for global prevention of PTB was an important part of the discussion.

3.7. Day 2 session 3: Iatrogenic PTB-The poor cousin to spontaneous PTB?

There were three excellent presentations:

1) Nutrition and pregnancy outcome and several of the studies on obesity that were presented at the Modena SM were discussed considering the increase incidence of obesity world-wide.
2) An excellent presentation was given by Jane Hirst of Oxford on the prevention of PTB with a better understanding of the importance of **gender** differences on fetal growthbased on the Intergrowth Fetal Growth Chart Project initiated by Jose Villar [167,168].
3) In addition, there was a discussion led by Al Brann, a neonatologist from Atlanta Georgia and a new member of PREBIC on the management of the woman at risk of recurrent extreme PTB with prevention rather than cure and a discussion on births between 16 and 24 weeks.

Table 11
PREBIC working groups.

Group 1	New/Young Investigators
Group 2	Systems Biology & PGP (Preterm Gene Project)
Group 3	Nutrition Group
Group 4	Biomarker & PBG (PTB Genes)
Group 5	Epidemiology Group
Group 6	Global Initiative Group (OPERA)

3.8. Day 3 session 4: PTB prevention-is it possible?

PTB Prevention-what is known and what is unknown? And recent reduction in rates of PTB in the United States-how did they do it? [81,82] And a lecture on a molecular solution to the progesterone conundrum by Sam Mesiano [61].

3.9. Day 3 session 5: The future of PREBIC

There was a final discussion of three important issues.

1) The Development of PREBIC Guidelines for the Global Prevention of PTB. How will OPERA help us accomplish the development of guidelines?
2) The Planning for the next PREBIC General Meeting
3) Discussion of Working Group Accomplishments for 2015

3.9.1. Final PREBIC Young Investigator meeting for 2015 | Seattle Washington (supported by GAPPs)

The title of this meeting was "Microbial Etiologies of Preterm Birth" and the following presentations provided the background for future planning of working groups lead by Young Investigator Groups (**YIG**).

1) The clinical research lecture was led by Joseph Hwang on the "Role of the Cervix in Preterm Birth"; Microbial/Inflammatory working group progress report by Angela Vinturache and the "Role of microbes, progesterone and PTB" by Cynthia Gyamfi-Bannerman.
2) The translational research lecture was led by Indira Mysorekar on the "Use of ultrasound to assess cervical competence" by Helen Feltovich and the "Biological pathways to PTB and fetal injury by Kristina Adams Waldorf followed by a feedback and advice by Ram Menon.
3) Finally, the basic science research lectures were moderated by Cynthia Gyamfi-Bannerman. The presentation on the "Placental Microbiome" was presented by Indira Mysorekar followed by a presentation of the "Oral Flora and PTB" by Yiping Han followed by feedback and advice from Calvin Hobel.

The key questions about the future of **YIG's** was discussed by Bo Jacobsson from Sweden on the importance of grant application, future working group symposia and the development of new research questions. The overall value of the above Satellite Symposium demonstrates the role that PREBIC identified to support the young investigator groups (**YIG**).

4. Final discussion & summary

During the first meeting of the PTB Collaborative in 2003, Xiaobin Wang gave the first comprehensive view of the interaction between genes, the environment and behaviors [7]. In addition, an update on the Human Genome Project (1990–2003) was provided. As a result, genetics became a focal point for the next two meetings of the 6 working groups to begin a search for the cause of PTB.

During the sixth meeting in 2008, Siobhan Dolan discussed the human genome epidemiologic (HUGE) study which was followed by a discussion of the role of the environment and stress and the risk of PTB by Ram Menon [26]. The next major step toward understanding the genetics of PTB was a lecture by Davey Smith at the PREBIC SM in Scotland (meeting #7, 2009) about the association between genes for adiposity and fat distribution and how BMI can be used as an indicator of future mortality secondary to CVD [43]. This was the first link where a risk factor during pregnancy and the risk for CVD was mentioned.

The next important step occurred during the eighth meeting in 2010 where Michael Kramer attempted to connect the risk of PTB to two pathways, the stress pathway and vascular pathway, both of which are also two important risk factors for CVD. It wasn't until the 9th meeting in 2011 that several geneticists re-addressed the complex interrelated constellation of pathways. In 2005 Lewis Muglia discussed the role of evolutionary genomics and the risk of PTL [37]. In 2011, Wildman et al. discussed the role of evolutionary genomics and the role they play during pregnancy to assure a successful pregnancy and what changes have occurred in the mother's genome and placenta to result in early PTD [169]. In addition, we returned to the issue of the risk of CVD by having K. Sutten-Tyrrell et al. discuss how low levels of sex hormone-binding globulin and high levels of free androgen index levels are related to the risk of CVD in women [71]. It is of interest that the first prospective study reported in 2016 on biomarkers for the identification of the risk of spontaneous PTB identified two markers insulin-like growth factor binding protein (IGFBP4) and sex hormone-binding globulin (SBG) ratio (IBP4/SHBG) that significantly predicted the risk of spontaneous PTB, again related to two genes that are associated with CVD risk [170].

Thus, in the past three years of PREBIC activities (2016, 2017 & 2018) [refer to PREBIC website for summary www.PREBICGlobal.org] there has been a tremendous advancement in identification of genes related to PTB. In 2017, a combined study of genetic investigators (Zhang G et al.) lead by Louis J. Muglia in a discovery and replication study of genetic associations with gestational duration and spontaneous PTB. Nine genes were identified at the level of the maternal genome [171]. The authors' conclusions of this genome wide association study identified genes associated with uterine development, maternal nutrition and vascular control. Thus, it appears that these studies support a connection between behaviors, the environment and vascular dysregulation supporting the possibility that PTB may be associate with major cardiovascular risk factors. This is supported by the recent epidemiologic study by Tanz LJ et al. showing a significant relationship between the history of PTB in women is significantly related to the subsequent early development of CVD [172]. PREBIC's goal for the next several years will be to take a global approach to begin a process of how to prevent PTB, since we now have an improve assessment of the cause of PTB. Refer to Appendix III: **PREBIC Global Initiative**.

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Appendix J. Supplementary data

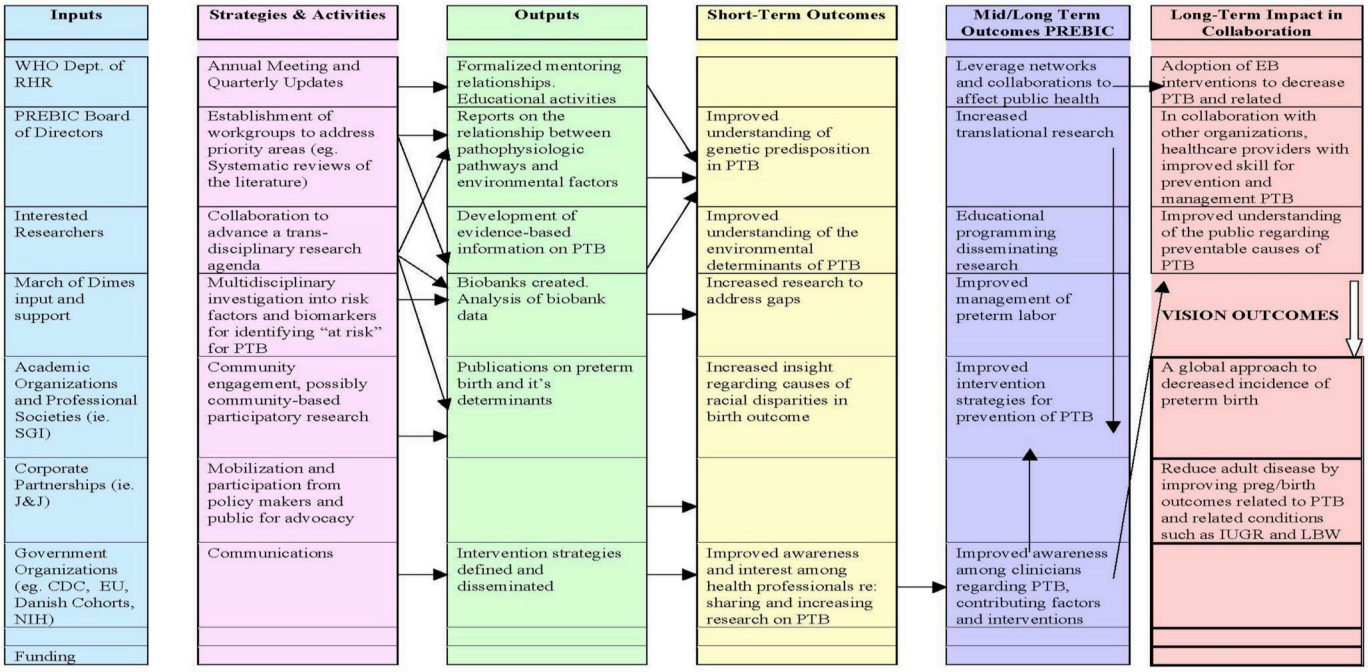
Supplementary data to this article can be found online at https://doi.org/10.1016/j.placenta.2019.03.008.

APPENDIX I

LOGIC MODEL.

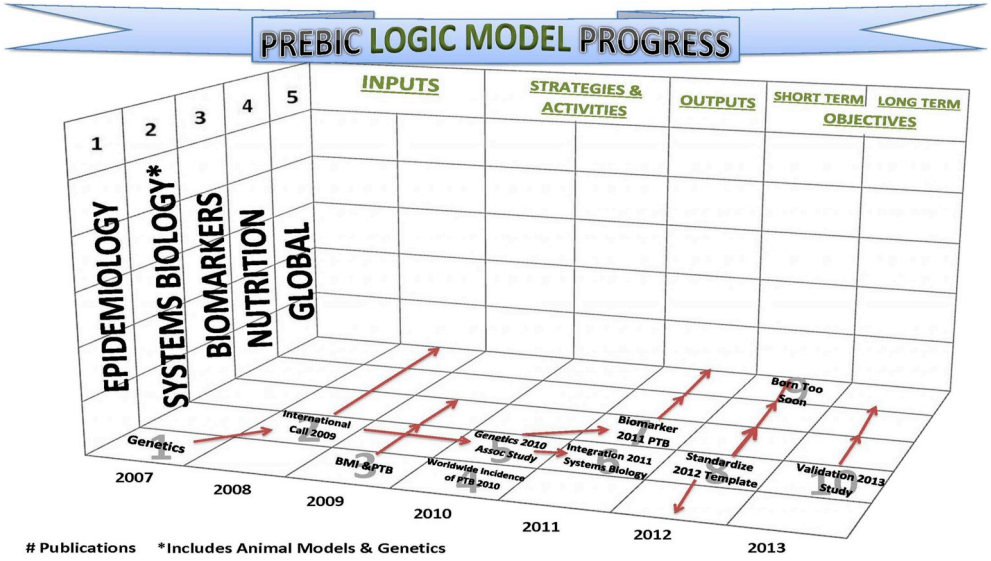
Logic Model for Preterm Birth International Collaborative (PREBIC)
Version of December 19, 2007

Principal Target Population(s): Researchers in Preterm Birth --- eventually clinicians and pregnant women



APPENDIX II

3D LOGIC MODEL SHOWING WORKING GROUPS & PUBLICATIONS.



APPENDIX III

PREBIC GLOBAL INITIATIVE.

The above global map lists the PREBIC branches: United States, South America, Africa and the Australasia Branch (China, South Korea and Australia). The red dots are locations of yearly PREBIC Meetings and the light green dots are PREBIC SMs.

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