ARRAY BIOPHARMA

Inventing, Developing & Commercializing Targeted Small Molecule Drugs for Patients Living with Cancer

Global Medicinal Chemistry and GPCR Summit

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Partnering and Outsourcing, Experiences from a Small Company Perspective

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Disclaimer

- All of the data to be presented has been taken from publicly available sources
- The presenter is an employee of Array BioPharma
- Any conclusions drawn or opinions stated are those of the presenter and do not necessarily reflect the official position of Array BioPharma

Outline

- Array Biopharma, background and history

- Collaborations
  - An integral part of our business model (past, present and future)
  - Various alliance structures utilized
  - Some case studies and discussion

- Outsourcing
  - Array is driving towards commercializing in 2018
  - Flexible business model
  - Strategic partnerships
  - Finding the right CRO's

Array BioPharma History at a Glance

- Small molecule drug discovery & development company
  - Boulder, Colorado, USA
  - Founded 1998
  - NASDAQ: ARRY
  - ~210 Employees
- Fully integrated discovery & development platform
- 23 INDs generated[1]
  - 70% Targeting Protein Kinases
  - ~16 compounds currently in clinical trials
- Binimetinib (MEK inhibitor) and Encorafenib (Raf inhibitor) - NDAs
- Partnerships with major pharma and emerging biotech
- Array assets have formed the basis of two new companies to date
  - VentiRx (Now part of Celgene) (2007): TLR8 agonist: VTX-378[2]
  - Loxo Oncology (2013): panTrk: LOXO-101 (Larotrectinib)[3]
  - Array received an equity stake in both companies[2,3]

1. http://www.arraybiopharma.com/discovery-collaborations/array-discovery-capabilities/
2. Array BioPharma Inc., 2008 10-K report
3. Array BioPharma Inc., 2014 10-K report

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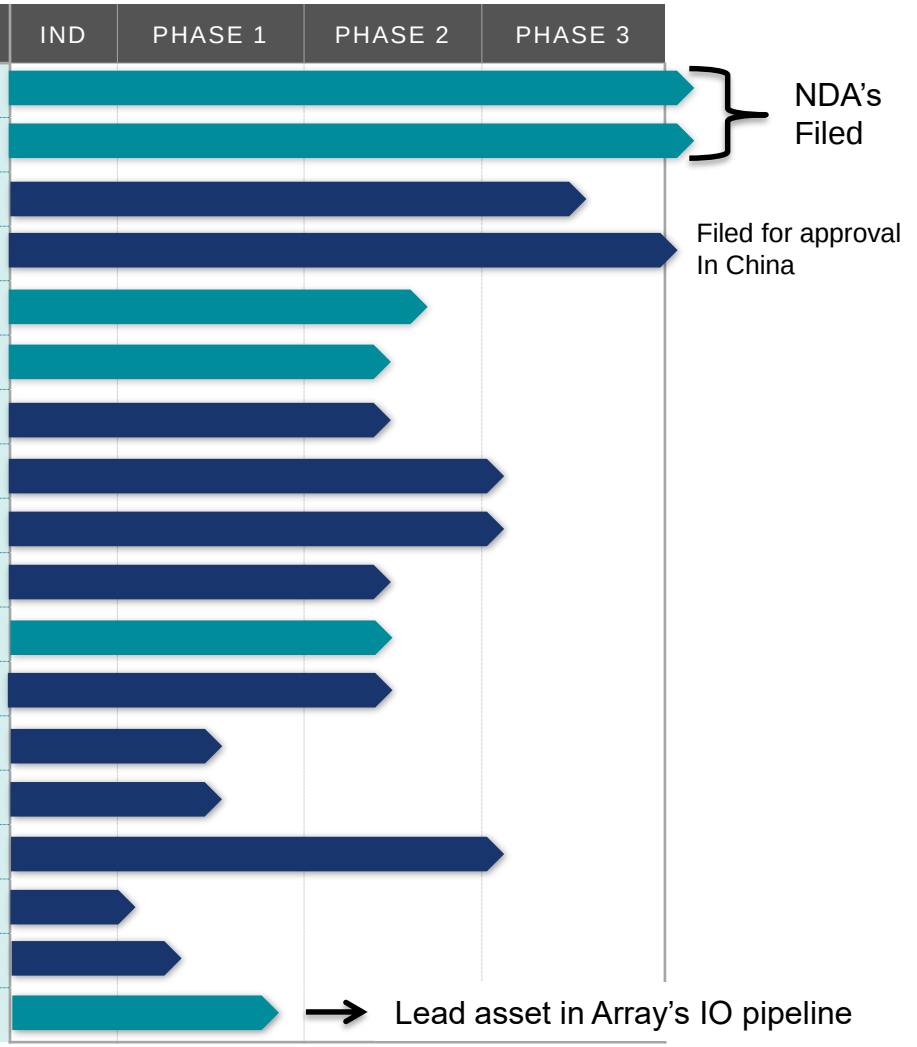
Robust Development Pipeline[1]

- Collaboration, partnering and licensing deals have been instrumental*

DRUG	INDICATION	TARGET
Binimetinib / MEK162*	Cancer	MEK
Encorafenib / LGX818	Cancer	BRAF
Selumetinib / AZD6244 (AstraZeneca)*	Cancer	MEK
Danoprevir / ASC08 (Roche)*	Hepatitis C	NS3 protease
Filanesib / ARRY-520	Multiple Myeloma	KSP
ARRY-797	LMNA-dilated DCM	p38
Motolimod / VTX-378 (Celgene)*	Cancer	TLR
Varlitinib / ASLAN001 (ASLAN)*	Cancer	Pan-HER
Ipatasertib /GDC-0068 (Genentech)*	Cancer	AKT
LY2606368 (Eli Lilly)*	Cancer	Chk-1
ARRY-502	Inflammation	CRTh2
ONT-380 (Cascadian)*	Breast Cancer	HER-2
GDC-0575 (Genentech)*	Cancer	Chk-1
GDC-0994 (Genentech)*	Cancer	ERK
LOXO-101 (Loxo Oncology)*	Cancer	Pan Trk
LOXO-195 (Loxo Oncology)*	Cancer	Pan Trk
LOXO-292 (Loxo Oncology)*	Cancer	RET
ARRY-382*	Immuno-Oncology	CSF1R



1. http://www.arraybiopharma.com/

What has Array brought to the table?

- Extensive expertise prosecuting kinase targets
- Novel and high quality lead chemical matter
- High quality protein crystallography
  - Several “original” structures
  - Experienced computational chemists
- Historically superior productivity and candidate quality[1,2]
  - Program cost efficiency ~35% better than industry average
  - Program time efficiency >15% better than industry standard
  - Attrition metric ~40 % better than industry standard

1. Paul et al. Nature Rev. Drug Dis. (2010) 9, 203-214.
2. Independent audit by external consulting company

Some collaboration strategies Array has utilized historically

- Partnering clinical stage asset – with co-development rights
  - MEK inhibitor (MEK162/binimetinib) with Novartis[1,2]
- Partnering clinical stage asset with additional research collaboration on the target
  - Glucokinase activator ARRY-403 with Amgen[3]
- Multi-target research deal with partner having option to develop resulting assets
  - Genentech[4]
  - Celgene[5]
- Partnering pre-clinical asset with additional research collaboration on further targets
  - Loxo oncology (formation of new company)[6]

1. Array BioPharma Inc. 10-K Report 2011; 2. Array BioPharma Inc. 10-K Report 2017;
3. Array BioPharma Inc. and Amgen Inc. Press Release, Dec. 14th, 2009; 4. Array BioPharma Inc. press release: Jan. 5th 2004;
5. Array BioPharma Inc. and Celgene Corp. Press release, Sept. 24th 2007; 6. Array BioPharma Inc., 2014 10-K report

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Aspects of a rewarding research collaboration

- Multiple year
- Partner engages in active and collaborative research on the targets
- Timely generation of IND's - adding value for the partner
- Partner exercises some options / develops assets
  - Milestone payments - adding value for Array
- Repeat business (adding targets / time to collaboration)
- Array FTE's funded - adding value for Array
- Array brings IP and/or expertise to the collaboration
- Expands the knowledge base of the organization
  - Enhances potential for extending or new collaborations

Case study 1- Genentech (Roche) collaboration - Model 1

- Collaboration began in 2003. Multiple extensions.
  - Research funded through January 2013[1].
- Initially two oncology targets – option to add targets[2]
- Two compounds moved to the clinic
  - GDC-0994; Erk inhibitor (Phase 1)[3]
  - DGC-0068 / Ipatasertib; Akt inhibitor (Phase 3, several Phase 2)[1]
- Array has received research funding, upfront and milestone payments ($26.5 million)[1]
  - Array is eligible to receive further milestone and royalty payments[1]
- Additional licensing agreement for Chk-1 inhibitor (GDC-0575)[1]
  - 2011; Array received upfront payment ($28 million) and is eligible to receive milestone and royalty payments[1]

1. Array BioPharma Inc. 2016-2017 10-K report; 2. Array BioPharma Inc. press release: Jan. 5th 2004;
3. http://www.arraybiopharma.com/product-pipeline/other-compounds/gdc-0994/

Case study 1 (Model 1) – key learnings

Checks all the boxes

- ✓ Multiple year
- ✓ Partner engages in active and collaborative research on the targets
- ✓ Timely generation of IND's - adding value for the partner
- ✓ Partner exercises some options / develops assets
  - ✓ Milestone payments - adding value for Array
- ✓ Alliance extensions (adding targets / time to collaboration)
- ✓ Array FTE's funded - adding value for Array
- ✓ Array brings IP and/or expertise to the collaboration
- ✓ Expands the knowledge base of the organization
  - ✓ Enhances potential for extending or new collaborations

Model 1 – additional learnings

- An effective collaboration model
  - Resource from both parties was applied
  - Good collaboration at the scientific level
  - Joint Research Committee to give feedback to team and help guide progress
  - Flexible agreement allowed for expansion and additional targets
  - Fruitful research collaboration helped enable subsequent licensing deal
- The needs of a collaborator can change over time
  - All good things will come to an end
  - Helpful to have a smooth winding down of research activities
  - 120 day “sun-set” clause[1]
- Reliance on a few larger collaborations
  - Takes time to replace

1. Array BioPharma Inc. 2013 10-K report

Case study 2 – Celgene collaboration - Model 2

- Collaboration began in 2007[1]
- Initial upfront payment to Array of $40 million[1]
  - Potential for milestone and royalty payments[1]
- Array to work on 4 targets (oncology and inflammation)[1]
- Array to progress through Phase 1 or 2a in the clinic[1]
  - Milestone payment at IND acceptance[2]
- Partner had ability to exercise an option on up to 2 programs[1]
- Amended in June 2009 (additional $4.5 million payment)[3]
- Partner waived rights to one program (September 2009)[3]
- Partner named remaining 3 targets (April 2010)[3]
  - CSF1R (oncology), TYK2 (inflammation) and PDGFR (fibrosis)[3]

1. Array BioPharma Inc. and Celgene Corp. Press release, Sept. 24th 2007
2. Array BioPharma Inc., press release, Nov. 30th 2010; Array BioPharma Inc. 2011 10-K report.
3. Array BioPharma Inc., 2010 10-K report

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Case study 2

- ARRY-382 (CSF1R inhibitor) – IND Nov. 2010[1]
  - $10 million milestone payment to Array[1]
- Additional agreement, July 2013[2]
  - Inflammation target[2]
  - $11 million upfront payment to Array[2]
- Two programs moved to clinical stage, two to preclinical candidate stage
- Partner did not exercise its option to develop any of the assets[3]
- Array retained rights to the programs[3]

1. Array BioPharma Inc., 2011 10-K report
2. Array BioPharma Inc., 2014 10-K report; Array BioPharma Inc., press release, July 29th, 2013
3. Array BioPharma Inc., 2013 10-K report; Array BioPharma Inc., 2016 10-K report

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Case study 2 (Model 2) – key learnings

Most boxes checked

- ✓ Multiple year
- \- Partner engages in active and collaborative research on the targets
- ✓ Timely generation of IND's - adding value for the partner
- \- Partner exercises some options / develops assets
  - ✓ Milestone payments - adding value for Array
- ✓ Alliance extensions (adding targets / time to collaboration)
- ✓ Array FTE's funded - adding value for Array
- ✓ Array brings IP and/or expertise to the collaboration
- ✓ Expands the knowledge base of the organization
  - ✓ Enhances potential for extending or new collaborations

Model 2 – additional learnings

- Looking at the big picture – can be viewed positively
- Array got to retain all the assets and IP
  - Research funded for >5 years
  - Valuable assets created
    - ARRY-382 (CSF1R inhibitor) – currently in active development
    - Other assets available for development or partnering
- Partner got a look at multiple targets – two at a clinical stage
  - Probably a reasonable value from their perspective
  - Reasonable investment for research on >4 targets over >5 years including two taken to an early clinical stage
  - Were able to make informed decisions on the targets

Considerations

- An upfront payment seems good at first ……
  - As time progresses and money is spent, *perception* may change
- Companies visions change with time
  - Don’t assume that what the collaborator says today will be the same a few years later
- Active research investment by the collaborator probably gives a better sense of commitment to a target than passive investment
  - But which model is preferred may be a matter of opinion
- It is disappointing to deliver a high quality candidate and for the partner to not take it forward
- Array retained rights to programs not progressed by partner
  - Ultimately still a “win” for Array

Other learnings

- Array was empowered to drive the program forward
  - Face to face / Joint Research Committee meetings quarterly
- Good when things go well and no unexpected issues
  - Can get on with research without disturbance
- But collaborators changing view of a target and where to take a drug candidate clinically (translational) can be missed
  - Clinical trial design considerations
- Array appreciated closer involvement with the partner as the collaboration progressed
- Ultimately decisions on whether to exercise an option made by a large corporation take into account a variety of considerations
  - Business, scientific
  - Have to accept it and move on
  - What is seen as valuable to a small corporation may not be for a large one

Comparing the two models

- Which is preferred may be a matter of risk tolerance
- Model 1 (i.e. Genentech collaboration)
  - ~10 years of steady research funding
  - Some compounds were moved into the clinic
  - A steady flow of modest milestone payments
  - Royalty payments may be realized
  - Not game changing for Array, but low risk and steady
- Model 2 (i.e. Celgene collaboration)
  - >5 years of research funding
  - Clinical and preclinical candidates produced
  - Lack of certainty whether the partner would exercise its options
  - Array ended up with the rights to all the assets being returned
  - But decision whether to sell or develop assets has to be made
    - Decided to develop CSF1R inhibitor – lead Immuno-oncology asset
  - Higher risk (but potentially game changing for Array)

What are potential partners looking for now?

- License clinical stage asset
  - Later stage clinical assets (Phase 2 data) are becoming increasingly difficult to find
  - Early clinical or late stage preclinical assets are being licensed
    - Incyte licenses Arginase Inhibitor CB-1150 from Calithera ($53 million)[1]
    - Compound was in early Phase 1 clinical trial

- Platform target research collaborations with options to license resulting drugs
  - Blueprint receives $45 upfront from Roche to work on up to 5 “immuno-kinase” targets[2]
  - Roche can exercise an option on up to at least 3 programs after Phase 1 clinical data has been generated

1. Fierce Biotech Jan. 30th, 2017
2. Fierce Biotech March 15th, 2016

What kind of collaboration is Array currently looking for?

- Platform research deal
  - Based on advanced pre-clinical (or early clinical) matter
  - Potential for expansion to additional targets

- Could be based around target or technology for example:
  - Immuno-oncology
    - Array has a number of ongoing IO kinase projects
  - Brain penetration
    - Array has the technology to discover brain penetrant compounds
    - A number of kinase programs with brain penetrant lead matter
  - Potentially outside of oncology
    - For example, recent collaboration with Amgen
    - Inflammation target discovered using Array's proprietary Kinase Directed Phenotypic Screening Platform[1]

1. Array BioPharma and Amgen press release: July 18th, 2017

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Outsourcing

- Array is driving towards commercialization (2018)
- Since ~2014 Array has adopted a flexible resourcing model
  - Internal research group
  - Strategic outsourcing
- CMC group sold (now part of Avista)[1]
  - Ongoing collaboration with Avista under agreement[1]
- Increased outsourcing of synthesis and medicinal chemistry
- Pharmacology, in-vitro ADMET, in-vivo PK
  - To supplement internal resource as required
- Immuno-oncology collaboration
  - Belfer Center for Applied Cancer Science (Dana-Farber)[2]

1. Array BioPharma Inc., 2016 10-K report; Accuratus Lab Services press release, June 2nd, 2015.
2. Dana-Farber Cancer Institute's Belfer Center press release, Feb. 1st , 2016

Synthesis / Medicinal Chemistry Outsourcing

- Determining the best ways to utilize
  - Low vs. high cost CRO
  - FTE arrangement vs. project based
  - Intermediate synthesis
  - Analog synthesis
  - Whether to utilize other services
    - In-vitro assays
    - In-vitro ADME
    - In-vivo PK (with or without bioanalytical)
    - Chiral separation

How has Array utilized outsourcing?

- Some US (high cost CRO)
  - Mainly CMC
  - Some chiral separation
  - Some in-vivo / pharmacology / toxicology
- Mainly low cost CRO's based in Asia (China, India)
  - For intermediate synthesis / medicinal chemistry analog synthesis
  - Cost is a factor – but not the only one
    - Reliability of vendor
    - Vendors experience with the chemistry
    - Communication – very important
    - Detail and thought put into the quote
    - Honesty is appreciated

Synthesis outsourcing

- Array has experimented with various formats
  - FTE based arrangements
    - Good flexibility for analog preparation
    - Balanced against longer term financial commitment
    - Not always easy for a smaller company to sustain
  - Individual project contracts
    - Smaller budget
    - Less flexible for making changes (but can be done)
      - Flexibility of the vendor can be important
    - Can “shop” projects around
      - Not committed to just one vendor
    - Most of what is currently being done
    - Forging trusting relationships with key vendors
      - Takes considerable time and effort to manage

Synthesis and beyond

- Low cost CRO
- Concerns at the outset about reliability of data
  - Difficult chemistry
  - Biological assay
  - In-vitro ADME
  - Pharmacokinetics / bioanalytical
- Our experience is that it can be done
- FTE Arrangement with CRO based in China
  - Accomplished some very challenging synthesis
  - In-vitro ADME and rodent PK data was high quality
    - On challenging chemo-types
  - Demonstrated ability to run biological assays
- Multiple individual synthesis projects with India based CRO

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