Roya Kabuki Program at Boston Children's Hospital
Progress report YEAR 1 (08/17-07/18)

Program team:
Milestone: recruit program team and establish operational basis
Olaf Bodamer MD, PhD, FAAP, FACMG (Director)
Emanuela Gussoni PhD (Co-Director)
Christina Hung MD, FACMG (Scientific Team Leader)
Tara Daly MSc (Program Coordinator)
Lee Chun Li MSc (Research Associate)
Asma Rashid MSc (Genetic Counselor)
Clara Hildebrandt MD (Genetics Fellow)
Julia Thomann MSc (Social Worker)
The program team meets on a weekly basis (Fridays 2pm-3pm).

Multidisciplinary clinic for Kabuki syndrome (start 1/2/18):
Milestone: establish multidisciplinary clinic by January 2018
The holistic approach to patient care in the Roya Kabuki Program is reflected through the multi-disciplinary approach. Kabuki sub-specialists (or "champions") were identified in Cardiology (Laura Mansfield MD), Endocrinology (Jessica Kremen MD), Immunology (Christina Yee MD), Neurology (Kerrie LaRovere MD), Neuropsychology (Ben Goodlett PhD), Nutrition (Krista Viau PhD), Ophtalmology (Anne Fulton MD) and Otolaryngology (Sukgi Choi, MD, Margaret Kenna MD PhD). Sub-specialists meet once per month to discuss individual patients, clinical research projects and collaborative efforts.

Patient outreach activities (in chronological order):
Milestone: not defined
November 17-18, 2017 ATK family event in Cleveland Ohio. Presented information on the established Roya Kabuki Program, actively recruited families to research protocol.
October 23, 2017 Kabuki Awareness Day. Letter introducing the Roya Kabuki Program, Halloween card and treats sent to 36 families.

January 11, 2018 Family event at BCH. Introduction of the Roya Kabuki Program to local families (12 families). Announcement of the opening of the Roya Kabuki interdisciplinary clinic, active recruitment of new families to research protocol and sample collection (blood and urine).
June 10, 2018 BCH Walk Team "Kabuki Friends". Raised $12,000 (26 participants).
July 13-14, 2018 ATK family event in Cleveland, Ohio. 27 new families scheduled to be consented to the Roya Kabuki Program.

Patient recruitment:
Milestone: Recruit 10-15 families/quarter, establish Biorepository
87 families have been in contact with the Roya Kabuki program since September 2017 (start date of the program coordinator Tara Daly). 54/87 families have been consented to the research protocol. 23/57 families have received the enrollment forms, but did not yet consent/signed. 46/54 families have sent complete sets of samples (including blood and urine), which have been processed and stored at -80^{o}C for analysis. These samples constitute the present (or current) Kabuki biorepository at Boston Children's Hospital.

Internet presence:
Milestone: establish a website
Information about the Roya Kabuki Program has been added to the BCH website: http://www.childrenshospital.org/centers-and-services/programs/f-_-n/roya-kabuki-program and the Bodamer laboratory website: www.bodamerlab.org

Collaborations:
Milestone: establish Kabuki network
A formal collaboration to facilitate clinical and translational research on Kabuki syndrome has been established with Cincinnati Children's Hospital (Andrew Lindsley MD PhD) and Children's Hospital of Philadelphia (Ko Izume MD PhD) as part of the GRIN (Genome Research Innovation) network. A first project on "Immune function in patients with Kabuki syndrome" has been initiated through Cincinnati Children's Hospital with participation of all Kabuki patients seen through the Roya Program.

Olaf Bodamer has joined the Takeda Kabuki Scientific Advisory Board to facilitate translational research on Kabuki syndrome between the US, Europe and Asia.

Scientific work:
Milestone: submit samples for biomarker screen
61 plasma samples (27 patients, 31 controls) and 44 urine samples (24 patients, 20 controls) were submitted to the Metabolomics Core at the Broad Institute (Clary Clish PhD) for targeted and untargeted metabolome analysis by LC-MS/MS (liquid chromatography tandem mass spectrometry). Raw data has been returned and is currently being analyzed.

Milestone: submit samples for transcriptome analyses
18 RNA samples from blood (12 patients, 6 controls) were submitted to BGI for transcriptome analysis. Raw data has been returned and is currently being analyzed.

Milestone: establish cell lines for drug screening and other functional testing
Cell lines from Kabuki patients are continuously being established. The main method is to establish lymphoblastoid cell lines by EBV transformation of lymphocytes from blood. If skin biopsies are available, primary fibroblast cell lines can also be established. Currently, lymphoblastoid cell lines from 1 KMT2D and 3 KDM6A patients and their family members have been established. We have one primary fibroblast cell line of a KDM6A patient.
Various translational read-through inducing drugs (TRIDs) have been purchased.

Grant submissions:
Milestone: submit one to two proposals per year

1) Harrington Discovery Institute Scholar-Innovator Award 2018 (submitted 5/17): – Disorders of epigenetic dysregulation- Budget $100,000 (not funded)
2) Takeda Pharmaceuticals (Cambridge MA) – "Kabuki Syndrome Natural History Study" (submitted 1/18). Budget $238,000 for one year (decision pending).
3) NIH U54 Rare Disease Consortium –"Disorders of Histone Modification" (deadline for submission 10/18). Budget $5 millions (1 million/year for five years).

Publications:
Milestone: not defined

1) Yap KL, **Bodamer O** et al. Congenital hyperinsulinism as the presenting feature of Kabuki syndrome: clinical and molecular characterization of 10 affected individuals. *Genet Med* 2018 (in press).
2) Adam M, **Bodamer O** et al. Clinical diagnostic criteria for Kabuki syndrome. *J Med Genet* 2018 (submitted).